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THE EFFICACY OF CUCURBITANE TYPE TRITERPENOIDS, GLYCOSIDES AND PHENOLIC COMPOUNDS ISOLATED FROM *MOMORDICA CHARANTIA*: A REVIEW

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ABSTRACT

Momordica charantia Linn. which has been used mainly for edible purposes at different countries of the world including South East Asia and has also been extensively used in traditional medicines for the cure of various ailments. *M. charantia* belongs to the cucurbitaceae family. Extensive research has been carried out on the fruit, leaves, and seeds of the plant. Most importantly, all these research works have shown its efficacy on various cancer cell lines like lymphoid leukemia, lymphoma, choriocarcinoma, melanoma, breast cancer, skin tumor, prostatic cancer, squamous carcinoma of tongue and larynx, human bladder carcinomas and on Hodgkin's disease. Clinical reports of some research on the use of *M. charantia* in diabetes and cancer patients showed promising results. The main active constituents of *M. charantia* are cucurbitane type triterpenoids which have some potent biological and pharmacological activities including antidiabetic, anti-obesity, anticancer, anti-HIV, anti-feedant and anti-oviposition activities. Since in the early 1960's the constituents of *M. charantia* have been investigated and several classes of secondary metabolites including cucurbitane-type triterpenoids, glycosides and phenolic compounds have been isolated and their structures were determined. This review summarizes the previous and current information regarding phytochemical constituents of *M. charantia* and their pharmacological effects that provide the scope for future research in this aspect.

INTRODUCTION: Plants and herb preparation have been traditionally use for the cure of various ailments from ancient times and even today all over the world, 80% of the population continues to use traditional medicine for primary health care. In the past decade, therefore, research has been conduct on scientific evaluation of traditional drugs of plant origin. *Momordica charantia* is one such plant that has been frequently used as medicine from time immemorial [1, 2].

Momordica charantia, a climber belonging to family Cucurbitaceae, is commonly known as bitter gourd or bitter melon in English and karela in Bengali. *Momordica* means, to bite (referring to the jagged edges of the leaf, which appear as if they have been bitten). All parts of the plant, including the fruit have bitter taste. The fruit is oblong and resembles a small cucumber; young fruit is emerald green that turns to orange-yellow when ripe. It is an herb, grows in tropical areas of Asia, Amazon, East Africa, and the Caribbean and cultivated throughout the world for its use as vegetable as well as folk medicine.

The plant has been used traditionally as medicine in developing countries like Brazil, Bangladesh, China, Colombia, Cuba, Ghana, Haiti, India Mexico, Malaya, New Zealand, Nicaragua, Panama and Peru. Some of its common uses in the above countries are for diabetes, as a carminative and in the treatment of colics [3-5]. Topically it is used for treatment of wounds, internally as well as externally for management of worms and parasites. It is also used as emmenagogue, antiviral for measles and hepatitis. In Turkish folk medicine, mature fruits of *M. charantia* are used externally for rapid healing of wounds and internally for treatment of peptic ulcers [5].

In Bangladesh, various medicinal properties are claimed for *M. charantia* that include antidiabetic, abortifacient, anthelmintic, contraceptive, antimalarial and laxative and is used for treatment of dysmenorrhea, eczema, emmenagogue, galactagogue, gout, jaundice, kidney (stone), leprosy, leucorrhea, piles, pneumonia, psoriasis, rheumatism and scabies. However, it is commonly consumed as vegetable [6].

During the last few decades tremendous research work has been carried out with *M. charantia* extract to see the antidiabetic, antiviral, antitumor, antileukemic, antibacterial, antihelmentic, antimutagenic, antimycobacterial, antioxidant, antiulcer, anti-inflammatory activities along with hypo-cholesterolemic, hypo-triglyceridemic, hypo- tensive, immunostimulant, and insecticidal properties [6-8]. This review aims to highlight the main phytochemical constituents of *M. charantia* with their biological properties which support for future research on this plant.

Phytochemistry: The reported data showed that cucurbitane type triterpenoids are the main and common phytochemicals present in the *Momordica charantia*. More than 50 cucurbitacins so far have been isolated from this plant together with glycosides, saponins, alkaloids, fixed oils, proteins, steroids, flavonoids and phenolic compounds. Research has found that the leaves are nutritious sources of calcium, magnesium, potassium, phosphorus and iron; both the edible fruit and the leaves are great sources of the vitamins A, C and B [3, 8-9].

Cucurbitane type triterpenoids: The terpenoids, referred to as isoprenoids, are a class of natural products and related compounds formally derived from five carbon isoprene units. The cucurbitacins are a typical group of cucurbitane type triterpenoids found in plants and belonging to the cucumber family (Cucurbitaceae) and the main chemical constituents of *M. charantia*. The following cucurbitane type triterpinoid are isolated from different part of *M. charantia* (**Fig. 1**)

Charantin, a mixture of two compounds, namely, sitosteryl glucoside and stigmasteryl glucoside [10]; kuguacins A-S [11-12]; 3β, 25-dihydroxy-7β-methoxy cucurbita-5, 23(E)-diene, 3β-hydroxy-7β, 25-dimethoxy

cucurbita-5, 23(E)-diene, 3β, 7β, 25-trihydroxy cucurbita-5, 23(E)-diene-19-al, 5β, 19-epoxycucurbita-6, 23(E)-diene-3β, 19, 25-triol, 5β, 19-epoxy-19-methoxycucurbita-6,23(E)-diene-3β, 25-diol [13]; 3β, 25-dihydroxy-5β,19-epoxycucurbita-6, 23(E)-diene [12]; momordicine I, II and III [14]; karavilagenin A, B, C, D and E [15-16]; 19(R)-methoxy-5β,19-epoxycucurbita-6, 23-diene-3β, 25-diol, 5β, 19-epoxycucurbita-6, 23(E)-diene-3β, 25-diol [15]; 3β, 7β-dihydroxy-25-methoxy cucurbita-5, 23(E)-diene-19-al [17]; 23(E)-25-methoxy cucurbita-23-ene-3β, 7β-diol, 23(E)-cucurbita-5, 23, 25-triene-3β, 7β-diol, 23(E)-25-dihydroxy cucurbita-5, 23-diene-3, 7-dione, 23(E)-cucurbita-5, 23, 25-triene-3, 7-dione, 23(E)-5β, 19-epoxycucurbita-6, 23-diene-3β, 25-diol, 23(E)-5β, 19-epoxy-25-methoxy cucurbita-6, 23-diene-3β-ol [18]; cucurbita-5, 23(E)-diene-3β, 7β, 25-triol, 3β-acetoxy-7β-methoxy cucurbita-5, 23(E)-diene-25-ol, cucurbita-5(10), 6, 23(E)-triene-3β, 25-diol, cucurbita-5, 24-diene-3, 7, 23-trione [19]; (19R, 23E)-5β, 19-epoxy-19-methoxy cucurbita-6, 23,25-triene-3β-ol, (23E)-3β-hydroxy-7β-methoxycucurbita-5, 23, 25-triene-19-ol, (23E)-3β-hydroxy-,7β, 25-dimethoxycucurbita-5, 23-diene-19-ol, (19R, 23E)-5β, 19-epoxy-19, 25-dimethoxycucurbita-6, 23-diene-3β-ol, (19R, 23E)-5β, 19-epoxy-19-methoxy cucurbita-6, 23-diene-3β, 25-diol [20].

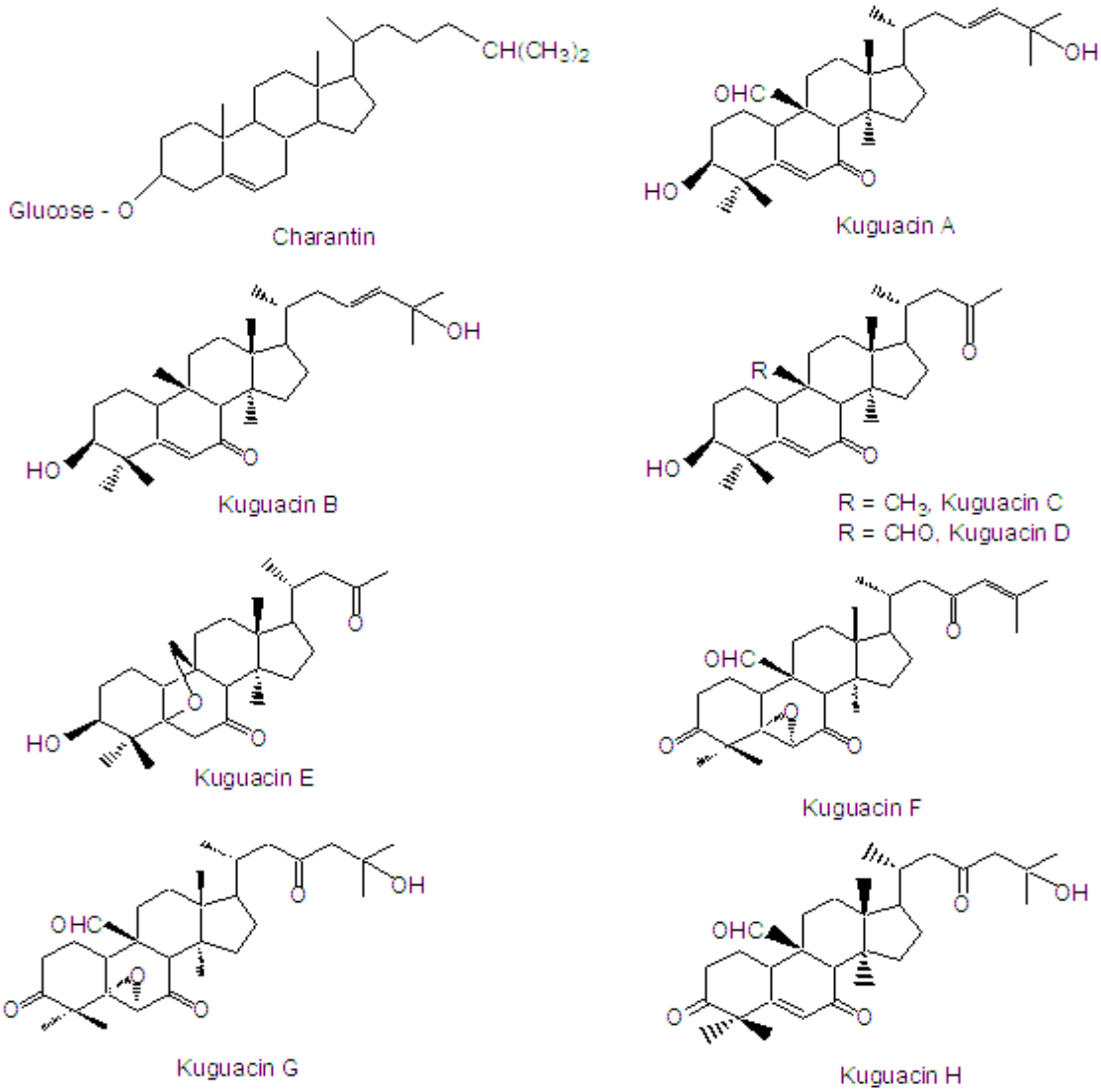


FIG. 1: MAJOR CUCURBITANE TYPE TRITERPINOID ISOLATED FROM *M. CHARANTIA* (CONTINUED)

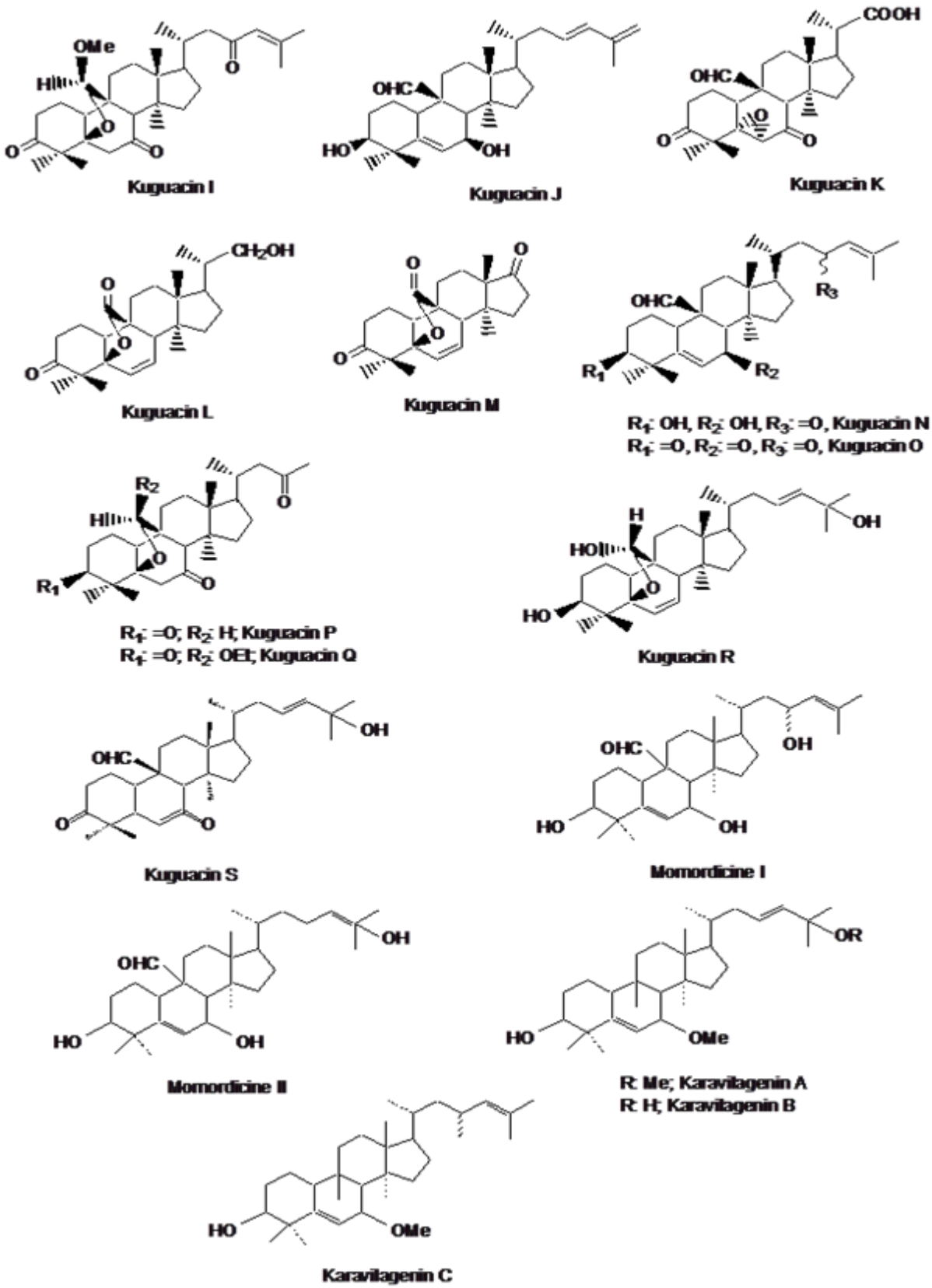


FIG. 1: MAJOR CUCURBITANE TYPE TRITERPINOID ISOLATED FROM *M. CHARANTIA*

Cucurbitane type triterpene glycoside: Cucurbitane glycoside, form with the substitutions at C-2 and/or C-3 position of the main skeleton of cucurbitanes, are abundant in the plants of genus *Momordica.* Momordicosides A-E [21-22], all lacking an oxygen function at C-11, the first cucurbitane glycoside have been isolated from the seeds of *M. charantia*. Following cucurbitane glycosides were also isolated (**Fig. 2**). Charantosides I-VIII [23]; momordicosides F1, F2, G, I, K, L, M, N, O, Q, R, S and T [24-26]; Karaviloside I, II, III, IV, V, VI, VII, VIII, IX, X and XI [15, 16]; 3-O-β-D-allopyranosyl, 7β, 25-dihydroxycucurbita-5, 23(E)-diene-19-al [13]; 3-O-β-D-allopyranosyl, 7β, 25-dihydroxy cucurbita-5(6), 23(E)-diene-19-al, 3-O-β-D-allo pyranosyl, 25-methoxy cucurbita-5(6), 23(E)- diene-19- ol [24]; Goyaglycoside- a, -b, -c, -d, -e, -f, -g and –h [27]. A new steroidal glycoside, 24(*R*)-stigmastan-3β, 5α, 6β-triol-25-ene 3-*O*-β-gluco pyranoside was also isolated from *M. charantia* [28].

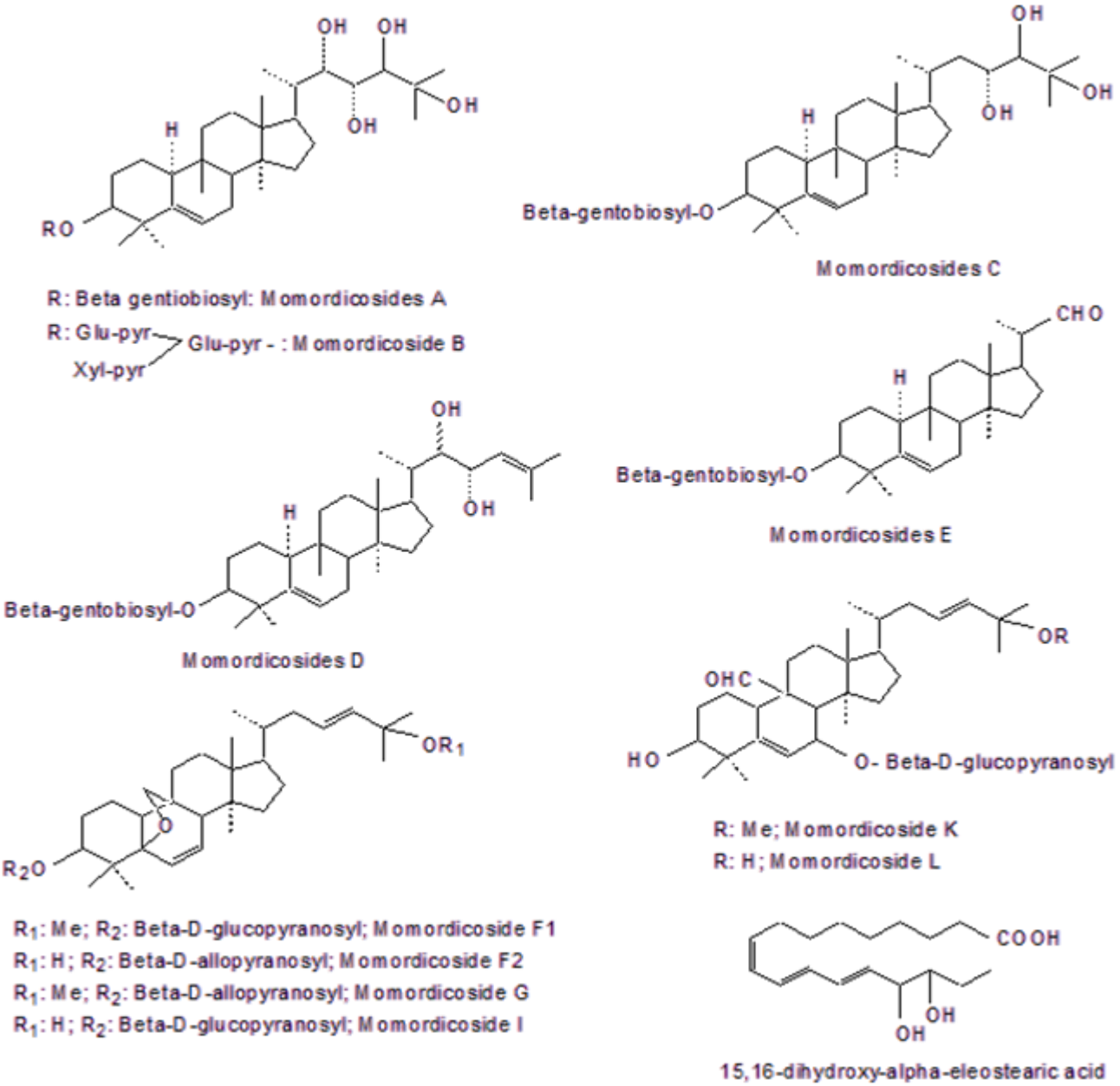
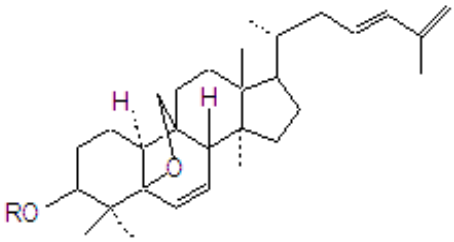
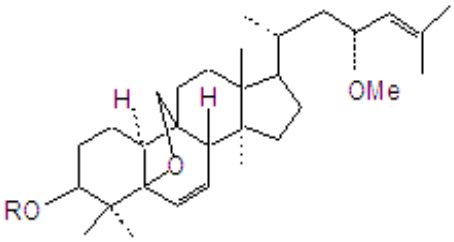


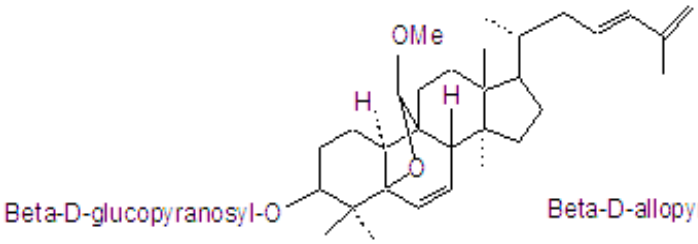
FIG. 2: MAJOR CUCURBITANE TYPE TRITERPINOID GLYCOSIDE ISOLATED FROM *M. CHARANTIA* (CONTINUED)



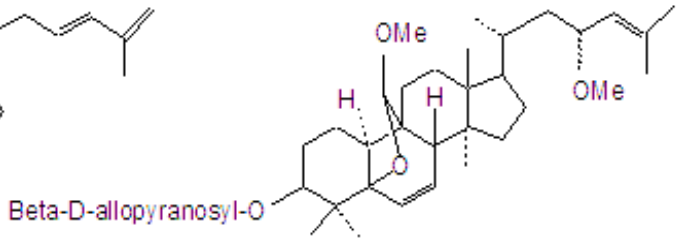
R: Beta-D-glucopyranosyl; Charantosides III
R: Beta-D-allopyranosyl; Charantosides IV



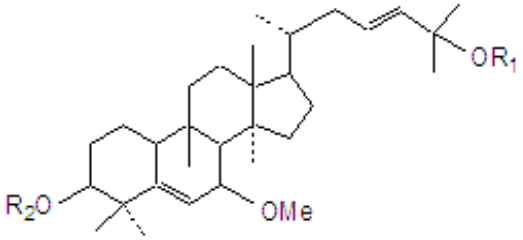
R: Beta-D-glucopyranosyl; Charantosides V
R: Beta-D-allopyranosyl; Charantosides VI



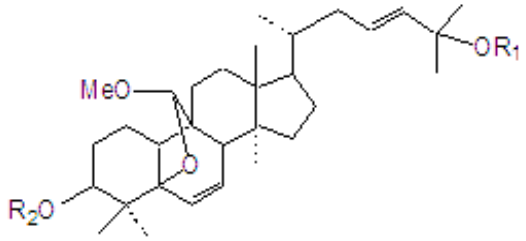
Charantosides I



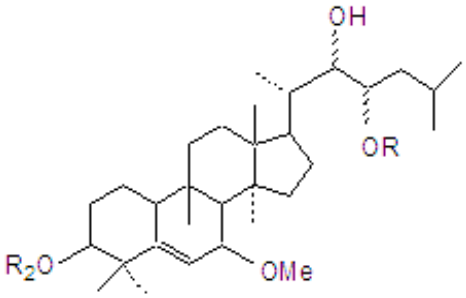
Charantosides II



R_1: Me; R_2: Beta-D-glucopyranosyl; karaviloside I
R_1: Me; R_2: Beta-D-allopyranosyl; karaviloside II
R_1: H; R_2: Beta-D-allopyranosyl; karaviloside III



R_1: H; R_2: Beta-D-glucopyranosyl; Goyaglycoside-a
R_1: H; R_2: Beta-D-allopyranosyl; Goyaglycoside-b
R_1: Me; R_2: Beta-D-glucopyranosyl; Goyaglycoside-c
R_1: Me; R_2: Beta-D-allopyranosyl; Goyaglycoside-d



R_1: Beta-D-glucopyranosyl; R_2: H; karaviloside IV
R_1: Beta-D-allopyranosyl; R_2: Beta-D-allopyranosyl; karaviloside V

FIG. 2: MAJOR CUCURBITANE TYPE TRITERPINOID GLYCOSIDE ISOLATED FROM *M. CHARANTIA* (CONTINUED)

Oleanane type triterpene saponins: Murakami *et al.,* [28] have reported the goyasaponins I, II and III present in the fresh fruit of Japanese *M. charantia*.

Phenolic and flavonoid compound: HPLC analysis has been proved that leaf, stem, fruit (green and ripe) contains phenolic compounds like galic acid, tannic acid, (+)-catechin, caffeic acid, p-coumaric, gentisic acid, chlorogenic acid and epicatechin [29-30] (**Fig. 3**).

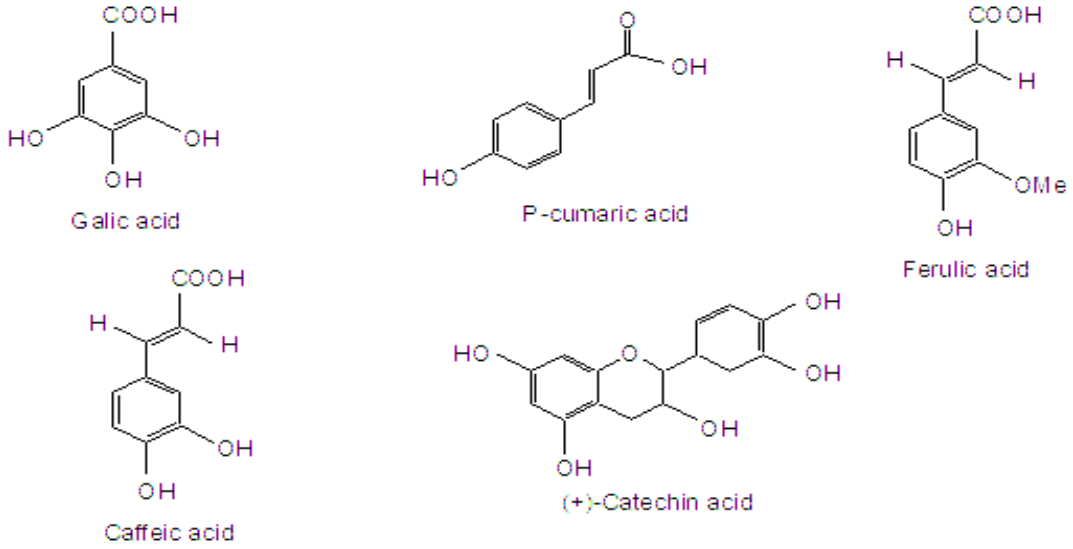


FIG. 3: PHENOLIC COMPOUND DETERMINED BY HPLC FROM *M. CHARANTIA*

Miscellaneous: The essential oil obtained from the seeds of *M. charantia* was analyzed by GC/MS. Twenty-five components, representing 90.9% of the oil, were identified and among them *trans*-nerolidol, apiole, *cis*-dihydrocarveol and germacrene D were the main constituents [31]. Trypsin inhibitors e.g. MCTI-II' and BGIT [32], elastase inhibitors [33], guanylate cyclase inhibitors [34] and α-glucosidase inhibitor e.g. D-(+)-Trehalose [35] are reported. Moreover, HIV inhibitory proteins like MRK29 (MW: 28.6 KDa) and MAP30 (MW: 30,000 KDa) and lectin were also documented [36]. α-eleostearic acid and its dihydroxy derivative, strongly inhibited the growth of cancer and fibroblast cell lines like HL60 leukemia and HT29 colon carcinoma, were also isolated from *M. charantia* [37].

Pharmacological Properties:

Antidiabetic activity: All parts (fruit pulp, leaves, seeds and whole plant) of *M. charantia* showed hypoglycemic activity in normal animals [38-40] and antihyperglycemic activity in alloxan induced method [41-43] or streptozotocin-induced method [44-46] as well as acts on genetic models of diabetes [47]. Moreover, a few isolated compounds like charantin, a polypeptide-p, momordin Ic, oleanolic acid 3-O-monodesmoside, and oleanolic acid 3-O-glucuronide of *M. charantia* also showed hypoglycemic activity [48-50].

Hypolipidemic effect: The treatment of diabetic rats with *M. charantia* extract resulted in significant reduction of blood lipid levels (total cholesterol and triglycerides) in diabetic rats. *M. charantia* also ameliorate PI-associated apoB and lipid abnormalities in HepG2 cells. Compounds in *M. charantia* improve lipid profiles. They reduce liver secretion of apolipoprotein B (Apo B) – the primary lipoprotein of low-density "bad" cholesterol; reduce apolipoprotein C- III expression, the protein found in very-low density cholesterol which turns into LDL/bad cholesterol; and increases the expression of apolipoprotein A-1 (ApoA1) - the major protein component of high density "good" cholesterol. It also lowers cellular triglyceride content [51].

Antioxidant effect: *M. charantia* extracts possess potent antioxidant and free radical scavenging activities [52-53] and this may be due to the presence of phenolic and flavonoid compounds like, galic acid, tannic acid, (+)-catechin, caffeic acid, p-coumaric, gentisic acid, chlorogenic acid and epicatechin [29-30].

Inhibition of protein Synthesis: The bitter melon plant (*Momordica charantia*) seeds also contain several lectins which, while not highly toxic to animals *in situ*, inhibit protein synthesis *in vitro* [54].

Hepatoprotective effect: The extract of *Momordica charantia* significantly reduces serum glutamic pyruvate ransaminase (SGPT), and serum glutamic oxaloacetate transaminase (SGOT) in rats. The hepatoprotective activity of *M. charantia* leaves may be attributed to the presence of flavonoids and ascorbic acid [55].

Antibacterial and antifungal activity: Clinically and experimentally, leaf extracts (Methanol, Ethanol and aqueous) of *M. charantia* have demonstrated a broad spectrum antimicrobial activity [56]. Meanwhile, essential oil of the seed of *M. charantia* showed antibacterial and antifungal activities may due to the presence of *trans*-nerolidol (61.6% of the total oil) [31].

Antiviral activity: Cunnick *et al.,* [57] clinically and experimentally demonstrated that the leaf extract of *M. charantia* have the ability to increase resistance against viral infections and to provide immunostimulant effects. Several isolated phytochemicals, e.g. α and β-momorcharin, lectin, MRK 29 and MAP 30, have been documented to have *in vitro* antiviral activity against Epstein-Barr, herpes, HIV, coxsackievirus B3 and polio-viruses and among them MAP 30 have promising anti HIV activity [58-59].

Anticancer activity: *M. charantia* extract and its several isolated compounds like momordin I, Id and Ie, α and β momorcharin and cucurbitacin B as well as MAP 30- have shown anticancer activity against lymphoid leukemia, lymphoma, choriocarcinoma, melanoma, breast cancer, skin tumor, prostatic cancer, squamous carcinoma of tongue and larynx, human bladder carcinomas and Hodgkin's disease [60-67]. kobori *et al*, [37] have depicted α-eleostearic acid present in the seed extract of this plant and its dihydroxy derivative strongly inhibited the growth of cancer and fibroblast cell lines like HL60 leukemia and HT29 colon carcinoma.

Abortifacient and antifertility activity: Literature review revealed the experimental documentation of abortifacient properties of *Momordica* proteins [68-72] and momorcharins produced abortifacient activity in early and midterm pregnancy [70-72].

Anti-ulcer activity: The traditional use of *M. charantia* in the treatment of ulcers is supported by research, suggesting the dried-powdered fruits in filtered honey have significant and dose-dependent anti-ulcerogenic activity against ethanol-induced ulcerogenesis in rats [73]. Matsuda *et al.,* [74] demonstrated momordin Ic (10 mg/kg, b.wt. p.o.) potentially inhibited ethanol induced gastric mucosal lesions.

Immunomodulatory activity: *M. charantia* extracts and its isolated constituents have a variable effect on the immune system. It has been shown to be immune stimulating in some studies and immunosuppressive in some conditions (allograpft rejection) [75]. α- and β-momorcharin showed immunosuppressive activity *via* lymphocytotoxicity or to a shift in the kinetic parameters of the immune response[76]. However, its immunostimulant activity has been attributed to increase the interferon production and natural killer cell activity [57].

Analgesic and anti-inflammatory activity: Momordin Ic and its aglycone, oleanolic acid are active principles with antirheumatoid activity [77-78].

Hypotensive and anti prothrombin activity: Wang and Ng [79] observed mild hypotensive response with Momordin. In another study, *M. charantia* prolonged

prothrombin time by inhibiting activation of factor X by factor VIIa-tissue factor complex or factor IXa [80].

Antiobesity: *M. charantia* and its isolated compounds increase the activity of adenosine-5-monophosphate kinase (AMPK), an enzyme that facilitates cellular glucose uptake and fatty acid oxidation. Hypoglycemic agents in *M. charantia* promote efficient oxidation of glucose into fuel, and conversion into starch. (Glycogen or animal starch is stored in the liver and muscle cells). During glucose shortages, fats/fatty acids are used as fuel. Continued demand for energy in the absence or shortage of glucose causes fat cells to release their fat contents to maintain energy balance. This increased fatty acid oxidation eventually leads to weight loss [81].

Toxicity and Drug interaction: The seed contains vicine and therefore can trigger symptoms of favism in susceptible individuals. In addition, the red arils of the seeds are reported to be toxic to children. Many *in vivo* clinical studies have demonstrated the relatively low toxicity of all parts of the *M. charantia* plant when ingested orally. Pregnant women should not eat bitter melon as it stimulates the uterus and may cause premature birth [82].

CONCLUSION: Recent years, ethno-botanical and traditional uses of natural compounds, especially of plant origin received much attention as they are well tested for their efficacy and generally believed to be safe for human use. It is the best classical approach on searching new molecules for management of various diseases. Thorough screening of literature available on *Momordica charantia* depicted the fact that it is a popular remedy among the various ethnic groups, Ayurvedic and traditional practitioners for the treatment of various ailments. Today, evidence based studies are needed to establish these facts so that these wonder drugs with lot of therapeutic activities can be traditionally use safely (excluding the toxic components) to cure the various diseases of suffering humanity with high efficacy and least side effects. Like *M. charantia* lot of other medicinal plants are available and the time is coming to explore the efficacy and best use of such effective secondary plant metabolites which reduce the use of synthetic modern medicine having severe side effects.

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