

# Anti-cancer properties of bioactive compounds isolated from *Momordica charantia*: A mini review

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## ABSTRACT

Cancer is a major global disease where abnormal cells rapidly proliferate having the ability to migrate to different parts of the human body via a process called metastasis. Cancer is also one of the leading causes of death worldwide and is a burden financially and on the quality of human lives in both well-developed and less-developed countries, especially as the population is increasing. For centuries, Ayurveda culture has recommended the use medicinal plants to treat a variety of diseases maintaining health prior to the advent of modern medicine. Over time, much information and knowledge have been gathered about the properties of medicinal plants by personal experimentation, local custom, anecdote and folk traditions leading to the formation of several traditional medicine systems and therapies. One such plant is *Momordica charantia*, which acts as a functional food to prevent and to treat diabetes mellitus and associated complications as well as cancers. Research in the last few decades, utilizing modern techniques, has revealed anti-cancer activities of *M. charantia*. Several groups of investigators have reported that treatment of number on cancer cell lines with *M. charantia*-related extracts and compounds have been very successful. These agents exert their anti-cancer effects by inducing cell cycle arrest and apoptosis without adversely affecting normal healthy cell growth. This review focuses on recent advancements in anti-cancer effectiveness and chemo-preventive ability of *M. charantia* and its active constituents with special emphasis on cucurbitane-type glycosides, ribosome-inactivating inhibitors and conjugated fatty acids.

**Keywords:** *Momordica charantia*, cell proliferation, cucurbitane, conjugated fatty acids, antitumor.

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## INTRODUCTION

A multitude of plants have been identified and used for the treatment of diseases throughout the world (Taylor, 2002). In developing countries, a majority of the population continues to use traditional medicine and over the past decades research has been focused on scientific evaluation of traditional drugs of plant origin. *Momordica charantia* (MC) belongs to a short-fruited group of the Cucurbitaceae family and is one such plant that has been frequently used as medicine. The Latin name *Momordica* means, "to-bite" referring to the jagged edges of the leaves, which appear as if they have been bitten.

In botanical terms, the plant is referred to as

- a. Family: Cucurbitaceae
- b. Genus: *Momordica*

- c. Species: *charanti*

- d. Synonyms: *Momordica chinensis*, *Momordica elegans*, *Momordica indica*, *Momordica operculata*, *Momordica sinensis* and *Silyos fauriei*.

All parts of the plant, including the fruit, stems and leaves, taste bitter. This tendril-bearing vine grows to 5 m. It bears simple alternate leaves 4 to 12 cm across, with three to seven deeply separated lobes. Each plant bears separate yellow male and female flowers (Taylor, 2002).

MC are perennial climbers cultivated in many wet tropical countries of the world including parts of South America and Amazon basin including Brazil, Guyana and the Caribbean, Asia including India, China, Sri Lanka,

Pakistan, Nepal, Malaysia and tropical and subtropical regions of East Africa (Taylor, 2002).

### Ethno-medical uses

Research has shown that *M. charantia* has been used as traditional medicine since ancient times for its various medicinal properties (Joseph and Jini, 2013). It has been used (fruits, leaves, stems and roots) and recommended for centuries in Ayurveda as a traditional medicine to treat diabetes and other disease. At present, in India and the Pacific islands, a host of other various medicinal properties are associated with *M. charantia*. These include antidiabetic, abortifacient, antihelmintic, contraceptive, antimalarial and laxative. The plant is also used for treatment of dysmenorrhea, eczema, emmenagogue, galactagogue, gout, jaundice, kidney (stone), leprosy, leucorrhoea, piles, pneumonia, psoriasis, rheumatism and scabies (Grover and Yadav, 2004). It is used as a repellent in Tanzania against ants, weevils, mosquitoes and moth (Bryant, 1909). Similarly, in several African countries *M. charantia* is used as a sedative for irritable stomach, for the treatment of boils and roundworms and as an earache remedy (Chhabra et al., 1983; Chhabra et al., 1989; Goldstein et al., 1937). In Turkish folk medicine, the fruits of *M. charantia* are used externally for healing of wounds, and internally for treatment of ulcers and parasites (Yesilada et al., 1999). *M. charantia* also possesses anti-hypertensive properties, but its most common use is in treatment of diabetes mellitus and colics (Yesilada et al., 1999).

In the past decades and with the aid of modern techniques and tools, hundreds of studies have been done with MC crediting it with antidiabetic, antiviral, antitumor, antileukemic, antibacterial, antihelmintic, antimutagenic, antimycobacterial, antioxidant, antiulcer, anti-inflammatory, hypocholesterolemic, hypotriglyceridemic, hypotensive, immunostimulant, and insecticidal

properties (Basch et al., 2003; Raman and Lau, 1996).

### Phytochemical properties

Medicinal benefits of *M. charantia* lie in the bioactive phytochemical components. These constitute chemicals that help to generate physiological effects on the human immune system, protecting it from various diseases (Raman and Lau, 1996). The constituents of *M. charantia* have been investigated since the 1960's and numerous reports on phyto-chemical screen of *M. charantia* have revealed several classes of primary metabolites (proteins, and sugars), while secondary metabolites include flavonoids, alkaloids, tannins, steroids, phenolic acid, saponins, glycosides, triterpenes, essential oil, etc (Raman and Lau, 1996). The young fruit is a good source of vitamin A, vitamin C, phosphorous and iron (Xie et al., 1998; Zhang et al., 2009; Braca et al., 2008).

Today, around 228 different compounds have been isolated from various parts of *M. charantia* (Taylor, 2002). These different compounds have been classified into different chemical types. These include proteins, triterpenes, lipids, inorganic, phenyl-propanoids, carotenoids, steroids, alkaloids, monoterpenes, alkene to C3, carbohydrates, benzenoids, alkanol C5 or more and other unknown structures. Of the 228 different compounds, most of these fall under the groups of proteins and triterpenes.

With respect to inhibition, MC is an inhibitor of trypsin (Miura and Funatsu, 1995), elastase (Hamato et al., 1995), guanylate cyclase (Takemoto et al., 1980) and alpha-glucoside inhibitor (D-(+)-trehalose) (Matsuura et al., 2002). HIV inhibitory proteins (MAP 30, MRK 29) have also been documented by researchers (Husain et al., 1994). Over the last two decades, numerous phytochemicals have been isolated from MC showing interesting biological and pharmacological activities (Table 1).

**Table 1.** Phyto-chemical constituents of *Momordica charantia*.

Sources	Phytochemicals	References
Plant body	Momorcharins, momordenol, momordicilin, momordicins, momordicinin, momordin, momordolol, charantin, charine, cryptoxanthin, cucurbitins, cucurbitacins, cucurbitanes, cycloartenols diosgenin, elaeostearic acids, erythrodiol, galacturonic acids, gentisic acid, goyaglycosides, goyasaponins and multiflorenol	Xie et al. (1998), Yuan et al. (1999) and Parkash et al. (2002)
Plant leaves	Glycosides, saponins, alkaloids, fixed oils, triterpenes, proteins and steroids	Raman and Lau (1996)
Fruit	Momorcharins, momordicine, charantin, polypeptide-p insulin, ascorbigee, amino acids, aspartic acid serine, glutamic acid, threonine, glutamic acid, threonine, alanine and g-amino butyric acid. Other constituents include pipercolic acid, luteolin and a number of fatty acids such as lauric, myristic, palmitic, palmitoleic, stearic, oleic, linoleic, linolenic acid	Lotlikar and Rao (1966) and Yuwai et al. (1991)
Seeds	Urease, amino acids—valine, threonine methionine, isoleucine, leucine, phenylalanine.	Orlovskaya and Chelombitko (2007)

## Pharmacological activities

### Anti-diabetic properties

*M. charantia* is most widely studied with regard to its anti-diabetic effect. Active fractions from the fruit of *M. charantia* have been reported by several researchers to have significant hypoglycemic activity and anti-diabetic effects (Jayasooriya et al., 2000). Charantin (a saponin), isolated from the fruits and leaves contains the polypeptide gurmarin, which is similar in composition to insulin and is a promising anti-diabetic substance for treatment of diabetes (Lee et al., 2009). Studies have shown that all parts of the plant can produce hypoglycaemic activity in normal animals, and dose-dependent anti-hypoglycaemic activity in *alloxan*-induced or *streptozotocin*-induced and also in genetic models of diabetes mellitus (Grover and Yadav, 2004). Pari et al. (2001) demonstrated, using animal studies, that poly-herbal preparation containing *M. charantia* resulted in a significant reduction in blood glucose, glycosylated haemoglobin and increase in plasma insulin.

### Antibacterial properties

Extract of *M. charantia* leaves can be used as an antibacterial agent against many infections caused by *Escherichia coli*, *Salmonella paratyphi*, *Shigella dysenteriae* and *Streptomyces griseus* (Taylor, 2002; Omoregbe et al., 1996; Frame et al., 1998). The whole plant also possesses antiprotozoal properties killing successfully *Entamoeba histolytica* (Khan et al., 1998).

### Antiviral properties

*M. charantia* and its components are also known to have antiviral activity against many viruses including HIV, herpes, Epstein-Barr, coxsackievirus B3 and polio (Grover and Yadav, 2004). Immuno-stimulant effects have also been observed *in vivo* with increased resistance to viral infection (Joseph and Jini, 2013).

MAP 30, a protein isolated from the plant is found to be responsible for the plants anti-HIV activity. A clinical study established improved efficacy of anti-HIV therapy when MAP 30 was combined with low doses of dexamethasone and indomethacin (Bourinbaier and Lee-Huang, 1996). Alpha- and beta-momorcharin extracts from MC also possess anti-HIV properties by inhibiting HIV-1 integrase (Au et al., 2000).

### Other properties

Various studies have revealed other pharmacological properties of the plant. Some of these include anti-poliovirus activity (Foa-Tomasi et al., 1982) (where ribosome-inactivating proteins, which are present in *M.*

*charantia*, inhibit protein synthesis, resulting in the inhibition of poliovirus replication), anti-ulcer activity (Matsuda et al., 1999), anti-malaria activity (Munoz et al., 2000), anti-herpes activity (Foa-Tomasi et al., 1982), anti-oxidant activity (Kubola and Siriamornpun, 2008) and anti-inflammatory activity (Choi et al., 2002).

## CANCER OVERVIEW

Cancer is a lethal global disease which is caused by uncontrolled division of abnormal cells in a specific part of the body. The cells rapidly proliferate having the ability to migrate to different parts of the body via a process called metastasis. It is one of the leading causes of deaths worldwide and it is a burden on both well-developed and less developed countries, especially as the population is increasing. In 2012 alone, there were 8.2 million deaths caused by cancer (Torre et al., 2015). Breast cancer is the leading cause of deaths in females worldwide with an estimated 1.7 million diagnosed cases and 521,900 deaths in 2012 accounting for 25% of all cancer cases and 15% of cancer deaths among females (Torre et al., 2015). Other leading causes of deaths by cancer include colorectal cancer, prostate cancer, cervical cancer, liver cancer, and stomach cancer (Torre et al., 2015).

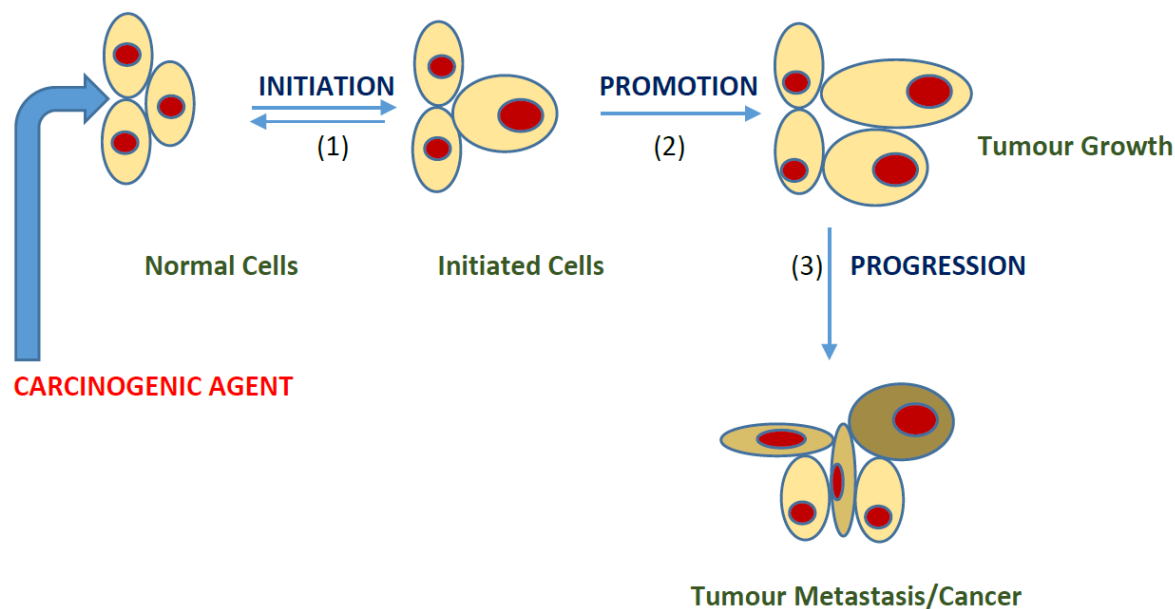
Cancer is a disease in which the cell presents itself with unrestricted proliferative potential that involves dynamic changes in the genome. Classes of cancer genes have been identified through their alteration in human and animal cells and by elucidation and transition of normal cells towards cancerous phenotypes in experimental models (Foulds, 1954; Bishop and Weinberg, 1996; Hanahan and Weinberg, 2000). Figure 1 shows a schematic diagram of the multi-cycle steps of a cancer progression.

Induction of cell cycle arrest or apoptosis by dietary compounds presents an excellent approach to inhibit the promotion and progression of carcinogenesis. However, cancer is a complex disease process and a single molecular target for therapeutic purpose might not be sufficient to stimulate the anticipated outcome. Therefore, relevant *in vitro* and *in vivo* studies, available in the literature and also related to anti-cancer of *M. charantia* sites, proposed its usefulness in signaling cascades processing for its anti-cancer and/or chemo-preventive efficacy. Mechanisms of action of the role of *M. charantia* in these studies include increased apoptosis, decreased cell proliferation and inhibition of tumours (Jilka et al., 1983; Kohno et al., 2002; Nagasawa et al., 2002; Xiong et al., 2009).

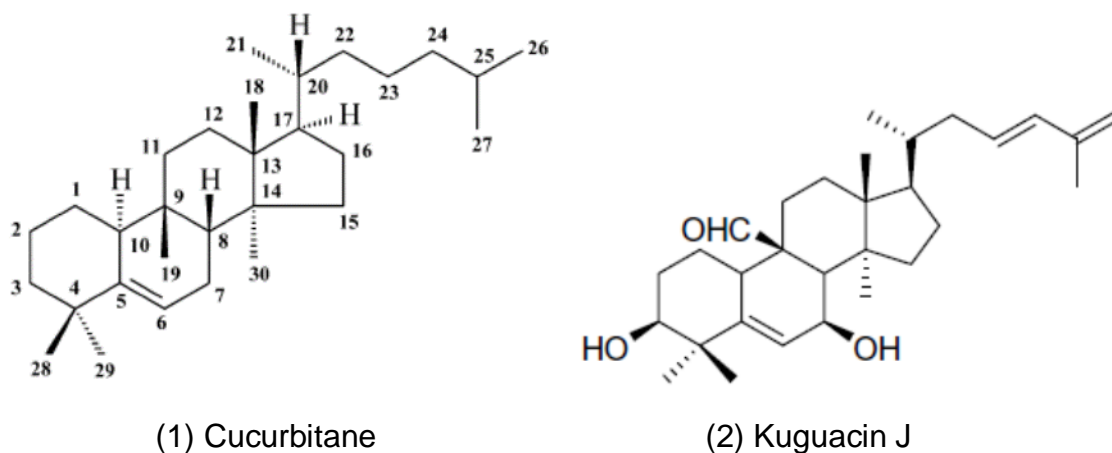
### Potential active constituents of *Momordica charantia* for anti-cancer properties

#### Cucurbitane-type triterpenoids

Cucurbitacins are a group of cucurbitane-type triterpenoids



**Figure 1.** A schematic diagram of multi-step cancer progression process. The process of carcinogenesis is complex and results in distinct cellular and molecular alterations. In simplified terms, it consists of the following stages: (1) initiation, whereby cells are exposed to a carcinogenic agent or other insults, (2) promotion, when abnormal cells persist and results in cell cycle alterations and (3) progression, when uncontrolled cell growth results in multidrug resistance towards anticancer drugs and metastasis follows (Hanahan and Weinberg, 2000).



**Figure 2.** (1) The basic chemical structure of cucurbitanes [19-(10 $\rightarrow$ 9 $\beta$ )-abeo-10 $\alpha$ -lanost-5-ene] and (2) the chemical structure of the triterpenoid Kuguacin J (Chen et al., 2005).

found in plants belonging to the cucumber family and are well-known for their bitterness and toxicity. Terpenoids, (referred to as isoprenoids) are a class of natural products that differ in sizes and composition and they are the largest groups of naturally occurring chemicals. They are derived from five-carbon isoprene units and consist of a C30 skeleton (Figure 2).

Structurally, they are characterised by the tetracyclic cucurbitane nucleus skeleton with a variety of oxygen substitutions at different positions and are arbitrarily

divided into twelve categories (A–T).

Numerous cucurbitane-type triterpenoids have been reported and isolated from various plants (Murakami et al., 2001; Kimura et al., 2005; Chang et al., 2006; Nakamura et al., 2006; Akihisa et al., 2007; Chang et al., 2008; Ma et al., 2010; Liu et al., 2009; Chen et al., 2008; Chen et al., 2009), with many showing biological activities (Chen et al., 2005). Moreover, many studies have confirmed different pharmacological activities of crude triterpenoids extract from *M. charantia*. These include

antidiabetic (Tan et al., 2008; Harinantenaina et al., 2006), antiviral (Yasui et al., 1998), anti-obesity (Bao et al., 2013; Hasani-Ranjbar et al., 2009), anti-proliferation (Sun et al., 2010; Lavhale et al., 2009; Yasuda et al., 2010; Pitchakarn et al., 2011; Ray et al., 2010; Battelli et al., 1996), and anti-HIV (Grover and Yadav, 2004; Beloin et al., 2005).

Today, more than 50 triterpenoids have been isolated from *M. charantia*, however, their biological activities, especially anti-tumour activities (including underlying mechanisms) remain to be explored in detail. Research work within the last decade, as it relates to anti-cancer activity from triterpenoids in *M. charantia*, has been promising (Yang et al., 2007; Escandell et al., 2008; Zhang et al., 2009; Tannin-Spitz et al., 2007). Akihisa et al. (2007) isolated thirteen cucurbitanes-type triterpene glycosides from a methanol extract of *M. charantia* 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. *M. charantia* can also induce inhibitory effects on EBV-EA induction, with IC<sub>50</sub> values of 200 to 409 mol ratio/32 pmol TPA. Selected compounds exhibited marked inhibitory effects in both 7, 12-dimethylbenz[a]anthracene and peroxy-nitrite-induced mouse skin cancer (Chang et al., 2008). Yasuda et al. (2010) have shown that Cucurbitacin B induces apoptosis via reactive oxygen species-dependent mechanism in human colon adenocarcinoma cells, while Pitchakarn et al. (2011) demonstrated apoptosis in androgen-dependent human prostate cancer by Kuguacin J, a triterpenoid isolated from the leaf of *M. charantia*.

Recently, Zhao et al. (2014) isolated (and structural elucidation) six new triterpenoids from the stems and leaves of *Momordica charantia*. One of these compounds, (momordicines VII), showed weak cytotoxicity against five human cancer cell lines with IC<sub>50</sub> values of 14.2 to 20.5 µmol/L.

### **Ribosome-inactivating proteins (RIPs)**

Ribosome-inactivating proteins, initially discovered in castor oil, are a family of plant enzymes that inhibit polypeptide chain elongation *via* N-glycosidase activity and potentially inhibit cellular protein synthesis (Stirpe, 1982). These proteins have gathered great research interest due to their potential use in cancer research. Importantly, they exhibit strong toxicity towards cancer cells while demonstrating low toxicity towards healthy cells. Plant RIPs are classified into three main categories (type 1 to 3) based upon their physical properties. *Momordica* anti-HIV protein (MAP 30) and Alpha-Momorcharin (α-MMC) (both type 1) are two major RIPs components in MC and they have been found to be potent inhibitors of protein synthesis due to their ribosome-specific N-glycosidase activity (Zeng et al., 2015).

There has been intense research activity over the past decade on the role of MAP 30 and α-MMC as an anti-tumour/anti-HIV agent (Tumer and Li, 2012) and this has also led to an increase in the demand for consumption of the fruit and its extracts. During the last 5 years, there have been promising reports of anti-tumour activity of ribosome-inactivating protein (RIP) from *M. charantia* by covalent attachment of polyethylene glycol leading to significant reductions of immunogenicity (Meng et al., 2012; Li et al., 2009; Bian et al., 2010).

### **Anti-tumor activity of MAP 30 and α-MMC RIP**

Accordingly, MAP30 and α-MMC have shown to exhibit antitumor activity in various cancer cells in both *in vitro* and *in vivo* studies (Lee-Huang et al., 1995; Lee-Huang et al., 2000; Fan et al., 2008; Hlin et al., 2016; Tsao et al., 1990; Ng et al., 1994; Battelli et al., 1996; Manoharan et al., 2014; Pan et al., 2014). MAP 30 has displayed anti-tumor activity in several human tumour cell lines (Lee-Huang et al., 1995), where anti-tumour activity was measured by metabolic labelling of protein synthesis in tumour cells. Subsequent work by these researchers (Lee-Huang et al., 2000) also showed that MAP 30 could effectively inhibit breast cancer (MDA-MB 231) cells via down regulating the expression of human epidermal growth factor receptor-2 (HER2). Fan et al. (2008) provided strong evidence that recombinant MAP 30 can induce the apoptosis of human colorectal carcinoma LoVo cells, while recent research by Hlin et al. (2016) confirmed that MAP30 recombinant protein inhibited the growth of bladder cancer 5637 cells by inducing apoptosis of target cells in a dose- and time- dependent manner.

α-MMC showed cytotoxicities against various cell lines (Tsao et al., 1990) with cytotoxic action being most sensitive towards choriocarcinoma and melanoma cells. Human tongue carcinoma cells, human skin fibroblasts and human nasopharyngeal carcinoma cells manifested an intermediate sensitivity while the most resistant cell line was Hepatoma. Subsequent work by Ng et al. (1994) further demonstrated the strong anti-tumour growth activity of α-MMC against human placental choriocarcinoma and sarcoma S180 cell lines. α-MMC was tested on human bladder carcinoma cells, particularly on the T24 cell line (Battelli et al., 1996). A time course of exposure, followed by further incubation without the immunotoxins, showed that maximum inhibition of protein synthesis by T24 cells was reached after 2 h of contact. Bian et al. (2010) found that α-MMC RIP from MC produced different degrees of inhibition on many tumour cells. Fifteen different tumour cell lines, including lung, colon, liver, epidermis, breast cancer and melanoma cells were utilized to test the anti-tumour activities of α-MMC. Manoharan et al. (2014a) investigated the anti-cancer effects and the cellular mechanisms of action of α, β momocharin (200 to 800

µM) on 1321N1, Gos-3, U87-MG, Sk Mel, Corl-23 and Weri Rb-1 cancer cell lines compared to normal healthy L6 muscle cell line measuring cell viability using MTT assay kit, Caspase-3 and 9 activities, cytochrome c release and intracellular free calcium concentrations  $[Ca^{2+}]_i$ . Their results showed that  $\alpha$ ,  $\beta$  momorcharin can evoke significant dose-dependent, decreases in the viability (cell death) of 1321N1, Gos-3, U87-MG, Sk Mel, Corl-23 and Weri Rb-1 cancer cell lines compared to healthy L6 muscle cell line and untreated glioma cells. Moreover,  $\alpha$ ,  $\beta$  momorcharin (800 µM) also evoked significant increases in caspase-3 and 9 activities,

cytochrome c release and elevation of mitochondrial calcium leading to calcium overload and consequently, cancer cell death.

Under normoxic and hypoxic conditions,  $\alpha$ -MMC preferentially exhibited inhibitory effect on nasopharyngeal carcinoma (NPC) cells partly by blocking survival signalling (Pan et al., 2014). Recently, Cao et al. (2015) examined the effect of  $\alpha$ -MMC on the inhibition of human breast cancer and assessed its general toxicity to find the therapeutic window *in vivo* for its potential clinical use. A summary of these two RIPs and their effects on different types of cancer are shown in Table 2.

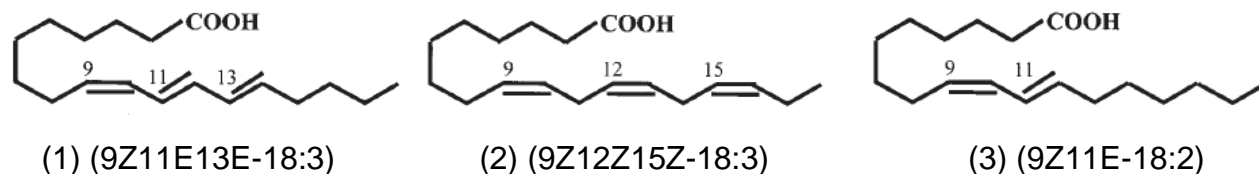
**Table 2.** Anti-tumour activities of MAP 30 and  $\alpha$ -MMC ribosome-inactivating proteins.

Ribosome inhibiting proteins	Tumour types	Cell lines	References
Momordica anti-HIV 30 (MAP 30)	Bladder cancer	5637	Hao et al. (2014)
	Breast cancer	BT20	Lee-Huang et al. (1995)
		MDA-MB 231	Lee-Huang et al. (2000)
	Epidermoid cancer	A431	Lee-Huang et al. (1995)
	Colon cancer	LoVo	Fan et al. (2008)
	Glioma	U87MG	Lee-Huang et al. (1995)
	Melanoma	Malme-3M	Lee-Huang et al. (1995)
	Liver/hepatoma cancer	HEP-38	Lee-Huang et al. (1995)
	Lung cancer	A549	Pan et al. (2014)
	Prostate cancer	DU145	Lee-Huang et al. (1995)
$\alpha$ -Momorcharin	Breast cancer	MCF-7, MDA, EMT-6	Bian et al. (2010),
		MDA-MB-231, MB-453, MCF-7	Cao et al., 2015, Battelli et al. (1996)
	Bladder cancer	T24	Bian et al. (2010)
	Colon cancer	SW480, SW620	Bian et al. (2010)
	Epidermoid	A431, Hep-2	Bian et al. (2010)
	Liver/haepatoma cancer	Hep G2, SMMC-7721	Bian et al. (2010)
	Lung carcinoma	Corl-23	Bian et al. (2010)
		Sk Mel	Tsao et al. (1990)
	Melanoma	A549, NCI-H460	Manoharan et al. (2014a)
		B16, M14, A2068	Manoharan et al. (2014)
Nasopharyngeal carcinoma	NPC, HK1	Pan et al. (2014)	
	NPC CNE2, NP69	Tsao et al. (1990)	
Neck squamous carcinoma	LICR, HN11	Tsao et al. (1990)	
	JAR	Tsao et al. (1990)	
Placental choriocarcinoma	JAR	Ng et al. (1994)	
Tongue carcinoma	LICR, HN4	Hao et al. (2014)	

### Conjugated fatty acids (CFAs)

Conjugated fatty acids (CFAs) (conjugated dienes, trienes, and tetraenes) are 18-carbon compounds found

in nature with conjugated double bonds (Suzuki et al., 2001). They have received increased interest because of their beneficial effects for human health, including anti-carcinogenic effects. Conjugated linoleic acids (CLAs),



**Figure 3.** Diagrams showing the chemical structures of (1)  $\alpha$ -Eleostearic acid, (2) Conjugated Linolenic acid and (3) Conjugated Linoleic acid.

conjugated linolenic acids (CLNs) and  $\alpha$ -eleostearic acids ( $\alpha$ -ESA) are examples of conjugated fatty acids which have been reviewed extensively for their biological properties (Suzuki et al., 2001). Various CLA isomers exist in nature due to geometrical and positional isomerism of the conjugated bonds in the structure (Suzuki et al., 2001). The most abundant natural isomer is 9Z11E-18:2. Figure 3 shows the chemical structures of *conjugated fatty acids* present in foods such as milk fat and meats from ruminant (Chin et al., 1992; Precht and Molkenin, 1997). Unlike CLA that occurs at concentration of about 1% in nature, CLN (9Z12Z15Z-18:3) and  $\alpha$ -ESA (9Z11E13E-18:3) are present in high amounts in some seed oils. In *M. charantia*,  $\alpha$ -ESA is the principal component of its seed oil, contributing between 50 and 60% of oil (Tsuzuki et al., 2004; Yasui et al., 2005).

Initially, CLAs were shown to possess anti-carcinogenic effect about three decades ago (Ha et al., 1987). Numerous researches have shown that CLAs can inhibit the growth of human breast (Shultz et al., 1992; colon (Tsuzuki et al., 2004; Yasui et al., 2005; Shultz et al., 1992; Palombo et al., 2002; Beppu et al., 2002), hepatoma (Tsuzuki et al., 2004), glioblastoma (Schfnberg and Krokan, 1995), lung (Tsuzuki et al., 2004; Schfnberg and Krokan, 1995), melanoma (Shultz et al., 1992) and prostate (Palombo et al., 2002) cell lines.

Research has also shown (Tsuzuki et al., 2004; Igarashi and Miyazawa, 2000; Grossmann et al., 2009) that CLNs have a stronger antitumour effect than CLAs.  $\alpha$ -ESA, which is converted *in vivo* to CLA, possesses a stronger suppressive effect on tumour cell growth of DLD-1 human colon cancer cells by inducing apoptosis *via* lipid peroxidation mechanism (Tsuzuki et al., 2004).  $\alpha$ -Eleostearic acid from *M. charantia* extract strongly inhibited the growth of HL60 leukaemia and HT29 colon carcinoma after 24 h incubation at 5  $\mu$ M concentration (Kobori et al., 2008). Anti-proliferative and apoptosis-inducing effect of free fatty acids (9c,11t,13t-CLN) prepared from *M. charantia* using human colon cancer Caco-2 cell lines revealed that this extract induced apoptosis through up-regulation of growth arrest and DNA damage inducible gene 45 (GADD45), peroxisome proliferator-activated receptor (PRAR) $\gamma$  and p53 gene (Yasui et al., 2005). The effects of  $\alpha$ -Eleostearic acid was also investigated on human breast cancer cell lines (MDA-MB-231 and MDA-ER $\alpha$ 7) by Grossmann et al.

(2009) where they showed that  $\alpha$ -ESA at a concentration of 40  $\mu$ mol/L inhibited proliferation of both cells lines in the range of about 70 to 90%. A summary of conjugated fatty acids and their effects on different types of cancer are shown in Table 3.

### Other studies

In addition to the various isolated compounds of *M. charantia* to kill different cancers and their cell lines, much work was also done on the alcohol, water and chloroform-isolated extract of *M. charantia* as an anticancer therapeutic agent. Several studies have shown (Ray et al., 2010; Li et al., 2012; Manoharan et al., 2014b) that the extract was more potent than individual compounds. In one such study by Ray et al. (2010), human breast cancer cells, MCF-7 and MDA-MB-231, and primary human mammary epithelial cells were used as an *in vitro* model to assess the efficacy of bitter melon (*M. charantia*) extract (BME) as an anticancer agent. BME treatment of breast cancer cells resulted in a significant decrease in cell proliferation and induced apoptotic cell death. Apoptosis of breast cancer cells was accompanied by increased poly (ADP-ribose) polymerase cleavage and caspase activation. Their results showed that BME modulates signal transduction pathways for inhibition of breast cancer cell growth and can be used as a dietary supplement for the prevention of breast cancer. In other studies (Kwatra et al., 2013; Li et al., 2012), methanol extract of *M. charantia* (MEMC) was used to evaluate the cytotoxic activity on four human cancer cell lines, Hone-1 nasopharyngeal carcinoma cells, AGS gastric adenocarcinoma cells, HCT-116 colorectal carcinoma cells, and CL1-0 lung adenocarcinoma cells. MEMC showed cytotoxic activity towards all the cancer cells tested, with the approximate IC<sub>50</sub> ranging from 0.25 to 0.35 mg/ml at 24 h. MEMC also induced cell death in a time dependent manner in these cells. Similarly, a study by Manoharan et al. (2014b) showed that a water soluble extract of *M. charantia*, ranging from 200 to 800  $\mu$ g/ml, can kill 1321N1, Gos-3, U87-MG, Sk Mel, Corl-23 and Werl Rb-1 cancer cell lines compared to healthy L6 muscle cell line and untreated glioma cells. The extract evoked its lethal effect on the different cancer cells via apoptosis and mitochondrial calcium overloading.

**Table 3.** Summary of anti-tumour activities of conjugated fatty acids.

Conjugated fatty acids	Tumour type	Cell lines	References
	Breast cancer	MCF-7	Shultz et al. (1992)
		HT-29, MIP-101	Palombo et al. (2002)
		CACO-2 (HTB-37), HT-29, DLD-1	Beppu et al. (2002)
	Human colon carcinoma	CACO-2	Yasui et al. (2005)
		DLD-1	Tsuzuki et al. (2004)
		HT-29	Shultz et al. (1992)
CLAs	Hepatoma	Hep2G	Tsuzuki et al. (2004)
	Human glioblastoma	A-172	Schfnberg and Krokan (1995)
	Lung adenocarcinoma	A549	Tsuzuki et al. (2004)
		A-427, SK-LU-1, A549	Schfnberg and Krokan (1995)
	Melanoma	M21-HPB	Shultz et al. (1992)
	Human prostate	PC-3	Palombo et al. (2002)
	Breast cancer	MDA-ER- $\alpha$ 7	Kobori et al. (2008)
	Hepatoma	Hep2G	Tsuzuki et al. (2004)
CLNs	Promyelocytic leukemia	HL60	Tsuzuki et al. (2004)
	Lung adenocarcinoma	A549	Tsuzuki et al. (2004)
	Human colon carcinoma	CACO-2	Yasui et al. (2005)
	Breast cancer	MCF-7	Igarashi and Miyazawa (2000)
		MDA-MB-231	Grossmann et al. (2009)
	Promyelocytic leukemia	HL60	Kobori et al. (2008)
	Human colorectal	HT-29	Kobori et al. (2008)
		DLD-1	Tsuzuki et al. (2004)
		DLD-1	Igarashi and Miyazawa (2000)
$\alpha$ -EAS	Human embryonic lung fibroblast	W138	Kobori et al. (2008)
	Human colon carcinoma	CACO-2 (HTB-37), COLO-320	Li et al. (2012)
	Hepatoma	HepG2	Igarashi and Miyazawa (2000)
	Melanoma	B16	Kobori et al. (2008)
	Tubular adenocarcinoma stomach	MKN-7	Igarashi and Miyazawa (2000)

## CONCLUSION

Various studies reviewed in this report suggest promising anti-tumour effects for *M. charantia* and its different isolated compounds. Anticancer activity of *M. charantia* against numerous cancers suggests that the plant contains the compounds that have anti-cancer potentials and properties. In spite of progress, further studies are still needed to understand the precise therapeutic dose of

each compound or the extract, combination therapy of these compounds and their ability to prevent drug resistance following treatment. MAP30 holds therapeutic promise over other RIPs because, not only it is active against infection and replication of both HSV and HIV, but is non-toxic to normal cells. The role of *M. charantia* in cancer therapy and drug resistance is of paramount importance as this plant serves various purposes in patients and most importantly, it is cost effective and



easily available in tropical countries. The plant is promising as a key therapeutic tool to treat non-communicable diseases globally including cancers, obesity, diabetes mellitus and where possible reducing co-morbidities.

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