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Momordica charantia L. (Karela): A bitter plant fruit with immense value in Nutraceutical and Pharmaceutical industries

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Abstract : Bitter gourd (Momordica charantiaL.) is a member of the Cucurbitaceae family and a popular vegetable crop used in Indian traditional medicine since ancient times. This vegetable is very high in bitter content and very low in calories. It has potential antidiabetic, lipid lowering and antioxidant activity. It has a cleansing action in the body by removing accumulated receptacles of old waste materials and used for the treatment of diabetes and many other diseases among the indigenous population of Asia, South America, India and East Africa. Different parts of this plant extract and its bioactive components have been used in various traditional systems of medicine and pharmaceutical industries as nutraceuticals for the treatment of various diseases. The fruit is pickled in brine which is rich of minerals, acids, vitamins, phenolic compounds, terpenoids, alkaloids, various glycosides, saponins, triterpenes, steroids, carotenoids, flavonoids, peptides which exhibits its potential as antidiabetic, antibacterial, antiviral, antiulcer, anticancer, antifertility, immunomodulator, antipsoriasis, and cardioprotective agent. It is now considered as a valuable resource of several inimitable products for the medicines against various diseases and also for the development of some novel industrial medicinal products. The current investigation aims to focus on the extravagance of *M. charantia* with respect to its phytoconstituents, comprehensive information on the pharmacological actions, nutraceutical values and recent progress in phytochemical based nanomedicines for effective treatment of various diseases. Keyboard : Momordica charantia, Charantin, antidiabetic agents, Marketed products, Phytosomes, Nanomedicines

Introduction:

Momordica charantia is a tropical and subtropical vine of the Cucurbitaceae family. It is widely grown in Asia and Africa for its edible fruit. Its several varieties differ substantially in the shape and bitterness and arise in India and will be launch into China in the 14th century [1]. It is widely used in East Asian, South Asian, & Southeast Asian cuisine. The plant is a tropical plant widely cultivated in Asia, East Africa and South America for its intensely bitter fruits that are generally used in cooking and as a natural remedy for treatment of

Muhammad Arif *et al* / International Journal of PharmTech Research, 2021,14(1): 01-14. DOI= <u>http://dx.doi.org/10.20902/IJPTR.2021.140101</u> diabetes [2]. In India, it is usually cultivated upto an altitude of 1500 m. Bitter guard is the trade name of plant, in hindi it is known Karela, Kareli, Karola and in Ayurveda Karavella, Sushavi, Ambuvallika, Brihadvalli[3]. The fruit is most often eaten green, or as its start to turn yellow. At this point, the fruit's flesh is watery and crunchy in texture (alike cucumber, chayote or green bell pepper, but bitter). The skin is tender and edible. Some sources claim the flesh (rind) becomes somewhat tougher and more bitter with age, but other sources claim that at least for the usual Chinese variety the skin does not change and bitterness decreases with age. The Chinese varieties are best harvested light green possibly with a marginal yellow tinge or just before. The pith becomes sweet and intensely red; it can be eaten uncooked in this state, and is a well liked ingredient in some Southeast Asian salads. When the fruit is fully ripe, it turns orange and mushy, and splits into pieces which curl back dramatically to expose seeds covered in bright red pulp. It is a monoecious annual climber with a slender, branched, angled and grooved stem that grows up to 5meter. Its leaves are alternate, petiolate, orbicular, 5-7 lobed, 5-12cm in diameter, both surfaces glabrous and prominently nerved. Tendrils are simple and slender. Flowers pale yellow to orange, solitary and unisexual. Fruits dark green to whitish pepo, 5-25 cm long, oblong, ribbed with many tubercles. Seeds brownish, compressed, 12-16 mm long, embedded in bright red pulp[4]. At present, many commercial products of *M. charantia* fruits are available in the market for commercial and medicinal purpose hence the present review will possibly act as bridge between nutraceutical food and industrial pharmaceutical potentials of *M.charantia*. This topic provides an overview of the medicinal uses, phytoconstituents, nutritional and pharmacological potentials, marketed and New Drug Delivery System formulations of numerous bioactive component of *M. charantia*.



Fig.1: Momordicacharantia twig with leaves, flower and fruits.

Vernacular Names [5]

Arab	:	Quisaul – barri
Assam	:	Kakiral, Kakral
Bengali	:	Karela, Uchchhe, Kerula
English	:	Bitter gourd, Balsam pear, Balsam apple.
Guajarati	:	Karela
Hindi	:	Karela, Kardi
Kannada	:	Hagal
Malayalam	:	Kaipp, Kaippavlli, Paval
Nepali	:	TeetaKarela
Oria	:	Kalara, Salara
Sanskrit	:	Sushavi, Karavella
Tamil	:	Pakal, Pavaka, Chedi, Paharkai
Telgu	:	Koekara, Kaaya
Urdu	:	Karela

Origin and phyto-geography:

The genus Momordica holds great interest dates back to Linnaeus for the study of its evolution. Evolutionarily, Momordica genomes are labile, therefore large genetic diversity of Bitter gourd are originate in different parts of the world. In India, this plant has been cultivated with two forms: creeping form, cultivated in the field during hot season; and climbing form, cultivated during the rainy season. The bitter gourd more typical of India has a narrower in shape with pointed ends, and a surface covered with jagged, triangular "teeth" and ridges whitish green color. Some is having miniature fruit of only 2.4–3.9 inch (6–10 cm) in length, which may be served as individually stuffed vegetables. These miniature fruit are well liked in Bangladesh, India, Pakistan, Nepal and other countries in South Asia. The sub-continent variety is well liked in Bangladesh and India [6-7].

Phytochemical Significance

Medicinal value of bitter melon has been attributed to its high antioxidant properties due in part to proteins, alkaloids, terpenes, saponins, triterpenoides and steroids all of which confer a bitter taste. The presence of different cucurbitacins (steroidal and triterpenoid substances) are wellknown for their bitterness property. It is the characteristic property of the family Cucurbitaceae [8]. It involved a collection of more than 30 triterpenoids and more than 10 steroids which have been isolated from roots, stems leaves, fruits and seeds [9]. Various phytoconstituents such as α and β -momorcharins, momordenol, momordicilin, momordicins, momordicinin, momordin, momordolol, charantin, charine, cryptoxanthin, cucurbitins, cucurbitacins, cucurbitanes, cycloartenols, diosgenin, elaeostearic acids, erythrodiol, galacturonic acids, gentisic acid, goyaglycosides, goyasaponins, multiflorenol, have been isolated from *M. charantia* [10-11]. Nineteen cucurbitacins named kuguacins A-E from the roots of *M.charantia* and kuguacins F-S from the vines and leaves of *M. Charantia* been isolated. Two new cucurbitane-type triterpene glycosides, charantagenins D and E, and has one new sterol, 7-oxo-stigmasta-5,25-diene-3-O- β -d-glucopyranoside, also been isolated from *M. charantia*. Some other category of phytoconstituents separated from this plant includes cytokinins, zeatin, zeatin, ribosides from seeds, lectins (I&II in seeds), a phytosphingosine from leaves and a pyrimidine derivative vicine from seeds which is a glycol alkaloid exhibiting hypoglycemic effects on non-diabetic fasting rats [12-13]. In M.charantia various volatile constituents such as: 1-penten-3-ol, cis-3-hexanol, cis-2-penten-1ol, trans-2-hexenol, cis-sabinol, myrtenol, benzyl alcohol have been identified [14]. Essential oil from seeds has exhibit the existence of menthol, squalene, nerolidol, etc [15]. A new ribosome-inactivating protein (RIP); (δ momorcharin) and a candidate RIP (ε -momorcharin) have been isolated respectively from the seeds and fruits of the *M. charantia* by afinity chromatography on Ag-gel blue gel and ion exchange chromatography, a fast protein liquid chromatography (FPLC) system [16].

Alkaloids





Fig. 2: Phytoconstituents of M. charantia

Nutrient Profile:

The analysis of the fruits of *M. charantia* depict the several nutritional certitude per 100 gm of fruits shown in table 1 [17-18].

 Table 1: The analysis of the fruits of M. charantia portrays the following nutritional component (per 100 gm of fruits).

Moisture	83.2%
Protein	5.3g
Total Carbohydrate	3.3g
Phosphorus	99mg
Ascorbic acid	88mg
Magnesium	85mg
Calcium	84mg
Iron	2.04mg
Niacin	1.11mg
Riboflavin	0.362mg
Thiamin	0.181mg
Folate	128ìg
Nicotinic acid	0.5 ìg
Vitamin A	1734IU
Total Omega 3 fatty acids	0mg
Total Omega 6 fatty acids	Omg

Pharmacological Activities and Therapeutic Benefits:

Momordica charantia known to possess extensive range of phytochemicals in its leaves and fruits that impart enormous medicinal value to the plant. These active constituents offer medicinal value to the plant. Pharmacological importance of the plant fruits has been evaluated by several researchers through in vitro and in vivo advances. It has shown antidiabetic, antibacterial, antiviral, anti-HIV, antiherpes, antipoliovirus, anticancer, antifertility, anti ulcer, immunomodulatory, antipsoriasis, analgesic & antinflammatory, hypotensive, anti prothrombin, hypocholesterolemic, anti-oxidant, antiobesity and cardioprotective activities. *Momordica charantia* has also documented to possess abortifacient, anthelmintic, antimalarial, contraceptive, and laxative properties [19].

Analgesic, Anti-inflammatory and Antipyretic Activity:

Ethanolic extracts of *M. charantia* has explored for analgesic effect (acetic acid-induced writhing and tail immersion tests in mice) and antipyretic property (yeast-induced pyrexia in rats). Intestinal and systemic anti-inflammatory responses have been observed [20]. Addition of wild bitter gourds reduced the inflammation biochemical markers (like GOT,GPT, C-RP, and NO concentrations) and pro-inflammatory cytokines TNF-a, IL-1 and IL-6, and compared to those of the sepsis group [21]. *M. charantia* exhibits anti-rheumatoid activitydue to its phytoconstituents- MomordinIc and its aglycone, oleanolic acid [22].

Abortifacient and Anti-fertility Activity:

Various investigations have proved the abortifacient property of *M. charantia*. The plant showed activity is due to the presence of proteins (β -momorcharin) which is present in the seeds. They inhibited the mitogenic responses of mouse splenocytes to phytohaemagglutinin, concanavalin A and lipopolysaccharide in a dose-dependent manner [23]. Biosynthesis of cultured endometrial cells was also inhibited by β -momorchrin. Abortifacient activity of β -momorchrin possesses due to the hatching of embryos from the zonapellucid and decrease in the outgrowth of trophoblast and inner cell mass development disruption. Methanolic seed extract of *M. charantia* showed anti-ovulatory and antiimplantation (early abortifacient) activity [24]. Oral administration of aqueous extracts of *M. charantia* caused a significant decrease in progesterone and estrogen in a dose dependent manner in Low, Moderate and High dose groups when compared with the control [25]. It has shown

to possess antifertility effects in females as well as male animals. Therefore, it is very essential to consider the teratogenic and abortifacient properties of *M. charantia* before its use in pregnancy.

Anthelmintic activity:

Different formulations of *M. charantia* have showed several anthelmintic properties than piperazine hexahydrate against *Ascaridiagalli* worms. Chloroform extract of *M. Charantia* seeds (20mg/ml) showed the best anthelmintic property against Indian earthworm *Pheretima posthuma* compared to standard Albendazole. The extract produces paralysis within 3 minutes and finally death within 8 minutes [26].

Anti-allergic activity:

An investigation showed that Momorcharin significantly depressed the delayed-type hypersensitivity reaction and the humoral antibody formation. It also suppressed the migration of macrophages provoked by thioglycollate. Another study stated that *M. charantia* extract in different concentrations increased the active basophils, thus it may possess a non-allergic type-I like hypersensitivity in susceptible individuals [27].

Antibacterial activity:

Various extracts of different parts of *M. charantia* have established its broadspectrum antimicrobial prospective[28]. The leaves extract has revealed antimicrobial activity against *E. coli, S. typhi, Shigella dysenterae* and *Streptomyces griseus*. It has also reticent the growth of *Mycobacterium tuberculosis* in a phase II study. The entire plant extract has showed antiprotozoal activity against *Entamoeba histolytica*[29]. The fruit extract has shown its probable resistant to*H. pylori* with MICs-1.95 and 250 µg/ml. A food preservative peptide has also isolated and evaluated from *Momordicacharantin*[30].

Anticancer activity:

M. charantia extract and its isolated fractions have showed cytotoxic property against lymphoma, lymphoid leukemia, prostatic cancer, breast cancer, choriocarcinoma, Hodgkin's disease, skintumor, melanoma, squamous carcinoma of tongue and larynx etc[31].*M. charantia* contains various active constituents which inhibit cell growth and proliferation and induce apoptosis [32]. Momordin I, I_d and I_e showed anticancer activity against human cancer cell lines and it was found to inhibit the protein synthesis of human choriocarcinoma and trophoblasts[33].

Antimalarial activity:

Methanolic extract of *M. charantia* leaves confirmed larvicidal and pupicidal effects against malarial vector *Anopheles stephensi* Liston (Diptera: Culicidae). The extract also exhibited a weak *in vitro* antiplasmodial activity and moderate *in vivo* activity against rodent malaria *P. vinckeipetteri*279 [34].

Antioxidant activity:

Various extracts of *M. charantia* were studied for determination of antioxidant activity (DPPH &hydrogen peroxide radical scavenging). The ethanolic extract showed the highest radical scavenging activity with IC_{50} values of $120.07 \pm 0.77 \mu g/ml$ in DPPH and $175.78 \pm 0.63 \mu g/ml$ in & Hydrogen Peroxide radical scavenging activity. An investigation was carried out to determine the antioxidant potential of aqueous extracts of leaf, fruit and stem by *invitro* assays [35].

Anti-ulcer activity:

Antimicrobial property against *Helicobactor pylori* has been exhibit by *M. charantia*, thus depicting its use as anti-ulcer agent [30]. Momordin Ic (10 mg/kg, p.o.) showed inhibiting the ethanol influence gastric mucosal lesions. *M. charantia* fruits methanolic extract in doses of 100 mg/kg and 500 mg/kg healed the gastric ulcer and also prevented the development of duodenal and gastric ulcers in rats. The ulcer index, free acidity, total acidity and pepsin content significantly declined in pylorus-ligated rats [36].

Antiviral activity:

The fruits of *M. charantia* contain antiretroviral protein-MAP 30 and α and β -momorcharins which have potential action against HIV infection. Mode of action of MAP 30 for its anti-HIV potential includes inhibition of transcription &transactivation and inhibition of viral integrase[37]. In an investigation, the efficacy of MAP-30 was enhanced by its combination withlow doses of dexamethasone and indomethacin. The anti-HIV activity of Recombinant MAP-30 (re-MAP30) was measured by viral coreprotein p24 expression [38].

The protein isolated from the fruits like MAP 30 and GAP 31 from *M. charantia* are also effective against *Herpes simplex* virus with effective concentrations for 50% inhibition (EC50) $0.1-0.2 \mu$ M for HSV-2, and 0.3-0.5 M for HSV 1 for MAP30 and GAP31, respectively[39].

Ribosome-inactivating proteins from *M. charantia* inhibited poliovirus replication by inhibiting protein synthesis [40].

The methanolic extract formulation of *M. charantia* with five other herbal extracts was used to study the anti-dengue activity based on cytopathic effects (CPE) denoted by degree of inhibition upon treating DENV1-infected Vero E6 cells [41].

Hepatoprotective activity:

M. charantia fruit juice and seed extract showed the significant elevation in alkaline phosphatase (P < 0.01-0.001) and serum gamma-glutamyltransferase(P < 0.001). There were no significant histopathological changes in liver of control and plant treated group[42].

Anti-lipidemic activity:

Numerous studies have been carried out to find outthe hypo-cholesterolemic potential of *M. charantia*. The findings of a study showed that the extracts of *M. charantia* have anti-obesity effects. It was hypothesized that in order to improve blood cholesterol profiles, *M. charantia* alters bile acidregulating proteins and hepatic gene expression of cholesterol[43].

Immunomodulatory activity:

It has been observed that components of *M. charantia* exhibit immune-suppressive as well as immunestimulatory activity. In a study, the immune-suppressive property of α - and β -momorcharin will be seen due to lympho-cytotoxicity or to a shift in the kinetic parameters of the immune reaction while an another investigation showed increase in interferon manufacture and natural killer cell to demonstrate its immunestimulant property[44]. The ethanolic extract of *M. charantia* extract at doses of 25, 50 and 100 mg/ kg body weight showed a stimulatory effect on both humoral and cellular functions in mice[45].

Anti-diabetic activity:

All parts of *M. charantia* plant (seed, leaves, whole plant, fruit pulp & juice) have been explored for their diabetic probable. Numerous findings have proved their anti-diabetic activity in normal animals in streptozotocinor alloxan induced and even the genetic models of diabetes [46-47]. Some of the phytoconstituents isolated from *M. charantia* like Polypeptide k, Polypeptide-p, Charantin, momordinIc, oleanolic acid, oleanolic acid 3-O-glucuronide and 3-O-monodesmoside have shown anti-diabetic activity [48].

Marketed Formulations:

In present study, the herbal formulations were prepared by mixing different ratios of lyophilized hydroalcoholic extracts of the selected plant materials which protects thermo labile compounds. In the study the combinations of *M. charantia* extracts with other plants extracts were formulated by keeping *M. charantia* extract at higher ratio [49].

Diabecon manufactured by Himalaya which increases peripheral utilization of glucose, increase hepatic and muscle glucagon contents; promote β -cells repair and regeneration and increase c peptide level. It is an ayurvedic product used as an adjuvant for the treatment of diabetes mellitus. Bitter Melon tablets helps to

achieve a positive sugar regulating effect by suppressing the neural response to sweet taste stimuli. It helps to regulate blood sugar levels and using it over a long period of time it significantly reduces glucose levels in the blood and urine. Bitter Melon is rich in vitamins B1, B2, B3,C and contains potassium, calcium, iron and β -carotene and works as an excellent blood purifier. It treats worm infestations, stimulates pancreas and liver and it is very useful in normalizing the digestive tract and also helps in improving peristaltic movements in the body. It also supports the immune-system and keeps body functions operating normally [50].

Pancreas Tonic is an Ayurvedic dietary supplement, contains *M. charantia* and other plants extracts shown to possess hypoglycemic activity [51].

Madhumehari Vati is very effective in the management of Type 2 Diabetes, formulated by Dr Vasishth's Ayu Remedies, named as Glycie tablet. This formulation contains *M. charantia* in higher content with other plants extracts. To overcome the problems of palatability, feasibility, shelf life with the powder form of drug, tablets were formed. The compounds of Madhumehari Vati were analyzed and standardized scientifically through qualitative and quantitative analysis by physico-chemical parameters and High Performance Thin Layer Chromatography (HPTLC) and pharmacognostical measures [52].

Dabur Madhurakshak is a polyherbal formulation containing powders of twelve different herbs by keeping *Momordica charantia* in higher ratio have been evaluated for anti-diabetic activity [53].

Hyponidd is a herbo-mineral formulation and has 12 blended plant extracts including *Momordica charantia* have been used in diabetes. There are no adverse events were noted in patients treated with Hyponidd[54].

Kerala Ayurveda Dhanwantharam Kwath is an Ayurveda formulation that helps relieve Vata disorders and postnatal difficulties in women. It helps in reducing the symptoms associated with degenerating diseases, rheumatic complaints, trauma, etc. It also proves beneficial in vaginal problems, painful micturition and helps restore natural strength after delivery [55].

Nanomedicines

Novel drug delivery is a technique in which active chemicals are made presented to a specified target at a rate and duration designed to achieve an anticipated effect. At present, herbal drugs form a major line of the treatment in the management of diabetes and few herbal pharmacologically active constituents can currently be administered through Novel drug delivery System [56-57].

Transdermal patches

Transdermal drug delivery system (TDDS) generally refers to topical application of drugs to well intact skin either for limited to a small area treatment of tissues or for systemic therapy.[58] TDDS can transport certain medication to systemic circulation in a more suitable and effective way than is probable with conventional dosage form. TDD Scan reduce first-pass metabolism associated with gastrointestinal administration of drugs and maintain steady drug level in blood[59]. A number of transdermal patches of herbal drug extracts have been developed by various investigators to achieve controlled release for extended duration. The Transdermal film contain the fractionated component from Ethanolic extract of *M.chirantia* fruits were prepared with hydroxy propyl methyl cellulose as a polymer. The films were evaluated for weight variation, folding endurance, thickness, drug contents and *in vitro* diffusion studiesand *in vivo* parameters like acute and subacuteanti diabetic activity in diabetic rats. The percentage release of active constituents from Transdermal patches of *M. charantia* (2cm²; 10 mg/patch) was found to be satisfactory. The Transdermal route reveals the negligible skin irritation and *in vivo* results revealed that the patches effectively decrease the blood glucose level [60-61].

Phytosomes

Phytosomes are one of the technologies to improve the penetration, absorption and bioavailability of herbal extracts orphytoconstituents. Phytosomes are micelles or littlecells like configuration contain the standardized herba lextracts or active phytoconstituents which combine to phospholipids and producing lipid compatible molecular complexes and with this nature of phytosomes can improve its penetration through the skin [62].



Fig. 3:Phytosome of phytoconstituents

Phytosomes are the nano-sized structure appropriate for transdermal delivery in the form of patches and can be used for various skin diseases [63]. Some formulations of *M. chirantia* extract were developed by using phosphatidylcholine. They are characterized, in terms of morphology, particle size distribution, zeta potential and entrapment efficiency. The phytosomes of *M. chirantia* spherical shape, particle size was 282.3 ± 16.4 nm, zetapotential value at -39.2 ± 0.14 mV and entrapment efficiency of 90.06 ± 1.07 %. *M. chirantia* extract loaded phytosomes with phosphatidylcholine1:3 was selected as an optimal formula with appropriate characteristics for transdermal delivery. Indena India Private Limited Bangalore patented the technology of phytosomes® and launches many products in market under this having diverse therapeutic benefits [64-65].

Liposomes

The liposomes are spherical particles usually 0.05-5.0µm in diameter that encapsulate a fraction of the solvent, in which they freely diffuse or float into their interior[66]. They are constructed of polar lipids which are characterized by having a lipophilic and hydrophilic group on the same molecules. Upon interaction with water, polar lipids self-assemble and form self-organized colloidal particles. One of the interesting properties of liposomes is their ability to target tumours and facilitate the cellular uptake of therapeutic agents compared to the agent alone. Liposomes can be prepared from SPC (Soy phosphatidylcholine) and HSPC (Hydrogenated soy phosphatidylcholine) phospholipids [67].



Fig. 4:Liposome containing hydrophilic and hydrophobic Phytoconstituents.

Natural drugs like *Momordica charantia* fruit extracts can be incorporated in liposome formulations. These liposomes can be were analysed by investigating, the resultant size, size distribution and zeta potential of the vesicles. The extract of *Momordica charantia* were mixed with liposomes and checked for the efficacy of the anticancer-liposome formulations on the viability of glioma cell lines and the molecular mechanism of the cell death were also investigated. The results show that liposomes prepared by the hydration with *Momordica charantia* extracts, the lipid phase had significantly larger size and wider size distribution as compared to drug free liposomes and exerted cytotoxic effects against glioma cells 1321N1, Gos-3 and U87-MG whereas *M.charantia* extracts without liposomes showed slight or no significant effect on the normal glial cells

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[68].Cosmetochem International AG is a Swiss-based company; part of the Lipoid Group of Companies launches Herbasec® technology in marketed which are the liposomal preparations of various herbal constituents used in cosmetics because of their anti oxidant effects for prevention of aging [69].

Conclusion:

Over the years many researchers have verified many of the traditional uses of *Momordica charantia* that continue to be an important natural remedy for various diseases. Different plant extracts can be found in various herbal formulations that are marketed today. *M.charantia* extract formulations are becoming more widely offered in the United State aswell as rest of the world and are employed by practitioners of natural health for treatment of diabetes, viral diseases, hepatic disorder, cancer and psoriasis. However, few studies have established biological activity of *M.charantia* phytochemical such as charantin, MAP30, momordin, α and β -momorcharins, but the therapeutic application with its phytochemical profile need to be more scientifically explored based on its different activities. *M.charantia* extracts can be used in formulating novel drug delivery system like transdermal patches, phytosomes and liposomes which will be safe, valuable, convenient and economically affordable drug delivery.*M. charantia* protein (MAP30) has potential anti-viral and anticancer, it would be better if MAP30 are used in combination with current armoury of antiretroviral drugs. In developing countries like Africa where both cancer and viral disease like AIDS are common, *M. charantia* can be advocated as a dietary aid.

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