Expert Opinion on Therapeutic Patents

ISSN: 1354-3776 (Print) 1744-7674 (Online) Journal homepage: http://www.tandfonline.com/loi/ietp20

Bioactivity and pharmacological Properties of α-mangostin from the mangosteen fruit: a review

Guoqing Chen, Yong Li, Wei Wang & Liping Deng

To cite this article: Guoqing Chen, Yong Li, Wei Wang & Liping Deng (2018): Bioactivity and pharmacological Properties of α-mangostin from the mangosteen fruit: a review, Expert Opinion on Therapeutic Patents, DOI: 10.1080/13543776.2018.1455829

To link to this article: https://doi.org/10.1080/13543776.2018.1455829

Accepted author version posted online: 20 Mar 2018.

Bioactivity and pharmacological Properties of α-mangostin from the mangosteen fruit: a review

Guoqing Chen[1], Yong Li[1], Wei Wang[2] and Liping Deng[1,2]*

Affiliations

[1]Department of Chemistry and Chemical Engineering, Shaoxing University, Shaoxing 312000, P.R.China

[2]Shaoxing University Yuanpei College, Shaoxing University, Shaoxing 312000, P.R.China

*** Corresponding author**

Telephone: +86-575-88342813, Email: wwdlp@126.com

Abstract

Introduction

Mangosteen as a rare and precious fruit looks like a queen crown, known as "Queen of Fruit". α-Mangostin (α-MG) is the most representative xanthone isolated from the pericarp of mangosteen, possessing extensive biological activities and pharmacological properties, which can be considered as an antineoplastic agent, antioxidant, anti-proliferation and induces apoptosis in various types of human cancer cells, and has protective effect on induced apoptotic damage.

Areas covered

The bioactivity and pharmacological Properties of α-MG are being actively investigated by various industrial and academic institutions. The bioactivities of α-MG have been summarized in several previous reviews, which were worthy of high compliment. However, recently, many new literatures about the bioactivities of α-MG have been further reported from 2016 to 2017. Herein, the activities of α-MG are supplemented and summarized in this text.

Expert opinion

As previously said, α-MG has anticancer potential and can be used as a chemoprevention or agent for breast cancer, colon cancer, pancreatic cancer, cutaneum carcinoma and oral cancer, etc. It also has anti-inflammatory, anti-bacterial, anti-malarial, anti-obesity action. Furthermore, α-MG has the effect of maintaining cardiovascular system and gastrointestinal health and controlling free radical oxidation. In recent years, α-MG has more applications in cosmetics, with the effects of anti-aging, anti-wrinkle, acne treatment, maintenance of skin lubrication. The application of α-MG in treating rheumatoid arthritis has been disclosed and the MG-loaded self-micro emulsion (MG-SME) was designed to improve its pharmacokinetic deficiencies. As mentioned above, α-MG can be a promising drug, also worthy of developing, and further research is crucial for the future application of α-MG.

Key word: α-Mangostin, biological activities, chemopreventive, pharmacology

Article highlights

- In this review, we focus on the new founding about bioactivity and pharmacological properties of α-MG.
- Several preclinical studies on depositing α-MG nanoparticles to sebaceous gland area for acne treatment were performed.
- α-MG inhibits DMBA/TPA-induced skin cancer through regulating PI3K/Akt/mTOR signaling pathway in mice.
- The first discovery of the effect of α-MG on cardiac function, leading to myocardial relaxation dysfunction.
- α-MG has a potential therapeutic effect on Osteoarthritis(OA), and that this effect may be achieved by inhibiting the mitochondrial apoptosis of chondrocytes induced by an activation of the NF-kB pathway.
- α-MG has a potential protective effect on apoptotic damage cells.

1. *Introduction*

To date, many human diseases associated with oxidative stress have been ubiquitous in the world, including diabetes, cardiovascular disease, inflammation and especially obesity and cancer. Excess adiposity and obesity are the root cause of at least 27 diseases that cause considerable lifelong morbidity and, in many scenarios, eventual cardiovascular mortality [1]. In addition, cancer is also the leading cause of high incidence and mortality in the world. At present, chemotherapy is still a significant treatment for malignant tumors, but its side- effects also seriously affect the life of patients [2]. As a result, cancer is one of the most serious clinical problems in the world, and needs a great deal of effort to find a new therapeutic agent [3]. In recent years, fruit as important dietary ingredients contain high bioactive ingredients, which have been dismissed as a promising source for developing safety and effective anticanncer medicines. The studies of epidemiological and experimental have shown that having fruits and vegetables regularly can diminish the incidence of cancer [4]. In addition, curcumin, sulforaphane, and caffeic acid phenyl ester etc., which are normally referred to as "phytochemicals", have been identified that possessing the characteristics of cancer chemical prophylaxis [5]. Mangosteen, known as "queen of fruits", which is a tropical evergreen tree cultivated in Southeast Asian nations. The pericarp of mangosteen was used as a traditional medicine for the treatment of abdominal pain, diarrhea, dysentery, infected wound, suppuration, and chronic ulcer. Recently, mangosteen products in the form of juices and dietary supplements have attracted scientists' interests [6, 7]. Lots of evidences from in vitro and in vivo researches have demonstrated that α-MG (**Fig. 1**) showed extensive pharmacological activities, including anticancer, antioxidant, antibacterial, antimalarial and anti-obesity activities as well as neuroprotective properties in Alzheimer's disease (AD), hepatoprotective and cardioprotective properties [8, 9, 10, 11]. This review provides an update analysis of the pharmacological activities and pharmacokinetics profile of α-MG, as well as describes the protection of α-MG on the apoptosis damage.

2. *Main pharmacological effects of α-MG*

2.1. *The anticancer properties*

The anticancer properties of *α*-MG were showed in **Table 1**. The current treatments for

cancer have not achieved good results. Chemotherapy is one of the most effective ways to diminish the incidence of cancer. In order to overcome the cancer and other diseases which endanger human health, and researchers continue to discover new drugs from plants. In recent years, anticancer effect of α-MG has gradually been confirmed. At present, the researches on α-MG treatment of high incidence of cancer such as mammary cancer, lung cancer, colon cancer, gastric cancer, prostate cancer, pancreatic cancer and skin cancer, which have achieved good results and elucidated the anticancer and cytotoxic activities of mangosteen [12]. The inhibitory effect of α-MG on cell viability in five HCC cell lines was studied by Hsieh et al. [13]. The healthy primary hepatocytes cells were treated with α-MG (0-40 μM) for 24 and 48 h, the 50% growth suppression concentration (IC_{50}) values as cytotoxic effects. The MTT assay showed that α-MG in both dose- and time-dependent ways to growth inhibition of SK-Hep-1 cells. However, there was no significant colonchanges in cell viability in normal hepatocytes. Furthermore, they researched the influence of α-MG on the suppression of colony formation of bacteria, and found that the cells treated with α-MG showed a remarkably diminish in the quantity of colonies in different concentrations. The experiment showed that α-MG had fairly good anti-hepatoma activity and low cytotoxic effect on normal hepatocytes. To measure the incidence of fibrotic nodules on the liver, the serum levels of the liver enzymes aspartate transaminase (AST) and alanine transaminase (ALT), the rats were divided into 3 groups and injected intraperitoneally with TAA 3 times a week for per week for 8, 12 and 16 weeks. A group was blank test, while the others were treated with 100 mg/kg α-MG or vehicle alone (80% DMSO, 20% water). The expression of liver cirrhosis-related genes and p53 protein level in liver were analyzed through the quantitative reverse transcription western-blot analysis. The results showed that the liver treated with TAA for 12 or 16 weeks obviously formed fibrotic nodules. The nodules were diminished by treatment of α-MG compared with treating with the vehicle dimethyl sulphoxide (DMSO). In addition, the serum levels of the liver enzymes AST and ALT were decreased after treating with α-MG compared with DMSO alone. There was no significant difference in liver cirrhosis-related gene expression, whereas the p53 protein level in liver displayed that α-MG drastically reduced the liver fibrosis' risk through the decline in p53 expression as compared to treatment of TAA or DMSO. It showed that α-MG had a beneficial

therapeutic effect in the TAA liver cirrhosis model [14]. The anti-proliferative effect of α-MG on HCC cells was investigated in another study, and found that the percentage of CD133, CD44 and EpCAM positive stem-like HCC cells were diminished by α-MG treatment. Moreover, the expression of key stemness transcription factors, such as Bmi-1 and c-Myc were also suppressed following α-MG treatment. In conclusion, α-MG had anti-proliferative effects in HCC cells and malignantly transformed hepatic cells [15].

In three human colon cancer cell lines, Kumazaki et al. [16] picked out epigallocatechin-3-gallate (EGCG), resveratrol (RES) and α-MG, combining with the treatment of the anti-cancer drug 5-FU. The numbers of viable cells were consistently diminished by treatment with EGCG, RES or α-MG in among three cell lines tested at more than 10 μM. All compounds primarily induced cells apoptosis and suppressed the PI3K/Akt signaling pathway. Additionally, α-MG not only had the greatest PI3K/Akt inhibition activity, but also inhibited the MAP kinase (MAPK)/Erk1/2 signaling. It indicated that α-MG was functioned as chemosensitizers when combined with antineoplastic drugs through the regulation of apoptotic and growth-related signaling pathways. In another similar research, α-mangostin and γ-mangostin had been researched as inhibitors of Wnt/β-catenin signalling. The transcriptional activity of TCF/ β-catenin and protein expression of β-catenin in colon cancer cells were all suppressed. Whereas the levels of cGMP and cGMP-dependent kinase were increased by mangostins treatment, which indicated that the β-catenin gene regulation gives rise to suppression of β-catenin. It showed that α- and γ-mangostin inhibited the proliferation of colon cancer cells via β-catenin gene modulation in Wnt/ cGMP signaling [17].

Several investigators utilized the nude mice models to assess chemoprevention efficiency of α-MG. A metastatic cancer model was developed by implanting the BJMC3879luc2 cells, a murine mammary cancer, into syngeneic BALB/c mice, which was similar to the human breast cancer. They confirmed that α-MG remarkably inhibited tumors' growth and the multiplicity of lymph node metastasis [18]. Meanwhile, α-MG could significantly suppress the FAS expression and its activity that results in the decrease of intracellular fatty acid accumulation, as well as decreased cell viability and induced apoptosis in human breast cancer cells. Moreover, α-MG induced apoptosis associated with HER2/PI3K/Akt and

mitogen-activated protein kinase (MAPK) signaling pathways. So α-MG may be used as food supplement or a potential therapeutic compound for breast cancer [19, 20].

The tanshinone IIA and α-MG were inserted into the AuNPs, PEI and CD complexes, respectively, through a simple green synthesis method. The preliminary biological tests showed that encapsulation of these natural compounds enhanced their efficiency against prostate cancer cell lines PC-3 and DU145. The in vivo tests confirmed the ability of the carrier to reach the tumoural tissues [21]. Li et al. used α-MG to treat with two prostate epithelial cancers cell lines, 22Rv1 and LNCaP, procured from two patients and assessed by reverse transcription-PCR(RT-PCR), Western blot, fluorescent microscopy and siRNA transfection to evaluate ER stress. They also assessed the α-MG for microsomal stability, pharmacokinetic parameters, and anticancer activity in nude mice. The α-MG significantly increased ER stress markers in prostate cancer cells. Moreover, the CHOP knockdown enhanced α-MG-induced apoptosis in prostate cancer cells. α-MG significantly suppressed tumor growth in a xenograft tumor model without obvious toxicity [22]. By above knowable, the anticancer properties of α-MG against several types of cancer have adequate foundation. But the effects and mechanism of α-MG against lung cancer haven't been reported yet and required further investigation. In recent years, the investigation indicated the increasing risks of the small cell lung cancer (NSCLC) in China and South Asian countries. The mechanism of action of α-MG on lung cancer was further investigated by Zhang et al [23], and cultured the non-small cell lung cancer cells A549 in DMEM complete medium supplemented with 10% FBS. The cultured A549 cells were treated with different concentrations of α-MG（0-10 μM） for 24 h. Taking out parts of the α-MG-treated A549 cells and determined the induction of apoptosis via the flow cytometry using Annexin V-FITC apoptosis kit. Determination by the Annexin V/PI staining, the amount of A549 cells poptosis increased to 18% by treatment of 5 μM α-MG. While treatment of 10 μM α-MG, the apoptosis up to 38% as well as the reactive oxygen species (ROS) increased. It confirmed that α-MG could make A549 cells apoptosis and the ROS played an important role.

Then the rest of α-MG-treated A549 cells were placed in the upper portion of the Boyden chamber containing serum free medium. The cells were immersed in a culture medium containing FBS, stained with crystal violet thus formed the crystal violet complex. Then

dissolved them in 10% acetic acid, measured the absorbance at 600 nm. According to the relationship between absorbance and the extent of migration, the extent of cell migration was obtained. Cells, which were treated with 5 μM α-MG, the amount of cells migration were inhibited up to 33%, and treatment of 10 μM α-MG, migration were inhibited by 60%. Overall, it concluded that ROS played a significant role in α-mangostin-mediated cytotoxicity in NSCLC cells.

Pancreatic cancer is one of the most lethal and aggressive cancers in the world and currently has no effective treatment for it. To investigate the inhibitory effect of α-MG on viability of pancreatic cancer cells, Xu et al [24] treated pancreatic cancer cells BxPc-3 and Panc-1 with varying concentrations of α-MG (0-32 μM) for 6, 12, 24, and 48 h. Then assessed cells viability by the MTT assay, measured α-MG-induced apoptosis in BxPc-3 and Panc-1 cells by flow cytometry and performed cell cycle analysis by PI/flow cytometry. Cells, which were treated with 32 μM α-MG resulting in loss of cell viability in both pancreatic cancer cell lines to more than 80%. Treatment of 16 μM α-MG increasing the apoptosis population of both of the cell lines to 30% above. The pancreatic cancer cells significantly accumulated in the G1/G0 phase after treatment with 8 μM α-MG, while cells became larger in G1/G0 phase after treatment of 16 μM α-MG. Furthermore, α-MG not only significantly inhibited the activity of pancreatic cancer, but also retained the biological characteristics of the original cells, which had a relatively higher clinical relevance. Meanwhile, the mangostin-encapsulated PLGA nanoparticles (Mang-NPs), and administrated intraperitoneally have been produced into KPC (about 4 weeks old males and females) mice. About ten weeks later, the researchers not only examined the effects of Mang-NPs on the expression of stem cell markers (CD24 and CD133) and pluripotency maintaining factors (c-Myc, Nanog and Oct4), but also examined the effects of Mang-NPs on the components of Shh pathway as well as its downstream targets in tumor tissues derived from KPC mice. The populations of both stem cell markers and pluripotency maintaining factors were down-regulated, and Mang-NPs also down-regulated the expression of Gli1, Gli2, Patched-1, Patched-2 in KPC mice. It suggested that Mang-NPs offered new hope for the treatment and/or prevention of pancreatic cancer by targeting CSCs. Mang-NPs could inhibit carcinogenesis by targeting CSC population, and inhibit the self-renewal capacity of CSCs

isolated from pancreata of human and KrasG12D mice. Mang-NPs also inhibited pancreatic cancer progression from PanINs to PDAC and metastasis in KPC mice by suppressing Shh pathway [25].

The researches on the treatment and/or prevention of pancreatic cancer have never stopped. They recently cultured the human pancreatic cancer TMIA PaCa-2 and PANC-1 cells, and treated with α-MG or γ-MG at varying concentrations. After 48 or 72 h, they were then subjected to TUNEL assay, western blotting and miRNA assay to determine the anti-cancer effect of α-MG and γ-MG. The results indicated that α-MG and γ-MG could reduce the viabilityof MIA PaCa-2 and PANC-1, induce apoptosis of MIA PaCa-2 and PANC-1, and induce autophagy in pancreatic cancer. Furthermore, treatment of MIA PaCa-2 or PANC-1 with gemcitabine alone or combined with α-MG or γ-MG at IC_{50} for 72 h, and measured the cells viability. They found that α-MG and γ-MG showed synergistic effects for gemcitabine on cell viability of MIA PaCa-2 compared to treatment of gemcitabine alone [26].

Skin cancer is also the most common type of cancer and no good treatment has been found yet. Moreover, it was not yet clear what the role of α-MG in skin cancer. The effect of α-MG on DMBA/TPA-induced skin cancer in mice was evaluated for the first time. Mice treated with two doses of α-MG in the experiment. At the end of experiment (20 weeks), they found the model group developed tumors significantly in the skin. Nevertheless, no tumor formed in α-MG-treated group. The results explicated that α-MG significantly inhibited the skin tumorigenesis, and decreased the tumor incidence rate and multiplicity. They then examined the expressions of inflammatory factors in skin tumor and blood by the enzyme-linked immunosorbent assay (ELISA). And found the down-regulation of pro-inflammatory factors while the anti-inflammatory factorwas significantly up-regulated. The results showed that α-MG protected mice from DMBA/TPA-induced skin tumorigenesis by suppressing inflammation [27].

2.2. Antioxidant activity of α-MG

In **Table 2,** some antioxidant properties of a-MG have been summarized. Many diseases are correlated with antioxidant deficiency. Lipid peroxidation is a key link in many pathological events caused by oxidative stress. The unsaturated lipid oxidation resulted in destruction of membrane lipid producing malondialdehyde as breakdown products are mutagenic and carcinogenic [28]. The cells will be injured by oxidative modifications of proteins or lipid peroxidation when the cellular defenses were destroyed [5]. α-MG possesses strong antioxidant activity and gradually have been confirmed in recent years. The researchers found that α-MG was able to purge singlet oxygen, superoxide anion and peroxynitrite anion in a concentration dependent way. It was concluded that α-MG could directly purge the reactive oxygen species (ROS) and possessed a neuro protective effect against 3-NPin primary cultures of CGNs, which was associated with its ability to improve the ROS production of 3-NP cells [29].

Cui et al. isolated two compounds, α-mangostin and γ-mangostin (γ-MG), which exhibited analgesic effects respectively. In their research, α-MG and γ-MG displayed the ability of scavenging reactive oxygen species in each dose-dependently. Furthermore, they explored its ability of free radical scavenger and analyzed its monoanion through the corresponding theory. From the HAT mechanism they found α-MG and its deprotonated forms are pretty good free radical scavengers, possessing more activities [30]. Later the absorption and antioxidant effects of MG-based functional drinks in the human body were investigated. The research was conducted in the generally healthy male and female adults of different ages, which were randomly split into treatment and placebo two sets via the placebo-controlled clinical trial. The subjects were took the beverage or placebo once a day and collected their blood samples in different time periods then analyzed them. The analytic results showed that the bioavailability of human body has been fully exploited and capacity of antioxidant levels was also markedly improved more than six hours. The endogenous antioxidant activity of α-MG could be enhanced through the activation of Nrf2 pathway [31]. Subsequently the researchers conducted a controlled clinical trial of 30 male and 30 female again, ages 18 to 60, the same as the previous experiment and the trial duration was 30 days. It was found that the group given the mangosteen-based drink formula showed 15% more antioxidant capacity in the blood stream than the placebo group, while no significant decreases for the same biomarker

was observed in the placebo group. In addition, they investigated the effect of mangosteen-based beverage on hepatic function. Their results indicated that there are no harmful effects on human hepatic and kidney functions after the 30 days consumption of the beverage, and the antioxidant capacity was significantly increases by α-MG-based formula. They also found that it possesses anti-inflammatory benefits with no side effects on immune, hepatic, and renal functions for long-term consumption [32, 33].

2.3. Anti-inflammatory, antibacterial and antimalarial activity of α-MG

The studies of the anti-inflammatory, antibacterial and antimalarial activities of α-MG have been studied and summarized in **Table 1**. Several studies have demonstrated anti-inflammatory, antibacterial and antimalarial activity properties of xanthones and extracts obtained from Mangosteen.

2.3.1. Anti-inflammatory activity of α-MG

Liu et al. [34] investigated the anti-inflammatory activity of α-MG in 2012. In their research, the U937 and EL4 cells in the lipopolysaccharide (LPS) were treated with different concentrations of α-MG for 4h. And the anti-inflammatory effects of α-MG was measured by the levels of tumor necrosis factor (TNF)-α and interleukin (IL)-4 in cell culture media, which were determined with enzyme-linked immunosorbent assay kits. The conclusion showed α-MG diminished the LPS expression of the inflammatory cytokines TNF-α and IL-4, and decreased the gene expressions in oncostatin M signaling through the mitogen-activated protein kinase (MAPK) pathways. α-MG was used as anti-acne agent to prepare nanoparticles highly loaded with α-MG and the mangostin nanoparticles at the hair follicles in acne patients were excellently sustained, as well as significantly improved the acne vulgaris condition with mangostin nanoparticles twice a day. It elucidated that the capability of the obtained particles can make α-MG eventually permeate into synthetic sebum [35]. Preparingthe primary Microglia, Midbrain neurons, Midbrain neuron-glianeuronal cultures and Transwell cocultures to explore the effects of α-MG to ensure the radioactivity in DA absorptionand analyze the proteins expression with Western blot. The results indicated that the increased levels of pro-inflammatory cytokines can be inhibited by α-MG. Moreover, α-MG protected

the neurotoxicity with α-synuclein-induced microglial, which inhibited microglial activation induced by *α*-synuclein by targeting NADPH oxidase [36]. SIRT-1 is a nuclear histone deacetylase, which could influence cellular function by the inhibition of NF-kB signaling. It reported that the ROS can inhibit SIRT-1 activity to enhance the NF-kB signaling resulting in inflammatory responses. From the response of inflammatory injury, Franceschelli et al. [37] investigated the NF-kB signaling pathway, and determined there were some links between these signaling molecules, as well as the anti-inflammatory mechanism of a-MG. It showed that a-MG significantly increased SIRT-1 expression in U937 cells, and the anti-inflammatory effect of α-MG was mediated by the NF-kB regulation through SIRT-1. Twenty-five patients (α-MG group) were treated with SRP and the subgingival application of mangostana gel was used as local drug delivery. The same number of placebo group were treated with SRP and placebo gel. Three month later, all of the patients were probed the pocket depth, clinical attachment level, bleeding index, plaque index, all clinical parameters were significantly reduced in the MGA group compared to the placebo group from baseline to the third month. Their conclusion showed that 4% α-MG gel can be used as an adjunct to SRP to provide a new dimension to periodontal therapy [38].

Osteoarthritis (OA) is a joint disease characterized by inflammation and cartilage degradation. Tianlong Pan et al [39, 40] used rat chondrocytes and an OA rat model induced by destabilization of the medial meniscus (DMM). And the rat chondrocytes were pretreated with α-MG or saline every other day. Additionally, they used the hematoxylin, eosin and Safranin-O-Fast green staining to evaluate the severity of cartilage lesions up to 8 weeks following surgery. The results suggested that the production of NO and PGE2 were inhibited by α-MG, and the IL-1β induced phosphorylation of the NF-kB signaling pathway was inhibited by α-MG. Furthermore, the cartilage treated with α-MG showed attenuated degeneration compared with the control group. These results showed that α-MG had potential therapeutic value in the treatment of OA.

2.3.2. Antibacterial activity of α-MG

Staphylococcus epidermidis beyond its local homoeostasis characteristics on human skin as a commensal flora, it has been well recognized for the most frequent cause of health

care-associated bloodstream infections and biomaterialassociated infections. Sivaranjani M et al. [41] investigated the rapid killing efficacy of α-MG on planktonic cells of S. epidermidis by performing time kill curve assay. As anticipated, α-MG displayed rapid concentrationdependent killing of S. epidermidis cells at concentrations above 4× MIC (5 g/mL) and 2× MIC (2.5 μg/mL) of α-MG, achieving 6 log and 4 log reduction of viable count within 5 min of exposure time, respectively. A less than 2 log reduction of viable counts was achieved while treating with 1× MIC (1.25 g/mL) of α-MG.

In parallel to these studies, the antibiofilm activity of α-MG against the three Staphylococcus aureus was investigated and strains by using a 96-well plate model for the formation of biofilm at 37℃for 24h, one of which was methicillin-resistant S. aureus (MRSA) and the other two strains were methicillin sensitive S. aureus (MSSA). They used the crystal violet to quantified biofilm biomass and observed cells viability with the confocal microscopy. It can be seen that the biomass was markedly reduced. Furthermore, assays used human red blood cells that indicated α-MG caused significant membrane damage with 50% of cell lysis occurred at concentration of about 36 mmol/ L. The results indicated that α-MG not only possessed sterilization, but also inhibited the formation of biofilm [42].

In S. epidermidis, biofilm formation is the most imperative virulence trait making this commensal inhabitant as hazardous to implantedmedical device usage. The effect of α-MG on immature and mature biofilms of S.epidermidis was assessed at 37 °C and the biofilms were visualized by using a Hitachi S-3000H scanning electron microscope. A visible growth reduction of S. epidermidis biofilm formation was observed at 1× MIC of α-MG. At 1/2 MIC, the biofilm was inhibited up to 80%. In addition, concentrations of α-MG from 4×, 8× and 16× MIC significantly eradicated the immature biofilms accordingly by 55, 73, and 93%. The immature and mature biofilms treated at 8× and 16× MIC of α-MG evidently decreased the viable bacterial load as well as the aggregation. α-MG was proficient enough to disrupt the preformed biofilms and effectively killed the biofilm embedded cells [41].

In another similar study showed the anti-biofilm had significant effects on candida biofilms and preformed biofilms. The xanthones in mangosteen-containing supplements should be used with extreme caution because α-MG will change the intestinal microbiome or promote dysbiosis. Recently, the researchers fed four mouse models with diet containing 0.1% α-MG

for a month. Feeding with α-MG significantly altered the four mice's cecal and colonic microbiota, reducing the number of beneficial bacterial groups while increasing the abundance of pathogenic bacteria [43].

2.3.3. Antimalarial activity of α-MG

Malaria still causes high morbidity and mortality in tropical countries, especially falciparum malaria, which have several factors associated with this situation. The most important factor is the resistance of parasite to current antimalarial drugs, including artemisinin. It is urgent to discover and develop new antimalarial drugs with a novel mode of action. Chaijaroenkul W et al. [44] investigated the antimalarial activities of crude ethanolic extract of Garciniamangostana Linn, including α-MG, β-MG. They found that the extracts targeted several metabolic pathways especially glucose and TCA metabolisms. It was hardly to detect the malatein culture medium of the exposed parasite, Malate is difficult to detect in parasite-exposed media, which may indirectly suggest that mangosteen is produced by blocking TCA metabolism. Moreover, not only the antimalarial activity of its rind extract was evaluated by other researchers but also the interaction with artemisinin against the Plasmodium falciparum 3D7 in vitro. They diluted these substances with DMSO and examined the antimalarial activity, either singly or in combination with artemisinin in vitro against Plasmodium falciparum 3D7 clone. The conclusions showed that the antimalarial activity of the extract and its synergistic effect with artemisinin is promising [45].

The antimalarial interaction of 9-hydroxycalabaxanthone and antimalarial activity of α-MG were investigated. Median (range) IC_{50} (drug concentration which produces 50% parasite growth inhibition) values of the 9-hydroxycalabaxanthone, α-MG, artesunate and mefloquine for 3D7 vs K1 clones were compared at different concentrations, respectively. α-MG combined with artesunate, exhibited a slight of antagonistic effect on antimalarial interaction, whereas α-MG-mefloquine combination had no interaction in both clones. The α-MG combined with 9-hydroxycalabaxanthone displayed the synergistic antimalarial interaction in both clones. Based on the previous reported about the antiplasmodial activities of several xanthones which were extracted from Garcinia mangostana [46]. The cytotoxic effects of α-MG and δ-MG were determined and compared with δ-MG (IC_{50} = 121.2±1.0 μM), α-MG

(IC_{50} = 0.2±0.01 μM) was more active against the resistant plasmodium falciparum. And they evaluated the therapeutic response according to administering the intraperitoneal route to mice, which had obtained the maximum therapeutic effect. It illustrated that these xanthones isolated from mangosteen husk have antimalarial effect because they diminished the parasitemia by approximately 80% [47].

2.3.4. Antiviral activity

The hepatoma cells (HepG2) were cultured in dengue virus (DENV) medium for 24, 48, 72 h, and infected with four serotypes of DENV respectively. Treatment of DENV-infected cells with varying concentrations of α-MG. After a period, as compared to the untreated DENV infected cells, treatment of α-MG (10-20 μM) could significantly reduce the amount of infected cells. At least 87% cell viability was observed in all of the conditions used. The average percent of HepG2 infected with DENV-1, DENV-2, DENV-3, and DENV-4 were 64%, 79%, 68%, and 66%, respectively. Exposure of α-MG caused 55%, 48%, 50%, and 47% reduction of infected cells when HepG2 cells were infected with DENV-1, DENV-2, DENV-3, and DENV-4, respectively. The results demonstrated that α-MG could reduce DENV infection and production of all four DENV serotypes [48].

3. Inhibitory and inductive effects of α -MG

3.1. Inhibition of cell proliferation

The effects of *α*-MG on anti-proliferative, induction of apoptosis and cell cycle arrest, which were summarized in **Table 3**. The MDA-MB-231 human breast cancer cell line was used as a model system to evaluate the anti-proliferative and apoptotic potential of α-MG. The MDA-MB-231 cells were cultured in different concentrations of α-MG, which took on dose and time dependant inhibition of cell viability and cell proliferation. The anti-proliferative effect of α-MG was evaluated by morphological findings and MTT. The anti-proliferative effect was associated with cell apoptosisusing DNA fragmentation analysis evidence [49]. Treatment the T47D cells with α-MG at various concentrations and times to determine the effect of α-MG on cell viability. The results showed that α-MG decreased cell viability in T47D human breast cancer cells and inhibited colony formation and proliferation of breast

cancer cells in a dose- and time-dependent manner [50]. The result of these researches indicated the potential anti-proliferative activity and apoptosis induction by α-MG.

3.2. Inhibition of angiogenesis

Currently, it is very limited to see the researches about the effects of α-MG on phase I and II enzymes and corresponding signaling pathways. It is necessary for further investigations. Wihastuti et al. demonstrated that extract of mangosteen pericarp can promote the formation of anti-angiogenesis through H_2O_2, HIF-1α, NF-κB, and that inhibition of iNOS in rats given a high-fat diet [51]. It was the first time for researchers reported the phosphorylation of KDR which inhibited by α-MG, and it also inhibited phosphorylation of the Y1175 residue of KDR (10 μM). Moreover, the bioassays were used to test inhibitory effects of α-MG on proliferation of human umbilical vein or artery endothelial cells, as well as the migration and tubule formation of HUVECs. The research has revealed that the inhibition of the phosphorylation of KDR tyrosine kinase is closely associated with the anti-angiogenic activity of α-MG. However, the anti-angiogenic effect of α-MG is closely related to the formation of ROS in bovine retinal endothelial cells (REC) [52].

The ROS formation in hypoxia-treated REC was markedly reduced by α-MG，and α-MG also inhibited VEGF-induced increases in permeability, migration, tube formation in REC, blocked angiogenic sprouting in the ex vivo aortic ring assay. In addition, α-MG was able to inhibit the phosphorylation of VEGFR2 which was induced by VEGF. It turned out that either oxidative stress or the VEGF-induced angiogenesis were limited by α-MG through the process involving abrogation of VEGFR2 and ERK1/2-MAPK activation [53].

3.3. Induced cancer cells apoptosis and protect the induced apoptotic damage

Won et al. [54] performed the flow cytometry assay to test whether or not α-MG induces apoptosis of MCF-7 cells. MCF-7 and MDA-MB-231 cells were stained with Hoechst 33258 dye after exposure to α-MG, then which were observed with fluorescence microscopy. Treatment with α-MG significantly increased chromatin condensation and apoptotic body formation in MCF-7 cells. On the other hand, incubation of MCF-7 cells with 1, 5, and 10 μM

α-MG for 48 h resulted in a dose-dependent accumulation of sub-G1 phase cells. These findings clearly showed that α-MG specifically induces apoptosis of MCF-7 cells. In another similar experiment, treatment of MCF-7 and MDA-MB-231 cells for 24 h with α-MG to analyze the apoptotic effects of α-MG. It found that α-MG induced breast cancer cells apoptosis in a dose-dependent manner, reaching very high levels at 4 μM concentration. The amount of MCF-7 cells early apoptosis was 9.29%, the late apoptotic cells were up to 18.67%, as well as MDA-MB-231 cells early apoptosis was up to 29.58%, late apoptotic cells were 13.76% [55]. α-MG increased the expression level of DR5 to effectively induce its transfer from the cytoplasm to the surface membrane of tumour cell for oligomerization. α-MG as a sensitizer of TRAIL-induced apoptosis, a naturally occurring chemo-preventive compound. It induces the apoptosis by double effects, thereby could inhibit the growth of tumour cell, and regulate the intracellular signal transduction pathway during apoptosis and proliferation [56].

Lee et al. [57] also found that α-MG could make the 5-FU-resistant SNUC5/5-FURcolon cancer cells apoptosis through its mediating of the activation of the extrinsic and intrinsic pathways. The Fas receptor levelin SNUC5/5-FUR cells had much lower Compared with the SNUC5 cells. The study illustrated that α-MG could overcome chemoresistance against 5-FU by activating apoptosis pathway, that it might be regarded as an efficient apoptosis sensitizer. In addition, visible light can cause the photochemical reactions in the oxygen-rich environment of the outer retina, resulting in the liberation of cytotoxic ROS. That ROS could induce the oxidative stress and damage the mitochondria and lipids. It is one of the most major factors of onset of the death of retinal pigment epithelial. Despite the retinal damage was induced by the photochemical and photo-oxidative mechanisms, the light-induced photoreceptor injury would be protected by α-MG through the structural and functional protection, and the ARPE-19 cells would be protected from oxidative stress-induced damage [58]. α-MG in non-toxic concentrations improved the viability of the iodixanol-treated cells up to 90.42% compared with contrast-induced damage in LLC-PK1 cells. Thus, α-MG had a potential protective effect on apoptosis of LLC-PK1 cells. In addition, the co-treatment with α-MG made the phosphorylation of LLC-PK1 cells decrease remarkably. α-MG could protect the contrast-induced apoptotic damage through inhibiting the activation of MAPKs and caspase [59].

3.4. Induced cell cycle arrest

α-MG can induced G1 arrest by the induction of cyclin-dependent kinase inhibitors (CDKIs). Nevertheless, addition to the role of p53-p21CIP1 axis, the mechanism of α-MG inducing cell cycle arrest remains unclear. α-MG inhibited proliferation and differentiation of HCT116 cells in a dose-dependent manner had been observed in the study conducted by Korm S et al. Consistent with previous reports, the reduction of p53 protected the cell cycle arrest from the influence of a-MG, but p21Cip1 expression was only slightly delayed in the loss of p53 after α-MG treatment. Instead, they found that the activation of p38 mitogen activated protein kinase (MAPK) and the subsequent reduction in Bmi-1 was also conducive to the induction of p16Ink4a, which was cause of G1 arrest upon α-MG treatment. The results indicated that α-MG exerts cytostatic effects on colon cancer cells by induction of G1 arrest via the p38MAPK-p16INK4a axis [60]. Although the effects of α-MG have been researched in many studies, the figures of the effects on human oral squamous cell carcinoma (OSCC) were limited. To quantify apoptosis in the early, late stage and necrosis, cells were cultured with 8–10 μM α-MG for 24 h, and harvested and processed for apoptosis assay using annexin V-FITC apoptosis detection kit (Enzo, Farmingdale, NY), and examined using a CYTOMICS FC500 flow cytometer system (Beckman Coulter, Porterville, CA). After 24 hours, α-MG was found to induce morphological changes such as membrane blebbing, cell shrinkage, and rounding in OSCC cells, but not in PDLF cells. These findings suggest that α-mangostin treatment induces cell death and morphological changes in OSCC cells. Moreover, treatment of OSCC cells with α-MG clearly obtained the evidence of apoptosis, such as nuclear fragmentation and accumulation of annexin V and PI-positive cells on OSCC cells, as well as led to the collapse of mitochondrial membrane potential and activated the expressions of the mitochondria-related proteins. So they viewed that α-MG may be an effective anticancer agent against human OSCC cells and treatment with α-MG also specifically induced G1 phase arrest [61].

4. Anti-obesity activity of α-MG

Obesity has become a worldwide epidemic proportions. In this condition, its related diseases, such as diabetes and cardiovascular disease, have become major public health challenges [62].

Treatments of those diseases with α-MG are summarized in **table 1**. Taher et al. [63] found that α-MG could be a potential prevention for metabolic diseases such as obesity particularly among type 2 diabetics via two ways in *vitro* systems. On one hand, α-MG decreased intracellular fat accumulation significantly (up to 44.4% relative to MDI-treated cells) via decreasing PPARγ expression. On the other hand, α-MG improved the glucose uptake (P<0.05) and free fatty acid release by increasing GLUT4 and leptin expression. Additionally, a hypothesis was that α-MG may improve hepatic steatosis and obesity in vivo systems. The α-MG supplementation to high-fat diet-induced obese mice decreased body weight gain significantly (13.8%), fat mass accumulation and the biochemical serum profiles including cholesterol, triglyceride and fatty acidlevels. Their researches suggested that α-MG exhibits anti-obesity properties via activating hepatic AMPK, SirT1 and PPARγ expression. Furthermore, the anti-obesity effect of α-MG supported the potential of α-MG to improve metabolic disorders [64]. In another study researched the effects of α-MG supplementation in HF-STZ induced type 2 diabetic rat models on biochemical and physiological parameters. The researchers found that α-MG supplementation could restore ocular blood flow (OBF) and improve blood-retinal barrier (BRB) permeability. Leakage of the BRB and reduction of OBF were related with hyperglycemia and the accumulations of free radicals, advance glycation end products (AGEs), receptor of advance glycation end products (RAGE), tumour necrosis factor alpha (TNF-α), and vascular endothelial growth factor (VEGF) in the retinal tissues. In vivo experiment, α-MG supplementation improved retinal microangiopathy via its anti-hyperglycemic, antioxidant, anti-inflammatory and antiglycation properties. α-MG may be considered as a candidate to prevent retinal microvascular complications in type 2 diabetic patient [65].

5. Neuroprotective properties in Alzheimer's disease and Parkinson's disease

Alzheimer's disease (AD), the most common type of dementia, is currently one of the largest global public health challenges. The amyloid beta (Aβ) deposit in the brain is the fundamental cause of the disease, Therefore, Aβ clearance strategy is being actively pursued as a promising disease modifying therapy. It found that α-MG exhibited significant inhibition of self-induced

β-amyloid (Aβ) aggregation. The neuroprotection of α-MG against Almertz's disease are summarized in **Table 4**.

α-Mangostin, Gartanin, Garcinone C and γ-Mangostin，isolated from the pericarps of Garcinia mangostana Linn, showed better antioxidant properties to scavenge Diphenyl-1-(2,4,6-trinitrophenyl) hydrazyl (DPPH) free radical, as well as potent neuroprotective effects against glutamate-induced HT22 cell death partly via the up-regulation of HO-1 protein level and then scavenging reactive oxygen species [66].

Yao et al. [67] disclosed their achievement what utilized *α*-MG as a novel potential therapy of Alzheimer's disease (AD). They found that α-MG increased the cellular uptake and degradation of $A\beta_{1-42}$ via upregulating the low density lipoprotein receptor (LDLR) expression in AD model mice. Furthermore, its nano formulation, loading *α*-MG into the core of poly (ethylene glycol)–poly (l-lactide) (PEG-PLA) nanoparticles [NP (*α*-MG)], showed lots of positive properties including ameliorating the biodistribution in both the brain and liver, enhancing the brain clearance of $A\beta_{1-42}$ and decreasing Aβ deposition attenuating neuroinflammatory responses as well as improving neurologic changes and reversing behavioral deficits.

Additionally, the enzyme-linked immunosorbent assay (ELISA) was utilized to measure the Aβ and soluble amyloid precursor protein α (sAPPα) in culture medium of cortical neurons. The interaction between α-MG and β- or γ-secretases by molecular docking, which further researched the effect of α-MG on β-amyloid (Aβ) production and its molecular mechanism. The measurement results showed that α-MG significantly diminished $A\beta_{40}$ and $A\beta_{42}$ production. However, the expression of enzymes involved in nonamyloidogenic and amyloidogenic pathways is unaffected, with a significantly decrease in β-secre activity. The molecular docking proved that α-MG interacted with β-site amyloid precursor protein cleaving enzyme 1 and presenilin 1 to interfere with their active sites. In result, their figures demonstrated that α-MG decreased Aβ production through inhibiting activities of β-secretase and likely γ-secretase in the amyloidogenic pathway. The current data and previous study unanimously indicated that α-MG can be a novel neuroprotective agent through intervention of complex pathological processes of AD [68].

To investigate the effect of α-MG on cells viability and explore its mechanism in vitro model

of Parkinson's disease (PD) induced by rotenone. The SH-SY5Y cells were exposed to 10 nM–1 μM α-MG in the presence of 10 μM rotenone for 24 h. α-MG concentration-dependently alleviated rotenone-induced cell death compared with cells that were treated with 10 μM rotenone alone. The most significant cytoprotective effect of α-MG was observed at a concentration of 0.3 μM. The researchers used western blot to investigate the effects of α-MG on the protein expression of α-synuclein and TH. After 24 h treatment with 10 μM rotenone, protein expression of α-synuclein increased by 159% ($p < 0.01$ vs. control group) and protein expression of TH protein decreased by 52.1% ($p < 0.01$ vs. control group), respectively. Compared with rotenone group, α-synuclein protein expression was downregulated by 43.1% following co-treatment with α-MG ($p = 0.008$, < 0.01 vs. rotenone group) and TH protein expression was upregulated by 32.7% following co-treatment with α-MG ($p = 0.04$, < 0.05 vs. rotenone group). Consistent with these western blot results, confocal microscopy analysis revealed that α-MG attenuated rotenone-induced increases in the red fluorescence intensity of aggresomes. Furthermore, the mitochondrial membrane potential reflects the proton motive force of the mitochondrial electron transport chain. Interestingly, treatment with α-MG (0.1, 0.3 μM) increased ΔΨm by 10.5 and 22.5% compared with the rotenone group. These results suggest that α-MG has neuroprotective effects against PD-related neuronal injury through the inhibition of α-synuclein aggregation and mitochondrial dysfunction [69].

6. Pharmacokinetic studies of α-MG

Table 4 indicates that the pharmacokinetic studies have played an increasingly important role in the drug discovery and development process, which could help us comprehend its actions in vivo, and explain a variety of events bearing on the efficacy and toxicity of the relevant herbs. In order to compare its pharmacokinetic properties, researchers used mice to assess the safety of *α*-MG in preclinical levels for the first time. And they also made a safety evaluation on the pharmacokinetics as well as the tissue distribution, in vitro metabolism, and plasma protein binding in mice. After the mice treatment with mangosteen not only increased the

absorption of α-MG, but decreased hepatic metabolism of α-MG. This finding contributed to interpret the pharmacokinetics of α-MG and the safety of mangosteen extract, as well as conduced to study the efficacy and safety investigation of α-MG or promote the development of clinical level [70]. Nevertheless, α-MG as a drug had low bioavailability and minimal oral absorption. The bioavailability of α-MG was improved with vegetable oil as the dispersion, thus developed a soft capsule. After intravenous and oral administration in mice, the pharmacokinetics and tissue distribution in rats got much easier to determined, researchers successfully affirmed them through the validated method and determined the concentration of α-MG in biological samples with an HPLC assay. The pharmacokinetic study found the absolute bioavailability of low, medium and high doses were 61.1%, 51.5% and 42.5%, respectively, indicating that the absolute bioavailability was effectively improved [71]. Furthermore, α-MG still has a significant deficiency in pharmacokinetic. The α-MG-loaded self-microemulsion (MG-SME) was prepared by encapsulation efficiency, size distribution, and morphology for the improvement of pharmacokinetics and potential clinical efficacy of α-MG, as well as evaluated its potential as a drug loading system based on the pharmacokinetic performance and tissue distribution feature. Researchers determined the solubility of α-MG in various conventional mediums to choose suitable components and optimized the formula of MG-SME by an orthogonal test and employed the optimized high performance liquid chromatography method (HPLC) to determine concentrations of α-MG and characterized the pharmacokinetic and tissue distribution features of α-MG in rodents. They found that SME as a nano-sized delivery system efficiently promoted the digestive tract absorption of α-MG and modified its distribution in tissues. The targeting feature and high oral bioavailability of MG-SME promised a good clinical efficacy, especially for immune diseases [72].

7. Concluding remarks

From above, it can be seen a series of experimental results were reported in recent years. The remarkable pharmacological effects and biological activity of α-MG were gradually performed. In addition, the pharmacological effects of α-MG in the major organ systems were showed good safety. Combination with other chemotherapeutic agents provided them distinctive properties such as higher therapeutic efficacy and lower toxicity, compared with the traditional chemotherapeutics alone. In addition, in the management of complex diseases such as AD, α-MG can simultaneously attack multiple targets, which provides a better choice for the treatment of these diseases [73]. Furthermore, α-MG can treat the acne and scavenge free radical generation of human skin, and inhibit the proliferation of melanoma cells. α-MG has some whitening effects, as a potential cosmetic [51, 35, 74]. The chemical prophylactic activity of α-MG was due to its inhibitory effects on proliferation of abnormal cell, cell cycle and apoptosis. These evidence strongly supported that α-MG may be a valuable compound and a promising candidate drug. It is hoped that the pharmacokinetic properties of the α-MG will be improved, the pharmacodynamic properties will be enhanced, as well as their targeting effects will be enhanced in further clinical investigation.

8. Expert opinion

Mangosteen has been used as a traditional medicine to treat diverse medicinal conditions for a long time, with xanthone derivatives as the major bioactive constituents. Of all xanthones isolated from mangosteen till now, α-MG has attracted most attention due to its wide variety biological activities, which is being actively investigated by various industrial and academic institutions. The current review focuses on the anticancer, anti-inflammatory, anti-oxidant and treatment of Alzheimer's disease potential of α-MG. As previously said, α-MG has the effect of maintaining cardiovascular system, gastrointestinal health and controlling free radical oxidation. Some studies have shown that α-MG has anticancer potential and can be used as a chemoprevention or agent for breast cancer, colon cancer, pancreatic cancer, cutaneum carcinoma and oral cancer, etc. The physiological action of α-MG is mild and the toxicity and side effects are minimal. Interestingly, the hydroxyl citric acid was also contained in mangosteen pericarp that can inhibit ATP citrate lyase, thereby preventing the formation of acetyl-CoA. Thus α-MG can be used in weight-loss foods. However, excessive intake may be

harmful to people's health. The benefits of α-MG for various tissues have been reported, but its effect on the heart has not been clarified. Recently, the effects of α-MG on cardiac function have been reported. It demonstrated that α-MG acutely altered cardiac function by directly inhibiting SERCA activity, leading to prolonged cytosolic Ca^{2+} removal and a subsequent ventricular diastolic dysfunction. The effect of α-MG appeared to be specific to SERCA and not to other ATPase enzymes [75]. The in vivo study also confirmed the suppressive effect of α-MG on cardiac function. Additionally, α-MG was increasingly valued by the food and cosmetic industry in view of possessing excelllent antioxidant activity, anti-bacterial, anti-inflammatory and anti-allergic effects. At present, there are many well-known manufacturers have produced a mangosteen-based beverage and mangosteen-based cosmetics series in Japan, South Korea, Europe and the United States. The study found that after the 30-day consumption of the mangosteen-based beverage, the antioxidant activity of human cells significantly increases and can be part of the diet possibly against inflammation and chronic diseases. Meanwhile, there were no side effects on human hepatic and kidney functions. Further studies ought to explore the mechanisms on the in vivo antioxidant interactions with metabolites and the mediation of inflammation pathways. Although entrapment of nanoparticles of appropriate sizes at hair follicles has been clarified, there is no report on specific clinical application of this finding. However, in the past two years, the researchers experimented on the skin of 10 acne patients for 4-week, it found significant improvement in acne vulgaris condition on the side twice daily applied with α-MG nanoparticles. The current mangosteen-related cosmetics have exfoliating lotion, mangosteen yogurt mask, etc. With the development of the research on the application of α-MG in the field of beauty and skin care continues. It is believed that the applications of mangosteen in the food and cosmetics fields will be increasingly extensive. Interestingly, α-MG possesses significant pharmacokinetic shortages. To augment its clinical efficacy, MG-loaded self-microemulsion (MG-SME) was recently designed and prepared by Xu WK et al. It found that MG-SME as a nano-sized delivery system efficiently promoted the digestive tract absorption of MG and modified its distribution in tissues. The targeting feature and high oral bioavailability of MG-SME promised a good clinical efficacy, especially for immune diseases. However, the current understanding of the chemical composition and content of mangosteen

peel is not yet clear enough and complete. Physical and chemical extraction methods of α-MG still need to be explored in depth. However, the current understanding of many action mechanisms of α-MG is not yet clear enough and complete. Physical and chemical extraction methods of α-MG still need to be explored in depth.

Funding

This study was financially supported by Zhejiang Provincial Natural Science Foundation of China under Grant （No. LQ13H300001 and No.Y2100872）, and supported by the National Science Foundation for Young Scholars of China under Grant (No. 81202411 and No.81100241).

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Reference

1. Lepor NE, Fouchia DD, McCullough PA. New vistas for the treatment of obesity: turning the tide against the leading cause of morbidity and cardiovascular mortality in the developed world. Rev Cardiovasc Med. 2013;14(1):20-39.
2. Wang HW, Yu JF, Jing J. Chemotherapy and chemotherapy effects of traditional Chinese medicine for cancer in modern medical system, J World Journal of Integrated Traditional and Western Medicine. 2017;12(1), 134-7 . (In Chinese)
3. Huang RZ, Hua SX, Wang CY, et al. 4-Methylumbelliferones Analogues as Anticancer Agents: Synthesis and in Cell Pharmacological Studies. J Anticancer Agents Med Chem, 2017;17(4):576-89
4. Pratheeshkumar P, Son YO, Korangath P, et al. Phytochemicals in Cancer Prevention and Therapy. J Biomed Res Int. 2015; 2015(2):1-2.
5. Zhang KJ, Gu QL, Yang K, et al. Anticarcinogenic Effects of α-Mangostin: A Review. J Planta Medica, 2016; 83(03/04):188-202.
6. Mohamed GA, Ibrahim SR, Shaaban MI, et al. Mangostanaxanthones I and II, new xanthones from the pericarp of Garcinia mangostana. J Fitoterapia, 2014; 98:215-21.
7. Hafeez BB, Mustafa A, Fischer JW, et al. α-Mangostin: A Dietary Antioxidant Derived from the Pericarp of Garcinia mangostana L. Inhibits Pancreatic Tumor Growth in Xenograft Mouse Model. J Antioxidants & Redox Signaling, 2014; 21(5):682-99.
8. Lee HN, Jang HY, Kim HJ, et al. Antitumor and apoptosis-inducing effects of α-mangostin extracted from the pericarp of the mangosteen fruit (Garcinia mangostana L.) in YD-15 tongue mucoepidermoid carcinoma cells. J International Journal of Molecular Medicine, 2016; 37(4):939-48.
9. Upegui Y, Robledo SM, Gil Romero JF, et al. In vivo, Antimalarial Activity of α-Mangostin and the New Xanthone δ-Mangostin. J Phytotherapy Research, 2015, 29(8):1195-1201.
10. Ibrahim MY, Hashim NM, Mohan S, et al. α-Mangostin from Cratoxylum arborescens : An in vitro, and in vivo, toxicological evaluation. J Arabian Journal of Chemistry, 2015; 8(1):129-137.

11. Wang SN, Li Q, Jing MH, et al. Natural Xanthones from Garcinia mangostana, with Multifunctional Activities for the Therapy of Alzheimer's Disease. J Neurochemical Research, 2016; 41(7):1806-17.
12. Mohamed GA, Al-Abd AM, El-Halawany AM, et al. New xanthones and cytotoxic constituents from Garcinia mangostana fruit hulls against human hepatocellular, breast, and colorectal cancer cell lines. J Journal of Ethnopharmacology, 2017; 198:302-312.
13. Hsieh SC, Huang MH, Cheng CW, et al. α-Mangostin induces mitochondrial dependent apoptosis in human hepatoma SK-Hep-1 cells through inhibition of p38 MAPK pathway. J Apoptosis An International Journal on Programmed Cell Death, 2013;18(12):1548-60.
14. Supawadee S, Thanet S, Wisut P, et al. Investigation of Therapeutic Effects of α-Mangostin on Thioacetamide-Induced Cirrhosis in Rats. J Journal of the Medical Association of Thailand=Chotmaihet thangphaet, 2015; 98 Suppl 9:S91-7.
15. Cai N, Xie SJ, Qiu DB, et al. Potential effects of α-mangostin in the prevention and treatment of hepatocellular carcinoma. J Journal of Functional Foods, 2016; 26:309-318.
16. Kumazaki M, Noguchi S, Yasui Y, et al. Anti-cancer effects of naturally occurring compounds through modulation of signal transduction and miRNA expression in human colon cancer cells. J Journal of Nutritional Biochemistry, 2013;24(11):1849-58.
17. Yoo JH, Kang K, Jho EH, et al. α- and γ-Mangostin inhibit the proliferation of colon cancer cells via, β-catenin gene regulation in Wnt/cGMP signaling. J Food Chemistry, 2011; 129(4):1559-1566.
18. Shibata MA, Iinuma M, Morimoto J, et al. α-Mangostin extracted from the pericarp of the mangosteen (Garcinia mangostana Linn) reduces tumor growth and lymph node metastasis in an immunocompetent xenograft model of metastatic mammary cancer carrying a p53 mutation. J BMC Medicine, 2011; 9(1):69.
19. Li P, Tian W, Ma X. Alpha-mangostin inhibits intracellular fatty acid synthase and induces apoptosis in breast cancer cells. J Molecular Cancer, 2014; 13(1):138.
20. Kritsanawong S, Innajak S, Imoto M, et al. Antiproliferative and apoptosis induction of α-mangostin in T47D breast cancer cells. J International Journal of Oncology, 2016; 48(5):2155-65.

21. Qiu S, Granet R, Mbakidi JP, et al. Delivery of tanshinone IIA and α-mangostin from gold/PEI/cyclodextrin nanoparticle platform designed for prostate cancer chemotherapy. J Bioorganic & Medicinal Chemistry Letters, 2016; 26(10):2503-6.
22. Li G, Petiwala SM, Nonn L, et al. Inhibition of CHOP accentuates the apoptotic effect of α-mangostin from the mangosteen fruit (Garcinia mangostana) in 22Rv1 prostate cancer cells. J Biochemical & Biophysical Research Communications, 2014; 453(1):75-80.
23. Zhang C, Yu G, Shen Y. The naturally occurring xanthone α-Mangostin induces ROS-mediated cytotoxicity in non-small scale lung cancer cells. J Saudi Journal of Biological Sciences, 2017.
24. Xu Q, Ma J, Lei J, et al. α-Mangostin Suppresses the Viability and Epithelial-Mesenchymal Transition of Pancreatic Cancer Cells by Downregulating the PI3K/Akt Pathway. J Biomed Research International, 2014; 2014(6):546353/1-546353/13.
25. Verma RK, Yu W, Shrivastava A, et al. α-Mangostin-encapsulated PLGA nanoparticles inhibit pancreatic carcinogenesis by targeting cancer stem cells in human, and transgenic (KrasG12D, and KrasG12D/tp53R270H) mice. J Scientific Reports, 2016; 6:32743.
26. Kim M, Chin YW, Lee EJ. α, γ-Mangostins Induces Autophagy and Shows Synergistic Effectwith Gemcitabine in Pancreatic Cancer Cell Lines. J Biomolecules & Therapeutics, 2017; 25(6):609-17.
27. Wang F, Ma H, Liu Z, et al. α-Mangostin inhibits DMBA/TPA-induced skin cancer through inhibiting inflammation and promoting autophagy and apoptosis by regulating PI3K/Akt/mTOR signaling pathway in mice. J Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie, 2017; 92:672-80.
28. Tjahjani S, Widowati W, Khiong K, et al. Antioxidant Properties of Garcinia Mangostana, L (Mangosteen) Rind. J Procedia Chemistry, 2014; 13:198-203.
29. Pedrazachaverrí J, Reyesfermín LM, Nolascoamaya EG, et al. ROS scavenging capacity and neuroprotectiveeffect of alpha-MG against 3-nitropropionic acid in cerebellar granule neurons, J Experimental &Toxicologic Pathology, 2009;61(5), 491-501.

30. Cui J, Huand W, Cai Z, New medicinal properties of mangostins: Analgesic activity and pharmacological characterization of active ingredients from the fruit hull of Garciniamangostana, L, J Pharmacology Biochemistry & Behavior, 2010;95(2):166-72.
31. Martínez A, Galano A, Vargas R. Free Radical Scavenger Properties of α-Mangostin: Thermodynamics and Kinetics of HAT and RAF Mechanisms. J Journal of Physical Chemistry B, 2011;115(43):12591-8.
32. Xie Z, Sintara M, Chang T, et al. Functional beverage of Garcinia mangostana (mangosteen) enhances plasma antioxidant capacity in healthy adults. J Food Science & Nutrition, 2015; 3(1):32-8.
33. Xie Z, Sintara M, Chang T, et al. Daily consumption of a mangosteen-based drink improves in vivo antioxidant and anti-inflammatory biomarkers in healthy adults: a randomized, double-blind, placebo-controlled clinical trial. J Food Science & Nutrition, 2015;3(4):342-348.
34. Liu SH, Lee LT, Hu NY, et al. Effects of alpha-mangostin on the expression of anti-inflammatory genes in U937 cells. J Chinese Medicine, 2012;7(1):1-11.
35. Pan-In P, Wongsomboon A, Kokpol C, et al. Depositing α-MG nanoparticles to sebaceous gland area for acne treatment, J Journal of Pharmacological Sciences, 2015;129, (4):226-232.
36. Hu ZY, Wang W, Ling J, et al. α-Mangostin Inhibits α-Synuclein-Induced Microglial Neuroinflammation and Neurotoxicity. J Cellular\s&\smolecular Neurobiology, 2016;36(5):1-10.
37. Franceschelli S, Pesce M, Ferrone A, et al. A Novel Biological Role of α-Mangostin in Modulating Inflammatory Response Through the Activation of SIRT-1 Signaling Pathway. J Journal of Cellular Physiology, 2016; 231(11):2439-51.
38. Mahendra J, Mahendra L, Svedha P, et al. Clinical and microbiological efficacy of 4% Garcinia mangostana L. pericarp gel as local drug delivery in the treatment of chronic periodontitis: A randomized, controlled clinical trial. J Journal of Investigative & Clinical Dentistry, 2017;8(4):e12262.
39. Pan T, Chen R, Wu D, et al. Alpha-Mangostin suppresses interleukin-1β-induced apoptosis in rat chondrocytes by inhibiting the NF-κB signaling pathway and delays the

progression of osteoarthritis in a rat model. J International Immunopharmacology, 2017; 52:156-62.

40. Pan T, Wu D, Cai N, et al. Alpha-Mangostin protects rat articular chondrocytes against IL-1β-induced inflammation and slows the progression of osteoarthritis in a rat model. J International Immunopharmacology, 2017; 52:34-43.
41. Sivaranjani M, Prakash M, Gowrishankar S, et al. In vitro activity of alpha-mangostin in killing and eradicating Staphylococcus epidermidis, RP62A biofilms. J Applied Microbiology & Biotechnology, 2017; 101(8):3349-3359.
42. Phuong NTM, Quang NV, Mai TT, et al. Antibiofilm activity of a-mangostin extracted from Garcinia mangostana L. against Staphylococcus aureus, Asian Pacific Journal of Tropical Medicine, 2017;10(12): 1154-60.
43. Gutierrezorozco F, Thomasahner JM, Galley JD, et al. Intestinal microbial dysbiosis and colonic epithelial cell hyperproliferation by dietary α-MG is independent of mouse strain, J Nutrients, 2015, 7(2):764-784.
44. Chaijaroenkul W, Mubaraki MA, Ward SA, et al. Metabolite footprinting of Plasmodium falciparum, following exposure to Garcinia mangostana, Linn. crude extract. J Experimental Parasitology, 2014; 145(1):80-6.
45. Tjahjani S. Antimalarial activity of Garcinia mangostana, L rind and its synergistic effect with artemisinin in vitro. J Bmc Complementary & Alternative Medicine, 2017; 17(1):131.
46. Chaijaroenkul W, Nabangchang K. The in vitro antimalarial interaction of 9-hydroxycalabaxanthone and α-mangostin with mefloquine/artesunate. J Acta Parasitologica, 2014;60(1):105-11.
47. Upegui Y, Robledo SM, Gil Romero JF, et al. In vivo Antimalarial Activity of α-mangostin and the New Xanthone δ-mangostin. J Phytotherapy Research, 2015; 29(8):1195-1201.
48. Tarasuk M, Songprakhon P, Chimma P, et al. Alpha-mangostin inhibits both dengue virus production and cytokine/chemokine expression. J Virus Research, 2017; 240:180-89.
49. Xia Y, Li Y, Westover KD, et al. Inhibition of Cell Proliferation in an NRAS Mutant Melanoma Cell Line by Combining Sorafenib and α-Mangostin. J Plos One, 2016;

11(5):e0155217.

50. Kritsanawong S, Innajak S, Imoto M, et al. Antiproliferative and apoptosis induction of α-mangostin in T47D breast cancer cells. J International Journal of Oncology, 2016; 48(5):2155-65.
51. Wihastuti TA, Sargowo D, Vasa vasorum anti-angiogenesis through H_2O_2, HIF-1α, NF-κB, and iNOS inhibition by mangosteen pericarp ethanolic extract (Garcinia mangostana Linn) in hypercholesterol-diet-given Rattus norvegicus Wistar strain, J Vascular Health & Risk Management, 2014;10(default), 523.
52. Shiozaki T, Fukai M, Hermawati E, et al. Anti-angiogenic effect of α-mangostin. J Journal of Natural Medicines, 2013;67(1):202-6.
53. Jittiporn K, Suwanpradid J, Patel C, et al. Anti-angiogenic actions of the mangosteen polyphenolic xanthone derivative α-mangostin. J Microvascular Research, 2014; 93:72-9.
54. Won YS, Lee JH, Kwon SJ, et al. α-Mangostin-induced apoptosis is mediated by estrogen receptor α in human breast cancer cells. J Food & Chemical Toxicology, 2014;66:158-65.
55. Li P, Tian W, Ma X. Alpha-mangostin inhibits intracellular fatty acid synthase and induces apoptosis in breast cancer cells. J Molecular Cancer, 2014; 13(1):138.
56. Minami K, Haruka S, Kohei T, et al. Understanding of tolerance in TRAIL-induced apoptosis and cancelation of its machinery by α-mangostin, a xanthone derivative. J Oncotarget, 2015; 6(28):25828-42.
57. Lee J, Kang J S, Choi B Y, et al. Sensitization of 5-Fluorouracil-Resistant SNUC5 Colon Cancer Cells to Apoptosis by α-Mangostin. J Biomolecules & Therapeutics, 2016;24(6):604-9.
58. Yuan F, Su T, Qiu X, et al. Protective effect of alpha-mangostin against oxidative stress induced-retinal cell death. J Scientific Reports, 2016; 6:21018.
59. Lee D, Choi YO, Kim KH, et al. Protective effect of α-mangostin against iodixanol-induced apoptotic damage in LLC-PK1 cells. J Bioorganic & Medicinal Chemistry Letters, 2016; 26(15):3806-9.
60. Korm S, Jeong HC, Kwon OS, et al. α-Mangostin induces G1 cell cycle arrest in HCT116 cells through p38MAPK-p16INK4a pathway. J Rsc Advances, 2015; 5(44):34752-34760.

61. Hyun-Ho K, In-Ryoung K, Hye-Jin K, et al. α-Mangostin Induces Apoptosis and Cell Cycle Arrest in Oral Squamous Cell Carcinoma Cell. J Evid Based Complement Alternat Med. 2016; 2016:5352412.
62. Liu QY, Wang YT, Lin LG. New insights into the anti-obesity activity of xanthones from Garcinia mangostana. J Food & function, 2015;6(2):383-93.
63. Taher M, Susanti D, Ichwan SJA, α-MG improves glucose uptake and inhibits adipocytes differentiation in 3T3-L1 cells via PPARγ, GLUT4, and Leptin expressions, J Evidence-based Complementary and Alternative Medicine, 2015; 2015: 740238.
64. Choi YH, Bae JK, Chae HS, et al, α-MG regulates hepatic steatosis and obesity through SirT1-AMPK and PPARγ pathways in high-fat diet-induced obese mice, J Journal of Agricultural & Food Chemistry, 2015;63(38), 8399-406.
65. Jariyapongskul A, Areebambud C, Suksamrarn S, et al. Alpha-mangostin attenuation of hyperglycemia-induced ocular hypoperfusion and blood retinal barrier leakage in the early stage of type 2 diabetes rats. J Biomed Research International, 2015; 2015(3):1-10.
66. Wang SN, Li Q, Jing MH, et al. Natural Xanthones from Garcinia mangostana, with Multifunctional Activities for the Therapy of Alzheimer's Disease. J Neurochemical Research, 2016, 41(7):1806-17.
67. Yao L, Gu X, Song Q, et al. Nanoformulated alpha-mangostin ameliorates Alzheimer's disease neuropathology by elevating LDLR expression and accelerating amyloid-beta clearance. J Journal of Controlled Release Official Journal of the Controlled Release Society, 2016; 226:1-14.
68. Zhao LX, Wang Y, Liu T, et al. α-Mangostin decreases β-amyloid peptides production via modulation of amyloidogenic pathway. J Cns Neuroscience & Therapeutics, 2017; 23(6):526-34.
69. Hao XM, Li LD, Duan CL,et al. Neuroprotective effect of α-mangostin on mitochondrial dysfunction and α-synuclein aggregation in rotenone-induced model of Parkinson's disease in differentiated SH-SY5Y cells J J Asian Nat Prod Res, 2017; 19(8):833-845.
70. Choi YH, Han SY, Kim YJ, et al. Absorption, tissue distribution, tissue metabolism and safety of α-mangostin in mangosteen extract using mouse models. J Food & Chemical Toxicology, 2014; 66:140-6.

71. Zhao Y, Tang G, Tang Q, et al. A Method of Effectively Improved α-Mangostin Bioavailability. J Eur J Drug Metab Pharmacokinet, 2016;41(5):605-13.
72. Xu WK, Jiang H, Yang K, et al. Development and invivo, evaluation of self-microemulsion as delivery system for α-mangostin. J Kaohsiung Journal of Medical Sciences, 2017;33(3):116-23.
73. Wang MH, Zhang KJ, Gu QL, et al. Pharmacology of mangostins and their derivatives: A comprehensive revi. J Chinese Journal of Natural Medicines, 2017; 15(2):81-93.
74. Wu **X**X, Yu HM, Jiang **X**T, Wang, XL, Huang WY, A plant compound sunscreen and its preparation and application patent CN 106420489 A. 2017.
75. Phungphong S, Kijtawornrat A, de Tombe PP, et al. Acute inhibitory effect of alpha-mangostin on sarcoplasmic reticulum calcium-ATPase and myocardial relaxation. J Journal of Biochemical & Molecular Toxicology, 2017; 31(10).

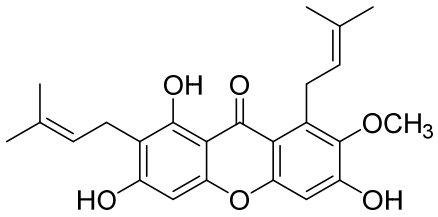

Fig. 1 The chemical structure of α–MG

Table 1 Main bioactivities and pharmacological effects of α-MG

Effect	Reference
Anticancer and cytotoxic properties of α-MG	
α-MG induces the mitochondrial dependent apoptosis, and the annexin V-positive cells were increased to 23.86 and 34.6 %.	Hsieh SC et al. (2013).
α-MG showed therapeutic effects on thioacetamide-induced cirrhosis in rats, decreased the p53 expression, reduced risk of liver fibrosis.	Supawadee S et al. (2015).
α-MG showed that has anti-proliferative effects in HCC cells and malignantly transformed hepatic cells.	Cai N et al. (2016).
α-MG regulates the expression of miRNA in human colon cancer cells by regulating signal transduction.	Kumazaki M et al. (2013).
α- and γ-Mangostin inhibit the proliferation of colon cancer cells via β-catenin gene regulation in Wnt/cGMP signaling.	YOO JH et al. (2011).
α-MG reduces tumor growth and lymph node metastasis in an immunocompetent xenograft model of metastatic mammary cancer carrying a p53 mutation.	Shibata MA et al. (2011).
α-MG induced breast cancer cell apoptosis by suppressing FAS expression and inhibiting intracellular FAS activity	Li P et al. (2014).
α-MG induces the apoptosis in T47D breast cancer cells and inhibits its proliferation.	Kritsanawong S et al. (2016).
α-MG deliveried from gold/PEI/cyclodextrin nanoparticle platform designed for prostate cancer chemotherapy.	Qiu S et al. (2016).
α-MG accentuates the apoptotic effect of in 22Rv1 prostate cancer cells through inhibition of CHOP.	Li G et al. (2014).
α-MG induces ROS-mediated cytotoxicity in non-small scale lung cancer cells.	Zhang C et al. (2017).
α-MG suppresses the viability and epithelial-mesenchymal transition of pancreatic cancer cells by downregulating the PI3K/Akt pathway.	Xu Q et al. (2014).
α-Mangostin-encapsulated PLGA nanoparticles inhibit pancreatic carcinogenesis by targeting cancer stem cells in human.	Verma RK et al. (2016).
α- or γ- mangostin as active ingredient for treating, preventing or alleviating pancreatic cancer.	Kim M et al. (2017).
α-mangostin significantly suppressed skin cancer cells formation and growth, and markedly reduced the incidence rate	Wang F et al. (2017).
Anti-inflammatory, antibacterial, antimalarial and antiviral activity of α-MG	
Anti-inflammatory of α-MG	
α-MG inhibited the expression of anti inflammatory gene in U937 cells	Liu et al. (2012)
α-MG deposited nanoparticles to sebaceous gland area for acne treatment.	Pan-In P et al. (2015)

Table 1. *Cont.*

α-MG inhibits α-synuclein-induced microglial neuroinflammation and neurotoxicity	Hu ZY et al. (2016)

α-MG inhibits p65 acetylation and down-regulates the pro-inflammatory gene products as COX-2, iNOS via SIRT-1 activation.	Franceschelli S et al. (2016)
4% mangostana gel significantly reduced clinical parameters, such as probing pocket depth, clinical attachment level, bleeding index, plaque index, and Td.	Mahendra J et al. (2017)
α-MG has a potential therapeutic effect on OA by inhibiting the mitochondrial apoptosis of chondrocytes induced by an activation of the NF-kB pathway.	Pan T et al (2017)
Antibacterial activity of α-MG	
α-MG displayed rapid concentrationdependent killing of S. epidermidis cells at concentrations above 4× MIC (5 g/mL) and 2× MIC (2.5 μg/mL) of α-MG.	Sivaranjani M et al. (2017)
α-MG prevented biofilm formation effectively, and significant damage the membrane with 50% of cell lysis occurred at concentration of about 36 mmol/L.	Phuong NTM et al. (2017)
α-MG significantly altered the four mice's cecal and colonic microbiota, reducing the number of beneficial bacterial groups while increasing the abundance of pathogenic bacteria.	Gutierrezorozco F et al.(2015)
Antimalarial activity of α-MG	
α-MG combined with 9-hydroxycalabaxanthone showed the synergistic antimalarial interaction in both clones.	Chaijaroenkul W et al. (2014)
The extract of mangosteen and its synergistic effect with artemisinin have anti-malarial effects.	Tjahjani S (2017)
α-MG was more active against the resistant Plasmodium falciparum chloroquine-resistant (FCR3) strain than δ-mangostin. The parasitemia was reduced by approximately 80%.	Upegui Y et al. (2015)
Antiviral activity of α-MG	
Treatment of DENV-infected cells with α-MG (2002μM) significantly reduced the infection rates of four DENV serotypes by 47–55%.	Tarasuk M et al. (2017)
Anti-obesity activity of α-MG	
α-MG improved glucose uptake and inhibits adipocytes differentiation in 3T3-L1 Cells via PPARγ, GLUT4, and Leptin expressions.	Taher M et al. (2015).

Table 1. *Cont.*

α-MG regulated hepatic steatosis and obesity through SirT1-AMPK and PPARγ pathways in high-fat diet-induced obese mice.	Choi YH et al. (2015).
α-MG restore OBF and improve the BRB integrity, indicating its properties closely associated with anti-hyperglycemic, antioxidant, anti-inflammatory, and antiglycation activities.	Jariyapongskul A et al. (2015).

Table 1. *Cont.*	
α-MG improved glucose uptake and inhibits adipocytes differentiation in 3T3-L1 Cells via PPARγ, GLUT4, and Leptin expressions	Taher M et al. (2015).
α-MG regulated hepatic steatosis and obesity through SirT1-AMPK and PPARγ pathways in high-fat diet-induced obese mice.	Choi YH et al. (2015).
α-MG restore OBF and improve the BRB integrity, indicating its properties closely associated with antihyperglycemic, antioxidant, anti-inflammatory, and antiglycation activities.	Jariyapongskul A et al. (2015).

Table 2 Antioxidant properties of α-MG.

Effect	**Reference**
α-MG is able to scavenge directly several ROS and has a neuroprotective effect against 3-NP in primary cultures of CGNs	PedrazaChaverría et al. (2009)
α-MG dose-dependently scavenge reactive oxygen species and possess potent peripheral and central antinociceptive effects in mice	Cui J et al. (2010)
α-MG is a good free radical scavenger through the HAT mechanism.	Martínez et al. (2011)
α-MG activates Nrf2 pathway to enhance the endogenous antioxidant activity.	Xie Z et al. (2015)
α-MG-based drink formula increased antioxidant capacity of human blood plasma and the C−reactive protein was also significantly decreased by 46%.	Xie Z et al. (2015)

Table 3 Inhibitory and inductive effects of α-MG

Effect	*Reference*
Inhibition of cell proliferation	
α-MG inhibited the viability and cell proliferation of MDA-MB-231 human breast cancer cells with dose and time dependant.	Atluri N et al. (2013).
α-MG inhibited the NRAS mutant melanoma cell proliferation, and reduced autophagy, eventually leading to apoptosis.	Xia Y et al. (2016).
Inhibition of angiogenesis	
α-MG inhibited the proliferation, migration and tubule formation of human umbilical vein endothelial cells (HUVECs).	Shiozaki T et al. (2013).
α-mangostin reduces oxidative stress and limits VEGF-induced angiogenesis through a process involving abrogation of VEGFR2 and ERK1/2-MAPK activation.	Jittiporn K et al. (2014).
Induced cancer cell apoptosis	
α-mangostin has effect on cell growth inhibition and induction of apoptosis in MCF-7 ERα-positive human breast cancer cells.	Won YS et al. (2014).
α-MG inhibits intracellular fatty acid synthase and induces apoptosis in breast cancer cells	Li P et al. (2014).
α-MG canceled the resistance by increasing the expression level of DR5 through down-regulation of miR-133b and effectively induced the translocation of DR5 to the cancer cell surface membrane in TRAIL-resistant DLD-1 cells.	Kumazaki K et al. (2015)
α-MG sensitizated the 5-fluorouracil-resistant SNUC5 colon cancer cells to apoptosis	Lee J et al. (2016).
Induced cell cycle arrest	
α-MG induces G1 cell cycle arrest in HCT116 cells through p38MAPK-p16INK4a pathway	Korm S et al. (2015).
Protective effect of α-MG against induced apoptotic damage	
α-MG protected oxidative stress induced-retinal cell death	Yuan F et al. (2016).
α-MG protected the iodixanol-induced apoptotic damage in LLC-PK1 cells	Lee et al. (2016).

Table 4 Neuroprotective properties and pharmacokinetic studies of α-MG

Effect	Reference
Neuroprotective properties in Alzheimer's disease and Parkinson's disease	
02 ± α-MG potent neuroprotective effects against glutamate-induced HT22 cell death partly via up-regulation of HO-1 protein level and then scavenging reactive oxygen species.	Wang SN et al. (2016)
Nanoformulated α-MG ameliorated Alzheimer's disease neuropathology by elevating LDLR expression and accelerating amyloid-beta clearance.	Yao L et al. (2016).
α-MG decreased Aβ production through inhibiting activities of β-secretase and likely γ-secretase in the amyloidogenic pathway, and intervented the multiple pathological of AD	Zhao LX et al. (2017).
Neuroprotective effect of α-MG on mitochondrial dysfunction and α-synuclein aggregation in rotenone-induced model of Parkinson's disease in differentiated SH-SY5Y cells	Hao XM et al. (2017)
Pharmacokinetic studies of α-MG	
The mouse models were used to study the absorption, tissue distribution, tissue metabolism and safety of α-MG.	Choi YH et al. (2016).
A soft capsule, with vegetable oil as the dispersion matrix, improved the bioavailability of α-MG.	Zhao Y et al. (2016).
MG-loaded self-microemulsion (MG-SME) makes up for the shortage of α-MG pharmacokinetics and increase the potential clinical efficacy of α-MG.	Xu WK et al. (2017).