Pharmacology of mangostins and their derivatives: A comprehensive review

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[ABSTRACT] Mangosteen (Garcinia mangostana Linn.) is a well-known tropical tree indigenous to Southeast Asia. Its fruit’s pericarp abounds with a class of isoprenylated xanthones which are referred as mangostins. Numerous in vitro and in vivo studies have shown that mangostins and their derivatives possess diverse pharmacological activities, such as antibacterial, antifungal, antimalarial, anticarcinogenic, antiatherogenic activities as well as neuroprotective properties in Alzheimer’s disease (AD). This review article provides a comprehensive review of the pharmacological activities of mangostins and their derivatives to reveal their promising utilities in the treatment of certain important diseases, mainly focusing on the discussions of the underlying molecular targets/pathways, modes of action, and relevant structure-activity relationships (SARs). Meanwhile, the pharmacokinetics (PK) profile and recent toxicological studies of mangostins are also described for further druggability exploration in the future.

[KEY WORDS] Mangostins; Derivatives; Pharmacological activities; Pharmacokinetics; Toxicology

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Introduction

Garcinia mangostana Linn., belonging to the Guttiferae family, is a kind of tropical plant native to Southeast Asia and its fruit, mangosteen, is known as "the queen of fruits". For hundreds of years, the pericarp of mangosteen has been used as a traditional medicine to treat inflammation, ulcer, skin infection, wound healing, amoebic dysentery, and diarrhe 

hydroxyl groups. Numerous in vitro and in vivo studies have revealed that mangostins exhibit a wide range of pharmacologic activities, including antibacterial, antifungal, antimalarial, anticarcinogenic, and antiatherogenic activities as well as neuroprotective properties in Alzheimer’s disease (AD) 

Pharmacological Properties

Anti-infectious properties

In recent years, serious drug-resistance and lack of effective therapeutics in the treatment of infectious diseases cause serious havoc to human beings. Therefore, we urgently need new anti-infectious drugs with novel targets to solve these problems. Mangostins have been reported to exert outstanding inhibitory activities against various pathogenic microorganisms, including multi-drug resistant (MDR) strains, by distinctly different modes of action 

These authors have no conflict of interest to declare.
Antibacterial activity

Anti-methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococci (VRE)

Staphylococcus aureus and Enterococci are two of the leading causes of nosocomial infections in healthcare facilities. However, the methicillin-resistant S. aureus (MRSA) and vancomycin-resistant Enterococci (VRE) have become particularly troublesome [6]. Inspiringly, α-mangostin (1) has been reported to have direct inhibitory effect and synergism against several strains of MRSA and VRE [7-9]. A recent study by Koh et al. has provided a detailed analysis of the antibacterial action of α-mangostin (1) against S. aureus and MRSA. In their work, low minimum inhibitory concentration (MIC) values of 0.78–1.56 μg·mL–1 and a rapid in vitro bactericidal action (3-log reduction within 5 min) were revealed. They have found that α-mangostin disrupts evolutionarily conserved bacterial cytoplasmic membranes and this property successfully gives it the ability of overcoming drug resistance [10]. These results support the tremendous potential of α-mangostin in controlling MRSA and VRE through a new mode of action.

To improve the antimicrobial activity and selectivity of α-mangostin (1), Koh and colleagues have mimicked the action of cationic antimicrobial peptides (CAMPs) through introducing different amine groups or cationic amino acids to C-3 and C-6 hydroxyl groups [11-12]. According to their research, the modified structures with amine groups of high pKa values display good antibacterial properties and improved selectivity, whereas groups of low pKa values reduce α-mangostin (1)’s antibacterial activity. Among these compounds, compound 4 (MIC = 0.39 μg·mL−1) is the most potent one (Fig. 2) [11]. The other series containing amino acids, especially arginines, exert further decreased toxicity and increased selectivity, such as compounds 5 and 6 (Fig. 2) which are also found to be effective in a mouse model of corneal infection by S. aureus and MRSA [12]. Ulteriorly, this research group has extended the concept of fragment-based drug design by proposing a pharmacophore model that is composed of one hydrophobic scaffold and two cationic terminal groups for the ab initio design of membrane active molecules against Gram-positive pathogens [13]. Overall, these studies provide general guidelines for the design and synthesis of small-molecule-based membrane active antimicrobials which could maintain the essential key characteristics of CAMPs.

Dharmaratne et al. have conducted an antibacterial activity assay on γ-mangostin (3), showing inhibitory effects against several strains of MRSA, methicillin sensitive S. aureus (MSSA), VRE, and vancomycin-sensitive Enterococcus (VSE) with MIC values being 3.13, 6.25, 6.25, and 6.25 μg·mL−1, respectively [14]. In the subsequent SAR study, some derivatives based on α-mangostin (1) or γ-mangostin (3) possessing a common 2, 8-diprenylated-1, 3, 6, 7-tetraoxygenated xanthone skeleton with different functional groups (7–10) (Fig. 2) are obtained. However, they are less active against MRSA and VRE than compounds 1 and 3. Moreover,
6-deoxy-γ-mangostin (11) is devoid of antimicrobial activity against MRSA strains as reported by another study [15]. It is concluded that C-3 and C-6 hydroxyl groups, together with C-2 prenyl side chain in the 1, 3, 6, 7-tetraoxegenated xanthone are essential for a high antibacterial activity. *Anti-Streptococcus mutans and Enterococcus faecalis*

*Streptococcus mutans* is the most prevalent and costly oral infectious pathogen of dental caries. The formation of the extracellular polysaccharide (EPS)-rich biofilm matrix, acidification of the milieu, and the maintenance of acidic pH microenvironment are key virulence attributes of *S. mutans* for the disease [16]. Nguyen et al. have shown that α-mangostin (1) is a potent inhibitor of acid production of *Streptococcus mutans*’s planktonic cells [17]. More importantly, their studies have also revealed that brief exposures to α-mangostin (1) could disrupt some of the virulence properties of *S. mutans*: (i) perturbation of insoluble EPS-matrix assembly at least in part by inhibiting glucosyltransferases (Gtfs) activities, (ii) compromising the mechanical stability of biofilms, and (iii) reducing acidogenicity by affecting the accumulation of intracellular iodophilic polysaccharides (IPS), the activities of the F(H⁺)-ATPase and phosphotransferase (PTS) system [18].

*Enterococcus faecalis* is considered one of the most resistant species in the oral cavity and is associated with persistent root canal infections [19]. α-Mangostin (1) is effective against *E. faecalis* with low toxicity to human periodontal ligament cells *in vitro*, whose representative MIC and minimum bactericidal concentration (MBC) values are 1.97 and 3.94 μg·mL⁻¹, respectively. The activity of α-mangostin (1) is higher than that of chlorhexidine at 2 × MBC and 4 × MBC, respectively, and equal to sodium hypochlorite at the same concentration level. These properties render it a promising novel root canal irrigant and a useful alternative for patients who are allergic to chlorhexidine or sodium hypochlorite [20].

*Anti-tuberculosis*

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, is the world’s number one killer among infectious diseases and the leading cause of death among women of reproductive age [21]. α-, β- and γ-Mangostins (1–3) have been reported to possess significant antitubercular potential against *M. tuberculosis* at MICs of 6.25, 6.25 and 25 μg·mL⁻¹, respectively [22]. Sudha et al. have explored the hydroxyl moieties at C-1, C-3 and C-6 positions and isopentenyl moiety of α-mangostin (1) in an extended SAR study [23]. All O-substituted α-mangostin analogues have no enhancement in anti-mycobacterial activity when compared with parent compound 1, whereas mono-O-alkylated tetrahydro α-mangostin analogues display increased activity. Interestingly, the analogues 12–14 (Fig. 3) are highly active against not only *M. tuberculosis* H₃₇Ra, but also virulent H₃₇Rv and the MDR clinical isolates. Therefore, analogues 12–14 are promising leads for new drug discovery. From the SAR point of view, some features can be pointed out: (i) the isopentyl at C-2 and C-8 together with methoxyl at C-7 positions of α-mangostin (1) improves the antituberculosis activity; (ii) C-6 or C-7 methoxyl groups together with C-1 hydroxyl of tetrahydro α-mangostin structure are important for high antituberculosis activity; and (iii) as the length of carbon chain increases, the activity of the monoalkylated and monoacylated tetrahydro α-mangostins reduces. In addition, Arunrattiyakorn et al. have found that the microbial metabolism of α-mangostin (1) results in isolation of four new xanthone derivatives 15–18 [24] (Fig. 3). Compound 15 shows a higher antitubercular activity than that of 1 (MIC = 6.75 and 15.24 μmol·L⁻¹, respectively), whereas the other three compounds without prenyl chains at C-2 or C-8 show a total loss of activity, suggesting the importance of the prenyl group at C-2 or C-8 for the anti-mycobacterial activity.

**Fig. 3** Anti-mycobacterial mangostin derivatives (compounds 12–18)

*Antifungal activities*

Gopalakrishnan et al. have reported that α- and γ-mangostins (1, 3) are active against three phytopathogenic fungi (*Fusarium oxysporum* vasinfectum, *Alternaria tenuis*, *Fusarium oxysporum* f. sp. *corollae*, and *Fusarium oxysporum* f. sp. *nepalense*). α-Mangostin (1) is more potent than chlorhexidine against *Fusarium oxysporum* whereas γ-mangostin (3) is more effective against *Alternaria tenuis* [25]. The mechanism of action of α-mangostin (1) is through the inhibition of F(H⁺)-ATPase and phosphotransferase (PTS) system [18].

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and Dreschlera oryzae) [25]. Candida albicans is the most important invading microorganism implicated in oral candidiasis. Kaomongkolgit et al. have found that α-mangostin (1) is effective against Candida albicans with higher MIC and minimum fungicidal concentration (MFC) values (1 000 and 2 000 µg·mL⁻¹, respectively) and faster killing speed than Clotrimazole and nystatin [26]. More interestingly, α-mangostin (1) is not toxic to normal human gingival fibroblasts at 4 000 µg·mL⁻¹ (2 × MFC) for 8 h. However, the antifungal mechanism of α-mangostin (1) has not been determined yet. It is assumed that α-mangostin (1) might act through attacking the structure of fungal cells, especially ergosterol which is the main lipid component in the membranes of fungi but not present in animals.

**Antimalarial properties**

Plasmodium falciparum, major species of human malaria parasite, has developed resistance to nearly all available antimalarial drugs [5]. Inspiringly, α-mangostin (1) significantly inhibits the resistant P. falciparum chloroquine-resistant FCR3 strain in vitro, with a low IC₅₀ of 0.2 µmol·L⁻¹. In vivo study indicates that intraperitoneally (i.p.) administration of α-mangostin (1) at a dose of 100 mg·kg⁻¹ twice daily for 7 days could attenuate parasitemia by approximately 80% without noticeable toxicity in the malarial murine model infected with Plasmodium berghei [27].

When evaluated for in vitro antimalarial activity against another resistant strain P. falciparum K1 (chloroquine and pyrimethamine-resistant), α-mangostin (1) shows a moderate activity with an IC₅₀ of 17 µmol·L⁻¹ [28]. Subsequently, a novel series of α-mangostin derivatives (19–32) (Fig. 4) have been synthesized by function of C-3 and C-6 hydroxyl groups and the SAR analysis has been made. It has been found that: (i) when hydroxyl groups are blocked by methyl (19), acyl (20) and alklycyan (21, 22), a dramatic decrease in activity is observed (IC₅₀ > 17 µmol·L⁻¹); (ii) dihydroxypropyl derivatives (23, 24) do not increase the activity, while a dihydroxypropyl group attached at C-6 (25) leads to an increase in activity (IC₅₀ = 7.4 µmol·L⁻¹); (iii) substitution with a hydroxypropyl group at C-6 (26) and carbamide at hydroxyl groups (27, 28) increases activity (IC₅₀ = 5.3, 4.5 and 8.3 µmol·L⁻¹, respectively); and (v) the alkylamino derivatives exhibit a considerable increase in activity (IC₅₀ < 1 µmol·L⁻¹), among which compound 29 is the best, with an IC₅₀ of 0.05 µmol·L⁻¹. Besides, the their studies have also indicated that cyclisation of C-2 prenyl side chain of the active amino derivatives substantially decreases the antimalplasmodial activity, such as compound 30, and modification of prenyl side chains also lower the activity, such as compounds 31–33 (Fig. 4). In conclusion, the presence of 3-OH and C-2-prenyl side chain contributes to the antimalplasmodial activity of mangostin.

The mechanism by which of α-mangostin and its derivatives’ exert their anti-P. falciparum properties has not been clarified yet. However, the hydroxyxanthones have been proposed to exert their antimalplasmodial activity through targeting hemoglobinolysis in the parasite digestive vacuole, where they form the soluble complex with heme, thereby inhibiting hemozoin formation [29-30]. Moreover, to enhance the interaction with heme propionate groups and to target the parasite acidic digestive vacuole, modification of the simple hydroxyxanthones by introducing side chains with protonatable nitrogen atoms could dramatically increase their antimalplasmodial activity [31-32]. It remains unknown whether α-mangostin, a prenylated hydroxyxanthone, and its alkylamino derivatives act by a similar mechanism.

**Anti-carcinogenic effects**

The anticancer effects of mangostins were first observed in various leukemia cell lines, even at low concentrations (< 10 µmol·L⁻¹) [33-34]. Thereafter, mangostins have been shown to inhibit or retard the growth of a wide range of cancer cells in vitro and implanted tumors in vivo [35-36]. Moreover, it is
noteworthy that they preferentially target cancer cells over non-cancerous cells, indicating that they may avoid conventional chemotherapeutics-induced side effects.\(^{37}\)

### Effects on skin cancer

Melanoma is the most aggressive form of skin cancer, whose incidence is increasing at the fastest rate.\(^{38}\) Wang et al.\(^ {39-40}\) have reported that α- and γ-mangostins (1, 3) inhibit the growth of human melanoma SK-MEL-28 cells in a concentration-dependent manner (IC\(_{50} = 5.92\) and 3.55 \(\mu\)g·mL\(^{-1}\), respectively), which is executed through the induction of G\(_1\) cell cycle arrest and mitochondrial apoptotic pathway. Also, many research groups have confirmed the significant anti-metastatic effects of α-mangostin (1) in melanoma cell lines.\(^ {41-42}\) Ultraviolet (UV) radiation has been implicated as a potential contributing factor to the pathogenesis of various types of skin cancers, including melanoma.\(^ {43}\) α-Mangostin (1) has been found to possess potent UV-screening activity, so that it could protect skin from the UV-induced carcinogenesis.\(^ {44}\)

### Effects on brain cancer

Kaomongkolgit et al.\(^ {45}\) have found that α-mangostin (1) at 3 \(\mu\)g·mL\(^{-1}\) for 48-h exposure displays moderate cytotoxicity against head and neck squamous cell carcinoma cell lines (HN-22, HN-30, and HN-31 cells) with inhibition rates of 45%-60%.\(^ {46}\) The mechanism was associated with inducing apoptosis through p53-dependent B-cell lymphoma-2-associated X protein (Bax) upregulation. In a study by Chao et al., α-mangostin (1) markedly decreased cell viability of glioblastoma GBM8401 and DBTRG-05MG cells in vitro (IC\(_{50} = 6.4\) and 7.3 \(\mu\)mol·L\(^{-1}\), respectively) and completely inhibited the clonogeneity of both cancer cell lines.\(^ {46}\) α-Mangostin (1) administered intraperitoneally (i.p.) at 2 mg/kg body weight (BW)/day for 4 weeks to mice bearing glioblastoma xenografts led to an approximately 50% reduction in tumor size compared to the control group.\(^ {47}\) The mechanism is triggering autophagic cell death via the activation of liver kinase B1 (LKB1)/AMP-activated protein kinase (AMPK) pathway and subsequent inactivation of mTOR complex 1 (mTORC1). These evidences support a promising future of α-mangostin as a candidate or lead compound for brain cancer therapy.

### Effects on breast and prostate cancers

Ibrahim et al.\(^ {48-50}\) have revealed that mangostins inhibit proliferation of both estrogen receptor (ER)-negative human breast cancer MDA-MB-231 cells and ER-positive human breast cancer MCF-7 cells at micromolar concentrations, resulting in cell cycle arrest concomitant with an increase in reactive oxygen species (ROS) as well as apoptosis through both the extrinsic and intrinsic pathways. Another study by Jiang et al. has revealed that the anticancer effect of α-mangostin (1) against breast cancer cell lines is mainly attributed to the suppression of fatty acid synthase (FAS)\(^ {51}\). In MCF-7 cells, α-mangostin (1) has been reported by Won et al. to exert anticancer effect by restraining the expression of estrogen receptor α (ERα)\(^ {52}\). Leão et al. have proposed that α-mangostin (1) abrogates the negative effect of murine double minute 2 (MDM2) on p53, thus restoring the p53-dependent growth inhibition and cell cycle arrest in the MCF-7 cells.\(^ {53}\) Intra gastric administration of α-mangostin (1) to Sprague-Dawley rats implanted with rat mammary adenocarcinoma LA7 cells at doses of 30 and 60 mg·kg\(^{-1}\) BW showed a significant reduction in the tumor volume (74.1% and 79.2%, respectively), when compared with the control group.\(^ {49}\) Of note, in another xenograft model of breast cancer induced by transplanting murine metastatic mammary adenocarcinoma cells BJMC3879 into syngeneic BALB/c mice, α-mangostin (1) administered by orally gavage at 20 mg·kg\(^{-1}\) BW not only prolonged the survival rates, but also suppressed the tumor volume and the multiplicity of lymph node metastases.\(^ {54}\)

Johnson et al. have demonstrated that α-mangostin (1) significantly reduces the cell viability of human prostate cancer LNCaP, 22Rv1, DU145, and PC3 cells in a concentration-dependent manner (IC\(_{50} = 5.9, 6.9, 22.5\) and 12.7 \(\mu\)mol·L\(^{-1}\), respectively) and inhibits the growth of 22Rv1 cells in athymic nude mice without obvious toxicity.\(^ {55-56}\) Moreover, α-mangostin (1) has been observed to directly inhibit cyclinD1/cyclin-dependent kinase 4 (CDK4) in a cell-free biochemical kinase assay, with the proposed mechanism being competitive inhibition in the binding site of CDK4 using molecular modeling methods.\(^ {55}\) Recently, researchers have reported that endoplasmic reticulum is a potential anticancer target for α-mangostin (1).\(^ {56-57}\) It has been found to selectively promote endoplasmic reticulum stress in prostate cancer cells to increase the apoptotic indices, while exerting little influence on normal prostate epithelial cells.\(^ {58}\)

### Effects on cancers of the digestive system

α-Mangostin (1) (3–10 \(\mu\)g·mL\(^{-1}\)) inhibits proliferation and promotes apoptosis in gastric adenocarcinoma BGC-823 and SGC-7901 cells, in concentration- and time-dependent manners, possibly by suppressing the activation of signal transducer and activator 3 (STAT3) and the expression of its regulated genes, B cell lymphoma-extra large (Bcl-xL) and myeloid cell leukemia-1 (Mcl-1).\(^ {58}\) A short-term administration of α-mangostin (1) elicits potent chemopreventive effects on chemically induced colon carcinogenesis in both mouse and rat models, suggesting that prolonged exposure may result in the suppression of tumor development.\(^ {59-60}\) The positive effects of mangostins on the treatment of colon cancer have been reported in many in vivo and in vitro studies, and some novel mechanisms responsible for their anticancer effects have been put forward, such as the involvement of miR-143/ERK5/c-Myc signaling pathway in colon cancer DLD-1 cells,\(^ {64}\) the inhibition of non-classical Wnt/β-catenin signaling in HCT116 and SW480 cells,\(^ {65}\) and the inhibition of topoisomerases I and II in HCT116 cells.\(^ {66}\)

Hafeez et al. have reported that α-mangostin (1) suppresses the growth of pancreatic cancer cells in vitro and...
in vivo. α-Mangostin (I) treatment results in a concentration-dependent increase in apoptosis in pancreatic cancer cells (PL-45, Panc-1, BxPC3, and ASPC1) and cell cycle arrest at G(0)/G(1) phase without having any effects on normal human pancreatic duct epithelial cells [2-6]. Besides, α-mangostin (I) administration (6 mg·kg−1 BW, i.p., 5 days a week) significantly suppressed both primary (PL-45) and secondary (ASPC1) pancreatic cancer cell-derived orthotopic and ectopic xenograft tumors in athymic nude mice [2, 68]. The underlying mechanism is related to its simultaneously hitting multiple signaling molecules that are aberrantly expressed and involved in proliferation, initiation, development, and chemoresistance of pancreatic cancer cells, including K-Ras, sonic hedgehog (Shh), NF-κB, and STAT3 signaling networks. The treatments that are able to limit migration and block invasion have been pursued to promote the survival rate of pancreatic cancer patients [68]. Under the control of extracellular signal-regulated kinase (ERK) or phosphatidylinositol 3-kinase (PI3K)/v-Akt murine thymoma viral oncogene homolog (Akt) pathway, α-mangostin (I) exhibits potent anti-metastatic effects on various pancreatic cancer cells (MIA PaCa-2, BxPC-3 and Panc-1 cells) by reducing the expressions of matrix metalloproteinases (MMPs) and suppressing the progression of epithelial-mesenchymal transition (EMT) [69-70]. In a recent study by Lei et al., α-mangostin (I) has been observed to suppress hypoxia-induced pancreatic stellate cells activation and pancreatic cancer cell invasion through inhibition of hypoxia inducible factor-1α (HIF-1α) stabilization and glioma-associated oncogene homolog 1 (GLI1) expression [71].

Anticancer activities in combination therapy

Besides being used in mono-therapy, mangostins can also be used in combination with other chemotherapeutic agents to increase therapeutic efficacy and/or minimize the chemotherapy-induced toxicity [72]. α-Mangostin (I) exhibits synergistic effect on 5-fluorouracil (5-FU)-induced growth inhibition in human colon cancer DLD-1 cells at low concentrations (< 5 μmol·L−1) [64]. This finding indicates that a decrease in the clinical dose of 5-FU is possible, thereby lowering his systemic toxicity of 5-FU and increasing its therapeutic index [64]. α-Mangostin (I) protects renal epithelial cells from cisplatin (CDDP)-induced apoptosis via inhibition of p53 induction and ROS generation [73]. On the other hand, it attenuates oxidative/nitrosative stress, inflammatory, and fibrotic markers, offering a renoprotective effect against CDDP-induced renal injury in rats [74-75]. In addition, mangostins possess protective effects against doxorubicin (Dox)-induced neuronal toxicity through inhibiting the production of tumor necrosis factor alpha (TNF-α), inducible nitric oxide synthase (iNOS), and NO, ameliorating the oxidative damage, and regulating pro-apoptotic and anti-apoptotic proteins [76].

Mangostin derivatives as anticancer agents

A preliminary analogue development study by Ren et al. [77] has revealed that both 3, 6-diacetylation (34) and 6-benzylation (35) slightly enhance the cytotoxicity of α-mangostin (I). Also, cyclization at C-2 and C-3 (33, 36) retains the initial cytotoxic potency of I, whereas cyclization at C-1 and C-2 (37) and 3, 6-dimethylation (19) greatly reduce such activity. Consistently, another study has indicated that di-O-alkylated α-mangostin derivatives display reduced cytotoxicity, compared to I [78]. Recently, Fei et al. [79] have synthesized a lot of novel α-mangostin analogs through substitution of the hydroxyl groups at C1, C3, and C6 (20, 34 and 38-49), cyclization at C-2 and C-3 (6 and 50), modification at C4 (51-53) and at C7 (54 and 55). Cytotoxicity activity screening study has identified potent cytotoxic agents such as 12, 20, 40, 46, 51 and 52, but all of them show reduced activity, compared with I. Compounds 20, 40, 49, 51 and 53 show a remarkably increased kinetic solubility, compared with I. The present SAR study has revealed that both of fitioere hydroxyl groups at C-3 and C-6 are essential for the activity and C4 modification can improve both anticancer activity and drug-like property. He et al. have reported that the microbial transformation of α-mangostin (I) by Cunninghamamella blakesleiana produces two new glycosylated products, 56 and 57 [80]. The cytotoxicity of 56 turns out to be comparable with α-mangostin (I), while 57 has an extremely low activity. The structures of all the anticancer derivatives are shown in Fig. 5.

Anti-atherosclerosis properties

Antioxidant activity

Low-density lipoprotein (LDL) oxidation is an early event in atherosclerosis and oxidized LDL (ox-LDL) contributes to atherogenesis, so antioxidant protection against LDL has become a focus of research in the related field [81-82]. Williams et al. have found that α-mangostin (I) acts as a free radical scavenger, lowering the oxidation of LDL induced by copper or peroxyl radical, and decreases the consumption of α-tocopherol induced by ox-LDL [83]. In the subsequent SAR study, Mahabusarakam et al. have synthesized several α-mangostin derivatives and tested their in vitro antioxidant activity [84]. The authors have suggested that structural modifications significantly affect their antioxidant activity: (i) derivatization of the C-3 and C-6 hydroxyl groups with methyl (19), acetate (20), nitrile (21, 22) or propane diol (23, 24) substantially decreases antioxidant activity; (ii) derivatization of C-3 and C-6 with aminomethyl enhances antioxidant activity, among which diethylaminoethoxy derivatives 58 and 59 (Fig. 6) show the most potent antioxidant activity; and (iii) cyclisation of prenyl side chains, such as compound 60 (Fig. 6), exert little influence on antioxidant activity. In hypercholesterolemia-diet-fed Rattus norvegicus Wistar rats, the mangosteen ethanolic extract (containing mangostins) at dose of 800 mg·kg−1 BW has been reported to exert antioxidant and anti-inflammatory activities to lower atherosclerosis markers, such as H2O2, TNF-α, NF-κB, HIF-α, and iNOS, inhibit foam cells formation, and decrease vasa vasorum angiogenesis [85-86].
Anti-proliferative activity against human aortic smooth muscle cells

It is widely believed that suppression of human aortic smooth muscle cells (HASMC) growth induced by HASMC growth factors, such as platelet-derived growth factor (PDGF), is useful to prevent atherosclerosis. Nishihama et al. [87] have made structural modifications of α- and γ-mangostins (1, 3) through halogenation, electrochemical oxidation, and 3-chloroperoxybenzoic acid (mCPBA) oxidation to examine their anti-proliferative activity against HASMC (Fig. 7). The halogenated derivatives 53 and 61–63 and electrochemical oxidized derivatives 64–67 show moderate anti-proliferative activity at 1 µmol·L–1, whereas mCPBA oxidized derivatives 68 and 69 demonstrate potent inhibitory effects.

Inhibition of acid sphingomyelinase

Robust evidences support that acid sphingomyelinase (aSMase)―ceramide pathway is tightly associated with the pathogenesis of atherosclerosis, which promotes lipoprotein retention within early atheromata and accelerates lesion progression [88]. Okudaira et al. [89] firstly demonstrated the inhibitory effect of α-mangostin (1) on aSMase with an IC50 of 14.1 µmol·L–1, and it showed potent selectivity against the neutral sphingomyelinase (nSMase) (IC50 = 113 µmol·L–1). Subsequently, a handful of α-mangostin (1) derivatives have been synthesized (Fig. 8), and preliminary SAR analysis has been performed. The inhibitory activity of benzophenone derivative 70 is comparable to that of 1, but the cytotoxicity is 1/10-fold less [90]. Both prenyl side chains are required to express potent and selective inhibitory activity against aSMase: compound 71 without C-2 prenyl group, maintains its activity but diminishes its selectivity; compound 72 without C-8 prenyl group keeps selectivity, while reducing activity [90]. The olefinic moiety is perhaps not necessary for the activity against aSMase, but affects selectivity because tetrahydro-derivative 12 retains activity, while its selectivity is reduced [90]. The free hydroxyl groups at C-3 and C-6 positions contribute to the activity against aSMase, which is evidenced by the inactivity of diacetyl derivative 34 [90]. Our research group has devoted major efforts to search effective and selective aSMase inhibitors based on the role of aSMase—ceramide pathway in the development of atherosclerosis and some of them are comparable to or more...
potent than the lead compound, such as compound 73, with an inhibition rate of 88.9% (positive control α-mangostin, 73%) [91].

**Neuroprotective properties in Alzheimer's disease**

Alzheimer’s disease (AD) is an age-related neurodegenerative disorder characterized by diverse cognitive impairments. Multiple factors, such as β-amyloid (Aβ) deposits, deficits of acetylcholine (ACh), τ-protein aggregation, and oxidative stress play significant roles in the pathophysiology of the disease [92]. Given the multifactorial nature of AD and the fact that a single drug attacking specific target has limited therapeutic success, the drug design strategy is gradually moving to the multi-target-directed ligand (MTDL) based on the “one-molecule, multiple-target” paradigm [93-94]. It has been suggested that mangostins may serve as promising multifunctional agents to combat AD, due to their multiple biological functions, such as ROS-scavenging [95-97], metal-chelating [98], acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) inhibitory [99-101], and Aβ aggregation-reducing [102] activities.

**Inhibition of β-amyloid aggregation**

According to the “amyloid hypothesis”, the production and accumulation of oligomeric aggregates of Aβ is a central event involved in the pathogenesis of AD and they are believed to initiate the pathogenic cascade, ultimately resulting in neuronal loss and dementia [103]. Accordingly, the blockade of Aβ-aggregation is a pragmatic therapeutic strategy for slowing and/or preventing the progress of AD. It is interesting to find that α-mangostin (1) displays significant protective effect against neurotoxicity induced by Aβ-(1-40) or Aβ-(1-42) oligomers (EC50 3.89 and 4.14 µmol·L–1, respectively). It maintains normal morphology of mammalian neurons, enhances their normal physiological function and disturbs the pathological process of AD [102]. The underlying mechanism is ascribed to its ability to inhibit the Aβ aggregation cascades, which is realized by disaggregating toxic β-sheet-rich aggregated Aβ oligomers and later-stage Aβ fibrils as well as suppressing Aβ fibril formation.

**Inhibition of cholinesterase**

The “cholinergic hypothesis”, as suggested by Davies and Maloney [104], attributes learning and memory dysfunction to the significant decrease in ACh level. In fact, most of the current clinically approved drugs for AD are cholinesterase inhibitors. There are two major types of cholinesterase responsible for the hydrolysis of ACh and regulation of cholinergic neurotransmission, AChE and BChE [105]. α-Mangostin (1) shows significant inhibitory effect against AChE and BChE with IC50 values being 2.14 and 5.41 µmol·L–1, respectively, which is identified as an AChE selective inhibitor. On the other hand, γ-mangostin (3) has almost equal selectivity towards both AChE and BChE (IC50 = 1.31 and 1.78 µmol·L –1, respectively) and is classified as a dual inhibitor [99]. Given that possessing dual inhibitory effect represents an additional therapeutic strategy for AD [106], γ-mangostin (3) should have greater clinical efficacy and are valuable in the management of AD. Molecular docking studies have revealed strong hydrogen bonding and π-σ interactions at the active site of both the enzymes, which might possibly contribute to the potency of both compounds. AChE has been shown to mediate the processing and deposition of Aβ peptide beyond cholinergic function, which is independent of its catalytic active site (CAS) and relates to peripheral anionic site (PAS) [107]. Interestingly, α-mangostin (1), despite being less active against AChE than that of γ-mangostin (3), could act by blocking the PAS of the enzyme and elicit additional benefits besides the inhibitory activity [99].

**Other activities**

Some researchers have also reported mangostins’s other important activities like hepatoprotective activity and...
could totally reverse alleviation of oxidative stress. Dismutase, and reduce glutathione, which results in the decrease of lipid peroxidation, increase the level of superoxide dismutase, and glutamate pyruvate transaminase in HL-7702 cells. It could also significantly decrease the level of oxaloacetate transaminase and glutamate pyruvate transaminase in HL-7702 cells. It could also significantly decrease the level of lipid peroxidation, increase the level of superoxide dismutase, and reduce glutathione, which results in the alleviation of oxidative stress. α-Mangostin (1) also has hepatoprotective activity on part of hepatic steatosis and obesity, according to Young Hee Choi et al. They have found that, when compared with the high fat diet states, an α-mangostin supplement could up-regulate hepatic AMPK, SirT1, and PPARγ levels, which significantly attenuate hepatic fat accumulation. Muhammad Taher et al. have mainly paid their attention to α-mangostin’s activity on glucose uptake and adipocyte differentiation of 3T3-L1 cells which reveal α-mangostin’s effectiveness on the management of obesity. They have found that α-mangostin could inhibit cytoplasmic lipid accumulation and adipogenic differentiation.

**Pharmacokinetic and Toxicological Studies**

PK studies have been elaborated in other reviews, which describe that mangostins can be absorbed and distributed to various tissues to regulate different cellular processes. However, they have low oral bioavailability due to extensive first-pass metabolism and poor absorption. In the below section, we will focus on the description of recent toxicological studies of mangostins (pure compound or as a constituent of mangosteen fruit extract).

Jujun et al. have performed acute and subacute toxicity studies of mangosteen ethanolic extract in rats. The results revealed that acute toxicity at the highest oral dose of 5 000 mg·kg⁻¹ BW and 28-days oral toxicity at doses of 50, 500, and 1 000 mg·kg⁻¹·d⁻¹ did not trigger any significant dose-related changes in average body weight, relative organ weight, hematological parameters, clinical biochemistry or histopathology of organs. Consistently, another study has also indicated no sign of toxicity of mangosteen extract at a maximum single oral dose of 5 000 mg·kg⁻¹ BW (acute toxicity) and daily oral dose of 2 000 mg·kg⁻¹ BW for 14 days (subacute toxicity). Mangosteen hydroethanolic extract has also been demonstrated to have no toxicity when mice are treated with at single intragastric doses of 2 000 and 5 000 mg·kg⁻¹ BW for 14 days (subacute toxicity). More importantly, for the subchronic toxicity study, mangosteen hydroethanolic extracts administered orally to rats at daily doses of 400, 600, and 1 200 mg·kg⁻¹ BW for 12 weeks did not cause any changes in general behavior and physiological status throughout the study period. After the 12-week period, no significant dose-related differences in blood biochemical parameters were observed among the female groups, whereas dose-related increases in direct bilirubin were detected in all male groups, compared that with the control group. However, neither gross necropsy nor histopathological examination of vital organs revealed any abnormalities regardless of gender. Recently, Ibrahim et al. have performed a complete in vitro and in vivo toxicological evaluation of pure α-mangostin (1). It showed low cytotoxic effects against normal liver cells (WRJ-68) in vitro. Oral gavage with α-mangostin (1) at single doses of 100, 500, and 1 000 mg·kg⁻¹ BW (acute toxicity) did not produce any toxicity in ICR mice, which was demonstrated by no treatment-related adverse effects on body weight, organ weight, serum biochemistry, histopathology, and oxidative stress biomarkers.

In view of these evidences, pure mangostin or mangosteen extracts at tested oral doses and duration do not produce acute, subacute or subchronic toxicity in rats or mice. But the long-term safety of mangostins should be determined by additional studies. It is particularly noted that two randomized, double-blind, placebo-controlled clinical trials conducted recently show that the consumption of a mangosteen-based beverage for 30 days has no side effects on immune, hepatic, and renal functions.

**Conclusion**

The aforementioned data demonstrate that mangostins and their derivatives have diverse pharmacological activities, with favorable PK and safety profiles. These evidences strongly support that mangostins or their derivatives might be valuable lead compounds or promising candidates for drug discovery. Among their multiple bioactivities, antibacterial activity and anticancer activity are two of the most outstanding properties. Targeting the bacterial membranes offers them a potential ability to prevent the emergence of resistant bacteria. Combination with other chemotherapeutic agents provides them distinctive properties such as higher therapeutic efficacy and lower toxicity, when compared with the traditional chemotherapeutics alone. In addition, in the management of complex diseases such as atherosclerosis and AD, mangostins can simultaneously attack multiple targets, which provides a better choice for the treatment of these diseases. The SAR studies have afforded important information on the relationship between structure and pharmacological activities, which may be helpful to design and develop more effective analogues in the future. However, few clinically pharmacodynamic studies of mangostins or their derivatives have been validated until now, which seriously impedes their promotion from empirical studies to an evidence-based, clinically applicable pharmacotherapy. It is hoped that, with further clinical investigations, mangostins or their derivatives will be widely used as efficient pharmacotherapy and first-line clinical choice for specific diseases in the near future.

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Abbreviations

AD, Alzheimer’s disease; SAR, structure–activity relationship; PK, pharmacokinetics; MDR, multidrug-resistant; MRSA, methicillin-resistant S. aureus; VRE, vancomycin-resistant Enterococci; VCM, vancomycin hydrochloride; GM, gentamicin; MIC, minimal inhibitory concentration; CAMPs, cationic antimicrobial peptides; EPS, extracellular polysaccharide; Grif, glycosyltransferases; IPS, iodophilic polysaccharides; PTS, phosphotransferase; MBC, minimum bactericidal concentration; TB, Tuberculosis; MFC, minimum fungicidal concentration; IC50, inhibitory concentration 50%; UV, Ultraviolet; Bx, B-cell lymphoma-2-associated X protein; BW, body weight; LKB1, liver kinase B1; AMPK, AMP-activated protein kinase; mTORC1, mTOR complex 1; ER, estrogen receptor; ROS reactive oxygen species; HSP70, heat shock 70 kDa protein; TUB, Tuberculosis; MDR, multidrug-resistant; MRSA, methicillin-resistant Staphylococcus aureus [J]. Fitoterapia, 2009, 80(2): 102-104.

References


