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ANTIDIABETIC EFFECTS OF KARVELLAK (*Momordica charantia*) : A REVIEW

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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, Karvellak (*Momordica charantia*), commonly referred to as bitter gourd, karela and balsam pear. Its fruit is also used for the treatment of diabetes and related conditions amongst the indigenous populations of Asia.

Karvellak (*Momordica charantia*) is an excellent source of vitamins and minerals that made it extensively nutritious. Moreover, the seed, fruit and leave of the plant contain bioactive compounds with a wide range of biological activities that have been used in traditional medicines in the treatment of several diseases, including inflammation, infections, obesity and diabetes.

The hypoglycemic effect of Karvellak or Karela (*Momordica charantia*) has been reported from many laboratories. To our knowledge the underlying biochemical mechanism of action of this important clinical effect has not been reported. During the course of investigation of this aspect of the herbal fruit, it was reported from our laboratory that ethanolic extract of *Momordica charantia* suppressed gluconeogenesis in normal and streptozotocin (STZ) induced diabetic rats by depressing the hepatic gluconeogenic enzymes fructose-1, 6-bisphosphatase and glucose-6-phosphatase.

Keywords: *Momordica charantia*, Hypoglycaemic agents, Diabetes, Bitter melon, Medicinal plant, Bioactive compounds, Insulin, Glucose metabolism.

Introduction: According to World Health Organization (WHO), medicinal plants are an accessible, affordable and culturally appropriate source of primary health care for more than 80% of Asia's population [1]. Despite all the progress in synthetic chemistry and biotechnology, plants are still an indispensable source of medicinal preparations, both preventive and curative. Hundreds of species are recognized as having medicinal values and many of those are commonly used to treat and prevent specific ailments and diseases [2]. *Momordica charantia*

(called bitter melon or bitter gourd in English or Karela in Bangla) is a tropical and subtropical vine of the family Cucurbitaceae, widely grown in Asia, Africa and the Caribbean for its edible fruit, which is among the most bitter of all fruits, is one of the well known medicinal plants.

In the last few years there has been an exponential growth in the field of herbal medicine and these drugs are gaining popularity both in developing and developed countries because of their natural origin and less side effects. Many traditional medicines in

use are derived from medicinal plants, minerals and organic matter ^[3]. In Indian systems of medicine most practitioners formulate and dispense their own recipes ^[4].

Momordica charantia, also known as bitter melon, is a member of the cucumber family, Cucurbitaceae. It is grown in the tropical and subtropical regions of the world. All parts of the plant, including the fruit, taste bitter. Fruits and seeds of bitter melon possess medicinal properties such as anti-HIV, anti-ulcer, anti-inflammatory, anti-leukemic, anti-microbial, anti-tumor and anti-diabetic activity. It can be used as alternative therapy for lowering blood glucose levels in diabetic patients ^[5]. This is attributed to the complex action of multiple compounds in bitter melon extract ^[6]. The bioactive compounds responsible for its hypoglycemic effect are a mixture of steroidal saponins known as charantins, insulin-like peptides and alkaloids ^[7].

Metabolomics is the comprehensive measurement of all endogenous metabolites in a biological fluid ^[8]. Through this approach, changes in metabolites profile of the biofluids can be identified. Therefore, metabolomics have been applied to diagnose diabetic patients and to identify the potential biomarkers ^[9]. The same approach can be used to study the medicinal properties of herbs as well. Thus, the underlying mechanisms of alteration in metabolic pathway associated with mechanism of medicinal herbs to treat a disease can be identified ^[10].

As diabetes has become a serious global health problem that getting more concern from nation worldwide, studies should be carried out to deliver the problem. Since there are lots of natural plant products that exhibit anti-diabetic potential, research should focus on herbal remedy as alternative therapy for diabetes treatment to reduce dependence on the synthetic drugs. One of such plants is *M. charantia*. However, the results of the previous research on *M. charantia* in the treatment of diabetes were still based on glucose and insulin analysis. More research needs to be done on a holistic analysis of metabolites in biofluids.

Plant Description: *M. Charantia* (bitter melon or bitter gourd) (Figure 1) is a flowering vine

in the family Cucurbitaceae. It is a tropical plant that is widely cultivated in Asia, India, East Africa, and South America for its intensely bitter fruits that are commonly used in cooking and as a natural remedy for treating diabetes ^[11]. It is a climbing perennial that usually grows up to 5 m, and bears elongated fruits with a knobby surface. It is a useful medicinal and vegetable plant for human health and one of the most promising plants for diabetes ^[12].



Figure 1: *M. Charantia* (bitter melon or bitter gourd)

Scientific classification

Kingdom:	Plantae
(unranked):	Angiosperms
(unranked):	Eudicots
(unranked):	Rosids
Order:	Cucurbitales
Family:	Cucurbitaceae
Genus:	<i>Momordica</i>
Species:	<i>M. charantia</i>
Binomial name	<i>Momordica charantia</i>

Plant Specification

Habitat: Common in coastal thickets, along creeks and streams and also cultivated

Parts used: Fruits, leaves and seeds

Leaves: Alternate, petiolate, blade with 5-7 deep palmate lobes and quite variable in size

Flowers: Unisexual, tubular, 5-lobed moderate sized, pole yellow to orange

Fruits: Pepo with black seeds embedded in a reddish pulp

Propagation: Via seeds and vegetation.

Nutritional value per 100 g (3.5 oz)

Energy	79 kJ (19 kcal)
Carbohydrates	4.32 g
Sugars	1.95 g
Dietary fiber	2 g
Fat	0.18 g
Protein	0.84 g

Vitamins Value per µg

Vitamins	Quantity (µg)	Percentage
Vitamin A equiv.	6 µg	(1%)
beta-carotene	68 µg	(1%)
lutein zeaxanthin	1323 µg	
Thiamine (B1)	0.051 mg	(4%)
Riboflavin (B2)	0.053 mg	(4%)
Niacin (B3)	0.28 mg	(2%)
Pantothenic acid (B5)	0.193 mg	(4%)
Vitamin B6	0.041 mg	(3%)
Folate (B9)	51 µg	(13%)
Vitamin C	33 mg	(40%)
Vitamin E	0.14 mg	(1%)
Vitamin K	4.8 µg	(5%)

Minerals Value per mg

Minerals	Quantity (mg)	Percentage
Calcium	9 mg	(1%)
Iron	0.38 mg	(3%)
Magnesium	16 mg	(5%)
Manganese	0.086 mg	(4%)
Phosphorus	36 mg	(5%)
Potassium	319 mg	(7%)
Sodium	6 mg	(0%)
Zinc	0.77 mg	(8%)

Other constituents

Other constituents	Quantity (g)
Water	93.95 g

Biological Activities: The different parts of the Karela contain following various biological activities

Root: Acrid, astringent, bitter.

Leaf: Antipyretic, bitter, emetic, purgative.

Fruits: Acrid, anthelmintic, anti-diabetic, anti-inflammatory, appetizer, bitter, depurative,

digestive, purgative, stimulant, stomachic, thermogenic^[13].

Ayurvedic Properties

Momordica charantia Linn. (Karela), a vegetable/ medicinal plant is used in the Ayurvedic system of medicine for treating various diseases including diabetes mellitus, measles, fever, hepatitis, itch etc.

According to Ayurveda it Contains

S.No.	Gunna (properties)	Laghu (light), ruksh (dry)
1.	Rasa (taste)	Katu (bitter) and tikta (pungent)
2.	Virya (potency)	Vshna (hot)

Combination of these properties makes karela a magic potion for diseases^[13].

Biochemical Constituents: The main constituents of bitter melon (Karela) are triterpene, protein, steroid, alkaloid, inorganic, lipid, and phenolic compounds^[14]. *Momordica charantia* (Karela) consists the following chemical constituents those are alkaloids, momordicin and charantin (Figure-2), charine, cryptoxanthin, cucurbitins, cucurbitacins, cucurbitanes, cycloartenols, diosgenin,

elaostearic acids, erythrodiol, galacturonic acids, gentisic acid, goyaglycosides, goyasaponins, guanylate cyclase inhibitors, gypsogenin, hydroxytryptamin es, karounidiols, lanosterol, lauric acid, linoleic acid, linolenic acid, momorcharasides, momorcharins, momordenol, momordicillin, momordicin, momordicosides, momordin, momordolo, multiflorenol, myristic acid, nerolidol, oleanolic acid, oleic acid, oxalic acid, pentadecans, peptides, petroselinic acid,

polypeptides, proteins, ribosome-inactivating proteins, rosmarinic acid, rubixanthin, spinasterol, steroidal glycosides, stigmastadiols, stigmasterol, taraxerol, trehalose, trypsin inhibitors, uracil, vacine, v-insuline, verbascoside, vicine, zeatin, zeatinriboside, zeaxanthin, zeinoxanthin Amino acids- aspartic acid, serine, glutamic acid, thscinne, alanine, g-amino butyric acid and pipercolic acid, ascorbigen, b-sistosterol-d-glucicide, citruline, elasterol, flavochrome, lutein, lycopene, pipercolic acid^[15-17].

Chemical Constituents

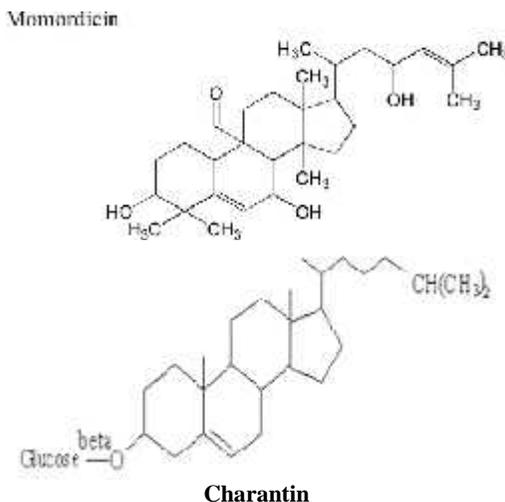


Figure-2: Phytochemicals : Momordicin and Charantin (Source: Kumar et al., 2010)

Traditional and Medicinal Uses: Karela has been used in various Asian traditional medicine systems for a long time, as useful for preventing and treating various diseases. Fruits of *Momordica charantia* (karela) used in asthma, burning sensation, colic, constipation, cough, diabetes, fever (malaria), gout, helminthiases, inflammation, leprosy, skin diseases, ulcer and wound. It has also been shown to have hypoglycaemic properties (antidiabetic) in animal as well as human studies. Juice of the Karela leaves used to treat piles completely. Karela is used as a blood purifier due to its bitter tonic properties. It can heal boils and other blood related problems that show up on the skin. Juice of karela is also beneficial in treating and preventing the liver damage^[19, 20].

Leaves are used in treatment of menstrual troubles, burning sensation, constipation, fever (malaria), colic, infections, worms and parasites, as an emmenagogue,

Fruits consists glycosides, saponins, alkaloids, reducing sugars, resins, phenolic constituents, fixed oil and free acids^[18].

Leaves are nutritious and have been reported as a source of calcium (1%), magnesium (4%), potassium (7%), phosphorus (5%), and iron (3%); fruits and leaves are great source of B vitamins; Thiamine (vit.B₁) 4%, Riboflavin (vit.B₂) 4%, Niacin (vit.B₃) 2%, (vit.B₆) 3%, Folate (vit.B₉)13%^[15-16].

2. www.rain-tree.com/bittermelon.htm

measles, hepatitis and helminthiases^[21]. In Guyana traditional medicine, leaf tea is used for diabetes, to expel intestinal gas, to promote menstruation, and as an antiviral for measles, hepatitis, and feverish condition. It is used topically for sores, wound, infections and internally and externally for worms and parasites^[22].

Seeds are used in the treatment of ulcers, liver and spleen problems, diabetes, intestinal parasites, high cholesterol, and intestinal gas, heal wounds and stomachache etc.^[16].

Roots are used in the treatment of syphilis, rheumatism, boils, ulcer, septic swellings, ophthalmia, and in *Prolapsus vagenae*^[16, 19].

Karela juice helps to reduce the problem of Pyorrhoea (bleeding from the gums). Karela capsules and tinctures are widely available in the United States for the treatment

of diabetes, viruses, colds flu, cancer, tumors, high cholesterol and psoriasis^[23].

Ethnomedical Uses: In India, *Momordica charantia* Linn. (Karela) used by tribal people for abortions, birth control, increasing milk flow, menstrual disorders, vaginal discharge, constipation, food, diabetes, hyperglycemia, jaundice, stones, kidney, liver, fever (malaria), gout, eczema, fat loss, hemorrhoids, hydrophobia, intestinal parasites, skin, leprosy, pneumonia, psoriasis, rheumatism, scabies, snakebite, vegetables, piles, tonic, anthelmintic, purgative^[14].

Medicinal Properties of Karela (*M. charantia*): Karela (*M. charantia* or Bitter melon) is traditionally known for its medicinal properties such as antidiabetic, anticancer, anti-inflammation, antiviral, and cholesterol lowering effects. It contains many phenolic compounds that may have the potential as antioxidant and antimutagen^[24]. The fruit, stems, leaves and roots of bitter melon have all been used in traditional medicine to help treat ailments such as hyperlipidemia, digestive disorders, microbial infections and menstrual problems^[25]. Bitter melon has been shown to possess powerful antiviral properties that can stimulate the immune system and activate the body's natural killer cells to help fight off viruses such as white spot syndrome virus and human immunodeficiency virus^[26-28]. Studies have also shown that bitter melon has anti-carcinogenic properties and can be used as a cytotoxic agent against many types of cancer^[29]. Ray *et al.* showed that the extract of bitter melon modulates signal transduction pathways for inhibition of breast cancer cell growth and can be used as a dietary supplement for prevention of breast cancer^[30].

Bitter melon extract can also be used as a broad-spectrum antibacterial agent to fight off infections caused by *Escherichia coli*, *Salmonella*, *Staphylococcus aureus*, *Staphylococcus*, *Pseudomonas*, and *Streptobacillus*^[31]. In addition, the plant possesses anti-helminthic properties, which are effective in the treatment of malaria. Traditionally, bitter melon has also been used as an abortifacient agent used to induce abortions. Therefore, pregnant women are advised to avoid consumption of the plant^[14].

The extract of the seed also have antispermatogenic effect^[32].

Phytochemical Properties: The medicinal values of Bitter melon lies in the bioactive phytochemical constituents that are non nutritive chemicals that produce definite physiological effects on human body and protect them from various diseases. In *M. charantia* primary metabolites are common sugars, proteins and chlorophyll while secondary metabolites are alkaloids, flavonoids, tannins and so on^[33].

Anti-diabetic effect of *M. charantia*: There are many traditional herbal remedies that have been used to treat diabetes in Asia and other developing countries^[34, 35-37]. *M. charantia* is one of the plants that have been investigated thoroughly for the treatment of diabetes^[38]. 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^[39-40]. Investigation of the traditional uses of *M. charantia* in India revealed that it is one of the most important plants for lowering blood glucose levels in patients with diabetes^[41].

Pharmacological Activity

Antioxidant Activity: Different parts of this plant have been used in the Indian medicinal system for a number of ailments besides diabetes. Antioxidant activity of extracted phenolic compound from bitter melon has been reported by^[42]. Antioxidant properties of *Momordica charantia* (Karela) Seeds on Streptozotocin induced-diabetic rats has been studied and results clearly suggest that seeds of *Momordica charantia* (Karela) may effectively normalize the impaired antioxidant status in streptozotocin induced-diabetes^[43].

Antidiabetic Activity: Karela contains bitter chemicals like, charantin, vicine, glycosides and karavilosides along with polypeptide-p a plant insulin, which are hypoglycemic in action and improve blood sugar levels by increasing glucose uptake and glycogen synthesis in the liver, muscles and fat cells. Reports indicate that they also improve insulin release from pancreatic beta cells, and repair or promote new growth of insulin-secreting beta cells. P-Insulin, a polypeptide from the fruits and seeds rapidly decreased and normalized

the blood sugar level in rats. Bitter melon contains another bioactive compound i.e. lectin that has insulin like activity. The insulin-like bioactivity of lectin is due to its linking together 2 insulin receptors. This lectin lowers blood glucose concentrations by acting on peripheral tissues and, similar to insulin's effects in the brain, suppressing appetite. This lectin is a major contributor to the hypoglycemic effect that develops after eating Karela. Charantin extracted by alcohol, is a potent hypoglycemic agent composed of mixed steroids which is sometimes used in the treatment of diabetes to lower the blood sugar levels^[18, 44-47].

Anticancerous and Antitumor Activity:

Bitter melon and its extract inhibit cancer and tumor formation. A novel phytochemical in karela has clinically demonstrated the ability to inhibit an enzyme named guanylate cyclase. This enzyme is thought to be linked to the pathogenesis and replication of not only psoriasis, but leukemia and cancer as well^[48-49]. Other phytochemicals that have been documented with cytotoxic activity are a group of ribosome-inactivating proteins named alpha and beta momorcharin, momordin and cucurbitacin B. In 1996, Lee-huang et al.^[50] have developed and patented one more chemical compound "MAP-30", which was able to inhibit prostate tumor growth. Momordin, another phytochemical has clinically demonstrated anti cancerous activity against Hodgkin's lymphoma in vivo^[51] and several other in vivo studies have shown the cytostatic and antitumor activity of the entire plant of bitter melon. Further studies reported that a water extract blocked the growth of rat prostate carcinoma and a hot water extract of the entire plant inhibited the development of the mammary tumors in mice^[49]. Numerous in vitro studies have also demonstrated the anti-cancerous and anti-leukemic activity of bitter melon against numerous cell lines including liver cancer, human leukemia, melanoma and solid sarcomas^[48-49].

Antimicrobial Activity: Sankaranarayanan and Jolly^[52] have clinically demonstrated broad spectrum antimicrobial activity of leaf extracts of Karela. They have reported the in vitro antibacterial activities of water, ethanol,

and methanol leaf extracts of Karela against *E. coli*, *Staphylococcus*, *Pseudomonas*, *Salmonella*, *Streptobacillus* and *Streptococcus*; an extract of the entire plant have shown anti-protozoal activity against *Entamoeba histolytica*. In another study, a fruit extract of Karela has demonstrated anti bacterial activity against the stomach ulcer-causing bacteria *Helicobacter pylori*^[53].

Various plant species possessed antimicrobial activity against different microorganisms^[54-56]. The antifungal potential of crude ethanolic extract of kaffir lime, bitter cucumber and tobacco has been studied by Thanaboripat et al., (2006)^[57] against *Aspergillus flavus*. Jagessar et al., (2008)^[22] evaluated antibacterial and antifungal activity of leaf extracts of *Momordica charantia* (Karela) against *Candida albicans*, *Staphylococcus aureus* and *Escherichia coli* and reported that the ethanol extracts of *Momordica charantia* (Karela), can be used for controlling *E. coli* and *S. aureus* induced diseases.

Antifertility Activity: Stepka et al., (1974)^[58] have demonstrated in vivo antifertility effect of fruit and leaf of bitter melon in female animals.

Antiviral Activity: Karela and its isolated phytochemicals, also has been documented with in vitro antiviral activity against numerous viruses including Epstein-Barr, herpes and HIV viruses^[59-60]. In an in vivo study, a leaf extract demonstrated the ability to increase resistance to viral infections as well as to provide an immunostimulant effect in humans and animals (increasing interferon production and natural killer cell activity)^[61]. Two proteins known as alpha-and beta-momorcharin (which are present in the seeds, fruit and leaves) have been reported to inhibit the HIV virus in vitro^[59-60]. In one study, HIV-infected cells treated with alpha-and beta-momorcharin showed a nearly complete loss of viral antigen while healthy cells were largely unaffected^[62]. In 1996 the inventors of the chemical protein along MAP-30 filed a U.S. patent, stating it was "useful for treating tumors and HIV infections. In treating HIV infection, the protein is administered alone or in conjunction with conventional AIDS therapies^[63]. Another clinical study showed

that MAP-30's antiviral activity was also relative to the herpes virus in vitro^[64].

Anti-Genotoxic Activity: Balboa and Lim-Sylianco, (1992)^[65] have reported that *Momordica charantia* (Karela) decreases the genotoxic activity of methylnitrosamine, methanesulfonate and tetracycline, as shown by the decrease in chromosome breakage.

Anti-Helminthic Activity: *Momordica charantia* (Karela) was found more effective in the treatment of *Ascaridia galli*^[66]. Ethanol (95%) extract of fruit juice, was found active on *Ascaridia galli*, whereas, hot water extract of seed at concentration of 1:50 was active on *Haemonchus contortus*^[67].

Anti-Malarial Activity: Karela is traditionally regarded by Asians, as well as Panamanians and Colombians, as useful plant for preventing and treating malaria. Laboratory studies have confirmed that various species of Karela have anti-malarial activity. Leaves brewed in hot water to create a tea to treat malaria^[68].

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 diabetes.

The *M. charantia* able to partially fix the altered metabolism of diabetic patients as indicated by the shifting of some metabolites profile (glucose, succinate, lactate, creatine, creatinine, urea and phenylacetyl glycine) to normal level. Hence, the *M. charantia* demonstrated to be potential anti-type 1 diabetic agent, as it is able to alter the main pathway leading to diabetic condition in treated rats although not all metabolites were shifted to normal level.

Diabetes Mellitus is a growing global metabolic epidemic. The use of karvellak (*M. charantia*) in Diabetes Mellitus is common and old but in lack of adequate better controlled human trials, we are still far from recommending it as a routine antidiabetic herbal food.

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