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A REVIEW ON ANTIDIABETIC POTENTIAL OF *M. CHARANTIA* LINN.

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Abstract: The plant *Momordica charantia* belongs to the family cucurbitaceae and is commonly known as bitter melon. Bitter melon grows in tropical and subtropic areas, including parts of East Africa, Asia, the Caribbean, and South America, where it is used as a food as well as a medicine. It produces beautiful flowers and prickly fruit .The fruit of this plant lives up to its name—it tastes bitter. Although the seeds, leaves, and vines of bitter melon have all been used, the fruit is the safest and most prevalent part of the plant used medicinally. Bittermelon contains steroidal saponins known as charantin, insulin-like peptides and alkaloids, which gives it hypoglycemic ability. Charantin stimulates the release of insulin and blocks the formation of glucose in the bloodstream, which may be helpful in the treatment of diabetes particularly in non-insulin dependent diabetes. Charantin posesses pancreatic and extra-pancreatic action, and has a slight antispasmodic and anticholinergic effect. The immature fruit of *M.charantia* is cucurbitacius. Cucurbitacius is comprised of a group of triterpenes including momordicosides, A-E, K, L, and momardicius I, II and III.

Keywords: *Momordica charantia,* diabetes mellitus, cucurbitaceae, charantin, momordicosides, p-insulin.

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INTRODUCTION

One of the major chronic illnesses associated with the development of cardiovascular disease is diabetes mellitus. This disease has become a pandemic in many developed countries and is causing the Canadian health care system up to $9 billion dollars per year.[1]

Diabetes mellitus, commonly referred to as diabetes, is a medical condition associated with abnormally high levels of glucose (or sugar) in the blood (hyperglycemia).[2,3] Diabetes mellitus is a clinical syndrome characterized by hyperglycaemia due to irresponse of Insulin or Diabetes mellitus is characterized by hyperglycaemia, glycoseuria, hyperlipidemia, negative nitrogen balance and sometimes ketonemia. The two major types of diabetes mellitus were given names descriptive of their clinical presentation are Type I or IDDM (Insulin-dépendent diabètes mellitus) & Type II or NIDDM (Non insulin-dépendent diabètes mellitus).[4] Type-1, also known as juvenile diabetes, is less common and often develops during childhood in individuals with a malfunctioning pancreas that produces little or no insulin. The most common type of diabetes is type-2, which used to be called adult-onset diabetes since the disease usually develops in adults. In type-2 diabetes, the pancreas can produce insulin, but the body's cells do not respond to it.[5] The number of individuals diagnosed with type-2 diabetes is continuing to rise worldwide, and the incidence in children and adolescents is also increasing.[6]

Diabetes is also associated with oxidative stress that plays an important role in the development of diabetes complications. An advanced production of free radicals due to diabetes causes membrane damage and further promotes lipid peroxidation.[7] Medications such as sulfonylurea are generally utilized in the management of type II diabetes, however, they are accompanied with side effects. Recently, some researchers had manifested an increasing interest towards traditional medicinal plants. Many traditional plants have been identified to have hypoglycemic activities.[8] One of these plants is *Momordica charantia* (MC), also known as karalla or bitter melon that belongs to the

cucurbitacea family. MC is consumed in South Asia, Africa, South America and oriental countries as a food item and medicinal plant for treating various diseases such as diabetes mellitus.[9]

Fig. Bitter-melon fruit

The hypoglycemic activity of MC fruit extract[10] MC seed[11]and whole plant extract[12] has been confirmed in experimental animals. MC is competent in lowering fasting serum glucose in patients with type II diabetes[13] and improving the glucose tolerance.[14] Previous studies had reported that MC enhances insulin secretion[11] and increases the number of pancreatic B-cells in the islets of Langerhans[15]

There are several possible mechanisms of hypoglycemic activity of MC. Some previous studies had also revealed that MC increases the glucose uptake in liver via promoting glucose-6-phosphate dehydrogenase and declining glucose-6- phosphatase activities. In addition, it could also increase the mRNAexpression of glucose transporter 4 (GLUT4) proteins in skeletal muscles. Mahomoodally et al. (2007) suggested that MC fruit extract can reduce glucose transport via the brush border of small intestine in albino rats. Wu and Ng (2008) had reported free radical scavenging activities of MC aqueous and ethanol extracts. The antioxidant compounds of MC include phenolic phytochemicals and vitamins such as C and A which were isolated from this plant. Recently, cucurbitane-type triterpenoids were isolated from the stems of MC and demonstrated their antioxidant activity.[16]

Morphology

The plant of *M. charantia* is annual herb with long, much branched, angled and grooved, more or less pubescent or hairy. Tendrils simple, slender, elongated stem. Leaves are almost orbicular in outline, 5-12.5 cm diameter, pubescent or subglabrous on both sides, cordate at base, deeply divide into 5-7 lobes, the lobes acute or subacute, apiculate, coarsely spinous-dentate.petioles 2.5-5 cm long, channelled, pubescent. Flower are monoecious. Male flowers solitary; peduncles 5-10 cm long, glabrous or pubescent, calyx 8-10 mm long, elliptic subacute.corolla somewhat irregular, lemon yellow, segment obtuse, 1.6- 2 cm long veined. Female flower: peduncles 5-10 cm long, slender, bracteates usually at near the base. Fruit bright orange coloured, 5-15 cm long pendulous, fusiform, usually pointed, ribbed. Seeds are 8-13 mm long, compressed, corrugate on the margin, sculptured on both faces.[17,18]

Phytochemical Nature

The major constituent is Charantin (1:1 mixture of stigma- stadienol β-D-glucoside and β-sitosterol β-D- glucoside), momordicosides A & B, vicine a non protein nitrogenous base. Others constituents are Triterpene glycosides like momordicosides C, D, E (from seed), momordicosides G, F_1, F_2, I, and two bitter momordicosides K and L, momordicines I & II, cycloeucalenol, spinasterol, stigmasterol, goyaglycosides -a, -b, -c, -d, -e, -f, -g and -h and goyasaponins I, II, and III. Steroidal glucoside like momorcharaside A and B, cucurbitane Pentacyclic triterpenes like Momordocin, momordocinin, momordocilin. Sterol like momordenol, monocyclic alcohol, momordol isolated from fruits, α- and –βmomorcharin from

seeds. Seed oil contains fatty acid like stearic acid, two types of sterols like 4- monomethyl sterol and 4-desmethyl sterols[19,20,21]

Lodikar et al[22]has isolated a non-nitrogenous substance identified as a "charantin." from the fruits of *M. charantia*. Charantin is a mixture of sitosteryl-3β-D-Glucoside and 5, 25-stigmastadiene-3 β-ol D-Glucoside. It is a whitish crystalline material melting at 266-268 ^{0}C with decomposition.

Baldwa et al[23] has isolated Gamma-aminobutyric acid and an insulin-like compound from the fruits and tissue cultures of *M. charantia L.* this plant insulin has 17 amino acids in two chains bound together with sulfide bonds. The infra-red spectrum was super imposable of that on standard zinc crystalline bovine insulin. This plant insulin is stable at 4^{0}C and is denatured by heat.

Ulubelen et al[24] has isolated and identified Additional compounds from the tissue cultures of the unripe fruits of *M. charantia*. These are diosgenen β-sitosterol, 7-stigmasten-ol, 5-stigmasten-3 β, 25 diol, 5, 25-stigmastadiene-3 β -ol and 7, 25-stigmastadiene-3 β -ol. The leaves yielded additional compounds such as n-octacosans (C28H58), triacontanol (C30H62O) and a new phytosphingosin. Okabe et al[25] has isolated two triterpene glycosides, momordicosides A and B, from the seeds on *M.charantia L.* Structures were shown as the 2-O-β -gentiobioside and 3-O- β –Dxylopyranosyl of cucurbit-5-ene-3 β,22(s),13(R),25-pentaol.

Miyahara et al[26] has isolated three triterpene glycosides named momordicosides C, D and E from the seeds of *M. charantia*. The structures were determined as 3-O- β -gentiobiosides of cucurbit-5ene-3 β,23,24,25-tetraol;cucurbita-5, 24-diene-3 β,22,23, triol and 3 β -hydroxy-23,24,25,26,27-penanor-20(Ę)-cucurbit-en- 22-al, respectively.

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 fruit is also rich in minerals including potassium, calcium, zinc, magnesium, phosphorus and iron, and is a good source of dietary fiber[27]

An insulin-like hypoglycemic protein known as polypeptide-p or p-insulin was isolated from the fruits, seeds and leaves of bitter melon and shown to lower blood glucose levels in gerbils, langurs and humans when injected subcutaneously[28]

The other major compound that has been isolated from the seeds of bitter melon is a glycoalkaloid known as vicine. This pyrimidine nucleoside has been shown to induce hypoglycemia in non-diabetic fasting rats by intraperitoneal administration.[29]

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.[30]

Antidiabetic activity of *M. charantia*

An alternative to using synthetic antidiabetics to help control blood glucose is the use of herbal plants. There are many traditional herbal remedies that have been used to treat diabetes in Asia and other developing countries. One plant that has received the most attention for its anti-diabetic properties is bitter melon, *Momordica charantia*, commonly referred to as bitter gourd, karela and balsam pear.[31]Chronic administration of hydro alcoholic Karela fruit extracts along with seeds in crude form (100mg/kg) for 14 days significantly reduces the blood glucose level. There was significant decrease in the blood glucose level in the 7th[$p<0.01$] and 14th [$p<0.001$] days of the diabetes induction, showing antidiabetic effect. Each bar represent the mean ± SEM (n=6).*$p<0.01$,**$p<0.001$ when compared against control group .The data were analyzed by one way ANOVA followed by post –hoc Newman-Keuls multiple comparison test.[32]

The effects of dietary bitter melon (*Momordica charantia*) freeze-dried powder on serum glucose level and lipid parameters of the serum and liver were studied in rats fed diets supplemented with and without cholesterol. Rats were fed the diets for 14 days containing bitter melon freeze-dried powder at the level of 0.5, 1 and 3% without an added dietary cholesterol (experiment I) and those containing bitter melon at the level of 1% with or without 0.5% cholesterol and 0.15% bile acid (experiment II). Dietary bitter melon resulted in a consistent decrease in serum glucose levels in rats fed cholesterol-free diets.[33]

Charantin administered at a 50mg/kg dose reduced hyperglycemia in rabbits by 42%. Charantin posesses pancreatic and extra-pancreatic action, and has a slight antispasmodic and anticholinergic effect.[34] P-isulin (or v-insulin, for vegetable insulin) is a large polypeptide structurally and pharmacologically comparable to bovine insulin. Subcutaneous and intramuscular administration of p-insulin produced hypoglysemic effects in diabetic patients, the peak effect was observed after 4-8 hours as compared to 2 hours for bovine insulin.[35]

In diabetic rabbits the glycemia decreased by 15.93% ten hours after the administration of the alcoholic extract in dose of 2 ml/kg body weight; the seeds of Momordica charantia Linn. reduced glycemia by 27.42% when administered in dose of 1.5 g/kg body weight. In alloxan recuperated rabbits, 5 hours after administration of the seeds, glycemia dropped 19.26%.[36] Orally administered *M. charantia* extracts lower glucose concentrations independently of intestinal glucose absorption and involve an extra pancreatic effect.[37] The hypoglycemic mechanism, the *M. charantia* extract seems to act like insulin or via insulin secretion from the pancreas, like the action of sulfonyl ureas.[38]

Hypoglycemic effects of fruit pulp, seed, and whole plant of *M. charantia* on normal and diabetic model rats showed that in the NIDDM model rats the saponin-free methanol extract of juice produced a significant hypoglycemic effect both in fasting and in postprandial states. Methanol extracts of seed and of whole plant, and saponin-free methanol extract of whole plant produced no hypoglycemic effects in normal or IDDM model rats either in fasting or in postprandial states.[39]

Wistar rats rendered hyperglycemic by streptozotocin (50 mg/kg b.w., i.p.) were maintained on a semisynthetic diet containing freeze dried bitter gourd powder at 0.5% level for 6 weeks. Dietary bitter gourd did not show any beneficial hypoglycemic influence as evidenced by the blood glucose levels as well as the excretion of diabetes related metabolites.[40]

M. charantia fruit extract, 500 mg kg-1, depressed the plasma glucose levels by 10-15% at 1 h. *M. charantia* extract (500 mg kg-1) caused a 4-5-fold increase in the rate of glycogen synthesis from U-14C-glucose in the liver of normally fed rats. These data suggest that the mechanism of action of *M. charantia* could be partly attributed to increased glucose utilization in the liver rather than an insulin secretion effect.[41]

M. charantia fruit juice on the distribution and number of alpha, beta and delta cells in the pancreas of streptozotocin (STZ)-induced diabetic rats using immunohistochemical methods suggested that oral feeding of *M. charantia* fruit juice may have a role in the renewal of beta cells in STZ-diabetic rats or alternately may permit the recovery of partially destroyed beta cells.[42]

CCl4 + C6H6 MC soft was selected for pharmacological interaction study with metformin and glibenclamide in 15 patients of NIDDM, with ages ranging 52–65 years. CCl4 + C6H6 MC soft significantly increases the hypoglycemic effect of – half dose (0.25 g) of metformin by 10% (F) and 17% (PP), half dose (2.5 mg) of glibenclamide by 11% (F) and 15% (PP) and half doses both of metformin and glibenclamide in combination by 13% (F) and 21% (PP) in comparison to the hypoglycemic effect obtained by their full doses.[43]

Extracts of Momordica charantia have also been shown to rapidly decrease and normalize blood sugar levels in alloxan- or streptozotocin-induced diabetes mellitus. A water-soluble peptide fraction of Momordica was found to be effective in normalizing blood sugar levels with oral administration.[44] Different fractions of the fruits and seeds exhibited antilipolytic activity, resembling insulin by inhibiting hormone-induced lipolysis.[45] Two of the active compounds were identified as peptides with similar aminoacid compositions.[46] The effect of the insulin-like peptide on the lipid profile is not clear since it had no action on steroidogenesis, but other studies demonstrated antilipolytic activity.[47]

Extracts of the fruit reversed some of the complications of diabetes in the liver and kidneys in experimental diabetes, with effective glucose control,[48] and reversed the effect of chronic diabetes on the modulation of both P450-dependent monooxygenase activities and GSH-dependent oxidative stress.[49] In a clinical study of Momordica in diabetic patients, hypoglycemic effects were accompanied by significant adaptogenic properties indicated by a delay in the appearance of cataracts and other secondary complications of diabetes.[50] The treatment of *M. charantia* to the diabetic induced animals showed the decrease of lactate and slight increase of pyruvate.[51]

A clinical trial of nine patients with confirmed Type-1 diabetes found that subcutaneous injection of an MC extract containing crystalline p-insulin resulted in statistically significant decrease in blood sugar levels compared with controls. Fasting blood sugar was drawn prior to administration of p-insulin and plasma glucose levels were used to determine dosage of p-insulin given to each patient. The onset of p-insulin effect was noted 30-6- minutes after administration, with peak effect ranging widely from 4-12 hours.[52]

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