Therapeutic use of bitter melon for diabetes.

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Abstract

Diabetes mellitus is among the most common disorder in developed and developing countries, and the disease is increasing rapidly in most parts of the world. It has been estimated that up to one-third of patients with diabetes mellitus use some form of complementary and alternative medicine. One plant that has received the most attention for its anti-diabetic properties is bitter melon, *Momordica charantia* (*M. charantia*), commonly referred to as bitter gourd, karela (India) and balsam pear (Africa). Its fruit is also used for the treatment of diabetes and related conditions amongst the indigenous populations of Asia, South America, India and East Africa. Abundant pre-clinical studies have documented in the anti-diabetic and hypoglycemic effects of *M. charantia* through various postulated mechanisms.

Keywords: *Momordica charantia*, hypoglycemic agents, Diabetes, Bitter melon, Medicinal plant, bioactive compounds, Insulin, Glucose metabolism

Introduction

Diabetes mellitus is considered as one of the five leading causes of death in the world [1]. Diabetes mellitus is a major global health concerning with a projected rise in prevalence from 171 million in 2000 to 366 million in 2030[2]. It is a syndrome of disordered metabolism, usually due to a combination of hereditary and environmental causes, resulting in abnormally high blood sugar levels (hyperglycemia)[3]. Being a major degenerative disease, diabetes is found in all parts of the world and it is becoming the third most lethal disease of mankind and increasing rapidly [4]. In India, there are estimated 77 million people above the age of 18 years are suffering from diabetes (type 2) and nearly 25 million are prediabetes (at a higher risk of developing diabetes in near future). More than 50% of people are unaware of their diabetic status which leads to health complications if

not detected and treated early. Adults with diabetes have a two- to three-fold increased risk of heart attacks and strokes. Combined with reduced blood flow, neuropathy (nerve damage) in the feet increases the chance of foot ulcers, infection, and the eventual need for limb amputation. Diabetic retinopathy is an important cause of blindness and occurs as a result of long-term accumulated damage to the small blood vessels in the retina. Diabetes is among the leading causes of kidney failure [5].

Prevalence of diabetes and trends over time

Impaired glucose tolerance (estimates) [20-79 years]	Year-2019	Year-2045
Number of people (million)	25.2	35.7
Rank	4	3
Diabetes (estimates) [20-79 years]		
Prevalence (%)	8.9	-
Age adjusted prevalence (%)	10.4	-
Number of people (million)	77.0	134.2
Rank	2	2
Diabetes (estimates) [>65 years]		
Number of people (million)	12.1	27.5
Rank	3	2

Undiagnosed diabetes (estimates)		
Prevalence (%)	57.0	-
Number of people (million)	43.9	-
Rank	2	
Healthcare expenditure on diabetes		
Mean expenditure per person with diabetes (USD)	92.0	-
Deaths related to diabetes		
Total deaths (million)	1.0	-

Ref - *USD - US dollars; Source IDF Diabetes Atlas 2019

Plant-based anti-diabetic medicine

Plant-based medicine has been used cost-effectively worldwide to treat diabetes. In fact, in many parts of the world, especially poor countries, this may be the only form of therapy available to treat diabetic patients. There are several reviews by different authors about anti-diabetic herbal plants [1],[6]–[7]. Ayurveda and other traditional medicinal systems for the treatment of diabetes describe a number of plants used as herbal drugs. Hence, they play an important role as alternative medicine due to less side effects and low cost. The active principles present in medicinal plants have been reported to possess pancreatic β cells regenerating, insulin releasing and fighting the problem of insulin resistance [8]. Hyperglycemia is involved in the etiology of development of diabetic complications. Hypoglycemic herbs increase insulin secretion, enhance glucose uptake by adipose or muscle tissues and inhibit glucose absorption from intestine and glucose production from liver [9]. Insulin and oral hypoglycemic agents like sulphonylureas and

biguanides are still the major players in the management, but there is quest for the development of more effective anti-diabetic agents.

From the current literature, it is evident that *M. charantia* is the most widely used and popular anti-diabetic plant. Thus, this review will concentrate mainly on *M. charantia* and its anti-diabetic properties.

Nutrient profile

Bitter melon is a powerful nutrient-dense plant composed of a complex array of beneficial compounds. These include bioactive chemicals, vitamins, minerals and antioxidants which all contribute to its remarkable versatility in treating a wide range of illnesses. The fruits contain high amounts of vitamin C, vitamin A, vitamin E, vitamins B1, B2 and B3, as well as vitamin B9 (folate). The caloric values for leaf, fruit and seed were 213.26, 241.66 and 176.61 Kcal/100 g respectively [10].

The fruit is also rich in minerals including potassium, calcium, zinc, magnesium, phosphorus and iron, and is a good source of dietary fiber (bitter melon "monograph", 2008). Medicinal value of bitter melon has been attributed to its high antioxidant properties due in part to phenols, flavonoids, isoflavones, terpenes, anthroquinones, and glucosinolates, all of which confer a bitter taste [11].

Fig. 1 Table content are for 100 gram of bitter melon [12].

Name	Amount	Unit
Water	91.3	g
Energy	41	kcal
Protein	0.82	g
Total lipid (fat)	2.72	g
Carbohydrate, by difference	4.19	g
Fiber, total dietary	1.9	g
Sugars, total including NLEA	1.89	g
Calcium, Ca	9	mg
Iron, Fe	0.37	mg
Magnesium, Mg	16	mg
Phosphorus, P	35	mg

Name	Amount	Unit
Potassium, K	309	mg
Sodium, Na	127	mg
Zinc, Zn	0.75	mg
Copper, Cu	0.032	mg
Selenium, Se	0.2	µg
Vitamin C, total ascorbic acid	31.9	mg
Thiamin	0.049	mg
Riboflavin	0.051	mg
Niacin	0.271	mg
Vitamin B-6	0.056	mg
Folate, total	49	µg
Folic acid	0	µg
Folate, food	49	µg
Folate, DFE	49	µg
Choline, total	10.7	mg
Vitamin B-12	0	µg
Vitamin B-12, added	0	µg
Vitamin A, RAE	17	µg
Retinol	11	µg
Carotene, beta	71	µg
Carotene, alpha	0	µg
Cryptoxanthin, beta	0	µg
Lycopene	0	µg
Lutein + zeaxanthin	1280	µg
Vitamin E (alpha-tocopherol)	0.48	mg
Vitamin E, added	0	mg
Vitamin D (D2 + D3)	0	µg
Vitamin K (phylloquinone)	6.9	µg
Fatty acids, total saturated	0.684	g
SFA 4:0	0.018	g
SFA 6:0	0.013	g
SFA 8:0	0.007	g
SFA 10:0	0.017	g
SFA 12:0	0.02	g
SFA 14:0	0.064	g
SFA 16:0	0.378	g
SFA 18:0	0.141	g
Fatty acids, total monounsaturated	0.905	g
MUFA 16:1	0.014	g
MUFA 18:1	0.871	g

Name	Amount	Unit
MUFA 20:1	0.012	g
MUFA 22:1	0	g
Fatty acids, total polyunsaturated	0.833	g
PUFA 18:2	0.747	g
PUFA 18:3	0.086	g
PUFA 18:4	0	g
PUFA 20:4	0.001	g
PUFA 20:5 n-3 (EPA)	0	g
PUFA 22:5 n-3 (DPA)	0	g
PUFA 22:6 n-3 (DHA)	0	g
Cholesterol	2	mg
Alcohol, ethyl	0	g
Caffeine	0	mg
Theobromine	0	mg

Anti-diabetic effect of bitter melon

There are many traditional herbal remedies that have been used to treat diabetes in Asia and other developing countries [13],[14]–[16]. *M. charantia* is one of the plants that has been investigated thoroughly for the treatment of diabetes [17]. With the traditional use supported by modern scientific evidence of the beneficial function of *M. charantia*, it is one of the most promising plants for diabetes today [18],[19]. Investigation of the traditional uses of *M. charantia* in India revealed that it is one of the most important plant for lowering blood glucose levels in patients with diabetes [20].

Possible modes of action of M. charantia and its extraction method

M. charantia and its various extracts and components are believed to exert their hypoglycemic effects via different physiological, pharmacological and biochemical modes [21]–[23]. The possible modes of the hypoglycemic actions of *M. charantia* and its various extracts and compounds are its hypoglycemic effect[24],[25], stimulation of peripheral and skeletal muscle glucose utilization[26],[27], inhibition of intestinal glucose uptake[28]–[30], inhibition of adipocyte differentiation[31], suppression of key gluconeogenic enzymes[32],[33], stimulation of key enzyme of HMP pathway[32], and preservation of islet β cells and their functions[34]. Today, over 140 different studies worldwide have investigated anti-hyperglycemic and hypoglycemic effects of the

different extracts and ingredients of *M. charantia* in both human and animal models [32],[33]

According to Kim and Kim, *M. charantia* extract suppressed the activation of mitogen-activated protein kinases (MAPKs) including stress-activated protein kinase/c-Jun N-terminal kinase (SAPK/JNK), p38, and p44/42, and the activity of NF-κB [35]. The findings suggest that *M. charantia* protects pancreatic β-cells through down-regulation of MAPKs and NF-κB in MIN6N8 cells. A similar study suggest that *M. charantia* improves the serum and liver lipid profiles and serum glucose levels by modulating PPAR-γ gene expression [36]. According to Ragasa *et al.*, clerosterol and 5α-stigmasta-7-en-3β-ol were isolated as sterols from *M. charantia* having significant hypoglycemic effects [24]. *M. charantia* was identified to possess a potent neuroprotective activity against global cerebral ischemia-reperfusion induced neuronal injury and consequent neurological deficits in diabetic mice [37]. Protein tyrosine phosphatase 1B (PTP1B), a negative regulator of insulin signaling, has served as a potential drug target for the treatment of type 2 diabetes [38]

Bioactive compounds

Based on the multitude of medical conditions that bitter melon can treat, scientists are more and more interested in studying its bioactive compounds and their actions on the body. However, as many studies report, there has been substantial emphasis on the anti-diabetic compounds and their hypoglycemic properties [41],[42]. A number of reported clinical studies have shown that bitter melon extract from the fruit, seeds, and leaves contain several bioactive compounds that have hypoglycemic activity in both diabetic animals and humans[32],[33].

Momordicine II and 3-hydroxycucurbita-5, 24-dien-19-al-7, 23- di-O-β-glucopyranoside (4), were isolated as saponins from *M. charantia*. Both compounds showed significant insulin releasing activity in MIN6 β-cells at concentration of 10 and 25 µg/mL [43]. The major compounds that have been isolated from bitter melon and identified as hypoglycemic agents include charantin, polypeptide-p and vicine.

Charantin

Charantin is a typical cucurbitane-type triterpenoid in *M. charantia* and is a potential substance with antidiabetic properties [44],[45]. Pitiphanpong *et al.* demonstrated that charantin could be used to treat diabetes and can potentially replace treatment. It is a mixture of two compounds, namely, sitosteryl glucoside and stigmasteryl glucoside [46]. Chen *et al.* isolated 14 cucurbitane triterpenoids, kuguacins, including two

pentanorcucurbitacins, one octanorcucurbitacin, and two trinorcucurbitacins, along with six known analogues from the vines and leaves of *M. charantia* [47]. The charantin from bitter melon fruit was extracted and estimated by high performance thin layer chromatographic method [48].

Studies have reported that the compound is more effective than the oral hypoglycemic agent tolbutamide [49]. In a study, two aglycones of charantin were isolated and identified as sitosterol and stigmastadienol glycosides, however, when tested separately for their hypoglycemic effects *in vivo*, these two constituents did not produce any notable changes in blood glucose levels [50]. This is an indication that charantin may contain other specific components, yet to be identified, that are responsible for the hypoglycemic activity observed in diabetics.

Polypeptide-p

Bitter melon is one of the most commonly used vegetable that contains polypeptide-p and is used to control diabetes naturally [51]. Polypeptide-p or p-insulin is an insulin-like hypoglycemic protein, shown to lower blood glucose levels in gerbils, langurs and humans when injected subcutaneously [52]. The p-insulin works by mimicking the action of human insulin in the body and thus may be used as plant-based insulin replacement in patients with type-1 diabetes [53]. Recently, Wang *et al.* have cloned and expressed the 498 bp gene sequence coding for the *M. charantia* polypeptide p gene and have also proved the hypoglycemic effect of the recombinant polypeptide in alloxan induced diabetic mice [54]. The oral intake of the extract from bitter melon seeds does produce hypoglycemic effects in streptozotocin (STZ) induced type-1 diabetic rats [55]. This indicates that compounds in bitter melon seeds other than p-insulin may also be effective in the treatment of type-1 diabetes.

Vicine

The other major compound that has been isolated from the seeds of bitter melon is a glycol alkaloid known as vicine [56]. This pyrimidine nucleoside has been shown to induce hypoglycemia in non-diabetic fasting rats by intraperitoneal administration [57]. However, vicine found in fava bean has been shown to induce favism, an acute disease characterized by hemolytic anemia, in individuals with a hereditary loss of the enzyme glucose-6-phosphatedehydrogenase [58]. Although there have been no reports on favism induced by bitter melon, individuals susceptible to the disease should avoid eating the fruit. Further studies are required to ensure the safety and efficacy of using vicine to treat hyperglycemia.

Other components

Many other bitter melon constituents have been identified and isolated by various extraction techniques. The first study to show the *in vivo* hypoglycemic activity of the major compounds of bitter melon was done by a group of Japanese scientists. They isolated 11 compounds by fractionation of a methanol extract from dried bitter melon fruits. The structure of three cucurbitane triterpenoids were determined, as well as two other major compounds that were tested and shown to significantly lower blood glucose levels in diabetic mice[59]. Four compounds that may be responsible for the bitter taste of the plant were isolated and identified as momordicosides K and L, and momordicines I and II. The last two compounds isolated were identified as sitosterol and stigmastadienol, the aglycones of charantin [50].

Bitter melon and glucose metabolism

its insulin-like effects on skeletal muscle cells, daily oral intake of bitter melon fruit juice over a period of 10 weeks significantly reduced the amount of Na^+ and K^+-dependent ^{14}C-D-glucose absorbed by rat jejunum brush border membrane vesicle compared to vesicles obtained from STZ-induced diabetic rats[41]. Taken together, these results clearly demonstrated that *M. charantia* and its extracts can directly regulate blood glucose via two mechanisms. Firstly, it can regulate how much glucose is absorbed by the gut into the blood following a meal and secondly, it can stimulate glucose uptake into skeletal muscle cells just like insulin. Moreover, it seems to exert its effect via the same intracellular signaling pathways as insulin in regulating glucose metabolism in the body [42].

Conclusion

The concept of food as medicine is a central theme in dietetic and nutritional sciences. *M. charantia* has been used as dietary supplements and ethnomedicine throughout centuries for relieving symptoms and conditions related to what we know in modern days as diabetes. To date, *M. charantia* has been extensively studied worldwide for its medicinal properties to treat a number of diseases [19]. It is described as a versatile plant worthy of treating almost any disease inflicted on mankind. This may be due to the fact that the

plant possesses over 225 different medicinal constituents [21]. These different compounds may act either separately or together to exert their medicinal effects. In relation to diabetes, only charantin, insulin-like peptide and alkaloid-like extracts possess hypoglycemic properties similar to the plant itself or its crude extracts. These different compounds seem to exert their beneficial effects via several mechanisms to control and treat diabetes mellitus.

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