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REVIEW

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A comprehensive review on bitter gourd (*Momordica charantia* L.) as a gold mine of functional bioactive components for therapeutic foods

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Abstract

Bitter gourd is a tropical wine grown mainly in India, China and South East Asia. The plant is cultivated mainly for its fruit part which is edible. Bitter gourd is unaccepted widely due to its bitter taste. Nevertheless, the fruit is a source of several key nutrients. The plant, as a whole contains, more than 60 phyto-medicines that are active against more than 30 diseases, including cancer and diabetes. Currently, the incorporation of the bioactive compounds isolated from bitter gourd into functional foods and beverages finds a new horizon. Nanoencapsulation and novel green extraction methods can be employed to improve the yield and quality of extracted compounds and their stability while incorporation into food products. The present review is an attempt to throw light to nutritional aspects, various bioactive compounds present and important nutraceutical properties of the bitter gourd plant in detail.

Keywords: Bitter gourd, Bioactive, Nutraceutical, Extraction, Encapsulation

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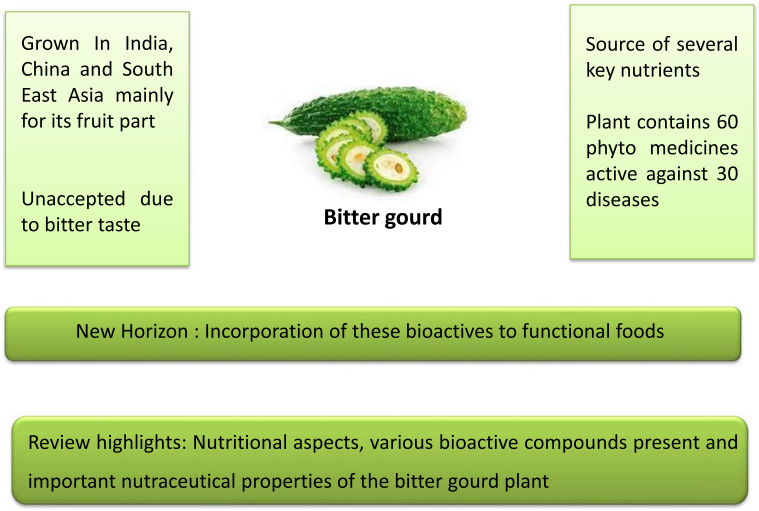
Graphical Abstract



Introduction

Bitter gourd (*Momordica charantia* L.) known also as bitter apple or bitter melon or balsam pear, is a tropical vine belonging to the order Cucurbitales, family Cucubitaceae and genus *Momordica.* The plant is cultivated as medicinal as well as vegetable crop widely in India, China and South East Asia (Behera et al. 2008). Even though whole plant is palatable in nature, bitter gourd is mainly grown for its fruit part. Fruits, flowers and young shoots are used as flavouring agents in various Asian dishes. Fruits are cooked with other vegetables especially in soups for the slight bitter taste. However, in Indian cuisines, fruits are mainly used after blanching or par boiling or soaking in salt water to reduce bitterness (Saeed et al. 2018). Fruits can also be canned or pickled or dehydrated in addition to cooking or deep frying. It is considered widely as a folk lore medicine against diabetes amongst the indigenous population of Asia, South America, India and East Africa (Joseph & Jini 2013). Apart from fruits, the roots, leaves and vines are used as a suppressant for tooth ache, diarrhoea and furuncle. Various products of bitter gourd like bitter gourd tea, which is known as gohyah or herbal tea made from dried slices of bitter gourd, is gaining popularity as herbal medicine (Jia et al. 2017).

Researches have proved that bitter gourd contains an insulin like principle which is often being designated as plant insulin, which has positive effects in lowering the blood and urine glucose content (Janagal et al. 2018). It has also been shown to have anti-cholesterol (Saeed et al. 2018), anti-cancer (Bai et al. 2016), anti-dementia (Joshi et al. 2017), anti-bacterial & anti-fungal (Mahmood et al. 2019), antioxidant and anti-inflammatory (Bortolotti et al. 2019) activities. All part of the plants mainly the fruits and seeds, contain more than 60 phyto-medicines active against more than 30 diseases including cancer and diabetes (Kole et al. 2020). The present review covers nutritional aspects of bitter gourd plant, important nutraceutical properties attributed to the bitter gourd and various studies conducted to prove it.

Bitter gourd: plant description

In general, the plant is a monoecious slender, tendril climbing annual vine of almost 2 to 4 m high. The plant possesses characteristic leaves with serrate margins which typically giving a look like bites. Each plant has separate yellow coloured male and female flowers. Different varieties of bitter gourd have different shapes of fruits, being discoid or ovoid or ellipsoid to oblong and pointed towards the end (Kole et al. 2020). Usually fruits are 2 to 10 cm long. The exterior of the fruits are warty and the cross section is hollow with a thin layer of flesh. Flattened seeds and pith are seen in the central cavity which is surrounded by the thin flesh layer (Gupta et al. 2011). The immature fruits are whitish or pale green in colour whereas the mature ones can be seen in light green, green and dark green depending on the varieties and while ripening the colour turns to orange yellow. The fruit of bitter gourd takes 45 to 80 days to gets mature (Sorifa 2018). The seed of bitter gourd is 8 to 15 mm long which are straw coloured and they are covered with flesh: white in unripe fruits and red in ripened ones (Poolperm & Jiraungkoorskul 2017).

Table 1 Nutritional composition of bitter gourd (Adapted from Behera et al. 2008; Nagarani et al. 2014; Sorifa 2018; Saeed et al. 2018)

Constituents	Amount
Water (%)	83.2–92.4
Lipids (%)	0.1–1
Carbohydrates (%)	4.2–9.8
Proteins (%)	1.6–2.9
Fiber (%)	0.8–1.7
Ash (%)	7–18
Calcium (mg/100 mg)	20–50
Phosphorus (mg/100 mg)	70–140
Iron (mg/100 mg)	2.2–9.4
Magnesium (mg/100 mg)	16
Sodium (mg/100 mg)	3–40
Potassium (mg / 100 mg)	8–170
Zinc (mg/100 mg)	0.1
Manganese (mg/100 mg)	0.08–0.32
Copper (mg/100 mg)	0.18–5
Vitamin A as carotenes	210–220 IU
Vitamin C	70–120 mg
Thiamine (mg)	0.05
Riboflavin (mg)	0.03
Niacin (mg)	0.4

Table 2 Amino acid composition of bitter gourd mature fruit and seed (Adapted from Nagarani et al. 2014; Sorifa 2018)

Amino acid	*M. charantia* mature fruit (mg/g protein)	*M. charantia* mature seed (mg/g protein)
Cystine	22.3	16.5
Aspartic acid	93.8	78.0
Threonine	25.2	17.4
Serine	55.0	43.5
Glutamic acid	96.0	124
Proline	54.4	49.7
Glycine	44.9	39.9
Alanine	51.2	46.7
Valine	42.2	36.7
Isoleucine	30.8	30.7
Leucine	64.9	60.5
Tyrosine	59.4	44.7
Phenylalanine	40.2	34.5
Methionine	27.6	23.6
Histidine	72.8	40.9
Lysine	101	98.7
Arginine	45.6	80.8

Nutritional profile

Bitter gourd is an often discarded vegetable, due to its bitter taste despite the fact that it is a source of several key nutrients. It has a higher nutritional value than other cucurbits such as squash, pumpkin, cucumber and zucchini owing to its high mineral and vitamin content (Krawinkel & Keding 2006). The fruit is rich in vitamins namely vitamin A, vitamin E, thiamine, riboflavin, niacin, folate and vitamin C. Similarly, it also has high amount of potassium, iron, calcium, magnesium, phosphorous and zinc. It contains a good amount of dietary fibre. Detailed nutritional composition of bitter gourd fruit is given in Table 1.

The calorific value for leaf, fruit and seed were 213.26, 241.66 and 176.61 kcal / 100 g respectively (Joseph & Jini 2013). Vitamin C is one of the abundant compounds in the plant (Goo et al. 2016). It was pointed out that leaf contains an average of 205 mg/100 g DW and fruits contain an average of 2022 mg/100 g DW and also noted that the content was higher in young stage fruits. The seeds of bitter gourd also are a rich source of quality proteins and they meet amino acid requirements/standards laid down by FAO/WHO/UNU for preschool children. The detailed amino acid composition of bitter gourd fruit and seed protein is given in Table 2. The bitter gourd seeds contain 35 to 40% of oil with fatty acid profile containing monounsaturated fatty acids (3.33%), saturated fatty acids (36.71%) and poly unsaturated fatty acids (59.96%) (Saeed et al. 2018). Bitter gourd is one of the few edible fruit which contains conjugated α linolenic acid in its seeds. The presence of a long chain PUFA, α eleostearic acid has been reported in bitter gourd seed oil (Yoshime et al. 2016). They are one of the naturally best sources of chromium (5.65 mg / 100 g) and zinc (45.45 mg / 100 g) (Saeed et al. 2018).

Bioactive compounds present in bitter gourd

The primary metabolites in bitter gourd are common sugars, proteins and chlorophyll while secondary metabolites are phenolics, carotenoids, curcubitane triterpenoids, alkaloids, saponins etc. Secondary metabolites are responsible for the nutraceuticals properties of bitter gourd which scarcely contribute to the nutritional value but produce beneficial physiological effects in the body (Daniel et al. 2014). Around 228 different compounds were identified from different parts of *M. charantia* (Nagarani et al. 2014) and the important compounds are given in Table 3.

Aqueous extract of bitter gourd contained carbohydrates, proteins, amino acids, sterols, flavonoids, phlobatannins, terpenoids, cardiac glycosides and saponins. Qualitative tests found out the presence of carbohydrates, proteins, amino acids, phenolics, saponins, sterols, alkaloids, cardiac glycosides, cholesterol and phlobatannins in the ethanolic extract of bitter gourd.

Table 3 List of different bioactive compounds identified from different parts of bitter gourd plant

Broad category	Compounds identified	Plant parts	References
Phenolic compounds	Flavonoids such as catechin, epicatechin Non flavonoids such as gallic acid, gentisic acid, chlorogenic acid, tannic acid, tannins	Fruits Leaves Stem	Ullah et al. 2011; Ingle & Kapgatte 2018; Nagarani et al. 2014; Mahwish et al. 2018
Carotenoids	Lutein, α & β carotene, zeaxanthin, β cryptoxanthin, lycopene	Fruits	Shubha et al. 2018
Cucurbitane Triterpenoids	Charantin, kuguacins A – S, momordicine I, II and III, Karavilagenin A, B, C, D, E, saponins (triterpenoid glycosides), goyasaponins, sapogenins such as diosgenin	Fruits and Leaves	Ullah et al. 2011; Ingle & Kapgatte 2018; Ummi et al. 2018; Shubha et al. 2018; Mahwish et al. 2018; Li et al. 2015
Phytosterols	Decortinone, clerosterol, ergosterol peroxide, stigmasterol, campesterol, β sitosterol	Fruits	Ullah et al. 2011; Ummi et al. 2018; Shubha et al. 2018; Kim et al. 2013
Alkaloids		Fruits & Leaves Seeds	Shubha et al. 2018; Ingle & Kapgatte 2018; Mahwish et al. 2018

Hexane extract showed the presence of alkaloids, cardiac glycosides, saponins and cholesterol. Methanolic extract was found to contain alkaloids, glycosides, cholesterol, saponins, flavonoids and terpenoids (Supraja et al. 2015). Barua et al. (2020) extracted bioactive compounds from fruits of two varieties of *M. charantia* with petroleum ether, ethyl acetate and ethanol. Phytochemical screening of the obtained extracts revealed the presence of alkaloids, flavonoids, saponins and tannins while the ethanolic extract showed higher phenolic content which may have the potential for food application. The essential oil obtained from the seeds of *M. charantia* was analysed by GC/MS and 25 constituents representing 90.9% of the oil were identified; the main constituents being *trans*- nerolidol, apiole and *cis* – dihydrovarveol (Braca et al. 2008). Kumari et al. (2017) concluded that the phytochemical composition of bitter gourd genotypes exhibited genetic diversity in phytochemical composition in flesh of bitter gourd and this variation may be due to genotype, level of phytochemicals present in genotypes, agro climatic condition and other agricultural practices.

Nutraceutical properties of *M. charantia*

Numerous researches has been conducted and proved the nutraceutical properties attributed to the bitter gourd. Some of the important properties, as shown in Fig. 1, are highlighted in the following section:

Anti- diabetic activity

Diabetes mellitus is a metabolic disease characterised by hyperglycaemia resulting from defects in insulin secretion, insulin action or both. *M. charantia* is a traditional remedy used since ages for management of diabetes in alternative and complementary medicine. Extensive research has been conducted to identify the compounds and the mechanism of anti-diabetic activity attributed to the bitter gourd is enlisted in Table 4.

Anticancer property

In last few decades, a number of preliminary trials have been conducted to reveal and establish the anti-cancer property of *Momordica charantia.* Studies suggest the role of bioactives in *M.charantia* in the regulation of cervical cancer, breast cancer, liver cancer, nasopharyngeal carcinoma, leukemia, colon cancer etc. Although several trials have been conducted in vitro and in vivo to explore the activity against carcinoma, systematic clinical trials are needed in cancer patients to establish the anti-cancer effects of *M. charantia.*

In vitro anticancer activity of ethanolic extract of *M charantia* whole fruit on cell lines representing breast and cervical carcinomas was established by Shobha et al. (2015). Cytotoxicity assay on HeLa (cervical cancer) and MCF 7 (breast cancer) cell lines showed 50% ethanolic extract is more potent based on IC_{50} value. The effect was directly attributed to the higher content of phenolic acids in the ethanolic extract. Güneş et al. (2019) also reported that the ethanolic whole fruit extract exhibited a higher anti-cancer activity. They investigated and compared the anti-carcinogenic effect of *M. charantia* fruits and seed extracts on human cancer cell lines which included lung cancer (A 549), breast cancer (MCF 7), chronic myeloid leukemia (K 562) and T cell leukemia (Jurkat cells). These were incubated with ethanol and acetone extracts of fruits and seeds of bitter gourd. Among the acetone and ethanolic seed and fruit extracts, ethanolic fruit extract showed the highest anti-tumour activity (90, 92, 85, and 87% against K562, A549, MCF 7 and Jukart cell lines respectively) and they suggested the ethanolic extract as a potential source for development of anti-cancer compounds.

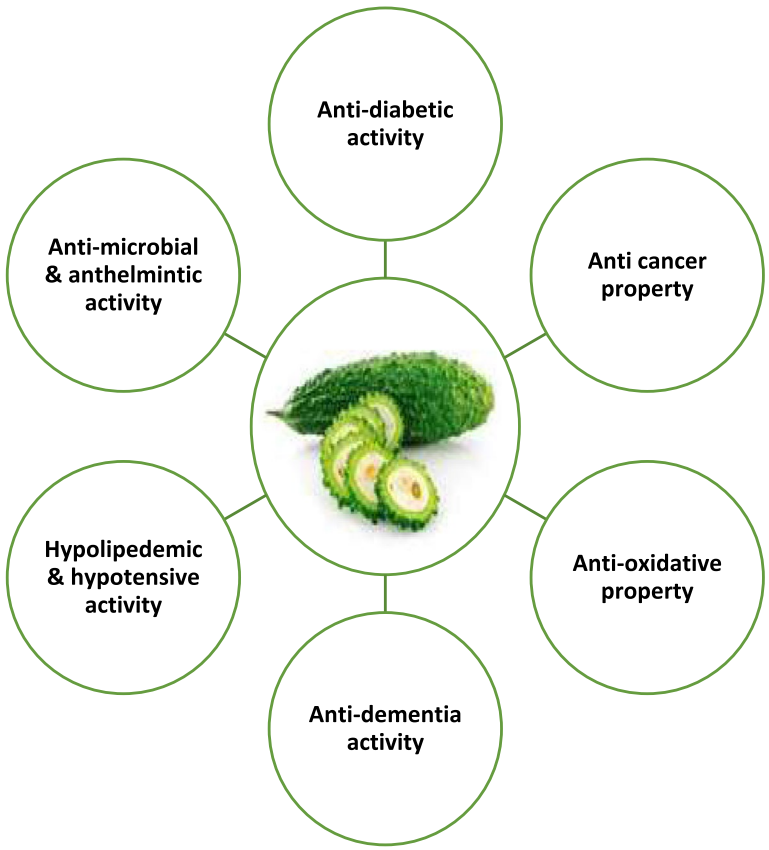


Fig. 1 Nutraceutical properties of *M. charantia*

Fang et al. (2012) studied the activity of *Momordica charantia* lectin, a type of ribosome inactivating protein from bitter gourd on two nasopharyngeal carcinoma cell lines, NPC CNE 1 and CNE 2 using in vivo assay in nude mice. Lectin was purified from bitter gourd seeds. The protein showed potent cytotoxicity towards both the cell lines CNE 1 and CNE 2 at the half maximal inhibitory concentration (IC50) of 6.9 and 7.4 respectively. An intraperitoneal injection of lectin (1 mg/kg/d) led to an average remission of NPC xenograft tumours subcutaneously inoculated in mice. A similar study was also reported in which MAP 30 protein, isolated from bitter gourd seeds, promoted the apoptosis in liver cancer cells in vitro and in vivo. Inhibition in cell viability with an IC_{50} value of 28.6 µM for 24 hrs and 7.8 µM for 48 hrs was obtained in Hep G2 cells and the anti-tumour potential was also effective in Hep G2 bearing mice (Fang et al. 2012). Dia and Krishnan (2016) reported a novel anticancer peptide, BG-4 isolated from *M. charantia* seeds showed a trypsin inhibitory activity 8.6 times higher than soybean trypsin inhibitor, which can be a possible reason for BG-4 to cause cytotoxicity to human colon cancer cells HCT-116 and HT-29 with median effective dose (ED50) values of 134.4 and 217 µg/ml respectively. The report was first to establish and anti-cancer potential of a novel bioactive peptide isolated from *M charantia.* However, in vivo models were not conducted to address the results.

Similarly Bai et al. (2016) pointed out the potential of a triterpenoid from bitter gourd in inhibiting the growth of breast cancer cells by conducting an in vitro assay in MCF 7 and MDA-MB- 231 breast cancer cell lines. The triterpenoid 3β, 7β, 25 -trihydroxycurcurbita 5,23 (E)-dien-19- al (TCD) was isolated from whole *M. charantia* plant. Suppression in proliferation of MCF-7 and MDA-MB-231 breast cancer cell lines with IC50 values at 72 h of 19 and 23 µM respectively via a PPAR γ independent manner was established. Yung et al. (2016) suggested the use of crude bitter melon extract as a supplement to improve the efficacy of cisplastin based chemotherapy in ovarian cancer. Important studies showing anti-cancer activity of *M.charantia* are detailed in Table 5.

Anti-oxidative property

Oxidative stress is the main cause for the development of various life style diseases including hypertension, diabetes, obesity etc. Researches are being conducted

Table 4 Studies showing anti-diabetic properties of bitter gourd fruit and extracts

Sl No	Nature of study	Treatment given	Results obtained	Ref
1	In vivo trial in streptozotocin induced diabetic rats	Bitter gourd in powder form incorporated at 10% level at expense of equivalent amount of corn startch in AIN 76 basal diet for 45 days	Improved diabetic status by significant reduction in glomerular filtration rate	Shetty et al. 2005
2	In vivo study in insulin resistant db/db mice	Administration of whole fruit powder, a lipid fraction, a saponin fraction or the hydrophilic residue of bitter gourd at a daily dosage of 150 mg/ kg body weight for 5 weeks	Lower glycated Hb level in all treatment groups Saponin and lipid fraction treated group shown reduced lipid peroxidation in adipose tissue Reduced protein tyrosine phosphate 1 B (PTB 1 B) activity in skeletal muscles (first study to demonstrate PTB 1 B regulation)	Klomann et al. 2010
3	Multicentre, randomised, double blind, active control trial in newly diagnosed type 2 diabetes patients	Bitter melon capsule with 500 mg of dried powder of fruit pulp containing 0.04 – 0.05 (w/w) of charantin at the rate of 500/1000/2000 mg bittermelon per day and 1000 mg metformin per day for 4 weeks.	Modest hypoglycaemic effect and significant reduction in fructosamine levels from baseline in 2000 mg treated patients. But less effect than metformin 100 mg per day	Fuangchan et al. 2011
4	Randomised clinical trial on diabetic patients	45 ml of bitter gourd fermented beverage as a morning drink	Significant improvement in reducing symptoms of diabetes, reduced fasting and post prandial blood sugar	Devaki & Premavalli 2014
5	In vivo rat model with induced diabetes with streptozotocin	Administration of fruit extract at the rate of 1.5 g /kg of rats for 28 days after induction of diabetes	Improved vascular compilation by decreasing blood pressure, serum total cholesterol, triglyceride levels, aortic tissue MDA level Increased aortic nitrous oxide level	Abas et al. 2015
6	Preliminary clinical trial on non-insulin- dependent diabetes mellitus patients	Powdered bitter gourd made into a tablet having a polypeptide of 20 mg. Dose of 4 to 6 tablets per day half an hour before meals, t.d .s for 8 weeks	Effective oral adjunt hypoglycemic effect without no reportable clinical side effects	Salam et al. 2015
7	In vitro alpha amylase and alpha glucosidase activities	Spectrophotometric assay of protein extracts from two varieties of bitter gourd	Inhibition of alpha amylase and alpha glucosidase activity on par with acarbose.	Poovitha & Parani 2016
8	In vivo assay in streptozotocin induced diabetic rats	10 mg/ kg body weight of protein extract from bitter gourd cultivars was fed to rats. Blood drawn after 10, 30,60 and 120 min of oral administration	Significant reduction in peak blood glucose and area under the curve	Poovitha & Parani, 2016
9	In vivo study on diabetes induced mice by streptozotocin	Aqueous and ethanol extracts of bitter gourd at the rate of 200 mg / kg weight of mice for 3 weeks	Significant reduction in blood glucose level	Yousaf et al. 2016
10	In vivo study in high sucrose diet induced diabetic rats	Skin, flesh and fruit powder at the rate of 150 and 300 mg / kg body weight for 56 days	Decrease in blood glucose level & increasing serum insulin level at the arte of 300 mg	Mahwish et al. 2018
11	Randomized placebo controlled single blinded clinical trial with 52 individuals with prediabetics	Daily bitter gourd consumption of 2.5 g of powder over a course of 8 weeks: Cross over design, 8 weeks for each study period & 4 weeks wash out.	Lowered fasting plasma glucose	Krawinkel et al. 2018

Table 5 In vitro and in vivo assays showing anticancer activities by bitter gourd

Sl No	Nature of study	Activity shown by	Assay conducted	Anti-cancer effect	References
1	In vitro assay in human nasopharyngeal carcinoma cells	Lectin purified from bitter gourd seeds	Flow cytometric apoptosis assay	Potent cytotoxicity towards cell lines CNE 1 and CNE 2 at IC50, 6.9 and 7.4 respectively	Fang et al. 2012
	In vivo assay in athymic nude mice		TUNEL staining assay	Average remission of NPC xenograft tumours in mice	
2	In vitro study in liver cancer cell lines In vivo studies in nude mice	MAP protein from *M charantia* seeds	Flow cytometric assay in Hep G2 cells and Hep G2-bearing mice	Inhibition in cell viability with an IC_{50} value of 28.6 µM for 24 hrs and 7.8 µM for 48 in Hep G2 cells and effective anti-tumour potential in Hep G2 bering mice	Fang et al. 2012
3	In vitro study on cervical and breast cancer cell lines	Ethanolic extract of bitter gourd	Sulforhodamine – B assay	Effective cytotoxicity towards HeLa and MCF7 cell lines	Shobha et al. 2015
4	In vitro assay on breast cancer cell lines	3β, 7β, 25 -trihydroxycurcurbita 5,23 (E)-dien-19- al (TCD) isolated from whole plant	MTT assay	Suppression in proliferation of MCF-7 and MDA-MB-231 cell lines with IC50 values of 19 and 23 µM respectively at 72 hrs	Bai et al. 2016
5	In vitro assay in human colon cancer cell lines	Novel protein BG 4 isolated from *M charantia* seeds	Flow cytometry apoptosis assay	Cytotoxicity towards HCT-116 and HT-29 cell lines with ED50 values of 134.4 and 217 µg/ml respectively	Dia & Krishnan 2016
6	In vitro assay in lung cancer (A 549), breast cancer (MCF 7), chronic myeloid leukemia (K 562) and T cell leukemia (Jurkat cells)	*M.charantia* fruit and seed, ethanol and acetone extract	MTT assay	Anti-tumour activity of 90, 92, 85, and 87% against K562, A549, MCF 7 and Jukart cell lines respectively by ethanolic extract	Güneş et al. 2019

on the effect of *M. charantia* and specific compounds in it against oxidative stress, most of them showing bitter gourd has the potential antioxidant properties. Bitter gourd showed good anti-oxidant capacity in comparison with colocasia (*Colocasia esculenta)* (Gayathri 2014) and pumpkin (*Curcubita pepo)* (Hamissou et al. 2013). Various in vitro studies have been carried out to establish the antioxidative activity of *M. charantia* whole fruit pulp, extracts, seed powder, leaves and stem (Kubola & Siriamornpun 2008; Padmashree et al. 2011; Leelaprakash et al. 2011).

An in vivo study in mice fed with appropriate doses of bitter gourd polysaccharide showed that they would scavenge the peroxide free radicals produced in vivo, block the free radical chain reaction and play a certain role in anti-oxidation and anti-ageing processes. Superdioxide mutase is an important antioxidant defense in living cells by balancing the oxidation and anti-oxidation. Similarly, catalase protects cells from oxidative damage caused by hydroxyl anion. The level of malonidialdehyde reflects the severity of free radical attack. The in vivo measurement results showed that the high and medium doses (300 μg and 150 μg/g respectively) of bitter gourd polysaccharides had a significant increase in SOD and CAT activities in serum, liver and brain of mice and reduction in MDA in the same to an extent (Tsai et al. 2011). Chen and Huang (2019) assessed the effect of derivatization of bitter gourd polysaccharides, obtained by water extraction and ethanol precipitation and chemically modified by carboxymethylation and acetylation, on the anti-oxidant activities. The different chemical modification showed different enhancement on the antioxidant capacities of bitter gourd polysaccharide which was assessed by hydroxyl radical scavenging capacity and DPPH radical scavenging capacity and anti-lipid peroxidation capacity. Ekezie et al. (2016) synthesized zinc nanoparticles from ethanol extract of bitter gourd and evaluated in vitro anti-oxidant efficacy of the particles. The results of DPPH and superoxide scavenge assays indicated that the nanoparticles exhibit potent antioxidant activity. Similarly, a dose dependent scavenging activity was exhibited in the superoxide radical scavenging assay.

Aminah and Anna (2011) investigated the influence of ripening states on phenolics and the corresponding antioxidant potential of bitter melon fruits. No significant differences in the FRAP and DPPH value of bitter gourd on the ripening stages was reported. However, further clinical trials are required to prove the anti-oxidant activity of bitter gourd plant parts.

Anti-dementia activity

Neurodegenerative diseases are illnesses which affect the brain cells causing a miscommunication and there by leading to irreversible effects in movement, memory, speech and intelligence. These diseases are untreatable and are described by a degeneration of certain neurons in a progressive manner occurs due to certain metabolic or toxic stress (Valarmathi et al. 2020). Some examples for neurodegenerative diseases are dementias, Parkinson's disease and PD related disorders, prion Disease, motor neuron diseases (MND), Huntington's disease (HD), spinocerebellar ataxia (SCA) and spinal muscular atrophy (SMA). Dementia is the term used to depict a group of neurodegenerative disorders which affect the memory keeping power of the brain. Alzheimer's disease, vascular dementia, Lewy body disease and frontotemporal dementia are some are the most common type of dementias. Various preclinical trials are being conducted to establish various neuroprotective effects particularly the anti -dementia activity of the compounds isolated from *M. charantia.*

Tamilanban (2018) isolated charantin from *M. charantia* and evaluated its neuropretective effect by in vitro studies performed in SH-SY5Y neuroblastoma cell lines. Charantin is a steroidal glycoside which exist as a mixture of sigmasterol gucoside and β sitosterol glucoside (Desai & Tatke 2015). The neuronal damage in cell lines was produced by MPP+ (1-methyl 4- phenylpyridinium) and tunicamycin, a bacterial toxin which causes endoplasmic reticulum stress which is common in Alzheimer's and Parkinson's diseases. The cell viability analysis and IC50 determination were performed by MTT assay and neuronal red uptake assay. The study revealed that charantin which was added at 8 hand 16 h after MPP+ treatment at a concentration of 1 mg/ ml showed a cell viability of 44 and 36% respectively. The positive effect was because of the possible free radical scavenging properties of charantin. Similar neuroprotective effect was found in tunicamycin induced neurotoxicity also. The percentage cell viability was found to be 35, 45 and 95% at 0.1, 0.5 and 1 mg/ml of charantin. The report was in accordance with another study conducted by Kuanhuta et al. (2014) in which charantin exhibited a high butyrylcholineesterase inhibitory activity. Gong et al. (2015) found out that *M. charantia* polysaccharide could protect against cerebral ischemia/reperfusion injury and the mechanism of protection could be at least in part attributed to the anti-oxidant activities proved by in vitro oxygen glucose deprivation (OGD) model. In another study, Ju and Kim (2018) also attributed the protective effect of *M. charantia* ethanol extract to the anti-oxidant and anti-apoptotic properties of bioactive compounds in the extract, against oxidative stress induced neuronal cell death. Oxidative stress was induced by hydrogen peroxide. *M. charantia* ethanol extract significantly reduced the H2O2 induced cell death in human neuroblastoma SK-N-MC cells.

In vivo studies establishing the effect of *M. charantia* are limited in regard to the memory impairment diseases. Miri et al. 2019 studied the effect of hydroalcoholic extract of *M. charantia* on the avoidance of memory alterations in mice using step-through model. The extract of the soaked plant was administered to the mice at doses of 10, 25, 50, 100 and 200 mg/kg by intragastric tube (gavage) method. A dosage of 25 mg/kg of extract indicated the ability to restore scopolamine induced memory corruption through step-through passive avoidance test. Pathakota et al. (2017) also demonstrated the anti-dementia activity of ethanol extract of bitter gourd through inhibiting lipid peroxidation and decreasing acetylcholinesterase activity in brain in mice. Behavioural tests (rectangular maze test and Morris water test) were also conducted which showed a general decrease in the transfer latency in all ethanol extract treated groups compared to the control group in which the memory loss effect of scopolamine induction is prominent. A similar reverse amnesia effect in scopolamine induced rats was reported by Joshi et al. (2017) also, by providing a dose of 5 to 2000 mg per kg of bitter gourd paste. Huang et al. (2018) investigated the effect of combined treatment of *M. charantia* and lithium chloride, which also has some neuropretective effects against Alzheimer's disease, in vitro and in vivo. They found out that combined treatment could be a potential strategy for the treatment of Alzheimer's disease.

Hypolipidemic and hypotensive activity

Hyperlipidemia is a condition in which blood has abnormally high levels of lipids namely cholesterol and triglycerides mainly occur due to unhealthy food choices, chronic stress and obesity. It is considered as a potential risk factor for cardiovascular diseases. Researches are undergoing in exploring the role of bioactive ingredients from *M. charantia* fruit and its parts against this condition.

The possibility of using of *M. charantia* juice as a hypolipidemic agent was investigated by (Sharmin et al. 2017). Norwegian rats were fed with high fat diet and the hypolipidemic effect of *M. charantia* juice was compared to atorvastatin, a commonly used hypolipidemic drug. A reduction of serum total cholesterol, low density lipoprotein cholesterol and triglycerides was observed in bitter gourd juice fed group which was similar to those fed with the drug. Arshad et al. (2018) compared the hypolipidemic effect of ethanolic extract of over dried peel, flesh and seeds powder and concluded that bitter gourd seed is helpful in controlling the hyperlipidemia more than other bitter gourd components through rat model. Another such comparative study showed bitter gourd whole fruit powder had the highest hypolipidemic activity, when the bitter gourd skin, flesh and whole fruit powders were fed to rats. They also reported a slight increase in high density lipoprotein (Mahwish et al. 2018).

Studies are also reported specifically to establish the anti-hypertensive effect of *M. charantia*. Lestari and Mahayasih (2017) positively correlated the presence of phenolic compounds in bitter melon and increased anti-hypertensive activity. The study conducted was to examine the effect of bitter melon leaves extract and its fractions (n hexane, ethyl acetate and n butanol) against hypertension by checking the angiotensin converting enzyme inhibition activity using ACE kit – WST. They concluded that the ethyl acetate fraction from the 80% ethanolic extract of bitter melon leaves provided highest inhibition activity against Angiotensin Converting Enzyme with I50 value 4.29 µg/ml and the same fraction showed highest flavonoid and tannin content. The ethanolic and methanolic extracts of leaves inhibited the angiotensin 1 converting enzyme in vitro, higher activity being shown by methanolic extract. In another study of Tan and Gan (2016), a functional polysaccharide was isolated from lyophilised *M. charantia* fruits and anti-hypertensive activity was determined in vitro. The result showed that the isolated polysaccharide had a higher inhibitory activity (94.1%) in comparison to other polysaccharide sources such as almond, pistachio and chickpea (Joshi et al. 2017). Priyanto et al. (2015) identified two novel angiotensin 1 converting peptides, VY-7 and VG-8, from a thermolysin digest of bitter melon seed proteins and inhibitory activity was evaluated using ACE inhibitory assay. The study showed that the VY-7 showed the best IC50 value in vitro in a simulated gastro intestinal digestion and the inhibition type was competitive. Significant anti-hypertensive effect was also shown in vivo in which the average systolic blood pressure of spontaneously hypertensive rats reduced from 220 to 180 mmHg at 8 h after oral administration.

Anti-microbial and anthelmintic activity

Bitter gourd is a folk lore medicine for various skin and stomach ailments owing to anti-microbial activities and the potential of bitter gourd as an antimicrobial agent is proven (Braca et al. 2008; Saeed et al. 2018). The ethanol extract of leaves of *M. charantia* was found effective against proliferation of *Eschericia coli, Staphylococcus aureus, Bacillus subtilis, Pseudomonas aeruginosa, Salmonella typhi, Klebsiella pneumonia* (Leelaprakash et al. 2011; Ingle & Kapgatte 2018) and *C. albicans* (Jagessar et al. 2008). The inhibition activity observed was attributed to the presence of alkaloids, flavonoids, saponins, tannins, anthraquinones and terpenoids. Jagessar et al. (2008) observed that the antimicrobial activity was

solvent dependent, in which ethanol extract being more potent than aqueous. Ingle and Kapgatte (2018) was also in accord with that. Mahmood et al. 2012 reported that the methanolic extract of ground bitter gourd fruit and seed pulp had antimicrobial activity against *Staphylococcus aureus, Salmonella typhi, Pseudomonas aeruginoisa* and *Eschericia coli* and against fungal strains *Penicillium expansum* and *Aspergillus niger*. Saengsai et al. (2015) isolated plumericin, an iridoid lactone from *M charantia* vine and proposed that its inhibition against *Enterococcus faecalis* and *Bacillus subtilis* was better than that of cloxacillin. In addition this, the extracts of leaf, fruit and seeds also reported to have anthelmintic activity against *Ascaris suum, Ascaridia galli, Fasciola hepatica, Stellantchasmus falcatus, Strongyloides spp, Caenorhabditid elegans* and *Eisenia foetida* in birds and mammals (Poolperm & Jiraungkoorskul 2017). Leaf extract of bitter gourd also reported to have activity against *Aeromonas hydrophila*, the most common bacteria that affect fresh water fish (Masithoh et al. 2019).

Methods of extraction of bioactive components from bitter gourd

Owing to the above said nutraceutical properties of bioactive compounds from *M. charantia*, recently much attention is being paid to the extraction techniques of those compounds. It is very much important that the extraction should not affect quality of the compounds and the extract should not be toxic, as it has to be incorporated ultimately to a food. Similarly, the technique must provide maximum yield along with maximum bioactive content. Solid liquid extraction is the most used method for the extraction from fruits and vegetables in which plant material is mixed with the extraction solvent and let the soluble phytochemicals diffuse out of the plant cell walls (Sutanto et al. 2015). A wide range of studies are being conducted using different solvents namely water, ethanol, methanol, acetone, hexane and butanol to find out the suitable method which gives highest bioactive content in the bitter gourd extract as depicted in Table 6. Extraction using water is the safest and easiest procedure even though the yield of phytonutrients is a matter of questioned. Jain and De (2016) suggested an optimum condition for water extraction of proteins and polyphenols with an optimum temperature and fruit water ratio. However, even after optimization the yield was found to be lower when compared to alcohol based extraction. In contrast, another report suggested that the aqueous method could be optimised to give an extraction yield of phenolic compounds equivalent to that obtained with the best organic solvent tested (80%) alcohol and less solvent and less time was required with water than with 80% alcohol (Tan et al. 2014). However, in the case of extraction of flavonoids particularly, acetone was the best solvent among water, n - butanol, methanol and ethanol even though after trying with optimised conditions for water extraction (Tan et al. 2014).

Studies have also investigated alternate extraction procedures, such as ultrasound assisted extraction of bioactive compounds from bitter gourd fruit. This method reduces both extraction time and temperature (Sutanto et al. 2015). Another study compared two sonication modes namely normal and pulsed mode and optimised the variables. Among them pulsed mode sonication showed better performance than that of normal mode sonication with marginally lower vegetable to solvent ratio but higher bio active content and it was suggested as a promising method with respect to conventional methods for production of bitter gourd aqueous extract for medicinal and functional applications (Chakraborty et al. 2020). An attempt was also made to extract β-carotene from enzyme treated ripe bitter melon pericarp using supercritical fluid extraction using carbon dioxide as a solvent and ethanol as a modifier to enhance the yield (Patel et al. 2019). Further, another study also put forward the use of super critical carbon dioxide extraction in extracting charantin from dried bitter gourd fruit promising a better yield of charantin with ethanol as a modifier. However, the highest yield of charantin was obtained by soxhlet extraction with water as solvent and lowest yield with supercritical extraction using pure carbon dioxide when a comparative study was done. When supercritical carbon dioxide extraction method was modified with ethanol, the extraction was more effective than conventional method. Thus it was proposed as a 'green extraction method' than a conventional method (Zaini et al. 2018). Microwave assisted ethanol extraction of saponins were also tried from *Momordica cochinchinensis* seeds and use of full fat seed powder was recommended for better yield (Le et al. 2018).

Significance of encapsulation of bitter gourd

Encapsulation is a technique to create an external membrane or coating of one of the material over another material, which is applied for the protection and/or preservation of bioactive, volatile and easily degradable compounds from biochemical and thermal deterioration (Rezaul et al. 2019). The technique can improve stability of various bioactive compounds isolated from bitter gourd while incorporating them to functional foods or beverages which may require undergoing different acidic, alkaline and thermal conditions while processing. Some attempts have been made by researchers to optimise the encapsulation conditions of extracts from bitter gourd. An optimised method for encapsulating aqueous bitter melon extract was proposed in which spray drying was

Table 6 Studies showing extraction of bitter gourd and parts using different methods and different solvents

Method	Plant part used	Target compounds	Optimum extraction conditions	Yield	References
Aqueous extraction	Fruit	Phenolic compounds	Temperature: 80 °C Time: 5 min Water to powder ratio: 40: 1 ml/g Particle size 1 mm	10.6 mg GAE/g dry basis	Tan, Stathopoulos, et al. 2014
Aqueous extraction	Fruit	Flavonoids	Temperature: 40 °C Time: 15 min Water to fruit powder ratio: 100: 1 ml/g	1.24 mg RE/g	Tan, Parks, et al. 2014
Ultra sound assisted extraction	Fruit	Total phenolic content	Temperature: 25 °C Time: 5 min		Sutanto et al. 2015
Aqueous extraction	Fruit	Proteins, Polyphenols	Fruit water ratio: 0.48 g/mL Extraction time: 95 min Extraction temperature: 68 °C	Proteins: 131.7 mg/L Polyphenols: 23.1 mg GAE per 100 ml	Jain & De 2016
Super critical carbon dioxide extraction with ethanol as modifier	Fruit	Charantin	Time: 2.5 h	0.7817 mg / g sample	Zaini et al. 2018
Super critical fluid extraction	Ripe bitter melon pericarp	β carotene	Pressure: 390 bar Flow rate: 35 mL/min Temperature: 70 °C Time: 190 min	90.12%	Patel et al. 2019
Pulsed mode ultra sound assisted extraction	Fruit	Total polyphenol content and total soluble proteins content	Temperature: 68.4 °C Time: 12 min Fruit to water ratio: 0.25 g/mL	104.5 mg GAE/g and 42.1 mg/ 1000 mL respectively	Chakraborty et al. 2020

GAE Gallic acid equivalent, *RE* Rutin equivalent

done with maltodextrin (MD) and gum Arabic (GA) as coating material (Tan et al. 2015). The aqueous extract was prepared from the ground freeze dried bitter melon using a shaking water bath at a temperature of 40 °C for 15 min. The optimal formulation for encapsulation was 35% (w/w) stock solution (MD: GA, 1:1) and a ratio of 1.5:1 g/g of the extract to the stock solution. Inlet temperature was set at 150 ± 2 °C and the outlet temperature at 85 ± 2 °C and the aspiration at 100%. They also optimised the inlet and outlet temperatures for spray drying as 140 °C and 80 °C using the same combination of MD and GA as encapsulating agents (Tan et al. 2015). Another study was also conducted for encapsulating aqueous homogenised bitter gourd extract. Maltodextrin and gum Arabic were used as the wall materials and optimum the core to wall ratio was 1:3. The optimum drying inlet air temperature was 160 °C (Raj & Priya 2016).

An attempt was made to produce nanoencapsulated probiotic bitter gourd juice powder using spray dryer at three different temperatures (140, 150 and 160 °C) with three different encapsulating agents (30% each of maltodextrin and gum Arabic and mixture of both maltodextrin (15%) and gum Arabic (15%)). The feed solution also contained *L. casei.* The results showed that the viability of the *L. casei* in the developed nanoencapsulated probiotic bitter gourd juice powder was considerably good when encapsulated with maltodextrin there by retaining the powder properties. The reason was attributed to the thermo protection effect of maltodextrin (Kalal et al. 2016). In another research, extraction and loading of bitter melon extract was performed at different concentrations of extract and lecithin (Rezaei et al. 2019). Nanoliposomal formulation produced with 0.5% extract and 1% lecithin was the best considering the particle size and encapsulation efficiency.

Conclusions

Bitter gourd is a wonder fruit which has nutritional and functional properties but due to its bitter taste, usage among population is limited. Not only the fruit but other parts of the plant also have proven functional attributes. Numerous researches had identified the bioactive compounds present in the bitter gourd and different parts of the plant. In vitro and in vivo studies have also extensively investigated bioactive properties such as anti-diabetic, anti-cancer, hypocholesterolomic, anti-dementia activities among others. Various novel technologies and concepts like nanoencapsulation and green extraction

methods enhance the possibilities of bitter gourd as a functional food thereby adding the need of value addition. However, researches are still at its infancy. The applications of bitter gourd and the identified phytochemicals in food and pharmaceutical industries are yet to be explored widely. The long term effects of consumption of bitter gourd have not been studied and moreover the bioactivities are proven mostly in vitro and in vivo trials. Proper clinical trials are required to know the efficient and effective positive effects of these properties on human systems.

Abbreviations

DW: Dry weight; FAO: Food and Agricultural Organisation; WHO: World Health Organisation; UNU: United Nations University; GC/MS: Gas chromatography-mass spectrometry; MCF7 : Michigan Cancer Foundation; NPC: Nasopharyngeal Carcino; DPPH: 2,2 - Diphenyl - 1 - picrylhydrazyl; FRAP: Ferric Reducing Antioxidant Power; ACE: Angiotensin Converting Enzyme.

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GKS prepared the draft of the manuscript. JAJ read and edited the manuscript. All authors read and approved the manuscript.

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Declarations

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