Volume:1 **Issue:**2
Year: 2020

International Journal of Traditional and Complementary Medicine Research

Publisher
Duzce University

REVIEW

A Review: *Momordica charantia* L.'s Biological Active Components and Its Potential Use in Traditional Therapies

Gulsah Aydin[1*] **Ertugrul Kaya** [1,2]

[1] Traditional and Complementary Medicine Application and Research Center, Duzce University, Duzce, Turkey
[2] Department of Pharmacology, Medicine Faculty, Duzce University, Duzce, Turkey

*Corresponding Author: Gulsah Aydin, e-mail: gulsahaydinn@gmail.com

Received: 27.05.2020 Accepted: 04.08.2020

Abstract
The use of herbs for therapeutic purposes has been widespread since ancient times. In traditional treatments, plants are applied in a variety of forms, either directly or prepared by isolation and / or enrichment of biologically active ingredients. *Momordica charantia* L. (bitter melon) is a popular bush that has traditional use as a supplement in the treatment of various diseases with its rich bioactive ingredient content. The plant has common pharmacological potential, including antimicrobial, antimutagenic, antifertility, antidiabetic, antioxidant, antilipolytic, hypoglycemic, anticancer, antimicrobial, antiviral and hepatoprotective activities. This review provides a short overview of the in vitro, in vivo and clinical studies conducted to evaluate the therapeutic efficacy and safety of *Momordica charantia*.
Keywords: *Momordica charantia*, Bitter melon, Traditional Medicine.

INTRODUCTION

The use of medicinal and aromatic herbs in traditional treatments dates back to very old years. There are many of traditional and herbal medicinal products that are used as supplements for the treatment of many diseases. Most known drug active substances are molecules that have been isolated from natural products and have been tested for efficacy. The use of molecules isolated from plants as medicine dates back to the 1800s. The vast majority of drugs approved until 1990 are molecules with natural products or derivatives[1]. In addition, the mixture of many active substances obtained by extraction of natural products with various solvents can show a synergistic effect and respond much more effectively to traditional treatment than a single chemical molecule will show. Therefore, extraction, purification and efficacy studies of natural products in the field of traditional medicine is an area that is always explored from ancient times until today without losing its importance. Evidence-based assessment of the efficacy and safety of components isolated from medicinal and aromatic plants is important for traditional medicine to be based on safe foundations. For purposeful safe applications of herbal supplements, it is necessary to conduct experiments to determine the effectiveness of natural products commonly known in traditional therapy with in vitro, in vivo and clinical studies.

All parts of the *Momordica charantia* L. (bitter melon) plant from the Cucurbitaceae family have bitter taste. Members of the Cucurbitaceae family have medicinal and nutritionally beneficial plants that contain many components with pharmacological activity. *M. charantia* is rectangular like and looks like a small cucumber. The young fruit becomes emerald green and turns orange yellow when it ripens. The seeds are reddish in color. Despite being of Asian origin, it has a wide distribution in various parts of the world, including Central and South America and Africa[2]. *M. charantia* contains many biologically active compounds such as glycosides, oils, alkaloids, proteins, triterpenes, saponins and steroids.

Unripen fruits are a storage of vitamin C, but also have phosphorus, Vitamin A, and iron content. Bioactive compounds are isolated from fruit, seeds and leaves of the plant[3,4]. As a result of phytochemical analysis studies on *M.* charantia plant, it was determined that the plant contains cardiac glycoside, alkaloid, tannin, flavonoid, saponin and steroid group chemicals[5,6]. Phytosterol groups with up to 30 carbon atoms in total have been reported to have anticancer, atherosclerotic, anti-inflammatory and antioxidant activities[7-9]. Terpenoid derivatives are known to have anti-inflammatory and anticancer activities[10,11]. Six new triterpenoids isolated from *M. charantia* have been reported to cause up to 72.4% blockade and no cytotoxicity on proliferation of vascular smooth muscle cells. Thus, it has been noted that *M. charantia* is rich in supportive bioactive molecules in the treatment of cardiovascular diseases through inhibition of proliferation of vascular smooth muscle cells[12]. *M. charantia* has high level of fatty acids. It contains fatty acids, that reduce the risk of developing cardiovascular disease such as omega-3[13]. It has been reported that the fatty acid content may act as antimicrobial agents against bacteria[14] and fungi[15]. Phenolic compounds containing coumarins, phenolic acids, lignins, tannins, lignanes and flavonoids are among the secondary metabolites that are abundant in the plant[16,17]. Phenolic compounds in *M. charantia* have important activities such as antimicrobial, antioxidant, anticancer and anti-HIV-1 activities[18-20]. These activities of *M. charantia*, which is a plant species rich in biological activity, are thought to originate from rich complex chemical compounds such as flavonoids, tannins, carbohydrates, resins, terpenoids, anthraquinones, saponins, sterols, phylobatamines, amino acids, glycosides, fatty acids and phenolic compounds[21,22]. Bioactive compounds can be extracted with the help of many different organic solvents using traditional extraction techniques and new technological techniques[23-25]. Polysaccharides are primary active ingredients that perform various pharmacological activities of *M. charantia*. There are studies investigating the blood sugar levels of the polysaccharides isolated from the plant and their biological activities on the regulation of antioxidant, antibacterial, antitumor and immune system functions[26]. MAP30, a 30 kDa protein isolated from seeds, has been proposed as the agent responsible for antiviral and antineoplastic properties[27-30]. *M. charantia*'s chemicals responsible for hypoglycemic action are a mixture of steroidal saponins known as charantins, alkaloids and insulin-like peptides[31] Therefore, it is recommended to consume *M. charantia* fruit extracts for antihyperglycemic activity[32].

It is known that *M. charantia* provides a very good supportive treatment in the treatment of diabetes in lowering blood glucose levels, in the treatment of inflammatory wounds, in nutritive disorders such as stomach and intestines[33]. It is also known to be used as a supportive in the treatment of various infections, in preventing tumor formation, in the treatment of measles, hepatitis, HIV and AIDS viruses, in the treatment of diseases such as infertility, gastrointestinal cramps, cancer, eczema and psoriasis. α- and β- momarcharin are two proteins in the *M. charantia* that are known to inhibit the AIDS virus[34]. It is known to use both internally and externally for the prevention of worms and parasites locally for the treatment of wounds. Ripen fruits are used for traditional therapies for skin wound healing externally and against to peptic ulcer internally in Turkey[35]. Studies on antidiabetic, antitumor, antioxidant, antileukemic, antibacterial, immunostimulant, anthelmintic, antiviral, antimutagenic, hypocholesterolemic, antiulcer, anti-inflammatory, insecticidal, hypotriglyceridemic, hypotensive and antimycobacterial properties of *M. charantia* are common[31,36,37].

POTENTIAL BIOLOGICAL ACTIVITIES OF *M. CHARANTIA*

Hypoglycemic activity

There are numerous in vitro, in vivo and few clinical studies supporting the use of *M. charantia* as whole fruit, extract or dried powder, which can lower blood sugar levels. In line with these studies, it is common to use *M. charantia* as an alternative to decrease blood sugar levels in the treatment of

type 2 diabetes[38,39]. In the component analysis of *M. charantia* extract, it has been shown that the components showing structural similarities to animal insulin are responsible for the hypoglycemic effect [30]. In general, it has been suggested that *M. charantia* polysaccharides have a significant effect on hypoglycaemia[40]. Polysaccharides have been reported to have protective and reparative effects on pancreatic islet tissue and the ability to reduce blood sugar[40]. Polysaccharides are thought to exhibit antihyperglycemic activity by improving glucose tolerance, glucose intestinal absorption, or improving glucose metabolism[41]. In addition, a mixture of polypeptides called "polypeptide p" isolated from seeds and two steroid glycosides specified as "charantin" are other chemical molecules reported to have hypoglycemic properties[42-44]. *M. charantia* aqueous extract has been reported to be a safe alternative for lowering blood sugar levels[45]. Glucosaminoglycans isolated from plant fruits have been found to have beneficial effects on diabetes metabolism[46]. It has been reported that the mixture of maximum molecular weight alkali polysaccharides extracted from *M. charantia* polysaccharides has the best antihyperglycemic effect and can lower blood sugar levels through increased insulin secretion from Beta cells[47].

A water-soluble polysaccharide isolated from *M. charantia* fruits has been reported to reduce blood glucose levels and increase glucose tolerance in alloxane-induced diabetic mice. Water-soluble polysaccharides can increase insulin secretion in streptozotocin-induced diabetic mice by repairing injured pancreatic islet tissues[48]. Another study has shown that by reducing the amount of *M. charantia* polysaccharides, the glucose level increases significantly and *M. charantia* polysaccharides can be a potential antidiabetic agent[49]. *M. charantia* methanol extract has been shown to exhibit hypoglycemic activity in diabetic albino rats due to alloxan [38,50-52]. Various *M. charantia* extracts have been reported to lower high glucose levels in diabetic rats [53-55]. In diabetic rat models, the ethanol extract of fruit pulp at a dose of 500 mg / kg body weight has been reported to reduce glucose levels 1 hour after administration[56]. It has been reported that aqueous extract and alkaline chloroform extract reduce blood sugar levels 1 hour after application[57]. In diabetic rats and glucose-dependent hyperglycemic rats, it has been reported that the blood sugar levels of the fruit of the plant are lowered half an hour after administration of the methanol extract and water extract[58]. It has also been observed that the extract increases thyroxine levels, normalizes glucose levels, and maintains the normal lipid profile in diabetic rats fed a normal diet or fed a high-fat, low-carb diet[59,60]. It has been reported that the glucose level is normalized and the effect is protected for 15 days in diabetic rats fed with the acetone extract of the fruit for a long time[61]. Hypoglycemic effects of the aqueous extract of the whole plant have been reported in rats[62]. The plant reduced plasma and hepatic triglyceride content and tissue fat accumulation [63]. It has been noted that plasma and liver lipid parameters improve in diabetic rats fed a cholesterol-rich diet and a high-fat diet[64]. The possible hepatoprotective effect of *M. charantia* in diabetic rats has been investigated. A group of male Sprague Dawley rats were treated with *M. charantia* ethanol extract after treatment according to known protocols. The liver of the animals was examined at 10 weeks, blood was collected by cardiac puncture and centrifuged to collect the serum. While blood glucose levels increased consistently in all groups without *M. charantia* treatment, the increase in blood glucose levels in the group treated with ethanol extract became close to normal. It has been reported that while the markers of liver damage showed a significant increase in the group that did not receive *M. charantia* treatment, it could be used as a supplement in alleviating liver damage in the treatment group[65]. In another study, the mechanisms of the renoprotective effects of *M. charantia* in diabetic rats were investigated. The application of *M. charantia* extract has been reported to restore kidney function, reduce weight loss and restore blood sugar levels to normal levels[66]. The effect of *Lactobacillus plantarum*-

fermentation on the antidiabetic functionality of *M. charantia* was investigated using a type 2 diabetic rat model. Fermented *M. charantia* juice administration has been reported to reduce hyperinsulinemia, hyperglycemia, hyperlipidemia and oxidative stress well than its non-fermented counterpart in diabetic rats. Diabetic rats treated with fermented *M. charantia* juice showed higher concentrations of acetic acid, propionic acid, butyric acid, total short-chain fatty acids and lower pH values in colonic contents than rats treated with unfermented *M. charantia* juice. These results showed that *L. plantarum*-fermentation increases the antidiabetic property of *M. charantia* juice by disrupting the regulation of the intestinal microbiota and the production of short-chain fatty acids[67,68]. *M. charantia* has been shown to permanently normalize blood sugar levels comparable to healthy rats. In treated rats, the expression of insulin and Pdx1 genes increased, and Glut2 expression decreased. Liver ALT, AST and ALP enzyme activities have fallen to the normal range in the treatment group to support the protective effect of *M. charantia*. These data showed that the plant improves pancreatic function by activating pancreatic beta cells and protecting liver tissue[69].

The juice of *M. charantia* has been reported to improve glucose tolerance in 73% of patients with beginner diabetes, while 27% of patients are unable to respond[70]. The effects of *M. charantia* PEG and *M. charantia* adsorbed with nanofraction extracts on blood rheological parameters in hyperglycemic patients were clinically investigated. Blood samples of 56 normoglycemic individuals and 26 hyperglycemic patients were collected, their general characteristics, rheological parameters and hematological features were determined. Whole blood viscosity was evaluated after treatment with PEG microspheres adsorbed with *M. charantia* extract, PEG and *M. charantia* nanofraction extracts. Although the viscosity of the blood of hyperglycemic patients is higher than that of normoglycemic individuals, it has been noted that the nanoparticles of *M. charantia* extracts reduce blood viscosity equally in normo and hyperglycemic individuals.

It has been noted that PEG microspheres do not reduce blood viscosity in hyperglycemic patients but PEG microspheres adsorbed with plant nanofraction extract reduce blood viscosity. Based on clinical study data, it has been reported that the use of nanoparticle extract of *M. charantia* and PEG microspheres adsorbed with nanofraction extract may play a role in the treatment of blood disorders in diabetic patients[71]. The effects of *M. charantia* on blood sugar levels in patients with type 1 or type 2 diabetes were investigated. For diabetic patients treated with *M. charantia*, an average decrease in serum glucose levels was noted within 30 minutes. At the end of the 4-hour period, the maximum decrease in serum glucose levels was observed with a rate of 49.2%, while after 12 hours, a permanent 28% decrease was observed[72]. A clinical study was conducted with a group of 9 type 2 diabetic patients, 8 of whom received simultaneous sulfonyl urea.

Subjects were initially given 50 ml of *M. charantia* juice and received 0.23 g of *M. charantia* fruit daily over the next 8-11 week period, and then glucose tolerance tests were performed. The test results, which were applied 1 hour after 50 ml of juice consumption, showed a 12% decrease in blood glucose level. The test, performed 1 hour after the intake of 0.23 g of fruit, showed a decrease of about 6% in glucose levels. It has been noted that after consuming 0.23 g of *M. charantia* for 8-11 weeks, an 8% decrease in glucose levels was observed from the first value[54]. In another clinical study, the effect of *M. charantia* juice on blood glucose levels was investigated in a case series of 18 patients diagnosed with type 2 diabetes. Individuals were given 100 ml of *M. charantia* juice 30 minutes prior to glucose loading. When the glucose tolerance test results before supplementation were compared with the results after treatment, it was observed that 13 patients showed a moderate improvement after taking *M. charantia*[70]. A clinical study was conducted with a group of 12 patients with type 2 diabetes who were not treated other than diabetic diets for 3 weeks. 5 patients received 3 g of dried fruit powder 3 times a day. In 7

patients, 100 ml of the extract of 100 g *M. charantia* powder prepared by boiling in water was given once every morning. While a 25% decrease in blood sugar level was observed in the patient group receiving dry powder, a significant decrease was observed in the blood sugar level with an average of 54% in the patient group receiving an aqueous extract[73].

When evaluating in vitro, in vivo and clinical studies, *M. charantia* extracts have been reported to show a moderate hypoglycemic effect. It is reported that the use of as a supportive therapy in diabetic patients may be an important traditional herbal supplement if it is evaluated and adjusted in dosage with co-consumed drugs.

Antibacterial activity

Poultry-related *Bacillus* spp and α-glucosidase activities and antiobesity properties of *M. charantia* fruit extract were evaluated. As a result of the test, it was observed that the ethanolic extract showed pronounced antibacterial properties against *B. licheniformis*[74]. The antiobesity potential of fruit extracts has been shown for porcine pancreatic lipase activity. The ethanolic extract of *M. charantia* fruits has been observed to cause inhibition of the pancreatic lipase enzyme. When the data obtained in the study were evaluated, it was reported that *M. charantia* fruits may be effective in inhibition of bacterial pathogens related to poultry[74].

Polysaccharides isolated from *M. charantia* have been reported to have significant inhibitory effects on bacteria. It has been shown that the main components of *M. charantia* responsible for antimicrobial functions are polysaccharides[26]. It has been reported that *M. charantia* polysaccharides have a good bacteriosis activity in *B. subtilis*, *S. aureus*, *S. typhimurium* and *E. coli* and the most obvious effect is the effect on *S. aureus*[40]. In the study conducted to determine different concentrations and pH values of *M. charantia* polysaccharides acting on *S. aureus*, *A. niger*, *E. coli and A. oryzae*, it was shown that antibacterial effect of polysaccharides was significantly affected by pH value and showed a positive correlation with the concentration[26].

Immunomodulatory activity

In vitro experiments have shown that *M. charantia* olisaccharides can increase immunity by stimulating the activation of lymphocytes and macrophages[75]. In another in vitro study, *M. charantia* polysaccharides have been reported to have significant immunomodulatory activity[76]. It has been reported that the water-soluble polysaccharide isolated from *M. charantia* may increase endothelium-derived relaxing factor production in the cell proliferation, the development of the inflammatory and immune response, and stimulate splenocytes and thymocytes[77].

In immunosuppressed mice from cyclophosphamide, it has been reported that carbolic particle clearance index, production of serum hemolysis, spleen index, thymus index and natural killer cell cytotoxicity can be increased to normal control levels by *M. charantia* polysaccharides. It has been reported that the aqueous extract can increase the phagocytic index and the percentage of adhesion of high doses of neutrophils to nylon buffers increased significantly compared to normal control animals[78].

Anti-inflammatory activity

It is known that oxidative stress and inflammation activate each other and oxidative stress plays a role in chronic infectious diseases[79]. The beneficial properties of *M. charantia* appear to be due to anti-inflammatory and antioxidant activities. *M. charantia* shows anti-inflammatory effects by acting on several important signal pathways involved in inflammation[80,81]. Momordicoside G, one of the bioactive components of *M. charantia*, has been reported to contribute to the repair of lung injuries[82]. The anti-inflammatory properties of BG-4, a new bioactive peptide isolated from *M. charantia* seed, have been evaluated and reported to have an anti-inflammatory effect by reducing the production of intracellular reactive oxygen species[83].

The wound-healing activity of the olive oil macerate of *M. charantia* was investigated in the linear incision and circular excision wound models. It has been noted that *M. charantia* olive oil

macerate shows healing activity in incision and excision wound models and shows 31.3% anti-inflammatory activity. Experimental data have shown that *M. charantia* has wound-healing and anti-inflammatory effects[84]. It is known that *M. charantia* plays a role in wound healing by increasing oxygenation by accelerating the production of growth factors, ensuring the proliferation of fibroblast cells and accelerating capillary circulation. The antioxidant and antimicrobial effects of phytochemicals in the plant content are thought to play a role in accelerating the wound healing process[33]. *M. charantia* supplements are thought to play a role in reducing inflammation, obesity and insulin resistance in obese mice by normalizing the serum levels of cytokines[85]. *M. charantia* powder supplementation has been reported to reduce systemic inflammation in obese mice fed a high-fat diet [86,87].

The therapeutic role of polysaccharides in *M. charantia* and their mechanisms of action against gastric ulcers from ethanol have been investigated and reported to play a role in suppressing gastric inflammation[88]. *M. charantia* fruit extract supplement has been reported to significantly reduce neuro-inflammation and contribute to the improvement of neurodegenerative diseases[89].

M. charantia extracts have been found to alleviate *P. acnes*-induced bacterial skin inflammation in mice. It has been reported that this effect may be due to the anti-inflammatory effects of phenolic compounds[90]. In mice fed high-fat diets for 16 weeks, it was observed that *M. charantia* juice reduced fat inflammation by 60% and prevented inflammation of colon and intestinal microbial dysbiosis. Based on these, *M. charantia* has been reported to have the potential to be supportive in the treatment of inflammatory diseases such as obesity and type 2 diabetes[91].

In a clinical study performed by applying *M. charantia* to 38 patients with primary knee osteoarthritis and placebo supplementation to 37 patients for 3 months, the effect of *M. charantia* on reducing pain in patients with primary knee osteoarthritis was evaluated. After 3 months of supplementation, *M. charantia* group significantly reduced body weight, body mass index and fasting blood sugar, and significant improvements in knee osteoarthritis were observed. The study showed that *M. charantia* can offer an alternative to reducing the need for analgesic drug consumption by reducing pain and improving symptoms in diseased individuals[92].

Antioxidant activity

The antioxidant activities of *M. charantia* polysaccharides have been extensively studied and have been shown to exhibit significant antioxidant activity[77,93,94]. While polysaccharides are reported to be the main source of antioxidant activity, it has been noted that uronic acid and proteins can strengthen antioxidant activity[95]. It has been reported that pectin polysaccharide isolated from *M. charantia* has a significant effect on the removal of hydroxyl radicals depending on the dose and may prevent lipid peroxidation[77]. The hydroxyl and superoxide radical scavenging capabilities of the three water-soluble polysaccharide fractions isolated from *M. charantia* have been evaluated, all of which have been shown to have powerful hydroxyl radical scavenging and weak superoxide radical scavenging effects[93]. Sulfated modification of *M. charantia* polysaccharides has been reported to show better antioxidant activity in vitro. In addition, it has been shown that polysaccharides can lead to improved antioxidant activity by increasing water solubility by chemical modification[96-98].

It has been noted that the treatment of neuroblastoma cells with *M. charantia* extract reduces cytotoxic oxidative stress from H_2O_2 by increasing intracellular cleansing activity[99]. Triterpene glycosides isolated from *M. charantia* stems and fruits have been reported to significantly inhibit xanthine oxidase activity [100]. Triterpenoids isolated from *M. charantia* bodies exhibited an inhibitory effect on cleaning activities and xanthine oxidase activity[101]. The antioxidant compounds in *M. charantia* seed powders have been reported to inhibit lipid peroxidation by demonstrating potential natural antioxidant activity[102]. The antioxidant activity of *M. charantia* against oxidative damage caused by peroxynitritis has been

evaluated in vitro and has been clearly shown to contribute to improvement[103].

There are also studies evaluating the antioxidant effects of *M. charantia* polysaccharides in mouse models. It has been reported in vivo that water-soluble polysaccharides significantly increase GSH-PX activities in superoxide dismutase and liver homogenate and reduce maleic dialdehyde content by 25.6% [104].

In mouse models treated with *M. charantia* polysaccharides for 28 days, it has been reported that the activity of superoxide dismutase and catalase in serum, liver and cerebrum is significantly increased and maleic dialdehyde level is decreased. The in vivo antioxidant mechanism of *M. charantia* polysaccharides has been linked to its contribution to improving antioxidant enzyme activities against damage caused by free radicals[98].

Antitumor activity

M. charantia extract has been reported to have promising potential as adjuvants in traditional anticancer therapies[105]. The effectiveness of *M. charantia* extracts and / or components isolated from *M. charantia* against different tumor cells was evaluated. Anti-proliferative and immunomodulatory effects have been reported in most studies[106]. *M. charantia* has been shown to modulate proteins associated with different cancer pathways[107]. The cell cycle is stopped by modulation of the signal path and cell cycle proteins, and an antitumor effect is shown by inducing apoptosis or other cell death pathways[108,109] *M. charantia* polysaccharides have been reported to inhibit proliferation of human leukemia cell line K562[110]. Sulfate modification of *M. charantia* extract has been shown to significantly inhibit the growth of HepG2 and Hela cells, and it has been reported that sulfated modification may increase anti-tumor activity[111].

The effects of Momordicoside G, an important bioactive component of M. charantia, on lung injury and carcinoma lesion were investigated. It is reported that Momordicoside G induces apoptosis with morphological changes in M1-like macrophages by decreasing the amount of reactive oxygen species and promoting autophagy when applied at a dose that has no effect on cell viability in M2-like macrophages[82].

Three triterpene glycosides isolated from *M. charantia* have been reported to show significant antitumor activity in cell lines derived from liver carcinoma[112]. Given the effect of *M. charantia* extracts on several inflammatory-related signaling pathways, it is thought to play an important role as an anti-tumor agent[107].

The effectiveness of *M. charantia* juice against PanC pancreatic cancer cells has been demonstrated in vitro. Autophagy inhibitors significantly prevent cell death of cancer cells. *M. charantia* juice has been reported to cause cell death by activating the autophagic pathway in drug-resistant pancreatic cancer (AsPC-1) cells[113]. In another study evaluating the effect of *M. charantia* juice on targeting pancreatic cancer-related cancer stem cells (PanC-CSCs), it was reported that the supplement may cause a decrease in the expression of genes and proteins involved in the regeneration and reproduction of PanC-CSC[114].

9 compounds containing three cucurbitan-type triterpen glycosides isolated from the immature fruit of *M. charantia* L, antihepatic fibrosis activity against murine hepatic stellate cells (t-HSC / Cl-6) and It was investigated for antihepatoma activity against two types of liver cancer cell line (HepG2 and Hep3B). Karavilosid III has been reported to cause inhibition of the t-HSC / Cl-6 cell line and exhibit cytotoxic activity against the Hep3B and HepG2 cell lines. It has also been developed as a chemotherapy agent for the treatment of liver fibrosis or carcinoma[112]. MAP30 has been reported to have in vitro antineoplastic effects. These effects are thought to be due to the ability to reduce the expression of growth factor receptors attached to the breast factor, such as the transmutran tyrosine kinase receptor encoded by the HER2 oncogene[30,115]. It was determined in vivo that tumor growth in S180 sarcoma and H22 liver tumor mice was significantly inhibited by *M. charantia* polysaccharides[116].

In another study, *M. charantia* polysaccharides have been shown to suppress the activity of apoptotic markers Bax and caspase-3 and increase

the level of anti-apoptotic protein Bcl-2 that promotes cell survival[88].

In the study where ribonuclease, which has a molecular weight of 14 kDa isolated from *M. charantia*, is injected daily into mice bearing HepG2 tumors, it was noted that tumor growth was significantly reduced[117]. Lectin isolated from *M. charantia* has been reported to significantly inhibit tumor growth in mouse cells carrying nasopharyngeal carcinoma[118]. In vivo study of a mouse model with PC3 prostate cancer, the leaf extract of *M. charantia* was reported to inhibit tumor growth. Cancer has been observed to metastasize to the lymphatic nodes, but no evidence has been found to metastasize to other organs[119].

The progression of the tumor towards malignancy is strongly associated with chronic inflammation responsible for tumor invasion and angiogenesis of normal tissues in the environment. *M. charantia* components also have the potential to have antitumor effect by modulating the inflammatory state. *M. charantia* extract treatment has been shown to be more effective in inhibiting tumor growth in mouse models with aggressive triple negative breast cancer (TNBC) compared to ER positive breast tumor growth. It has been shown that abnormal irregularity of lipid metabolism is associated with breast cancer progression, and treatment causes decreased esterified cholesterol accumulation in TNBC cell lines compared to control cells. Moreover, expression levels of acyl-CoA and cholesterol acyltransferase 1 (ACAT-1) were evaluated in TNBC cells treated with *M. charantia* extract, and the extract was shown to inhibit ACAT-1 expression in TNBC cells. It has been reported that *M. charantia* therapy may have therapeutic potential in human breast cancer by suppressing TNBC cell growth[120]. Considering the performed in vitro and in vivo studies, it is thought that consumption of *M. charantia* supplement may help reduce the risk of cancer.

Other biological activities

It has been reported that *M. charantia* polysaccharides have a neuroprotective effect that can reduce neuronal death caused by thrombin in primary hippocampal neurons[121,122]. The hepatoprotective effect of *M. charantia* water soluble polysaccharides has been investigated on the CCl4 liver damaged mouse model, and it has been shown that plant water soluble polysaccharides can reduce mouse serum ALT damage to 10.6% and AST damage to 30.7% [104]. In another study, the effects of pectic polysaccharide supplement isolated from *M. charantia* against female reproductive toxicity and infertility triggered by sodium arsenite in Wistar rats were investigated. Pectic polysaccharide has been reported to significantly reduce ovarian and uterine lipid peroxidation and the formation of reactive oxygen species from sodium arsenite by regulating superoxide dismutase, catalase and glutathione peroxidase activities. It has been noted that pectic polysaccharide therapy reduces sodium arsenite toxicity by modulating S-adenosine methionine pool components such as B12, folate and homocysteine. Thus, a successful fertility was reported in rats receiving supplements instead of infertile conditions[123]. MAP30 isolated from *M. charantia* has been reported to inhibit the HIV viral integrase and cause irreversible relaxation of super-helix viral nucleic acids. These changes caused by the MAP30 protein have been reported to prevent viruses from integrating themselves into host cell genomes[29].

TOXICITY

Although there have been many studies on *M. charantia*, strong enough, randomized, placebo-controlled clinical trials are needed to properly determine safety and effectiveness before being routinely recommended. It is likely to cause additional side effects, especially when taken with other glucose-lowering agents. There are no other data on pediatric dosages. Convulsions and hypoglycemic coma were observed in two children, whose glycemia decreased strongly 1-2 hours after *M. charantia* tea was given on an empty stomach[124]. It has been reported as the most serious side effect known to humans. Other known side effects of *M. charantia* are the reduction of fertility in mice, an increase in γ-glutamyltransferase and alkaline phosphatase levels and headaches in

animals receiving oral juice and seed extract[37,125]. It has been reported that favism disease caused by glucose-6 phosphate dehydrogenase enzyme deficiency may develop after consumption of *M. charantia*. The disease is defined by other symptoms such as hemolytic anemia, headache, stomach pain, and coma[31]. It was determined that this was due to the glycosidic compound named "vicin" in the composition of *M. charantia*[126].

It has been reported that the fertility rate of mice fed with M. charantia juice supplement decreased. It has been reported that particular attention should be paid to the use of plants in pregnant women, since the proteins in the composition of *M. charantia* significantly reduce fertility in animal models and pose a risk of losing the baby[127-130]. It has been reported that spermatogenesis is inhibited in dogs fed with *M. charantia* fruit extract[131]. In the study performed with MAP30 protein isolated from *M. charantia*, it was stated that human sperm was not affected[132].

In diabetic animal models, it was reported that hepatotoxicity symptoms were not observed based on histological and biochemical observations after treatment with *M. charantia*[65]. Even if histopathological changes do not occur in animals with liver disease, caution should be exercised as transaminase increase is reported.

Many in vitro and in vivo studies have been conducted in which the beneficial effect of *M. charantia* on the heart has been reported. In a study conducted to investigate the potential developmental toxicity on fetal heart development using zebrafish (Danio rerio) embryos, seed extract was reported to be lethal with LD_{50} values. In addition, multiple anomalies were detected in zebrafish embryos at these concentrations[133]. In the same study, it has been reported that the fruit extract can be used safely without harming zebrafish embryos at a concentration of 200 µg / mL. However, it has been reported that severe cardiac hypertrophy develops in embryos treated with fruit extract over time and the cardiac myoblast specification process is impaired in zebrafish embryos. It was emphasized that the supplement should be used with caution to prevent possible damage to the development of the fetus in pregnant diabetic patients due to the teratogenicity of the seed extract and fruit extract cardiac toxicity[133].

A case of acute interstitial nephritis has been reported in a man with type 2 diabetes and hypertension using the hyponidd drug containing *M. charantia*[134]. Anuria was defined in 2-3 days following edema and urinary reduction in the patient who took one tablet daily for a week. Kidney toxicity has been reported in mice treated with *M. charantia* for more than a week[135]. It has been reported that *M. charantia* seeds and the outer shell contain lectin, which inhibits protein synthesis in the intestinal wall, but this is not related to clinical signs or symptoms in humans[136]. *M. charantia* can cause additional side effects when taken with blood sugar lowering agents. It has been observed that glucose-lowering effects are enhanced in rats supplemented with sulfonylurea tolbutamide together with *M. charantia* juice. Additional glucose-lowering effects were observed in 8 of 9 patients who took *M. charantia* juice or fruit powder with sulfonylurea[54]. In a woman with type 2 diabetes, it has been reported that the use of *M. charantia* and garlic supplements containing sulfonylurea chlorpropamide and curry caused additional glucose-lowering effects[137].

Safety data are derived from animal models rather than clinical studies. Clinical findings indicating that long-term use of *M. charantia* at high doses may cause kidney conditions should be tested by better organized clinical trials. In a meta-analysis study, it was reported that better structured studies are needed by emphasizing the scarcity of clinical data[138]. People who report allergies to other herbs from the Cucurbitaceae family should avoid the use of *M. charantia*.

CONCLUSION

It is known that the majority of the world population prefer traditional folk medicine products to industrial products. One of the main reason for the increased interest in herbal medicinalproducts is that natural products will be considered less toxic, but this is often a false perception. In health problems, many components

of vegetable origin obtained from natural products have the potential to act as supplements, alone or in mixtures. Due to the synergistic effect, many active compounds may have therapeutic potential much higher than the effects they can give alone when given as a herbal preparation.

M. charantia plant is a natural product known to be used for many years in the treatment of type 2 diabetes. There are many scientific studies supporting the anti-inflammatory and antioxidant properties of the plant, and it is a strong candidate that can clearly contribute to reducing the consumption of plant glycemia as well as reducing analgesic drug consumption in infectious diseases. There are also studies showing its effectiveness in the treatment of obesity, wound healing and supporting the immune system. Many in vitro and in vivo studies have been conducted on the investigation of the anticancer activity of *M. charantia*. The ability of *M. charantia* bioactive components to modulate a variety of cell cycle regulating proteins located in different signal paths has been clearly demonstrated in studies showing anticancer activity. The plant is known to play a vital role in cancer development and progression in cell signaling cascades. The *M. charantia* plant remains popular in the discovery of natural products, with its ability to suppress tumors by targeting multiple oncogenic signaling pathways. More studies are needed where *M. charantia* extracts or bioactive chemicals isolated from the plant are combined with chemotherapeutic drugs to see if they increase drug effectiveness or reduce side effects. There is also a gap in the field of clinical testing of all activities. Few clinical studies on *M. charantia* focused only on the effects on type 2 diabetes and were performed on a small number of subjects. Better clinical studies are needed on hyperglycemic efficacy. In addition, plant efficacy should be verified by increasing in vitro, in vivo and well-organized clinical trials in other areas where its use has traditionally been reported. It is known that the use of *M. charantia* herb together with the drugs used in the treatment of diabetes causes rapid decreases in blood sugar. Better safety studies are needed to perform the safety tests of the plant, to clarify the side effects and to adjust the doses in a controlled manner.

REFERENCES

1. Lij W, Veseras J. Drug Discovery and Natural products: end of an era or an endless frontier?[J]. *Science.* 2009;325(5937):161-165.
2. Ji Y, Luo Y, Hou B, Wang W, Zhao J, Yang L, Xue Q, Ding X. Development of polymorphic microsatellite loci in M. charantia (Cucurbitaceae) and their transferability to other cucurbit species. *Scientia horticulturae.* 2012;140:115-118.
3. Choi JS, Kim HY, Seo WT, Lee JH, Cho KM. Roasting enhances antioxidant effect of bitter melon (M. charantia L.) increasing in flavan-3-ol and phenolic acid contents. *Food Science and Biotechnology.* 2012;21(1):19-26.
4. Yaldız G, Sekeroglu N, Kulak M, Demirkol G. Antimicrobial activity and agricultural properties of bitter melon (M. charantia L.) grown in northern parts of Turkey: a case study for adaptation. *Natural product research.* 2015;29(6):543-545.
5. Mada S, Garba A, Mohammed H, Muhammad A, Olagunju A, Muhammad A. Antimicrobial activity and phytochemical screening of aqueous and ethanol extracts of M. charantia L. leaves. *Journal of Medicinal Plants Research.* 2013;7(10):579-586.
6. Oragwa Leonard N, Efiom Otu O, Okwute Simon K. Phytochemicals, anti-microbial and free radical scavenging activities of M. charantia Linn (Palisota Reichb) seeds. *African Journal of Pure and Applied.* 2013;7(12):405-409.
7. Ramprasath VR, Awad AB. Role of phytosterols in cancer prevention and treatment. *Journal of AOAC International.* 2015;98(3):735-738.
8. Uddin MS, Sarker MZI, Ferdosh S, Akanda MJH, Easmin MS, Bt Shamsudin SH, Yunus KB. Phytosterols and their extraction from various plant matrices using supercritical carbon dioxide: a review. *Journal of the Science of Food and Agriculture.* 2015;95(7):1385-1394.
9. Zhu Y, Soroka D, Sang S. Oxyphytosterols as active ingredients in wheat bran suppress human colon cancer cell growth: identification, chemical synthesis, and biological evaluation. *Journal of agricultural and food chemistry.*

2015;63(8):2264-2276.

10. Li C-J, Tsang S-F, Tsai C-H, Tsai H-Y, Chyuan J-H, Hsu H-Y. M. charantia extract induces apoptosis in human cancer cells through caspase-and mitochondria-dependent pathways. *Evidence-Based Complementary and Alternative Medicine.* 2012;2012.
11. Zhang J, Huang Y, Kikuchi T, Tokuda H, Suzuki N, Inafuku Ki, Miura M, Motohashi S, Suzuki T, Akihisa T. Cucurbitane triterpenoids from the leaves of M. charantia, and their cancer chemopreventive effects and cytotoxicities. *Chemistry & biodiversity.* 2012;9(2):428-440.
12. Tuan NQ, Lee D-H, Oh J, Kim CS, Heo K-S, Myung C-S, Na M. Inhibition of proliferation of vascular smooth muscle cells by Cucurbitanes from M. charantia. *Journal of natural products.* 2017;80(7):2018-2025.
13. Delgado-Lista J, Perez-Martinez P, Lopez-Miranda J, Perez-Jimenez F. Long chain omega-3 fatty acids and cardiovascular disease: a systematic review. *British Journal of Nutrition.* 2012;107(S2):S201-S213.
14. Alva-Murillo N, Ochoa-Zarzosa A, López-Meza JE. Short chain fatty acids (propionic and hexanoic) decrease Staphylococcus aureus internalization into bovine mammary epithelial cells and modulate antimicrobial peptide expression. *Veterinary microbiology.* 2012;155(2-4):324-331.
15. Urbanek A, Szadziewski R, Stepnowski P, Boros-Majewska J, Gabriel I, Dawgul M, Kamysz W, Sosnowska D, Gołębiowski M. Composition and antimicrobial activity of fatty acids detected in the hygroscopic secretion collected from the secretory setae of larvae of the biting midge Forcipomyia nigra (Diptera: Ceratopogonidae). *Journal of insect physiology.* 2012;58(9):1265-1276.
16. Žilić S, Serpen A, Akıllıoğlu Gl, Gökmen V, Vančetović J. Phenolic compounds, carotenoids, anthocyanins, and antioxidant capacity of colored maize (Zea mays L.) kernels. *Journal of Agricultural and Food Chemistry.* 2012;60(5):1224-1231.
17. Khoddami A, Wilkes MA, Roberts TH. Techniques for analysis of plant phenolic compounds. *Molecules.* 2013;18(2):2328-2375.
18. Alves MJ, Ferreira IC, Froufe HJ, Abreu R, Martins A, Pintado M. Antimicrobial activity of phenolic compounds identified in wild mushrooms, SAR analysis and docking studies. *Journal of applied microbiology.* 2013;115(2):346-357.
19. Ghasemzadeh A, Jaafar HZ. Profiling of phenolic compounds and their antioxidant and anticancer activities in pandan (Pandanus amaryllifolius Roxb.) extracts from different locations of Malaysia. *BMC complementary and alternative medicine.* 2013;13(1):341.
20. Hu Q-F, Zhou B, Huang J-M, Gao X-M, Shu L-D, Yang G-Y, Che C-T. Antiviral phenolic compounds from Arundina gramnifolia. *Journal of natural products.* 2013;76(2):292-296.
21. Sathya A, Ambikapathy V, Panneer S. Studies on the phytochemistry, antimicrobial activity and antioxidant properties of Cassia occidentalis L. *Asian Journal of Plant Science and Research.* 2012;2(4):530-533.
22. Sood A, Kaur P, Gupta R. Phytochemical screening and antimicrobial assay of various seeds extract of Cucurbitaceae family. 2012.
23. Dar UK, Owais F, Ahmad M, Rizwani GH. Biochemical analysis of the crude extract of M. charantia (L.). *Pakistan journal of pharmaceutical sciences.* 2014;27(6):2237-2240.
24. Tan SP, Parks SE, Stathopoulos CE, Roach PD. Extraction of flavonoids from bitter melon. *Food and Nutrition Sciences.* 2014;2014.
25. Yeo YL, Chia YY, Lee CH, Sow HS, Yap WS. Effectiveness of maceration periods with different extraction solvents on in-vitro antimicrobial activity from fruit of M. charantia L. *Journal of Applied Pharmaceutical Science.* 2014;4(10):16-23.
26. Zhang F, Lin L, Xie J. A mini-review of chemical and biological properties of polysaccharides from M. charantia. *International journal of biological macromolecules.* 2016;92:246-253.
27. Bourinbaiar AS, Lee-Huang S. The Activity of Plant-Derived Antiretroviral Proteins MAP30 and GAP31 against Herpes Simplex Virus Infectionin Vitro. *Biochemical and biophysical research communications.* 1996;219(3):923-929.
28. Lee-Huang S, Huang PL, Chen H-C, Huang PL, Bourinbaiar A, Huang HI, Kung H-f. Anti-HIV and anti-tumor activities of recombinant MAP30 from bitter melon. *Gene.* 1995;161(2):151-156.
29. Lee-Huang S, Huang PL, Bourinbaiar A, Chen H, Kung H. Inhibition of the integrase of human immunodeficiency

virus (HIV) type 1 by anti-HIV plant proteins MAP30 and GAP31. *Proceedings of the National Academy of Sciences.* 1995;92(19):8818-8822.

30. Lee-Huang S, Huang PL, Sun Y, Chen HC, Kung HF, Murphy W. Inhibition of MDA-MB-231 human breast tumor xenografts and HER2 expression by anti-tumor agents GAP31 and MAP30. *Anticancer Research.* 2000;20(2A):653-659.
31. Raman A, Lau C. Anti-diabetic properties and phytochemistry of M. charantia L.(Cucurbitaceae). *Phytomedicine.* 1996;2(4):349-362.
32. Ali L, Khan AKA, Mamun MIR, Mosihuzzaman M, Nahar N, Nur-E-Alam M, Rokeya B. Studies on hypoglycemic effects of fruit pulp, seed, and whole plant of M. charantia on normal and diabetic model rats. *Planta medica.* 1993;59(05):408-412.
33. Kisacik ÖG, Güneş ÜY. Yara iyileşmesinde kudret narının etkisi. *Spatula DD.* 2017;7(2):53-59.
34. F Fang E, B Ng T. Bitter gourd (M. charantia) is a cornucopia of health: a review of its credited antidiabetic, anti-HIV, and antitumor properties. *Current molecular medicine.* 2011;11(5):417-436.
35. Grover J, Yadav S. Pharmacological actions and potential uses of M. charantia: a review. *Journal of ethnopharmacology.* 2004;93(1):123-132.
36. Ng T, Chan W, Yeung H. Proteins with abortifacient, ribosome inactivating, immunomodulatory, antitumor and anti-AIDS activities from Cucurbitaceae plants. *General Pharmacology: The Vascular System.* 1992;23(4):575-590.
37. Basch E, Gabardi S, Ulbricht C. Bitter melon (M. charantia): a review of efficacy and safety. *American Journal of Health-System Pharmacy.* 2003;60(4):356-359.
38. Joseph B, Jini D. Antidiabetic effects of M. charantia (bitter melon) and its medicinal potency. *Asian Pacific Journal of Tropical Disease.* 2013;3(2):93-102.
39. Palamthodi S, Lele S. Nutraceutical applications of gourd family vegetables: Benincasa hispida, Lagenaria siceraria and M. charantia. *Biomedicine & Preventive Nutrition.* 2014;4(1):15-21.
40. Wu L, Ke L, Huang X, Liu S, Chen H, Rao P. Separation and characterization of the active ingredients of M. charantia L. and their protective and repairing effect on HIT-T15 cells damaged by alloxan in vitro. *J Chin Inst Food Sci Tech (Chin).* 2006;6(4):24-28.
41. Xu X, Shan B, Liao C-H, Xie J-H, Wen P-W, Shi J-Y. Anti-diabetic properties of M. charantia L. polysaccharide in alloxan-induced diabetic mice. *International journal of biological macromolecules.* 2015;81:538-543.
42. Ng T, Wong C, Li W, Yeung H. Insulin-like molecules in M. charantia seeds. *Journal of ethnopharmacology.* 1986;15(1):107-117.
43. Ng T, Wong C, Li W, Yeung H. Isolation and characterization of a galactose binding lectin with insulinomimetic activities: from the seeds of the bitter gourd M. charantia (family Cucurbitaceae). *International journal of peptide and protein research.* 1986;28(2):163-172.
44. Wong C, Ng T, Yeung H. Screening of Trichosanthes kirilowii, M. charantia AND Cucurbit a maxima (family cucurbitaceae) for compounds with antilipolytic activity. *Journal of ethnopharmacology.* 1985;13(3):313-321.
45. Virdi J, Sivakami S, Shahani S, Suthar A, Banavalikar M, Biyani M. Antihyperglycemic effects of three extracts from M. charantia. *Journal of ethnopharmacology.* 2003;88(1):107-111.
46. Kumar GS, Vijayalakshmi B, Salimath P. Effect of bitter gourd and spent turmeric on constituents of glycosaminoglycans in different tissues in streptozotocin induced diabetic rats. *Molecular and cellular biochemistry.* 2006;286(1-2):53.
47. Dong Y, Zhang H. Studies on Components Wıth Antihyperglycemic Effect of M. charantia L. Polysaccharıdes. *Acta Nutrimenta Sinica.* 1956(01).
48. Bin X, Dong Y, Zhang H, Cui H, Qi L. The antihyperglycemic effects of polysaccharide from M. charantia in STZ-induced diabetic mice. *Acta Nutrimenta Sinica.* 2004(05).
49. He X, Liu Z. Study on HTS anti-diabetic antagonists from M. charantia L. *Food Science.* 2007;28(2):313-316.
50. Simpson R, Morris GA. The anti-diabetic potential of polysaccharides extracted from members of the cucurbit family: A review. *Bioactive Carbohydrates and Dietary Fibre.* 2014;3(2):106-114.
51. Ahmed I, Lakhani M, Gillett M, John A, Raza H. Hypotriglyceridemic and hypocholesterolemic effects of anti-diabetic M. charantia (karela) fruit extract in streptozotocin-induced diabetic rats. *Diabetes Research and Clinical Practice.* 2001;51(3):155-161.

52. Nkambo W, Anyama N, Onegi B. In vivo hypoglycemic effect of methanolic fruit extract of M. charantia L. *African health sciences.* 2013;13(4):933-939.
53. Akhtar MS, Athar MA, Yaqub M. Effect of M. charantia on blood glucose level of normal and alloxan-diabetic rabbits. *Planta Medica.* 1981;42(07):205-212.
54. Leatherdale B, Panesar R, Singh G, Atkins T, Bailey C, Bignell A. Improvement in glucose tolerance due to M. charantia (karela). *Br Med J (Clin Res Ed).* 1981;282(6279):1823-1824.
55. Higashino H, Suzuki A, Tanaka Y, Pootakham K. Hypoglycemic effects of Siamese M. charantia and Phyllanthus urinaria extracts in streptozotocin-induced diabetic rats (the 1st report). *Nihon yakurigaku zasshi Folia pharmacologica Japonica.* 1992;100(5):415-421.
56. Sarkar S, Pranava M, MARITA AR. Demonstration of the hypoglycemic action of M. charantia in a validated animal model of diabetes. *Pharmacological Research.* 1996;33(1):1-4.
57. Day C, Cartwright T, Provost J, Bailey C. Hypoglycaemic effect of M. charantia extracts. *Planta medica.* 1990;56(05):426-429.
58. Chaturvedi P. Antidiabetic potentials of M. charantia: multiple mechanisms behind the effects. *Journal of Medicinal Food.* 2012;15(2):101-107.
59. Chaturvedi P, Akala H. Thyrogenic responses of M. charantia. *J Applied Zool Res.* 2003;14:191-194.
60. Nerurkar PV, Lee YK, Motosue M, Adeli K, Nerurkar VR. M. charantia (bitter melon) reduces plasma apolipoprotein B-100 and increases hepatic insulin receptor substrate and phosphoinositide-3 kinase interactions. *British journal of nutrition.* 2008;100(4):751-759.
61. Singh N, Tyagi S, Agarwal S. Effects of long term feeding of acetone extract of M. charantia (whole fruit powder) on alloxan diabetic albino rats. *Ind J Physiol Pharmac.* 1989;33(2).
62. Ojewole JA, Olayiwola G, Adewole SO. Hypoglycaemic and hypotensive effects of M. charantia Linn (Cucurbitaceae) whole-plant aqueous extract in rats: cardiovascular topics. *Cardiovascular Journal of South Africa.* 2006;17(5):227-232.
63. Senanayake GV, Maruyama M, Shibuya K, Sakono M, Fukuda N, Morishita T, Yukizaki C, Kawano M, Ohta H. The effects of bitter melon (M. charantia) on serum and liver triglyceride levels in rats. *Journal of ethnopharmacology.* 2004;91(2-3):257-262.
64. Chaturvedi P. Role of M. charantia in maintaining the normal levels of lipids and glucose in diabetic rats fed a high-fat and low-carbohydrate diet. *British journal of biomedical science.* 2005;62(3):124-126.
65. Offor U, Naidu EC, Ogedengbe OO, Aniekan PI, Azu OO. M. charantia mitigates hepatic injury following adjuvant treatment with antiretroviral drugs in diabetic animal models. *Toxicological Research.* 2020;36(1):37-44.
66. Offor U, Coleridge Stephen Naidu E, Olalekan Ogedengbe O, Isaac Jegede A, Imo Peter A, Azu Onyemaechi O. Renal histopathological and biochemical changes following adjuvant intervention of M. charantia and antiretroviral therapy in diabetic rats. *Iranian Journal of Basic Medical Sciences.* 2019;22(11):1359-1367.
67. Gao H, Wen J-J, Hu J-L, Nie Q-X, Chen H-H, Xiong T, Nie S-P, Xie M-Y. Fermented M. charantia L. juice modulates hyperglycemia, lipid profile, and gut microbiota in type 2 diabetic rats. *Food research international.* 2019;121:367-378.
68. Hartajanie L, Fatimah-Muis S, Heri-Nugroho HS K, Riwanto I, Sulchan M. Probiotics Fermented Bitter Melon Juice as Promising Complementary Agent for Diabetes Type 2: Study on Animal Model. *Journal of nutrition and metabolism.* 2020;2020.
69. Malekshahi H, Bahrami G, Miraghaee S, Ahmadi SA, Sajadimajd S, Hatami R, Mohammadi B, Keshavarzi S. M. charantia reverses type II diabetes in rat. *Journal of food biochemistry.* 2019;43(11):e13021.
70. Welihinda J, Karunanayake E, Sheriff M, Jayasinghe K. Effect of M. charantia on the glucose tolerance in maturity onset diabetes. *Journal of Ethnopharmacology.* 1986;17(3):277-282.
71. França EL, Ribeiro EB, Scherer EF, Cantarini DG, Pessôa RS, França FL, Honorio-França AC. Effects of M. charantia L. on the blood rheological properties in diabetic patients. *BioMed research international.* 2014;2014.
72. Baldwa V, Bhandari C, Pangaria A, Goyal R. Clinical trial in patients with diabetes mellitus of an insulin-like compound obtained from plant source. *Upsala journal of medical sciences.* 1977;82(1):39-41.
73. Srivastava Y, Venkatakrishna-Bhatt H, Verma Y, Venkaiah K, Raval B. Antidiabetic and adaptogenic properties of M. charantia extract: an experimental and clinical evaluation. *Phytotherapy Research.* 1993;7(4):285-289.

74. Gupta C, Khusro A, Salem AZ. Susceptibility of poultry associated bacterial pathogens to M. charantia fruits and evaluation of in vitro biological properties. *Microbial pathogenesis.* 2019;132:222-229.
75. Cai Y, Liu M, Wu X, Wang Z, Liang C, Yang Y. Study on the antitumor and immune-stimulating activity of polysaccharide from M. charantia. Pharm. *Clin Res.* 2010;18(2):131-134.
76. Zhang L, Zhang M, Huang W, Zhang Y, Zhang R, Wei Z. Optimization on cellulase and ultrasonic wave assisted extraction technology of M. charantia polysaccharides. *Nongye Jixie Xuebao= Transactions of the Chinese Society for Agricultural Machinery.* 2010;41(11):142-147.
77. Panda BC, Mondal S, Devi KSP, Maiti TK, Khatua S, Acharya K, Islam SS. Pectic polysaccharide from the green fruits of M. charantia (Karela): structural characterization and study of immunoenhancing and antioxidant properties. *Carbohydrate research.* 2015;401:24-31.
78. Meera S, Nagarjuna CG. Antistress and immunomodulatory activity of aqueous extract of M. charantia. *Pharmacognosy Magazine.* 2009;5(19):69.
79. Biswas S. Does the interdependence between oxidative stress and inflammation explain the antioxidant paradox? Oxidative Med Cell Longev 2016: 1–9. In:2016.
80. Dandawate PR, Subramaniam D, Padhye SB, Anant S. Bitter melon: a panacea for inflammation and cancer. *Chinese journal of natural medicines.* 2016;14(2):81-100.
81. Chao C-Y, Sung P-J, Wang W-H, Kuo Y-H. Anti-inflammatory effect of M. charantia in sepsis mice. *Molecules.* 2014;19(8):12777-12788.
82. Du Z, Zhang S, Lin Y, Zhou L, Wang Y, Yan G, Zhang M, Wang M, Li J, Tong Q. Momordicoside G regulates macrophage phenotypes to stimulate efficient repair of lung injury and prevent urethane-induced lung carcinoma lesions. *Frontiers in pharmacology.* 2019;10:321.
83. Jones LD, Pangloli P, Krishnan HB, Dia VP. BG-4, a novel bioactive peptide from M. charantia, inhibits lipopolysaccharide-induced inflammation in THP-1 human macrophages. *Phytomedicine.* 2018;42:226-232.
84. İlhan M, Bolat IE, Süntar İ, Köklü HK, Çankal DAU, Keleş H, Akkol EK. Topical application of olive oil macerate of M. charantia L. promotes healing of excisional and incisional wounds in rat buccal mucosa. *Archives of oral biology.* 2015;60(12):1708-1713.
85. Bao B, Chen Y-G, Zhang L, Xu YLN, Wang X, Liu J, Qu W. M. charantia (Bitter Melon) reduces obesity-associated macrophage and mast cell infiltration as well as inflammatory cytokine expression in adipose tissues. *PLoS One.* 2013;8(12).
86. Bai J, Zhu Y, Dong Y. Response of gut microbiota and inflammatory status to bitter melon (M. charantia L.) in high fat diet induced obese rats. *Journal of Ethnopharmacology.* 2016;194:717-726.
87. Bai J, Zhu Y, Dong Y. Obese rats supplemented with bitter melon display marked shifts in the expression of genes controlling inflammatory response and lipid metabolism by RNA-Seq analysis of colonic mucosa. *Genes & genomics.* 2018;40(6):561-567.
88. Raish M, Ahmad A, Ansari MA, Alkharfy KM, Aljenoobi FI, Jan BL, Al-Mohizea AM, Khan A, Ali N. M. charantia polysaccharides ameliorate oxidative stress, inflammation, and apoptosis in ethanol-induced gastritis in mucosa through NF-kB signaling pathway inhibition. *International journal of biological macromolecules.* 2018;111:193-199.
89. Nerurkar PV, Johns LM, Buesa LM, Kipyakwai G, Volper E, Sato R, Shah P, Feher D, Williams PG, Nerurkar VR. M. charantia (bitter melon) attenuates high-fat diet-associated oxidative stress and neuroinflammation. *Journal of neuroinflammation.* 2011;8(1):64.
90. Huang W-C, Tsai T-H, Huang C-J, Li Y-Y, Chyuan J-H, Chuang L-T, Tsai P-J. Inhibitory effects of wild bitter melon leaf extract on Propionibacterium acnes-induced skin inflammation in mice and cytokine production in vitro. *Food & function.* 2015;6(8):2550-2560.
91. Nerurkar PV, Orias D, Soares N, Kumar M, Nerurkar VR. M. charantia (bitter melon) modulates adipose tissue inflammasome gene expression and adipose-gut inflammatory cross talk in high-fat diet (HFD)-fed mice. *The Journal of nutritional biochemistry.* 2019;68:16-32.
92. May LS, Sanip Z, Shokri AA, Kadir AA, Lazin MRM. The effects of M. charantia (bitter melon) supplementation in patients with primary knee osteoarthritis: A single-blinded, randomized controlled trial. *Complementary therapies in clinical practice.* 2018;32:181-186.

93. Li J, Wang Y, Huang J, Xu X, Xiang C. Characterization of antioxidant polysaccharides in bitter gourd (M. charantia L.) cultivars. *J Food Agric Environ.* 2010;8(3&4):117-120.
94. Tan H-F, Gan C-Y. Polysaccharide with antioxidant, α-amylase inhibitory and ACE inhibitory activities from M. charantia. *International journal of biological macromolecules.* 2016;85:487-496.
95. Deng Y-Y, Yi Y, Zhang L-F, Zhang R-F, Zhang Y, Wei Z-C, Tang X-J, Zhang M-W. Immunomodulatory activity and partial characterisation of polysaccharides from M. charantia. *Molecules.* 2014;19(9):13432-13447.
96. Liu X, Chen T, Hu Y, Li K, Yan L. Catalytic synthesis and antioxidant activity of sulfated polysaccharide from M. charantia L. *Biopolymers.* 2014;101(3):210-215.
97. Wang Z-J, Xie J-H, Shen M-Y, Tang W, Wang H, Nie S-P, Xie M-Y. Carboxymethylation of polysaccharide from Cyclocarya paliurus and their characterization and antioxidant properties evaluation. *Carbohydrate polymers.* 2016;136:988-994.
98. Xie J-H, Zhang F, Wang Z-J, Shen M-Y, Nie S-P, Xie M-Y. Preparation, characterization and antioxidant activities of acetylated polysaccharides from Cyclocarya paliurus leaves. *Carbohydrate Polymers.* 2015;133:596-604.
99. Kim KB, Lee S, Kang I, Kim J-H. M. charantia ethanol extract attenuates H2O2-induced cell death by its antioxidant and anti-apoptotic properties in human neuroblastoma SK-N-MC cells. *Nutrients.* 2018;10(10):1368.
100. Lin Z-Y, Liu X, Yang F, Yu Y-Q. Structural characterization and identification of five triterpenoid saponins isolated from Momordica cochinchinensis extracts by liquid chromatography/tandem mass spectrometry. *International Journal of Mass Spectrometry.* 2012;328:43-66.
101. Liu C-H, Yen M-H, Tsang S-F, Gan K-H, Hsu H-Y, Lin C-N. Antioxidant triterpenoids from the stems of M. charantia. *Food chemistry.* 2010;118(3):751-756.
102. Padmashree A, Sharma GK, Semwal AD, Bawa AS. Studies on the antioxygenic activity of bitter gourd (M. charantia) and its fractions using various in vitro models. *Journal of the Science of Food and Agriculture.* 2011;91(4):776-782.
103. Kim HY, Sin SM, Lee S, Cho KM, Cho EJ. The butanol fraction of bitter melon (M. charantia) scavenges free radicals and attenuates oxidative stress. *Preventive nutrition and food science.* 2013;18(1):18.
104. Zhou R, Tu N-y, Cong M, Kan G-s, Ren D-m, Chen H-m. Purification and hepatoprotective effect of Momordica polysaccharides. *Food Science and Technology.* 2013;2.
105. Salehi B, Zucca P, Sharifi-Rad M, Pezzani R, Rajabi S, Setzer WN, Varoni EM, Iriti M, Kobarfard F, Sharifi-Rad J. Phytotherapeutics in cancer invasion and metastasis. *Phytotherapy Research.* 2018;32(8):1425-1449.
106. Nerurkar P, Ray RB. Bitter melon: antagonist to cancer. *Pharmaceutical research.* 2010;27(6):1049-1053.
107. Farooqi AA, Khalid S, Tahir F, Sabitaliyevich UY, Yaylim I, Attar R, Xu B. Bitter gourd (M. charantia) as a rich source of bioactive components to combat cancer naturally: Are we on the right track to fully unlock its potential as inhibitor of deregulated signaling pathways. *Food and Chemical Toxicology.* 2018;119:98-105.
108. Huang X, Nie S. The structure of mushroom polysaccharides and their beneficial role in health. *Food & function.* 2015;6(10):3205-3217.
109. Wu J, Zhou J, Lang Y, Yao L, Xu H, Shi H, Xu S. A polysaccharide from Armillaria mellea exhibits strong in vitro anticancer activity via apoptosis-involved mechanisms. *International journal of biological macromolecules.* 2012;51(4):663-667.
110. LI Z-t, ZHANG J, XIE J, SUN R-g. The inhibition effect of two different M. charantia polysaccharides on the proliferation of human leukemia cell in vitro. *Journal of Shaanxi Normal University (Natural Science Edition).* 2013;2.
111. Guan L. Synthesis and anti-tumour activities of sulphated polysaccharide obtained from M. charantia. *Natural product research.* 2012;26(14):1303-1309.
112. Yue J, Sun Y, Xu J, Cao J, Chen G, Zhang H, Zhang X, Zhao Y. Cucurbitane triterpenoids from the fruit of M. charantia L. and their anti-hepatic fibrosis and anti-hepatoma activities. *Phytochemistry.* 2019;157:21-27.
113. Somasagara RR, Deep G, Shrotriya S, Patel M, Agarwal C, Agarwal R. Bitter melon juice targets molecular mechanisms underlying gemcitabine resistance in pancreatic cancer cells. *International journal of oncology.* 2015;46(4):1849-1857.
114. Dhar D, Deep G, Kumar S, Wempe MF, Raina K, Agarwal C, Agarwal R. Bitter melon juice exerts its efficacy against pancreatic cancer via targeting both bulk and cancer stem cells. *Molecular carcinogenesis.* 2018;57(9):1166-

1180.
115. Wang Y-X, Jacob J, Wingfield PT, Palmer I, Stahl SJ, Kaufman JD, Huang PL, Huang PL, Lee-Huang S, Torchia DA. Anti-HIV and anti-tumor protein MAP30, a 30 kDa single-strand type-I RIP, shares similar secondary structure and β-sheet topology with the A chain of ricin, a type-II RIP. *Protein Science.* 2000;9(1):138-144.
116. Ping-ping Z, Jin-fu L, Chang-lu W, Yan-ting Y, Jin-hai X. Study on the Antimicrobial Activities of the Extracts from M. charantia L. *Natural Product Research & Development.* 2008;20(4).
117. Fang EF, Zhang CZY, Fong WP, Ng TB. RNase MC2: a new M. charantia ribonuclease that induces apoptosis in breast cancer cells associated with activation of MAPKs and induction of caspase pathways. *Apoptosis.* 2012;17(4):377-387.
118. Fang EF, Zhang CZY, Ng TB, Wong JH, Pan WL, Ye XJ, Chan YS, Fong WP. M. charantia lectin, a type II ribosome inactivating protein, exhibits antitumor activity toward human nasopharyngeal carcinoma cells in vitro and in vivo. *Cancer Prevention Research.* 2012;5(1):109-121.
119. Pitchakarn P, Suzuki S, Ogawa K, Pompimon W, Takahashi S, Asamoto M, Limtrakul P, Shirai T. Kuguacin J, a triterpeniod from M. charantia leaf, modulates the progression of androgen-independent human prostate cancer cell line, PC3. *Food and chemical toxicology.* 2012;50(3-4):840-847.
120. Shim SH, Sur S, Steele R, Albert CJ, Huang C, Ford DA, Ray RB. Disrupting cholesterol esterification by bitter melon suppresses triple-negative breast cancer cell growth. *Molecular carcinogenesis.* 2018;57(11):1599-1607.
121. Duan Z-Z, Zhou X-L, Li Y-H, Zhang F, Li F-Y, Su-Hua Q. Protection of M. charantia polysaccharide against intracerebral hemorrhage-induced brain injury through JNK3 signaling pathway. *Journal of Receptors and Signal Transduction.* 2015;35(6):523-529.
122. Gong J, Sun F, Li Y, Zhou X, Duan Z, Duan F, Zhao L, Chen H, Qi S, Shen J. M. charantia polysaccharides could protect against cerebral ischemia/reperfusion injury through inhibiting oxidative stress mediated c-Jun N-terminal kinase 3 signaling pathway. *Neuropharmacology.* 2015;91:123-134.
123. Perveen H, Dey A, Nilavar NM, Chandra GK, Islam SS, Chattopadhyay S. Dietary CCPS from bitter gourd attenuates sodium arsenite induced female reproductive ailments cum infertility in wistar rats: anti-inflammatory and anti-apoptotic role. *Food and Chemical Toxicology.* 2019;131:110545.
124. Hulin A, Wavelet M, Desbordes J. Intoxication aiguë par M. charantia (Sorrossi)(à propos de deux cas). *Médecine d'Afrique Noire.* 1988;35(9):671-674.
125. Tennekoon KH, Jeevathayaparan S, Angunawala P, Karunanayake EH, Jayasinghe K. Effect of M. charantia on key hepatic enzymes. *Journal of ethnopharmacology.* 1994;44(2):93-97.
126. Dutta P, Chakravarty A, Chowdhury U, Pakrashi S. Studies on Indian Medicinal-Plants. 64. Vicine, A Favism-Inducing Toxin From Momordica-Charantia Linn Seeds. *Indian Journal of Chemistry Section B-Organic Chemistry Including Medicinal Chemistry.* 1981;20(8):669-671.
127. Aguwa C, Mittal G. Abortifacient effects of the roots of Momordica angustisepala. *Journal of ethnopharmacology.* 1983;7(2):169-173.
128. Chan W, Tam P, Yeung H. The termination of early pregnancy in the mouse by β-momorcharin. *Contraception.* 1984;29(1):91-100.
129. Leung S, Yeung H, Leung K. The immunosuppressive activities of two abortifacient proteins isolated from the seeds of bitter melon (M. charantia). *Immunopharmacology.* 1987;13(3):159-171.
130. Stepka W, Wilson K, Madge G. Antifertility investigation on Momordica. *Lloydia.* 1974;37(4):645c.
131. Dixit V, Khanna P, Bhargava S. Effects of M. charantia L. fruit extract on the testicular function of dog. *Planta medica.* 1978;34(07):280-286.
132. Schreiber CA, Wan L, Sun Y, Lu L, Krey LC, Lee-Huang S. The antiviral agents, MAP30 and GAP31, are not toxic to human spermatozoa and may be useful in preventing the sexual transmission of human immunodeficiency virus type 1. *Fertility and sterility.* 1999;72(4):686-690.
133. Khan MF, Abutaha N, Nasr FA, Alqahtani AS, Noman OM, Wadaan MA. Bitter gourd (M. charantia) possess developmental toxicity as revealed by screening the seeds and fruit extracts in zebrafish embryos. *BMC complementary and alternative medicine.* 2019;19(1):1-13.
134. Beniwal P, Gaur N, Singh S, Raveendran N, Malhotra V. How harmful can herbal remedies be? A case of severe acute tubulointerstitial nephritis. *Indian journal of nephrology.* 2017;27(6):459.

135. Mardani S, Nasri H, Hajian S, Ahmadi A, Kazemi R, Rafieian-Kopaei M. Impact of M. charantia extract on kidney function and structure in mice. *Journal of nephropathology.* 2014;3(1):35.
136. Marles RJ, Farnsworth NR. Antidiabetic plants and their active constituents. *Phytomedicine.* 1995;2(2):137-189.
137. Aslam M, Stockley I. Interaction between curry ingredient (karela) and drug (chlorpropamide). *The Lancet.* 1979;313(8116):607.
138. Akter S, Goto A, Mizoue T. Smoking and the risk of type 2 diabetes in Japan: a systematic review and meta-analysis. *Journal of epidemiology.* 2017;27(12):553-561.