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REVIEW OF POLYHERBAL MEDICINES FOR THE MANAGEMENT OF TYPE 2 DIABETES MELLITUS

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ABSTRACT

The review article highlights the increasing prevalence of diabetes and its associated complications, emphasizing the need for effective management strategies. It delves into the potential of herbal therapies as a promising avenue for addressing the challenges posed by diabetes. The review addressed studies on the hypoglycemic and hypolipidemic effects of some herbal substances, including *Butea monosperma*, *Terminalia arjuna*, and *Cuminum cyminum*. This review article suggest that these herbal medicines may offer benefits in managing diabetes and its complications. Furthermore, this review article discussed the chemical constituents of these herbs and their potential mechanisms of action in the context of diabetes management. For instance, it highlights the free radical scavenging properties of flower extracts from *Butea monosperma* and the anti-inflammatory and neuroprotective effects of *Nigella sativa*. This review also discussed clinical experiments involving diabetic patients, which demonstrated the potential of *Nigella sativa* in reducing blood glucose and lipid levels. Additionally, the manuscript provides insights into the effects of *Trigonella foenum-graecum* seeds on type 2 diabetic patients, emphasizing the importance of monitoring clinical signs and serum toxicity variables. Overall, the review presents a wealth of scientific evidence supporting the potential of polyherbal medicines in managing type 2 diabetes mellitus. It underscores the importance of further research and clinical investigations to elucidate the efficacy and safety of these herbal therapies. The review article serves as a valuable resource for researchers, healthcare professionals, and individuals interested in alternative approaches to diabetes management.

KEYWORDS: Polyherbal Medicine, Diabetes, Mellitus, *Nigella Sativa*

Abnormalities in insulin secretion and insulin resistance of primary target tissues define diabetes mellitus (DM), the most severe non-communicable metabolic illness as stated by Green *et al.,* in 2007. Forecasts indicate that by 2025, the total number of people with diabetes will have increased from 285 million in 2010 to 438 million 2025, representing a 54% increase, according to the International Diabetes Federation (IDF) (IDF Diabetes Atlas, 2009). Based on their causes, diabetes mellitus (DM) may be categorized as either type I (T1DM) or type 2 (T2DM). Hyperglycemia owing to an absolute or relative insulin shortage characterizes type 1 diabetes, a chronic metabolic disease. About 90% of patients with diabetes have the most common forms of diabetes, known as type 2 (Khunti *et al.,* 2000). Hyperglycemia due to an insulin secretion or function impairment, or both, is a hallmark of many illnesses and disorders. Hamden and co-workers. (2008) found that Damage to tissues and subsequent complications are major outcomes of persistently elevated blood glucose levels (Hamden 2008). Diabetes mellitus (DM) is connected to a number of metabolic and physiologic issues, including arterial disease, hypertension, atherosclerosis (high triglyceride levels and low levels of high-density lipoproteins), and high cholesterol. Many long-term complications can develop from diabetes mellitus (DM), including impairment to the eyes, kidneys, nerves, heart, and central vascular system. The monetary toll that diabetes has on individuals, communities, and nations is substantial. Despite the availability of insulin and other insulin analogues as hypoglycemic agents when used to treat diabetes, the side consequences linked with these drugs are increasing interest in herbal therapies for the disease. According Erasto (2005), this has contributed to the notion that natural goods are safer due to their compatibility with biological systems (Erasto *et al.,* 2005). The pancreatic β-cell can regulate blood glucose levels by reacting to small rises in plasma glucose levels. Hyperglycemia, a symptom of kind 2 diabetes, which is brought on by the gradual loss of pancreatic β-cells, which in turn leads to reduced insulin production (TIDM and T2DM). The liver, being an insulin-sensitive organ, is particularly important for glucose homeostasis maintenance because it controls the relationship between glucose use and gluconeogenesis. Consequently, pancreatic and liver damage are critical to the development and progression of type 1 and type 2 diabetes. Therefore, it would be fascinating to study the

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effects of nutritional supplements on organs like the pancreas and liver that control glucose metabolism.

The potential of antioxidant supplements to reduce diabetes-related complications is an encouraging sign of progress in our knowledge of how oxidative stress contributes to various illnesses. A lengthy history of diabetic treatment has included herbal remedies made from herbal remedies (Modak *et al.,* 2007). Researchers are currently looking into these compositions' antioxidant and antidiabetic capabilities (Mutalik *et al.,* 2005). The Palash, scientifically known as Butea monosperma (BM) Lam., belongs to the Fabaceae family and has numerous medicinal uses, including damaging antifungal, estrogenic, anti-inflammatory, antistess, and anticonceptive effects. However, the primary chemical constituents of BM flower extract are butrin, isobutrin, medicarpin, flavone glycoside, butin, palasonin, coreopsin, and β-sitosterol. Panda *et al.,* (2009) and Somani *et al.,* (2006) are two examples of studies that have investigated the hypoglycemic and hypolipidemic effects of BM using this compound model of diabetes. A type 2 diabetes model in newborn rats has only recently shown, Bavarva and Narasimhacharya (2008) shown that BM has anti-hyperglycemic and anti-hyperlipidemic properties (Bavarva *et al.,* 2008).

Problems with insulin synthesis, functioning of insulin, or both lead to chronic hyperglycemia and disturbances in the metabolic processes of carbohydrates, lipids, and proteins define metabolic condition of different etiologies, which is referred to as diabetes mellitus (DM). A person with diabetes cannot make or effectively utilize insulin. The pancreas secretes insulin, a hormone that the body uses to transform carbs and other nutrients into energy. Diabetes may cause damage, malfunction, and eventual organ failure over time. Diabetes is characterized by a loss of weight, increased thirst, decreased vision, and frequent urinating. A non-ketotic hyperosmolar state or ketoacidosis can develop in severe situations, which can cause stupor, coma, and ultimately death if treatment is not successful. It may take a long time to diagnose hyperglycemia since symptoms aren't always severe or nonexistent, even though it's been shown to induce pathological and functional alterations. Diabetic complications can emerge over time and pose serious health risks. These include potential blindness from retinopathy, kidney failure from nephropathy, foot ulceration, amputation, charcot joints, and autonomic dysfunction presenting as sexual dysfunction from neuropathy. Blood clots, arterial disease, and cerebrovascular illness are more common in people with diabetes than in people in general (Song *et al.,* 2019).

The prevalence of diabetes mellitus is increasing in India, with a rate of 2.4% in rural regions and 11.6% in urban centers (Ramachandran *et al.,* 2002). The Worldwide Diabetes Federation's Diabetes Atlas 2006 predicts that by 2025, the population of diabetics in India will have jumped from 40.9 million in 2006 to 69.9 million in 2025, barring immediate action to avoid the disease (Sicree 2006).

RISK FACTORS

Genetic Predisposition

Hereditary susceptibility greatly favors type 2 diabetes. Its route of inheritance remains unknown, despite the fact that it exhibits familial aggregation and a high proportion (80%) in monozygotic twins. A polygenic illness may be at play here. Siblings and children of There is an elevated risk of developing type 2 diabetes in individuals who already have diabetes. Inheritance of the disease, prior experience with diabetes during pregnancy mellitus, or a family or personal history of diabetes all raise the risk of acquiring type 2 diabetes hyperglycemia a baby born weighing more than 9 pounds.

Environmental Factors

Excessive calorie consumption, obesity with extra fat around the middle (visceral), lack of physical activity, etc., are causes of type 2 diabetes in surroundings that work in tandem with a person's genetic susceptibility. Even while insulin levels in type 2 diabetes patients may remain normal or even rise for a long period (particularly when obesity is present), they may fall as the illness progresses.

Medical Conditions

Type 2 diabetes may be linked to subclinical Excessive production of cortisol is the hallmark of this condition cortisol (Iwasaki *et al.,* 2008). About 9% of people with diabetes have subclinical Cushing's syndrome (Cho *et al.,* 2000). According to Taniguchi (2008), removing pituitary microadenomas may increase insulin sensitivity in diabetic individuals (Taniguchi *et al.,* 2008). It is still unclear how exactly testosterone improves insulin sensitivity, however hypogonadism is often linked to elevated cortisol levels, and low testosterone levels are related with type 2 diabetes. Although it is very rare, polycystic ovarian syndrome (PCOS) and metabolic syndrome are danger signs that could lead to type 2 diabetes.

Medications

Medications utilized for managing a broad range of diseases may be able to cause drug-induced hyperglycemia by interfering with the insulin control system. Below are a few instances, along with the corresponding molecular mechanisms.

Somatropin - Might make people less insulin sensitive, particularly those who are already at risk.

Protease Inhibitors - Block the process by which proinsulin is transformed into insulin.

Phenothiazines - Inhibit insulin secretion.

Nicotinic acid and glucocorticoids- impair insulin action

Niacin - induces a rise in insulin resistance because it promotes the mobilization of free fatty acids to increase.

Fluoroquinolones - Blocks ATP-sensitive potassium channels, which in turn inhibits insulin release.

Corticosteroids - Lead to gluconeogensis and peripheral diabetes.

Calcium Channel Blockers - Blocks insulin secretion by preventing the release of calcium from the cytosol.

Beta-blockers - Inhibit insulin secretion.

Atypical Antipsychotics - Change how the receptor binds, which makes insulin resistance worse.

Others that could put you at risk for type 2 diabetes including the following:

Age

A substantial risk factor risk of acquiring type 2 diabetes? is advancing age. The danger starts to increase dramatically at about the age of 45 and continues to do so far beyond the age of 65. Teens and young adults are seeing a faster increase in the in comparison to other age groups for type 2 complications of diabetes, while the illness is still most frequent in people aged 40 and higher.

Obesity

Along with the epidemic of childhood obesity, it is more common in today's youth than in previous generations.

Sex

Type 2 diabetes affects men and women at about the same rate worldwide.

Race

Type 2 diabetes is more common among people of color, Native Americans, Hispanics, and Japanese Americans compared to whites who do not have a Hispanic heritage (Harris *et al.,* 1995).

Hypertension/High blood pressure (>140/90 mm Hg)

High-fat diet/High blood triglyceride (fat) values, such as triglyceride levels over 150 mg/dl or high-density lipoprotein (HDL) cholesterol levels below 40 mg/dl

Diagnosis of Diabetes

Those who suffer from type 1 diabetes mellitus do not produce enough insulin, making it impossible for them to maintain normal blood glucose levels. One typical reason for this is when the immune system mistakenly destroys the beta cells in the pancreas that produce insulin. Rarely is type 1 diabetes diagnosed before symptoms appear. Diagnosing diabetes involves looking for symptoms, certain lab results, and signs of immune system damage (Knip *et al.,* 2005). Most people are perfectly healthy and at an acceptable weight when they initially start to experience problems.

Symptoms — Symptoms of hyperglycemia, or elevated blood sugar, are encountered by most patients prior to identification of either type of diabetes is made. Some of these symptoms could include things like eyesight problems, extreme thirstiness, lethargy, weight loss, or frequent urination. Symptoms of diabetic ketoacidosis (DKA) or hyperosmolar nonketogenic coma (HTN) may manifest at the time a diagnosis of type 2 diabetes or, less frequently, the first form of diabetes.

Laboratory Tests Blood sugar levels are measured using a battery of tests; this one is considered the most accurate way to diagnose diabetes. The kind and severity of diabetes may be determined with the use of further testing. To be sure they are still unusually high, the blood tests need to be again the next day.

Random Blood Sugar Test — It makes A random blood sugar test can be done at any point throughout the day, regardless of when you last ate. When a patient's random blood sugar level hits 200 mg/dl (11.1 mmol/l) or above, diabetes has been identified in patients presenting characteristic hyperglycemia characteristics.

Fasting blood sugar test After an 8- to 12-hour period of fasting, a person's blood sugar level is measured (usually overnight). Typically, while 126 mg/dl (7.0 mmol/l) or higher is considered high, fasting glucose levels are below 100 mg/dl (5.6 mmol/l) indicates the presence of diabetes. To establish the diagnosis of diabetes, however, the test has to be repeated the following day.

Glycosylated Hemoglobin Test (HbA1c) — Analyzing calculated as the mean blood sugar level throughout the preceding two to three months HbA1c blood test is all about. It is typically reserved for use in diagnosing diabetes and tracking blood sugar management in those who already have the condition. An average blood sugar level of 120 mg/dl (6.6 mmol/l) is indicated by a normal result for HbA1c, which is typically 6.1% or below. If you have type 1 diabetes, your doctor should check your hemoglobin A1c levels three or four times a year.

Markers of Immune Destruction - The presence Evaluation of fasting diabetic hyperglycemia is the initial indicator of immune destruction markers, including islet cell self-antibodies insulin autoantibodies, and glutamic acid decarboxylase (GAD) self-antibodies in 85 to 90% of individuals with Type 1 diabetes. Along with Hashimoto's thyroiditis, Graves' illness, and Addison's disorder, these individuals may also have additional autoimmune illnesses.

Insulin Resistance - Insulin resistance makes it more probable that people with type 2 diabetes often require extremely high insulin dosages (>0.7 units/kg/day) in order to maintain control of the blood sugar levels of their patients while taking insulin. People with insulin resistance often exhibit symptoms such abdominal obesity, high blood pressure, aberrant lipid profiles, atherosclerosis, and hyperuricemia; moreover, they do not show signs of having antibodies that target beta cells specifically.

Complications

Three serious acute complications may occur in people with diabetes (Mohan 2012).

Diabetic Ketoacidosis

Glucagon excess and insulin insufficiency both cause ketoacidosis. It is the only complication that may occur in those who suffer from type 1 diabetes. Two main factors, stress and insufficient insulin ingestion, are responsible with this disease. Lipolysis occurs when insulin is absent and adipose tissue is broken down into free fatty acids. The liver creates ketones, such as acetoacetic acid and β-hydroxybutyric acid, by absorbing free fatty acids and oxidizing them with the enzyme acetyl coenzyme-A. Nevertheless, the efficiency with which various organs can absorb these ketone molecules is not balanced, leading to ketonaemia and ketonuria. Dehydration prevents the urine elimination of ketone bodies, leading to systemic metabolic ketoacidosis. In a clinical setting, this disorder manifests as anorexia, nausea, vomiting, rapid and deep breathing, disorientation, and coma.

Hyperosmolar nonketogenic coma

In most cases, type 2 diabetes will cause hyperosmolar nonketogenic coma. Patients with elevated blood glucose levels will experience the osmosis-induced expulsion of water from their cells into the bloodstream. In addition to 'dumping' glucose into the urine, the kidneys are also losing water, which raises the blood osmolality. Serum osmolality may become extremely high as a result of the osmotic action of both elevated glucose levels and water loss in the absence of injectable or oral replenishment of fluids (dehydration). With the body's draws water out of cells and excretes it, cells may become more and more dry. Additionally, electrolyte abnormalities are prevalent. If these changes persist for an extended period of time, it may lead to lethargy, which is defined as a decreased degree of awareness or consciousness, and even coma. Because blood is so thick, thrombotic and bleeding problems are common. In hyperosmolar nonketotic coma, the death rate is rather high.

Hypoglycemia

In type-1 diabetes, hypoglycemia is a much more prevalent condition. Symptoms like as uneasiness, tremor, hunger, and perspiration are common during bouts of hypoglycemia that occur throughout the day. Insomnia, bad nightmares, or a headache first thing in the morning are all indications of hypoglycemia, which may happen throughout the night or not at all. Patients with diabetes run the risk of hypoglycemia if they take too much insulin, skip meals, or exercise too much. For insulin doses to be accurately measured, it is critical that the patient and prescribing physician have a solid rapport. In reaction to low blood sugar, the body secretes more of the hormones cortisol, adrenaline, norepinephrine, and growth hormone, all of which boost blood sugar levels. Consequently, hyperglycemia (a reversal of blood sugar levels) is a common outcome. A popular name for this occurrence is the somoghi phenomenon.

Recurrent spikes in Long-term effects of diabetes are worsened by elevated blood glucose concentration. Diabetes may lead to serious long-term problems, such as:

Atherosclerosis

The risk of atherosclerosis is two to three times greater in diabetes patients compared to non-diabetic individuals. Hypolipidemia, low HDL (high-density lipoprotein) Although the precise cause of atherosclerosis

is unclear, possible factors include elevated levels of non-enzymatic glycosylation, increased platelet adhesiveness, obesity, and associated hypertension in diabetes. Heart disease, silent MI, stroke, gangrene of the foot or toes, and cerebrovascular illness are all possible complications of diabetic dyslipidemia among other consequences.

Diabetic Microangiopathy

A condition where the inner layer of small blood arteries and capillaries thickens. This can happen in musculoskeletal tissues (such as the skin, skeletal muscle, eye, and kidney) and non-muscular cells (such as peripheral nerves, renal tubules, and Bowman's capsule) is the cause of microangiopathy, which develops as a consequence of persistently high blood sugar levels.

Diabetic Nephropathy

Damage to the kidneys, known as diabetic nephropathy, may cause chronic renal failure and, in the worst case scenario, death.

In diabetic nephropathy, four distinct lesions are outlined;

- Diabetic glomerulosclerosis
- Vascular lesions
- Diabetic pyelonephritis and necrotizing renal papillitis
- Tubular lesions or Armanni-Ebstein lesion.

Diabetic Neuropathy

It is unclear what causes diabetic neuropathy, however it could be because of hyperglycemia-induced protein glycosylation or because of myoinositol insufficiency caused by sorbitol and fructose buildup. Although all sections of the nervous system are susceptible to diabetic neuropathy, the condition is most often identified by systemic peripheral neuropathy.

Diabetic Retinopathy

Serious eye condition known as diabetic retinopathy may cause blindness. Background retinopathy lesions include microaneurysms, hemorrhage, exudates, and retinal edema; proliferative retinopathy lesions are distinct from the former (with newly formed vessels, scaring, retinitis preoliferens, vitreous hemorrhage and retinal detachment). Diabetes increases a patient's risk of developing retinopathy, cataracts, and glaucoma at an earlier age.

Infections

Insulin ulcers are more likely to occur in people with diabetes, pyelonephritis, otitis, carbuncles, and TB. Several causes might be at play here, including hyperglycemia, altered leucocyte functions, diminished cellular immunity, and inadequate blood flow caused by vascular involvement.

OTHER COMPLICATIONS

Dental Disease

Diabetes increases the risk of periodontal (gum) disease. Diabetic risk is almost double in young people compared to non-diabetic individuals. Loss of gum-to-tooth attachment of 5 mm or more is seen in roughly one-third of individuals with diabetes who suffer from advanced gum disease.

Complications of Pregnancy

Significant birth abnormalities occur in 5–10% of births and 15–20% of fetuses as a result of uncontrolled diabetes before conception and throughout the first trimester of pregnancy. Both the mother and the child are put at danger when the diabetes is not well managed throughout the second and third trimesters of pregnancy, especially if the baby is born too big.

Foot Damage

A number of foot problems might develop in the event of nerve injury or inadequate blood circulation to the feet. Infections may develop from wounds and blisters if not addressed. Toe, foot, or even limb amputation may be necessary in cases of severe injury.

Hearing Problems

A higher probability of hearing loss is linked to diabetes.

Treatments

There is an immediate need to enhance management due to the rising incidence of the illness during the last 20 years. There has been tremendous growth in the use of pharmaceuticals to treat diabetes in recent years. New classes of antidiabetic drugs have emerged, bringing both new potential and new obstacles to diabetes management. In table 4 you can see all of the available anti-diabetic medications for diabetes treatment. In addition to their major pharmacological activities, several of the medicines used in diabetes medication also have antioxidant characteristics.

INSULIN

Treatment with Insulin

The existing diabetes mellitus categorization system recognizes a subset of individuals whose ability to secrete insulin is severely impaired and whose life is predicated on the use of exogenous insulin. Between five and ten percent of Americans with diabetes fall into this insulin-dependent category (type-1). While insulin from outside sources is not necessary for the life of most type-2 diabetics, many can only reach their healthiest when they augment their endogenous secretion with insulin from outside sources (Li 2014). Insulin pump infusion and injection are the only methods for administering insulin at the present time.

Oxidative Stress

An excessive formation of free radicals or Oxidative stress can be caused by either an increase in reactive oxygen species (ROS) or a decrease in the levels of antioxidant defenses, or both (Batty *et al.,* 2022). Nonradical species like hydrogen peroxide (H2O2) and hydrochlorous acid (HOCl) are also part of the reactive oxygen species (R.O.S.), as are free radicals like superoxide (•O2-), hydroxyl (•OH), peroxyl (•RO2), and hydroperoxyl (•HRO2- (Batty *et al.,* 2022). If one ROS is produced, it could trigger the development of other ROS as a result of radical chain reactions. The production of O2- occurs through the reduction of oxygen by one electron under certain circumstances, by NAD (P) H oxidase, xanthine oxidase, cyclooxygenase, and even eNOS. It also happens when the electron transport chain in mitochondria is normally doing oxidative phosphorylation, which is a crucial step in ATP production (Batty *et al.,* 2022). In normal conditions, antioxidant defense systems quickly eliminate •O2-. Superoxide dismutase enzymes, one residing in the cytoplasm (Cu-SOD) and the other in the mitochondria (Mn-SOD) dismutase •O2- to H2O2 (Batty *et al.,* 2022). Within the mitochondria, glutathione peroxidase (GSH-Px) and in the lysosomes, catalase (CAT) convert H2O2 to water and oxygen, respectively. Iron and copper are transition elements that may convert H2O2 to the very reactive •OH radical. Proteins, lipids, and DNA are all negatively impacted by extreme quantities of reactive oxygen species (ROS) (Juan *et al.,* 2021). Free radicals assault and destroy nucleic acids, lipids, and proteins if antioxidants inside cells do not neutralize them. Damage to energy metabolism, cell signaling, transport, and other vital biological processes may result from free radical assault byproducts that are oxidized or nitrosylated. When these kinds of injuries build up, cells eventually die via necrosis or apoptosis. Besides damaging macromolecules inside cells, reactive oxygen species (ROS) can activate mechanisms that are vulnerable to stress, which regulate gene expression and, in the end, lead to cell death (Juan *et al.,* 2021). Endogenous anti-inflammatory mechanisms, which are present inside cells, neutralize ROS to guarantee proper cellular activity. The most efficient methods for replenishing reduced glutathione (GSH), a major cellular antioxidant, are glutathione reductase and decreased nicotinamide adenine dinucleotide phosphates, as stated by Vairetti and colleagues (2021).

Anti-Diabetic Drug

Antioxidants have the ability to alleviate the symptoms of diabetes since oxidative stress is strongly implicated in the beginning, advancement, and maintenance of the disease, according to maritime *et al.,* (2003). Consequently, a drug that lowers blood sugar levels while simultaneously bolstering or maintaining the antioxidant defense system—that is often weak—would be an appropriate treatment for diabetes mellitus. The selection of hypoglycemic medications is severely restricted at the present time. Here are some qualities that a perfect anti-diabetic medicine should have:

1. It should orally active.

2. It should improve diabetes associated complications.

3. It should ameliorate impaired insulin secretion.

4. It should decrease insulin resistance.

5. It should cause only a small degree of adverse reactions. It should not cause hypoglycema.

6. It should have specific effects on the impaired metabolism of liver, muscle and fat tissue, intending for the extra pancreatic action.

7. It should supplement dietary management and should not replace it

8. It should have anorectic action to aid weight reduction.

Plants Selected for Antidiabetic Research Work

It was agreed that studies might be conducted for additional investigation of those plants that are according to existing research, conventional wisdom, and current practise, it may be anti-diabetic. However, there is a guideline for choosing plants for more research (Marles *et al.,* 1995). Many experts stated that at least five factors may be used to prioritise the selection of species in order to "accelerate" research on the anti-diabetic properties of plants:

1. The prevalence of plants

2. Usage that is customary in one or more nations

3. Evidence from experiments showing minimal toxicity

4. Hypoglycemic activity determined through experiment

5. Lack of knowledge on hypoglycemic components

Numerous plant species with identical morphological characteristics have been shown to have diverse chemical compositions. Even extensively used medicinal plants include adulterants that are added for commercial gain without regard for their therapeutic value or toxicity. Regarding the long-term usage of plants as a medicine, the time of collecting and processing, such as cleansing and detoxification, should be given equal weight. Such plants should only be the subject of very careful research. The following five plants were chosen for this study project.

Polyherbal mixtures refer to formulations that incorporate multiple herbs, each contributing to the overall therapeutic effect. In the context of antidiabetic polyherbal mixtures, these formulations often combine various medicinal plants known for their potential in managing diabetes. These mixtures leverage the synergistic effects of different herbs, targeting multiple pathways involved in glucose metabolism, insulin sensitivity, and related processes. Here are some details about antidiabetic polyherbal mixtures:

Mechanisms of Action

Polyherbal mixtures often target multiple pathways involved in diabetes to provide a comprehensive therapeutic approach. These mechanisms may include:

- Improved insulin sensitivity.
- Enhanced glucose uptake by cells.
- Inhibition of carbohydrate digestion and absorption.
- Modulation of Functions of pancreatic beta-cells and insulin secretion.
- Minimization of oxidative damage and inflammation associated with diabetes.

Clinical Studies

- Research studies and scientific studies have examined the efficacy and safety of antidiabetic polyherbal mixtures.
- Researchers have shown that people with type 2 diabetes can improve their glycaemic control, lower their fasting blood glucose levels, and become more insulin sensitive.
- However, the outcomes can vary, and more robust, to determine the safety and efficacy over a long period of time, carefully planned clinical trials are required efficacy of these formulations.

Synergistic Effects

- The synergy among different herbs in a polyherbal mixture is a key aspect of its effectiveness. The combined action of various bioactive compounds may result in enhanced therapeutic outcomes compared to individual herbs.
- Synergistic effects may also contribute to minimizing side effects and improving overall tolerability.

Formulations and Dosage

- Antidiabetic polyherbal mixtures are available in various formulations, including capsules, tablets, powders, and teas.
- The dosage and formulation may vary depending on the specific mixture and manufacturer's recommendations.
- It's crucial for individuals it is important to adhere to the dosage instructions and seek advice from physicians before incorporating these mixtures into their diabetes management plan.

Safety Considerations

- While many herbs included in polyherbal mixtures have a history of safe use, potential interactions with medications and individual variations in response should be considered.
- Adverse effects are generally mild, but individuals with pre-existing patients should proceed with caution and consult a medical expert if they have any preexisting diseases or are on any other drugs.

Antidiabetic polyherbal mixtures offer a holistic approach to diabetes management by combining the therapeutic potential of multiple herbs. While promising, further research and to determine their effectiveness, safety, and potential long-term advantages in treating diabetes, well-designed studies are required. diabetic people should consult healthcare professionals before incorporating polyhedral mixtures into their regimen.

Some important polyherbal Medicinal plants having anti-diabetic property have been studied with ethnobotanical description and possibilities to extend in detail, such as:

Herbal Drugs

These herbal drugs were reported to be effect on DM and are described below:

Table 1: The herbal drugs for management of Diabetes Miletus

S.No	Herbs name
1	*Butea monosperma*
2	*Terminalia Arjuna*
3	Black seed *(Nigella sativa),*
4	Fenugreek *(Trigonella foenum),*
5	Flax seeds *(Linum usitatissimum),*
6	Cumin *(Cuminum cyminum)*
7	Walnut oil
8	Wheat germ oil
9	Sesame oil

Butea monosperma

Common Name(s): Dhak, Palash, Flame of the forest, Parrot tree

Beneficial Effect of Flower

Butea monosperma flowers has been shown to possess a number of properties being bitter, aphrodisiac, emmenagogue, diuretic, expectorant, tonic, good in biliousness, inflammation and gonorrhoea. Earlier flowers have been used as astringent for the digestive tract, "Kapha" sickness, gout, skin conditions, burning, strangulation, thirst, leprosy, and eye disorders (Burlia *et al.,* 2007). Dye made from flowers is heated up in water and used to color clothing and create antibacterial creams for the skin. Because of its anti-inflammatory, menstrual-flow-promoting, and depurative properties, flowers have been used to treat a variety of urinary tract infections in both sexes (Burlia *et al.,* 2007). As an added bonus, reducing body heat and chronic fever has been achieved by crushing flowers in milk and sugar. According to researcher leucorrhoea may be cured by soaking flowers in water overnight. According to Badhe and Pande (1988), the butea monosperma flower may be used as both a dye and an antiseptic, particularly in cases of roundworm, threadworm, and Giardiasis illnesses (Badhe *et al.,* 1990).

Some Biological Activities

Antistress Activity

It has been shown that the extract reduces the stress associated with water immersion, as well as the levels of corticosterone and serotonin in the blood and the brain (Kasture *et al.,* 2002).

Hepatoprotective and antitumorigenic properties

Indians utilize a floral extract of *Butea monosperma* to treat liver problems; researchers there identified two flavonoids, isobutrin and butrin, that are antihepatotoxic (Wagner *et al.,* 1986). One possible explanation for the extract's Isobutrin and butrin, its active components, have chemo preventive consequences for reactive oxygen species, tumour promoter activated signs, and hepatic carcinogenesis. By evaluating its hepatoprotective benefits against acute liver injury, a 2011 study by Sharma and Shukla validated the conventional utilization of a water-based extract from the flowers of the species Butea monosperma (Sharma *et al.,* 2011). The results of another study examined the impact of an aqueous extract from Butea monosperma flowers on cancer and hepatotoxicity. There has been recent news that an aqueous extract from B. monosperma flowers may preserve the liver's nuclear morphometry and function as both a hepatoprotective and antitumorigenic agent (Mathan *et al.,* 2011).

Anticonvulsive Activity

Flowers have an influence on memory and behavior that is mediated by monoamine neurotransmitters, according to research published by Kasture *et al.,* (2002)(Kasture *et al.,* 2002). The presence of a triterpene might be the reason for its anticonvulsive effect, as suggested by Kasture *et al.,* (2002) (Kasture *et al.,* 2002). To learn more about its efficacy in treating epilepsy, more research is needed.

Antiestrogenic and Antifertility Activity

It was shown that flowers have antiestrogenic properties by Shah *et al.,* in 1990. There was a notable reduction in uterine weight increase, cornification of the vaginal epithelium, and typical histological alterations.

Free Radical Scavenging

The in-vitro models The reducing power assay, radical scavenging of 2,2 diphenyl-1-picrylhydrazyl (DPPH) radial, radical nitric oxide, radical superoxide anion, radical hydroxyl, and inhibition of blood cells hemolysis using 2,2' azo-bis (amidinopropane) dihydrochloride (AAPH) were all utilized to evaluate the free radical-scavenging properties of flower extracts (Lavhale *et al.,* 2007). Scavenging free radicals was extremely effective in the methanolic extract, ethyl acetate fraction, and butanol fraction. One possible explanation for the observed action is that the extracts include larger amounts of phenolic compounds.

Anti-inflammatory Activity of *Butea monosperma* Flowers

The effectiveness of a butea monosperma methanol extract in reducing inflammation flowers was investigated in a study that included albino rats (Shahavi *et al.,* 2008). The rats were given carrageenin to cause Paw swelling and granuloma of cotton pellets. A new study looked at how a water-soluble extract from Butea monosperma flowers could reduce inflammation (Choedon *et al.,* 2010). In addition, the anti-inflammatory benefits of butrin, isobutrin, and butein, which are components of BM, were studied for the treatment of inflammation caused by mast cells. Inflammatory and other disorders involving activated mast cells may benefit from this novel approach to learning about the BM's molecular base and its components' claimed anti-inflammatory properties (Rasheed *et al.,* 2010).

Antidiabetic Activity

Several preliminary research has been conducted to examine the antidiabetic activity of BM using different part of the extract like seed, leaves, bark and flowers but none meets to upto mark. Some preliminary studies have shown the hypoglycemic property of BM flowers. A single pilot research in rats with type 1 diabetes examined the effects of butea monosperma seeds on blood sugar and cholesterol levels have been reported (Bavarva *et al.,* 2008). Moreover, antidiabetic and antioxidant activity of leaves of BM have been investigated. stigmasterol, isolated from *B. monosperma* bark has been suggested to possess anti-diabetic and antiperoxidative properties due to thyroid inhibitory and insulin stimulatory nature. Butea monosperma flowers have recently been studied for their antihyperglycemic and antioxidative properties in diabetic mice produced by alloxan(Sharmna *et al.,* 2009).

Terminalia arjuna

Common Name(s): Arjun, Arjuna, Koha, Kahu, Arjan, Vellamatta

Some Biological Activities of *Terminalia arjuna* (TA) Bark

Cardioprotective and antioxidant activities

Some studies have shown that TA extracts have cardioprotective and antioxidant properties, including the presence of naphthanol glycoside and rjunaphthanoloside (Ali *et al.,* 2003), Arjunic acid, arjungenin, arjunetin, and arjunglucoside II are glucosides of these compounds (Pawar *et al.,* 2005). The bark of Terminalia arjuna contains arjunic acid, a powerful free radical capture, which was discovered by Sun and colleagues in 2008. The bark of the TA tree has a long history of use in the treatment of heart conditions.

Several researchers have investigated the cardioprotective benefits of TA bark in rats, rabbits, and mice using an isoproterenol-induced myocardial ischemia model (Tandon *et al.,* 1996). An evaluation was conducted to determine the impact of arjunolic acid, which is generated from TA, on several parameters such as electrocardiographic alterations, antioxidant status, lipid peroxide, myeloperoxidase (MPO), and antiplatelet activity. According to Sumitra and coworker (2001), arjunolic acid may provide cardioprotection by preventing damage from myocardial necrosis (Sumitra *et al.,* 2001). Recent research has investigated the antioxidant effects of TA on the hearts of rats that have been perfused with ischemia. The results showed that the rat heart's natural antioxidant chemicals were enhanced and oxidative stress was prevented by the crude bark of TA. Arjunglucoside II, a glucoside of the oleanane terpenoid arjungenin, has recently been demonstrated to impede the growth of cancer cells in human polymorphonuclear cells. Some previous research has shown that TA bark extract may protect organs from oxidative stress after exposure to carbon tetrachloride (Manna *et al.,* 2007) and N-nitrosodiethylamine (Sivalokanathan *et al.,* 2005) in rats. These results strongly suggest the results TA has antioxidant properties that it produces internally. Together, the data from the aforementioned studies and those from previous ones (Karthikeyan *et al.,* 2003) provide experimental evidence that TA is significantly involved in protecting the heart and LDL cholesterol from oxidative damage. According to Parmar and co-workers (2006), changes in thyroid hormones may mediate the cardioprotective action of TA bark extract (Parmar *et al.,* 2006). On top of that, research has shown that bark extract may have a cardioprotic impact because of its antioxidant properties (Sinha *et al.,* 2008). Research in rats with isoproterenol-induced chronic heart failure has uncovered the processes that account for the cardioprotective benefits of Terminalia arjuna bark extraction (Parveen *et al.,* 2011). According Biswas and colleagues (2011), diabetic rats have also shown that extracts from the bark and leaves have antioxidant activity and reduce oxidative stress (Biswas *et al.,* 2011).

Cardiotonic Activities

The cardiotonic and stimulating effects of TA bark were first shown in early physiological investigations on rabbit and frog hearts in isolation. Subsequent research indicated that the glycoside, derived from TA bark, caused an increase in blood pressure when

administered intravenously. It was later discovered that the bark powder has diuretic qualities as well as cardiotonic ones. Following this, research in rat atria and isolated frog hearts demonstrated chronotropic and inotropic effects of the bark's aqueous extract (Karamsetty *et al.,* 1995). Sandhu and company performed the research (2010) examined the cardiotonic effects of TA bark extract in young individuals who were otherwise healthy (Sandhu *et al.,* 2010).

Coronary Flow

There was a boost in coronary flow in the Langendorff's rabbit heart planning, which is an isolated cardiac when injected with the bark's aqueous extract. The antiplatelet activity has been evaluated impacts both healthy individuals and those suffering from arterial disease using TA ethanolic bark extract (Malik *et al.,* 2009).

Hypotensive Effects

Sustained hypotension and bradycardia were observed by Singh *et al.,* (1982) and were dosage dependent. Additional research using TA aqueous extract has shown hypotensive effects. A research conducted the thoracic aorta of rats by means of an extract made from water shown that the separated aortas contracted and then relaxed. Hypotensive effects were seen in both the extract in water and the portion of the component that included tannin-related chemicals. The pharmacological foundation of the enhanced coronary flow after TA infusion may be explained by increased prostaglandins activity (Bhatia *et al.,* 1998). It is possible that this is one of the reasons why TA helps CAD patients.

Effects on Lipids

Even though they were provided with a high-cholesterol diet, rabbits administered TA bark had substantially lower total cholesterol levels than those in the control group, in accordance with case-control studies by Tiwari *et al.,* (1990) (Subramaniam *et al.,* 2011). Subsequent research provided additional confirmation of these results (Khanna *et al.,* 1996). According to a study, TA was shown to be the most effective hypolipidemic drug out of the three Terminalias (Khalil 2005). Of note, it has the additional effect of increasing HDL cholesterol levels. It exhibited anti-atherogenic characteristics, including hypolipidemia and partial prevention of aortic atherosclerosis.

Anti-ischemic activities

Multiple groups of researchers have looked at the effectiveness of TA treatment in coronary artery disease and stroke (Dwivedi *et al.,* 2005). When it comes to treating type 2 diabetes mellitus (T2DM) that is accompanied by hypertension, ischemic heart disease, and dyslipidemia, Dwivedi and Aggarwal (2009) outlined the function of TA.

Effect on Endothelial Dysfunction

Bharani and co workers (2004) found that its high bioflavonoid concentration makes it an excellent agent for reversing endothelial dysfunction and a powerful antioxidant (Bharani *et al.,* 2004).

Anticancer Activity

Due to its antioxidant and immunomodulatory activity it has been described to prevent liver disorders. Moreover, it plays a beneficial role on hepatocellular carcinoma in vivo and in vitro and possess anti carcinogenic activity. Furthermore, it has profound effects against DLA tumour cells (Ganesan *et al.,* 2010).

Antiulcer Property

Bark of TA has been shown to possess antiulcer and ulcer healing property most likely because of the free radicals that it scavenges (Devi *et al.,* 2007).

Wound Healing Property

Some studies have evaluated the wound healing property of TA.

Black seed (Nigella sativa)

Common Name: Kalo jira, Black cumin, Kalonji, Sanskrit: Krishana jira,

Medicinal uses

N. sativa seeds are medically applied to cure a number of illnesses such as bronchitis, diarrhoea, rheumatism, asthma, and skin conditions. It has liver-toning, anti-diarrheal, appetite-stimulating, and emmenagogue properties. It is used to treat digestive issues, boost immune system, and improve milk production in nursing women in order to battle parasite infections (Al-Ali *et al.,* 2008). Due to their extremely low degree of toxicity, seeds are also employed as flavoring additives in pickles & breads (Yarnell *et al.,* 2011). Seeds can be used to treat skin outbreaks and worms. Oil has antimicrobial and local anaesthetic properties when applied topically. Consumption of roasted black seeds is administered to alleviate nausea and vomiting (Morsi 2000)**.**

Antidiabetic Effects of Nigella sativa

Researchers looked at the possibility of L-carnitine, lipoic acid (-LA), or a mix of these as a treatment for diabetes in animals that had been resulted

after a single intravenous administration of streptozocin (65 mg/kg). Researchers also measured insulin, responsiveness to insulin, C-peptide, HOMA, and pyruvate activity in addition to fasting blood sugar in order to study how glucose is metabolized. The increased blood glucose level was effectively lowered by either – lipoic acid (-LA) or *N. sativa.*

The level of insulin and C-peptide was dramatically raised by the combination of three chemicals. Combining -LA, L-carnitine, and *N. sativa* will considerably increase the metabolism of carbohydrates in diabetic rats, increasing the likelihood that DM will be successfully managed (Salama 2011)**.**

Diabetes sufferers in Kuwait have reportedly used a combine extracts of *N. sativa*, asafoetida, gum, myrrh and aloe, according to Al-Awadi and Gumma (Al-Awadi *et al.,* 1987).

The researchers investigated the impact of rats were tested for the effectiveness of various medications in decreasing The concentration of glucose in the blood. A person's glucose levels -lowering property of the plant extract containing Nigella was found to be caused by the inhibition of hepatic gluconeogenesis, according to additional research, and the plants extracted phytoconstituents prove according to research (Al-Awadi *et al.,* 1987; Mohamed *et al.,* 2009), it is a very effective therapy for the treatment of NIDDM-II. Administration to the volatile oil of N. sativa resulted in a significant reduction in blood glucose levels in both healthy and diabetic rabbits, regardless of changes in insulin levels (Al-Hader *et al.,* 1993).

Two doses of treatment were associated with a decrease in elevated plasma glucose levels in diabetic patients, according to a recent investigation rabbits generated by alloxan, thanks to the seed extract. Another study reviewed the effects of N. sativa oil on insulinotropic mechanisms in hamsters with streptozotocin and nicotinamide-induced diabetes mellitus. Serum albumin levels increased significantly and blood sugar levels decreased noticeably following over the course of four weeks, with *N. sativa* oil (Darakhshan *et al.,* 2015). The study also confirmed that n-Hexane and the raw extract of *N. sativa* seed can prevent diabetes (Abo-Atya *et al.,* 2021).

Thymoquinone (TQ), which , with a molecular weight of and a chemical formula of C10H12O2 164.20 g mol^{-1}, is the primary bioactive substance in *N. sativa* (Tiruppur Venkatachallam *et al.,* 2010). TQ is made up of the enol, keto, and mixed forms.

According to TQ's pharmacological properties, the main type is keto form (Alkharfy *et al.,* 2011). TQ has a great sensitivity to light and degraded quickly after being exposed to it. Furthermore, it exhibited unstable in water, especially at pH values higher than neutral (Salmani *et al.,* 2014). Focusing on the restorative benefits of the primary *N. sativa* ingredient (TQ) in neurological illnesses. According to the facts we present, TQ should be looked into further as a potential treatment for several neurodegenerative illnesses.

Results from 60 diabetic patients participated in the clinical experiment, and the results showed that N. sativa considerably reduced overnight blood glucose, LDL cholesterol, and total lipids, suggesting that it can be useful as an adjunctive treatment for insulin resistance DM syndrome (Najmi *et al.,* 2008)(Najmi *et al.,*, 2008). Using the STZ model to induce diabetes in rats, Hamdy and colleagues (2009) investigated the effects of TQ and *N. sativa* seed oil on neuropathy and oxidative stress (Hamdy *et al.,* 2009). When control group compared with the test group, it showed a substantial rise in dopamine and norepinephrine levels and a marked drop in serotonin level. Administration of NS oil or TQ orally partially reverted these results.

The majority of STZ's negative side effects, including mitochondrial dysfunction, DNA rippling, and heterochromatin aggregation, vacuole formation and disintegration, were significantly reduced by TQ. These effects of STZ were also reversed, albeit to a lower degree, from the water-based hydrosol of *N. sativa*. Normal insulin levels were restored with *N. sativa* oil; however normal serum glucose levels were not achieved. The biochemical and ultrastructural data imply that TQ and *N. sativa* extract have anti-STZ-diabetic and therapeutic effects through reducing oxidative damage and maintaining the normal physiology of pancreatic beta-cells. The observed hypoglycemic impact might be caused by improved -cell ultrastructure, which would raise insulin levels. Diabetes treatment and cell defense against oxidative stress may both benefit therapeutically from *N. sativa* and TQ (Abdelmeguid *et al.,* 2010)**.**

Neuroprotective / Neuro-pharmacological Activities

Alzheimer's Disease

A devastating neurological disorder, Alzheimer's disease (AD) destroys brain cells, reducing cognitive abilities and leading to memory loss. It seems that its processes contribute to inflammation and cellular oxidative stress. Multiple investigations have demonstrated that flavonoids, thanks to their antioxidant qualities, are useful in treating AD (Alhebshi *et al.,*

2013). In addition to reducing Ab1-42's brain damage, TQ also protected against oxygen depletion and possible excitability the mitochondria. The main cortical and hippocampal neurons' inhibition of synaptic vesicle recycling was improved by TQ. In contrast to Ab1-42, TQ exhibits therapeutic and neuroprotective effects in the rat hippocampus via reducing oxidative stress, according to a 2008 study by Saeed *et al.*,, One of the key roles played by beta-amyloid peptides in the development of AD. In the treatment of AD, natural compounds can prevent the pathways connected to A-induced neurotoxicity (Di Matteo *et al.,* 2007).

Effects on Epilepsy

Investigators looked at TQ's ability to help safeguard the brain from harm in a rat model of SE using lithium-pilocarpine. Given the crucial role that Nrf2 is the antioxidant response, it is a transcription factor, it can prevent cells against infections and hazardous chemicals (Espinosa-Diez *et al.,* 2015)**.**

According to this study, TQ therapy (10 mg/kg ip) reduced brain damage brought on by SE via altering the Nrf2 signaling pathway, which is responsible for activating the defense mechanism that includes antioxidants. The actions made by studies also showed that TQ enhanced memory and learning abilities. A distinct study 20 discovered that TQ (10 mg/kg ip) reduced seizures in a lithium-pilocarpine seizure paradigm via reducing NF-kB transcription, which regulates proinflammatory responses (Shao *et al.,* 2017).

Thymoquinone enhanced electroencephalography profiles, decreased mortality, lessened the intensity of seizures, and enhanced learning and memory (Baluchnejadmojarad *et al.,* 2013). According to one study, TQ has a curative role in the rat intrahippocampal 12ainite prototypical of temporal lobe epilepsy. Malondialdehyde (MDA), nitrate, and severe seizure activity were all reduced by TQ administration (10 mg/kg) in the hippocampus tissue (Dariani *et al.,* 2013)**.**

Depression

One of the serious mood disorders, major depressive disorder (depression) alters how people typically handle daily tasks including thinking, working, eating, feeling, or sleeping for at least two weeks (Spitzer *et al.,* 1995). The pathophysiology of depression is linked associated with tumour necrosis factors (TNF), interleukin-6 (IL-6), and C-reactive protein (CRP), which are markers of inflammation Depression is largely influenced by neuroinflammation (Dowlati *et al.,* 2010). It has been demonstrated that medicinal herbs, such as Nigella sativa, may have therapeutic effects in contrast to depressive-like behaviour in rodent models. Hosseini and co-workers, 2012 investigated the impacts of an alcohol-based hydrocarbon *N. sativa* (TQ) in rodent model of depression-like behaviour brought on by lipopolysaccharide (LPS) (100 g/kg, ip) (Hosseini *et al.,* 2012). The male rats were split up into several groups, including: In contrast to the LPS group, *N. sativa* and TQ were administered separately, however coadministration of NS (400 mg/kg) with TQ resulted in the lowest immobility periods. Additionally, in the FST test, *N. sativa* and TQ reduced the number of treated mice that crossed over. They demonstrated neuroprotective activities induced by LPS, depression-like behaviour in rats when combined with *N. sativa* and TQ.

Trigonella foenum-graecum (Fenugreek)

Common Name: *Sagmethi, Methi, Kasurimethi*

Phytochemical Constituents in Fenugreek

One of the many chemical constituents of fenugreek is steroid sapogenins (Figure 2.3). It has been demonstrated that fenugreek has diosgenin in its hydrophobic embryo. Fenugreek contains two furastanol glycosides, also known as hederagin glycosides, which are F-ring opening diosgenin precursors. Trigocoumarin, nicotinic acid, trimethyl coumarin, and trigonelline are just a few of the alkaloids found in the stem. The mucilage in the seeds is one element that stands out in particular. The stem has 28% mucilage, a volatile oil, two alkaloids like trigonelline and choline, 5% of an oil with a greater scent and a definite bitterness, 22% proteins, and a substance that gives it a yellow tint (Khare 2004)**.**

1. **Steroidal saponins**. Diosgenin and yamogenin (0.1% to 2.2%) are the two most significant steroidal saponins. Tigogenin, Gitogenin, Sarsapogenin, Yuccagenin, and Smilagenin are further sapogenins. Fenugreekine, a sapogenin peptide ester, is also present in the seeds (Anis 1985).

2. **Alkaloids**. Trigonelline, an alkaloid of this plant, has been isolated in concentrations up to 36%. The seed also contains gentanin and carpaine choline as alkaloids (Salehi Surmaghi 2008).

3. **Oils.** Fixed oil with 6% to 10% of odourless, golden-yellow unsaturated fatty acids can be found in fenugreek seeds. Ether, benzene, sulphur, and petroleum ether are excellent solvents for dissolving oil. There is antibacterial action in fenugreek oil.

4. **Proteins.** This plant has a high protein content (between 22 and 25%), with a concentration of

arginine, lysine, tryptophan, and histidine in lesser amount. It has high quantities of lysine, arginine, and gelicin but valin, threonine, and methionine, which are sulfur-containing amino acids, can be found in trace amounts (Mirzaei *et al.,* 2012).

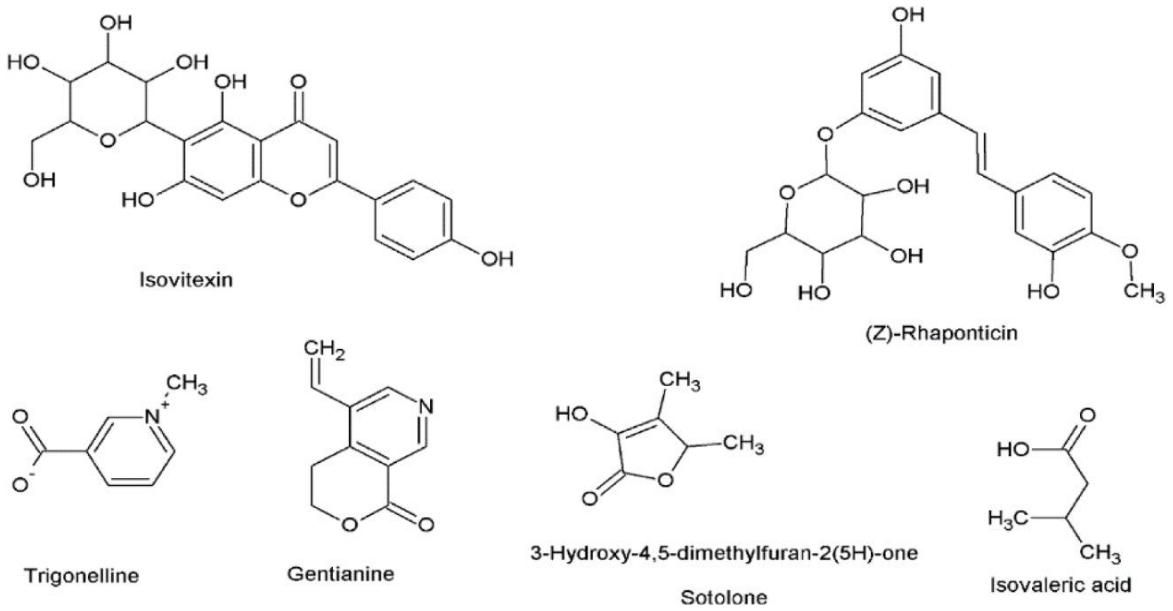


Figure 1: Important Phytoconstituents of fenugreek (Some important chemical structure)

Recent Medicinal Uses and Pharmacologic Activities

In Diabetes

In light of the widespread usage of fenugreek that has been documented and its great therapeutic potential, numerous studies on the various impacts of this plant have been carried out in the present to confirm the application of useful elements and the processes by which they work to cure diseases. New studies have shown that this plant has a wide range of effects in treating many diseases. The following list of pharmaceutical effects highlights their importance. Studies on humans and animals reveal that fenugreek seed consumption lowers both chronic and acute blood sugar levels. In a test on rats intended to compare the effects of fenugreek dry extract and insulin, it was discovered that a 15 mg/kg dose of the herb had the same blood sugar-lowering effects as insulin in that it reduced blood sugar by 1.5 units per kilogramme. When cellular factors were examined, it became clear that fenugreek extract was to blame for the decline in sugar and glucose tolerance through stimulating the synthesis of insulin in adipocytes and liver cells.

Studies on cellular factors revealed that fenugreek extract was the cause of the decline in blood sugar and glucose tolerance via promoting insulin production as reported by Vijayakumar *et al.,* (2008) in hepatocytes and adipocytes. In order to develop hypercholesterolemia in rats, a diet was prepared with fenugreek at concentrations of 15%, 30%, and 60%. The quantity of cholesterol and bile acids passed out in the stool increased as the dose increased, and the amount of serum cholesterol increased significantly at each of the three dosages (P .001) (Sharma 1984).

Toxicological Studies

The effects of *T. foenum-graecum* seeds (Methi)) on 60 type 2 diabetic patients over the course of 24 weeks were studied. The study tracked changes in weight, clinical signs, and serum toxicity variables such as Alanine transaminase (AspAT/ASAT/AAT), serum glutamic pyruvic transaminase (SGT), creatinine, blood urea, alkaline phosphatase, and bilirubin. Control group and treated groups received 300 gm of carbs per day for the first seven days of the trial. After that, samples of blood were obtained to assess the base size of the variables. The standard diet of diabetic individuals received a total of 25 g of fenugreek seed powder on day 7. Fenugreek seed recipients experienced a non-significant weight change of 1 ± 1.6 kg. After 3 to 4 days, several patients who got fenugreek leaves symptoms like diarrhoea and cramping disappeared. Blood factors did not significantly change, and no negative effects on the liver or kidneys were noticed (Sharma *et al.,* 1996).

The majority of information on the adverse effects of fenugreek ingestion came from investigations with lab rodents. In addition to detecting pathological abnormalities in the kidney and liver, lower body weight,

and high uric acid levels in the blood in Sudanese chicks fed fenugreek, it was also observed that use of fenugreek appeared to cause myopia. According to Mishra and co-workers (2011), the reduction of tri-iodothyronine (T3) synthesis in rodents led to a drop in body weight (Mishra *et al.,* 2011). Its derivatives like Coumarin, which have anti-coagulants property, are included in fenugreek formulations (Panda *et al.,* 2023). In people using blood-clotting medications like warfarin, this will show synergistic effects with coumarin, which increases the risk of internal bleeding.

Linum usitatissimum L. (Flax)

Common name: *flax or linseed*

Antidiabetic Properties

Daily ingestion of flaxseeds improves blood sugar management in pre-diabetic overweight men and women. As they lower levels of quick plasma glucose (FPG) in both type 2 diabetes and preconception. Hutchins found that flaxseeds at a dosage of 13 grammes per day were found to lower fasting plasma glucose. Consuming low glycemic index foods helps reduce insulin resistance and the problems that result from it (Hutchins *et al.,* 2013). A person intake a low dose of 20grm/day for 3 months in different research. The low-dose therapy of flaxseeds dramatically improved insulin sensitivity while lowering levels of FPG concentrations and insulin resistance (Javidi *et al.,* 2016).

The anti-diabetic properties of flaxseed and its constituent parts. Flaxseeds and flax lignin help to better regulate blood sugar levels. Flaxseeds contain the primary lignan of flaxseeds, secoisolariciresinol diglucoside (SDG), as well as the flax lignan complex. In a rat study, SDG was found to lower the incidence of diabetes. Patients with coronary heart disease who also had diabetes were the subject of a study. They received flaxseed oil as a supplement for three months, and the results showed that it did not affect the levels of the genes encoding LDLR, IL-8, and TGF-β, PPAR-γ, lipoprotein (a) LP(a), interleukin-1 (IL-1), and TNF- α (Hashemzadeh *et al.,* 2017).

An examination of phytochemistry *of L. usitassimum* reveals that tannins are present. The tannoids inhibit aldose reductase in vivo and stop lens opacification brought on by hyperglycemia in organ culture. Additionally, it prevents the synthesis of sorbitol in the lens and may mitigate the oxidative stress brought on by the polyol pathway. So, according to Suryanarayan and colleagues (2007), tannoids are helpful in preventing the development of cataracts caused by diabetes in rats (Suryanarayana *et al.,* 2007). The extract's high phenol concentration supports its anti-amylase activity. According to Rohan and co worker (2002), phenolic compounds can interact with and/or inhibit proteins and enzymes (Rohn *et al.,* 2002). Alkaloids are detected positively in *L. usitassimum*'s phytochemical analysis. This extract contains alkaloids that are known to lower levels of glucose in bloodstreams. Quinones found in flax seed aid to combat inflammatory conditions like arthritis, one of diabetes mellitus' consequences. Terpenoids found in flax exhibit pharmacological properties including antiviral, antimalarial, antibacterial, cholesterol synthesis inhibition, anti-inflammatory and anti-cancer properties.

Cuminum cyminum (Cumin)

Common name: Cuminum seed, Safed jeera, jeera

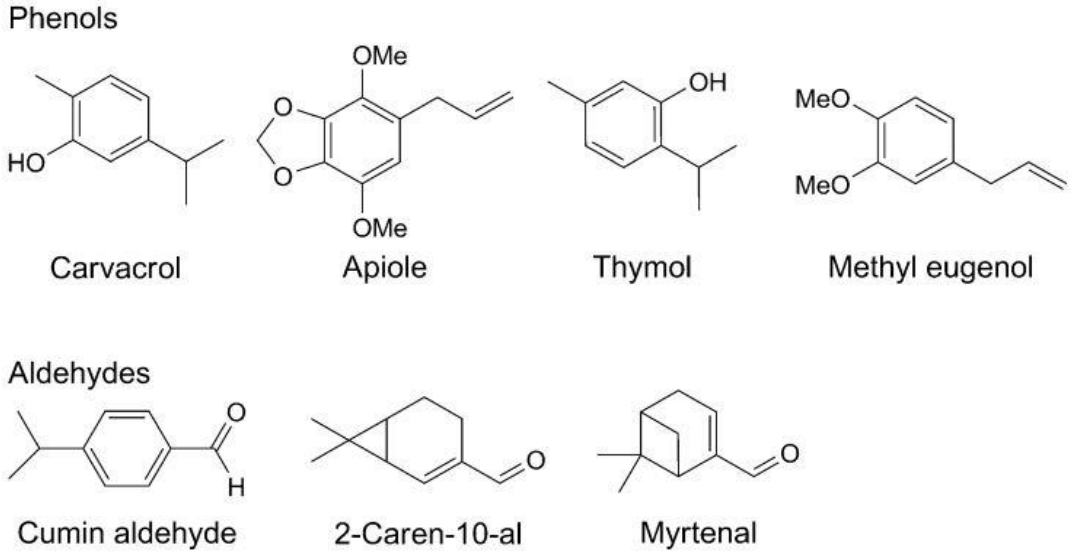


Figure 2: Important chemical compounds of Cumin (Chemical Compound's Structure)

Pharmacological Activities

Antidiabetic, antioxidant, antifungal, antibacterial, immunomodulatory, anti-inflammatory, and insecticide activities are listed as the most significant medical benefits of cumin documented in literature (Figure 2).

According to Roman-Ramos (1995) and Dhandapani and co-worker (2002), cumin seeds exhibit antidiabetic effects on hypolipidemic effect on diabetes-prone rats and streptozotocin-induced diabetic mice rats (Roman-Ramos *et al.,* 1995, Dhandapani *et al.,* 2002). According to Sultana *et al.,* (2010), cuminaldehyde produced from cumin seeds has aldose reductase and glucosidase inhibitory actions as well as antioxidant characteristics (Sultana *et al.,* 2010).

Up to 14.5% of cumin seeds are lipid-rich. They reportedly include 14 flavonoid glycosides, including 7 from the apigenin group, 5 from the luteolin group, and 2 from the chrysoeriol group.

Antioxidant Properties

Cumin essential oils exhibit outstanding antioxidant properties, and their phenolic levels rise with age. The active ingredients and pure extracts of European cumin have both been assessed and found to be quite successful. According to Mohamed, Hamed, and Fouda (2018) cumin extract has contains 19.013 milligrammes of quinoxaline and 24.021 milligrammes of gallic acid per gramme of gather, respectively, respectively (Mohamed *et al.,* 2018).

Anti-inflammatory Properties

Numerous inflammatory indicators, including TNF-α, C-reactive protein, adiponectin are significantly affected by treatments that include C. cyminum, according to the literature. A thorough description of *C. cyminum*'s anti-inflammatory activities was also provided by Srinivasan and colleagues (Srinivasan 2018).

Immunomodulatory Properties

Cumin is an efficient immunomodulatory drug, dramatically It elevated CD4+ and CD8+ T cell counts and modulated T lymphocyte transcription in a dose-dependent manner. Literature has also reported in-depth immunomodulatory and other positive characteristics of *C. cyminum* (Chauhan *et al.,* 2010)**.**

Antidiabetic Activities

C. cyminum supplementation has allegedly improved measurements of fasting blood glucose and glycosylated haemoglobin. Additionally, it was noted that C. cyminum essential oil exhibited the highest antidiabetic inhibitory efficacy of -amylase (Tahir *et al.,* 2016)**.**

In an additional research, Roman-Ramos *et al.,*, 1995 administered water, tolbutamide (a hypoglycemic drug), and conventional preparations of 12 edible plants via the gastric route to a group of 27 healthy rabbits to evaluate the antihyperglycemic effects of cumin. Subcutaneously, a dextrose solution was injected. The findings showed that cumin dramatically reduced blood glucose levels. When Willatgamuwa *et al.,*, 1998, administered a food regimen containing 1.25 percent cumin powder to diabetic rats induced by streptozotocin, they saw a reduction in hyperglycemia and glucosuria (Willatgamuwa *et al.,* 1998). This impact was noticed to become more significant near the end of the eighth week after the diet's administration, around the third week.

Additionally, the body weight also improved, and there were alterations in the diabetic animals' metabolism, such as a reduction in blood urea and creatinine excretion. More recently, after giving an ethyl alcohol (EtOH) extraction of cumin to STZ diabetic rats, Srivsatava *et al.,*, 2011, observed significant lowering of glucose levels and a reduction in triglycerides (Srivsatava *et al.,* 2011). Cumin has also shown a promising potential for usage as a dietary supplement to guard against diabetic DNA damage and stop diabetes complications (Hannan *et al.,* 2021).

***Walnut* (Juglans regia) Oil**

Common name: Walnut

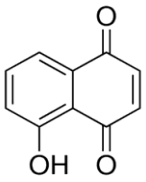
Plant Description

According to Wu and colleagues 2010, walnuts, which are the seeds of the *Juglans regia* L. (Juglandaceae) tree, are a very healthy food (Figure 2.7) (Wu *et al.,* 2010). In Asia and Europe, they are also utilized as a traditional remedy oncology, gastrointestinal issues, and respiratory infections (Andrews *et al.,*, 2023). Since linoleic and oleic acid make up most of walnuts' fat, they may offer additional antiatherogenic properties. Among the many beneficial polymorphic lipids, walnuts are particularly rich in omega-3 and omega-6. Potentially pivotal in warding off coronary cardiovascular disease are omega-3 polyunsaturated fatty acids., according to epidemiological and clinical studies (Bucher *et al.,* 2002)**.**

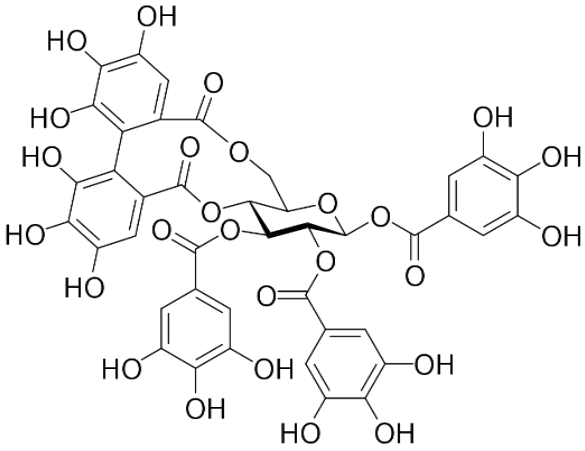
Phytoconstituents

Its vast range of medicinal advantages are caused by the existence of substances comprising nitrogen, polyphenols, alkaloids, and flavonoids, and other carotenoids components (Figure 2.8) and (Figure 2.9)) (Gupta *et al.,* 2019).

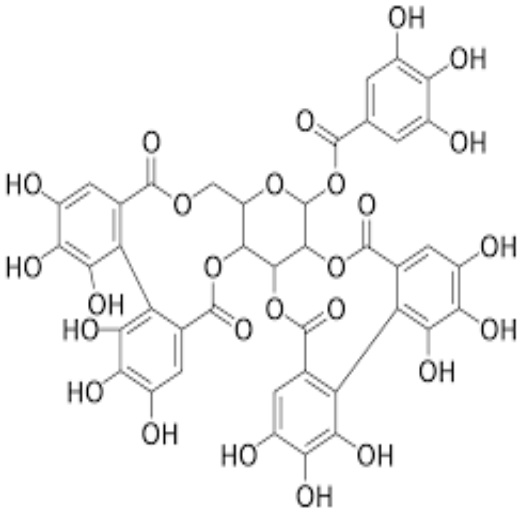
Some Chemical Structure of Medicinal Value



Juglone



Telimagrandin-I



Casuarictin

Figure 3: Important phytoconstituents of Walnut oil

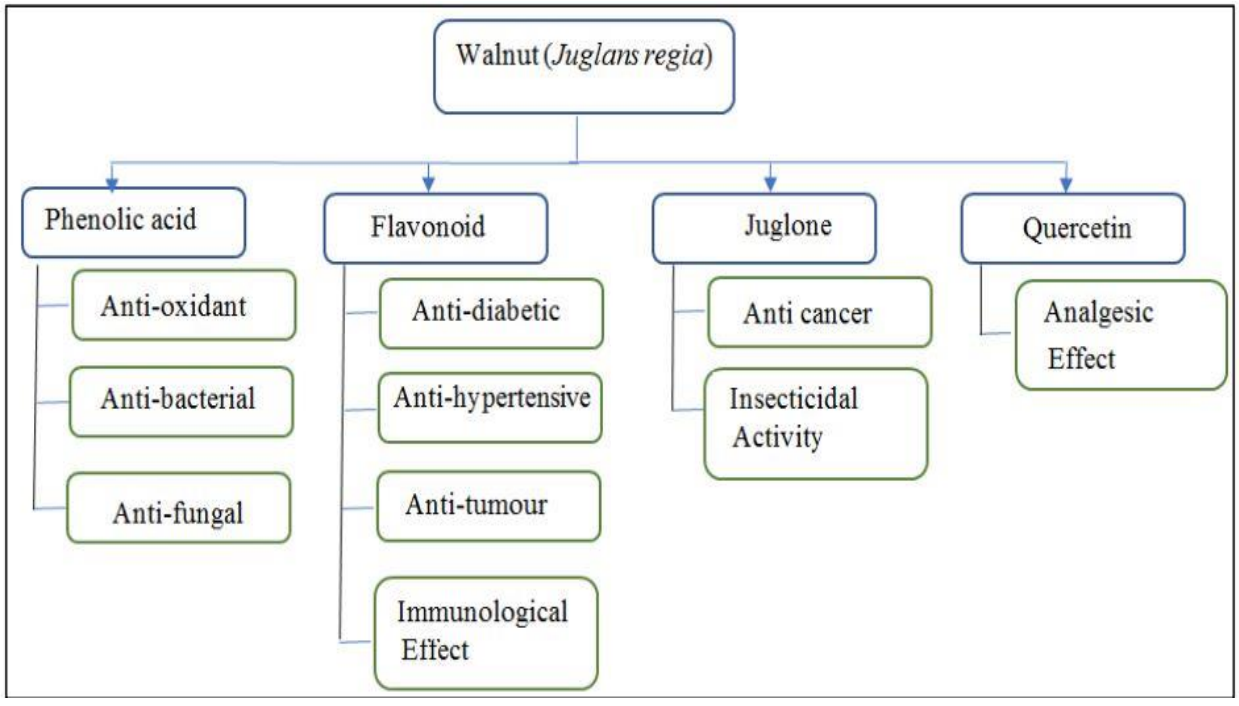


Figure 4: Pharmacological Properties of walnut

Anti-diabetic Properties

Finding novel ways to treat and prevent diabetes while also reducing its bad side effects is crucial now more than ever because of the increased number of people who are contracting the condition. More than 1200 medicinal herbs have been shown to have potential benefits for the management of insulin resistance and its consequences, according to ayurvedic studies. The discovery of a parasite-killing compound in walnut leaves opened the door to exploring them for use in managing

hyperglycemia and tuberculosis (TB). Infusing walnut leaves, either in combination with olive leaves or on their own, is known to lower levels of blood sugar in people with diabetes. Possible glycemic control benefits of walnut extraction include stimulating the remaining pancreatic beta cells to secrete more insulin, increasing insulin sensitivity, acting like beta cells, and preventing the small intestine from absorbing dietary carbohydrates, thereby increasing glucose uptake. According to Mohammadi and co-workers (2012) the insulin-dependent glucose transporter is also known as the peripheral glucose transporter (Mohammadi *et al.,* 2011). The anti-diabetic impact of in rats that developed diabetes after being exposed to streptozotocin Juglans regia leaves was studied.

After receiving therapy with Juglans regia extracts, When diabetic and glycosylated haemoglobin amounts rose, triglyceride, LDL, and total cholesterol levels fell sharply significantly (Mohammadi *et al.,* 2011)**.**

Anti-cancer Properties

The chloroform abstract of walnut root was discovered by Zhang *et al.,* (2015) to be cytotoxic to a variety of human cancer cells, including those from the skin, breast, lung, prostate, and colon (Zhang *et al.,* 2015). Phenolic chemical impact on cells with cancer, inflammation, angiogenesis, and radiation resistance have been demonstrated to be devastating. Research has demonstrated that consuming a diet rich in polyphenols can diminish the likelihood of developing cancer. This is to cause cells to die in breast cancer cells and prostate cancer cells, respectively, extracts of walnut green husk and root bark in methanol, chloroform, and n-hexane increased expression of caspase 8, caspase 3, and Bax genes while decreasing expression of Bcl-2 genes. According to the study, the bioactive compounds discovered in walnut green husks have the potential to be utilized in the creation of drugs that combat cancer (Croitoru *et al.,* 2019)**.**

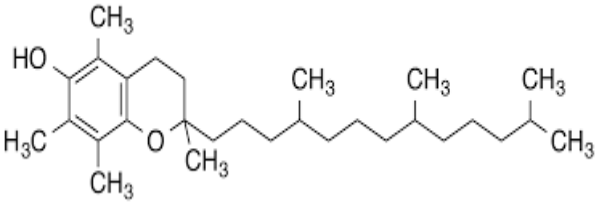
Wheat Germ *(Trititum Vulgare)* Oil

Common name: Wheat Germ Oil

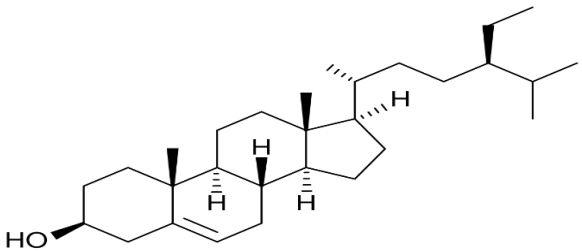
Phytoconstituents

Numerous tocopherols and phenol chemicals found in wheat germ oil (WGO) have antioxidant, antidiabetic, hepatoprotective and anti-inflammatory properties (Figure 2.10 A & B) (Niu *et al.,* 2013). It also contains vitamin E and poly-unsaturated fatty acids like linolenic and linoleic acids, which inhibit oxygen radical production in living organisms (El-Shafey *et al.,* 2022).

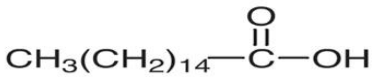
Some Important Chemical Structure



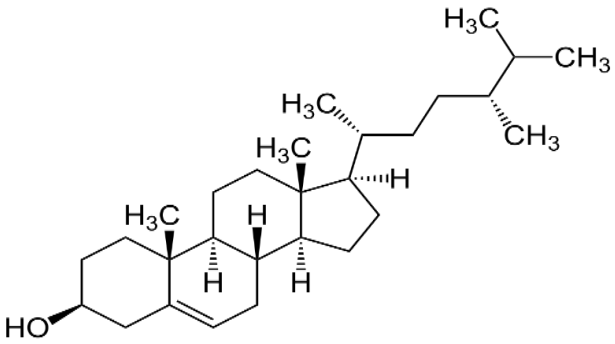
Alpha-tocopherol



Phytosterol



Palmitic acid



Campesterol

Figure 5: Important structure of chemical constituents found in WGO

Medicinal Properties

However, refined WG that eliminates the bran and oil drastically lowers the nutritious value of the finished product. Recent studies by several researchers have demonstrated that Wheat germ oil to reduce swelling, increase antioxidant capacity, and inhibit carcinogenesis in the majority of cancer models (Reddy *et al.,* 2000). Due to their increased levels of vitamin E and vital fatty acids, they produced strong protective benefits. WGO can also reduce oxidative stress and improve lipid metabolism (Reddy *et al.,* 2000).

Antidiabetic Properties

The germ oil from wheat has historically been used by patients with a range of health issues, and wheat

has been referred to as the "staff of life." Polyunsaturated fatty acids are present in abundant amount along with vitamin E, acts as a potent antidiabetic activity (Dass *et al.,* 2018)**.** WGO may aid to lessen oxidative stress. Contains policosanol as well, a compound that may be useful in reducing elevated Irmak *et al.,* (2005) found that blood sugar and total cholesterol levels are related. According to Hassanein and Abedel-Razek (2009), since the WGO contains more tocotrienols and alpha, beta, and gamma-tocopherols than any other natural source on Earth (Hassanein *et al.,* 2009).

The WGO accelerates the lipid peroxidation (LPO) process by inducing via the tocopherol-mediated redox pathway and blocking prostaglandin synthesis, Additionally, the Wheat germ oil contains anti-oxidant properties due to zeaxanthin, lutein and beta-carotene and fat-soluble carotenoids (Leenhardt *et al.,* 2008).

Anticancer Properties

In the most common cancer models, several studies have recently demonstrated that the chemo-preventive mechanisms of WG and WGO include anticarcinogenic effects antioxidant, and anti-inflammatory (Arslan *et al.,* 2020). They produced strong protective effects because of the greater levels of vitamin E and important fatty acids in them**.** WGO can also reduce lipid peroxidation and enhance lipid metabolism (Emam *et al.,* 2022).

Eight naturally occurring isoforms of vitamin E, which is a fat-soluble antioxidant, exist: tocotrienol isoforms and tocopherol isoforms. Multiple investigations to evaluate the potential of -tocopherol, a prominent form of vitamin E, in combating cancer, based on the concept that elevated levels of oxidative stress cause or influence the progression of nearly every cancer. Tocopherol can interact with the tocotrienols' anticancer isomers when taken as an antioxidant, that is the reason several clinical trials using it failed to yield notable outcomes (Yang *et al.,* 2020)

Protective Actions for the CNS

Many beneficial fatty acids, including linoleic and linolenic acid, are found in this oil, as well as vitamins like vitamin E (tocopherols), A, D, and B6 (Khedr 2017). These fatty acids promote endurance, lower cholesterol levels, and improve muscle dystrophies and other neuromuscular illnesses, as well as brain growth and cognitive capabilities in both healthy and pathological situations (Hussain *et al.,* 2013, Anwar *et al.,* 2015). The vitamin E in WGO is a powerful antioxidant that directly scavenges harmful radicals to protect the brain from oxidative stress. Improving the process of brain dysfunction and preventing oxidative damage to DNA and cell membranes. Additionally, -carotenes, which are also antioxidants, are present in WGO declared that WGO not only stops unsaturated fatty acids from 18oxidizing, but it also protects DNA (Leenhardt *et al.,* 2008).

Sesame *(Sesamum indicum Linn.)*

Common name : Sesame

Pharmacological Properties

According to reports, sesame seed oil has antioxidant, anti-inflammatory, antihypertensive, antithrombotic, antimutagenic, and cardioprotective characteristics. All of these bioactive substances are thought to be protective and are probably synergistic in their effects (Figure- 2.13.) (von Hanstein *et al.,* 2020).

Supplementing the standard diet of both healthy and diabetic female Wistar rats with 6% sesame seed oil considerably decreased factors that affect blood sugar levels, including lipid peroxidation and antioxidant status (Ramesh *et al.,*, 2005). On the other hand, factors related to hemology, electrolyte/mineral balance, insulin, and hepatic enzyme activity are different were not tested in the first study. Additionally, Ramesh and colleagues utilised sesame oil that was bought commercially for their tests and employed female Wistar rats; they did not specify the oil's quality (Ramesh *et al.,* 2005)**.**

Many people believe sesame to be among the most promising crops for utilised as medicine since prehistoric times. In particular cultures like the Aztec and Chinese, this was already thought of as the one-of-a-kind and unusual form of herb with amazing benefits. It has decreased the commonness of cardiac failure in diabetic mice (Donaghue *et al.,* 2009).

Hypertensive rats given sesame oil show improvements in cardiac cardiac hypertrophy in terms of mass, left heart the thickness, and cardiomyocyte distance across, suggesting that the oil could ameliorate the problem these animals. Recent research shows that sesame and its liganads have a remarkable impact on diabetes treatment, prevention, and improvement (ElSayed *et al.,* 2023). It has been observed that the combined effects of glibenclamide and sesame oil not only will generally lower nevertheless this will also significantly improve the health of those with type 2 diabetes by lowering their blood sugar and total triglyceride levels (Libby *et al.,* 2005).

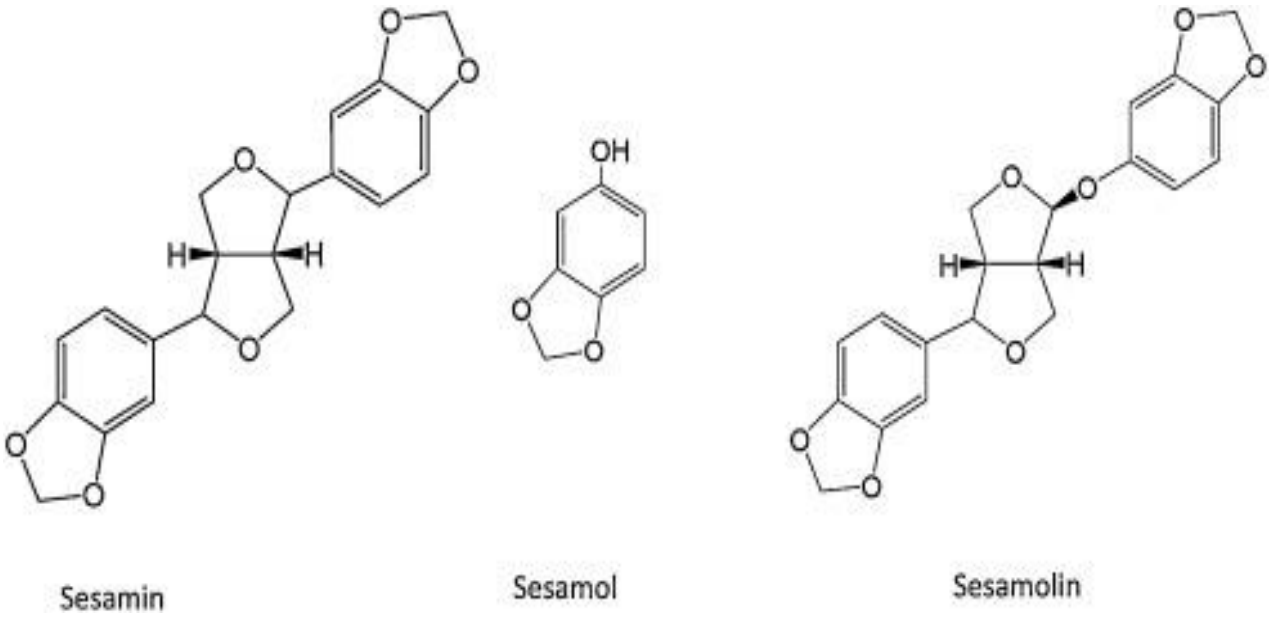


Figure 6: Phytoconstituents of sesame (Some Important Chemical Structure)

CONCLUSION

This review article emphasize the promising role of polyherbal medicines in the management of type 2 diabetes mellitus. It could highlight the need for further research and clinical trials to validate the efficacy and safety of these herbal therapies. Additionally, the this review might underscore the importance of integrating traditional herbal knowledge with modern scientific approaches to develop effective treatments for diabetes and its associated complications. This review article could also encourage collaboration between researchers, healthcare professionals, and traditional medicine practitioners to explore the full potential of polyherbal medicines in addressing the global burden of diabetes.

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