LATEST TRENDS IN PHARMACY PRACTICE

Dr. Dinesh Kumar Upadhyay
Renuka Jyothi S
Rishi Kapoor Poddar

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CONTENTS

CHAPTER 1

A COMPREHENSIVE STUDY ON NOVEL ADVANCEMENTS IN DIABETES MELLITUS TREATMENT

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ABSTRACT:

Diabetes mellitus (DM) is defined by high blood sugar involving disruptions in carbohydrate, lipid, as well as protein metabolism caused by abnormalities in insulin in the body, insulin production, or even both. Diabetes is becoming more common all across the world at an alarming speed. The rising incidence of diabetes globally is a reason to be concerned, including both associated with significant morbidity as well as growing healthcare expenditures. DM is a group of metabolic disorders defined by elevated blood sugar levels resulting from inadequate insulin synthesis or cells that do not release insulin. Type I, Type II, and gestational diabetes are the three forms of diabetes. Insulin method for treating diabetes by administering exogenous insulin. This study focuses on diabetes care, with a particular emphasis on the most recent anti-diabetic drugs, and alternate insulin methods of delivery, as well as the artificial pancreas and also this study explores the new diabetes technology to enhance blood glucose management, reduce long-term problems, and also improve the patients' quality of lives. Although these emerging technologies are appealing to be used, they must enhance results like blood glucose management or avoid long-term consequences to achieve efficiency as well as be widely accepted.

KEYWORDS:

Diabetes Mellitus (DM), Insulin, Type 1Diabetes Mellitus (T1DM), Type 2 Diabetes Mellitus (T2DM).

1. INTRODUCTION

Glucose is a basic sugar that may be present in food. It is a nutrient that would be required for the proper development of the body's tissues. Food is prepared in the stomach lining for glucose as well as other nutrients after mealtime. The glucose in food particles is taken into circulation through the intestinal epithelium or transported by the blood to all cells in the human body. Therefore, glucose cannot penetrate the cell on its own. It requires the help of insulin to enter the cell membranes. Insulin, as a result, regulates glucose metabolism within the body. Insulin is known as the "hunger hormone." During a carbohydrate-rich meal, the accompanying insulin levels increase, eventually reducing the blood glucose level, or sugar is carried out from the bloodstream into the cells producing energy.

According to World Health Organization (WHO) statistics, India has 32 million diabetics in 2001. The "International Diabetes Federation (IDF)" estimates that there are around 40.9 million

diabetics in India, with this figure expected to climb to 69.9 million by 2025 [1]. The great majority of diabetes patients come in two main comprises a broad range of groups presently known as type-I or type-II diabetes. Sugar must be transported from the circulation by the hormone insulin. Beta cells in the pancreas create insulin (an organ that produces insulin). This mechanism is slowed in people with diabetes. Diabetes develops so when pancreatic type-I diabetes is characterized by an inability to generate adequate insulin, or by an increase in insulin production is faulty type 2 diabetes cannot transfer sugar from the bloodstream. Either insufficient insulin is produced, or the insulin production is defective and cannot transfer glucose from the bloodstream. Diabetes mellitus belongs to a collection of illnesses that all have increased blood sugar levels as a defining feature. The two most common general categories of this condition are type 1 diabetes and type 2 diabetes[2].

1.1.Diabetes Mellitus Type 1 (T1DM):

Type 1 diabetes can occur at any age, although it appears to be more common in children and youth.Diabetes type-1 is responsible for 5-10% of all diabetes cases in the US. Type-1 diabetes seems to have a genetic component, while the origins remain unknown. Treatment for type 1 diabetes is best accomplished in the framework of a medical provider and contains aspects such as insulin delivery, glucose monitoring, meal preparation, or screenings for comorbid diseases or diabetes-related disorders [3]. T1dm is distinguished by pancreatic -cell loss, resulting in complete insulin insufficiency. There are 2 types recognized: A Type 1A is caused by a cell-mediated autoimmune response,however, type 1B is significantly less prevalent, seems to have no known etiology, and also is usually found in people of African or Asian ancestry with varying degrees of insulin deficiency among rare occurrences of ketoacidosis.

Type 1 diabetes has progressed from a disorder with a high mortality rate before insulin delivery to one that is at a higher risk of long-term sickness or fatality. A major shift in type 1 diabetes therapy is unlikely unless we can break the loops through artificial endocrine pancreas implants, islet transplantation, and stem cell development. In the meantime, people with type 1 diabetes and their healthcare providers should focus their efforts on the therapeutic strategies which have the greatest potential to reduce risks, like hypoglycemia and diabetic ketoacidosis in the short to medium term, as well as microvascular illness or psychological distress over a longer period [4].

1.2.Diabetes Mellitus Type -2 (T2DM):

The winning emotion associated with the gluco-centric approach («beat the sugar and save the patient») or strict glycemic control in T1DM was quickly generalized to T2DM. Meanwhile, the United Kingdom Prospective Diabetic Study (UKPDS) research, reported in 1996, revealed very moderate results: despite a considerable decrease in micro-vascular problems, there was no considerable improvement in macro-vascular outcomes in the subgroup with well-controlled diabetics[5]. Type 2 diabetes is far more frequent, accounting for90% and 95 percent of all diabetes cases adults are the most typically affected by type 2 diabetes, however, this has lately started to occur in youngsters. Type 2 diabetes, lack of physical activity, as well as overweight all have a significant link. Dietary variables could contribute to the emergence of t2d Insulin sensitivity is common among type 2 diabetics [6].

This indicates that their pancreatic is producing insulin, but this is not doing as it should. The pancreas begins to produce more insulin by working harder. It eventually runs out of energy to maintain the proper glucose equilibrium, so blood glucose levels rise. Maintaining a healthier life

might postpone the need for medications and/or insulin. Therefore, it is critical to understand that if you do require pills and/or insulin, this is simply the natural evolution of the illness. The probability of getting diabetic problems could be decreased by taking pills and/or injections as early as they are required [7].

2. LITERATURE REVIEW

Carolina M. Casellini and Aaron I. Vinik stated in a study that ***diabetic*** neuropathies are a diverse set of illnesses characterized by a wide variety of defects. They might be proximal or distal, localized or diffuse, and influence both the autonomicand somatic nervous systems. Diabetes neuropathy causes serious illness and mortality, as well as a decrease in a person's quality of life or daily activities. The disease's therapy is complicated and needs a particular approach. This review discusses current improvements in the prevention of chronic neuropathy signs as well as the basic pathogenesis [8].

LinaXu et al. conducted a study that which epidemiological research has shows that diabetic Mellitus (DM) becomes a pandemic worldwide, along with metabolism or hormonal problems. The vast majority of diabetic individuals develop type -2 diabetes mellitus (T2DM), which would be distinguished by insulin resistance and also increased insulin abnormalities. Despite their therapeutic advantages in the treatment of T2DM, many medications must have had some unfavorable adverse effects. Natural products (NPS) have emerged as major bioactive agent resources for anti-T2DM drug development, given the pathophysiology of T2DM. The goal of this review was to provide a summary of the actions and mechanisms underlying of NPs in the treatment of t2dm. The increased understanding of LNPS for their many regulatory impacts on diverse target or signal pathways would substantially allow the development of anti-T2DM medicines [9].

YananWang et al. proposed in a study that This analysis has thoroughly described the accurate nanomedicine implementation, real-time properties, patient-friendly, in the profession of diabetes prognosis as well as the ability to monitor, and it has emphasized the distinct potential of different nanoparticle carriers (– for example, synthetic polymer nanomaterials, lipid membranes, microcapsules, microparticles, microspheres, and so on.) in the treatment of diabetes as well as problems. Furthermore, the successful nanomedicine for the treatment of different main diabetes problems with dramatically enhanced life quality in diabetic patients was thoroughly reviewed. Following a study of the research, various essential challenges of nanomedicine-based strategy applications, stability as well as long-term stability implications in vivo, a lack of formulation delivery guidelines, scale-up feasibility, as well as other challenges must be resolved. Therefore, the study gives insights into the development, benefits, and limits of innovative nanomedicine applications in diabetes diagnosis, tracking, as well as treatments [10].

3. DISCUSSION

A malfunction of this autoregulation framework either as the pancreas's inability to synthesize any or inadequate insulin, pancreas overburden from ingesting too many artificial sweeteners over a lengthy amount of time, and over compensatory response, or a mixture of these - problems such as lack of insulin and thus high blood sugar. This is a defining feature of diabetes mellitus (commonly called diabetes).

1. Fasting glucose (100 to 125 milligrams per deciliter is damaged).

2. Insulin resistance (fasting glucose just under 126 milligrams per deciliter or two-hour levels of glucose between 140 and 199 milligrams per deciliter.

3.1.Insulin, Chemistry, or Metabolism:

Insulin is a polypeptide hormone composed of Two disulfide bridges connecting two strands of 21 or 30 amino acids formed by the hydrolysis of the C peptide. It has a hypoglycemic impact and is secreted by the ß cells within the pancreas of Langerhans. It relates to the IGF (insulin-like growth factor) and somatomedin peptide family.

3.1.1. Insulin biosynthesis:

Insulin is generated by beta cells that make up 75 percent of the pancreaticLangerhans islets Alpha cells produce glucagon, whereas delta cells produce somatostatin. Insulin is generated as a solitary polypeptide chain, preproinsulin, which would be turned into proinsulin that is processed by furin proteases to provide insulin or C peptide (C for linking, since it connects the two chains A and B). Insulin, which is bonded to two zinc atoms, is kept in granules as polymers, most likely a hexamer shows in Figure 1.

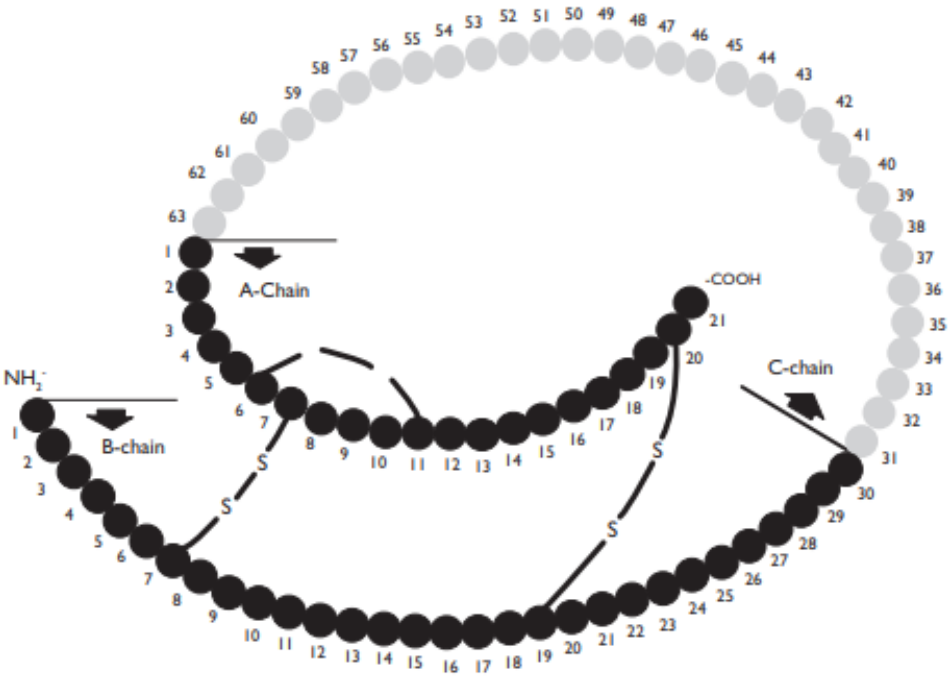

Figure 1:Displays the Structure of Insulin with Different Chains [11]**.**

Insulin is produced in the pancreas's beta cells as preproinsulin, which may be the major source, as well as the gene for it is discovered on chromosome 11 around the "Insulin-Like Growth Factor-2" (IGF-2)shows in Figure 2. Vesicles are responsible for the secretion of proinsulin. These activities of prohormone converse 2 or 3, as well as carboxypeptidase, continue the transformation of proinsulin to insulin in developing granules. Microtubules or microfilaments serve to transport developing granules[12].

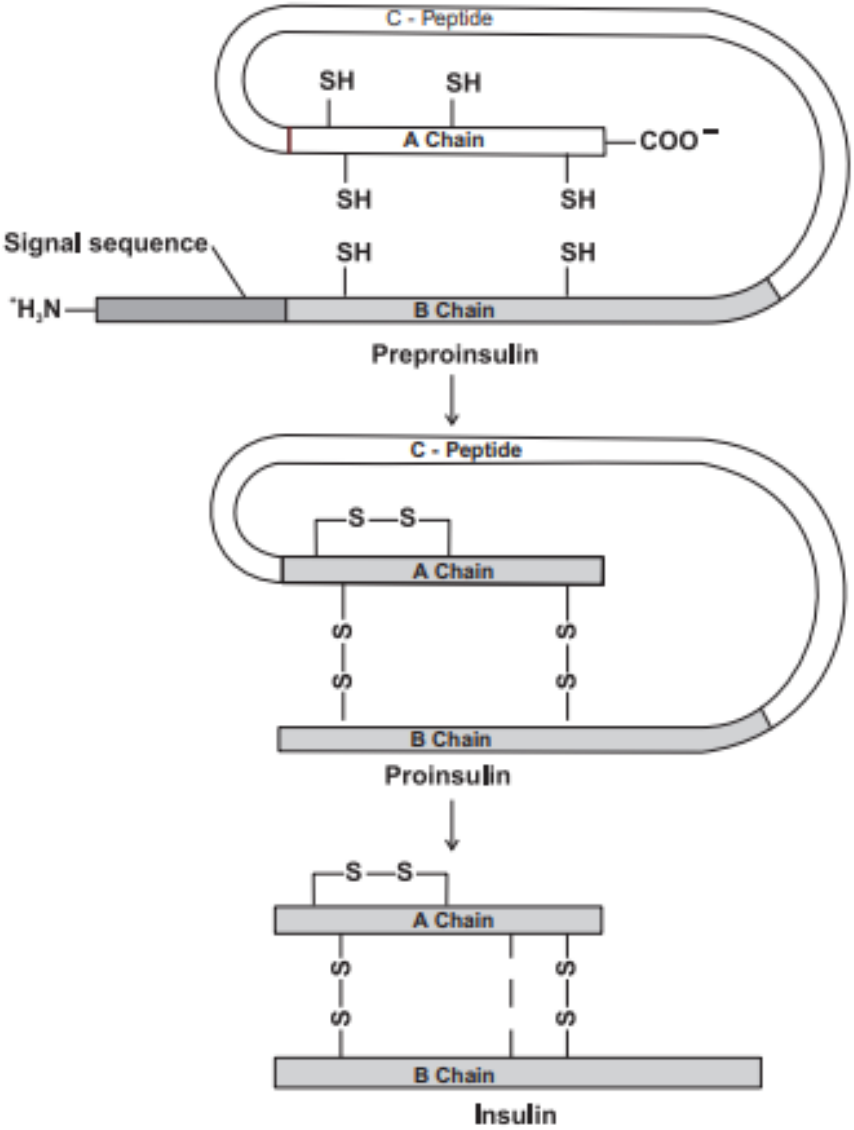

Figure 2: Displays the Insulin biosynthesis by Removing the C-Peptide[11]**.**

3.2.Secretion of Insulin:

Exocytosis releases insulin and C peptide into the portal venous system, which directs it to the liver, where it accounts for roughly half of the total. The remaining insulin is spread to other organs. There isanincrease in secretion associated with feeding, with such a baseline release of roughly 40 micrograms/h in fasted circumstances. Pulsatile secretion spikes are overlaid on these sluggish fluctuations. The goal of exogenous insulin therapies is to approximate the physiologic pattern of release. Glucose is the primary stimulator of insulin production; it causes a bilayer release: an initial impact of limited duration as well as a prolonged effect. Tight connections link the cell of the islets to facilitate the movement of ions, compounds, and secondary messages from one cell to another and hence play a vital role in synchronization secretions[13].

3.3.Insulin stimulation takes place in various conditions:

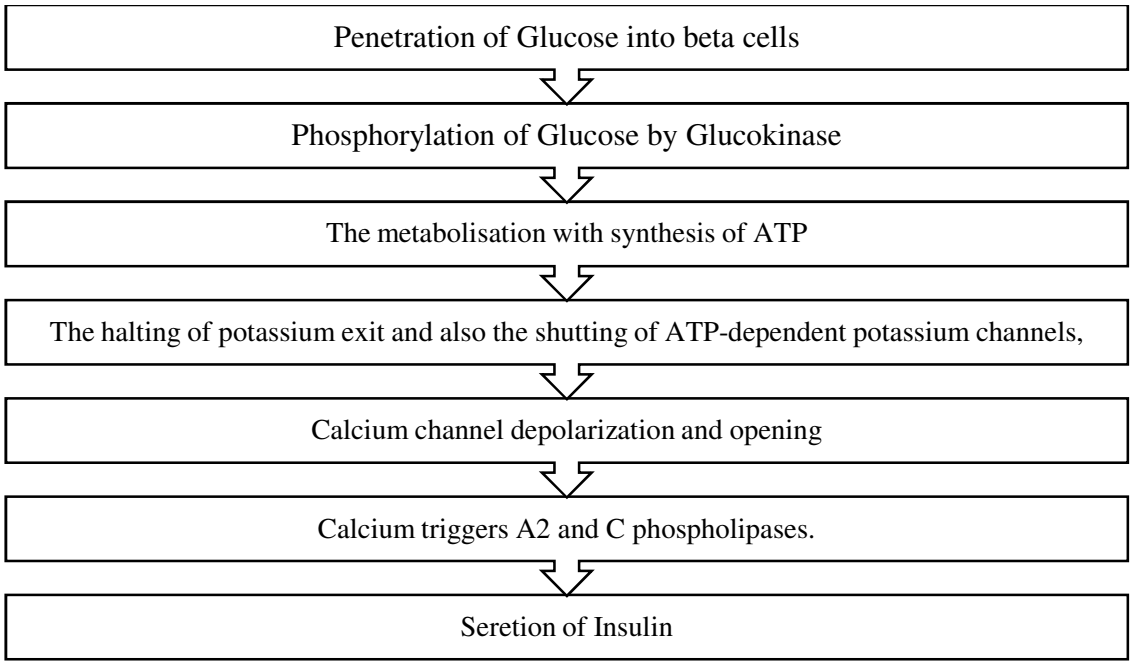

Figure 3: Displays the Flow Chartof Insulin Secretion Metabolic Regulation.

1. Glucose penetration into beta cells via Glutathione 2 carriers, irrespective of the production of insulin.
2. Glucokinase phosphorylates glucose, which is then metabolized with the creation of Adenosine Triphosphate (ATP), which intracellular concentration rises shows in Figure 3. This rise in ATP causes the closure of ATP-dependent ion channels as well as the halting of potassium exit, resulting in depolarization as well as the opening of voltage-dependent calcium influx. Calcium entry causes the stimulation of A2 or C phospholipases as well as the production of insulin [14].

3.4.Type 1 Diabetes Mellitus:

Insulin shortage originates from the loss of insulin-producing beta cells within pancreatic islets of Langerhans in type 1 diabetes. The major cause of this beta-cell death is an autoimmune assault mediated by T cells. There is no known preventative treatment for type 1 diabetes; it accounts for roughly 10percent of diabetic patient occurrences in North America and Europe (although it varies by geographical region), as well as a greater portion in certain other places.

- *Treatment:*

Diabetes mellitus is now a clinical syndrome with no cure, therefore medical attention should be focused on managing/avoiding potential short- and long-term diabetes-related complications. Patient education, dietetic assistance, reasonable exercise, and self-monitoring of blood sugar levels all play a significant role in maintaining that all these short-range and long blood sugar levels are within normal limits. Proper management is required to limit the possibility of long-term problems. This one is potentially possible with a mixed diet, exercise, or loss of weight

(type 2), different oral diabetic treatments (only type 2), as well as insulin usage (type 1 and type 2 who do not react to oral meds, especially people with long-term diabetes) [15].

3.5.Type-2 Diabetes Mellitus:

There is no loss or mild decline in the cell population, insulin in circulating is low, average, and even strong, and no anti-cell antibody is found; there is a high degree of hereditary susceptibility, and the disease often manifests late (past middle age) Over 90percent of patients have type 2 diabetes mellitus causes:

1. A cellular glucose-receptor abnormality causes them to respond to increased glucose concentrations or absolute cell shortage. Reduced insulin responsiveness of peripheral tissues; decrease in the number of insulin releases.
2. Obesity can cause an insulin deficiency deficit due to the accumulation of hyperglycemic hormones (glucagon).

- *Treatment:*

If the mother has gestational diabetes, it is critical to keep her blood sugar levels under control. This includes frequent blood sugar (glucose) tests, a well-planned diet, and staying active seen in Table 1.

Table 1: Depicts the Comparison between Diabetes Mellitus Type 1 to Diabetes Mellitus Type 2 [16]**.**

Characteristics	**Diabetes Type I**	**Diabetes Type II**
The age of beginning	At the age of 40	After 40 years, it's finally here.
The type of onset	Harsh and abrupt	Slow and insidious
Weight	Normal	Obesity
Frequency	10-20%	80-90%
Human leukocyte antigens (HLA)	HLA-D linked	No HLA association
Genetic locus	Unknown	Chromosome 6
Pathogenesis	Auto-immune	Insulin -resistance
Islet cell differentiation	Beta-cell depletion, Insulin	There was no insulitis, but there was some beta-cell depletion.
Antibodies against islet cells	Yes	No
Insulin levels in the blood	Insulin levels have dropped.	No
Complications that occur suddenly	Keto-acidosis	Hyperosmolar-coma
Clinical administration	Diet and Insulin	Drugs and Diet

3.6.Diabetes mellitus advances:

3.6.1. Transplantation of Islet Cells:

A novel islet cell transplant approach has shows potential in Type 1 Diabetes patients. The transplantation, known as the 'Edmonton' procedure, reportedly succeeded in 7 patients remaining insulin-free for up to Fourteen months following therapy. Clinical studies are now being conducted at ten national diabetes clinics to see whether insulin reversing may be effective in a larger number of patients. The Edmonton procedure employs islet cells (pancreatic cells) from 2 or more donors' pancreatic islets. The cells are implanted into a diabetic patient, but then specific drugs are administered to prevent the new cells from being rejected. One complication with transplantation would be that, while a person may no longer require insulin, the drugs to avoid rejection of new tissue should be taken for the rest of their lives. These drugs have negative side effects [17].

3.6.2. Therapy using Genes:

Two recent studies discuss gene therapy techniques for several elements of diabetes. These papers are at the vanguard of what will undoubtedly be continuous and intriguing research as a result of genome sequencing decoding.

1. SH2domain-containing inositol phosphatase-2 (SHIP2), a gene discovered by scientists, appears to control insulin. SHIP2 is now a prospective gene therapy targeted for type 2 diabetes therapy, to improve insulin consistency.
2. A protein that inhibits blood vessel formation in the eye is being researched as potential regenerative medicine for retinopathy. A new survey showed that treating a mouse model of retinopathy with the protein pigment epithelium-derived factor, abbreviated PEDF, inhibited excessive new blood vessel creation. It could be used to treat macular degeneration as well [18].

3.7.A Look towards the Future:

3.7.1. Insulin Administration Methods:

i. Insulin inhalation:

The lungs' vast surface area (more than 100 m2), combined with their thin or highly vascularized epithelial, makes them an appealing target for fast insulin uptake. Many aerosol techniques have been introduced for inhaling insulin in a powder form or solution, as well as clinical studies are now underway. These are primarily concerned with the administration of relatively tiny short-acting and rapid-acting insulin dosages for 'top-up' at mealtime. In the studies, the primary insulin infusion dosage is administered through traditional injection. The pulmonary pathway of absorption is comparable to or quicker than a subcutaneous injection of rapid-acting insulin, as well as the impact is long-lasting. Absorption variability within an individual is minimal, and it is significantly influenced by concurrent respiratory circumstances.

ii. Insulin taken orally:

Over the last three decades, several attempts to create an oral insulin formulation have been described, including liposome-encapsulated insulin or different polymer-wrapped insulins. No one has offered a suitable barrier against proteolytic degradation as well as an efficient boost to absorption to provide appropriate bioavailability. An alkyl polyethylene-glycol conjugated

hexyl-insulin (HIM2) in laboratory trials with Nobex and GSK is a recent promising addition. A particulate 'Nano cubicle' dispersion, as well as a polylactide microcapsule [18].

iii. Insulin, both buccal and nasal:

Buccal insulin administration is being tested in clinical trials by Generex and Lilly under the brand names Oralin® in Europe and Oralgen® in the United States. An aerosol (RapidMist®) delivers a thin spray directly into the buccal mucosa, comparable to asthma treatment. The nasal epithelium has very poor insulin absorption and therefore is vulnerable to inter-current localized diseases or irritation. Surfactants as well as other absorbing boosters boost bioavailability but have not resulted in a sustainable delivery system owing to disruptions in the nasal epithelium's stability.

iv. Insulin for the Liver:

Subcutaneous insulin injections would not mimic the usual physiological distribution of glucose into the circulating blood, exposing the liver to greater insulin levels than the peripheral. Insulin coupled with thyroxine is being studied for preferred transport to the liver [19].Insulin pump technology has advanced significantly, and implanted pumps are now available to certain patients. Insulin biosensors are a novel family of drugs that induce a gene to create more insulin-controlled proteins. These proteins extract glucose from the circulation, hence increasing insulin bioavailability. It also reduces the body's synthesis of glucose. Type I diabetes is also being treated with pancreas or islet cell transplantation [20].

4. CONCLUSION

Diabetes is a slow-killing illness with really no known cure. Diabetes can strike at any age. Therefore, the probability of developing diabetes rises as people age. Novel medicines are being developed at various levels, with some showing encouraging outcomes in clinical trials. Increasing the treatment arsenal's options by incorporating new mechanisms that may assist improve results and lower the financial strain of this illness in the long run. Curing diabetes has long been a pipe dream. A massive amount of research has been carried out in the hopes of finding a cure. The goal of this review article is to offer an introduction to diabetes mellitus clinical tests and their current state. The biggest achievement in research and treatment, therefore, has been in diabetes treatment, with little advancement forward toward a diagnosis. Current diabetic treatments pancreatic transplantation, islet transplantation, modified pancreatic beta cells, islet regeneration, and the virtual pancreas, are the five types. More discoveries in disease research are continually being made, paving the door for diabetes to be treated quickly and cheaply.

The outcome of ongoing or planned intervention trials would determine the future of T1DM medication treatment. Immunomodulation, alone or in combination with immunosuppressive medication, appears to help lower C-peptide depletion following diagnosis. Human immune system research lags behind even the mouse or rat. An international network of clinical research centers financed by the National Institutes of Health has built a framework for experiments detecting or treating Type 1 diabetes. Patient education is an essential element of insulin treatment. Patients must be trained on insulin preservation, needle usage, insulin mixture, injection or meal scheduling, correct site selection, as well as injection technique. Patient

learning involves SMBG or hypoglycemia control. Better glycemic control can be achieved by patient education or thorough assessment.

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CHAPTER 2

ROLE OF TNF-ALPHA, IFN-GAMMA, AND IL-10 ON PULMONARY TUBERCULOSIS PATHOGENICITY

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ABSTRACT:

Tumor necrosis factor-alpha (TNF-α), which was first recognized as a factor that produces tumor necrosis, has more recently, been shows to have additional significant actions as a pathogenic factor of autoimmune illnesses. TNF-α is responsible for activating two separate signaling pathways via its interactions with two different receptors. These pathways end up producing a wide array of biological reactions, like the continuation of cell life, cell division, and cell expansion. This study focuses on the cytokine, which has synergistic effects with Interferon-gamma (IFN-gamma), stimulates the formation of Reactive Oxygen and Nitrogen Intermediates (RNIs), modulates macrophage tuberculostatic function, and stimulates immune cell migration into the infected area, and also the formation of granulomas, which also tries to control the disease progression. The main immunological cytokine, IFN-gamma, activates macrophages, which function as microbicides throughout the body. Despite the lack of conclusive studies that investigated an obvious dichotomy between T-helper cell Th-1 and Th-2 responses, which included protective immunity and also the risk of illness, researchers could recommend that knowledge of these responses based on the applicable expression levels could help to explain the immune reaction associated with Mycobacterium tuberculosis (MTB) safety.

KEYWORDS:

Cytokine, Interferon-gamma (IFN-gamma), Interleukin, Mycobacterium Tuberculosis (MTB), T-helpers cell (TH-1, TH-2), Tumor necrosis factor-alpha (TNF-α).

1. INTRODUCTION

Tuberculosis (TB) is an infectious disease that most commonly causes shortness of breath and also could infect any part of the human body. This could form when germs proliferate through air droplets. Although tuberculosis could be lethal, it is often prevented and treated. Tuberculosis may be acquired by inhaling Mycobacterium tuberculosis (MTB) bacteria. The most contagious kind of tuberculosis has been the one that affects the lungs, even though it is usually acquired through close contact with someone who has this TB [1].

It can have possible for someone to have TB viruses in their body without ever showing any symptoms of the disease. The immune systems of the vast majority of individuals are capable of keeping germs away, therefore stopping them from replicating or developing diseases. In certain circumstances, a person may have tuberculosis (TB) infection with tuberculosis (TB) but still have no symptoms of the disease. Latent tuberculosis is the name that physicians give to this condition. There is a possibility that an individual may not even show any symptoms, so as a result, they will be unaware that they have been contaminated. Additionally, there is no possibility of passing on a dormant illness to another individual. A person who has latent TB, on either hand, is required to get treatment anyway [2]. The body would be unable to absorb tuberculosis germs. This is more likely whenever the immune system is compromised owing to sickness or the use of certain drugs. Whenever this occurs, the bacteria will grow or create signs, culminating in active tuberculosis. Patients with active tuberculosis could transmit the illness. Without invasive surgery, TB develops active in 5–10 percent of those infected. According to the Centers for Disease Control and Prevention (CDC), approximately half of these individuals show signs of improvement within two to five years [3]. The following factors increase the likelihood of getting active tuberculosis:

i. Someone with a compromised immune system.
ii. Everyone who becomes infected during the last 2–5 years.
iii. Elderly people and young children.
iv. Patients who haven't yet previously gotten adequate TB therapy.

A family of cytokines known as tumor necrosis factors (TNFs) is produced by macrophages and may trigger cell damage in some tumor cell types. Tumor Necrosis Factor Alpha (TNF α), Tumor Necrosis Factor-beta (TNF-β) one of the first two members of this family to be found was a cytokine that is known more popularly as Lymphotoxin-alpha.

This kind of cytokine is suppressed by interleukin 10, which was one of the first cytokines ever identified. TNF-α, or tumor necrosis factor-alpha, plays a significant part in the growth, development, and death of cells, as well as in the regulation of lipid metabolism and thrombosis. TNF is also known as TNF (TNFA), Tumor Necrosis Factor Superfamily (TNFSF2), or (TNFSF1). TNF is a transmembrane glycoprotein that is degraded to a soluble form by a metalloproteinase. Its action is derived from the synthesis of trimers that attach to TNF cell surface receptors, of which there are two kinds, Tumor Necrosis Factor Receptor (TNRF-1) and (TNRF-2).

Both receptors may detect antiapoptotic or proinflammatory signals; TNRF1 could trigger the caspase cascade, resulting in death. Experiments in mouse models for the receptor genes suggest that the TNRF1 receptor is required for TB defense, but TNRF2 may moderate TNF activity. The activity of both is different since TNRF1 is triggered by the TNF monomer whereas TNRF2 is only activated by trimers [4].

TNF and TNF receptors serve critical roles in modulating immune function in acute and chronic inflammation. During the last century, TNF antagonist medicines such as anti-TNF monoclonal and also TNF fusion protein was used to treat inflammatory diseases like arthritis, psoriatic arthritis, spondylitis, inflammatory bowel disease, and many others [5].

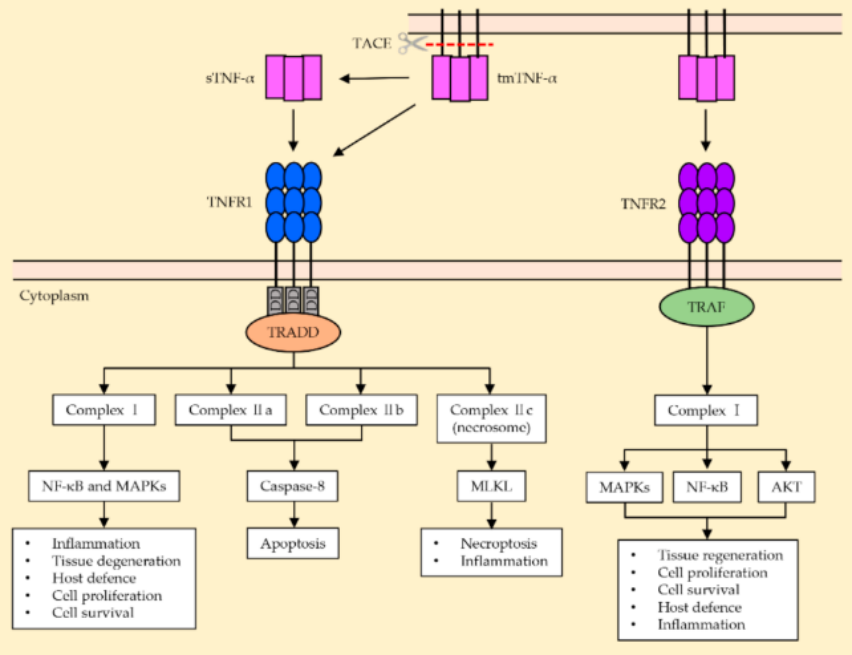

Figure 1:Displays the Tumor Necrosis Factor Receptors TNFR1 and TNFR2 are part of the TNF Signaling Pathway [6]**.**

The TNF-1 activation could result in the development of several signaling complexes known as complex Interleukin, ILa, ILb, or ILc, that result in unique cellular functions. During the assembly of complex I activating TNFR-1 attaches to TNFR1-Associated Death Domain Protein (TRADD), which is followed by the linkage and also the interactions of other components. Mitogen-Activated Protein Kinases (MAPKs) or nuclear factor B (NF-B) are the targets of this signaling pathway [7]. Apoptosis is caused by the production of complexes ILa or ILb (also known as apoptosomes). Complex Ilc (also referred to as necrosome) is created once the complexes have been uncleaved, and the Receptor-interacting Kinases (RIPK-1) or (RIPK-3) join with one another to create the combinations ".The "Lineage Kinase Domain-Like Protein" is phosphorylated by the complex Innate lymphoid cell (ILc) through RIPK3, causing apoptotic cell death as well as inflammation shows in Figure 1 [8].

2. LITERATURE REVIEW

Noha A. Ghallab et al. conducted a study to investigate the feasibility of detecting salivary levels of IFN- γ, TNF- γ, and sTNFR-2 from Erosive Oral Lichen Planus (ELP) patients for therapeutic application. In this research, authors included 20 ELP patients and 20 age-sex-matched controls. ELISA was used to analyze salivary profiles in ELP patients who had been treated with prednisone. It was reported by authors that before therapy, ELP patients had considerably greater levels of IFN- γ ($P \leq .01$), TNF- γ ($P \leq 0.0001$), and sTNFR-2 ($P \leq .01$) than controls. Salivary levels of IFN-γ TNF, and sTNFR-2 reduced considerably after therapy as compared to pretreatment values. Authors concluded that salivary IFN- γ, TNF- γ, and sTNFR-2 levels may be detected in ELP patients and drop considerably following prednisone therapy, suggesting that these disease-related biomarkers might be used in the diagnosis and monitoring [9].

Soumajyoti Sarkar et al. stated in a study that immunotherapy against Psoriasis and psoriatic arthritis has been revolutionized by the discovery of TNF-α. However, patients who use this drug

are at a greater risk of infection, which may lead to pathological changes in their bodies. It was anticipated that there will be 10 million new cases of tuberculosis in 2016, with India having the highest TB case incidence at 2.79 million in 2016. Infliximab, an anti-TNF medication, was recently psoriatic arthritis or psoriasis patients in India may now be treated with this medication. However, prolonged use of such medicines increases the chance of latent TB reactivation. Patients with psoriatic arthritis or psoriatic arthritis in India who use anti-TNF medicine are more likely to develop TB [10].

Joanna Matowicka-Karna et al. conducted a study to determine T. gondii's influence on immune response indicators. In their study, T. gondii-infected women (ages 18–42) received antiparasitic therapy. IgM (index) and IgG exceeded 300 IU/ml in all cases. 40 healthy women aged 18–46 comprised the control group. IgE, IL-5, IL-6, IL-10, IL-12, and TNF-α levels were measured by the authors in the study and control groups. It was found that T. gondii patients showed double greater IL-5 and IL-6 levels than healthy ones, confirming an inflammatory condition. Toxoplasmosis increased IL-10 fivefold compared to healthy controls. IL-12 and TNF- α levels were similar to healthy controls. In this study, authors concluded that T. gondii-infected individuals produce more humoral response cytokines, whereas cell response cytokines remain stable [11]. Carola Seifart et al. conducted a case-control research that looked at TNF-308, TNF-α 252, IL-6-174, IL-10-819, and IL-10-10-1082 in lung cancer patients and controls. 117 lung cancer patients (77 with NSCLC, including 40 with Squamous Cell Carcinoma and 26 with Adenocarcinoma, and 40 with SCLC), 117 matched controls without pulmonary illness, and 243 healthy persons were studied (population control). Using matched-pair analysis, genotype frequencies didn't vary. IL-10-1082 genotypes containing the G allele were more common in SCLC than in controls ($p = 0.006$) [SCLC: 84.6%, controls: 64.6%]. This gives SCLC a 3.01 odds ratio (95% CI: 1.21-7.48). Other polymorphisms were not associated. The research suggests a link between IL-10-1082 G and SCLC in Germans. Functional IL-10-1082 polymorphism links with changed IL-10 levels and may affect lung cancer risk by altering airway inflammation [12].

Amanda Mootoo et al. discussed in a study that TNF- α is an important component of the host's innate defense response toward pathogenic assault. However, it could also contribute significantly to the pathophysiology of some diseases, like TB. This condition illustrates TNF-'s role as a "double-edged sword," because it may cause significant tissue damage in addition to managing Mycobacterium TB infection. TNF- α has an extremely complicated network of relationships, and most of its functions are still unknown [13]. Peter Vandenabeele et al. stated in a study that TNF has 2 major effects: one is good regarding its ability to fight infection or tumors, as well as its negative impact on the immune system and cytokine. These effects are regulated by two receptors (TNF-R), although their specific involvement in distinct cell types is unknown. TNF causes receptor oligomerization, which is thought to link the receptor to downstream signal transduction. According to new research, some TNF-R-associated proteins, including kinases, might begin cytoplasmic signaling pathways [14].

3. DISCUSSION

The genus Mycobacterium has about 100 recognized species with a wide geographical range, ecological variety, or relationships with the other species, over 20 species are hazardous to humans. TB is often caused by the intracellular facultative bacillus M. tuberculosis (MTB). The WHO aims to halve TB infections and illness deaths by 2015 [15]. Even so, the proportion of instances of tuberculosis resistance to many drugs is increasing, putting control of the disease at

risk. The immunological state is linked to TB progression. The host's adaptive immune response to this virus is recognized to be regulated by cell-mediated immunity, with particular cytokine or Th1 cells playing essential roles [16]. Recognizing the processes that occur in this reaction, particularly the operation of the cytokine network that has been linked to the development of this illness is critical for progress in the development of effective management or preventive strategies [17].

3.1."Cytokines":

Cytokines were chemicals generated by several cell types that primarily facilitate intercellular communication in the immune response. Cytokines have pleiotropic or regulatory actions that play a role in host defense, inflammation, as well as tissue regeneration. Different cytokines, like IL-12, IL-23, IL-27, IL-18, IL-1, IL-7, as well as IL-15 are interleukin-12 (IL-12) family members and have been already recognized as playing a role in TB. MTB often lives in nonactivated macrophages, where it survives in the intracellular compartment by inhibiting the combination of the phagosome and the lysosome, preventing prolonged contact with a low pH, which are both critical to its death.

Type-1 helper cells (TH-1) cytokine production is stimulated by the 19 kDa lipoprotein and other MTB factors such as cord factor. Figure 2 shows how the immune system begins to fight against M. tuberculosis. T-helper 1 (Th1) cell proliferation is stimulated by the host immunological response to mycobacterium, which is aided by several cytokines, including IL-12, IL-17, or IL-23. The Th1/IFN/TNF cytokines and their role in mediating anti-mycobacterial cytokine cascades are well-established. This is due to the granuloma's creation and maintenance, driven by TNF- α and IFN- working synergistically to produce cytokines and signaling molecules [18]. IL-1's role in host resistance was shows in a study by creating antibodies against the cytokine, which led to an increase in mortality during chronic infection. Numerous cytokine-mediated processes are critical to the development of MTB resistance and also the emergence of resistance mechanisms.

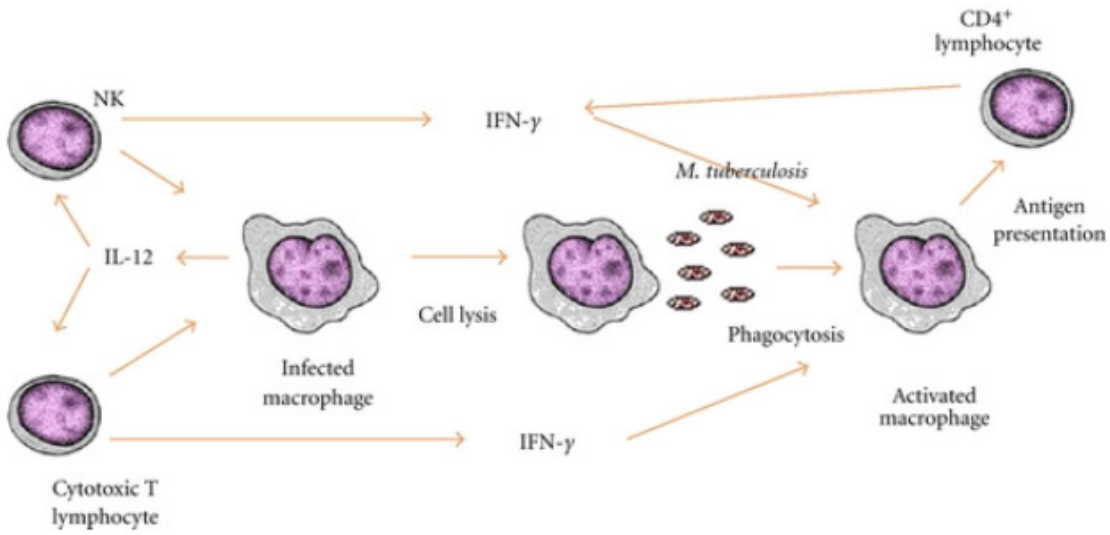

Figure 2: Displays The First Defensive Response To The M. Tuberculosis-Th1 Combination [19]**.**

3.1.1. M. tuberculosis immune response:

In clusters of differentiation 4(, CD4+) T cells,macrophage function is regulated by cells other than cytolytic (CD8+) lymphocytes. The functional activity of macrophages in bacterial eradication is controlledby cytokines that are produced by T cells, more especially by tumor necrosis factor (TNF) beta or interferon beta.

3.2."TNF-α (Tumor Necrosis Factor)":

The tumor necrosis factor (TNF), had first been identified as an in vivo necrosis inductor in malignant tumors. TNF is a cytokine that promotes inflammation with several physiological effects. TNF- α expression is closely regulated because that can transmit the harmful consequences of septic shock-like arterial hypotension, disseminated vascular coagulation, as well as fatal hypoglycemia. TNF- α appears to play a pivotal role in mycobacterial infection management, operating on a wide range of cell types. Primary producers include T lymphocytes, dendritic cells, or macrophages. These cytokines enhance the activity of macrophages in the fight against tuberculosis. TNF- α also increases immune cell migration to the sites of infection, which contributes to the creation of granulomas, which are capable of regulating the progression of the disease [20].

A study specifically looked into the role of the protein called (NOD- 2) when identified in human alveolar macrophages, the nucleotide-binding oligomerization domain protein-2 was found to bind "Muramyl Dipeptide (MDP)" to ligands, which would, in turn, stimulated the synthesis of interleukin 1, interleukin 6, or TNF. The MDP administration of air-sac macrophages increased M. tuberculosis intracellular development control, an action linked with considerable TNF- α and IL-6 production. Indications that TNF has anti-inflammatory characteristics are provided by a variety of sources is the discovery that individuals with rheumatoid arthritis. Patients who received TNF- α antagonists (monoclonal antibodies that directly target TNF- α or TNF- α soluble receptors) had a considerably greater chance of activating latent TB. TNF- α is one of the most crucial elements in the migration of monocytes and also the powerful activation of apoptosis. However, cell death is linked to the bacterial host's rupture, the release of live M. tuberculosis, or the degradation of tissue. TNF is another important cytokine implicated in this occurrence [21].

3.3.Interferon –Gamma (INF-γ):

Interferons (IFNs) are molecules discovered in virus-infected cellular culture supernatants that seemed to interact immediately with transcription and replication, thus the name. Type I IFNs, which are split into 2 primary kinds, are induced or efficient in viral responses: IFN is produced by fibroblasts and released by leucocytes. T lymphocytes and Natural Killer (NK) cells create Type II interferon, often known as IFN, in responses to immunologic or inflammation stimuli, not the viral illness itself. The most important TB cytokine is "natural killer cells." One of the two types of T lymphocytes, either CD4 or CD8 or NK cells, may create it. IFN- about mycobacterial activation may be produced by natural killer T cells (NKT) or T-lymphocytes, which have a limited repertoire for detecting pathogens but can also offer protection from Mycobacterium tuberculosis in both in-vitro and vivo.

Morosini et al. focus on the information that they discovered in their research that there is a difference in human IFN while interleukin-12 synthesis occurs primarily in the lungs and

interleukin-10 in the peripheral circulatory system, these two components are not mutually exclusive. IL-18 was discovered to be much more essential in the human immune response to M. tuberculosis by researchers, indicating that IL-18 may serve as an IFN-activator in the lungs and have immunoregulatory impacts on the peripheral circulation at the same time [22]. According to preliminary findings, the administration of M. tuberculosis and also the development of immunopathology contribute to sickness and death in TB patients. A broad range of IFN-IL-17 levels was observed in people with positive Purified Protein Derivative (PPD) screens or healthy persons in response to multiple M. tuberculosis antigens, and so this variability also was identified in the quantities of IL-17 and IFN- produced in response to various antigens.

3.4.Interleukin-10(IL-10):

T-cell cytokine production is limited by the cytokine synthesis inhibitor IL-10. There is also evidence to suggest that IL-10 inhibits both the T- helper type1 (Th1) and Th2 populations in vitro. IL-10 reduces pro-inflammatory cytokine production (IFN-, TNF- α, and IL-12) and antigen-presenting cell activity, inhibiting T lymphocyte activation by reducing MHC class II expression. It has immune-regulatory characteristics. The "Bacillus Calmette-Guérin" (BCG) immunization has been associated with an elevation in IL-10 expression in several human populations. IL-10 gene polymorphisms linked to the emergence of infectious disorders have been studied, and the results show that this variation is critical to the immune system's development or inflammation. Increased IL-10 synthesis, in particular, could depress the immune reaction and encourage the development of the disease. For the immunopathology of tuberculosis, the immunosuppressive impact of IL-10 is undeniable. Furthermore, several studies have shows no indication of a response to Mycobacterium TB antigens in Peripheral blood mononuclear cells (PBMCs) from persons with medical tuberculosis leading to raised levels of this cytokine in these cells.

4. CONCLUSION

Innate immunity, which includes the bacillus' interaction with dendritic cells and macrophages, is where the host's resistance to M. tuberculosis infection starts. However, the transition from illness care to the formation of chronic infections is largely unclear, due in part to a dearth of relevant animal research. The significance of TNF- α in the establishment of latent MTB infection is well recognized. Many animal research and clinical observations demonstrated that individuals with auto-immune diseases who were treated with TNF- α inhibitors acquired. As a consequence, this archetypal proinflammatory cytokine may potentially have anti-inflammatory properties; however, the mechanism remains unknown. Decoding this complex system of TNF-α activities, and interactions within an integrated immune response to MTB infection is crucial and necessitates more investigation, particularly considering the serious clinical implications. The author found that there is no clear evidence demonstrating that Th1 and Th2 responses, which include self-protective immune responses or disease susceptibility, are well differentiated. Understanding the host's immunological defenses against M. tuberculosis is aided by Th1 and Th2 cells.

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CHAPTER 3

SAFINAMIDE IN THE MANAGEMENT OF PARKINSON'S DISEASE (PD): AN ANALYSIS OF CLINICAL TRIALS AND RAT MODELS

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ABSTRACT:

A complex interplay between the depletion of dopaminergic and non-dopaminergic neurotransmitter systems results in "Parkinson's disease (PD)", a neurodegenerative condition. Today, the primary method of treating motor deficits involves medications that work on dopaminergic pathways. The available treatments for PD mainly involve Carbidopa / Levodopa, the use of which usually results in unwanted complications. The focus of the current study is to highlight the use of safinamide as an adjunctive therapy, its effects in clinical trials, and its mechanism of action in animal models. Safinamide is a special drug that enhances the transmission of dopaminergic signals and inhibits monoamine oxidase B. Additionally, it has anti-glutamatergic properties, which help lessen dyskinesia, a side effect that restricts the use of most dopaminergic therapies. When used as an add-on therapy to levodopa in patients having advanced PD, safinamide has been shows to extend duration without inducing troublesome dyskinesia. It has been discovered that it works well as a supplement to dopamine agonists in early PD. The potential role of neuroprotection is yet to be explored more in the human species.

KEYWORDS:

Glutamate, MAO-B Inhibitor, Motor Fluctuations, Parkinson's Disease (PD), Safinamide.

1. INTRODUCTION

The second leading cause of mortality and the primary cause of disability globally, respectively, are neurological disorders. Especially in low- and middle-income nations, neurological disease-related mortality and impairments have increased significantly during the past 30 years. Further increases are anticipated internationally due to population growth and aging. This increase in the absolute number of afflicted persons indicates that attempts to prevent and treat severe neurological disorders have not made enough headway in reversing demographic trends throughout the world [1]. PD is one of the neurological disorders that worsen with age. The source of the neurodegenerative process in PD is unknown; various processes are implicated in its development, involving mitochondrial dysfunction, oxidative stress, proteasomal dysfunction, and inflammatory modifications [2]. The diagnostic process of PD is mostly clinical, however, imaging methods such as single positron or photon emission computed tomography and

magnetic resonance can help in some cases. Major and early motor fluctuations are caused by the loss of "dopaminergic neuronal cells" in the "substantia nigra pars compacta". This causes a lack of dopamine transmission in the nigrostriatal pathway, which leads to stiffness, bradykinesia, and tremor that define PD [3].

The most significant requirements in the therapeutic PD treatment are the elimination of motor abnormalities caused by dopaminergic treatments, the alleviation of non-levodopa responsive features, the management or control of non-motor manifestations, and the management of the disease. OFF periods and motor complications are important drivers of "quality of life (QOL)" in PD, as well as reducing two aspects i) severity and ii) duration can help in the improvement of motor function considerably [4], [5].

This goal can be aided in part by the discovery of efficient dopamine-replacement drugs. Monoamine oxidase (MAO)-B inhibitors, dopamine agonists (DAs), and Levodopa are the ones that fall under the first-line treatment for motor manifestations. The first one Levodopa is particularly efficient in treating the motor complications of PD, but its administration in the long-term is frequently constrained by the emergence of motor fluctuations, such as response oscillations between "bad (off')" and "good (on)" symptom control and dyskinesia induced by treatment. As a result, adding additional medications to levodopa for PD treatment entails adding "MAO-B inhibitors, amantadine, catechol-O-methyltransferase (COMT) inhibitors, and Das" [6].

Long-term levodopa treatment, despite being effective, can cause several debilitating side effects, including dyskinesia and motor abnormalities. Treatment approaches that postpone and reduce the need for levodopa are desired since these adverse effects are made worse by the dosage and length of levodopa treatment. It is possible to supplement levodopa/carbidopa therapy with catechol- O -methyltransferase inhibitors [7].

These medications increase the amount of unmetabolized levodopa that reaches the substantia nigra by preventing COMT from converting levodopa to 3- O -methyldopa in the stomach. However, in sensitive people, COMT inhibitors can cause dyskinesia. Early PD can be successfully treated with DA agonist alone, which can significantly postpone the need to administer levodopa. The dopamine transporter decreases or decline of F-18-dopa uptake in the striatum was less severe in individuals originally given DA agonists like pramipexole or ropinirole than in those first given levodopa. However, there are now problems with the use of DA agonists because all DA agonists, including non-ergolinic DA agonists like pramipexole and ropinirole, can cause edema of the lower limbs, sleep attacks, and compulsive disorders. The use of MAO-B inhibitors, one of the important enzymes that are involved in dopamine metabolism in the brain, is another method for treating PD. MAO-B medications reduce PD motor symptoms by boosting dopamine levels at synapses. Some MAO-B inhibitors have also been found to have neuroprotective effects.

1.1. Dopamine Catabolism and its role in PD:

"Monoamine oxidase (MAO)" and "Catechol-O-methyl transferase (COMT)" catalyze the enzymatic breakdown of DA into its inactive metabolites. MAO-A and B, the isoforms of MAO can execute this metabolizing activity. It should be highlighted that glial cells are the primary source of COMT expression. In neurons, this enzyme is either missing or present at minute concentrations. MAO-A is primarily found in catecholaminergic neurons such as SN cells while

MAO-B is mostly present in "astrocytes". MAO converts dopamine to generate "dihydroxyphenylacetaldehyde (DOPAL)", conversion of which was carried out into the form "dihydroxyphenylacetic acid (DOPAC)" by the enzyme's aldehyde dehydrogenase. The enzyme COMT transforms DA to 3-methoxytyramine in another pathway of DA metabolism. The 3-methoxytyramine is then converted by MAO to "Homovanillic acid (HVA)" and excreted in the urine as illustrated in Figure 1. Thus, MAO inhibition has been proposed as an additional treatment for conditions such as PD and Alzheimer's [8].

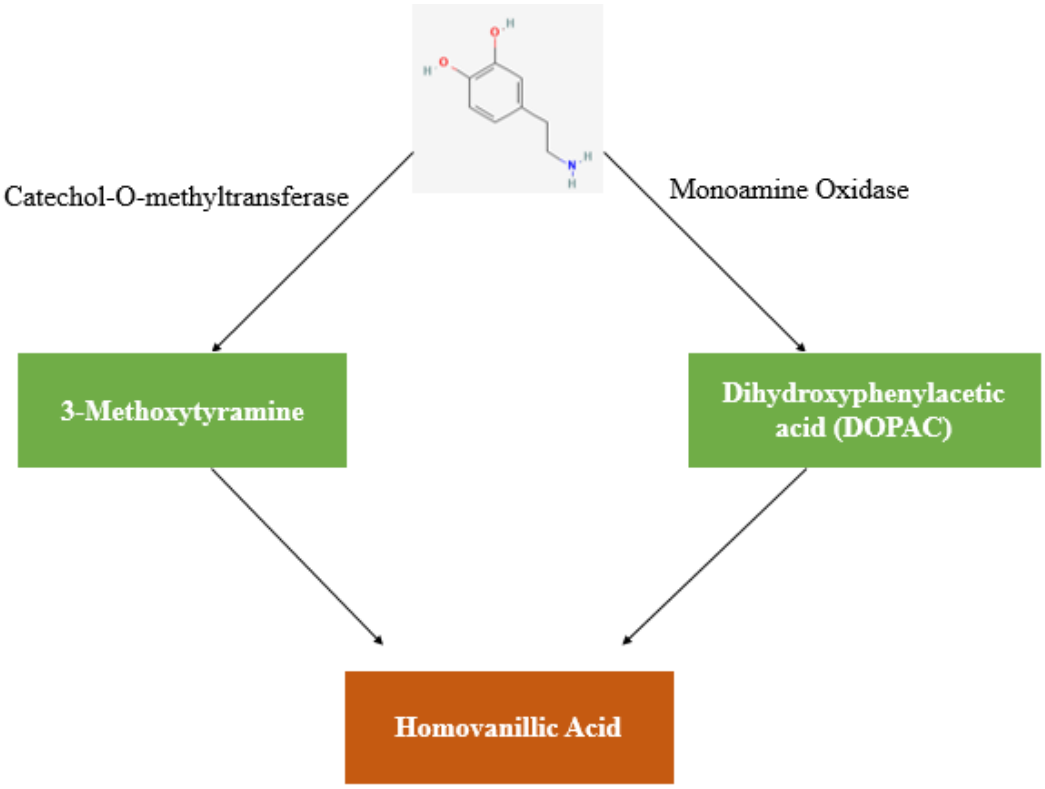

Figure 1: Illustrating the Pathways and the Enzymes Involved in the Catabolism of Dopamine (DA).

1.2. Characteristics of Safinamide:

Safinamide (Xadago), a first-generation anticonvulsant, is an MAO-B inhibitor that possesses pharmacological features that are intriguing in the setting of neurodegenerative disorders, prompting an investigation into its possibility as an adjunctive treatment to levodopa in the management of PD. Approaches to alleviating delayed symptoms and lessening disease development (e.g., by sparing dopaminergic neurons from premature death) have yet to be identified. Although promising findings have been produced experimentally with numerous classes of drugs, clinical evidence of arrest or postponement of neuron loss in PD remains a problem. The 2-D structure of the safinamide is given in Figure 2 and the characteristics are enlisted in Table 1.

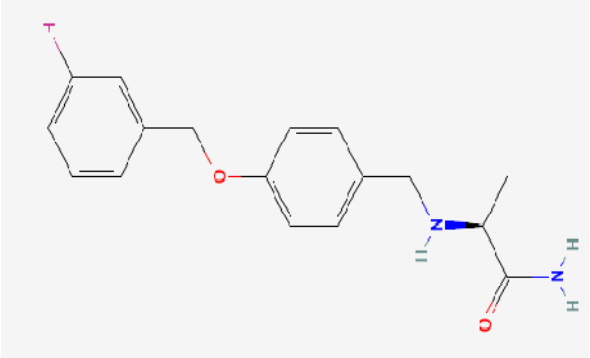

Figure 2: Illustrating the Two-Dimensional Structure of Safinamide with Different Elements.

Table 1: Enlisting the Characteristics of Safinamide with Brand Name, Molecular Formula, Route of Administration, Pharmacological class, and Mechanism of Action.

Drug Name	**Safinamide**
Brand Name	Xadago
Molecular Formula	$C_{17}H_{19}FN_2O_2$
Administration Route	Oral
Pharmacology Description	Monoamine oxidase B Inhibitor
Mechanism of Action	Reversible inhibition of selective MAO-B as a mesylate salt

In the present study, the author discussed the fundamentals of treatments involved in PD treatment with the drawbacks they pose while treating patients with PD in the early to late stages. In Section 1, a brief background about the topic is given with the limitations of the current treatments as well as the fundamentals of safinamide with its characteristics. In Section, 2 a thorough review of clinical studies to check the safety and efficacy of safinamide is discussed. In addition to that different proposed mechanisms of action, safinamide is also reviewed in rat models. In Section 3, a discussion of the reviewed studies and their limitations is provided. In section 4, the conclusion about safinamide is given as a potential drug for effective management of non-motor and motor complications.

2. LITERATURE REVIEW

2.1. Clinical Studies Involving Safinamide for the management of PD

Research by Anthony H et al. investigated the efficacy as well as the profile of its safety in the Levodopa treated patients who are having motor fluctuations. PD Patients were randomized in a 1:1 ratio to receive a placebo or double-blind supplementary safinamide for 168 days. Every day with breakfast, patients received 1 pill of safinamide or a placebo. By day 14, the initial dose of 50 mg was raised to 100 mg if no problems with tolerance had occurred. 549 were randomly assigned to 274 mg of safinamide and 275 mg of placebo at 119 locations. Safinamide caused a mean change of +1.42 hours daily on time without bothersome dyskinesia from a baseline of 9.30 hours compared to a placebo shift of +0.57 hours from a baseline of 9.06 hours. Therefore, the results of their study suggested the use of safinamide as a levodopa adjunctive treatment in individuals with PD and motor abnormalities to treat symptoms on schedule, prevent severe dyskinesia, and shorten the period between doses [9].

Carlo et al. studied and evaluated the efficacy of Safinamide 100mg/day on patients with PD for the long-term. They involved 352 patients to investigate the effectiveness and the effect of safinamide in different groups of patients that were taking levodopa monotherapy or other Parkinson's treatment and thus checked the effects of safinamide on the QOL of the patients as well as the improvement in the motor fluctuations. They found that safinamide if used as an add-on to that other monotherapy can help in motor fluctuations complications. In addition to that, they also observed an improvement in QOL in subgroups. Therefore, their study suggested that safinamide can be considered as an adjunct therapy which still needs further confirmation in large trials [10].

Another study by Geroin et al. investigated 13 PD patients having pain with safinamide of 100mg/day dose for 12 weeks duration. The primary and the secondary measures were then used in terms of several scales. To evaluate possible modifications in the processing of nociceptive stimulus, LEPs were utilized. The frequency of treatment-emergent adverse events and the dropout rate were used to evaluate the safety profile. The primary and secondary outcomes showed a substantial improvement after 12 weeks of safinamide medication. LEP complexes showed no observable substantial alterations. None of the participants experienced any adverse effects as a result of the treatment during trial completion. These early results suggest that safinamide 100 mg/daily dose can be a safe as well as effective pain treatment option for PD patients who have motor fluctuations [11].

Bianchi et al. also researched to investigate the effectiveness profile of safinamide for nonmotor complications in idiopathic PD patients. In their study, they performed data collection retrospectively from 20 subjects with PD undergoing treatment with Levodopa monotherapy and other combinations. They included cognitive assessment, Physical and mental Fatigue, Hoehm and Yahr stage, “Scales for Outcomes in Parkinson’s Disease (SCOPA)” as the secondary endpoints, “PD questionnaire-8”, and then the “questionnaires/scales performed at T1” or baseline. To analyze the efficacy, mean and standard deviations were used to treat continuous variables with descriptive analysis. In addition, a nonparametric test called the “Friedman test” was used to assess the statistical importance of the data. The results demonstrated a significant decrement in, the PDQ-8 and SCOPA motor scale which demonstrated that there is a positive effect of safinamide treatment on complications other than motor complications in PD patients [12].

Another research by Tsuboi et al. investigated safinamide efficacy in Levodopa-treated PD patients. They used different endpoints in their study involving the alterations from the baseline in mean daily "OFF-time", unified "PD rating scores", and "PDQ-39 scores". However, the primary endpoint was chosen to be the change from the baseline in the men's daily "ON-time" without dyskinesia at 364 days of treatment. A total number of 142 patients out of 203 patients completed the study of 52-week treatment. The results showed that 78.3% of total individuals reported adverse events which caused discontinuation in 10.8%. They also found that the means of daily ON-time without dyskinesia got an increase from the baseline whereas there a change of -1.40h was also observed in OFF-time which demonstrated that the adjunct therapy of Safinamide with other PD treatments is well tolerated and also improved ON-time and other PD symptoms [13].

Cattaneo et al. investigated the long-term effectiveness of Safinamide for 2 years in chronic pain caused by PD using a post hoc analysis which was focused on the scores "PD QOL questionnaire-39" as well as the reduction of concomitant pain treatment. It has been found that the administration of Safinamide when compared to the placebo improved unpleasantly hot and cold and painful cramps and spasms. It was also noted that the treatment with safinamide reduced the concomitant paint treatment by 26.2%. Therefore, their study suggested that safinamide can be used in chronic pain management in PD patients as it demonstrated long-term efficacy [14].

Stocchi et al. carried out another safety open-label study to evaluate the potential risk of changing from rasagiline treatment to safinamide treatment using twenty objects with PD of advanced level on treatment with levodopa and rasagiline. They found that there were no cases of serotonin syndrome which usually results when changing between the MAO-B inhibitors. There were no major changes observed in the primary endpoint involving a mild increase in the 24-h mean blood pressure, slightly higher values of 24-h diastolic and systolic BP values as well as there was no variability documented between the two ABPM evaluations. Therefore, this study also suggested that switching from one type of MAO-B inhibitor to any other type specially safinamide which is well tolerated in patients with PD [15].

2.2. Safinamide Studies in Animal Models

A study by Gardoni et al. studied safinamide effects on dyskinesia induced by the levodopa in rats with "6-hydroxydopamine (6-OHDA)–lesion". The parameters such as neurochemical, behavioral, and molecular parameters were evaluated. Three groups of rats were treated with levodopa, saline, and levodopa in combination with safinamide. The analysis of different parameters involving GABA, glutamate release motor performance, and abnormal involuntary movements was carried out. They found that the administration of safinamide inhibited the increase in the release of glutamate induced by the use of levodopa. These data collectively point to a possible role for the striatal glutamate-modulating aspect of safinamide's action in its therapeutic outcomes, where safinamide use in long-terms as a levodopa add-on treatment considerably improves motor fluctuations [16].

Another study by Sciacculuga et al. investigated and evaluated the electrophysiological effect of safinamide on the synaptic as well as intrinsic characteristics of the "spiny projection neurons (SPNs)" and thus defined the anticipated antiparkinson activity of safinamide. In striatal slices from untreated DA-denervated rats and 6-hydroxydopamine-lesioned animal model that had received prolonged levodopa treatment, "patch-clamp recordings" were used to examine the

electrophysiological effects of safinamide. LIDs evaluation in vivo with and without prolonged safinamide therapy and the motor deficit was performed with the help of a stepping test. They found that the safinamide administration reduced glutamatergic synaptic transmission and SPNs firing rate in all groups. Therefore, their study suggested the efficacy of safinamide with a specific pathway for antiparkinson activity at a clinically relevant dosage [17].

Another research by Xu et al. investigated the neuroprotective effects of safinamide in endothelial cell lines and Ischemic rat models. In their research, they looked at how it affected brain endothelial cells in animals with abruptly induced strokes. They created a mouse model of a transit stroke by inducing middle cerebral artery occlusion (MCAO). During ischemia and reperfusion and before MCAO, mice received 90 mg/kg/daily dose of safinamide. According to the findings, safinamide treatment greatly reduced the amount of cerebral infarct brought on by MCAO, as well as the result of the BB barrier disruption, neurological impairment, and defective expression of the proteins ZO-1 and occludin. They also noted that the pretreatment with safinamide reduced glucose and oxygen deprivation/reperfusion-induced cytotoxicity and promoted cell viability [18].

The above studies have studied and evaluated the clinical efficacy of safinamide as an adjunctive therapy for the patient undergoing levodopa and other combination of drugs for the management of the PD using a multitude of a clinical trial under different conditions at different doses dominated by 100mg/day. In addition to that, another section of the literature review provided a body of proposed mechanisms of action for the anti-Parkinson's activity of Safinamide and its potential using animal models predominantly rats. Whereas the present study provides a fundamental and review of recent research studies which can collectively help researchers to find out the possible drawbacks of the implementation of safinamide in the treatment of PD both in combination or alone.

3. DISCUSSION

Safinamide works with both modes of action named non-dopaminergic as well as dopaminergic in the patients having PD which is briefly illustrated in Figure 3 below. Safinamide controls the release of glutamate by acting on N-type calcium and voltage-gated sodium channels. It is converted into several inactive metabolites and mainly eliminated through the urine. Enzymes for CYP/CYP450 are neither inhibited nor stimulated by it.

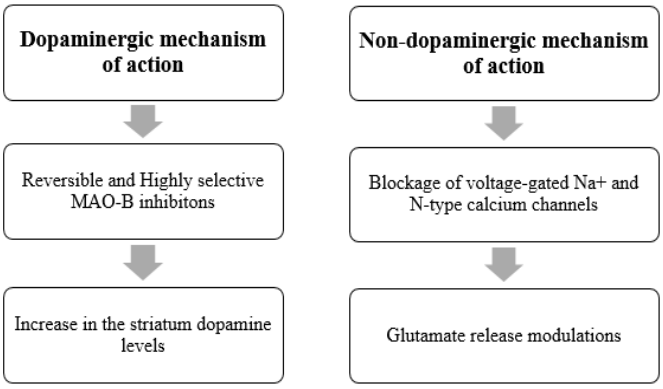

Figure 3: Illustrating the Mechanisms of Action; i) Dopaminergic and ii) Non-Dopaminergic.

It must not be used along with SNRIs, dextromethorphan, TCAs, certain opioids, other MAO inhibitors, cyclobenzaprine, or other drugs that when combined can result in serotonin syndrome. Taking safinamide does not place restrictions on the foods you can eat that contain tyramine. On March 21, 2017, the FDA authorized safinamide as an adjunct for individuals with PD with OFF time. On February 24, 2015, the European Commission approved safinamide for sale in the entire European Union as a supplementary treatment to levodopa, either by itself or in conjunction with other PD drugs.

The costs related to PD impose a significant financial strain on healthcare systems. A critical analysis of cost-utility based on findings of indirect comparison, and systematic review projected that safinamide will be more beneficial and less expensive than rasagiline in individuals with PD taking levodopa monotherapy or in conjunction with other PD drugs. To further understand the cost-effectiveness of adjunct therapy like safinamide in the population of patients, additional information from the well pharmaco-economic evaluations is required. No human studies on the neuro-protective benefits of safinamide are investigated, even though animal studies have shows it to have these properties, which may be partially related to its nondopaminergic (glutamatergic) activity. To completely understand the possible neuroprotective benefits of safinamide in PD patients, if any, more study is required. Finally, the dose of "50-100 mg/day" was observed to be of greater tolerability as well as effective as an adjunct to levodopa and also other dopaminergic drugs in patients with PD. Safinamide appears to be an effective therapeutic choice in this situation, although further research is required, including comparative studies and long-term trials.

Although it is not currently expected to be used as monotherapy, safinamide will be accessible for use in early or later diseases if it does show to be effective. Due to MAOB overlapping and the potential to increase the likelihood of a tyramine effect, using safinamide with either selegiline or rasagiline is most likely not viable. As a result, it will serve as an alternative for patients who have not yet started taking an MAO-B as an addition to either levodopa or a dopaminergic agonist. Safinamide is not intended to be used as a single medicine to start treating Parkinson's disease (PD), however, this could change depending on the outcomes of clinical trials and research. The role of safinamide in PD treatment remains unknown. The good side-effect and pharmacokinetic profile, as well as the possibility of lowering the levodopa dosage when safinamide is given, indicate that safinamide is a beneficial chemical in the treatment of PD.

4. CONCLUSION

A unique molecule called safinamide combines non-dopaminergic and dopaminergic modes of action. It is a very powerful, highly specific, and reversible MAO-B inhibitor. As a result, it lessens the motor fluctuations of PD and can be administered without causing tyramine-related dietary restrictions. Safinamide has good linear dose-dependent pharmacological properties. It has a favorable once-daily dosage regimen comparable to other MAO-B inhibitors because of its good oral bioavailability and extended half-life. Despite having a large amount of biotransformation, it doesn't interact significantly with CYP proteins or interacts significantly with other drugs. As the potential of the symptomatic treatment of PD is being reached, researchers are looking for neuroprotective drugs. Numerous compounds, including levodopa, MAO-BIs, DA, and even safinamide, have been shows in animal experiments to also have neuroprotective effects. Therefore, even though numerous drugs have proved to have a

neuroprotective benefit in animal models and tissue cultures, these treatments have not yet been shows to have a similar effect in human clinical trials. Therefore, larger trials and exploratory studies are still needed to know the exact potential of safinamide in neuroprotection.

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CHAPTER 4

A COMPARATIVE EVALUATION OF GLIMEPIRIDE WITH OTHER TREATMENTS IN PATIENTS OF TYPE 2 DIABETES MELLITUS

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ABSTRACT:

"Type 2 diabetes mellitus (T2DM)" is becoming more common across the world; thereby managing glycemia is an important aspect of preventing significant diabetic complications. For many years, sulfonylureas have been used to treat T2DM. Glimepiride, which is an oral hypoglycemic drug, is widely used to treat T2DM. This evaluation study aims to assess and review the effectiveness of glimepiride in comparison to other treatments including glyburide, Linagliptin, canagliflozin, ginsenoside, liraglutide, and empagliflozin. In comparison to other sulfonylureas, glimepiride was associated with a lower incidence of weight gain and hypoglycemia in clinical investigations. Because of its absence of side effects, glimepiride could be safer in people with cardiovascular diseases (CVDs). It lowers postprandial glucose, glycosylated hemoglobin levels, and fasting plasma glucose, and is a cost-effective and viable treatment for T2DM.

KEYWORDS:

Cardiovascular Disease (CVD), Glimepiride, Insulin, Type 2 Diabetes Mellitus (T2DM), Sulfonylureas, World Health Organization.

1. INTRODUCTION

Type 2 diabetes is recognised as a serious public health issue that has an enormous effect on both patient mortality and healthcare expenditures. Due to fast economic expansion and urbanisation, diabetes has increased in prevalence in many parts of the world [1]. A person with diabetes has the worse quality of life (QOL), which causes significant morbidity and early mortality. Furthermore, it was brought up for discussion that individuals under the age of sixty account for more than one-third of mortality linked to diabetes [2]. These modifications are linked to increased intake of sedentary lifestyles and unhealthy foods, which elevate fasting plasma glucose and BMI. The likelihood of developing type 2 diabetes is increased in those with higher BMIs. Because diabetes primarily affects elderly persons, another issue is the ageing of the global population [3].

The cost of treating diabetes is at least 3.2 times greater than the national average for per-person healthcare expenditures, and when complications are present, the cost jumps to 9.4 times higher. Many patients' blood sugar, blood pressure, and other objectives continue to be insufficiently controlled. A portion of this has been attributed to a lack of awareness of diabetes and preventative treatment. According to the 2021 UN world population, 10.5%, 10.2%, and 10.8%

of individuals aged 20 to 79 worldwide were predicted to have diabetes, respectively. Diabetes prevalence rises with age, with individuals aged 75-79 having the highest prevalence of 24%. Men were more likely to be affected than women between the ages of 25 and 69 (Figure 1).

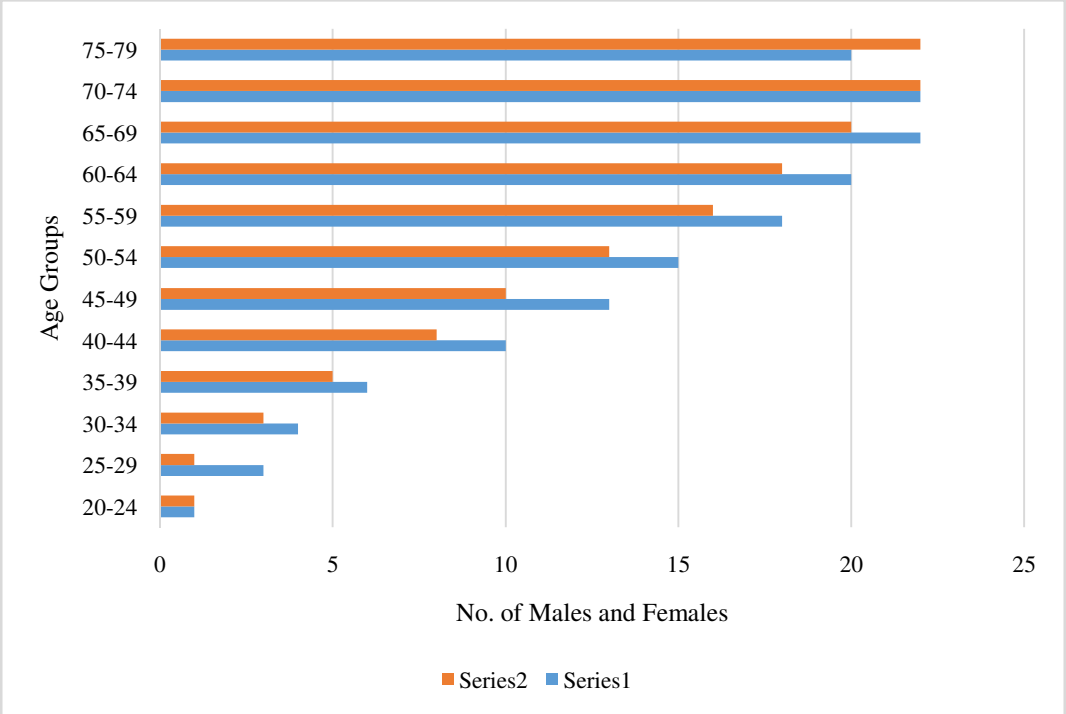

Figure 4: Graph Showing the prevalence of T2DM among different Age Groups; Series 1 Represents Males and Series 2 Represents Females.

The present study has attempted to highlight the fundamentals of glimepiride with more emphasis on its comparison to other treatments. The first section provides an understanding as well as a background behind the global burden of T2DM, its current treatments, and its drawbacks. The second provides a thorough insight into the current literature about the comparison of glimepiride to other treatments and their safety as well as their efficacy. Furthermore, the third section provides a critical discussion about the use of glimepiride and its implications. The last, and fourth section provides a concluding remark about the topic.

2. LITERATURE REVIEW

Type 2 Diabetes Mellitus patients needs attentions and improved care to increase the longevity within this patient group, adding to their numbers. Diabetes significantly raises the risk of microvascular and macrovascular complications and vascular disease account for a large proportion of the T2DM burden. Taking into account the number of individuals with T2DM and its sequelae is critical for governments and healthcare professionals, not only because it places a significant strain on already limited health resources. This is especially true for emerging countries of the world, where the highest increase in diabetes cases is expected. Diabetes affects 415 million people globally, according to the World Health Organization. Global trends indicate that the prevalence rate will rise by roughly 2.5 % every year.

2.1.Diabetes Mellitus and Treatment:

A chronic metabolic disorder known as diabetes mellitus (DM) is characterised by problems in the production, secretion, or activity of the hormone insulin. Diabetes is classified into two types based on pathophysiology and etiology: "type 1 diabetes" and "type 2 diabetes", with the T2DM accounting for approximately 90% of all cases [4]. It develops over time in humans, particularly elderly adults, and often goes unreported and undiagnosed. Dietary changes and increased physical exercise can and should be used to address this problem [5], [6]. In its severe stages, the condition necessitates therapeutic intervention with insulin therapy or blood glucose-lowering drugs. The diagnosis is either incidental or brought on by the development of coronary atherosclerotic plaque, a long-term diabetes consequence. Obesity and overweight (20% are obese and 60% of persons with diabetes are overweight), poor eating behavior, and insufficient physical exercise all raise the risk of acquiring type 2 diabetes (Figure 2) [7].

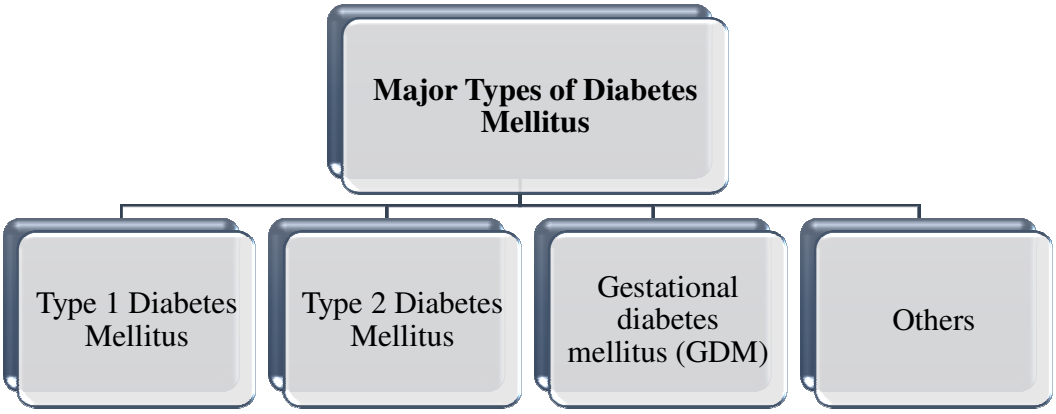

Figure 5: Major Types of Diabetes Mellitus; i) Type 1 Diabetes Mellitus, ii) Type 2 Diabetes Mellitus, iii) Gestational Diabetes Mellitus (GDM), and iv) Others.

The "life expectancy" of a 60-year-old person with diabetes and CVD is 12 years less than that of the general population, as per epidemiological statistics [8]. Diabetes reduces lifespan on average by 6 years. The disease causes long-term impairment and a considerable decline in QOL throughout the years of its progression. The possibility of a significant reduction in life expectancy should also be taken into account as one of the key factors. Diabetes is classified as a lifestyle disease due to its continually rising patient population and significant risk of dangerous complications. It has been identified as one of the major global health priorities since it is one of the most prevalent causes of mortality in highly developed nations. A multidisciplinary strategy with an integrated approach is required due to the special properties and manifestations of Diabetes.

Controlling the advancement of the disease and preventing the development of related morbidity focus on early treatment and diagnosis designed to restore normal glycemic control. Diabetes is commonly left untreated for years due to its insidious nature and gradually developing symptoms. The time of diagnosis is frequently already followed by sequelae including retinopathy, neuropathy, and nephropathy. A regimen of food and exercise has traditionally been the first step in a sequential treatment strategy to achieve glycemic control. Oral medication therapies—with or without insulin—are then added if exercise and nutrition are unable to return blood sugar levels to normal. For the treatment of T2DM, several pharmaceuticals are available,

such as insulin, a-glucosidase inhibitors (miglitol and acarbose), derivatives of the amino acid d-phenylalanine (nateglini), meglitinide analogs (repaglinide), thiazolidinediones (pioglitazone and rosiglitazone), and biguanides (metformin). The most popular anti-hyperglycemic medications for the treatment of T2DM patients are sulfonylureas.

The polar, hydrophilic changes in first-generation sulfonylureas are often small. The larger, nonpolar, lipophilic substitutions in second-generation sulfonylureas, which allow them to more readily cross cell membranes, are responsible for their improved effectiveness. Acetohexamide, Tolbutamide, and chlorpropamide are examples of second-generation sulfonylureas that are equally effective in lowering hyperglycemia as first-generation sulfonylureas. In contrast, second-generation sulfonylureas are favored due to their higher potency and typically better safety characteristics. However, even among the second-generation sulfonylureas, there are considerable differences in terms of safety.

2.2. Glimepiride:

Glimepiride was first made available in 1995 and belongs to the second-generation sulfonylurea (SU) therapeutic family. It is used to treat T2DM and promote glycemic control. Glimepiride increases peripheral tissue sensitivity to insulin, which increases glucose absorption and lowers plasma blood glucose levels as well as levels of glycated hemoglobin (HbA1C) [9]. It also accelerates the insulin granules release from the "pancreatic beta cells". As depicted in Figure 3 and enlisted in Table 1, Glimepiride with the chemical formula of $C_{24}H_{34}N_4O_5S$ has a 491 kd molecular weight and it is marketed under the brand names Tandemact, Duetact, and Amaryl. Apart from all these properties, it is classified as a small molecule.

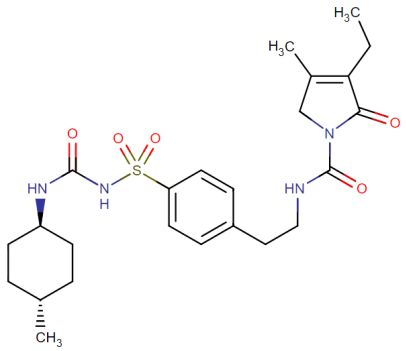

Figure 6: Chemical Structure of Glimepiride.

Table 2: List of Generic Name, Brands, Types, Molecular Weights, and Chemical Formula of Glimepiride.

Generic Name	Glimepiride
Brands	Tandemact, Duetact, Amaryl
Type	Small molecule
Molecular Weight	490.62
Chemical Formula	$C_{24}H_{34}N_4O_5S$

It helps lower postprandial glucose, glycosylated hemoglobin levels, and fasting plasma glucose, and is regarded as a viable, cost-effective therapeutic option for T2DM management. Glimepiride was licensed by the US "Food and Drug Administration (FDA)" in 1995 for the treatment of T2DM. It is generally marketed as "oral pills" under the trade name "Amaryl" and is normally used once a day.

Rosenstock *et al.* carried out a randomized control trial to investigate the comparative study on Glimepiride effects versus Linagliptin on the CVD outcomes in T2DM patients. They carried out their study using a total of 6042 participants in 43 countries, 607 hospital facilities as well as primary care sites based on selected features involving adults with CVD risk and T2DM. In their study, the participants were randomized to receive linagliptin at the dose of 5mg/daily, and on the other hand, glimepiride was given at 1-4mg\daily. The author concluded that Lintagliptin uses for a median of 6.3 years was associated with a non-inferior risk of composite CVD outcomes among individuals with relatively early-onset T2DM [10].

Another study by Garvey *et al.* carried out a study to compare glimepiride and canagliflozin against inflammatory biomarkers and adipokines in T2DM using a 52-week trial study. The results revealed an increase in median serum adiponectin by 17% and a decrease in median serum leptin by 25% with canagliflozin when compared to glimepiride. In addition to that authors also found an increase in median serum TNFalpha by 7% and a reduction in median serum IL-6 by 22% which was then followed by the correlational studies which indicated that Canagliflozin can have a beneficial impact on CVD and insulin sensitivity [11].

Yang *et al.* also carried out a metabolic study of glimepiride and ginsenoside in rats with T2DM. In their study, they developed an in Vitro incubation system using "type 2 diabetic rat liver microsomes (TRLM)" and "normal rat liver microsomes (NRLM)" followed by the analysis of metabolism chromatography coupled with mass spectrometry. The results of their study revealed the increase in TRLM and RLM using glimepiride after the treatment with ginsenoside potentially due to the synergistic effect of both [12].

Nystrom *et al.* investigated the variability in subjects with T2DM receiving glimepiride or liraglutide involving a total of 62 individuals with T2DM. The included individuals were then randomized to a 4mg/daily dose of glimepiride and 1.8mg liraglutide both in combinatorial treatment with 1mg of metformin. In the liraglutide-treated group, there was a continuous rise in "diurnal HR" that was preceded by a considerably elevated HR during daytime [13].

Tamura *et al.* carried out another comparison to assess the effects of glimepiride and empagliflozin in patients with T2DM with a randomized controlled trial. They carried out the study using a total number of 63 patients having T2DM receiving glimepiride and empagliflozin followed by setting the primary and the secondary outcome. The results of their study revealed that there is no significant difference between both glimepiride and empagliflozin. However, the use of empagliflozin demonstrated a significant reduction in body fluid volume potentially due to the heart failure risk reduction.

Glimepiride and other second-generation SUs have been compared in several research. Dills and Schneider compared the outcomes of "glimepiride" vs "glyburide" in a multicenter trial that included 577 Patients with T2DM. After a year of treatment, it was observed that there were no

obvious changes between the two groups for PPG, FPG, or HgbA1C. Furthermore, glimepiride was associated with a lower incidence of hypoglycemia than glyburide (1.7 vs 5.0 percent, respectively; p = 0.015), which is defined as a patient reporting hypoglycemic symptoms without having them confirmed by blood glucose tests [14].

Another research by Tandon *et al.* also carried out a pharmacoeconomic analysis for the comparison of the cost-effectiveness of teneligliptin+metformin and glimepiride+metformin using patients with T2DM for the total course of 8 weeks. A cost-effective analysis was then performed which suggested that the latter combination of glimepiride+metformin is much more cost-effective when compared to the first combination of teneligliptin+metformin. When used in the initial stage [15].

Hamaguchi *et al.* investigated the effectiveness of glimepiride in patients that were treated with glibenclamide using a multicenter study. They performed the study involving a total of 66 outpatients with diabetes and the switching to glimepiride from glibenclamide. The results revealed a significant lowering in "fasting plasma IRI" in patients after 6 months of treatment. In addition to that, they also observed a weight reduction, therefore suggesting that glimepiride can improve insulin resistance in patients that are hyperinsulinemic and are treated with glibenclamide [16].

The above studies provide a comparative assessment of glimepiride with various other treatments that have been provided in each study. In addition, its efficacy with other drugs in combinatorial treatment was also assessed. Whereas this paper provides a thorough review of the current comparison.

3. DISCUSSION

In the U.S. and many other countries across the world, T2DM is quickly rising to the top of the list of the most common chronic diseases. After 0, 1, and 6 years of treatment, the condition can cause significant long-term sequelae such as renal failure, blindness, and impaired cardiac h-Cell function in patients. Patients with T2DM are also more likely to experience sexual dysfunction, amputations, and other complications as a result of aberrant insulin levels, high blood sugar, and abnormal lipid levels due to vascular impairment. These serious diabetes consequences can be avoided with early diagnosis, close monitoring, and pharmacological management. In the therapy of diabetes, strict lifestyle changes, such as diet and exercise, are crucial, but they frequently fall far short in regulating hepatic glucose production and hyperglycemia.

Drugs known as sulfonylureas have been used for many years because they work effectively and are well tolerated. However, several of the original second-generation sulfonylureas are linked to weight gain and hypoglycemia, making them potentially inappropriate for patients who are predisposed to hypoglycemia, as well as those who are overweight or have compromised renal function. Investigations into glimepiride, the newest second-generation sulfonylurea, have shows several characteristics that might help it overcome some of these drawbacks. Additionally, glimepiride has a positive safety profile and has been shows to successfully lower FPG, A1C, and PPG, concentrations. Controlled trials including more than 5000 individuals with T2DM have proven the sulfonylurea's effectiveness and safety, especially in the case of glimepiride. Glimepiride was equally effective in double-blind studies although there were discernible variations between treatment groups.

Most T2DM patients are overweight. When these individuals lose weight, their clinical and metabolic profiles, particularly HbA1c, significantly improve. SUs, insulin, and thiazolidinediones are all thought to cause weight gain, despite research showing that glimepiride has no effect on weight in T2DM patients. Weight gain brought on by T2DM therapies has become a major problem in clinical practise and a major obstacle to achieving optimal glycemic control. In patients with T2DM, glimepiride is associated with weight-neutral effects and comparable metabolic management compared to other drugs in this class.

3.1. The dilemma of Precise Mechanism

Although the precise mechanism of the beneficial effects of glimepiride is unknown, it has been suggested that glimepiride inhibits insulin secretion less than other SUs. Furthermore, glimepiride lowers blood sugar in a variety of non-pancreatic mechanisms, such as by reducing endogenous glucose synthesis and increasing peripheral glucose absorption. These effects might explain why using glimepiride causes weight loss or weight neutrality.

3.2. Effective Dose

Glimepiride is commonly started with 1-2 mg given just before breakfast. Self-monitoring blood sugar levels are used to adjust the dose, which is then progressively increased until glycemic control is reached. Although dosages as high as 32 mg/day have been employed in clinical studies, the highest suggested dosage is 8 mg/day. The usual dosage ranges from 1-4 mg per day. The mean HbA1c before and after therapy was shows to be lower at higher doses (6–8 mg/day). In individuals whose T2DM is not managed by SUs, it may also be used in conjunction with other T2DM therapy options, such as insulin. However, glimepiride and insulin together require a lower initial dose of insulin.

3.3. Tolerability and other considerations

Patients with T2DM, even the elderly, seem to tolerate glimepiride well. In patients who are elderly, disabled, or malnourished, it should be taken with caution. While it can be utilized in situations of “renal insufficiency”, individuals should be monitored for hypoglycemia symptoms and glimepiride doses should be lowered in these cases.

3.4.Side effects

Hemolytic anemia, thrombocytopenia, agranulocytosis, leukopenia, aplastic anemia, and pancytopenia are only a few of the rare but dangerous hematological side effects of glimepiride. With SUs, especially glimepiride, hepatic porphyria responses and disulfiram-like events have been seen. There have been instances of hyponatremia documented, most frequently in individuals who are taking other medications or have illnesses that are known to cause hyponatremia. It has been recommended that some SUs, such as glimepiride, could increase the peripheral activity of antidiuretic hormone and/or amplify its release.

In this current study, a summary of a comparative assessment of glimepiride with several other medications is provided including glyburide, Linagliptin, conagliflozin, ginsenoside, liraglutide, and empagliflozin. In these studies, it has been observed that there is much heterogeneity in the results of clinical trials and other multicenter studies. A study revealed that patients with very early T2DM and increased cardiovascular risk showed noninferiority in the risk of major negative cardiovascular events when using linagliptin compared to glimepiride. “Canagliflozin”

may improve adipose tissue function and cause changes in “IL-6”, “serum adiponectin”, and “leptin” according to studies by Garvey et al., which would improve insulin sensitivity and reduce the risk of cardiovascular disease. According to the results of Yang et al., ginsenoside Rg3 and glimepiride can be used in combination to treat T2DM.

4. CONCLUSION

In course of the type 2 diabetes management, feasible, pharmacologic treatments should be introduced as part of current therapy regimens to achieve effective glycemic control. Glimepiride can be taken once daily, at any time of the day, and provides 24-hour glycemic control by efficiently lowering blood glucose concentrations at lower dosages than other SUs. The findings from clinical trials point to a possible reduction in the risk of cardiovascular adverse outcomes with glimepiride treatment compared to glibenclamide, as well as a decreased risk of hypoglycemia (including exercise-induced episodes) was also recorded when glimepiride is used.

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CHAPTER 5

ASSESSING THE EFFICACY AND SAFETY PROFILE OF DIFFERENT DRUG TREATMENTS IN THE MANAGEMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

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ABSTRACT: A chronic autoimmune condition that can affect every organ and tissue, systemic lupus erythematosus (SLE) is common across the world with a presence in developed as well as developing countries. It has been documented that disease activity and further development are influenced by a combination of factors ranging from hormonal factors to genetic factors and environmental factors. The great heterogeneity of clinical symptoms, manifestations, and organ damage has also been found in previous studies which further highlights the standard treatment or therapy to be developed for effective management because of the side effects caused by the existing ones. Therefore, the role of this review is to provide critical insights into the burden of SLE, epidemiology, clinical manifestations as well as the factors affecting the risk of its development. Apart from that, an intense review of existing literature on the efficacy and safety of different drugs in the treatment of SLE has also been provided. The findings of this study revealed that there are great disparities that affect the outcomes of the treatment when used in the management of SLE. Therefore, this study can provide a path for further development of an effective drug against SLE which require a fundamental to be established before pondering the process of novel drug development.

KEYWORDS: Autoimmune Disease, Environmental Factors, Systemic lupus erythematosus (SLE), Rituximab (RTX).

1. INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with diverse symptoms and a cause that has yet to be completely explained but is thought to be complex [1]. Epidemiological research on SLE reveals significant age, gender, ethnic, temporal, and geographical differences, pointing to genetic, hormonal, and environmental disease factors. There are significant gender differences in SLE burden, with women having a greater illness prevalence than males. Based only on clinical findings, it was determined that the condition primarily afflicted females in 80-90 percent of cases [2]–[4].

SLE is a chronic systemic autoimmune disease that leads to a variety of physiological and immunologic abnormalities as well as clinical manifestations. Lupus susceptibility is inherited. As a result, environmental factors or other causes are frequently acknowledged as illness triggers. Lupus can affect nearly every organ system, most notably and fatally, the neurological & renal systems. Individuals severity ranges from little cutaneous effect to severe organ malfunction, with results varying from death to long-term remission. Moreover, disease activity

can fluctuate greatly, with the vast majority of patients experiencing flares followed by prolonged periods of remission. Clinical symptoms and signs of SLE differ not only from case to case but also exhibit substantial geographical or ethnic variability among groups. The first section of this review study aims to the critical insights into the epidemiological profile of the diseases, clinical symptoms and manifestations, and the factors influencing the risk of developing the disease. In addition to that recent literature on the clinical efficacy and treatment of SLE are also provided with their safety profile. In the second section, a discussion on the development of novel therapeutics as well as the considerations is provided which is then followed by the third section conclusion.

1.1. Epidemiology and Clinical Manifestations:

The prevalence and incidence of autoimmune disease, SLE have been reported to be 30-50 per 100,000 people, corresponding to around 250000 in the United States and 500000 patients in Europe. As illustrated in Figure 1, a study published found that ancestry, race, and ethnicity all had a significant influence on the symptoms and degree of SLE [5]. Asian, Black, and Hispanic people have a greater prevalence and incidence of SLE than white people, and they have a more serious and persistent disease, with long-term health damage and higher death. Differences in seen are mostly due to genetic variations and interaction with local environmental factors that may or may not be modifiable. It has also been noted that 90% of patients are females of reproductive age. Although symptoms might differ, frequent symptoms are rash, arthritis, and constitutional symptoms. Individuals on the opposite end of the range may present with life-threatening organ problems such as autoimmune cytopenias, lupus nephritis, or nervous system dysfunction [6].

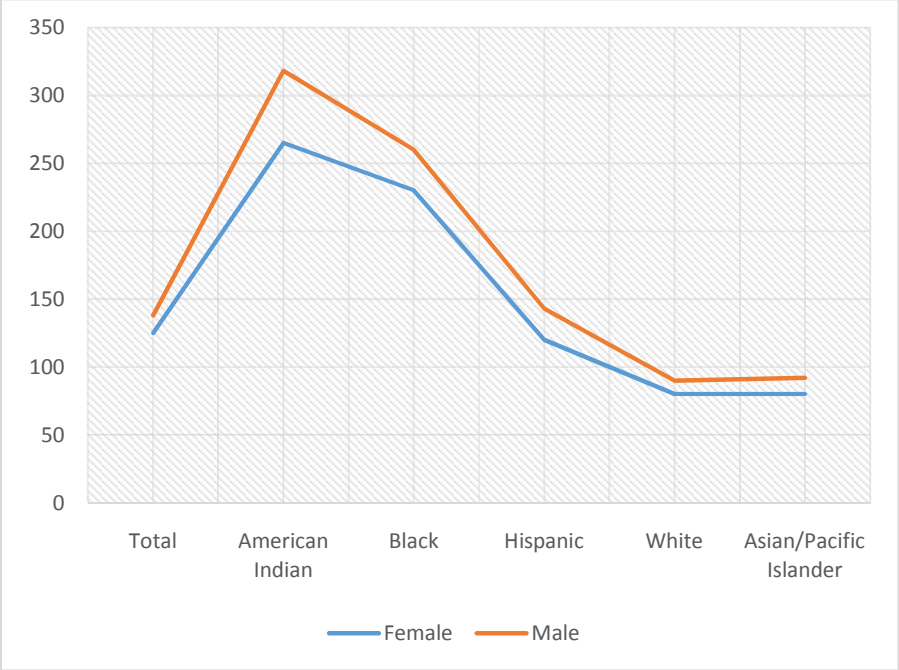

Figure 7: Illustrating the Prevalence of Systemic Lupus Erythematosus (SLE) in Terms of Race/Ethnicity and Sex.

SLE patients can show a range of systemic symptoms. Arthralgias, arthralgias, malaise, fever, myalgias, headache, lack of appetite, and body weight are among the general symptoms. Arthralgia, fatigue, and fluctuations in weight are the most prevalent symptoms in new cases that are being reported or recurring active SLE flares. The most common constitutional symptom, Fatigue, connected with SLE, can be caused by active SLE, medications, concurrent fibromyalgia, mood disorders, active SLE, and lifestyle factors. Fatigue caused by active SLE normally appears in association with other laboratory markers and clinical manifestations. Another prevalent but a nonspecific symptom of SLE is fever which can develop from a range of sources, the most common of which is infection, active SLE, and fever-induced by any treatment drug [7]. A thorough history may help in distinguishing between these. The clinical manifestations of SLE by different body systems are enlisted in Table 1 below.

Table 3: Enlisting the common manifestations of Systemic Lupus Erythematous (SLE) sorted by different body systems.

Neurologic	Coma, Lethargy, confusion, Seizure, Psychosis
Renal	High blood pressure, Impaired renal function, Presence of protein and blood in the urine, kidney failure.
Cutaneous	Alopecia, Skin lesions, disfigurement
Hematologic	Lymphadenopathy, thrombocytopenia, anemia, leukopenia, splenomegaly
Immunologic	Malaise, headache, fever, myalgias, arthralgias
Cardiopulmonary	Pericarditis, vulvar damage, heart failure, conduction defects

1.2.Factors Involved in SLE risk and disease development

According to earlier studies, environmental factors and exposure to them could be responsible for over 60% of the risk of SLE, with Gene-Environment (G-E) combinations contributing to some of this risk. This frequently results from environmental stimuli of epigenetic changes (such as DNA methylation) that support differential gene expression. This may help to explain why, despite having equivalent genetic risk factors, one person with SLE manifests while the other does not. The exposome consists of the whole range of personal exposures encountered during one's lifetime, including endogenous and biological, psychological, and behavioral exposures, all of which can influence gene expression via G-E interactions. A study by Leffers and Jacobsen studies the interactions between the exposome and genome in the development of SLE. Their study revealed that genetic factors and environmental factors alone cannot explain the risk of the development of SLE. Their work supported that gene and environment interactions can potentially add to the risk of the development of SLE intensifying the need to explore more basic the interactions involved in the development of the disease for a better understating of the SLE complexity [8]. The risk of SLE has been linked to several chemicals, physical, and other modifiable external factors, but only a small number of researchers have looked at whether these

exposures interplay biologically with hereditary variables. The factors influencing the risk of SLE development are categorized into three categories namely environmental exposures, Gene-environment interaction, and third, being genetic factors as illustrated in Figure 2 below.

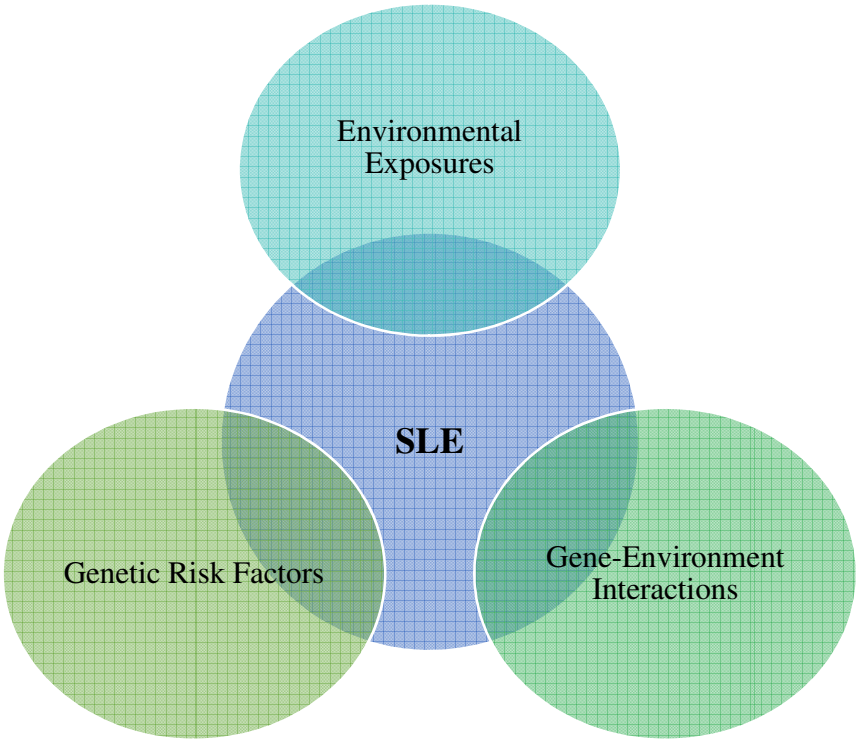

Figure 8: Illustrating the different factors influencing the risk of SLE Development.

There is a significant genetic link to SLE susceptibility, as evidenced by the concordance rates of 24-58% in monozygotic twins and 2-5% in dizygotic twins. It is further backed up by the fact that SLE as well as other autoimmune diseases are more common in families of SLE patients than in the general community. Generally, it seems that 8–10% of cases of familial SLE occur, with percentages comparable in communities of Afro-Caribbeans, African Americans, Europeans, Latin Americans, and certain Asians [9].

Choi et al. investigated the association of healthy lifestyle factors with SLE and its lower risks. Their study includes a total number of 185,962 women patients. They performed a calculation of the healthy lifestyle index score based on the baseline followed by the assignment of the scores after 2 years of monitoring based on different factors such as smoking, diet, body mass index, and other factors like alcohol consumption. The results of their study demonstrated that a higher score of HLIS was found to be associated with a lower frequency of SLE in individuals under study supervision. Therefore demonstrates that modification of healthy lifestyle factors can potentially reduce the risk of the development of SLE by 50%.

1.3.Pathogenesis of SLE:

An interplay of environmental triggers, hormonal, immunological, and genetic predisposition are all the components of the individual necessary for SLE to manifest clinically. Immunological tolerance to self-antigens is lost in this context of toleration combined with pro-

inflammatory stimuli such as cytokines including type 1 interferons. Then comes autoimmune disease, which is triggered by a complex combination of impaired neutrophil extracellular traps, immune complex sensing, lymphocyte biology, interferon pathways, impaired clearance of apoptotic debris, and improper extracellular trapping by neutrophils.

The 11–50% monozygotic twin concordance and greater risk in family members point to a genetic vulnerability. Numerous genes, most of which code for immunological components including ITGAM, IRF5, BLK, CTLA4, HLA, and STAT4 among others, have been linked to a propensity to get lupus. Numerous environmental factors have been linked to lupus. The most well-known examples are ultraviolet radiation, medicines, and supplemental agents like echinacea and trimethoprim-sulfamethoxazole also smoking, and infections. Additionally, a 50 % higher chance of getting lupus has been associated with psychological stress [10].

Both the adaptive and innate immune systems, which are linked in a feedback loop, are known to be disrupted in lupus. Lupus causes complicated T-cell aberrations that are dysfunctional. There is a polarisation toward Th17 over Tregs and insufficient IL-2 production. Double-negative T cells are in excess. In SLE, T lymphocytes support B cells excessively. Despite overall B cell lymphopenia, there are indications of an overabundance of auto-reactive B cells. A novel biologic treatment was created as a result of the BAFF pathway, a mechanism for T cell-independent B cell survival or hyperactivation of the BLyS.

1.4.Clinical Efficacy of SLE Treatments:

A fusion protein known as abatacept is made up of the Fc region of immunoglobulin IgG1 and the extracellular domain of CTLA-4. It limits the co-stimulatory association between B and T lymphocytes, obstructing B-cell response by inhibiting co-stimulatory T-cell activation. It attaches CD86 and CD80 more tightly than CD28 and has a greater affinity for both of these molecules. Initially, abatacept was licensed for the management of severely and moderately active rheumatoid arthritis (RA) that was resistant to typical "disease-modifying anti-rheumatic drugs (DMARD)" or an antitumor necrosis factor (TNF) drug. Later, it was also permitted to treat juvenile polyarticular idiopathic arthritis. Although this biologic agent is still being tested in clinical studies for the treatment of SLE, the positive outcomes might open up new possibilities for SLE patients. There are a lot of clinical trials published on the internet for assessing the efficacy of different treatments and their safety profiles [11].

Furie et al. investigated the efficacy and the safety profile of abatacept (ABA) against a placebo in patients having lupus nephritis. The study included a multicenter, double-blind study, open-ended trial for 24 months. A total of 405 patients were included and randomized in the study. The results of the study revealed that the patients treated with abatacept demonstrated a lot of improvement in proteinuria which lead to the early improvement. The safety profile was also reviewed for 2 years which was demonstrated to be favorable [12].

Another study by McCarthy et al. carried out a study to investigate the short-time efficacy of rituximab (RTX) in 270 patients with refractory SLE. In their study, they performed the analysis of the disease activity, rates of infection, and baseline characteristics followed by defining the responses. The responses were achieved from 49% of the patients. The results of the study showed that RTX was associated with a great safety and efficacy profile in the improvement of patients with refractory SLE. Serious infection was also observed in the patients after 3 months of RTX therapy which can be further improved with early vigilance [13].

Serris et al. also carried out a study to assess the safety and efficacy of RTX in patients with SLE associated with cytopenias using a multicenter retrospective cohort study. Standard definitions were then used to assess responses. 61 women with 2 male patients were included in the study. The results of their study revealed the relapse in 24; successful retreatment for 16 patients. The study also showed very less severe infections after treatment with RTX without any fatal outcome with no further cases of neutropenia induced by RTX which demonstrates that RTX seems to be an option that is very effective in treating SLE [14].

Gottenberg et al. investigated Epratuzumab efficacy in 1584 patients with SLE associated with Sjögren's Syndrome. Two patient population was randomized into two groups; namely patients with SLE and associated with SS or SLE without SS. Different parameters were then used to assess the safety and efficacy profile of Epratuzumab using British Isles Lupus Assessment Group (BILAG) biologic markers (including IgM, IgG, IgA, and B cells), BILAG-based Combined Lupus Assessment (BICLA) clinical response to treatment, total score. The result of their study revealed that SLE patients with SS treated with epratuzumab demonstrated greater efficacy and further improvements in the patients which were potentially due to bioactivity and the decrease in the B cell number [15].

Another study by Tanaka & Tummala investigated a monoclonal antibody, Anifrolumab for the treatment of SLE. The results of their study revealed that anifrolumab of 300mg with monthly interventions was associated with a difference of >16% with control in a study of 52 weeks. The results of the study also supported the efficacy of the Anifrolumab from combined data. In addition to that, as with another study, it has been noted that only 8-16% of the individuals demonstrated the superiority of the anifrolumab [16].

The above research studies have undertaken different investigations to assess the efficacy and safety of different treatments for SLE management targeting the molecular mediators involved in the onset of the development of the disease. However, the role of this study is to provide researchers to go deep insight into the fundamental of the pathophysiology as well as the clinical manifestation of the disease with also the factors influencing its development for better development of possible therapeutic.

2. DISCUSSION

A summary of all the fundamentals of SLE with different factors influencing its development, epidemiology as well as the associated clinical manifestations are provided above. In addition to that clinical trials, multicentre studies, and other placebo-controlled studies of different treatments of SLE are also summarized above with a focus to provide one-stop for researchers to go through the safety and clinical efficacy profile of trials involving different treatments attempting to manage SLE. Patients with rheumatoid arthritis, hypertension, or diabetes, have resulted in significant improvements due to effective treat-to-target approaches. Initiatives in SLE have established therapeutic objectives by using a similar approach [17]. The number of cases who responded in the standard-of-care groups in lupus nephritis and extra-renal clinical trials has been appallingly low, despite the presence of several treatments. Even if patients in the population may have not been reflected in the research populations. Numerous pharmaceutical firms have recognized the urgent need for better and more efficient treatments, which has sparked an unprecedented level of clinical trial engagement in SLE. The methods used are as diverse as the disease itself. However, the drug development process has proven to be extremely difficult, with many phases 2 and 3 clinical studies failing to achieve their main

objectives. Numerous factors contribute to this, such as flawed study design (glucocorticoid-sparing strategies and inadequate outcome measures), poorly define targeted population (rituximab appears to be effective in refractory patients or patients with new-onset lupus nephritis), and possibly poorly defined targets. Interventional research is being conducted on several strategies that target extracellular and intracellular targets, including novel cellular strategies, blocking of stimulation, anti-cytokine targeting, blocking of intracellular signaling pathways, enhanced B-cell depletion, and immunomodulatory concepts (such as low dose IL-2 treatment). All drugs and their profile are not covered in this study because there are so many different avenues being investigated; instead, we focus on the most important ones. Patients suffering from SLE have a five-fold higher risk of death than the general population, owing mostly to comorbidity complications. Even though it is difficult to distinguish between treatment-related or disease-related morbidity, there is an indication that SLE patients have higher infectious, osteoporotic, malignant problems (lung cancer, hepatobiliary cancer, and non-Hodgkin lymphoma), venous (atypical and typical), metabolic, arterial (cardiovascular and cerebrovascular) complications [18].

The management of various comorbidities is outlined in consensus recommendations; nonetheless, they mostly reflect standard clinical practice. The use of a low dosage of aspirin in patients with complications with antiphospholipid antibodies as a preventative measure against osteoporosis or thrombosis prophylaxis is not dependent on specific kinds of evidence for SLE patients, but it should still be taken into consideration. A double-blind trial supports sunscreen use for UV light protection in patients with SLE. Similarly, people with greater cardiovascular risk should consider weight management, immunizations, exercise, and quitting smoking. For certain people, statins plus antihypertensive medication may be necessary. Antimalarials should be used in all SLE patients due to their wide-ranging benefits that go beyond their anti-inflammatory benefits and their correlation to improved survival [19]. Usually, long-term follow-up studies may show lower damage accumulation and comorbidities risk factors (such as coronary heart disease, hypertension, infections, atherosclerosis, dyslipidemia, and osteoporosis) are present. The understanding of possible genetic and environmental variables that influence the occurrence of SLE in particular populations has advanced during the past several years. Various candidate genes underlying disease susceptibility have been discovered by GWAS investigations, and numerous environmental factors have been proposed by large cohort studies. Unfortunately, no one gene (or gene combination) or range of stressors has yet been identified, which may account for more than a small portion of people who eventually develop SLE. To partially evaluate the elements of the presently obscure portion of genetic heredity, investigations for rare gene variations with high cumulative effects have been prompted by the limited capacity of common variants to explain the genetic basis of complex disorders. The highest risk for SLE development is thought to result from a mix of genetic and environmental risk factors, and synergistic G-E interactions can be the most significant mechanism influencing the risk of SLE. The investigation of SLE-specific G-E interactions also has a great deal of potential to shed light on the pathophysiologic mechanisms underlying the disease and may identify specific regions worth further investigation in gene expression studies and epigenetics, as has been suggested for IFN signaling in SLE. Another crucial group of factors affecting the severity of SLE is environmental triggers, such as infections and UV radiation. Infectious pathogens may cause immunoregulatory disruption, tissue injury, and the release of antigens to cause the start of SLE. The pathophysiology of SLE in the local Aborigine population is considered to be influenced by the high incidence of serious bacterial infections in some parts of Australia. The keratinocyte

death caused by UV radiation may produce nuclear antigens that may trigger an autoimmune reaction. Therefore, differences in SLE burden between nations may be caused by differences in sunlight exposure, partially explaining the higher frequency of disease in the north of Australia and the south of Europe.

3. CONCLUSION

Since cellular and molecular mediators, as well as pathogenic pathways underpinning SLE, are becoming better known, novel biological treatment options targeted against the disease and its molecular mediators are being developed. The pathophysiology of SLE is still not entirely understood. However, further research is required. Novel biological therapies are quickly becoming available. There is still a long way to go until there are new therapeutic alternatives for SLE. To assess the effectiveness, safety, and immunologic profiles of all drug treatments, assessment studies must be conducted. Despite the obvious challenges, phase II as well as phase III trials should get standardized, and effectiveness endpoints need to be appropriately established and tailored to a particular SLE population, to particular clinical symptoms, organ involvement, and other comorbidities. When assessing the efficacy, cost-effectiveness , and long-term safety of these novel therapies, post-marketing surveillance and registry data are also essential. Because of this, new biological treatments must go through a protracted and expensive process once they are developed before they can be considered strong contenders as the main methods of therapy for SLE.

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CHAPTER 6

A STUDY ON EMERGING PERSONALIZED MEDICINE IN CANCER TREATMENT WITH A SPECIAL EMPHASIS ON BIOMARKERS

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ABSTRACT:

Chemotherapy has subsequently undergone a revolution in terms of advancement and improvement. Despite this, a substantial population of patients has primary treatment failures or relapses with the development of resistant malignancy. To move away from the "one-treatment-fits-all" approach, the scientific community began to accept the necessity for a personalized medicine approach. Advancing personalized medicine can help mitigate treatment failures in the cancer patient. Therefore, this paper aims to review personalized medicine, and its fundamental context to different types of cancers such as colorectal cancer, gastric cancer, and breast cancer. In addition to that, this study also provides a review of the recent studies investigating novel biomarkers associated with a wide variety of cancers which can help in the early diagnosis of cancer at different stages. Therefore, the study provides a path for future researchers to further investigate the discovered biomarkers to take them from bench to bed.

KEYWORDS:

Biomarkers, Cancer, Chemotherapy, Colorectal cancer, Personalized Medicine.

1. INTRODUCTION

Every year, millions of individuals are given cancer diagnoses globally, and more than 50% of those who receive a cancer diagnosis die as a result of their disease. As a result, cancer is a huge health burden for everyone. Cardiovascular disease and cancer are the two conditions that cause the majority of deaths worldwide today. However, it is unquestionable that as a result of significant advances in the detection, prevention, and treatment of CVDs, cancer will eventually overtake other causes of death as the number one killer in many countries around the world. The fact that elderly people are by far the most vulnerable population means that it will likely be a significant health problem. According to Global Cancer Statistics (GLOBOCAN), “lung cancer” is the most frequent kind of cancer globally in terms of both prevalence and mortality, followed by breast, lung, prostate, and colorectal cancer. It is predicted there will be more than 21.7 million newly diagnosed cases of cancer globally by 2030, with 13 million deaths from the disease happening annually owing to aging and population growth alone. In low- to middle-income countries, where 60% of cancer-related deaths now occur, this trend is expected to become much more obvious [1], [2].

Cancer is a complex hereditary disorder that causes abnormal cells to grow and divide uncontrolled throughout the body and to spread to other organs. “Breast cancer” is the most prevalent type of cancer among women. Annually, "Pink Ribbon Day" is commemorated to increase public awareness of this condition. One of the most dangerous life-threatening diseases

a woman may experience in her lifetime, it is diagnosed in 150 out of every 100,000 women each year. It accounts for around 16% of all malignancies in women and is thought to be responsible for 500,000 mortality annually. Although breast cancer affects males less commonly than it does women, it nonetheless claims the lives of and affects about 2,000 men each year in the US. Figure 1 shows the Graphical Representation of New Cases of Different Types of Cancer in Females in a Year, WHO. Figure 2 shows the Graphical Representation of New Cases of Different Types of Cancer in Males in a Year, WHO.

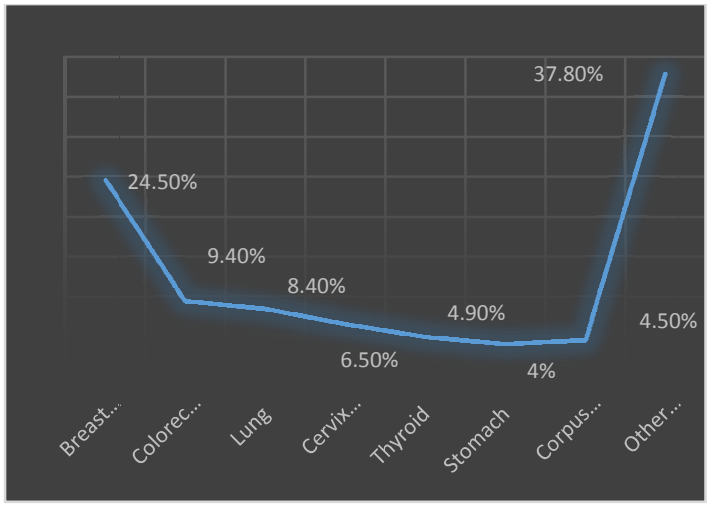

Figure 9: A Graphical Representation of New Cases of Different Types of Cancer in Females in a Year, WHO.

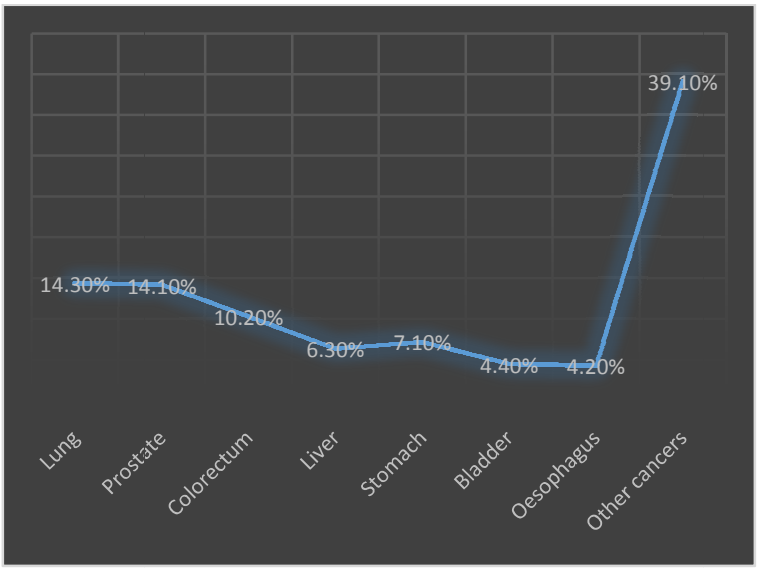

Figure 10: A Graphical Representation of New Cases of Different Types of Cancer in Males in a Year, WHO.

Surgery, chemotherapy, radiation therapy, and immunotherapy are the four primary categories of standard cancer treatments. Some patients will only need one therapy, but the most effective way to combat resistance is usually with a combination of therapies. When solid tumors do not spread

and are situated in accessible parts of the body, surgery may be an option; however, since many cancers do metastasize, more aggressive interventions, such as radiation and chemotherapy, are required [3]. To eradicate cancer cells and reduce the tumor, these methods require high doses of radiation and medications, which, regrettably, sometimes result in extra harm to healthy cells.

Despite their widespread usage, they do have problems, such as low effectiveness, which is not confined to only chemotherapy but also other modern cancer treatments. It is projected that any given class of cancer drugs is useless in a startling 75% of patients. Importantly, the kind, stage, and location of cancer in addition to the age and general condition all affect how successful these treatments are. This implies that several individual aspects should be taken into account before selecting a cancer treatment. Figure 3 shows the Influence of Different Factors on Drug Response and Associated Variations.

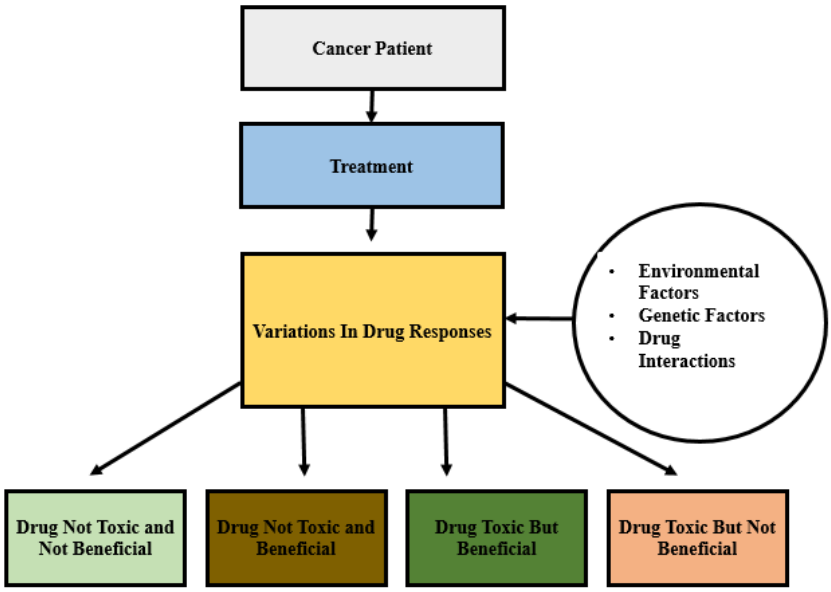

Figure 11: Illustrating the Influence of Different Factors on Drug Response and Associated Variations.

Cancer incidence and prevalence are rising alarmingly, but treatment progress has been gradual and the duration of its effects ranges from weeks to months. Traditionally, clinicians have treated patients based on disease symptoms, pathological examination, and medication history. Numerous cancer types may now be found early on due to improvements in diagnostic technology and early detection markers. These epigenetic, epigenetic, biochemical, metabolomics, genetic, imaging, and proteomic markers are used [4]. With the option of multiplexing, technologies may be employed to find these markers in clinical samples. The use of multiple markers in the same sample often improves the specificity and sensitivity of cancer detection and helps in making an early and accurate diagnosis by a physician. As could be inferred from the profiles of markers outlined above, this information is extremely important since it allows for the formulation of personalized treatment regimens depending on the existence and stage of cancer. The gold standard in clinical practice is still pathological diagnosis, although molecular diagnosis using new data may differ from pathological diagnosis.

1.1. Need for Personalization in Cancer Treatment

Cancer may result from somatic or inherited genetic anomalies. Following cancer, genetics can help researchers understand hereditary cancers, which represent a significant part of medical genetics. Only 10 to 15% of all cancers are inherited, while the rest are impacted by the environment, infections, and lifestyle factors. Scientists can use this data to estimate a human lifetime of developing cancer. Only a small number of cancer-disposing syndromes are defined by the autosomal dominance of an allele, which raises the chance of cancer. Mutations and other genetic changes are also influenced by non-genetic factors. Additionally, it has been shows that people without a family history of cancer can develop cancer[5]–[8].

Inherited genetic differences in genes involved in drug metabolism and processing also affect how patients respond to treatment, in addition to genetic variations. These changes could make some drugs more toxic. The science of "pharmacogenomics," which determines whether people would react to a particular medicine according to their genetic information, has been made possible by this understanding. Utilizing the right drug at the right dose, with minimum or no toxicity, for the “right patient” at the “right time” is the aim of personalized medicine.

1.2. Personalized Medicine

The term "personalized medicine" refers to a special method of personalizing medical treatment to each patient's particular needs. Precision medicine is also a term used to describe personalized medicine. Using the genetic structure of the genome, these treatments are developed. The prevention, diagnosis, and treatment of any condition become its top priority, and individualized medicine is founded on “genomics” and “pharmacogenomics”. Personalized medicine for treating the condition will be strengthened by the development of molecular profiling expertise to get access to protein, DNA, and RNA. Precision medicine has several benefits over conventional medicine, including the need for less treatment than is necessary, increased efficacy and safety, a reduction in adverse drug reactions, improved patient compliance, and a lower proportion of failed clinical trials. Targeted treatments like personalized medicine are effective for a variety of diseases, including “lung cancer”, “autoimmune disorders”, “prostate cancer”, and “brain tumors” [9]. Figure 4 shows the Different Omics Involved in Personalized Medicine.

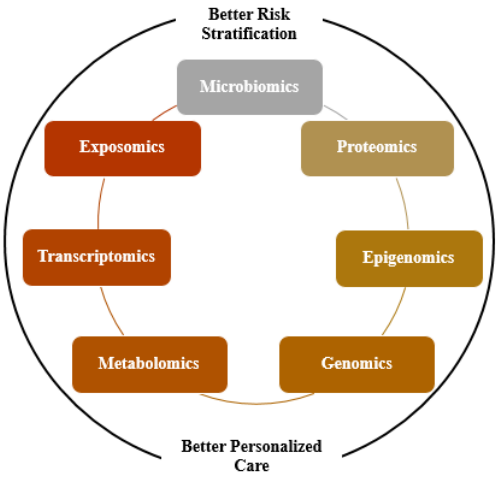

Figure 12: Illustrating the Different Omics Involved in Personalized Medicine.

A form of targeted therapy known as personalized medicine is beneficial for a variety of diseases including brain cancer, lung cancer, prostate cancer, rheumatoid arthritis, autoimmune disorders, etc. To provide patients with more accurate care, a highly functional customized treatment system will benefit from technologies like improved knowledge of genomics, phenomics, and other "-omics" (such as exosomes, metabolomics, and proteomics,). Therapeutic biomarkers may be prognostic, predictive, or both at once. The progress of a disease within a population that is not being treated can be determined independently by prognostic biomarkers. The overall clinical outcome of an individual is correlated with the absence or presence of a biomarker (such as the risk of mortality and recurrence). In different forms of cancer, prognostic biomarkers offer treatment-independent predictive data on patient outcomes [10]–[12].

Taylor *et al.* studied the population of breast cancer to determine the combination of "single-nucleotide polymorphisms" that are related to various disease subtypes. Targeted genes linked with the risk of developing disease in these categories were investigated, accompanied by the discovery and assessment of existing active chemical compounds as therapeutic repurposing options. The findings of their analysis indicated 175 gene targets associated with genes important to diverse subgroups of breast cancer patients. TGM2 and P4HA2 have high appropriating possibilities and a powerful deterministic link to breast cancer, illustrating that a comprehensive study of combination genomic (and others) features can be utilized for the precise stratification of patient populations and recognize potential drug candidates [13].

Yu *et al.* examined 127 serum samples from colorectal cancer plus 90 serum samples from healthy controls using "matrix-assisted laser-desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry" and magnetic beads. By using "tandem mass spectrometry (MS/MS)", the protein "threonine/serine kinase 4 (MST1 or STK4)" was discovered. An enzyme-linked immunosorbent test and western blotting were then used to confirm the finding. When combined with carcinoembryonic antigen and FOBT, they demonstrated that "MST1" was downregulated in colorectal cancer patients, with a specificity of 100 % and a sensitivity of 92.3 % for the diagnosis of "colorectal cancer". Additionally, their research suggested that "MST1" could function as a marker for distantmetastasis [14].

In a different study, by Quesada-Calvo *et al.* label-free proteomics was used to analyze 76 colorectal tissue samples from inflamed or normal mucosa, as well as early stages of colorectal cancer. Immunohistochemistry was used to characterize the three chosen biomarker candidates. 561 proteins having a significantly altered distribution among patient and control groups were found out of the 5258 proteins that were found. Distributions of OLFM4, KNG1, and "Sec24C" were confirmed in tissue and demonstrated variable levels of expression, particularly in 2 early stages of colorectal cancer [15].

Comprehensive proteome analysis of adjacent tissues (AT) and paired tumors utilizing high-resolution "Fourier-transform mass spectrometry" and a unique technique of quantitative pathway analysis was presented in separate research by Hao *et al.* According to the findings of this study, 12380 proteins were identified, and 740 of those were thought to have a 4-fold change that was characteristic of colorectal cancer [16]. Fatahi *et al.* examined the function of "lncRNAs" as oncogenes or tumor suppressors, which makes them promising bio-markers for the "diagnosis" and "prognosis" of gastric cancer. Their conclusions suggested that lncRNAs such as HOTAIR, "tissue differentiation-inducing non-protein" coding, "UCA1", "PVT1",

"UCA1", and "LINC00152" may be useful prognostic and diagnostic indicators for people with gastric cancer [17].

Liu *et al.* performed a thorough investigation to determine the expression profile and clinical implications of "m6A-related genetic targets" in "BRC". Several tests and analyses demonstrated that these targets were different expression profiles in "BRC tissues". "TMA IHC" staining revealed that the majority of targets were considerably changed at the protein level (either up-regulated or down-regulated), which correlated to changes in the genomic profile. In BRC cell lines, IF analysis revealed the subcellular localization of "m6A-related" genetic targets. Additionally, they found that "KIAA1429 (P=0.032)", "YTHDF3 (P=0.001)", and "YTHDF1 (P=0.049)", overexpression indicated a poor prediction in terms of overall survival (OS) [18].

2. DISCUSSION

Late diagnosis accounts for a major amount of cancer morbidity and mortality when surgery and pharmacological treatments are less successful. As a result, early cancer detection can be critical and very useful, finding cancers before they spread and allowing personalized medicines to be provided as soon as feasible. Accurate biomarkers have been intensively researched to answer the critical requirement for cancer detection, diagnosis, prognosis, and monitoring, with an emphasis on low or non-invasiveness. Cell-free tumor DNA, derived from necrotic or apoptotic tumor cells, as well as circulating tumor cells, has emerged as an exciting target for liquid biopsies (e.g., semen, urine, blood). Liquid biopsies have yielded promising outcomes in cancer biology for identification, therapeutic response, and prognosis of malignancies such as Ewing sarcoma, pancreatic, osteosarcoma, urothelial, and urothelial, lymphoma, and other hematologic cancers. Some assays can detect numerous malignancies, and multisite prospective observational clinical studies are underway.

To give an even earlier diagnosis of these tumors, could liquid biopsies be included in the present population-based cancer routine screening? Could there eventually be a population-based cancer screening program that uses a simple test to detect a variety of malignancies that is broadly and simply accessible (e.g., even in remote areas without specialist equipment)? Would such a target population further be segmented to allow for more specialized screening frequencies, allowing those at higher risk (Positive for oncogenes in panel testing or others with understood high environment exposure) to be vetted more commonly than those at lower risk? In Australia, a precise method similar to this is already being used for screening cervical cancer, with the risk classification of participants into various screening paths being informed by the findings of an HPV test.

It is crucial that everyone has access to an early diagnosis of cancer and follows suitable treatment options. A specific solution to this problem would make use of big data collection and analysis, evidence-based technological improvements, and public health strategies to guarantee equity and effectiveness. The objective is to enable everyone in a population (the n of many) to obtain adequate screening procedures (both test kind and test frequency) to detect the greatest variety of malignancies at the earliest stage and then offer all cancer patients the most suitable precision therapy.

Predictive biomarkers, which foretell patient response to therapy, are crucial tools in the quickly expanding field of research for personalized medicine because they help identify patients most likely to benefit from the treatment. This helps ensure that the right patient receives the right

therapy while preventing unnecessary overtreatment. An ongoing area of study is the quest for predictive biomarkers, which may include proteomic, genomic, or machine-learning methods. Predictive biomarkers make it possible to pinpoint breast cancer patients who will likely benefit from a certain therapy and to forecast both the effectiveness of a given treatment and tumor resistance.

The development of personalized medicine for patients with breast cancer depends on the discovery of novel prognostic biomarkers. The discovery of predictive molecular or imaging biomarkers with high accuracy is being pursued using novel technologies, such as -omics and artificial intelligence. The search for CRC biomarkers has seen some fascinating breakthroughs. The discovery of novel biomarker testing methods, including the recent characterization of liquid biopsies, patient-derived xenografts, CMS, and organoids, represents an opportunity for advancing and improving biomarker discovery. To prospectively confirm the use of biomarkers, it is crucial to keep in mind that the gold standard for their development has not yet been defined. The third most frequent cancer-related cause of death, after colorectal and breast cancer, with a 5-year survival rate of around 30–35%. Since early detection is linked with a reduced death rate, the discovery of new biomarkers for earlier detection and proper treatment of patients with the best therapeutic response is extremely important.

3. CONCLUSION

Recent progress in precision and personalized treatment for cancer and associated symptoms are highlighted by recent advancements in cancer treatment. Modern diagnostics and therapeutics have resulted in significant breakthroughs over conventional medicine. The use of data mining, novel biomarkers, and therapeutic targets is becoming increasingly important in research. As a result, this paper summarized some of the novel biomarkers that have been discovered and investigated in studies from 2016 to 2021 against a variety of cancers with special emphasis on colorectal cancer, breast cancer, and gastric cancer.

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CHAPTER 7

APPLICATION POTENTIAL OF ANTI-DIABETIC MEDICINAL PLANT SPECIES AND PHYTOMOLECULES CHARACTERIZATION

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ABSTRACT: "Diabetes mellitus (DM)" is a long-lasting metabolic condition defined by hyperglycemia brought on by insufficient insulin production, resistance to insulin action, or a combination of the two. In the US and more lately, worldwide, DM has achieved epidemic proportions. A significant amount of health care costs is expected to be attributed to the morbidity and death brought on by diabetes. For the treatment of diabetes mellitus, several drugs are now used, however, phyto-based treatments are of utmost importance. The current investigations concentrated on a review of the anti-diabetic perspective of several plant species including Aloe barbadensis miller, Berberis lyceum, Allium cepa, and many others highlighting the significance of herbal or traditional medication in the treatment of Diabetes patients with a more intensive review of recent literature investigating medicinal plants and their phytomolecules having anti-diabetic properties with a wide variety in the mechanism of action. Thus, providing a clear snapshot for researchers, scientists, and health practitioners on the phytocompounds and plant species for more exploration in the context of diabetes treatment.

KEYWORDS:

Diabetes Mellitus, Herbal Medicine, Insulin, Medicinal Plants, Phytomolecule, Traditional Medicine.

1. INTRODUCTION

Diabetes is recognized as a serious public health issue that has a major influence on both human beings and healthcare expenses. Diabetes has grown more common in so many areas of the world due to fast economic expansion and urbanization. Diabetes diminishes the functional ability of the individual as well as their quality of life (QOL), leading to significant mortality and morbidity [1]. Recently, concern has been raised that more than one-third of diabetes-related mortality occurs in individuals under the age of 60. Such modifications have been related to increased intake of unhealthy products and low physical activity, each of which results in greater BMI and fasting plasma glucose levels [2], [3]. Type 2 diabetes is more likely to occur in those with higher BMIs. The aging of the worldwide population is yet another cause, as diabetes specifically targets elderly individuals. Whenever comorbidities are evident, the cost of treating diabetes is at least 3.2 times greater than the national average for healthcare costs per person and rises to 9.4 times. Many individuals still struggle to regulate their blood sugar, blood pressure, and other targets. This can be attributed in part to a lack of awareness about diabetes and preventative treatment. Based on the projected 2021 UN world population, the diabetes prevalence in adults aged 20 to 79 years will be 10.5% globally, 10.2% in women, and 10.8% in men. Age affects the rate of diabetes, with people aged 75 to 79 with the highest frequency (24%).

There are numerous categories of anti-diabetic drugs available on the market for the treatment of the condition, including thiazolidine, insulin analogs, dipeptidyl peptidase-4 inhibitors, biguanides, sulphonylureas, alpha-glucosidase inhibitors, among others. Each of these drugs has a unique mechanism for reducing the elevated glucose level [4], [5]. However, the long-term use and side effects of the present hypoglycemic drugs are creating a large need for effective, low-side-effect, and cost-effective treatments for diabetes. Table 1 shows the Synthetic Treatments of Diabetes Mellitus, their Pharmacological Class, and Side Effects. Figure 1 shows the Chemical Structures of Most Marketed Diabetes Mellitus Treatment Drugs.

Table 1: Enlisting the Synthetic Treatments of Diabetes Mellitus, their Pharmacological Class, and Side Effects.

Treatments	Types of Drug	Side Effects
Glimepiride	Sulfonylureas	Low blood sugar level
Pioglitazone	Thiazolidinediones	Weight Gain, Liver Toxicity, Effects on Cardiovascular Health
Exetinide	GLP-1 Agonist	Thyroid cancer, Hypoglycemia
Rapaglidine	Meglitinide	Gastrointestinal effects, Hypoglycemia
Pramlintide	Amylin Analogue	Allergy, Hypoglycemia
Saxagliptin	DPP-4 Inhibitor	Hepatitis, Kidney impairment, Pancreatitis, Cancer risk
Regular insulin	Insulin Analogue	Weight gain, Insulin allergy, Hypoglycemia

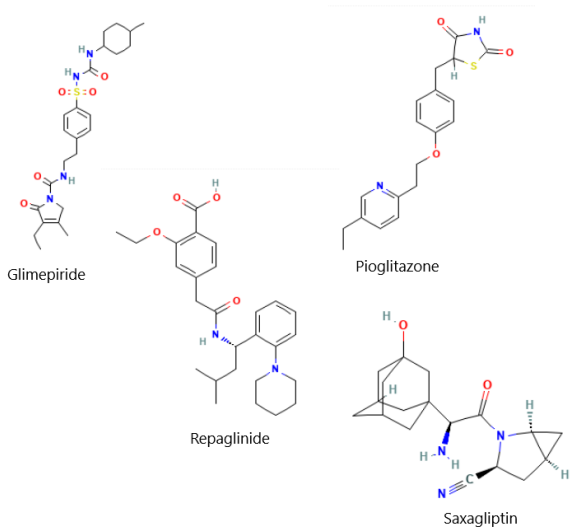

Figure 1: Illustrating the Chemical Structures of Most Marketed Diabetes Mellitus Treatment Drugs.

1.1. Role of Traditional Medicine

In addition to being used for nutritional purposes like food, nutrition, etc., herbal products also play a significant part in the treatment of several diseases. Herbal medicine often referred to as herbal drugs or botanical medicine, or phytomedicine is a type of conventional medicine that makes use of various plant components, including their fruits, seeds, flowers, bark, leaves, berries, and roots, for therapeutic purposes. Over the past few decades, the usage of traditional medicine has accelerated significantly [6]. Around the world, conventional healthcare practices including Ayurveda, Unani, and traditional Chinese medicine are all practiced. Due to its availability, cost, cultural acceptability, and public trust, traditional medicine is only the major source of healthcare in a few countries. Around four billion people depend on traditional medication as their key form of health care in underdeveloped nations as Illustrated in Figure 2.

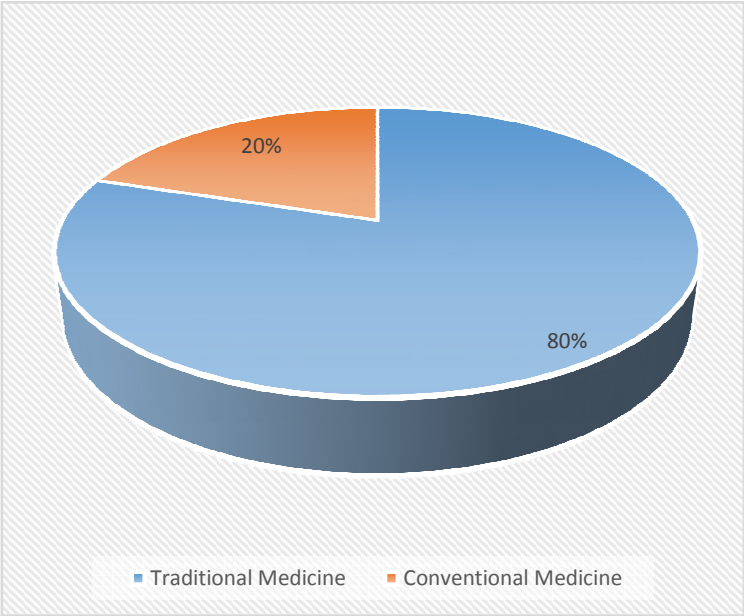

Figure 2: Illustrating the Proportion of the Population using Conventional and Traditional Medicine, WHO Report.

Traditional medicine has been used in the treatment of a wide range of disease conditions that are given below in Figure 3.

Similar results indicate that DM patients are using more natural products. This is an outcome of the cumulative negative effects that come with long-term usage of oral hypoglycemic drugs and insulin in DM patients, including digestive disturbances (vomiting, nausea, and diarrhea), edema, hypoglycemia episodes, and hepato-renal abnormalities.

1.1. Traditional Medicine in Diabetes

The biggest problem facing medical professionals is how to treat diabetes mellitus without having any negative consequences. 800 medicinal plants are reportedly used to manage DM, based on the international ethnobotanical report. Approximately 450 medicinal plants have been shown to have anti-diabetic activities in studies, and only 109 medicinal plants have a whole mode of action defined. For the treatment of many diseases including cancer, heart disease, and

diabetes in the past, both physicians and laymen employed traditional medicinal plants with their active ingredients and properties. In India and China, traditional plants have been utilized for diabetes treatment for a very long time [7], [8].

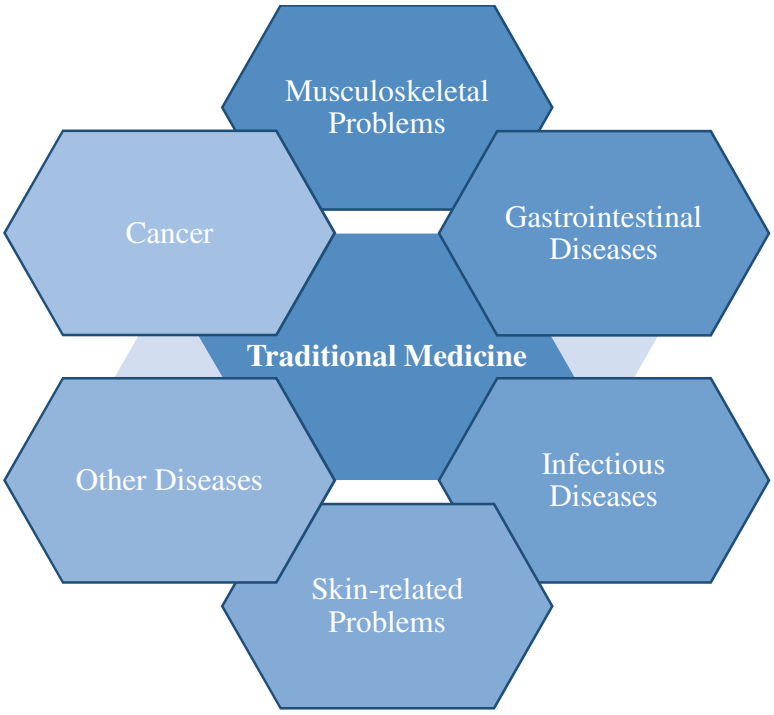

Figure 3: Illustrating the Variety of Uses of Traditional Medicine for the Treatment of a Wide Range of Diseases.

Because they have fewer side effects and negative consequences than synthetic drugs, herbal drugs are a preferable option. Formulations made from plants are commonly accessible without a prescription. Life-threatening diseases are treated with these natural medicines. When chemical medicines fail to effectively treat a disease, these treatments are also employed. These medications are natural and safe and they have no hazardous side effects. Although synthetic treatments do not consistently cure diseases, herbal drugs consistently heal the patient and treat the disease.

Herbal remedies include extracts of natural herbs, fruits, and vegetables that help treat a variety of conditions without causing any negative side effects. Chemical medications, on the contrary hand, are made synthetically and also have negative effects. In comparison to allopathic pharmaceuticals, herbal formulations are less expensive. Eco-friendly herbal formulations are available. Herbal preparations are made from natural ingredients, whereas allopathic medications are made from naturally occurring substances that have been transformed chemically. Herbal products are accessible without a license and prescription, but all allopathic medications require them. Figure 4 illustrates the benefits provided by herbal medicines.

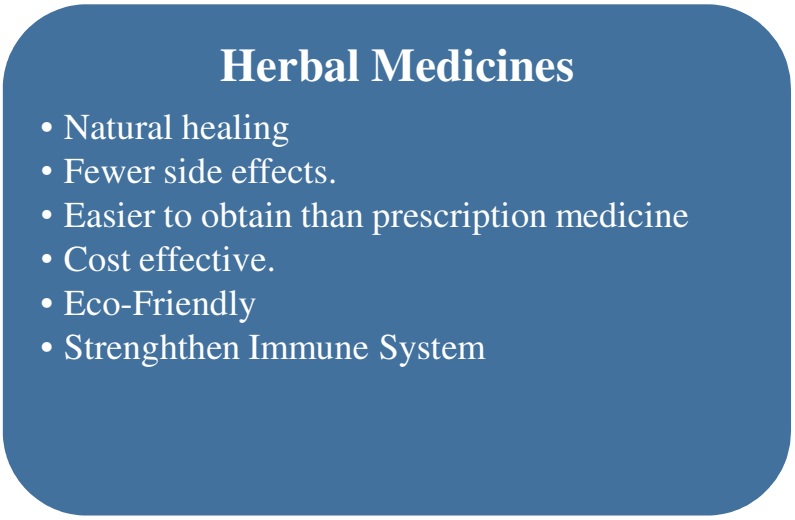

Figure 4: Illustrating the Benefits of Herbal Medicine in the Treatment of Diabetes Patients.

"Natural products", specifically those with a botanical source, are the key to discovering good lead candidates and are crucial to future drug development initiatives. Plant-based remedies are the most effective treatments now accessible, especially in rural regions, due to their "accessibility", "affordability", and "lack of negative side effects". In addition, many plants offer a plentiful supply of bioactive compounds, which have potent pharmacological benefits without any negative side effects. Many of the pharmaceuticals that are now on the market were either directly or indirectly derived from plants, which have long been an excellent source of drugs.

1.1.1. Aloe barbadensis miller

Aloe vera has been utilized for centuries to cure a variety of diseases and contains anti-oxidant, anti-inflammatory, and wound-healing properties. Wistar diabetic rats induced with streptozotocin (STZ) were utilized in a study by Noor *et al.* to examine the possible protective effect of *A. vera* extracts on pancreatic islets. Male "Wistar rats" were separated into 4 groups of six for the study after acclimatization.

The findings of their study revealed that normal blood glucose levels were restored along with an elevation in insulin levels. When comparing rats suffering from diabetes administered with *A. vera* extracts to the untreated diabetic rats, morphologic examination of pancreatic sections showed a qualitative and quantitative increase in terms of diameter, number, volume, and the surface of the pancreatic islets [9].

1.1.2. Allium sativum

Kun-Yan *et al.* isolated and recovered polysaccharides (GPSs) from raw garlic bulbs using "gradient ethanol precipitation (GEP)" combined with "three-phase partitioning (TPP)". The findings of their investigation indicated that GPS80 had greater uronic acid (12.89% 0.09%) and greater carbohydrates (86.68% 0.90%) concentrations. Additionally, GPS80 had the highest antioxidant potential, inhibiting impacts on alpha-amylase and alpha-glycosidase, as well as nitric oxide stimulatory activities in "RAW264.7 macrophage cells" in vitro [10].

1.1.3. Allium cepa

Jini and Sharmila *et al.* used *Allium cepa* to undertake the green production of silver nanoparticles for diabetes. *In vitro*, anti-diabetic action studies demonstrated that the nanoparticles exhibit greater levels of "α-glucosidase" and "α-amylase" inhibitory activities. It also had higher levels of antioxidant potential and lower cytotoxicity. It was found that green synthesized silver nanoparticles can be employed as a potential phyto-drug for diabetes treatment [11].

1.1.4. Berberis lyceum

Mughal and Ali *et al.* studied the effects of α-glucosidase and α -amylase inhibition on *in-vitro* antidiabetic efficacy. In addition, they calculated the *in-vivo* antidiabetic properties of alloxan-induced "Swiss albino mice". Mice were also given an aqueous extract (200 mg/kg b.w.) of root bark for a total of 4 weeks. The findings of their investigation indicated that when administered with *B. lycium Royle* root bark extract, blood-glucose levels, and other bounds were dramatically stabilized, suggesting that *B. lycium Royle* has an anti-diabetic effect [12].

1.1.5. Momordica charantia

In research by Ru *et al.*, a new *Momordica charantia* L Se-MCPIIa-1 selenium-bound polysaccharide was created using selenylation modification. By using spectroscopic methods, the physicochemical and morphological characteristics were studied. Their findings demonstrated that Se-MCPIIa-1 has anti-diabetic effects in vivo by dramatically lowering fasting blood glucose levels, increasing insulin levels, and improving antioxidative enzyme activities in diabetic mice when administered at an optimum dose of 20 mg/kg/body weight. Additionally, histopathology studies revealed that Se-MCPIIa-1 could defend against the effects of diabetes on the liver, pancreatic islets, and kidneys [13].

1.1.6. Cassia auriculata

Nambirajan *et al.* studied *C. auriculata* L. flowers and buds in ethanol extracts. LC ESI/MS analysis identified particular phytochemicals found in CABE and CAFE. CABE and CAFE were discovered to have in vitro anti-diabetic action by inhibiting digestive enzymes. Furthermore, in vivo anti-diabetic tests demonstrated that CABE is more effective than CAFÉ, confirming *C. auriculata's* promise in diabetes therapy [14].

1.1.7. Cinnamomum zeylanicum

Niroshani M *et al.* used spectrophotometry to investigate the "Proanthocyanidin content" (PC, vanillin assay), "total phenolic content" (TPC, Folin-Ciocalteu technique) "α-glucosidase and α-amylase inhibition" of extract. They measured IC_{50} values for "α-amylase" and "α-glucosidase" inhibition, as well as phytochemical profiling. According to the findings, pressured water and elixirs are promising methods for extracting anti-diabetic components from cinnamon. The primary chemicals found were benzyl alcohol, cinnamyl alcohol, benzoic acid, and 4-Allyl-2,6-dimethoxyphenol [15].

Salehi *et al.* presented a review of the extensive literature on medicinal plants and their active chemicals in diabetes treatment in addition to the previous investigations, placing particular attention on *in vitro* and *in vivo* activity. An overview of recent research on the effects of

medicinal herbs and plants and the compounds linked with them on various targets in clinical investigations was also presented [16].

2. DISCUSSION

Synthetic medicinal chemistry has provided numerous promising molecules to treat various infections and chronic diseases, but there are still several chronic and newly emergent diseases for which treatment must be developed. However, drug manufactured by synthetic medicinal chemistry has several unwanted consequences. People in developing countries frequently turn to traditional medicine due to the high expense of healthcare services.

The primary source for finding viable lead candidates is natural compounds, particularly those with plant sources, and they are crucial to the next drug-development projects. Plant-based treatments are the dominant performer among all accessible medications, particularly in rural areas due to their easiness of accessibility, low cost, and few adverse effects. Furthermore, a variety of plants offer a rich supply of bioactive compounds that have potent pharmacological effects without any negative side effects. Many of the medications that are now accessible are derived directly or indirectly from plants, which have historically been an excellent source of pharmaceuticals.

For decades, several plants have been regarded as a primary source of strong anti-diabetic medications. Medicinal plants, particularly, are utilized to cure diabetes in impoverished nations to alleviate the load of the high cost of conventional treatments. Currently, medicinal herbs and plants are advised for the treatment of conditions such as diabetes because they contain phytoconstituents such as “terpenoids”, “alkaloids”, “flavonoids”, “carotenoids”, “saponins”, and “glycosides” that may have anti-diabetic properties. Diabetes is becoming more common, raising worries among the medical establishment and the general population. Despite the availability of oral hypoglycemic agents on the market, medicinal plants are frequently effective in treating diabetes. There are several remarkable therapeutic choices for diabetes treatment all around the world, including herbal treatments and botanical components with minimal toxicity and no adverse effects.

The various plants listed above have been utilized either singly or in combination with other ingredients to treat diabetes and its consequences. This herbal composition has several significant flaws, one of which is a lack of clarity regarding the active constituents. To analyze the therapeutic efficacy of the product and standardize it, it is crucial to understand the active ingredient and their molecular interaction. Aiming to better understand how some of these plants work, model systems are now being used in the investigation process.

Due to their usage by unlicensed or uncertified professionals and self-medication, traditional medicines are viewed with great concern by both the general public and international health authorities. When they became ill, several participants claimed that they would look for herbal healers in the bushes near their homes or would buy them from nearby friends, herbalists, and family members. The fact that traditional remedies don't include any ingredients, according to some FGD and IDI participants, makes them safe. Participant perception of the chemical composition of traditional treatments was also shows by other investigations. The natural chemicals found in plants, however, include some hazardous ones [17].

The development of new antidiabetic drugs has been greatly aided by developments in traditional medicine research. It is important to note that only a small number of medicinal plants have had human effectiveness studies. The bulk of stories omitted information regarding the components of formulations, processing methods, and actual identities of the plants. The majority of clinical trial methodologies were poorly developed, which frequently produced inconsistent results. More effective clinical investigations are thus required for further validation. However, struggles should be made to identify the anti-diabetic components found in anti-diabetic plants. Furthermore, in the future, the medicinal herbs and plants mentioned could help develop novel functional meals with anti-diabetic benefits or in preventing the hyperglycemic effects of particular diets, such as those high in simple carbohydrates.

While each therapeutic benefit claim is examined for herbal medicine, there is a chance that severalof these treatments may increase the range of drug treatments accessible, thus until comprehensive safety profiles are published, caution must be used. Patients with serious diseases should elude herbal agents without first seeing a doctor, in addition to circumventing them during breastfeeding, and pregnancy. With extreme caution, the items should not be mixed with prescription or over-the-counter medications. If a pharmacist recommends a substance that causes harm, the implications for malpractice lawsuits against them should be taken into account. The gathering and reporting of data on the negative effects of medications, including those from herbal products, is still the responsibility of pharmacists, doctors, and other healthcare professionals.

3. CONCLUSION

This study has provided a list of anti-diabetic plants that are used to treat diabetes mellitus. It was discovered that these plants contain hypoglycaemic properties and can be utilized to treat a variety of secondary problems associated with diabetes mellitus. For the treatment of many different types of sickness, plants have proven a reliable source of medication; nevertheless, many plants and the active components extracted from them have not yet undergone thorough characterization. Additional research must be done to determine the precise mechanism of action of therapeutic plants with antidiabetic and insulinmimetic activities. It is a common misconception that plants are safe, yet so many plant products are toxic to humans. As a result, toxicity studies of these plants must be addressed before their consumption.

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CHAPTER 8

AN UPDATE ON ANTIMICROBIAL ACTIVITY OF *ABUTILON INDICUM LINN.* AGAINST HUMAN PATHOGENS

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ABSTRACT:

The burden of infectious diseases is increasing day by day because of emerging and re-emerging pathogenic microorganisms including bacteria, viruses, and fungi which further points out the need to explore alternative medicine. Abutilon indicum is one of the miraculous plants that are native to any part of the world, having significant therapeutic potential in a wide variety of human diseases from cardiovascular diseases to cancer. However, this study aims to highlight the antimicrobial activity of A. indicum and its various extracts. This study also provides studies investigating the antimicrobial activity of nanoparticles derived from A. indicum extracts. The findings of this work revealed that the whole plant of A. indicum or any part whether leaves, buds, fruits, and flower contains a range of bioactive compounds having different mechanisms of action against human pathogens.

KEYWORDS:

Antibiotics, Antimicrobial Activity, Abutilon Indicum, Infectious Disease, Nanoparticle.

1. INTRODUCTION

The world has developed a sophisticated global health system to protect itself from risks posed by infectious diseases, including known and unknown. The system is composed of numerous informal and formal network systems of organizations that collaborate with different stakeholder groups, possess various goals, processes, and tiers of accountability, continue to perform at different regional levels, as well as time frame the for-profit, public, and nonprofit sectors. The worldwide health system has significantly impacted efforts to protect and enhance human health. But infectious disease threats are still there everywhere in the world, whether they are new or recurrent. The incidence and severity of these threats differ significantly. Moreover, they have a variety of effects on mortality, and morbidity, as well as a variety of economic and social consequences. They are also, to varying degrees, amenable to alternate solutions, such as regulation, the supply of clean water, and biological countermeasures [1].

The term "infectious diseases" refers to clinically apparent illnesses brought on by the presence and proliferation of harmful biological agents in a particular host organism. It is frequently used interchangeably with the terms "contagious diseases" or "transmissible diseases." Nearly 50,000 people die from infectious diseases each day, making them the leading cause of premature mortality worldwide [2]. Drug resistance to human pathogenic microorganisms has recently been widely documented worldwide. Infectious diseases are a serious threat to global health since they are a leading source of morbidity and death. Up until recently, research and development (R&D) initiatives provided novel treatments in time to treat pathogens that developed resistance to

antibiotics. In the present and the future, nature-based alternatives to antibiotics are going to be crucial for society. And among the genera with significant medicinal relevance is Abutilon, which has several species [3], [4].

The Abutilon genus includes over 150 perennial or annual shrubs, herbs, or even small trees that are found in subtropical or tropical parts of Asia, America, Africa, and Australia. These plants are members of the Malvaceae family. It only needs heat and sunlight to flourish, even in dry, poor soils. It grows often after the rains and blooms throughout the winter in India, where it is extremely prevalent on roadsides and waste areas. It is grown for decorative purposes in Poland as well. The pharmacological and therapeutic properties of many plants belonging to the Abutilon genus have long been praised. There is plenty of literature that supports the therapeutic use of several plants from this species in the management of various disorders and diseases [5].

There has recently been a resurgence in scientific interest in studying the species, some of whose plants are rare and valuable Ayurvedic herbs. In ethnobotanical studies carried out by ethnobotanists and in conventional medical systems like Ayurveda, the different components of the plant Abutilon, including its seeds, leaves, and roots, are known to possess diverse therapeutic properties.

The scientific evaluation of the extracts from the whole plant Abutilon focused on their tonic, augment, vardhaka, oja, and ojas properties—the elusive essence of all vital fluids that promote harmony, health, and spiritual development. Since then, the genus Abutilon has yielded a wide range of compounds, the majority of which are steroids, terpenoids, flavonoids, and phenolic compounds.

Additionally, some Abutilon species are used to extract valuable fibers. The fibers are derived from plants such as *A. polyandrous, A. indicum, and A. asiaticum* and are used to make “cordages”, “jute dyes”, “ropes”, “carpets”, “wrapping cloth”, “rubber”, “tissue papers”, “coarse cloth”, “medicines, “cigarette paper”, “tires”, “textiles”, and “shoe polishes”, among other products. Chinese jute, a valuable fiber, is produced by the plant Abutilon Avicenna. The Abutilon plant species noted above have all been studied for their antibacterial properties, but A. indicum has received the most attention.

1.1. Abutilon indicum

South Asia is home to the Abutilon indicum plant, often known as "Kanghi" or "Thuthi" in Hindi. The profession of pharmacy benefits greatly from nature. Natural treatments work effectively and have no negative side effects. A plant with a height of up to 3 m, Abutilon indicum (Linn.) is also known as "Country Mallow." The 1.90–2.50 cm long, oval, toothed, acuminate, occasionally subtrilobate leaves have teeth. The flowers are “yellow” and have a peduncle joint just above the center. Petioles that range in length from 3.8 to 7.5 cm, axillary solitary, pedicels that are frequently 2.5 to 5 mm long, stipules that are 9 mm long, and joined very nearly at the top, calyxes that are divided in the middle, 12.8 mm long, with lobes that are apiculate, ovate and corollas that are 2.5 cm in diameter and yellow. The fruits have prominent, straight-spreading beaks and are capsule-shaped, highly pubescent, and edible. The branching, pubescent, sturdy stems measure between one and two meters tall. The 3-5 mm reniform seeds are dark brown or black, tuberculate, or minutely stellate-hairy.

Figure 13: A Pictorial representation of the Flower of A. indicum.

Figure 14: A Pictorial Representation of the Fruit body of A. indicum.

Figure 15: A Pictorial Representation of Leaves of A. indicum.

Figure 16: A Pictorial Representation of the Whole Plant of A. indicum.

In the tropics and subtropics, A. indicum grows in bare, open areas. It is reported from savannas, lakesides, beaches, low bushes, dunes, and roadside.

1.1.1. Botanical Classification of Abutilon indicum

Table 4: Illustrating the botanical classification of Abutilon indicum.

Kingdom	Plantae - Plants
Subkingdom	Tracheobionta - Vascular plants
Superdivision	Spermatophyta - Seed plants
Division	Magnoliophyta - Flowering plants
Class	Magnoliopsida - Dicotyledons
Subclass	Dilleniidae
Order	Malvales
Family	Malvaceae -Mallow family
Genus	Abutilon Mill. - Indian mallow
Species	Abutilon indicum (L.) Sweet – monkey-bush

1.1.2. Chemical constituents in A. indicum

Numerous studies have investigated the phytochemistry of Abutilon indicum and discovered that it contains a variety of chemical components. Mucilaginous compounds and asparagines are present throughout the entire plant. As the primary classes of compounds, they have alkaloids, n-alkane mixtures (C22-34), hexoses, flavonoids, saponins, and alkanol. Abutilon-A, vanillic acid, Beta-sitosterols, fumaric acid, galatonic, Para—Beta-D-glycosyloxybenzoic, Para-hydroxybenzoic, Para-coumaric acid, caffeic acid, and amino acids are some significant components identified in the plant. Caryophyllene oxide, geraniol, Alpha-pinene, Endemol, borenol, elemene, farnesol, geranyl acetate, and alpha-ciniole are among the main components of the EOs found in the plant A. indicum, along with several other minor components [6], [7].

"8, 9-methylene heptadec-8-enoic (malvalic) acid", "9, 10-methylene octadec-9-enoic (sterculic)", and "Cis-12, 13-epoxyoleic (vernolic) acid", are all present in the seed oil of the plant. Along with farnesol, elemene, cineole, borneole, and eudesmol. The seed oil contains steric, palmitic, oleic, and linolenic acids. The aerial portions of the plant also include certain gossypetin-8- and -7-glucosides, cyaniding-3-rutinosides, tocopherols, flavonoids, and beta-sitosterol. Sapogenins, carbohydrates, steroids, and flavonoids are all present in the leaves. Gallic acid can also be found in the roots of the plant. Essential oil of flowering tops includes caryophylline, alpha-cineole, farnesol, alpha-pinene, geraniol acetate, borenol, geraniol, and caryophylline oxide.

The pharmacological activities of Abutilon indicum include immunomodulation, wound healing, hepatoprotection, analgesia, antibacterial, antimalarial, and hypoglycemic activity. But the purpose of the present study is to provide recent research on the antibacterial properties of A. indicum, its extracts, and its essential oils.

2. METHODOLOGY

The information provided in the present review paper is obtained from Scopus, google scholar, Web of Science, PubMed, and other databases with a range of relevant keywords which were then narrowed down to get more accurate and precise information about the objective of the study. The Keywords used for the literature search are Abutilon indicum, Pharmacological properties, phytochemical screening, antibacterial activity, Medicinal plants, and so on. The literature search was also performed using a combination of the above-mentioned keywords. The methodology of the present work is detailed in Figure 5 below.

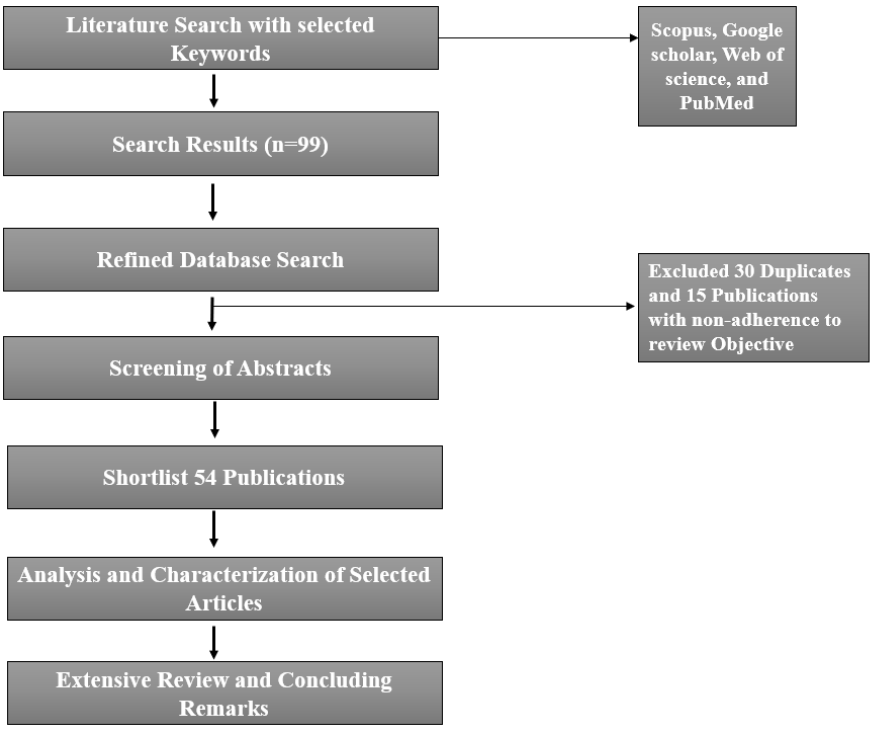

Figure 17: Illustrating the Methodology Used in Carrying out the Present Review.

2.1. Antimicrobial Activity of Abutilon Indicum

Mustafa et al. revealed for the first time the presence of a novel component "syringaldehyde" isolated from ethyl acetate extract leaves and assessed by “HPTLC”. As tested, syringaldehyde demonstrated significant wide-spectrum antibacterial effectiveness against Klebsiella pneumoniae (KP) and Bacillus subtilis (BS). CLSM study also demonstrated that the compound can inhibit biofilm development in the fungus A. fumigatus, validating its antifungal and antibacterial activities [8].

Shashikala and Meena used in Vitro and in silico approaches to recognize the bioactivities of A. indicum fruit. They prepared the ethanolic extract and then screened it for antibacterial activity

against "*Enterococcus faecalis", "Staphylococcus aureus", and the fungus "Aspergillus niger"* in vitro. "*Aspergillus niger", "E. faecalis", and "S. aureus"*is moderately resistant to an ethanolic fruit extract, which has a MIC of 25 g/l, according to the results. Leads against the target "cyclooxygenase 2" were identified as "AI 1005", "AI 1004", and "AI 1003"`, which all had strong hydrogen bond interactions and advantageous pharmacokinetic characteristics. A further finding from DFT studies was that molecules AI 1005 and AI 1004 had the lowest energy gap and the most promising reactivity [9].

In a different study, Edupuganti et al. examined the antibacterial effects of several plant leaf extracts in ethanol against "*S. aureus"*, "*E. coli"*, and "*Candida parapsilosis" & "A. niger"*. To assess the antibacterial activity, the disc diffusion technique was employed. The results demonstrated that *A. indicum*, even at a low concentration of 5 g/ml, has greater antibacterial activity against "*E. coli" and "Staphylococcus aureus"* when compared to others [10].

Mohanta et al. synthesized electrically charged AgNPs from the leaf extract of *A. indicum*. The produced AgNPs were investigated for both antifungal (*Candida kruseii*) activity, and antibacterial (*Pseudomonas aeruginosa*), and both showed promising antimicrobial action. The fundamental cause for the antibacterial effect of produced nanoparticles might be related to charge transfer processes occurring between nanoparticles and microorganisms. Furthermore, AgNPs demonstrated potent cytotoxic and antioxidant effects against the MCF-7 BC cell line [11].

Ahmad et al. produced NiO nanoparticles with Phyto molecule coatings in another work by using a green approach and utilizing leaf extract from Abutilon indicum. The diffusion experiment was used to test the antibacterial action of the produced nanoparticles against various bacteria in comparison to regular treatment and plant extract. According to the findings of their study, NiO nanoparticles coated with phytomolecules had the largest zones of inhibition against, and S. aureus, B. subtilis, B. bronchiseptica, E. coli [12].

To conduct the green production of copper oxide nanoparticles, Ilaj et al. employed leaf extract from the *A. indicum* plant. They then utilized the diffusion technique to examine the antibacterial property. The outcomes of their research showed that CuO nanoparticles had strong bactericidal activity against Bacillus subtilis and Klebsiella, with zones of inhibition of 15 mm and 14 mm, respectively [13].

Binigha et al. examined the antibacterial activity of *A. indicum* and *Tecoma stans* leave extracted in ethanol. The bacteria *E. faecalis* were grown on nutrient agar slopes. The powder of the two herbs was extracted using a "Soxhlet extractor" and condensed to a dry residue using the diffusion technique. Bacterial strains were added to the nutritional broth. The result demonstrated the antibacterial ability of Abutilon indicum and Tecoma against the oral pathogen E. faecalis. When compared it was found that Abutilon indicum outperformed Tecoma stans in terms of inhibitory activity [14].

The above studies used different methodologies to assess the antimicrobial and other activities of extracts made from A. indicum. However, we realized the need to compile the data on the antimicrobial efficacy of the A. indicum as well as nanoparticles derived from using its extracts to provide researchers and health practitioners as well as a pharmacist with the antimicrobial potential of A. indicum.

3. DISCUSSION

The irresponsible use of antibiotics in the treatment of human diseases has fast resulted in the condition referred to as antimicrobial or antibiotic resistance, which occurs when microscopic organisms become resistant to the spectrum of conventional antibiotics and are also referred to as multidrug resistance. Such pathogens are commonly referred to as antibiotic- or drug-resistant pathogens. It has reduced the number of treatment alternatives available to the medical community to combat these strains. Antibiotic-resistant microorganism infections frequently come with high mortality and morbidity rates as well as a significant financial burden on the world's healthcare system. Unfortunately, community-acquired infections are gradually identifying MDR pathogens. In addition to the overuse of antibiotics in human treatment, antibiotics used in animal medicine have contributed to the evolution of antibiotic resistance. As a result, natural-source compounds are gaining popularity.

As illustrated in Figure 6, Abutilon indicum also has immunomodulatory, analgesic, wound healing, hepatoprotective, antibacterial, antimalarial, and hypoglycemic effects. Anti-inflammatory and anti-proliferative properties are seen in the ethanolic extract of leaves of *A. indicum*. The study revealed an interaction mechanism of bioactive compounds of the plant with the MAP Kinase pathway. The ethanol leaf extract may have the potential to provide innovative anti-inflammatory and anti-cancer medications in the future [15]. In another investigation, A. indicum demonstrated considerable hepatoprotective efficacy by lowering paracetamol-induced and carbon tetrachloride-induced abnormalities in biochemical parameters, as evidenced by enzymatic analysis. It was found that the plant extract can inhibit free radical production, which may result in hepatoprotective activity [16]. Other studies have also reported the ability of the plant to induce apoptosis [17]. According to Wu et al., A. indicum exhibits cytoprotective, strong antioxidant, and DNA protective effects, which give pharmacological support for its overall biological action. Further studies will also concentrate on identifying bioactive substances and the molecular mechanisms behind potential therapeutic uses in the healing of cellular oxidative damage caused by disease [18].

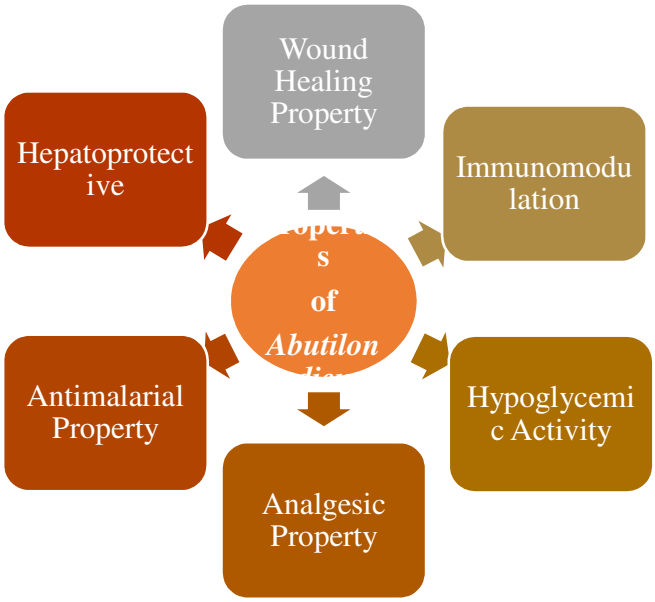

Figure 18: Illustrating the Pharmacological Properties of Abutilon indicum.

Glycosides, carbohydrates, tannins, flavonoids, steroids, and phenolic compounds are the principal chemical constituents. As a result of this review, an effort has been made to gather and assemble information on the antibacterial activity of A. indicum notes that will be valuable to society as it ventures into the realm of alternative medical systems. Based on the findings of this study, it is clear that extracts from the entire plant of A. indicum, as well as its components, have the potential for biological uses as an antibacterial and antioxidant agent. Although further in vivo and toxicity research are needed to validate this. The hazardous effects of an experimental substance on multiple species, tissues, and dosages are disclosed via preclinical toxicity studies on a wide range of biological systems. Chemical toxicity may be investigated by (a) examination of unintentional exposure to substances, (b) in vitro study using "cells" or "cell lines", and (c) in vivo exposures to test animals. Consequently, there is a need to research the different experimental models and safety evaluation methods for *A. indicum* and its bioactive components. Pre-clinical toxicological studies help determine the "No Observed Adverse Effect Level," which is necessary to start the clinical investigation of experimental items.

4. CONCLUSION

According to studies, the Malvaceae plant A. indicum has a wide range of activity against several human ailments. The current study, however, assessed the antibacterial properties of several extracts. Additionally, this study offers nanoparticles and rods made from A. indicum for their antibacterial or antifungal properties. The overall findings of this work showed that A. indicum possesses a significant amount of bioactive components that are responsible for its antibacterial activity against species of streptococcus, klebsiella, and staphylococcus as well as its antifungal activity against species of Aspergillus. The results of the few in Vivo studies that have been conducted thus far to demonstrate A. indicum potential have not yet been validated.

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CHAPTER 9

INVESTIGATION OF PLANT SOURCES FOR EFFECTIVE TREATMENT OF RESPIRATORY DISEASES

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ABSTRACT:

The use of traditional medicine is widespread, and its economic significance is increasing rapidly. Traditional medicine is typically the only readily available and reasonably priced form of treatment in developing nations. The practice of traditional medicine is common in many Asian nations. Several diseases such as those associated with the renal system, cardiovascular system, digestive system, and hepatic system are currently being treated using botanical sources, especially medicinal plants. There is a relatively less comprehensive approach used to combine the research studies evaluating the efficacy of botanical sources against respiratory diseases. Therefore, the present study attempts to investigate the plant-based treatment efficacy against asthma and Chronic obstructive pulmonary disease (COPD). They provided a critical review of the recent literature with an analytical discussion on the barriers confronted in the pathway of using Plant extracts and phytochemicals such as safety doses and low expertise in herbal medicine. The paper also provides some recommendations, addressing which can result in reaping the full potential of botanical sources.

KEYWORDS:

Asthma, Chronic Obstructive Pulmonary Disease (COPD), Medicinal plant, Respiratory Diseases, Traditional Medicine.

1. INTRODUCTION

Around the world, respiratory diseases are a frequent and important cause of illness and death. The significant and most common cause of pediatric hospital visits in 2012 was respiratory disorders. Acute respiratory infections, comprising 20% of lower respiratory tract infections and 80% of upper respiratory tract infections make up 30-60% of hospital patients in Pakistan who are admitted outside. Bronchitis, asthma, the common cold, whooping cough, and cough are the most prevalent respiratory disorders. Each breath introduces the human lung to allergens and airborne contaminants. Along with air pollution and exposure to air pollutants at work, tobacco smoking, especially passive smoke exposure, is the main cause of respiratory disease burden. Respiratory diseases, both chronic and acute are brought on by contact with smoke from flames used for heating and cooking. It has been noted that 3.5 million premature deaths per year are

brought on by the hazardous effects of indoor and outdoor air pollution, which are frequently exposed to by over two billion people [1], [2]. Women and children, particularly those living in low-income families, suffer a disproportionate amount of diseases and deaths caused by exposure to poor indoor air quality. As per the report of WHO 2016, global health estimates revealed a total death percentage of 11.9% comprising respiratory diseases and respiratory infections which is then followed by all other causes of disease as illustrated in Figure 1 below.

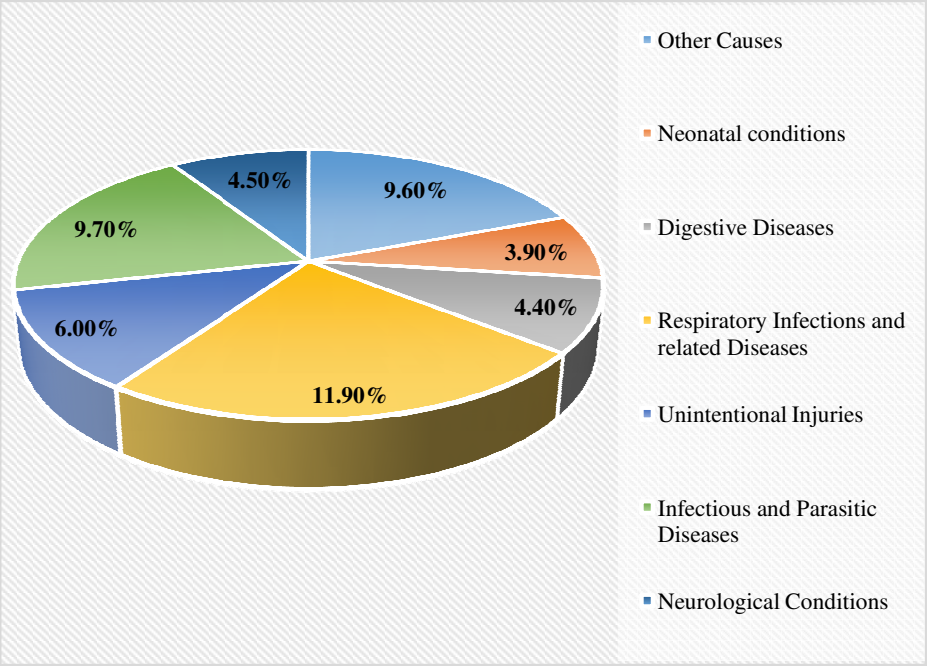

Figure 1: Illustrating the Estimated Percentage of All-Cause Deaths Worldwide, WHO Estimates; 2016.

The cost of prevention is far lower than that of respiratory disease treatment. Public health measures, such as raising awareness, capacity building, and training, are essential to the global control and eradication of respiratory diseases. To enhance disease diagnosis, management, and prevention, research is necessary in advancing our understanding of how diseases develop. Multiple health improvements have been brought about by medical advancements, although not necessarily in the areas where they are most needed.

The financial stability of several countries is being threatened by rising healthcare expenditures. Resources are severely depleted by respiratory diseases, which also place a heavy impact on global health. With insufficient access to medical care and pharmaceuticals, a vicious cycle emerges in which poor health drives countries to become more impoverished health causes poverty. To maximize the advantages of investigation within the context of each country, improvements in health care involve systematic research, a well-trained and available labor force, education, and an effective medical system.

Due to several factors, including climatic conditions and the lack of adequate medical facilities, respiratory diseases are a typical occurrence. For the treatment of different respiratory

conditions, the locals rely on local plant resources. In various cultures across the world, herbal treatments are frequently used to treat respiratory conditions. Since the beginning of time, humans have used phytotherapeutic agents to treat diseases, but only recently has their use skyrocketed. As illustrated in Figure 2, the estimation provided demonstrates that 80% of the global population uses phytotherapeutic agents to meet their basic medical needs and that 11% of all prescribed medications are made from plants.

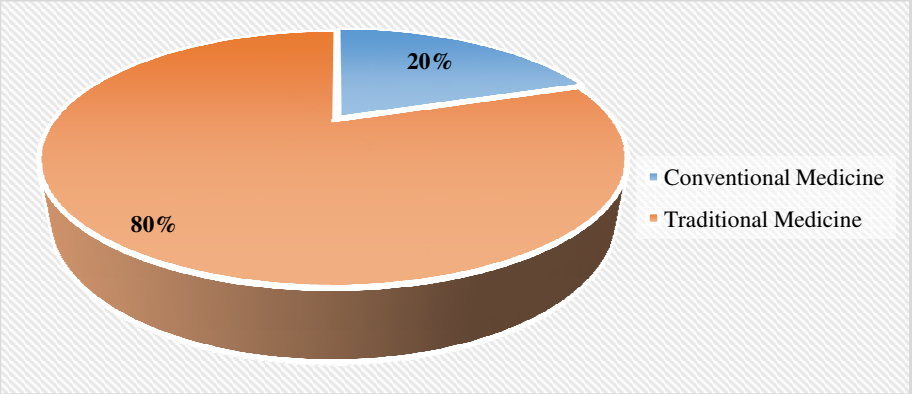

Figure 2: Illustrating the Estimated Percentage of Population Using Conventional and Traditional Medicine in Developing Countries; WHO Estimates.

As there are many plant sources having efficacy in respiratory disease treatment. There is still a lack of comprehensive and compilation studies compiling all research studies documenting and suggesting different plants, plant extracts, and essential oils for the treatment of a variety of respiratory conditions.

Therefore, the study attempts to provide a comprehensive approach for combining the research studies on the efficacy of plant extracts and their employment and outcome for respiratory diseases.

The present review study is carried out in a total of sections where the first section defines the fundamentals and the significance of the study, the second section describes the methodology used to carry out the review work followed by the third section reviewing and compiling the literature findings. In addition to that, a critical discussion on the barriers and opportunities is using herbal medicine for respiratory diseases has also been provided which is then followed by a concluding remark in the section.

2. METHODOLOGY

Information from electronic data searches, including those conducted on Research Gate, Scopus, Science Direct, and PubMed, was used to carry out the present review work. To find the pertinent information, a combination of specific keywords including "herbal Medicine," "Medicinal Plants," "Medicinal Herbs," "Respiratory conditions," "Respiratory diseases," "Traditional Medicine," and "Respiratory infections" was utilized in the search process. The exclusion of records was then done using various criteria such as based on the language. Figure 3 below shows how the present review was carried out.

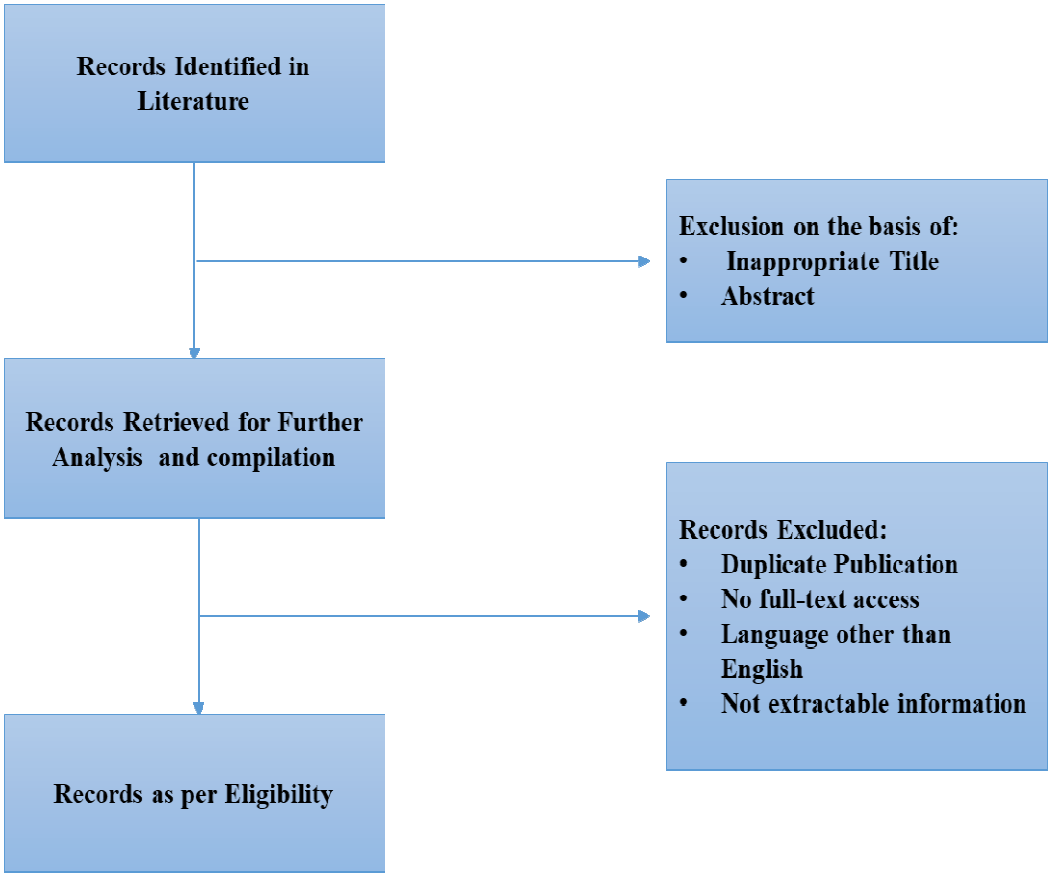

Figure 3: Illustrating the Methodology Used to Carry Out the Present Review Work.

3. LITERATURE REVIEW

There is an ample number of studies documenting the benefits of botanical and other sources for different diseases. However, there are relatively scarce studies on their effect on the treatment of respiratory diseases. Some studies are evaluating different plants against different subgroups of respiratory diseases such as COPD and asthma, and so on. A list of Medicinal Plants and their Compounds for the Treatment of "Chronic obstructive pulmonary disease (COPD)" and "Asthma" are represented in Table 1.

3.1. Chronic obstructive pulmonary disease (COPD)

COPD refers to a wide array of diseases that cause and induce impairment in respiration and further impede airflow. Chronic bronchitis and emphysema are among them. A substantial proportion of the population has COPD but has not gotten treatment or a diagnosis. There is no effective treatment for COPD, however, it can be managed with a variety of interventions. As chemical interventions and treatments are having unintended side effects and high costs with low efficacy, alternative sources are being explored.

Ghorani et al. the efficacy of an important medicinal plant, *Zataria multiflora Bioss* for respiratory symptoms, pulmonary function tests, and inflammatory cytokines in patients having COPD. To carry out the study, they divide the patients into a total of three groups where the patients received two different doses of the extract which were set as 3 and 6mg/kg/day along with a placebo group. The results of their study revealed a significant reduction in the IL-8 and TNF-α over 2 months. In addition, the study revealed an increase in forced expiratory volume, "peak expiratory flow (PEF)" and "forced vital capacity (FVC)", also found highlighting the significance of the plant and its extract for the treatment and management of the symptoms of the respiratory disease like COPD.

The effects of botanical sources have also been investigated for the respiratory conditions induced by smoking. Possebon et al. investigated a total of four medicinal herbs *Equisetum arvense, Mikania glomerata Spreng Plantago major,* and *Arctium lappa* to study the anti-inflammatory properties in the COPD model using Wistar rats. In their study, they first artificially exposed Wistar rats to cigarette smoke, and 4% of the extracts were then evaluated to check the efficacy. The results of their study revealed no toxicity. In addition to that, a significant reduction in macrophages, mast cells, and leukocyte influx in bronchoalveolar lavage along with the prevention of tracheal metaplasia and pulmonary congestion demonstrates the efficacy of the plants as a potential therapeutic strategy [3].

Nabissi et al., the extracts of thyme were evaluated for COPD patients. They looked into the effectiveness of a commercialized thyme extract in raising Ca^{2+} levels, CBF, and cAMP, in a MucilAir 3D human COPD airway epithelia reconstructed in vitro experiment utilizing "YM976", "isoproterenol", "GSK1016790 A", "salmeterol", as positive controls. The results revealed that thyme extracts increased levels of cAMP beginning 12 hours after treatment, improved CBF in airway epithelia, and reduced extracellular Ca2+ levels [4].

3.2. Asthma

Asthma is characterized as the most frequent and prevalent chronic disease in children. It is a common non - communicable disease (NCD) affecting both children as well as adults. Symptoms are caused by the inflammation and narrowing of the narrow airways of the lungs, which results in chest tightness, wheezing, coughing, and shortness of breath. The primary treatment is inhalers, which are gadgets that let patients breathe in the medicine. In addition to that synthetic drugs are also required in severe cases which are sometimes ineffective.

Sharif et al., the efficacy of the plant *Aerva lanta* extract was evaluated for its potential for anti-inflammatory action in a mice model with induced asthma. In their study, the mice model was used and the administration of three different extracts was carried out for continuous one week. The results of their study revealed that there was a significant improvement in the count of inflammatory cells. In addition to that, a significant reduction of IgE antibodies and TNF-α with also a significant reduction in IL-4,5 and 13 which was possibly attributed to various anti-oxidant phytocompounds revealed in the GC-MS study.

Xia et al. carried out a study on the anxiolytic and Anti-inflammatory activities of *Euphorbia hirta* extract with the help of rat models. In their study, they first performed the phytochemical screening which was then followed by the evaluation of anti-asthmatic activity with the help of a

total of four groups of asthmatic rats. The results of the efficacy of the extract were recorded in terms of histopathological analysis, apoptosis, antioxidant marker, and another indicator. The results revealed a significant reduction in various factors and markers including cyclooxygenase-2, IL-6, eosinophils, and lipid peroxidation along with the reduced mRNA expression of various enzymes and markers responsible for the development of asthma [5].

Rouibah et al. characterized the chemical composition of *Zineb Rouibah* and evaluated anti-oxidant activity in an allergic asthma model using different oxidative stress parameters. The results of their study revealed that the administration of two different extracts considerably enhanced the anti-oxidant capacity in asthma and demonstrated a link between the strong antioxidant activity of olive leaf extracts and phenolic components.

Table 1: Enlisting the Medicinal Plants and their Compounds for the Treatment of "Chronic obstructive pulmonary disease (COPD)" and "Asthma".

Respiratory Disease	Plant Species	Phytocompounds	References
Asthma	*Scutellaria baicalensis,*	Flavone	[6]
Asthma	*Curcuma longa*	Curcumin	[7], [8]
	Ginkgo biloba	Biflavones	[9]
	Adhatoda vasica	luteolin-6,8-di-C-glucoside	[10]

4. DISCUSSION

Due to their exceptional abilities to intensify positive effects for the consumer with a little amount required, plants and herbs are of considerable interest. The production of medicines made from plants is continually changing, with the present emphasis being placed on plant molecular farming and nanomedicine employing conventional agents. New bioactive compounds are being discovered in plants through phytochemical and pharmacological investigations as a result of the ongoing developments in the disciplines of biotechnology and analytical chemistry. It is not a novel idea to use plants in traditional medicine. This results in the major limitation of

insufficient amounts, required for the development and clinical usage of novel medications with natural active components, as well as the necessity of enhanced isolation extraction procedures.

Herbs, in contrast to conventional treatments, are frequently asserted to be non-toxic due to their biological origin and extensive usage as traditional treatments. The long-term usage toxicities, drug-herb interactions, and inaccurate identification of species of plants, though, can also result in a variety of problems. On the other hand, it is debatable whether or not the pharmacist's recommendations and expertise were adequate and met patients' requirements. Even though herbalists are not licensed healthcare providers, the usage of homemade herbal remedies during the pandemic increased in all nations. However, it is important to determine if the recommendations made by herbalists are consistent with the evidence-based guidelines or not. In addition to that as respiratory issues can be caused by a variety of factors as illustrated in Figure 4 and lead to the same disease condition which further necessitates a look into the compounds of the plants. A particular compound can also be efficacious against the disease condition with a particular inducing factor.

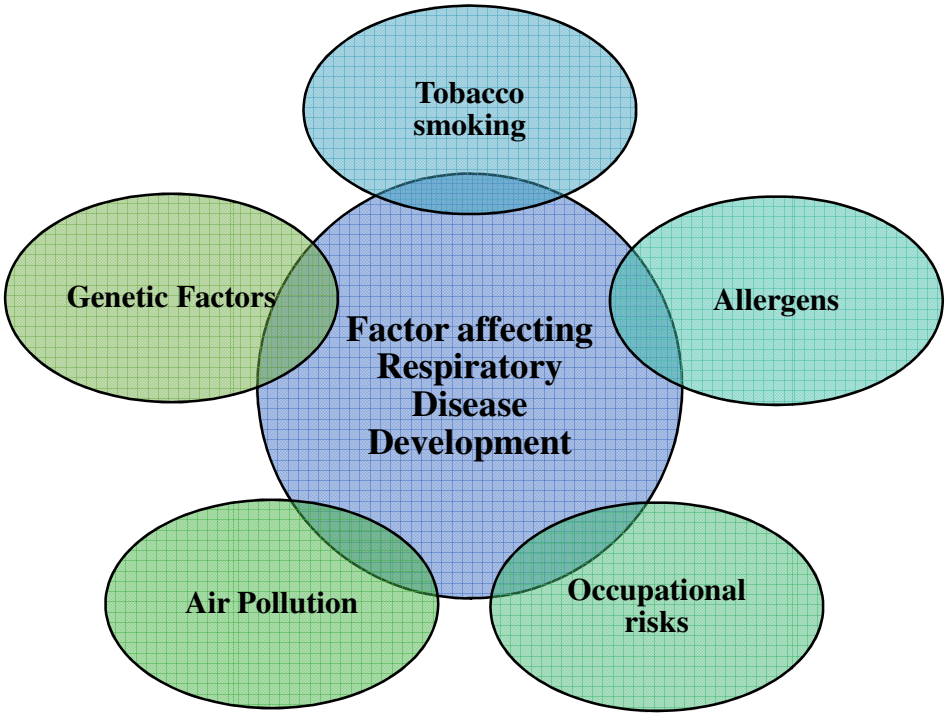

Figure 4: Illustrating the Different Factors Responsible for the Development of Respiratory Diseases.

Public health concerns and questions about the safety of herbal medicinal products are becoming more widely recognized as their use throughout the world increases and a large number of new products are released into the market. The majority of plants used to treat and prevent respiratory diseases may include toxic compounds (phenol, colchicine, etc.) that, in the case of an overdose, can result in a range of health problems. As a result, it is vital to assess the efficacy and safety of the examined herbal medications.

5. CONCLUSION

In recent times, it has turned out to be gradually crucial to collect essential data from local folklore about the therapeutic utilization of plants for treating respiratory conditions and to place more emphasis on the beneficial therapeutically and phytoconstituents evaluation of medicinal plants for the separation of new compounds as well as for their usefulness, protection, and effectiveness in treating respiratory disease.

The variety of plants is still important for humans, offering the medical system a wide range of both contemporary and conventional treatments. People in developed nations continue to rely on the traditional healthcare system even in the current scientific and technological era since it is less expensive and has fewer side effects than contemporary allopathic medicines.

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CHAPTER 10

PHYTOCHEMICAL ANALYSIS AND EVALUATION OF PHARMACOLOGICAL PROPERTIES OF *SANTALUM ALBUM LINN*

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ABSTRACT: Indian sandalwood having the scientific name "Santalum album L.", is a beautiful everlasting woody tropical tree that produces one of the costliest essential oils in the world from its matured heartwood. Sandalwood commonly known as Chandana in Sanskrit is mostly known for its scent and cosmetic properties. However, its uses are beyond cosmetics, beauty, and lovely fragrances. Therefore, the present study aims to explore another aspect of sandalwood use which lies in the therapeutic or medicinal properties using a literature review using electronic databases search from PubMed, Science Direct, Google Scholar, Scopus, and Research Gate. In addition to reviewing the medicinal properties of sandalwood, this study also provides a thorough review of the phytochemical composition which can help relate the bioactivity of sandalwood in different diseases with the composition of phytochemicals present in it. As this plant is only used in folk medicine, its use in contemporary medicine requires large clinical trials as well as toxicity studies.

KEYWORDS: Medicinal Properties, Pharmacological Properties, Phytochemical, Santalum Album, Sandalwood.

1. INTRODUCTION

One of the most precious trees in the world is "*Santalum album L.",* a member of the "Santalaceae" family. "Srigandha (Sanskrit)", "Safed Chandan (Hindi)", and "White sandalwood (English)" are all names for this treasured botanical resource that is intertwined into the traditions and culture of India. India produces 85% of the sandalwood which is followed by Indonesia and other nations as Illustrated in Figure 1 [1]. With almost 2000 years of continuous existence, sandalwood has maintained its distinction as the desired fragrance element from ancient to present times. The *Santalum album* has been stated throughout ancient scriptures, folklore, and Indian mythology [2]. The sandal tree grows in a variety of edaphic and eco-climatic environments. Given the significant genetic difference between provenances, it is determined that sandal adapts extremely well to varied geographical variables in terms of heartwood, growth, and oil content [3]. The plant has mostly been used to produce sandalwood oil, which is derived by steam distillation of its roots and heartwood. Sandalwood, as well as its oil, symbolizes gold, hence the norms and regulations controlling its cultivation and handling are rigorously enacted by the government [4]–[8].

There is much domestic use of sandalwood as illustrated in Figure 2. In addition to its primary uses as an expectorant, stimulant, sedative, and coolant, sandalwood also has astringent, diuretic, and sedative properties that make it beneficial as a genitourinary and bronchial tract disinfectant. Sandalwood oil is valuable in the perfume business because of its smoky, enduring, and sweet

scent [9]–[11]. Sandalwood is used in the Ayurvedic medical system for several additional conditions, including inflammation of the umbilicus, eye infections, poisoning, vomiting, diarrhea with bleeding intrinsic hemorrhage, and piles. It is also utilized as a restorative for the stomach, heart, and liver, as well as an anti-poison, memory improvement, fever, and blood purifier.

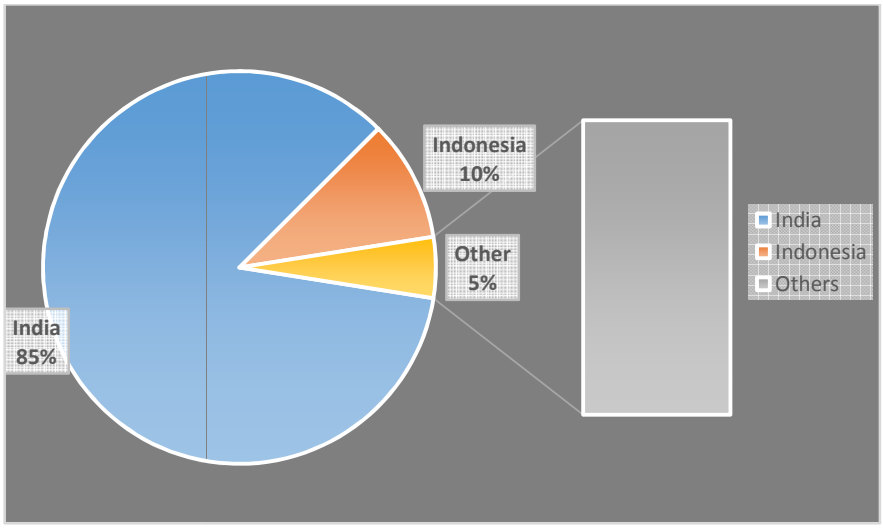

Figure 1: Illustrating the Estimated World Sandalwood *(Santalum album)*Production by Countries.

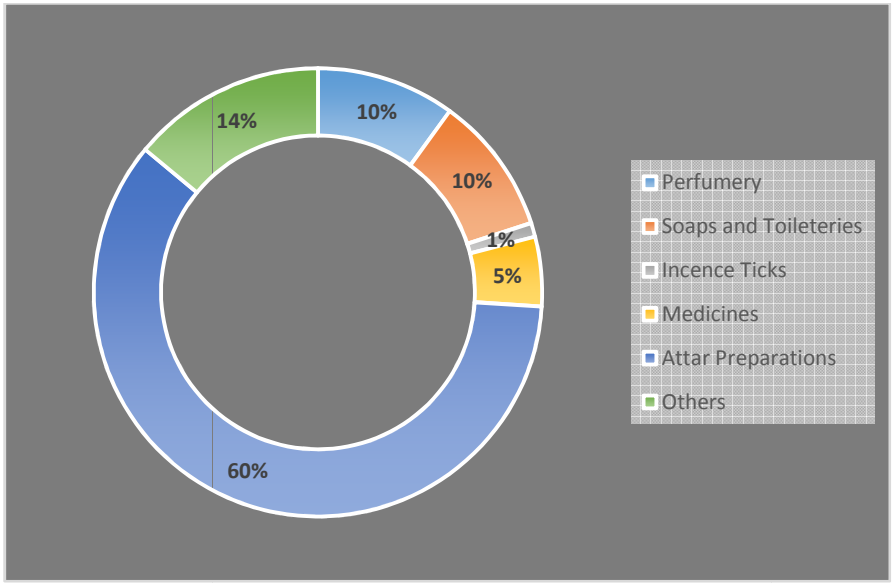

Figure 2: Illustrating the Domestic Consumption of Sandalwood *(Santalum album)* by Different Sectors.

Despite its very little use in medicine, it is now getting increasing attention for its promising pharmacological properties. Therefore, this study aims to provide a comprehensive approach to combining the evidence of its various medicinal properties with the help of an intensive literature review.

This paper is divided into a total of five sections where the first section provides a fundamental and the significance of carrying out the review study, the second section discusses the methodology, and section 3 provides an intensive review of literature on morphology, phytochemistry as well as the pharmacological properties of sandalwood. The Fourth section provides the barriers and opportunities in the pathway of using sandalwood in medicine. In addition to that, the last section provides a concluding remark.

2. METHODOLOGY

An electronic database search is carried out on PubMed, Scopus, Science Direct, Research Gate, and Google Scholar to find the relevant records. To review records, a strategy using a combination of keywords is utilized involving keywords: sandalwood, *Santalum album L.*, Pharmacological properties, Phytochemistry, Phytochemical screening, and so on. A thorough search on the first 10 pages of Google Scholar is also carried out in case of missing any recent research studies. The exclusion of the records is performed based on "No complete information" Non-Extractable Data" and "language other than English". The whole methodology of carrying out the review is provided in Figure 3 below.

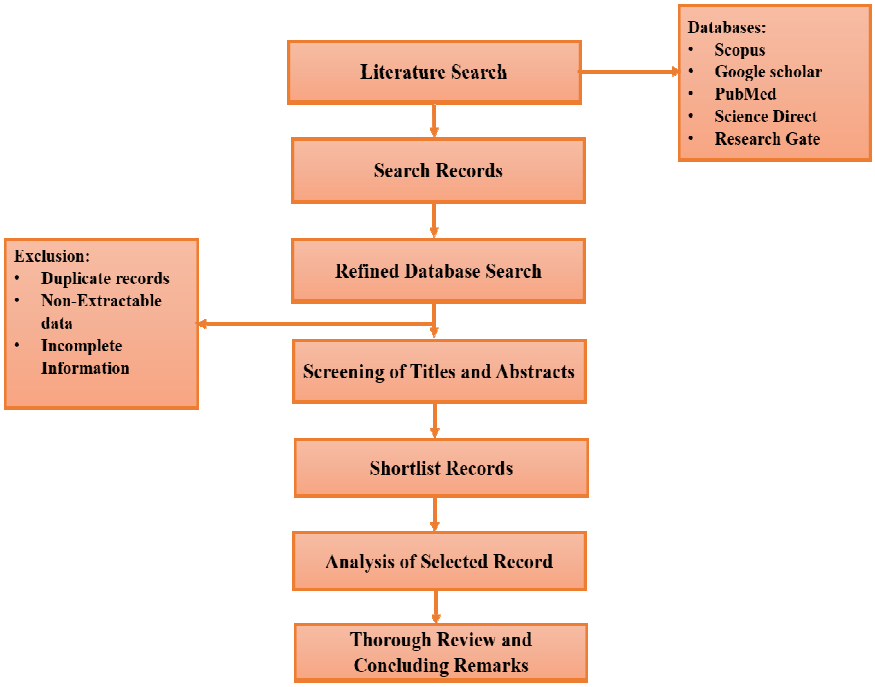

Figure 3: Illustrating the Methodology Used to carry out the Review Study.

3. LITERATURE REVIEW

There is an ample amount of research studies documenting morphologic characteristics, phytochemical analysis, and pharmacological properties.

3.1. Morphologic Characterization and Classification

S. album is characterized as a little evergreen tree that can reach 4 meters in Australia, although it may reach 20 meters in India, with 2.4 meters of diameter and delicate branchlets with drooping nature. The bark is reddish, dense, dark brown, dark grey, or practically black, rough

with deep fissures that are vertical in older trees, red on the interior, and smooth in young trees. Leaves are typically opposing, thin, glabrous, ovate or oblong elliptical, 3-8 x 3-5 cm, and bright green above, glaucous and somewhat lighter underneath; tip rounded or pointy; 5-15 cm long; stem grooved, venation visibly reticulate. Figure 4 below illustrates the pictorial representation of flowers, leaves, and trees of Sandalwood *(S. album).*

Figure 4: Illustrating the Flowers, Leaves, and tree of *S. album (S. album).*

Scientific Classification

The scientific classification of the *Santalum album(*sandalwood) is detailed below with "kingdom", "clade", "order", "family", "genus", "species", "scientific name", and "common name".

i. "Kingdom: Plantae

ii. Clade: Angiosperms

iii. Clade: "Eudicots"

iv. Order: Santalales

v. Family: Santalaceae

vi. Genus: Santalum

vii. Species: album

viii. Scientific name: *Santalum album*

ix. Common name: Sandalwood"

The refine and processed Sandalwood is illustrated in Figure 5 (left; white sandalwood and right; red sandalwood) which is one of the most common forms of domestic use and international trade.

Figure 5: Illustrating a Pictorial Representation of White and Red Sandalwood.

3.2.Phytochemical Screening

The characterization of phytoconstituents becomes important because of their traditional use in a variety of therapeutic applications. Several studies have been conducted with variations in an experimental procedure to reveal every constituent. In a recent study performed by Sharifi-Rad et al., the phytochemical analysis of sandalwood is carried out on the naturally growing 30 years of sandalwood tree with the help of the distillation process which revealed a diverse array of compounds such as 90% of santalol where the α-santalol accounted for the 52% of santalol as well as β-santalol which accounted for 23%. In addition to that other phytocompounds such as β- and α- santalenes, α-santalic acid, cis-lanceol, pi-β-santalene, cis-nuciferol, trans- α -bergamotene, di-hydro-β-santalic acids [12].

It has also been noted that the difference and making variations in the process to extract oil from sandalwood can either increase or decrease the yield of the oil. Kusuma demonstrated that adding more air to the microwave hydrodistillation process can raise the sandalwood oil yield produced, which is inversely related to the airflow rate. It has been found that the sandalwood oil composition that was microwave air-hydro distilled, was more than that of another approach in terms of identification. When compared to microwave hydrodistillation, "microwave air-hydrodistillation" yields extracts with higher aroma/fragrance quality [13]. Another separate study by Hudha et al. also attempted to develop a variation for extracting the higher yield of sandalwood oil which revealed that mass variation and dry wind treatment can escalate the yield produced [14]. As demonstrated by several other research studies, a comprehensive approach carried out by Kumar et al. also revealed "α-santalol" and "β-santalol" as the major chemical compounds present in sandalwood. Figure 6 illustrates the chemical structure of the most important compounds, as well as other major phytochemicals, revealed in the phytochemical screening of sandalwood oil [15].

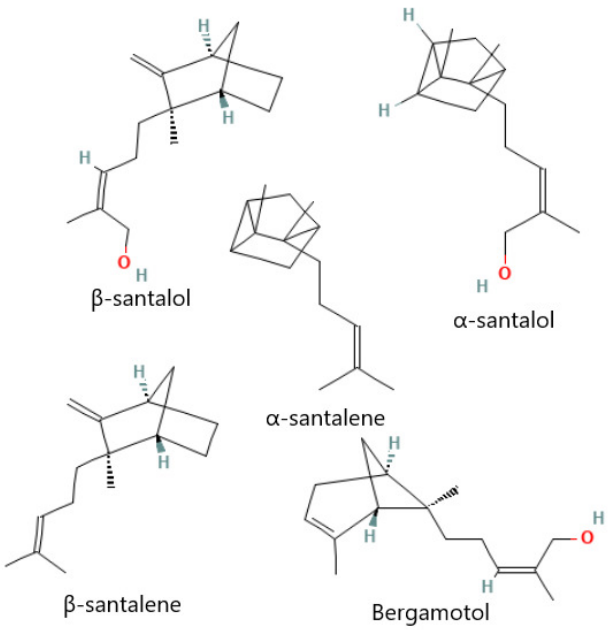

Figure 6: Illustrating the Major Phytochemical Compounds Present in Sandalwood.

3.3. Pharmacological Properties

A lot of comprehensive studies are available that document the evidence of the therapeutic application of sandalwood and its phytochemicals. A recent comprehensive study carried out by Bommareddy et al. investigated and presented the medicinal properties of the majorly present natural phytochemical of sandalwood oil. The findings of their study revealed that the compound has major bioactivity as an anti-cancer agent. Alpha-santalol has been shown in numerous models of cancer to cause cell death via cell cycle arrest and apoptosis. Therapy with alpha-santalol resulted in a considerable decrease in markers of inflammation in skin tissue models [16]

In another study carried out by Mishra and Dey, the phytocompound from sandalwood is docked with different protease and kinases which make up the majority of target proteins in several diseases like infections, cancer, and many others. The results of their study revealed that the compound Cyclosaplin has the most affinity against a range of target proteins like VEGFR2, p38, EGFR, and PKB demonstrating the potential as kinase and protease inhibitors [17].

Pushpawati and Rita evaluated extracts(n-hexane) of *santalum album* for its anti-inflammatory activity(topical) using an animal model with induced edema. Hydrocortisone and extract of sandalwood leaf applied topically considerably decreased rat ear edema caused by croton oil, with respective percentage inhibitions of 36, 52, and 73%. However, compared to the negative control, it did not substantially decrease inflammation at a greater dosage of 40 mg/ear. The results of the histology examination also showed that hydrocortisone and extract at dosages of 10 and 20 mg/ear greatly reduced leukocyte infiltration [18].

In addition to the anti-cancer and anti-inflammatory, there is also evidence of neuroprotective effects of sandalwood. Suganya et al. investigated the extract of sandalwood and its neuroprotective effects on human SH-SY5Y neuroblastoma cells. The results of their study revealed that the extracts of sandalwood significantly raised the mRNA levels of MxA, IFN-α, and IFN-β. In addition to that, the findings of their study also revealed a decrease in CCL2, IL-6, IP-10, and CXCL8 demonstrating the potential for neuroprotection [19].

4. DISCUSSION

One of the most well-known and commonly utilized plants in perfumes and cosmetics is the Santalum album. Sandalwood is used for a variety of pharmacological purposes in addition to its usage in perfumes and cosmetics, making it one of the most significant plants used in medicine. Over the past 20 years, several investigations on this plant have been carried out, but more research is still needed before sandalwood can be fully utilized for the benefit of humans. For more than a century, scientists have been focusing on the study of intriguing chemical components, particularly sesquiterpenoids of sandalwood, to understand their structure, synthesis, & pharmacological efficacy.

Sandalwoodhas been cultivated in India and is renowned across the world for its aromatic oil, which is delicious, long-lasting, and valuable for therapeutic purposes. In many ancient medical systems, including Ayurveda, Siddha, and Unani medicine, *S. album* and the EOs made are utilized in the prevention and treatment of a broad range of diseases. This paper is attempt to highlight the multifaceted therapeutic and medical significance related to its abundant supply of phytochemicals, notably sesquiterpenes.

It has traditionally been used as a nervine tonic, diuretic, gastroprotective, exhilarating, cardiotonic, antiseptic, blood purifier, expectorant, analgesic, and anti-inflammatory. As a result, it is beneficial in the treatment of gastrointestinal, cutaneous, respiratory, cardiovascular, integumentary, locomotor, and urogenital diseases. It has antiviral, sedative, analgesic, antibacterial, antioxidant, anti-inflammatory, and anticancer activities, as well as effects on the cardiovascular and gastrointestinal systems. As a result, this research strongly supports the fact that sandalwood and its oil contain a variety of pharmacological activities. However, there is still a need for clinical trials to demonstrate the above pharmacological actions in diverse disorders.

Sandalwood availability and output have dramatically decreased owing to overharvesting and poaching of environmental assets. Adulterations are also being performed as it is one of the scarce species. Some adulterations are easy to identify; however, adulteration performed by a professional using the proper components may be extremely difficult to detect. The physical and chemical characteristics of genuine oil are influenced when it is adulterated with (semi) synthetic additions.

The quality control measure is strongly suggested to combat the risk of adulterations. Unlike traditional approaches, identification, and quantification of adulterants in sandalwood oil may be accomplished with ease using techniques such as Gas chromatography and GC coupled with Mass spectroscopy as well as other physicochemical methods. To authenticate oil and assure a high-quality ingredient, one or a combination of these approaches can be used as a quality control procedure. Furthermore, it is recommended that regulatory bodies or certifying bodies closely monitor quality control and authentication for high-priced Sandalwood oil.

The sandalwood plant has several chemical compounds, both significant and small. Alpha-santalol, a significant phytochemical ingredient of the sandalwood plant, was examined for toxicity. In experimental models, sandalwood oil and its derivatives were shown to have minimal acute oral and cutaneous toxicity. According to the literature research, there are extremely few reports of sandalwood oil causing irritation or hypersensitivity. However, data on sandalwood oil toxicity is still limited. Even though the plant has long antiquity of usage with no recorded harmful effects and is deemed safe.

5. CONCLUSION

In the present study, an attempt has been made to review the morphological characteristic, phytochemical composition, and pharmacological properties of *Santalum album L.* The study reviews the phytochemical composition which demonstrates a range of important phytochemicals in context with various therapeutic applications. The sandalwood used in therapeutic has only been observed in traditional and folk medicine, despite its genuine efficacy. However, to use sandalwood, its extracts, and oil in modern medicine, more studies and randomized clinical trials are needed to confirm the findings.

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CHAPTER 11

AN ASSESSMENT OF ANTI-CARCINOGENIC EFFECTS OF *CROCUS SATIVUS L.* FOR CANCER CHEMOPREVENTION

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ABSTRACT:

Cancer is considered one of the most frightening diseases in the world, and both advanced and emerging countries are experiencing a significant rise in its prevalence. Cancer patients now have a wider range of therapeutic alternatives, however, these options are only temporary and curative. Because of this, continuous research into better, safer medications has been carried out for many years to overcome these limitations, and as a consequence, some phytoconstituents have been shows to have anti-cancer properties. The most significant and costly spice studied for its anti-cancer effects is Crocus sativus L. Therefore, the present study evaluates the anti-cancer activity of Crocus sativus and its chemical compounds on various types of cancers such as prostate, breast, and colon-rectum cancers while starting with a preliminary study on the morphology of Crocus sativus L. as well as its phytochemical composition. In addition to that this review also provides a critical discussion on the barriers and opportunities that can be presented by this spice for the chemoprevention of various types of cancers. Therefore, there is an immediate need to fill the gaps by applying the recent findings on the potential of saffron in cancer prevention and early management of patients that are susceptible to developing it.

KEYWORDS:

Anti-Cancer, Breast Cancer, Cancer, Crocus Sativus, Phytochemical.

1. INTRODUCTION

Cancer is caused by a pathologic malfunction in the mechanisms that regulate specific cell growth, differentiation, and death. The word "carcinoma" refers to the malignant cells that most frequently develop tumors and come from tissue known as epithelial (also known as tissue with a secretory or lining function). Most cancers are carcinomas in various organs, including the breast, lungs, colon, and others. The etiology of various cancers is highly varied, even if they share certain traits, and their responses to treatment might vary greatly [1]–[4].

There were 10 million cancer-related deaths in 2020, making it the second biggest cause of death globally. Most of the cancer burden is borne by low- and middle-income countries. A total of 70% of cancer-related fatalities in 2020 surpassed those in high-income countries by a margin of around 10 million. Even more shockingly, 90% of new cases and fatalities from cervical cancer—a type of cancer that may be prevented—occur in low- and middle-income nations. The significant barriers that cancer imposes on national health systems are beyond the capacity of the developing world, which has very few resources [5], [6].

The fundamental driver driving increases in cancer incidence, mortality rates, and healthcare expenditures is frequently thought to be population aging. However, the reality is more complicated. Age-standardized cancer mortality is currently dropping in all age categories in high-income countries, even though those over the age of 70 represent more than half of all cancer deaths. It has also been noted that there is no barrier to the occurrence of cancer whether it is country, sex, race, and ethnicity. However, a significant variation in the number of deaths and new cases can be seen in the context of the above-mentioned factors. As per recent data of GLOBOCAN 2018, the most number of new cancer cases is from Asia followed by Europe, America, Africa, and Oceania (Figure 1).

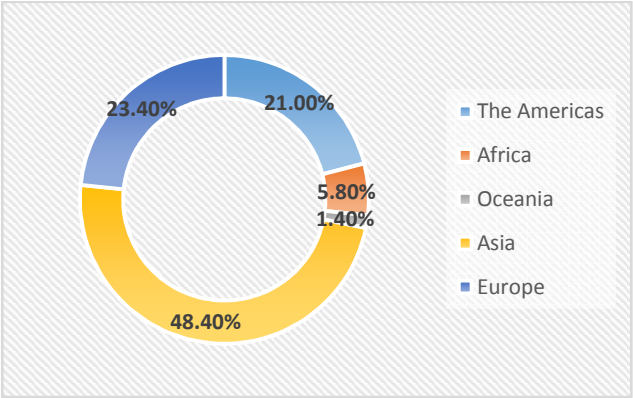

Figure 1: Illustrating the Global Cancer Incidence by Countries; GLOBOCAN 2018.

As per the recent estimates given by World Health Organization 2021, a significant increase in cancer cases. The new cancer case estimates are enlisted in Table 1 below as per the cancer types. Lung cancer was found to be associated with most deaths attributed to cancer reaching 1.80 million deaths in 2020 followed by 916000 deaths caused by colon and rectum cancer, 830000 deaths by liver cancer, and 769000 deaths by stomach cancer.

Table 1: Enlisting the New Cases of Cancer by Types as per Recent WHO Estimates.

Cancer types	Number of New Cases
Colon and Rectum Cancer	1.93 Million
Breast Cancer	2.26 Million
Lung Cancer	2.21 Million
Prostate Cancer	1.41 Million
Skin Cancer	1.20 Million
Stomach	1.09 Million

The current candidates for treatment for cancer include surgical excision of cancer and radiotherapy for the huge accumulating mass of cancer, which is frequently accompanied by systemic chemotherapy for management [7]–[10]. The most widely used chemotherapy drugs are hormones, and molecular targeting drugs, anti-tubulin drugs (like taxanes), DNA-interactive

drugs (like doxorubicin and cisplatin), and antimetabolites (like methotrexate). Recurrence of cancer, drug resistance, and adverse effects on tissues and organs not targeted are the primary problems of chemotherapy. These concerns might constrain the application of anticancer treatments and lower the quality of life for patients. The quest for novel anticancer drugs with improved efficacy and fewer side effects is ongoing to address the shortcomings of therapeutic strategies.

Botanical Sources have been proven to be effective against a variety of cancers. Crocus sativus L. is one of the botanical sources for a variety of compounds. The dried red stigma of Crocus sativus L., a member of the “Iridaceae” family (also known as "Kesar"), is extensively grown in Iran as well as other countries like India and Greece. More than 150 volatile compounds and aroma-producing substances, mostly terpenes, as well as their esters, are present in saffron. A lot of research has been going on to explore the health benefits of saffron. But more research is now being focused on its anti-cancer activities. This plant is mostly produced in Iran, which produces approximately 90% of global saffron production. All around the world, including west Spain, India, Greece, Italy, Azerbaijan, Europe, and Morocco, *C. sativus* grows in moderate regions. It is notably common in Iran and East Asia. The size of the world saffron market by application is illustrated in Figure 2 below. The growth of the market for saffron in pharmaceuticals and cosmetics is projected to be a major market driver during the projected period.

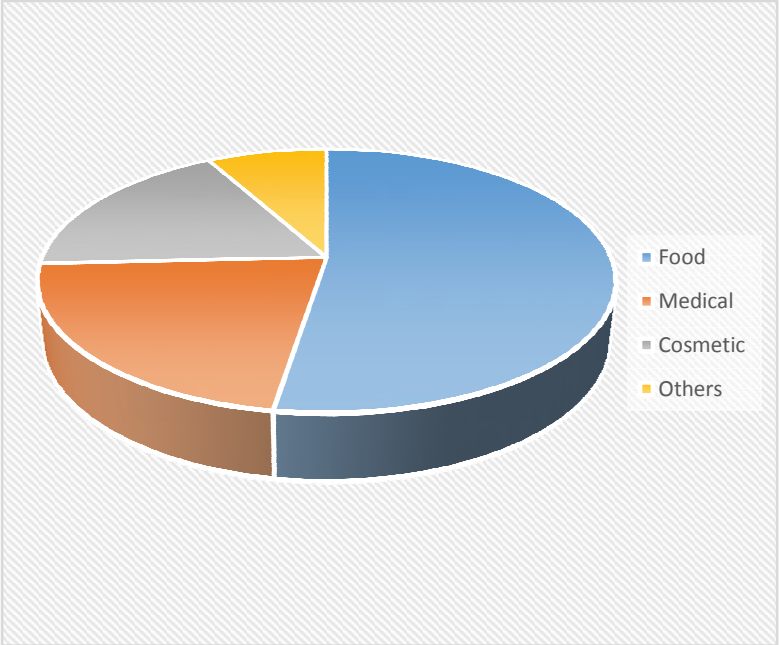

Figure 2: Illustrating the Global Market of Saffron by Application; 2020.

Therefore, the present review study aims to combine the evidence of the anti-cancer activity of saffron with the help of intense review literature available online on various databases. This paper is divided into a total of five sections, where the first section discusses the introduction and the significance of carrying out the review study, the second provides the methodology, and the third section provides the intensive review of the effect of saffron on different types of cancers. In addition to that, a critical discussion on the opportunities and the barriers to using Saffron for the treatment of cancer has been discussed with a concluding remark.

2. METHODOLOGY

The present review study is carried out using a database search on PubMed, Google Scholar, Research Gate, Science Direct, and so on. The review strategy utilized a combination of keywords such as "Saffron" "Crocus sativus L.", "Cancer", " Anti-cancer" "Medicinal Plants, and "Herbs".

The Preliminary screening of the records was performed with title and abstract Screening. And further, the Records were excluded in case of duplicate studies, non-extractable data, and incomplete information. The design used to carry out the review study is detailed in Figure 3 below.

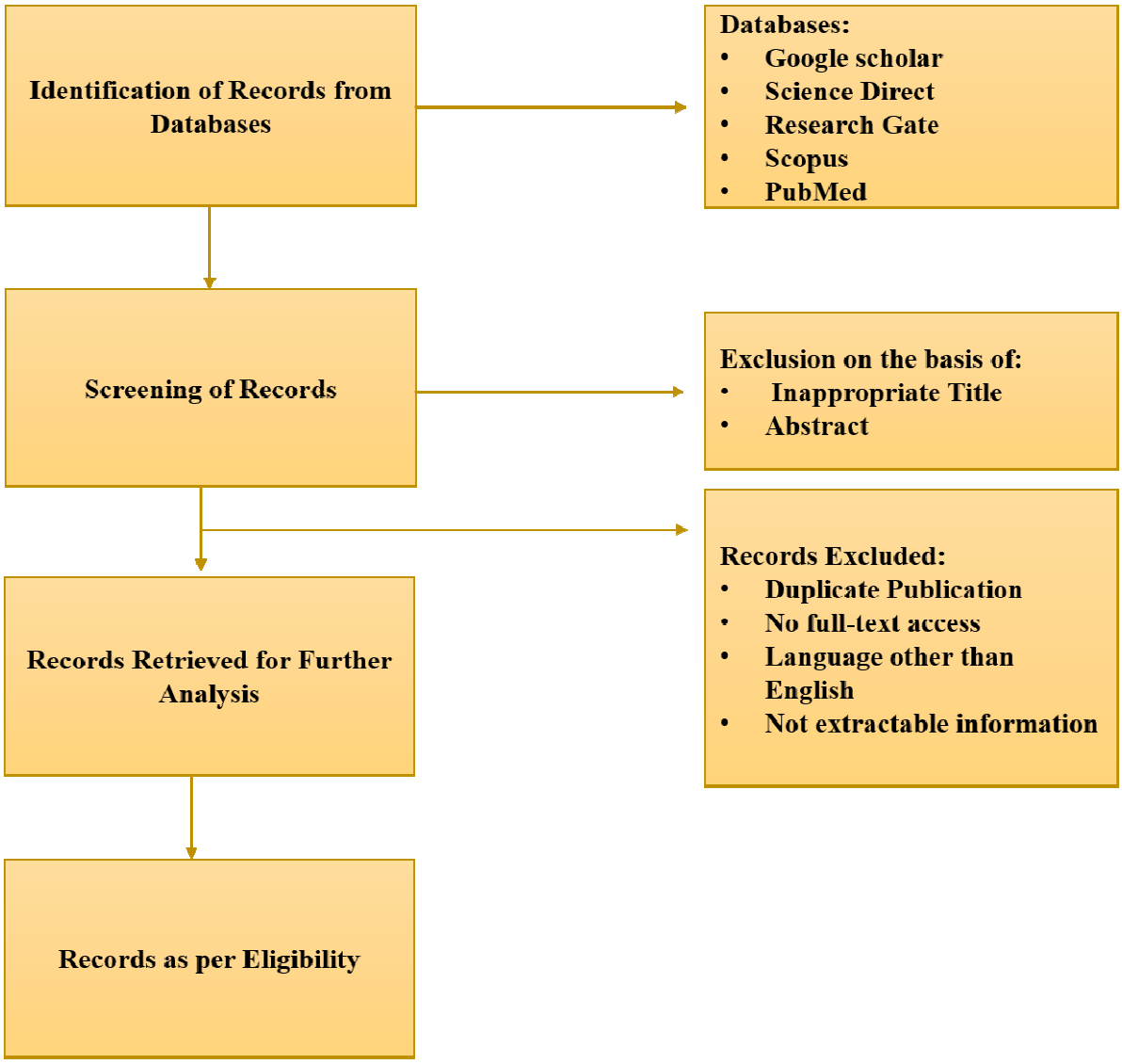

Figure 3: Illustrating the Design used to carry out the Review Study.

3. LITERATURE REVIEW

3.1. Morphologic traits and Scientifc Classification

Iridaceae family member C. sativus is a sterile, triploid perennial plant. A corm is present in Crocus sativus, and it houses the flower stem, leaves, and bracts. The corm beneath shields them from damage. Purple flowers frequently come into bloom in the autumn on C. sativus. From 10 to 30 cm in height, the plant grows. *C. sativus* contains 24 chromosomes because it is a triploid (2n = 3x = 24), which has three times as many as a haploid. By failing to link chromosomes during meiosis, as a result, the plant turns sterile. Figure 4 below illustrates the flower and stigma of *C. sativus.*

i. Kingdom: Plantae
ii. Clade: Tracheophytes
iii. Clade: Angiosperms
iv. Clade: Monocots
v. Order: Asparagales
vi. Family: Iridaceae
vii. Genus: Crocus
viii. Species: *C. sativus*

Figure 4: Illustrating the flower of Crocus sativus L. and Separatef Stigmas.

3.2. Phytochemical Screening:

There are around 150 aroma-producing and volatile chemicals in saffron. It also contains a large number of nonvolatile active compounds, a majority of which are carotenoids, such as "α- and β- carotenes", "lycopene", and "zeaxanthin". According to phytochemical studies, the color is mostly caused by the oxidized carotenoid components crocin and crocetin, the flavor is primarily due to safranal (3), and the sharpness is due to glucoside picrocrocin [11]–[13].

3.3. Anti-Cancer Activity:

There is an ample number of studies reporting the anticancer genic action of saffron. Apart from that activity of several compounds was also tested against a lot of cancer types. Shakeri et al. provided a snapshot of the "in-vitro" and "in-vivo" molecular modes of action for anti-cancer action, cancer prevention, and protection properties of extracts from saffron. Saffron has been known to have selective toxicity and preventative impacts on malignant cells while having no negative influence on normal cells, and it inhibits tumor growth. Saffron appears to lessen the toxicity of anti-cancer treatments. When used in large quantities, saffron exhibits toxicity implications that are substantially larger than those seen in human food culture [14].

3.3.1. Colon and Rectum Cancer:

When the cells lining the colon or the rectum develop into aberrant tumors and proliferate uncontrollably, colorectal cancer is the result. It is crucial to have routine colorectal cancer screenings since symptoms frequently do not manifest until the cancer has progressed. The phase of cancer determines how colorectal cancer is treated [15], [16]. Cancer's stage reveals its severity. Chemotherapy, surgery, and radiation therapy are all possible treatment options [17].

Chen et al. evaluated the effectiveness of "crocin" against cell lines "A549" and "SPC-A1". Crocin increased G0/G1 arrest and decreased cell growth in a concentration-dependent mode. It also caused apoptosis. Crocin put the expression down of "B-cell lymphoma 2 (Bcl-2)" while increasing the mRNA expressions of "B-cell lymphoma 2-associated X protein (Bax)", and p53. Additionally, crocin demonstrated a higher inhibitory impact when paired with cisplatin or pemetrexed than it did when used alone.

Amin et al. investigated saffron and its active compounds against colon cancer cells using cell lines such as "HCT116+3 (inserted MLH1)", "HCT116+5 (inserted MSH3)", "HCT116+3+5 (inserted MLH1 and MSH3)", and "HCT116". The results of their study revealed that extracts inhibited (up to 70%) growth in colonal cells with inadequate "MMR" (HCT116) compared to competent "MMR". When fed with saffron, defective MMR cells outperform competent MMR cells (up to 90%) [18].

3.3.2. Breast Cancer:

Arzi et al. carried out a comparative evaluation of the anti-metastatic properties of saffron carotenoids, crocetin, and crocin, as well as their effects on the pathway called Wnt/-catenin. The results of their study revealed that the survival of 4T1 cells was discovered to be inhibited by crocetin and crocin. Other experiments revealed that the non-toxic dosages markedly reduced invasion, invasion, cell mobility, and migration while also lessening adherence to the extracellular matrix. The genes for FZD7, NEDD9, VIM, and VEGF- were all expressed at lower levels by crocin whereas E-CAD was elevated. Similar anti-invasion abilities were shows by crocetin and crocin on 4T1 cells [19]. Nezamdoost et al., the effects of saffron and High-intensity training were evaluated for the anti-cancer activity of female BALB/c mice. The results of their study revealed that in comparison to the control and HIIT groups, the HIIT + SAE group had higher levels of SIRT1 mRNA [20].In vitro, in vivo, and silico experiments were conducted to assess the impact of saffron carotenoids on breast cancer. The results of their study revealed a reduced Superoxidase dismutase activity by Cro/Crt both in the MCF-7 cell line and in vitro. SOD activity was elevated in breast cancer mouse models by Cro/Crt. In addition to that they

found that in vitro, Cro/Crt exhibits radical scavenging potential. They cause significant modifications to the SOD kinetics and structure [21].

3.3.3. Prostate Cancer:

Cells in the prostate gland tend to multiply uncontrolled, which leads to the development of prostate cancer. Only men are known to have the prostate gland. Some of the fluid of sperm is produced by it. The bladder, which is described as an organ holding urine, is above the rectum, and the prostate is in front of it. Ahmadnia et al. researched to assess the potential anticancer impact of saffron stigma extract on L929 (mouse fibroblast cells) as control cells and human prostate cancer (PC3). The saffron extract did not affect normal cells in fibroblast cell lines after 24 hours, and they were morphologically intact. Cell mortality and cellular shape alterations, as well as significant granulation, were seen after 4 days in cells with the greatest dose (1600g/mL). The only alterations identified in prostate cell lines after 1 day were in cells with a dosage of 1600 g/mL. The cells were granular, and the morphology was spherule. Following 72 hours, significant granulation was detected in the group with a concentration of 1600 g/mL, as well as a drop in cell count and the death of certain cells [22].

The above studies have demonstrated different saffron extracts and their various active components against prostate, breast and colon, and rectum cancer. However, there is a very less comprehensive approach to the effects of this important spice and its chemical constituents on a variety of cancers combining the evidence to fill the gap in the use of saffron for its medicinal property in cancer prevention. Therefore, the present study helps in reviewing the evidence on saffron, its extract, and its ingredients on cancers like prostate, breast colon, and rectum cancers.

4. DISCUSSION

Since the beginning of time, scientists have worked to use the natural resources at their disposal and pinpoint the beneficial properties of medicinal plants that might have a large positive influence on human health. The saffron crocus, commonly known as Crocus sativus L., is one of these plants. Studies show that the active ingredients of saffron are protective against a multitude of diseases, particularly cancer. Scientists from all over the world are increasingly drawn to suggest that saffron consumption is positively correlated with a decreased risk of many forms of cancer, and they have also looked into the potential role of the numerous phytochemicals in saffron. These phytochemicals crocetin, crocins, picrocrocin, and safranal as illustrated in Figure 5 are among the most often studied in both in vitro and in vivo research because they are thought to have the highest medical bioactivity. These findings indicate that the compounds in saffron may have powerful anticancer and antitumor action with high selectivity against cancer cells, without harming healthy cells or having any negative side effects like those associated with traditional cancer treatments or drug resistance.

Given the documented benefits of saffron on cancer cell removal, saffron extracts could well be utilized in the treatment and prevention of cancers if human clinical studies are completed. Saffron extracts have a high IC50 in normal cells, which limits their cytotoxicity to non-cancerous cells and makes their users safe. Additionally, studies have demonstrated that saffron could be beneficial in the fight against cancer, especially in cases of other prevalent malignancies and nervous system cancers. According to studies, saffron extract possesses anti-drug properties, suggesting a novel therapeutic method for reducing medicinal toxicity and paving the way for prospective clinical uses. Furthermore, studies on the benefits of saffron extracts on lymphomas

are recommended. There is a need for human clinical study in this field since it has been challenging to translate the result of animal studies to humans and determine the safest and best dose.

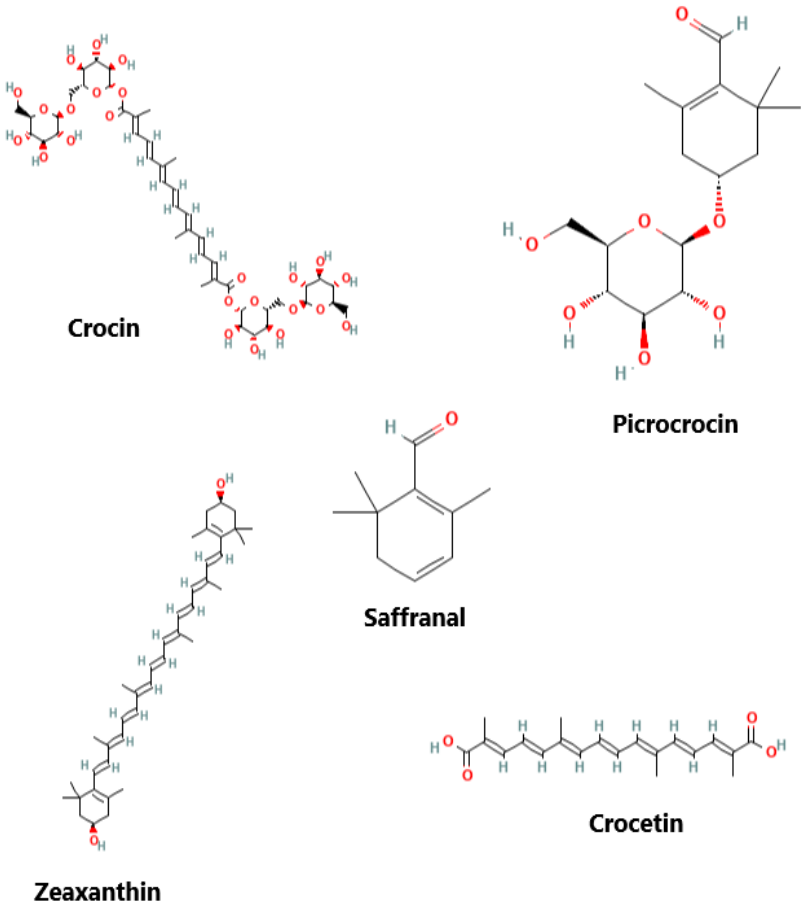

Figure 5: Illustrating the Major Phytocompounds Found in Crocus Sativus L.

5. CONCLUSION

Approximately 8 million people die of cancer each year, which makes it the most important cause of mortalities in the world. While the vast majority of conventional clinical studies have concentrated on treating tumors once they manifest, wise researchers are looking for natural molecules that may prevent the formation of cancers very early on. Instead of chemotherapy, this commendable objective is known as chemoprevention. In the present study, the summarized effects of saffron and its biologically active compounds were reviewed which highlights the potential of traditional medicine and the role it can play in the future. However, a lot of research on toxicity and safe dosage is still required with large clinical trials.

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CHAPTER 12

EVALUATION OF ANTI-VIRAL ACTIVITY OF MEDICINAL PLANTS AND THEIR EXTRACTS

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ABSTRACT:

Every year, three to five million patients are affected by viral infections. Herbal products have been utilized for medical purposes since ancient times and are renowned for their antiviral activities and much more tolerable adverse reactions, whereas frequently utilized antiviral drugs frequently exhibit limited efficiency and substantial negative effects. As the side effects and the limited efficiency of synthetic anti-viral drugs are increasingly known by the modern population. Therefore, researchers are now investigating natural sources for alternative medicine against a variety of viruses causing severe infections. The present study aims at investigating the effects of the anti-viral activity of various medicinal plants and their plant extracts. In addition to that, the study also provides a critical discussion on the opportunities and barriers confronted by medicinal products for treating viral infections. However, there are still gaps that need to be addressed for harnessing the full potential of natural sources, especially medicinal plants.

KEYWORDS:

Anti-viral, Herbs, Medicinal plants, Infections, Viruses.

1. INTRODUCTION

A major global concern for medical professionals today is viral infection because of the uncontrolled incidence of mortality and morbidity. As illustrated in Figure 1, the World Health Organization reported the prevalence of different diseases where infectious diseases accounted for 24% which further needs immediate attention. Out of the various infectious diseases, human health has been impacted for many years by several viruses that can cause death, such as herpes simplex virus (HSV), influenza virus, and hepatitis virus subtypes A, B, and C (HAV, HBV, and HCV), the human immunodeficiency virus (HIV), and others. In addition to these pre-existing viruses, coronavirus-2 (SARS-CoV-2) has started to become a worldwide problem as of 2019. The severe acute respiratory illness associated with the coronavirus infection, commonly known as "the novel coronavirus disease" (COVID-19), has an extremely high mortality rate.

There are still several viral infections that have significant fatality rates. Antiviral treatments are still required even if antiviral chemotherapy has made excellent progress. A potential issue for effective therapy is the formation of drug-resistant infections during treatment. Additionally, it's possible to find brand-new viral infections. Viral inhibitors have long been recognized as biologically active compounds with plant origins. These antiviral substances can be obtained from sources like higher plants, which have, for a variety of reasons, been studied far less than the conventional ones.

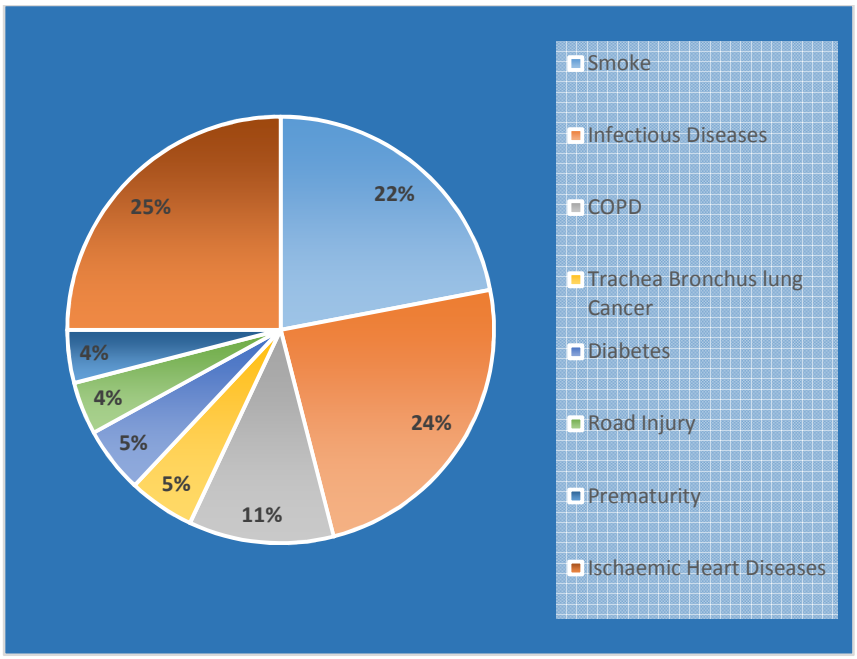

Figure 1: Illustrating the Prevalence of Different Diseases, Injuries, and Conditions (WHO).

Natural products have been used extensively for hundreds of years to keep people healthy and wealthy all over the world. Herbs are frequently employed in the treatment of a variety of diseases. According to a recent survey, consumers prefer alternative medicine over mainstream care in the majority of emerging nations today as reported by WHO. An estimated 80% of the population in developing countries rely on traditional medicine as illustrated in Figure 2.

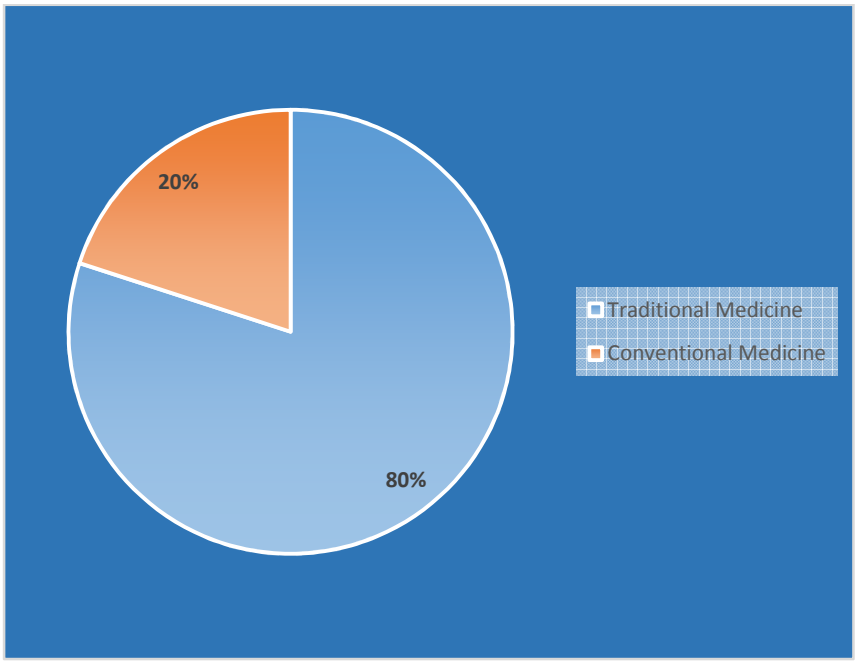

Figure 2: Illustrating the Estimated Use of Traditional and Conventional Medicine in Developing Countries (WHO Estimates).

Numerous publications and books assert that herbs are effective in treating a variety of ailments, including hepatitis, cirrhosis, and other fatal conditions. It has been generally noted that traditional medicines and medicinal plants serve as a standard for preserving health. A growing market for the use of products made from medicinal plants has been discovered during the development of several drugs.

Herbal remedies for mild disorders have gained popularity as a means of maintaining personal health. There is a high probability that the world's remaining medicinal plants will vanish due to rising demand. Consequently, medicinal plants play a significant role in the country of India's health care system.

The possibility of medicinal plants producing new drugs is threatened by the alarming loss of biodiversity; according to recent estimates, one in five plant species on earth faces extinction. Even though herbal medicines have long been considered a reliable source of safe and effective treatments with the ability to generate new ones, this potential is now in danger.

To establish a relationship between the ethnomedicinal use of medicinal plants and drug discovery in modern medicines, scientists working on drug discovery are urgently documenting and researching the bioactivity of numerous ethnobotanical medicinal plants.

As many plants and herb species are having great antimicrobial properties against a diverse range of microbial pathogens, there is still a lack of combining all the evidence that is published in the form of research studies, case reports, and systematic reviews. Therefore, this study aims to combine the evidence on the plant species having anti-viral activity against different economically important viruses.

The paper is divided into a total of five sections. The first section provides an understanding of the topic and the face of the review study as well as the significance of carrying out this review. The second section provides a methodology that is employed to find the relevant papers for review work.

In addition to that, the third section provides an intensive review of the literature published online documenting the anti-viral activity of various herbs which is then followed by section 4 explaining the opportunities and challenges of herbal treatments for viral infections. In addition to that, section 5 five provides a concluding remark.

2. METHODOLOGY

The review work is carried out using an electronic database search. The databases used to retrieve the records were PubMed, Google Scholar, Research Gate, Science Direct, and other websites. The review approach employed terms such as "Herbs," Anti-viral activity," "Virus," "Infectious disease," and "Anti-microbial effect."

The preliminary examination of the records was based on title and abstract screening. In addition, the Records were excluded due to non-extractable data, redundant research, and insufficient information. More information on the approach used to perform the review research may be seen in Figure 3 below.

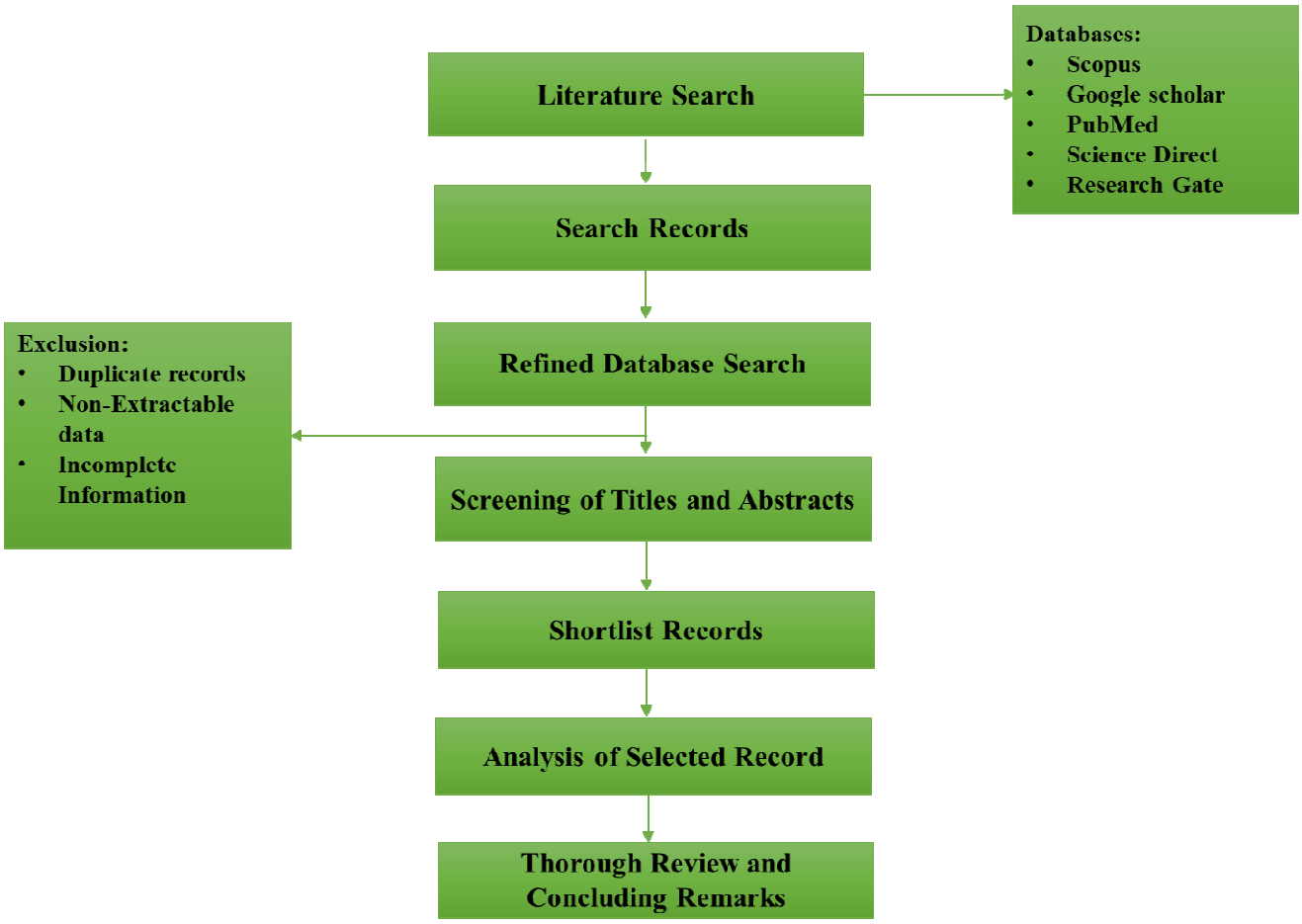

Figure 3: Illustrating the Design Used to Carry out the Review Study.

3. LITERATURE REVIEW

Since the beginning of time, many different plants have been employed in medicine and are renowned for their potent medicinal benefits. Many of these botanicals have been used to treat highly contagious diseases like viral infections in conventional medicine.

3.1.Zingiber officinale (Ginger)

Kaushik et al. tested *Z. officinale* which is commonly known as Ginger for anti-viral activity against chikungunya in an animal cell culture model. *Z. officinale* rhizome was used to make the therapeutic plant extract. The anti-viral activity was investigated by analyzing the cytopathic effects and cell viability as evaluated by the MTT experiment. The maximum non-toxic dosage of ginger plant extract was determined to be 62.5 g/ml. As a result, rhizome extracts of Z. officinale show a strong potential to cure CHIKV [1].

Camero et al. investigated ginger essential oil (GEO) for antiviral efficacy against CpHV-1 in vitro. GEO was discovered to be an efficient cell-free viral virucide, inactivating CpHV-1 up to 100%. The destruction of the herpesvirus envelope and its related structures, which are required for virus adsorption and entrance into the human host, is most likely responsible for virucidal action [2].

3.2.Curcuma longa L. (turmeric)

Numerous studies have demonstrated that the pharmacological and biological characteristics of extracts of curcuminoids and turmeric rhizomes have demonstrated anti-viral action against a variety of viruses, including hepatitis B and C viruses, influenza virus, human immunodeficiency virus, etc.

Hadhrami et al. reported a case of a 10-year-old child with herpetic vesicular-ulcerative lesions who was addressed with turmeric coupled with systemic acyclovir, resulting in full healing by the third day of treatment.

Mounce et al. described the antiviral effects of curcumin in which they demonstrated that adding curcumin before infection reduced the virus titer by much more than 0.5 log10 without causing toxicity. Curcumin revealed an IC50 of 1.9 M for Zika and 3.89 M for Chikungunya, respectively [3].

3.3. Allium sativum L.(Garlic)

Khubbar et al. reported that garlic is one of the most effective natural treatments against a wide range of viruses. Immuno-modulatory effects of this healthful spice are attributed to flavonoid and organosulfur molecules. Severe acute respiratory CoV-2 structural protease helps speed up viral multiplication. The active site areas of this serine-type protease establish hydrogen bonds with garlic bioactive, which suppresses the COVID-19 outbreak. Therefore, they demonstrated that Garlic and its derived products used regularly as an adjuvant therapy may alleviate side effects and toxicity of the main treatments while lowering the amount required [4].

3.4. Azadirachta indica (Neem)

Using simulated molecular binding investigations, Roa et al. determined the effects of particular small molecules of neem on human and viral proteins related to several pathways. The findings of their investigation showed that the naturally occurring neem compounds Gedunin and Pongamol showed significant binding energies against dengue virus protein, thereby indicating that they might operate as possible Dengue virus treatments [5].

3.5. Ocimum basilicum (Basil)

Nandi and Khanna explained how thymol, a naturally occurring substance in basil worked in A549 cells to prevent influenza. They used the MTT test to determine the toxicity of thymol, and they found that 50% of the minimal toxic concentration was at 49.4 g/ml. Quantitative RT-PCR and western blotting were used to evaluate the inhibiting effect of thymol. The results of their study revealed that only 50 and 25 g/ml of thymol treatments demonstrated suppression of expression at the RNA and protein levels at 24 hours when compared to the control.

4. DISCUSSION

There is a growing demand for antiviral compounds since treating viral diseases with conventional antiviral drugs as frequently as possible induces viral obstruction. Viral contaminations are being remedied entirely with present antiviral treatment with unfavorable clinical effects. It is well-accepted that plants offer immense potential for treating a wide range of infectious diseases. Eliminating viral infections is challenging because there are still several viruses that need efficient antiviral medications and vaccines for prevention. It is critical to

continue developing effective antiviral chemotherapeutic drugs that are cost-effective and have few side effects, and so that can also be used in conjunction with other treatments to enhance the treatment of patients. Because there are no preventive vaccines or active antiviral treatments available to treat the symptoms of several viruses, eradicating these viral infections appears difficult and troublesome. Nevertheless, the variety found in natural products is a great resource for the development of new structure-activity relationships, novel antivirals, and efficient therapeutic/protective approaches to viral diseases. There are many advantages of herbal treatments over synthetic treatments which are illustrated in Figure 3 below.

A considerable portion of the global population relies on herbal medicine for at least primary health care since its usage is particularly prevalent in underdeveloped nations. It raises the question of why herbal medicine is not utilized more commonly as authorized therapies in the developed world given the study and proof of some efficacy in treating viral infections with it. The fact that these medications have not been subjected to adequate testing or monitoring throughout patient usage is one major factor. As a result, it is uncertain how, if at all, these treatments work to treat viruses.A variety of natural materials and herbal compounds have been shown to have potent antiviral activity; these findings can be used to develop derivatives and therapeutic approaches.

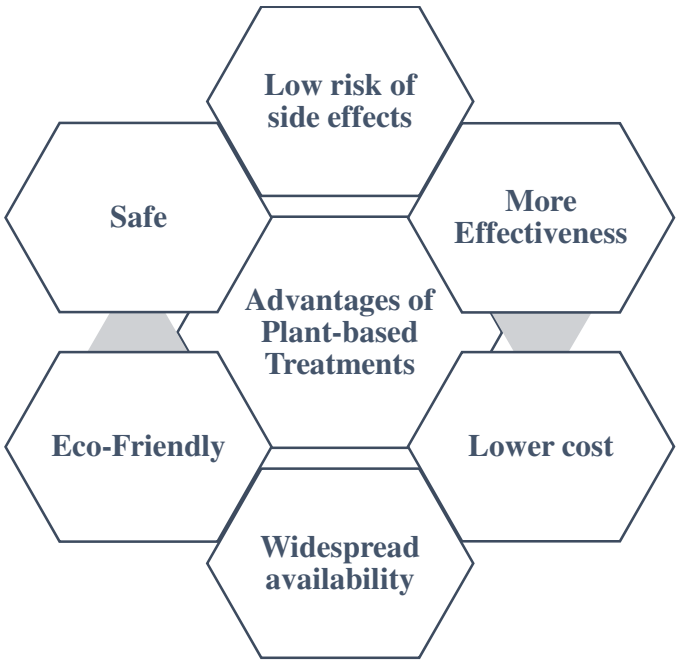

Figure 3: Illustrating the Advantages of Plant-based Treatments over Synthetic Drugs.

5. CONCLUSION

Many viral infections and diseases are still fatal and/or untreatable, even though some can be controlled with life-prolonging medications, which seem to be costly and out of reach for the majority of people. As a result, one of the top universal situations in drug research is the development and implementation of effective, safe, and low-cost antiviral compounds. This review provides evidence of different plant species having anti-viral activity. However, there are

still limitations, for example, the information about the effects of medicinal plants on biological systems is lacking. Only indigenous people have had experience with a specific plant or phytochemical to cure a condition.

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CHAPTER 13

A COMPREHENSIVE DISEASE OF EARLY CLINICAL DIAGNOSIS AND MANAGEMENT OF HUNTINGTON'S DISEASE

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ABSTRACT:

Huntington's disease (HD) is a kind of Neurodegeneration that is inherited in an autosomal dominant manner and is an uncommon genetic illness. Although Huntington's disease (HD) has a recognized genetic cause, numerous alternative approaches are believed to be connected to Neurodegeneration, and numerous pre-clinical and diagnostic research studies have been carried out to evaluate the efficacy of treatment interventions targeting some of these processes. Although many studies examining novel approaches with the potential to be disease-modifying strategies are still being conducted at the pre-clinical level, accepted healthcare studies may aid in the identification or precision of alternative therapies that are probable to enhance the quality of life for those with HD. This study concentrates on the early phases of Huntington's disease a neurological illness that is inherited in an autosomal dominant manner, and the diagnostic methods and pharmaceutical treatments now available for those with the disease. This study also focuses on diagnostic techniques and pharmacological therapy options for the early stages of the illness. Given the lack of success in finding a cure or altering existing treatments, this overview will focus only on symptomatic and supportive measures.

KEYWORDS:

Huntington's Disease (HD), Dystonia, Dementia, Motor Symptoms, Neurodegeneration.

1. INTRODUCTION

George Huntington identified Huntington's disease (HD) in 1872 as a kind of progressive neurodegeneration that is passed down mostly via the maternal line. Huntington's disease (HD) is a hereditary neurodegenerative condition that causes motor, cognitive, and behavioral symptoms. In the initial stages of Huntington's disease, neuronal death occurs mostly in the caudate nucleus. This is due to the functional and structural alteration of a ubiquitous protein called huntingtin[1]. The condition affects approximately 1 in 10,000 people, frequently manifesting itself in middle life (though the age at which symptoms first appear may vary widely), and typically lasting for approximately 20 years [2]. Progressive motor abnormalities, behavioral problems, and cognitive impairment are the results of Huntington's disease is a rare genetic neurological disorder. It's possible to get an HD treatment at any point in one's life, although it often happens around the time of middle adulthood. Although HD worsens with time, even in its earliest stages, it may cause mild symptoms such as involuntary movements, trouble with executive skills, and depression [3].

However, this does not prevent these people from continuing to live on their own. Patients need care as the condition advances. As a result, they can lose their ability to drive and/or work.

Coordination and the ability to solve problems deteriorate and falls become more often. Late-stage HD patients may lose the ability to talk, swallow, and move on their own accord, become bedridden, and rely on feeding tubes as their condition progresses. Further, dementia at this point in the course of the illness is often severe and may impact all facets of cognition. Infections, especially aspiration pneumonia, are the leading cause of mortality, occurring at a median of 18 years following the beginning of symptoms [4].

Although there is currently no medication shown to delay or slow the course of HD, treating chorea symptoms based on the revealed neurochemical pathology may be beneficial in some individuals and may have a positive effect on motor function, quality of life, and safety. Dystonia, other movement problems, and the non-motor features of HD might all be targets for clinical therapy [5]. Approximately 3% to 7% of the population of every 100,000 people will have the full clinical condition, whereas roughly 20% of the population of every 100,000 people will be carriers of the faulty gene. Both walking and agility are severely hampered by dementia, a loss of muscular coordination, and the aberrant, abrupt, jerky motions known collectively as chorea. Although chorea may appear at any time from infancy to old age, it most often develops in the middle years (around 33–44 years of age) [6].

The caudate nuclei, which are found in the lateral ventricle of the brain, are particularly vulnerable to degeneration in HD since they are a component of the basal ganglia. The putamen is less likely to show signs of degeneration than the caudate nuclei, which might show mild to severe symptoms. In addition to the lack of gliosis in the early stages, severe disease is characterized by higher neuronal loss from the caudate and also the formation of the grey matter of the caudate containing reactive astrocytes and microglia. Neostriatal neurons and glial cells that have persisted include mutant Htt in their cell bodies and synapses. Htt, interestingly enough, is not exclusively found in the brain but is instead a widely distributed protein [7].

2. LITERATURE REVIEW

Manon van Kampen et al. stated in their study that The Netherlands developed Passivities of daily living (PDL) for chronic patients. PDL is patient-centered and focuses on stability and permanent impairments. One late-stage HD patient from Atlanta's HD center is included. Two weeks of observation and monitoring. In the first week, typical attention is given. In week 2, PDL-trained caregivers wash and clothe the patient. PACSLAC-D measures patient pain and discomfort. The BORG Rating of Perceived Exertion Scale measures care's physical strain. The author expects late-stage HD patients to feel decreased pain and suffering with PDL vs. conventional treatment. The author also anticipates less physical hardship for caretakers [8].

Researchers Marie N. Hellem and colleagues used fluorodeoxyglucose (FDG) positron emission tomography (PET) and magnetic resonance imaging (MRI) of the brain to examine structural and metabolic brain anomalies in premanifest HD gene-expansion carriers and to determine whether metabolic issues precede structural abnormalities. The author selected 21 presymptomatic HD gene-expansion carriers and 17 control subjects from the Neurogenetics Clinic at Rigshospitalet in Denmark. Added to the (cytosine, adenine, guanine) and CAG was repeating locus 39 and motor 5 on the Unified HD rating system. In HD gene expansion carriers, striatal metabolism was reduced ($p=0.028$) compared to gene-negative controls, but striatal volume was unaffected. There was a strong relationship between striatal metabolism and CAG-Age-Product (CAP) score, as well as striatal volume and CAP scoring system. Heightened ventral striatal volume, and decreased metabolic rate. To better understand the dynamics of change, research on larger

cohorts utilizing hybrid FDG-PET/MRI is required the author concludes that striatal hypometabolism precedes atrophy [9].

James A. Bourgeois O.D et al. discussed in their study that in Patients with agile the effects of a CGG extended form in the permutation part of the gene for "fragile X mental retardation 1 (FMR1)", the known cause of X-associated tremor/ataxia syndrome (FXTAS), a brain condition, were studied. FXTAS patients were evaluated neurologically, psychiatrically, and neuropsychologically. Seven instances had dementia, while seven had mood and/or anxiety issues. Neuropsychological testing revealed 12 impairments. Physicians examining dementia patients should examine this newly discovered illness, particularly in individuals with mobility issues and a mental retardation family history. If FXTAS is suspected, doctors may do FMR1 DNA testing; positive test results need MRI, neurology, and genetic counseling [10].

Jane Simpson et al. evaluated in their study the usefulness of the concept of irritability in terms of those who suffer from Huntington's illness. In November 2018, the author looked through Scopus, Web of Science, Academic Search Ultimate, PsycINFO, and CINAHL for relevant articles, and these results informed a scoping literature review. The first return included 453 documents, but only 40 were deemed reviewable. The 40 studies showed various features of irritability in HD patients that affect its reliability as an independent entity. A gold standard for irritation has not been found, hence it is rated inconsistently in the research. Evidence suggests that irritation is more of a multifaceted notion than a pathogenic state in HD significantly related to melancholy and anxiety. The author stated that the clinical literature lacks an agreement on how to operationalize and quantify irritation in HD patients. Further study is needed to understand irritability's behavioral, cognitive, and emotional components in HD [11].

Stefan Kloppel et al. stated in their study that clinically, presymptomatic Huntington's disease is characterized by irritability, depression, and anxiety (HD). While undergoing functional magnetic resonance imaging, the participants (16 PSCs and 15 controls) were instructed to choose which of two alternate squares was shows to them. People were often informed they were incorrect even if they correctly identified the bigger square. The differences in size were barely perceptible, but they were enough to make the criticisms sound reasonable. The findings suggest that PSCs have abnormal emotion processing circuits due to reduced sensitivity to cues about their own or others' emotional states. Irritability and other HD-related mental symptoms may arise later in life as a result of this impairment [12].

3. DISCUSSION

Common motor symptoms, which may or may not be accompanied by a family background of HD are used to make a diagnosis of HD. Changes in personality, as well as cognitive and behavioral symptoms, might be apparent at the moment of presentation or even before a diagnosis of HD is made. Confirming the treatment plan in symptomatic individuals could be accomplished through the use of a DNA test that reveals the htt gene has undergone an aberrant CAG expansion. People at high risk for HD who are treated by experienced physicians may undergo DNA analysis with adequate genetic counseling as well as the patient's request.

Recently, scientists have gained a deeper understanding of the pathophysiological mechanisms that underlie neuronal failure and, eventually, the distinctive neurodegenerative pattern seen in HD. Despite this progress, however, no successful disease-modifying therapy has yet been established. As a result, treatment is still symptom-based and limited to individually tailored

forms of supportive care. Still, it's important to stress that HD symptomatic therapy now is far more advanced than it was, say, 20 years ago. Nonetheless, there should be a significant increase in the amount of emotional and social help provided to patients and their loved ones [13].

Symptoms often appear between the ages of 30 and 40 and affect both sexes equally. Initiation of HD symptoms occurs between the ages of 1 and 90. Juvenile onset describes the subset of instances in which symptoms appear in people under the age of 20. Most instances in children are passed on from father to son, and although chorea is a common symptom, patients may also show Parkinsonian symptoms such as bradykinesia, dystonia, tremors, and cognitive deficits. When diagnosing HD, the Westphal subtype is used if the patient exhibits more hypokinetic symptoms (such as bradykinesia and dystonia) than hyperkinetic ones (chorea) [14].

3.1.Neuroimmunology: The Brain's Defense Against Infection:

It was formerly believed that the brain could not mount humoral or cellular immune responses, making it an immunologically privileged organ. The blood-brain barrier (BBB), which protects the central nervous system (CNS) from the rest of the immune system, lends more support to this theory. However, this is only the case if there is no underlying immune system disorder or inflammatory condition affecting the brain and spinal cord. The central nervous system's immune system is triggered in response to trauma, axotomy, ischemia, and degeneration. In a normal brain, microglial cells the CNS's resident macrophages lie dormant and do not actively defend against pathogens. In response to stimulation, microglial cells alter their surface antigen expression and release inflammatory cytokines [15]. Myeloid progenitor cells, Microglial cells, astrocytes, T cells, and neurons near begin talking to one another after the production of cytokines including IL-6, IL-12, and TNF-. Extensive brain injury and induce apoptosis may result from the production of these inflammatory cytokines, as well as from chronic inflammation. These effects may be exacerbated by NMDA-mediated excitotoxicity and caspase activation[16].

3.2.Huntington's Disease Manifestations:

Huntington's disease (HD) manifests itself primarily via motor, cognitive, and mental signs and symptoms, known together as the nuclear sign and symptoms. Among the less-recognized but commonly devastating HD characteristics include extreme weight loss, sleep and circadian rhythm problems, and autonomic nervous system dysfunction. Average onset ages are in the 30s to 50s, with a wide age spread (from 2 to 85) possible. The average lifespan is 17-20 years with this condition. As the illness worsens, patients become more reliant on others for care and eventually pass away. Pneumonia is the leading killer, followed closely by self-harm.

i. The indications and symptoms of motor dysfunction:

Dystonia is indicated by aberrant posture brought on by slow, tight motions that raise the muscular tone, such as torticollis or the rotation of the trunk or limbs. The earliest motor symptom of Huntington's disease is often a kind of dystonia, such as torticollis. Tics are another kind of involuntary movement, and they are similar to those found in people with Tourette syndrome; however, they are unusual. It is possible for cerebellar symptoms, such as hypo and hypermetria, to manifest on an intermittent basis. The way they walk is often compared to that of someone who is inebriated or who has cerebellar ataxia. It takes a lot of practice to tell the

difference between choreographed walking and ataxic walking. Signs in the shape of a pyramid (the Babinski symbol) may be seen inadvertently[17].

Dystonia is characterized by aberrant posture brought on by slower movements and increased muscular tone, such as torticollis, as well as twisting of the trunk or limbs. Dystonia is often the presenting motor sign of Huntington's disease (such as torticollis). Tics, which are involuntary muscle movements similar to those observed in Tourette syndrome, are another example of such behavior but are far less common. Similar to the appearance of hypo- and hypermetria, cerebellar symptoms might pop up at random. One's gait may be compared to that of someone who is inebriated or who has cerebellar ataxia. Choreographed walking and ataxic walking are difficult to tell apart. The presence of a pyramidal sign (also known as a Babinski signal) is coincidental. Tongue sticking out, mouth slightly open, and pouting lips [18].

Behavioral and mental health indicators: It is very uncommon for psychiatric symptoms to present themselves at the onset of motor symptoms in the initial stages of the illness. Psychiatric symptoms are often evident at the earliest stages of the disease, sometimes before motor symptoms appear. Psychiatric symptoms might be present in anywhere from 33–76% of patients, depending on the research design. These symptoms and indicators often have a profoundly deleterious effect on both individual and family functioning. Most people experience some kind of depression. Difficulty in diagnosis is compounded by the fact that HD is also characterized by a decrease in appetite, apathy, and physical activity. Low self-esteem, guilt, and worry are common symptoms [19].

Difficulty in diagnosis is compounded by the fact that HD is also characterized by a decrease in appetite, apathy, and physical activity. Common symptoms include a lack of confidence, excessive self-criticism, and excessive worry. Disease progression correlates with apathy but not with anxiety or sadness. Early symptomatic people and premanifest gene carriers are at increased risk for suicide. The highest rates of suicide attempts and completion occur roughly when independence declines and the gene test is administered. In addition, 34%-61% of people experience anxiety, often because they don't know when or how their illness may manifest. Both irritability and aggressiveness are symptoms of obsessive-compulsive disorder, which may significantly disrupt a patient's daily life. In hindsight, irritability is the initial indicator; nonetheless, it manifests itself in all phases of the disease [20].

ii. Dementia:

Cognitive decline is another important symptom of HD, and it may occur before the most severe phases of the disease, the emergence of motor symptoms might be very mild. Alterations to the brain's structure and function, especially in the area of executive functioning. When everything is running smoothly, our thoughts and actions are planned and purposeful. Patients with HD are unable to recognize what is important and what is unimportant, a skill that is normally possessed by healthy people. The patients have lost the ability to organize their lives and carry out formerly routine tasks. They become unable to shift their mindset and adapt to new circumstances. It becomes tricky when doctors make mistakes and patients don't respond the way they used to or as those around them anticipate they would. There is a minimum of foul language. There will be a loss of memory, although semantic memory may be preserved to some degree. There is a significant slowing of all psychomotor functions.

The research for innovative and efficient treatments for HD continues to be a top priority because there is currently no solution for this devastating condition and the medications that are now available for HD mostly concentrate on the management of symptoms. Within the context of this situation, the potential effectiveness of a large number of different treatment methods for HD is now being investigated via clinical studies. Intervention and the possible method of action are shows by it, as indicated in Figure 1.

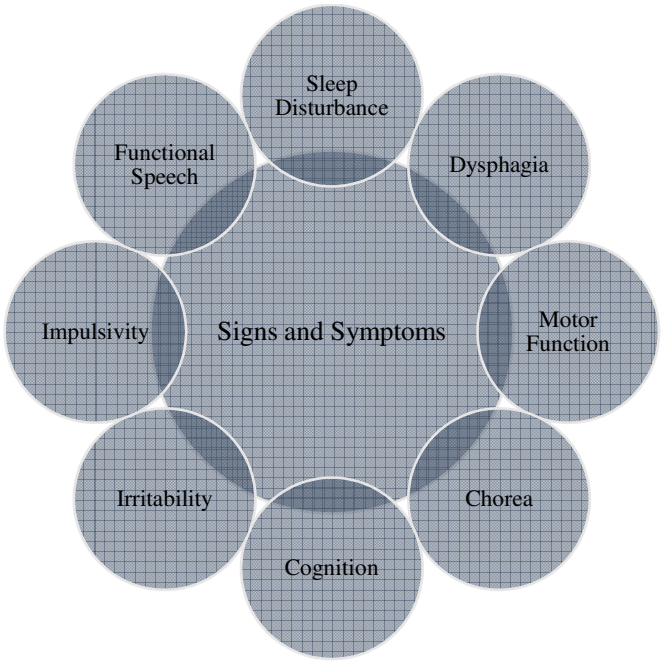

Figure 1: An overview of the clinical studies that are currently being conducted for Huntington's disease.

3.3.Experimental Therapeutic Strategies in Pre-Clinical Settings:

Although a genetic foundation for HD has been discovered for almost 30 years, therapy options are still limited despite progress in understanding the processes underlying the illness. There is now no treatment that will stop the progression of this disease, but there is hope that future clinical studies may lead to the identification of a cure or at least the identification of treatments that will significantly enhance the lives of individuals already afflicted. In light of this, significant efforts are still concentrated in the pre-clinical stage, with several research presently looking at the possible benefits of novel therapeutic approaches.

3.3.1. Neurotrophic Factors:

iii. "Brain-Derived Neurotropic Factor (BDNF)":

Restoring BDNF levels may be done in many different ways. So, the author zeroes focus on how to artificially boost these neurotrophin levels, whether by protein infusion, genetic approaches, or pharmaceuticals, while increasing BDNF levels is attainable via nutritional changes, environment enrichment, and physical exercise [21].

Several researchers have employed animal models to study HD to examine the impact of increasing BDNF protein expression or gene expression. BDNF mini-pumps, BDNF-expressing adenovirus intrastriatal injections, and BDNF-expressing cell implantation are all potential methods of administration that have all been demonstrated to produce striatal neuroprotective properties and cognitive improvements. Although these findings are encouraging, they must be interpreted cautiously because of the side effects associated with mini-pumps. There is, to start, the possibility that this procedure's level of invasiveness will make it impractical or impossible to use in a clinical context. Furthermore, the infusion site is likely to become the origin of a steep concentration gradient, it might lead to alterations in the infused tissue as well as unpleasant side effects including swelling. For this reason, clinical investigations in HD are now looking more favorably at other approaches to successfully give appropriate concentrations of BDNF to the brain [22].

iv. Glial Cell Line-Derived Neurotropic Factor (GDNF):

Dopaminergic neuronal growth and neuroprotection both rely on GDNF, and it has been shows that GDNF is essential for both processes. A preliminary investigation employing a QA lesion model found that administering GDNF Intra Cerebro ventricular 30 minutes before QA injection reduced neuronal degeneration. While these results seemed encouraging, it was still unclear whether or not GDNF might be neuroprotective after quinolinic acid had already caused damage to the striatum. While GDNF may not be able to reverse the damage already done to the striatum, it is not unreasonable to hope that it may alleviate some of the symptoms. Later research evaluated whether or not increasing the expression of growth differentiation-promoting factor (GDNF) using an AAV containing the GDNF gene (AAV-GDNF) would have any protective benefits. When given 3 weeks before quinolinic acid, AAV-GDNF prevented the death of striatal neurons [23].

3.4.Pharmacological methods:

Since the timing of symptomatic treatment does not affect the neurodegenerative process, it should be carefully addressed depending on the requirements of the patient. The goal should be to provide the highest possible standard of living. There has to be frequent, individualized evaluations of both intended benefit and negative effects. Early in the course of the illness medication treatment should be commenced only at the patient's request and not at the urging of family members who, for example, may be ashamed of the patient's involuntary movements or unable to stand by while they perceive their loved one is in pain. Anticonvulsants, benzodiazepines, glutamate antagonists, glutamate reuptake inhibitors, monoamine oxidase inhibitors, and medications that deplete these neurotransmitters are all examples of neuroleptics are only a few of the many medications that have been tried and shows to be effective in reducing choreatic movements. However, double-blind controlled therapy studies are urgently required as there is not enough information to provide suggestions for the long-term management of HD-related movement disorders.

v. Tetrabenazine:

Tetrabenazine (TBZ), a monoamine depletory, is recommended for the treatment of chorea in HD by both American and European recommendations. The danger of tardive dyskinesia with TBZ is lower than with regular or atypical neuroleptics. In the early phases of choreatic movement disorder, TBZ is a viable choice for medical therapy since it is often well tolerated. 37

Depression, Parkinsonism, sleeplessness, akathisia, and sedation are all possible adverse reactions. The recommended starting dose of TBZ is 12.5 mg daily; it may be raised by 12.5 mg three times a day, once a week. Although the daily maximum is debatable, most experts agree that it shouldn't exceed 100 mg.

vi. Neuroleptics:

Neuroleptics, which work by inhibiting dopamine transmission, may be favored if chorea is accompanied by other mental symptoms such as agitation or psychosis. Even though atypical neuroleptics are preferred because of their lower risk of side effects, traditional medications like haloperidol, fluphenazine, or chlorpromazine may be necessary for patients with really severe chorea or psychosis that is characterized by hostility. If a patient with HD develops Parkinsonian-like symptoms, they need immediate medical intervention. Parkinsonism symptoms may become more severe when using most neuroleptic medications. Chorea in HD patients may be treated with one of many atypical neuroleptics. Chorea has been claimed to improve with the use of olanzapine, risperidone, and aripiprazole, albeit the evidence is limited.

vii. Benzodiazepines:

It is well-known that chorea may intensify in the face of psychological stress or other similar conditions. Therefore, benzodiazepines may be introduced to the treatment plan gradually to lessen the severity of the emotional side effects. Yet, the potential for drug misuse and addiction must be taken into account.

viii. Amantadine:

Since current study findings are inconsistent, amantadine's effectiveness (suggested dosages: 300–400 mg/day) in the management of chorea is unclear. As a result, this NMDA receptor antagonist may be a choice for certain individuals with chorea. However, although it is suggested by the American Academy of Neurology recommendations as a second-line treatment following tetrabenazine, in our practice it is not given at the onset of symptoms.

4. CONCLUSION

HD is characterized by a predominance of immunological activity in both the brain and the rest of the body, a progressive age-dependent neuropathological condition. Neurodegeneration and persistent neuroinflammation are hallmarks of HD clinical symptoms, which seem to be triggered by aggregation of mutant Htt. Keeping tabs on the disease's development would be made easier with the support of research that identifies new immunological biomarkers and their plasma and central nervous system concentrations. Complement overexpression in presymptomatic HD may serve as a helpful immunological biomarker for tracking the development of the illness. Clinicians can treat the symptoms of this terrible illness until clear neuroprotective therapies are established. Although there is strong evidence that TBZ is effective in treating difficult chorea, different individuals will have different responses to different medications, therefore the decision should be made on an individual basis. To create and evaluate treatments that may halt or reverse HD's progression, the researchers must find biomarkers of its progression that are simple to acquire, trustworthy, and resilient. Many hopeful therapeutic compounds are now in various stages of development, thus there is still hope for better therapy or even preventative medication in HD.

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CHAPTER 14

AN ASSESSMENT OF *ACARBOSE* FOR EFFECTIVE MANAGEMENT OF DIABETES MELLITUS

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ABSTRACT:

An effective way to manage postprandial blood sugar is to take acarbose, an inhibitor of -glucosidase. It works by inhibiting small intestine brush border glucosidase competitively and reversibly, preventing the degradation of starch and sucrose, as well as a delay in the digestion of fructose and glucose. Due to the mechanisms of action of acarbose, dietary starch content may affect hypoglycemic response.

Chinese people follow a traditional Eastern diet that emphasizes fruits, seafood, whole grains, legumes, and vegetables. This study examined Acarbose's history of use and its current status as a diabetic therapy option. The main aspects of acarbose that were examined in this study were its tolerance and safety for use in the management of pre-diabetes and diabetes type 2. Acarbose medication over a long period may be beneficial for those with prediabetes and type 2 diabetes. Acarbose is likewise safe and well tolerated, with few significant side effects, according to the author's study.

KEYWORDS:

Acarbose, Diabetes Mellitus, Glucose level, Insulin.

1. INTRODUCTION

Acarbose is an anti-diabetic medication commonly prescribed for type 2 diabetes and is sometimes used to treat prediabetes as well. It is marketed under the brand names Glucobay (Bayer AG), Precose (Bayer Pharmaceuticals), and Prandase (Pfizer Canada) in China and Europe (Bayer AG), and its chemical structure of Acarbose is shows in Figure 1. It's inexpensive and common in China, but not in the United States.

One doctor said the drug's lack of efficacy in the United States means its diarrheal and flatulent side effects aren't worth it. A large Asian population with type 2 diabetes found "acarbose to be effective, safe, and extremely well absorbed." These contrasting views may arise from the fact that acarbose seems to be much more beneficial for those who have a moderately high-carbohydrate Eastern diet [1].

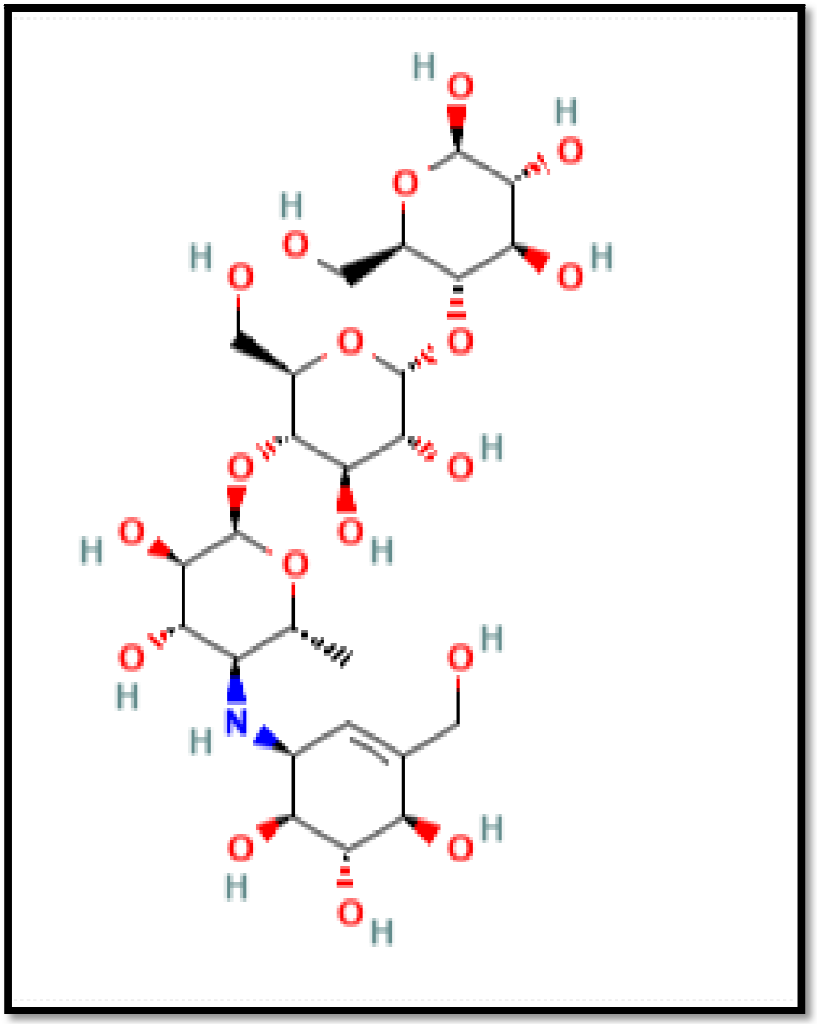

Figure 1: Displays the 2-D chemical structure of *Acarbose*.

It prevents glucose from being released from bigger carbs by inhibiting the intestinal enzyme alpha-glucosidase. Includes a reducing end that is maltose and an acarviosin moiety. The glucosidase cyclomaltodextrinase produced by the gut bacteria Lactobacillus plantarum breaks down acarbose into maltose and acarviosin. Type 2 diabetes mellitus (T2DM) is increasingly prevalent, making it a serious public health concern worldwide. However, its origin and development remain mysterious. Maintaining tight control of blood sugar levels in diabetic individuals is an important part of treatment. The research suggests that the consequences of diabetes may be mitigated if blood glucose levels are kept under control [2]. In those with type 2 diabetes, the body uses insulin inefficiently, which results in uncontrolled blood sugar levels and is treated with acarbose (together with diet alone or diet plus additional drugs). To treat diabetes, acarbose inhibits enzymes responsible for converting meals into glucose (sugar) in the blood. Reducing the rate at which food is digested may reduce the rapid increase in blood sugar that occurs after eating [3].

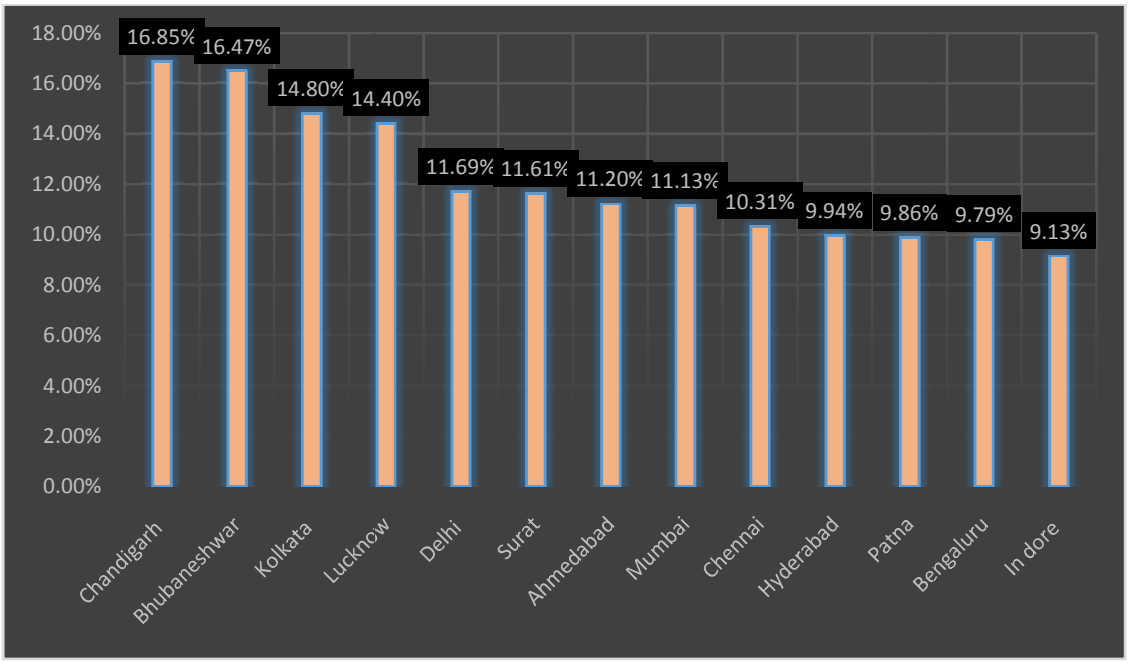

Figure 2: Displays the Estimated percentage of Indian respondents who will have diabetes in 2020, subdivided by city.

In 2020, about 18 percent of respondents from the city of Chandigarh had diabetes, according to the findings of a large-scale study performed throughout India. As of the same year, the next highest percentage of diabetes responders came from Bhubaneshwar, at almost 16.5 percent, followed by more than roughly 15 percent from Kolkata. This concerning pattern was associated with harmful behavior, as seen in Figure 2. Type 2 diabetes will be one of the most difficult medical problems to solve in the new millennium [4]. There were 366 million individuals with diabetes in 2011, and by 2030, that number is expected to climb to 552 million, according to projections from the "International Diabetes Federation". Type 2 diabetes, which makes up more than 90% of all instances of the condition, is becoming more commonplace worldwide. The fact that the sickness is being discovered at an earlier stage is the only positive aspect of the rising number of new cases. This is crucial since it's the only method to prevent or at least postpone serious consequences for the patient.

Long-term disability and death may result from diabetes and high blood sugar symptoms including nerve damage, loss of eyesight, heart disease, stroke, and kidney failure. Monitoring daily blood sugar levels frequently, taking any prescribed medications, making any necessary adjustments to your lifestyle (such as diet, exercise, and smoking cessation), and keeping your A1C in the normal range may all contribute to better diabetes management. Treatment of diabetes may lessen the probability of health issues such as hypertension, cholesterol overload, diabetes, neuropathy (tingling or numbness in the limbs or feet), vision changes or loss, gum disease, and diminished sexual drive in men and women.

When dietary and exercise adjustments alone aren't enough to keep blood sugar levels in the normal range, pharmacological treatment options are part of the toolkit for managing type 2 diabetes. For almost 20 years, acarbose's alpha-glucosidase inhibitor has been a cornerstone of type 2 diabetes care, especially at its onset. Several nations have given their blessing to the

management of prediabetes utilizing it. In this report, we focus on patients' perspectives on acarbose treatment for a range of medical issues.

2. LITERATURE REVIEW

Acarbose, an inhibitor of alpha-glucosidase, was used, the authors of the research Jean-Louis Chiasson et al. looked at the impact of treating individuals with impaired glucose tolerance (IGT) by lowering their blood sugar after meals. 1429 IGT patients were randomized, and only 1368 were available for the more concise intent-to-treat analysis since 61 were omitted due to a lack of IGT or post-randomization information. Participants included both males and females, having a mean (SD) BMI of 30.9 and a median (SD) age of 54.5 (4.2). During the 3.3 (1.2) years of observation, patients were analyzed. Hypertension (140/90 mm Hg) and also included are significant cardiovascular events such as heart attacks, cardiac deaths, heart failure, strokes, and problems with blood vessels in the brain and extremities. The author concludes that acarbose significantly reduces use in the treatment of IGT raising the danger of cardiovascular disease and high blood pressure [5].

In their research, Qingrong Pan et al. evaluated how metformin and acarbose medication affected the excretion of albumin in the urine of Chinese patients who have just been diagnosed with low-grade albuminuria and diabetes. There were a total of 589 people who had just been diagnosed with type 1 diabetes, and they were divided into two groups: Group I (UACR 10 mg/g; n=331) and Group II (UACR 10-30 mg/g; n=258). After 48 weeks of treatment with metformin and acarbose, the effects on the UACR, blood pressure, body mass index, blood sugar, lipids, and the "homeostasis model assessment of insulin resistance (HOMA-IR)" were evaluated. Diastolic blood pressure, hyperglycemia, "low-density lipoprotein cholesterol," and the "homeostasis model assessment index (HOMA-IR)" were all significantly higher in Group II compared to Group I ($P < 0.05$). Group II, which used metformin plus acarbose, had a decrease in UACR ($P<0.001$), although acarbose was more effective ($P<0.05$). While both groups saw considerable improvements in body mass index, hyperglycemia, hypertension, and HOMA-IR, UACR was not significantly decreased in Group I despite these improvements. In Chinese people who had just been diagnosed with type 2 diabetes but weren't yet receiving treatment, “low-grade albuminuria (UACR 10–30 mg/g)” was linked to metabolic traits. Metformin and acarbose lower albumin excretion [6].

The diabetic risk was lowered by 36% in those with IGT who were treated with acarbose according to research by Sophie Delorme and Jean-Louis Chiasson study in the journal Diabetes Care. The risk of cardiovascular events was also reduced by 49% in those who followed this diet. One study found that the development of acarbose treatment delayed certain people's carotid intima-media thickness increases by 50%. Last but not least, acarbose medication was linked to a 35% Acarbose is beneficial in controlling diabetes, as indicated by a meta-analysis of seven longitudinal studies, and it also reduces the risk of cardiovascular disease. Acarbose's hypothesized heart-protective effect may result from its ability to mitigate the oxidative damage brought on by a postprandial increase in blood sugar [7].

In the randomized STOP-NIDDM study, Uwe Zeymer et al. showed that reducing Acarbose treatment for persons with reduced glucose tolerance may benefit from taking measures to reduce their blood sugar after meals. The results of an electrocardiographic sub-study that analyzed the impact of acarbose on silent ischemic episodes according to the Minnesota code. ECG substudy comprised 1181 individuals. 72 individuals demonstrated substantial baseline-to-

end ECG alterations, Acarbose patients numbered 33, whereas placebo patients numbered 39. Myocardial infarctions were significantly more common in the placebo group, but no other ECG abnormalities were different between the groups "(P=0.07 with Fisher's Exact test and P=0.023 with Chi-square test)". Patients with poor glucose tolerance were shows to benefit from Acarbose's ability to lower postprandial hyperglycemia and hence avoid silent myocardial infarctions in this study of prospective intervention. There needs to be a pilot study of this approach in populations at high risk [8].

3. DISCUSSION

Medical practitioners in the United States and throughout the globe are beginning to treat people with type 2 diabetes mellitus, which is a serious public health issue, developing at younger and younger ages. When used in conjunction with either diet alone or diet with exercise, the medication acarbose is efficient in treating type 2 diabetes mellitus. This exercise is useful for individuals of a multidisciplinary team that administers acarbose to patients since it provides a thorough overview of the drug's indications, contraindications, interactions, surveillance, and other treatment considerations. Acarbose is an oral antidiabetic medication that does not affect insulin. Acarbose has a unique method of action that allows it to regulate glucose metabolism all day long by aiding in the generation of insulin, in addition to its direct and vital involvement in the absorption of carbs from meals into the blood[9].

3.1.Mechanism of Action:

Acarbose, a complex oligosaccharide, inhibits pancreatic alpha-amylase and intestinal membrane-bound alpha-glucoside hydrolase competitively and irreversibly. In the small intestine, alpha-amylase from the pancreas acts as a digestive catalyst for starch and cellulose, converting them into simpler sugars. Alpha-Glucosidase Hydrolase Activity in the Small Intestine converts complex carbohydrates like sucrose and maltose into simpler sugars like glucose and fructose at the intestinal brush border. Acarbose lowers postprandial glucose levels by slowing the digestion of carbs, which reduces glucose absorption. By elevating glucagon-like peptide-1, acarbose may lead to significant weight reduction . Drugs that do not reduce insulin levels have been the subject of substantial study for their potential to aid persons with type 2 diabetes in their weight reduction efforts, as shown by the work of Lazzaroni E. et al. Weight loss with acarbose was less than 3.2%, with canagliflozin ranging from 3.2-5%, and with tripeptide being higher than 5% [10].

Although this, acarbose is now suggested in several recommendations for treating diabetes and is even favored above other oral glucose-lowering medicines because of its shows potential to lessen cardiovascular events. When used slowly, acarbose is typically well tolerated even though it might cause some gastrointestinal adverse effects including flatulence.

In addition to its antiplatelet actions, acarbose has been shown to promote vascular health. Last but not least, acarbose has been proven to produce euglycemia by reducing postprandial glucose and lipid surges and raising concentrations of "glucagon-like peptide 1 (GLP-1)". AGIs function in the digestive system like false carbs. They do this by inhibiting -glucosidase enzymes at the intestinal epithelium's brush border. These enzymes help break down complex carbohydrates like oligosaccharides and polysaccharides into simpler sugars like monosaccharides that the body may more readily absorb [11].

3.2.*Combination therapy:*

The addition of acarbose to the standard in some randomized studies, anti-diabetic medications like sulfonylureas, metformin, and insulin have been examined, in double-blind clinical studies conducted on People in China who have type 2 diabetes.

i. As a supplement to sulfonylureas, acarbose:

Patients with poorly controlled sugar who had been taking a fixed dose of sulfonylureas for 4 weeks before the questionnaire had significantly lower HbA1c and blood glucose levels after 12 weeks of medical intervention with acarbose 50 mg tid, according to a multicenter, randomized, double-blind study conducted in the People's Republic of China. These trials demonstrate that acarbose is an acceptable and effective therapy for Asians with uncontrolled type 2 diabetes despite dietary and sulfonylurea restrictions [12].

ii. Acarbose as a supplement to metformin treatment:

In addition to sulphonylureas and metformin, acarbose may help Type 2 diabetics in China have their blood sugar and hemoglobin A1C under control. Adults in Taiwan who suffer from type 2 diabetes have not shows improvement. For the last 12 weeks of treatment, patients who had been receiving lower doses of patients who were taking either acarbose (50 mg bid) or glibenclamide (2.5 mg bid) in addition to their metformin monotherapy (1,500 mg OD) were given increased dosages of both drugs. While both therapies lowered HbA1c levels, only acarbose resulted in statistically significant reductions in markers of oxidative stress "(MAGE; 5.6 mmol/L vs. 4.0 mmol/L, P0.001)", body mass index (BMI); "69.8 kg vs. 68.3 kg, P0.01)", and "serum triglycerides (1.2 mmol/L vs. 0.9)" [13]. The study's authors found that there was not a significant risk of hypoglycemia with the Acarbose with metformin in a fixed dosage combination. Thus, they hypothesize that it might be used to successfully treat type 2 diabetes [14].

iii. Acarbose as a supplement to insulin treatment:

Diabetic Type 2 Patients who lived in China and had an HbA1c of less than 6.5% were studied for their glycemic variability. Every patient received premixed insulin twice a day, and 86 individuals additionally took acarbose 50 mg twice a day for two weeks. A CGM system was used to examine each subject.

The MAGE, as well as the mean of daily variations, were both reduced by a substantial amount after combination treatment with acarbose compared to the group receiving just insulin "(40 and 15%, respectively, P<0.01 and P<0.05)". Furthermore, hypoglycemia episodes occurred far less often (2% vs. 24%, P<, 0.01). Researchers found that hypoglycemia episodes were reduced and glycemic variability was decreased with a combination treatment consisting of premixed insulin bid and acarbose [15].

Similar to the results of the research, further medication with 100 mg tid of acarbose improved insulin sensitivity and glycemic control in Asians with type 2 diabetes were not effectively managing blood sugar. Particularly, decreases in both 1-hour postprandial glucose "(1.33 mmol/L vs 0.67 mmol/L, P=0.029)" and HbA1c (0.5%) were observed more effective when paired with acarbose than when using a placebo alone [16].

3.3.Acarbose action mode and cardiovascular implications:

Acarbose's beneficial effects on blood glucose levels are seen in the decreased production of substances that promote atherosclerosis. Acarbose's immediate and secondary effects are summarized in Figure 3.

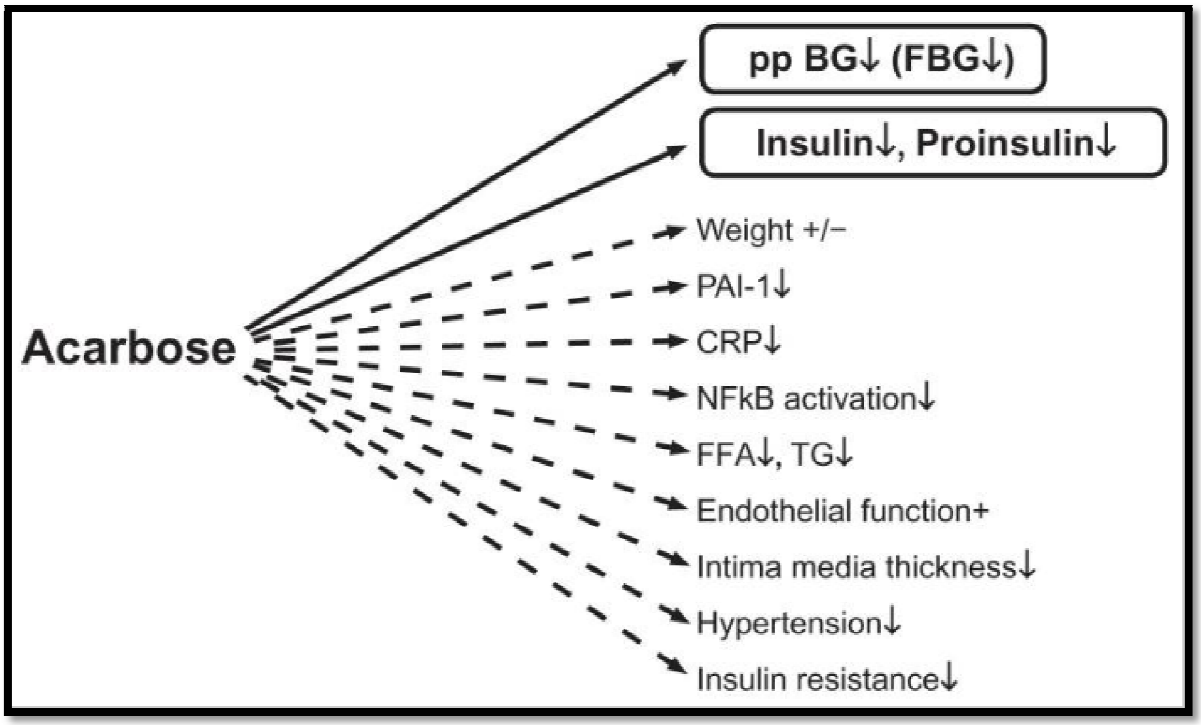

Figure 3: Acarbose affects hormones, metabolism, and inflammatory factors in different ways [17]**.**

Because of the increased synthesis of superoxide at high glucose levels, nitric oxide is less bioavailable, leading to a weaker vascular response and lessened vasodilation. An additional effect of hyperglycemia is an escalation in blood clotting and platelet aggregation. Thrombotic plaques arise when there is an increase in the production of substances involved in adhesion and the process by which monocytes attach to endothelial cells. C-reactive proteins and cytokines are produced at higher rates in people with hyperglycemia. Triglyceride levels, clotting time, C-reactive protein, nuclear factor kappa B, endothelial function, intima-media thickness, and blood pressure are all inflammatory markers that have all been reported to improve with acarbose administration in certain trials [18]. Even individuals with poor glucose tolerance exhibit higher arteriosclerotic alterations and enhanced cardiovascular health due to vasculotoxic processes that start at a relatively early illness stage. The STOP-NIDDM study is a placebo-controlled "(Study TO Prevent Noninsulin-Dependent Diabetes Mellitus)" study that showed that acarbose improved cardiovascular clinical outcomes [5].

3.4.Toxicity:

The overdose of acarbose will not result in hypoglycemia, but it may have more severe gastrointestinal side effects. When recovering from an overdose, patients should avoid consuming any carbs for 4 to 6 hours. Because acarbose inhibits the degradation of sucrose (table sugar) and delays glucose absorption, patients using acarbose in addition to other antidiabetic

medications should be told to use glucose in the event of hypoglycemia (gel, pills, etc.). In cases of severe hypoglycemia, it may be necessary to provide glucose intravenously or glucagon intramuscularly.

3.5.Improving Healthcare Team Results:

Acarbose is often prescribed for Diabetic Type 2 Patients. The medication has certain helpful applications, but it is not a very powerful agent when taken alone. Due to the drug's mechanism of action, stomach distress and bloating are those that people often report experiencing. As a result, it is the responsibility of the pharmacist, nurse, and certified diabetes educator to instruct the patient on proper medication administration. Patients should also be advised to avoid cola drinks, which may exacerbate stomach discomfort. The risk of hypoglycemia is quite low while using this medication, but if it does occur, alternative antidiabetic medications should be considered. The patient has to be treated for hypoglycemia and then advised on how to avoid future bouts of low sugar. An interdisciplinary group of medical professionals is ideal for administering acarbose treatment, as is the case with any other drug that regularly communicates about the patient's progress and any changes in their condition. This is the only way to effectively mitigate the drug's adverse effects.

3.6.Adverse Effects of Acarbose:

Diarrhea and abdominal discomfort are three of the unpleasant effects that occur most often. These negative GI symptoms may be amplified by eating a diet heavy in carbohydrates. For therapy, gastrointestinal symptoms often improve. Because of its potential for unpleasant side effects, acarbose medication adherence might be difficult. Acarbose treatment has been associated with increased levels of serum transaminases. In most cases, patients have no symptoms from their elevations, and they return to normal when pharmacological treatment is discontinued. Acarbose monotherapy should not result in hypoglycemia. However, when used with hypoglycemic antidiabetic drugs such as sulfonylureas or insulin, the treatment might raise the risk of hypoglycemia. Using an inhibitor of alpha-glucosidase has been linked to very uncommon incidences of pneumatosis cystoid intestinalis, according to post-marketing research.

Studying the effects of medication on muscle mass and function in patients with type 2 diabetes, Jiang L. et al. lower their plasma glucose levels in retrospective cross-sectional research [19]. When compared to drug-naive individuals and those receiving insulin, metformin, or sulfonylureas monotherapy, acarbose caused the greatest decreases in skeletal muscle indexes, physical functioning, and walking ability.

4. CONCLUSION

Acarbose seems to lower the incidence of cardiovascular risk with just a little increase in the risk of hypoglycemia. Tolerable gastrointestinal side effects from acarbose might be seen on occasion if the drug is begun at a low dosage and increased gradually. Acarbose, like metformin, is an excellent pharmacological alternative for avoiding diabetes in prediabetic patients and should be used as such.

Further, larger, longer-term studies examining acarbose in diabetes patients and other patient groups would be helpful to establish its health benefits and low toxicity. Maintaining its site of action over time is an additional benefit of acarbose therapy.

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CHAPTER 15

AN EVALUATION OF GINGER (*ZINGIBER OFFICINALE ROSCOE)* IN THE TREATMENT OF DEGENERATIVE DISEASES AND THE PREVENTION OF AGING

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ABSTRACT:

Ginger (*Zingiber officinale*) is a typical food additive that improves the flavor and taste of dishes, it is well known to include certain possible phytochemical components that may have beneficial medical properties. One of the most significant active components is a six-shogaol, while the other is a six-gingerol. Ginger may offer certain health benefits, such as antioxidant and anti-inflammatory properties, but research on its possible neuroprotective properties has gotten less attention. Increased lifespan has also contributed to an increase in the frequency of neurodegenerative disorders (NDs), which are characterized by comparable neuropathological indicators such as protein misfolding, oxidative stress, neuroinflammation, aging, degenerative illnesses, and ginger. Studies of osteoarthritis, type 2 diabetes Mellitus (T2DM), high blood pressure, Parkinson's disease (PD), Alzheimer's disease (AD), and osteoporosis. This investigation ought to spark interest in ginger and its potential applications, such as the development of nutrient-dense foods or pharmaceutical supplements for the treatment of chronic illnesses, such as the development of nutrient-dense foods or pharmaceutical supplements for treating chronic illnesses.

KEYWORDS:

Alzheimer's Disease (AD), Ginger (*Zingiber officinale*Roscoe), Gingerols, Oxidative Stress, Paradols, Shogaols.

1. INTRODUCTION

Ginger, the actual since ancient times, "*Zingiberaceae family*" and "*Zingibe*r" genus member "*Roscoe"* was employed as a spice and herbal medicine. Several common illnesses may be alleviated or treated with ginger root, including migraines, the common cold, motion sickness, and nausea and vomiting. Ginger contains several bioactive components, including phenolic and terpene chemicals. The different bioactivities of ginger may be attributed to the phenolic chemicals, namely gingerols, shogaols, and parasols [1]. The vast majority of the organic compounds found in nature are produced by plants and other members of the vegetable kingdom. Plants can biosynthesize complex molecular structures with many different roles in the human body. The molecules that ensure the growth and health of cells are known as primary metabolites. Secondary metabolites are synthesized by plants from these substances through very intricate biochemical pathways and aid in defense response and adaptability.

Ginger is one of the world's oldest and most widely used medicinal plants. It's been shown effective in treating gastrointestinal distress, inflammation, and rheumatic conditions. Carminative, digestive, perspiration, anti-flu, and stimulant qualities have all been attributed to its root. Ginger is a popular spice and flavor in culinary applications due to its fiery and revitalizing effects. Beverages and baked goods including bread, cakes, cookies, and preserves all start with this ingredient. Because of its pleasant aroma, it is widely used in the cosmetics sector [2]. Ginger is perennial, herbaceous in appearance, and generates an articulated rhizome. It also possesses adventitious roots and distal leaves, a solitary flower per basilar, and destroyed floral bracts. In appearance, ginger rhizomes are long and narrow, with a small convexity at their base. Their color may range from pale yellow to a deep, leathery brown, and they are striated lengthwise. The endoderm is yellow, and there are many fibrovascular bundles and oil cells throughout the tissue. The smell and taste are both nice and fragrant, but the latter is also rather intense [3]. More than 25 centuries have passed since ginger was first utilized in Chinese and Indian medicine [4]. The Spanish introduced ginger to Mexico, and the country is now one of the world's leading producers [5]. Ginger is often used in traditional Mexican medicines to alleviate digestive problems. Different chemotypes of ginger have been created since its introduction to tropical nations[6]. For those who suffer from motion sickness, ginger is an excellent anti-nausea cure. It also acts as an anti-inflammatory, pain reliever, temperature regulator, and cholesterol-lowering herb. Clinical studies without bias support its use for this purpose.

The empirical pharmacological effects of this therapeutic spice have sparked a fresh wave of research into isolating and identifying its bioactive ingredients and verifying them in the lab. Illustrated by Figure 1 Compounds found in ginger have several useful pharmacological effects, including those that reduce inflammation, fight cancer, lower blood sugar, and lower cholesterol. In the last decade, researchers have learned a great deal about the bioactive components of ginger and its positive biological effects on health.

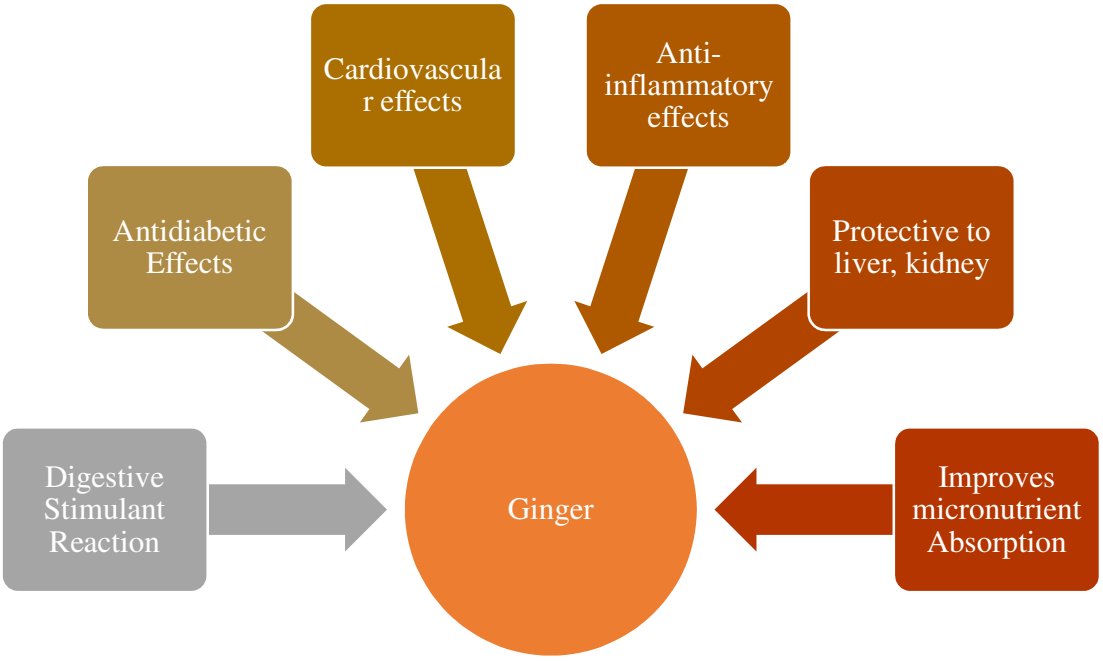

Figure 1: Displays the Health benefits of ginger (*Zingiber officinalis*)

Aging has been defined as a steady decline in physiological integrity, characterized by functional impairment and increased susceptibility to several diseases [7]. In this context, "elderly" means those aged 60 and above. In 2050, the share of the global population over 60 is projected to almost double from its current level of 962 million to 2.1 billion, as reported by the World Health Organization. Adults in this age range will outnumber kids under the age of five in 2020. In addition, by 2050, low- and middle-income nations will host 80% of the world's senior population. In part, the aging of the population may be attributed to the fact that the mortality rate has been on the decline since 1970 when it was very high. Globally, there were 2.1 children born to every woman in 2010, down from 4.95 in 1970. The mortality rate decreased from 15.3 per 100,000 in 1980 to 4.6 per 100,000 in 2010 [8].

Age-related neurodegenerative illnesses have become more common as the elderly population in Western nations has expanded. More than 26 million individuals throughout the globe are now living with Alzheimer's disease, making it the most prevalent pathology. By 2050, this figure is projected to triple. Neurodegenerative disorders that are a result of aging currently have no viable therapies, proceed irreversibly, and have high individual and societal costs. Because of this, age-related decline in organ or tissue function and structure is often linked with degenerative illnesses [9]. Deterioration of an organ or tissue causes a reduction in health and well-being, raises the chance of illness, and ultimately may cause death. The term "degenerative disease" is used to describe conditions in which tissues and cells gradually stop functioning as well as they once did [10]. Cardiovascular disease, hypertension, and “type 2 diabetes mellitus”, “Alzheimer's disease (AD)”, “Parkinson's disease (PD)”, atherosclerosis are all examples of degenerative illnesses (DM) [11].

In light of this, the goal of this study is to provide a succinct overview of the data showing that ginger may help prevent several neurological disorders, including Parkinson's disease, multiple sclerosis, and Alzheimer's disease. Through the use of the Web of Science, Scopus, Science Direct, and PubMed databases, research involving ginger was looked for. With a few notable deviations from the original publication in those earlier works of considerable value, the publications chosen have all been published within the recent decade.

2. LITERATURE REVIEW

According to the research done by Ken Tanaka et al., it is crucial to have a thorough grasp of the bioactive ingredient in traditional herbal remedies to examine their genuine therapeutic activity. The author used “liquid chromatography-mass spectrometry (LC-MS)” to examine the chemical characteristics of both dietary and therapeutic ginger variants. Results from principal component analysis (PCA) suggest gingerol's acetylated derivatives are the pharmacological indicator, not gingerol or shogaol. Z., a fresh ginger variety, was newly developed. Commiphora officinale CV. The chemical contents and rhizome output of Ogawa Umare, also known as "Ogawa Umare" (OG), indicate that it has the potential as a cutting-edge facility for making ginger-based herbal treatments [12].

Keiichiro Sugimoto et al. performed a placebo-controlled crossover research was conducted on healthy, cold-sensitive women to determine the beverage's ability to make them feel warmer. In a room maintained at a constant 21 degrees Celsius, six women drank either a beverage containing 0.07 percent ginger extract or a control (both volumes were 280 milliliters) and both groups saw an elevation in palm temperature shortly after drinking. Palm temperature rose for 20 minutes after drinking the ginger beverage, but returned to normal after drinking the placebo.

Consumption of ginger led to a sustained rise in palm temperature that was statistically significant and longer lasting than the placebo effect ($p < 0.05$). Some participants who drank the ginger beverage reported feeling warmer than usual long thereafter, following a questionnaire. A beverage containing ginger extract may, therefore, lessen the negative effects of being exposed to cold [13].

According to research by Faizul Azam et al., ginger (*Zingiber officinale*) has a variety of possibly bioactive phytochemicals with useful therapeutic characteristics, despite being a common seasoning used to enhance the flavor of food. The author is interested in finding out more about the bond formation between ginger's active ingredients and several pharmaceutical targets for treating Alzheimer's disease utilizing molecular docking experiments. Using the Autodock 4.2 program and a Lamarckian genetic algorithm strategy, researchers docked 13 distinct target proteins with 12 ligands. All co-crystallized ligands were docked into their native binding cavities since the docking technique was confirmed by a good correlation coefficient value ($r2=0.931$) among experimental measurements and docking anticipated attributes. Additionally, the Osiris property analyzer and the Molinspiration online toolbox were used to assess the drug-likeness score as well as the molecular characteristics necessary for a favorable pharmacokinetic profile. Because none of the compounds violated Lipinski's rule of five, they are all potentially useful therapeutic options for Alzheimer's disease [14].

The therapeutic uses of ginger that Nguyen Hoang Anh et al. have been studying are getting a lot of attention because of the advantages they may have for patients. In their study, the author looked at randomized controlled trials of ginger's effects following PRISMA guidelines for publishing systematic literature reviews and meta-analyses. To that end, all relevant data from 109 publications were gathered, including information on the studies' methods, populations, assessment methods, adverse effects, and primary findings. Improvements were shown in biomarkers for colorectal cancer, inflammation, metabolic disorders, the gastrointestinal tract, and nausea and vomiting during pregnancy, but predictions for other functions were more contentious. Only 43 clinical trials (36.4%) met the criteria for "high quality of evidence". and also the problems in ginger clinical studies went beyond the quality assessment outcome. To confirm the claimed therapeutic benefits of ginger, further studies using suitable research approaches are needed [15].

3. DISCUSSION

In terms of prevalence, Parkinson's disease ranks only behind Alzheimer's as the second most frequent form of neurodegeneration. Alpha-synuclein protein builds up within neurons, where it forms tangles called Lewy neurites and clumps called Lewy bodies, which are hallmarks of the disease, and a rise in incidence with age are the hallmarks of this age-related disorder [16]. Iron buildup in the brain and oxidative stress are two of the several environmental and genetic elements linked to the beginning of Parkinson's disease. Research by Medeiros et al. shows that people with Parkinson's disease have significantly higher levels of oxidative stress and inflammatory markers [17]. Inhibiting the inflammatory reaction, boosting concentrations of nerve development factors, and encouraging synapse formation are all ways in which the active ingredient in ginger may help alleviate the cognitive impairment that often accompanies it.

3.1.Properties of Ginger's Bioactive Compounds:

Active components, like phenolic and terpene chemicals, are plentiful in ginger. Ginger's primary phenolic constituents include parasols, shogaols, and gingerols. Common polyphenols in fresh 10-gingerol, 6-gingerol, and 8-gingerol are all components of ginger, all of which are known as gingerols. Gingerols may be converted to their equivalent shogaols by heat treatment or prolonged storage. Hydrogenation changes shogaols into paradols. Furthermore, ginger contains a wide variety of phenolic chemicals, Inherent in the ginger family of bioflavonoids include quercetin, zingerone, gingerenone-A, and 6-dehydrogingerdione. The essential oils of ginger may include terpene elements such as a-bisabolene, a-curcumene, zingiberene, a-farnesene, and a-sesquiphellandrene. Additionally, ginger contains polysaccharides, lipids, organic acids, and dietary fiber [18].

Dried ginger gets its characteristically pungent flavor from shogaols, which have been formed when gingerol analogs experience dehydration processes to generate the equivalent shogaols, superior to their forebears in terms of stability and pharmacological effects. Rhizomes undergo this chemical transformation throughout the drying and storing processes. Figure 2 depicts the metabolic pathway by which 6-shogaol is transformed into 6-paradol by bacteria. Quercetin, zingerone, gingerenone-A, and 6-dehydrogingerdione are some of the other phenolic chemicals found in ginger [19]. Both the biosynthesis as well as the concentration of bioactive chemicals in ginger are affected by some variables, including the cultivar, environment, and treatment processes. Furthermore, it has been stated that the chemical makeup of black ginger and regular ginger varies from country to country. Differentiating between conventional ginger, which contains phenolic acids unrelated to gingerol, and black ginger, which contains methoxyflavones.

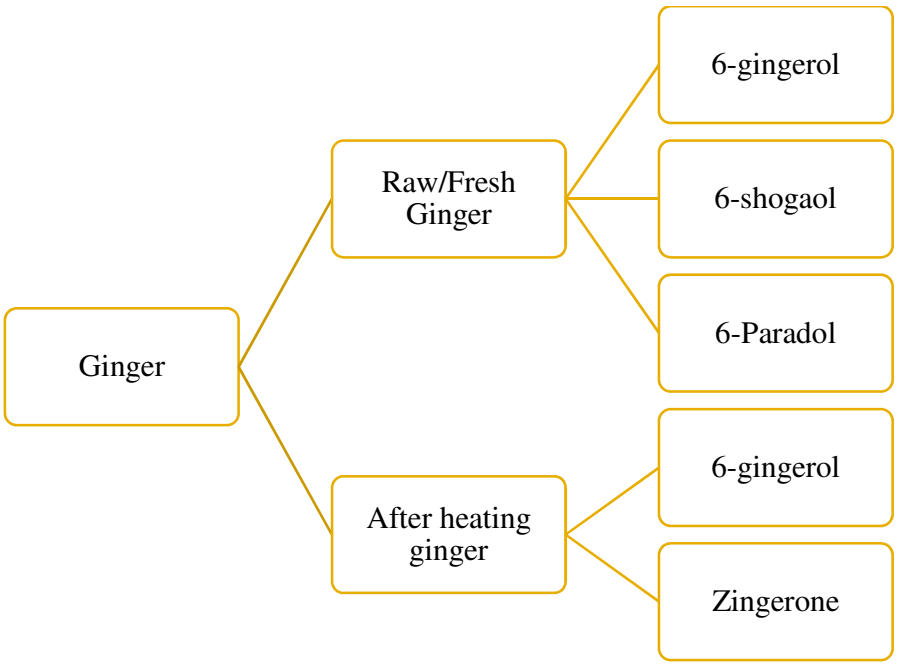

Figure 2: Illustrates the Bioactive substances in ginger: chemical structures and activities.

Although ginger is a widely used spice, nothing is known about its metabolites or metabolism. The only way to completely comprehend ginger's mode of action and therapeutic potential is to

evaluate its bioactivity. The widespread use of dietary supplements derived from food is occurring despite little understanding of their efficacy and safety. Gingerol is the bioactive component of ginger that has received the greatest attention from researchers [20].

3.2.The Scientific Evidence Relating to Health Effects:

There has been constant observation of ginger's effects on the digestive system, which makes sense given that ginger and its compounds seem to congregate in this organ. For thousands of years, people have utilized ginger to treat a variety of ailments, from the common cold to cancer, and is thought to have a wide range of significant therapeutic and preventative properties. There is no controlled scientific data to back up the various claims made for therapeutic plants, so most of the information has been passed down orally. In contrast, more thorough scientific research has recently been done on the functions and objectives of ginger and its many constituents.

3.2.1. Antioxidant and Inflammatory Properties of Ginger:

Most neurodegenerative illnesses, for example, may be traced back to an increase in oxidative stress brought on by radical production that may cause damage to cells, like nitrogen reactive species (NOS) and reactive oxygen species (ROS). The antioxidant bioactive chemicals should be broadly distributed throughout several dietary matrices such as many edible flowers, cereals, herbs, and veggies. Furthermore, recent studies have shows that ginger's bioactive components are effective antioxidants and anti-inflammatory agents. Antioxidant, antibacterial, anticancer, anti-inflammatory, anti-allergic, and protection against neurodegenerative illness are only some of the many biological functions shows by gingerols and shogaols [21]. Dry ginger outperforms fresh, stir-fried, and carbonized varieties when it comes to antioxidant activity in in vitro tests. This is because the polyphenol content is greater in dried ginger, whereas the gingerols in fresh ginger may be converted into the less potent shogaols during cooking processes like stir-frying and carbonization.

Inflammation is a defensive reaction that occurs in the body in response to microbial invasion, antigen exposure, or cell/tissue injury. As a result, numerous different kinds of cells, mediators, receptors, and signaling pathways are all involved. Atherosclerosis, cancer, diabetes, rheumatoid arthritis, and senescence are only a few of the disorders in which one of the main contributors to the cause is chronic inflammation. Multiple scientific investigations have established that ginger's active ingredients have anti-inflammatory properties. It was previously believed that ginger's anti-inflammatory properties stemmed from an inhibitory effect on prostaglandin and leukotriene production.

3.2.2. Antinausea Agent:

Historically, ginger has most often been used to combat motion sickness. Several randomized controlled trials have shows that ginger is typically beneficial as an antiemetic, and this has prompted a comprehensive evaluation of the advantages and hazards of herbal therapy for liver and gastrointestinal problems. The use of ginger root is more effective than the use of dimenhydrinate (Dramamine) or a placebo in addressing the signs of motion sickness, making it a popular recommendation for those who may be susceptible to being seasick. The subjective intensity of seasickness in navy cadets may be reduced by 1 g of ginger, according to follow-up research. Evidence shows that ginger inhibits serotonin receptors and performs its antiemetic direct effects on the central nervous system and also the digestive system, however, the precise

mechanism by which ginger works to prevent nausea and vomiting is still unclear. The usefulness and safety of ginger for managing vomiting and nausea have been challenged in the past due to the sometimes inconsistent outcomes obtained, although the antiemetic properties of ginger are the most well-studied properties of this spice and have been examined extensively. However, ginger is still suggested for those experiencing morning sickness due to pregnancy, chemotherapy, or recent surgical treatment.

3.2.3. The Effects of Ginger on DNA Damage and Cancer Prevention:

Some of the effects of 6-GN have been hypothesized to be in the areas of cancer prevention, inflammation regulation, tumor suppression, and apoptosis induction. Several types of cancer have shows relevant impacts. Chromatin control and DNA damage-associated cell cycle regulation, and apoptosis are only a few of the underlying biological mechanisms. Differential impacts on normal and cancerous cells are highlighted by these effects, and the fact that they do not harm healthy cells bodes well for their use in therapeutic settings in the future.

Lima et al. [22] used a modified experimental design to find that high concentrations of 6-GN reduced cell viability in murine sarcoma cell lines relative to some other antineoplastic drugs. Micronuclei were examined using a cytogenetic method of analysis, and the presence of nucleoplasmic bridges and nuclear buds at high quantities was accompanied by an uptick in death. An exciting observation is that pre-treatment adding 6-GN to gastric cancer cell lines may increase IR-induced apoptotic cell death.

3.2.4. Cardioprotective Activity:

Growing older is a major contributor to the danger of cardiovascular disease. Risk factors for cardiovascular disease and stroke include dyslipidemia and hypertension. Ginger and several of its active ingredients have shows promise in recent research for their potential to reduce lipid profile, blood pressure, and platelet activation. It has been observed that fresh ginger extracts administered intravenously reduce blood pressure in sedated rats; this action is due to an inhibitory impact on voltage-dependent calcium channels. Pretreatment with ginger rhizomes reduced blood pressure and inhibited Nitric oxide (NO), a vasodilator, generated by the NOS inhibitor L-NAME in a rat model of hypertension although boosting ACE and arginase activity.

An effective way to reduce blood pressure in middle-aged people is by taking ginger supplements twice a day (>3 g) for two months, as shows in a clinical trial meta-analysis. Atherosclerosis is widely believed to result from an increase in blood lipids. In high-fat diet-fed rats, blood levels of triglycerides (TG), low-density lipoprotein (LDL), and total cholesterol all decreased, but levels of "good" cholesterol did not were increased with aerobic exercise mixed with ginger extract. These results suggest that ginger may provide some amount of protection against atherosclerosis.

3.2.5. Skin Ageing and Degenerative Disease:

The skin not only acts as a barrier against a wide range of harmful environmental factors but also serves a significant aesthetic purpose. Alterations to the skin's appearance are a common telltale indicator of advancing years. As we become older, our skin loses its elasticity and becomes loose and wrinkled. It is well known that chronic radiation from the sun's ultraviolet rays is the primary factor in the development of visible signs of skin aging (extrinsic aging) [23]. A neurodegenerative condition called Alzheimer's disease (AD) causes memory loss and other

cognitive problems. The anti-inflammatory and antioxidant benefits of *Zingiber officinale* are the primary reasons for exploring its application in neurological illnesses like Alzheimer's. Clinical research has revealed that ginger aids memory by increasing the expression of nerve growth factor (NGF), which facilitates long-term hippocampus enhancement by decreasing its complexity and speeding neurite development.

Adult-onset and complicated, as a type of neurodegeneration, in terms of prevalence, Parkinson's disease (PD) is second only to Alzheimer's. The pathogenic basis of this condition is the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc), a region of the midbrain. This loss is accompanied by insoluble masses of poorly folded alpha-synuclein protein (Lewy bodies). As a result of neurodegeneration, the SNpc loses its dopaminergic projections to the striatum, which messes with how the basal ganglia normally work [24]. Two environmental and genetic variables that have been connected to the onset of Parkinson's disease include oxidative stress and iron buildup in the brain. So, it's safe to say that neuroinflammation is a major contributor to the onset and progression of Parkinson's disease and other neurodegenerative conditions. Oxidative stress is evident in PD because of mitochondrial dysfunction and a chronic inflammatory response. As a consequence of this tension, reactive oxygen and nitrogen species (ROS and RNS) are generated (RNS). Due to their reaction with excess iron, reactive species kill off dopaminergic neurons in the substantia nigra.

3.3. Adverse Effects of Ginger:

Heartburn, diarrhea, burping, and overall stomach pain are some of the moderate side effects that may occur. The potential for unwanted consequences rises when dosages over 5 grams per day are routinely used. When taken topically for a limited amount of time, ginger may not have any adverse effects. Some people's skin may get irritated by it. Reports indicate that pregnant rats take ginger extracts well when given orally (1000 mg/kg) and that it has no negative effects on either the mothers or the developing babies. Another research found that when pregnant rats were given ginger tea, they had double the embryo loss but had heavier surviving babies compared to untreated controls. While ginger oil was shows to cause chromosomal abnormalities in mice, ginger rhizome extract at doses ranging from 0.5 to 10.0 g/kg given intraperitoneal injection had no such impact.

Heavy menstrual bleeding and elective cesarean sections are both associated with an increased risk of diarrhea, as observed in two separate trials. In addition to this, gastrointestinal symptoms also included epigastric discomfort, bloating, and gas. Also, patients who were given ginger before laparoscopic surgery reported fewer cardiovascular and respiratory problems. There were no outward signs of abnormality in any organs, and hematological and blood biochemical indicators showed no changes between the treated and untreated animals. At the highest dosage (2000 mg/kg), the only discernible impact was a modest reduction in the relative and absolute weight of the testes. Treatments for morning sickness during pregnancy that contained ginger was not associated with any teratogenic effects in human-controlled studies.

4. CONCLUSION

Ginger's antioxidant and anti-inflammatory properties come from its abundance of gingerols, shogaols, and paradols are all examples of bioactive chemicals that may be useful in treating neurological illnesses by lowering inflammation and oxidative stress. Some inflammatory, oxidative, and immunopathological factors contribute to their progression, and the medications

used to treat them have limited effectiveness and might cause undesirable side effects. Ginger's antioxidant, anti-inflammatory, and immunomodulatory qualities suggest it may slow the development of MS, and also epilepsy, Parkinson's, Alzheimer's, and migraine. More ginger's bioactive components need to be isolated and defined before its biological activities and underlying mechanisms of action can be studied in depth. To prove ginger's effectiveness against numerous illnesses in humans requires well-designed clinical studies of ginger and its many bioactive components

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CHAPTER 16

CLINICAL FEATURES, PATHOGENESIS, PREVENTION, AND TREATMENT OF DYSKINESIA INDUCED BY LEVODOPA IN PARKINSON'S DISEASE

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ABSTRACT:

"Parkinson's disease (PD)" is successfully treated with the dopamine replacement therapy levodopa (LD), a progenitor to dopamine. For more than 40 years, oral levodopa has been used extensively, often in conjunction with a dopa-decarboxylase inhibitor (DDCI) which decreases numerous treatment problems, increases its half-life, and the brain's availability of levodopa is increased. Moreover, drug-induced dyskinesias and day-to-day fluctuations in motor responsiveness might complicate long-term therapy for LD. Reduced levodopa dose, dopamine agonists as the first treatment for Among the treatments and preventative approaches for "levodopa□induced dyskinesia(LID") mentioned in this study include Parkinson's disease, neurosurgery, amantadine, atypical and neuroleptics. LID may have a detrimental influence on both the cost of healthcare and the quality of life. According to the author's conclusion, Levodopa either slows down Parkinson's disease progression or has an ongoing effect on its symptoms. Neuroimaging evidence, on the other hand, suggests that levodopa either hastens the degeneration of dopamine nerve terminals in the nigrostriatal region or that its pharmacological actions alter the dopamine transporter. Possible long-term consequences of levodopa on Parkinson's disease are yet unknown.

KEYWORDS:

Levodopa (LD), Levodopa□Induced Dyskinesia (LID), Motor Symptoms, Parkinson's Disease (PD), Parkinsonism.

1. INTRODUCTION

Dr. James Parkinson initially recognized Parkinson's disease (PD) in 1817; it is a chronic, advanced neuro-degenerative condition involving motorized and nonmotor indications under the name "shaking palsy". The gradual degeneration of movement and muscular control caused by the illness has a profound clinical effect on patients, families, and caretakers. Evidence of neuronal loss in non-dopaminergic areas shows that there may be other reasons for motor signs in PD besides the loss of striatal dopaminergic neurons. Motor signs of PD, such as resting tremors, bradykinesia, and muscular rigidity, are collectively referred to as "parkinsonism." However, PD is not the only reason someone has PD, it is not the only possible cause. Other illnesses and pharmacological side effects may also lead to Parkinsonism [1]. Several nonmotor

manifestations, like sleep difficulties, depression, and cognitive alterations, have been linked to PD's pathophysiological changes before the development of motor characteristics. Research into protective or preventative medicines has been fueled by evidence from this early, preclinical stage [2].

The condition develops slowly but becomes worse with time. One of the first signs is tremor, and bradykinesia and stiffness may follow. Most people don't notice they have postural instability until the latter stages of the condition, but it may have a major effect on their daily lives. It's also worth noting that some people have autonomic symptoms before they experience motor symptoms. Most individuals are diagnosed after a thorough review of their medical history and current symptoms. In circumstances where certainty cannot be established, SPECT scans may be used to rule out other neurological illnesses. People in their thirties and forties are not immune to developing PD, despite the disease's reputation as one that primarily affects the elderly. The disease strikes men at a higher rate than women by a factor of 3:2, with the difference in onset time between the sexes discussing how estrogen protects women's nigrostriatal dopaminergic systems from damage [3].

The basal ganglia are affected by PD, as are the numerous other nuclei that make up this brain region. Multiple regions of the cerebral cortex send signals to the striatum, both excitatory and inhibitory. The primary disease that causes the symptoms is the expiry of dopaminergic neurons. Pesticide, herbicide, and other industrial chemical exposure have been linked to PD as a cause. Injecting "1-methyl-4-phenyl-1, 2, 3, and 6-tetrahydropyridine" (MPTP)". has been connected to Parkinsonian-like symptoms in certain individuals Within the mitochondria, this chemical is built up. There is also evidence that the thalamic nuclei may be damaged due to oxidation and also the production of free radicals.

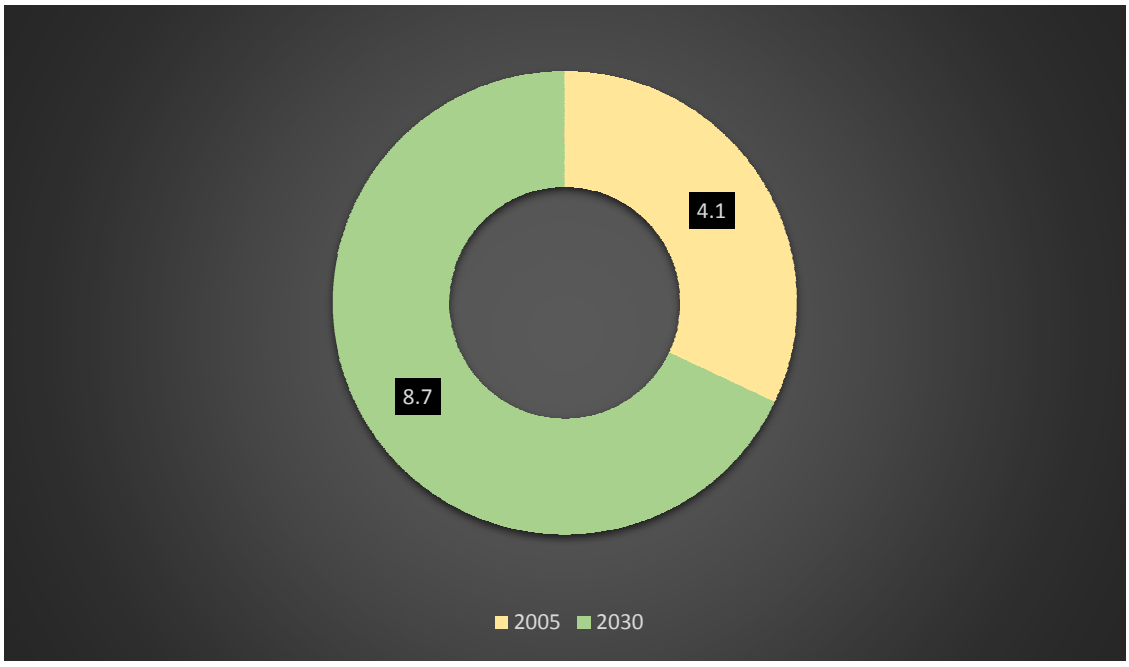

Figure 1: Displays that the frequency of "Parkinson's disease" is expected to rise significantly all over the globe.

Figure 1 shows the estimated worldwide frequency of PD between 2005 & 2030. PD affected 4.1 million individuals worldwide in 2005, but by 2030, that number is projected to increase to 8.7 million. Levodopa transforms into dopamine in the brain when taken orally. Levodopa, a dopamine replacement medication, is often used by physicians to treat "PD" signs. It's the best drug for enhancing the lives of those with idiopathic PD, and it's used primarily to alleviate the slow, uncoordinated movements that characterize the condition (called bradykinesia). Levodopa is often the next course of action after other antiparkinsonian drugs are unable to relieve a patient's Parkinson's disease symptoms. Also, patients with carbon monoxide poisoning or post-encephalitic Parkinsonism might benefit from taking this medication [4].

The golden ordinary for PD symptomatic effectiveness in medication treatment remains to be levodopa (LD), which has been used therapeutically for more than 40 years. Lower scores indicate greater improvement in motor control with dopamine replacement with LD compared to other dopaminergic treatments on the "Unified Parkinson's Disease Rating Scale (UPDRS)". Levodopa medication may be given for a very long time without causing dyskinesias in certain people. The incidence of peak-dose dyskinesias may be influenced by genetic variables. There is evidence that some variations in the dopamine receptor D2 gene are linked to a lower propensity for peak-dose dyskinesias.

More and more evidence suggests that motor issues (particularly dyskinesia) brought on by prolonged LD treatment are due to the nonphysiologic pulsatile activation of striatal dopamine receptors. Because the LD molecule does not necessarily have the property of inducing motor complications [5], Evidence for using LD in the diagnosis of PD will be reviewed, and the question of LD administration as a potential contributor to the drug's tendency to cause motor issues will be discussed. For immediate-release LD formulations, the half-life is just 90 minutes.

2. LITERATURE REVIEW

In their research, Catherine Ding et al. stated in their study the dopaminergic drugs and rate of motorized improvement in PD. Examination of off-phase motorized scores using linear mixed-effects regression revealed a yearly decrease of 2.3% of the maximum impairment rating. More severe motor dysfunction at the start of therapy was associated with more rapid improvement. Patients with dementia also had significantly worse motor performance than controls ($P = 0.02$), and it deteriorated more rapidly in terminally ill patients. The study's author suggested that these findings should be used to guide the development of clinical trials for medicines with potential neuroprotective characteristics [6].

For those suffering from "Deep Brain Stimulation (DBS)", "Parkinson's disease" of the "Subthalamic Nucleus (STN)" and levodopa are two of the most common treatment choices, which David S. May et al. assessed in their research. Expanding the Balance Evaluation Systems Test (BEST test), this cross-sectional research evaluated participants' balance while they were ON-medication/ON-stimulation with when they were OFF-medication/OFF-stimulation due to PD and STN-DBS (BESTest). Scores on the BESTest were compared between the untreated and the treated conditions to determine general equilibrium. The variations in various components of balance across treatment conditions were evaluated by comparing scores on the BESTest's six parts. The sample size was 29 (21 males, 8 females; average age, 65.0± 6.9 years). After accounting for multiple comparisons, we found that our scores on the treated state of the BESTest were considerably better than the untreated condition ($p < 0.05$). These authors' findings offer sustenance to the hypothesis that STN-DBS and levodopa aid recovery poise in general,

and represent a primary stage for evaluating the influence of these medications on particular aspects of stability [7].

Evaluation of the association between dopamine replacement treatment and other clinical characteristics and point prevalence estimates for four ICDs in PD, as reported by Daniel Weintraub et al. The researchers conducted a cross-sectional analysis of 3,900 people with medicated idiopathic PD from 46 clinics in the US and Canada, randomly assigning rates depending on whether or not the patients were taking medication. Five percent of patients suffered from gambling addiction, while 3.5 percent exhibited compulsive sexual conduct. Treatment with a dopamine agonist was associated with an increased risk of impulsivity issues "(17.1% vs 6.9%; OR, 2.72; 95% CI, 2.08-3.54; P .001)". Comparing pramipexole and ropinirole, the rates of impulse control disorder were comparable "(17.7% vs. 15.5%; OR, 1.22; 95% CI, 0.94-1.57; P =.14)". Dopamine agonist treatment for PD raises the likelihood of ICD by a factor of 2 to 3.5. This connection reflects ICD drug classes. Other demographic and clinical characteristics and ICDs reveal a complicated link that needs more study to maximize preventative and treatment options [8].

The researcher Marina Svetel et al. set out to determine the likelihood that PD patients will have hallucinations and what variables would increase that likelihood (PD). One hundred eighty successive PD patients short of dementia participated in this cross-sectional investigation. 24 people (or around 13% of the total) may have had hallucinations. Levodopa-induced dyskinesia ($p = 0.002$), nightmares ($p = 0.025$), and the duration of their occurrence ($p = 0.021$) were all associated with greater H-Y illness stages. Hallucinations in PD were shows to be significantly associated with both the length of time someone has had PD ($p = 0.024$) and the total number of points on the Neurological Symptom Inventory ($p = 0.002$) [9].

As mentioned in their paper, A. Rizos et al. conducted an observational study to define the spectrum and characteristics of emergencies that neuroleptic malignant syndrome (NMS) in a longitudinal unit of PD patients who experience EMO periods. Consistent with previous publications, our findings show that EMO episodes are widespread and affect 59.7% of participants throughout all illness stages. Yet critically, EMOs were linked to NMS in 88.0% of those cases. Most people had symptoms including the need to go to the bathroom quickly, limb paresthesia, dizziness, anxiety, dribbling saliva, pain, and sadness. NMS linked to EMO. Based on the patients' reported dopaminergic treatment regimens, this research suggests that a continuous or time-release medication delivery method may help reduce EMO-related NMS. More knowledge, identification, and proper treatment of EMO and NMS may enhance 24-h PD management. There is a need for Instruments designed specifically for measuring motor and NMS EMO symptoms [10].

3. DISCUSSION

Over the last 40 years since its debut, levodopa's effectiveness in PD has been generally recognized. Prior worries that levodopa may have toxic consequences for the brain have been largely disregarded, and it is generally considered that there is no need to postpone the commencement of levodopa, at least in terms of toxicity. Parkinson's disease is characterized by substantia nigra degeneration. This condition causes a decrease in dopamine in the striatum by affecting the nigrostriatal circuit. Levodopa can cross the blood-brain block, but dopamine is unable to (BBB). In the brain and throughout the body, levodopa is metabolized into dopamine. Carbidopa and benserazide are examples of peripheral decarboxylase blockers used in

conjunction with levodopa to improve absorption and reduce side effects (such as carbidopa and benserazide). Inhibiting the enzyme that catalyzes the change of levodopa to dopamine in the peripheral, known as dopamine decarboxylase, increases the level of levodopa that can pass the blood-brain barrier. After being metabolized, it serves as a replacement for declining levels of endogenous dopamine by activating postsynaptic dopaminergic receptors [11].

3.1.Levodopa as a Therapeutic Agent:

Parkinson's plus syndrome and other conditions that are sensitive to dopa are still the primary focus of levodopa's therapeutic applications. The clinical effectiveness of levodopa varies depending on the subgroup of symptoms being treated Motorized signs such as bradykinesia and inflexibility are characteristic of PD and are often successfully treated with levodopa. In many cases, the motor signs of PD may be alleviated with the use of levodopa, including bradykinesia and stiffness. Even while levodopa is helpful, it does not come without serious side effects that are a major part of the patient's sickness, especially when the disease is advanced. Some of the adverse effects of levodopa are due to the drug's conversion into dopamine by DOPA decarboxylase outside of the central nervous system (peripheral conversion). Combining levodopa with peripheral inhibitors of DOPA decarboxylase may reduce these adverse effects, as will be discussed more below. Prolonged usage is associated with serious motor problems including dyskinesias and extreme swings in motor function [12].

In this case, the tremor's response is subtler. Other motor symptoms, including speech and swallowing problems, postural instability, and frozen gait, also often have a poor response rate. Levodopa treatment has a low success rate in treating nonmotor symptoms, such as mental health problems (such as dementia or depression) or physiological problems (such as autonomic dysregulation or sleep disturbances). Some people may benefit from taking levodopa at night to help them sleep. Dyskinesia and motor fluctuations have both been linked to long-term levodopa therapy [13].

When medicine is at its most effective dosage, it may cause dyskinesias, which are characterized by uncontrollable, hyperkinetic twisting motions. There is a fine line to walk between achieving optimal management of motor symptoms and avoiding side effects when troublesome dyskinesias occur as a result of levodopa treatment. To manage motor symptoms at a lower levodopa dosage, deep brain stimulation may be explored for patients who have reacted well to levodopa in the past but who have acquired troublesome dyskinesias [14]. The least effective dosage, dose fractionation, and the administration of other dopaminergic therapies are all methods used to mitigate levodopa's negative effects. Previously, "levodopa vacations" were used, however, this practice is now discouraged. DOPA decarboxylase inhibitors, such as benserazide and carbidopa, are used in tandem with levodopa to lessen its peripheral adverse effects. By specifically blocking levodopa's peripheral conversion to dopamine, these chemicals reduce levodopa's peripheral side effects without crossing the blood-brain barrier [15].

3.2.The epidemiology and potential contributing factors:

The epidemiological study of Parkinson's disease has some logistical hurdles shows in Table 1. Even in massive population studies, only a small percentage of people will have PD. Consequently, the margin of error in any one research may be large. This is especially difficult in analytic investigations when the causes of illness vary amongst groups. Furthermore, testing

ideas incorporating numerous factors would need huge populations, which is problematic given the degree to which the causation of PD is complex.

Table 1: Demonstrates the challenges that the epidemiological investigation experienced "Parkinson's disease".

Diagnostic Procedure	Challenges
Currently, there is no reliable diagnosis	A professional examination is the most trustworthy method. There are no diagnostic criteria for pathology.
An Extensive Preclinical Phase	It may take years of exposure before symptoms appear.
Disorder of late life	Identification of risk factors in hindsight Low diagnostic fidelity in family members
Comparatively Rare	A large base population is required.

When planning and evaluating epidemiological studies of PD, it is helpful to keep in mind the potential role that diagnostic ambiguity might play. Underestimates or overestimates of the prevalence of PD might result from including or excluding people based on their health status. In case-control studies or family studies, including case participants who do not have Parkinson's disease (PD) may obscure a causal association or even lead to correlations with characteristics indicating a different condition. The pattern of transmission of a genetic disorder within a family might sometimes be misunderstood.

Imaging methods include "positron emission tomography (PET)" and "single photon emission computed tomography (SPECT)", which may identify and show how radiolabeled tracers are distributed throughout the body. Even in its early phases, PD patients had less tracer accumulation in the striatum lateral to the afflicted limbs, suggesting a dysfunction in the presynaptic dopaminergic pathway. There is some evidence that ultrasonography may help diagnose nigral damage in PD, and this has been proposed by others.

Early-onset Parkinson's patients are more likely to experience "levodopa-induced dyskinesia". Patients with a disease beginning between the ages of 40 and 59 had a 50% chance of LID during the next 5 years, whereas those with a disease onset beyond the age of 70 had a 16% risk. Because of the distinct kinetics of levodopa, although the underlying cause is unknown, it has been postulated that Parkinson's disease may contribute to this predisposition as people age. Important things to think about are whether nigral denervation is present and how severe it is (disease severity). LID virtually invariably develops in patients with idiopathic PD when levodopa is treated at the doses used in clinical practice; healthy individuals and those with additional neuro-logical illnesses do not grow LID [16].

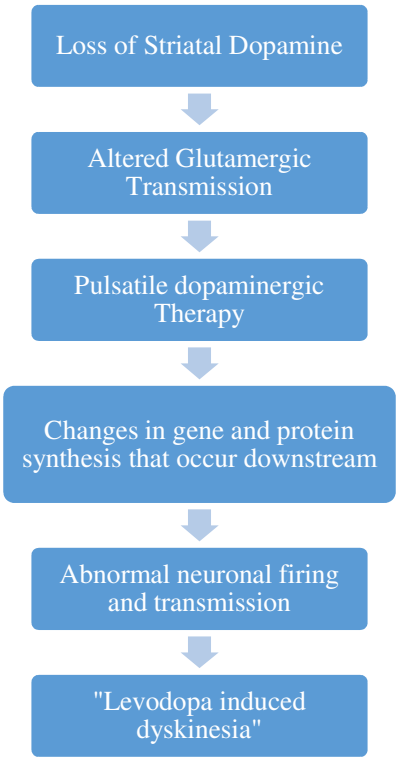

Figure 2: Levodopa-induced dyskinesia (LID): a schematic depiction of the processes leading up to the onset of the condition.

Figure 2 shows Levodopa-induced dyskinesia (LID): a schematic depiction of the processes leading up to the onset of the condition. Emerging evidence suggests that LID may be traced back to alterations in both dopaminergic and non-dopaminergic transmission, with the latter resulting in the genetic and protein alterations characteristic of the disorder. Striatal neurons respond to high glutamate concentrations by increasing the production of Fos and Fos-related proteins (FRA). The 20 FRAs form activator protein1AP1 complexes with the transcription factor JunD, which can regulate some genes and proteins such as encephalin, dynorphin, and NMDA receptors [17].

Smaller dosages are better for starting treatment, and the suggested daily dose is 300–1200 mg (more if tolerated), given in 3–12 equally spaced doses. The dosage should be titrated up by 100 mg every three to four days. When administered orally, levodopa causes some people to experience gastrointestinal (GI) distress.

Patients should take their levodopa either 1 hour before or 2 hours after a meal high in protein for optimal absorption. If taken with a high-fat, high-calorie meal, levodopa absorption may be reduced by two hours. A high-protein diet may also make it harder for levodopa to be absorbed due to interactions with amino acid transporters. Before ingestion, oral dissolving tablets must be fully dissolved on the tongue. Levodopa comes as an extended-release capsule and may be taken either with or without meals. If a patient has difficulty swallowing, they may open the capsule and scatter the ingredients over meals [18].

i. Orally Administration:

In addition to carbidopa\levodopa, the FDA authorized an inhalation variant of the drug in 2018 for PD treatments. Levodopa is also available as a dry powder for inhalation, which allows it to avoid the gastrointestinal tract and the liver completely.

ii. Infusion:

A nasojejunal infusion may be given over 16 hours as an alternative route of administration. There is evidence that levodopa infusion is not related to the low plasma trough concentrations seen with oral medication delivery. The negative consequences of motor problems have been demonstrated to lessen in recent investigations of such infusions. Pulsatile dosing of levodopa, according to some research, may lead to greater motor problems than continuous treatment. As there is a lack of data on the use of levodopa in children, it is not advised for use in individuals under the age of 18.

3.3.Adverse Effects of Levodopa:

Nausea, dizziness, headaches, and sleepiness are frequent Levodopa side effects. Carbidopa dosage increases are indicated for nausea relief, with domperidone as a possible backup plan. Due to potentially increased sensitivity to central nervous system (CNS) impacts, aged people need special care. Confusion, hallucinations, delusions, psychosis, and agitation are among the most prevalent adverse reactions of levodopa in elderly people. Due to a possible increase in hip fracture risk in the elderly, levodopa may cause a slight rise in homocysteine levels. It has been shown that patients with idiopathic Parkinsonism on levodopa are at increased risk for low blood vitamin B12 concentrations, increased methylmalonic acid levels, and sensorimotor peripheral neuropathy [19].

Some individuals using antihypertensive drugs must lower their dosages or stop taking them altogether because they cause cardiovascular side effects including dizziness and postural hypotension. Cardiac arrhythmias have also been reported by researchers. One of the documented side effects of levodopa is sleepiness. It may strike suddenly and without notice, so drivers must take extra care. Clinicians should advise patients who suffer extreme daytime drowsiness to stop using the medicine. Levodopa's potential side effects become more apparent with prolonged usage. Permanent alterations to motor function brought on by substance abuse may have terrible consequences on the value of the lifecycle of a patient. Fifty percent of people using levodopa for 5-10 years will have motor problems during that time. If Parkinson's disease was diagnosed at a young age, the motor problems are more severe.

3.4.Toxicity:

Neuronal cells are vulnerable to levodopa toxicity, according to research. Apoptosis may be triggered by the free radicals produced during levodopa oxidation in the body. When levodopa is decarboxylated in the peripheral, it may cause an increase in the concentrations of dopamine, norepinephrine, and epinephrine in the blood. Because catecholamines activate alpha and beta-adrenergic receptors, an excess of these hormones has negative effects. Levodopa may pass through the placenta and be metabolized by the fetus in pregnant women. The safety of using levodopa during pregnancy has not been well studied, unfortunately. Caution is required when the medicine is given to nursing mothers since it is contained in breast milk. Toxicities are

treated with life-sustaining interventions including gastric lavage, airway management, and intravenous (IV) fluid administration.

4. CONCLUSION

The primary care physician needs to be aware of the patient of PD symptoms since L-effects dopa's are temporary and the patient may need to begin taking additional drugs. In this case, the doctor may benefit from being alerted quickly to changes in the patient's condition thanks to the constant monitoring performed by the nursing staff. If additional agents are required, the pharmacist should contact the doctor to assess any drug-drug interactions and doses. Furthermore, a gastroenterologist and urologist may requirement to be seen for PD patients who exhibit some autonomic symptoms. Despite the circumstance that there is no known treatment for PD, the prognosis may be improved with interprofessional cooperation. There has been a dramatic uptick in the use of dopamine, a remarkable drug, in contemporary treatments ever since its breakthrough discovery by Carlsson. Levodopa has been called "the chemical of the century," yet the work of other researchers and academics is essential to its discovery and development.

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CHAPTER 17

EVALUATION OF POTENT ANTI-CANCER ACTIVITY OF ISOFLAVONOID "GENISTEIN"

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ABSTRACT:

Genistein is an isoflavonoid that is abundant in soybeans. It is being examined extensively for its tumoricidal properties since it contains a diverse variety of bioactive. Investigations into the mechanisms of anti-cancer efficacy have shows a variety of paths, including cell proliferation stimulation and tyrosine kinase repression. There have been a lot of concerns associated with conventional medications and treatments for cancer which can also be life-threatening. Nowadays, people are more concerned about the side effects associated with cancer treatments. Hence, a lot of studies are now being conducted to explore phytocompounds. One of those phytocompounds is genistein which is gaining a lot of traction for a variety of cancer. Hence, the present study aims at reviewing the effects of this isoflavonoid on cancer patients. In addition to that, the author also provides a discussion on the future consideration and opportunities which need to be refined for making genistein a potential lead molecule.

KEYWORDS:

Anti-Cancer, Breast Cancer, Isoflavone, Inflammation, Genistein.

1. INTRODUCTION

Immune system protection against infection or damage is inflammation. Inflammation serves to get rid of dangerous and alien stimuli and to go back to normal physiological and tissue functions. Chronic and acute inflammatory responses are two different forms of inflammation that can exist [1]. The term "chronic inflammation" refers to an inflammatory reaction that lasts more than a few days and is distinguished from acute inflammation, which develops right once after damage. Chronic inflammation can develop as a result of inadequate treatment of acute inflammation, which may accelerate the deterioration of tissue, resulting in functional limitations. As it contributes significantly to the development of "asthma", "cancer", "neurodegenerative disease", "multiple sclerosis", "atherosclerosis", "osteoarthritis", "chronic obstructive pulmonary disease", "inflammatory bowel disease", and "obesity" is now cited as a significant trigger in several conditions [2]. One of the major diseases which is becoming a cause f concern is cancer both in men and women.

Epidemiological research has already demonstrated that soy products significantly reduce the incidence and mortality rates of prostate cancer and breast cancer. The bulk of the soy isoflavones sometimes referred to as soy phytoestrogens, which seem to be present in substantial

concentrations in soy products include genistein (60%) and daidzein (30%), as well as trace amounts of glycitein (10%). Depending on the tissues and the presence of coregulator proteins, phytoestrogens function as naturally occurring, selective estrogen receptor (ER) modulators. Owing to their purported estrogen-antagonistic effects, it has been hypothesized that they may lessen the risk of hormone-dependent malignancies. Figure 1 shows the Graphical Representation of Cancer prevalence by Region as per Global Cancer Observatory (GLOBACAN; 2018).

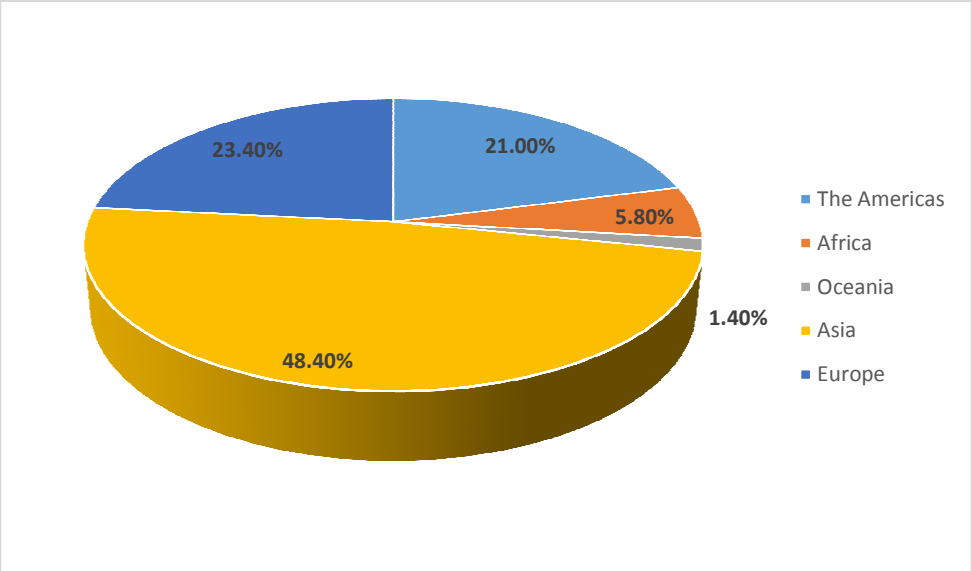

Figure 1: A Graphical Representation of Cancer Prevalence by Region as per Global Cancer Observatory (GLOBACAN; 2018).

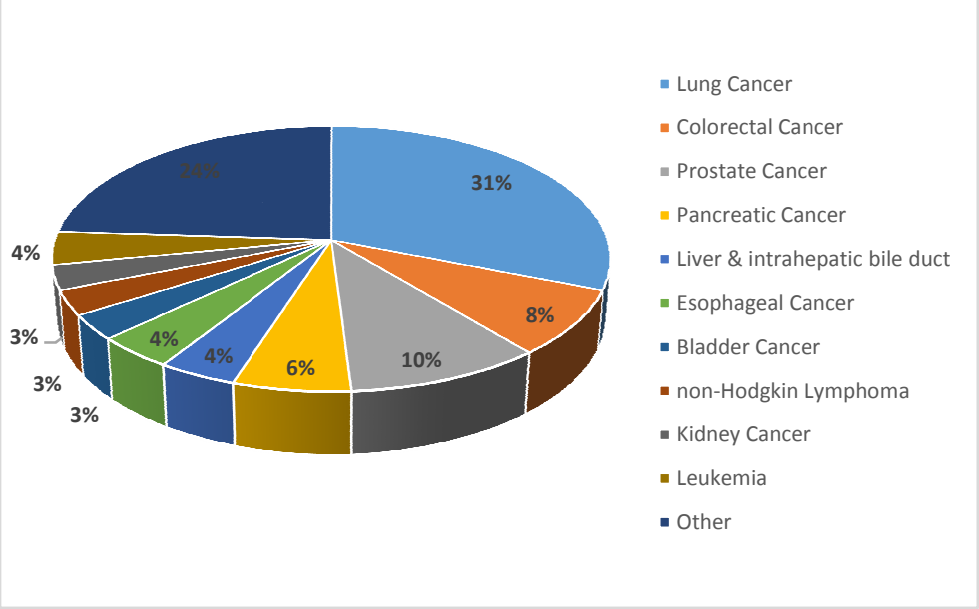

Figure 2: A Graphical Representation of Cancer Prevalence by Types.

Figure 2 shows the Graphical Representation of Cancer Prevalence by Type. Genistein, a member of the isoflavones, has undergone significant research to identify its chemoprotective and medicinal effects. Genistein has been found to prevent the development of non-hormone-dependent cancers like stomach, lung, colon, and pancreatic tumors in several in vivo and in vitro investigations[3], [4]. The regulation of genes that regulate the cell cycle and death is how genistein produces its different modes of action. Genistein may also work throughout its molecular targets to prevent angiogenesis and antioxidant events. Therefore, the present study aims at reviewing the anti-cancer activity of Genistein with a special emphasis on the mode of action associated with it.

The current paper is divided into a total of five sections: the first section converses the importance of conducting the work; the second section offers a comprehensive review of the literature; the third section discusses the method used to perform the study; the fourth section discusses the future consideration and the fifth section offers a concluding comment.

2. LITERATURE REVIEW

2.1.Genistein

A phytoestrogen isoflavone known as Genistein, which ranges in concentration from 0.2 to 0.6 mg per 100 grams of legumes and ripe seeds, is readily accessible. Its high solubility in several polar solvents, including "dimethylsulfoxide", "acetone", and "ethanol", and "low water solubility", maybe the cause of its decreased oral bioavailability. Genistein is well absorbed after being administered orally, with a tmax (transport maximum) of 5 to 6 hours and a t1/2 of 8 hours. When Genistein crosses the blood-brain barrier and placenta, it spreads quickly all through the body. In the digestive system and liver tissue [5].

It functions as an antineoplastic and anticancer drug by inhibiting the activities of protein topoisomerase-II (DNA topoisomerases, type II) and tyrosine kinase. In mouse and human cell lines, it has been demonstrated through experimentation to cause G2 phase arrest. Genistein also functions as an antihelmintic[6]–[8]. It is the component in *Felmingia vestita,* a plant historically used to treat worms. Table 1 shows the Molecular Formula, Synonyms, and Molecular weight of Genistein. Poultry cestode, pork trematode, and common liver fluke have all been successfully treated with it. Furthermore, genistein, a phytoestrogen, can selectively modulate estrogen receptors. It has been studied in clinical trials as a possible substitute for traditional hormone treatment to assist postmenopausal women to prevent cardiovascular disease. Kudzu, tofu, fava beans, and lupin are a few natural sources of genistein. Figure 3 shows the Chemical Structure of "Genistein". Figure 4 shows the Major Biological Sources to obtain Genistein.

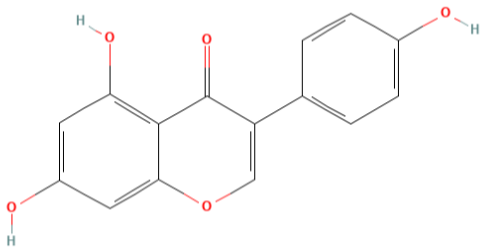

Figure 3: Illustrating the Chemical Structure of "Genistein".

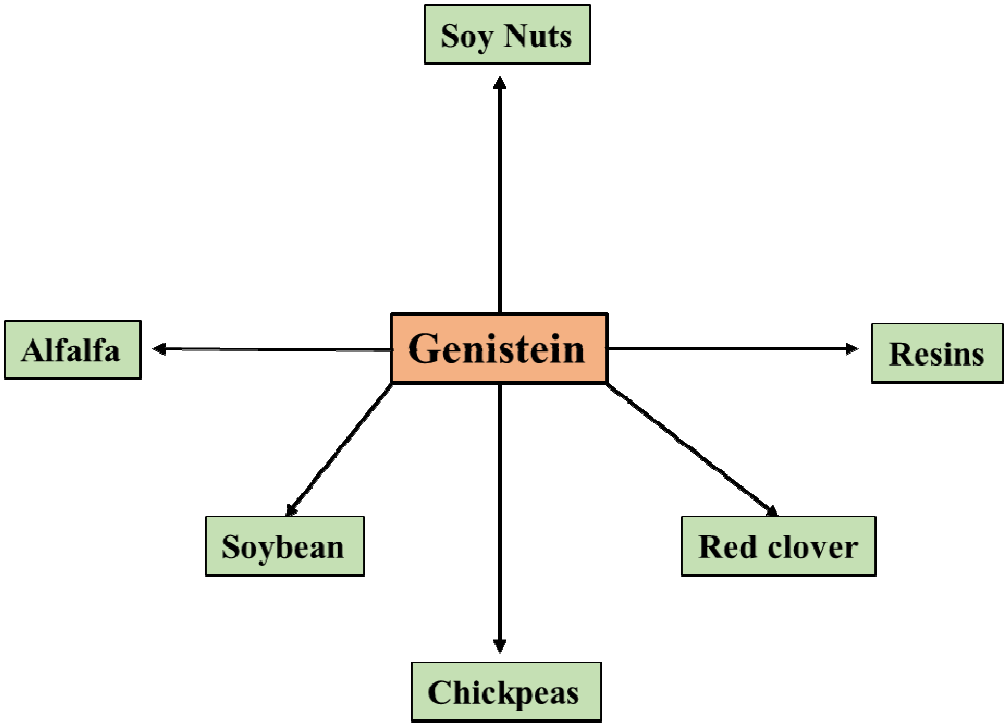

Figure 4: Illustrating the Major Biological Sources to Obtain Genistein.

Table 1: Enlisting the Molecular Formula, Synonyms, and Molecular Weight of Genistein.

Compound Name	Genistein
Molecular Formula	$C_{15}H_{10}O_5$
Synonyms	446-72-0, 4',5,7-Trihydroxyisoflavone, Prunetol, Genistein
Molecular Weight	270.24

2.2.Effects of Genistein on Cancer

The scientific world has been interested in genistein because of its possible helpful effects on human severe illnesses such as cancer. Genistein's mechanistic understanding exposes its potential for antimetastatic, antiangiogenic, cell cycle arrest, apoptotic induction, and anti-inflammatory actions. Among all types of cancers, genistein is investigated and is now intensively being investigated for breast, lung, and prostate cancer.

2.2.1. Breast Cancer

Kabaa et al. conducted research using two cancer lines, MDA-MV-231 and MCF-7. In cell viability experiments, the study found a significant dose-dependent response. Genistein has an IC50 value of 47.5 M. Isoflavonoids triggered death both in cell lines in a “dose-dependent” and “time-dependent” manner, with isoflavonoids being much more active in MCF-7 cells [9].

Andrade et al. showed that genistein consumption following a tamoxifen response reduced the elevated probability of reappearance in the children while having no impact on the control offspring. The offsprings of obese dams showed a marked rise in the number of inflammatory Enterobacteriaceae and Prevotellaceae and a decrease in the production of short-chain fatty acids by "Clostridiaceae". These alterations and elevated levels of the gut metabolite N-acetylcholine, which are associated with a rise in all-cause mortality, were both reversed by genistein supplementation [10]. Figure 5 shows the various mechanism by which genistein exhibits anti-cancer effects in breast cancer patients.

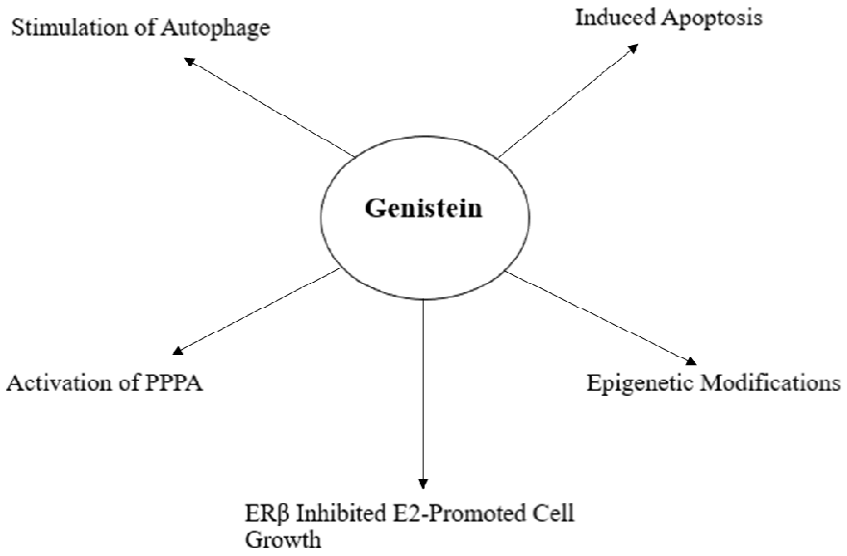

Figure 5: Illustrating the various mechanism by which genistein exhibits anti-cancer effects in breast cancer patients.

2.2.2. Prostate Cancer

Soy isoflavones may lessen the side effects of radiation and chemotherapy. Furthermore, in men with prostate cancer, soy isoflavone compounds may improve the effectiveness of "chemotherapy" and "radiation treatment". A decreased risk of various malignancies has been linked to soy diet consumption. Additionally, eating soy-based foods while receiving cancer therapy may improve results and lengthen survival. These findings sparked "*in vitro" and "in vivo"* research to clarify the biological effects of numerous chemicals found in soybeans.

Many of the biological processes involved in the initiation and advancement of cancer are modulated by soy isoflavones, which have been proven to have substantial biological impacts. Furthermore, their selective estrogen receptor modulation properties, these c also possess epigenetic properties, antioxidant, and anti-inflammatory, that might also attempt to clarify their potential importance in cancer prevention [11].

Shafiee et al. looked into the "genistein" influence on "p38 mitogen-activated protein kinase (p38MAPK)" and "caspase-3", which are the primary cellular signaling pathways in PC3 cells. Therefore, their study demonstrated that By lowering the potential for metastasis and controlling the "caspase-3" and "p38MAPK pathways" at various protein and transcription levels, genistein demonstrates its advantageous anticancer characteristics on PC3 cells.

2.2.3. Lung Cancer

Fu et al. looked at whether FoxM1 and MnSOD activity was accountable for the anticancer effects of “genistein” on “cancer stemlike cells (CSLCs)” from lung cancer cells. The results of their study demonstrated that sub-cytotoxic quantities of genistein hindered lowered expression of Bmi1, CD44, CD133, and Nanog and sphere formation activity in LCSLCs. Genistein additionally inhibited invasive and the migratory activity of LCSLCs. FoxM1 and MnSOD knockdown increased the inhibitory activity on CSLC features of LCSLCs.

Chan et al. discovered that genistein might increase intracellular ROS production, reduce mitochondrial activity, and mitochondrial membrane potential, and upregulate the transcription of proteins related to mitochondrial apoptosis. Additionally, the investigation found that genistein dramatically raised the expression of PUMA and FOXO3a in NSCLC.

The above studies have demonstrated the efficacy of genistein on a variety of cancer predominantly “prostate cancer”, “breast cancer”, and “lung cancer” with a variety of proposed mechanisms of action involved in cellular signaling pathways. However, the present study is conducted to combine the recent evidence to make a concluding remark for future consideration.

3. METHODOLOGY

Google Scholar, PubMed, Science Direct, Hindawi, and Research Gate are just a few of the internet databases that were used to gather the material for this review research. The following keywords are used to categorize and choose the research and review papers: "Prostate Cancer," "Genistein," "Soy Products," "Lung Cancer," "prostate cancer," "Cancer," "Anti-cancer agent," "Breast cancer" "Mammary cancer," and "Health Issues." In addition to that, to get other relevant records that were missed in keyword searches were manually gathered with google scholar searches on the first five pages. Figure 6 below provides the block diagram of the process to conduct the review.

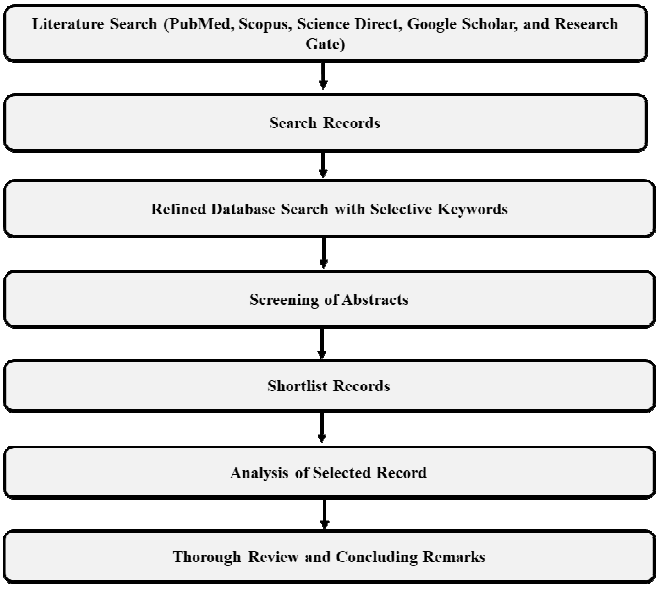

Figure 6: Illustrating the Methodological Design to Retrieve Relevant Records for Review Study.

4. DISCUSSION

A soy-rich diet and cancer prevention were linked by several observational studies. The above research studies were prompted by findings indicating prostate and breast cancer rates in Asia, such as China and Japan wherein foods are abundant in soy products, are significantly lower than in the Europe and United States. It's been shown in several meta-analyses that eating soy products lowers the chance of males developing prostate cancer and lowers the risk of Asian women developing breast cancer. In Western women, this link was not verified. In addition, a recent meta-analysis discovered that eating soy isoflavones can reduce the risk of developing breast-related cancers in Asian women who are pre- and postmenopausal.

We examined the current data about the encouraging potential of genistein as cancer preventative. Genistein may have a therapeutic effect in treating various cancers, according to several preclinical and clinical studies. It is well known that the development of negative outcomes in cancer treatment, such as “drug resistance”, “a greater risk of recurrence”, and the “absence of or ineffectiveness of therapies” including chemotherapy, phototherapy, surgery, and radiation, occurs. To increase the effectiveness of chemotherapeutic therapy and reduce side effects, attention has recently been focused on natural therapies. Genistein can be categorized as one of these substances since it exhibits synergistic activity when combined with popular anticancer medications including docetaxel, tamoxifen, and adriamycin indicating a possible role in combinatorial treatment.

As a result, it is plausible to assume that genistein will have a major clinical outcome when supplied at pharmacological dosages (hundreds of micromolar) but will have little or no impact when delivered at chemopreventive levels (1 M). Most probably, the reality is much more complicated than we can ever fathom. We can postulate pleiotropic antitumor action arising from synergistic processes attributed to the abundance of different substances whenever genistein is adsorbed at low quantities with other bioactive compounds present in the food (or their metabolites). Conversely, one might assume that genistein has consequences at smaller concentrations that differ from those observed at high levels, dependent on the biological background and molecular target under investigation.

5. CONCLUSION

According to several epidemiological and experimental studies, genistein may have promise as a chemopreventive or curative medication against cancers. In addition to its hormonal actions, genistein has anticancer properties that are connected to multiple cell signaling pathways. Because the therapeutic efficacy of cancers is complicated by the buildup of chemoresistance, genistein is expected to play a role in activating multi-resistant cancer cells and have comparable efficacy with standard chemotherapeutic drugs. Even though clinical studies are being carried out to evaluate the functionality of genistein as an anticancer agent against different types of cancer, there is still a lack of large clinical trials with a variety of factors to confirm the efficiency of genistein.

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CHAPTER 18

USE OF HERBAL MEDICINE IN THE TREATMENT OF SKIN DISEASE

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ABSTRACT:

The acceptance and recognition of herbal medicine are increasing day by day. One of the important reasons for increasing this interest is the awareness of natural remedies being more efficacious and less harmful than synthetic drugs. Numerous skin conditions are common health issues that affect people of all ages, from newborns to the elderly, as well as being harmful in a variety of ways. A healthy body depends on having good skin. Cancer, herpes, and cellulitis are among the skin disorders that many people might contract. These disorders are routinely treated using certain wild plants and their parts. The utilization of plants predates the existence of mankind. Natural medicine is reportedly safe and inexpensive. It is a good basic material for creating new synthetic substances as well. The most prevalent type of illness that affect people of all ages is skin disorders. The study's objective is to recommend treatments for human skin disorders as well as to highlight the necessity for a thorough investigation of medicinal plants that may yield new treatment ideas for other terrible diseases.

KEYWORDS:

Antibiotic, Disease, Herbal, Medicine, Skin Disease.

1. INTRODUCTION

The largest organ in the human body is the skin, which covers the outside of the body. It also serves as the initial line of defense. Many specialized cells or structures make up the skin. Epidermis, dermis, as well as hypodermis, are the three major layers. Each layer has a unique effect on the properties of the skin as a whole. The thickness of the epidermis, the top layer of the skin, varies from one part of the body to another. It is thinnest (0.05 mm) on the eyelids as well as thickest (0.5 mm) on the palms or soles (1.5 mm). The thickness of the dermis varies according to where the skin is located [1], [2].

The hypodermis is a subcutaneous connective tissue that connects the dermis to the skin. The major blood vessels and nerves are found in the subcutaneous tissue, which is a layer of fat or connective tissue. This layer is critical for controlling either internal or exterior body temperatures. This layer's thickness differs from individual to individual across the body. The three primary elements of the skin are sweat glands, hair follicles, as well as sebaceous glands [3], [4].

1.1. Common Skin Problem

Skin problems are a common illness that can cause a variety of injuries and impact individuals of all ages, from babies to the elderly. There are nine major kinds of skin disorders, even though there are over a thousand ailments that can harm the skin. Rashes A rash is a red, inflamed area of skin or a cluster of different spots. Inflammation, infections, allergies, underlying disorders, or anatomical faults like blocked pores or faulty oil glands can all cause this. Rashes include dermatitis, eczema, pityriasis rosea, hives, and psoriasis [5], [6].

In infections caused by yeast on the skin's surface, harmless fungi are always present. Infection occurs when these microorganisms enter the body. These infections, which are generally superficial and affect the skin, hair, or nails, include athlete's foot, ringworm, and lock itch. Furthermore, in people with compromised immune systems or who have just taken antibiotics for a lengthy period, the fungus might spread deep into the body, leading to a more serious sickness.

1.1.1. Rashes:

A rash is a patch of red, irritated skin or a collection of distinct patches. These can be brought on by inflammation, allergies, infections, underlying diseases, or structural flaws like clogged pores or dysfunctional oil glands. Acne, eczema, dermatitis, pityriasis rosea, hives, and psoriasis are a few examples of rashes.

1.1.2. Parasitic Infections:

These happen when a virus enters the skin's inner layers through the stratum corneum. Warts, shingles (herpes zoster), and herpes simplex are a few examples of viral skin diseases. Measles or chicken pox are two examples of systemic viral diseases that can have an impact on the skin. Antibiotics cannot treat viral illnesses.

1.1.3. Bacterial Illnesses:

Staphylococci or streptococci are the two most prevalent forms of bacteria that cause such illnesses. The follicles, the deeper layers of skin, or the epidermis can all get infected with bacteria. These infections might spread throughout the entire body if improper care is not taken to treat them. Examples include cellulitis, Lyme disease, or impel folliculitis. Antibiotics work better for treating bacterial illnesses.

1.1.4. Infection caused by Parasites:

These occur when a virus travels through the stratum corneum to the inner layers of the skin. Viral skin diseases include shingles, warts (herpes zoster), and herpes simplex. Measles or chicken pox are two examples of systemic viral infections that can cause damage to the skin. Viruses cannot be treated with antibiotics. Bacterial infections The two most common types of bacteria that cause such diseases are staphylococci and streptococci. The bacteria can damage the follicles, the deeper layers of the skin, and the epidermis [7], [8]. If these diseases are not treated properly, they can spread throughout the body. Lyme disease, cellulitis, or impale folliculitis are some examples. Antibiotics are the most effective technique for treating bacterial infections.

1.1.5. Problems with Skin Pigmentation:

The amount of pigment in the skin is controlled by the body's generation of melanin. Hypopigmentation, or the lack of pigment, can be caused by the absence of melanocytes,

chemical or cold exposure, damaged cells, c or certain illnesses. Hyperpigmentation or an enhancement in pigment can be caused by skin irritation, hormone changes, aging, a metabolic condition, and any other underlying issue. Freckles, Melasma, or age spots are examples of hyperpigmentation. Vitiligo is an example of poor pigmentation.

1.1.6. Neoplasms and Cancers:

When skin cells start to divide more quickly than usual, these growths develop. Skin growths do not always indicate malignancy. Some tumors are benign and won't grow. Every year, 800,000 Americans lose their lives to cancer, the majority of which are skin malignancies. 90% of the time, exposure to the sun is to blame. The three forms of skin cancer are basal cell cancer, squamous cell cancer, and malignant melanoma, with basal cell cancer being the most treatable and the most deadly form. One preventative measure is to protect the skin from UV rays that might damage it. The chance of treatment rises with early discovery. As a result, regular self-checks are advised. Figure 1 shows the Natural and Herbal medicine for the Treatment of Skin Diseases.

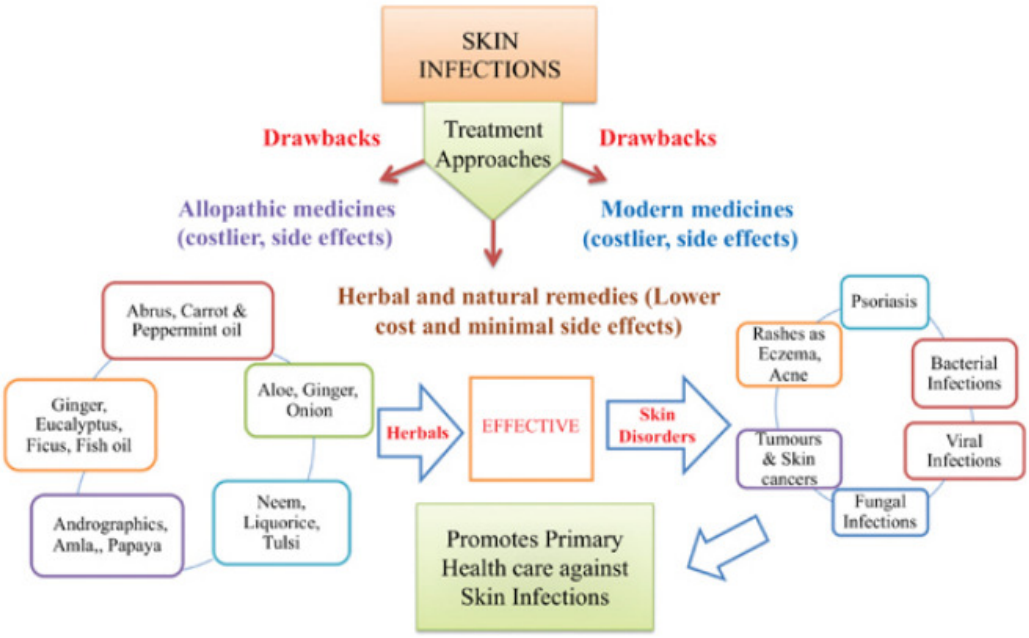

Figure 1: Illustrate the Natural and Herbal medicine for the Treatment of Skin Diseases [9]**.**

1.2. Treatment for Conventional Skin Diseases:

The common medications used topically include:

i. *Antibacterials:* Medicines that fight bacteria, such as Bactroban or Cleocin, are widely used to treat or prevent illnesses.
ii. Psoriasis can be treated with anthralin (drithocreme, mi canal, and other names), which helps to reduce inflammation.
iii. *Antifungal drugs:* Lamisil, Lotrimin, or Nizoral are examples of common topical antifungal drugs used to treat skin conditions including ringworm or athlete's foot.

iv. *Benzoyl peroxide:* Use lotions and other acne treatments that contain benzoyl peroxide.
v. *Coal tar:* This topical treatment is available either with or without a prescription, or its dosages range from 0.5% to 5%. Coal tar is used to treat psoriasis and seborrheic dermatitis, among other conditions (often in shampoos). Coal tar is presently infrequently used due to its slow action and risk of seriously staining clothing or bedding.
vi. Different corticosteroids are utilized to treat skin conditions including eczema in the form of foams, lotions, ointments, or creams.
vii. *Retinoids:* These medications, such as Retin A and Tazorac, are creams or gels derived from vitamin A and used to treat conditions including acne.

Salicylic acid is a medication that comes in a variety of forms, including patches, lotions, soaps, gels, or shampoos. Due to the possibility of negative consequences from applying more and more to the body at once, it should be used with caution. Salicylic acid, an active ingredient in several skin care products, is used to treat warts as well as acne.

2. LITERATURE REVIEW

Kalyani Pathak and Ratna Jyoti Das study discusses the function and benefits of numerous medicinal herbs for various skin conditions. Skin diseases are the most common ailments that afflict people of all ages.

Skin diseases are among the common opportunistic infections among immunocompromised individuals due to the rising complexity of HIV/AIDS, making skin health an important part of basic healthcare in many areas. Skin problems are responsible for a great deal of pain, suffering, disability, and financial loss. In addition, they have a significant disadvantage due to their visibility in society. However, thanks to recent advancements, skin grafting, laser treatment, and plastic surgery can all effectively eliminate cutaneous scars [10].

A Gupta studied the treatment of numerous skin problems, and examine the ethnobotanical knowledge base. Because of the increasing difficulty of HIV/AIDS, skin illnesses are among the typical opportunistic infections in immunocompromised persons, making skin health an essential component of primary healthcare services across several communities. The use of therapeutic plants in traditional medicine in India is extensive. In India, several formulas have been used to treat burns, cuts, and other skin conditions. In this study, we found a variety of medicinal plants that individuals utilize to treat dermatological conditions. Additional thorough ethnobotanical, as well as ethnopharmacological research, may result in the creation of therapeutic plants for skin diagnosis and services [11].

Thomas M Walter et al. in their studies examined the individual plants and made-up medications listed in traditional Siddha Indian medicine as effective treatments for skin conditions. Individuals are aware of the therapeutic benefits of the foods they eat daily. The foundation of traditional remedies is made up of the priceless bioactive chemicals that medicinal herbs are naturally endowed with. Herbal treatments have been used to cure a variety of infectious disorders throughout human history. The inclusion of phytochemical elements like tannins, glycosides, alcohols, and aldehydes, among others, is what causes this effect. These elements are beneficial for future generations as well as for the development of medicinal medicines. People are vulnerable to several lifestyle ailments, particularly skin illnesses, as a result of their fast-paced lifestyles and contaminated environment [12].

3. DISCUSSION

Folk herbal therapy has been used to address skin health issues for tens of thousands of years. Even the great apes, who are physiologically our closest cousins, employed herbs for self-care. Depending on what was available, different continents have employed herbs in a variety of ways. Due to its link to the "Human Immunodeficiency Virus and Acquired Immunity Deficiency Syndrome" (HIV/AIDS), skin conditions have recently gained significant attention.

Over 80% of people in underdeveloped nations rely on traditional medicine to take care of their basic medical requirements, according to the "World Health Organization".

Given that it has the greatest worldwide collection of medicinal plants, India is regarded as the botanical garden of the world. In addition to being nontoxic and easily accessible, medicinal plants play a vital role in pharmacological research and drug development, but they are also used as therapeutic agents directly or as starting materials for the synthesis of drugs [13], [14].

Uses for the skin The skin's primary purposes are as follows:

i. The defense of the body.
ii. Sensation, or the act of sending information about the environment to the brain.
iii. Control of temperature.
iv. Immunity, which is the function of skin inside the immune system
v. Allows for development and mobility without risk of harm. Excretion of certain waste products from the body.
vi. Endocrine function, such as concerning vitamin D.

From newborns to the elderly, skin disorders are the most prevalent health concern. These conditions aren't simply basic; they hurt the skin in many different ways and are frequently the signs of more serious underlying conditions like herpes, cancer, or cellulitis.

Since herbs offer more benefits than other medications, it is necessary to understand skin problems and how to treat them. Many different ailments are frequently treated using plants. Since the dawn of humankind, these plants have been utilized. Both affordable and secure [14], [15].

They serve as valuable raw materials in the creation of fresh synthetic substances. This review looks at several plants that can be used to cure certain ailments.

3.1. Herbal Medicine for Skin Disease:

Owing to several benefits, including frequently fewer side effects, improved patient tolerance, being comparatively less expensive, and being accepted due to a long history of usage, natural medications derived from plants are becoming more and more popular. Additionally, herbal remedies offer logical ways to cure a variety of illnesses that are difficult to treat and incurable using conventional medical practices.

For these reasons, several plants have been researched as potential treatments for conditions affecting the skin, from itchiness to skin cancer. Over the previous 17 years (1995-2012) of study, 31 plants have so far been reported to be useful in treating a variety of skin conditions. Some of them are listed below in Figure 2.

Figure 2: Illustrate the pictorial representation of some plants that are widely used in the treatment of skin disease. a) Ricinus communis, b) aloe vera,c) Tea Tree, d) Catharanthus roseus.

3.1.1. For Acne, Use Tea Tree Oil:

Acne may be treated naturally with tea tree oil. Acne is a common skin illness that often starts as you enter adolescence. The American Pharmaceutical Association Practical Guide to Natural Medicines reports that after three months of use, tea tree oil significantly reduced the number of acne lesions. Additionally, it revealed a decreased prevalence of negative side effects such as irritability, burning, dryness, or itching. The activity is brought about by plant terpenes as well as their related alcohols' anti-inflammatory properties. It should only be used topically; inside use might result in toxicity.

3.1.2. Use Garlic for Bacterial and Fungal Infections:

Garlic's antimicrobial and antifungal qualities are essential in the treatment of a variety of fungal and bacterial skin illnesses, including athlete's foot, ringworm, and fungal nail infections. Ajoene, a substance found in garlic, has antifungal properties. When purchasing ointments to treat a fungal infection, you should also keep an eye out for this substance. Garlic is thought to be harmful to consume when expecting or nursing, so stay away from it. Apply crushed garlic juice twice a day to the afflicted region and wash it off with water after 30 minutes [16], [17].

3.1.3. Use Aloe Vera for Burns and Wounds:

Aloe Vera has been utilized to heal burns and wounds for ages. It helps heal frostbite and chronic leg ulcers while reducing itchiness and burning sensations. Aloe vera contains salicylic acid, which works as an analgesic or anti-inflammatory drug by preventing the formation of prostaglandins. When administered topically, it might occasionally result in allergic contact dermatitis, so take caution. Here are some other tips for removing burn scars and markings at home.

3.1.4. Leafy Vegetables for Psoriasis:

Cabbage leaves are effective at treating psoriasis symptoms when applied to irritated skin. It has a high sulfur content, which helps psoriatic sufferers' skin feel less irritated and inflamed. Wash only a few cabbage leaves, smash them with a rolling pin, as well as warm them to create a

poultice. To treat skin irritation and itching, apply this paste directly to the affected area. Additionally, learn about the 7 ways to avoid a psoriasis flare-up.

Skin cancer that begins in the basal layer of the skin's cells is known as “basal cell carcinoma” (BCC). Basal cells in their natural state border the epidermis. Keratinocytes are skin cells that divide to produce new skin cells. Cancer of the basal cells leads to tumors on the skin's surface. These tumors frequently exhibit sores, lumps, scars, growths, or red patches as symptoms**.** Although BCC seldom metastasizes (spreads to other regions of the body), it can nonetheless result in deformity. In rare circumstances, it may spread to other bodily areas. If this occurs, it might become life-threatening. BCC is the most prevalent kind of skin cancer [18], [19].

3.1.5. Turmeric:

For hundreds of years, turmeric, an herb or spice, has been used in alternative medicine. It is known that turmeric has several health advantages, and it is referenced in traditional Ayurvedic remedies. Curcumin, a potent antioxidant found in turmeric, helps to inhibit the growth of cancer. The afflicted area should be covered with a thick paste made of turmeric and water for around 20 minutes. The use of turmeric has also been demonstrated to increase immunity against all illnesses.

Herbal medicine is a success of widely accepted medicinal variety. Medicinal plants almost always play a vital role and serve as the foundation of traditional medicine. The establishment of criteria for quality, safety, and efficacy is a crucial first step in ensuring the safe use of these medications. In the majority of the nations where ethnomedicine is frequently used to treat cut wounds, skin infections, aging, mental illness, swelling, cancer, diabetes, jaundice, asthma, scabies, venereal diseases, eczema, snakebite, or gastric ulcers, tribal healers teach locals how to make herbal medicines [20]. They don't retain any records, and knowledge is mostly verbally transmitted from one generation to the next. The WHO has shows a strong interest in gathering information about medicinal plant use by indigenous peoples throughout the globe. There is a need for a worldwide campaign to preserve medicinal plants and revive regional cultures' old medical practices. The need for medicinal plants is gradually rising while the woods are steadily getting less. This has led to an unscientific and excessive use of the forest's therapeutic plants.

4. CONCLUSION

The majority of people in the globe live in rural locations, where they are more likely to develop skin conditions such as pittosporum, Versicolor, papilloma, eczema, psoriasis, pigmented nevi, and melanoma. These skin conditions are brought on by microorganisms like fungi, bacteria, and viruses that are all around us. Skin diseases not only cause people to become physically and emotionally unwell, but they also cause them to spend a lot of money on treatment when they reach a chronic stage. Humans can save a lot of money if these diseases are treated early on. Therefore, herbal medicines that are affordable and have few side effects will be useful for treating illnesses in all individuals, particularly those in developing nations. There are several medicinal herbs that tribal people have historically utilized for skin disorders. In the current study, researchers discovered a few of the therapeutic herbs that individuals utilize to treat dermatological conditions. Additional thorough ethnobotanical or ethnopharmacological research may result in the creation of medicine for the treatment and care of the skin.

The use of herbs to treat various skin conditions has a lot of potential. More than 80% of Indians treat skin disorders with a variety of plant-based drugs and traditional medicine. They can be very beneficial to the people of India in general, and the poor people in particular, because they are far more economical than conventional allopathic treatments. Herbs are full of active compounds and have the potential to treat a wide range of skin conditions, from rashes to deadly skin cancer, in a method that is both less risky and more economical. Habitat loss, habitat degradation, urbanization, as well as other human activities may represent a danger to these species since more than half of the plant species that are useful for treating skin conditions are often limited to forests. The urgent need is to preserve these plants with local support and to carry out in-depth studies in this area to increase the potential for using herbal remedies to treat skin conditions.

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CHAPTER 19

THERAPEUTIC EFFECTS OF NATURAL MEDICINE ON ISCHEMIC STROKE

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ABSTRACT:

Ischemic stroke is a leading cause of mortality worldwide. During the recovery period of a stroke, significant alterations in the Central Nervous System (CNS) can be seen, including emotional, cognitive, and behavioral impairments. Brain ischemia impacts a considerable number of individuals worldwide, resulting in lifelong impairment or death. There is no long-term medication that can restore neurological impairment and increase blood flow to the injured region. Since there are now no effective therapies for stroke, many scientists are looking into the best plants or medications to treat it. To address this issue, newer remedial procedures are needed because this treatment has several downsides. Utilizing medicinal plants as a therapy method is the most cost-effective choice with fewer negative effects. Hence, the present study aims at exploring the effects of medicinal plants for managing ischemic stroke. In addition to that, the study also provides future considerations which can help fill the gap for harnessing the potential of herbal medicine.

KEYWORDS:

Herbal remedies, Ischemia, Ischemic stroke, Neuroinflammation, Stroke.

1. INTRODUCTION

A stroke is an abrupt impairment of brain activity and one of the primary causes of disability and death. It is mostly brought on by a disruption in the blood supply to the brain (referred to as an ischemic stroke in popular culture) or by the collapse of capillaries or vessels in the brain (that is hemorrhagic stroke). The brain cells (neurons) in the afflicted region of the brain die as a result of abnormalities in the blood flow or blood vessel rupture. The neurologic condition known as brain ischemia/stroke is vascular generated and is characterized by the sequential pathological events known as the "ischemic cascade," which include oxidative stress, energy failure, inflammation, excitotoxicity, apoptosis, etc. Reduced/blocked blood flow is what causes all of these negative repercussions [1], [2].

For the brain to function normally, blood flow must continuously carry oxygen and glucose into the brain; any disruption of this blood supply causes significant brain damage. The rapid loss of blood flow accompanied by the subsequent resuscitation of the ischemic region causes a cascade of molecular and cellular processes that lead to ischemic brain damage. The epicenter of the ischemic territory (also known as the ischemic core), in which the blood circulation is the lowest, seems to be where brain damage occurs faster and more severely in ischemia, which is caused by

blockage of the cerebral arteries primarily caused by the middle cerebral arteries, the much more common type of stroke. The primary cause of neuronal cell death in the ischemic core area is energy failure. In the past three decades, an increasing number of studies examining the pathophysiology and processes of stroke have concluded that neuroprotection is an effective stroke therapy method. Even though their pre-clinical effectiveness has been shown, all neuroprotective medications have so far failed in clinical studies [3]–[5]. Natural remedies are becoming more popular as a result of the absence of efficient therapeutic approaches for the treatment of stroke. Natural medicine, in contrast to Western medicine, works by giving the body exogenous stimulants to help it maintain and restore its internal equilibrium. Recently, the overall effects of certain herbal remedies on stroke have been studied. According to the research, using natural remedies may help the microcirculation of the brain, reduce neuroinflammation and oxidative stress, and alter microglia polarization. These effects may all help prevent ischemic/reperfusion damage. Figure 1 shows the Graphical Representation Illustrating the Variety of Causes Contributing to the Total Burden of Neurologic Disease Burden.

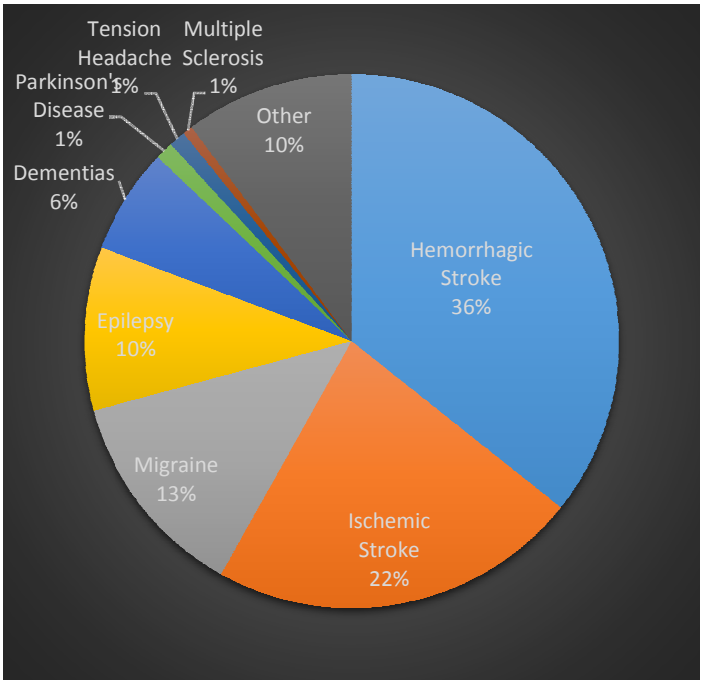

Figure 1: A Graphical Representation Illustrating the Variety of Causes Contributing to the Total Burden of Neurologic Disease Burden.

The ethnobiological method stands out as a key technique for the identification of new neuroactive natural compounds derived from plants that are consumed or employed as culinary or therapeutic ingredients by various cultural (ethnic) groupings. On the impact and possible advantages of traditional Eastern medicine (TEM) in stroke, various evaluations have been published in recent years. According to reports, several herbal remedies or their derivatives may be able to guard against ischemia/reperfusion injury, restore microcirculation in the ischemic brain, and suppress apoptosis, having neuroprotective qualities, which would support their use in patients suffering from ischemic stroke. The current paper is divided into a total of five sections: the first section discusses the importance of conducting the study; the second section offers a comprehensive review of the literature; the third section discusses the method used to conduct

the study; the fourth section discusses the future consideration and the fifth section offers a concluding comment.

2. LITERATURE REVIEW

The development of novel therapeutic agents for a wide range of human disorders can be greatly aided by herbal medicines, which are often derived from plants. The complicated stroke pathophysiology and the multifaceted effects of herbal medicine and its active ingredients may point to the bright future of natural medicine for stroke treatment. Herbal medications are thought to be effective in the treatment of stroke because of their anti-oxidant, anti-inflammatory, anti-apoptotic, neuroprotective, and vascular protective effects. Compared to allopathic therapy, herbs often have fewer adverse effects recorded and may be safer to use for a longer period of time. For persistent medical issues like stroke, herbal remedies are thought to be more efficient. The findings of laboratory studies on several medicinal plants and their active ingredients are encouraging. The use of herbal medicine in stroke, however, faces significant challenges as a result of the failure to convert laboratory animal studies into clinical trials. Efforts should be made to continue using treatment methods that have been shown to be helpful up until and unless scientifically thorough proof of the efficacy and safety of herbal medicine in ischemic stroke patients is obtained. Several medicinal plants have been investigated for their ant-stroke properties.

2.1.Allium sativum

Zhang et al. conducted a study to better understand how allicin affected rat cerebral ischemia/reperfusion (I/R) damage. Transient middle cerebral artery occlusion (MCAO) was performed on rats for 1.5 hours, followed by 24 hours of reperfusion. Random assignments of rats were made to the MCAO, sham surgery, and MCAO + allicin groups. The findings revealed that allicin decreased TNF levels, MPO activities in the serum, brain water content, cerebral infarction area, and neuronal apoptosis. According to the findings of the current study, allicin has anti-inflammatory and anti-apoptotic properties that safeguard the brain from cerebral I/R damage [6].

Figure 2: Illustrating Different Medicinal Plants and their Plants Having Efficacy Against Stroke; *Allium sativum, Ginkgo biloba, Allium cepa, Smyrnium olusatrum, and Punica granatum*.

Another study by Lin et al. demonstrated that sphingosine kinases 2 (Sphk2) were considerably expressed both in vitro and in vivo when allicin was present. An Sphk2-mediated pathway was implicated in the allicin-induced protection in experimental models, as evidenced by the partial reversal of the protective role of allicin towards MCAO and OGD damage after administration with the Sphk2 inhibitor ABC294640, therefore suggesting that a neuroprotective approach for ischemic stroke may be possible with a post-injury injection of allicin, according to the data taken together [7].

2.2. Ginkgo biloba:

Using the GRADE (Grading of Recommendation Assessment, Development, and Evaluation) technique, Chong et al. evaluated the evidence's degree of confidence. 12 randomized controlled trials with 1466 participants were discovered. According to combined data, ginkgo Biloba administration may have improved neurological function in AIS patients as measured by a 2.87-point decline on the National Institutes of Health Stroke Scale (95% CI: 4.01-17.74, p0.001). The use of *Ginkgo biloba* was also linked to an enhancement in activities of daily living and outcome measures (Mean Difference: 9.52; 4.66-14.33, p0.001). According to subgroup analysis, utilizing an injected version of Ginkgo biloba had a greater impact than using the oral form [8].

2.3.Allium cepa:

Saurabh Kumar et al. investigated how pretreatment with an aqueous extract of A. cepa protects against retinal damage brought on by ischemia/reperfusion (I/R). In their investigation, C57BL/6J mice had their pterygopalatine arteries (PPAs) tied for two hours before reperfusion. At 7, 14, and 28 days following surgery, the effect of oral pretreatment with an aqueous extract of A. cepa (300 mg/kg) on the expression of several genes was examined in comparison to the control and injury-only groups. In the retina at 14 and 28 days following treatment with A. cepa, compared to the damage-alone group, molecular analyses at various periods revealed enhanced expression of BCl-2, GDNF, GFAP, and Brn3b [9].

2.4.Smyrnium olusatrum

Hasan Yousefi-Manesh et al. looked into the impact of myrrh-like furanosesquiterpene isofuranodiene pre-treatment on inflammatory response and oxidative stress in experimental animals of ischemic stroke. Myrrh-like furanosesquiterpene was obtained by the crystallization of Smyrnium olusatrum essential oil, and its composition and quality were validated by NMR and HPLC investigations. The results of the study revealed that Acute pre-treatment with furanosesquiterpene (10 mg/kg i.p.) dramatically lowered the levels of the inflammatory cytokines IL-1, expression of pNF-B/NF-B, and TNF-alpha, and the lipid peroxidation biomarker MDA [10].

2.5.Punica granatum

In Wistar rats, Viswanatha et al. tested the cerebroprotective effect of Punica granatum methanolic leaf extract (MePG). According to the findings of their research, MePG possesses high antioxidant activity. Furthermore, in LPS-induced RAW 264.7 cell lines, MePG dramatically decreased the production of nitrite, ROS, and TNF-. Furthermore, as compared to sham controls, global ischemia followed by reperfusion resulted in substantial alterations in neurological and behavioral functioning in I/R control animals [11].

3. METHODOLOGY

The data for this review was gathered and assembled using electronic resources including Research Gate, Science Direct, PubMed, Scopus, and Google Scholar. A variety of relevant keywords and their combinations were used to find and sort the appropriate publications. Stroke, Ischemic stroke, Medicinal plants, herbs, botanical sources, and Neurological diseases, were among the keywords. The procedure utilized to find relevant records is shows in Figure 3 below.

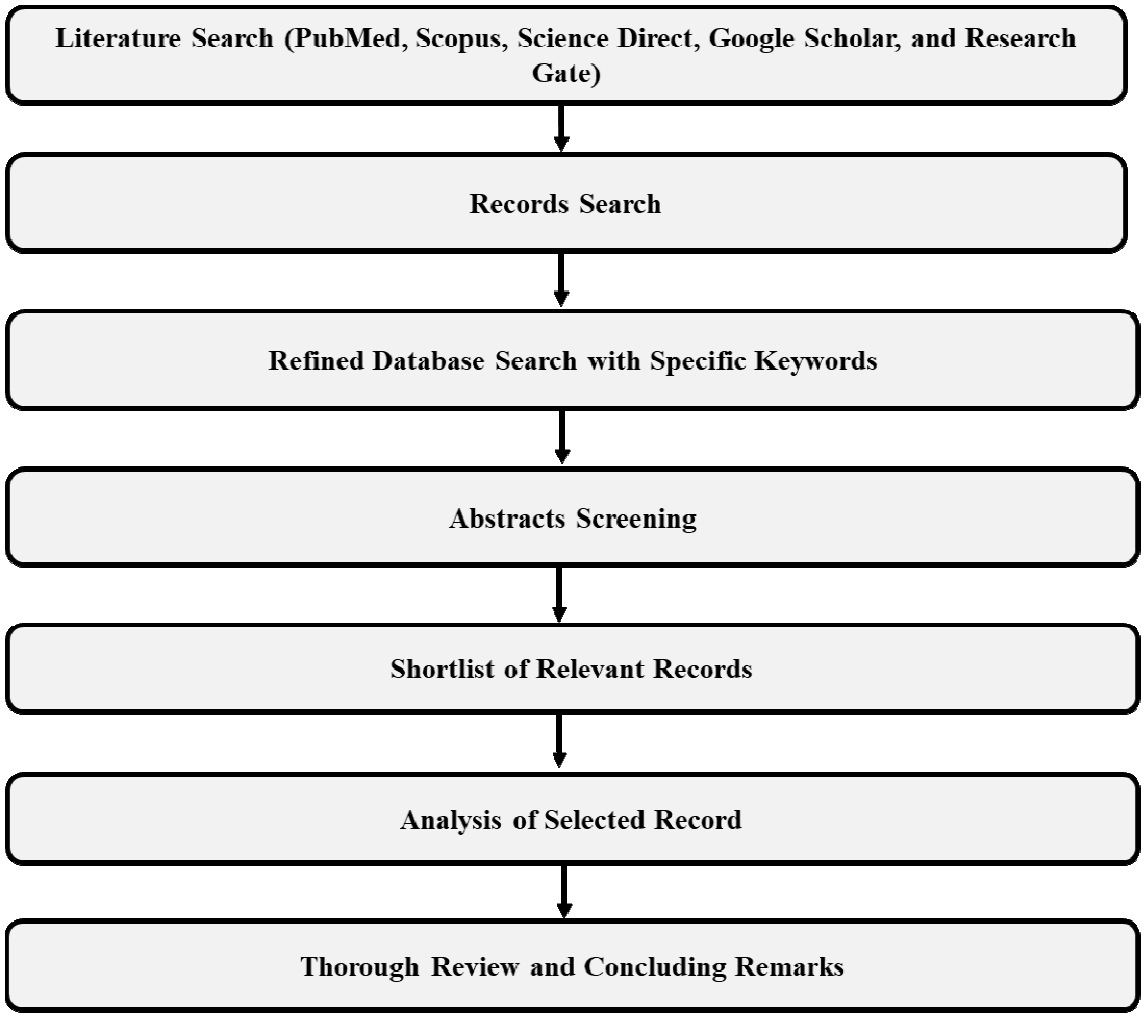

Figure 3: Illustrating the Methodological Design to Retrieve Relevant Records for Review Study.

4. DISCUSSION

Through the inhibition of oxidative stress, the reduction of neuroinflammation, and the attenuation of apoptosis, natural medicines show promising neuroprotective characteristics in the acute phase of cerebral ischemia. The active compounds of natural remedies, in contrast to the pharmacological pharmaceuticals employed in Western medicine, are frequently not identified, and the underlying processes that cause the neuroprotective benefits are still not fully understood. The evaluation and interpretation of the findings might be complicated by the

variability across formulations and batches of natural medicines utilized in the same study. In an I/R injury model, further research is required to clarify the specific function that natural remedies play in the ischemic cascade following a stroke. To comprehend the role of natural remedies in Ischemic stroke, it is also important to understand the factors that contribute to it which are illustrated in Figure 4.

Research into new applications for thrombectomy, stem cell therapy, and neuroprotection are among the emerging therapies in the field of Ischemic stroke care. It is unclear if thrombectomy would still be beneficial for individuals with less favorable imaging features, even though sophisticated imaging is increasingly being utilized to identify people who will benefit from it. Additionally, even though numerous herbal remedies show neuroprotective benefits in ischemic stroke animal models of experimentation, none of them have been successfully applied in clinical conditions. One of the main causes of the failure is that these studies were conducted primarily on healthy young adult rodent models instead of on older animals, even though stroke is more common in older people and the effects of natural remedies on older rodents could differ from their neuroprotective effects on younger animals. Consequently, it is strongly advised to use older animals to investigate the effects of natural medicine on stroke to realize their therapeutic applicability.

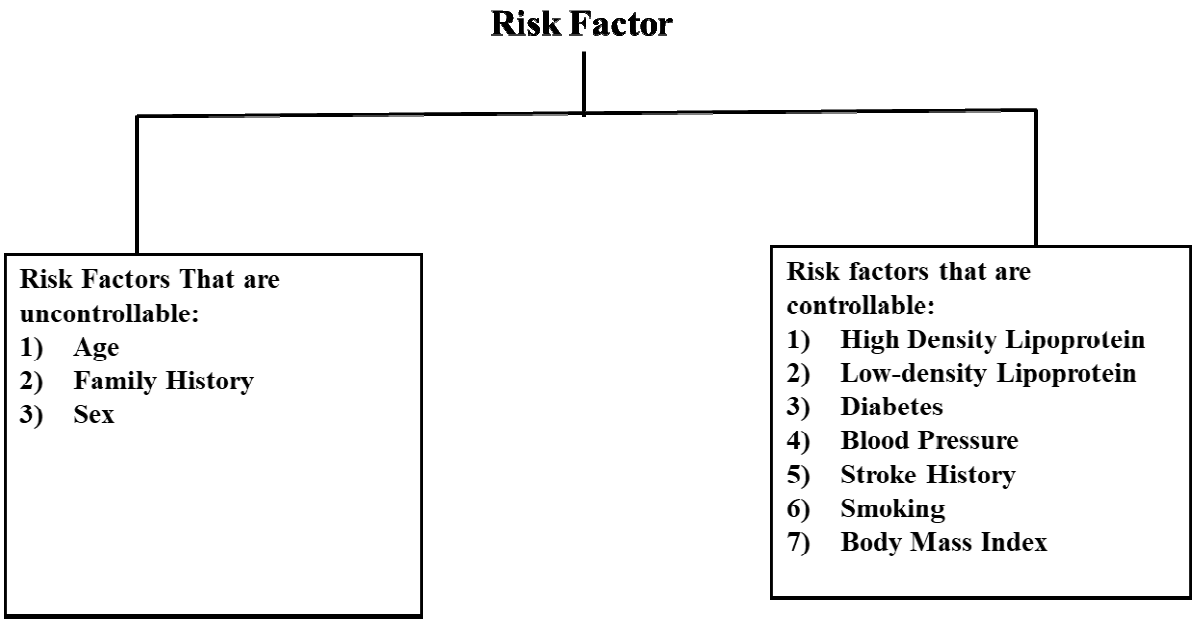

Figure 4: Illustrating the Controllable and Uncontrollable Risk Factors of Ischemic Stroke.

Salvaging brain tissue from the penumbra region of the ischemic brain is particularly crucial for the management of ischemic stroke. The neurologic deterioration brought on by cerebral ischemia and reperfusion includes neuroinflammation as one of its key pathophysiological mechanisms. As a result of increased production and accumulation of inflammatory cytokines and chemokines after a stroke, neuronal impairment, and neurovascular injury are exacerbated. To treat ischemic stroke linked to severe neuroinflammation, reducing inflammation is a viable technique.

For reducing neuroinflammation and halting the progression of cerebral ischemia-reperfusion damage, natural substances are a rich supply. However, it is important to note that during ischemic brain damage, several inflammatory mediators are generated at various times, and different inflammatory cell types are activated. The process makes the inflammatory processes, particularly complex due to the interactions between cytokines, chemokines, adhesion molecules, and small molecules. It is challenging to differentiate how each element contributes to the response of the inflammatory network to ischemia-reperfusion damage in the brain.

Accordingly, the majority of research on the anti-inflammatory and neuroprotective properties of herbal products is still cursory and lacking in detail since it is difficult to pinpoint the precise inflammatory factors or cells that natural substances are meant to target. To comprehend the complicated pathogenic process and create new medications that target the vital signaling pathways to preserve ischemic/hypoxic cells, more thorough research is required. Additional in-depth analyses of the most important inflammatory variables at various phases of an ischemic stroke provide promising targets for creating innovative therapeutic approaches to treat ischemic stroke. In their study, there were six investigations, where there had been no reports of serious adverse events following the use of herbal medications. To determine if herbal remedies are effective against ischemic stroke, more research is necessary.

5. CONCLUSION

The efficacy of medicinal herbs in the treatment of ischemic stroke was generally demonstrated in all of the selected publications. The aforementioned research evaluated the benefits of herbal remedies in minimizing brain damage through several elements and enhancing brain perfusion. However, the main difficulty in assessing the efficacy of herbal treatments was the lack of a standard evaluation protocol for these investigations. The limited population size and brief follow-up following therapy were two additional drawbacks. Last but not least, these drawbacks and the possibility of bias in certain studies necessitate more research to demonstrate the effectiveness of herbal remedies in treating ischemic stroke.

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CHAPTER 20

AN ANALYSIS OF THE COGNITIVE IMPACT OF NICOTINE AND ITS EFFECTS ON HUMAN BEINGS

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ABSTRACT: Nicotine is a compound that has stimulant and depressive alkaloid properties. It is present in Solanaceae family plants. It is synthesized in the roots of plants and accumulates in their leaves. During harvesting, nicotine is also metabolized into several therapeutically significant chemicals. These include tobacco-specific nitrosamines. Numerous biological mechanisms, including the management of hormone secretion, enzyme activity, and gene expression, have been revealed to be impacted by nicotine. This study's goal was to present an overview of nicotine's physiological effects and metabolism. To discover age-related health impacts of oral exposure and examine the mechanisms behind these repercussions, the author of this reviews both preclinical and human clinical studies. In the future, this paper will present a different perspective on nicotine and make others aware of its advantages and disadvantages. This paper will set a platform for other researchers to provide a new basis for their research. In the future, this paper will present a different perspective on nicotine and make others aware of its advantages and disadvantages. This paper will set a platform for other researchers to provide a new basis for their research.

KEYWORDS: Blood Cancer, Cancer, Lung Cancer, Nicotine, Smoking.

1. INTRODUCTION

The brain's nicotinic cholinergic systems have been associated with several prominent mental illnesses, particularly schizophrenia, ADHD, and attention-deficit or hyperactivity disorder (ADHD) [1]. The central nicotinic networks' significance in cognition, education, and memory is substantiated by both human clinical trials and animal experimentation [2]. The model nicotinic acetylcholine receptor (nAChR) [3] agonist is nicotine, which has strong consequences on attention as well as interactions with presynaptic nAChR to promote the neurotransmitters to be released associated with learning and memory, including glutamate [4], dopamine, norepinephrine, serotonin, and g-aminobutyric acid [5]. Numerous studies have shown that nicotine facilitates student concentration. Additionally, it has been established that nicotine and nicotinic substances have neuroprotective properties, which are likely administered by nicotinic signal transduction. In vitro b-amyloid deposition of nicotine has recently been demonstrated to be inhibited [6]. As a proof of concept for proposed therapies to enhance mental performance, nicotine may be administered to individuals with cognitive problems by skin patch or injection [7].

This methodology was adopted by the author to demonstrate the effectiveness of nicotine therapy in a variety of groups, including healthy non-smoking individuals, attention-deficit patients,

schizophrenic patients, and people with ADHD [8]. It is also possible to evaluate the effectiveness of nicotinic therapy for enhancing cognitive functioning using animal models. Importantly, selective nicotinic ligands, local infusion, and lesions may be used in animal models to understand the mechanisms of nicotinic activity [9]. For the early assessment of the effectiveness of new nicotinic medicines, experimentally induced models are crucial. The establishment of nicotinic therapies for cognitive impairment benefits from the knowledge provided by concurrent clinical and experimental animal investigations [10]. During harvesting and fermentation, nicotine is also metabolized into a variety of physiologically significant chemicals. Particular nitrosamines from tobacco are the most noticeable. Numerous studies have been performed on the effects of nicotine on humans, animals, and other cell systems [11]. The main effects of nicotine on an entire, unharmed animal or human being are an increase in heart rate, blood pressure, plasma-free fatty acids, blood sugar mobilization, and the percentage of catecholamines in the blood [12]. Additionally, it has been shown that rats given a high-fat diet and nicotine exhibit altered antioxidant defense systems [13]. The stimulation of nicotinic receptors increases the production and exocytic release of many hormones, especially norepinephrine, and epinephrine, at the cellular level [14]. Chronic nicotine consumption has also been observed to activate tyrosine hydroxylase, the first and rate-limiting enzyme in catecholamine manufacturing, in addition to the release of these hormones. Additionally, c-fos and c-jun gene products have been demonstrated to be generated by nicotinic receptor activation, and the intracellular levels of transforming growth factors have been stabilized [15]. Nicotine also causes sister chromatid exchange and chromosomal abnormality, increased production of heat shock proteins, reduction of cell growth, and prevention of apoptotic at the cellular level.

1.1.Chemical Properties and Structure of Nicotine:

Nicotine is a naturally existing alkaloid that is largely present in plants in the solanaceous plant family, including tobacco, potatoes, tomatoes, and green peppers [16]. Before a few years back, nicotine was first synthesized and identified as the main component of tobacco. It exists as a stereoisomer and has an active center. According to Figure 1; the structure of nicotine [1-methyl-2- (3-pyridyl-pyrrolidine), C10H14N2] [17] was proposed by researchers and confirmed by the synthesis of pure nicotine is a clear liquid with a characteristic odor whereas it turns brown on exposure to air [18]. It can mix with an equal amount of water. However, it partitions preferentially into organic solvents. Thus, it can easily be extracted from aqueous solutions by solvent extraction. It is a strong base and has a boiling point of 274.5 8C at 760 Torr.

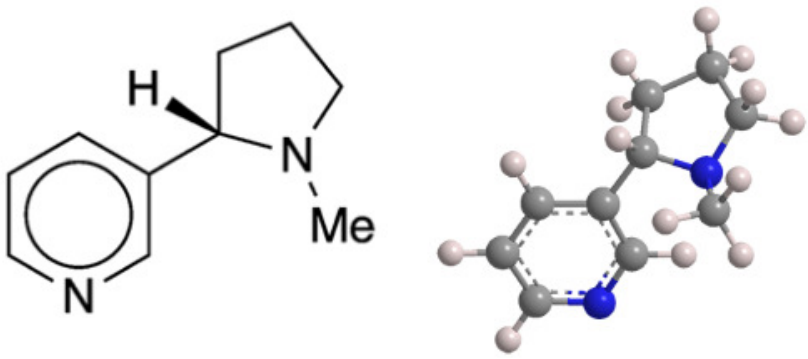

Figure 1: Illustrated the Chemical Structure of the Nicotine [19]**.**

In Table 1, it represents the properties of nicotine i.e. this leads to the formation of various metabolites like cotinine and nornicotine, dimethyl cotinine, trans-3-hydroxy-cotinine, and d-(3-pyridyl)-g-methylaminobutyric acid [20]. Thereafter in phase II, there is N'-and O' glucuronidation of the metabolites and excretion via urine, feces, bile, saliva, sweat, etc. 5.0-10.0% of elimination is by renal excretion of unchanged nicotine, however, there is reabsorption from the bladder when the urinary pH is high [21]. There is evidence that nitrosation of nicotine in vivo could lead to the formation of N-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1- butanone (NNK), which are known to be highly carcinogenic. Inflammation in the oral cavity increases the risk of endogenous nitrosation [22].

Table 1: Illustrated the different properties of Nicotine.

Sr. No.	**Properties**	
1.	Formula	$C_{10}H_{14}N_2$
2.	Molecular Weight	162,234 $g.mol^{-1}$
3.	Melting point	-79°C
4.	Boiling point	247°C
5.	Rotatory index (S)	aD = -168 at 20° C
6.	Density	d=1010
7.	Refractive index	N=1530
8.	Comments	*i.* Pale yellow to dark brown liquid with a slight, fishy odor when warm. *ii.* Insecticide.

In this paper, the author has discussed nicotine. Nicotine has many disadvantages, on the other hand, nicotine can also be used in the form of medicine in different circumstances. According to various research, it has been confirmed that nicotine can also be used in the medical sector.

2. LITERATURE REVIEW

S. Mahajan et al. illustrated that Nicotine, the primary therapeutic component of tobacco, gives it its significant propensity for addiction and physical dependence, which makes tobacco cessation therapy challenging to administer. Nicotine addiction often begins in this age group because the enlarged adolescent brain is particularly susceptible to the neuro-inflammatory effects of nicotine. A growing body of research suggests that microglial cells, the brain's primary physiological sensor, have a role in following drug dependence and behavioral effects, particularly in the developing adolescent brain. Long-term nicotine addiction can result from microglial activation and microglia association with nicotine throughout childhood and adolescence, both of which are marked by neuro-inflammation. This non-systematic review explores the neuroscience of nicotine addiction, the genetics of adolescent nicotine addiction,

and the potential mechanisms behind nicotine's effects on inflammatory signaling pathways in microglia to better understand how nicotine affects the adolescent brain. The author said according to the research, modulating the homeostatic balance in microglia may have interesting therapeutic potential for adolescent smokers, who experience neuronal processes related to withdrawal, tolerance, and abstinence when using tobacco products [23].

T. Asadishad et al. illustrated that the harmful pharmacological effects of smoking on many organs have been motivated by the fact that smoking is one of the causes of many diseases. Nicotine can affect the smooth muscles of the colon, which in turn affects gut motility and alters how quickly digested food moves through the digestive tract. Optical detection technologies offer the advantages of non-contact and high sensitivity for probing the early effects of nicotine on cells. Consequently, we used an optically elliptical technique to measure the quick and precise effects of nicotine on colon cells. The authors' findings, which were illustrated, demonstrated that by prolonging the duration of smoke exposure on the cell over a specified maintenance time, the phase difference between each polarizer increased, and also caused a general red-shift. The author demonstrated visually that cigarettes, which contained the addictive component nicotine, had a direct effect on colon cells cultivated on the plasmonic chip using varying exposure times to cigarette smoke. By using a label-free, non-invasive plasmonic approach to introduce nicotine into the system, it exhibited significant changes in the amplitude and phase of the interacting light [11].

M. Ren et al. stated that in various countries, smoking remains the number one avoidable cause of death. Although tobacco-free products have replaced flammable cigarettes, nicotine consumption is increasing among susceptible groups, including children, adolescents, and pregnant mothers. Nicotinic acetylcholine receptors are dynamically expressed throughout the lifespan, allowing nicotine to exert diverse effects on certain areas of the brain at different developmental stages.

In addition to being a health risk to adults, nicotine exposure has neurotoxic consequences on fetuses, infants, children, and adolescents. This review would like to draw attention to the changing roles played by pregnancy, adolescence, and maturity. The author also provides clinical and preclinical evidence of the effects of nicotine exposure on neurodevelopment, cognition, and behavior at different stages of development. This in-depth analysis reveals specific nicotine effects on lifespan to elucidate medical and public health strategies to shield vulnerable groups from nicotine exposure.

3. DISCUSSION

Nicotine is the main cause of addictions in cigarette smokers and studies on both humans and animals have shows that nicotine has negative effects on many organs. Its biological effects are widespread and affect many bodily systems, including the respiratory, reproductive, renal, and cardiovascular systems. Several investigations have documented the carcinogenicity of nicotine. By modulating cell growth, angiogenesis, and malignant pathways, it aids in tumor growth. This results in chemotherapy drug resistance. The use of nicotine replacement therapy (NRT) helps cessation programmers to be more successful by reducing withdrawal symptoms. It is still uncertain whether nicotine has any real health benefits for people. Nicotine should only be used when supervised by experts skilled in smoking cessation, thus its sale should also be closely controlled. It naturally follows that the focus should be on research into safe nicotine replacement.

3.1.Harmful Effects of Nicotine on the Human Body:

Nicotine is a dangerous and highly addictive chemical. It can cause an increase in blood pressure, heart rate, the flow of blood to the heart, and a narrowing of the arteries which are vessels that carry blood. Nicotine may also contribute to the hardening of the arterial walls, which in turn, may lead to a heart attack nicotine is also responsible for another disease which is mentioned in Figure 2 below:

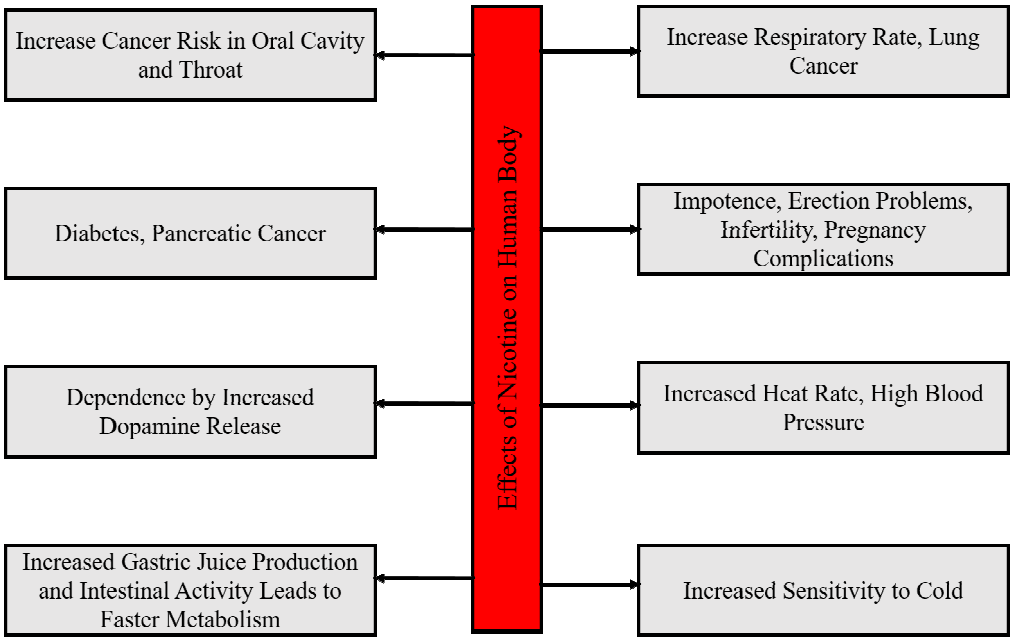

Figure 2: Illustrated the Effects of Nicotine on the Human Body.

3.1.1. Increase Cancer Risk on Throat:

Throat cancer occurs when cells in your throat develop genetic mutations. These mutations cause cells to grow uncontrollably and continue living after healthy cells would normally die. The accumulating cells can form a tumor in your throat. It's not clear what causes the mutation that causes throat cancer. But doctors have identified factors that may increase your risk.

i. Prevention:

There's no proven way to prevent throat cancer from occurring. But to reduce your risk of throat cancer, you can:

1. *Stop Smoking or Don't Start Smoking:* If you smoke, quit. If you don't smoke, don't start. Stopping smoking can be very difficult, so get some help. Your doctor can discuss the benefits and risks of the many stop-smoking strategies, such as medication, nicotine replacement products, and counseling.
2. *Drink Alcohol Only in Moderation:* If you choose to drink alcohol, do so in moderation. For healthy adults, that means up to one drink a day for women and up to two drinks a day for men.

3. *Choose a Healthy Diet full of Fruits and Vegetables:*The vitamins and antioxidants in fruits and vegetables may reduce your risk of throat cancer. Eat a variety of colorful fruits and vegetables.
4. *Protect Yourself from HPV:*Some throat cancers are thought to be caused by the sexually transmitted infection human papillomavirus (HPV). You can reduce your risk of HPV by limiting your number of sexual partners and using a condom every time you have sex. Ask your doctor about the HPV vaccine, which may reduce the risk of throat cancer and other HPV-related cancers.

3.1.2. Increase Respiratory Rate and Lung Cancer:

Sometimes, lung cancer tumors grow in a way that blocks airways, put pressure on the lungs, or causes inflammation in the respiratory system. All of these situations can prevent your respiratory system from working properly, leading to problems getting in enough air. Shortness of breath is a common symptom. There are some other factors related to Lung Cancer:

1. *Blocked Airways:* Lung tumors can grow into or press against the airway, narrowing the passage and making it difficult to get enough air in and out of the body.
2. *Fluid Buildup:* In some patients with lung cancer, lung cancer cells invade the space between the lungs and the chest wall, called the pleural space. This condition, called pleural effusion, causes fluid to build up around the lungs, making it harder for the lung to fully expand and take in enough air.
3. *Low Levels of Oxygen in the Blood:* Lung cancer can decrease red blood cells, which are responsible for transporting oxygen from the lungs up to the heart and the rest of the body.

i. Preventions:

The best way to prevent lung cancer is to stop smoking or avoid it altogether. According to the Centers for Disease Control and Prevention, smoking is the main contributor to avoidable diseases in the country. The immediate health benefits of quitting smoking reduce smokers' chances of lung cancer. When you quit smoking, your entire body begins to perform better, from lower blood pressure and less chance of heart attack to higher levels of energy and greater lung function. Another preventive method is to reduce radon exposure. Surprisingly, radon exposure ranks second in the country after smoking as a cause of lung cancer. Radon is a naturally occurring gas that can seep through foundation cracks into homes and groundwater. Fortunately, there are many places to obtain radon testing kits, including online and at some home improvement stores. If you discover excessive levels of radon in your home, you can install a mitigation system that closes seams and cracks when purifying water for drinking, cooking, and bathing. A healthy, balanced diet and exercise can help reduce the risk of cancer.

3.2.Beneficial Effects of Nicotine:

Would you be surprised to learn that most Americans think nicotine solves the riddle of schizophrenia or that a cancer-causing drug can also successfully cure neurodegenerative conditions like Parkinson's? May be used to develop novel weight loss treatments or to aid in relaxation. Despite the prevalence of nootropics, which are sometimes referred to as "smart pills" or study drugs many people are unaware of the fact that nicotine has been shows to boost

memory and other cognitive abilities. Researchers are actively researching new ways that nicotine can help people live better lives, even though it is commonly misunderstood by both the public and condemned in the media. The following examples demonstrate that nicotine can have a positive effect in specific situations:

i. As a Cognitive Enhancer:

Nicotine seems to be neuro-protective, preventing neurological problems that worsen over time. Additionally, it appears that people who choose to use nicotine may benefit from some of the same properties that make it an effective potential weapon against neurological conditions such as Parkinson's disease. According to a Professor of Psychology at the University of Sussex (UK), nicotine is the most trusted cognitive enhancer we currently have. It enhances working memory and visual attention at the moment. A large group of people Nicotine has the strongest cognitive-enhancing benefit of any substance. There was even research exploring the ability of nicotine to affect memory. The ability to remember and complete tasks set for the future by a person, such as remembering oneself to contact someone at a given time, is known as memory.

ii. As Fat Burner:

Nicotine has long been known to help people lose weight. Smokers often gain weight after stopping. But new research shows how nicotine affects metabolism, causing the body to initiate a process called thermogenesis, which causes the body to burn certain types of fat cells. By triggering the CHRNA2 nicotinic acetylcholine receptor, thermo genic fat cells are triggered. The CHRNA2 receptor, which is affected by nicotine or acetylcholine, is the same receptor that controls nicotine dependence in brain cells. Mimics the effect of acetylcholine.

iii. Improve Short-Term Memory:

Several studies have shown that nicotine improves short-term memory. It is one of the most well-known benefits of nicotine. In a typical nicotine or memory study, University of Surrey (UK) researchers provided nicotine gum or a placebo to 10 smokers and 10 non-smokers and then had them perform short-term memory tasks at predetermined intervals for four hours. The findings suggest that nicotine improved memory reaction times. According to the authors, when individuals were questioned about knowledge that was already stored in short-term memory, correct positive answers were given; but, when the information was not stored in memory, the exact negative responses did not affect the subjects' reaction times. It has been hypothesized that nicotine makes it easier for short-term memory to process input information.

iv. Improve Reaction Time:

Several studies have determined that nicotine either shortens or lengthens reaction times during experimental tasks. The University of London's Institute of Psychiatry evaluated 113 smokers, and researchers found that smoking cigarettes in a realistic environment increased a smoker's performance in an IQ-related activity. Researchers from the University of Auckland in New Zealand tested 29 participants in a similar study under conditions of smoking, spurious smoking, and low, medium, and high nicotine cigarettes and found that nicotine reduced or improved decision-making time while smug smoking acted as if you're smoking while holding a cigarette without lighting it increases decision-making time. Whether the test person was a heavy or moderate smoker regularly, the effect was clear.

v. Improve performance:

It's understandable why players would want to test nicotine as a performance-enhancing substance. Improved short-term memory and reaction speed are desirable traits, especially in complex team sports. The sport's governing organizations consider nicotine legal. A 2017 meta-analysis of research on the relationship between smoking and sports performance showed that players find nicotine improves their performance. Baseball and American football players especially often use smokeless tobacco, while the great athletes of Sweden, Finland, and Norway often use snus. In 2002, 25% of the more than 400 Finnish athletes supported by their National Olympic Committee used snus. According to the players, the consumption of smokeless tobacco reduces dryness of the mouth, controls weight, provides relief, and increases the speed of thought and attention.

4. CONCLUSION

Nicotine pathways and the enzymes constituting a part of them have been completely determined by extensive investigations on nicotine metabolism. Since not all enzymes required for nicotine absorption have yet been fully identified and identified, further research in this area will be needed. Genetic polymorphism studies in nicotine metabolism have revealed traits of individual variations in nicotine response, including nicotine ingestion, addiction, and lung cancer progression. Currently, it is believed that the type and function of enzymes that absorb nicotine have a major impact on how quickly nicotine is administered and how much nicotine is needed to be consumed.

The link between excision and a lower chance of contracting the disease may aid in understanding how nicotine and cigarette smoke may prevent disease in smokers. Nicotine's restriction on the apoptosis process, which normally kills cancer-causing cells, and stimulation of tumor growth in some preclinical studies may also have an effect on nicotine-induced carcinogenesis. To further understand the specific mechanisms by which nicotine promotes cancer, more research on the metabolic activities, cell growth and apoptosis of nicotine will be necessary. Since its discovery, dopamine has been associated with a variety of biological functions, most of which have dual effects, making pinpoint analysis methods more challenging. Several studies have been and are being conducted to elucidate the controversial effects of nicotine, particularly in the areas of mitochondrial dysfunction, necrosis, and cell proliferation. Oxidative stress is often caused by high nicotine levels, while it seems to be reduced in small doses. Parkinson's disease, which is associated with increased mitochondrial dysfunction in smokers, may emerge less frequently because of nicotine's inhibitory effect on oxidative stress. More research is still needed to fully understand the physiological effects of nicotine under various experimental conditions.

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CHAPTER 21

AN ESSENTIAL STUDY ON THE IMPORTANCE OF VITAMIN C AND ITS DEPLOYMENT HUMAN HEALTH

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ABSTRACT:

The discovery of vitamin C ties into a long history of relentless investigation into the origins of the ancient hemorrhagic disease scurvy. Vitamin C, which was first isolated in 1928, is important for the development and maintenance of connective tissues. It is important for bone development, wound healing, and maintaining gum health. Vitamin C is an essential dietary component for the formation of collagen, being a co-factor in the biosynthesis of catecholamines, cholesterol, L-carnitine, amino acids, as well as some peptide hormones. Vitamin C deficiency leads to scurvy, a degenerative disease that weakens blood vessels, damages connective tissue as collagen production is impaired, and eventually leads to mortality due to generalized degeneration. Additionally, protection against cardiovascular or cancer diseases may be aided by vitamin C. The effects of vitamin C on the neurological system and individuals with chronic diseases have also been studied. Vitamin C is a useful supplement to prevention strategies for these pathological conditions because of its ability to combat inflammation and the resulting oxidative damage, which are important contributors to the onset and development of many chronic or acute diseases. The purpose of this review is to provide an overview of current and well-recognized developments in vitamin C research and their clinical consequences. In the future, through this study, people well aware of the importance of vitamin C for human health.

KEYWORDS:

Ascorbate, Antioxidant, Collagen, Health Benefits, Vitamin C.

1. INTRODUCTION

Some metabolic activities in our bodies require vitamin C, a water-soluble vitamin also known chemically as ascorbate or ascorbic acid. Although many animals naturally produce vitamin C, which is one of the nutrients best for treating colds and coughs, humans must consume meals high in vitamin C to get its health benefits. The body needs vitamins for several physiological and biochemical activities. Vitamins are necessary nutrients. Since the majority of vitamins cannot be produced by the body, their replenishment in the diet is crucial [1]. It occurs as dehydroascorbic acid in reduced or oxidized forms, both of which are physiologically active, easily interconvertible, and serve as significant antioxidants. Oxygen, alkali, as well as high temperatures, may all quickly oxidize vitamin C or destroy it. The majority of animal and plant species can produce vitamin C from both glucose and galactose via the uronic acid route, but humans and other primates are unable to do so because they lack the enzyme gluconolactone

oxidase necessary for its manufacture. This enzyme's deficiency is the product of a mutation that happened around 40 million years ago [2], [3].

Vitamin C is essential for the body's basic physiological processes. It aids in the hydroxylation of glycine, lysine, praline, carnation, or catecholamine, as well as the formation or metabolism of tyrosine, tryptophan, and folic acid. It makes it easier for cholesterol to be converted into bile acids, which decreases blood cholesterol levels. Converting ferric to ferrous also boosts the absorption of iron in the gastrointestinal tract. As an antioxidant, it defends the body against the harmful effects of free radicals, poisons, and pollution. Linus Pauling studied the medicinal effects of vitamin C, but his later work on the topic was very contentious even though he was a well-respected scientist [4], [5].

The lack of this vitamin commonly results in anemia, bleeding gums, infections, scurvy, poor wound healing, muscle degradation, atherosclerotic plaques, capillary hemorrhage, or neurotic symptoms. High doses of vitamin C are commonly given to address the deficiency, however, unlike fat-soluble vitamins, toxicity is rare. Recent research has also looked at how vitamin C affects infection or immunity. Given the wide spectrum of biological, physiological, or therapeutic impacts of vitamin C, this process of setting to compile several relevant pieces of knowledge.

1.1. Functions and Metabolism of Vitamin C:

Green plants naturally produce VitC, a tiny carbohydrate (3-keto Lgulofuranlactone), through a two-step process that primarily uses L-galactose or D-galacturonic acid. Due to a deficiency in the L-gluconolactone oxidase (GLO) enzyme, humans are unable to produce vitamin C and must thus exclusively obtain it from an external source, which is shows in Figure 1.

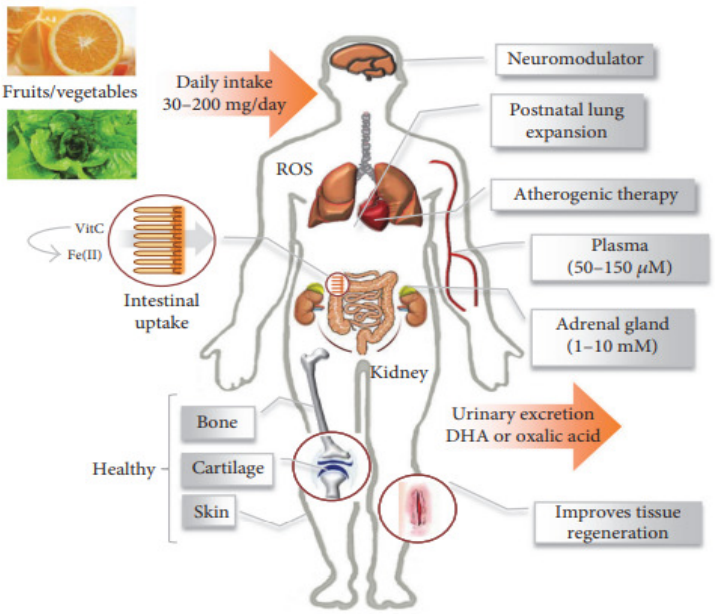

Figure 1: Illustrate the Metabolism and Actions of Vitamin C. Humans Need to Get Vitamin C Everyday Through Their Diets. It Is Essential For both the Regeneration and Repair of Tissues as well as the Normal Operation of Healthy Tissues and Organs.

Oxidative catabolization of vitamin C results in the formation of dehydroascorbate (DHA), which is then broken down into oxalic acid. Urinary excretion is the major method of getting rid of vitamin C and DHA. One of the main end products of vitamin C degradation in humans is oxalate, which can lead to the development of calcium oxalate kidney stones and nephrocalcinosis in susceptible individuals.

2. LITERATURE REVIEW

Juliet M. Pullar et al. studied the role of vitamin C in skin health. The strength, suppleness, and nutrient retention of the epidermis is ensured by both the inner dermal layer and the highly cellular, barrier-functioning epidermal outer layer. Normal skin contains high levels of vitamin C, which supports a variety of well-known and important functions, such as promoting collagen synthesis and helping the body's defense mechanisms against UV-induced photodamage. This information is frequently cited as support for the use of vitamin C in topical treatments, but there is little evidence to support the efficacy of this approach over increasing dietary vitamin C intake. Authors compare the effectiveness of ingesting vitamin C versus applying it topically, pinpoint the areas where a lack of evidence prevents us from understanding the potential advantages of vitamin C for skin health, and make recommendations for which aspects of the skin are most likely to gain from increased dietary vitamin C intake [6].

Raakhuis studied Vitamin C, a crucial nutrient, that may lessen the negative consequences of exercise-induced oxidative stress, such as exhaustion, immunological dysfunction, and muscle injury. Reactive oxygen species, but even so, may be responsible for the positive take all appropriate measures that vitamin C attenuates. In fact, out of a total of 12 studies, vitamin C at doses >1 g/d1 significantly decreased sports performance in four of the four studies, possibly by lowering mitochondrial biogenesis, whereas another four studies found no statistically significant differences. Vitamin C doses of 0.2 g/d1 may be adequate to minimize oxidative stress or offer other health advantages without compromising training adaptations if they are taken in through five or more servings of fruits and vegetables [7].

Callen Pacier studied the importance of vitamin C as a way to prevent scurvy has been known for centuries. Numerous elements of vitamin C will be assessed, including inadequate vs optimum blood plasma levels, sufficient daily dosages required to maintain ideal levels, and the safety of greater doses, in this review of the scientific literature. Additionally, it will highlight the significance of vitamin C as a potent bioactive component and how to use it to prevent and treat many chronic illnesses. It is vital to convey the significance of alternative healthcare practices in either clinical or preventative care in this study. Due to its strong antioxidant capability, enormous physiological ramifications, and extremely low risk of adverse effects, vitamin C was chosen as a symbol of this notion. The research author examined in this review evaluated the value of vitamin C for the human health of all involved human subjects [8].

Melissa A. Moser et al. studied the findings of existing epidemiologic research on vitamin C and its potential role in “cardiovascular disease” (CVD). According to certain studies, vitamin C can help with lipid profiles, vascular stiffness, or endothelial function. Observational cohort studies have found conflicting results on the impact of the vitamin on CVD risk and death, while other researchers have not been able to replicate these findings. In general, current evidence indicates that vitamin C insufficiency is linked to an increased risk of CVD mortality but that vitamin C might also improve lipid profiles as well as endothelial function in select populations, particularly those with low plasma vitamin C levels. In addition, several studies have revealed

that vitamin C may have advantages for the heart when consumed in quantities greater than those needed to avoid deficiency as traditionally described [9].

3. DISCUSSION

3.1. Health Benefits of Vitamin c:

3.1.1. Vitamin C's Function in Skin Health:

Vitamin C, which is one of the top anti-aging compounds in the cosmetic industry, is the secret to giving oneself a clear, radiant complexion. In addition to being essential for the creation of collagen, a crucial molecule for enhancing the skin, Vitamin C's abundance of antioxidant capabilities also supports skin regeneration, which aids in the body's ability to heal damaged skin cells. To satisfy our nutritional needs, Mother Nature has given us a broad variety of foods rich in vitamin C, but there is no assurance that they will be absorbed by the skin. To suit the needs of the skin, it must be applied topically in the form of oils or serums. But to our great joy, the market is presently swamped with skincare essentials that incorporate this wonderful beauty component. Whether it's for uneven skin tone, fine wrinkles, rough texture, acne scars, general dullness, or sagging skin, there's a strong possibility that vitamin C-based skin-care products will be recommended as a therapy.

3.1.2. Bioavailability of vitamin C:

Vitamin C's efficient absorption from the gut and renal excretion are the two main factors that determine its bioavailability or effective concentration. Vitamin C is absorbed by the epithelial cells of the small intestine through SVCT1 or diffuses into the peritubular capillaries and the circulatory system after being taken by diet or dietary supplements. Through a general filtration process, circulating AA is filtered from the renal capillary bed into Bowman's capsule. Through the SVCT1 transporter in the proximal convoluted tubule, AA is reabsorbed. Renal excretion is the difference between the quantity of AA filtered and reabsorbed [10], [11].

3.1.3. Healing Tissue with Vitamin C:

It is also generally accepted that to restore the injured tissue's tensile strength, wound healing calls for the production, accumulation, or cross-linking of collagen. An early study showed that vitamin C administration increased the strength properties of scar tissue in guinea pigs to its maximal level. Since then, several studies have been conducted to assess the function of AA in the regeneration and repair of wounds because it promotes the production of collagen.

A sufficient level of AA is necessary for proper healing, especially in postoperative patients. Because AA is quickly depleted during the postoperative period for collagen production at the site of wounds or burns, providing 500 mg to 1.0 g/day of AA is recommended to speed up the healing process. Proven that AA pre-treatment was beneficial in irradiation wound healing and advocated a vitamin C-related therapeutic strategy to accelerate wound repair in such conditions and cases of mixed damage.

3.1.4. Fertility and Vitamin C:

This vitamin boosts the generation of progesterone or iron absorption. Increased C seems to support fertility in women with luteal phase deficiency, a condition defined by inadequate progesterone. It aids in enhancing the health as well as motility of sperm in males. On empirical grounds, vitamin C has been used to treat male infertility, particularly in the presence of non-

specific seminal infections. Several publications have found its presence in high concentrations in the seminal plasma of healthy people, ranging from 2.5 to 12 mg/dL. However, the specific effect of vitamin C on male reproduction is yet unknown. The structural and functional integrity of androgen-dependent reproductive organs was dependent on AA. Low vitamin C concentrations caused significant degenerative alterations in the testes, epididymis, and vas deferens of scorbutic guinea pigs [12], [13]. Along with the spermatogenic epithelium's loss, the levels of plasma testosterone or steroid genesis also decreased. On the other side, high vitamin C consumption has been linked to male reproductive failure. On Leydig cells of guinea pigs, they were unable to detect any definite effects of vitamin C treatment. AA comprises up to 65% of the total chain-breaking antioxidant capacity of fertile men's seminal plasma as the primary antioxidant. Seminal plasma has a concentration that is almost ten times greater than plasma. In several investigations, it was discovered that the amount of AA in the seminal plasma of fertile as well as infertile men was considerably different, as well as the proportion of sperm with normal morphology strongly connected with seminal AA in both groups.

3.1.5. Cardiovascular Diseases and Vitamin C:

The plasma testosterone or steroidogenesis levels fell together with the loss of the spermatogenic epithelium. On the other hand, excessive vitamin C intake has been connected to male reproductive failure. They were unable to identify any distinct effects of vitamin C therapy on guinea pig Leydig cells. As the main antioxidant, AA makes up 65.00% of the total chain-breaking antioxidant capability of seminal plasma from fertile males. Plasma concentration is nearly 10 times lower than that of seminal plasma [14], [15]. In multiple studies, it was shows that both productive and infertile men had significantly varied amounts of AA in their seminal plasma and that both groups' ratios of sperm with normal morphology were highly correlated with seminal AA. Vitamin C enables proper folding into the triple helical collagen molecule, which is then released to produce the extracellular matrix or, in the case of type IV collagen, to serve as a component of the basement membrane. Vitamin C also facilitates the creation of collagen. The lack of ascorbate results in friable arteries, most notably capillaries that are more susceptible to rupture, which in turn causes the distinctive petechial hemorrhages and ecchymoses seen in scurvy and the cerebral cortex of SVCT2 knockout mice. Vitamin C has been demonstrated to prevent apoptosis in both congestive heart failure patients and cultured endothelial cells by preventing the effect of inflammatory cytokines or oxidized LDL. Vitamin C supplementation also decreased the creation of endothelium microparticles [16], [17].

3.1.6. Vitamin C's Role in Patients with Serious Illnesses:

According to reports, critically sick patients frequently have subnormal vitamin C concentrations in their plasma or leukocytes, which are inversely related to the failure of numerous organs and directly related to survival. The possible therapeutic role of vitamin C in the treatment of different infections has long been researched since sepsis is linked to increased generation of ROS or peroxynitrite, which deplete antioxidant molecules as well as damage proteins and lipids. Indeed, it has been demonstrated that patients with sepsis who get enteral administration of vitamin C as well as other antioxidants recover more quickly than those who receive parenteral treatment, which also reduced morbidity and death [18]. The significance of ascorbate in avoiding the loss of barrier function in sepsis conditions by both reducing endothelial cell death and increasing their proliferation is one potential mechanism for such effects. Furthermore, in human subjects with acute inflammation or who have received an injection of LPS, vitamin C

improves the arteriolar ability to respond to vasoconstrictors (angiotensin, norepinephrine, and vasopressin) as well as prevents inhibition of endothelium-dependent vasodilation responses to acetylcholine, preventing hypotension in sepsis as well as, consequently, edema. Another way that ascorbate affects endothelial permeability is by scavenging superoxide, preventing the creation of nitric oxide or peroxynitrite, as well as lowering the oxidation products that are created when peroxynitrite reacts with cell proteins.

3.1.7. Vitamin C's effects on the Nervous System:

Ascorbate has been shows to have a variety of impacts on the nervous system. Vitamin C may efflux from several cell types, including neurons, due to its hydrophilic characteristics and a negative charge at physiological pH. Vitamin C promotes neurotransmission as well as a range of effects on behaviors including memory, learning, or motility. It appears that many brain cell lines are accessible to the vitamin C entrance [19], [20]. The performance of 15-month-old mice on a passive avoidance task was enhanced by oral ascorbate treatment when combined with vitamin E, but not when ascorbate was administered alone, according to experimental animal models. The treatment of ascorbate intraperitoneally helped mice with memory problems recover. In contrast to a previous study in which five days of acute pre-test ascorbate treatment resulted in poor performance, ascorbate treatments administered intraperitoneally for 14 days as well as orally for 30 days improved both attraction and retention in just this passive avoidance task in addiction.

3.1.8. Ocular Diseases and Vitamin C:

The role of Vitamin C in preventing ocular disease has been studied, and it has been shows that ascorbate influences the development of cataracts and that combining ascorbate with some other antioxidant minerals and nutrients slows the progression of highly developed age-related macular degeneration as well as loss of visual acuity in people who have symptoms of this disease. The usefulness of vitamin C as a therapy for diabetic retinopathy has also been investigated, although further research is needed to demonstrate that it has a substantial impact on its progression.

3.1.9. Vitamin C's Immunomodulatory Function:

An intricate system of protection, the immune system includes both innate and adaptive responses. To restore the harm, the innate immune system detects and eliminates "non-self" rebuffs through inflammatory processes, which is shows in Figure 2. White blood cells (WBC) migrate to contaminated locations thanks to vitamin C, and it also regulates the formation and function of innate and adaptive immune cells, as well as the production of antibodies and phagocytosis, which is the process by which microorganisms are killed. There is evidence that vitamin C may improve the health of pneumonia sufferers.

According to earlier research, mice lacking in vitamin C had poorer outcomes after contracting the H3N2 (hemagglutinin type 3 and neuraminidase type 2) influenza due to lower levels of IFN-a/b and higher levels of IL-1a, IL-1b, and tissue necrosis factor-a (TNF-a). These cytokine storm expression patterns were eliminated in animals given vitamin C supplements. In patients with acute Epstein-Barr virus infection (EBV), a high IV vitamin C dosage (7.5–50 g) resulted in decreased EBV-IgG (immunoglobulin G) profiles, but EBV-IgM antibody profiles were inversely linked with rising plasma ascorbate concentrations.

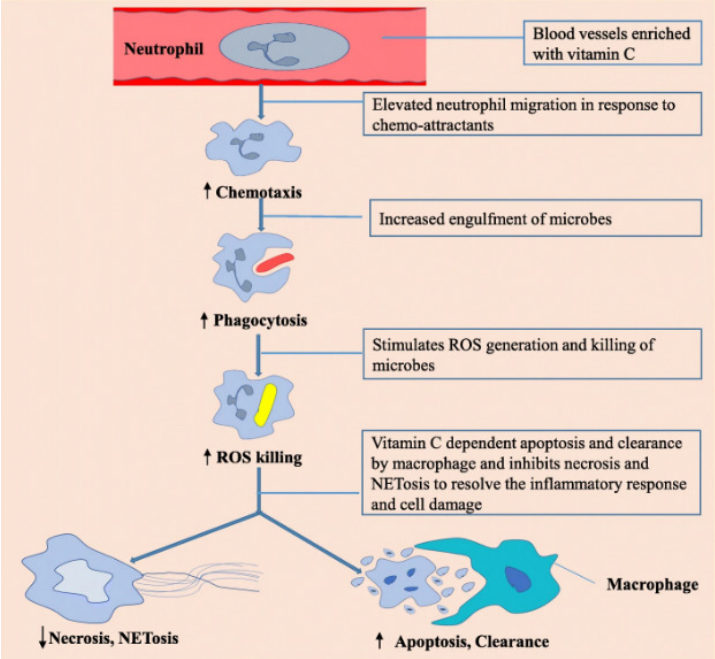

Figure 2: Illustrate the action of immune cells and vitamin C.

A water-soluble substance with a very significant nutritional value is vitamin C. By defending the body against cardiovascular illnesses, skin aging, and eye ailments, it strengthens the immune system. Even the prevention of cancer is a benefit, which is shows in Figure 3. By combating nitrates or free radicals, it does this. This potent antioxidant also aids in tissue regeneration and repair. According to studies, you need to consume more than 500 mg of vitamin C daily to reap all of its health advantages.

Figure 3: Illustrating the Health Benefits of the Vitamin C.

3.1.10. Reduces High Blood Pressure:

High blood pressure patients are more likely to suffer from cardiovascular problems. It is crucial to alter nutrition to control blood pressure levels. An important factor in regulating the levels is vitamin C. According to studies, vitamin C has also sped up the healing process for hypertensive individuals.

3.1.11. Fights Cancer:

Fresh fruit and vegetable consumption has been related to a lower risk of cancer. They are crucial to a balanced diet. You can be guaranteed to acquire all the minerals or vitamins from them, especially vitamin C. According to research, increasing your vitamin C intake can lower your risk of developing malignancies of the mouth, rectum, throat, lungs, or vocal cords.

3.1.12. Decreases the risk of a stroke:

The risk of stroke can be decreased by increasing vitamin C consumption through vegetables and fruit. With sufficient consumption of vitamin C, this cardiovascular illness can be prevented. This regulates blood pressure and lessens the likelihood of heart attacks. Additionally, it gets rid of the body's free radicals, which are the primary cause of stroke.

3.1.13. Avoids Scurvy:

If untreated, scurvy is a fatal condition that can cause death. It is directly related to inadequate consumption of vitamin C. Scurvy can result from a diet that is deficient in vitamins or lacking altogether. It causes tight muscles, curled hair, weakness, or weariness. Additionally, there are instances when it causes gum disease, a drop in red blood cell count, as well as bleeding. The signs and symptoms might worsen if ignored. The bleeding or infection may result in the patient's death. It is also quite easy to treat scurvy. A complete recovery might be aided by taking vitamin C pills for a few weeks. Rarely, drinkers and individuals with mental illnesses can also get scurvy.

3.1.14. Stimulates Blood Flow:

Another extremely significant advantage of vitamin C. It enhances the body's blood circulation. By lowering oxidative stress, it can stop vascular dysfunction. As it will enhance circulation, it is also advised for people with postural tachycardia syndrome. It also lessens mental tension and aids in controlling children's blood pressure. It is advised that smokers consume large amounts of vitamin C.

4. CONCLUSION

This review's objective is to outline recent and well-recognized developments in vitamin C research and their therapeutic implications. Vitamin C is an effective tool to use in humans for the prevention of such pathologic conditions because it can combat inflammation and the oxidative damage that follows, both of which play a significant role in the initiation and progression of a variety of chronic or acute diseases. The particular effects of ascorbate on physiological systems or disease pathology at the molecular level remain unknown, even though

many of the well-known therapeutic advantages of vitamin C use are only understood at the phenomenological level. To identify new possible therapeutic implications for vitamin C, deeper comprehension of its mechanisms of action is crucial. It serves as a treatment for a variety of illnesses and ailments. The immune system is strengthened by vitamin C, which also lessens the intensity of allergic responses and aids in the prevention of infections. However, there is still debate over the importance of vitamin C and its curative effects concerning human diseases including cancer, diabetes, atherosclerosis, neurodegenerative illness, and metal toxicity. Therefore, more sustained, uninterrupted work may offer up new perspectives for understanding its importance in the therapy of disease. This review's objective is to present an overview of recent, widely acknowledged advancements in vitamin C research and their therapeutic implications. Through this study, individuals will become more aware of the significance of vitamin C for human health in the future.

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CHAPTER 22

ANTI-CANCER EFFECTS AND MECHANISM OF APIGENIN FOR EFFECTIVE CHEMOPREVENTION

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ABSTRACT:

In the United States and other industrialized nations, cancer is a significant public health burden, accounting for around 7 million deaths annually. Worldwide, there are significant regional and demographic variations in cancer rates, particularly between developing and industrialized countries. Within areas, trends of cancer prevalence change as people age or urbanize more and more. Changes in eating patterns and variances in cancer rates have both been influenced by migration. These epidemiological data imply that environmental variables, especially the largely controllable diet, have an impact on cancer rates. Chemoprevention or dietary cancer prevention are two complementary strategies to cancer prevention. Apigenin is one the compound which is now being investigated a lot for its anti-cancer activities against a variety of cancers including breast cancer, prostate cancer, lung cancer, and many others. Therefore, the present study aims at exploring and investigate the evidence for the effectiveness of apigenin. In addition to that, the study also provides a discussion on the associated challenges confronted by Phytomolecule like apigenin to be used as an anti-cancer agent.

KEYWORDS:

Anti-cancer, Apigenin, Cancer, Chemoprevention.

1. INTRODUCTION

A huge worldwide problem for both advanced and developing nations, cancer is a serious public health problem. According to estimates, there were 18.1 million new cases of cancer reported globally in 2018, and by 2030, that number is expected to rise to 23.6 million. Given the high notoriety, treating it has been an ongoing battle with only somewhat successful results. Surgical excision of cancer and radiation therapy is now the only alternatives for treating it. Systemic chemotherapy is often used as a maintenance treatment after the vast accumulating biomass of cancer has been treated with radiation therapy [1], [2]. Antimetabolites, such as methotrexate, DNA-interactive substances, such as doxorubicin and cisplatin, anti-tubulin substances, such as hormones, taxanes, and molecular targeting substances are the main chemotherapeutic drugs that are now on the market. Chemotherapy's main drawbacks include drug resistance, cancer recurrence, and harmful effects on tissues that aren't being treated, which may limit the use of anticancer medications and lower the quality of life for patients. Finding novel, potential anticancer drugs with more effectiveness and fewer side effects are still being done to address the issues with current treatment.

Man has always had a close relationship with nature and relied on it to survive from the beginning of time. Man relies on his surroundings to meet his requirements for fundamental necessities including food, shelter, and healthcare. Plants met his need for food and medication in addition to basic basics. Man has begun employing animal products and other natural bioresources, such as those found in plants, to prepare medicines alongside the use of plants. As a consequence, many systems of traditional medicine have developed in various nations depending on the cultural, social, and environmental contexts of the respective ethnic groups. Around the globe, traditional and contemporary therapeutic systems both use plants as key natural resources. Several thousand years ago, people first discovered the medicinal use of plants and plant-based products. Several ancient writings from Egypt, China, Greece, Rome, Babylonia, Rome, and other places know the therapeutic effects of plants with other therapies.

Today, there is a resurgence of interest in herbal therapy, with both optimistic and realistic perspectives. Herbal medicines are complex mixtures of various elements of a single plant or several herbs, which sometimes have synergistic effects with one another and result in the drug's enhanced therapeutic potential. An essential prerequisite for quality control is the identification of the physiologically active component that provides a product with its therapeutic properties [3]. Therefore, it is crucial to assure the quality of herbal medicine, which is a factor in both its safety and effectiveness, and to perform a proper identification and quality evaluation. Based on their photochemical components, herbal formulations have therapeutic effects. To standardize, evaluate the quality, and increase the effectiveness of herbal medicines, photochemical studies of the medicinally significant plants should be conducted. As a result, pharmacognosy is regarded as a crucial instrument for the research of medicinal plants to establish their identification, validity, and standardization. Figure 1 shows the estimated number of cancer cases, Global cancer data 2018. Figure 2 shows the estimated number of cancer deaths, Global cancer data 2018.

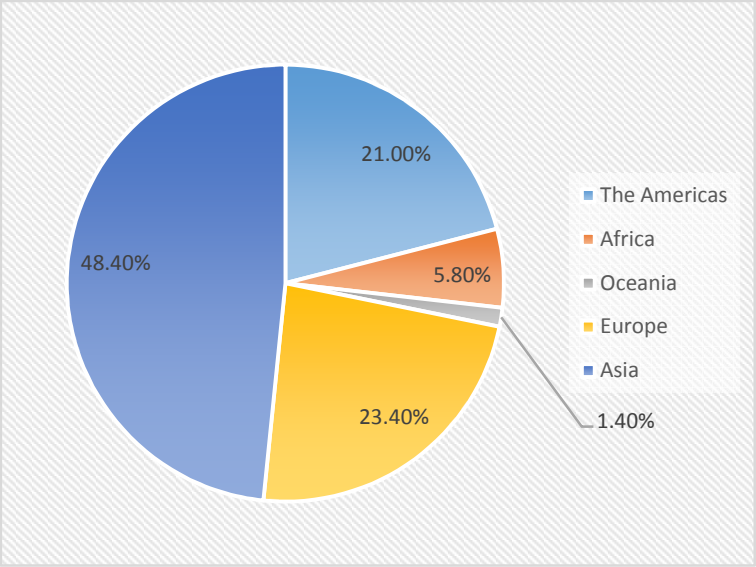

Figure 1: Illustrating the estimated number of cancer cases Global cancer data 2018.

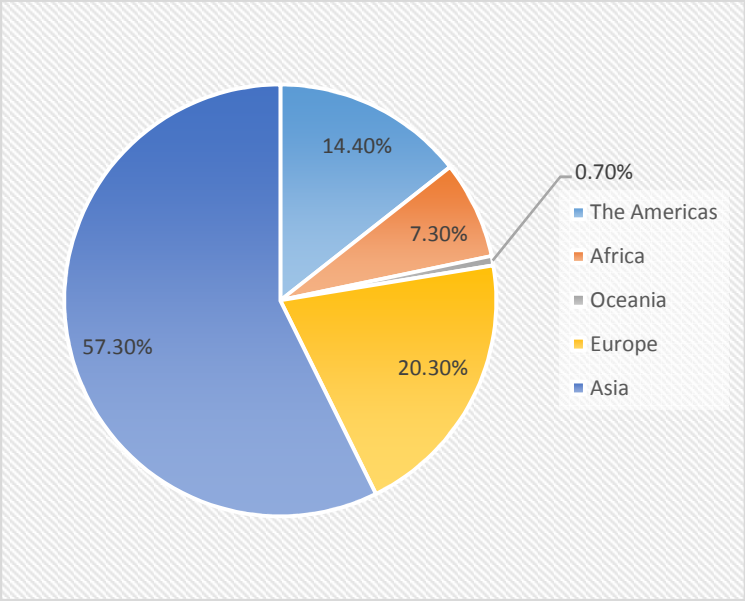

Figure 2: Illustrating the estimated number of cancer deaths, Global cancer data 2018.

Plants are still utilized as a conventional form of treatment in the current age of medicine to treat certain disorders. Through the production of some compounds or bioactive components that are not nutritional but are important lines of defense, plants may defend themselves against pathogenic microorganisms, dangerous insects, and harsh environmental changes. These would be referred to as phytochemicals, which are similar to essential oils. In addition to plants, it may shield people and animals against several diseases that are brought on by bacteria or the poisons those microorganisms create [4], [5]. This is a result of its antibacterial quality. The use of phytochemicals as chemopreventive agents is possible in the future. Because of differences in chemical composition, a variety of phytochemicals have been identified as significant categories so far. The primary categories of phytochemicals include terpenoids, carotenoids, flavonoids, saponins, alkaloids, aromatic acids, aromatic acids, phytosterols, organic acids, essential oils, and protease inhibitors. The anti-inflammatory, antigenotoxic, antiproliferative, anticarcinogenic, antimutagenic, anthelmintic, antibacterial, and antioxidative capabilities make them capable of acting as a direct or indirect defense mechanism against infections or hazardous conditions.

Throughout the last three decades, advancements in cancer therapy have dramatically increased cancer patients' chances of survival and quality of life. The three main cancer treatment options available today are chemotherapy, surgery, and radiation therapy. Recently, efforts to treat cancer using immunotherapy have increased. One of the best cancer therapies now available is chemotherapy [6], [7]. While there is constant research and development into new medications and treatment approaches, the state of chemotherapy today is far from ideal. Chemotherapy's effectiveness is limited, and severe drug-related adverse effects are frequent with a few noteworthy exceptions. It is thought that extended chemotherapy treatments impair the body's immune system, making patients more vulnerable to various illnesses and infections. Surgery is the typical cancer therapy that has the least amount of side effects, although not all cancers can be cured by surgery. Another alternative for treating cancer is radiation therapy, although it has a variety of potentially dangerous side effects, such as diminished resistance to other illnesses and

the potential to be carcinogenic in and of itself. Consequently, it is crucial to create cancer management strategies based on mechanisms. With pharmaceutical therapies focusing on prevention rather than cure, the practical objectives of this strategy should be to reduce the incidence of invasive cancer and early-onset cancer fatalities. Chemoprevention is the name given to such an intervention.

Chemoprevention is a fast-expanding field of oncology that focuses on utilizing naturally occurring or manufactured medicines to prevent cancer. This pharmaceutical strategy depends on identifying healthy people who are thought to be more likely to have cancer and for whom a pharmacological medication may successfully delay the start of the disease. Chemoprevention has a role in avoiding the development of invasive and metastatic qualities in existing neoplasms, in addition to reducing or delaying the initiation of neoplasia by blocking neoplastic genesis [8], [9]. Hence, chemoprevention of cancer differs from cancer therapy in that its objective is to reduce the occurrence of cancer. Many cell culture systems and animal tumor models have shown that a range of plant-derived nutrients and non-nutritive components can suppress the development of cancer. This has caused a greater focus to be placed on cancer prevention techniques that make use of these dietary components. Cancer chemoprevention and dietary cancer prevention are the two main diet-related cancer prevention techniques that have emerged, and there is a significant amount of overlap between them.

Cancer chemoprevention often entails the use of manufactured or naturally occurring substances in pharmacologic intervention to stop, halt, or reverse carcinogenesis or stop the growth of invasive cancer. Contrarily, diets rich in fruits, vegetables, and other plant-derived substances are preventative against several illnesses, including epithelial malignancies. Data from epidemiological research, including a variety of case-control and cohort studies, strongly show an inverse relationship between eating fruits and vegetables and the risk of developing cancer. Certain eating habits are useful forms of dietary cancer prevention. Micronutrients, dietary fiber, and different polyphenolic agents are just a few of the ingredients in fruit and vegetables that may help them reduce the chance of developing cancer. The main plant-derived substances believed to prevent cancer are flavonoids and dietary fiber. The most prevalent and extensively dispersed polyphenolic chemicals are flavonoids, which are incessantly present in meals of plant origin. Over 5,000 different chemicals are classified as flavonoids, which are characterized chemically as having a common phenylchromanone structure and one or more hydroxyl replacements.

2. LITERATURE REVIEW

Yan et al. described the signaling pathways that apigenin modulates, including the PI3K/AKT, MAPK/ERK, JAK/STAT, NF-KB, and Wnt/-catenin pathways, and we concentrate on the most recent discoveries on the anti-cancer properties of apigenin and their underlying mechanisms. We also go through how to utilize apigenin in combination with other anti-cancer drugs to increase its effectiveness against different cancers and how to use it as an adjuvant chemotherapy agent to treat malignancies that have become resistant to other drugs or to lessen the side effects of chemotherapy. Also, a summary and discussion of apigenin's actions on cancer stem cells are provided. These results showed that apigenin is a potential drug for cancer treatment. Both as a dietary supplement and as an adjuvant chemotherapeutic drug for cancer treatment, apigenin looks to have the potential to be developed[10].

He et al. in their study talked about the active ingredients of many traditional Chinese remedies, vitexin, and isovitexin, which were discovered in a variety of medicinal plants. The pharmacological activities of vitexin (apigenin-8-C-glucoside), which include but are not limited to antioxidant, anti-cancer, anti-inflammatory, anti-hyperalgesic, and neuroprotective actions, have lately attracted more attention. The isomer of vitexin known as isovitexin (apigenin-6-C-glucoside), which is often purified alongside vitexin, also demonstrates a variety of biological functions. Recent studies have revealed that vitexin and isovitexin may be used as adjuvants for difficult-to-treat illnesses or as prospective replacement medications for a variety of disorders. To serve as a guide for future research and therapeutic applications, this study compiled the most current data on the numerous pharmacological actions and associated signaling pathways of vitexin and isovitexin[11].

Lim et al. examined in the current work the anti-cancer effects of apigenin on choriocarcinoma cells (JAR and JEG3). Both the JAR and JEG3 cells were affected by apigenin, which also promoted apoptosis and inhibited mitochondrial membrane potential. In addition, apigenin treatment of JAR and JEG3 cells mostly lowered the phosphorylation of AKT, P70RSK, and S6 while dose-dependently increased the phosphorylation of ERK1/2 and P90RSK. Moreover, apigenin and pharmacological inhibitors of PI3K/AKT (LY294002) and ERK1/2 (U0126) have synergistic anti-proliferative effects when used together in the treatment of JAR and JEG3 cells. All of these findings showed that apigenin is a good chemopreventive drug that controls the PI3K/AKT and ERK1/2 MAPK signal transduction mechanisms to prevent the development and metastasis of choriocarcinoma cells[12].

In this work, Lee et al. looked at how apigenin affected human MDA-MB-231 cells to prevent cancer. Initially, an MTT test was used to assess apigenin's cytotoxicity against MDA-MB-231 cells. The molecular mechanism behind apigenin's anticancer action was then investigated, along with its impact on the cell cycle and apoptotic processes. The cell cycle was arrested in the G2-M phase and there was an increase in early apoptosis as a result of apigenin's dose-dependent inhibition of cell growth. The expression of CDK6, cyclin Dl, and cyclin Bl were both downregulated, while p21 was upregulated, which was strongly correlated with the cell-cycle inhibitory impact. Cleaved PARP and cleaved caspase-3,-7, and-9 expression were elevated in response to apigenin's activation of apoptosis[13].

The goal of the current study by Hong et al. was to encapsulate apigenin with whey protein isolate (WPI) using a pH-cycle approach and then evaluate the physical and chemical characteristics, the anticancer effects against human colorectal HCT-116 and HT-29 cancer cells in vitro, and the in vivo bioavailability. With an encapsulation efficiency of up to 98.15% and a loading capacity of up to 196.21 mg/g-WPI, apigenin up to 2.0 mg/mL was nanoencapsulation with 1.0 mg/mL WPI. After being enclosed, apigenin developed an amorphous state, whereas nanodispersions remained stable throughout storage. Apigenin's ability to inhibit cell proliferation was unaffected by nanoencapsulation or in vitro digestion. As compared to apigenin that was not nanoencapsulated, the cellular absorption, pro-apoptotic effects, and bioavailability in the mice's blood and colon mucosa were all increased. To add lipophilic phytochemicals into functional drinks for disease prevention, the current work may be crucial.

3. DISCUSSION

Pure Apigenin is unstable and not highly soluble in organic or water-based solvents. Because of these characteristics, apigenin cannot be used in its pure forms. Foods naturally contain apigenin

largely in the form of acylated derivatives and glycoside conjugates, which are more water-soluble than the parent molecule. Although these properties may require enzymatic cleavage by human or microbial glucosidases, the moiety with which apigenin is conjugated is a significant factor in determining its absorption and bioavailability. According to studies, human absorption of the quercetin glycoside found in onions is much higher than that of quercetin itself. This suggests that apigenin's highest bioavailability may come from its native form coupled with ßglycosides.

Once in the gut, apigenin undergoes significant metabolism via a dual recycling system that includes both enteric and enterohepatic recycling. According to studies, apigenin is quickly converted by the enzyme UDP glucuronosyltransferase UGT1A1 into glucuronide and sulfate conjugates, which are more easily carried through circulation and eliminated via bile or urine.

According to Gradolatto et al. oral ingestion following a single dosage of radio-labeled apigenin in rats led to a 51% recovery of radioactivity in urine, 12% in feces, 1.2% in blood, 0.4% in the kidneys, 9.4% in the gut, 1.2% in the liver, and 24.8% in the rest of the body after 10 days. After taking oral apigenin for 24 hours, radioactivity was detected in the blood. Apigenin's blood kinetics showed a comparatively long elimination half-time of 91.8 h when compared to other dietary flavonoids. These findings imply that even though apigenin has poor bioavailability, its delayed pharmacokinetics may cause an accumulation of this flavonoid in the tissues, which would effectively impart its chemopreventive properties.

Since that cancer cells contain several genetic mutations, a combinatorial therapeutic approach is necessary for cancer treatment to be successful. Combinatorial cancer therapy's major goals are to increase the antitumor effects of chemotherapeutic drugs and get around the problem of acquired drug resistance. When taken alone at human physiological doses, apigenin is an effective anti-cancer drug but has only modest anti-cancer effectiveness. Hence it makes sense to co-treat with additional chemo drugs to increase their anti-cancer effects. Table 2 provides a summary of how apigenin and other chemo drugs work together. Moreover, the majority of the combination therapies improved both in vitro and in vivo anti-cancer activity.

In the clinic, chemotherapy medications like cisplatin and paclitaxel are often used to treat cancer. While these medications significantly contribute to the extension of cancer patients' overall survival rates, their unintended toxicity has long been a source of worry for doctors and patients. Co-administration with other targeted medications has undergone extensive testing and is very effective in clinical settings to maximize their antitumor effects and reduce their limitations. According to research, apigenin co-administration considerably increases the anti-cancer efficiency of chemotherapeutic medications and aids in overcoming their limitations in treating different kinds of malignancies by targeting several signaling pathways.

Clinical studies have examined recombinant Apo2L/tumor necrosis factor-related apoptosis-inducing ligand, a potent anticancer drug that promotes cancer cell death without harming healthy cells. Nevertheless, because of developed resistance, TRAIL therapy only shows modest anti-cancer effects in several malignant tumors. The Apo2L/TRAIL pathway chemotherapy requires overcoming this resistance. Apigenin inhibits adenine nucleotide translocase-2 and increases DR5 to break down Apo2L/TRAIL resistance in prostate cancer DU145 and LNCaP cells. Moreover, apigenin's ability to increase DR5 expression and Apo2L/TRAIL-induced apoptosis was reduced when ANT2 was silenced by siRNA, demonstrating the need for ANT2 inhibition. TRAIL therapy alone is ineffective against NSCLC A549 and H1299 cells. In a p53-

dependent way, apigenin exposure increases DR4 and DR5 expression and makes those cells more susceptible to TRAIL-induced apoptosis. Moreover, Kim et al. demonstrated that via altering the Bcl-2 family of proteins, apigenin synergistically increased the cytotoxicity of TRAIL in anaplastic thyroid cancer cells.

MicroRNAs are small, non-coding RNAs with 20–24 nucleotides that control gene expression post-transcriptionally. A variety of transcripts may be impacted by aberrant miRNA expression, which may also have a significant impact on signaling pathways involved in cancer. MiRNAs may thus have a role in the development of malignancies as oncogenes or tumor suppressors. Apigenin-induced anticancer effects might be strengthened by modification of miRNA expression. Glioblastomas have elevated levels of miR-423-5p, which helps glioma stem cells. With a change in the Bax/Bcl-2 ratio, an increase in cytochrome c level, Apaf-1 induction, and caspase-3 activation, miR-423-5p downregulation promotes apigenin-induced cell death in glioma stem cells. In contrast, miR-138 overexpression greatly increased apigenin-induced cell death and lowered cell viability and colony formation capabilities in vitro, and successfully inhibited tumor development in vivo in malignant neuroblastoma SK-N-DZ and SK-N-BE2 cells.

Co-treating with a second agent to lessen the negative effects of one medicine is another popular method in the treatment of cancer. It is well known that apigenin demonstrates a wide range of biological actions, including anti-inflammatory and antioxidant effects. One of the side effects that restrict the use of cisplatin in cancer treatment is nephrotoxicity. To protect Wistar Albino mice from cisplatin-induced nephrotoxicity, Hassan et al. discovered that co-administration with apigenin dramatically decreased blood urea nitrogen, serum creatinine, TNF-, IL-6, COXI, COXII, and MDA levels and raised GSH levels. 4-Hydroxy-2-nonenal is one lipid peroxidation product that has been linked to the development of neurological diseases. Apigenin dramatically reduced 4-HNE-mediated cell death in neuronal-like catecholaminergic PC12 cells in another research via restoring ER homeostasis. Consequently, apigenin not only exhibits considerable protective properties and reduces chemo-drug-mediated adverse effects but it may also be employed as an adjuvant chemotherapeutic agent to overcome drug resistance.

Verdicts

Plant flavonoids may provide significant health advantages, which is supported by a large body of research. It takes a methodical and thorough approach to design diet-derived chemopreventive therapies. Before beginning clinical trials, the most logical method for developing novel drugs is to test them on particular molecular and cellular targets in a suitable animal model to assess their effectiveness and bioavailability. Epidemiological research offers a wealth of knowledge and may provide important recommendations for the creation of chemopreventive drugs. However, before beginning clinical trials, it is crucial to validate the resulting hypothesis using experimental data from cell culture and the relevant animal models. Often found in fruits and vegetables, apigenin is a common non-mutagenic plant flavonoid that has shown outstanding potential as a strong chemopreventive drug. Apigenin-mediated cancer prevention and therapy has been associated with a variety of mechanisms of action, including estrogenic/anti-estrogenic activity, antiproliferative activity, induction of cell-cycle arrest and apoptosis, inhibition of oxidation, induction of detoxification enzymes, control of the host immune system, and alterations in cellular signaling.

Significant developments have been made in evaluating apigenin's effectiveness in pre-clinical cancer models. Ongoing efforts are required, with a particular emphasis on new pre-clinical investigations of different cancer animal models that closely resemble human tumors, which may then be confirmed in clinical trials. Apigenin has a huge amount of promise for future development as a promising cancer chemopreventive drug, according to a substantial body of accumulating information.

CONCLUSION

Glycoside form, which is found in dietary sources, is broken down into apigenin itself in the gastrointestinal lumen for absorption and distribution. Due to this, tissues in other sites are not exposed to the same levels of apigenin as the gastrointestinal tract epithelium. Epithelial malignancies of the gastrointestinal system would also fall under this category. We evaluate the evidence regarding apigenin's potential to function in ways that prevent the spread and progression of gastrointestinal malignancies. It has been shown that apigenin suppresses cell proliferation, makes cancer cells more susceptible to death by apoptosis, and prevents the creation of blood vessels to support the expanding tumor. Also, it takes steps to change how cancer cells interact with their surroundings. The chemokine signaling pathways that control metastasis into other sites are inhibited by apigenin, which also inhibits the remodeling of the extracellular matrix, cell adhesion molecules that contribute to cancer growth, and glucose absorption by cancer cells. Apigenin could thus be able to inhibit the spread of metastatic illness more slowly than other medications already on the market.

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CHAPTER 23

AN EXPLORATORY STUDY ON PHARMACEUTICAL PROPERTIES OF AZADIRACHTA INDICA

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ABSTRACT:

One of the most promising plants, the neem tree, may potentially be useful to everyone in the world. There is probably no other plant that produces as many different products or as many usable byproducts. Neem is essential in solving several issues relating to human health. Due to the chemical components found in neem, a doctor tree, it has a wide range of biological activities connected to it and is now used in a worldwide context. Neem has become a popular treatment option in contemporary medicine due to its extensive usage in Ayurveda, and homeopathic treatments.

Ayurveda brought the neem tree to the awareness of natural product chemists. Concerning the physiological functions and therapeutic uses of neem, significant progress has been made during the past 50 years. The goal of this paper is to use the therapeutic benefits of the entire neem plant in treating a variety of human illnesses. In the future people will be aware of the various benefits and pharmaceutical properties of Azadirachta Indica.

KEYWORDS:

Antifungal, Antibacterial, Antifungal, Azadirachta Indica, Medicinal.

1. INTRODUCTION

Neem is a naturally occurring plant that is derived from the neem tree, also known as Azadirachta indica or Indian lilac. The extract is made from the tree's seeds but has a variety of historical applications. In addition to being used in hair as well as dental treatments, neem is well-recognized for its pesticide and insecticide capabilities. Originally, the neem tree's leaves, blossoms, seeds, roots, fruits, or bark have all been used to cure fever, infections, inflammation, skin conditions, or dental issues. Neem leaf's therapeutic benefits have been specifically discussed [1]. The anti-inflammatory, antihyperglycemic, antibacterial, antiulcer, antiviral, immunomodulatory, antimalarial, antifungal, antimutagenic, antioxidant, but also anticarcinogenic activities of neem leaf or its components have been proven, as shows in Figure 1. The extensive spectrum of pharmacological functions of neem leaf is summarized in this study [2].

Figure 1: Illustrate the pictorial representation of Azadirachta Indica (Neem), such as a) leaves, b) flowers, and c) fruit.

According to legend, planting a neem tree in front of your home will get you to paradise. To ward against evil, neem leaves are put in front of doors or gates. To expose the newborn to a protective aura, the brides will bathe in water that has been mixed with neem leaves during wedding ceremonies. Through the improvement of antioxidant activity, suppression of bacterial growth, or modification of genetic pathways, plant products as well as natural products demonstrate an essential role in the prevention and treatment of illnesses. Due to their low side effects and accessible qualities, several plants are still being eagerly explored for their potential medicinal roles in the management of illnesses. It is common knowledge that allopathic medications cost a lot of money and have detrimental effects on healthy tissues and a variety of biological processes. It is well acknowledged that many pharmacologically effective medications are made from natural resources, such as medicinal plants [3].

The Bible and the Quran are only two examples of religious texts that promote the use of herbs for treatment and prevention. Islamic viewpoint also supports the use of herbs in the management of ailments, and Prophet Mohammed advocated the use of different plants and fruits in the treatment of illnesses. Many viral, metabolic, or malignant disorders are treated using neem components in Ayurveda, homeopathy, Unani, and contemporary medicine. Neem trees and their various components have been employed in Indian traditional Ayurvedic treatment for centuries [4].

In traditional medicine, intestinal helminthiasis, leprosy, respiratory problems, constipation, or general health promotion have all been treated with neem oil, bark extracts, and leaf extracts. Its efficacy in the treatment of rheumatoid arthritis, persistent syphilitic ulcers, and latent ulcers has also been demonstrated. Neem oil is used to treat several skin ailments. Bark, leaf, flower, root, and fruit all work together to treat, skin ulcers, itching, and blood disorders [5].

1.1. Neem: A Botanical Description

The Meliaceae family, which includes the neem tree, is widely distributed in tropical or semitropical areas like India, Pakistan, Bangladesh, and Nepal. It is a tree that grows quickly, reaching a height of 20 to 23 m. Its straight trunk measures around 4-5 feet in diameter. Each of the compounds, imparipinnate leaves has between 5 and 15 leaflets. It produces green drupes that mature to golden yellow from June through August. Azadirachta indica's taxonomic status (neem) [5].

Position of Azadirachtaindica in the Taxonomy

1. Order – Rutales
2. Suborder – Rutinae
3. Family – Meliacese
4. Subfamily – Melioideae
5. Tribe – Melieae
6. Genus – Azadirachta
7. Species – Indica

1.2. History:

The first known medicinal system for humans dates back to between 10,000 and 4000 BC, it was characterized as a prophylactic against death. The great sacred tree Neem was the first plant to be named in this medical system by the Great Sage Agathiyar. Data were recorded on palm leaves throughout the ancient period, but these documents are known as palm leaf manuscripts. In 1992, British archaeologists excavating at Mohenjo-Daro or Harappa discovered clay vessels made of neem as well as a skull that had undergone cranial surgery [6]. This incident demonstrates the development of the old medical system, which included surgery as well as phytopharmacology. In this paper, the author talks about the medicinal value of Azadirachta Indica (Neem) and its health benefits.

2. LITERATURE REVIEW

Alok Maithani et al. studied various health benefits of neem. Most developing nations employ traditional medicine or medicinal plants as a normative foundation for the preservation of good health, as has been well documented. Based on the knowledge gathered from traditional healers, around 121 medicinal medicines have been discovered in the past century. The creation of novel medications from medicinal plants has greatly benefited from the simplification of chemical principles from natural sources. Because of the numerous phytoconstituents, it contains and the numerous pharmacological properties linked to it, Azadirachta indica is among the most lucrative plants farmed in India [7].

Haider Ali Quraishi et al. studied about medicinal and Therapeutical properties of Neem (Azadirachta indica). Most developing nations employ traditional medicine or medicinal plants as a normative foundation for the preservation of good health, as has been well documented. Based on data gathered from conventional scientists and doctors, 130 medicinal items have been discovered in the previous century. The development of new drugs from medicinal plants has been greatly aided by the simplification of chemical fundamentals from natural sources. As a result, the market for plant-derived chemicals, fragrances, flavors, pharmaceuticals, as well as color ingredients alone now exceeds several billion dollars annually. The current review emphasizes research on Unani medicine as well as botanical, taxonomic, and pharmacological discussions on neem [8].

S. Susmitha et al. studied about antimicrobial activity of Neem. By using the cup diffusion method, aqueous extracts of Azadirachta indica (Neem) were put through an in vitro antibacterial experiment against human pathogenic Salmonella and Escherichia sp. Secondary plant metabolites (alkaloids, terpenoids, tannins, steroids, glycosides, flavonoids) and reducing sugars were found using a qualitative phytochemical study. For the examination of lipids, alkaloids, and

flavonoids contained in leaf extracts, thin layer chromatography (TLC) was also carried out using various solvent systems. The current study would be successful in determining candidate plants with various antimicrobial activities that could be further utilized for phytochemical characterization and isolation in the treatment of infectious diseases, particularly in light of the emergence producing more potent antimicrobial agents [9].

Garima Pandey et al. studied about Evaluation of the Phytochemical, Antibacterial properties of Neem. Following HPTLC examination, phytoconstituents in a 50% ethanolic extract of neem leaves were subjected to quantitative and qualitative quantification. To further understand the antioxidant capacity of neem leaves, the DPPH free radical scavenging activity was carried out. Using a well-diffusion experiment, the antibacterial activity of the extract was investigated against Gram-positive Staphylococcus aureus as well as Gram-negative Escherichia coli. Both E. coli and S. aureus were susceptible to the extract's antibacterial effects, albeit S. aureus was more successfully suppressed than E. coli. The findings imply that the leaves of A. indica have strong antibacterial or antioxidant activities, as well as phytoconstituents that could be involved in its therapeutic effects [10].

3. DISCUSSION

A database search on PubMed, Science Direct, Google Scholar, Research Gate, and other sites was used to conduct the current review study. Combining keywords like "Antifungal, Antibacterial, Antifungal, Azadirachta Indica, and Medicinal" were used in the review technique. The records preliminary review employed title and abstract screening. Insufficient information, redundant research, and non-extractable data were some reasons to exclude the Records. More details about the review study's methodology are provided in Figure 2 below.

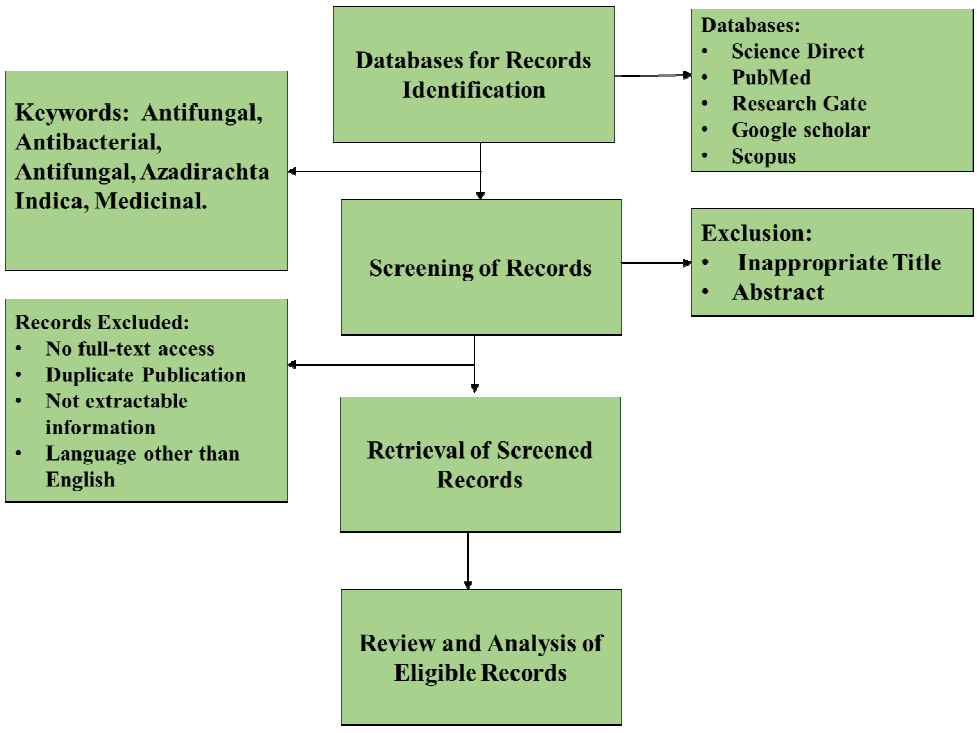

Figure 2: Illustrate the Design of the Methodology of the Current Work.

Neem is a naturally occurring plant that is derived from the neem tree, also known as Azadirachta indica or Indian lilac. The extract is made from the tree's seeds and has a variety of historical applications. In addition to being used in hair and dental treatments, neem is well-recognized for its pesticide and insecticide capabilities. Traditionally, the neem tree's leaves, blossoms, seeds, fruits, and roots, instead of bark have all been used to cure fever, infections, inflammation, skin conditions, and dental issues. The main crude extract made from the oil of Neem seed kernels is called nimbidin. Tetranortriterpenes like Nimbin, Nimbidinin, Nimbolide, Nimbinin, or Nimbidic acid may be isolated from Nimbidin. In formalin-induced arthritis in rats, nimbidin as well as sodium nimbidate have anti-inflammatory action.

They also have antiulcer and antihistamine properties by inhibiting H2 receptors. In both humans and rats, nimbidin has spermicidal action. Additionally, tests have been conducted on fasting rabbits using oral Nimbidin administration, which lowers blood glucose levels. Additionally, it has antifungal properties against Mycobacterium tuberculosis or Tinea rubrum. Administration of sodium nimbidate results in diuresis in dogs, proving that sodium nimbidate is a diuretic. Nimbolide has anti-fungal and anti-malarial properties against Plasmodium falciparum as well as antibacterial properties against Staphylococcus aureus as well as Staphylococcus coagulase. Azadirachta Indica L. Neem's Pharmacological Actions in the Treatment of Illnesses Regulate a Variety of Activities, as shown in Figure 3.

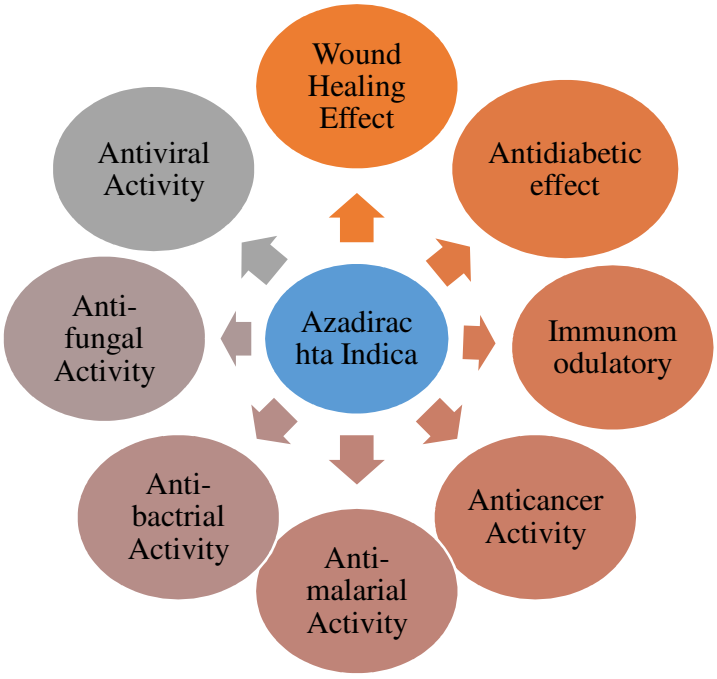

Figure 3: Illustrate the Regulation of Numerous Activities by Azadirachta Indica L. Neem's Pharmacological Actions in the Treatment of Illnesses.

3.1. Medicinal Property of Neem:

3.1.1. Antiviral:

Neem leaves have been proven to be effective against Dengue virus type 2 in that it prevents the virus from replicating in vitro as well as in lab animals. Although Neem does not treat, it can

prevent chickenpox, smallpox, or fowl pox by inhibiting the entry of the Herpes simplex virus type 1 into natural target cells. During the germination of horse grain, neem seed extract's antioxidant activity was proven in real-time.

3.1.2. Antifungal Activity:

An experiment was made to evaluate the efficacy of various extracts of neem leaf on seed-borne fungi Aspergillus and Rhizopus and results confirmed that the growth of both the fungal species was significantly inhibited and controlled with both alcoholic and water extract. Furthermore, the alcoholic extract of neem leaf was most effective as compared to the aqueous extract for retarding the growth of both fungal species. Another discovery demonstrated the neem cake's antimicrobial properties in preventing the growth of three sporulating fungi, including H. pennisetti, C. lunata, and C. gloeoporioides f. sp. mangiferae. Additionally, the study's findings demonstrated that methanolic and ethanolic extracts of Azadirachta indica reduced the development of Aspergillus flavus, Alternaria [11]. Previous researchers have noted the antifungal properties of aqueous extracts of many neem sections, including neem oil and its main constituents. To investigate Azadirachta indica L.'s antifungal properties, research was conducted. Against Alternaria solani Sorauer, the findings showed that ethyl acetate fraction, with MIC of 0.19 mg, was more efficient in slowing fungal growth. This fraction was also more effective than fungicide (mancozeb + metalaxyl), with MIC of 0.78 m.

3.1.3. Antibacterial:

The methanol extract of A. indica leaves has antibacterial action against Salmonella typhi, Staphylococcus aureus, Bacillus subtilis, and Proteus Vulgaris, and very moderate activity against Pseudomonas aeruginosa, although it is infective against Escherichia coli. A. Indica leaf extracts in petroleum ether or methanol were very efficient in killing Candida albicans. A. India bark extract in hexane also has antibacterial action against Escherichia coli. Staphylococcus aureus, Escherichia coli, Staphylococcus pyogenes, or Pseudomonas aeruginosa are among the microorganisms that cause ophthalmic illness, while the seeds of Azadirachta indica have antibacterial properties [12], [13].

3.1.4. Hypoglycemic:

Neem leaf aqueous extract dramatically lowers blood sugar levels and guards against adrenaline- or glucose-induced hyperglycemia. Recently, either normal or diabetic rabbits induced with alloxan showed hypoglycaemic effects with leaf extract as well as seed oil.

3.1.5. Immunoregulation:

Neem bark or leaf aqueous extract also has immunostimulant as well as anticomplementary effects. Neem oil has been demonstrated to be active by specifically engaging the immunological processes of the cell to provide an improved response to a future mitogenic or antigenic stimulus.

3.1.6. Hepatoprotective:

By administering carbon tetrachloride to rats as an acute hepatotoxic agent and using silymarin as a typical hepatoprotective agent, young stem bark extract of Azadirachta indica was employed to analyze the hepatoprotective efficacy. For the experiments, a dosage of 200 mg/kg or 500 mg/kg was used. When Azadirachta indica is administered, it boosts the quantity of total protein and stabilizes the levels of serum bilirubin, glutamate pyruvate transaminase, glutamate

oxaloacetate transaminase, or alkaline phosphatase. As a result, this plant indicates an improvement in the liver cells' functional state [14], [15].

3.1.7. Antidiabetic:

Rats with diabetes caused by a high-fat diet were given the oral effective dosage of A. indica leaf extracts (400 mg/kg body weight [b.wt]) once a day for 30 days. Fasting blood sugar, oral glucose tolerance, levels of insulin signaling molecules, glycogen, serum lipid profile, or glucose oxidation in the gastrocnemius muscle were all evaluated after the trial.

3.1.8. Central Nervous System Impact:

The leaf extract was shows to have varying degrees of the central nervous system (CNS) depressing action in mice. Significant CNS depressing activity was detected in leaf fractions of acetone extract.

3.2. Poultry Uses:

When chicken feed is contaminated with aflatoxin, Aspergillus flavus is formed. Neem oil is utilized to prevent this, and the extract from Neem leaves inhibits Penicillium expansion's formation of patulin. The processed Neem cake, which is utilized as chicken feed, has excellent culinary quality as well as wormicidal efficacy. Additionally, neem leaves include a sizable quantity of protein, minerals (apart from zinc), digestible levels of crude protein, or total digestible proteins that provide superior nutrition for poultry animals like sheep, goats, and cows. According to a study, the main parasite infesting goat husbandry in Malaysia is Haemonchus contortus, and neem leaf water extract may be able to lower the number of eggs it produces [16], [17]. After just two weeks, the Neem leaf water extract loses its effectiveness as an antihelminth, and subsequent weeks reveal a rise in the egg count when the feces are examined under a microscope. As a result, the dose needs to be adjusted, and the dosage for the test animal needs to be optimized.

3.3. Fertilizer:

Neem cake, which is left behind after neem oil is extracted from the seed, may be used as a biofertilizer to feed plants and boost agricultural yields. Additionally, a study was conducted to clarify the effects of Neem leaves, wood ash, as well as modified Neem leaves (wood ash +Neem leaves) on tomato development and the impacts of extracts on the soil after the tomato was harvested. According to the study, when compared to applying Neem leaves or wood ash separately, the modified Neem leaves provide the highest levels of plant height, leaf area, stem girth, and tomato plant branching. Comparing poultry manure to Neem leaf extracts, you can see that the height stem girth is enhanced. When compared to poultry manure or individual applications of Neem leaves and wood ash, the modified Neem leaves extract displays the best value of Nitrogen, organic matter, Potassium, Calcium, Phosphorus, or Magnesium in the soil [18], [19].

3.4. Pesticide:

According to a study, soaking a banana corm and pseudostem with neem cake extract, neem seed powder in water, neem kernel powder, or neem oil emulsion would interfere with the settling response, and larval feeding of Cosmopolites sordidus, egg laying, also known as the banana corn borer.

4. CONCLUSION

Since these revered Neem plants have a wide range of therapeutic benefits. Therefore, research should be done on combining Azadirachta indica's bioactive components with other medicinally important plants to treat disorders that have not been fully cured by modern medicine or that have become resistant to the existing therapies. Secondary metabolites from medicinal plants are abundant and have promise as medication sources and therapeutic value. The utilization of plant extracts as medicinal agents is gaining more and more attention. Neem is a plant with pharmacological potential for usage as a cure-all. According to the literature review, mango is a possible source of anticancer, anti-inflammatory, anti-diabetic, or antibacterial medications. It is also utilized as a radioprotective, cardioprotective, and memory-enhancing substance, among other things. The gathered data on Azadirachta indica's traditional usage of their effectiveness and popular belief that natural substances, especially those of plant origin, are safe for human use. To cure a range of human disorders, the medicinal advantages of the entire neem plant are the focus of this study. People will be aware of the different advantages and medicinal characteristics of Azadirachta indica in the future.

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CHAPTER 24

MORPHOLOGY, PHYTOCHEMISTRY, AND PHARMACOLOGICAL PROPERTIES OF *CYMBOPOGON CITRATUS* (LEMONGRASS)

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ABSTRACT:

In the world, one of the most widely used plants is Cymbopogon citratus (Poaceae), which is also one of the most widely distributed. There are several pharmacologic properties in the various C. citratus extracts. Among many others, the anticancer, anti-inflammatory, antibacterial, and antimicrobial properties are widely known. Depending on the application, C. citratus may be utilized either alone or in combination with other phytoconstituents. Numerous research has been conducted to characterize the chemical constituents of volatile and nonvolatile substances as a result of the ethnopharmacological uses of C. citratus. Citronella oil is employed as a fragrance in toiletries, insecticides (bio-pesticide), cosmetics, and wasted grass in agriculture, as well as in chemical and pharmaceutical industries to produce soaps, detergents, perfumes, scents, cosmetics, aftershaves, and as a culinary taste in food industries. Here, the present study aims at reviewing the morphology, phytochemistry, and pharmacological properties of lemongrass. The findings of the study revealed that lemongrass can be used for its therapeutic potential for anti-microbial, anti-inflammatory, and anti-cancer properties.

KEYWORDS:

Antimicrobial, Cymbopogon Citratus, Medicinal Herbs, Lemongrass.

1. INTRODUCTION

Medicinal herbs have been the most important and safest drugs from time immemorial and therefore play an important role in public and basic health care. Medicinal herbs are therapeutic agents that are essential in the primary healthcare system to preserve excellent well-being and health. The Stone Age may have been the origin of unproven and unproven ethnopharmacological understanding of therapeutic plants. Unexpected advances in the utilization of herbs in the primary healthcare system have lately been noted on both the African and Asian continents [1]. In the past, a rising number of customers have been seeking new herbal products with distinct properties that give pleasurable moments while also providing enough health advantages. Herbal medications were developed as a result of scientific or systematic research into bioactive ingredients, ethnopharmacology, or traditional knowledge of therapeutic plants. This is the foundation for phytochemical progress. Nearly 10,000 therapeutic plants have been identified in recent years, with around 4500 having been tested for bioactive components and pharmacological tests. *C. citratus* is one of the therapeutic plants with enormous pharmacological activity [2].

Citronella grass or lemongrass is another name for Cymbopogon citrates staff. This species is a member of the Gramineae family, which includes around 500 genera and 8,000 plant species. Lemongrass is a 1-meter-tall tufted perennial grass with multiple stiff leafy stems emerging from short rhizomatous roots. It comes with a 5-year economic lifecycle. The leaf blade is straight, tapering at both sides and grows to 50 centimeters in length and 1.5 cm in breadth. The tubular leaf sheath functions as a pseudostem. Glaucous, long, green leaves with a linear tapering above and down the edges[3]. At the adult phases of development, this plant produces flowers. Flowering, on the other hand, has never been seen under planting because of the short harvesting period. The inflorescence is a 1-meter-long spike. Flowers are produced on decompound spatheate, with panicles ranging in length from 30 to 60 cm. The rhizome sends forth new suckers, which grow vertically as tillers to create thick clusters.

Because of its economically important essential oils, *Cymbopogon citratus* is of great interest and is frequently employed in food science and technology in addition to traditional medicine. Because of the introduction of new illnesses, individuals are becoming more aware of health problems. Because of the dangers connected with synthetic medications, treating with plant-based medicine looks to be an alternate method [4]. Lemongrass is used in traditional medicine to treat elephantiasis, leprosy, malaria, flu, coughs, gingivitis, headaches, ophthalmology, pneumonia, and vascular problems. Lemon grass contains antibacterial and antifungal effects, according to studies. It's a home remedy for menstruation problems and nausea when combined with pepper.

Lemon grass is an effective cleanser that aids in the detoxification of the liver, kidney, bladder, & digestive system. It lowers excess fats, cholesterol, uric acid, and other toxins in the system while increasing blood circulation, digestion, and lactation; it also relieves gastroenteritis and indigestion. Lemon grass is also reported to assist with skin care by decreasing pimples and acne and acting as a muscular and tissue toner. It may also help lower blood pressure. Lemon grass, according to new research conducted by the Food and Nutrition Research Institute of the Department of Science and Technology (DOES), may aid in cancer prevention. The current study is organized into five parts, the first of which explains the fundamentals of the agenda, the second of which gives linked works of the study of recent literature, and the third of which describes the approach. The fourth section then presents the research study's findings and discusses future research suggestions, which are accompanied by the conclusion in section 5.

1.1. Morphology and Phytochemistry of Lemongrass

Lemongrass is another name for the plant Cymbopogon, a Poaceae family member. As shows in Figure 1, Lemongrass is a perennial grass that can reach up to one meter tall and has several stiff, greenish stems that sprout from tiny, rhizomatous roots. In the Indonesia and Philippines, perennial fragrant grasses described as Cymbopogon citratus are frequently planted. Additionally, it is grown in America and Asia, notably in their tropical climates. Although it is primarily an Indian native herb, the herb is also cultivated in several other tropical and subtropical countries [5]–[7].

Because it contains more citral than other plants, lemongrass (Cymbopogon citratus) is well recognized. Either early or late lemongrass harvesting has an impact on essential oils and citral concentration. Temperatures, light output, soil moisture, fertilizer, and maturation all had an impact on the essential oils and citral components. The plant transitions from the vegetative to the reproductive phase as it ages. Generally, there is a strong correlation between the production

of plant biomass and the yield of essential oils. The proportion of younger to older leaves determines whether essential oils are of higher quality and contain more citral (75%) when collected at a certain time. Alternative methods, such as solvent, rapid solvent dense CO2 and the solid phase matrix, Soxhlet, and super-critical fluid extraction techniques, are often used to get lemongrass essential oils. Owing to the intricacy of the chemical constituents, modern methods like high-performing liquid chromatography in combination with gas chromatography (HPLC-GC) are the recommended analytical method. A sample may be placed into a GC for a greater level of separation, however, HPLC is more effective for a wide class separation. Common phytochemical constituents of lemongrass are illustrated in Figure 2 below.

Figure 1: A Pictorial Representation of Cymbopogon citratus, Lemongrass.

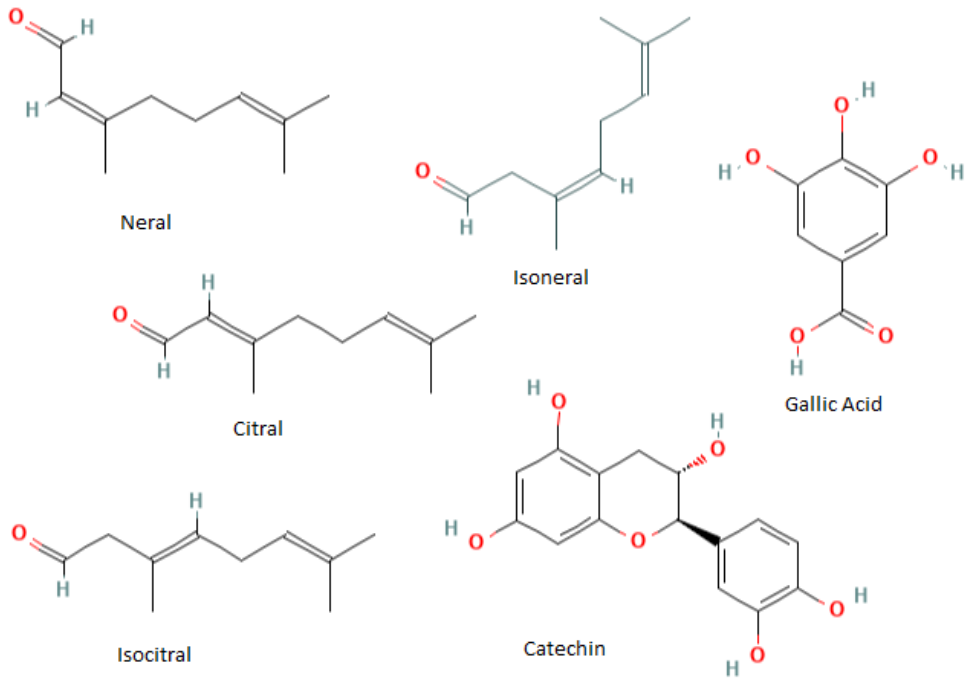

Figure 2: Illustrating the two-dimensional structures of common phytoconstituents found in lemongrass.

1.2.Pharmacological Properties

Major pharmacologic applications of lemongrass have been reviewed in this study, as illustrated in Figure 3 below.

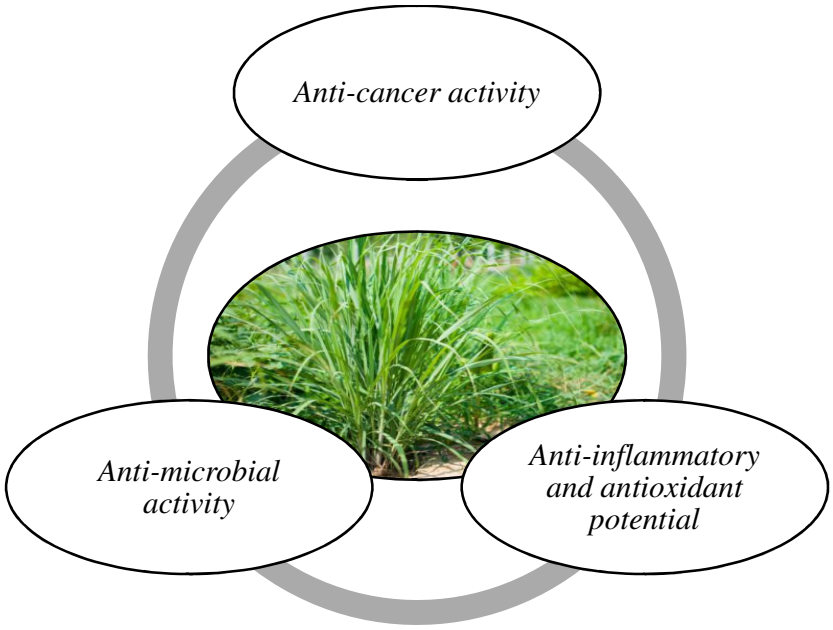

Figure 3: Illustrating the major three pharmacologic applications of Lemongrass.

1.2.1. Anti-microbial activity

In an in vitro investigation, Shanjun Gao examined the efficiency of lemongrass (Cymbopogon flexuosus) essential oil as well as its pharmacological component citral against dual-species biofilm communities produced by Candida and Staphylococcus aureus species. According to their findings, both lemongrass essential oil and citral were effective to diminish cell viability and biofilm biomass of each species in the biofilm. Microscopic studies demonstrated these compounds interfered with the adhesion qualities of each species and disturbed the biofilm matrix by counteracting proteins, nucleic acids, and carbohydrates in the biofilm [8].

Syed Nyamath and B Karthikeyan tested preparations of lemon grass leaves (fresh and dried) for antibacterial activity against several microorganisms in hot, cold, and diverse solvents including methanol and ethanol. As opposed to other species, staphylococcus aureus had a larger inhibition zone (12.50mm) at 1000 ppm concentrations in ethanol dry leaf extracts. Pseudomonas aeruginosa (2.0mm) had the smallest zone of inhibition in hot water fresh leaf extracts at 250 ppm [9].

Essam Hebishy found that combining gum Arabic (GA), whey protein hydrolysates (WPH), soy lecithin (SL), and their ternary admixture with high-intensity ultrasound scans can enhance the thermal, physical, oxidative stability, and color, as well as the antibacterial properties, of lemongrass essential oil (LEO) nanoemulsions (NEs).

Monika Yadav et al. examined the antibacterial activity of essential oils EOs of Tulsi (Ocimum sp.), Clove (Syzygium aromaticum), and Lemongrass (Cymbopogon citratus), to discover the

most efficient EO against various kinds of foodborne microorganisms. The findings revealed that each of the microorganisms tested positive for clove EO, with the maximum zone of inhibition reported in P. funiculus (40.344.83 mm), C. globosum (39.531.69 mm), and A. niger (41.565.05 mm), and the lowest in E. coli 1 (11.070.52) and S. aureus (9.770.93) [10].

1.2.2. Anti-cancer activity

Gomes et al. studied the anticancer and chemotherapeutic properties of lemongrass in prostate cancer cells line (DU-145). DU-145 cells were subjected to various doses of lemongrass aqueous extract (30; 100; 300; 500; and 1000 g/mL), alone and in conjunction with docetaxel, for 1 and 3 days. Lemongrass was shows to have an anticancer impact and increased docetaxel chemotherapy efficacy by lowering colony formation and proliferation. Furthermore, we discovered increased cell cycle arrest in the G0/G1 phase and oxidative stress [11].

Priyanka Kumari et al. conducted research on the production of cellulose nanocrystals (CNC) from the lignocellulosic biomass of lemongrass following oil extraction using a hydrolysis reaction. CNC was shows to be non-cytotoxic in A431 cells and human reticulocytes at various doses (2-10 g/ml) using an in-vitro MTT and hemolysis test. Curcumin-loaded CNC demonstrated greater cytotoxicity and higher cellular absorption as compared to curcumin alone, although CNC was harmless. According to the research, CNC that comes from nature might be employed as a medication carrier system.

1.2.3. Anti-oxidant and anti-inflammatory activity

Deeksha Salaria et al. conducted in vitro and also in silico investigations to assess the antioxidant and anti-inflammatory capabilities of C. citratus essential oil (CEO). In vitro, antioxidant activity was assessed, whereas its anti-inflammatory activity was assessed using the egg albumin denaturation technique. Molecular docking of major phytoconstituents of CEO was performed using Autodock vina software against human cyclooxygenase 2 (PDB ID: 5IKQ) proteins and human peroxiredoxin 5 (PDB ID: 1HD2), which were then analyzed using molecular dynamics (MD) simulation revealed that β--caryophyllene can be utilized as a possible contender to synthetic anti-inflammatory drugs with adverse effects, as well as act as natural antioxidants [12].

Martins et al. demonstrated the potential of gelatin and maltodextrin as encapsulants and proved the practicality of freeze-drying C. citratus essential oil microparticles. The thermal and oxidative stability of oil were increased via microencapsulation, giving protection against environmental conditions and volatilization. M1 had a closed, pore-free surface, according to scanning electron microscopy. M1 demonstrated a better yield and microencapsulation efficiency, indicating a significant commercial potential due to lower storage, transportation, and distribution costs [13].

2. METHODOLOGY

Databases including Scopus, Google Scholar, Research Gate, PubMed, and Science Direct have been searched to discover the papers describing morphology, phytochemistry, and pharmacological properties of lemongrass. Furthermore, a manual screening from 20 pages of Google Scholar was done to look for any significant papers and materials. The block diagram illustrating the technique utilized for the current study is shows below in Figure 4.

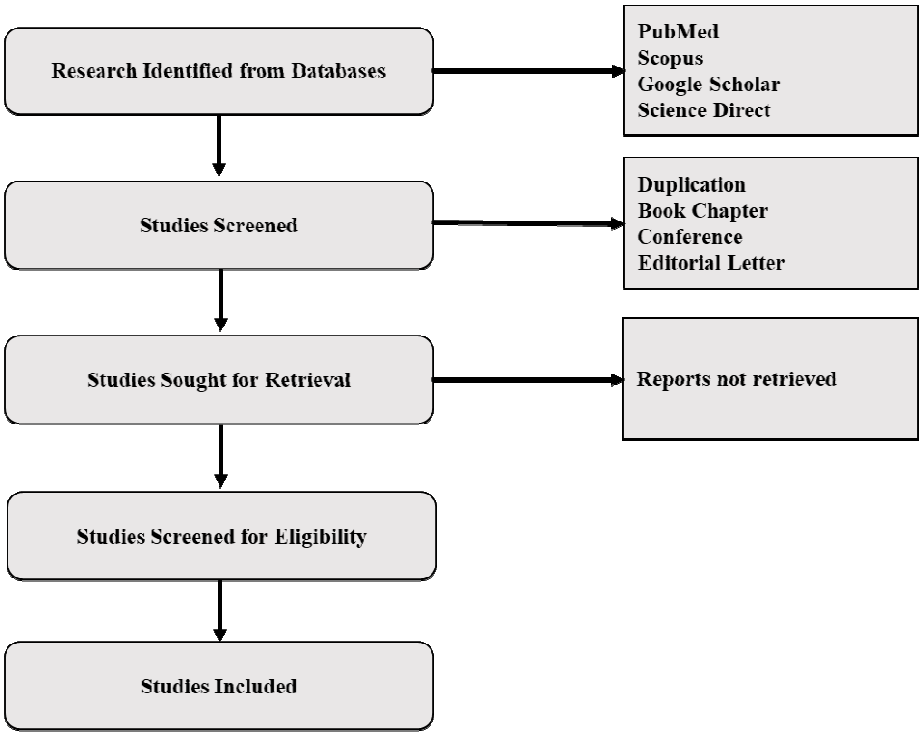

Figure 4: Illustrating the Methodology used to carry out the present review study.

3. DISCUSSION

The majority of research studies on lemongrass tea and derivatives are conducted using decoction, infusion, or organic solvent extraction without taking into account the effects of other variables including harvesting time, cultivation method, controlled fermentation/oxidation, roasting/frying, and withering conditions. Prior studies have shows that these parameters influence the content, physicochemical qualities, and biological characteristics of tea from various sources. If the above-mentioned circumstances are taken into account, the qualities of lemongrass tea may be impacted as well. Furthermore, traditional solvent extraction procedures are used in the bulk of investigations on lemongrass. Other extraction-assist technologies, such as ultrasonic-aided extraction, microwave-aided extraction, high-pressure processing, subcritical water extraction, enzymatic-aided extraction, and supercritical fluid extraction, have not been well investigated, if at all.

These unique strategies have been found to increase product production and biological characteristics. When compared to hydro-distillation, supercritical fluid extraction of lemongrass essential oil yielded a greater yield. Additionally, efforts have been undertaken to examine the impact of ultrasonic processing on the formation of lemongrass essential oil-alginate nanoemulsions. This will ultimately raise the bioavailability of the lemongrass essential oil by increasing its absorption into the food matrix. Moreover, although it has been stated that beverage clarity improves appearances and drinking quality, no research on lemongrass tea has indeed been reported. All of the topics which have been discovered ought to be the attention of future lemongrass researchers.

Researchers concluded that Lemongrass has good therapeutic potential owing to phytonutrients including such plant flavonoids, carotenoids, lignans, sterols, terpenoids, saponins, sulfides, and fiber as shown in Figure 5, that have a preventative function in oxidative stress and numerous human diseases. Lemongrass essential oil is used in fragrances, cosmetics, soap manufacturing, and insect repellant. Lemongrass contains a significant bioactive constituent with several therapeutic potentials, notably anti-cancer, anti-hypertensive, and anti-mutagenicity. Moreover, it shouldn't be consumed as a tea just for its traditional taste, rather than for its intended function. The development of lemongrass-based therapeutic meals and functional drinks is thought to have had the potential to be employed in diet-based treatments.

Figure 5: Illustrating the major classes of Phytonutrients present in Lemongrass.

Since lemongrass is commonly ingested alongside other physiologically active compounds, additional study on its possible interaction with other medications is needed to determine its influence on their pharmacokinetics and bioavailability.

Lemongrass has long been used for aesthetic, therapeutic, and nutritional purposes. Lemongrass has medicinal properties that may be utilized to prevent a variety of physiological risks. As a result of its distinctive scent and biological uses, including anti-inflammatory, immune-boosting, and anti-malarial properties, in addition to its ability to cure digestive disorders, it is primarily drunk as tea. In this light, lemongrass does have the ability to be employed in a wide range of functional food items to benefit mankind due to its polyphenol-rich profile and therapeutic uses.

4. CONCLUSION

Human beings rely heavily on medicinal plants to maintain their health. The pharmacological examination of several plants utilized in Indian traditional medicine is becoming more popular. Lemongrass piqued people's attention because of its economically lucrative essential oils, which are extensively employed in culinary technology and traditional medicine. Because of the

renewed interest in natural products derived from lemon grass, a thorough phytochemical and pharmacological investigation is necessary, which will open up new pharmacological possibilities for this exquisite plant, which will aid in clinical research and the creation of innovative medications.

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CHAPTER 25

AN EVALUATION OF PHYTOCHEMISTRY AND PHARMACOLOGICAL PROPERTIES OF *BOERHAAVIA DIFFUSA* (PUNARNAVA)

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ABSTRACT:

There are many different diseases in the world today due to different factors like aging, environmental triggers, and genetic risk factors. To control or treat these diseases, a vast amount of drugs are used daily. Thus, whether voluntarily or involuntarily, people are compelled to keep a large number of toxic/harmful compounds in their bodies. Thus, these previously stored chemicals cause a new disease in human bodies, and now the new drug is then required to treat which adds to the stack of chemicals in the body. Therefore, natural compounds are gaining traction in today's world because of their safety profile and increasing efficacy. Hence, this paper aims to provide the phytochemical and pharmacological properties of a reputed medicinal plant which is known as Boerhavia diffusa. B. diffusa is said to have a wide range of activities against cancer, cardiovascular disease, asthma, microbial diseases, and many more which have a significant impact on disease burden and healthcare affordability/availability across the world. The current review also focuses on the particular portion of the plants and their morphological and anatomical properties which are known to be rich in different bioactive compounds. This study can pave the path to explore more about the possible mechanism of action of bioactive compounds present in plant extracts for future drug development against a wide variety of diseases.

KEYWORDS:

Boerhaavia Diffusa, Boeravinone, Punarnava, Ethnopharmacology, Phytochemicals.

1. INTRODUCTION

Herbal cures are intended for the natural and herbal sectors, according to an adage that dates back to ancient times. For medicinal purposes, more than 80,000 plant species are employed globally. The World Health Organization (WHO) estimates that 70 to 80 percent of the populace in underdeveloped countries rely on alternative medicines, primarily made from botanical sources, for their healthcare [1]. Growing allopathic drug side effects, the absence of a cure for several medical conditions, growing treatment rates, antimicrobial tolerance, and developing disorders are all factors contributing to this increasing concern.

Historically, the use of medicinal plants as a type of therapy for the reduction of pain has been documented. To strategically advance the development of novel lead compounds for natural

product drug discovery, the chemical components of plants will be explored, and pharmacological and phytochemical screening will be performed. Finding and developing a novel, effective, and active chemical with lower toxicity for systemic activities is the goal and focus of many researchers. It has always been quite exciting to research biologically active compounds and secondary metabolites from natural sources to treat various diseases. The traditional knowledge system of tribal communities is being used to treat various ailments. Various types of herbs can be used to prevent diseases that can affect different organs in both humans and animals. The discovery of the bioactive compounds in drugs and their advancements begins with the use of herbs. Because they are plants that naturally occur, indigenous plants are the natural inhabitants. Because native species have frequently developed to adapt to particular environments and circumstances, it is crucial to preserve them. Indigenous species have been discovered to have specific qualities that have been utilized to create specialized treatments to save lives. Therefore, the present study discusses the morphological, anatomical, phytochemical, and pharmacological properties of the reputed medicinal plant "*Boerhaavia diffusa L. red spiderling"* followed by a critical discussion on the limitations of presently published studies to evaluate the anti-disease properties of various extracts of *B. diffusa.* Which was then concluded by a concluding remark in the next section.

1.1. Boerhaavia diffusa Linn.

A perennial plant with the common name Spreading Hogweed is *B. diffusa Linn.* which belongs to the family Nyctaginaceae. Although its rich green patch in the arid areas is really lovely, its habitat is a dry wasteland. More commonly visible after a rainy season, it is a trailing plant. It is a type of wild vegetation with well-developed, convoluted roots that do not grow when the weather gets adverse. The first rainfall causes the branches and leaves to grow, bearing the name Punarnava (That which rejuvenates). On a stem that is greenish-purple, it bears thin, spreading branches. It also has leaves that are oppositely positioned, glabrous, and ovate-shaped. It features unique pink funnel-shaped flowers. Its glabrous leaves are a real food source that includes important nutritional ingredients including carbohydrates, fats, proteins, fiber, minerals, and vitamins. Several tribal regions in India and other nations have reported using it as a healthy alternative food source [2].

1.2. Botanical Classification

Table 5: Representing the List of the Botanical Classification of *Boerhaavia diffusa*.

Kingdom	:	Plantae
Division	:	Tracheophyta
Class	:	Magnoliopsida
Order	:	Caryophyllales
Family	:	Nyctaginaceae
Genus	:	Boerhavia L. spiderling
Species	:	*Boerhaavia diffusa* L. red spiderling

A well-known Ayurvedic herb by the name of *B. diffusa*, sometimes referred to as Punarnava, is utilized in several significant formulations, including Punarnavadi mandura, Punarnavastaka kwatha curna, Punarnavadyarista Punarnavasava, and Sukumara ghrita. Inflammation, hepatic, edema, ascites, renal, cardiovascular, and cerebrovascular disorders are treated with these formulations. Due to its widespread use around the world, it has been used for a variety of ethnopharmacological purposes, including the treatment of skin diseases, ophthalmic issues, hepatoprotection, cardiovascular problems, and a variety of endocrine and reproductive abnormalities. Numerous studies proving its pharmacological effects as hepatoprotective, anti-inflammatory, anti-diabetic, nephroprotective, and anti-edematous have been published, mostly over the past 35 years, as a result of its widespread use in traditional texts and ethno - medicinal reports. It has simultaneously produced a large diversity of compounds including over 150 components. Rotenoid, a structurally unique type of "isoflavonoid", has been found with significant structure diversity in its root portion.

As illustrated in Figure1, Flowers of *B. diffusa* are very "small" in size having an ovoid shape, and upper portion in color pink with the lower part greenish, with a shape like a funnel, 10–25 cm, in umbels, arranged on long-stalks, small, acute, bracteoles, axillary and in terminal panicles, 4–10 corymb perianth tube. Small umbels of flowers, measuring between 10 and 25 mm in length, are internally sessile. The fruit is a single, seeded nut that is spherical, glandular, and about 0.5 cm in length. It is also clavate, 6 mm long, and plainly 5 ribbed. As illustrated in Figure 2, *B. diffusa* has asymmetrical, suborbicular, or ovate-oblong leaves with rounded or slightly pointed apexes and rounded or subcordate bases. Larger leaves measure 25–37 mm in length, whereas smaller leaves measure 12–18 mm. The color of the leaves is greenish below, while they are white above. For certain instances, the dorsal side of the margin is pink. It is whole or sub undulates, has thin petioles that are almost as long as the blade and is also thick in texture. As illustrated in Figure 3, *B. diffusa* roots are tapering, cylindrical, fusiform, elongated, slightly tuberous or tortuous, 0.2 to 1.5cm diameter, smooth surface to touch but rough owing to root scars and minute longitudinal fracture and striations. *B. diffusa* has roots that spread out horizontally and vertically, penetrating the ground deeply. The scars left by fallen rootlets on old roots are frequently tangled and ragged. The flavor of the roots is somewhat, bitter, sweet, and pungent; they do not have a distinctive smell. They have exceptionally delicate skin and are cream-colored or light brownish-yellow.

Figure 19: Illustrating the flower structure of the *B. diffusa* plant; Ovoid, Pink and Small in Size.

Figure 20: Illustrating the Leaves of *B. diffusa* plant; Asymmetrical, Suborbicular, or Ovate-oblong.

Figure 21: Illustrating the Roots of *B. diffusa* plant; tapering, Cylindrical, Fusiform, Elongated.

1.3. Geographical Distribution

Boerrhaavia species can be found in subtropical, hot, and warm regions. Around 40 different species can be found throughout the temperate regions of the world. In countries like Benin, Egypt, Somalia, Rwanda, Sudan, Senegal, Zambia, Ghana, Ethiopia, South Africa, and Nigeria, among many others, the continent of Southern and Northern America and Africa is home to many species of Boerhaavia. All across Asia, in nations like Malaysia and China, Pakistan, Cambodia, the Philippines, Kuwait, Saudi Arabia, Nepal, Myanmar, Afghanistan, and India.

"B. repens", "B. chinensis", "B. diffusa", "B. repanda", "B. rubicunda", and *"B. erecta"* are six of the 40 species in this genus that are generally found in India. "*B. diffusa*" is a native of India as well. It may be found throughout warm regions of India and up to an altitude of 2000 meters in the Himalayan area. After the rainy season, it thrives in wastelands and fields. West Bengal has some growth of this plant as well.

1.4.Phytochemical screening

B. diffusa contains a variety of secondary metabolites, including hormones, alkaloids, proteins, flavonoids, lipids, triterpenoids, carbohydrates, lignins, and glycoproteins. Lipids and proteins are in massive quantities in the roots and shoots. The root has 14 amino

acids, involving 7 total essential amino acids (AAs), on the other hand, the shoot has 15 amino acids, comprising 6 essential AAs. To find the chemical composition and determine its function in the pharmacological action of the plant, several investigations have been conducted. It may be difficult to divide these many constituents into their active components since they may work together synergistically. Similarly, the change in the chemical constituents is based on plant origins, drying techniques, harvest seasons, and other factors.

A study by Jayachaitra *et al.* performed the characterization of *Boerhaavia diffusa* using thin-layer chromatography. The results of their study revealed the presence of phenols, terpenoids, glycosides, flavonoids, tannins, and alkaloids. The mineral composition was also estimated which revealed the presence of Na, Ca, and Mg in large quantities while low quantities of Zn and Cu [3].

Another study by Sinan *et al.* also carried out HRMS/LC-MS analysis to chemically characterize the compounds present in *B. diffusa*. The UHPLC-HRMS analysis was used to dereplicate and identify 37 specialized metabolites present in the samples under study. Analysis indicated that there were two additional glycosides, 12 fatty acids, 15 hydroxybenzoic, seven flavonoids, one rotenoid, hydroxycinnamic, and acyl quinic acids and their glycosides [4].

Kangavalli U *et al.* carried out a comparative phytochemical investigation of different extracts of *B. diffusa* including ethanol, hexane, aqueous, chloroform, and ether extracts further different qualitative methods are used to validate the presence of the compounds. The results of their study showed the presence of “phenols”, “alkaloids”, “tannins”, “carbohydrates”, and “saponins” [5].

Priya & Sharma carried out a study undertaking the phytochemical screening and further estimations of saponin composition. In their study, they used the extract of *B. diffusa* for further investigation. The results of their study demonstrated the presence of “saponins”, “flavonoids”, “phenolic compounds”, and “alkaloids”, and the further saponin estimation revealed that the methanolic extract of the plant was having 3mg/g of saponin content whereas the 4.5mg /g in the aqueous extract of root [6].

“Quercetin 3-Orobinobioside”, “Eupalitin 3-O-galactosyl (1–2) glucoside”, “3,4-Dihydroxy-5-methoxycinnamoyl rhamnoside”, and “Kaempferol 3-O-robinobioside” are examples of secondary metabolites. The extract of the roots and leaves of *B. diffusa* was found to contain “eupalitin-3-O- [-D-galactopyranoside]”. In another study, the bioassay method was used to separate the methanolic extract from *B. diffusa* root into 5 rotenoids compounds, including the well-known “boeravinone E”, “boeravinone D”, “C5”, and two new compounds called “boeravinone H” and “boeravinone G”. Spasmolytic activity was demonstrated by boreavinone G, boreavinone E. Different amounts of chemical components, such as alkaloids, are distributed throughout the plant. From the stems, leaves, and roots, two quinolizidine alkaloids known as “punarnavine-II” and “punarnavine-I” have also been isolated.

1.5. Pharmacological Screening

1.5.1. Anti-diabetic properties:

Oyebode *et al.* conducted an *in vitro* and *in silico* study to investigate the antidiabetic, anti-obesogenic, and well as antioxidant properties of ethanol, water, and extract of *B. diffusa* especially the aerial parts of it. Different methods for estimating the antioxidant properties were used like DPPH and FRAP were used. The enzyme inhibitory potential of extracts for pancreatic

lipase and glucosidase was also examined followed by the analysis of bioactive components with GC-MS. The outcomes of their study revealed that the ethanol extracts exhibit the most anti-oxidant activity. In addition to that increased super oxidase dismutase and catalase activity as well as increased GSH levels. In their In silico study, they found the compounds present in the extracts namely xanthone, xanthene, and stigmasterol showed a significant binding affinity to the diabetes target protein such as alpha-glucosidase and lipase [7].

Another study by Alam *et al.* investigated the extracts of "*B. diffusa* root" for its anti-diabetic activity in "streptozotocin-induced diabetes" in an animal model(rats). The findings of their study showed a significant enhancement in blood plasma enzymes like "SGPT", "SGOT", and "ALP" and a great enhancement in blood glucose. In addition to that rats treated with extracts were also found to have significant improvement in serum insulin, total protein, weight loss, and liver glycogen [8].

Akhtar *et al.* also investigated a study on the therapeutic efficacy of *B. diffusa* using rat models with experimental diabetes, oxidative stress, and diabetes-linked hyperlipidemia. Diabetes-induced rats were then given treatment with methanol extracts of *B. diffusa* (D-MT), partially isolated bio-active fraction(D-BT), or glibenclamide. The results of their study demonstrated alleviation of glycated hemoglobin and fasting blood glucose in the treatment groups of D-BT and D-MT after 14 weeks. In addition to that, "plasma lipid profile", "lipid hydroperoxide (LOOH)", "HMG-CoA reductase (HMG-R) activity", "phospholipids (PLs)", "free fatty acids (FFAs)", "malondialdehyde (MDA)", and a "conjugated diene (CD)", were also found to be ameliorated in all groups demonstrating the antidiabetic effect of *B. diffusa* extract [9].

Panda K.C. also demonstrated the inhibitory activity of *B. diffusa* on enzymes involved in the development of diabetes such as α-glucosidase. The findings of their study revealed that the extracts of roots and leaves of *B. diffusa* exhibited strong inhibitory activity against α-glucosidase [8].

1.5.2. Anti-Cancer Activity:

Boerhavia can have potential as an anticancer agent, according to recent studies. Despite having significant adverse effects, the cancer available treatments of surgery, chemotherapy, and radiotherapy, are quite successful. Additionally, as the progress of treatment, cancer cells become less responsive. Scientists are working hard to identify natural cancer treatments to get around it.

By using the "MCF-7 (Michigan Cancer Foundation-7) breast cell line", Remya *et al.* conducted in vitro experiments to assess the cytotoxicity of an extract from *B. diffusa* root. After being incubated for 48 hours with the "breast cell line", the *B. diffusa* test sample at 800 g/ml demonstrated cyto-toxicity of around 65.1 ± 1.2 highlighting the potential of extracts from *B. diffusa* to combat cancer.

Muthulingam & Chaithanya *et al.* also investigated the anti-cancer activity of methanol extracts of *B. diffusa* leaf against the MCF-7 cell line. The cytotoxic effects were evaluated by observable changes in "MCF-7 cell morphology", "a yellow tetrazolium", and "3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT)". The results of their study revealed a dose-dependent cytotoxic activity of the extracts of 13.9%, 27.96%, 43.65%, and 52.86% at varying concentrations [10].

Another Study by Sahu *et al.* carried out a computational study of phytochemicals from B. diffusa with "cyclin-dependent kinase 2- associated protein 1". In their study, they screened different phytochemicals of *B. diffusa* like "Boeravinone A, B, C, D, E, F, G, H, I, and J". Homology modeling, docking, and Molecular simulations were used to file the binding affinity which revealed a significant binding affinity of -7.9kcal/mol [11].

1.5.3. Hepatoprotective Effects:

Thajudeen *et al.* investigated compounds from *B. diffusa* roots for their hepatoprotective effects specially boerovinone B and caffeic acid. When compared to conventional sylimarin, caffeic acid (200 g/mL) and boeravinone B (200 g/mL) demonstrated the most substantial hepatoprotective action in HepG2 cells produced by galactosamine 40 mM toxicity. The results validated the traditional usage of *B. diffusa* as a functional food with positive effects on human health.

Balkrishna *et al.* investigated a herbal formulation, livogrit from three plants *Solanum nigrum, Phyllanthus niruri,* and *B. diffusa* for treatment and the management of hepatocellular toxicity in the zebrafish model. The results of their study demonstrated the normalization of deregulated liver function parameters and further minimization of the risk of liver dysfunction. In addition to that, liver cytology demonstrated a steady decline in death of hepatocyte cell potentially due to the therapeutic effects of Livogrit.

1.5.4. Nephroprotective Effects:

There is broad consensus among researchers who have looked at the renal effects of *B. diffusa* extract that it has a diuretic effect. Gaurav *et al.* carried out a study to assess the nephroprotective effects of *B. diffusa* in combination with *Tinospora cordifolia* nephrotoxicity induced by diclofenac. The results of their experimentations showed that the herbal combination of both plants demonstrated nephroprotective activity against oxidative stress, inflammation, and nephrotoxicity induced by diclofenac.

1.5.5. Antimicrobial Activity

B, diffusa is also investigated for its antimicrobial activity ranging from anti-bacterial to antiviral properties. Kaviya *et al.* carried out an antimicrobial test of extracts from *B. diffusa* roots against the growth of *Staphylococcus aureus* and *Pseudomonas aeruginosa* which resulted in a zome of inhibition of 8mm to 20mm at the concentration of 200 Nephroprotective potentials of *Tinospora cordifolia* and *B. diffusa* herbal combination against nephrotoxicity that is diclofenac induced. In addition to that, they found, that the compound "2-(1,2 dihydroxyethyl)-5-[[2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-3,4-dihydrochromen-6-yl]oxy]oxolane-3,4-diol" showed the minimum binding score demonstrating the highest affinity in the complex formation.

Another Oluwabusayo *et al.* carried out a study to evaluate the *in vitro* inhibitory activity of leaf extracts of *B. diffusa* against salmonella. They performed an agar disk diffusion method to evaluate the anti-salmonella demonstrating the zone of inhibition of 35.21±0.47 mm at the concentration of 200mg/ml with the ethanolic extract. In addition, the broth dilution method demonstrated a significant reduction in cell growth.

The above studies have carried out the evaluation of the plant and its extracts for different kinds of inhibitory activities against renal, microbial, cardiovascular, and other diseases with the

dominance of laboratory studies. However, this paper summarizes a lot of activities of the plant extracts with as much as evidence possible to support the therapeutic value of the plant.

2. DISCUSSION

According to the findings of the preceding investigations, the species *Boerhavia* has long been used in the traditional medicinal system across the world, most notably in cancer, liver, and kidney-related problems, and microbiological infections. Different compounds were identified in the extracts to be responsible for different activities of extracts against a range of disease conditions beneficial substances from this species. Various flavonoids and rotenoids have been identified and extensively researched for their anticancer, antioxidant, and anti-inflammatory properties.

Additionally, according to the research compiled here, plant extracts have a strong anti-cancer activity which has been demonstrated by several research studies published on the internet. Its anti-inflammatory, nephroprotective, and hepatoprotective properties, which were shows by pharmacological research, make it more suited for the treatment of several disorders and other associated conditions. Given that oxidative stress is a major contributor to many diseases, it has been noted that the extracts of *B. diffusa* have anti-inflammatory and antioxidant properties. Plant extracts also showed anti-diabetic, adaptogenic, analgesic, and antioxidant properties in additional animal studies [9], [12].

However, there is relatively little clinical research available, and the various pharmacological actions of the plant extract and extracted phytochemicals have only been tested in in vitro experiments employing laboratory animals. Therefore, it's possible that the outcomes won't always apply to human situations. There is little understanding of its applications in tumors or malignancies, experimental results demonstrated that the plant *B. diffusa* has a high cytotoxic effect against tumor cells, which should be investigated further to identify novel antineoplastic drugs. It suppresses experimental metastasis, and breast cancer, and protects against radiation-induced damage to skin cancer. *B. diffusa* extracts revealed no adverse side effects or cytotoxicity, indicating that they can be used for an extended length of time. However, research on long-term survivors has revealed several delayed toxicities of anticancer treatment. Given the possible function of *B. diffusa* as an anti-metastatic drug and its usage in traditional medicine, a toxicity test particularly during extended treatment, is required.

3. CONCLUSION

Over the centuries, *B. diffusa* has developed into a wonderful medicinal plant with a wide range of active compounds that are useful against a wide range of diseases. In traditional herbal treatments used all across the world, the plant is very important. *B. diffusa* is a renowned plant in ethnobotanical and traditional medicinal systems across the world. It contains a variety of chemical substances that have medicinal properties such as anticancer, anti-inflammation, diuresis, immunomodulation and hepatoprotection, nephroprotection, and antimicrobial. However, it has yet to gain a base in the herbal market. In the present landscape of plant-based formulations, *B. diffusa* has the potential to be an effective and economical product for the management of a wide variety of diseases. It is also a resource of chemically novel “rotenoid” and “flavonoid” compounds, that can be used to design novel semi-synthetic derivative chemical compounds for novel applications.

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