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A Review: Anti Diabetic Medicinal Plants Used For Diabetes Mellitus Bioactive Compounds in Anti-Diabetic Plants: From Herbal Medicine to Modern Drug Discovery

Sheetal Choudhary[1], Dr. Kehar Singh Dhaker[2]
[1]Research scholar, School of Pharmacy, LNCT University, Kolar Road, Bhopal, Madhya Pradesh, India, 462042
[2]Professor, LNCT University, Kolar Road, Bhopal, Madhya Pradesh, India, 462042
Correspondent author
Mrs. Sheetal Choudhary[1*]
Research scholar, School of Pharmacy, LNCT University, Kolar Road, Bhopal, Madhya Pradesh, India, 462042

Abstract: *Hyperglycemia in the pancreatic β-cells leads to the chronic condition known as diabetes mellitus. Among all non-communicable illnesses, diabetes mellitus ranks high in prevalence worldwide. Type 1 diabetes mellitus, in which the pancreas does not produce enough insulin, and Type 2 diabetes mellitus, in which the body becomes resistant to insulin, are both causes of hyperglycemia. Managing and reducing blood glucose levels in the blood vessels to a normal level is the primary focus of modern diabetic mellitus treatments. But there are a lot of adverse effects with most contemporary pharmaceuticals, and they can cause some major health problems while you're taking them. For this reason, traditional remedies have served as an alternative to modern treatment for quite some time. Although it has not yet reached pandemic proportions in many underdeveloped and newly industrialized nations, it is now the fourth worst killer among the world's wealthiest countries. We must confront this grave danger in the twenty-first century. Herbs and plants have been used as medicine for a very long time. Herbal remedies for a variety of illnesses were addressed in Ayurveda and other Indian texts. Less than one percent of the approximately 250,000 higher plants have undergone pharmacological screening, with even less tested for diabetes mellitus. In addition, novel plant-based bioactive medicines have demonstrated impressive antidiabetic performance in clinical trials, outperforming oral hypoglycemic medications. There is hope for the treatment of diabetes mellitus in traditional medicine, which has shown promising clinical results. According to the World Health Organization, achieving universal health coverage would need a concerted effort to reduce the prevalence of diabetes and its consequences. So, to help those who are diabetic, this study provides a brief overview of the pharmacological properties and active ingredients of a few well-known plants. Examining the antidiabetic effects of different medicinal plants is the focus of this research.*
Keywords: *Diabetes mellitus, Anti-Diabetic Plants, traditional medicines*

INTRODUCTION:

Diabetes is a complex, fast growing, chronic and non-communicable endocrine disorder of global concern associated with high risk of developing metabolism related complications in patients. Diabetes is characterized by hyperglycaemia, hyperlipidemia and oxidative stress, which further leads to chronic complications affecting various organs in body including, eyes, blood vessels, nerves and kidneys. According to World Health Organization (WHO), it is an epidemic disease having high risk of morbidity and mortality. About 387 million people are suffering with this disease globally and projected to be exceed over 640 by 2040 [1].

Diabetes comprises of four types, that is, type 1 diabetes, type 2 diabetes, gestational diabetes, and specific types of diabetes due to other causes. Among these, type 2 diabetes is the most common form of diabetes along with increasing patients every year characterized by tissue resistance to the insulin activity coupled with a relative deficiency in insulin secretion. Consequently, development has been taken place for search of potential therapeutic agents with higher efficacy to fight its complications. However, the efficacy of these therapeutic agents is not sufficient due to their side effects or any individual agent acts only on a part of the pathogenic process keeping considerable portion of the pathogenesis untreated [2].

Multiple problems are associated with the pathophysiology and treatment of diabetes and therefore, use of a single therapeutic agent for the reversal of all the aspects of the disease is almost impossible. Hence, the unidirectional therapeutic approach in the management of diabetes does not appear to be the way to treat the diabetes mellitus. To keep the glucose level close to normal is the most important task in the patients of type 2 diabetes. The treatment of diabetes as glycemic control is achieved through oral

hypoglycaemic agents, insulin therapy, dietary guidance, regular physical activity, and psychosocial support [3].

Although, currently available treatments are effective but frequently combined with unwanted complications, like obesity and hypoglycaemia, etc. Therefore, there is always a high demand of a new, safe and cost effective anti-diabetic drug. Traditional medicinal formulations from plants and their active phytoconstituents are used globally as a therapy for diabetes and in its complications. Several traditional medicines as well as herbs are well-known for prevention and treatment of diabetes. These herbal medicines are reported to delay the development of diabetes related complications and alter the metabolic abnormalities. Moreover, plants derived constituents exhibiting anti-diabetic properties have been isolated and they have displayed higher potential than the synthetic drugs [4].

Natural products like nopal, fenugreek, bitter guard, gymnema, ginseng, tronadora and α-lipoic acid are commonly used for the treatment of diabetes. Foods and dietary constituents with combined anti-glycation and anti-oxidant nutrients can exert their effects on different hormones, metabolic enzymes, and physiological processes of organ systems involved in carbohydrate metabolism thus playing significant role in the prevention and treatment of diabetes [5].

Appropriate herbal medicine can be discovered to control diabetes by considering numerous additional vital factors than the blood glucose, hemoglobin A1c (HbA1c) and insulin level. However, most of the herbs are not systematically investigated using in vitro and animal models and clinical trials in human. Thus, mechanism based studies are necessary for providing the scientific evidences for these natural medicines. Moreover, the pharmacological, toxicological, and phytochemical analysis is required before clinical trials. Furthermore, proper botanical/taxonomic identification along with detection of active constituents, evaluation of possible side effects and toxicity improves the quality and authenticity of herbal drug under investigation. Similarly, developing comprehensive database containing sound information on medicinal plants/herbs/herbal drugs and their use in curing various diseases will decrease excessive high cost and improve the research productivity [6-7].

In recent times, researchers are paying greater attention to the drugs of plant origin and functional foods to modulate physiological properties to cure diabetes and its complications. Therefore, natural anti-diabetic drugs from plant origin offer an attractive approach to control diabetes [8-10]. Considering these facts, this review is attempted to assess the available scientific information on medicinal plants used for the prevention and management of diabetic complications, current drugs or molecules available for diabetes treatment and their action mechanism and active natural products of plant origin for new drug discovery for the treatment of diabetic complications [11]. Patients with diabetes are at increased risk for metabolic-related consequences; the disease is complicated, rapidly expanding, chronic, and non-communicable, making it an endocrine illness of worldwide significance. The chronic complications of diabetes impact several organs in the body, such as the kidneys, blood vessels, nerves, and eyes. The disease is characterized by high blood sugar, high cholesterol, and oxidative stress. The World Health Organization (WHO) has classified it as an epidemic disease with a high potential for death and serious illness. The current global prevalence of this condition is estimated to be 387 million, with estimates suggesting that it could surpass 640 million by 2040 [1].

There are four distinct forms of diabetes: type 1, type 2, gestational diabetes, and additional forms of the disease. Type 2 diabetes, which is marked by tissue resistance to insulin action and a relative shortage in insulin production, is the most prevalent kind of diabetes and is rising in prevalence each year. As a result, research into more effective treatment drugs to combat its consequences has progressed. Unfortunately, these therapeutic drugs can have adverse effects or only target a component of the pathogenic process, leaving a significant section of the pathogenesis untouched, therefore their effectiveness is insufficient [2]. Because diabetes has several interrelated pathophysiological and therapeutic components, it is very unlikely that a single therapy drug will reverse all of these features of the illness. Therefore, it appears that treating diabetes mellitus with a unidirectional treatment strategy is not the best course of action. For people with type 2 diabetes, maintaining a normal blood sugar level is of utmost importance. Glycemic management is the goal of diabetic treatment, which includes insulin administration, dietary recommendations, physical exercise, psychological support, and oral hypoglycaemic medications [3].

Although the medicines that are now available work, they often come with side effects that patients don't desire, such as obesity and low blood sugar. As a result, novel anti-diabetic drugs that are both safe and cost-effective are always in demand. Diabetes and its consequences are treated worldwide with traditional

medicinal formulations derived from plants and their active phytoconstituents. It is well-known that certain herbs and traditional remedies can help prevent and cure diabetes. Reportedly, these herbal remedies can change metabolic irregularities and postpone the onset of diabetes-related problems. In addition, anti-diabetic components originating from plants have been identified, and they have shown more promise than the synthetic medications [4].

Many people often utilize natural remedies such as nopal, fenugreek, bitter guard, gymnema, ginseng, tronadora, and α-lipoic acid to cope with diabetes. As a result of their effects on various hormones, metabolic enzymes, and physiological processes of organ systems involved in carbohydrate metabolism, foods and dietary components with combined anti-glycation and anti-oxidant nutrients can play a significant role in the prevention and treatment of diabetes [5].

Several other important parameters than blood glucose, hemoglobin A1c (HbA1c), and insulin level can be considered while finding the right herbal treatment to manage diabetes. Many herbs, however, have not been well studied through human clinical trials, animal studies, or in vitro investigations. Therefore, in order to provide scientific proof for these natural medications, mechanism based research are essential. Clinical studies cannot begin without first conducting pharmacological, toxicological, and phytochemical analyses. The quality and authenticity of the herbal medication under research are enhanced by correct botanical/taxonomic identification, detection of active ingredients, evaluation of probable side effects and toxicity, and possible drug analysis. A similar strategy to reduce wasteful spending and increase research productivity is to compile reliable information on medicinal plants, herbs, and herbal medications and their usage in treating a wide range of disorders in a comprehensive database [6-7].

The use of functional foods and medications derived from plants to alter physiological characteristics in the treatment of diabetes and its consequences has recently attracted more scientific interest. It follows that plant-based anti-diabetic medications provide a promising strategy for diabetes management [8–10]. In light of these facts, the purpose of this review is to evaluate the current state of knowledge regarding medicinal plants used to treat diabetes and its complications, the action mechanism of the drugs and molecules currently available to treat diabetes, and the potential of active natural products derived from plants to aid in the development of new drugs to treat diabetic complications [11].

Diabetes progression and complications

Development of insulin resistance: Understanding the progression of diabetes complications has come a long way in recent years. The pathophysiology of diabetes has been elucidated via the use of current research methods. Several theories regarding the genesis, development, and insulin resistance of diabetes have been postulated. We know a lot about systemic inflammation, endoplasmic reticulum stress, and lipid accumulation in ectopic tissues. When insulin activity is out of whack for various reasons, it can be because of a combination of the aforementioned processes. The endocrine system degenerated due to the stress caused by changes in glucose and lipid metabolism as well as the extra efforts needed to maintain this metabolic balance [12].

The oxidative stress that develops as a result of persistent low-grade inflammation initiates the process of insulin resistance associated with obesity. Type 2 diabetes and its complications, including dyslipidemia, are specifically linked to subclinical inflammatory disorders and immune system misdirection. Dyslipidemia, which leads to insulin resistance, has been associated with the secretion of cytokines, such IL-6 and tumor necrosis factor (TNF)-β, by adipose tissue. An further important route associated with inflammation is the Janus kinases and signal transducer and activator of transcription proteins (JAK/STATs), which includes NF-kB, c-jun terminal NH2-kinase (JNK), and mitogen-activated protein kinases (MAPK) [13].

Three mechanisms in which β-cell activity is negatively impacted by chronic hyperglycemia include glucose desensitization, β-cell expression, and glucose toxicity. In the islet of diabetes mellitus patients, glycolysis leads to a negative correlation between the weight of β-cells and the oxidative imbalance linked to the expression of DNA damage. The activation of endoplasmic reticulum stress is triggered by the functional overload of β-cells caused by the increased demand for insulin in hyperglycemic and insulin-resistant conditions. The ability to maintain glucose homeostasis is unaffected by the fact that normal sensitivity for glucose level varies greatly among individuals. Nevertheless, as hyperglycemia worsens glucose tolerance, the sensitivity of β-cells to glucose decreases over time [14].

Similar to how insulin secretion is changed during diabetes, it is rhythmic and biphasic. The coordinated secretion of insulin from the millions of islets in the pancreas causes these oscillations. In order to coordinate the secretory property from the β-cell clusters, there has to be substantial coordination within

the islets and the pancreas for the creation of collective secretory bursts. Most of the insulin that the body produces is released via this rhythmic process. Prior to the physiological occurrence, β-cell dysfunction happens, and subsequent elements like high blood sugar, high cholesterol, cellular oxidative stress, altered hormone and cytokine activity, and impaired blood flow all play a role in its advancement [15].

To keep blood glucose levels stable and prevent the worsening of diabetes, it is crucial to keep the bulk of β-cells at a recognizable level. The bulk of β-cells is reduced due to an imbalance in cytokines, which promotes cell death and reduces their ability to replenish. According to clinical evidence, autopsy of diabetes patients show a decrease of 50-60% in β cell mass [16].

Progression of diabetes: The β-cells of the pancreatic islets are mainly stimulated by an elevated blood glucose level. Constant problems arise from maintaining a high blood glucose level. Diabetes nephropathy, diabetic retinopathy, diabetic neuropathy, and many other problems begin as a result of micro-vascular lesions caused by high blood sugar. Depression, erectile dysfunction, and dementia are further complications of hyperglycemia [17].

Hyperglycemia, hyperlipidemia, inflammation, adipokines, and impaired insulin secretion all have a significant influence on insulin sensitivity. The development of diabetes is accelerated by obesity, which triggers oxidative stress in the endoplasmic reticulum and cells, the secretion of cytokines, abnormal lipid profiles, and impaired protein tyrosine phosphatase signaling. Dysfunction of cells, DNA damage, organelle injury, membrane structural changes, and oxidative stress-induced reactive oxygen species (ROS) are all possible outcomes of cellular stress (Chang & Chuang, 2010). Adipose tissue is the destination for extra calories when dieting to excess. But adipose tissue experiences hypoxia if its threshold capacity is exceeded. Thus, when hypoxia inducible factor-1 (HIF-1) is activated, inflammation in adipose tissue is caused by an increase in the expression of inhibitor NF-κB kinase (IKK) and c-Jun N-terminal kinase (JNK) [18].

Adipocyte apoptosis and inflammation are both exacerbated by elevated levels of inflammatory cytokines, which in turn suppress the peroxisome proliferator activated receptor (PPAR). Lipoprotein lipase, which is activated by insulin resistance, hydrolyzes lipoprotein triglycerides and produces free fatty acids (FFA). As a result, lipotoxicity is induced by the excessive outflow of free fatty acids from adipocytes into circulation, which are then transported and accumulated in other organs. An increase in free fatty acid levels leads to the buildup of ceramide and diacylglycerol (DAG), which in turn impede the insulin pathway's function via serine phosphorylation and by increasing the isoforms of protein kinase-C (PKC). When fatty acid levels are too high, it leads to lipotoxicity, which in turn causes normal cell malfunction. The release of cytokines and NF-κβ occurs in the liver when Kupffer cells are activated. In addition, insulin resistance is enhanced because ceramide stimulates the JNK and NF-Ⅱ/IKK pathways. All the organs that absorb a lot of glucose, including skeletal muscle, etc., acquire insulin resistance in this manner. Insulin resistance develops over time as a result of changes in glucose metabolism brought about by hyperglycemia and hyperlipidemia [19].

Current pharmaceutical treatment of diabetes and approved drugs

Because insulin production is limited in type 1 diabetes, insulin injections are the backbone of treatment (American Diabetes Association, 2018). Blood glucose-lowering (hypoglycemic) medications were necessary for the majority of persons with type 2 diabetes, even if some patients were able to reach their goal levels by healthy eating and regular exercise. The plasma glucose level can be decreased by the modification of metabolic pathways by many kinds of chemicals. Here is a list of all the hypoglycemic agents that have been authorized, except insulin. Many considerations are considered when deciding which of these agents to employ, including the type of diabetes, blood glucose level, age, other medical conditions, medication usage, and other personal circumstances [20].

The healthcare professional may recommend a single medicine or a combination of medications to help you reach your goal blood glucose level, taking into account all of these considerations. One of the first lines of defense against high blood sugar in people with type 2 diabetes is metformin, a member of the biguanides family of drugs. Here are some additional medications that can lower glucose levels: sulfonylureas, meglitinides, thiazolidinediones, α-glucosidase inhibitors, dipeptylpeptidase-4 (DPP-4) inhibitors, bile acid sequestrants, dopamine-2 agonists, sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, etc. [21].

Antidiabetic effect of folklore medicinal plants

Allium sativum and its application to Diabetes Mellitus: Allium sativum is the scientific name for garlic, which is a plant species in the family of Amaryllidaceae. Garlic is known to have various health benefits

such as lowering cholesterol, improving blood pressure, and boosting the immune system. Garlic has also been shown to have potential benefits for individuals with diabetes. Research has suggested that garlic may help lower blood sugar levels and improve insulin sensitivity, which can be beneficial for diabetes.
The major phytochemicals present in garlic include allicin, which is one of the most well-known phytochemicals in garlic and is responsible for its pungent odor; sulfur compounds, including diallyl disulfide and diallyl trisulfide, which have antioxidant, anti-inflammatory, anti-diabetes, and anti-cancer properties, flavonoids, including quercetin and kaempferol, which are known for their antioxidant properties; saponins, which are natural detergents that have cholesterol-lowering properties; and fructans, which are a type of carbohydrates that can act as prebiotic candidates [22].

Brassica juncea: It is commonly used spice in various food items in Tamilnadu. B. juncea is a traditional medicinal plant which belongs to family Cruciferae. B. juncea aqueous seed extract has a potent hypoglycemic activity which was investigated in STZ induced diabetic male albino rat. Doses which have hypoglycemic activity was reported as 250, 350, 450 mg/kg [23].

Figure 1: Plant Brassica juncea

Eugenia jambolana Eugenia jambolana (E. jambolana) popularly known as Jamun or Indian blackberry has been indicated in Ayurveda, an ancient system of Indian medicine, for use in DM. In accordance to its claimed anti-diabetic effect in traditional medicine, E. jambolana has been reported to have hypoglycemic effects both in experimental models and clinical studies[24].

Figure 2: Plant Eugenia jambolana

Alangium lamarckii: Antidiabetic effect of alcoholic extract of Alangium lamarckii (A. lamarckii). Alcoholic leaves extract 250 and 500 mg/kg bw was used for these studies. A. lamarckii have significant antidiabetic activity in STZnicotinamide induced diabetic rat[25].

Figure 3: Plant Alangium lamarckii

Albizia odoratissima: Antidiabetic effect of methanolic bark extract of Albizia odoratissima (A. odoratissima) in alloxan induced diabetic mice. The methanolic extracts were fed to the animals at a dosage of 250 and 500 mg/kg body weight. The significant reduced in the levels of serum cholesterol, triglycerides, SGOT, SGPT, alkaline phosphatase and decrement [26]

Figure 4: Plant Albizia odoratissima

Artemis sphaerocephala: Krasch Antioxidant effect of Artemis sphaerocephala (A. sphaerocephala) gum on STZ induced diabetic rat. Levels of serum and liver tissue thiobarbituric acid reactive substances (TBARS) and +OH were increased in STZ induced rat. The activity levels of liver and serum superoxide dismutase were decreased. After administration of extract of A. sphaerocephala, levels of TBARS and +OH were decreased in serum and liver tissue. The significant increments in the levels of liver and serum SOD. A. sphaerocephala is very good antioxidant activity [27].

Figure 5: Plant Artemis sphaerocephala

Axonopus compressus: The anti-diabetic effect of the methanolic leaf extract of the plant. Diabetes was induced in the rats by injection of alloxan. Methanolic leaves extract 250, 500 and 1 000 mg/kg bw was used for these studies. Methanolic leaf extract of Axonopus compressus (A. compressus) at all the doses (250, 500 and 1 000 mg/kg) were significant reduction (by 31.5%, 19.8% and 24.5%) of the blood glucose levels in the diabetic rats when compared to the control group. A. compressus may possess very good antidiabetic property [28].

Figure 6: Plant Axonopus compressus

Berberis vulgaris: Hypoglycaemic effect of Berberis vulgaris (B. vulgaris) L. in streptozotocin-induced diabetic rats B. vulgarisis a traditional medicinal plant which belongs to family Berberidaceae. The results indicated that water extract and saponins shows significant hypoglycemic effect. The serum cholesterol and serum triglycerides levels were significantly increased [29].

Figure 7: Plant Berberis vulgaris

Caesalpinia digyna: Antidiabetic effect of bergenin from the roots of Caesalpinia digyna (C. digyna). The levels of plasma total cholesterol (TC), triglycerides (TG) and LDL-C were significantly increased, whereas levels of (HDL-C) were significantly decreased in diabetic rats when compared to control. After administration of bergenin (10 mg/ kg; p.o.) the lipid profile were significantly increased when compared with that of glibenclamide (10 mg/kg; p.o.). The activity levels of antioxidant enzymes such as SOD and Cat were decreased. The level of TBARS was significantly increased in diabetic rat compared to control rat. The administration of bergenin (10 mg/ kg; p.o.) significantly increased the SOD and CAT respectively and reduced TBARS [30].

Figure 8: Plant Caesalpinia digyna

Catharanthus roseus: Hypoglycemic effect of the methanolic leaf extract of Catharanthus roseus (C. roseus) in alloxan induced diabetic rats. The levels of blood glucose were significantly decreased when compared with Control rat. The blood glucose lowering effect of C. roseus methanolic extract was more pronounced than Glibenclamide and Metformin [31-32].

Figure 9: Plant Catharanthus roseus

Aloe Vera L. Burm. (Asphodelaceae): Aloe vera is the popularly medicinal plant ever known and the most applied medicinal plant especially in the cosmetic industry, and antidiabetic mediation (Figure 8). This traditional medicinal plant belongs to the family Liliaceae. It is original to Africa and Mediterranean

countries. It is reported to be distributed widely in the islands of Cyprus, Malta, Sicily, Cape Verde and India [33].

Figure 10: Plant Aloe vera

Pterocarpus marsupium (Fabaceae): Pterocarpus marsupium (P. marsupium) is a large, high tree that can grow up from 15 to 30 m tall (Figure 9). It belongs to the Fabaceae family and distributes in India, Nepal, and Sri Lanka, which is widely used in 'Ayurveda' as 'Rasayana' for the management of various metabolic disorders including hyperglycemia [34]

Tinospora cordifolia (T. cordifolia): It has been commonly known as "Amrita" or "Guduchi", belong to the Menispermaceae family. It has been one of the important drugs of Indian Systems of Medicine for a long time. Guduchi is native to India and mainly distributed in tropical areas such as Myanmar and Sri Lanka. In India, this plant has been reported as the main source of treatments for many diseases such as fever, dyspepsia and urinary diseases in folk medicine.

T. cordifolia, containing polysaccharide isolated from this plant exposed the β-cell regenerative properties which could be pointed to develop antidiabetic medicine with few side effects. Oral administration of the extract of T. cordifolia roots for two weeks experimented with induced type 2 diabetic rats resulted in this plant can promote insulin secretion and inhibit glucosgenolysis process and therefore improve the regulation of blood glucose level in the body [103]. In 2011, Patel also studied the hypoglycemic effects of alkaloidal fraction of T. cordifolia extract. This investigation demonstrated the antidiabetic activity of T. cordifolia due to the promoting of insulin-releasing, improving insulin sensitivity and inhibiting gluconeogenesis process [35]

Figure 11: Plant Tinospora cordifolia (Menispermaceae)

Tinospora crispa (Menispermaceae): Tinospora crispa (T. crispa) is a precious medicinal climbing plant. As a kind of vines, its body is very rough, light brown, long to 6–7 m or more. orally administrated extract of T. crispa exhibited a potential antidiabetic effect. The mechanisms of these activities were predicted so that this plant could stimulate insulin secretion through the modulation of β-cell Ca^{2+} concentration. In Noipha's experiment, T. crispa extracts improved the glucose transport activity of L6 myotubes by increasing GLUT1 transporter. Thus, it can be further used as an antidiabetic agent for the treatment of type II diabetes [36].

Gymnema sylvestre (Apocynaceae): Gymnema sylvestre (G. sylvestre) belonging to the Apocynaceae family, originated from tropical forests of The Southern and Central India and Sri Lanka. The major biological active ingredient of G. sylvestre is Gymnemic acids—a group of triterpenoid saponins isolated and identified successfully (Figure 11). Several studies have reported that the main biological activity of this plant is antidiabetic activity. the action of Gymnemic acids in diabetic treatment was reported to be able to stimulate pancreatic cell production, thereby increasing insulin production, increase insulin sensitivity and insulin activity, help to control and stabilize blood glucose concentration in the body. Gymnemic acids were also reported to be able to inhibit the absorption of glucose in the small intestine and inhibit the conversion glycogen in live to glucose molecules in blood [37]

Cyamposis tertragonoloba (Fabaceae): Cyamopsis tetragonoloba L. Taub is commonly known as Cluster Bean or Guar, belongs to the Fabaceae family. The plant is a very small drought-resistant herb and widely cultivated in India. This plant was reported to contains a high amount of carbohydrates and fiber. ecause of the presence of flavonoids and other phenolic compounds of the plant, Cyamopsis tetragonoloba showed a marginal antihyperglycemic effect on blood glucose level in normal fasted rats, however, the blood glucose-lowering effect was significant in alloxan-induced hyperglycemic rats. Other studies showed that this herb could improve insulin release and decrease the amount of HbA1c. Gopalsamy Rajiv Gandhi et al. reported that polyphenols identified in C. tetragonoloba beans showed hypoglycemic action and protected β-cells. Hence this plant can be considered for use in the management of type 2 diabetes mellitus [38].

Ocimum sanctum L. (Lamiaceae): Ocimum sanctum L. is a small tree, up to 1 m tall, commonly known as 'Sacred basil' or 'Holy basil' or "Hương Nhu Tía" in Vietnam, is grown as a household plant in many countries for medicinal purposes like Vietnam and India (Figure 13). It belongs to the Lamiaceae family. The whole plant has a pleasant aroma. The phytochemistry of Ocimum sanctum is identified in all parts of this plant, containing many nutrients and bioactive constituents. However, the quantity of these constituents depends on many natural factors, including growing, harvesting, storage conditions. eaf power extract lowered plasma glucose level by the presence of many active phytochemicals including eugenol, carvacrol, linalool, caryophylline, β-sitosterol which have been studied about potent hypoglycemic effects efficiency. The other investigation has reported the antidiabetic and hypoglycemic activities of a triterpenoid (16-hydroxy-4,4,10,13-tetramethyl-17-(4-methyl-pentyl)-hexadecahydro-cyclopenta[a]phenanthrene-3-one) isolated from Ocimum sanctum by in vivo investigation [129]. The mechanisms of the antidiabetic and hypoglycemic potential of this compound were elucidated to increase the pancreatic secretion of insulin from β-cells, and enhance glucose utilization. It was suggested that this triterpenoid should be considered to be developed as a potential antidiabetic medicine. This evidences support that O. sanctum has many benefits in the management of diabetes, and this plant should be encouraged to be a potential anti-diabetic activity [39]

Promising natural products for the management of diabetes and its complications

Based on the preliminary results from the screening of extracts and their constituents on different in vitro and in vivo studies, various plant-based natural products (phytochemicals) are studied in detail for their mechanism of action against diabetes. Some of these compounds are discussed in detail in following sections.

Berberine: Berberine, an active compound of Berberis spp., Coptidis spp., Hydrastis xanthorhiza, Mahonia spp., Phellodendron amurense, T. cordifolia, and many others species, has been commonly utilized for the adjuvant administration of type 2 diabetes since a long time. Berberine controls the glucose and lipid metabolism as demonstrated by several studies in different animal model. Significant reduction (upto 20%) in glycated hemoglobin (HBA1c), postprandial blood glucose, fasting blood glucose and plasma triglycerides were recorded in persons treated with berberine. Similarly, reduction in body weight and level of plasma triglycerides and improvement in insulin function was observed in Wistar rats fed with high fat diet by the treatment of berberine. Berberine up-regulated the expression of gene associated with energy consumption in mice tissue adipose and muscle and down regulated the genes involved in lipogenesis [40]. Berberine treatment also improved hyperglycemic conditions by increasing AMP-activated protein kinase (AMPK) action in adipocytes and L6 myotubes. It also improves glucose uptake by increasing translocation of GLUT-4 in muscle cells by regulating phosphatidylinositol 3-kinase, and inhibit lipid deposition in adipocytes. It also elevates the level of glucogen like protein (GLP-1), inhibit production of ROS, normalize mitochondrial dysfunction, reduce endothelial micro-particle-mediated oxidative stress, and suppress inflammation. Based on a meta-analysis review, berberine was found

beneficial for controlling blood glucose level in the treatment of diabetic mellitus. Berberine also found effective as comparable to conventional oral hypoglycaemic drugs. Interestingly berberine is also reported to inhibit αglucosidase enzyme activity. Therefore, effectiveness of berberine against anti-dyslipidemic and other diabetes complications needed to be further authenticated by detailed. Intervention of berberine with improved lifestyle tended to decrease the level of fasting plasma glucose post-prandial glucose and glycated hemoglobin than lifestyle improvement alone or with the treatment of placebo demonstrated no significant difference between berberine and oral hypoglycaemic drugs [41]. Berberine treatment with lifestyle intervention was found better than intervention in lifestyle for the treatment of hyperlipidemia. Also, berberine in combination of the drug lower the lipid level and found more effective in lowering triglycerides and LDL-C level and increasing HDL-C level than the lipid controlling drugs alone. Various mechanism of action of berberine in treatment of diabetes and its complications are reported along with the activity of berberine derivatives and its combination with other molecules. Berberine is also reported to regulate non-coding RNAs to exert its therapeutic action in diabetes [42-44]

Ginsenosides: Ginsenosides are chemical constituents of a perennial plant species ginseng (Panax ginseng), which used in traditional medicine in China, Japan, Korea and other countries. Ginsenosides exhibited antihyperglycemic and anti-obesity activity through the PPAR-mediated pathway. PPAR-γ mRNA expression in patients of diabetes mellitus was significantly increased after 2 weeks treatment of ginsenosides. Similarly, it improved lipid metabolism by decreasing the level of triglyceride, total cholesterol and blood glucose as compare to the control individuals. Ginsenoside Rb1 exhibited cardio-protection activity against ischemia reperfusion injury [45-48].

CONCLUSION:

Patients, their families, and society as a whole bear the financial burden of diabetes mellitus. In addition, blindness, renal failure, and heart failure are among the severe chronic consequences that can develop from untreated diabetes. Researchers are focused on developing novel antidiabetic drugs to help alleviate this condition. Many traditional treatments have gained attention due to the negative consequences of contemporary therapy. In addition, combinatorial therapy including plant extracts and conventional medications are becoming increasingly feasible. A reduction in blood sugar levels and management of diabetic complications are both achieved through the unique active components found in each plant. Isolating, purifying, and identifying bioactive compounds in plants will be the focus of future study. The purpose of this evaluation is to supply the data needed for diabetes management. Our analysis incorporates a comprehensive inventory of plants with anti-diabetic properties culled from the Vietherb database. Improving understanding of the creation of functional foods and drugs to combat diabetes depends on the isolation and identification of bioactive phytochemicals derived from these plants. Traditional herbal remedies for diabetes mellitus were covered in this overview. Traditional medicinal herbs are more commonly employed in rural regions due to the abundance of therapeutic plants found there. For this reason, the prospect of treating diabetes mellitus with chemicals derived from plants that are both easily accessible and do not necessitate the time-consuming pharmaceutical manufacture is quite appealing. Researchers in the fields of pharmacology and therapeutics may find this review helpful as they endeavor to examine antidiabetic medicinal plants for the purpose of developing new antidiabetic medications.

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