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. Uncontrolled hepatic glucose output and reduced uptake of glucose by skeletal muscle with reduced glycogen synthesis leads to hyperglycemia. 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.

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.

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
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 diseases, 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.

Hence, a 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 diabetic.

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

It is proposed that inhibition of alpha-glucosidase and α-amylase may influence the gastrointestinal absorption and metabolic effects of carbohydrate that may help in the treatment of postprandial hyperglycemia. 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.

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. They are proposed that herbal plants may contain bioactive compounds or metabolites like alkaldoids, flavonoids, phenols, tannin etc that can affect the activity of these enzymes.

Chromatographic separation of extraction of Phyllanthus urinaria leaves give gallic acid, corilagin and macatamin B that performed inhibitory action against α-amylase of pancreas. 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 herb showed its inhibition against the activity intestinal sucrase, maltase, α-amylase and catalase.

Corchorus olitorius leaves have large number of flavonoids and polyphenolic compounds which showed the inhibitory activity against α-glucosidase and of α-amylase and used to manage hyperglycemia and complication of diabetes via oxidative stress. 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 enzyneso-amylase and α-glucosidase via delaying the absorption of intestinal glucose.

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 membrane, the end there is tissue damage including the tissue of pancreas. 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.

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 disposing damage 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 factors.

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. Twigs extracts were applied on gas chromatography-mass spectrometry and resultant data revealed 12 bioactive compounds, namely, dl-α-tocopherol, 2-hexyl-1-decanol, n-hexadecanoic acid, stigmastanol etc. Study found that Stigmastanol 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 which could increase the inhibitory activity using medicinal herbs.

Phyllanthus urinaria exhibits antioxidant effect and suppressed the oxidative stress and reinstates antioxidant ability. The ethanolic extract of Aloe vera gel powder exhibited maximum flavonoid, polyphenol, and DPPH radical scavenging activity in diabetic rats. Hence, gel powder of Aloe vera may be preventative oxidative stress in diabetic rats. Correspondingly, the seed extract of Trigonella foetida extracts of Aloe vera was used to treat oxidative stress and diabetes. The extract of Aloe vera gel powder prevented oxidative stress and recovered the levels of blood glucose. The extract of Aloe vera gel powder prevented oxidative stress and recovered the levels of blood glucose in diabetic rats.

The antioxidant activity of fresh Allium sativum 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. Likewise, animal studies have confirmed that Thymus marschallianus can decrease microvascular complication of diabetes by decreasing oxidative stress and reinstates antioxidant ability.

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The antioxidant activity of fresh Allium sativum 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. 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.

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. 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 resistance.

Oil extract of Allium sativum exhibited to improve glucose tolerance and insulin secretion, expression of GLUT4 and gluconeogenesis in diabetic mice. Aqueous extract of garlic (500 mg/kg) was given to diabetic rats. After three of usage of extract ther is a significant increase in the level of circulating antioxidant with reduced values of blood glucose.
On the other hand, the ethanolic extract of bark of Symplosocochinchinensis 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 Helicertas augustofolia root was found to markedly increase the level of blood glucose, circulating insulin and insulin resistance in diabetic animal38.

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 sugar as well as insulin resistance in diabetic rats. Meanwhile, the sensitivity index for insulin related with function of beta-cell was higher in experimental animal40. 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 glucose in cells. The study also showed this may increase sensitivity of insulin with decrease insulin resistance40.

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 animals30.

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 diabetes41. 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 pancreas36.

The extracts of bark of Chloroxylon swietenia bark increase the level of circulating insulin in diabetic animals and control the level of blood sugar43. Similarly, ethyl acetate leaves extract of Forsythia suspensa in diabetic animal significantly raise the level of circulating insulin as well reduce the level of blood glucose43.

It is therefore said that medicinal herbs play an important role in improvement of diabetics disorders amending the no of β-cells of pancreas, increasing the secretion of 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 insulin43.

Various herbs which are studied have multiple mode of antidiabetic actions including renewal of beta cells of pancreas, increases sensitivitiy of insulin, enhance utilization of glucose and antioxidant ability43.

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, anti-oxidant, anti-inflammatory, immunomodulatory and other effects43. Motivate insulin secretion from beta cells, sparing effect of insulin, increase the consumption of glucose, antioxidant, and anti-inflammatory43.

In addition, the seed of fenugreek has multiple antidiabetic effects due to its alkaidal. These may include its glycemic control via glycogenesis, antioxidant, and anti-inflammatory43. The active ingredients of Catharanthus roseus: vindoline, catharanthine and tetrahydrodrolastine showed hypoglycaemic effect via increase glycolysis, proteolysis, and lipolysis. Hypoglycaemic 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 pancreas, enhancement of insulin secretion via the action of the β-cells of pancreas44. The herb extract of fenugreek will increase the uptake of glucose by muscles and adipose tissue and improve the glucose utilization via increasing the activity of glucose-6-phosphate dehydrogenase45.

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 provide to induce antidiabetic effect of C. chinensis via the process of oxidation of glucose, glucogenesis and glycogenolysis45.

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Catharanthus roseus shows antioxidant effect via increase of activity of α-glucosidase and inhibit the digestion of carbohydrates46. 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 due to the presence of diverse ingredients present in the extract of herbs46. Conversely the aqueous extract of bark of A. africana exhibit anti-atherogenic abilities and prevent many complications of diabetes43. Whereas the leaves extract of Urtica dioica can secretre insulin, inhibit the activity of alpha-glucosidase and act as anti-atherogenic agent for treatment of diabetes43.

The active ingredients of Forsythia suspensa are phyllrin, forsythia ester A, and rosin-β-D-furan. The extract of plant showed that due to the presence of ingredient there is an improvement of uptake of glucose in adipocytes under insulin resistance. Study observed that phyllrin significantly increase the consumption of glucose and improve expression of glucose transporter and insulin resistance50. Conversely the hexane treated extract of Symplosocochinchinensis leaves showed hypoglycaemic effect in rats. It improves the sensitivity of insulin and reduction in serum insulin, lipid profile and raise glycogen of liver in diabetic animal50. 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 pancreas in diabetic animals50.

**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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