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Role of Medicinal Plants in the Management of Diabetes Mellitus: A Review

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Diabetes mellitus is a worse metabolic condition in which level of glucose and lipid increased in blood circulation due to insufficient insulin functionality that may lead to worse the complication like atherosclerosis, dyslipidemia, gangrene, limb amputation, kidney failure, and many more. Furthermore, high concentration of glucose in blood stream can directly produce reactive oxygen species which ultimately more worsen the conditions like dyslipidemia, atherosclerosis etc. This disorder is expected to affect 9.3% of the global population in 2019, increasing to 10.2% by 2030 and increasing 10.9 % by 2045. Medicinal plants are used as medicine to treat many ailments since a long time ago. But now they have been rediscovered with having specific constituents to treat diseases and many more yet to discover. There are so many active phytoconstituents of plants which are being extracted, purified, tested and formulated for patient convenience. In the present review, various plants used to treat diabetes mellitus due to have negligible side effects as compared to allopathic treatment (oral hypoglycemic drugs) are described. Many plants with hypoglycemic effect of many plants have been reported, and the mechanisms of action of these plants with these hypoglycemic behaviors are being examined through in vitro and in vivo studies. Some of these 22 medicinal plants and their active constituents related to antidiabetic activity are discussed in this review.

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1. INTRODUCTION

Diabetes mellitus (DM) is a worse metabolic condition marked by high glucose level in circulation, hyperlipemia, hyperaminoacidemia, and hypoinsulinemia which occurs in a reduction in insulin secretion and operation. It is linked to the progression of minor and major vascular disorders including nephropathy, cerebrovascular disease, neuropathy and cardiovascular diseases. This disease is related to a poorer quality of life as well as an increased risk of death and morbidity. Long-term hyperglycemia plays a major role in onset up to worsening of micro and macrovascular complications [1]. Diabetes is expected to affect 9.3% of the global population (46.3 crore people) in 2019, increasing to 10.2% (57.8 crore) by 2030 and 10.9% (70 crore) by 2045. The incidences are greater in urban areas (10.8%) than rural areas (7.2%) and in high-income countries (10.4%) than low-income countries (7.2%). One-half of those with diabetes (50.1%) are unaware that they have the disease [2]. Insulin and various oral antidiabetic drugs such as sulfonylureas, biguanides, alpha-glucosidase inhibitors, and glinides are the currently available treatment for DM [3]. Materials are costly and hard to acquire in developing countries. Due to the adverse effects which are associated with oral hypoglycemic drugs (therapeutic agents) for the treatment of diabetes mellitus, nowadays herbal medicines are becoming increasingly popular [4]. As a result, conventional herbal remedies extracted from plants are primarily used and play a specific and effective role in the treatment of DM [1]. The hypoglycemic effect of many plants used as anti-diabetic treatments has been confirmed, and the mechanisms of these plants' behavior are being examined. Herbal or plant-based ingredients are high in phenolic content, terpenoids, flavonoids, coumarins and other constituents that help lower blood sugar levels [5].

Traditional therapeutics and alternative remedies derived from traditional medicinal plants are also discussed in this study. Orthodox medicines extracted from widely accessible medicinal plants carry a lot of promise for the development of new anti-diabetic medications. WHO (World Health Organization) has compiled a list of 21,000 medical herbs used around the world [6]. A list of medicinal plants with anti-diabetic and other positive properties, as well as herbal medicines used in diabetes care, has been compiled. The data for this study were retrieved from Web of Science, PubMed, Chemical Abstracts, Science Direct, SciFinder, Dr. Dukes Phytochemical and Ethnobotany, CIMER and InteliHealth.

2. MEDICINAL PLANTS WITH ANTI-DIABETIC POTENTIAL

2.1 *Allium cepa*

Allium cepa is widely known as onion, a spice plant that belongs to the Liliaceae family. It has been used in the prevention of several diseases since earlier civilizations. Bora and Sharma described a comprehensive review on therapeutic potential of *Allium cepa* [7]. Hypoglycemic activity is one the most significant effects in diabetes mellitus, among its many health benefits. Sulphur compounds (S-methyl cysteine) and flavonoids (quercetin) are largely responsible for hypoglycemic activity, which helps in reducing glucose, lipids in circulation, oxidative stress. Onion extracts have been shown to have hypoglycaemic and hypolipidemic impact. In preliminary clinical trials, slices of *Allium cepa* were found to be safe to eat by diabetic patients and to have adequate hypoglycemic function [8]. Silver nanoparticles of *Allium cepa* were also prepared by green synthesis for diabetes treatment. Ultra Violate-visible spectroscopy, Fourier Transform Infrared Spectroscopy and Scanning Electron Microscopy were used to classify the synthesized silver nanoparticles. The particles have higher levels of a-amylase and inhibitory activities of alpha-glucosidase, according to the in vitro reports. Besides that, it had higher antioxidant activity and lower cytotoxicity. The green synthesized silver nanoparticles were reported to be an effective phytomedicine for the treatment of DM [9].

2.2 *Azadirachta indica*

Azadirachta indica, commonly known as neem is a tropical and semi-tropical tree local to the Indian subcontinent. The ethanolic components of plant leaves were studied and found that plant enriched in antioxidant and antidiabetic flavonoid and these were nicotiflorin, rutin, isoquercitrin, quercitrin and astragalin [10]. The use of flower extract enhanced functional recovery,

especiallyin the areas of motor and sensory functions. Malondialdehyde levels were significantly reduced, while superoxide dismutase activity and axon density were significantly increased [11]. Reports suggested that the extract of plant's leaves decrease the level of glucose, cholesterol, and triglycerides in serum but there was an increase in weight of the body, tissue antioxidants, vascular endothelial growth factor contents and total collagen [12].

2.3 *Aegle marmelos* Correa

Aegle marmelos is commonly named as Bael is a fruit tree with fruits belonging to the Rutaceae family, widely grown all over the world. This plant has been getting prominence popularity due to its immense classical medicinal usage. Bael fruit has flavonoids, fibers, terpenoids, carotenoids, coumarins, phenolics and alkaloids [13]. The essential oil of Aegle marmelos also revealed that it has inhibitory activities against many important enzymes which are related to DM and has mild antioxidant ability [14]. In streptozotocin-induced diabetic rats, the effect of a chloroform extract of the plant was observed. Total and specific advanced glycation end products, protein carbonyl formation, and collagen solubility tests were used to assess antiglycation activity *in vitro* [15].

2.4 *Allium sativum*

Allium sativum Linn. (garlic) (family: Alliaceae) is commonly used as a worthwhile ingredient and a common cure for a range of infections and diseases. *Allium sativum* is grown almost everywhere in the world and it seems to have arisen in Asia before expanding to other areas of the globe. *Allium sativum*is a major source of S-binding components, the most significant of which is alliin. *Allium sativum* has a characteristic odour, flavour, and biological and medicinal properties owing to volatiles like allicin and sulphur compounds(lipid-soluble) like diallyl disulphide, ajoene, diallyl trisulphide, diallyl sulphide, and dithiins [16]. Dyslipidemia, a major risk factor for cardiovascular disease, is often linked to diabetes. According to existing data, *Allium sativum* has a good reputation for treating diabetic dyslipidemia. When compared to placebo, monitor, or baseline, the groups treated with garlic had significantly lower serum TG (19 to 36%) and fasting blood glucose (FBG, 18 to 56%). In patients who are suffering from Type 2 DM, mixing garlic with metformin increased glycemic regulation and lipid profile [17].

2.5 *Aloe barbadensis Miller*

Aloe was formerly classified as part of the Liliaceae tribe, but it is now classified as a separate family, Aloaceae. Its origins are in South and East Africa, as well as the Mediterranean. It has over 400 species and can be found all over the world, though it is mainly found in subtropical areas [18].Aloe-emodin, aloin, aloesin and emodin, are the major active constituents of aloe. Aloe–emodin, in particular, has emerged as a potential antimicrobial, antidiabetic, cytotoxic, cardioprotective and also anti-inflammatory and skin protective activity [19].

2.6 *Aloe ferox* L

Aloe ferox L., a perennial succulent commonly named as cape aloe that is belonging to the family Liliaceae and is described as having massive stemless leaves with a narrow edge and spongy dense scimitar leaves. In vitro experiments revealed that leaf of *Aloe ferox*extracts inhibited α-glucosidase but had no effect on α -amylase inhibition. Isoferulic acid-3-glucuronide, oleic acid, and stearic acid were found in *Aloe ferox* leaf powder.Isorhamnetin, cinnamic acid, and were present in *Aloe ferox* water extract. Reports revealed that *Aloe ferox* leaf powder showed promise in preventing weight gain and possibly having a hypoglycemic impact in animals who fed on high lipid diet possibly due to inhibitory activity of α-glucosidase that helped in the regulation of the glucose in circulation [20].Supplementing with *A. ferox* resulted in a modest rise in serum insulin but no improvement in end-point plasma glucose levels. A. ferox, on the other hand, reported that there was a clinically significant improvement in the status of a diabetic person [21].

2.7 *Ficus religiosa*

Ficus religiosa commonly named as sacred fig and peepul is a member of the Moraceae family. There are some countable species of trees found with the largest varieties in Southeast Asia, tropical South America, and Australia [22].It is reported that with the multiple organs of this tree Diabetes and many more diseases have all been treated. The use of *F. religiosa* bark extract showed in a substantial decrease in glucose in circulation in rats, with the effect being more articulated at 50 and 100 mg/kg than at 25 mg/kg. This has also been shown to have a critical anti-lipid peroxidative effect on diabetic

rat's pancreas. The findings suggest that bark aqueous extract has anti-diabetic effects [23].

2.8 *Momordica charantia*

*Momordica charantia (*Family: Cucurbitaceae) is a tropical and subtropical plant, commonly named as bitter gourd or bitter melo, balsam pear or karela [24].It is grown in China, India, East Africa, and Central and South America.*M. charantia* is primarily used for food, the whole plant, especially the seeds and fruit, has long been used as classical medicine for the treatment of DM and its complications [25].Major changes were reported inthe absorption of glucose (61%) and release of adiponectin (75%) that were correlated with the drug mixture water extract and insulin compared to control doses [26].The anti-adipose activity of *M. charantia* extract is contradicted by its inhibitory effect on leptin expression [24].The important chemical constituents of *M. charantia* are: 1) heteropolysaccharides 2) proteins and peptides3)Cucurbitanes and cucurbitacins: terpenoids and saponins;4) flavonoids and phenolic extracts; 5) essential oils, sterols, amino acids and fatty acids. Water makes up 93.2 percent of a fruit's dry weight, while protein and lipids make up 18.02 and 0.76 percent, respectively [27]. Bitterness in bitter-gourd is caused by triterpene glycosides, specifically momordicoside K and momordicoside L. *M. charantia* juice showed significant antidiabetic capacity [28].

2.9 *Lagenaria siceraria*

The fruit of the bottle gourd (*Lagenaria siceraria*) belongs to the cucurbitaceae family [29].Bottle gourd has been reported as an anti-diabetic and anti-cancer agent in some trials [30]. Administration of pulp powder showed in a substantial low ($p<0.01$) in triglyceride and level of VLDL-c, as well as a significant rise ($p<0.01$) in HDL-c. These findings indicate that bottle gourd pulp powder (DBPP) has therapeutic potential and may show improved effects if ingested for a longer period of time [29]. Saponins and flavonoids are reported in Lagenaria siceraria fruit extract. Saponin has the capability to bind with cholesterol in the lumen of the intestine, preventing it from being absorbed, and it also boosts lipoprotein lipase function [31]. The fruit extract of Lagenaria siceraria is sometimes used as potent Nutraceutical having important effects like lowering the lipid level in circulation and also showed antioxidant effects, and can be useful as a symptomatic measure for people who are at risk of cardiovascular disease [32]. Fruits of L. siceraria possesses outstanding antioxidant effect and alpha-amylase inhibitory effect [33].

2.10 *Ocimum sanctum*

Ocimum sanctum also known as Holy Basil, is a Southeast Asian Ayurvedic herb with a long history of cultural use [34]. In O. sanctum, many chemical compounds are reported. The major compounds include eugenol methyl ether, caryophyllene , germacrene D , -elemene , and copaene . The key constituent in O. sanctum is eugenol methyl ether [35].Methanol extract and its effective fractions (ethyl acetate/butanol) have been shown antidiabetic activity due to polyphenolic compounds [36,37].

2.11 *Eugenia jambolana*

It is commonly known as black plum or Jamun belonging to Myrtaceae family. It is a large evergreen tree found throughout the Indian subcontinent [38].The seed of *Eugenia jambolana* was reported to contain a variety of biologically active chemical constituents, including saponin, flavonoids, triteripenoids, gallic acid, glycosides and ellagic acid [39]. E. jambolana has been reported the antidiabetic and anti-oxidant propertyagainst streptozotocin-induced diabetic rats [40]. In experimental, diabetes induced rats gave treatment with ethanolic extract of kernel at a mentioned dose per body weight substantially improved glucose, urea and cholesterol in circulation that boosted tolerance of glucose and whole protein and liver glycogen levels [41].

2.12 *Pterocarpus marsupium*

The *Pterocarpus marsupium*, also known as the Indian Kino Tree or Vijyasara, Bija, belongs to the family of Fabaceae and is found throughout India [42]. Pterostilbene, (-) epicatechin, pterosupin, marsupin, tannins, and other bioactive principles found in the heart wood of this woody tree are responsible for its anti-diabetic function [43]. The results of an experimental study design for diabetic neuropathy screening the animals revealed that diabetic animals had neuroprotective behaviour. A study also reported that P. Marsupium pretreatment led to substantial lowering the level of glucose [44].

2.13 *Trigonella foenum*

It is a dicotyledonous plant with an annual harvest, commonly known as fenugreek and Methi in hindi belonging to the Papilionaceae subfamily of the Fabaceae family [45]. It was found that fenugreek extract causes phosphorylation of insulin receptors present in adipose tissues [46]. S. Sharma and V. Mishra et al were found the protective effect on the DNA damage by removing free radicals that cause oxidative stress [47]. Trigonella foenum seeds were high in saponins, notably dioscin or diosgenin, which had been isolated and screened for α-glucosidase inhibitory activity in vitro, confirming natural anti-diabetic agents with minor toxicity [48]. (9Z,12Z)-N-((3R,4R,5S)-4,5-Dimethyl-2-oxotetrahydrofur-3-yl) octadeca-9,12-dienamide (N55) , a positive GLP-1 signaling modulator obtained from fenugreek seeds was reported as effective for treatment of diabetes [49].

2.14 *Gymnema sylvestre*

Gymnema sylvestre, commonly known as gurmar, a vulnerable and slow-growing plant belongs to Apocynaceae family and has historically been used to treat a number of diseases. It is found in India, Africa, Australia, and China as a wild herb [50].The main chemical constituents of *G.sylvestre*are gymnemic acids, which are triterpenoid saponins and are believed to have anti-diabetic properties due to their biological activity [51]. Gymnemic acids possess anti-sweetener, anti-diabetic, and anti-inflammatory potential. Gymnemic acid molecules have an atomic structure as molecules of glucose. These molecules bind to taste binding site, blocking sugar molecules in food from inducing them and thereby reducing sugar cravings [52]. Further studies was shown that triterpene glycoside inhibit pancreatic amylase, glucosidase, sucrase, and maltase activity which were derived from *Gymnema sylvestre* [53].

2.15 *Carica papaya*

Carica papaya is a small herbaceous plant in the Caricaceae family. This plant is commonly grown for its edible, tasty fruit, which has a high nutritious value and is easy to digest [54]. As the diabetes disrupted the integrity of working heart, *Carica papaya* help to restore the myocardial contractility and prevent the cell death induced by diabetes [55]. Ethanolic extract of *C. papaya* leaf reported to havehighest concentrations of tannins and steroids and both steroids and quinones were detected in the largest concentrations in chloroform extract [56]. It was also reported thatthe aqueous extract of *C. papaya* was found to retain body weight by activating the few residual β-cells, resulting in insulin release and decreased liver glycogen content [54].

2.16 *Costus igneus*

Costus igneus, commonly name insulin plant, Fiery Costus or Spiral Flag, is a herbaceous plant belongs to the family of Costaceae. It is grown in India to treat DM [57]. Three main proteins present in this plant are; Aglycin, Viglycin and ILP(insulin like protein) that directly stimulate IRs(Insulin Receptor)and promote secondary stimuli until all glucose uptake are done [58]. ILP act via insulin signaling pathway was further demonstrated by Mansi R. Hardikar et al through studied mechanism of action by experimenting on L6 myotubes(immortalized rat skeletal myoblast cell line) [59]. A stable and effective silver coated nanparticles were also prepared and characterized for oral drug delivery [60]. It was also reported that Costus igneus-ZnO nanoparticles were more effective than simple leaf extract of *C. igneus* [61].

2.17 *Cinnamomum zeylanicum*

This traditional medicine is obtained from bark of trees belonging to the family of Lauraceae and also believed that plant has many health benefits such as reducing triglyceride, LDL, total cholesterol [62]. Cinnamon extracts showed inhibitory effect on metabolic enzymes like α-amylase and α-glucosidasein rat pancreatic tissues [63]. Chemical profiling of aq. Extract showed total phenolic content and proantocynidin content in which cinnamaldehyde and cinnamic acid were main chemical constituent having alpha-glucosidase inhibitory and alpha amylase inhibitory activity [64]. Phenolic extract of plant is responsible for antioxidant and free radical scavenging activity also [65].

2.18 *Zingiber officinale*

It consists of fresh and dried roots of plant belongs to family of zingiberacae, cultivated in india, South East Asia, Mexico and other parts of the world [66]. Zingerone was important chemical constituent and also found to be more antioxidant than BHA [67]. Ginger also showed the inhibitory

action against alpha glucosidase enzyme which is helpful to treat type 2 DM [68]. Methanolic extract of plant rhizomes found to be effective in weight management, reduction in higher lipid content and glucose level [69].In vivo studies suggested that daily consumption of 1.2 g of ginger for 90 days effectively treat DM type 2 patients by decreasing blood sugar, total cholesterol and LDL [70].

2.19 *Berberis aristata*

It is spinous herb commonly known as Daruhaldi, Darhald, chitra or Indian beri beri, belonging to the family Berberidaceae. It is widely distributed throughout the Himalayan region [71]. Root bark of the plant contained protoberberine alkaloid like oxyberberine, karachine, berberine and berbamine & flavor contained polyphenolic flavonoids like rutin [72]. Meta-analysis studies showed that plant has the acitivity to reduce LDL, total cholesterol and glucose and also have the effect to increase the level of HDL [73].

2.20 *Rubia cordifolia*

It is herbaceous climbing plant with thin red bark, commonly known as majith, belonging to the family of Rubiaceae [74]. Further investigations showed that certain solvent fractions like ethyl acetate and and n- butanol fractions have significant antidiabetic effect [75]. Tripathi YB et al found Rubiadin, dihydroxy anthraquinone, is main active chemical constituent has the antioxidant activity. Aq. root extract was found to have antidiabetic activity with lowering serum triglyceride level effect [76].

2.21 *Jasminum grandiflorum*

It is the medicinal plant commonly known as Cameli, Jati or Spanish jasmine, belonging to family Oleaceae (olive family) used to treat many ailments [77]. Phenolic compounds were active chemical constituents of dried flower bud has the antioxidant activity [78]. Ethanolic extract of flower has diabetic wound healing capacity by impairing angiogenesis. Further it has maximum wound breaking strength through maximizing collagen synthesis, that also showed antioxidant activity [79]. In vivo and *in vitro* studies showed an antioxidant and anti-inflammatory effect of methanolic extract of leaves [80].

2.22 *Mangifera indica*

Mangifera indica, commonly known as Mango, belongs to the family Anacardiaceae. Traditionally, parts of plants used to treat many ailments including diabetes type 2 to some extent [81].there are so many active chemical constituents including polyphenols, phenolic acid and various flavonoids are reported as free radical scavenger activity [82]. Aq. Extract of leaves of plant has significant effect to reduce the high glucose level, when fed simultaneously only, it suggested that it may be due to hindrance in absorption of glucose in intestine [83]. It has been also reported that extract from acid hydrolysis has maximum antioxidant property as compared to the ethanolic extract [84].

3. DISCUSSION

The present review emphasized medicinal plants which are very effective to treat Diabetes mellitus. Diabetes is increasing sharply to crisis point (also with obesity), with disastrous consequences including accelerated atherosclerosis, gangrene and limb amputation, kidney failure, neuropathy, and blindness. Adult brains need glucose as a supply of energy, and blood glucose monitoring represents the need to retain sufficient fuel supplies in the face of reduced food consumption and fluctuating metabolic demands. Extra calories are stored in the form of glycogen or fat. During fasting, the accumulated energy must be metabolized in a controlled way. Insulin is the most powerful regulatory hormone. Excess calories are stored as glycogen or fat. During fasting, these energies stored needs to be metabolized in a regulated manner. Insulin induction is stimulated by elevated blood glucose levels. Insulin release is influenced by the amount of glucose consumed. Insulin secretion is more efficient when glucose is given orally rather than intravenously. In diabetics, glucose has a lower ability to secrete insulin. The prevalent b cell is found in the center of individual islet, which is covered by a mantle of A cells bestrew D and PP cells. B cells also secrete islet amyloid polypeptide or amylin, a peptide that delays gastric emptying and inhibits insulin by inducing glycogen breakdown in striated muscle and C peptide. Glucagon works in opposition to insulin, increasing blood glucose and stimulating muscle protein breakdown. Insulin and glucagon synthesis is inhibited by somatostatin. It's widely spread outside the pancreas, and it's also released from the hypothalamus, inhibiting pituitary gland growth hormone release.

In diabetic patient, there is an increment in mobilization of fatty acid i.e. lipolysis from

adipose tissues to blood circulation that ultimately cause the high level of ketone bodies in circulation. As this fatty acids have both structural and functional requirements in every cell but in excess amount it may lead to disease that is treated by some medicinal plants like *Trigonella foenum-graecum* [48], *Eugenia jambolana* [39],*Lagenaria Siceraria* [32], *Caricapapaya* [54].

In DM, high concentration of glucose may directly cause can directlymake reactive oxygen species that lead to disparity among enzymatic and non-enzymatic antioxidant protection and also intensify the metabolism of glucose by a way of polyol (sorbitol) pathway as a result in increased production of reactive oxygen species (ROS). ROS can trigger low-density lipoprotein (LDL) oxidation, which results in the formation of ox-LDL, that is not identified by the LDL receptor but can also be grabbed by scavenger receptors in macrophages, contributing to foam cell formation, atherosclerotic plaques and complications of DM [85]. Some reports suggest that some plants like *Allium cepa* [9], *Azadirachta indica* [10] and *Aegle marmelos* [14] having antioxidant ability to treat the complications of DM.

4. CONCLUSION

The study highlights the efficacy of "herbal medicine" which is an ancient tradition, used in some parts of India. This ancient concept should be carefully evaluated in the light of modern medical science and can be utilized partially if found suitable. Many medicinal plants are reported to have anti-diabetic activity but many of them have don't have much data regarding mechanism of action and clinical trial, therefore it is suggested that a lot of scope is there on medicinal plants for finding mechanism of action and further clinical trial for benefits of human being.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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