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Promise of bitter melon (*Momordica charantia*) bioactives in cancer prevention and therapy

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Abstract

Recently, there is a paradigm shift that the whole food-derived components are not ‘idle bystanders’ but actively participate in modulating aberrant metabolic and signaling pathways in both healthy and diseased individuals. One such whole food from *Cucurbitaceae* family is ‘bitter melon’ (*Momordica charantia*, also called bitter gourd, balsam apple, *etc.*), which has gained an enormous attention in recent years as an alternative medicine in developed countries. The increased focus on bitter melon consumption could in part be due to several recent pre-clinical efficacy studies demonstrating bitter melon potential to target obesity/type II diabetes-associated metabolic aberrations as well as its pre-clinical anti-cancer efficacy against various malignancies. The bioassay-guided fractionations have also classified the bitter melon chemical constituents based on their anti-diabetic or cytotoxic effects. Thus, by definition, these bitter melon constituents are at cross roads on the bioactivity parameters; they either have selective efficacy for correcting metabolic aberrations or targeting cancer cells, or have beneficial effects in both conditions. However, given the vast, though dispersed, literature reports on the bioactivity and beneficial attributes of bitter melon constituents, a comprehensive review on the bitter melon components and the overlapping beneficial attributes is lacking; our review attempts to fulfill these unmet needs. Importantly, the recent realization that there are common risk factors associated with obesity/type II diabetes-associated metabolic aberrations and cancer, this timely review focuses on the dual efficacy of bitter melon against the risk factors associated with both diseases that could potentially impact the course of malignancy to advanced stages. Furthermore, this review also addresses a significant gap in our knowledge regarding the bitter melon drug-drug interactions which can be predicted from the available reports on bitter melon effects on metabolism enzymes and drug transporters. This has important implications, given that a large proportion of individuals, taking bitter melon based supplements/phytochemical extracts/food based home-remedies, are also likely to be taking conventional therapeutic drugs at the same time. Accordingly, the comprehensively reviewed information here could be prudently translated to the clinical implications associated with any potential concerns regarding bitter melon consumption by cancer patients.

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Keywords

Bitter melon; Bitter gourd; *Momordica charantia*; Cancer chemoprevention; Phytochemicals

1. Introduction

The plant of bitter melon (*M. charantia*, family Cucurbitaceae) is a climber and bears oblong fruits resembling cucumber in shape; the young fruits are emerald green in color and turn to orange-yellow on ripening (Fig. 1) [1–3]. *M. charantia* has been cultivated as a vegetable and used traditionally as folk medicine [1–3]; the shape and size of *M. charantia* fruit varies considerably between different genotypes and cultivars [1,4,5]. Traditionally, bitter melon has been used in non-developed and developing countries (such as: China, India, Sri Lanka, Brazil, Cuba, Haiti, Thailand, Vietnam, Mexico, Panama, Peru, *etc.*) for its several health benefits including presumed anti-diabetic effects [1–3,6,7]. Bitter melon has been also consumed for various other benefits such as abortifacient, anthelminthic, contraceptive, gout, kidney-stone, piles, rheumatism, galactagogue, *etc.* [1–3,6,7]. The increased focus on bitter melon consumption in developed countries, could in part be due to several recent pre-clinical efficacy studies demonstrating bitter melon potential to target obesity/type II diabetes-associated metabolic aberrations [2,3,6,7]. Some preliminary clinical studies also show that bitter melon improves glucose tolerance, reduces blood glucose levels, and lowers hemoglobin A1C (A1C) levels in patients with type-II diabetes; though some studies have shown no improvements in A1C levels [8–11]. The past clinical studies with bitter melon, investigating these beneficial effects, have been small, short-term or uncontrolled and thus warrant careful interpretations [8–11]. Though the exact mechanism of glucose lowering by bitter melon is unknown, several mechanistic studies have shown that bitter melon causes hypoglycemia, stimulates peripheral skeletal muscle glucose utilization, inhibits intestinal glucose uptake, suppresses key gluconeogenic enzymes, and preserves pancreatic β cells and insulin secretory function [2,3,6,7].

Notably, bitter melon is now also extensively evaluated for its anti-cancer efficacy against various malignancies [2,12–16]. In various pre-clinical studies, bitter melon extract or its isolated constituents have shown significant anti-cancer efficacy against lymphoid leukemia, lymphoma, and breast, skin, prostate, colon, bladder and pancreatic cancers, as well as Hodgkin's disease [2,17]. Given the vast literature reports on the bioactivity and beneficial attributes of bitter melon constituents, this comprehensive review focusses on the bitter melon components and the overlapping beneficial effects, together with possible bitter melon drug-drug interactions. To avoid any discrepancies related to different nomenclatures used in published reports with reference to bitter melon fruit, hereafter, bitter melon is referred to as *M. charantia*.

2. Cultivation, harvesting and morphology of bitter melon (*M. charantia*)

M. charantia is extensively cultivated in China, India, and Southeast Asia; in the United States it is primarily grown in small farms in California and Florida [1,18]. The plant can be grown in tropical and subtropical climates; it is mainly cultivated during the spring, summer,

and rainy seasons as an annual crop, but can grow as a perennial in mild-winter regions [1,18]. The development of plant is impeded in cool temperatures, while frost totally damages it. Plants are ideally grown by direct seeding in well drained sandy or silt loam, but it can also be grown in any good soil with proper agricultural management [1,18]. The plant is a fast growing trailing or climbing vine with thin stems and tendrils and is day neutral; a trellis is required to support the climbing vine. A single plant bears both male and female flowers, though male flowers appear first and exceed the number of female flowers [1,18]. The flowers open at sunrise, remain open for only one day and require insects for pollination; approximately 10–12 fruits are borne per plant [1,18].

The fruits have a characteristic pebbly surface with smooth/rough length wise ridges. Unripe, immature fruits (4–6 in. long) are light green, firm, oblong with white flesh and are the ones harvested for consumption [1,18]. During maturation, fruit surface gradually turns to yellow or orange and ripe fruits become spongy, tend to split open, revealing orange flesh and bright red inner tissue structures to which the seeds (tan and oval) are attached; there are about 5–7 seeds per gram of fruit [1,18]. Ripe fruits are relatively bitterer than unripe ones and lose their market value. The USDA recommends storage of unripe fruits at 53–55 °F at 85–90% relative humidity. The approximate storage life of fruits is 2–3 weeks and should be isolated from ethylene producing produce to prevent postharvest ripening.

When used for culinary purposes, *M. charantia* fruits are blanched, parboiled or soaked in salt water before cooking to reduce the bitter taste (the bitter flavor is considered desirable for consumption and has been selected for domestication) [1,19]. The bitterness has been attributed to the cucurbitacin –like alkaloid momordicine and triterpene glycosides (momordicoside K and L) [1,19]. The fruits are cooked, stuffed, stir-fried or added in small quantities to soups and curries to provide a slightly bitter flavor. Young shoots, leaves and fruit extracts have been also used in the preparation of tea; additionally the fruits can be dehydrated, pickled or canned. For medicinal purposes, traditionally, the juice of the fruit is consumed early morning on an empty stomach for controlling glucose levels in hyperglycemic states [1,2,6,19].

3. Isolation and identification of bitter melon (*M. charantia*) constituents

Published reports have described that *M. charantia* fruit is a rich source of minerals (potassium, calcium, zinc, magnesium, phosphorous and iron); vitamins (C, A, E, B1, B2, B3, and B9 as folate); and glycosides, saponins, alkaloids, fixed oils, triterpenes, triterpene glycosides, proteins, and steroids [1–3,6,20–23]. The ‘bitter’ constituents have been characterized as momordicosides K and L, and momordicines I and II [1–3,22,23].

Depending upon *M. charantia* varieties, origin, and harvest times including maturity stages (immature, mature, and ripe fruits), the proportion of the chemical constituents differs in different *M. charantia* accessions [24–26]. A number of research labs have put considerable efforts in compiling comprehensive data about the variable environmental and genetic factors that impact the presence of active ingredients in different genotypes and cultivars [1,19,24–27]. Since some of the biological properties of *M. charantia* can be influenced by these variations in the chemical constituents this could be a primary reason why

experimental results differ widely in different studies. Also in many studies, researchers have ambiguously mentioned the variety of *M. charantia* and the extraction procedure employed to isolate the active ingredients which could be another factor that differentially impacts the observed biological effects across various experimental studies. Thus it is imperative that research groups involved in either pre-clinical and clinical evaluation studies should employ standardized preparation of *M. charantia* and provide comprehensive details of extraction procedure used to isolate either the active ingredient or list clearly the details of the extraction solvent used (e.g water, ethanol, methanol, *etc.*).

Over the course of four decades, many bitter and non-bitter cucurbitane-type triterpene glycosides and their aglycones have been reported as the chemical constituents present in *M. charantia* [1,2,22,23,28]. Yoshikawa and group have characterized many triterpene glycosides from *M. charantia* sourced from different geographical locations including, Japan, Indonesia, Sri Lanka, Thailand, and India [21,29]. In 2001, using fresh *M. charantia* whole fruits with immature seeds (from Okinawa, Japan), the Yoshikawa research group reported the isolation and structure elucidation of goyaglycosides a, b, c, d, e, f, g, and h; goyasaponins I, II, and III; and momordicosides A, C, F₁, I, and K [29]. Briefly, these cucurbitane-and oleanene-type triterpene glycosides were isolated from methanolic extract of the fresh fruit which was further partitioned into an ethyl acetate extract and an aqueous phase. The aqueous phase was next extracted with 1-butanol to obtain 1-butanol extract and aqueous extract fraction. Subjecting the 1-butanol extract to normal- and reverse-phase silica gel column chromatography and high-performance liquid chromatography (HPLC) finally yielded the above glycosides [29]. Using the same Japanese variety of *M. charantia*, in 2005, Akihisa and group reported the isolation of three new cucurbitane-type triterpenoids from the methanolic extract of this fruit [30], which were established as (19*R*, 23*E*)-5 β ,19-epoxy-19-methoxycucurbita-6,23,25-trien-3 β -ol, (23*E*)-3 β -hydroxy-7 β -methoxycucurbita-5,23,25-trien-19-al, and (23*E*)-3 β -hydroxy-7 β ,25-dimethoxycucurbita-5,23-dien-19-al. Along with these new compounds, two known cucurbitane-type triterpenoids: (19*R*, 23*E*)-5 β ,19-epoxy-19,25-dimethoxycucurbita-6,23-dien-3 β -ol and (19*R*, 23*E*)-5 β ,19-epoxy-19-methoxycucurbita-6,23-diene-3 β ,25-diol were also reported in these fruits [30]. Notably, *M. charantia* was identified as the first natural source of these tetracyclic triterpenoids [30]. In 2006, in continuation of their study on *M. charantia* varieties, Yoshikawa and group [21] reported the isolation and structure elucidation of three new cucurbitane-type triterpenes called karavilagenins A, B, and C and five new cucurbitane-type triterpene glycosides called karavilosides I, II, III, IV, and V from the dried fruit of *M. charantia* variety cultivated in Sri Lanka. Along with these new compounds, two known cucurbitane-type triterpenes, 19(*R*)-methoxy-5 β , 19-epoxycucurbita-6,23-dien-3 β ,25 -diol and 5,19-epoxycucurbita-6,23-diene-3,25-diol, and nine known cucurbitane-type triterpene glycosides, goyaglycosides b, c, and d, and momordicosides F₁, F₂, G, I, K, and L were also isolated from these fruits [21].

In 2007, Zhao and group [31] isolated and identified three new cucurbitane-type triterpenoids saponins, 23-*O*- β -D-allopyranosyl-5 β ,19-epoxycucurbita-6,24-diene-3 β ,22 (*S*), 23(*S*)-triol-3-*O*- β -D-glucopyranoside; 23-*O*- β -D-allopyranosyl-5 β ,19-epoxycucurbita-6,24-diene-3 β ,22(*S*), 23(*S*)-triol-3-*O*- β -D-allopyranoside; and 23-*O*- β -D-allopyranosyl-5 β ,19-epoxycucurbita-6,24-diene-3 β ,19 (*R*),22(*S*), 23(*S*)-tetraol-3-*O*- β -D-allopyranoside (named

momordicoside M, N, and O, respectively), and a known saponin momordicoside L from the ethanolic extract of the fresh fruits of *M. charantia* cultivated in Beijing, China [31]. In 2008, Khan and group [32] reported the isolation and characterization of two new cucurbitane-type triterpene saponins, 7 β ,25-dimethoxycucurbita-5(6),23(*E*)-dien-19-ol 3-*O*- β -D-allopyranoside and 25-methoxycucurbita-5(6),23(*E*)-dien-19-ol 3-*O*- β -D-allopyranoside as well as nine known compounds: momordicosides A, F₁, F₂, G, K, and L; goyaglycoside c and d; and 3 β ,7 β ,25-trihydroxycucurbita-5,23(*E*)-dien-19-ol from the air-dried and powdered fruits of *M. charantia* cultivated in India [32]. This group further developed the analytical methods for reliable and accurate determination of five main triterpene and triterpene glycosides of *M. charantia* to address authentication of different *M. charantia* varieties [33]. In a 2009 study, Qui and group [34] isolated three new cucurbitane triterpenoids: 19(*R*)-*n*-butanoy-5- β ,19-epoxycucurbita-6,23-diene-3 β ,25-diol 3-*O*- β -glucopyranoside; 23-*O*- β -allopyranosyle-cucurbita-5,24-dien-7 α ,3 β ,22(*R*), 23(*S*)-tetraol 3-*O*- β -allopyranoside; and 23(*R*),24(*S*),25-trihydroxycucurbit-5-ene 3-*O*-{[β -glucopyranosyl (1 $\rightarrow$ 6)]-*O*- β -glucopyranosyl]-25-*O*- β -glucopyranoside; and one new steroidal glycoside, 24(*R*)-stigmastan-3 β ,5 α ,6 β -triol-25-ene 3-*O*- β -glucopyranoside from the methanolic extracts of *M. charantia* cultivated in Yunnan province, China [34]. Along with these new compounds, ten other known compounds: karaviloside II and III; momordicoside K, L, M, N, B, S, and A; and kuguaglycoside B were also isolated from this fruit variety [34]. In 2009, Zhao and group further reported the isolation and identification of guanosine as well as dihydrophaseic acid 3-*O*- β -D-glucopyranoside from the Chinese variety of *M. charantia* fruits [35]. In a 2010 study, using the methanolic extracts of dried fruits of *M. charantia*, cultivated in Thai Binh province Vietnam, Kim and group [36] reported the isolation and identification of three new cucurbitane-type triterpene glycosides: (19*R*,23*R*)-5 β ,19-epoxy-19-methoxycucurbita-6,24-diene-3 β ,23-diol 3-*O*- β -D allopyranoside; (23*R*)-5 β ,19-epoxycucurbita-6,24-diene-3 β ,23-diol 3-*O*- β -D-allopyranoside; and (19*R*)-5 β ,19-epoxy-19,25-duhydroxycucurbita-6,23(*E*)-diene-3 β -ol 3-*O*- β -D-glucopyranoside. Clearly, a plethora of natural products chemistry efforts have been put in place over the years to isolate and identify a wide class of natural agents present in *M. charantia*, which were also instrumental in driving the field for the biological efficacy of *M. charantia* in various settings.

4. Bioassay guided fractionations of bitter melon (*M. charantia*) extracts

Based on structure activity relationships as well as bioassay guided fractionations, the biological role of some of the isolated chemical constituents of *M. charantia* fruits has also been elucidated. The structures of some of the chemical constituents are depicted in Fig. 2.

4.1. Metabolic regulatory effects

The bioassay guided fractionations have attributed the anti-diabetic benefits of *M. charantia* to a mixture of steroidal saponins (*e.g.* charantin), alkaloid (vicine), polypeptide-p (also known as plant insulin), and other cucurbitane-type triterpenoids [16,22,23,37–40]. A 2006 bioassay guided fractionation study by Asakawa and group [23] reported the antidiabetic screening based fractionation in ether and ethyl acetate of methanolic extracts of *M. charantia* fruits cultivated in India. The major isolated compounds (pure cucurbutanoids) in

ether fraction: 5 β ,19-epoxy-3 β ,25-dihydroxycucurbita-6,23(*E*)-diene, and 3 β ,7 β ,25-trihydroxycucurbita-5,23(*E*)-dien-19-al showed significant decrease in blood glucose levels in alloxan-induced diabetes in male ddY mice [23]. On the other hand, the aglycones of charantin (sitosterol and stigmastadienol) did not show any hypoglycemic effects [23]. Since the quantity of the compounds fractioned in ethyl acetate was less, as such this fraction was not evaluated for the hypoglycemic activity. Another 2006 study by Chuang et al. [41] reported that ethyl acetate fraction of *M. charantia* fruits significantly activated peroxisome proliferator receptors (PPAR) α and γ . Notably, the fraction rich in 9 cis, 11 trans, 13 trans-conjugated linolenic acid from *M. charantia* significantly activated PPAR α [41]. This isolated fraction also significantly induced acyl CoA oxidase activity in a PPAR-responsive murine hepatoma H4IIEC3 cell line [41].

In 2010, Kim and group [39] screened the compounds isolated from the methanolic extract of the *M. charantia* fruits (Vietnamese variety) for their anti-diabetic activity by evaluating their inhibitory activity against α -glucosidase. Results indicated towards the potential of some of these isolated compounds to inhibit the α -glucosidase enzyme activity; the most polar compounds (momordicoside A and momordicoside M) among the cucurbitane-type triterpene glycosides displayed the strongest enzyme inhibition potential [39]. In another 2010 study, Ma et al. [20] reported the isolation of a new cucurbitane-type triterpenoid glycoside momordicoside X along with five known cucurbitane-type triterpenoids and related glycosides from the whole plant material of *M. charantia* sourced from Raintree Nutrition Inc. (Carson City, NV, USA). Using MIN6 β -cells based insulin secretion assay, the isolated new compound was shown to moderately effect insulin secretion [20]. On similar lines, a 2011 study by Keller et al. [38] screened the ethanolic extract, saponin-rich fraction, and five purified saponins and cucurbitane triterpenoids: 3 β ,7 β ,25-trihydroxycucurbita-5,23(*E*)-dien-19-al; momordicine I and II; 3-hydroxycucurbita-5,24-dien-19-al-7,23-di-*O*- β -glucopyranoside; and kuguaglycoside G for their effects on insulin secretion using MIN6 β -cells. Screening results demonstrated significant insulin stimulating effects of momordicine II, kuguaglycoside G, and the saponin rich fraction [38].

Tan et al. in 2008 [40] reported the isolation of four new cucurbitane-type triterpenoid glycosides momordicosides Q, R, S, and T and karaviloside XI. The compounds momordicoside S, karaviloside XI and their aglycones increased AMPK activity and stimulated GLUT-4 translocation from cytosol to membrane in L6 myotubes and 3T3-L1 adipocytes [40]. Furthermore, when administered to both insulin-sensitive and insulin-resistant mice, the momordicosides enhanced glucose disposal from the circulation and fatty acid oxidation [40]. On mechanistic front, Iseli et al. [42] reported in a 2013 study that the *M. charantia* derived triterpenoids do not activate AMPK directly in an allosteric manner nor was the activation as a result of inhibition of cellular respiration, rather the activation of AMPK was LKB1-independent and Ca²⁺-dependent, and mediated *via* CaMKK β as a key upstream kinase. In a 2014 study, Takahashi et al. [43] reported that linolenic acid derivative, 13-Oxo-9(*Z*),11(*E*),15(*Z*)-octadecatrienoic acid, present in *M. charantia* has the potential to activate PPAR γ , and thus stimulates glucose uptake in adipocytes and induces adipogenesis *via* induction of PPAR γ -target genes in adipocytes.

Further in a 2014 study, Zeng et al. [44] reported the isolation of four new cucurbitane-type sapogenins together with eight known compounds from the acid-hydrolyzed fruit extracts of *M.charantia*. On screening for their biological activity, these compounds showed significant inhibition of a tyrosine phosphatase, protein tyrosinephosphatase 1B (PTP1B), which is implicated in type II diabetes. The inhibitory activity was shown to be associated with the presence of —OH groups.

In a 2015 study, Chen et al. [37] reported the isolation of five new cucurbitacins kuguacins II–VI from the methanolic extract of dried *M. charantia* fruits (sourced from Yunnan province, China) along with five known analogues. The compounds were screened for their anti-gluconeogenic activity; of the compounds tested, four of the cucurbitacins showed significant inhibition of glucose production from liver cells [37].

4.2. Anti-cancer effects

Table 1 summarizes the anti-cancer effects of various constituents of *M. charantia* [15,16,45–51]. Briefly, in 2007, Akihisa et al. [45], in continuation of their work on the Japanese variety of *M.charantia*, reported the isolation of eight new cucurbitane-type triterpene glycosides charantosides I, II, III, IV, V, VI, VII and VIII, and five known compounds goyaglycoside c, d; momordicoside F₁, F₂; and karaviloside I from the methanolic extract of the dried fruits. These isolated compounds along with the five cucurbitane-type triterpenoids reported earlier by the same group were subjected to *in vitro* screening assays for determining their anti-tumor promoting potential [45]. In these preliminary experiments, all eighteen compounds displayed their potential against 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced activation of Epstein-Barr virus early antigen (EBV-EA). These results are significant as inhibition of EBV-EA induction is recognized to be correlated with anti-tumor promoting activities in cancer chemoprevention studies [45]. Importantly, in these assays, the five cucurbitane-type triterpenoids (without the glycosyl moieties) exhibited the most potent inhibitory activity. On further investigation, these five cucurbitane-type triterpenoids were also found to possess nitric oxide (NO) scavenging activity in a screening model based on the activation of NOR1, a NO donor [45]. Based on these significant inhibitor effects in *in vitro* screening experiments, two of the most effective cucurbitane-type triterpenoids: (19*R*, 23*E*)-5β,19-epoxy-19-methoxycucurbita-6,23,25-trien-3β-ol and (19*R*, 23*E*)-5β,19-epoxy-19,25 - dimethoxycucurbita-6,23-dien-3β-ol were also evaluated for their efficacy against skin carcinogenesis in an *in vivo* model [45]. Both these compounds displayed significant inhibition of 7,12-dimethylbenz[a]anthracene (DMBA)- and peroxyxynitrite (ONOO⁻)-induced and TPA-promoted skin tumorigenesis in two-stage mouse skin carcinogenesis model [45].

In a 2009 study, Mizushina and group [49] screened the purified fractions obtained from the methanolic extract of *M. charantia* [obtained commercially as bitter melon juice (Sahodhara-3, Japan)] for their potential to inhibit DNA polymerase (pol) activity. In this study, monogalactosyl diacylglycerol (MGDG, a glycolipid) containing two α-linolenic acids (C18:3) was isolated and identified as a potent and selective inhibitor of mammalian pol species such as α, γ, δ, and ε sub-types [49]. The isolated compound

MGDG-C18:3-C18:3 also caused strong growth inhibition of A549 lung cancer cells, BALL-1 acute lymphoblastoid leukemia cells, HCT116 colon cancer cells, HeLa cervix cancer cells, HL60 promyelocytic leukemia cells, and NUGC-3 stomach cancer cells; however no growth inhibitory effect of this compound was observed in normal human cells namely, human umbilical vein endothelial cells and human dermal fibroblasts [49].

In 2011, Huang and group [52] screened the isolated compounds, obtained after ethyl acetate and ethanol-based sequential extraction of *M. charantia* fruits of the Taiwanese variety, for their effects on estrogen activity. Using a transactivation assay for estrogen receptor (ER) α and β , the screening assays showed that the non-saponifiable fraction of the ethyl acetate extract activated ERs, while four of the isolated compounds antagonized the transactivation of 17 β -estradiol via both ER α and β ; three of these compounds also showed weak agonist activity for ER α and β [52]. In summary, this study concluded that cucurbitane-type triterpenoids from *M. charantia* have partial agonist/antagonist activity for ER and could be partly responsible for interference in the reproductive hormone signaling pathway and thus, may be associated with infertility-inducing adverse effects of this fruit [52].

In 2012, Yuqing Zhao and group [51] reported the isolation of two new cucurbitane-type triterpene glycoside charantagenins D and E (in addition to charantagenins A, B, and C reported previously by them) together with a new sterol, 7-oxo-stigmasta-5,25-dien-3-*O*- β -D-glucopyranoside and other eight known compounds from ethanolic extract based fractions of *M. charantia* fruits (Shanxi province, China). The isolated compounds were screened for their cytotoxic effects against a panel of cancer cell lines using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) based viability assays [51]. Of all the compounds tested, charantagenin D and goyaglycoside-d with an —OCH₃ substituent group in the side chain showed significant cytotoxic effects against A549 lung cancer cells and U87 glioblastoma cells while compounds charantagenin E, momordicoside K, and stigmasta-7,25(27)-dien-3 β -ol showed moderate cytotoxic effects [51]. On similar lines, Hsiao et al. [16] performed bioassay-guided fractionation of ethanolic extract of *M. charantia* fruits (Taiwanese variety) and screened the isolated compounds for their cytotoxicity against MCF-7 (breast cancer), WiDr (colon cancer), HEp-2 (laryngeal cancer), and Doay (medulloblastoma) cell lines. Notably, the compounds with 5 β ,19-epoxy ring and C(25)-*O*-methyl functional groups: kuguaoside A; momordicoside I, F₁, and K; and goyaglycoside-b displayed cytotoxic effects on these cancer cells [16]. Additionally, out of all the compounds tested, the compound 3-*O*- β -D-allopyranoside showed significant hypoglycemic activities in the glucose uptake assay in C2C12 myoblast cells [16].

In a 2013 study, Weng et al. [15] reported that the cucurbitane-type triterpene 3 β ,7 β -dihydroxy-25-methoxycucurbita-5,23-diene-19-al, isolated from whole plant of wild *M. charantia* (from Taiwan), had strong cytotoxic effects against MCF-7 and MDA-MB-231 breast cancer cells which was mediated through activation of PPAR γ and downstream modulation of PPAR γ -targeting signaling pathways. This triterpene further inhibited mTOR-p70S6K signaling *via* Akt downregulation and AMPK activation [15].

4.3. Anti-oxidant and anti-inflammatory effects

The damage to cells caused by oxidative stress due to the presence of free radicals is recognized to play a causal role in the development of cancer and other health conditions [53]. Studies have shown that *M. charantia* is a rich source of antioxidants and thus could be potentially useful against the damaging effects induced by the free radicals [24,25]. Specifically, pericarp and seeds of *M. charantia* are rich in phenolic compounds which have shown strong anti-oxidant activity [24,25]. According to studies by Horax et al. [24], the maximum number of total phenolics can be extracted from pericarp or seeds when 80% ethanol is used as an extraction solvent. The main phenolic constituents identified were catechin, gallic acid, gentisic acid, chlorogenic acid, and epicatechin; the kinetic behavior of the ethanolic extract showed that these phenolics had slow free radical scavenging activity in the 2,2-diphenyl-1-picrylhydrazyl based free radical scavenging assay [24]. Notably, the amount and type of *M. charantia* phenolics was found to change during the growth and maturity of the fruit which could be correlated to their differential antioxidant activity [24].

In a 2011 study, Lin et al. [54] screened the isolated cucurbitane-type triterpene glycosides from the methanolic extract of the stems and fruits of *M. charantia* (Taiwanese variety) for their antioxidant activity using various *in vitro* assays. The newly identified cucurbitane-type triterpene glycoside taiwacin A as well as other known isolated glycosides displayed either radical cation or superoxide-anion scavenging activity as well as inhibited xanthine oxidase activity, indicating their potential against reactive oxygen species (ROS)-induced deleterious effects [54].

Chronic inflammation is recognized as one of the primary triggers that lead to various diseases including cancer [55,56]. This chronic inflammation related cancer triggering potential can be mediated by inflammatory mediators which generate an inflammatory environment in tumors and lead to the activation of transcription factors which in turn coordinate the production of inflammatory mediators and activation of signaling molecules involved in cancer growth and progression [55,56]. Importantly, several studies have reported the anti-inflammatory effects of *M. charantia* constituents. For example, in continuation of their work on the isolation of cucurbitane-type triterpene glycosides from the *M. charantia* fruits of the Vietnamese variety, Kim and group in 2012 [57] screened seventeen of these compounds for their anti-inflammatory potential. Using *in vitro* HepG2 cell culture based assays, two compounds showed significant inhibition of TNF α -induced NF κ B activation and decreased the induced mRNA levels of iNOS and COX-2 [57]. In PPAR subtype transactivation assays, one of the compounds caused significant PPAR γ transactivation [57].

Further in 2015, Liaw et al. [48] reported the isolation and identification of five new 5 β ,19 epoxycucurbitane triterpenoids, taikuguasins (A–E) along with 5 β ,19-epoxy-25-methoxycucurbita-6,23-diene-3 β ,19-diol from the ethanolic extract of fresh *M. charantia* fruits (Taiwanese variety). These compounds were screened for their anti-inflammatory and cytotoxic activity; out of which, taikuguasin C and D showed significant inhibition of lipopolysaccharide (LPS)-induced NO production in the mouse macrophage RAW 264.7 cell line as well as showed significant cyto-toxic effects (in MTT assay) against MCF-7 (breast

cancer), HepG2 (hepatocellular cancer), HEp-2 (laryngeal cancer), and WiDr (colon cancer) cells [48].

5. Biologically effective novel proteins from bitter melon (*M. charantia*)

Apart from the chemical constituents, many novel protein and enzymes with specific biological effects have also been isolated from *M. charantia* fruits. Table 2 summarizes the biological effects of various novel proteins from *M. charantia*. Notably, Vesely et al. [58] and Claflin et al. [59] reported that an aqueous extract of *M. charantia* fruits inhibits guanylate cyclase activity by its potential as a non-competitive inhibitor of guanylate cyclase activity and by lowering GMP levels *in vivo*. Since guanylate cyclase-cyclic GMP was recognized to be involved in cell growth, DNA and RNA synthesis and malignant transformation, studies were carried to determine *M. charantia* effects on prostate cancer cells and lymphocyte proliferation [59–61]. Aqueous extract of the fruits was found to cause G2-M cell cycle arrest and inhibit proliferation of rat prostate cancer cells with no effect on normal human prostate cells [59]. Furthermore, Takemoto et al. [61,62] reported partial purification and characterization of the guanylate cyclase inhibitor from the *M. charantia* extract, and showed that the aqueous extract has both cytostatic and cytotoxic effects on human lymphocytes with stronger cytotoxic effects against human leukemic lymphocytes. Importantly, in murine lymphoma systems in animal models, the crude extract significantly inhibited tumor formation [60].

In another study, Lee-Huang et al. [63] reported the isolation and purification of a 30 kDa anti-viral protein momordica anti-human immunodeficiency virus protein (MAP30) from *M. charantia* seeds. MAP30 was shown to exhibit potent *in vitro* anti-HIV activity by its potential to cause topological inactivation of viral DNA and ribosome inactivation [63–65]. It was also found to work in synergism with other therapeutics for regulation of HIV replication [64], and also shown to be effective against herpes simplex virus infections [66]. MAP30 has been also shown to inhibit proliferation and cause apoptosis in a panel of cancer cells from prostate, breast, lung, hepatocellular, and brain glioblastoma [65,67]. In 2012, Fang et al. [67] reported the purification and characterization of a 14 kDa ribonuclease (RNase MC2) from *M. charantia* seeds. RNase MC2 was shown to possess absolute specificity for uridine and to cause RNA-cleavage in baker's yeast tRNA and tumor cell rRNA [67]. Importantly, RNase MC2 inhibited cell proliferation and induced apoptosis in MCF-7 (breast cancer) and HepG2 (hepatocellular cancer) cells and xenograft tumors [67,68].

The isolation of type II ribosome inactivating protein (*M. charantia* lectin) and type I ribosome inactivating protein [α -momorcharin (α -MMC)] has also been reported from *M. charantia* seeds, which exhibited significant anti-tumor efficacy against human nasopharyngeal cancer cells in culture and in xenograft tumors [67,69]. A combination of type I ribosome inactivating proteins α -MMC and β -MMC known as MCP-30 has been previously shown to induce apoptosis in premalignant (PIN) human prostate cells as well as malignant prostate cancer (PCa) LNCaP and PC3 cells and xenograft with no effect on normal prostate cells [70]. These inhibitor effects of MCP-30 were associated with its potential to inhibit histone deacetylase-1 activity in these cancer cells [70]. Furthermore, a d-

galactose-specific lectin isolated from *M. charantia* seeds (MCL) has been reported to have insulinomimetic activity with a strong type I and a weak type II ribosome inactivating protein activity [71]. MCL has shown strong growth inhibition of Ehrlich ascites carcinoma under both *in vitro* and *in vivo* conditions [71].

Using high-speed counter-current chromatography (HSCCC) coupled with a reverse micelle solvent system Li et al. [72] have also reported the separation of a new protein (unidentified) together with protein P-B and pentatricopeptide repeat-containing proteins from *M. charantia*. The new unidentified protein has shown significant anticancer activity against human gastric cancer SGC-7901 cell line [72]. Furthermore, Hsiang and group (2013) have reported the isolation of a trypsin inhibitor named *M. charantia* insulin receptor (IR)-binding protein (mcIRBP) from the aqueous extract of *M. charantia* seeds [73,74]. These researchers showed that the novel IR-binding protein could stimulate PI3K/Akt signaling pathway and also increase glucose uptake in adipocytes *in vitro*, and when administered to animals (under diabetes state as well as during glucose tolerance tests), the mcIRBP protein could significantly reduce blood glucose levels as well as modify the genes involved in insulin-signaling pathways [73,74].

6. Biological efficacy of whole bitter melon (*M. charantia*) fruits

Apart from the evaluation of biological properties of chemical constituents isolated from the fruits of *M. charantia* using bioassay-guided fractionation assays and structure activity-based relationships, the whole bitter melon (*M. charantia*) fruit extract or juice, either as such or in dried or lyophilized form, has also been evaluated for its biological properties in various *in vitro* and *in vivo* pre-clinical assays (Table 1 summarizes the anti-cancer effects). Some of these benefits are also listed below.

Extensive mechanistic studies conducted *in vitro* as well as *in vivo* have shown that *M. charantia* causes hypoglycemia, stimulates peripheral skeletal muscle glucose utilization, inhibits intestinal glucose uptake, inhibits adipocyte differentiation, suppresses key gluconeogenic enzymes (glucose-6-phosphatase and fructose-1,6-biphosphatase), preserves pancreatic β cells and insulin secretory function, and reduces serum lipid levels [2,3,6,7,22,75]. It also increases both hepatic and red-cell shunt enzyme glucose-6-phosphate dehydrogenase [75]. *M. charantia* has been also shown to modulate host metabolism within the gut-hepatic axis [76–78]. For example, in high fat-fed rodent models, bitter melon feeding reduces hepatic triacylglyceride (TAG) level, attenuates hepatic steatosis, and decreases hepatic cholesterol level that is mediated through an increased secretion of neutral steroids without effecting cholesterogenesis [76–78].

The whole bitter melon (*M. charantia*) fruit is now also extensively evaluated for its anti-cancer efficacy against various malignancies including our own work in pancreatic cancer [2,12–17,47,79–92]. Table 1 summarizes these anti-cancer effects. Briefly, oral administration of aqueous extract of *M. charantia* has been shown to afford protection against DMBA and croton oil exposure-associated two-stage skin carcinogenesis progression in Swiss albino mice [93]. *M. charantia* juice has been shown to inhibit proliferation and to induce apoptosis in MCF-7 and MDA-MB-231 breast cancer cells; this

effect was associated with modulation of expression levels of cell cycle regulatory molecules [94]. Methanolic extracts of *M. charantia* have also shown significant inhibition of proliferation and clonogenicity of HT29 and SW480 colon cancer cells *in vitro* [95]. These inhibitory effects were associated with activation of AMPK-mediated signaling pathways and autophagy induction. However, dietary feeding of freeze dried and powdered fruits of *M. charantia* has been shown to provide no protection against azoxymethane (AOM)-induced colon carcino-genesis in Wistar rats [96]. Aqueous extract of *M. charantia* has also demonstrated strong anti-cancer efficacy against PCa cell cycle progression *in vitro* and also delayed the progression of prostate tumorigenesis in a pre-clinical PCa *transgenic adenocarcinoma of the prostate* (TRAMP) model [13]. Furthermore, studies from our group using *M. charantia* juice (after removing pulp and seeds) have shown its significant growth inhibitory effect against a panel of pancreatic cancer cells including Mia PaCa-2 xenograft tumors [12]. These inhibitory effects were associated with significant decrease in cell proliferation and apoptosis induction under both *in vitro* and *in vivo* conditions, and were associated with an increase in AMPK activation [12]. Our studies have also demonstrated the potential of *M. charantia* juice to target both gemcitabine sensitive and resistant pancreatic cell lines; the growth inhibitory effects on gemcitabine resistant cells were associated with a decrease in both Akt and ERK1/2 phosphorylation [14]. Overall, these findings suggest the cancer chemopreventive and anti-cancer efficacy of the whole bitter melon (*M. charantia*) fruit against several cancers, and advocate more detailed pre-clinical studies in additional models which could support its use in clinical conditions to control various malignancies.

7. Drug–drug interactions with bitter melon (*M. charantia*)

A multitude of pre-clinical *in vitro* and *in vivo* studies in animal models, including our research efforts over the years [7,97–106], have also shown that many phytochemicals contain potent compounds with pleotropic effects, which are able to affect a plethora of enzyme systems and signaling cascades involved in the pathogenesis of certain diseases. Due to these presumed/reported health effects, phytochemicals intake as dietary supplements or raw food components, including *M. charantia* consumption, has been steadily increasing in recent years. Importantly, a large proportion of individuals, taking such supplements/phytochemical extracts/food based home-remedies, are also taking conventional therapeutic drugs at the same time [97]. Many *in vitro* studies have already reported effects of several phytochemicals on various cytochrome-P450 (CYP) isoforms, on phase II conjugation enzymes and on drug transporters [97]. Similarly, various studies have also reported such effects of *M. charantia* [50,107–115]; Table 3 summarizes these effects. In accordance with the findings in Table 3, phytochemicals in *M. charantia* may interfere with absorption, distribution, metabolism and excretion of therapeutic drugs, altering the pharmacokinetics of the latter. By induction or inhibition of various metabolism-associated enzymes and drug transporters, *M. charantia* can enhance the toxicity or reduce the therapeutic effect of another drug. This raises serious concerns about the uncontrolled consumption of phytochemicals, including *M. charantia* (mostly consumed world-wide for its beneficial effects in controlling/treating diabetes and in recent times for its anti-cancer effects), and warrants detailed investigations exploring these drug-drug interactions.

8. Concluding remarks

In brief, the bioassay-guided fractionations of bitter melon (*M. charantia*) have mostly classified its chemical constituents based on their anti-obesity/type II diabetes associated metabolic aberrations or cytotoxic effects towards various cancer cells. Thus, by definition, these *M. charantia* constituents are at cross roads on the bioactivity parameters; they either have selective efficacy for correcting metabolic aberrations or targeting cancer cells, or have beneficial effects in both conditions (summarized in Fig. 3). Importantly, the recent realization that there are common risk factors associated with obesity/type II diabetes-associated metabolic aberrations and cancer and the fact that in certain cancers there are additional increased risks combined with obesity and/or type II diabetes [116], the dual efficacy of *M. charantia* against the risk factors associated with both diseases could potentially impact the course of malignancy to advanced stages. Notably, several funding agencies have recently supported various grants to evaluate in detail the efficacy and associated molecular mechanisms of the whole bitter melon (*M. charantia*) fruit against various malignancies and other disease conditions. It remains to be seen what kind of fruition these efforts bring regarding the efficacy of bitter melon (*M. charantia*) fruit against various malignancies as well as other ailments.

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Chinese Green

Indian Green

Fig. 1.
Images of bitter melon genotypes.

Fig. 2.
 Chemical structure of some of the major A) phenolic compounds, B) cucurbitane-type triterpenes, and C) cucurbitane-type triterpene glycosides isolated from bitter melon (*M. charantia*).

Fig. 3.

Illustration depicting overlapping cellular and molecular mechanisms driving biological effects of bitter melon (*M. charantia*) in metabolic regulation and anti-cancer efficacy.

Center image shows different bitter melon genotypes: Chinese green (left); Indian green (right); and standardized preparation of lyophilized bitter melon fruit juice in vials.

Table 1Anti-cancer effects of Bitter Melon (*M. charantia*) and its chemical constituents.

Cancer type	Agent or part studied	Cancer model	Anticancer effects	References
Skin cancer	Peel, pulp, seed, and whole fruit extract	Skin papilloma in Swiss albino mice	↓ DMBA-induced skin papilloma by topical treatment	Singh et al. [79]
	Whole fruit aqueous extract	Skin papilloma in Swiss albino mice	↓ DMBA-induced skin papilloma by oral treatment	Ganguly et al. [93]
	Fruit extract	Skin papilloma and melanoma tumorigenesis in Swiss albino mice	↓ DMBA-induced skin papilloma and melanoma tumorigenesis by oral treatment	Agrawal and Beohar [80]
	Isolated compounds (19 <i>R</i> , 23 <i>E</i>)-5β,19-epoxy-19-methoxycucurbita-6,23,25-trien-3β-ol and (19 <i>R</i> , 23 <i>E</i>)-5β,19-epoxy-19,25-dimethoxycucurbita-6,23-dien-3β-ol	Skin papilloma in Swiss albino mice	↓ DMBA or peroxynitrite-induced skin papilloma by oral treatment	Akihisa et al. [45]
Breast cancer	Powdered freeze-dried fruit	Mammary tumorigenesis in Sprague Dawley rats.	↓ DMBA-induced mammary tumorigenesis by dietary treatment	Kusamran et al. [87]
	Whole fruit-hot water extract	Spontaneous mammary tumorigenesis in SHN mice.	↓ Spontaneous mammary tumorigenesis by oral treatment with whole fruit-hot water extract	Nagasawa et al. [89]
	Juiced fruit extract	<i>in vitro</i>	↓ Viability of MCF-7 and MDA-MB-231 breast cancer cells	Ray et al. [94]
	Isolated compound α-eleostearic acid	<i>in vitro</i>	↓ Proliferation of MDA-MB-231 and MDA-MB-231-ERα breast cancer cells	Grossmann et al. [46]
	Isolated compounds kuguaside A; momordicoside I, F ₁ , and K; and goyaglycoside-b	<i>in vitro</i>	↓ Viability of MCF-7 breast cancer cells	Hsiao et al. [16]
	Isolated compound 3β,7β-dihydroxy-25-methoxycucurbita-5,23-diene-19-ol	<i>in vitro</i>	↓ Viability of MCF-7 and MDA-MB-231 breast cancer cells	Weng et al. [15]
	Isolated compounds taikuguasin C and D	<i>in vitro</i>	↓ Viability of MCF-7 breast cancer cells	Liaw et al. [48]
Prostate cancer	Juiced fruit extract	<i>in vitro</i>	↓ Growth and proliferation of rat prostate adenocarcinoma (G) cells	Claflin et al. [59]
	Juiced fruit extract	<i>in vitro</i> and TRAMP mice	↓ Cell-cycle progression of PC-3 and LNCaP prostate cancer cells and oral treatment delays progression of prostate tumorigenesis	Ru et al. [13]
	Leaf extract	<i>in vitro and in vivo</i>	↓ Invasiveness of PLS-10 prostate	Pitchakarn et al. [90,91]

Cancer type	Agent or part studied	Cancer model	Anticancer effects	References
			cancer cells by dietary treatment	
Stomach cancer	Leaf extract and isolated compound Kuguacin J	<i>in vitro</i>	↓ Viability of LNCaP prostate cancer cells	
	Fruit extract	Forestomach papillomagenesis in Swiss albino mice	↓ Benzo (a) pyrene-induced forestomach papillomagenesis by dietary treatment	Deep et al. [83]
	Isolated compound MGDG-C18:3-C18:3	<i>in vitro</i>	↓ Viability of NUGC-3 stomach cancer cells	Matsui et al. [49]
Colon cancer	Methanolic extract of leaves	<i>in vitro</i>	↓ Viability of AGS gastric cancer cells	Li et al. [88]
	Ethanol extract of fruit	AOM-induced aberrant crypt foci formation in F344 rats.	↓ AOM-induced aberrant crypt foci formation by oral treatment	Chiampanich-ayakul et al. [82]
	Seed oil rich in conjugated linoleic acid	AOM-induced aberrant crypt foci formation and colon tumorigenesis in F344 rats.	↓ AOM-induced aberrant crypt foci formation and colon tumorigenesis by dietary treatment	Kohno et al. [85,86]
	Powdered freeze-dried fruit	AOM-induced colon tumorigenesis in Wistar rats.	No preventive effect on AOM-induced colon tumorigenesis by dietary treatment	Kupradinun et al. [96]
	Methanolic extract of leaves	<i>in vitro</i>	↓ Viability of HCT116 colon cancer cells	Li et al. [88]
	Methanolic extract of fruit	<i>in vitro</i>	↓ Proliferation and clonogenicity of HT29 and SW480 colon cancer cells/cancer stem cells ↑ Sensitivity of HT 29 colon cancer cells to doxorubicin	Kwatra et al. [95,111]
	Isolated compound α-eleostearic acid	<i>in vitro</i>	↓ Viability of HT29 colon cancer cells	Kabori et al. [47]
Pancreatic cancer	Isolated compound MGDG-C18:3-C18:3	<i>in vitro</i>	↓ Viability of HCT116 colon cancer cells	Matsui et al. [49]
	Isolated compounds kuguaside A; momordicoside I, F ₁ , and K; and goyaglycoside-b	<i>in vitro</i>	↓ Viability of WiDr colon cancer cells	Hsiao et al. [16]
	Isolated compounds taikuguasin C and D	<i>in vitro</i>	↓ Viability of WiDr colon cancer cells	Liaw et al. [48]
	Juiced fruit extract (freeze-dried)	<i>in vitro</i> and xenograft tumors	↓ Viability of BxPC-3, MiaPaCa-2, and AsPC-1 pancreatic cancer cells ↓ Growth of MiaPaCa-2 xenograft tumors by oral treatment	Kaur et al. [12]
	Juiced fruit extract (freeze-dried)	<i>in vitro</i>	↓ Viability of gemcitabine-resistant MiaPaCa-2 and AsPC-1 pancreatic cancer cells	Somasagara et al. [14]

Cancer type	Agent or part studied	Cancer model	Anticancer effects	References
Leukemia	Crude fruit extract (ammonium sulfate precipitated)	<i>in vitro</i>	↑ Cytotoxicity towards leukemic lymphocytes	Takemoto et al. [61]
	Crude fruit extract (ammonium sulfate precipitated)	Lymphoma tumors in mice.	↓ CBA/DI T-cell based lymphoma tumors by <i>i.p</i> injection	Jilka et al. [60]
	Ethanol extract of seed	<i>in vitro</i>	↓ Proliferation of Su9T01, HUT-102, and Jurkat adult T-cell leukemia cells	Kai et al. [84]
	Isolated compound α -eleostearic acid	<i>in vitro</i>	↓ Viability of HL60 promyelocytic leukemia cells	Kabori et al. [47]
	Isolated compound MGDG-C18:3-C18:3	<i>in vitro</i>	↓ Viability of BALL-1 acute lymphoblastoid and HL60 promyelocytic leukemia cells	Matsui et al. [49]
Head-Neck cancer	Juiced fruit extract	<i>in vitro</i> and xenograft tumors	↓ Proliferation of Cal27, JHU-22, and JHU29 head and neck squamous cell cancer cells ↓ Growth of Cal27 xenograft tumors by oral treatment	Rajamoorthi et al. [92]
	Isolated compounds kuguaoside A; momordicoside I, F ₁ , and K; and goyaglycoside-b	<i>in vitro</i>	↓ Viability of HEp-2 laryngeal cancer cells	Hsiao et al. [16]
	Isolated compounds taikuguasin C and D	<i>in vitro</i>	↓ Viability of HEp-2 laryngeal cancer cells	Liaw et al. [48]
	Methanolic extract of leaves	<i>in vitro</i>	↓ Viability of HONE1 nasopharyngeal cancer cells	Li et al. [88]
Adrenocortical cancer	Fruit extract	<i>in vitro</i>	↓ Proliferation of both mouse and human adrenocortical cancer cells	Brennan et al. [81]
Cervical cancer	Isolated compound MGDG-C18:3-C18:3	<i>in vitro</i>	↓ Viability of HeLa cervical cancer cells	Matsui et al. [49]
	Leaf extract and isolated compound Kuguacin J	<i>in vitro</i>	↑ Sensitivity of KBV1 cervical cancer cells to vinblastine	Pitchakarn et al. [50]
Lung cancer	Methanolic extract of leaves	<i>in vitro</i>	↓ Viability of CL 1-0 lung cancer cells	Li et al. [88]
	Isolated compound MGDG-C18:3-C18:3	<i>in vitro</i>	↓ Viability of A549 lung cancer cells	Matsui et al. [49]
	Isolated compounds charantagenin D, goyaglycoside-d, charantagenin E, momordicoside K, and stigmasta-7,25(27)-dien-3 β -ol	<i>in vitro</i>	↓ Viability of A549 lung cancer cells	Wang et al. [51]
Brain cancer	Isolated compounds charantagenin D, goyaglycoside-d, charantagenin E, momordicoside K, and stigmasta-7,25(27)-dien-3 β -ol	<i>in vitro</i>	↓ Viability of U87 glioblastoma cells	Wang et al. [51]
	Isolated compounds kuguaoside A; momordicoside I, F ₁ , and K; and goyaglycoside-b	<i>in vitro</i>	↓ Viability of Doay medulloblastoma cells	Hsiao et al. [16]

Cancer type	Agent or part studied	Cancer model	Anticancer effects	References
Liver cancer	Isolated compounds taikuguasin C and D	<i>in vitro</i>	↓ Viability of HepG2 hepatocellular cancer cells	Liaw et al. [48]

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Table 2Biologically effective novel proteins from Bitter Melon (*M. charantia*).

Protein/enzyme name	Isolated from plant part	Biological effects	References
Guanylate cyclase inhibitor	Aqueous extract of fruits	<ul style="list-style-type: none"> • Non-competitive inhibitor of guanylate cyclase activity • ↓ GMP levels in vivo • ↓ Proliferation of rat prostate cancer cells; in vitro treatment with aqueous extract of fruits. No effect on normal prostate cells • ↓ Tumor formation in murine lymphoma models: in vivo treatment with crude extract • Cytostatic and cytotoxic effects on human lymphocytes and cytotoxic effects against human leukemic lymphocytes: in vitro treatment with partially purified inhibitor in aqueous extract 	Vesely et al. [58]; Claflin et al. [59]; Jilka et al. [60] ; and Takemoto et al. [61,62]
Momordica anti-human immunodeficiency virus protein (MAP30)	Seeds	<ul style="list-style-type: none"> • Anti-HIV activity • Topological inactivation of viral DNA and ribosome inactivation • Synergistic effect with other therapeutics for regulation of HIV replication • Effective against herpes simplex virus infections • ↓ Proliferation and induced apoptosis in a panel of cancer cells from prostate, breast, lung, hepatocellular, and brain glioblastoma 	Lee-Huang et al. [63–65]; Bourinbaier et al. [64,66] ; and Fang et al. [65,67]
Ribonuclease (RNase MC2)	Seeds	<ul style="list-style-type: none"> • Ribonuclease activity • Absolute specificity for uridine • Causes cause RNA-cleavage in baker's yeast tRNA and tumor cell rRNA • ↓ Proliferation and induced apoptosis in MCF-7 breast cancer cells and HepG2 hepatocellular cancer cells 	Fang et al. [67,68]
<i>M. charantia</i> lectin	Seeds	<ul style="list-style-type: none"> • Type II ribosome inactivating protein • Anti-tumor efficacy against human nasopharyngeal cancer cells in culture and in xenograft tumors 	Fang et al. and Pan et al. [67,69]
α-Momorcharin (α-MMC)	Seeds	<ul style="list-style-type: none"> • Type I ribosome inactivating protein • Anti-tumor efficacy against human nasopharyngeal cancer cells in culture and in xenograft tumors 	
MCP-30	Seeds	<ul style="list-style-type: none"> • Type I Ribose inactivating proteins (combination of α-MMC and β-MMC) • Induces apoptosis in premalignant and malignant human prostate cells and xenograft s • No effect on normal prostate cells • ↓ histone deacetylase-1 activity in prostate cancer cells 	Xiong et al. [70]

Protein/enzyme name	Isolated from plant part	Biological effects	References
MCL (D-galactose specific lectin from <i>M. charantia</i>)	Seeds	<ul style="list-style-type: none"> • Strong Type I and a weak type II ribosome inactivating protein activity • Insulinomimetic activity • ↓ Growth of Ehrlich ascites carcinoma under both <i>in vitro</i> and <i>in vivo</i> conditions 	Kabri et al. [71]
New protein, protein P-B, and pentatricopeptide repeat-containing proteins	Fruit juice	<ul style="list-style-type: none"> • Anti-cancer activity • ↓ Proliferation of SGC-7901 human gastric cancer cells; and: <i>in vitro</i> treatment with new unidentified protein 	Li et al. [72]

Table 3Effect of Bitter Melon (*M. charantia*) on CYP enzymes and drug transporters.

ENZYME/TRANSPORTER	Effect of <i>M. charantia</i> or its constituent	MODEL and METHODS	Results/Validation	References
P-gp	–Reverses P-gp mediated drug resistance –Inhibits P-gp activity –Directly binds to P-gp –Decreases P-gp levels	–Cervical carcinoma KB –V1 cells (sensitive/MDR resistant) –Radio labelled drug accumulation –Insect cells P-gp expressing –Bioguided fractionation of <i>M. charantia</i> -leaves/fruits – <i>M. charantia</i> treatment of cervical cancer patients; blood and NK cells sampling	–Reversal of multi drug resistance –Decreased expression of P-gp in NK membrane of <i>M. charantia</i> treated patients –Kuguacin J-binds to P-gp substrate binding sites	Pongnikorn et al.; Limtrakul et al.; and Pitchakarn et al. [50,112,113]
	Inhibits P-gp activity	–Caco-2 cells and rhodamine uptake –Bioguided fractionation of <i>M. charantia</i> water extract	1-monopalmitin (monoglyceride) as P-gp inhibitor	Konishi et al. [109,110]
Aminoglycoside resistance	–Modifies antibiotic activity due to altered resistance	–Methicillin-resistant <i>S. aureus</i> and antibiotics (aminoglycosides) uptake	–Modifies antibiotic activity due to altered resistance	Coutinho et al. [108]
P-gp, BCRP, MRP-2, and PXR	–Decreases MDR gene expression –Decreases PXR promoter activity –Enhances DOX-uptake and reduces drug efflux	–HT29 cells and DOX-uptake/sensitization –MDCK cells overexpressing efflux transporters (P-gp, BCRP, MRP-2) –Luciferase based assay for PXR promoter activity	–Reversal of multi drug resistance –PXR is involved in activation of Phase I/II metabolizing enzymes and efflux transporters; <i>M. charantia</i> inhibits its promoter activity	Kwatra et al. [111]
CYP-450 enzymes	–modulates enzyme expression and catalytic activities of different CYP's (in tissue and iso-enzyme specific manner)	–STZ induced diabetic rats –Microsomal mono-oxygenase activity was measured –WB analysis for protein expression	–Modulation of xenobiotic metabolism	Raza et al. [114,115]
	–modulates enzyme expression and catalytic activities of phase I and phase II enzymes –differential effect of Thai vs. Chinese fruits	– Wistar rats fed with <i>M. charantia</i> (Thai vs. Chinese variety) in diet – Hepatic mono-oxygenases, glutathione-S-transferase, and <i>in vitro</i> metabolic activation of carcinogens aflatoxin B1 and benzo[a]pyrene was measured	–increases activity of some phase II detoxification enzymes –decreases activity of some Phase I enzymes	Kusamran et al. [90]
	–Inhibits CYP2C9	–E.coli transfected with CYP's –CYP inhibition assays and <i>M. charantia</i> -leaves	–Inhibits CYP's	Opong et al. [110]

Abbreviations: P-glycoprotein (P-gp); Breast cancer resistance protein (BCRP); Multi-drug resistance associated protein-2 (MRP-2); Pregnane X receptor (PXR); Doxorubicin (DOX); Streptozotocin (STZ); Cytochrome-P450 enzymes (CYP's).