DIABETES MELLITUS

A Review on the Medicinal Plants and Diabetes Mellitus

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ABSTRACT

Background: **Diabetes mellitus is a group of metabolic disorders sharing the common underlying feature of hyperglycemia. In developed countries, use of medicinal plants has recently increased as scientific evidence about their effectiveness has become broadly available. This article is to review the efficacy and safety of medicinal plants commonly used for diabetes mellitus.**

Materials and Methods: **We carried out a literature search in several electronic data bases such as: Pubmed, Pubmed Central, Google, Google Scholar, Scopus and Medline from 2000 to 2020 to acquire the status of information concerning this concept.**

Results: **Medicinal plants have long been used in traditional systems of medicine for diabetes. Some recent reports on the medicinal plant with anti-diabetic effects have provided evidence for possible mechanisms of action. Nonetheless, the majority of investigators only speculated on a wide range of possible mechanisms or simply demonstrated an antihyperglycemic effect for the crude plant extracts or the isolated compounds of interest.**

Conclusion: **This review articles hope that this will be beneficial as a starting point to consider the discussed products for further investigations to identify and develop new medicinal remedies with potential alternative or complementary use in controlling diabetes.**

KEY WORDS

medicinal plant, diabetes mellitus, hyperglycaemia, *Paederia foetida*

INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic disorders sharing the common underlying feature of hyperglycemia. DM is resulting from insulin deficiency, characterized by abnormal increase in the blood sugar level, altered metabolism of carbohydrates, protein and lipids, and an increased risk of vascular complications[1,2]. Uncontrolled hepatic glucose output and reduced uptake of glucose by skeletal muscle with reduced glycogen synthesis leads to hyperglycemia[3]. Along with hyperglycemia, diabetes is associated with micro and macro-vascular complications, which are the major causes of morbidity and death in diabetic subjects.

Diabetes is one of the major health and development challenges of the 21st century. According to the International Diabetes Federation, there are currently 371 million people living with diabetes and another 28 million people are at high risk of developing the disease. Factors like aging, physical inactivity, obesity, smoking, history of gestational diabetes, increase population and urbanization can increase the prevalence of diabetes worldwide. The prevalence was increasing from 9.1% in the year of 2014 to 13.9% in the year of 2030, and 17.9% in the year of 2060[4].

The currently available antidiabetic agents include sulfonylureas, biguanides, thiazolidinediones and alpha glucosidase inhibitors and are widely used to control the hyperglycemia. These drugs fail significantly to alter the course of diabetic complications. They have limited use because of undesirable pathological conditions and high rates of secondary failure. Thus, it is essential to look for more effective antidiabetic agents with fewer side effects. Apart from conventional allopathic medicines, traditional/alternative therapy plays a significant role in treating DM.

Traditional medicinal plants having antidiabetic properties can be a useful source for the development of safer and effective oral hypoglycemic agents. More than 350 traditional plants are used in the treatment of diabetes mellitus, which have been recorded. Only a small number of these have received scientific and medical evaluation to assess their efficacy. However, plant remedies are the mainstream of treatment in underdeveloped regions. This review focuses on diabetes mellitus and the role of plants in the treatment of diabetes mellitus.

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MATERIALS AND METHODS

We conducted our literature search in several electronic data bases such as: Pubmed, Pubmed Central, Google, Google Scholar, Scopus and Medline from 2000 to 2020 to obtain the current status of information regarding our concept using such keywords as: obesity, type of obesity, comorbidities, cardiovascular disease and others. We got the findings from these data bases, which are hereby reported in this review.

Benefits of study

Different groups of antidiabetic medications are available in the market like sulphonylureas, insulin analogue, biguanides and α-glucosidase inhibitors, etc with different mechanisms for regulation of blood glucose level. However, these drugs may have a number of side effects. Whereas, medicinal herbs have negligible side effects, more effective and affordable for treatment of diseasess, this motivates the researchers to take interest in herbal medicine. In Malaysia and the rest of the world, the discovery of the antidiabetic herbal drugs could be beneficial due to the negligible efficacy and safety concerns of antidiabetic drugs for a lot of people[5].

Hence, the present review of studies was carried out to collect information on commonly available medicinal plants to treat diabetes. This review is focused on the herbal remedies that may have a role in prevention or treatment of diabetes, including the mechanism by which these herbs regulate the level of blood sugar of diabetic patients.

Medicinal plant and different stages of diabetes

Medicinal herbs or plants may have a role to manage diabetes in different stages of disease via inhibiting the enzyme that takes part in digestion of carbohydrate, controlling the secretion of insulin, level of blood sugar, oxidative stress as well as resistance of insulin and helps in regulation of glycemic index. However, there is a need to know the history of the diabetic patient and the therapeutic usefulness of herb for suitable management of the diabetics[6].

Role of medicinal herbs in digestion of carbohydrate through via inhibition of enzyme

It is proposed that inhibition of alpha-glucosidase and a-amylase may influence the gastrointestinal absorption and metabolic effects of carbohydrate that may help in the treatment of postprandial hyperglycemia[7]. In humans, the main action of alpha-glucosidase is to help in digestion of dietary starches and carbohydrates and to form glucose which is absorbed via the intestine and results in an increase in the level of blood glucose. The inhibitor of alpha-glucosidase competitively inhibits the activity of intestinal alpha-glucosidase. This inhibition reduced the absorption of glucose and increased the time of digestion[8].

Pancrease releases α-amylase in response to food containing carbohydrate. This enzyme converts carbohydrates into monosaccharides in GIT. The monosaccharide is further acted by α-glucosidases and converts into glucose which after absorption enters blood circulation and increases the level of blood glucose. It is therefore necessary to use the inhibitor of these two enzymes for suppressing the digestion of carbohydrate and reduce the uptake of glucose and the level of circulating glucose[9,10]. They are proposed that herbal plants may contain bioactive compounds or metabolites like alkaloids, flavonoids, phenols, tannin etc that can affect the activity of these enzymes[11].

Chromatographic separation of extraction of *Phyllanthus urinaria* leaves give gallic acid, corilagin and macatannin B that performed inhibitory action agains alpha amylase of pancrease[12]. Conversely phytochemical investigation proved that leaf extract of *Ocimum basilicum* (basil) contains flavonoids, saponins, cardiac glycosides, tannins, and steroids. The flavonoid and polyphenol content of leaf extract of the herbshowed its inhibition against the activity intestinal sucrose, maltase, α-amylase pancrease[13].

Corchorus olitorius leaves have large number of flavonoids and polyphenolic compounds which showed the inhibitory acitivity against α-glucosidase and of α-amylase and used to manage hyperglycemia and complication of diabetes via oxidative stress[14]. On the other hand, *Glycine max (L.) Merrill* or soybean contain large number of polyphenolic compounds like isoflavones. Studies showed that phenolic extracts of soybean inhibit the activity of enzymesα-amylase and α-glucosidase via delaying the absorption of intestinal glucose[15].

It is clear from studies that the herbal medicines may be a natural choice to conventional α-glucosidase and α-amylase inhibitors used in the treatment of diabetes and thus control postprandial hyperglycemia by impeding the absorption of carbohydrate.

Antidiabetic and Antioxidant Effects and of Medicinal Plants:

There is a direct link between oxidative stress and diabetes mellitus. Chronic hyperglycemia encourages auto-oxidation of glucose to produce ROS or reactive oxygen species and improper states of tissue that imbalance the creation of ROS and protective mechanisms of cells which may results oxidative stress, functional change, destruction of cell and at the end there is tissue damage including the tissur of pancrease. In patients with diabetes, oxidative stress may be a reason of defect in insulin secretion, insulin resistance, dysfunction of β-cell, altered glucose tolerance as well as vascular complications. It is stated that oxidative stress may be the reason of dysregulation of adipocytokine and dysregulation and suppress the signals of insulin and causing insulin resistance and may take part in the pathogenesis of T2DM[16].

The antioxidant activity of herbs, vegetables and fruits may be from polyphenol compounds such as flavonoids and phenolic acids. It is proposed that these compounds interact with free radical, their scavenging function results in dislocation of added electron over the phenolic antioxidant and stable the timbre effect of aromatic ring nucleus, which stops the continuance of the chain reaction of free radicle. Furthermore, the fundamental mechanisms of antioxidants of herb are to target signal transduction pathways, via antioxidant response elements like transcription system[17].

Paederia foetida is an edible plant that has antioxidant and antidiabetic activities in an *in vitro* evaluation. *Paederia foetida* is found in Asian countries used to treat many diseases, especially diabetes. The powdered form of twigs of Paederia foetida were extracted using chloroform, hexane, and methanol solvents independently. Twig extracts were applied on gas chromatography-mass spectrometry and resultant elute revealed 12 bioactive compounds, namely, dl-α-tocopherol, 2-hexyl-1-decanol, n-hexadecanoic acid, stigmastanol etc. Study found that Stigmasterol and n-hexadecanoic acid are metabolites of *P. Foetida* which may bind with α-glucosidase and α-amylase and form α-amylase-stigmasterol and α-glucosidase-n-hexadecanoic acid complexes with the inhibitory concentration (IC50) of 600.3 and 1349.01 μg/mL respectively. *P. foetida* supplementation or metformin reversed the clinical manifestation of Type 2 diabetes mellitus, but *P. foetida* alleviated biochemical alteration of Type 2 diabetes mellitus better than metformin[18].

The antioxidant activity of fresh *Allium sativum L.* is due to organosulphur compounds. It is found that extract of fresh garlic allows to stand for a period of 20 months produces extract of aged garlic extract having organosulphur compound which is stable and water solvable and helps to prevent oxidative injury by scavenging of free radicals[19]. Likewise, animal studies have confirmed that *Thymus marschallianus* can decrease microvascular complication of diabetics by decreasing oxidative stress and reinstates antioxidant ability[20].

The ethanolic extract of Aloe vera gel powder presented maximum flavonoid, polyphenol, and DPPH radical scavenging activity in diabetic rats. Hence, gel powder of Aloe vera may be preventoxidative stress in diabetic rats[21]. Correspondingly, the seed extract of Trigonella foenum-graecum at a dose of 100 mg/kg is given for 15 days to a diabetic animal. The study observed that animals showed hypoglycemic effect and improved the impair levels of malondialdehyde and hydrogen peroxide along with the activities of glutathione peroxidase, superoxide dismutase and catalase as well as transcription of these genes in the liver and the brain of diabetic rats[22,23].

The majority of the diabetic patients are suffering from T2DM due to the development of resistance to the endogenous insulin by the cells and tissues of the body. Resistance to the cells can be reverted to sensitivity using medicinal herbs[24].

The uses of hydroalcoholic extract leaves of Urtica dioica exhibit hypoglycaemic effects, decrease values of serum insulin, and reduce index of insulin resistance. The study concluded that insulin to the cells and tissues has been raised by the leaves extract of herb as proved by reducing levels of blood glucose[25]. As wise the ethanolic extract of leaves of Anacardium occidentale with a dose of 100 mg/kg in diabetic rats exhibited noteworthy reductions in levels of fasting blood sugar, serum insulin level and index of fasting insulin resistnace[26].

Oil extrac of Allium sativum exhibited to improve glucose tolerance and insulin secretion, expression of GLUT4 and gluconeogenesis in diabetic rats. Aqueous extract of garlic (500 mg/kg) was given to diabetic rats. After three of usage of extact ther is a significant increase in the level of circulating antioxidant with reduced values of blood glucose[27,28].

On the other hand, the ethanolic extract of bark of Symplocos cochinchinesis bark (250 mg/kg and 500 mg kg daily) notably reduced the level of blood glucose and insulin resistance and improve the insulin sensitivity of the cells in diabetic rats Similarly, 200 mg/kg and 400 mg/kg/day of ethanolic extract of root of Helicterus angustifolia root was found to marked reduction in the level of blood glucose, circulating insulin and insulin resistance in diabetic animal[29].

Besides the 100, 200 mg/kg and 400 mg/kg extract of Pleurotus ostreatus. The study observed that aqueous extract of P.ostreatus decreases the level of blood sugaer as well as insulin resistance in diabetic rats. Meanwhile the sensitivity index for insulin related with function of beta cell was higher in experimental animal[30]. On the other hand, supplementation of resveratrol in a dose 100 to 150 mg/day showed a significant antidiabetic effect in an experimental model by Enhancing vasodilator function and may help to lessen insulin resistance. The study also found that it may stimulate the uptake of glucose, transport of glucoe in cells. The study also showed this may increase sensitivy of insulin with decrease insulin resistance[31].

Recently, research outcomes have discovered that chemicals present in medicinal plants can treat diabetes mellitus via various mechanisms like insulin signalling regulation that induce protein and gene expression; the elevation of secretion of insulin; the upgrading of function of β-cell; and the re-absorption of glucose in experimental animals[32].

Oil of Cuminum cyminum used at a dose of 25 μg/mL for 40- 50 days increases the secretion of insulin 3-4 folds. Additionally, it can protect beta cells with no side effects, and it may be used in the treatment of diabetes[33]. Likewise ethanolic extract of Aloe vera leaf gel, at a dose of 300 mg/kg found to raise the level of insulin via regenerated beta-cells of pancrease[34].

The extracts of bark of *Chloroxylon swietenia* bark increase the level of circulating insulin in diabetic animals and control the level of blood sugar[35]. Similarly, ethyl acetate leaves extract of *Forshythia suspense* in diabetic animal significantly raise the level of circulating insulin as well reduce the level of blood glucose[36].

It is therefore said that medicinal herbs play an important role in improvement of diabeticdisordervia amending the no of β-cells of pancrease, increasing the secretionof insulin and shield the beta-cell from obliteration, however, further research is needed to find exact mode of action of these plants on secretion of insulin[37].

Various herbs which are studied have multiple mode of antidiabetic actions including renewal of beta cells of pancrease, increases sensitivity of insulin, enhance utilization of glucose and antioxidant ability[38].

Garlic extract in a daily dose of 0.5 to 1.5 gma have many biological functions and may be useful for human due to its hypoglycaemic, antioxidant, antimutagenic, immunomodulatory and other effects[39]. Motivate insulin secretion from beta cells, sparing effect of of insulin, increase the consumption of glucose, antioxidant, and anti-inflammatory[40].

In addition, the seed of fenugreek has multiple antidiabetic effects due to its alkaloid. These may include its glycemic control via glycogenolysis, proteolysis, and lipolysis. Hypoglycemic effect of alkaloid of herb is due to its antioxidant effect and modulation of secretion of insulin. Besides delayed absorption of glucose, regeneration of β cells of pancrease, enhancement of insulin secretion via the action of fenugreek to control hyperglycema. Besides, the herb extract of fenugreek will increase the uptake of glucose by muscles and adiposetissue and improve the glucose utilization via increasing the activity of glucose-6-phosphate dehydrogenase[41].

Coptis chinensis showed antidiabetic effect via rebirth of cell size of beta cell and increase the secretion of insulin, increase the GLUT 4 expression, and enhance the uptake of glucose in adipose and muscle tissue. It is proved that downregulation of gene of liver that provide antidiabetic effect of *C. chinensis* via the process of oxidation of glucose, glucogenesis and glycogenolysis[42].

The active ingredients of *Catharanthus roseus:* vindoline, catharanthine and tetrahydroalstonine showed hypoglycaemic effect via increase glucose uptake, increase activity of glucokinase to facilitate the process of phosphorylation of glucose and posses glycemic control. It also increases the activity of maladehydrogenase and involve in citric acid cycle and helps in utilization of glucose by the cells of liver. It shows antioxidant effect via increase the level of reduced form of glutathione. On the other hand, vindoline in *C. roseus* inhibit the activity of tyrosine phosphatase which imitates the function of insulin and its sensitivity. Besides, it inhibits the activity of α-glucosidase and inturn inhibit the digestion of carbohydrates[43].

It is therefore found that multimodal mode of action of herbal extract effectively control the diabetes by reducing the level of blood glucose, increase the number of β-cells, inhibit glucose absorption, and give antioxidant effect against reactive oxygen species etc is mainly duet to the presence of diverse ingredients present in the extract of herbs[44]. Conversely the aqueous extract of bark of *A. africana* exhibit antihyperglycemic abilities and prevent many complications of diabetes[45]. Whereas the leaves extract of *Urtica dioica* can secrete insulin, inhibit the activity of alpha-glucosidase and act as anti-hyperglycemic agent for treatment of diabetes[46].

The active ingredients of *Forsythia suspense* are phillyrin, forsythia ester A, and rosin-*β*-D-furan. The extract of plant showed that due to thes ingredient there is an improvement of uptake of glucose in adipocytes under insulin resistance. Study observed that phillyrin significantly increase the consumption of glucose and improve expression of glucose transporter and insulin resistnace[47]. Conversly the hexane treated extract of *Symplocos cochinchinensis* leaves showed hypoglycemic effect in rats. It improves the sensitivity of insulin and reduction in serum insulin, lipod profile and raise glycogen of liver in diabetic animal[48]. Whereas ethanol treated leaf extract of *Coccinia grandis* caused marked reduction in blood glucose and increase the level of serum insulin. It also reduces oxidative stress and restore the function of beta cells of pancreae in diabetic animal[49,50].

CONCLUSION

Use of medicinal plants is continued in both ancient times and present society for the avoidance, comfort and management of diabetes. Various medicinal plants display antidiabetic function by controlling the secretion of insulin, sensitivity of insulin to the cells, glucose disruption, and help in controlling the glycemic index of diabetics. Medicinal plants are chosen as options for managing the disease including diabetes by patients due to their affordability, and negligible side effects. Thus, laboratory research is carried out via clinical trials and marketed preparation or formulation.

However, the rapid development of the medicinal plants in managing diabetes immediately necessitates the authenticate protocol of testing to assess the quality and quantity of bioactive compounds of medicinal plants, that will ultimately test a human being and certified by the authorities of the state for the efficacy and safety of the herbal preparation. This review articles hope that this will be beneficial as a starting point to consider the discussed products for further investigations to identify and develop new medicinal remedies with potential alternative or complementary use in controlling diabetes.

DISCLOSURE STATEMENT

No potential conflict of interest was reported by the authors

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