Bitter melon (Momordica charantia): a natural healthy vegetable
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ABSTRACT
Bitter melon provides health benefits against various ailments for improving the quality of life. It is nutrient dense plant-based food containing versatility of bioactive compounds such as alkaloids, polypeptide, vitamins, and minerals. Owing to presence of bioactive compounds, it has the ability to fight against various lifestyle related disorders, e.g. cancer insurgence, diabetes mellitus, abdominal pain, kidney (stone), fever, and scabies. Amongst bioactive moieties, p-insulin is similar to insulin whose subcutaneous injection significantly lower blood glucose levels in diabetic patients. It also contains steroidal saponins called charantin, act alike peptides and certain alkaloids that effectively control sugar level in blood. The therapeutic perspectives have been also highlighted as they are helpful in regulating blood cholesterol thus protecting the body from cardiovascular disorders like atherosclerosis. Whole fruit, seeds and leaves of bitter melon regulates impaired antioxidant status and suppress fat accumulation. Moreover, curative potential of its bioactive components and their utilization in value added food products are also the limelight of article.

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Introduction
In the field of nutrition, plants and their products have significant importance not only for providing basic nutrients but also for prevention of various maladies. They indeed improve the quality of life[1] throughout the globe. Plant-based traditional medicines are also in use[2,3] since immemorial times, however, their standardizations is essential in order to assess their potential.[4] Epidemiological data portrayed inverse correlation between their consumption and declining incidence of several ailments. Fruits and vegetables contain array of compounds broadly categorized as phytochemicals that have profound influence especially for disease prevention. The recent era witnessed more coherent and systematic studies regarding these bioactive molecules and results in development of a segregated section, i.e. functional and nutraceutical foods. These health promoting commodities are gaining attention of the consumer due to higher acceptability and raised level of awareness. These biologically active components are widely distributed in food such as spices, herbs, tea, fruits, & vegetables and show considerable antioxidant activity in vivo & in vitro with significant health consequences.[5] The aforementioned debate is incomplete if we do not look at our lifestyle. Currently, the lifestyle matters a lot in a variety of ways, e.g. ease of life, less eventful with lavish/relish palatability. These all factors cumulatively resulted in diversified eating habits.[6] The metabolic reactions occurring in the body leads to production of some toxic metabolites like free radicals and indeed energy uptake and lack of physical exercise further worsen the health status of individuals.

The widespread prevalence of various ailments including coronary hear diseases, diabetes mellitus, cancer insurgence, degenerative disorders, and lack of body inherent defense mechanism are
often attributed to the lifestyle changes. The plants and their metabolites offer protections against such maladies if incorporated in the diet. They possess anticarcinogenic, hypocholesterolimic, hypoglycemic, and other beneficial properties. Their consumption is also linked with improved immunity to protect against oxidative stress and allied disorders. Some of these phytochemicals dense plants are bitter or astringent in their nature and usually receive less attention of the consumers and their acceptability is limited. However, these plants offer wide range of protection against various ailments.\textsuperscript{[7,8]} \textit{Momordica charantia} is one such sample that holds rich phytochemistry and effective agent in dietary regimens to prevent against different maladies.\textsuperscript{[9,10]} Brief about the bitter melon, it is used as a vegetable in many countries but since time immemorial, it is also used for administration of numerous ailments comprising ulcer,\textsuperscript{[11]} diabetes mellitus,\textsuperscript{[12,13]} and inflammation,\textsuperscript{[10,14]} etc. BM (bitter melon) is innate to subtropical and tropical areas in Asia and some other parts of the globe. It belongs to family cucurbitaceous and in Indian cuisines it is usually pronounced as \textit{karela}. All portions of the BM are palatable in nature but frequently grown for the fruit that is bitter of all.\textsuperscript{[15]} As far morphology of the plant is concerned, it is herbaceous plant that grows around 5 m and bears simple/alternate leaves of 4–12 cm with 3–7 deeply separate lobes. Bitter melon is similar to a small cucumber, usually rectangle and oblong in shape and eaten green. Bitter gourd is filled with pulp and large flat seeds, which surrounding a comparatively thin layer of flesh.\textsuperscript{[16,17]} BM (bitter melon) also rich in various bioactive components containing minerals, alkaloids, vitamins, steroidal saponins, polypeptide, and aromatic volatile oil, apart from its usage as vegetable. Bitter melon has ability to fight against numerous life style associated disorders, due to the presence of bioactive components.\textsuperscript{[15,18]} In this review, main focus of discussion is advancement of bitter melon and its active constituent regarding their health promoting mechanism. The therapeutic perspectives are the limelight of the manuscript. The curative potential of biter melon and its bioactive components demands attention of the researchers and it is the focus of the article too that bitter melon should be used in value added food products.

### Classification of \textit{Momordica charantia}

| Kingdom      | Plantae         |
|--------------|-----------------|
| Common Name  | Karela, Bitter gourd. |
| Order        | Cucurbitales   |
| Species      | M. charantia    |
| Genus        | Momordica       |
| Family       | Cucurbitaceous  |
| Class        | Magnoliopsida   |
| Division     | Magnoliophyta   |

### Chemical composition

Regarding the nutritional composition, \textit{Momordica charantia} contains 91.8% water, 0.20% fat, 4.2% carbohydrates, and 1.4% fiber. The proteins present in bitter melon seeds are of indeed quality and meet the amino acids requirements/standards laid down by (FAO/WHO/UNU) for preschool children. The proteins are fractionated into albumin, globulin, and glutelin that are present in the amounts of 49.3, 29.3, and 3.1%, respectively. The molecular weight of these proteins usually varies from 45 to 55 kDa.\textsuperscript{[19,20]} The bitter melon seeds contain nearly 35% to 40% of oil and the fatty acid profile indicates that the seeds contain 3.33% and 36.71% of MUFA (monounsaturated fatty acid) and SFA (saturated fatty acids). The largest amount (59.96%) of PUFA (polysaturated fatty acids) are found to be present in bitter melon. Amongst PUFA, α-eleostearic acid (54.26%) is a conjugated linolenic acid and is of significance importance.\textsuperscript{[21, 22]} The mineral profile of bitter melon seed is little different as it contains potassium, magnesium, calcium, sodium, and phosphorous in the
highest amounts and are more abundant in fruit and leaves.\textsuperscript{[22]} However, seeds are one of the naturally best sources of chromium and zinc, i.e. amounts of 5.65 and 45.45 mg/100 g, respectively.\textsuperscript{[22]} Bitter melon has been demanded to comprise glucosides, mineral matters, charantin, steroidal saponin, alkaloids, momordium, carbohydrates, and ascorbic acid, etc.\textsuperscript{[10]} By using Folin-Ciocalteu reagent, the quantitative examination of entire phenolic compounds shown the occurrence of 42.36 mg GAE/g in bitter gourd. The occurrence of Gallic acid in bitter melon as main phenolic acid has been showed by HPLC examination of phenolic content. Many other phenolic components are found to be present in bitter melon extract such as epicatechin, chlorogenic acid, catechin, and gentisic acid and gallic in bitter acid.\textsuperscript{[19,23–25]} The extract of BM has been demonstrated as slow rate free radical scavenging agents by free radical scavenging assay, which use 2,2- DPPH (diphenyl-1-picrylhydrazyl).\textsuperscript{[19,23,24]}

A diversity of bioactive compounds are present in BM (bitter melon), which comprises two classes of saponins recognized as oleanane and cucurbitane-type triterpenoids.\textsuperscript{[26]} From the whole plant of the MC one new cucurbitane-type triterpenoid glycoside, momordicoside U,\textsuperscript{[1]} along with five well-known cucurbitane-type triterpenoids and associated glycosides, kuguaglycoside G,\textsuperscript{[6]} 3-hydroxycucurbita-5,24-dien-19-al-7,23-di-O-β-glucopyranoside,\textsuperscript{[5]} momordicine I,\textsuperscript{[3]} 3β,7β,25-trihydroxycucurbita-5,23 (E)-diен-19-al\textsuperscript{[2]} and momordicine II\textsuperscript{[4]} have been isolated.\textsuperscript{[10]} Through GC/MS, the vital oil which attained from MC (Momordica charantia) seeds was evaluated. About 25 constituents which demonstrated 90.9% of the oil had been recognized. Main components which were identified in the oil are germacrene, trans-nerolidol apiole, and cis-dihydrocarveol.\textsuperscript{[27,28]} Alphaelostearic acid is abundant in oil, which has strong properties of lowering blood fat, inhibiting the proliferation of tumour cell, inhibiting CVD, anticancer, and anti-inflammatory.\textsuperscript{[22]} On those polysaccharides or proteins, minerals particularly Zn and Cr may had a strong effect and form a stouter anticipation of cholesterol, hyperlipidemia, and hyperglycemia.\textsuperscript{[29]} Fruit, seeds, and leaves hold different health promoting phytochemicals such as resins, vitamins, minerals, alkaloids, steroidal saponins, polypeptides, and aromatic volatile oil. Standard constituents of bitter melon are charantin, momordicine, and p-insulin which are steroidal saponin, alkaloid and polypeptides in nature, respectively.\textsuperscript{[25,30]} Fruit pulp of bitter melon contain no free pectic acid, but has soluble pectin. From the pulp of bitter melon, galacturonic acid has also been obtained. Momordicine and charantin are predominantly responsible for the health encouraging effect and the bitterness of M. charantia.\textsuperscript{[31,32]}

**Therapeutic use**

The bitter melon is natural product with ability to overcome or delay the process of aging due to presence of bioactive molecules. A variety of functional ingredients are found to be present in bitter melon comprise phytochemical components essentially terpenoids, glucosides, flavonoids, phenolic, alkaloids, charantin, and tannins. The plant of *Momordica charantia* is also rich in numerous saponins including kuguacin, momordin, karavilose, momordin, momordicoside, and karavilagenin.\textsuperscript{[33]} In one study, the obese rats fed on bitter melon continued to live at least a month longer as compared to control.\textsuperscript{[34]} Owing to these functional components, bitter melon possess wide range of pharmacological activities for instance, antioxidant,\textsuperscript{[32]} antifungal,\textsuperscript{[35]} anti-diabetic,\textsuperscript{[36]} ant obesity, stomachic, anticancer, hypotensive, and blood cholesterol lowering effects.\textsuperscript{[37,38]} The diabetes mellitus and associated complications are true example of lifestyle related disorders. The sedentary lifestyle, high intake of dietary energy, and obesity are amongst various causes leading to metabolic syndrome and diabetes mellitus.\textsuperscript{[39,40]} No doubt, drug used for the treatment of diabetes mellitus are effective but the side effects associated with their use often call for alternative from traditional medicines. The role of diet and dietary interventions is being highlighted in numerous scientific studies and the role of plants and their products are of significance importance.\textsuperscript{[41]} The bitter sensation of the under discussion plant is considered to be effective in preventing diabetes mellitus and curing associated complications. In general, bitter
Compounds like oleanolic acid 3-O-glucuronide, charantin, polypeptide-P, olea- 

Insulin resistance has been created by the particles which encompassing rigorous ethanolic extract of BM (bitter melon). Under high fat fed situations, BM extract supplementation enhanced the insulin sensitivity and glucose tolerance. As compared to placebo, the insulin-stimulated IRS-1 tyrosine phosphorylation was also enhanced. Moreover, bitter melon can reduce triglyceride and low-density lipoprotein. Momordicoside, an active compound, showed moderate insulin secretion activity. In diabetic rats body weight and the high level of fasting blood glucose has been improved by the administration of BM extracts about 13.33 g pulp per kg body weight/day. Compounds like oleanolic acid 3-O-glucuronide, charantin, polypeptide-P, olea- 

Moreover, bitter melon can reduce the number of β-cells and reduced the level of glucose in blood. No substantial difference of serum glucose concentration (93.7±9.63 vs. 88.35 ± 6.31 mg/dl) and serum sialic acid (57.95 ± 4.90 vs. 57.6 ± 5.56 mg/dl) has been shown by the patients who follow the treatment of bitter melon. It has been shown by histopathological studies that rosiglitazone administration with MC prohibited the hepatic damage and improved the volume of islet cell in pancreas. In one more study, the insulin secretion level and glycogen synthesis of alloxan-induced hyperglycemic mice raised with enhanced glucose tolerance and the blood glucose of alloxan-induced hyperglycemic mice reduced, when treated with saponin fraction of bitter melon about 500 mg per kg weight. In alloxan diabetic albino rats, acetone extract of BM (bitter melon) about 50, 25, and 75 mg per 100 g body weight lowered the level of glucose in blood from 13.30 to 50% after the treatment of 8 to 30 days. In islets of Langerhans, various stages of β-cells recovery has been shown by the histological observations. From pre-existing islet cells the neoformation of islets has been reflected by the existence of small scattered islets. During oral glucose tolerance test the levels of insulin and plasma glucose considerably increased. The lowering of glucose is partly due to increased serum insulin levels.

Insulin secretion can also be enhanced using saponin-rich fraction @ 10 and 25 μg/ml. The possible reasons for increased insulin concentration include reducing the extent of pancreatic damage thus increasing β-cells. The reduced level of glibenclamide was also observed by some researchers. Research stated that bitter melon fruit pulp @ 400 mg/kg/day can increased the β-cells by two folds in the diabetic rats with abundant insulin granules. Insulin resistance has been categorized by substantial down-regulation of hepatic insulin signalling such as recognized by over-expression of phosphotyrosine phosphatase 1B, reduced protein kinase B, phosphorylation of IR (insulin receptor), insulin receptor substrates 1 and 2 and phosphoinositide-3 kinase. In HFD-fed mice, BMJ not only increases the insulin and glucose tolerance but also reduces the phosphorylation status of insulin receptor (IR) and its downstream signaling molecules and lowers plasma apoB-48 and apoB-100. As compare to the liver of extract cured animals, the liver of alloxan diabetic rats exhibited necrosis, hydropic degeneration, and fatty change. Obesity and high energy intake are related with degenerative syndromes such as kidney damage, ecognitive decline, and liver damage. During obesity and over nutrition, increased metabolic flux to the brain can orchestrate blood-brain barrier (BBB) disruption, stress response, recruitment of inflammatory immune cells from microglial cells activation, and peripheral blood leading to neuroinflammation. Bitter melon has a neuro-protective effect on the stress, neuro-inflammatory cytokines, and HFD (high-fat diet)-associated BBB disruption. Moreover, as compared to high fat diet-fed mice, pro-inflammatory cytokines and plasma antioxidant enzymes were regulated in mice fed high fat diet. In obesity
and linked diabetes mellitus the activity of 11β-HSD1 (β-Hydroxysteroid dehydrogenase type 1) is a significant etiological feature. The capsules of BM (bitter melon) extract comprise minimum one constituent with selective β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitory action.\[67\] The level of glucose in blood is significantly reduced by the bitter melon. In diabetic nephropathy the thickening of the GBM (glomerular basement membrane) is well categorized in renal failure. Bitter melon feeding considerably reduce the increase in the glycoconjugates components during diabetes. The supplements of bitter melon significantly lowered the diabetes related elevation in the actions of enzyme which involved in the degradation and synthesis of GAGs (glycosaminoglycans).\[68,69\] Bitter melon supplementations also significantly improves the antioxidant status of the body as shown by normal levels of reduced glutathione and low levels of TBARS.\[11,47\] In BM (bitter melon) two isomers of CLnA (conjugated linolenic acid) are present, which are useful against oxidative stress in diabetes.\[70,71\]

Fructose diet-induced hypoadiponectinemia has been reversed by BM (bitter melon). In improving insulin sensitivity, fructose diet-induced hypoadiponectinemia which is reserved by BM offers a therapeutic advantage to insulin resistance. In WAT (white adipose tissue), bitter melon decreased the expression of leptin and improved the expression of PPAR gamma (peroxisome proliferator-activated receptor gamma). Moreover, in skeletal muscle bitter melon considerably increases the protein of GLUT4 (glucose transporter 4) and the expression of mRNA.\[18\] BM considerably declined the level of resistin mRNA and adipose leptin and also decrease the weights of visceral fat and epididymal white adipose tissue. The effects of bitter melon partly be through PPAR alpha-mediated pathways to improve the profiles of plasma lipid and a portion of effects is due to be through PPAR gamma-mediated pathways, which result in improving insulin resistance and lowering the levels of glucose.\[72\] Adiponectin expression and cell viability of bitter melon extract was affected through the decrease in accumulation of lipid in differentiating 3T3-L1. At least five different triterpenoids must be contained by bitter melon extract and decreased preadipocyte viability with an LC50 concentration after 72 h determined to be 0.310 ± 0.01 mg/mL, 0.402 ± 0.04 mg/mL for 24 h, and 0.314 ± 0.01 mg/mL for 48 h.\[73,74\] Charantins a mixture of compounds reduced the levels of blood glucose in diabetic along with normal rats.\[75\] In contrary, p-insulin or polypeptide-p results in glucose clearance when injected directly in the blood. However, when the same compounds were ingested than their effects were limited due to their susceptibility to the digestive enzymes in the stomach. However, the hypoglycemic properties of bitter melon when ingested orally are due to presence of charantins. In another study, it was proved that against high blood glucose the water extract of bitter melon was found to be more effective as compared to ethanolic extract. Glucose lowering effect of BM might be due to higher availability of phytochemicals in water.\[24,69\] Researchers described that incorporation of about 150 mg/Kg body weight of seed extract results in reduced TBARS and blood glucose as well as GST, GPx, glutathione, SOD, and catalase in the kidney and liver of diabetic rats.\[76\]

Normal kidney has a normal glomerulus surrounded by Bowmen’s capsule, convoluted tubules without any changes in a normal person. Diabetic person kidney has a degenerated glomeruli and thick basal membrane that disturb normal functioning of kidneys. In rat modeling, bitter melon extract extended apart in healing glomerulus and basal membrane as well as suppresses the inflammation and hyaline deposition in kidneys. Furthermore, extract was found to be effective against tissue necrosis.\[77,78\] Bitter melon in the form of capsules significantly decreases the A1c levels amongst patients of type-2 diabetes taking capsules. With IC 50 values of 12.0, 8.3, and 3.7 mg/mL for MIF, AE, and MF, bitter melon extracts dose-dependently repressed the sucrase action of intestinal mucosa. By inhibiting the activity of alpha-glucosidase, bitter melon repressed postprandial hyperglycemia. The most valuable constituent which is present in the LT 1,300 fraction obtained from MF.\[26,32,79\] In the digestion alpha-glucosidase shows a significant role. While α-glucosidase inhibitor retarded the use of dietary carbohydrate and prevent it from postprandial hyperglycemia and suppress the activity of carbohydrate digesting enzyme. The activity of enzyme has been suppressed by aqueous extract of bitter melon.\[32,80\] Results from numerous animal modeling studies
revealed that BM has hypoglycemic effects against STZ induced diabetes mellitus. In the current past, numerous randomized controlled trials were conducted in human subjects and presented varying pictures. On the regulation of blood glucose, the effect of bitter melon extract containing beverage amongst prediabetics has been evaluated by Boone and his coworkers during OGTT (oral glucose tolerance test). A considerable reduction has been found in postprandial glucose response by the intake of acute bitter melone. But insulin response has not been effected by the acute intake of BM.

### Bitter melon and cancer insurgence

The revolution of cancer is a current day curse for the nutritionists and pharmaceutical industries. There is widespread progress in the growth of anticancer therapies due to increased prevalence of cancer world wide. In order to decrease the risk of cancer and to control cancer revolution, anticipations of approaches are more significant. Bitter melon extract control the growth of cancer cells and has no side effect in humans as well as in animals. Several components isolated from bitter melon exhibited anticancer perspectives that include momordin I, I.e. and Id, α and β momorcharin, and cucurbitacin B as well as MAP-30. Bitter melon is not sufficiently effective for breast cancer, which is a severe public health problem amongst women. In breast cancer, the anti-proliferative action of BME (bitter melon extract) has been estimated. In preclinical model, BME (bitter melon extract) inhibits the growth of breast cancer by encouraging autophagic cell death. A third important reason of death in several populations of the world is prostate cancer. Kuguacin J which is extracted from BM has ability to constrain the prostate cancer growth. The ways of activities include hindering the expression of active forms of MMP-9 and MMP-2 and cell cycle arrest (Cdk4, CD1 and Cdk2). It has been examined that experimental and trial diets were having 12.5% and 6.25% of ground BM (bitter melon). In both kinds of prostate cancer cells MCL induced mitochondrial injury, apoptosis, DNA fragmentation, and G(1)-phase arrest. MCL induced apoptosis has been attended by an increase in cleavage of poly (ADP-ribose) polymerase and caspase-3, survivin levels reduction, attributable to augments of Bad/Bcl-xL and Bax/Bcl-2. The cell proliferation in adrenocortical carcinomas has been reduced by BME (bitter melon extract) in dose-dependent manner. The apoptosis induction has been facilitated through mitogen-activated protein kinase expression caspase-3 activation, enhanced cellular tumour antigen p53, inhibited G1/S-specific cyclin D3, D1, and D2, cyclin-dependent kinase inhibitor 1A and cyclic AMP-dependent transcription factor-3 levels. As compared to lower doses, α-momorcharin about 6.25 mg per kg body weight has been stated to possess immunotoxicity and immunogenicity. In leukemia cells, apoptosis has been induced by dihydroxy-α-eleostearic acid and α-eleostearic acid. These constituents have been found to inhibit azoxymethane-induced colon carcinogenesis in rat. It has been detected that protein-DNA interaction and nuclear transcription machinery inhibit tumour promoting signals. A-ESA may block the proliferation of breast cancer cell and induce apoptosis through an oxidation dependent mechanism.

Through RNases (ribonucleases) the revolution of cancer can be controlled. Bitter melon seeds contained natural 14-kDa RNase-MC-2. It has been suggested that for its cytotoxic and cytostatic activities against MCF-7 breast cancer cells through increased production of Bak and cleavage of PARP and activation of caspase (caspase9, caspase7, and caspase8), resulting in apoptotic response. Bitter melon can inhibit 7,12-dimethylbenz (a) anthracene (DMBA)-induced mammary gland carcinogenesis due to its phase II detoxificating enzymes inducing propertiest. Bitter melon extract treatment inhibited cyclin D1 and cyclin B1 expression and enhanced pChk1/2, p53, and p21 and proposing a mechanism which involved cell cycle regulation. BME modulates signal transduction pathways for inhibition of breast cancer cell growth and can be used as a dietary supplement for prevention of breast cancer.

Previously, it has been shown that bitter melon seed, pericarp and placenta extracts induce apoptosis in HL60 human leukemia cells. In HL60 cells apoptosis induced by α-eleostearic acid @ 160 µM. The growth of Hela cells and HepG2 cells has been inhibited by a native
polysaccharide (MCP2) from bitter melon and its sulphated derivatives, which indicated that the anti-tumour activity of MCP2 might be enhanced by sulphated modification.\textsuperscript{[103]}

The MAP30 has been tested highly meta-static human breast tumour MDA-MB -231 cells and estrogen-independent cells. The revolution of cancer might be controlled by using MAP30 which results in inhibition of expression of the HER2 gene and inhibition of cancer cell proliferation \textit{in vitro}. In human prostate cancer cells, similar impact of MCP30 has been detected.\textsuperscript{[104,105]} In Swiss albino rats, the extract of bitter melon leaf and fruit employ chemopreventive effect and decrease number and yield of papillomas and incidence of tumour. By using 1000 and 500 mg per Kg body weight reduction in tumour volume had been observed and life span of the rats had been increased upto 30 days.\textsuperscript{[91,106,107]} The main components of innate immunity are the NK (natural killer) cells. These cells have ability to arbitrate anti-tumour action. Against neck and head cancer cells, the supplements of BM (bitter melon) ameliorates the natural killer-mediated toxicity.\textsuperscript{[108]} In the nutshell, cancer insurgence can be prevented with the help of bitter melon. However, most of the results are derived from animal modeling thus there is dire need of the time to conduct controlled randomized trials to warrant its application in chemotherapy for human subjects.

\textbf{Antihyperlipidemic activity}

Hyperlipidemia is a social problem nowadays and associated with diabetes leading to increase in morbidity and mortality. Major risk factor of high blood lipid concentration is associated with ischemic heart diseases, atherosclerosis, and cerebrovascular disease. \textit{Momordica charantia} significantly showed antihyperlipidemic effect. Metformin, a fraction of \textit{Momordica charantia} and other fractions such as flavonoids, saponins, tannins, triterpenes, and alkaloids effect total cholesterol level in diabetic rats. More recently, a different mechanism of bitter melon has been described which suggests that it repairs damaged β-cells thus increasing the levels of insulin and its sensitivity.\textsuperscript{[42]} It also stimulates the release and synthesis of adiponectin and thyroid hormones and by inhibiting the activity of glucosidase inhibits the absorption of glucose. BM enhances the action of AMPK (adenosine-5-monophosphate kinase) that is associated with fat release from fatty tissues and glucose uptake and thus causing in weight loss.\textsuperscript{[109]} Another study revealed that diabetic rats treatment with \textit{Momordica charantia} extract resulted in significant reduction of blood lipid levels. Hepatic production of triglycerides also contributes to the hyperlipidemic effect of HIV-1-protease inhibitors and that contain lipoprotein instead of lipoprotein clearance.\textsuperscript{[110]} The bitter gourd @ 3% can significantly reduce the cholesterol and TG levels. The decrease was mediated through enhanced excretion of fecal lipid excretion and their lymphatic transport.\textsuperscript{[111,112]} In HepG2 cells bitter melon also ameliorate lipid and PI-associated ApoB abnormalities. Along improving lipid profiles, phytochemicals also decrease apolipoprotein C-III and decrease liver secretion of apolipoprotein B (Apo-B). Apo-B protein known as lipoprotein used for the production of LDL. Apo-C-III is a lipoprotein which is involved in the synthesis of LDL and found to be present in VLDL. \textit{Momordica charantia} compounds increases Apo-A-1 (Apo lipoprotein A-1) which is basic protein component compulsory for HDL synthesis.\textsuperscript{[48]} Bitter melon was analysed at hyperinsulinemic high fat diet for less visceral fat mass.

In a dose-response (0.375, 0.75, and 1.5%) study, oral glucose tolerance was improved in rats fed a high fat (30%) diet supplemented with freeze-dried bitter melon juice at a dose of 0.75%–1.5%. At the highest dose, rats showed lower energy efficiency and less visceral fat mass. Addition of \textit{Momordica} juice did not change the fat absorption but it reduced the adiposity in rats. Results revealed that on lipid and glucose metabolism, BM juice have multiple influences.\textsuperscript{[36,113]} Saad et al.\textsuperscript{[114]} observed that BM has ability to reduce body weight, visceral fat, and the accumulation of high fat due to its anti-hyperlipidemic effect. Mahwish et al.\textsuperscript{[115]} investigated the formulations and the anti-hyperlipidemic and anti-hyperglycemic action of various parts of BM (bitter melon) and observed that BM (bitter melon) has substantial potential in lowering visceral fat, body fat, and also in improving the diabetic complications, consequently showing the anti-hyperlipidemic effects.
Antioxidant and antiinflammatory activity

Lipid peroxidation and liver damage may be caused by the generation of ammonium free radical. Increased ammonia and urea levels lead to liver damage in ammonium chloride induced rats. Excessive ammonia intake increases activation of NMDA receptors as well neuronal degeneration resulting in oxidative damage due to lipid peroxidation and suppresses the activity of antioxidants.\[116,117\] Induction of ammonium salts either chloride or acetate introduced toxicity of ammonia and oxidative stress resulting in formation of lipid peroxide and free radicals.\[118\] Oral administration of bitter melon normalized the levels of TBARS, hydroperoxides, ALT, AST, and GPx and these all are mainly responsible for liver damage and lipid peroxidation.\[116,117\] Highest value based on DPPH radical-scavenging activity and ferric reducing power was observed for leaf extract, while the green fruit extract showed the highest antioxidant activity on the bases of hydroxyl radical-scavenging activity, β-carotene-linoleate bleaching assay, and total antioxidant capacity.\[119\] Similarly, it was studied that water as well ethanolic extract of bitter melon possess significant DPPH radical scavenging activity and iron chelating activity better than Vit. E. Whereas free radical scavenging, xanthane oxidase, and anti lipid peroxidation activity was lower than that of Vit. E.

The antioxidants are capable of damaging and contracting free radicals.\[120,121\] The bitter melon and its ethanolic extracts contain high antioxidant activities that are well correlated with phenolic compounds.\[9,122\] By increasing the activities of catalase and levels of reduced glutathione, bitter melon inhibited stress-induced lipid peroxidation. It might be beneficial to include bitter melon in our daily life.\[123,124\] For keratinocytes, the protective action of the extract associated with oxidant dosage and a dose-dependent association of oxidant toxicity was only seen with H (2) O (2). At 300 and 200 microg/mL TPE, cytoprotection was dose-dependent against oxidants. At 50 μg/mL Extracts exert no effect on HX-XO toxicity. Any cytoprotection has not been shown by pretreatment with both the extracts.\[31,125\] Stronger antioxygenic activity has been possessed by bitter melon seed powder and pul[p at 20 g kg(−1) and their water/ethanol extracts. Other solvent extracts endorsed to the existence of higher amounts of flavonoids and phenolics. As compare to pulp portion, the seed portion of BM contained higher levels of total fat (238.9 g/kg), crude fibre (350.2 g kg, and total protein. As a major fatty acid the presence of α-eleostearic acid which is an isomer of conjugated linolenic acid has been indicated by fatty acid analysis of bitter melon seed oil. The results of this study confirmed the presence of antioxygenic compounds in both bitter melon pulp and seed. In particular, their ethanol/water extracts showed great potential as natural antioxidants to inhibit lipid peroxidation in foods.\[126,127\] Three new cucurbitane triterpenoids and one new steroidal glycoside, were isolated together with 10 known compounds from bitter melon.\[128,129\]

The exposure of HepG2.2.15 cells to MAP30 resulted in inhibition of HBV DNA replication and HBsAg secretion. After exposed to three different concentrations of MAP30 for 2, 4, 6, and 8 days respectively, the inhibition rates of extracellular HBV DNA, HBsAg, and HBeAg of each concentration decreased significantly. After 9 days of treatment, the inhibition rates of extracellular HBV DNA of the different concentrations differed greatly. The MAP30 could inhibit the production of HBV dose-dependently. The expression of HBsAg was significantly decreased by MAP30 dose-dependently and time-dependently. Lower dose of MAP30 (8.0 microg/ml) could inhibit the expression of HBsAg and HBeAg.\[130,131\] Previous studies have shown that extracts of wild bitter melon suppresses lymphocyte proliferation, and macrophage and lymphocyte activity.\[132,133\] Traditionally, the wild bitter melon leaves are crushed to obtain the juice for applying on the skin for treating insect bites, bee stings, burns, contact rashes, and wounds. Decoction of its leaves and fruits is drunk as preventative or treatment of stomachache, toothache, liver diseases, diabetes, hypertension, and cancer.\[134\] Furthermore, in vivo administration of bitter melon extract decreased PC3 human prostate cancer cell growth subcutaneously in nude mice and this effect was due primarily to the induction of apoptosis, with no significant differences in markers of proliferation or MVD between control and treated animal tumours. The selective induction of apoptosis in neoplastic cells is also a hallmark of a class of anti-tumour compounds known as HDAC inhibitors. HDACs, which catalyze the removal of acetyl groups...
from the N-terminus of histones, lead to chromatin condensation and transcriptional repression. Altered expression of individual HDACs in tumour samples has been reported and several HDAC inhibitors are in clinical trials for cancer therapy. Effects of MCP30 on HDAC1 in prostate-derived cell lines were observed because this particular HDAC was previously shown to be over expressed in human premalignant and malignant prostate lesions,[122,135] with the highest increase in expression in hormone refractory prostate cancer. HDAC1 activity is increased in premalignant and malignant prostate cancer cell lines as compared to the non-neoplastic RWPE cell line.

Furthermore, the Type I RIPs contained in MCP30 inhibit HDAC1 expression levels and activity selectively in the neoplastic cell lines. MCP30 may restore normal PTEN signaling as demonstrated by decreased activity of Akt by dephosphorylation at Ser-473, increased Ser-9 phosphorylation of GSK-3b, inhibition of canonical Wnt signaling, and decreased expression of Cyclin-D1 and c-Myc in the neoplastic prostate cells. It has been observed that 5-aza-20-deoxycytidine, a DNA methyltransferase inhibitor reactivates the transcription of PTEN in prostate cancer cells. Re-expression of PTEN mRNA and protein in PIN, LNCaP, and PC3 cells which may result from the inhibitory effect of MCP30 on HDAC-1 levels and activity. Eighteen HDACs have been identified in humans and it is possible that MCP30, genistein, and other dietary compounds modulate the expression and activity of multiple HDACs in a tissue-specific manner with resultant activation of a variety of tumour suppressor and pro-apoptotic genes. To our knowledge, this is the first report which states that Type I ribosomal inactivating proteins derived from dietary bitter melon possess HDACi activity and can selectively induce apoptosis in premalignant and malignant prostate cells and inhibit human prostate cancer cell growth in vivo.[136,137]

**Inflammation and bitter melon**

Inflammation is a complicated immune process that can be defined by the sequential release of mediators such as pro-inflammatory cytokines, including interleukin (IL)-1, tumour necrosis factor (TNF), interferon (IFN)-c, IL-6, IL-12, IL-18, and the granulocyte-macrophage colony stimulating factor. Inflammation is settled by anti-inflammatory cytokines such as IL-4, IL-10, IL-13, IFN-a, and the transforming growth factor (TGF)-b. Although inflammation is overall a protective response against xenobiotics, chronic and uncontrolled inflammation is detrimental to tissues,[138], which may cause chronic inflammation-derived diseases, such as cardiovascular diseases, autoimmune rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), cancers,[139] and aging-associated diseases, such as Alzheimer’s or Parkinson’s disease.[140] Thus, inhibition of the overproduction of inflammatory mediators, especially pro-inflammatory cytokines IL-1b, IL-6, and TNF-a, may prevent or suppress a variety of inflammatory diseases.[112] Previous reports indicated that the extract of bitter melon plant inhibits activation of nuclear transcription factor-κB (NF-κB) through stimulated by tumour necrosis factor-a (TNFa). It further induced the expressions of inducible nitric oxide synthase and cyclooxygenase-2 mRNA. The ethanolic extracts (250 and 500 mg/kg) showed an analgesic and antipyretic effect.[14] Bitter melon is beneficial for reducing LPS-induced inflammatory responses by modulating NF-kappaB activation.[112] Placenta extract of bitter melon suppressed lipopolysaccharide (LPS)-induced TNFa production in RAW 264.7 macrophage-like cells. Butanol-soluble fraction of bitter melon placenta extract strongly suppresses LPS-induced TNFa production in RAW 264.7 cells.

Gene expression analysis using a fibrous DNA microarray showed that the bitter melon butanol fraction suppressed expression of various LPS-induced inflammatory genes, such as those for TNF, IL1alpha, IL1beta, G1p2, and Ccl5. The butanol fraction significantly suppressed NFkappaB DNA binding activity and phosphorylation of p38, JNK, and ERK MAPKs. BM also exhibit antulcer activity. Ethanol induced gastric mucosal lesions has been inhibited through momordin-Ic about 10 mg per kg body weight. Against ethanol-induced ulcerogenesis in rats, dried BM powder with honey showed substantial anti-ulcerogenic activity. In diethyldithiocarbamate-induced ulcer models and indomethacin pretreated rats, ethanol fruits extract also exhibit gastric cytoprotective effects
against HCl-EtOH-induced ulcerogenesis.\textsuperscript{[11]} Bitter melon fruit also has a anti-\textit{Helicobacter pylori} activity.\textsuperscript{[11]} High intake upto 500 mg/kg of MC extract showed antiulcer activity and significantly reduced total acidity and pepsin activity while lower dose did not inhibit the ulcer proliferation. Compounds that are responsible for antiulcer activity are still not known, but it is assumed that flavonoids and steroids may be responsible for reducing the formation of gastric ulcer and similarly, carotenoids may also possess gastric cytoprotective action.\textsuperscript{[141]}

**Antimicrobial activity**

Clinical signs of broad-spectrum antimicrobial activity has been delivered by the extract of bitter melon leaf. It has been demonstrated that the whole plant extract has antiprotozoal activity and methanol, water, and ethanol extract of the BM leaves are considered to have an antibacterial action against \textit{Salmonella}, \textit{Pseudomonas aeruginosa}, \textit{E. coli}, \textit{Bacillus}, and \textit{Streptococcus} chain.\textsuperscript{[142]} Likewise, antimicrobial activity of \textit{Momodica} was investigated and it was revealed that \textit{Staphylococcus aureus} is mostly affected by essential oil of \textit{Momodica} even at a dose of 125–500 μg/ml while, \textit{E. coli} and \textit{C. albicans} both are also sensitive to a level 500 μg/ml.\textsuperscript{[143]} It was suggested that antibacterial properties of \textit{M. charantia} oil is related to its high trans-nerolidol and conjugated linolenic acids content which was tested previously. \textit{Momordica charantia} is a basis of natural products which derived from plant with antifungal-modifying and antiepimastigote activity.\textsuperscript{[144,145]} α-momorcharin due to its ribosome-inactivating protein (RIP) ability is effectual in inhibiting the fungal and bacterial growth. Their potential against \textit{Fusarium solani} (IC50 value: 6.23 μM), \textit{Fusarium oxysporum} (IC50 value: 4.15 μM), and \textit{Pseudomonas aeruginosa} (IC50 value: 0.59 μM) is described.

Santos et al.\textsuperscript{[144]} presented further arguments that bitter melon is useful to treat fungal and parasitic diseases, e.g. Chagas disease (Causative organism: \textit{Trypanosoma cruzi}). About 46.06 μg/mL ethanolic extract of BM killed 50%. Though, ≤ 1024 μg/mL was a MIC (minimum inhibitory concentration). Against 25 strains of Candida such as \textit{C. guilliermondii}, \textit{C. albicans}, \textit{C. parapsilosis}, \textit{C. glabrata}, \textit{C. tropicalis}, and \textit{C. krusei}, the antifungal action of bitter melon @ 10 mg/ml has been verified.\textsuperscript{[146]} Through disc diffusion method, a substantial inhibition has been measured. With minimum inhibitory concentration (MIC) value of 500 μg/ml the essential oil of plant has been found to prevent \textit{Staphylococcus aureus}.\textsuperscript{[27,147]} \textit{Momordica charantia} also has cytoxic and antiprotozoal activities. With IC50 value of 0.7–7 μg/ml bitter melon revealed good antiprotozoal activity against \textit{Trypanosoma brucei}.\textsuperscript{[148]} On four clinical strains of \textit{Cryptococcus neoformans}, \textit{Klebsiella pneumoniae}, \textit{Proteus vulgaris}, and \textit{Salmonella typhi} and four reference microorganisms (\textit{Staphylococcus aureus}, \textit{Pseudomonas aeruginosa}, \textit{Candida albicans}, and \textit{Escherichia coli}), the antimicrobial activity of bitter melon extract has been tested. Excluding \textit{Cryptococcus neoformans} and \textit{Proteus mirabilis}, on verified microorganisms bitter melon extracts revealed antimicrobial activity.\textsuperscript{[149,150]} Aqueous extract of the green bitter melon and its active ingredient Momordicatin are effective against kala-azar/leishmaniasis (Causative agent: \textit{Leishmania donovani}) with mean IC50 values of 0.6 & 0.02 mg/L, respectively. In vivo trials conducted in hamsters, the test dose of about 300 mg per kg body weight was effective in 100% parasite clearance. The mode of action includes inhibition of SOD which is one of the significant enzymes of the oxidative burst. The bitter melon and its bioactive molecules are potential candidates as chemotherapeutics against leishmaniasis.\textsuperscript{[10,151]} The larvicidal potential of bitter melon is also of significance. For this resolution, trials had been conducted against two types of mosquito vectors such as \textit{Culex quinquefasciatus} and \textit{Anopheles stephensi}.\textsuperscript{[152]} Trials which were conducted against mosquito species detected that the extract of extrtpetroleum ether (LC50 = 41.36; 15.62 ppm and 27.60/17.22 pm) had been found to be more effective. So it is expected that in future bitter melon extract may act as a useful biolarvicide against mosquitoes. In Asia, \textit{Momordica charantia} has been considered effective for the management and prevention of malaria. In Colombia and Panama for the treatment of malaria, tea from bitter melon leaves has been considered to be useful. It has been confirmed by laboratory studies that species which
are associated to BM (bitter melon) have anti-malarial activity. Major disease burden has been contributed by malaria and other vector-borne diseases. These diseases can be controlled by controlling the vectors. Crude ethanolic extracts from *Momordica charantia* has strong anti-malarial activity.

Oral administration of leaves showed strong antimalarial activity reduces the levels of parasitemia in plasmodium infected mice. The extract of *Momordica charantia* leaves has been examined for antimalarial action against *Plasmodium falciparum* cultured. It was found that *P. falciparum* growth was inhibited by extract. The IC50 values for *Momordica charantia* was 68.4 μg/mL. Some compounds from bitter melon showed moderate anti-HIV-1 activity with EC49 values of 8.45 and 25.62 microg/ml, and exerted minimal cytotoxicity. Amongst the various ribosome-inactivating proteins (RIPs) isolated from bitter melon, MAP30 (*Momordica* protein of 30 kDa) displayed anti-tumour activity. Adult T-cell leukaemia (ATL) is caused by human T-cell leukaemia virus type I (HTLV-I) infection and is resistant to conventional chemotherapy. The bitter melon seeds suppressed the proliferation of three cell lines. Hydroxy-pentanorcucurb-5-en-3-one and dioxo-pentanorcucurbit-5-en-22-oic acid extracted from bitter melon showed potent cytoprotective activity in tert-butyl hydroperoxide (t-BHP)-induced hepatotoxicity of HepG2 cells. Five cucurbitacins, kuguaicins A-E (1-5), together with three known analogues, 3beta,7beta,25-trihydroxycucurbita-5, (23E)-diene-19-al, 3beta,25-dihydroxy-5beta,19-epoxy cucurbita-6, (23E)-diene, and momordicine I, were isolated from roots of bitter melon.

**Anti-parasitic (anti-anthelmintic) effect of bitter melon**

Helminth infection is a prevailing problem, which is caused by nematodes, cestodes, and trematodes. The main target of helminthic infection is GI system that affects human and livestock's in the world. There are three ways that can efficiently treat the infection, i.e. medicinal use, lifestyle management, and dietary modification. As compare to lifestyle management and dietary modification, trend towards the use of medicine is more. Lifestyle management and the use of therapeutic diet have attained great interest as compare to medicinal use, because medicines cause a lot of side effects. In these days, as compare to other functional foods, bitter gourd considered as an important therapeutic medicinal food with antithelmintic action and its importance is due to the presence of functional ingredients involving saponins, i.e. momordin, momordicoside, momordicin, kuguacin, karavilsodie, and karavilagenin. The mechanism behind anthelmintic effect of BM (bitter melon) including inhibition of arachidonic acid metabolism, mico nicotinic agonists, oxidative phosphorylation inhibition, increased calcium permeability, acetyl cholinesterase inhibitors, and β-tubulin binding. Saponins paralysis the worms and lead their mortality by inhibiting the acetyl cholinesterase. Saponins affect the permeability of the cell membrane of worms and lead disintegration and vacuolization of tegument. Moreover, saponin can irritate the mucous membrane channel gastrointestinal of worms that interfere with the absorption of food. Alkaloids including steroidal alkaloid and oligoglycosides have neurotoxic properties, which effect on acetylcholine-stimulated body wall muscle contraction, so act as acetylcholinesterase inhibitors, course worm paralysis. Alkaloids act as an antioxidant and are capable of decreasing the generation of nitrate which may interfere in homeostasis that is important for helminthes development. Flavonoid compounds including apigenin can inhibit larval growth and inhibit the arachidonic acid metabolism which may lead to the degeneration of neurons in the worm’s body and lead to death. Tannins can be potentially act as anthelmintic effect by reducing migratory ability and survival of newly hatched larvae. They reduce worm burden and caused damage to the digestive tissues and of worms. Moreover, tannins inhibit energy generation of worms by uncoupling the oxidation phosphorylation and bind to glycoprotein on the cuticles of the worms and lead to death.
**Wound healing**

The juice of BM (bitter melon) has a healing potential against psoriasis, scabies, and ringworm. Bitter melon juice become more effective with the addition of one teaspoon of lime juice. In the susceptible areas of the world, bitter melon juice used in the inhibition of leprosy. In contrast to an ointment povidone iodine, *Momordica* fruit powder act as an ointment. In rats modeling wound healing potential of fruit powder has been assessed. A significant response has been shown by powder ointment in terms of period of epithelization, wound-contracting ability and wound closure time.\[171\] Absolute ethanolic extract of bitter melon fruits and leaves are very effective in wound healing. Approximately, 1% w/v of the 95% absolute ethanol-50% benzene *Momordica* fruit extract considerably improved the rate of epithelization and wound closure. The components which are present in the extract of *Momordica* fruit are responsible for effective wound healing.\[172\]

In bitter melon ribosomes inactivating proteins are presents. By inhibiting the synthesis of proteins which promote viral diseases, ribosome inactivating proteins constrain the reproduction of viruses. According to laboratory tests the bioactive components which are present in bitter melon can be useful in the management of HIV infection. Lectins and proteins are insulated from bitter melon have a strong influence on HIV, but these compounds are not well absorbed in patients. In infected people, oral intake of BM will slow the progression of HIV. It has been demonstrated by a clinical trial that bitter melon leaf extract provide an immunostimulant effects against viral infections particularly HIV and has an ability to treat various viral diseases. Numerous compounds such as MAP-30, MRK-29, momorcharin, and lectin are isolated from bitter melon, these compounds have a protective effect against viral infections. Varous studies in mice show that, by down-regulating the NF-κB inflammatory pathway, the seeds of BM had a cardio-protective effect. Lectin is an important bioactive component present in bitter melon. Due to non-protein-specific association to insulin receptors, lectin possess insulin-like activity. Lectin act on peripheral tissues and lower the concentration of blood glucose, related to the effect of insulin in brain, lectin is a main contributor to the hypoglycemic effect which develops after bitter melon ingestion.\[173,174\] Singh et al.\[175\] reported that when the extract of BM was applied to diabetic wounds, it prevents the regression of blood vessels and granulation tissue which results in improving and accelerating wound healing.

**Conclusion**

Towards the conclusion, it is anticipated that functional and health supportive potential of *Momordica charantia* needs to be explored for the curb various maladies. Numerous scientific evidences have come forward in support of these acclaimed benefits. But still, there is a need to consider the hidden potential of this great blessing of nature. Furthermore, there is a need to pay sincere contribution towards the exploration of these bioactive molecules. There has been sufficient research conducted on probing the hidden potential of bitter melon against ulcer, viral diseases, and various others microbial invasions. It has a great potential to fight against various lifestyle related disorders. In type-1 diabetic’s subcutaneous injection of insulin considerably lower the level of glucose and between bioactive moieties, P-insulin is related to that insulin. Apart of the health promoting functions, it may be deemed as efficient choice in value added food products.

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