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Bitter melon: a panacea for inflammation and cancer

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Abstract

Nature is a rich source of medicinal plants and their products that are useful for treatment of various diseases and disorders. *Momordica charantia*, commonly known as bitter melon or bitter gourd, is one of such plants known for its biological activities used in traditional system of medicines. This plant is cultivated in all over the world, including tropical areas of Asia, Amazon, east Africa, and the Caribbean and used as a vegetable as well as folk medicine. All parts of the plant, including the fruit, are commonly consumed and cooked with different vegetables, stir-fried, stuffed or used in small quantities in soups or beans to give a slightly bitter flavor and taste. The plant is reported to possess anti-oxidant, anti-inflammatory, anti-cancer, anti-diabetic, anti-bacterial, anti-obesity, and immunomodulatory activities. The plant extract inhibits cancer cell growth by inducing apoptosis, cell cycle arrest, autophagy and inhibiting cancer stem cells. The plant is rich in bioactive chemical constituents like cucurbitane type triterpenoids, triterpene glycosides, phenolic acids, flavonoids, essential oils, saponins, fatty acids, and proteins. Some of the isolated compounds (Kuguacin J, Karaviloside XI, Kuguaglycoside C, Momordicoside Q–U, Charantin, α-eleostearic acid) and proteins (α-Momorcharin, RNase MC2, MAP30) possess potent biological activity. In the present review, we are summarizing the anti-oxidant, anti-inflammatory, and anti-cancer activities of *Momordica charantia* along with a short account of important chemical constituents, providing a basis for establishing detail biological activities of the plant and developing novel drug molecules based on the active chemical constituents.

Keywords

Momordica charantia; Bitter melon; Anti-oxidant activity; Anti-inflammatory activity; Anti-cancer activity; Natural products

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Introduction

Nature is a rich source of natural products, among which medicinal plants and phytochemicals have gained immense attention in drug discovery because of their wide safety profile, multi-targeted activities and potential to treat a wide range of diseases. World Health Organization (WHO) has recently reported that about 80% of the world's population still rely on traditional system of medicine [1]. The major and old traditional systems of medicines are Indian and Chinese traditional medicinal systems that have compiled the therapeutic effects of many plants and plant products. Indian medicinal system is a source of such plant database [2] which either in the form of powder extracts, pills or liquid forms (solutions and suspensions) has been used widely in India for treatment of various diseases. The Indian medicinal plants described in Ayurveda such as bitter melon [3–4], turmeric [5–6], and bael [7–8], have proven their importance in recent years for treatment of various diseases, including diabetes and cancer. The development of science and technology in recent time makes it possible to discover the active constituents present in these plants and establish their biological targets for evolving them as a remedy for treating diseases. Further, identification of the active pure constituents of the plants will give an opportunity for pharmacologists to find out the exact mode of action and establishing their effects by conducting systematic clinical trials. The modern technology can be also used to carry out chemical modifications to evolve more potent and selective targeting molecules based on these natural scaffolds. Hence, more systematic studies on these plants and plant products are needed for full exploitation of their potential and evolving novel drugs based on these scaffolds.

In the present review, we are summarizing chemical constituents and biological activities of *Momordica charantia* (MC) that is one of the vegetable plants used in traditional medicinal systems. MC belongs to the family of Cucurbitaceae and is commonly known as bitter melon, bitter gourd, balsam pear, bitter cucumber, Karela, and African cucumber [9]. *Momordica* means "too bite", which refers to the jagged edges of the leaf appear as if it has been bitten. All parts of the plant, including the fruit, taste bitter. Hence, the fruits are usually cooked with different vegetables, stir-fried, stuffed or used in small quantities in soups or beans to give a slightly bitter flavor and taste. Several parts of MC, including fruits, flowers, and young shoots, are used in various Asian dishes as a flavoring agent. The shoots and leaves of MC are also cooked and consumed as vegetables and fruit extracts are also used in tea preparations [10–11]. Unlike other cucurbitaceous vegetables, the bitter fruit flavor of MC is considered desirable for consumption. This plant is cultivated in all over the world, including tropical areas of Asia, Amazon, east Africa, and the Caribbean, and used as vegetable as well as folk medicine. MC has been cultivated traditionally in developing countries like India, China, Brazil, Colombia, Cuba, Ghana, Haiti, Mexico, Malaya, New Zealand, Nicaragua, Panama, and Peru, and is commonly used for the treatment of diabetes and colics [12–13]. MC is also used as antiviral, anti-malarial, and anti-bacterial agent, while it is applied for wound healing and treatment of peptic ulcers in Traditional Turkish medicine. In Indian medicinal systems, MC is reported to possess anti-diabetic, abortifacient, anti- helminthic, anti-malarial, and laxative properties, while it is also used for

treatment of dysmenorrhea, emmenagogue, eczema, gout, galactagogue, kidney (stone), jaundice, leucorrhea, leprosy, pneumonia, piles, rheumatism, and psoriasis [14].

The plant has been studied for several decades because of its use as a food product and several traditional medical uses. Various extracts of MC are studied for biological activities, including anti-oxidant [15], anti-diabetic [16], anti-cancer [17], anti-inflammatory [18], anti-bacterial [19], antifungal [20], anti-viral [21], anti-HIV [22], anti-helminthic [23], anti-mycobacterial [24], hypotensive [25], anti-obesity [26], immunomodulatory [27], anti-hyperlipidemic [28], hepatoprotective [29], and neuropro-tective [30] activities. Several chemical constituents such as cucurbitane type triterpenoids, cucurbitane type glycosides, triterpene saponins, phenolic, and flavonoid compounds, and some protein fractions have been isolated from MC [31]. In the present review, we are summarizing some of the important reports dealing with anti-oxidant, anti-inflammatory, and anti- cancer activities of MC along with its reported chemical constituents and their biological activities.

Momordica charantia

The genus *Momordica* belongs to subtribe *Thladianthinae,* tribe *Joliffieae,* subfamily *Cucurbitoideae,* of the *Cucurbitaceae* [32], including 45 plant species domesticated in Asia and Africa [33]. The genus *Momordica* has monoecious group represented by only *M. charantia* L. and *M. balsamina* L., while dioecious group is constituted by *M. dioica* Roxb., *M. sahyadrica* Joseph & Antony, *M. cochinchinensis* (Lour.) Spreng., and *M. subangulata* Blume (ssp. *renigem* (*G.* Don) W.J.J. deWilde).

Occurrence and cultivation of MC

The plant grows in tropical areas of Asia, Amazon, east Africa, and the Caribbean. The core of MC domestication is likely to belong in eastern Asia, probably eastern India or southern China [34–35]. The members of the Indo-Aryan culture mentioned about wild or small-fruited cultivated forms of MC in Ayurvedic books from 2 000 to 200 BCE [36], suggesting an early cultivation of MC in India. Hence, it is thought that the most modern Hindi (Indian language) terminology “Karela” may ultimately be of Dravidian origin [37]. The Chinese written reference to MC was made in 1370 CE [38]. Both the domesticated and putative wild MC progenitors of MC are listed in floras of India, tropical Africa, and Asia as well as the New World tropics, where it first arrived in Brazil via the slave trade from Africa and then spread into Central America [39].

Momordica species grow well in hot, humid climate areas, but also grow abundantly in subtropical climates, and are day neutral. *Momordica* species are tolerant to a range of environments [40] and can grow in tropical and subtropical climates [41]. MC is chiefly cultivated during the spring, summer, and rainy seasons, with some winter production occurring in subtropical climates. Generally, it is cultivated throughout the year in tropical climates, while the temperature required for the plant growth is 25–30 ºC. Frost can kill the plants, and cool temperatures could retard development. The MC crop can grow above 18 ºC [42], with optimum temperature being 24–27 ºC [43]. MC grows well in full sun and is adaptable to a wide range of soil types, but grows best in a well-drained sandy loam soil that

is rich in organic matter. It also grows well in soils of shallow to medium depth (50–150 cm), and like most cucurbits, MC prefers well drained soils [44].

Morphological characteristics of MC

MC is herbaceous, tendril-bearing vine that grows up to 5 m bearing simple and alternate leaves 4–12 cm across, along with 3–7 cm deeply separated lobes having yellow male and female flowers. Usually flowering occurs during the months of June to July and fruiting during September to November in the Northern Hemisphere. The fruit is oblong shaped with a distinct warty exterior. The cross sections show hollow interior with a thin layer of flesh covering a central seed cavity contained large, flat seeds, and pith. Fruit is usually consumed when it is green or when it starts turning yellow, whereas at this stage it is crunchy and watery in texture. As fruit progresses to ripen, the rind becomes tough and even bitterer, while the pith becomes sweet and red colored. After full ripening, fruit turns orange and mushy and splits into segments which curl back dramatically to expose seeds covered in bright red pulp [44–45].

MC comes in a variety of shapes and sizes (Table 1). The Chinese variety of MC is in pale green color, usually 20–30 cm long, oblong in shape with bluntly tapering ends and with a gently undulating, warty surface, whereas the Indian variety has a narrower shape with pointed ends and a surface covered with jagged, triangular “teeth” and ridges. Indian MC is classified into two botanical varieties based on fruit size, shape, color, and surface texture. First variety is *M. charantia* var. *charantia* possessing large fusiform of fruits (not taper at both ends) and having several triangular tubercles appearing like a “Crocodile’s back”. The second variety is *M. charantia* var. *muricato* (Wild), with small and round fruits with tubercles, more or less tapering at each end [46]. Both varieties are widely cultivated throughout tropical and subtropical regions of India. Yang and Walters [38] have classified MC into three horticultural groups or types, as described in Table 1.

MC is a monoecious, scarcely to densely pubescent, slender climbing annual plant growing about 2–4 m height. The stems are round shaped, 12–15 cm long with internodes on 5–6 cm and tendrils are delicate in nature. The leaves are about 2.5–8 cm × 4–10 cm in size, reniform to orbicular or suborbicular in outline, deep and palmately 5–9 lobed, cordate at base, acute or acuminate at apex, lobes ovate or obovate, narrowed at base, sinuate to undulate margins, mucronate, petioles 1.5–5 cm long. The plant bears male and female flowers. Male flower stalks are slender with bract midway or toward the base; peduncle is 2–5 cm long, possess green colored reniform bract, diameter is 5–11 mm, pedicel is 2–6 cm long, receptacle-tube cup shape is 2 – 4 mm long and 2–3 men wide, sepals are pale green colored and ovate-elliptic shaped with a size of 4–6 mm × 2–3 mm, petals are obovate (10–20 mm × 7–15 mm), mucronate at apex, filaments are 1.5–2 mm long and inserted in the throat of the receptacle tube. Female flower peduncle is 1–6 cm long, bract is 1–9 mm diameter, pedicel is 1–8 cm long, and sepals are narrow, oblong and lanceolate in shape having size of 2–5 mm long. The petals are smaller (7–10 mm long) than or equal to that in males. Female flowers possess narrowly rostrate fusiform ovary (5–11 mm × 2–3 mm) with a style is of two rare long. Fruits (3–20 cm × 2–5 cm) are pendulous having 2–8 cm long stalk, discoid, ovoid, ellipsoid to oblong or blocky shape often narrowed at the ends (Fig. 1).

The fruits are white or green in color and possess orange color at maturity. The fruits have soft tuberculate with 8–10 broken or continuous ridges and – splitting from base in three irregular valves. The seeds are 5–30 in number, having a squarish rectangular shape ends subtridentete. The faces of seeds (5–9 × 3–6 rare) are compressed, sculptured with grooved margins and possess brown or black testa [38, 44–45].

Nutritional value of MC

The nutritional analysis has revealed that MC fruits are a rich source of carbohydrates, proteins, fibers, vitamins, and minerals. MC possesses the highest nutritive value among cucurbits [35, 43]. The vitamin C content of Chinese MC varies significantly (440–780 $mg \cdot kg^{-1}$ edible portion), while variation inin nutrient contents has been observed in MC including carbohydrates, proteins, zinc, iron, calcium, magnesium, phosphorous, and ascorbic acid [47]. The crude protein content of MC fruits (11.4–20.9 $g \cdot kg^{-1}$) is higher than that of tomato and cucumber [48]. The pulp around the seeds of the mature ripe fruit is a rich source of the carotenoid lycopene [49].

Chemical constituents of MC

MC is a rich source of phytochemicals; there are several studies reporting numerous chemical constituents isolated and purified from the plant and its parts by using extraction and chromatographic techniques. Some of them have shown biological activity; hence MC is an important medicinal plant to explore. The major chemical constituents are cucurbitane type triterpenoids, cucurbitane type triterpene glycoside, phenolic acids, flavonoids, essential oils, fatty acids, amino acids, sterols and saponins constituents and some proteins. In the following sections, we are summarizing some of the important bioactive constituents of MC.

Cucurbitane type triterpenoids

Cucurbitane type triterpenoids are the major class of compounds belonging to bitter melon chemical constituents (Fig. 2). Several cucurbitane type triterpenoids possess a wide variety of biological activities, including anti-cancer activity. (19*R*, 23*E*)-5*β*, 19-epoxy-19, 25-dimethoxy-cucurbita-6, 23-dien-3*β*-ol (**1**) and (19*R*, 23*E*)-5*β*, 19-epoxy-19-methoxy-cucurbita-6, 23, 25-trien-3*β*-ol (**2**) show moderate inhibitory effects against activation of NOR 1 which is a nitrogen oxide (NO) donor as well as inhibitory effects in both 7, 12-dimethylbenz-[*α*]-anthracene (DMBA) and peroxynitrite (ONOO-; PN)-induced mouse skin carcinogenesis test [50–51]. (19*R*, 23*E*)-5*β*, 19-epoxy-19-methoxy-cucurbita-6, 23-diene- 3b, 25-diol (**3**) shows cytotoxic activity against HL60 cell line [50, 52]. (23*E*)-5*β*, 19-epoxycucurbita-6, 23, 25-triene-3*β*-ol (**4**) exerts weak cytotoxic activity against MCF-7 (IC_{50} 41.74 $\mu mol \cdot L^{-1}$) and HL-60 (IC_{50} 99.89 $\mu mol \cdot L^{-1}$) cell lines [53]. (23*E*)-3*β*, 25-dihydroxy-7*β*-methoxycucurbita-5, 23-dien-19-al (**5**) and Karavilagenin D (**6**) show inhibitory effects on 12-*O*- tetradecanoylphorbol-13-acetate (TPA)-induced Epstein-Barr virus early antigen (EBV-EA) activation induced with in Raji cells as well as inhibitory activity on skin-tumor promotion in mouse skin carcinogenesis-induced by DMBA as initiator, and with TPA as a promoter [52], while the compound (23*E*)-3*β*,7*β*-dihydroxy-25-methoxy-cucurbita-5,23-dien-19al (**7**) also shows inhibitory activity against EBV-EA

activation induced by TPA as well as cytotoxic activity against HL60 (IC_{50} 1.7 ± 0.5 μmol·L^{-1}), CRL1579 (IC_{50} 17.2 ± 2.5 μmol·L^{-1}), A549 (IC_{50} 10.8 ± 1.3 μmol·L^{-1}), SK-BR-3 (IC_{50} 7.1 ± 1.2 μmol·L^{-1}), and AZ521 (IC_{50} 26.1 ± 2.5 μmol·L^{-1}) cell lines [52]. (23*S**)-3*β*-hydroxy-7*β*, 23-dimethoxy-cucurbita- 5, 24-dien-19-al (**8**) and (23R*)-23-*O*-methylmomordicine IV (**9**) also show cytotoxic activity against HL60 cell line with IC_{50} values being 6.2 ± 0.7 μmol·L^{-1} and 7.6 ± 0.5 μmol·L^{-1}, respectively [52]. 25, 26, 27-trinorcucurbit-5-ene-3, 7, 23-trione (**10**) and 3, 7-dioxo-23, 24, 25, 26, 27-penta-norcucurbit-5-en-22-oic acid (**11**) have cytoprotective effects in *tert*-butyl hydroperoxide (*t*-BHP)-induced hepatotoxicity of HepG2 cells [54]. Harinantenaina *et al*. have shown the blood glucose lowering effects of 3*β*, 7*β*, 25-trihydroxycucurbita-5, 23(*E*)-dien-19-al (**12**) and 5*β*, 19-epoxy-3*β*, 25-dihydroxycuc- urbita-6, 23(*E*)-diene (**13**) [55]. 3*β*-hydroxy-cucurbita-5(10), 6, 22(*E*), 24-tetraen-19-al (**14**) and 5*β*, 19-epoxycucurbita-6, 22(*E*), 24-triene-3*β*, 19-diol (**15**) have antagonizing effects of the transactivation of 17*β*-estradiol (E2) via both estrogen receptor (ER)-*α* and *β* receptors [56]. Weng *et al*. have shown that 3*β*, 7*β*-dihydroxy-25-methoxycucurbita-5, 23-diene-19-al induces apoptotic death in breast cancer cells via activation of PPAR-*γ* and also suppresses cyclin D1, CDK6, Bcl-2, XIAP, cyclooxygenase-2, NF-*κ*B, and ER-*α* expression [57]. Cheng *et al*. have evaluated the anti-inflammatory activities of 5*β*, 19-epoxy-25-methoxycucurbita-6, 23-diene-3*β*, 19-diol (**16**, EMCD) against TNF-*α*-induced inflammation via AMPK in FL83B cells. EMCD inhibits TNF-*α*-induced expression of iNOS, NF-*κ*B, protein-tyrosine phosphatase-1B, TNF-*α* and interleukin-1*β* [58]. Kuguacin C and E have been evaluated for inhibitory effects against HIV replication in C8166 cells, exhibiting moderate inhibitory activity with EC_{50} value being 8.45 and 25.62 μh·mL^{-1} respectively [59]. Kuguacin F–S also exhibit weak anti-HIV-1 activities *in vitro* [60]. Pitchakarn *et al*. have shown that Kuguacin J (**17**) exerts growth inhibitory activities against PC-3 cells with IC_{50} value of 25 μmol·L^{-1}. Kuguacin J causesG1-phase arrest in cell cycle and induces apoptosis in PC-3 cells. It also decreases cyclin D1 and E levels, and inhibits cyclin-dependent kinases (Cdk2 and Cdk4). Kuguacin J reduces survivin levels in PC3 cells and produces anti-invasive effects by inhibiting invasion and migration. It inhibits the secretion of active forms of MMP-2 and -9 as well as uPA in PC3 cells [61]. Some other cucurbitane type triterpenoids like Karavilagenin A–F [52, 62–63], Kuguacin A–S [59–61], Octanorcucurbitacin A–D [64] have been isolated and structurally characterized from MC.

Cucurbitane type triterpene glycoside

Numerous cucurbitane types of triterpene glycosides have been isolated from MC (Fig. 3) and evaluated for biological activities. Charantagenins A–E are isolated from MC and Charantagenin D (**18**) (IC_{50} 1.07, 1.08 and 14.01 μmol·L^{-1}/lit respectively) and Charantagenin E (**19**) (IC_{50} 3.82, 67.32 and > 100 μmol·L^{-1}/lit respectively) have been shown to exhibit anti-proliferative activity against A549, U87 and Hep3B cell lines [65]. Goyaglycosides a–h are identified from MC and Goyaglycoside-b (**20**) and -d (**21**) are cytotoxic to MCF-7 (IC_{50} 12.46 ± 0.21 and 10.80 ± 0.85 μg·mL^{-1}, respectively), Doay (IC_{50} 12.73 ± 0.84 and 10.12 ± 0.41 μg·mL^{-1}, respectively), HEp-2 (IC_{50} 15.64 ± 1.60 and 13.76 ± 0.32 μg·mL^{-1}, respectively) and WiDr (IC_{50} 14.64 ± 1.61 and and 17.02 ± 0.72 μg·mL^{-1}, respectively) cells [66–67]. Kuguaglycosides A–H [68] are also isolated from MC and Kuguaglycoside C (**22**) exerts cytotoxic activity against IMR-32 cells with IC_{50} value being

12.6 μmol·L^{-1} and also decreases survivin expression and induces cleaved PARP, as well as enhances the expression and cleavage of apoptosis- inducing factor (AIF) [69]. Hsiao *et al.* have studied the anti-proliferative effects of Kuguaoside A–D (**23–26**) against human cancer MCF-7, WiDr, HEp-2, and Doay cells. Kuguaoside A produces potent anti-proliferative effects with IC_{50} values being 12.60 ± 0.69, 19.37 ± 1.73, 15.89 ± 1.39, and 17.42 ± 0.79 μg·mL^{-1}, respectively [66]. Momordicoside A–E, F, F1, G, I, and K–W [67, 70–73] have been isolated and purified from MC. Momordicoside F1, F2, I, K, U (**27–31**) exert anti-proliferative effects against human cancer MCF-7, WiDr, HEp-2, and Doay cells [66]. Taiwacin A and B are another glycosides from MC that possess anti-oxidant activity [74]. Charantoside A–G [66, 70, 75] have been isolated and structurally characterized from MC. Karaviloside I–XIII [62, 76] have been isolated and structurally characterized from MC. Akihisa *et al.* have isolated and structurally characterized Charantoside I–VIII from the methanolic extract of the fruits of Japanese MC [51]. Momordicine I – VIII [54, 63, 77–79] are also found in MC.

Phenolic acid and flavonoids

MC is rich in phenolic acids and flavonoids (Fig. 4). It contains quinic acid (**32**), protocatechuic acid (**33**), ascorbic acid (**34**), gallic acid (**35**), chlorogenic acid (**36**), catechin (**37**), syringic acid (**38**), caffeic acid (**39**), rutin (**40**), 4-coumaric acid (**41**), myricetin (**42**), gentisic acid (**43**), vanillic acid (**44**), o-coumaric acid (**45**), t-cinnamic acid (**46**), *p*-methoxy-benzoic acid (**47**), which have been found to exert anti-oxidant activity [55, 80–81], whereas Hsu *et al.* have shown that phytol (**48**) and lutein (**49**) suppress pro- inflammatory cytokine and matrix metalloproteinase (MMP)-9 levels in P. acnes-stimulated THP-1 cells [82].

Essential oils

Braca *et al.* have isolated several anti-bacterial and antifungal essential oil compounds from MC, including α-pinene (**50**), β-pinene (**51**), octanal (**52**), 1, 8-cineole (**53**), β-phellandrene (**54**), *C*-dihydrocarveol (**55**) and trans- dihydrocarveol (**56**), carvone (**57**), (E)-anethole (**58**), safrole (**59**), methyl-eugenol (**60**), germacrene D (**61**), β-selinene (**62**), α-selinene (**63**), myristicin (**64**), δ-cadinene (**65**), trans- nerolidol (**66**), spathulenol (**66**), cedrol (**67**), β-bisabolol (**68**), and apiol (**69**) (Fig. 5) [83].

Saponins, fatty acids, and amino acids

MC contains numerous saponins, fatty acids, and amino acids (Fig. 6). Ahmad *et al.* have tested α-glucosidase and α-amylase inhibitory activity of fatty acid components from MC, including C10–0 (**71**, Capric acid), C12–0 (**72**, Lauricacid), C16–0 (**73,** Palmitic acid), C18–0 (**74,** Stearic acid), C18–1 (**75,** Oleic acid), C18–2 (**76,** Linoleic acid), and C20–0 (**77,** Arachidic acid) [84]. 9-cis, 11-trans, 13-trans- conjugated linolenic acid (**78**, 9*C*, 11*T*, 13*T*-CLN), or α-eleostearic acid, is one of the potential fatty acids from MC. It possesses anti-proliferative and apoptosis-inducing properties in colon cancer Caco-2 cells by decreasing bcl-2 expression, and up-regulating GADD45 and p53, PPAR-γ mRNA and protein levels [85]. MC contains amino acids, Polypeptide K, aspartic acid, glutamic acid, serine, glycine, histidine, arginine, threonine, alanine, proline, tyrosine, valine, methionine, cystine,

isoleucine, leucine, phenylalanine, lysine, and tryptophan [84]. Murakami *et al.* have isolated saponins from MC, namely Goyasaponins I–III [67].

Proteins

Several proteins have been isolated and characterized from MC and evaluated for their biological activity. α-Momorcharin is one of such proteins that inhibit incorporation of [3*H*] thymidine, [3*H*] leucine, and [3*H*] uridine into P388 (mouse monocyte-macrophage), JAR (human placental choriocarcinoma), J774 (Balb/c macrophage), and sarcoma S180 cell lines as well as increases the tumoricidal effect of mouse macrophages on mouse mastocytomal (P815) cells [86]. Meng *et al.* have developed PEGylated derivatives of α-momocharin and momordica anti-HIV protein (MAP30) which exerts about 60%–70% anti-proliferative in JAR choriocarcinoma cells and anti-viral activities as well as reduces 50%–70% immunogenicity when compared with their unmodified counterparts [87]. Manoharan *et al.* have shown that α- and β-momocharin treatment reduces the cell viability (increases in cell death) of 1321N1, Gos-3, U87-MG, Sk-Mel, Corl-23 and Weri Rb-1 cancer cell lines as compared to healthy L6 muscle cell line and untreated glioma cells [88]. Fang *et al.* have purified and characterized a 14-kDa Ribonucleases (RNase MC2) from the seeds of MC. RNase MC2 shows a potent RNA-cleavage activity against baker's yeast tRNA, tumor cell rRNA, and specificity for uridine. RNase MC2 exhibits both cytostatic and cytotoxic activities against MCF-7 breast cancer cells, causing nuclear damage (chromatin condensation, karyorrhexis, and DNA fragmentation) and resulting in early or late apoptosis. RNase MC2 is found to induce differential activation of MAPKs (p38, JNK and ERK) and Akt. RNase MC2 also activates caspases-7, -8, -9, and enhances the production of Bak as well as cleaved PARP, contributing to the apoptotic response [89]. Fan *et al.* have shown that MAP30 suppresses proliferation of LoVo cells, induces apoptosis, upregulates Bax, and downregulates bcl-2 expression [90]. Marmorin inhibits the proliferation of hepatoma Hep G2 cells and breast cancer MCF-7 cells [91].

Biological activities of MC

Antioxidant activity—Lu and colleagues have reported the protective effects of the ethanolic extracts of MC fruit against alcohol-induced liver injury in C57BL/6 mice. These protective effects are mediated by increase in antioxidant enzymes (GSH, GPx, GRd, CAT and SOD), reduction in lipid peroxidation (MDA) and lowering expression of pro-inflammatory cytokines (TNF-α, IL-1β and IL-6) in the liver [29]. Similarly, Thenmozhi & Subramanian have shown that MC extract provides protection by reversing the oxidant-anti-oxidant imbalance in ammonium chloride-induced hyperammonemic rats suggesting the involvement of anti-oxidant properties of MC extract in biological activity [92]. Wei and coworkers have shown that the free radical scavenging activity of MC extract is notably enhanced after the heat drying process. The extract is found to manifest a corresponding higher proliferation activity on NIT-1β-cells [15]. Liu *et al.* have synthesized sulfated derivatives of polysaccharide from MC with different degree of sulfation. MC polysaccharide with high degree of sulfation exhibits superior antioxidant activities as compared to the native polysaccharide from MC *in vitro*, indicating the advantage of sulfated modification for enhancing anti-oxidant activities [63]. Lin *et al.* have isolated a new cucurbitane-type triterpene glycosides taiwacin A and B from the stems and fruits of MC.

These compounds exhibit ABTS radical cation scavenging activity with IC_{50} values being 119.1 ± 4.3, and 204.5 ± 1.2 μmol·L^{-1}, respectively [93]. Kumar *et al.* have evaluated the anti-oxidant activity of the total aqueous extract (TAE) and total phenolic extract (TPE) of MC fruits by radical-scavenging methods and cytoprotective effects on hydrogen peroxide (H_2O_2)- and hypoxanthin-xanthin oxidase (HX-XO)-induced damage to rat cardiac fibroblasts (RCFs), NIH 3T3, and keratinocyte (A431). At 200 and 300 μg·mL^{-1} TPE, cytoprotection is dose-dependent against oxidants. Extracts have no effect on HX-XO toxicity at 50 μg·mL^{-1}, while pre-treatment with both the extracts does not show any cytoprotection [94]. Dhar *et al.* have examined the *in vitro* antioxid- ant activity of conjugated octadecatrienoic fatty acid (9-cis, 11-trans, 13-trans-18 : 3), α-eleostearic acid present in karela seed oil. A significant increase in respective peroxidation levels has been observed in diabetic control blood than the non-diabetic control blood. α-Eleostearic acid has decreased lipid peroxidation level against control samples in a dose- dependent manner [95].

Ching *et al.* have examined the effect of maternal high-fructose intake and whether metabolic control in the offspring could benefit from supplementing MC to the maternal diet. Their results indicate that supplementing MC to dams could offset the adverse effects of maternal high-fructose intake on lipid metabolism and anti-oxidant status in adult offspring [96]. Tripathi & Chandra have evaluated the anti-hyperglycemic and the anti-oxidative potential of aqueous extracts of MC pulp and found improved fasting blood glucose levels in rats. MC treatment improves the anti-oxidant activities (reduced glutathione content (GSH), superoxide dismutase (SOD), catalase (CAT), and glutathione-s-transferase (GST)) in kidney, heart, and liver tissues, and thiobarbituric acid-reactive substance (TBARS) levels, suggesting its protective role against diabetes-induced damage to vital organs [97]. These authors have investigated the effect of MC on anti-oxidant status and lipid peroxidation in heart tissue of normal and alloxan-induced diabetic rats and found that it reduces the elevated levels of fasting blood glucose with a decrease in lipid peroxidation and the increase in the activities of anti-oxidant enzymes in heart tissue of diabetic rats [98]. Chaturvedi & George have evaluated the effects of MC on glucose concentration, lipid profiles, and oxidative stress level in alloxan-induced diabetic rats receiving a chronic sucrose load. Their results show that MC maintains the normal glucose levels, decreases triglyceride as well as low-density lipoprotein levels, and enhances high-density lipoprotein levels. MC also improves the anti-oxidant enzyme status by reducing TBARS levels and normalizing reduced glutathione levels [99]. Teoh *et al.* have studied the protective effect of the MC extract on the kidneys of streptozotocin- induced diabetic Sprague-Dawley rats. The treatment with the MC extract (50 mg·kg^{-1} body weight, p.o.) reverses streptozo-tocin-induced hypercellularity and edema of the proximal tubules, thickening of the basement membrane of the Bowman's capsule, necrosis and hyaline deposits in the kidney. The anti-oxidant property of MC extract prevents the oxidative damage involved in the diabetic kidney, hence providing nephroprotective activity against diabetes [100]. The liver of the diabetic rats shows the involvement of the hepatocytes in the process of inflammation. MC treatment shows features of healing in the liver damage in the diabetic animals and found useful in reversing the changes in the liver in diabetes mellitus [101]. Xiang *et al.* have investigated the cellular reparative effects of MC boiling water extract (MCE) on the HIT-T15 Hamster pancreatic β-cells. The high molecular weight fraction of MCE (MW > 3 kDa)

shows the better effects in repairing alloxan damaged cells (cell proliferation rate = 32.1%) than that of the low molecular weight fraction (MW ≤ 3 kDa), while the latter shows the higher activity on enhancing insulin secretion of normal or damaged cells [102]. Sathishsekar & Subramanian have investigated the anti-oxidant activities of the aqueous extract of seeds of a country and hybrid variety of MC (MCSEt1 and MCSEt2) in streptozotocin-induced diabetic rats. The extract exerts rapid protective effects against lipid peroxidation by scavenging free radicals, thereby reducing the risk of diabetic complications. The effect of MCSEt1 is better than that of MCSEt2 [103].

Kavitha *et al.* have evaluated the anti-stress activity of ethanolic extract of MC fruits at a dose of 200 and 400 $mg \cdot kg^{-1}$ on stress-induced changes in Wister albino rats and *in vitro* lipid peroxidation in rat brain. Pretreatment with MC significantly reverts acute stress (immobilization for 150 min once only)-induced changes in levels of brain monoamine (5-hydroxytryptamine, norepinephrine, epinephrine, and dopamine) and the level of plasma corticosterone. This study has shown that the anti-stress activity of MC might be due to its anti-oxidant potential [104]. Nerurkar *et al.* have investigated the neuroprotective effects of MC on a high-fat diet (HFD)-associated blood-brain barrier (BBB) disruption, stress and neuroinflammatory cytokines in C57BL/6 female mice. MC ameliorates HFD-associated changes in BBB permeability. HFD-induced activation of glial cells and expression of neuroinflammatory markers including NF-κB1, IL-22, IL-16, and IL-17R are normalized in the brains of mice treated with MC. HFD-induced brain oxidative stress is decreased by MC treatment with a reduction in FoxO, normalization of Sirt1 protein expression and upregulation of Sirt3 mRNA expression. The plasma anti-oxidant enzymes and pro-inflammatory cytokines are also normalized in HFD-fed mice with MC as compared to HFD-fed mice. The investigators conclude that MC offers a therapeutic strategy to improve obesity-associated peripheral inflammation and neuroinflammation [105]. Malik *et al.* have evaluated the neuroprotective effect of lyophilized MC fruit juice against global cerebral ischemia and reperfusion-induced neuronal injury in diabetic mice. The treatment with lyophilized MC juice (200–800 $mg \cdot kg^{-1}$, p.o., o.d.) exerts dose-dependent attenuation of the cerebral oxidative stress and damage, as well as neurological deficits. It also possesses anti-hyperglycemic activity in diabetic mice. The study suggests that MC has potent neuroprotective activity against global cerebral ischemia-reperfusion-induced neuronal injury and consequent neurological deficits in diabetic mice [30]. Chaturvedi has studied the protective effects of MC extract on lipid peroxidation-induced by immobilization stress in rats. The results show that MC inhibits stress-induced lipid peroxidation by increasing the levels of reduced glutathione and activities of catalase in rats. Thus, this plant provides protection by strengthening the anti-oxidants like reduced glutathione and catalase [106]. Padmashree *et al.* have evaluated the anti-oxygenic activity of MC pulp and seed powders along with their different solvent extracts. MC pulp and seed powders exhibit stronger anti-oxygenic activity than other solvent extracts, while MC pulp and its extracts show slightly higher anti-oxygenic activity than MC seed and its extracts [107]. De *et al.* have found that fresh juices of MC and tomato could also protect from DMBA-induced DNA damage, but not as effectively as the single agents [108].

Anti-inflammatory activity—Xu *et al.* have studied the effects of MC on mitochondrial function during the development of obesity-associated fatty liver in C57BL/6 mice fed with HFD supplemented with freeze-dried MC powder through daily gavage at doses of 0.5 (HFD + 0.5 BG) and 5 (HFD + 5 BG) $g \cdot kg^{-1}$, respectively. After 16 week, the mice in the HFD + 5 BG group showed less body and tissue weight gain and less hyperglycemia and hyperlipidemia compared with those in the HFD group. In HFD + 0.5 BG and HFD + 5 BG groups, serum interleukin-6 concentration was lower than that in the HFD group. The serum C-reactive protein concentration was lower in the HFD + 5 BG group compared with the HFD group. The study suggested that MC prevents inflammation and oxidative stress, modulates mitochondrial activity, and inhibits lipid accumulation during the development of fatty liver [109]. Bao *et al.* have studied the effects of MC treatment for 12 weeks in C57BL/6 mice fed with HFD. The MC containing diets ameliorate HFD-induced obesity and insulin resistance as well as reduce macrophage infiltration into epididymal adipose tissues (EAT) and brown adipose tissues (BAT). MC lowers mast cell recruitments in EAT, and reduces pro-inflammatory cytokine monocyte chemotactic protein-1 (MCP-1) expression in EAT and BAT along with IL-6 and TNF-α expression in EAT. The MC containing diets also normalize serum levels of the cytokines suggesting the role of MC in reducing inflammation, obesity and insulin resistance in obese rats [110]. Hsieh *et al.* have studied the effects of administration of MC seed oil for 11 weeks on white adipose tissue (WAT) in mice. The results show that the WAT in mice subjected to long-term high dose MC seed oil administration is considered by decreased caveolae formation, enhanced ROS insult, tissue remodeling/repair, uncoupling of mitochondria, and stabilization of the actin cytoskeleton. It is suggested that the anti-adiposity effect of MC seed oil is associated with WAT delipidation, inflammation, and browning [111].

Jain and colleagues have investigated the effect of MC in the tibial and sural nerve transection (TST)-induced neuropathic pain in rats. TST leads to development of mechanical and heat hyperalgesia as well as cold allodynia, dynamic mechanical allodynia, and functional deficit in walking along with rise in the levels of TBARS and TNF-α. Treatments of MC (200, 400, and 800 $mg \cdot kg^{-1}$) attenuate TST-induced behavioral and biochemical changes. It is suggested that PPAR-γ agonistic activity, anti-oxidative potential and anti-inflammatory activity are critical for anti-nociceptive effect of MC in ameliorating neuropathic pain [112]. Hsu *et al.* have evaluated the inhibitory effect of MC on *Propionibacterium acnes*-induced inflammation. The results show that ethyl acetate (EA) extract of MC fruit *in vitro* potently suppresses pro-inflammatory cytokine and matrix metalloproteinase (MMP)-9 levels in *P. acnes*-stimulated THP-1 cells. The treatment (intradermal injection) with EA extract of MC to mice reduces *P. acnes*-induced granulomatous inflammation and ear swelling. It is also found that both saponifiable (S) and nonsaponifiable (NS) fractions of EA extract of MC suppress pro-inflammatory cytokine and MMP-9 levels [82]. Cheng *et al.* have investigated the effects of a purified triterpene from wild variant WB24 of MC viz. 5β, 19-epoxy- 25-methoxy-cucurbita-6, 23-diene-3β, 19-diol (EMCD), against TNF-α-induced inflammation via AMP-activated protein kinase (AMPK) in FL83B cells. EMCD suppresses the TNF-α-induced expression of inflammatory markers, including inducible nitric oxide synthase (iNOS), p65 subunit of NF-κB, TNF-α, protein-tyrosine phosphatase-1B, and IL-1β. EMCD possesses better anti-inflammatory

activity than epigallocatechin-3-gallate (EGCG) when tested simultaneously. The mechanistic study suggests that EMCD suppresses the activation of the Iκ-B kinase (IKK) complex and the NF-κB pathway, whereas the effect is likely to be through AMPK independent pathway [58]. Lii *et al.* have investigated the anti-inflammatory effect of MC on lipopolysaccharide (LPS)-stimulated RAW264.7 macrophages. The ethanol extract shows the greatest reduction of LPS-induced nitric oxide (NO) and prostaglandin E2 (PGE_2) production and iNOS and IL-1β expression. It has been shown that both the hot water and the ethanol extracts of MC inhibit NF-κB activation [113]. Kobori *et al.* have shown that the butanol-soluble fraction of the MC placenta extract reduces LPS-induced TNF-α production in RAW 264.7 cells. The MC butanol soluble fraction has decreased the expression of LPS-induced inflammatory genes, including those for IL-1α, IL-1β, TNF-α, G1p2 and Ccl5. The butanol soluble fraction also reduced NF-κB DNA binding activity and phosphorylation of p38, JNK, ERK as well as MAPKs [114]. Ou *et al.* have purified a novel *Momordica charantia* peroxidase (MCP) from fruits. MCP catalyzes the oxidation of ferulic acid (FA) to dehydrodimer (FA-2). FA-2 inhibits the phytohemagglutinin (PHA) and Con A-induced release of pro-inflammatory factors such as nitric acid (NO), TNF-α, and proliferation of spleen cells, while it promotes a greater DNA fragmentation of spleen cells than other complexes. These results suggest that MCP as a useful tool enzyme transforms some complexes such as FA to more active derivatives like FA-2 that possesses anti-inflammatory activity mediated by interfering with immune response in the process of inflammation [115].

Anti-cancer activities

Breast cancer: Weng *et al.* have evaluated 3-β, 7β-dihydroxy-25- methoxycucurbita-5, 23-diene-19-al (DMC), a cucurbitane- type triterpene isolated from wild MC, against breast cancer cells. DMC is found to activate PPAR-γ and suppress the expression of PPAR-γ targeted signaling effectors, including CDK6, cyclin D1, bcl-2, cyclooxygenase-2, NF-κB, XIAP, and estrogen receptor-α and induce endoplasmic reticulum stress, as shown by the induction of GADD153 and GRP78 expression. DMC inhibits mTOR-p70S6K signaling through downregulation of Akt and activation of AMPK. The property of DMC to activate AMPK in liver kinase (LK) B1-deficient MDA-MB-231 cells suggests that this activation is independent of LKB1-regulated cellular metabolic status. DMC induces a cyto-protective autophagy presumably through mTOR inhibition, which could be overcome by the cotreatment with the autophagy inhibitor chloroquine. Their results suggest the ability of DMC to modulate multiple PPAR-γ targeted signaling pathways provides a mechanistic basis to account for the anti-tumor activity of MC [116]. Fang *et al.* have purified and characterized a 14-kDa Ribonucleases (RNase MC2) from the seeds of MC. RNase MC2 shows a potent RNA-cleavage activity against baker's yeast tRNA, tumor cell rRNA, and specificity for uridine. RNase MC2 exhibits both cytostatic and cytotoxic activities against MCF-7 breast cancer cells, causing nuclear damage (chromatin condensation, karyorrhexis, and DNA fragmentation), resulting in early or late apoptosis. RNase MC2 has been found to induce differential activation of MAPKs (p38, JNK and ERK) and Akt. RNase MC2 also activates caspase-7, -8, and -9, enhanced the production of Bak as well as cleaved PARP, contributing to the apoptotic response [89]. Ray *et al.* have evaluated the anti-cancer activity of MC extract in MCF-7 and MDA-MB-231 human breast cancer cells and primary human mammary epithelial cells. MC treatment results in reduced cell proliferation and apoptotic

cell death in breast cancer cells. Apoptosis of breast cancer cells is accompanied by increased PARP cleavage and caspase activation. MC treatment of breast cancer cells also inhibits survivin and claspin expression. MCF-7 cells treated with MC are accumulated during the G2-M phase of the cell cycle. Further studies have revealed that MC treatment enhances p21, p53, and pChk1/2 and inhibits cyclin B1 as well as cyclin D1 expression, indicating an additional mechanism in the cell cycle regulation [117].

Eleostearic acid (α-ESA) is a conjugated linolenic acid that is present to the extent of 60% of MC seed oil. Grossmann *et al.* have studied the effects of α-ESA on both estrogen receptor (ER)-negative MDA-MB-231 (MDA-wt) and ER-positive MDA-ER-α-7 human breast cancer cells. It is found that alpha-ESA inhibits proliferation of both MDA-wt and MDA-ER-α-7 cells, while conjugated linoleic acid possesses weak anti-proliferative activity at 20 to 80 μmol·L^{-1}. α-ESA (40 μmol·L^{-1}) treatment leads to apoptosis (70% to 90%) for both cell lines, whereas conjugated linoleic acid (40 μmol·L^{-1}) results in only 5% to 10% apoptosis, similar to results for control untreated cells. Addition of α-ESA leads to loss of mitochondrial membrane potential and translocation of apoptosis-inducing factor as well as endonuclease G from the mitochondria to the nucleus. α-ESA causes a G2-M block in the cell cycle. These results suggest that α-ESA can block breast cancer cell proliferation and induce apoptosis through a mechanism that may be oxidation dependent [118]. Nagasawa *et al.* have studied the effects of chronic treatment with hot water MC extract on spontaneous mammary tumorigenesis in SHN virgin mice. The free access to extract of MC (0.5%) in drinking water to mice reduces the development of mammary tumors. MC extract inhibits uterine adenomyosis with a common pathological background to mammary tumors. There are no adverse effects of chronic treatment with these agents as estimated from food and water intake body weight, and various plasma component levels as well as external appearance [119]. Lee-Huang *et al.* have investigated the efficacy of MAP30 on estrogen-independent and metastatic human breast tumor MDA-MB-231 *in vitro* and *in vivo*. MAP30 treatment to MDA-MB-231 breast cancer cells results in inhibition of proliferation and reduction of HER2 gene expression *in vitro*. MAP30 treatment of the MDA-MB-231 human breast cancer bearing SCID mice at a dose of 10 μg/injection EOD for 10 injections results in significant increase in survival, with 20%–25% of the mice remaining tumor free for 96 days indicated efficiency against human breast cancer MDA-MB-231 *in vitro* and *in vivo* [120]. α-momorcharin exerts growth inhibitory activities against MDA-MB-231, MCF-7 and MDA-MB-453 with IC_{50} values being 15.07, 33.66 and 42.94 μg·mL^{-1}, respectively. It also induces apoptosis by enhancing caspase-3 activities, and G0/G1 or G2/M arrest. α-Momorcharin exerts anti-tumor activity in MDA-MB-231 and MCF-7 xenograft model in nude mice, but authors also conclude that α-momorcharin has narrow therapeutic window *in vivo* [121].

Colon cancer: In a recent study from our lab, Kwatra *et al.* have evaluated the efficacy of methanolic extracts of MC on colon cancer stem and progenitor cells. Both whole fruit and skin extracts show significant inhibition of cell proliferation and colony formation, with whole fruit possesses higher efficacy. The cells are arrested at the S-phase of cell cycle. The whole fruit induces the cleavage of LC3B, but not caspase 3/7, suggesting that the cells are undergoing autophagy, not apoptosis. The autophagy is further confirmed by Western

blotting analysis, showing the reduction of Bcl-2 and increase in beclin-1, Atg-7 and -12 upon whole fruit treatment along with reduced cellular ATP levels coupled with activation of AMPK, while the exogenous additions of ATP leads to revival of cell proliferation. The treatment with whole MC fruit extract exerts a dose-dependent reduction in the number and size of colonospheres. The extracts also decrease the expression of Doublecortin-like kinase 1 (DCLK1) and Leucine-rich repeat-containing G-protein coupled receptor 5 (*LGR5*) [4]. In addition, further study from our lab has determined effects of MC extract on anti-cancer activity and bioavailability of doxorubicin (DOX) in colon cancer cells. The pretreatment of MC extract enhances the effect of DOX on cell proliferation and sensitizes the cells toward DOX. There is both enhancement in drug uptake and reduction in drug efflux. The expressions of multidrug resistance conferring proteins (MDRCP) P-glycoprotein, MRP-2, and BCRP are reduced after MC treatment. MC extract suppresses DOX efflux in MDCK cells overexpressing the three efflux proteins individually, suggesting that MC extract is a potent inhibitor of MDR function. MC extract suppresses *pregnane X receptor* (PXR) promoter activity, thereby suppressing its expression. These results suggest that MC extract can enhance the bioavailability and efficacy of conventional chemotherapy [17].

Li *et al.* have evaluated the methanolic extract of MC (MCME) for cytotoxic activity on four human cancer cell lines, Hone-1, AGS, HCT116, and CL1–0, which show cytotoxic activity towards all cancer cells tested (IC_{50} value 0.25 to 0.35 mg·mL^{-1} at 24 h). MC-induced cell death is found to be time-dependent in these cells by inducing apoptosis and DNA fragmentation. MC treatment activates caspase-3 and enhances the cleavage of downstream DFF45 and PARP, leading to DNA fragmentation and nuclear condensation. After 24 h treatment of MCME, the bcl-2 expression is decreased, while Bax expression is increased, suggesting the involvement of mitochondrial pathway in cell death mechanism [122]. Li *et al.* have identified resistance-like protein P-B from MC by high-speed counter-current chromatography (HSCCC) coupled with a reverse micelle solvent system. Fractions I and III are identified as resistance-like protein P-B and pentatricopeptide repeat- containing protein, respectively, which are found in MC for the first time. The anti-cancer activities of these three proteins are tested in the human gastric cancer cell line SGC-7901. The results show that fraction II possesses anti-cancer activity with an IC_{50} value of 0.116 mg·mL^{-1} for 48 h treatment [123]. Fan *et al.* have cloned and expressed MAP30 and studied its effects on cell proliferation and apoptosis of human colorectal carcinoma LoVo cells. The results show that the proliferation of LoVo cells is suppressed by MAP30 in a time- and dose-dependent manner at a concentration ranging from 0.67 to 4.67 μmol·L^{-1}. The apoptotic nuclei of LoVo cells are induced by MAP30, and the genomic degradation is detected by single-cell gel electrophoresis (comet assay). The treatment increases the transcription and expression of Bax, and downregulates the transcription and expression of Bcl-2 [90]. Yasui *et al.* have investigated the anti-proliferative and apoptosis-inducing effects of free fatty acids prepared from the MC seed oil using colon cancer Caco-2 cells. The expression level of apoptosis suppressor Bcl-2 protein is decreased by the treatment. The GADD45 and p53, which play an important role in apoptosis-inducing pathways, are up-regulated with MC treatment in Caco-2 cells [124]. Deep *et al.* have tested the MC fruit extract against 3, 4-benzo(a)pyrene [B(a)P]-induced forestomach papillomagenesis in Swiss albino mice. MC Extract at concentrations of 2.5% and 5% of standard mice feed is used for the short-term and long-

term studies. A significant decrease in tumor burden is observed in short- and long-term treatment. The total tumor incidence is reduced to 83.33% with 2.5% dose and 90.90% with 5% dose in short term treatment, whereas tumor incidence is decreased to 76.92% with 2.5% dose and 69.23% with 5% dose of MC in long-term treatment [125]. Kohno *et al.* have studied the inhibitory effect of dietary administration of MC in azoxymethane (AOM)-induced colonic neoplasms in male F344 rats. The treatment causes significant reduction in the incidence and the multiplicity of colonic adenocarcinoma. The inhibition is associated with the increased content of CLA (c9, t11–18 : 2) in the lipid composition in colonic mucosa and liver while exhibiting enhanced expression of PPAR-γ protein in the nonlesional colonic mucosa [126]. Kohno *et al.* have also studied the modifying effects of dietary feeding of conjugated linolenic acid (CLN) isolated from the seeds of MC on the development of azoxymethane (AOM)-induced colonic aberrant crypt foci (ACF) in male F344. Dietary administration of CLN causes a significant reduction in the frequency of ACF, lowers the PCNA index and induces apoptosis in ACF. The findings suggest that the possible chemo-preventive activity of CLN in the early phase of colon tumorigenesis is through modulation of cryptal cell proliferation activity and apoptosis [127]. MC contains steroidal saponin known as Charantin (**79**) (Fig. 7) that is endowed with hypoglycemic activity. It is isolated from fruits of MC [128]. The compound is a 1 : 1 mixture of two steroidal saponins namely, β-sitosteryl glucoside ($C_{35}H_{60}O_6$) and 5, 25-stigmasteryl glucoside ($C_{35}H_{58}O_6$) [129]. It is tasteless, crystalline in nature, whitish in color and melts at 266–268 °C. Chemically it is a typical cucurbitane-type triterpenoid [130–131]. Charantin is reported for antidiabetic activity [132–133] and anti-bacterial activity [134]. Our unpublished study has demonstrated that charantin is a potent inhibitor of stem cells that are marked by DCLK1 in colon cancer. Moreover, charantin is a potent inhibitor of colon cancer xenografts grown in athymic nude mice. Therefore, charantin has potent anti-cancer activity.

Pancreatic cancer: Kaur *et al.* have examined the anti-cancer activity of MC juice against pancreatic carcinoma cells in BxPC-3, MiaPaCa-2, AsPC-1 and Capan-2 cells *in vitro* and in MiaPaCa-2 tumor xenograft in nude mice. MC (2%–5%, *V/V*) treatment decreases the cell viability in all pancreatic carcinoma cell lines by inducing apoptosis through caspases activation, altering the expression of Bcl-2 family members and releasing cytochrome-c into the cytosol. MC juice also reduces survivin and X-linked inhibitor of apoptosis protein, and increases the levels of CHOP, p21, and phosphorylated mitogen-activated protein kinases (extracellular signal- regulated kinase 1/2 and p38). MC juice also activates AMPK, which is a biomarker for cellular energy status. *In vivo*, oral administration of lyophilized MC juice (5 mg in 100 μL water per day per mouse) for six weeks inhibits MiaPaCa-2 tumor xenograft growth by 60%, without any noticeable toxicity in nude mice. IHC analyses of xenograft tumors show that treatment of MC juice results in decreased proliferation, apoptosis induction and AMPK activation *in vivo* [135].

Liver cancer: Fang *et al.* have studied the activity MAP30 against human hepatocellular carcinoma HepG2 cells and HepG2- bearing mice. Molecular studies suggest the involvement of caspase-8 regulated extrinsic and caspase-9, regulating intrinsic caspase cascades in MAP30-induced cell apoptosis. Cell cycle study suggests that MAP30 induces S-phase arrest. The MAP30 (2 mg·kg^{-1}, i. p.) is effective in reducing tumor volume as well

as tumor weight in HepG2-bearing nude mice. MAP30 treated tumors show significant necrosis as compared to control, while tumors also have a histological appearance with massive apoptosis, as assessed by the enhancement of activated caspase-3 cells, TUNEL-positive cells as well as cleaved PARP cells [136]. Fang *et al.* have investigated the effects of RNase MC2 on HepG2 cells. It is found that RNase MC2 treatment results in reduction in cell proliferation as well as induction of cell apoptosis *in vitro* and *in vivo*. RNase MC2 treatment also causes cell cycle arrest at the S-phase and apoptosis, associated with the activation of both caspase-8 and caspase-9, regulating apoptotic pathways. RNase MC2 downregulates the expression of Bcl-2 and increases Bak expression. The RNase MC2-induced apoptosis process also involves phosphorylation of ERK and JNK. RNase MC2 treatment suppresses the growth of HepG2 xenograft-bearing nude mice by inducing apoptosis as assessed by increased number of caspase-3 cells and PARP-positive cells, and TUNEL-positive cells in tumor tissues [137]. Zhang *et al.* have studied the anti-cancer effects of MC lectin *in vitro* in HepG2 and PLC/PRF/5 cells and *in vivo*. The treatment causes cell cycle G2/M phase arrest, autophagy, mitochondrial injury, and DNA fragmentation in HepG2 and PLC/PRF/5 cells. It also induces apoptosis mediated by caspase and MAPK pathway activation. MC lectin treatment also reduces growth of HepG2 xenograft tumor in nude mice [138].

Prostate cancer: Ru *et al.* have studied have the efficacy of MC against PC3 and LNCaP human prostate cancer cells. The treatment with MC extract arrests the prostate cancer cells are in the S-phase of the cell cycle and modulate the expression of cyclin D1, cyclin E, and p21. MC treatment also enhances expression of Bax and induces cleavage of PARP. The treatment of MC extract orally, delays the progression to high-grade prostatic intraepithelial neoplasia in TRAMP (transgenic adenocarcinoma of mouse prostate) mice (31%). Prostate tissue from MC extract-fed mice shows about 51% reduction of proliferating cell nuclear antigen expression [139]. Pitchakarn *et al.* have studied the effects of MC leaf extract and Kuguacin J, on androgen-dependent LNCaP human prostate cancer cells, leading to growth inhibition through G1-phase arrest and apoptosis. Kuguacin J treatment reduces the levels of cyclin-dependent kinases (Cdk2 and Cdk4), cyclins (D1 and E), and proliferating cell nuclear antigen, and causes an increase in levels of p21 and p27. The induction of apoptosis is accompanied by caspase and PARP cleavage, attributable to augment of Bax/Bcl-2 and Bad/Bcl-xL expressions and decrease of survivin levels. MC leaf extract and Kuguacin J treatment also decreases the expression of androgen receptor (AR), prostate-specific antigen (PSA), while it induces p53 protein level. The down regulation of p53 by RNA interference indicates that MC leaf extract and Kuguacin J treatment result in growth inhibition, which is partly mediated by p53-dependent cell cycle arrest as well as apoptosis pathways. The treatment of MC leaf extract and Kuguacin J is less toxic to normal prostate cell line PNT1A, suggesting their safety profile [140]. The anti-invasive effects of MC leaf extract on a rat prostate cancer cell line (PLS10) *in vitro* and *in vivo* have been investigated, showing that non-toxic concentrations of the MC leaf extract significantly inhibit the migration and invasion of cells *in vitro*. The results show that MC leaf extract reduces the secretion of MMP-2 and -9 as well as urokinase plasminogen activator (uPA) from PLS10 cells as assessed by zhymographic studies. The MC leaf extract treatment causes a decrease in gene expression of MMP-2 and -9, increase in the mRNA level of TIMP-2, and partial inhibition

of the collagenase type IV activity. In the *in vivo* study, MC leaf extract diet resulted in 100% survival rate in intravenous inoculation of PLS10 to nude mice as compared to 80% in the control mice. Although the treatment did not show any change in the incidence of lung metastasis, there was a slight decrease in the percentage lung area occupied by metastatic lesions [141]. Xiong *et al.* have isolated a protein MCP30 from MC seeds that induces apoptosis in prostatic intraepithelial neoplasia (PIN) and prostate cancer cell lines *in vitro* and suppresses PC-3 growth *in vivo* without affecting normal prostate cells. MCP30 also inhibits histone deacetylase-1 (HDAC-1) activity and promotes acetylation of histone-3 and -4 proteins. MCP30 treatment induces expression of PTEN in PIN and prostate cancer cell lines, resulting in inhibition of Akt phosphorylation. MCP30 treatment also causes the inhibition of Wnt signaling through reduction of nuclear accumulation of β-catenin and reduction in the levels of c-Myc and Cyclin D1 [142].

Skin cancer: Agrawal and Beohar have studied the effects of MC fruit and leaf extract on skin carcinogenesis in Swiss albino mice. The tumor incidence, tumor burden, tumor yield, and cumulative number of papillomas are lower in the mice treated with MC fruit extract or MC leaf extract, compared to control. MC treatment (500 and 1 000 $mg \cdot kg^{-1}$ for 30 days) shows increase in life span of mice and reduces the tumor volume, compared to control group in the melanoma model [143]. Ganguly *et al.* have studied the anti-cancer effects of aqueous extract of fruits of MC in a two-step skin carcinogenesis model in mice. The oral administration of the fruit extract at high concentration has an adverse effect on the general health and lifespan of the animals. But when this dose is reduced by half, the extract exerts protection from the development of skin tumors and increases life span expectancy [144]. Singh *et al.* have evaluated the inhibitory potential of the extracts of MC peel, pulp, seed, and whole fruit on mouse skin papillomagenesis with the modulatory influence of biotransformation system enzymes. Topical application of MC against DMBA results in the modulation of the tumor burden (tumors/mouse), the cumulative number of papillomas and the percent incidence of mice bearing papillomas, respectively. The results suggest the maximum chemopreventive potential is in the MC peel, indicating that biotransformation system enzymes may be the cause of this reduced papillomagenesis [145].

Cervical cancer: Pitchakarn *et al.* have used the bioguided fractionation method to identify the active components of MC leaf extract that are able to modulate the function of P-gp and the MDR phenotype in a human cervical carcinoma cell line (KB-V1). It is found that one of the active compound of MC leaf extract viz. Kuguacin J, increases sensitivity of vinblastine and paclitaxel in KB-V1 cells, suggesting that Kuguacin J directly interacts with the drug-substrate-binding site on P-gp [146]. Limtrakul *et al.* have studied the effects of extracts of MC leaves, fruits and tendrils for their abilities to modulate the functions of P-gp and the MDR phenotype in the multidrug-resistant human cervical carcinoma KB-V1 cells (high P-gp expression) and in wild type drug-sensitive KB-3–1 cells (lacking P-gp). Treatment of drug-resistant KB-V1 cells with MC leaf extracts causes enhanced sensitivity to vinblastine, but similar treatment of KB-3–1 cells shows no such effect, whereas the fruit and tendril extracts do not affect the MDR phenotype in either cell line [147].

Leukemia: Kai *et al.* have evaluated the inhibitory effects of 80% ethanolic extracts agricultural plants on the proliferation of seven Adult T-cell leukemia (ATL)-related human leukemia cells (Su9T01, HUT-102 and Jurkat), three ATL cell lines (ED, Su9T01 and S1T), two human T-cell lines transformed by human T-cell leukemia virus type I (HTLV-I) infection (HUT-102 and MT-2) and two HTLV-I-negative human T-cell acute lymphoblastic leukemia cell lines (Jurkat and MOLT-4). Seed extract of MC suppresses the proliferation of Su9T01, HUT-102 and Jurkat cells, proposing the use of MC for treatment of leukemia [148]. Kobori *et al.* have fractionated the ethanol extract of MC by liquid-liquid partition and silica gel column chromatographic techniques. Several fractions inhibit the growth and induce apoptosis in HL60 cells. Fraction 7 is identified as (9*Z*, 11*E*, 13*E*)-15, 16-dihydroxy-9, 11, 13- octadecatrienoic acid (15, 16-dihydroxy α-eleostearic acid), which possesses the strongest growth inhibitory and apoptosis inducing activity in HL60 cells [149]. Takemoto *et al.* have shown that an extract from the MC preferentially inhibits the soluble guanylate cyclase from leukemic lymphocytes which is correlated with its preferential cytotoxic effects for these same cells [150]. An anti-CD5 monoclonal antibody (mAb) is linked to the plant toxin momordin purified from MC, which is a type-1 ribosome-inactivating protein. The *in vitro* cytotoxicity of the immunotoxin is tested as measured by the inhibition of protein or DNA synthesis on isolated peripheral blood mononuclear cells (PBMC) as well as on human T-cell leukemia Jurkat. The activity of the immunotoxin on PBMC is very potent (IC_{50} 1–10 pmol·L^{-1}) and unaffected by blood components. The conjugate is also efficient in the inhibition of the proliferative response in a mixed lymphocyte reaction (IC_{50} 10 pmol·L^{-1}). The *in vivo* activity of the immunotoxin is evaluated in the model of nu/nu mice bearing Jurkat leukemia. A significant reduction of the tumor development (80%, $P < 0.01$) was observed in the animals treated with immunotoxin [151].

Miscellaneous cancers: Amongst other cancers examined after treatment with MC extract include adrenocortical cancer cells [152], human lung adenocarcinoma CL1 cells with different metastatic ability [153–154], human nasopharyngeal carcinoma CNE2 and HONE1 cells [155], and head and neck squamous cell carcinoma cells [156].

Summary and conclusions

Momordica charantia, commonly called as Bitter melon, is a tropical and subtropical vine of the family Cucurbitaceae, widely grown in Asia, Africa, and the Caribbean for its edible fruit. It is traditionally used in alternative system of medicines as one of the remedy for its anti-diabetic, laxative, anti-ulcer, anti-helminthic and anti-malarial activities and also for the treatment of respiratory diseases and rheumatism. MC contains diverse constituents that are involved in therapeutic activity of MC. Several *in vitro* and *in vivo* studies have been conducted to establish the therapeutic role of MC for treatment of diabetes, cancer, inflammatory diseases, malaria, HIV. Although MC exhibits multi-targeted activity against several cancers in animal models, systematic clinical studies are needed to establish the anti-cancer effects in patients with cancer. Additionally, further studies are required to develop novel drug delivery systems and to establish safety profile.

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Abbreviations

ABTS	2, 2'-Azino-bis(3-ethylbenzothiazoline-6-sulphonic acid)
ACF	Aberrant crypt foci
AIF	Apoptosis-inducing factor
AMPK	AMP-activated protein kinase
AOM	Azoxymethane
AR	Androgen receptor
ATL	Adult T-cell leukemia
BAT	Brown adipose tissues
BBB	Blood-brain barrier
CAT	Catalase
CDK	Cyclin-dependent kinase
CLN	Conjugated linolenic acid
DCLK1	Doublecortin-like kinase 1
DMBA	7, 12-Dimethylbenz-[*a*]-anthracene
DMC	3-β, 7β-Dihydroxy-25-methoxycucurbita-5, 23-diene-19-al
DOX	Doxorubicin
EAT	Epididymal adipose tissues
EBV-EA	Epstein-Barr virus early antigen
EGCG	Epigallocatechin-3-gallate
EMCD	5β, 19-Epoxy-25-methoxycucurbita-6, 23-diene-3β, 19-dio
ER	Estrogen receptor
FA	Ferulic acid
ABTS	2, 2'-Azino-bis(3-ethylbenzothiazoline-6-sulphonic acid)

RGC	Reduced glutathione content
GSK-3	Glycogen synthase kinase-3
GST	Glutathione-s-transferase
HDAC-1	Histone deacetylase-1
HFD	High-fat diet
HSCCC	High-speed counter-current chromatography
HX-XO	Hypoxanthin-xanthin oxidase
IHC	Immunohistochemistry
IKK	Iκ-B kinase
iNOS	Inducible nitric oxide synthase
LGR5	Leucine-rich repeat-containing G-protein coupled receptor 5
LK	Liver kinase
LPS	Lipopolysaccharide
MAP30	Momordica anti-HIV protein
MC	*Momordica Charantia*
MCE	MC boiling water extract
MCME	Methanolic extract of MC
MCP-1	Monocyte chemotactic protein-1
MCP	*Momordica charantia* peroxidase
MDRCP	Multidrug resistance conferring proteins
MMP-9	Matrix metalloproteinase-9
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NO	Nitrogen oxide
PARP	Poly (ADP-ribose) polymerase
PGE_2	Prostaglandin E2
PHA	Phytohemagglutinin
PIN	Prostatic intraepithelial neoplasia
PN	Peroxynitrite
PPAR-γ	Peroxisome proliferator-activated receptor gamma

PXR	Pregnane X receptor
RCFs	Rat cardiac fibroblasts
ROS	Reactive oxygen species
SOD	Superoxide dismutase
***t*-BHP**	*tert*-Butyl hydroperoxide
TAE	Total aqueous extract
TBARS	Thiobarbituric acid-reactive substance
TNF-*α*	Tumor necrosis factor-alpha
TPA	12-O-Tetradecanoylphorbol-13-acetate
TPE	Total phenolic extract
TRAMP	Transgenic adenocarcinoma of mouse prostate
TST	Tibial and sural nerve transection
uPA	Urokinase plasminogen activator
WAT	White adipose tissue
WHO	World Health Organization
***α*-ESA**	Eleostearic acid

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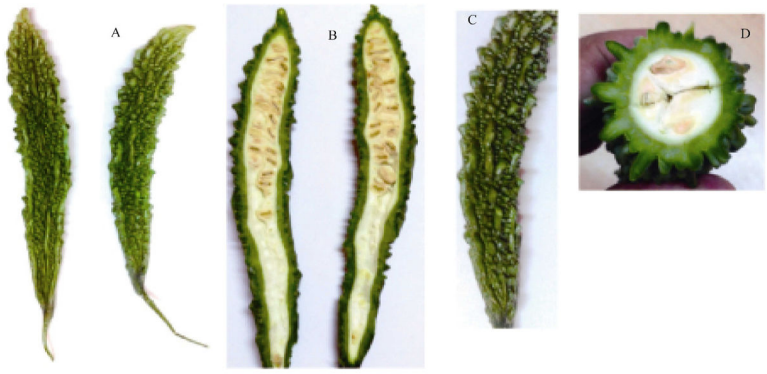

Fig. 1.

Pictures of *Momordica charantia* (Indian Variety) fruit (A), vertical section of the fruit (B), closer view of the fruit (C), and transverse section of the fruit (D)

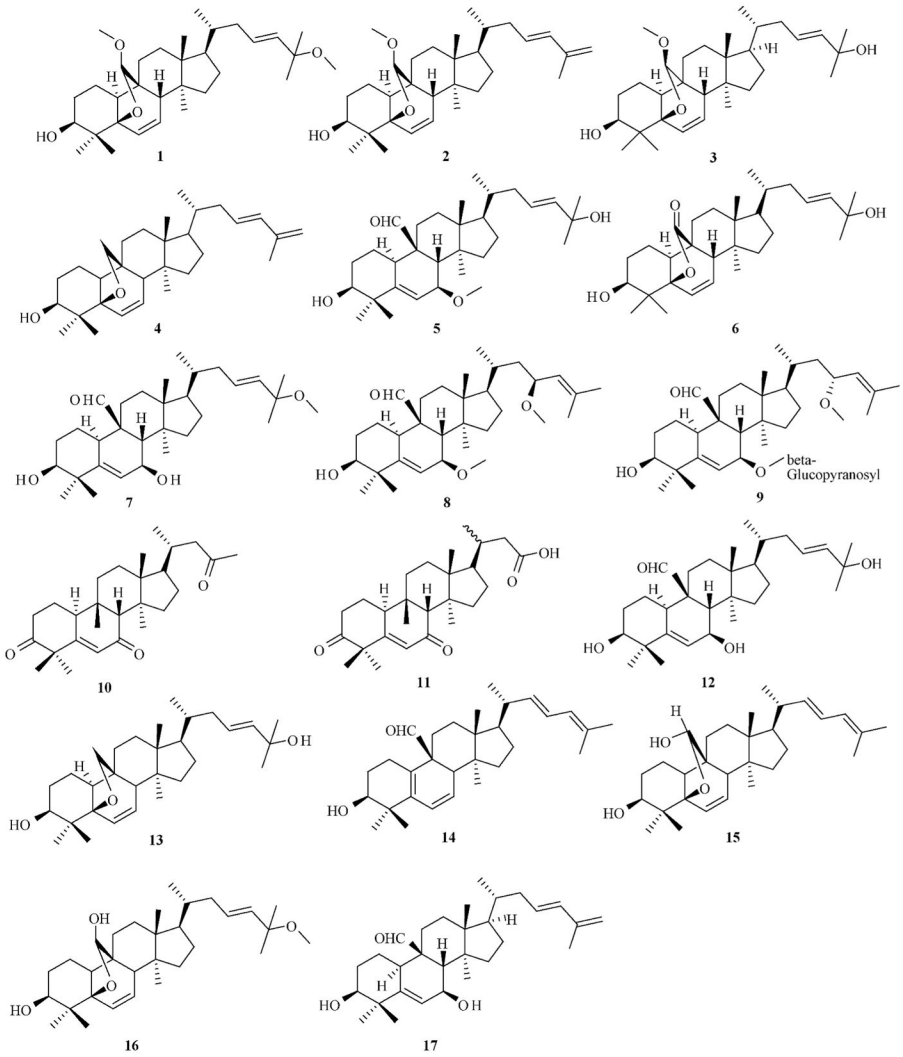

Fig. 2.

Chemical structures of cucurbitane type triterpenoids isolated from *Momordica charantia*

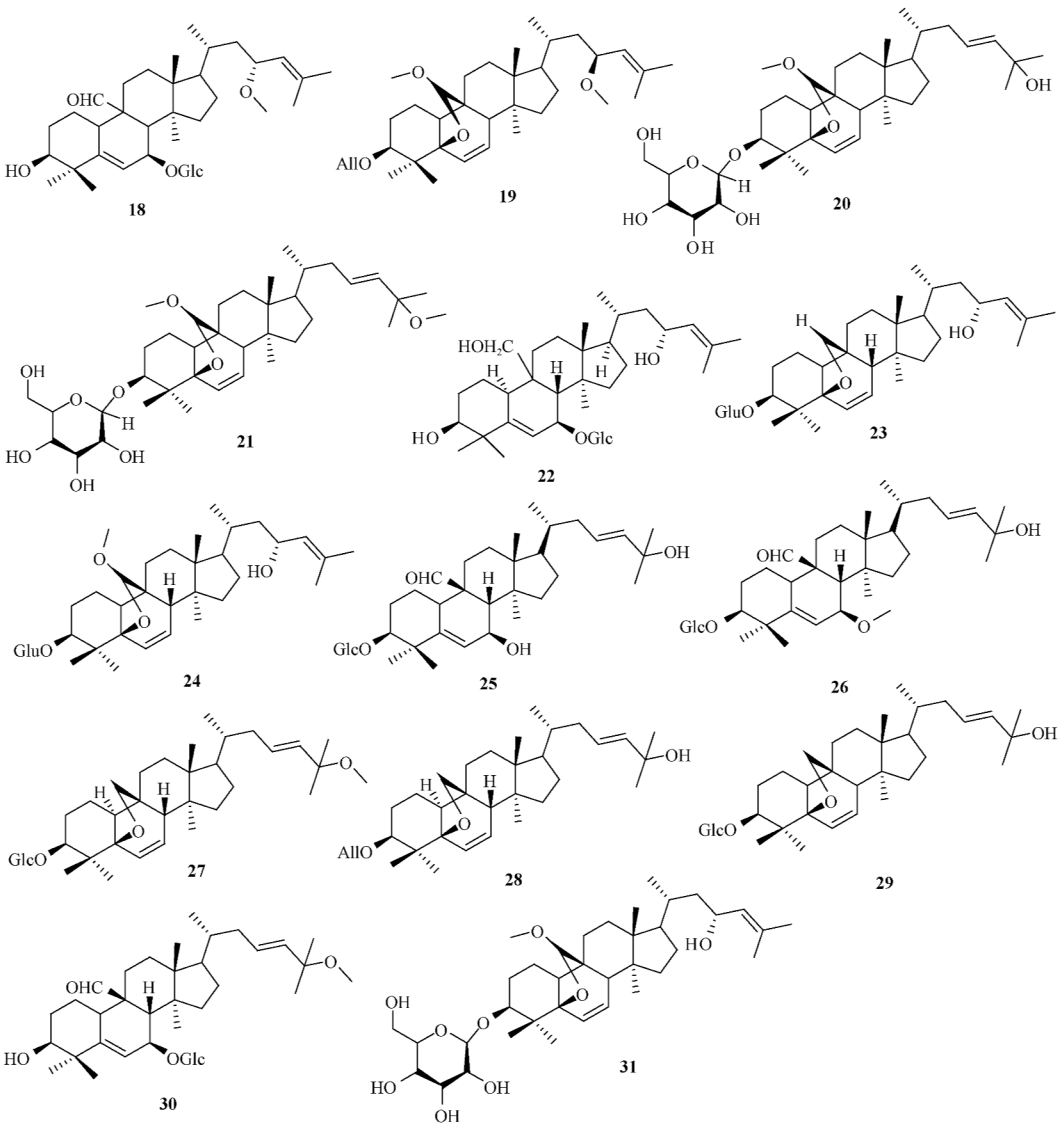

Fig. 3.

Chemical structures of cucurbitane type triterpene glycoside isolated from *Momordica charantia*

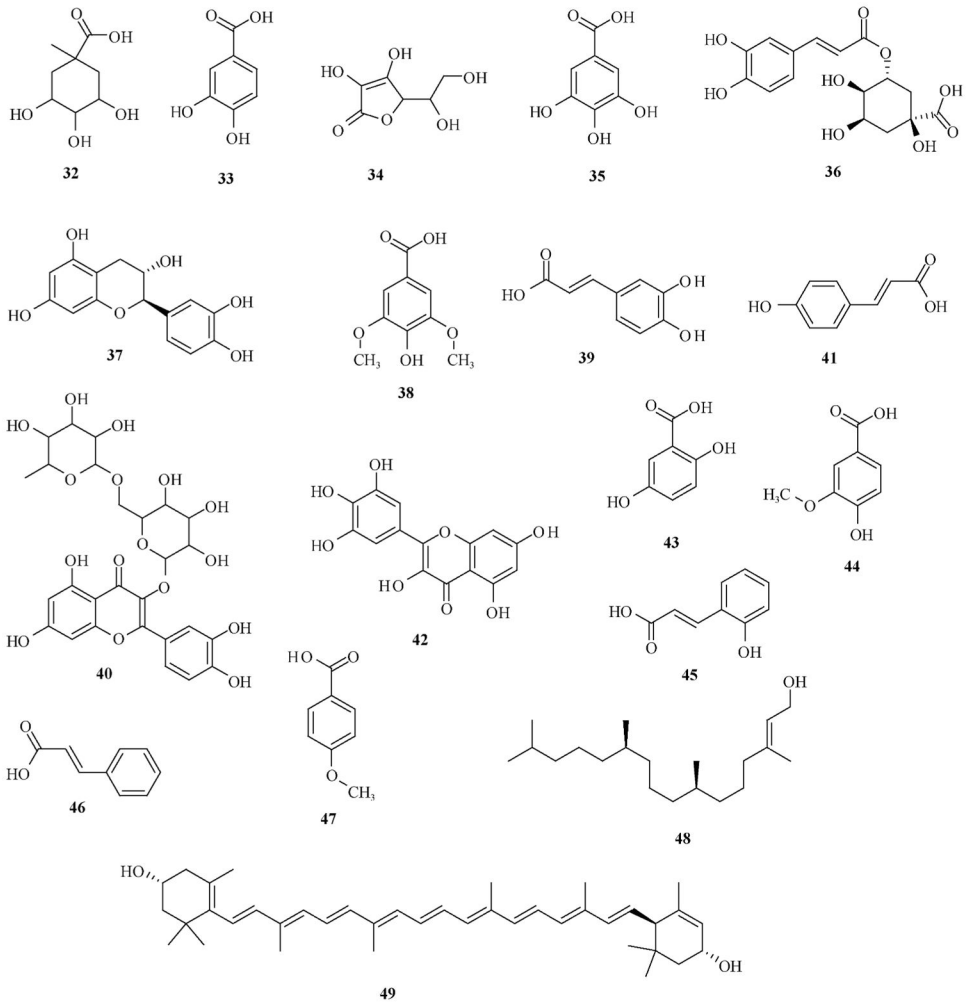

Fig. 4.
Chemical structures of phenolic acids and flavonoids isolated from *Momordica charantia*

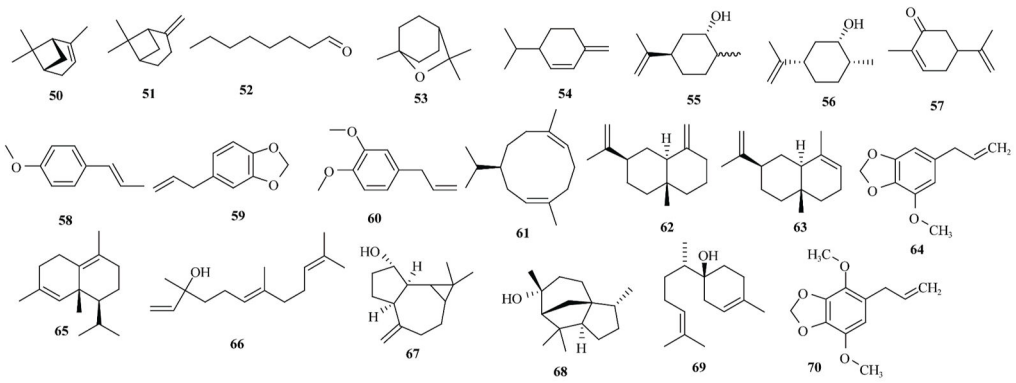

Fig. 5.
Chemical structures of essential oils isolated from *Momordica charantia*

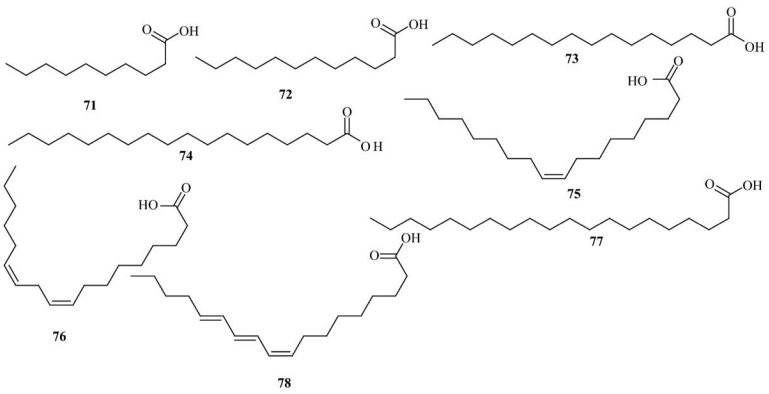

Fig. 6.

Chemical structures of saponins and fatty acids isolated from *Momordica charantia*

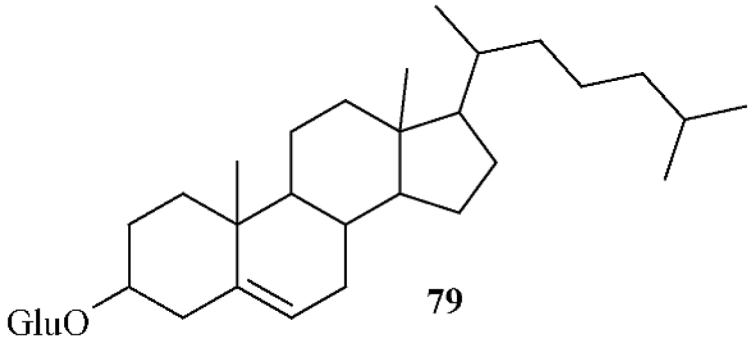

Fig. 7.
Chemical structure of charantin

Table 1

Classification of *M. charantia* species described by Yang and Walters [38]

Variety	Fruit size	Weight	Bitterness	Color
1	Small, 10–20 cm long	0.1–0.3 kg	Very bitter	Dark green
2	Long, 30–60 cm	0.2–0.6 kg	Slightly bitter	Light green with medium-size protuberances
3	Triangular-fruited type, cone-shape fruit, 9–12 cm long	0.3–0.6 kg	Moderately to strongly bitter	Light to dark green with prominent tubercles