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PERSPECTIVE

Bitter Melon: Antagonist to Cancer

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ABSTRACT The incidence of cancer is increasing worldwide, in spite of substantial progress in the development of anti-cancer therapies. One approach to control cancer could be its prevention by diet, which inhibits one or more neoplastic events and reduces cancer risk. Dietary compounds offer great potential in the fight against cancer by inhibiting the carcinogenesis process through the regulation of cell homeostasis and cell-death machineries. For centuries, Ayurveda (Indian traditional medicine) has recommended the use of bitter melon (*Momordica charantia*) as a functional food to prevent and treat diabetes and associated complications. It is noteworthy to mention that bitter melon extract has no-to-low side effects in animals as well as in humans. The anti-tumor activity of bitter melon has recently begun to emerge. This review focuses on recent advancements in cancer chemopreventive and anti-cancer efficacy of bitter melon and its active constituents. Several groups of investigators have reported that treatment of bitter-melon-related products in a number of cancer cell lines induces cell cycle arrest and apoptosis without affecting normal cell growth. Therefore, the effect of bitter melon should be beneficial for health, and use of the non-modified dietary product is cost effective.

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INTRODUCTION

Prevention by the use of naturally occurring dietary substances is considered a practical approach to reduce the increasing incidence of cancer. The intervention of multi-stage carcinogenesis by modulating intracellular signaling pathways may provide the molecular basis of chemoprevention with a wide variety of dietary phytochemicals (1). Cancer cells acquire resistance to apoptosis by overexpressing anti-apoptotic proteins and/or by the downregulation or mutation of pro-apoptotic proteins. Therefore, an excellent approach to inhibit the promotion and progression of carcinogenesis and to remove pre-malignant and malignant cells from the body is by induction of cell cycle arrest or apoptosis by dietary chemopreventive compounds.

Carcinogenesis is generally a complex and multi-step process in which distinct molecular and cellular alterations occur. In order to simplify the understanding of the different possible options for chemoprevention and chemotherapy in cancer development and progression, the following stages have been described: (i) initiation, when cells are exposed to a carcinogenic agent, (ii) promotion, when abnormal cells persist and initiate a preneoplastic stage (iii) progression, final phase of the tumorigenesis, when an uncontrolled cell growth occurs (Fig. 1). A cancer chemopreventive agent could be effective at any of the classically defined stages of carcinogenesis: initiation, promotion, and/or progression (2,3). The scope of the efficacy of such agents could be profound, because the natural course of the development of full-blown clinically evident cancer is relatively long and sometimes takes decades.

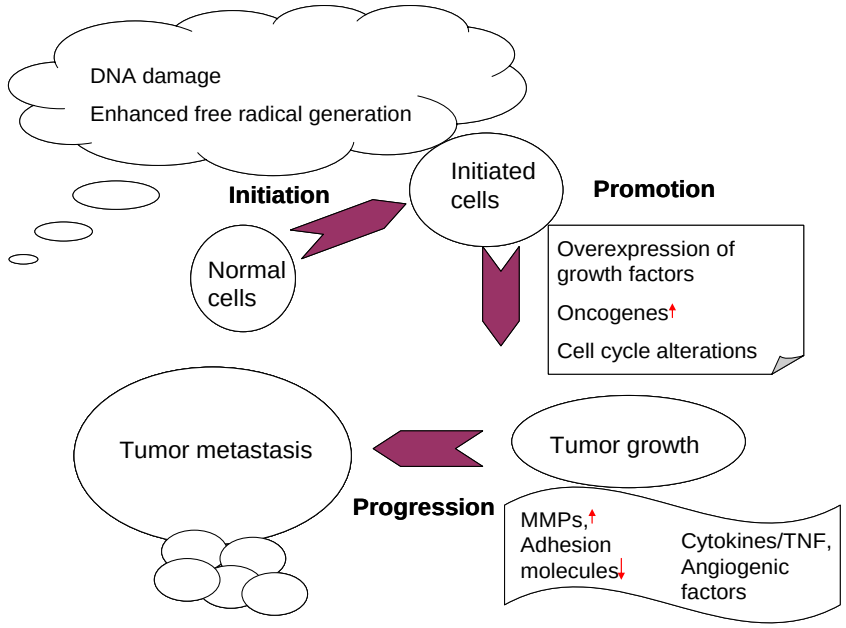

Fig. 1 Schematic diagram of multi-step cancer progression process.

The American Cancer Society publishes Nutrition and Physical Activity Guidelines to serve as a foundation for its communication, policy, and community strategies and ultimately to affect dietary and physical activity patterns among Americans (4). Greater consumption of vegetables and fruits has been associated with a lower risk of a number of cancers in the majority of epidemiologic studies. Fruits and vegetables represent a vast source of phytochemicals with varied chemical structure. Many fruits and vegetables have already been extensively studied for their potential anti-cancer or chemopreventive efficacy (2). Fruits and vegetables are major sources of vitamins, minerals and fiber, and intake of them is beneficial in maintaining good general health and helping to lower cancer risk.

In this review, we have focused our discussion on the advancements of bitter melon (*Momordica charantia)* and its active constituents regarding their cancer chemopreventive and anti-cancer efficacy as well as associated molecular mechanisms. *Momordica charantia*, also known as bitter gourd, balsam pear or *karela*, belongs to the family *Cucurbitaceae* and is widely cultivated in Asia, Africa, and South America. This fruit is extensively used in folk medicines as a remedy for diabetes, specifically in India, China, and Central America (5, and references therein). Over the years, there has been a worldwide interest in bitter melon as a dietary supplement because of its various beneficial effects, including lowering diabetes and lipidemia (5,6). All parts of the plant (fruit, seed, and leaves) were shown to possess hypoglycemic properties in normal and diabetic animal models. A recent study by us reveals that BME is well tolerated and has been termed as relatively safe in acute, subchronic, and chronic doses in animal studies (6). Moreover, clinical studies have used BM fruit or BM tea to evaluate its effects in diabetic patients (5,7).

BITTER MELON AND CANCER: EFFICACY AND MECHANISMS OF ACTION IN VARIOUS CANCER MODELS

Cancer is a disease in which the cell presents itself with unrestricted proliferative potential. The transition of normal cells towards cancerous phenotype occurs at different stages, as discussed by Hanahan and Weinberg (8). Since these defects are mostly due to aberrant signaling cascades involving numerous molecular players, targeting them by chemopreventive agents could be a rationalized approach in obtaining control of cancer. Generally, the growth rate of cancer cells exceeds that of normal cells due to dysregulation of their homeostasis machineries. Tumors also represent the culmination of multiple genetic abnormalities. As a consequence, the targeting of a single molecular target for therapeutic purposes might not be sufficient to elicit the desired outcome. Induction of cell cycle arrest or apoptosis by dietary compounds is an excellent approach to inhibit the promotion and progression of carcinogenesis. Bitter melon targets signaling cascades for its anti-cancer and/or chemopreventive efficacy. Additionally, Table I summarizes the most relevant studies available in the literature related to anti-cancer efficacy of bitter melon.

Bitter Melon Treatment and Cell Cycle Modulation

Almost two decades ago, the anti-tumor activity of crude bitter melon extract (BME) in murine lymphoma was reported (9). BME inhibited tumor formation in CBA/H mice which had been given intrperitoneal injections (77% of the untreated mice with tumors *versus* 33% of the treated

Table I *In Vitro* and *In Vivo* Studies Showing the Chemoprevention or Anti-tumor Activities of Bitter Melon

Derivatives of bitter melon	*In vivo* / *in vitro* model	Mechanism of action	Reference
Hot water extract of bitter melon	SHN virgin mice	↓Inhibition of mammary tumor	(16)
Compounds 1 & 2 (Bitter Melon seeds)	Mouse skin cancer	Inhibition	(17)
Alpha-eleostearic acid (alpha-ESA) and dihydroxy derivative	HL-60 leukemia, HT-29 colon carcinoma cells, DLD-1 colon cancer cells	↑Apoptosis	(18,19)
MCP-30 (Bitter Melon seeds)	Prostatic intraepithelial neoplasia (PIN) and PCa cell lines	↑Apoptosis	(13)
Alpha-ESA	Human breast cancer cells	↓Proliferation, G(2)-M block in the cell cycle, ↑Apoptosis	(20)
Bitter melon seeds	Cancer cells	↑Apoptosis	(14)
Seed oil of Bitter Melon	Colon carcinogenesis murine model	Inhibition of colonic aberrant crypt foci (ACF)	(15)
MAP-30	Xenograft model with human breast cancer cells	↓Proliferation	(12)
Bitter melon crude extract	CBA/H mice	Inhibit tumor formation	(9)

mice with tumors after 6 weeks). However, the mechanism of this activity was not studied in detail. Recently, we have observed that treatment of crude BME in cancer cells resulted in significant effect on inhibition of cell growth and induction of apoptosis. Progression of the cell cycle in eukaryotic cells is controlled by a series of protein complexes composed of cyclins and cyclin-dependent kinases (CDKs). Cyclins are central regulators of the cell division cycle. D-type cyclins interact with CDK4 and CDK6 to drive the progression through early/mid-G1 in response to mitogen stimulation. Cyclin E-cdk2 is active in mid G1 close to the restriction point, cyclin A-cdk2 from the beginning of S to M, whereas cyclin B-cdc2 is active at the G2/M transition. We have shown that BME treatment perturbs cell cycle regulation, and induces G2/M phase block (10) in breast cancer cells. The expression of critical cell cycle regulatory proteins, such as cyclin B1 and cyclin D1, was significantly decreased. BME treatment also modulates cell cycle regulation in prostate cancer cells (Ray R, unpublished observation).

Bitter Melon Treatment and Apoptosis

Cell death plays an important role in development, tissue homeostasis, and degenerative diseases. The two major forms of cell death are apoptosis and necrosis. Apoptosis, a morphologically and biochemically distinct form of cell death, is an important physiologic process in both normal development and pathological consequences. A diverse set of stimuli can trigger the apoptotic process in virtually all nucleated cells. One of the key regulatory steps for apoptosis is the activation of caspases. Active caspases then cleave many important intracellular substrates, leading to the characteristic morphological changes associated with apoptotic cells. We have shown that crude BME treatment in breast and prostate cancer cells also induces apoptosis and PARP cleavage. In breast cancer cells, BME also induces caspase activation (10). However, *in vivo* efficacy of the crude BME has yet to be tested.

POTENTIAL ACTIVE CONSTITUENTS OF BITTER MELON FOR ANTI-CANCER ACTIVITY

Chemical constituents of BM include, but are not limited to, glycosides, saponins, alkaloids, fixed oils, triterpenes, proteins and steroids that have been extensively reviewed elsewhere (11). Nutritional value of BM is attributed to its high mineral and vitamin contents, while bitterness is attributed to non-toxic alkaloids, momordicosides and momordicines. Regardless of its universal anti-diabetic properties, ongoing studies with crude BME indicate possible differences in chemical constituents. For instance, triterpene glycosides, oleanane-type triterpene glycosides, goyasaponins were identified from fresh fruits of Japanese *M. charantia*, while additional karavilagenins and karavilosides were identified in the methanolic extract obtained from the dried fruits of BM cultivated in Nuwara Eliya, Sri Lanka (12). Therefore, further studies are necessary to characterize the active constituents of bitter melon.

Among the various ribosome-inactivating proteins (RIPs) isolated from *Momordica charantia*, MAP30 (Momordica protein of 30 kDa) displayed anti-tumor activity (13). The efficacy of MAP30 has been tested in estrogen-independent and highly metastatic human breast tumor MDA-MB-231 cells. Treatment of MDA-MB-231 breast cancer cells with MAP30 resulted in inhibition of cancer cell proliferation as well as inhibition of expression of the HER2 gene *in vitro* (13). When MDA-MB-231 human breast cancer cells were transplanted into SCID mice, the mice developed extensive

metastases, and all mice succumbed to tumors by day 46. Treatment of the human breast cancer-bearing SCID mice with MAP30 resulted in significant increases in survival, with 20–25% of the mice remaining tumor free for 96 days. The effect of MCP30, isolated from bitter melon seeds, was examined in a number of human prostate cancer cell lines (14). Treatment of MCP30 selectively induces both cell cycle arrest and apoptosis in premalignant and malignant prostate cells (14). Administration of MCP30 decreased PC3 human prostate cancer cell growth in nude mice, and this effect was due primarily to the induction of apoptosis. Recent studies further indicate that chemical modification and reduction of BME RIP significantly reduced its *in vivo* immunogenicity, but retained its anti-proliferative activity as measured by DNA fragmentation and caspase-3 activation (15).

The bitter melon seed or fruit extracts were shown to display anti-cancer activity in a rat colonic aberrant crypt foci model (16) and a mouse mammary tumor model (17). Akihisa *et al.* (18) have isolated 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 Momordica charantia. Compounds 1 and 2 exhibited marked inhibitory effects in both 7,12-dimethylbenz[a]anthracene-and peroxynitrite-induced mouse skin cancer. Seed oil of bitter melon contains more than 50–60% alpha-eleostearic acid (α-ESA). α-ESA suppress the growth of DLD-1 human colon cancer cells by inducing apoptosis via lipid peroxidation (19). *α-ESA*, which is converted to conjugated linoleic acid *in vivo*, had a stronger suppressive effect than the conjugated linoleic acid on tumor cell growth. Treatment of α-ESA induces apoptosis in HL60 human promyelocytic leukemia cells (20). Grossmann *et al.* (21) have shown that that *α-ESA* blocks breast cancer cell proliferation and induces apoptosis. Although *α-ESA* strongly induced apoptosis in HL60 cells, the acetone extract of bitter melon seed, which is probably rich in α-eleostearic acid, did not induce apoptosis in the cells. Lipophilic components of pericarp and placenta in the acetone extract may blunt the apoptosis of HL60 cells. In fact, the acetone extract also did not suppress the colon cancer growth in xenograft model (19). Therefore, more work will be necessary to understand the *in vivo* activity of bitter melon.

CONCLUSION

Cancer prevention continues to evolve with the rapid integration of molecular approaches into its research and clinical practice. The use of dietary products to manage or arrest the carcinogenic process provides an additional therapy along with conventional medicine for treatment of the disease. The *in vitro* and *in vivo* studies reviewed above suggest a promising anti-tumor effect of bitter melon. This natural product may serve as potent agent for enhancing the therapeutic effects of chemotherapy, radiotherapy or other standard therapeutics for the treatment of human cancers. Although the beneficial effect of bitter melon in diabetes and lipid metabolism is well studied, its effect on cancer prevention and/or therapy has begun to emerge. Although we put forth the best effort to cite the most relevant references on better melon and cancer therapy, we could not include all for the purposes of this review.

FUTURE DIRECTION

Naturally occurring phytochemicals have shown promising chemopreventive effects in various *in vitro* and preclinical models, and in several cases, their mechanisms of action at the molecular level have been characterized (1,3). However, active constituents of bitter melon for cancer prevention and therapy are in their infancy stage. More studies are needed in high-risk populations for cancer of specific organs or sites with standardized bitter melon extract preparations to establish the dose regimen and to determine pharmacologically achievable levels of biologically active constituents in the target organ. These studies are also necessary to address any toxicity associated with long-term intake/administration of bitter melon. Therefore, in spite of this progress, much more work will be required to optimize the *in vivo* activity of bitter melon. Further, the consumption of bitter melon in diets has translational potential in the fight against cancer and is considered beneficial to the general population.

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