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A Review on Momordica charantia, a Nutraceutical Approach for Inflammatory Related Disease(Cancer)

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ABSTRACT : Momordica charantia, commonly called bitter gourd, is a plant belonging to the Cucurbitaceae family and has been known for centuries for its medicinal and nutritional properties. Due to the presence of many bioactive compounds, some of which have strong biological effects, this plant is used in folk medicine all over the world, primarily for diabetes, but also for other diseases related to cancer and inflammation.It is used to treat a variety of medical conditions, including: M. charantia extract has been widely proven to help lower blood sugar levels in patients with type 2 diabetes.Most of the existing research on M. Charantia's bioactive compounds have only been tested in cell lines and animal models. Therefore, the actual effects of bitter melon on human health are not fully established, and systematic clinical trials are needed to establish the efficacy and safety of bitter melon for patients.Additionally, both in vitro and in vivo studies have shown that bitter melon can cause toxic or harmful effects under various conditions.

The purpose of this review is to provide an overview of the anti-inflammatory and antitumor properties of bitter melon and discuss its pharmacological activities and possible side effects. Although there is a lot of literature on bitter gourd as an anti-diabetic agent, very few papers discuss the anti-inflammatory and anti-cancer properties of this plant.Cancer is the second leading cause of death worldwide. Many plant food products have shown promising anticancer effects.Bitter melon or bitter gourd (Momordica charantia) is a nutrient-rich medicinal plant grown in tropical and subtropical regions of many countries.Bitter melon, which has traditionally been used as a folk medicine, contains many bioactive components such as triterpenoids, triterpene glycosides, phenolic acids, flavonoids, lectins, sterols, and proteins, which can potentially be used without serious side effects.It shows strong anti-cancer effects.The preventive and therapeutic effects of crude extracts or isolated components have been studied in cell line-based and animal models of various types of cancer.This review summarizes recent advances in testing the cancer preventive and therapeutic effects of bitter gourd, focusing on the underlying molecular mechanisms.The crude extract and its components prevent many types of cancer by promoting the formation of reactive oxygen species. Inhibition of cancer cell cycle, cell signaling, cancer stem cells, glucose and lipid metabolism, invasion, metastasis, hypoxia and angiogenesis. Inducing apoptosis and autophagy cell death, as well as improving immunological protection. As a result, bitter melon has the potential to be a cancer preventative and therapeutic agent.

INTRODUCTION

Cancer is characterized by uncontrolled cell proliferation achieved by dynamic changes in the nuclear genome .Research has identified several risk factors that influence uncontrolled cell growth.These include: Inherent risks arising from natural mutations in DNA.external factors such as carcinogens, viruses, xenobiotics, and lifestyle factors such as smoking, alcohol abuse, nutritional intake, and physical activity Intrinsic factors related to an individual's immune system, metabolic patterns, response to DNA damage, and hormone levels . In the United States, cancer incidence is projected to be approximately 18 million in 2020, which equates to approximately 4,950 new cases per day.The number of deaths from cancer in 2020 is estimated to be approximately 600,000 people, which equates to more than 1,600 deaths per day . Prostate, lung, and colon cancers are the most common cancers in men (43% of all cases), breast, lung, and colon cancers are the most common in women (50% of all cases), but others The incidence of cancer is higher in women.Men The size of the pancreas, liver, oral cavity, pharynx (head and neck), and skin continues to increase Despite significant improvements in treatments in recent years, cancer remains the second leading cause of death, and population-based studies predict that the number of new cancer cases will dramatically increase to more than 22 million people worldwide by 2030.is predicted to

increase rapidly .Therefore, prevention and the development of specific treatments will be important options to treat this disease. Research suggests that prevention can be achieved by reducing risks due to external and lifestyle factors and through early detection . Once treated, the primary tumor can usually be removed by surgery. However, in some cases, surgery is difficult and useless for subclinical metastases and cannot remove cancer cells, leading to recurrence. In the case of targeted therapy, more effective drugs, appropriate doses, and combination treatment protocols with fewer toxic effects have been developed over the years.However, these methods have side effects and are sometimes expensive, and one of the main problems is that cancer cells eventually become resistant to treatment . A recent WHO report suggests that approximately 80% of the world's population uses traditional Chinese medicine for primary care . Several epidemiological studies have shown that fruits and vegetables play an important role in reducing cancer risk .This may be due to the cumulative effect of the many bioactive phytochemicals, vitamins, minerals, proteins, and fibers found in fruits and vegetables. Many herbal products, whether whole extracts or bioactive ingredients, can inhibit cancer development, at least in animal models. Numerous clinical trials are underway to test the safety and effectiveness of natural ingredients in preventing or treating cancer.

This review focused on the latest information on bitter melon (Momordica charantia) and its underlying mechanisms for cancer prevention and treatment.Bitter melon, bitter gourd, balsam pear, and karela belong to the Cucurbitaceae family and are widely cultivated in Asia, Africa, and South America. The medicinal properties of bitter gourd have been reported for a long time in the treatment of diseases such as toothache, diarrhea, boils, and diabetes . The beneficial effects of bitter melon crude extract or isolated compounds are associated with the reduction of diabetes and lipidemia, as well as antibacterial, antifungal and anti-HIV activities . Promising anticancer effects of bitter melon have been observed in various in vitro and in vivo studies .Here, we will summarize the molecular mechanisms of cancer prevention and treatment by bitter gourd. Therefore, this review could have far-reaching implications for the treatment of the disease and help advance it into clinical trials

BITTER MELON AND ITS CONSTITUENTS

Bitter melon is a bitter-tasting herbaceous plant grown in tropical and subtropical regions of many countries.Traditionally, bitter melon is used as a folk medicine in various countries. The fruit is also used as a side dish in Southeast Asia.Bitter melon tea, known as bitter gourd or herbal tea, is made from dried slices and used for medicinal purposes. Bitter melon has the highest nutritional value among cucurbits, containing carbohydrates, protein, fiber, vitamins (folate: C, A, E, B1, B2, B3, B9), minerals (potassium, calcium, zinc, magnesium, phosphorus, iron) .The biological activity of bitter gourd is dependent on its major chemical components, including cucurbitan-type triterpenoids, cucurbitan-type triterpene glycosides, phenolic acids, flavonoids, essential oils, fatty acids, amino acids, lectins, sterols, and saponins (goya saponins I, II). To do). III) Constituents and some proteins found in fruits, seeds, roots, leaves, and vines . Cucurbitan-type triterpenoids are the most common chemical constituents.Bitter taste is the result of cucurbitan-type triterpenoids: (momordicin I and II) and triterpene glycosides: momordicosides K

Researchers have developed various extraction methods to isolate pure compounds or plant extracts using different solvents such as water, methanol, ethanol, n-butanol, and acetone.Organic solvents are more suitable for the extraction of phenolic acids and flavonoids There are many different types of bitter gourd, with different origins, harvest times, and different proportions of chemical components depending on these parameters. The various main components found in different varieties and different parts of plants are summarized below .

THE ACTIVITY OF BITTER MELON ON CANCERS

Bitter melon extract and its active ingredients have been studied in cancer cell line-based laboratory models and preclinical animal models, but clinical studies on cancer types are lacking. In prevention studies, raw bitter melon extract prepared with water, methanol, or ethanol has been shown to be effective against mainly blood cancers, breast cancer, colon cancer, head and neck cancer, liver cancer, prostate cancer, skin cancer, and stomach cancer. is used for the treatment of It was done in an animal model. Therapeutic studies using crude extracts or isolated compounds have been conducted against blood, brain, breast, colon, stomach, head and neck, kidney, liver, lung, ovarian, pancreatic, prostate, skin and cervical cancers. Performed in vitro and in vivo models.

ROLES OF BITTER MELON IN CANCER PREVENTION AND THERAPY

BLOOD CANCER

The anticancer effects of raw bitter melon extract were first reported in a mouse model, where ammonium acetate precipitation of bitter melon water extract prevented tumor formation and enhanced immune function .However, the crude extract showed minimal effects on normal human peripheral blood lymphocytes compared to lymphocytes from chronic or acute leukemia patients.

Similarly, the bitter melon compound Momordica antiviral protein 30kD (MAP30) significantly inhibited proliferation in human acute myeloid leukemia (AML) cell lines HL-60, THP-1 cells and patient AML in a dose- and time-dependent manner., induced apoptosis. The art and path of cells . Fractions from seed extracts, namely Mc-1, Mc-2, Mc-3 and Mc-2Ac, induced the differentiation of leukemic cells HL60 in a dose-dependent manner .Another study found that (9Z,11E,13E)-15,16-dihydroxy-9,11,13-octadecatrienoic acid (15,16-dihydroxy-α-eleostearic acid), the main component of seeds, induced apoptosis.HL60 cells . α-Eleostearic acid isolated from ethanolic extraction of seeds inhibits the growth of leukemia cell lines ED and Su9T01, but has been reported to have minimal effects on peripheral blood, mononuclear cell .

BREAST CANCER

Both prevention and treatment studies have been conducted in breast cancer models. Fruit water extract inhibited the proliferation, induced apoptosis, and decreased cell viability by 80% in breast cancer cells MCF-7 and MDA-MB-231 in a time- and dose-dependent manner . Importantly, this extract showed no cytotoxic effects on primary mammary epithelial cells (HMECs) even after 5 days of treatment.Similar to the aqueous extract, the isolated compound MAP30 inhibited MDA-MB-231 cells in SCID mouse in vitro and in vivo xenograft models .Rephrase Continuous administration of water extract (0.5%) via drinking water prevented the spontaneous development of mammary gland tumors in virgin SHN mice without side effects .Oral administration of the extract (30% v/v) via drinking water inhibited tumor growth in syngeneic (mouse breast cancer cells 4T1 and E0771) and xenograft mouse models (human breast cancer cells MDA-MB-231). , autophagy was induced and tumor growth was inhibited Esterification of cholesterol . Bitter melon extract showed better effects on triple-negative breast cancer cells compared to ER-positive breast cancer cells in a mouse model.

COLON CANCER

Dietary bitter melon seed oil dose-dependently reduced the incidence and multiplicity of azoxymethane (AOM)-induced colon cancer in male F344 rats Free fatty acids isolated from bitter melon seed oil and his 9-cis, 11-trans, 13-trans conjugated linolenic acid reduce cell viability of Caco-2 cells .Furthermore, bitter melon seed extract in water, ethanol, or ethanol: water (1: 1) showed cytotoxic effects on human colon tumor 116 cells .However, the water extract had the best effect on the cells. Moreover, methanol extract from whole fruit inhibited the proliferation, colony formation, and sphere formation of HT-29 and SW480 cells and induced autophagy .Extracts prepared from whole peels were shown to have less effect on cell lines compared to extracts from whole fruits. None of the extracts showed cytotoxic effects on human benign foreskin fibroblasts (HFF).This extract also increased doxorubicin sensitivity in colon cancer cells . Konishietal. identified an active ingredient l-monopalmitine from a methanol extract that inhibits his P-glycoprotein in human epithelial colorectal adenocarcinoma cells Caco2 .α-Eleostearic acid also inhibited the proliferation of HT29 colon cancer cells .

GASTRIC CANCER

Short-term and long-term administration of fruit extract (2.

5% and 5%) inhibited benzo(a)pyrene [B(a)P]-induced forestomach carcinogenesis in Swiss albino mice .Long-term treatment showed better preventive effects in mice. Methanol extract of leaves showed therapeutic effect on gastric adenocarcinoma cells AGS . Bitter melon protein compounds (fractions I-III) isolated by high-speed countercurrent chromatography inhibited the human gastric cancer cell line SGC-7901 . Fraction II showed the highest anticancer activity.

HEAD AND NECK CANCER

This category includes cancers of the tongue, oral cavity, nasal cavity, sinuses, salivary glands, larynx, and pharynx. Bitter melon extract showed potential cytotoxic effects in Cal27, JHU029, and JHU022 cells in a time- and dose-dependent manner . Anticancer effects were associated with inhibition of cell proliferation, induction of apoptosis, inhibition of c-Met signaling, and reduction of glycolysis and lipid metabolism .Oral administration of the extract (30% v/v) prevented

xenograft and syngeneic tumor growth by reducing cell proliferation and inducing apoptosis in mice . Additionally, in a syngeneic model, the extract reduced infiltrating regulatory T cell (Treg) populations in tumors and spleen . In a subsequent study, continuous oral administration of water extract via drinking water (30% v/v) showed that 4-nitroquinoline-1-oxide (4-NQO) was shown to prevent the development of induced murine tongue squamous cell carcinoma. ossification, metabolism and immune system . In nasopharyngeal carcinoma cells, alpha-momorcarin (α-MMC), a component of bitter melon, showed cytotoxic activity against his CNE-1 and HONE1 cells, but not in non-cancerous human nasopharyngeal epithelial cells NP69. Minimal effects were observed .

LIVER CANCER

Oral administration of methanol extract (40 mg/kg) during pre- and post-carcinogenic stages inhibits diethylnitrosamine (DENA) and Prevented the development of carbon chloride (CCl4)-induced hepatocellular carcinoma and apoptosis . On the other hand, treatment with fruit extract (5% v/v) for 48h resulted in the death of 63% of HepG2 cells due to inhibition of apolipoprotein B secretion and hepatic triglyceride synthesis . MAP30 and α-MMC isolated from seeds showed potential cytotoxic effects on HepG2 cells . Map30 also inhibited the growth of HepG2 cell xenograft tumors in nude mice . No side effects of MAP30 were observed in animal models.

Cucurbitan-type triterpene glycosides, flupirone cucurbitan A, goya glycoside I, chalantagenin F, and nine other compounds exhibited antifibrotic activity against mouse hepatic stellate cells (t-HSC/Cl-6) and human We investigated the anticancer activity against liver cancer cells HepG2 and HepG2 Hep3B. Among the compounds, carabiroside-III showed the best inhibitory activity against t-HSC/Cl-6, Hep3B, and HepG2 cell lines.

LUNG CANCER

Aqueous and methanol extracts from leaves of bitter melon plants showed dose-dependent cytotoxic effects on human non-small cell lung cells A549 and lung adenocarcinoma cells CL1, but not on normal human embryonic kidney cells. HEK293 and lung cell WI-38 are less sensitive . α-MMC and MAP30 suppressed A549 cell proliferation and induced S-phase cell cycle arrest and apoptosis in a dose- and time-dependent manner . MAP30 showed stronger effects on cells than α-MMC .

PROSTATE CANCER

Oral administration of bitter melon fruit extract prevented the progression of prostatic intraepithelial neoplasia in TRAMP (transgenic murine prostate adenocarcinoma) mice by inhibiting cell cycle progression and proliferation . Dietary leaf ethanol extracts (1% and 5%) prevented the development of PC3 cell xenograft tumors without adversely affecting the body weight of mice .The same extract (0.1 and 1% in the diet) increased animal survival and decreased PLS10 cell-mediated metastasis in nude mice .Bitter melon extract induced over 90% cell death in PC3 and LNCaP cells, whereas primary prostate epithelial cells showed only a very moderate effect .Another study reported that whole amniotic fluid extract inhibited proliferation of rat prostate adenocarcinoma cells in vitro and induced cell cycle arrest in G2-M phase .

Ethanol leaf extract inhibited prostate cancer growth in in vitro and in vivo models .Bitter melon compound MAP30 (1-20 µg/ml) dose-dependently inhibited cell proliferation of human prostatic intraepithelial neoplasia (PIN) cells, PC-3 cells, and LNCaP cells without cytotoxic effects on normal prostate cells. and induced apoptosis (RWPE). Intraperitoneal administration of MAP30 also inhibited the growth of PC-3 xenograft tumors in mice .

PANCREATIC CANCER

Fruit water extract treatment inhibited cell proliferation and induced apoptosis in human pancreatic cancer cells BxPC-3, MiaPaCa-2, AsPC-1, and Capan-2 . This extract inhibited the proliferation and induced autophagy of gemcitabine-resistant AsPC-1 cells in a dose- and time-dependent manner . This extract also inhibited the CD44+/CD24+/EpCAMhigh pancreatic cancer stem cell (CSC) population, CSC-associated markers SOX2, OCT4, NANOG and CD44, and increased the sensitivity to gemcitabine in vitro and in vivo . In xenograft models, the extract reduced tumor volume and inhibited glucose and lactate transporters GLUT1 and MCT4 .

SKIN CANCER

Oral administration of fruit extracts prevents carcinogenic skin carcinogenesis in mice, increases survival, reduces lipid peroxidation, activates liver enzymes glutathione S-transferase, glutathione peroxidase, and catalase, and stimulates lymphocyte reduced DNA damage .Similarly, pretreatment or continuous topical application of methanol extracts of fruits and leaves (doses of 500 and 1000 mg/kg body weight) can induce dimethylbenz[a]anthracene (DMBA)/croton oil-induced cutaneous papilloma. significantly reduced the formation of micronuclei and prevented micronuclei formation and chromosome damage. Abnormalities and increased survival of Swiss albino mice . Cucurbitan-type triterpene glycoside compounds 1 and 2 isolated from methanol extracts of fruits prevented DMBA- and peroxynitrite-induced carcinogenesis in mouse skin .However, no further studies using these compounds have been reported. In a melanoma treatment model, doses of 500 and 1000 mg/kg body weight of fruit and leaf extracts in 50% methanol decreased B6F10 xenograft tumor growth and prolonged survival of C57 B1 mice .

OTHER CANCERS

Raw bitter melon extract or isolated compounds showed potential anti-cancer effects against other cancers such as adrenocortical cancer, glioma, ovarian cancer, and cervical cancer .This extract inhibited proliferation and induced apoptosis in human and mouse adrenocortical carcinoma cells, whereas extracts from blueberry, zucchini, and acorn squash showed no cytotoxic effects. MAP30 inhibited cell proliferation, migration and invasion and induced apoptosis in a time- and dose-dependent manner in glioma cell lines U87 and U251 . fruit methanol extract inhibited cell proliferation and increased cisplatin sensitivity in ovarian cancer cell lines A2780cp, A2780s, C13*, and OV2008 . No significant cytotoxicity of the extract was reported on immortalized human ovarian surface epithelial cells (HOSE 17-1). Intraperitoneal injection of the extract reduced ES2 xenograft tumor growth and increased cisplatin sensitivity in nude mice.

Similarly, ethanolic leaf extract inhibited the proliferation of the human cervical cancer cell line KB-V1 and induced sensitivity to the chemotherapeutic drugs vinblastine and paclitaxel in a dose-dependent manner .Hexane and diethyl ether fractions from the extract showed the strongest effects. However, extracts from fruits and vines had no effect on these cells. Kuguacin J (#4) isolated methanol extract from leaves showed cytotoxicity and induced drug sensitivity in cervical cancer cells KB-VI and ovarian cancer cells SKOV3 .The purified lectins momordin (MW: ·24 kDa) and agglutinin (MW: ·32 kDa) inhibited ehrlichaocyte tumors at an LD50 dose of 5 mg/kg body weight without any obvious animal toxicity.

MOLECULAR MECHANISM OF BITTER MELON IN CANCER PREVENTION AND THERAPY

The bioactivity of bitter melon depends on the cumulative effect of various bioactive components. The anticancer and therapeutic effects of bitter melon raw extract/pure compound depend on the time of administration, i.e., the time of administration. However, the molecular mechanisms of prevention and treatment were found to be similar at the stages before and after carcinogenesis. The molecular mechanism of bitter melon's anticancer effects has been extensively studied in in vitro cancer cell line models.

1) GENRATION OF REACTIVE OXYGEN SPECIES ANTI-INFLAMMATION AND CARCINOGEN ELIMINATION

Bitter melon crude extract and pure compounds increase the production of cellular reactive oxygen species (ROS) and decrease the inflammatory cytokines S100A9, IL23a, IL-1β, IL-6, TNFα, and various enzymes including glutathione S-transferase.induced the activity of detoxifying enzymes.

Superoxide dismutase and cataracein in different types of cancer .Since tumor cells increase their production of ROS, further increases in ROS levels along with induction of detoxifying enzymes impede tumor formation and progression and increase stress-induced cell death. Many natural products exert similar chemopreventive mechanisms . Acute inflammation is the main response to pathogen or oncogenic attack, whereas chronic inflammation caused by the induction of proinflammatory cytokines increases carcinogenic potential through increased ROS levels, mutations, and epithelial-to-mesenchymal transition (EMT). This is one of the reasons for the conversion. Angiogenesis and metastasis .Inhibition of proinflammatory cytokines with inhibitors or neutralizing antibodies has shown promising results in various clinical studies .On the other hand, detoxifying enzymes such as glutathione S-transferase, superoxide dismutase, and catalase serve as the first line of defense against oxidation and carcinogen metabolism, thereby preventing the initiation and progression of carcinogenesis . Therefore, bitter melon has potential preventive and therapeutic effects against various types of cancer.

2) MODULATION IN CELL SIGNALING

During cancer progression, cancer cells manipulate multiple signaling pathways to promote unregulated proliferation, motility, and survival . Many signaling molecules are being investigated as potential targets for cancer therapy. Bitter melon extract inhibited the c-Met/Stat3/c-Myc/Mcl-1 axis in head and neck cancer .The proto-oncogene MET encodes the receptor tyrosine kinase c-Met, which regulates multiple downstream events such as STAT3/c-Myc, PI3K/AKT, Ras/MAPK, JAK/STAT, SRC, and Wnt/ promotes tumor development and progression. β -catenin . Furthermore, this extract activated AMP-activated protein kinase (AMPK) and inhibited mTOR/p70S6K and/or AKT/ERK/FOXM1 (Forkhead Box M1) signaling cascade in ovarian cancer . Similarly, crude extracts regulated AMPK/mTOR and p38 MAPK signaling in breast, colon, and prostate cancers . Bitter melon compounds α-eleostearic acid, 3β, 7β, 25-trihydroxycucurbita-5,23(E)-diene-19-al, lectin and RNase MC2 have been implicated in signaling events in various cancers. showed a potential role in regulation .Several studies have suggested that c-Met, PI3K/AKT, or p38 MAPK signaling are attractive targets for the development of drugs that inhibit proliferation and resistance to apoptosis, and many of these drugs has shown promising efficacy in clinical trials against multiple cancers . Therefore, regulation of signaling events by bitter melon may be important for cancer prevention and treatment.

3) REGULATION ON CELL CYCLE

Cancer cells are characterized by uncontrolled cell cycle progression and defective cell cycle checkpoints, contributing to uncontrolled proliferation, genetic instability, and resistance to apoptotic cell death [82].

Bitter melon water extract inhibits cell cycle-promoting genes cyclin D1 and survivin and induces tumor suppressor genes p21 and p27 in head and neck cancer cells, as verified by cell cycle-specific qRT-PCR array and subsequent Western blot analysis [44] Water extract induces cell cycle arrest in S phase or G2-M phase, inhibits the expression of cyclin D1, cyclin E1, and cyclin B1, and inhibits the expression of p53, p21, and pChk1 in breast and prostate cancer cells.

/2 has been enhanced [27,61].

Similar effects of crude extract and bitter melon components α-MMC, MAP30, Kuguacin J (#4), and lectin have been observed in other cancers.

4) INHIBITION OF CANCER STEM CELL POPULATION

Cancer stem cells are a small subpopulation of cells within a heterogeneous tumor that, when transplanted into a host, give rise to a new tumor with the original tumor's phenotype, undergo self-renewal and differentiation, and undergo chemotherapy or radiation therapy. resistance to therapy, metastasis, and tumor recurrence . CSCs can be detected by various markers such as Sox2, Oct4, Nanog, CD24, CD44, CD133, CD90, EpCAM, and ALDH in different tumors .Targeting CSCs in combination with conventional treatments is considered an important approach to chemotherapy, and many clinical trials are currently underway for different types of cancer . Many natural phytochemicals exhibit anticancer properties by targeting CSC populations and their self-renewal .Bitter melon water extract could inhibit CD44+/CD24+/EpCAMhigh CSC population, decrease CSC markers SOX2, OCT4,NANOG and CD44, and increase gemcitabine sensitivity in a pancreatic cancer model .Similarly, methanol extract of fruit inhibited sphere formation and expression of CSC markers DCLK1 and Lgr5 in colon cancer cells

MAP30 decreased the expression of the self-renewing Wnt signaling pathway effector molecule β-catenin and its target genes c-Myc and cyclin D1 in glioma and prostate cancer cells . Therefore, bitter melon may have potential therapeutic effects against various cancers due to its effect on CSC.

5) INDUCTION OF APOPTOSIS AND AUTOPHAGY

Apoptosis and autophagy are considered to be interrelated pathways of cell death , and bitter melon induces both pathways leading to cancer cell death. Apoptosis is a caspase-mediated programmed cell death that is activated in response to various stresses such as DNA damage, growth factor deficiency, and oxidative stress .Genetic mutations or alterations generally cause solid tumors to lose the ability to undergo immediate and extensive apoptosis, the so-called first-order response that characterizes sensitive cells .Induction of apoptosis is an essential event for various types of anticancer drugs, and disruption of this mechanism can lead to widespread drug resistance and, in some cases, nonspecific side effects .

Bitter melon crude extract increases the expression of pro-apoptotic Bax, Bak, Bid, and p53, decreases anti-apoptotic Bcl2, activates caspase 3, 7, 9 and cytochrome c release, and induces various types of It was found to prevent PARP cleavage in cancer .

Similarly, induction of apoptosis by bitter melon compounds α, β-momorcarin, RNase MC2, 3β,7β,25-trihydroxycucurbita-5,23(E)-diene-19-al, MAP30, lectin, and BG-4 It was also observed that the Type of cancer. Autophagy is a self-degrading process that responds to various stresses such as nutrient deprivation, organelle damage, hypoxia, ROS

generation, ER stress, and drug treatment . The mechanism of autophagy in cancer is not clear. Autophagy can be tumor-induced or beneficial for cancer prevention, and excessive autophagy promotes massive cell death . Bitter melon extract induced autophagic cell death by converting LC3A to lipidated LC3B, increasing the accumulation of p62, and enhancing the expression of Beclin-1, ATG-7, and -12 . Bitter melon lectin also plays a dual role by inducing either apoptosis or autophagy . However, the mechanism of induction of autophagy or apoptosis in cancer after bitter melon treatment is unknown.

6) MODULATION IN IMMUNE SYSTEM

Suppression of the immune system is an important factor in the development of cancer.

Bitter melon fruit water extract reduced FoxP3+ infiltrating regulatory T (Treg) cell populations in tumors and spleen .Furthermore, the extract reduced the Th17 cell population within the tumor.

However, there was no change in Th1 and Th2 cell populations. Furthermore, treatment with this extract enhanced natural killer (NK) cell-mediated cytotoxic effects in head and neck cancer cells .

However, the extract showed no cytotoxic effect on her NK cells, but increased granzyme B accumulation, CD107a/LAMP1 translocation/accumulation, and CD16 and NKp30 expression.

RNA-seq analysis revealed that the water extract significantly modulated "immune system processes" that prevented tongue carcinogenesis in mice .

In the bitter melon treatment group, the significantly downregulated genes in this pathway were s100a9, IL23a, IL1β, and the immune checkpoint gene PDCD1/PD1. Increased expression of s100a9, IL23a, IL1β, and PD1 has been observed in several human malignancies. Drugs targeting s100a9 or PD1 have shown promising results in phase I–III clinical trials against various cancer types .Therefore, it can be seen that bitter melon extract has a potential role in cancer prevention and treatment.

7) MODULATION IN GLUCOSE AND LIPID METABOLISM

Metabolic reprogramming is one of the hallmarks of cancer, promoting rapid energy production, biosynthetic capacity, and resistance to therapy. RNAseq analysis shows downregulation of important glycolytic and lipid metabolism genes in the prevention of mouse tongue carcinogenesis by bitter melon water extract . Subsequent analysis of head and neck cancer cells revealed downregulation of key glycolytic genes SLC2A1 (Glut-1), PFKP, LDHA, PKM, and PDK3, as well as levels of pyruvate and lactate after treatment with the extract. and decreased glycolytic rate .In lipid metabolism, water extract inhibited the expression of fatty acid biosynthetic genes ACLY, ACC1, and FASN, and the levels of phosphatidylcholine (PC), phosphatidylethanolamine (PE), and plasmenylethanolamine (pPE) in head and neck cancer cells. In triple-negative breast cancer (TNBC) model, water extract reduced esterified cholesterol by inhibiting acyl-CoA:-cholesterol acyltransferase 1 (ACAT-1) . Subsequent studies showed a decrease in the expression of lipid metabolism genes SREBP-1/2, FASN, LDLR, and TIP47 by the extract and accumulation of lipid droplets in TNBC cells.Modulation of lipid metabolism by bitter melon induced ER stress-mediated apoptotic cell death . Water extract treatment also reduced the glucose transporter GLUT1 and the lactate transporter MCT4 in in vitro and in vivo models of pancreatic cancer . Therefore, regulation of metabolism is an important event in the prevention and treatment of cancer caused by bitter melon.

8) INHIBITION OF INVANSION , METASTASIS , HYPOXIA AND ANGIOGENESIS

Bitter melon water extract inhibited wound healing, migration, and invasion of the ovarian cancer cell line SKOV3 . Methanol extract from bitter melon leaves inhibited migration and invasion in human lung adenocarcinoma CL1 cells and suppressed the enzyme activities of MMP-2 and MMP-9 . Similarly, leaf ethanol extract inhibits the activity of MMP-2, MMP-9, urokinase plasminogen activator (uPA),
collagenase type IV, and the expression of induced TIMP2, thereby inhibiting the rat prostate. inhibited the migration and invasion of cancer cells (PLS10) (60). α-MMC, a component of bitter melon, decreased the expression of hypoxia-inducible factor 1-α (HIF1α) and vascular endothelial growth factor (VEGF) in hypoxic nasopharyngeal carcinoma cells and inhibited the proliferation of human umbilical vein endothelial cells. Overall, bitter gourd extract or pure compounds modulate multiple cellular events simultaneously to prevent cancer cell proliferation, survival, and metastasis.

HOW DOES BITTER MELON EXTRACT ENTER INTO CANCER CELLS

The extract modulates membrane integrity and then penetrates cells to exert biological effects.

To exert anti-cancer activity, bitter melon extracts/compounds must interact with cancer cell membranes and subsequently penetrate into cancer cells. Little is known about this mechanism.

A study revealed that bitter melon water extract could inhibit the expression of membrane lipid raft protein flotillin and modulate its localization in head and neck cancer cells . In the same study, bitter melon extract reduced levels of cell membrane components phosphatidylcholine,
phosphatidylethanolamine, and plasmenylethanolamine in head and neck cancer cells.

This suggests that the extract can interact with the lipid bilayer and modulate the integrity and permeability of cancer cell membranes. Lipid rafts are also receptor-mediated cell signaling hubs.

Therefore, the regulation of various signaling events mediated by bitter gourd may be through the regulation of membrane lipid rafts. Lectin-type compounds have been found to bind specifically to cell surface oligosaccharides and glycans and are transported into cells .Cancer cells change their membrane structure in many ways compared to normal cells. Among these, changes in membrane oligosaccharides are mainly observed in cancer cells .There are different types of lectins in bitter melon extract, which can likewise specifically penetrate cancer cells and exhibit biological mechanisms such as inhibition of ribosomes and induction of apoptosis and autophagic cell death. Various triterpene glycosides bind to cell membranes, interact with membrane lipids, form glycoside-sterol complexes within the membrane, form multimeric channels in sterol-containing lipid bilayers, and increase membrane permeability to ions and peptides. Saponin-like compounds also have the ability to bind to cell surfaces and form pores in membranes, disrupting the ionic balance within the membrane and causing cell lysis . Similarly, flavonoids readily bind to cell surfaces and penetrate intracellularly to exert cytotoxic effects Therefore, the types of triterpene glycosides, saponins, and flavonoids contained in bitter gourd are thought to enter cells through a similar mechanism and exert anticancer effects.However, detailed research is required to know the exact mechanism by which bitter melon is formed.

INTERACTION WITH CELLULAR MACROMOLECULES DNA, RNA AND PROTEINS

Bitter melon components α-MMC and MAP30 exhibit topological inactivation of DNase and DNA activities . These two components were shown to be effective inhibitors of protein synthesis due to their ribosome-specific N-glycosidase activity . MC2 RNase in bitter melon seeds showed strong RNA cleavage activity against tRNA of baker's yeast and rRNA of tumor cells, and absolute specificity for uridine . In the same study, RNase MC2 induced nuclear damage through nuclear disruption, chromatin
condensation, and DNA fragmentation, leading to early/late apoptosis in breast cancer cell line MCF7 .

Bitter melon lectin has type I and type II ribosome inactivating activity . In another study, a factor purified from bitter melon extract (equivalent to a molecular weight of 40 kDa) was shown to inhibit RNA and protein synthesis in intact tissue culture cells .The protein component present in the aqueous extract (molecular weight corresponding to 50–70 kDa) showed non-competitive inhibition of guanylyl cyclase .Bitter melon extract has P-glycoprotein inhibitory activity . The ABC transporter P-glycoprotein is highly expressed in tumor cell membranes and secretes hydrophobic drugs from cells in an ATP-dependent manner, causing drug resistance .

Bitter melon extract inhibits the activity of calcium-independent phospholipase A2 (iPLA2) in head and neck cancer cells . iPLA2 is ubiquitously expressed in mammalian cells and is involved in multiple biological processes including lipid metabolism, phospholipid remodeling, cell differentiation, maintenance of mitochondrial integrity, cell proliferation, signal transduction, and cell death.Studies suggest that flavonoids physically interact with DNA, RNA, and protein molecules, thereby regulating transcription, translation, protein function, and enzyme activity .Flavonoids form strong hydrogen bonds and bind strongly to nucleic acids and proteins. Bitter melon extract contains several flavonoids.

It appears that these components may behave similarly.There has been no research into how the components of bitter gourd enter the core. All evidence suggests that bitter melon compounds penetrate cells and regulate DNA, RNA, and protein function in cancer prevention and treatment.

EPIGENETIC MODIFICATION

Epigenetic regulation, such as DNA methylation at CpG dinucleotide sequences, histone modifications such as methylation and acetylation, and non-coding RNA-mediated regulation, is a reversible process and plays an important role in gene expression. Epigenetic changes are essential phenomena that regulate the activation of oncogenes and the repression of tumor suppressor genes, and are often observed in the early stages of carcinogenesis . Many medicinal plant extracts and active ingredients have anticancer properties as they can reverse epigenetic changes . The role of bitter melon in epigenetic modification has not been well studied.Bitter melon extract contains many phytochemicals, especially flavonoids.

Flavonoids have been shown to alter epigenetic mechanisms in cancer control . 3β,7β,25
trihydroxycucurbita-5,23(E)-diene-19-al (TCD), a bitter melon triterpenoid, inhibits histone deacetylases (HDAC1, HDAC2, HDAC3, and HDAC4) and thereby prevent the proliferation of breast cancer cells.

Bitter melon MCP30 inhibits histone deacetylase 1 (HDAC-1) activity and promotes acetylation of histones H3 and H4 in prostate cancer cells .MAP30 induces the histone acetyltransferase p300 and promotes histone H3 acetylation in leukemia cells . Bitter melon fruit extract exhibits anti-inflammatory effects in human lung epithelial cells by upregulating microRNA miR-221 and miR-222 .

This suggests that the regulation of gene expression by bitter gourd may be due to epigenetic modification activity. However, detailed studies are required to elucidate these mechanisms.

CONCLUSION

As discussed in this review, bitter melon is rich in many nutrients and active compounds, including triterpenoids, triterpene glycosides, phenolic acids, flavonoids, lectins, sterols, proteins, and saponins.

The anticancer and therapeutic effects of bitter gourd have been extensively studied using crude extracts in water, methanol, and ethanol as solvents.Both crude extracts and isolated compounds have demonstrated potential anti-inflammatory properties by inhibiting cancer cell proliferation, survival, and metastasis in multiple cancer types without causing significant toxicity to normal cells. It has cancer and therapeutic effects.

Anticancer effects include ROS generation, activation of detoxifying enzymes, inhibition of cancer stem cell populations and their self-renewal, cell cycle inhibition, cell signaling, invasion, metastasis, hypoxia, angiogenesis, and glucose and lipid metabolism. , related to induction. Relationship between apoptosis, autophagy and immune system regulation - Changes in multiple cellular events can be achieved simultaneously through regulation of membrane organization, interaction with DNA, RNA, and proteins, and epigenetic modification by bitter melon . Therefore, bitter melon may have the potential to improve cancer prevention mechanisms. On the other hand, extracts or pure compounds can be used as therapeutic agents in parallel with conventional treatments for additional cancer treatment management.

However, further evaluation of the active ingredient and detailed mechanistic studies in preclinical systems are needed, which may be important for the design of prospective studies of interventional therapies.

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