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Role of Karela in Diabetes: 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, *Momordica charantia* (*M. 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, South America, India and East Africa. Abundant pre-clinical studies have documented in the anti-diabetic and hypoglycaemic effects of *M. charantia* through various postulated mechanisms. However, clinical trial data with human subjects are limited and flawed by poor study design and low statistical power. The present review is an attempt to highlight the antidiabetic activity as well as phytochemical and pharmacological reports on *M. charantia* and calls for better-designed clinical trials to further elucidate its possible therapeutic effects on diabetes.

Keywords- Diabetes mellitus, Antidiabetic, Karela, Pharmacology.

I. 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]. It is the most common endocrine disorder, affecting 16 million individuals in the United States and as many as 200 million individuals worldwide. Diabetes has been a clinical model for general medicine[5]. Complementary and alternative medicine involves the use of herbs and other dietary supplements as alternatives to mainstream western medical treatment. A recent study has estimated that up to 30% of patients with diabetes mellitus use complementary and alternative medicine[6]. Medicinal plants and its products continue to be an important therapeutic aid for alleviating the ailments of human kind[7]–[9]. Herbs for diabetes treatment are not new. Since ancient times, plants and plant extracts were used to combat diabetes. Many traditional medicines in use are derived from medicinal plants, minerals and organic matter. The World Health Organization (WHO) has listed 21 000 plants, which are used for medicinal purposes around the world. Among them, 150 species are used commercially on a fairly large scale[1],[10]. *Momordica charantia* (*M. charantia*), also known as bitter melon, karela, balsam pear, or bitter gourd, is a popular plant used for the treating of diabetes-related conditions amongst the indigenous populations of Asia, South America, India, the Caribbean and East Africa[11],[12]. Its fruit has a distinguishing bitter taste, which is more pronounced as it ripens, hence the name bitter melon or bitter gourd. Biochemical and animal model experiments have produced abundant data and hypotheses accounting for the anti-diabetic effects of *M.*

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charantia. In comparison, clinical studies with human subjects are sparse and low quality in design. Diabetes mellitus is well known clinical entity with various late complications like retinopathy, neuropathy, nephropathy, *etc*. Natural products are known to play an important role in pharmaceutical biology[13]. Specific plant knowledge may provide insight for strategic consumption and sustainable use. The alternate medicine system is now gaining momentum with the knowledge of active principles identified from plant species[14]. *M. charantia* has significant antidiabetic as well as hypolipidemic activity so that it can be used as an adjuvant along with allopathic treatment of medicine to treat diabetes as well as to delay the late complications of diabetes. In the present review, we have elucidated the possible antidiabetic activity of *M. charantia* and its medicinal potency responsible for the hypoglycemic activity. Karela is one of the best gifts given by nature to us which has magical powers to treat a wide variety of diseases.

1.1. Geographical Distribution

Karela is obtained as fresh green fruit of the plant *Momordica Charantia* Linn., family Cucurbitaceae[15]. *M. charantia* is of the medicinal plants with hypoglycemic activity being studied majorly. It is a climber widely cultivated as food in Asia, Africa and South America. It is also cultivated all over India and cultivated upto an altitude of 1500 m. The word *Momordica* is derived from the Latin word *Mordeo* which means to bite and the species name is derived from Greek word and it means beautiful flower. Fruit of this plant is known as bitter melon, bitter gourd, balsam pear or African cucumber[16,17]. In the Amazon, local people and indigenous tribes grow bitter melon in their gardens for food and medicine. They add the fruit and/or leaves to beans and soup for a bitter or sour flavor; soaking it first with salt may remove some of the bitter taste. Medicinally, the plant has a long history of use by the indigenous peoples of the Amazon. Karela leaf tea is employed for diabetes; as a carminative for colic; topically for sores, wounds, and infections; internally and externally for worms and parasites; and as an antiviral for measles, hepatitis, and fever conditions[18,19].

In Brazilian herbal medicine, bitter melon is used for tumors, wounds, rheumatism, malaria, leucorrhea, inflammation, menstrual problems, diabetes, colic, fevers, worms, to induce abortions, and as an aphrodisiac. It is also employed topically for skin problems, vaginitis, hemorrhoids, itchy rashes and leprosy[20,21]. In Mexico the entire plant is used for diabetes and dysentery; the root is a majorly employed as aphrodisiac. In Peruvian herbal medicine, the leaf or aerial parts of the plant are used to treat measles, malaria, and all types of inflammation. In Nicaragua the leaf commonly is used for stomach pain, diabetes, fevers, colds, coughs, headaches, malaria, skin problems, menstrual disorders, aches and pains, hypertension, infections, and as an aid in childbirth[22,23,24,25].

Fig. 1: Geographical distribution of *M.charantia*

1.2. Scientific Classification[6]

Kingdom	-	PLANTAE
Order	-	CUCURBITALES
Family	-	CUCURBITACEAE
Genes	-	MOMORDICA
Species	-	*M.charantia*

1.4 Morphological Characters

Colour- Green when raw and yellowish when ripe, some species are white also.
Odour- slight to no smell.
Taste – bitter
Size- 20- 30 cm long generally
Shape - oblong with blunt tapering ends and pale green in colour[8]

1.5. Cultivation and Collection

It is a type of annual or perennial climbers found throughout India and is also cultivated Upto an altitude of 1500m. It is cultivated during warm season i.e. during April to July by using 2-3 seeds in a pit. [26] The pits are prepared at a distance of half a meter and provided with manures. Only one plant is retained and seedlings are watered once or twice a week. Plants begin to flower 30-35 days after sowing and the fruits are ready for harvesting 15-20 days after flowering. Bitter gourd, also known as balsam pear, is a tropical vegetable widely Cultivated in Asia, Africa and South America[27].

- **Best soil for bitter gourd farming:** The best medium for seeds is a fertile, well drained soil with a pH ranging from 5.5 to 5.7, enriched with organic matter, such as compost or dried manure. But it will tolerate any soil that provide a good drainage system (sandy loam soil, but it will grow in areas will grow in areas with poorer soils.) It should be in a free area and will prefer the climate with daytime temperatures between 24 C and 35 C. The soil must be prepared well by adding organic matter before planting. Seeds soaked in water will germinate sooner. Soil temperature for germination is at least 20 C to 25 C[28,29].
- **Time of sowing and seed rate in bitter gourd farming:** The seed is sown from January to march for summer season crop, june – july for rainy season crop in the plains and march to june in the hills. The seed rate is 4 to 5 kg/ha[30].
- **Method of sowing in bitter gourd farming:** The seed is sown by dibbling method at a spacing of 120*90

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cm. Generally 3 to 4 seeds are sown in a pit at 2.5 to 3 cm depth. The seeds are soaked in water over night before sowing for better germination. Seed germination was enhanced by soaking the seeds for 24 hrs in solution of 25 to 50 ppm GA and 25 ppm boron. In flatbed layout seeds are dibbled at the spacing 1*1 m[31].

- **Irrigation/water supply in bitter gourd farming:** Irrigation should be carried out in 3 to 4 days interval during the initial stages of plant vine growth. It is crucial to irrigate alternate days at the rime of flowering and fruiting stage. Irrigate the vines on need base, it does not require any irrigation rainy season or when there is a sufficient moisture in the soil. In case of flooding or heavy water stagnation, make sure to drain out the water problem areas, drip irrigation would be the best choice to utilize the water effectively[32].
- **Harvesting in bitter gourd farming:** The harvesting in bitter gourd farming starts from 60 to 65 days after sowing the seeds. Harvesting should be carried out when fruit

are young and tender at every alternate day. Fruits should be harvested carefully without damaging the plant vine. Unless, it grown foe seed purpose, they should not be allowed to ripe on the vines. The harvested bitter gourd can be stored for 2-3 days in cool conditions[33].

- **Yield in bitter gourd farming:** In most of the crops, yield depends upon the cultivar (variety), soil, type, climatic conditions and farm management practices. In bitter gourd farming, an average yield of 65 to 100 quintal/ha can be obtained[14].

1.6. Plant Parts Description

Leaves: simple, usually palmately 5-7 lobed, tendrils unbranched or 2 branched. The herbaceous, tendrils bearing vine grows to 5 m. It bears simple, alternate leaves 4–12 cm across, with 3–7 deeply separated lobes[35].

Fruit: ovoid, ellipsoid, or spindle shaped, usually ridged or warty, irregularly as a 3 valved fleshy capsule. The fruit has a distinct warty looking exterior and an oblong shape. It is hollow in cross-section, with a relatively thin layer of flesh surrounding a central seed cavity filled with large flat seeds and pith. Seeds and pith appear white in unripe fruits, ripening to red; the flesh is crunchy and watery in texture, similar to cucumber or green bell pepper.[36][37] The skin is soft and edible. Bitter melon comes in a variety of shapes and sizes. The typical Chinese type is 20–30 cm long, oblong with blunt tapering ends and pale green in colour, with a gently undulating, uneven surface. The bitter melon more typical of India has a narrower shape with pointed ends, and a surface covered with jagged, triangular "teeth" and ridges. Coloration is green or white. Some bear miniature fruit of only 6–10 cm in length, which may be served individually as stuffed vegetables. These miniature fruit are popular in Southeast Asia as well as India. In Panama bitter melon is known as Balsamino. The pods are smaller and bright orange when ripe with very sweet red seeds[38].

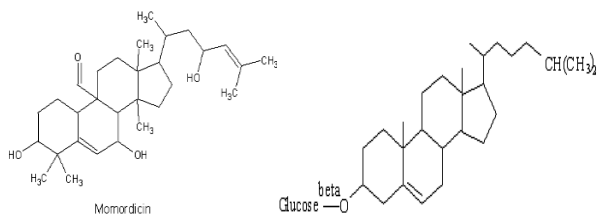
Flowers: Staminate flowers usually solitary on a bracteates scape, hypanthium shallow, calyx 5 lobed, petals 5, usually yellow, distinct, 1-3 with incurved scales at base, stamens usually 3, inserted toward base of hypanthium, filaments distinct, broad, anthers distinct or coherent, 2 of them dithecal, the other monothecal, cells curved or flexuous; pistillate flowers usually solitary on a bracteates scape, hypanthium ovoid to spindle shaped, perianth usually smaller than in staminate flowers, staminodes absent or 3, ovules numerous, horizontal, stigmas 3, 2 lobed. Seeds few to numerous, ovate, usually sculptured. Each plant bears separate yellow male and female flower[39].

Fig. 2: *M.charantia* Different Parts

1.7. Chemical Constituents

The active constituents of the fruits are triterpenes including momordicin and momordicinin, and a series of cucurbitanes, momordicosides, goyaglycosides and kuguacins; proteins including α, β and γ-momorcharins, and momordins a and b and polypeptide P, also known as vegetable or plant insulin (v- or p-insulin).[40] Pyrimidines such as such as vicine and charine are found particularly in the seed, and many sterols (including charantin), fatty acids and volatile compounds have also been identified in the fruit. The chemical composition of the leaf is less well-known, but it does contain goyasaponins[41].

Following is the list of all types of chemical constituents in the *M.charantia*. Glycosides; Momordin, charantin.



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Alkaloids; Momordicin
Others; Polypeptide-P
Oils (seeds only); Stearic acids, linoleic acids, oleic acids.
Glycoprotein; Alpha- momorcharin, beta-momorcharin, lectins.
Amino acids; aspartic acid, serine, glutamic acid, thscinne, alanine, g-amino butyric acid and pipecolic acid
Others; Vicine (pyrimidine nucleoside), protein[19,20].
The fruit pulp has soluble pectin but no free pectic acid.

1.8. Charantin

Charantin is steroidal glycoside and exist as equal mixture of stigmasterol glucoside and β-sitosterol glucoside. It has got blood sugar lowering property equivalent to insulin.

1.8.1 Description

1. It is a white crystalline, neutral and tasteless compound.
2. Charantin is freely soluble in non-polar solvents such as chloroform and dichloromethane whereas it is slightly soluble in polar solvents such as ethanol or ;methanol. Charantin is soluble in ether.
3. It's melting point ranges from 266-268 degree Celsius[21].

1.8.2 Phytochemistry

With Libermann-Burchard test charantin gives violet colour changing to blue, green and yellow. On hydrolysis with acid it produces glucose and sterol. It gives violet- blue colour and pink colour on spraying with anisaldehyde sulphuric acid reagent and vanillin sulphuric acid reagent, respectively[22].

1.8. 3 Isolation of charantin

Few attempts have been made to extract and isolate charantin from fruits of *M. charantia* using various chromatographic techniques.

Effect of different solvents (acetone, dichloromethane, ethanol and water), solvent composition (ethanol and water), solvent flow rate and temperature on extraction efficiency of charantin was evaluated. Ethanol was found to be the most effective solvent for extraction of charantin. Yield was increased with increase in temperature. Purification of charantin was done by treating extract using 50-70% of methanol solutions and pure hexane. T.B. Ng *et al.* isolated charantin from seeds of *M. charantia* by affinity chromatography, ion-exchange chromatography and gel filtration chromatography. Seeds were extracted with 10 mM Tris-HCl (pH 7.2). The extract was filtered and chromatographed on affinity column DEAE cellulose column, Affi-gel Blue gel and then by ion-exchange chromatography on Mono S column to get pure charantin. Charantin was extracted by mixing dry powder of fruits with water. The mixture was boiled and filtered. Different amounts of PEG, K2HPO4 and ethanol were added to various amounts of water extract and an aqueous two-phase system was prepared. The system was vortexed, centrifuged and charantin containing salt-rich layer was extracted with 95% ethanol. The ethanol extract thus prepared was kept overnight at 4 0C and salt was allowed to precipitate. Precipitates were removed and amount of charantin was estimated by UV spectrometry. Charantin was isolated from dried fruits by successive extraction with petroleum ether (60-80 0C) and 80% ethanol. The ethanol extract was concentrated to a small volume and basified with KOH. After 48 h, the ethanol solution was diluted with water and extracted with ether. The ether extract was washed with water, HCl and again with water. The aqueous and acid washings were discarded. The ether layer was distilled off and the residue was recrystallized several times using 95% ethanol to get charantin[23,24].

1.9. Pharmacological actions of Karela

Hypoglycaemic activity: Charantin isolated from fruits of *M. charantia* was tested for its hypoglycemic activity. In fasting rabbits, it gradually lowered blood sugar within one to four hours and recovered slowly to initial level. At an oral dose of 50 mg/kg, blood sugar level was declined by 42% at the 4th hour. The average blood sugar fall during 5 hours was 28%. Charantin was found to be more potent than tolbutamide however both compounds produced similar pattern of blood sugar change. The hypoglycaemic activity of charantin in depancreatixed cats was less, but abolished, indicating a pancreatic as well as extra-pancreatic action[42].

Cardiovascular effects: Effect of charantin on cardiovascular system was studied. At the dose of 800 mg/kg, 5-10% of blood pressure lowering of anaesthetized cat was observed. The contraction of isolated heart of frog was increased at dose of 5-10 mg and the same dose was effective to terminate action of acetylcholine[43].

Anti-sialogogue: Charantin at dose of 10-15 mg/kg delayed the onset of tremors but did not affect salivation produced by tremorine[44].

Anticancer: Bitter Melon and Bitter Melon Extracts inhibit cancer and tumor. A novel phytochemical in bitter melon 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. One clinical trial found very limited evidence that bitter melon might improve immune cell function in people with cancer, but this needs to be verified and amplified in other research. 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. A chemical analog of bitter melon proteins was developed and named MAP-30 and its inventors reported that it was able to inhibit prostate tumor growth.[45] The phytochemical momordin has clinically demonstrated cytotoxic activity against Hodgkin's lymphoma in vivo, and several other in vivo studies have demonstrated the cytostatic and antitumor activity of the entire plant of bitter melon. Further studies reportd that, a water extract

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blocked the growth of rat prostate carcinoma and a hot water extract of the entire plant inhibited the development of mammary tumors in mice. 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[46].

Digestive system: Leaf juice is purgative and emetic. It has been used in traditional Chinese medicine as an appetite stimulant, and a treatment for gastrointestinal infection. Bitter melon contains a bitter compound called momordicin that is said to have a stomachic effect[47].

Antiobesity: Five compounds in bitter melon increase the activity of adenosine 5 monophosphate kinase (AMPK), an enzyme that facilitates cellular glucose uptake and fatty acid oxidation. Hypoglycemic agents in bitter melon promotes efficient oxidation of glucose into fuel, and convertion into starch. (*Glycogen* or *animal starch* isstored in the liver and muscle cells). During glucose shortages, fats/fatty acids are used as fuel.[48] Continued demand for energy in the absence or shortage of glucose causes fat cells to release their fat contents to maintain energy balance. This increased fatty acid oxidation eventually leads to weight loss. Compounds in bitter melon improves lipid profiles. They reduce liver secretion of *apolipoprotein B (Apo B)* – the primary lipoprotein of low-density "*bad"* cholesterol; reduce apolipoprotein C- III expression, the protein found in *very-low density cholesterol* which turns into LDL/bad cholesterol; and increases the expression of *apolipoprotein A-1 (ApoA1)* - the major protein component of high density "good" cholesterol. It also lowers cellular triglyceride content. In other in vivo studies, bitter melon fruit and/or seed have been shown to reduce total cholesterol and triglycerisin both the presence and absence of dietary cholesterol. In one study, elevated cholesterol and triglyceride levels in diabetic rats were returned to normal after 10 weeks of treatment. The fruit and seed of bitter melon have demonstrated (in animal studies) to lower blood cholesterol levels. Persons on medications to lower blood cholesterol should monitor their cholesterol levels. Various cautions are indicated[49].

Skin: Fruit and leaves are used in leprosy. Bitter melon inhibits the enzyme guanylate cyclase, which may benefit people with psoriasis. This enzyme is thought to be linked to the pathogenesis and replication of psoriasis

Reproductive syatem: Leaves act as a galactogogue. The seeds, however, have demonstrated the ability to induce abortions in rats and mice, and the root has been documented with a uterine stimulant effect in animals. The fruit and leaf of bitter melon has demonstrated an in vivo antifertility effect in female animals; in male animals, it was reported to affect the production of sperm negatively. Bitter melon traditionally has been used as an abortive and has been documented with weak uterine stimulant activity; therefore, it is contraindicated during pregnancy. This plant has been documented to reduce fertility in both males and females and should therefore not be used by those undergoing fertility treatment or seeking pregnancy. The active chemicals in bitter melon have shown in animal studies to be transferred through breast milk; therefore, it is contraindicated in women who are breast feeding[50,51].

Liver: Fruit is useful in sub acute cases of liver and spleen. Another method for carcinogen-induced lipid peroxidation in liver and DNA damage in lympocytes were reduced by following treatment of *M.charantia.* The fruit extract was found to significantly active liver enzymes glutathione stransferase, glutathione peroxidase and catalase, which showed a depression following exposure to the carcinogen. The result suggest the preventive role of water soluble constituents of *M.charantia* fruit during carcinogensis, which is mediated possibly by their modulatry effect on enzymes of biotransformation and detoxification system of host[52].

Antimicrobial activity: In addition to these properties, leaf extracts of bitter melon have clinically demonstrated broad spectrum antimicrobial activity. Various water, ethanol, and methanol extracts of the leaves have demonstrated in vitro antibacterial activities against E. coli, Staphylococcus, Pseudomonas, Salmonella, Streptobacillus and Streptococcus; an extract of the entire plant was shown to have antiprotozoal activity against Entamoeba histolytica. The fruit and fruit juice has demonstrated the same type of antibacterial properties and, in another study, a fruit extract has demonstrated activity against the stomach ulcer-causing bacteria Helicobacter pylori. Although all parts of the plant have demonstrated active antibacterial activity, none have shown activity against fungi or yeast. Long-term use of this plant may result in the die-off of friendly bacteria with resulting yeast/candida opportunistic overgrowth. Cycling off the use of the plant (every 30 days for one week) may be warranted, and adding probiotics to the diet may be beneficial if this plant is used for longer than 30 days[54,55].

Antiviral activity: Bitter melon (and several of its isolated phytochemicals) also has been documented with in vitro antiviral activity against numerous viruses including Epstein-Barr, herpes, and HIV viruses. 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). Momordica Anti-human Immunovirus Protein (MAP30) activates natural killer cells, interferes with the ability of HIV viruses to divide and spread. It also increases the body's production of *interferon-gamma*, a natural substance that fights all types of viruses. Another clinical study showed that

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MAP-30's antiviral activity was also relative to the herpes virus in vitro. It contains three anti-HIV proteins: alpha- and beta momorcharin, and MAP-30, and charantin, beta-DSitosterl- beta-D-glucoside, 5,25-Stigmastadien-3-beta-Dglucoside, serotonin, and many kinds of amino acids[56-57].

Anti HIV activity: Bitter melon has also been suggested as a treatment for AIDS, but the evidence thus far is too weak to even mention. Laboratory tests suggest that compounds in bitter melon might be effective for treating HIV infection. As most compounds isolated from bitter melon that impact HIV have either been proteins or glycoproteins (lectins), neither of which are well-absorbed, it is unlikely that oral intake of bitter melon will slow HIV in infected people. It is possible oral ingestion of bitter melon could offset negative effects of anti-HIV drugs, if a test tube study canbe shown to be applicable to people. Clearly more research is necessary before this could be recommended. The other realm showing the most promise related to bitter melon is as an immunomodulator. One clinical trial found very limited evidence that bitter melon might improve immune cell function in people with cancer, but this needs to be verified and amplified in other research. If proven correct this is another way bitter melon could help people infected with HIV. 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 but research has only been demonstrated in test tubes and not in humans. Another study explained that HIV-infected cells treated with alpha- and beta-momorcharin showed a nearly complete loss of viral antigen while healthy cells were largely unaffected. "Useful for treating tumors and HIV infections. In treating HIV infections, the protein is administered alone or in conjunction with conventional AIDS therapies" stated by inventors of MAP-30 protein analog in U.S. Patent. The proteins (alpha and beta momorcharin) appeared to modulate the activity of both T and B lymphocytes and significantly suppressed the macrophage activity[58,59].

Larvicidal activity: *M. charantia* has shown good larvicidal activity against three container breeding mosquitoes[60].

Wound healing property: Researchers found that *Momordica charantia* Linn. Fruit powder, in the form of an ointment (10% w/w dried powder in simple ointment base), showed a statically significant response, in terms of wound contracting ability, wound closure time, period of epithelization, tensile strength of the wound and regeneration of tissues at wound site when compared with the control group, and these results were comparable to those of a reference drug povidone iodine ointment in an excision, incision and dead space wound model in rats[61]

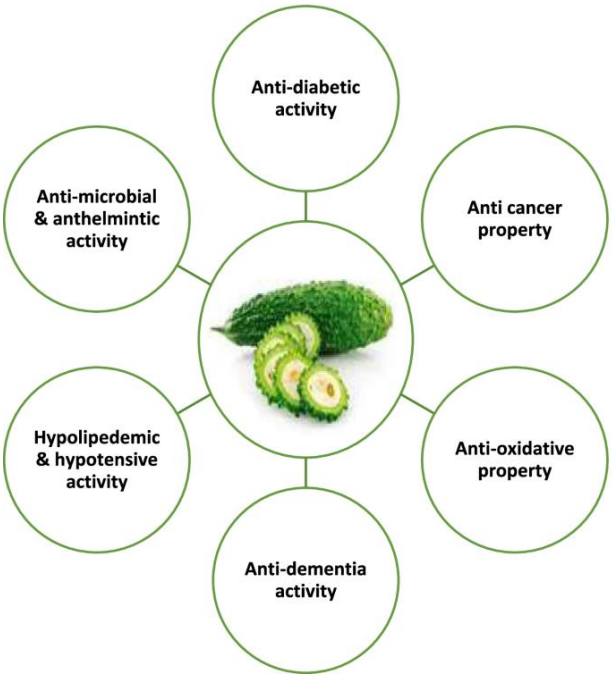

Fig. 3: Pharmacological activity of *M. charantia*

1.10 Traditional uses of Karela plant parts

Fruits- The fruit is considered as tonic, stomachic, stimulant, emetic, antibilous, laxative and alterative. The fruit is useful in gout, rheumatism and subacute cases of the spleen and liver diseases. It is supposed to purify blood and dissipate melancholia and gross humours. It has also been shown to have hypoglycaemic properties (antidiabetic) in animal as well as human studies. Fruit pulp, leaf juice and seeds are antihelimintic[62].

Fruit juice or leaf tea- The fruit juice and/or a leaf tea is employed for diabetes, malaria, colic, sores and wounds, infections, worms and parasites, as an emmenogogue, and for measles, hepatitis, and fevers[63].

Leaves- Leaves act as galactogogue

Roots- Root is astringent.

Other uses - Abortifacient, anthelmintic, aphrodisiac, burn, catarrh, constipation, digestion, demulcent, dermatosis, diabetes, diarrhoea, dyspepsia, eczema, emetic, emmenagogue, emollient, fever, febrifuge, hemorrhoids, hepatitis, hypoglycemic, inflammation (liver), leprosy, leucorrhoea, leukemia, malaria, menstrual colic, pain, pruritus, purgative, rheumatism, scabies, skin, tumor, wound, vaginitis, vermifuge, cancer (breast), food, glucosuria, halitosis, hematuria, polyuria, refrigerant, bite (snake), anaemia, colitis, kidney (stone), sterility (female), dysentery, gonorrhoea, appetite stimulant, insecticide, laxative, rage, rhinitis, contraceptive, dysmenorrhea, fat loss, galactagogue, gout, hydrophobia, piles, pneumonia, psoriasis, sore, asthma, headache, scald, sprue, stomachache, cold and cough[64].

1.11. Anti-diabetic effects of M. charantia

In order for the body to respond to high blood sugar levels, several systems must cooperate. A

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malfunction in any of the procedures involved in the regulation, secretion, absorption, or breakdown of insulin can result in the buildup of glucose in the blood. Damage to the insulin-producing cells is the cause of the symptoms of diabetes, such as continuous hyperglycemia. Numerous strategies have been used to lower the prevalence of diabetes. Although they are the mainstays of diabetes treatment, oral hypoglycemic drugs and insulin have noticeable side effects and have little effect on how diabetic complications develop. Dietary approaches that return blood glucose and lipoprotein levels to normal should lessen morbidity and death brought on by DM's aberrant carbohydrate and lipid metabolism.

Due to its propensity to reduce blood sugar levels, bitter melon, also known as bitter gourd (b.g), karela, or balsam pear, is a species of the Momordica genus (Yibchok-Anun et al. 2006). The results of this investigation showed that drinking MC fruit juice significantly reduced serum glucose and elevated serum insulin in both diabetic and pretreatment rats. The proportion of people with healthy -cells increased as well. Its extra-pancreatic and/or pancreatic actions may cause this to happen.[65]

These outcomes are in line with those attained by giving MC extract to diabetic rats caused by alloxan, where blood sugar levels were reduced and reduced serum insulin levels were elevated similarly to the effects of glibenclamide. Additionally, it was believed that, similar to oral hypoglycemic medications (such as sulfonylurea), it might increase insulin secretion from cells by depolarizing the membrane of those cells, changing ion flux, or interfering with receptors that recognise insulin secretagogues. These two methods are currently assumed to be used by all medications that release insulin.[66][67]

There is some evidence that MC can boost erythrocyte and adipocyte peripheral glucose oxidation while also reducing hepatic gluconeogenesis and boosting hepatic glycogen production. Our in vitro research revealed that MC juice can accelerate the uptake of glucose by diaphragms from normal and diabetic rats, indicating that this may be one of the mechanism(s) through which MC exerts its hypoglycemic impact. It has been demonstrated that MC and insulin work better together than they do separately. Amplification of insulin action and elevated insulin sensitivity in target tissues are potential causes. We obtain these results, which is consistent with these observations. The concentration of GLUT-4 protein increased in the muscle plasma membrane fraction following oral administration of MC. This may be the cause of improvements in diabetics' insulin sensitivity. This study also found an increase in antioxidant capacity and a decrease in ROS generation. [68] MC fruit extract contains antioxidant substances like polyphenols, flavonoids, and flavonols despite the extract's low molecular weight. The literature suggests that MC extract increases glucose absorption via enhancing the phosphatidyl inositol-3 kinase pathway. Numerous studies have linked MC's insulin-like activity to an increase in glucose and amino acid absorption into skeletal muscle cells. If insulin levels are increased while glucose levels are decreased, protein glycation may be decreased. This study discovered that drinking MC fruit juice lowered serum fructosamine levels in diabetic and MC-pretreated rats. When taken in significant quantities, fruits and vegetables have been found to lower plasma lipid levels. The findings of this study demonstrated that MC fruit juice also has lipid-lowering effects in diabetic animals. Whereas serum TC and TG levels in diabetic rats treated with MC or pretreated with MC increased significantly along with serum HDL-c levels, they decreased significantly in diabetic rats treated with MC and STZ. It is feasible to produce a hypolipidemic effect by modifying the hydrolysis of specific lipoproteins and controlling their preferential absorption and metabolism by different tissues. [69] There is some proof that MC's capacity to lessen the activity of NADPH and NADH cofactors in fat metabolism is what causes it to have an anti-hyperlipidemic impact. MC may produce its anti-hyperlipidemic action via oxidising NADPH. Insulin's effect reduces lipolysis and peripheral depot mobilisation by inhibiting hormone-sensitive lipase in adipose tissue. It's possible that MC fruit can mimic the effects of insulin or increase its efficiency in the body. According to the study's findings, MC fruit juice exhibits significant antioxidant activity, which may be the cause of its hypoglycemic effects. MC dramatically decreased the levels of MDA in the pancreas of the diabetic and control groups. This might be as a result of slower lipid peroxidation. After ingesting MC, serum TAOC and pancreatic GSH significantly increased in both the diabetic and the MC pretreatment groups. This could happen due to either an increase in the enzymatic antioxidant defence system's production of GSH and other antioxidant enzymes or a reduction in the oxidative stress that causes less of their breakdown. The extract has immediate preventive effects, reducing the risk of diabetes complications and lipid peroxidation, which free radicals scavenge. It was discovered that MC fruit juice prevented lipid peroxidation through the use of in vivo and in vitro models. In conclusion, oral administration of MC as prevention or therapy in STZ diabetic rats exhibited hypoglycemia, hypolipidemic, and potent antioxidant effects. It was able to counteract the pathogenic characteristics of STZ when given as a pretreatment before the development of DM by lowering hyperglycemia, hyperlipidaemia, and oxidative stress. Sadly, it wasn't enough to halt the disease's spread. The pancreas is the likely site of action for the powerful hypoglycemic effects of this natural agent, though its additional pancreatic actions, such as reducing insulin resistance and increasing glucose utilisation in the skeletal muscles, cannot be discounted. Elevated serum insulin levels, improved -cell function, and protection

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against islet destruction all point to the pancreas as the likely site of action. [70]

II. CONCLUSION

Nutritionists and dietitians place a strong emphasis on the idea of food's medicinal potential. M. charantia has been used as a food supplement and in traditional medicine for the treatment of diabetes and related disorders for millennia. As of now, M. charantia has been the subject of substantial international research into its potential as a medicine for treating a wide range of illnesses. The plant is so adaptable that it has the potential to cure nearly every illness that has ever plagued humankind. Perhaps this is because there are more than 225 different active ingredients in the plant that have therapeutic properties. The therapeutic benefits of these many substances may result from either independent or synergistic action. Only charantin, insulin-like peptide, and alkaloid-like extracts contain hypoglycemic effects similar to the plant or its crude extracts. The therapeutic benefits of these various substances in the management and treatment of diabetes mellitus appear to be exerted via a number of distinct pathways. Despite the wealth of information from biochemical and animal research, the available clinical data are frequently inaccurate due to small sample size, lack of control, and poor study designs, as discussed in the present article. This analysis confirms the importance of larger, more well-designed clinical studies of M. charantia as a dietary supplement for people with diabetes. Particularly among ethnic minorities with high diabetes prevalence and a preference for therapy based on natural products due to cultural beliefs, M. charantia may be a viable choice.

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