

Review

Cucurbitane-type triterpenoids in *Momordica charantia* Linn.

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***Momordica charantia* Linn, belonging to the family of Cucurbitaceae, is a useful medicinal and vegetable plant for human health and one of the most promising plants for diabetes. Cucurbitane-type triterpenoids are the main active constituents of *M. charantia* and have a number of potential biological and pharmacological activities including antidiabetic, anti-obesity, anticancer, anti-HIV, antifeedant and antioviposition activities. Since the early 1960's the constituents of bitter melon have been investigated and several classes of secondary metabolites including cucurbitane-type triterpenoids have been isolated. Charantin, an anti-diabetic compound, is a typical cucurbitane-type triterpenoid in *M. charantia* and is a potential and promising substance for the treatment of diabetes. This review summarized previous and current information regarding cucurbitane-type triterpenoids in *M. charantia* and provides new insights into its underlying chemical isolation and activities.**

Key words: Biological and pharmacological activities, charantin, cucurbitane-type triterpenoids, diabetes, *Momordica charantia* Linn.

INTRODUCTION

Momordica charantia Linn, belonging to the family of Cucurbitaceae, is an indigenous medicinal and vegetable plant found in the tropical and subtropical regions of the world and is commonly known as bitter gourd or bitter melon. All parts of the plant, including the fruit, taste bitter. The fruit looks usually oblong and resembles a cucumber (Basch et al., 2003; Krawinkel et al., 2006). The young fruit is emerald green that turns to orange-yellow when ripe. At maturity, the fruit splits into irregular valves that curl backwards and release numerous brown or white seeds encased in scarlet arils (Figure 1).

M. charantia is grown mainly for the production of immature fruits (Figure 2A) although the young leaves (Figure 2B) are edible as vegetable. It has been used extensively in traditional medicine as a remedy for

diabetes. With the traditional use supported by modern scientific evidence of the beneficial function of *M. charantia*, it is one of the most promising plants for diabetes today (Cefalu et al., 2008; Leung et al., 2009; Modak et al., 2007; Nahas et al., 2009). A number of studies have reported the effects of *M. charantia* unrelated to diabetes. Bitter melon has some interesting biological and pharmacological activities, e.g. anticancer, antiviral, antibacterial, analgesic, anti-inflammatory, hypotensive, anti-fertility, hepatotoxicity and antioxidant (Beloin et al., 2005; Grover and Yadav, 2004; Ng et al., 1992; Scartezzini et al., 2000; Zafar et al., 1991).

Since the early 1960's the constituents of bitter melon have been investigated and several classes of primary and secondary metabolites have been isolated from *M. charantia* fruit, seeds and whole plants (Raman and Lau, 1996). Bitter melon contains biologically active chemicals that include crude fat, crude protein, soluble dietary fiber, minerals, essential oil, flavonoids, phenolic acids, glycolipids, triterpenes. The immature fruits are a good source

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Figure 1. Fruit development of *M. charantia*: A) young B) mature and C) split fruit after full maturity.



Figure 2. Immature fruits (A) and young leaves (B) of *M. charantia* at the market in Siem Reap, Cambodia (The picture was taken in August, 2007).

of vitamin C and also provide vitamin A (Xie et al., 1998; Braca et al., 2008; Zhang et al., 2009).

Among the secondary metabolites of *M. charantia*, cucurbitane-type triterpenoids are one of the main bioactive constituents. These compounds and their aglycones showed some biological effects beneficial to diabetes and obesity. In addition, cucurbitane-type

triterpenoids have been reported to exhibit various pharmacological and biological activities including anticancer, anti-HIV, antidiabetic, antifeedant and antioviposition activities (Raman and Lau, 1996; Grover and Yadav, 2004; Beloin et al., 2005). This review presents previous and current information regarding cucurbitane-type and provide new insights into the underlying the chemical iso-

lations and biological activities of cucurbitane-type triterpenoids in *M. charantia*.

CUCURBITANE-TYPE TRITERPENOID IN *M. CHARANTIA*

Triterpenoids

The terpenoids, referred to as isoprenoids, are a class of natural products and related compounds formally derived from five-carbon isoprene units. Terpenoids of different sizes and composition are found in all classes of living things and are the largest group of naturally occurring chemicals (De las Heras et al., 2003). This class is subdivided according to the number of carbon atoms. The triterpenoids are terpenoids having a C₃₀ skeleton. These C₃₀ constituents are isolated and characterized from various sources in nature, particularly in resins and may occur as either esters or glycosides (Mahato et al., 1992; Connolly and Hill, 2008). More extensive backbone rearrangement of the protostane cation affords the cucurbitane skeleton. The cucurbitacins are a typical group of cucurbitane-type triterpenoids found in plants and belonging to the cucumber family (Cucurbitaceae). The natural cucurbitacins are well-known for their bitterness and toxicity (Hylands and Mansour, 1982; Chen et al., 2005).

Charantin

Charantin is a typical cucurbitane-type triterpenoid in *M. charantia* and is a potential substance with antidiabetic properties (Krawinkel and Keding, 2006). Pitiphanpong et al. (2007) demonstrated that charantin could be used to treat diabetes and can potentially replace treatment. This compound is a mixture of two compounds, namely, sitosteryl glucoside (Figure 3a) and stigmasteryl glucoside (Figure 3b). Pitiphanpong et al. (2007) established an efficient method, pressurized liquid extraction (PLE) of charantin from fruits of *M. charantia* using ethyl alcohol. Patel et al. (2006) developed a high performance thin layer chromatography (HPTLC) method for quantitative estimation of charantin in small, big, dried fruits used in formulations and different marketed antidiabetic polyherbal formulations (PHF). They found that the HPTLC method was reproducible, accurate and precise and detect charantin concentration at nanogram level. The developed HPTLC method would be an important tool in the quality control method of polyherbal formulations.

ISOLATION AND BIOLOGICAL ACTIVITIES OF CUCURBITANE-TYPE TRITERPENOID IN *M. CHARANTIA*

Chen et al. (2009) isolated fourteen cucurbitane triterpenoids, kuguacins F-S (1 - 14), including two pentanorcucurbitacins (6 and 7), one octanorcucurbitacin (8), and

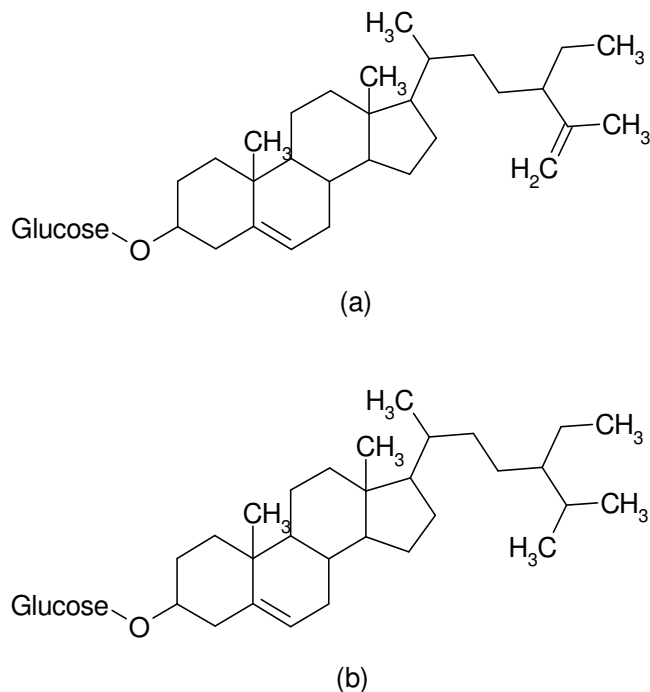


Figure 3. Chemical structure of (a) sitosteryl glucoside and (b) stigmasteryl glucoside

two trinorcucurbitacins (11 and 12), along with six known analogues from the vines and leaves of *M. charantia*. These compounds exhibited weak anti-HIV-1 activities *in vitro*. Akihisa et al. (2007) achieved the isolation of thirteen cucurbitane-type triterpene glycosides, including eight new compounds named charantosides I (6), II (7), III (10), IV (11), V (12), VI (13), VII (16), and VIII (17), and five known compounds, 8, 9, 14, 15 and 18, from a methanol extract of the fruits of Japanese bitter melon. They investigated these triterpene glycosides and five other cucurbitane-type triterpenes, 1 - 5, also isolated from the extract of bitter melon fruits, for their inhibitory effects on the induction of Epstein-Barr virus early antigen (EBV-EA) by 12-O-tetradecanoylphorbol-13-acetate (TPA) in Raji cells. These compounds exhibited inhibitory effects on EBV-EA induction with IC₅₀ values of 200 - 409 mol ratio/32 pmol TPA. Compounds 1 and 2 showed anticancer activity in induced mouse skin carcinogenesis tests. Four cucurbitane glycosides, momordicosides Q, R, S and T and stereochemistry-established karaviloside XI, were isolated from *M. charantia* by Tan et al. (2008). These compounds and their aglycones showed some biological effects beneficial to diabetes and obesity. Five cucurbitacins, kuguacins A-E (1-5), together with three known analogues, were isolated from bitter melon roots by (Chen et al., 2008). Compounds 3 and 5 showed moderate anti-HIV-1 activity and exerted minimal cytotoxicity. Harinantenaina et al. (2006) established the isolation of three new cucurbitane triterpenoids (1 - 3), together with eight known compounds

(4 - 11) from bioguided fractionation of the methanol extract of dried bitter melon. The major compounds, 5beta,19-epoxy-3beta,25-dihydroxycucurbita-6,23(E)-diene (4) and 3beta,7beta,25-trihydroxycucurbita-5,23(E)-dien-19-al (5) have been tested and have shown blood hypoglycaemic effects in the diabetes-induced male ddY mice strain at 400 mg/kg. They demonstrated that major pure cucurbitanoid compounds of *M. charantia* have *in vivo* hypoglycaemic effects.

Wang et al. (2008) developed a simple and specific analytical method for the quantitative determination of five cucurbitane-type triterpenoids isolated from the fruit of *M. charantia*. They suggested that the method was sensitive, quick and accurate for the determination of main triterpenes and saponins in bitter melon, and can be used for quality control of *M. charantia* and its related dietary supplements. Donya et al. (2007) studied the effect of various processing methods on the determination of momordicosides K and L contents. To identify momordicosides K and L in methanolic extracts of fresh and processed samples, a liquid chromatography-electrospray ionization-mass spectrometry (LC/ESI/MS) method was used. Only extracted ion chromatographs for blanched bitter melon and bitter melon with MY 68 agent showed the absence of momordicosides K and L. Four new cucurbitane-type triterpenes, cucurbita-5,23(E)-diene-3beta,7beta,25-triol (1), 3beta-acetoxy-7beta-methoxycucurbita-5,23(E)-dien-25-ol (2), cucurbita-5(10),6,23(E)-triene-3beta,25-diol (5) and cucurbita-5,24-diene-3,7,23-trione (6), together with four known triterpenes, were isolated from the methyl alcohol extract of the stems of bitter melon by Chang et al. (2008).

Liu et al. (2008) isolated two new (1 and 2) and eight known cucurbitane-type triterpene glycosides and one cucurbitane-type triterpene from the fruits of *M. charantia*. The glycosides (7beta,25-dimethoxycucurbita-5(6),23(E)-dien-19-al 3-O-beta-D-allopyranoside (1); 25-methoxycucurbita-5(6),23(E)-dien-19-ol 3-O-beta-D-allopyranoside (2); momordicosides A, F (1), F (2), G, K and L; and goyaglycoside-c and goyaglycoside-d) and the triterpene [3 beta,7beta,25-trihydroxycucurbita-5,23(E)-dien-19-al] were characterized by physical, chemical and spectroscopic techniques, including 1D- and 2D-NMR as well as by comparison with reported data. Three new cucurbitane-type triterpenoid saponins, named momordicoside M, N and O, respectively, along with one known saponin momordicoside L were isolated from the fresh fruits of *M. charantia* by Li et al. (2007). Nakamura et al. (2006) isolated three cucurbitane-type triterpene called karavilagenins A, B and C and new cucurbitane-type triterpene glycosides called karavilosides I, II, III, IV and V from the dried fruit of Sri Lanka bitter melon. Five cucurbitane-type triterpenes, (23E)-25-methoxycucurbit-23-ene-3beta,7beta-diol (1), (23E)-cucurbita-5,23,25-triene-3beta,7beta-diol (2), (23E)-25-hydroxycucurbita-5,23-diene-3,7-dione (3), (23E)-cucurbita-5,23,25-triene-3,7-dione (4) and (23E)- 5beta,

19-epoxycucurbita-6,23-diene-3beta,25-diol (5), together with one known triterpene, (23E)-5beta,19-epoxy-25-methoxycucurbita-6,23-dien-3beta-ol(6), have been isolated from the methanol extract of the bitter melon stems by Chang et al. (2006).

Kimura et al. (2005) reported that the structures of three new cucurbitane-type triterpenoids isolated from the methanol extract of the fruit of Japanese bitter melon were established as (19R,23E)-5beta,19-epoxy-19-methoxycucurbita-6,23,25-trien-3beta-ol (1), (23E)-3beta-hydroxy-7beta-methoxycucurbita-5,23,25-trien-19-al (2) and (23E)-3beta-hydroxy-7beta,25-dimethoxycucurbita-5,23-dien-19-al (3) on the basis of spectroscopic methods. These compounds were accompanied by the known (19R,23E)-5beta,19-epoxy-19,25-dimethoxycucurbita-6,23-dien-3beta-ol (4) and (19R,23E)-5beta,19-epoxy-19-methoxycucurbita-6,23-diene-3beta,25-diol (5). This is the first report on the isolation of tetracyclic triterpenoids possessing a delta23,25-conjugated diene system, viz., 1 and 2, from a natural source. Murakami et al. (2001) isolated eight cucurbitane-type triterpene glycosides called goyaglycosides-a, -b, -c, -d, -e, -f, -g and -h and three oleanane-type triterpene saponins termed goyasaponins I, II and III from the fresh fruit of Japanese bitter melon together with five known cucurbitane-type triterpene glycosides momordicosides A, C, F1, I and K.

ANTIFEEDANT AND ANTIOVIPOSITION ACTIVITIES OF CUCURBITANE-TYPE TRITERPENOIDS

Mekuria et al. (2005) reported that *Liriomyza trifolii* (the American serpentine leaf mining fly), whose larva feeds on more than 120 plant species is well known by its high degree of polyphagy. Investigations on the oviposition behavior by the American serpentine leaf mining fly demonstrated that among cucurbitaceous plants, *M. charantia* is rarely attacked by *L. trifolii*. The methanol extract of bitter melon leaves exhibited strong oviposition deterrent activity against *L. trifolii* females on the host plant leaf when it was dipped in the methanol extract at a concentration of 1 g of fresh leaf equivalent/ml. They isolated a new cucurbitane triterpenoid, 7,23-dihydroxy-3-O-malonylcucurbita-5,24-dien-19-al, along with another known compound, momordicine I from the bioguided fractionation of the methanol extract of the leaves of *M. charantia*. Both a new isolated cucurbitane triterpenoid and momordicine I, respectively, had significant ovipositing deterrent effect towards the adult females of *L. trifolii* on host plant leaves treated at concentrations of 3.25 and 33.60 microg/cm². In addition, They isolated a novel cucurbitane glucoside, 7-O-beta-D-glucopyranosyl-3,23-dihydroxycucurbita-5,24-dien-19-al, named momordicine IV, along with another known compound, momordicine II from the analysis of the polar fraction of the methanol extract of bitter melon leaves. Momordi-

cine II and IV deterred oviposition by *L. trifolii* significantly when bioassays were carried out on kidney bean leaves treated at 75.6 and 20.3 microg/cm² leaf surface, respectively. There was no synergistic effect on oviposition deterrent when the two compounds were combined in their natural abundance Mekuria et al. (2006). Kashiwagi et al. (2007) isolated a cucurbitane glucoside, momordicine V from bitter melon leaves, along with the previously reported compounds, momordicines I, II, IV and 3-O-malonylmomordicine I. The oviposition by *L. trifolii* on host plant leaves was obstructed by the treatment of momordicine V with 26.16 microg/cm² leaf surface.

CONCLUSION

Medicinal and vegetable plants are recommended for the essential source of nutrition and the prevention of human disease including cancer and diabetes that they have to offer. However, their phytochemicals and action mechanisms are poorly understood. *M. charantia* is a useful medicinal and vegetable plant for human health and one of the most promising plants for diabetes. Extensive research has studied the isolation of several classes of secondary metabolites including cucurbitane-type triterpenoids and the potential biological and pharmacological activities of natural products in *M. charantia*. Therefore, bitter melon is recommended as one of the most promising plants for diabetes. Charantin, a cucurbitane-type triterpenoid, is also recommended for the treatment of diabetes. The aim of this study is to gather all the possible information regarding cucurbitane-type triterpenoids in *M. charantia* with the aim of helping scientists to take action for future study in this discipline.

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