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A REVIEW ON MEDICINAL PLANTS WITH POTENTIAL ANTIDIABETIC ACTIVITY

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Abstract

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 hypoglycaemic properties, reported in the literature. The profiles presented include information about the scientific name, family, methodology used, the degree of hypoglycaemic activity and the active agents. Out of a large number of herbal drugs stated to possess anti-diabetic activity in the Ayurvedic system of medicine of India, *Cinnamomi cassiae* (Lauraceae), *Tournefortia hartwegiana* Steud, (Boraginaceae), *Averrhoa bilimbi Linn* (Oxalidaceae), *Commelina communis* L. (Commelinaceae), *Origanum vulgare* (Lamiaceae), *Caralluma attenuate* (Apocynaceae), *Murraya koenigii* (Rutaceae), *Aerva lanata* (Amaranthaceae), *Picrorrhiza kurroa* (Scrophulariaceae), and *Eugenia jambolana* (Myrtaceae) were widely used to treat diabetes by the traditional practitioners over many centuries. The present review circumscribes Indian plants that have been pharmacologically tested and shown to be of some value in Diabetes Mellitus. The effects of these plants may delay the development of diabetic complications and correct the metabolic abnormalities. Moreover, during the past few years some of the new bioactive drugs isolated from hypoglycaemic plants showed antidiabetic activity with more efficacy than oral hypoglycaemic agents used in clinical therapy.

Keywords: Hypoglycaemic, antidiabetic, medicinal plants, diabetes mellitus.

Introduction

Diabetes mellitus is a group of metabolic alterations characterized by hyperglycemia resulting from defects in insulin secretion, action or both. It has already been established that chronic hyperglycemia of diabetes is associated with long term damage, dysfunction and eventually the failure of organs, especially the eyes, kidneys, nerves, heart and blood vessels (Huang *et al*., 2005). The use of medicinal plants for the treatment of diabetes mellitus dates back from the Ebers papyrus of about 1550 B.C. A multitude of herbs, spices and other plant materials have been described for the treatment of diabetes throughout the world (Kesari *et al*., 2005). The medicinal plants provide a useful source of oral hypoglycemic compounds for the development of new pharmaceutical leads as well as a dietary supplement to existing therapies (Bailey and Day, 1989). Some of the plants which are being used for the treatment of diabetes have received scientific or medicinal scrutiny and even the WHO expert committee on diabetes recommends that this area warrant further attention (WHO, 1980).

India has about 45,000 plant species and many of them have medicinal properties. Out of a large number of herbal drugs stated to possess anti-diabetic activity in the Ayurvedic system of medicine of India, *Cinnamomi*

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cassiae (Lauraceae), *Tournefortia hartwegiana* Steud, (Boraginaceae), *Averrhoa bilimbi Linn* (Oxalidaceae), *Commelina communis* L. (Commelinaceae), *Origanum vulgare* (Lamiaceae), *Caralluma attenuate* (Apocynaceae), *Murraya koenigii* (Rutaceae), *Aerva lanata* (Amaranthaceae), *Picrorrhiza kurroa* (Scrophulariaceae), and *Eugenia jambolana* (Myrtaceae) were widely used to treat diabetes by the traditional practitioners over many centuries. The present review circumscribes Indian plants that have been pharmacologically tested and shown to be of some value in Diabetes Mellitus.

***Cinnamomi cassiae* (Lauraceae)**

Cinnamon is one of the traditional folk herbs used in Korea, China and Russia for diabetes mellitus (Bailey and Day, 1989; Chung, 1994). Cinnamon is the bark of the *Cinnamomi cassia* (Lauraceae). Cinnamic aldehyde (Wijesekera, 1978), cinnamic acid (Hiromu *et al*., 1974), tannin (Inokuchi *et al*., 1984) and methylhydroxychalcone polymer (MHCP) (Jarvull-Taylor *et al*., 2001) are its main componets. Jarvull-Taylor's research also showed that cinnamon increases the insulin sensitivity and glucose uptake in adipocytes (Jarvull-Taylor *et al*., 2001).

The effects of administration of cinnamon extract with 50, 100, 150 and 200 mg/kg to db/db mice were determined first by measuring food consumption, changes in body weight, food efficiency ratio (FER) and blood glucose levels. The differences in the body weight and food intake of the mice treated with cinnamon extract and control were not significant. Changes in body weight and FER did not differ between the groups. The decline in blood glucose levels reached its maximum after 2 weeks and remained almost constant after 4 and 6 weeks of cinnamon extract administration. The "high dose" of cinnamon extract, 200 mg/kg was the most effective dose in decreasing the blood glucose level. Serum insulin levels were found to be significantly higher in the cinnamon extract 200 mg/kg than the control group. Serum concentration of triglyceride in the cinnamon extract treated db/db mice decreased by 45.0% than in the control group. But the level of HDL–cholesterol significantly increased by 1.5 fold ($P < 0.01$) in the cinnamon extract-treated group. HDL–total cholesterol ratio (HTR) (%) was also found to be higher in the cinnamon-treated group than the control group. The small intestinal glycosidase activity was found to decrease in the cinnamon-treated db/db mice (Kham *et al*., 2003). So, the possible mechanism by which cinnamon extract brings about its hypoglycemic action in diabetic mice may be by potentiating the effect of insulin in serum or by increasing either the pancreatic secretion of insulin from the existing beta cells or its release from the bound form.

***Tournefortia hartwegiana* Steud, (Boraginaceae)**

Tournefortia hartwegiana Steud, (Boraginaceae) commonly known as "hierba rasposa", "clachichinol" or "tlachichinole", is a plant from the deciduous dry forest in Morelos, Mexico (Monroy-Ortiz and Castillo, 2000). In this region, decoction from dry leaves of this plant is used in traditional medicine as anti-diarrheic and anti-diabetic agent.

Tournefortia hartwegiana aerial parts decoction (10 g/1000 ml per day, aproximately) is claimed to be useful in Morelos, Mexico, for the treatment of diabetes and this decoction is orally taken by people during 10–14 days to control the disease (personal communication with Dr. Castillo-Espa˜na). Treatment with 310 mg of methanol Extract of *Tournefortia hartwegiana* /kg body weight/day on alloxan-induced diabetic and normoglycemic rats up to 10 days, showed an important reduction in blood glucose levels ($p < 0.05$). The effect was significant in diabetic and normoglycemic rats. *Tournefortia sarmentosa* allowed the isolation of benzenoids with antilipid-peroxidative activity (Lin *et al*., 2002). It was directed to isolate the active constituents from the methanolic extract of *Tournefortia harwegiana* to allow understanding its mechanism(s) of action (Ortiz-Andrade *et al*., 2005).

***Averrhoa bilimbi Linn* (Oxalidaceae)**

Averrhoa bilimbi Linn (Oxalidaceae) is a small–sized tree growing up to 15 m tall and 30 cm diameter. The chemical constituents of A.bilimbi that have been identified include amino acids, citric acid, cyanidin–3–O–h–D–glucoside, phenolics, potassium ion, sugars and vitamin A. It is used as antibacterial, antiscorbutic, astringent; post–partum protective medicine; treatment of fever, mumps, pimples, inflammation of the rectum and diabetes (decoction of the leaves); treatment of itches, boils, rheumatism, cough and syphilis (paste of leaves); treatment of scurvy, bilious colic, whooping cough, hypertension (Goh *et al*., 1995) and as a cooling drink (juice of preserved fruits); treatment of children's cough (syrup of flowers); treatment of stomach ache (fruits).

Some researchers showed that ethanolic leaf extract of Averrhoa bilimbi and its semi–purified fractions possesses hypoglycemic and hypolipidemic properties in Type I diabetic rats when administered intraperitoneally (Tan *et al*., 1996) as well as orally (Pushparaj *et al*., 1999; Pushparaj *et al*., 2000; Pushparaj *et al*., 2001). The semi–purified fractions of the ethanolic extract of Averrhoa bilimbi leaves such as AF (Aqueous Fraction) and BuF (Butanol Fraction) have potent hypoglycemic and hypotriglyceridemic properties in HFD–STZ–diabetic rats. AF (125 mg/kg BW) caused a significant hypoglycemic effect at 30 min, 60 min, 120–min and 180 min

when compared with vehicle control. The body weight, food and water intakes of the rats did not differ significantly in AF and BuF–treated diabetic rats. the semi–purified fractions of the ethanolic extract of *Averrhoa bilimbi* leaves such as AF and BuF ameliorated diabetes in HFD–STZ–diabetic rats. Moreover, AF is more potent than BuF in the amelioration of hyperglycemia and hypertriglyceridemia. However, the chemical nature of potential antihyperglycemic component (s) of AF and BuF remains to be elucidated.

***Commelina communis* L. (Commelinaceae)**

Commelina communis, commonly known as the Asiatic dayflower, is an herbaceous annual plant in the dayflower family. *Commelina communis* L. Leaf tea from *C. communis* L. has been in use in gargle for sore throat, diuretic, acute tonsillitis, urinary infections, dysentery, acute intestinal enteritis, obesity, and diabetes mellitus (Kim HS *et al*., 1999). Aqueous extracts of commelina leaves (CE-L) and whole plants (CE-W) inhibited the activity of α-glucosidase in vitro in a concentration-dependent Manner. CE-L inhibited the α-glucosidase more effectively than CE-W. Compared to control, the activities of α-glucosidase were inhibited 77.4%, 62.1% and 57.01% by 10 mg/ml of CE-L, CE-W and acarbose, respectively. Literature also provides an inhibitory effect of acarbose that has significant inhibitory effect on glucoamylase (90% inhibition), sucrase (65% inhibition), and maltase (60% inhibition) (Mooradian AD and Thurman JE, 2001), it seems that CE-L acts similar to acarbose. In addition, prolonged administration of CE-L at a dose of 100 mg/kg for 10 days caused a significant ($P < 0.05$) decrease in level of fasting blood glucose, and acarbose also showed a significant ($P < 0.01$) lowering effect on fasting blood glucose level compared to the STZ-induced diabetic control group.

These results support the fact that CE-L might improve diabetes by normalizing the post-prandial plasma glucose as well as fasting blood glucose (Joy KL and Kuttan R, 1999; Ji-Youn Youn *et al*., 2004). Although, in this study, we provided evidence for CE-L as a potent α-glucosidase inhibitor and has properties to normalize blood glucose, the exact mechanism by which CE-L improves the hyperglycemia in STZ-induced diabetic mice is not yet clear, and chemical nature of potential anti-hyperglycemic component of CE-L remains to be established.

***Origanum vulgare* (Lamiaceae)**

Origanum vulgare (OV) (Lamiaceae), locally known as "Zaatar" is a native plant widely distributed throughout the south-eastern region of Morocco (Tafilalet). This plant is traditionally used in diabetes control and treatment accord ing to our previous ethnobotanical survey in a great area of Morocco; Tafilalet region (Eddouks *et al*., 2002). In Tafilalet region, among 320 informants, the number of citation of the plant in diabetes treatment was 50 (Eddouks *et al*., 2002). The main known pharmacological activities of OV were; anti-bacterial (Harpaz *et al*., 2003; Burt and Reinders, 2003; Dorman and Deans, 2000), anti-oxidant (Stashenko *et al*., 2002; Vichi *et al*., 2001; Nakatani, 2000; Lagouri and Boskou, 1996; Lamaison *et al*., 1991) and anti-thrombin (Goun *et al*., 2002).

In diabetes phytotherapy, the effect of aqueous OV extract has never been demonstrated experimentally in either clinical or experimental type 1 diabetes mellitus. In the south-eastern region of Morocco (Tafilalet), OV leaves are recognised as potent hypoglycaemic agents by several traditional healers (Eddouks *et al*., 2002). Lemhadri (Lemhadri *et al*., 2004) reported, in normal rats, the blood glucose levels did not change after OV oral administration (20 mg/kg). In diabetic rats, a significant decrease of blood glucose levels was noted in OV treated groups when compared to baseline values. Pre-treatment blood glucose levels in diabetic rats, which were very high, dropped 6 h after a single oral administration of aqueous OV extract at a dose of 20 mg/kg ($P < 0.05$). In STZ diabetic rats, once daily repeated oral administration of the aqueous OV extract (20 mg/kg) caused a significant and cumulative de decrease of blood glucose levels. The basal plasma insulin concentrations did not differ significantly in the OV-treated groups when compared to untreated group in both normal and diabetic rats when treated once daily at a dose of 20 mg/kg. OV could normalise the blood glucose levels in diabetic rats by the restoration of normal insulin sensitivity.

The known main constituents of OV have been demonstrated to be volatile compounds such as linalool, alcohols, phenols (Garcia and Sanz, 2001; Daferera *et al*., 2000) and terpens (Mockute *et al*., 2001). Their eventual hypoglycaemic effect in type 1 diabetes mellitus has not been demonstrated. However, their potential effect on anti-bacterial and anti-oxidant activities have been proved (Harpaz *et al*., 2003; Burt and Reinders, 2003; Stashenko *et al*., 2002). Flavonoids are considered as active principles in many medicinal plants and natural products with positive effect for human health (Wollenweber, 1988). These natural compounds could act separately or synergistically to cause the hypoglycaemic effect. This could not exclude the intervention of other phytochemical constituents as bioactive hypoglycaemic agents. The precise mechanism(s) and site(s) of this activity and the active constituent(s) involved are still to be determined in addition to toxicological studies.

***Caralluma attenuate* (Apocynaceae)**

Caralluma attenuata is a thick, succulent perennial herb growing wild in dry hill slope regions of Hyderabad and in several districts of Andhra Pradesh, India. Locally it is known as 'Kundaetikommu', and is eaten raw as a cure for diabetes (personal information from users) and the juice of the plant along with black pepper is recommended in the treatment of migraine (Srinivasacharyulu Y and Yogarathnakaram, 1931). It reported the presence of luteolin-49-*O*-neohesperidoside (Ramesh M *et al*., 1999) with a significant anti-inflammatory and antinociceptive activity (AVN, *et al*., 1999). *Caralluma tuberculata*, growing both wild and cultivated in Pakistan is either eaten raw or cooked as a vegetable and is also reported to be a cure for diabetes and rheumatism (Ali SI, 1986; Chopra RN *et al*., 1956).

The fresh juice of *C. tuberculata* was shown to possess hypoglycemic activity (Ahmed MM *et al*., 1989). The luteolin-4-*O*-neohesperidoside has been isolated from *C. tuberculata* (Rizwani GH *et al*., 1990). The effect of *C. attenuata* extracts has prevented the increase in blood glucose levels significantly (*P*-0.001) after glucose administration; the maximum glucose tolerance was observed at the 30th min for butanol extract. Also, in alloxan-induced diabetic rats only the butanol extract has shown significant (*P*-0.001) and considerable fall (25%) in blood glucose level. It is generally accepted that alloxan treatment causes permanent destruction of bcells (Asres K, 1993; Pari L and Uma Maheswari, 1999). It is, therefore, conceivable that the hypoglycemic principles in the butanol extract of *C. attenuata* exert their effect by an extrapancreatic mechanism in diabetic rats.

***Murraya koenigii* (Rutaceae)**

Murraya koenigii (MK) is known as 'Curry Patta' in Hindi and is widely use as a spice and condiment in India and other tropical countries. It belongs to the family Rutaceae (citrus family). Ayurveda mentions its use as a treatment for diabetics (Satyavati *et al*., 1987). Spices and cereals like Fenugreek, MK, Brassica juncea as dietary constituents have been found to have beneficial effect on carbohydrate metabolism experimentally as well as clinically (Iyer and Mani, 1990; Vats *et al*., 2002; Khan *et al*., 1995). Yadav S. *et al*. (2002) investigated the efficacy of feeding curry leaves (MK) as dietary constituents in controlling hyperglycemia. Feeding of diet containing various doses of MK to the normal rats for 7 days did not show any profound hypoglycemia in this study and this is in contrast to the report of Khan *et al*., 1995. This may be possibly due to shorter duration (7 days) of the present study in comparison to 60-day duration in the Khan study. However, MK exerted profound antialloxan effect as diet containing higher proportion of MK significantly prevented the rise in blood glucose after administration of alloxan (35 mg/kg).

Alloxan and STZ produce hyperglycemia by selective cytotoxic effect on pancreatic b cells. One of the intracellular phenomenon for its cytotoxicity is through generation of free radicals demonstrated both in vivo and in vitro (Gandy *et al*., 1982; Papaccio *et al*., 1986). MK probably prevented the destruction of b cells of islets in the pancreas. This is an interesting finding and suggests that it may have antioxidant or free radical scavenger properties in preventing these changes. Antioxidant/ free radical scavenging property of MK leaves has been stated earlier by many authors (Tachibana *et al*., 2001; Khan *et al*., 1996, 1997; Ramsewak *et al.,* 1999). Thus MK may have a role in prevention of diabetes and its consumption should be encouraged in the early diabetic state.

***Aerva lanata* (*Amaranthaceae*)**

Aerva lanata (Family-*Amaranthaceae*) is an erect, hoary-tomentose herb available throughout India, Ceylon, tropical Africa, Java and Philippines. Its plant extract has been reported to possess diuretic, anti-inflammatory, antimalarial, anthelmintic, antivenin, analgesic and sedative activities (Chopra, 1933; Zagari, 1992; Gessler *et al.,* 1994; Selvanayagam *et al.,* 1994; Vetrichelvan *et al*., 2000). Also it is used to treat urinary calculi, hematemesis, bronchitis, nasal bleeding, cough, scorpion stings, fractures, spermatorrhoea, to clear uterus after delivery and to prevent lactation (Mukerjee *et al*., 1984; Shah and Gopal, 1985; Sikarwar and Kaushik, 1993; Girach *et al*., 1994). Phytochemical studies on *A. Lanata* revealed that it contains aerva flavonoid glycosides, aervitrin, aervolanine, aervoside, amyrin, betulin, campesterol, canthin-6-one, 10-hydroxy-canthin-6-one, carboline-1 propionic acid, chrysin, _-ecdysone, daucosterol, hentriacontane, narcissin, β-sitosterol, syringic acid, feruloyl tyramine and vanillic acid (Aiyar *et al.,* 1973; Zadorozhnii i., 1986; Wassel and Ammar, 1987; Mallabaev *et al.,* 1989; Chandra and Shastry, 1990; Zapesochnaya *et al.,* 1991, 1992; Pervykh *et al*., 1993). In folklore practice hot water extract of *A. lanata* has been reported to be useful in Diabetes Mellitus (Singh *et al.,* 1980).

The blood glucose data obtained clearly indicate that the alcoholic extract from *A. lanata* produce significant and consistent hypoglycaemic effects in alloxan-induced diabetic rats. The continuous treatment with AAL for a period of 15 days produced a significant decrease in the blood glucose levels of diabetic rats, but not in the normal rats. the flavonoids and terpenes present in the AAL are reported to be hepatoprotective agents (Merck, 1996; Mustaq Ahmad *et al.,* 2000) improvement of liver function and subsequent increase in uptake

of blood glucose and its utilization may be another mechanism of action of AAL.

***Picrorrhiza kurroa* (Scrophulariaceae)**

Picrorrhiza kurroa (Family—Scrophulariaceae) is a small herb available in the Himalayan region from Kashmir to Sikkim. Dried rhizomes of the plant are being used for medical treatment. The extract made from the rhizomes has been shown to have antioxidant activity equal to that of a-tocopherol and BHA (Ramesh *et al*., 1991). Recently it has observed that the *P. kurroa* extract could scavenge oxygen free radicals such as superoxides, hydroxyl radicals and inhibited lipid peroxidation induced by Fe2+ ascorbate system in rat liver homogenate (Joy and Kuttan, 1995). It has been known that alloxan induces its diabetogenic activity mainly by inducing oxygen free radicals and thereby damaging the pancreas (Hal liwell and Gutteridge, 1985). *P. kurroa* extract was found to reduce the glucose level in normal, glucose loaded animals and in animals made diabetic with alloxan. Alloxan has been shown to induce free radical production and cause tissue injury (Halliwell and Gutteridge, 1985). The pancreas is especially susceptible to the action of alloxan-induced free-radical damage.

It was reported earlier that *P. kurroa* extract can act as a free radical scavenger in vitro (Joy and Kuttan, 1995) and it indicates that administration of *P. kurroa* can reduce the level of serum lipid peroxides as well as ameliorate the destruction of WBC and confirms the possibility that the major function of the extract is on the protection of vital tissues including the pancreas, thereby reducing the causation of diabetes in these animals.

***Eugenia jambolana* (Myrtaceae)**

Eugenia jambolana (EJ) of family Myrtaceae (called black plum in English and Jamun in Hindi in India) is being widely used to treat diabetes by the traditional practitioners over many centuries (Nadkarni, 1954; Sharma *et al.,* 2006). It is a large evergreen tree growing up to 30 m high found widely in India. It is also found in Thailand and Philippines. Its fruits are oval to elliptical 1.5–3.5 cm long, dark purple or nearly black, luscious, fleshy and edible (Sharma *et al.,* 2006). The anti-hyperglycemic activity of seeds of EJ is well established (Shrotri *et al.,* 1963; Bansal *et al.,* 1981; Kohli, 1983; Achrekar *et al.,* 1991; Grover *et al.,* 2000; Vikrant *et al.,* 2001).

However, there is little information on the effect of this plant extract in different types of diabetes and its role in improving lipid profiles except for the one by Sharma *et al.* (2003). They compared the ethanolic extract's effect on severe diabetic (SD) rabbits (type-I or IDDM) where pancreas was near totally to destroy and when the mildly diabetic (MD) rabbits (type 2 or NIDDM) still had functional b cells.

Discussion and Conclusion

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. Moreover, uncontrolled diabetes leads to 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 methods used in the experiments are diverse. Transient hyperglycaemia can be produced by an oral glucose tolerance test (OGTT). However, the diabetic model that was most commonly used was the streptozotocin- and alloxan-induced diabetic mouse or rat to obtain type I diabetic models.

This review 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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Declarations of Interest

The authors report no declarations of interest.

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