World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Available online at: http://www.wjpsonline.org/
Review Article

Medicinal plants with antidiabetic activity - A review of herbal medicine

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Received: 19-09-2018 / Revised Accepted: 27-10-2018 / Published: 02-11-2018

ABSTRACT

Diabetes mellitus is one of the most common non-communicable diseases globally. It is the fourth leading causes of death in the most developed countries and there in substantial evendiced that it in epidemic in many developing and newly industrialized nations. This determines a serious threat to met within 21st century. Since ancient time plants have been exemplary source of medicine. Ayurveda and other Indian literature mentioned the used of plants in treatment of various ailments. Out of an estimated 250 000 higher plants, less than 1% have been screened pharmacologically and very few regard to diabetes mellitus. Medical plants play an important role in the management of diabetes mellitus especially in developing countries where resources are meager. This review presents the profiles of plants with hypoglycemic properties. The profiles presented include information about the scientific name, family, the degree of hypoglycemic activity and the active agents. The large number of plants described in this review clearly demonstrated the importance of herbal plants in the treatment of diabetes. It also shows the effort to isolate new potential antidiabetic agents Systematic studies on the folklore medicinal plants that combat diabetes mellitus are scanty.

Keywords: Hypoglycemic, Non-communicable disease, Antidiabetic agents, Medicinal plants

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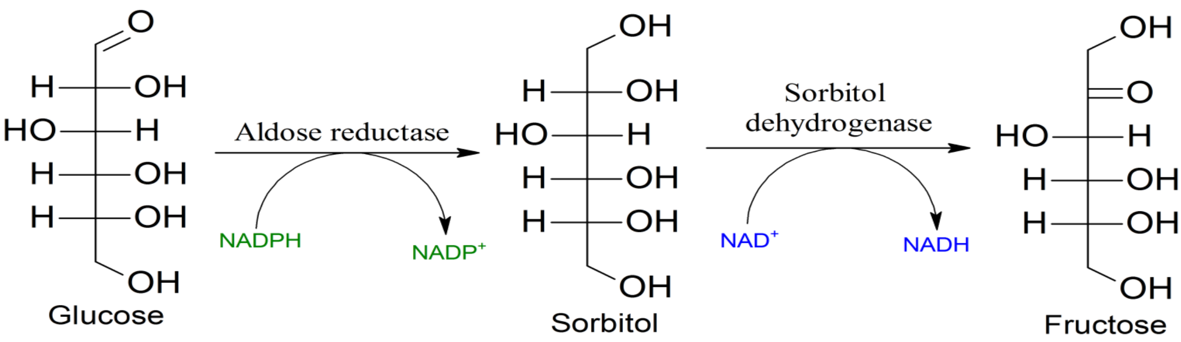
How to Cite this Article: Gaurav, Prince Raj, and Amit Singh. Medicinal plants with antidiabetic activity - A review of herbal medicine. World J Pharm Sci 2018; 6 (11): 84-92.

INTRODUCTION

Diabetes mellitus is a group of metabolic disorders with one common manifestation hyperglycaemia [1, 2]. Chronic hyperglycaemia causes damage to eyes, kidneys, nerves, heart and blood vessels [3]. It is cause by inherited and/or acquired deficiency in production of insulin by the pancreas, or by the ineffectiveness of the insulin produced. It results from either inadequate secretion of hormone insulin, an inadequate response of target cells to insulin, or a combination of these factors [4]. This disease requires medical diagnosis, treatment and changes in life style. There are many synthetic medicines developed for patients, but it is the fact that it has never been reported that someone had recovered totally from diabetes (5). According to World Health Organization the diabetic population is likely to increase up to 300 million or more by the year 2025 [6]. Currently available therapies for diabetes include insulin and various oral antidiabetic agents such as sulfonylurea's, biguanides and glinides. Many of them have a number of serious adverse effects; therefore, the search for more effective and safer hypoglycaemic agents is one of the important areas of investigation [7]. Aldose reductases, a key enzyme in the polyol pathway catalyze the reduction of glucose to sorbitol.



Polyol pathway [8]

Accumulation of sorbitol in the body causes various complications including cataract, neuropathy and nephropathy [8]. The hypoglycaemic effect of several plants used as antidiabetic remedies has been confirmed, and the mechanisms of hypoglycaemic activity of these plants are being studied. Natural products having antidiabetic potential, which acts through either insulinomimetic or secretagogues properties, are reviewed here [9]. Several medicinal plants have been used as dietary adjunct and in the treatment of numerous diseases without proper knowledge of their function. Although phytotherapy continues to be used in several countries, few plants have received scientific or medical scrutinity [10]. Moreover, a large number of medicinal plants possess some degree of toxicity. For example, it was reported that about one third of medicinal plants used in the treatment of diabetes are considered toxic [11].

The following potential hypoglycaemic plants are presented in the paragraphs. The scientific name of the plant, the family and the name of the country in which they are available are indicated. The description of methods used in the experiments, model animals, and the degree of hypoglycaemia, doses, toxicity and active ingredients are also included. Plants which did not show any significant hypoglycaemic effect were not included [12]. This review also focuses on the role of traditional therapeutic and natural medicines from traditional medicinal plants for diabetes. Traditional medicines from readily available medicinal plants offer great potential for the discovery of new antidiabetic drugs [13].

Natural Medicines Used for Diabetes Therapy

Recently, some medicinal plants have been reported to be useful in diabetes worldwide and have been used empirically as antidiabetic and antihyperlipidemic remedies. Despite the presence of known antidiabetic medicine in the pharmaceutical market, diabetes and the related complications continued to be a major medical problem [14]. Antihyperglycemic effects of these plants are attributed to their ability to restore the function of pancreatic tissues by causing an increase in insulin output or inhibit the intestinal absorption of glucose or to the facilitation of metabolites in insulin dependent processes [15]. More than 400 plant species having hypoglycemic activity have been available in literature, however, searching for new antidiabetic drugs from natural plants is still attractive because they contain substances which demonstrate alternative and safe effects on diabetes mellitus [16]. Most of plants contain glycosides, alkaloids, terpenoids, flavonoids, cartenoids, etc., that are frequently implicated as having antidiabetic effect. Species will be described in alphabetical order and information about each species will include in sequence: general botanical and taxonomic data, distribution in the world, experimental study and mechanism of action [17].

Annona muricata (Annonaceae)
Annona muricata played an important role in reduction of oxidative stress of pancreatic beta-cells of streptozotocin induced diabetic rats, which was confirmed by the increased area of insulin immunoreactive beta-cells and protection against degeneration of beta-cells[18].

Annona squamosa (Annonaceae)
Annona squamosa commonly called custard apple plant possesses antidiabetic activity. It acts by promoting insulin release from the pancreatic islets, increasing utilization of glucose in muscle and inhibiting the glucose output from liver [20].

Bougainvillea spectabilis (Nyctaginaceae)
The blood glucose lowering potential of ethanolic leaf extract of Bougainvillea spectabilis in streptozotocin induced type I diabetic albino rats was probably due to increased glucose uptake by enhanced glycogenesis in the liver and also due to increased insulin sensitivity [21].

Catharanthus roseus (Apocyaceae)
Dichloromethane methanol extract of leaves and twigs of Catharanthus roseus in carbohydrate metabolism, showed to enhance secretion of insulin. The extract was also found to be helpful in prevention of damage caused by oxygen free radicals [22].

Hibiscus rosa sinensis (Malvaceae)
Oral administration of ethanol extract of Hibiscus rosa sinesis at 250 mg/kg, p.o. showed mild but significant hypoglycemia which was mainly due to insulin release by stimulation of pancreatic beta cells [23].

Gymnema sylvestre (Asclepiadaceae)
Alcoholic extract of Gymnema sylvestre stimulated insulin secretion from the rat islets of Langerhans and several pancreatic beta cell lines. In another study, oral administration of a water-soluble leaves extract of Gymnema sylvestre at 400 mg/day, p.o. to 27 IDDM patients on insulin therapy lowered fasting blood glucose and insulin requirements [24]. Pancreatic beta cells may be regenerated or repaired in type II diabetic patients on Gymnema sylvestre supplementation; this is supported by the raised insulin levels in the serum of patients after supplementation. Gymnemic acid molecules dihydroxy gymnemic triacetate had the ability to release the insulin by the stimulation of a regeneration process and revitalization of the remaining beta cells. Aqueous extract of Gymnema sylvestre leaves stimulated insulin secretion from mouse cells and isolated human islets in vitro, without compromising cell viability [25].

Lepechinia caulescens (Lamiaceae)
Lepechinia caulescens significantly decreased glucose tolerance suggesting that Lepechinia caulescens has insulinomimetic activity [26].

Medicago sativa (Fabaceae)
Aqueous extract of Medicago sativa evoked stimulation of insulin secretion from the BRIN-BD11 pancreatic beta cell line in vitro. In another study it was found that insulin releasing activity of the methanol and water fractions is mainly due to the cumulative effect of its constituent present in it [27].

Ginkgo biloba (Ginkgoaceae)
Effect of Ginkgo biloba extract in humans and healthy rats shows that Ginkgo biloba significantly increased the insulin concentration [28].

Agrimony eupatoria(Rosaceae) :- Aqueous extract of Agrimony eupatoria evoked stimulation of insulin secretion from the BRIN-BD11 pancreatic beta cell line in vitro. The effect of extract was found to be glucoseindependent [29].

Coccinia indica (Cucurbitaceae)
Oral administration of dried extract of Coccinia indica at 500 mg/kg, p.o. for 6 weeks significantly increased insulin concentration in a clinical study. The plant extract showed to exert beneficial hypoglycemic effect in experimental animals and human diabetic subject possibly through an insulin secreting effect or through influence of enzymes involved in glucose metabolism [30].

Acacia arabica(Leguminosae) :- About 94% seed diet of Acacia arabica showed hypoglycemic effect in rats through release of insulin. However, powdered seeds of Acacia arabica at 2, 3 and 4 g/kg, p.o. exerted a significant hypoglycemic effect in normal rabbits by initiating the release of insulin from pancreatic beta cells [31].

Euccalyptus globulus (Myrtaceae)
Aqueous extract of Euccalyptus globulus (0.5 g/L of solution) increased peripheral glucose utilization in the mouse abdominal muscle and increased insulin secretion from the clonal pancreatic beta cell line [32].

Helicteres isora (Sterculiaceae)
Antihyperglycemic activity of butanol extracts of root of Helicteres isora at 250 mg/kg, p.o. in glucose loaded rats acts through insulin-sensitizing activity [33].

Aegle marmelos(Rutaceae) :- Aqueous leaf extract of Aegle marmelos showed antihyperglycemic activity in streptozotocin induced diabetic rats after 14 days treatment either by increasing utilization of glucose or by direct stimulation of glucose uptake through increased insulin secretion [34].

Boerhaavia diffusa (Nyctaginaceae)
Chloroform extracts of leaves of Boerhaavia diffusa showed antidiabetic activity in streptozotocin induced diabetic rats which mainly act by reducing blood glucose level and increasing insulin sensitivity [35]. Hypoglycemic and antihyperglycemic activity of aqueous leaf extract at 200 mg/ kg p.o. for 4 weeks in normal and alloxan induced diabetic rats showed to increase plasma insulin levels and improve glucose tolerance [36].

Caesalpinia bonducella (Cesalpinaceae)
Hypoglycemic activity of aqueous and ethanolic extracts of Caesalpinia bonducella in chronic type II diabetic model, showed an increase secretion of insulin in isolated islets [37].

Alangium salvifolium (Alangiaceae) :- Methanolic extract of Alangium salvifolium leaves possesses antihyperglycemic and antihyperlipidemic effects in dexamethasone induced insulin resistance in rats, which may be due to the antioxidant and insulinotropic effect of extract [38].

Ephedra distachya (Ephedraceae)
The alkaloids of Ephedra distachya herbs and l-ephedrine have shown antihyperglycemic effect in diabetic mice due to regeneration and restoration of atrophied pancreatic islets that induces the secretion of insulin [39].

Prunella vulgaris (Labiatae)
Jiangtangsu had been isolated from Prunella vulgaris and confirmed to have a remarkable blood sugar lowering effect in diabetic mice. The possible mechanism of Jiangtangsu is to repair cells of pancreatic islet to release insulin [40].

Psidium guajava (Myrtaceae)
Flavonoid glycosides such as strictinin, isostrictinin and pedunculagin are the effective constituents of Psidium guajava, which have been used in clinical treatment of diabetes due to improved sensitivity of insulin [41].

Radix rehmanniae (Scrophulariaceae)
The pectin type polysaccharide, obtained from the rhizome of Radix rehmanniae exhibited hypoglycemic activity in normal and streptozotocins induced diabetic mice by stimulating the secretion of insulin and reducing the glycogen content in the mice [42].

Allium sativum (Alliaceae)
Antihyperglycemic activity of ethyl ether extract of Allium satiyum at 0.25 mg/kg, p.o. was reported to be the most potent and active principle of Allium sativum (garlic) which was due to increased insulin like activity. Oral administration of the ethanol extract, juice and oil of Allium sativum has remarkably blood sugar lowering effect in normal and alloxan-induced diabetic rats or a rabbit mediated through stimulation of insulin secretion from parital cells of pancreas [43]. Allicin, a sulfur-containing compound showed to have significant hypoglycemic activity due to increased hepatic metabolism, increased insulin release from pancreatic beta cells. S-allyl cystein sulfoxide (SACS), the precursor of allicin and garlic oil, stimulated in vitro insulin secretion from beta cells isolated from normal rats. The beneficial effects of SACS could be due to its antioxidant and secretagogues activity [44]. Daily oral feeding of garlic extracts at 100 mg/kg increased plasma insulin level with concomitant decrease in plasma glucose levels. Effect of aqueous garlic (10% v/v) extracts on isolated pancreas were shown to potentiate glucose-induced insulin secretion[17]. Effect of garlic on high-fat diet feed rats for 2 weeks suggests that garlic is insulinotropic rather than hypoglycaemic [45].

Aloe vera (Liliaceae)
Hypoglycemic effect by bitter principle of Aloe vera in the rats is mediated through stimulation of synthesis or release of insulin from the beta-cells of Langerhans. Effect of pseudoprototinosaponin AIII and prototinosaponins AIII on glucose uptake and insulin release suggested their hypoglycaemic effects are due to actions on hepatic gluconeogenesis or glycogenolysis. Single as well as repeated doses of bitter principle of the Aloe vera showed hypoglycemic effect in diabetic rats, which was through stimulation of synthesis or release of insulin from pancreatic beta cells[46].

Capsicum frutescens
Capsicum frutescens increased serum insulin concentration in a high-fat (HF) diet-fed streptozotocin induced type 2 diabetes rats after 4 weeks treatment. The data of this study suggest that 2% dietary Capsicum frutescens is insulinotropic rather than hypoglycemic in the experimental methods [47].

Asparagus racemosus (Liliaceae)
The ethanol extract, hexane, chloroform and ethyl acetate fractions of Asparagus racemosus root were shown to have dose-dependent insulin secretion in

isolated perfused rat pancreas, isolated rat islet cells and clonal beta -cells. These findings reveal that constituents of Asparagus racemosus root extracts have insulinotropic activity [48].

Bauhinia variegata (Caesalpiniaceae)
Crude ethanolic extract of leaves of Bauhinia variegata and its major metabolite (6S, 7E, 9R)-9-hydroxymegastigma4,7-dien-3-one-9-beta-glycopyraroside (roseoside) have insulinotropic activity in insulin-secreting cell line INS-1 and it was found to be dose-dependent [49].

Berberine
Berberine promoted glucose-stimulated insulin secretion rather than basal insulin secretion in dose-dependent manner in rat's pancreatic islets. Berberine can enhance glucose-stimulated insulin secretion in rat islets, and probably exerts the insulinotropic effect via a pathway involving hepatic nuclear factor 4 alpha (HNF4) alpha and glucokinase, which is distinct from sulphonylureas[21]. Significant insulin sensitizing activity was observed in 3T3-L1 adipocytes which were given 50 M berberine plus 0.2 nM insulin to reach a glucose uptake level increased by 10 nM of insulin alone. This was associated with increased glucose transporter-4 translocation into the plasma membrane via enhancing insulin signalling pathways and the insulin receptor substrate-1-phosphoinositide 3 KinaseAkt. Berberine also increased glucose-stimulated insulin secretion and proliferation in Min6 cells via an enhanced insulin/insulin-like growth factor-1 signalling cascade. Data suggested that berberine can act as an effective insulin sensitizing and insulinotropic agent [50].

Biophytum sensitivum (Oxalidaceae)
Leaf extract of the Biophytum sensitivum stimulates pancreatic beta cells to release insulin in diabetic male rabbits and exerts hypoglycemic activity. Administration of the Biophytum sensitivum extract in 16-h fasted nondiabetic rabbits showed a significant rise in the serum insulin levels, which suggested a pancreatic mode of action of Biophytum sensitivum. The hypoglycaemic response of Biophytum sensitivum may be mediated through stimulating the synthesis/release of insulin from the beta cells of Langerhans [51].

Brassica nigra (Cruciferae)
Oral administration of aqueous extract of Brassica nigra for two months decreased serum glucose level, which was due to the release of insulin from pancreas [52].

Cinnamon zeylaniucm (Lauraceae)
In vitro incubation of pancreatic islets with cinnamaldehyde isolated from Cinnamon zeylaniucm resulted in enhanced insulin release. The insulinotropic effect of cinnamaldehyde was due to increase in the glucose uptake through glucose transporter (GLUT4) translocation in peripheral tissues [53].

Caffeine
Treatment with 0.01% caffeine solution in 90% pancreatectomized diabetic rats for 12-week reduced body weight, fats, and decreased insulin resistance. At the same time caffeine also enhanced glucose-stimulated first- and second-phase insulin secretion and beta-cell hyperplasia [54].

Camellia sinensis (Theaceae)
Epigallocatechin gallate, present in Camellia sinensis increases insulin activity and prevents oxidative damages in streptozotocin induced diabetic rats. Lower dose of Camellia sinensis on SD rats fed with high fat diet for 2 weeks showed insulinotropic effect in experimental condition [55].

Citrullus colocynthis (Cucurbitaceae)
Citrullus colocynthis pulp extract at 300 mg/kg, p.o. was found to significantly increase insulin and decrease plasma glucose levels in alloxan induced diabetic rats. Immunohistochemistry procedure showed that the amount of insulin in beta-cells of the islets of Langerhans is greater in Citrullus colocynthis treated-diabetic rats in comparison to the control group[28]. Administration of the ethanol extract of the dried seedless pulp of Citrullus colocynthis at 300 mg/kg, p.o had insulinotropic actions in alloxan-induced diabetic rats Aqueous extract of Citrullus colocynthis showed dose-dependent increase in insulin release from isolated islets. Different extracts such as crude extract, aqueous, alcoholic, purified extract and beta-pyrazol-1-ylalanine, the major free amino acid derivative present in the seeds significantly induced insulin secretion in vitro in the isolated rat pancreas and isolated rat islets [56].

Cornus officinalis (Cornaceae)
Alcoholic extract of Cornus officinalis can increase GLUT4 mRNA and its protein expression in NIDDM rats by promoting proliferation of pancreatic islets and by increasing postprandial secretion of insulin and therefore accelerating the glucose transport[15]. Methanol extract and its fractions had potent insulin mimic activity on phosphoenolpyruvate carboxykinase expression. The ability of fractions to protect beta-cell against toxic challenge, and to enhance insulin secretion strengthens the role of Cornus officinalis in diabetes therapy [57].

Elephantopus scaber (Asteraceae)
The acetone extract of Elephantopus scaber showed a significant decrease in blood glucose level by improving insulin sensitivity, augmenting glucose dependent insulin secretion and stimulating the regeneration of islets of Langerhans in pancreas of STZ-induced diabetic rats [58].

Enicostemma littorale (Gentianaceae)
Aqueous extract of Enicostemma littorale induced serum insulin levels in alloxan-induced diabetic rats at 8 h was associated with potentiation of glucose-induced insulin release through K+-ATP channel dependent pathway [59].

Eriobotrya japonica (Rosaceae)
Aqueous extract of Eriobotrya japonica and the compounds cinchonain Ib, procyanidin B-2, chlorogenic acid and epicatechin, were tested for insulin secretory activity in INS-1 cells, showed significantl increase of insulin secretion from INS-1 cells in dose-dependent manner [60].

Fermented unsalted soybeans
Effect of fermented unsalted soybeans in 90% pancreatectomized diabetic Px rats for 8-week enhanced insulin secretion. In addition, Chungkookjang potentiated insulin/IGF-1 signaling in islets via the induction of insulin receptor substrate-2 expression, leading to increased pancreatic duodenal homeobox-1, insulin promoter transcription factor. In parallel with the enhancement of the signaling, Chungkookjang elevated pancreatic beta-cell hyperplasia by increasing its proliferation and decreasing apoptosis [61].

Genistein
Genistein increases insulin secretion in both insulinsecreting cell lines (INS-1 and MIN6) and mouse pancreatic islets. It was found that genistein directly acts on pancreatic beta-cells, leading to activation of the cAMP/PKA signalling cascade to exert an insulinotropic effect [62].

Radix glycyrrhizae (Fabaceae)
Radix glycyrrhizae and glycyrrhetinic acid enhanced glucose-stimulated insulin secretion in isolated islets. In addition, they induced mRNA levels of insulin receptor substrate-2, pancreas duodenum homeobox-1, and glucokinase in the islets, which contributed to improve beta-cell viability [63].

Momordica charantia (Cucurbitaceae)
Significant reduction of blood glucose level and increased concentration of plasma insulin have been observed in diabetic rats that were treated with fruit juice of Momordica charantia. The observed effect was due to an increase in the number of beta cells in treated animals compared to untreated one. The phytochemical momordicin, charantin, and a few compounds such as galactose-binding lectin and insulin-like protein isolated from various parts of this plant have been shown to have insulin mimetic activity [64].

Nigella sativa oil (Ranunculaceae)
Significant decreases in blood glucose level, and increase in serum insulin level were observed on treatment with Nigella sativa oil for 4 weeks. Immunohistochemical staining of pancreas from Nigella sativa oil-treated group showed large areas with positive immunoreactivity for the presence of insulin [65].

Panax ginseng (Araliaceae)
Ginseng polypeptides isolated from the root of Panax ginseng, when injected subcutaneously at daily doses of 50 and 100 mg/kg for 7 successive days in mice resulted in decreased blood glucose, increased liver glycogen level and stimulated insulin secretion. The aqueous ethanolic extract of Korean red ginseng significantly evoked a insulin release in a glucose-independent manner [66].

Smallanthus sonchifolius (Asteraceae)
Administration of 2% Smallanthus sonchifolius to diabetic rats for 30-day increased levels of circulating insulin, which may be due to increased synthesis and secretion of insulin [67].

Stevia rebaudiana (Asteraceae)
Effect of stevioside in isolated mouse islets and the clonal beta cell line INS-1 was investigated and found that glycoside stevioside exerts antihyperglycaemic, insulinotropic, and glucagonostatic actions in the type 2 diabetic GK rat. In another study it was concluded that stevioside and steviol stimulate insulin secretion via a direct action on beta cells [62].

Tabernanthe iboga (Apocynaceae)
The effect of an aqueous extract of Tabernanthe iboga augmented glucose-stimulated insulin seceretion in a dose-dependent manner. Tabernanthe iboga contains water soluble insuliotropic compounds. the insulin secretary effect of Tabernanthe iboga might invove the closure of K^+ intensification of calcium influx through voltage-sensitive Ca^{2+} channels [68].

Results and Discussion
Diabetes is a metabolic disorder which can be considered as a major cause of high economic loss which can in turn impede the development of nations.9 Moreover; uncontrolled diabetes leads too many chronic complications such as blindness, heart failure, and renal failure. In order to prevent this alarming health problem, the development of

research into new hypoglycaemic and potentially antidiabetic agents is of great interest. The families of plants with the most potent hypoglycaemic effects include: Leguminoseae, Lamiaceae, Liliaceae, Cucurbitaceae, Asteraceae, Moraceae, Rosaceae, Euphorbiaceae and Araliaceae. The majority of the experiments confirmed the benefits of medicinal plants with hypoglycaemic effects in the management of diabetes mellitus. Numerous mechanisms of actions have been proposed for these plant extracts. Some hypotheses relate to their effects on the activity of pancreatic ß cells (synthesis, release, cell regeneration/revitalization) or the increase in the protective/inhibitory effect against insulinase and the increase of the insulin sensitivity or the insulin-like activity of the plant extracts. Other mechanisms may involve improved glucose homeostasis (increase of peripheral utilization of glucose, increase of synthesis of hepatic glycogen and/or decrease of glycogenolysis acting on enzymes, inhibition of intestinal glucose absorption, reduction of glycaemic index of carbohydrates, reduction of the effect of glutathione. All of these actions may be responsible for the reduction and or abolition of diabetic complications.

In conclusion, this paper has presented a list of anti-diabetic plants used in the treatment of diabetes mellitus. It showed that these plants have hypoglycaemic effects. Many new

Bioactive drugs isolated from plants having hypoglycaemic effects showed antidiabetic activity equal and sometimes even more potent than known oral hypoglycaemic agents such as daonil, tolbutamide and chlorpropamide. However, many other active agents obtained from plants have not been well characterized. More investigations must be carried out to evaluate the mechanism of action of medicinal plants with antidiabetic effect. The toxic effect of these plants should also be elucidated.

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