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Review on Antidiabetic Activity on Medicinal Plants

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Abstract

Medicinal plants have been proposed as rich yet unexploited potential sources for anti-diabetic drugs, even though used since ancient times for the treatment of diabetes mellitus. Many of the synthetic drugs were discovered either directly or indirectly from the plant source. The present study reviews of plants having anti diabetic property. Although many plants are recommendation, further pharmacological and chemical research should be done to elucidate the exact mechanism of hypoglycaemic activity.

Keywords: Diabetes mellitus, Medicinal plants, Anti-oxidants.

1. Introduction

Diabetes mellitus According to WHO, the term diabetes mellitus is defined as a metabolic disorder of multiple etiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The effects of diabetes mellitus include long-term damage, dysfunction and failure of various organs. Diabetes mellitus may have the characteristic symptoms such as thirst, polyuria, blurred vision and loss of weight [1].

2. Types of diabetes mellitus

2.1. Insulin Dependent Diabetes Mellitus (IDDM, Type 1)
2.2. Non-Insulin Dependent Diabetes Mellitus (NIDDM Type 2)
2.3. Gestational diabetes (Type 3)

3. Treatment of diabetes mellitus

3.1 Insulin and oral hypoglycemic drugs

Insulin therapy should aim to mimic nature, which is remarkably successful both in limiting postprandial hyperglycaemia and preventing hypoglycaemia between meals. Different preparations of insulin are available such as human insulin, beef insulin, pork insulin. Insulin therapy is no free from complications and adverse effects. The most important adverse effect are weight gain and hypoglycaemia when inappropriate dose of insulin is taken and when there is mismatch between meals and insulin injection. They bind to sulfonylurea receptors on the ß-cell plasma membrane, causing closure to ATP sensitive potassium channels, leads to depolarized the cell membrane. Administration of sulfonylurea's to type 2 DM patient's increases insulin release from the pancreas and also may be further increase insulin levels by reduce hepatic clearance of the hormones. It has been shown to increase peripheral uptake of glucose, and to reduce hepatic glucose output by approximately 20-30% when given orally but not intravenously. Impaired absorption of glucose from the gut has also been suggested as a mechanism of action [5].

3.2 Herbal treatment of diabetes

There are several literature reviews by different authors about anti-diabetic herbal products, but the most informative is the review by Atta-Ar-Rahman who has documented more than 300 plant species accepted for their hypoglycaemic properties. This review has classified the plants according to their botanical name, country of origin;

parts used and nature of active agents. One such plant is *Momordica charantia* (Family: Cucurbitaceae). WHO are listed 21,000 plants, which are used for medicinal purposes throughout world. Among these 2500 species are in India, out of which 150 species are used commercially on a fairly large scale. India is the largest producer of medicinal herbs and is called the botanical garden of the world [5].

4. Screening models for antidiabetes

4.1 Diabetes induced animal model

4.1.1. Alloxan

Diabetogenic action of alloxan is mediated by reactive oxygen species. Alloxan and the product of its reduction, dialuric acid, establish a redox cycle with the formation of superoxide radicals. These radicals undergo dismutation to hydrogen peroxide. Thereafter highly reactive hydroxyl radicals are formed by the fenton reaction .the action of reactive oxygen species with simultaneous massive increases in cytosolic calcium concentration causes rapid destruction of β cells. The action of alloxan in the pancreas is preceded by its rapid uptake by the β cells [27].

4.1.2. Streptozotocin

Streptozotocin2-deoxy-2-[3-[methyl-3-nitrosoureidp]-d-glucopyranose]] is synthesized by steptomycetes achromogenes and is used to induce both type-1 and type-2. Streptozotocin induces diabetes in almost all the species. diabetes dose varies with the species and the optimal dose required to produce diabetes in rat was found to be [50-60mg/kg i.p. or i.v],in mice 9175-200mg/kg i.p. or i.v] and in the dogs [`15 mg/kg for 3 days].Due to its low solubility the rapid i.v ;injection appears to be best route of administration [28].

4.1.3. Ferric nitrilotriacetate induction of diabetes mellitus

This rarely used procedure. Rats and rabbit`s parentrally treated with à large daily dose of ferric nitriloacetate manifestated diabetic symotoms such as hyperglycemia glycosuria ketonemia and ketourea after approximately 60 days of treatment the blood insulin response to oral glucose loading poor [28].

4.1.4. Non insulin dependent diabetes mellitus [NIDD] resembling animal models

By altering the dose and the dose of the STZ injection, the n-stz models exhibit various stages of type-2 diabetes mellitus, such as impaired glucose tolerance, mild, moderate and severe hyperglycemias neonatal stz-induced rat model of type 2 diabetes mellitus model is generated by injecting Wister rats on the day of their birth intravenously [28] [saphenous vein] or intraperitoneal with 100mg/kg of stz.

4.1.5. Harmone induced diabetes

Growth harmone induced diabetes; in intact adult dogs and cats repeated administration of growth harmone induces an intensively diabetic condition with all symptoms of diabetes including severe ketonemia and ketonuria ,corticosteroid induced diabetes: hyperglycemia, glycosuria, are observed in forced fed rats treated with cortisone, in guinea pig and rabbit <experimental corticoid diabetes could be obtained without forced feeding [28].

4.1.6. Insulin deficiency due to insulin antibodies

Bovine insulin [1mg] is injected subcutaneously to guinea pig at monthly intervals and is bleed by cardiac puncture two weeks after the second and subsequent doses of antigen. Intravenously injection [0.25-1.0ml] of guinea pig anti insulin serum to rats induces aldose of dependent increase of blood glucose. This effect is due to neutralization by insulin antibodies secreted by the injected animal.

4.1.7. Virus induced diabetes

Type-1 diabetes may due to virus infection and β-cell specific autoimmunity. The d-variant of the encephalamycarditis virus [emc-d] selectively infects and destroys the β cells in the male ICR Swiss mice similar to the human insulin dependent diabetic [30].

4.1.8. Genetically diabetic animals:

Several animal species, mostly rodents have been described to exhibit spontaneous diabetes mellitus on a hereditary basis E.g.; spontaneously diabetic rats like BB rat WBN/KOB rat etc [28].

4.1.9. Models of diabetes accelerated atherosclerosis

Accelerated cardiovascular disease is leading cause of both morbidly and mortality in diabetic patients. Aggressive therapy of dyslipidemia is necessary since the risk of myocardial infraction is the same as in non diabetic patients with previous myocardial infraction. Currently rats and mice are the most widely used models to study diabetes and atherosclerosis.

4.1.10. Genetic models of diabetes

A) Spontaneously develop diabetic rats

These models permit the evaluation of the effect of the natural product on an animal without an interference of the side effects induced by the chemical drugs like alloxan and STZ reported above. Several recent publications summarized the major advances in this field (ex; spontaneously diabetic Gotokakizakhi rat which is a genetic model of type-2 diabetes originating from selective breeding over many generations of glucose-intolerant non diabetic wister rats.

B) Genetically engineered diabetic mice

In this case, rodents may be produced to over or under express proteins thought to play an keyrole in the glucose metabolisms although significant advances in this field have arisen in recent years ,especially with the advent of transgenic mice, there have been no studies carried out involving natural products on this models [28].

5. Plants on diabetes mellitus

Natural products are the major mine for discovering promising lead candidates, which play an important role in future drug development programs. Ease of availability, least side effects and low cost make the herbal preparations are the main key player of all available therapies, especially in rural areas. The aim of this review is not to mention all the anti diabetic plants previously discussed in details in the textbook of "Traditional Medicines for Modern Times Anti diabetic Plants", but we will shed light on the most relevant data related to these popular plants [6].

5.1. *Acorus calamus* (Acoraceae):

Oral administration of methanolic extract of *A. calamus* rhizome restored the levels of blood glucose in Streptozotocin induced diabetic rats after 21 days. Further, lipid profile glucose 6-phosphatase, fructose 1, 6 bis phosphatase levels and hepatic markers enzymes were decreased [7].

5.2. *Aegle marmelos* (Rutaceae):

The aqueous extract of leaves at dose 1gm/kg for 30 days are controlled blood glucose, body weight, liver glycogen. The extract was comparison to insulin in restoring blood glucose and body weight to normal levels. Consequently, the active principle of marmelos extract had similar hypoglycaemic effect to that of insulin [8].

5.3. *Afzelia Africana* (Leguminosae):

The anti diabetic properties of aqueous extract from stem bark of *Afzelia africana*. The dose was 200 mg/kg that was reduced blood glucose level. In addition of hyperglycaemia, it also prevents various complication of diabetes [9].

5.4. *Alstonia scholaris* (Apocynaceae):

The extract of bark of *Alstonia scholaris* has found to anti diabetic and anti hyperlipidemic activity in induced diabetes in rats. Four week treatment with extract of bark dose 150 mg/kg and 300 mg/kg. Ameliorated the alterations in fasting blood glucose, serum triglyceride, serum cholesterol, liver glycogen, glycosylated hemoglobin and body weight in diabetic rats [10].

5.5. *Anacardium occidentale* (Anacardiaceae):

Oral administration of doses 35, 175 and 250 mg/kg are reduce blood glucose levels in diabetic rats. Hexane and ethyl acetate fractions are the most prominent actions suggesting the presence of non polar and polar hypoglycaemic compounds in the plant [11].

5.6. *Annona squamosa* (Annonaceae):

The aqueous extract of roots of *Annona squamosa* dose of 250 mg/kg and 500 mg/kg body weight. It reduces the blood glucose level and effects were compared with the glibenclamide [12].

5.7. *Anoectochilus roxburghii* (Orchidaceae):

A high yielding constituent from *Anoectochilus roxburghii*, involve in the hypoglycemic effect on streptozotocin diabetic rats and orally administered(15mg/Kg) and which is speculated to be partially attributed to modulating the activity of enzymatic antioxidants, scavenging free radicals [13].

5.8. *Artemisia pallens* Wall. Ex-DC. Besser (Asteraceae):

It is a shrub endemic to southern India especially in Mysore state and is used in folk medicine in parts of southern India. Oral administration of the methanolic extract doses (100, 500 and 1000 mg/kg) anti hyperglycaemic effect in glucose-fed hyperglycaemic and alloxanized rats (60 mg/kg). The effect was moderate in fasted normal rats but greater in diabetic rats [14].

5.9. *Artemisia dracunculus* L. (Asteraceae):

It is commonly known as "dragon herb". It is native to a wide area of the Northern Hemisphere from eastern Asia to India, western North America, and south to northern Mexico. At doses of 50-500mg/kg/day, the hypoglycaemic activity of the extract enhances 3-5-fold with the bio-enhancer Labrasol, making it comparable to the activity of the anti diabetic drug metformin. Tarralin, an ethanolic extract lowers elevated blood glucose levels by 24% receptor *in vitro* [15].

5.10. *Artemisia herba*-alba Asso (Med).(Asteraceae):

It is a perennial shrub that grows commonly on the steppes of Northern Africa, Arabian Peninsula, Western Asia and South Western Europe. Oral administration of 0.39 g/kg body weight of the aqueous extract of the leaves or barks produces a significant reduction in blood glucose level, while the aqueous extract of roots and methanolic extract of the aerial parts of the plant produce almost no reduction in blood glucose level. The extract of the aerial parts of the plant seem to have minimal adverse effect and high LD_{50} value [16].

5.11. *Azadirachta indica* (Meliaceae):

This is also known as Neem and is a tree native to India, Burma, Bangladesh, Sri Lanka, Malaysia and Pakistan and is growing in tropical and semi-tropical regions. A low (0.5g TID) and high (2g TID) doses of powdered part, aqueous extract and alcoholic extract of *Azadirachta indica* showed significant hypoglycaemic activity in high dose and can be successfully combined with oral hypoglycaemic agents in type-2 diabetic patients whose diabetes is not controlled by these agents [17].

5.12. *Bruguiera gymnorrhiza* (Rhizophoraceae):

Oral administration of ethanolic extract of B. gymnorrhiza root (400 mg/kg b.wt) significantly reduced the blood sugar level, total cholesterol, triglycerides, VLDL and LDL and significantly increased the HDL level of STZ induced diabetic rats [7].

5.13. *Biophytum sensitivum* (Oxalidaceae):

Oral administration of the ethanolic extract of *B. sensitivum* whole plant significantly decreased the blood glucose level, serum cholesterol level and increased the total protein level of induced diabetic rats [7].

5.14. *Caesalpinia bonducella* (Fabaceae):

The action of the extracts on diabetes induced hyperlipidemia significantly lowers the elevated cholesterol as well as LDL level. The drug has the potential to act as anti diabetic as well as anti hyperlipidemic [7].

5.15. *Camellia sinensis* (Theaceae):

Tea is known in folk medicine as a medicinal plant that used as a hypotension and anti diabetic. Its anti diabetic action is due to reduction of intestinal glucose absorption. The aqueous leaf extract (450 mg/kg) have a strong glucose lowering effect after oral administration in induced diabetic rats [10]

5.16. *Ficus benghalensis* (Moraceae):

The aqueous extract of *F. bengalensis* stem bark significantly reduced the blood glucose level of STZ induced diabetic rats [7].

5.17. *Ficus racemosa* (Moraceae):

The glucose-lowering efficacy of a methanol extract of the stem bark of *Ficus racemosa* Linn. was evaluated both in normal and alloxan-induced diabetic rats. The extract at the doses (200 and 400 mg/kg body weight) exhibited significant hypoglycaemic activity in both experimental animal models when compared with the control group. The activity was also comparable to that of the effect produced by a standard anti-diabetic agent, glibenclamide [20].

5.18. *Gymnema sylvestre* (Asclepidaceae):

It is a large woody, much branched climber with pubescent young parts in dry forest up to 600 m height. *Gymnema sylvestre* (400mg/day) is given to alloxan induced diabetic rats. It also known for its antidiabetic, anticancer and anti microbial properties. It is rich in phyto chemicals such as alkaloids, flavonoids, saponins, carbohydrates [21].

5.19. *Helicteres isora* L. (Malvaceae):

The hot water extract of fruit of *H. isora* exhibited anti oxidant activity and moderate anti-diabetic activity at 200 mg/mL doses. It showed glucose-up take activity and was found to have activity comparable to insulin and met formin. The ethanolic extract has insulin-sensitizing and hypolipidemic activity use in the treatment of type-2 diabetes [14].

5.20. *Justicia beddomej* (Acanthaceae)

It is a shrub, grows in shadow and moist area which belongs to family Acanthaceae. The leaves of the plant are reported to be useful in the treatment of diabetes. The ethanolic extract of leaves at dose 100 mg/kg reduced the serum glucose level in induced diabetic rats after administer i.p. route. Plant also has other effects like astringent, expectorant, anti-inflammatory, antispasmodic, antibacterial, diuretic, anthelmintic etc [10].

5.21. *Lantana camara* L. (Verbenaceae):

Once daily administration of *L. camara* leaf juice (1500 mg/kg/day for 14 days) showed significant hypoglycaemic effect in rats. However, the plant is hepatotoxic in nature [14].

5.22. *Momordica charantia* (Cucurbitaceae):

It is a popular herbal resource to treat diabetes. It increases the mitosis of pancreatic cells and partially recovers the destroyed cells. Various medicinal properties are claimed for *Momordica charantia* namely anti diabetic, abortifacient, anthelmintic, contraceptive, antimalarial and laxative and also in galactogogue, jaundice, leprosy, pneumonia and rheumatism. Charantin, vicine and p-insulin (polypeptide) are reported as the active ingredients [22].

5.23. *Morinda lucida* (Rubiaceae):

Methanolic extract and aqueous extract of *Morinda lucida* (Rubiaceae) has been found to have hypoglycemic activity in alloxan induced diabetic rats [10].

5.24. *Murraya koenigii* Linn (Rutaceae):

Neelesh Malviya, Sanjay Jain, et all 2014 has examined. In normal and alloxan diabetes the aqueous extract of the leaves of *M. koenigii* produced hypoglycaemic effect. Oral feeding of this plant for 60 days diet to normal rats showed an increase in the concentration of hepatic glycogen due to hypoglycaemic activity. It suppresses blood glucose level and was found to have beneficial effect on carbohydrate metabolism [23].

5.25. *Ossimum gratissium* (Labiatae):

The hypoglycaemic effects of aqueous leaves extract of *Opium gratisimum* was investigated in streptozotocin induced diabetic rats. The aqueous extract at the dose of 500 mg/kg significantly lowered blood glucose level of the diabetic rats by 81.3% after 24 hr of extract administration [10].

5.26. *Polyalthia longifolia* (Annonaceae):

Oral administration of the methanolic extract of *P. longifolia* bark (200 and 300 mg/kg b.w.) reduced the fasting blood glucose, moreover the elevated levels of SGOT, SGPT, ALP, triglycerides and total cholesterol were restored to near normal level in STZ induced diabetic rats [7].

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5.28. *Polygonati Odorati* (Liliaceae):

Its aqueous extract showed potent antidiabetic activity influencing glucose or carbohydrate metabolism through inhibiting α-glucosidase activity in the digestive canal and thus improving glucose and triglyceride metabolism [23].

5.29. *Sclerocarya birrea* (Anacardiaceae):

The methylene chloride/methanol extract (150 and 300 mg/kg bw) of *S. birrea* stem bark significantly reduced the blood glucose level, plasma cholesterol, triglyceride and urea levels to the normal level and increased plasma insulin level in STZ induced diabetic rats [25].

5.30. *Securinega virosa* (Euphorbiaceae):

Intraperitoneal administration of (100, 300 and 600 mg/kg b.w.) methanol extract from *S. virosa* leaves significantly reduced the blood glucose level of STZ induced diabetic rats [7].

5.31. *Swertiachirayita H. Karst.* (Gentianaceae) Chirata (Hindi):

It is mainly found in temperate Himalayas between the height of 1200 and 1300 m. Various crude extracts and its isolated fractions have shown hypoglycemic activity in various animal models. Oral administration of ethanolic extracts (95%) and hexane fraction of *S. chirayita* (10, 50 and 100 mg/kg) to normal, glucose-fed and STZ-induced diabetic rats significantly lowered blood glucose in all groups of animals [24].

5.32. *Tectona grandis* (Verbenaceae):

Methanolic extract of *Tectona grandis* roots has antidiabetic activity which was performed on alloxan induced diabetic albino rats. Its hypoglycemic action was compared with glibenclamide and hypoglycemic activity has been reported at the dose of 500mg/kg [25].

5.33. *Terminalia chebula* (Combretaceae):

An herbal formulation containing *T. chebula* named Triphala is traditional medicine for the treatment of diabetes. Anti diabetic effects of the chloroform extract of *T. chebula* Retz seeds in streptozotocin -induced diabetic rats was proved [23].

10. Conclusion

The World Health Organization estimated that about 30 million people suffered from diabetes in 1985 and the number increased to more than 171 million in 2000. It is estimated that the number will increase to over 366 million by 2030 and that large increases will occur in developing countries, especially in people aged between 45 and 64 years. Plant drugs and herbal formulations are considered to be less toxic and free from side effects than synthetic ones. Based on the WHO recommendations, hypoglycaemic agents of plant origin used in medicine are important. The attributed anti hyperglycaemic effects of these plants are due to their ability to restore the function of pancreatic tissues by causing an increase in insulin output or a decrease in the intestinal absorption of glucose. Hence, treatment with herbal drugs has effect on protecting cells and smoothing out fluctuation in glucose levels. In general, there is very little biological knowledge on the specific modes of action in the treatment of diabetes, but most of the plants have been found to contain substances like glycosides, alkaloids, terpenoids, flavonoids etc. that are frequently implicated as having anti diabetic effects. The research for alternate remedies (from the plant kingdom) for diabetes mellitus will continue all over the world as the disease poses many challenges not only to the physician but also to the researcher.

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