Research review

Bitter Melon (*Momordica charantia*)

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INTRODUCTION: Herbal medicine was the main form of treatment for illness before the advent of Western medical practice, and still is today in 75 to 90% of the rural areas of the world (1). Each area of the world has its own form of ethno-medicine based on the plants found in that area (1,2,3,4,5). Japan and China are two countries with a long history of exchanging herbal lore extendeding over many thousands of years (3,6). Their particular form of herbal medicine is called *Kampo* (3,6). The integration of Western medicine and Kampo in Japan, although slow, was not entirely antagonistic (6). In 1774, Gentaku Otsuki, pointed out in one book that both Eastern and Western medicine have their weaknesses and encouraged practitioners of both systems to adopt a positive attitude towards the West so that medicine could eventually evolve into a better system (6).

The first example of the integration of Eastern and Western medicine was achieved by Dr. Seishu Hanaoka (1760-1835). He developed the general anesthetic, tsusensan, from Kampo herbs and used it to perform a mastectomy for breast cancer (6). Since that time, the scientific study of many herbal medicines have revealed biologically active compounds that have been adopted into Western pharmaceuticals. The drugs isolated from plants are particularly useful as they are more often complex compounds yet they occur in a biologically active conformation. Because of their complexity, it is also very unlikely that the plant compounds would have been synthesized *a priori* in the search for new compounds (7). When herbal medicine leads are exploited, broad classes of compounds can be developed. A few examples of the variety of common pharmaceuticals of herbal origin are outlined below.

The well-known bronchodilator and antitussive ephedrine, comes from the herb *Ephedra sinica*, commonly used in Kampo prescriptions for conditions such as bronchial asthma (8). The discovery of morphine led to the development of all the narcotic analgesics (7). The bark of *Cinchona* was found to contain quinine which led to the development of the antimalarial drugs (3,7). The traditional herbal extract from rhubarb (*Rheum spp.*) contains several active compounds. These compounds mediate several medicinal effects of rhubarb such as its purgative action (sennosides), its anti-bacterial, anti-fungal, and antitumor activities (anthraquinones), its anti-inflammatory activities and analgesic activities (lindleyin), and its improvement of lipid metabolism (stilbenes) and nitrogen metabolism (rhatannin) (9).

Vincristine, derived from the Madagascar periwinkle (*Catharanthus roseus*), is highly effective and extensively used in the treatment of leukemias (8,10). However, the yield of vincristine from the periwinkle is extremely low and every available soil suitable for the growth of this plant is under development (1).

Many plant compounds have been identified with antiviral or cytotoxic antitumor characteristics (11-20). One such plant, *Momordica charantia*, will be discussed in detail in the following section.

Momordica charantia

The plant *Momordica charantia* belongs to the family CUCURBITACEAE and is known by many common names: balsam pear, African cucumber, cindeamor, bitter apple, bitter melon, bitter gourd, carilla plant, wild cucumber, margose, concombre Africain (4), the herb Kuguazi (China) (21), and Karela (Pakistan) (22). It is common in China, India, and Africa where it has a history of several medicinal uses (4). The species has become naturalized in the southern United States where the unripe fruit is eaten and used in home remedies for treating colds (3).

Momordica charantia is not only used for medicinal purposes, but also as a general insecticide, which is beneficial in tropical countries where insects are a common vector of many diseases (4).

Medicinal uses

The bitter melon plant is commonly used as a purgative agent. Alcoholic or aqueous extracts of the seed, mesocarp, or epicarp cause a relaxation of guinea pig ileum and rat jejunum, while alcoholic or aqueous extracts of the leaves produce contractions (4). The seeds and wall of the fruit contain a resin, a saponic glycoside yielding leaterin (a cucurbitacin), and alkaloids that cause vomiting and diarrhea (89).

M. charantia also has antibacterial and anthelmintic properties. Antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* have been reported using an aqueous extract of the roots and leaves (5,4). The juice of the leaves and fruits or seeds is used as an anthelmintic. In Brazil, the dose for anthelmintic use is two or three seeds (4).

Studies of antifertility action of this plant indicate that it is effective in males. Dixit *et al.* (23) concluded that an ethanol extract of the fruit will induce a state of infertility without altering general metabolic activities when administered chronically at 1.75 g/day for 60 days to male dogs (5).

The roots, fruit and seeds of the bitter melon are used as an abortifacient. Several constituents of the fruits, such as charantin, 5-hydroxytryptamine, diosgenin and ß-sitosterol, were observed to act as uterine stimulants (5). Oral administration of an alcoholic extract of the seed produced abortion in rats with the effect being more pronounced in early pregnancy. The extract can also be given intra-uterine to induce contractions of the rat uterus (4).

Two glycoproteins *a*-momorcharin and ß-momorcharin have been isolated from the seeds of *M. charantia*. Both momorcharins induce mid-term abortion and terminate early pregnancy in mice in a similar manner (24,21). Their molecular weights are 31,000 and 29,000, respectively. They contain about 2% carbohydrate and differ immunologically from each other (24,21). Mouse morulae and early blasto-

cysts develop normally to the late blastocyst stage in the presence of *a*-momorcharin in culture but normal embryonic development is inhibited when the blastocysts are implanted in pseudopregnant mice (25).

In vitro studies indicate that ß-momorcharin disturbs peri-implantation development by blocking the hatching of embryos from the zona pellucida, decreasing the incidence of successful attachment of the blastocyst, reducing the trophoblast outgrowth and disturbing the development of the inner cell mass. A possible cause of these effects on the developing embryo may be through inhibition of nucleic acid and protein synthesis. Preliminary results indicate that both *a*- and ß-momorcharin inhibit the uptake and the incorporation of ^{3}H-leucine and ^{3}H-uridine into protein and RNA of the mouse embryo (24).

Both momorcharins inhibited embryonic implantation (24,25). ß-momorcharin can act directly on the uterus by reducing its biosynthetic capacity, which is a prerequisite for proper decidual reaction. With a reduced decidual reaction, the uterine environment is unsuitable for embryonic implantation (26). This, in conjunction with the embryocidal effects of the protein, is the major cause of the termination of early pregnancy by ß-momorcharin.

Experimental tests and clinical trials using an extract of the dried fruit or ground dried seeds indicate that they have marked hypoglycemic properties (27,22,5,4). The antidiabetic effects of the bitter melon are clearly demonstrated using a rabbit model streptozotocin (STZ)-induced diabetes mellitus (28). The STZ induces an increase in blood sugar accompanied with an increase in blood urea, serum creatinine, serum cholesterol, free fatty acids and triglycerides, a fall of glycogen in liver and muscle and a loss of body weight. Ground bitter melon seed given with the rabbit food has a hypoglycemic effect on blood sugar levels which is accompanied by hypolipemia. The ß-cells of the pancreas are found to be activated by this treatment. The seed treatments have no effect on lowering blood urea and creatinine nor does this treatment improve impaired renal functions caused by STZ (28).

Yet others (28,29), found no hypoglycemic activity in an aqueous extract of the dried fruits of the bitter melon on alloxan induced diabetic mice. Alloxan induces diabetes by destroying all ß-cells of the pancreas. This indicates that the bitter melon hypoglycemic activity may work to some extent via these cells. This is partially supported through experiments conducted by Welinhinda *et al.* (30). These workers demonstrated that an aqueous extract of the unripe fruits of the bitter melon is a potent stimulator of insulin release from ß-cell-rich pancreatic islets isolated from obese-hyperglycemic mice. This induced release of insulin is not suppressed by epinephrine nor by the removal of calcium. These authors suggest that the insulin releasing effect is a

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result of membrane perturbations as the bitter melon extract is found to mimic the action of saponin in inhibiting the Ca^{2+}/H^+ exchange mediated by the ionophore A23187 and inhibiting the release of Ca^{2+} from preloaded liposomes (30).

The hypoglycemic effect is attributed to two factors: a substance labeled charantin, a crystalline fraction obtained from an alcoholic extract of the fruit, and a polypeptide (p-insulin, or v-insulin, for vegetable-insulin) obtained from the fruit, seed and tissue (31,27,4). Charantin, administered at 50 mg/kg doses reduces hyperglycemia in rabbits by 42%. Charantin possesses pancreatic and extra-pancreatic action, and has a slight antispasmodic and anticholinergic effect. Charantin helps to control diabetic patients (5), but should not be viewed as curative.

The p-insulin is structurally and pharmacologically comparable to bovine insulin. The purification of p-insulin can be carried out in a manner similar to the purification of insulin from the pancreas of animals (31). Amino acid analysis of p-insulin indicates that it has 166 residues composed of 17 different amino acids and a molecular weight of approximately 11,000. The p-insulin is found to be composed of two polypeptide chains bound together by disulfide bonds (31). Although similar in many aspects, immunoassays did not indicate any cross-reactivity between p-insulin and bovine insulin (27). Subcutaneous and intramuscular administration of the polypeptide, p-insulin isolated from the fruit, produced hypoglycemic activity in diabetic gerbils, langurs and humans. In juvenile diabetic patients, the peak effect was observed after 4-8 hours as compared to 2 hours for bovine insulin (31,27). Hypersensitivity reactions to p-insulin are absent in patients previously treated with animal insulin, but studies on long-term treatments with p-insulin have not been completed (31).

Other biologically active compounds

The immature fruit of *Momordica charantia* tastes bitter, due to the cucurbitacins found in it. Cucurbitacins comprise a group of triterpenes distributed in the cucurbitaceous plants. Five non-bitter cucurbitacins have been isolated from the seeds and are designated momordicosides A-E (32,33). The immature fruit of this plant has been the source of two bitter glycosides,

momordicosides K and L (34) and four non-bitter glycosides, momordicosides F_1, F_2, G and I (33). The leaves and vines contain three bitter principles which are glycosides named momordicins I, II, and III. These momordicins are very similar in structure to momordicosides K and L (35).

Two seed storage proteins have been isolated from the seeds of *M. charantia*. These proteins contain high concentrations of glutamic acid, glutamine and arginine. The proteins appear to consist of four subunits of 5,500 daltons (36).

The seeds are also the source of vicine, a toxin, which is a glycoside of a non-protein nitrogenous base. This toxin induces favism, an acute condition characterized by fever, headaches, abdominal pain, severe anemia, prostration and coma (37).

Tomita et al. (38) originally purified galactose binding lectins from *M. charantia* seeds by affinity chromatography using a Sepharose 4B column. Linn et al. (39), isolated and partially characterized a toxic and non-toxic lectin from the seeds of the bitter melon. The purified toxic lectin, momordin, has a molecular weight of 24,000 and inhibits protein biosynthesis in Ehlrich ascites tumor cells. The non-toxic lectin, momordica agglutinin, has a molecular weight of 32,000 and is able to agglutinate the human O type red blood cells at a concentration of 0.5 g/ml. The hemagglutination is inhibited by galactose and its derivatives as reported by Tomita et al. (38). The amino acid compositions of momordin and momordica agglutinin are different (39).

Further studies (40,41) of the hemagglutinating lectin indicate that it is a glycoprotein containing 10% hexoses and 2.5% hexosamine. The lectin has a molecular weight of 120,000 and is tetrameric in nature, containing two pairs of non-identical subunits of molecular weights 28,000 and 30,000. The lectin has two binding sites per molecule which bind galactose and related sugars independently of each other. There do not appear to be any additional low affinity receptors (40). Chemical modification studies found that tryptophan and tyrosine residues are important for the carbohydrate binding activity (41).

An ethyl ether extract of *M. charantia* seeds is found to contain two inhibitors of protein synthesis in a cell-free system (a lysate of rabbit reticulocytes) (42,43). The

inhibitors appear to act through an inhibition of peptide chain-elongation rather than through an inhibition of initiation as the extent of protein inhibition is the same when the extract is added before or well after starting the reaction (44). One inhibitor of protein synthesis is also a hemagglutinating lectin. The lectin has a molecular weight of 115,000 and consists of four subunits (43). The lectin is non-mitogenic to human lymphocytes (45). The second protein, a basic glycoprotein (pI >8) (46), has a molecular weight of 31,000 (46) and has no hemagglutinating properties (43). This second protein is called *Momordica charantia* inhibitor (MCI) and is a ribosome-inactivating protein (47). Several plants contain inhibitors of protein synthesis which inhibit the 60 S subunit of eukaryotic ribosomes (45,44) and inhibit the replication of plant viruses (45). These ribosome inactivating proteins affect mammalian ribosomes more than plant ribosomes and have no effect on homologous ribosomes (45). Abrin and ricin, two such inhibitors, are toxic to animals or cells *in vitro*, while many other inhibitors have low or no toxicity (44).

Both the *M. charantia* lectin and the inhibitor are capable of inhibiting protein and subsequently DNA synthesis in mitogen-stimulated, normal, human, peripheral blood lymphocytes and human leukemic lymphocytes (47). The inhibitor has a low toxicity (rats tolerated 100 mg/100 g body weight), while the hemagglutinating lectin has a more rapid and pronounced effect on cellular protein synthesis. This difference is probably due to better penetration of the lectin into cells (42,43,47). Although the *M. charantia* inhibitor contains sugar residues (mannose, glucose, xylose, fucose and glucosamine), these residues may not be necessary for the biological activity of the protein. The pokeweed antiviral protein isolated from the seeds of the pokeweed contained no detectable sugars and yet is a potent inhibitor of protein synthesis (48,46). The inhibitor contains some thiol groups which would allow it to be linked to antibodies for possible use as an immunotoxin (46).

The 31,000 dalton protein synthesis inhibitor from *M. charantia* exhibits antiviral activity in virally infected cells similar to other ribosome-inactivating proteins such as pokeweed antiviral protein (PAP), wheat germ inhibitors, gelonin and dianthins. Treat-

ment of virally infected cells with 200 g/ml of *M. charantia* inhibitor reduced the viral yield of polio virus infected cells by 98%. This reduction in virus is not due to inhibition of virus penetration in cells, but due to inhibition of protein synthesis in cells. The inhibitor decreased herpes simplex virus-1 plaque forming efficiency (the plaques were fewer and smaller). Protein synthesis was found to be inhibited more in virally infected cells than in uninfected cells (44).

Recently the 31,000 dalton protein, called MAP 30, has been purified and a partial sequence obtained. This protein has a sequence similar to ricin A chain but is not identical. This protein exhibited a dose-dependent inhibition of HIV-1 infection of H9 cells (50).

A crude aqueous extract of the fruit of the bitter melon contains many proteins and many biochemical activities. The ripe fruit and leaves of the bitter melon are the source of a guanylate cyclase inhibitor (51,52). This inhibitor is not a lipid as the inhibitory activity remained in the aqueous phase after a double extraction with ether: ethanol (4:1) followed by an extraction with chloroform:methanol (2:1) (52). The guanylate cyclase inhibitor is acid stable and heat labile. This partially purified inhibitor has the ability to decrease basal levels of guanylate cyclase and to impair chemical carcinogen-induced increases in guanylate cyclase activity. The guanylate cyclase inhibitor has no effect on adenylate cyclase (52).

As guanylate cyclase activity is found to be increased in many tumor cells and is associated with concanavalin A (Con A) stimulated lymphocytes (53), the guanylate cyclase inhibitor has been tested against tumor cells and mitogen-treated lymphocytes. The aqueous extract of the bitter melon ripe fruit and leaves is found to block the growth of rat prostatic adenocarcinoma *in vitro*, and inhibit the incorporation of ^{3}H-thymidine into DNA of Con A-stimulated cells. DNA histograms indicate that the extract inhibits at the $G_2 + M$ phase of the cell cycle (54,55). In low amounts, this material also inhibits the self associating reaction of bovine tubulin and prevents the polymerization of chick tubulin in a manner similar to

colchicine (56,55). The crude extract of the fruit of the bitter melon is preferentially cytotoxic for leukemic cells versus normal lymphocytes. This cytotoxicity correlates with the guanylate cyclase inhibitory activity (54,55,51). Testing of nine other plant extracts that are cytotoxic to cells revealed that only an extract from the Lawson's cypress, *Chamaecyparis lawsonianna*, exhibits comparable cytotoxicity and guanylate cyclase inhibition levels (51).

Partial purification of a guanylate cyclase inhibitor finds that it co-elutes as a single, trypsin sensitive peak with a molecular weight of 70,000. This purified protein exhibits preferential cytotoxicity to several human lymphoblastoid cell lines (57).

A second substance (58) can be purified with a molecular weight of 40,000 that is cytostatic to BHK-21 cells but has no effect on cellular cyclic GMP. The 40K molecule is sensitive to trypsin and to boiling and is able to inhibit RNA and protein synthesis in intact tissue culture cells and cell free systems. This cytostatic molecule also exhibits non-specific antiviral activity.

Another cytostatic molecule (59) which preferentially inhibits RNA synthesis in intact cells can also be purified from the crude extract. This molecule has an apparent molecular weight of 11,000 and is not sensitive to boiling or to treatments with trypsin, ribonuclease, or deoxyribonuclease. This molecule has no effect on guanylate cyclase nor phosphodiesterase.

As stated above, a crude extract of the fruit of the bitter melon can preferentially inhibit *in vitro* tumor cell growth (54,47,57,51). Jilka *et al.* (60) have shown that this crude aqueous extract also exhibits *in vivo* antitumor activity. The extract is able to inhibit tumor formation in CBA/H mice injected with CBA/DI tumor cells and tumor formation in DBA/2 mice injected with L1210 or P388 tumor cells. This *in vivo* antitumor activity requires both the prior exposure of tumor cells to the extract *in vitro* and intraperitoneal injection of 8 g protein extract twice a week.

Characterization of this anti-lymphoma moiety indicates that it is sensitive to treatment with trypsin and boiling, but insensitive to DNase or RNase. On SDS-

PAGE, this moiety has a molecular weight of 40,000 (Takemoto, unpublished data).

Splenocytes of animals injected twice a week with 8 mg protein of the bitter melon extract exhibited an enhanced mixed lymphocyte reaction, while thymocytes of these animals exhibited an enhanced incorporation of ^{3}H-thymidine into trichloroacetic acid-precipitable material after 48 hours of exposure to Con A (60). Resistance to L1210 lymphoma formation in DBA/2 mice, can be adoptively transferred by injection of peritoneal exudate cells, twice a week, from DBA/2 mice which have been injected with the bitter melon antitumor factor (Takemoto, unpublished data). Therefore, some of the antitumor activity of the bitter melon extract may be due to immunopotentiation (59).

Spreafico *et al.* (61) studied some of the immunomodulatory characteristics of the 30,000 dalton *Momordica charantia* inhibitor. They found that *in vitro* incubation of MCI with splenocytes decreased the responsiveness to the T cell mitogens, PHA and Con A, but not the B cell mitogen, LPS. *In vitro* or *in vivo* treatment of splenic or peritoneal macrophages with MCI is able to augment their natural cytotoxicity to TU5 cells in a 48 hour assay. They were unable to detect any activation of NK cells in the spleens of MCI treated mice and did not look at NK cytotoxicity in the peritoneal cavity of treated mice. *In vivo* treatment is also able to increase the time necessary for allograft rejection and decrease murine responsiveness (as measured by a plaque forming cell assay) to T dependent antigens while not affecting the T independent antigens. This group concluded that the MCI has no effect on the B cell arm of the immune response, but may exert its effect by inhibition of T-regulatory cells (61).

Recently, we have identified the affected immune cells as NK cells (62). These studies suggested that an *in vivo* anti-tumor effect is not due entirely to ribosomal inactivating activity. Rather, there are endogenous activators of the host's immune system..

It should be noted that the bitter melon extract is not toxic. In view of the many reports of its antitumor and anti-HIV activity, this plant should be further studied (62).

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