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Research Article

ANTICANCER POTENTIAL OF α-MANGOSTIN

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ABSTRACT

Objective: Mangosteen (*Garcinia mangostana* Linn.) is a tropical fruit originated from South East region. Mangosteen exhibiting a variety of pharmacological activities and is often used for traditional medicine. There are numerous chemical compounds contained in the pericarp of the mangosteen fruit. One of them is xanthone derivative which in some studies shows antioxidant and anticancer activity by preventing free radical and damaging cells. One of the xanthone derivatives that have the strongest anticancer properties is α-mangostin.

Methods: Anticancer potential of α-mangostin was reviewed from available literature.

Results: The α-mangostin shows anti-proliferative and apoptotic activity by suppressing the formation of carcinogenic compounds in various cancer cells. This review will summarize the anticancer properties of α-mangostin that may be exploited for effective cancer prevention.

Conclusion: Development of α-mangostin as a chemopreventive compound can provide new opportunities for effective cancer drug discovery. α-mangostin is useful as a complementary or alternative medicine and a chemopreventive tool against cancer.

Keywords: Mangosteen, Xanthones, α-mangostin, Anticancer.

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INTRODUCTION

Cancer is a large group of diseases that affect every part of the body leading to uncontrolled growth. Other terms of cancer are neoplasms and malignant tumors. New cells grow abnormally which can spread to other organs and are often called metastases. The major cause of death due to cancer is caused by metastases [1].

Cancer is the prominent causes of death in the worldwide. More than half of cancer cases happen in developing countries and cause about 60 million deaths. Existing anticancer treatment such as chemotherapy, surgery, and radiotherapy can only offer some benefits to cancer patients because toxicity issues and is not specific to cancer cells [2]. Therefore, research on cancer drugs is still heavily conducted. Many studies have been done to medicinal plants and foods to find effective cancer treatments. As a potential chemopreventive or therapeutic agent, a big number of medicinal plants have been evaluated [3]. Today, plants are still used as one of the main sources in the finding of new medicines. Therefore, the use of traditional medicine that can be obtained from nature becomes an important alternative in achieving better public health quality [4]. Mangosteen is one of the medicinal plants that become the object of the study.

Mangosteen is a fruit that widely used in Chinese, Jamu, and Ayurvedic medicine. Mangosteen fruit contains substances that have some activities such as antihistamine, chemoprotective effects, antiviral, and a class of natural polyphenol compounds called xanthones [5-7]. Xanthone is found in a secondary metabolite of some higher plant families, including fungi. These compounds are biologically active phenols among the constituents of the mangosteen pericarps and have demonstrated interesting biological activities [8,9]. Mangosteen fruit is also found to have efficacy for anti-obesity [10], dental health problem [11], skin infections and wounds, or malaria infections [12].

Currently, 200 xanthones are discovered to exist in nature, and 50 xanthones have been taken from the hull of the mangosteen fruit. All xanthones have the same skeletal structure; their peculiarities are on the side chains marked with carbon 1-8. Xanthones have six-conjugated groups in member ring structure with more double-bond carbon. This structure of xanthone is very stable and versatile [13].

Xanthones have significant biological properties, including antitumor, antioxidants, antibacterial, anti-inflammatory, antifungal, antiviral, and anti-allergic activity [14]. The anticancer properties of xanthones have recently been studied for their inhibitory effects in the carcinogenesis process. Molecular targets in tumor cells are inhibited by xanthones such as kinases, DNA polymerases, ribonucleotide reductase, and cyclooxygenases [3].

The greatest antitumor activity of all the xanthones has been shown by α-mangostin in prostate, breast, lung, and colorectal cancer [15]. This compound has a molecular formula $C_{24}H_{22}O_6$ and can be caught from the pericarps of the mangosteen fruit [16]. α-mangostin consists of several types including γ-mangostin and β-mangostin [17].

Since the discovery of α-mangostin in 1855 by W. Schmid, many studies have been done on this compound, both in isolation, structural, and biological properties [18]. Its pharmacological properties such as mosquitoes larvicide [19], antibacterial [20], therapeutic drugs [21], antifungal [22], anticancer [23], antioxidant [24], antituberculosis [25], and anti-inflammatory [26]. Among the many studies showed, the anticancer and cytotoxic properties of α-mangostin have been studied through a number of studies.

α-mangostin (10 μM) showed perfect inhibition of HL60 (human promyelocytic) leukemia cell line in humans through apoptotic induction [23]. Ca^{2+}-ATPase-dependent apoptotic induced by α-mangostin in PC12 (pheochromocytoma) cells induces through mitochondrial pathways [27]. Other studies show that IC_{50} values of α-mangostin are almost equal to 5-fluorouracil (5-FU) in the DLD-1 SLJJ-1 cell model [28]. Based on this data, the development of α-mangostin as an chemopreventive compound can provide new opportunities for

effective cancer drug discovery. Hence, this review may be help made to provide scientific information about the anticancer properties of α-mangostin that is rarely know to develop and build new remedies for cancer treatment and prevention.

Mangosteen

Tropical tree of Mangosteen (*Garcinia mangostana* Linn.) is cultivated in Indonesia, India, Singapore, Malaysia, Philippines, Thailand, and Sri Lanka. This tree is slow to grow and can spread 6-25 m. It has glabrous and leathery leaves. Mangosteen fruit has a slightly sour and sweet taste with a dark purple or reddish color. The fruit is edible, has white, soft, pleasant aroma, and juicy flesh. Typically, the entire fruit is 2.5-7.5 cm in diameter, equal to the size of a tangerine [29].

The chemical constituent of mangosteen pericarp

Mangosteen is found that obtain many vitamins and minerals such as vitamin C, riboflavin, niacin phosphorus, and iron in the pericarp of the mangosteen fruit contained natural polyphenols such as xanthones and substances that have chemoprotective and antihistamine effects [30].

Xanthones secondary metabolites in some higher plants [31] comprise an oxygenated heterocycles class. There are 5 groups of classified xanthones: (a) Oxygenated xanthones, (b) xanthonolignoids, (c) xanthone glycosides, (d) prenylated xanthones, and (e) miscellaneous xanthones [32]. Several studies on anticancer properties of xanthones from mangosteen hull can be seen in Table 1.

α-mangostin

α-mangostin is found on the hull of the mangosteen fruit (*G. mangostana* Linn.) and is a metabolite of 1,3,6,7-tetrahydroxy-2,8-di (3-methyl-2-butenyl) xanthone. The α-mangostin is a derivative of xanthones that are widely present in the hull of the mangosteen fruit. The molecular formula of α-mangostin is $C_{24}H_{22}O_6$ with molecular weight 410.46, and melting point 180-182°C [16].

Physical and chemical properties of α-mangostin

α-mangostin is a yellow amorphous crystal with melting point 180-182°C. This compound has a maximum wavelength at 215, 243, and 317 nm [33]. α-mangostin is soluble in methanol and has a water solubility 2.03×10^{-4} mg/L at 25°C. A qualitative analysis was performed by thin-layer chromatography (TLC) and detected by ultraviolet lamps with or without ammonia or using phenolic spray reagents. A quantitative analysis can be done with liquid chromatography [34,86].

The isolation of α-mangostin

α-mangostin can be isolated from the skin of the mangosteen fruit (*G. mangostana* Linn.) and recrystallized to obtain pure α-mangostin crystals. This recrystallization process uses two solvents. The choice of solvent is based on differences in the solubility of the compounds in both solvents. The solvent must be able to dissolve the desired compound, while the other solvent cannot dissolve the compound. α-mangostin is insoluble in water but soluble in methanol; hence, methanol-water is chosen as a solvent in the process of recrystallizing α-mangostin [7,34,35].

Isolation of α-mangostin begin with extraction of the samples of mangosteen peel skin powder and were extracted by maceration, using methanol solvent for 3×24 hrs. The methanol extract obtained was concentrated using a rotary evaporator. Furthermore, the concentrate extract was partitioned three times with a mixture of ethyl acetate:water = 1:1. The resulting ethyl acetate phase combined and evaporated to produce a dark-brown ethyl acetate extract [34].

The solid extract is then separated by liquid-vapor chromatography using a Merck 60 GF-254 kieselgel as the stationary phase with chloroform, chloroform-methanol, and methanol as eluents. Separation results are monitored with TLC. Fractions which have been shown to be a spot on the TLC are combined and purified by recrystallization using a suitable solvent. The obtained isolates were tested for purity by determining melting point and TLC. The molecular structure of the xanthone compound is determined by spectroscopic method and compared with α-mangostin [5,7].

Anticancer and cytotoxic activities of α-mangostin

Through a number of studies, the anticancer and cytotoxic activities of α-mangostin that isolated from the hull of the mangosteen fruit have been discovered. α-mangostin can control cancer cells by apoptotic mechanism (cell suicide process). The cell growth inhibition of human leukemia cell line HL60 was examined for 72 hrs, following cell incubation with α-mangostin at 5 or 40 μM. The strongest inhibitory activity was displayed by α-mangostin (IC_{50} 10 μM). Compared than other xanthones, α-mangostin was discovered to be effective from 10 μM. The leukemia cell lines such as NB4, K562, and U937 indicated that the α-mangostin has inhibited as well. The cell growth of leukemic cell lines can be inhibited by α-mangostin at 5-10 μM [23]. α-mangostin biological activity associated with apoptosis, such as topoisomerase inhibitory effect [36], silicotoxinasease acids [37-38], and Ca2-ATPase [39]. The enzyme is associated with apoptotic signaling [40-43].

Cell-cycle distribution analysis was conducted on DLD-1 cells, and human colon cancer was conducted to find the mechanism of antiproliferative effect of xanthone. Target for cancer therapeutics in most human cancer cells is cell-cycle machinery and check-point signaling pathway that are dysregulated [44-46]. Apoptosis in cancer cells related with p27 overexpression [47,48] and cyclin and cdc2 suppression [49-52].

The results showed antiproliferative mechanism of α and β mangostin caused by the inhibition of pass into S-phase so that G1-phase arrest induced. While in γ-mangostin, antiproliferative mechanism is caused by inhibition of entry into the G2/M-phase. Antiproliferative activity of four prenylated xanthones (methoxy-β-mangostin, α-mangostin, γ-mangostin, and β-mangostin) on DLD-1 cells. They concluded that antiproliferative effect of xanthone was connected to the number of hydroxyl groups [23].

The potency of α-mangostin on MCF-7 cell (human breast adenocarcinoma cell) as an anticancer agent against expression of matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9) was shown. Overexpression of proteolytic enzymes such as matrix metalloproteinase (MMPs) involves in metastasis [53]. Most extracellular matrix can be degraded by MMP-2 and MMP-9 forming the basal membrane [54]. The promoter of MMP-2 and MMP-9 shown

Table 1: Anticancer properties of xanthones isolated from mangosteen

Effect	References
Six hepatoma cell lines including HEp 3B, HA22T, HCC36, SK-HEp-1, and TONG were all sensitive antiproliferative effect of garcinone E	Ho *et al.* (2002) [77]
Growth inhibitory in human leukemia HL60 cells of six xanthones from the hull of mangosteen	Matsumoto *et al.* (2003) [23]
The ACF has been inhibited by dietary administration of crude α-mangostin	Nabandith *et al.* (2004) [78]
In four cells lines, antileukemic activity of mangosteen fruit rind (aqueous extract) shown	Chiang *et al.* (2004) [87]
Antiproliferative effect of mangosteen methanolic and ethanolic extracts on SKBR3 cells (human breast cancer)	Moongkarndi (2004) [88]
Three human cancer cell lines shown cytotoxic effect of mangostenone C, garcinone C, mangostenone D, garcinone-D, demethylcalabaxanthone, β-mangostin, gartanin, garcinone E, α-mangostin, mangostinone, and c-mangostin	Suksamrarn *et al.* (2006) [84]

ACF: Aberrant crypt foci

to contain necrosis factor-κB (NF-κB) and activator protein-1 (AP-1) elements is highly conserved [55-57].

Treating MCF-7 cell with α-mangostin >6 μM for 24 and 48 hrs resulted in dose- and time-dependent lack of cell viability. Cytotoxicity did not occur at doses below 6 μM performed for 24-48 hrs. Migration of MCF-7 cells and 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced invasion could completely be inhibited by α-mangostin in MCF-7 cells. The cytotoxicity of α-mangostin using MCF-7 cells with α-mangostin for 24 and 48 hrs at different concentrations (0-16 μM) was investigated, followed by an MTT assay. On the growth of MCF-7 cells, α-mangostin exhibited a time- and dose-dependent inhibitory effect. Cell viability was significantly decreased while cells were treated with 8-16 μM α-mangostin for 24 and 48 hrs.

α-mangostin is effective as an antimetastatic agent against expression of MMP-2 and MMP-9 in human breast adenocarcinoma cell MCF-7. α-mangostin stimulates a stable chemoprotective effect against TPA-mediated metastases. The antimetastatic effects of α-mangostin on TPA-induced MCF-7 cells may be due to inactivation of extracellular signal-regulated kinase 1/2 (ERK1/2) phosphorylation and reduction of DNA binding activity of AP-1 and NF-κB, leading to downregulation of MMP-2 and MMP-9 expression, and consequently, invasion and migration of cell inhibited [58].

α-mangostin gives antimetastatic effects against human prostate cancer cells PC-3. c-Jun N-terminal kinase, ERK1/2 or p44/42 mitogen-activated protein kinase (MAPK), and p38 MAPK are three major mammalian MAPKs. Treatment of cells with α-mangostin may decrease the following enzyme expression in a way that depends on the concentrations: MMP-2, MMP-9, and urokinase-plasminogen (u-PA) activator. The expression of MMPs and u-PA are regulating by p38 MAPK, ERK1/2, and c-Jun N-terminal kinase (JNK)/SAPK [59-61].

The effects on the phosphorylation of JNK1/2 and activation of NF-κB, c-Fos, and c-Jun are also shown by α-mangostin. The expression of MMP-2, MMP-9, and u-PA in PC-3 cells can also be reduced by treatment with a specific inhibitor of JNK. Based on these results, the metastases of PC-3 cells can be mediated by the ability of α-mangostin to the mechanism of reduction of MMP-2, MMP-9, and u-PA expression by suppressing the JNK1/2 signal pathway and inhibiting the binding activity of NF-κB and AP-1 [62].

The anticancer activity of α-mangostin on DLD-1 colon cancer cells was investigated. The signaling pathways of MAPKs modulate by various phytochemicals, including resveratrol [63], arucanolide [64], and epigallocatechin-3-gallate [62], leading to cell death and growth inhibition. In contrast with decreased amount of miR-143 in human colon cancer and in normal colon cell, a large amount of miR-143 is expressed [66-67].

Their results showed a reduced number of cancer cells with 20 μM α-mangostin. Apoptosis is found as a mechanism of the 20 μM α-mangostin cytotoxic effect. Although Western blotting showed no signs of caspase activation, apoptotic inhibitory results using caspase inhibitors and caspase activity, and the release of G-endonucleases from mitochondria with decreased mitochondrial membrane potential was demonstrated. The phosphate-ERK1/2 level increased up to 1 hr after the start of treatment in the early phase. The levels then decreased and increased again in the final phase. After 6 hrs of treatment, the phospho-Akt level showed a sharp decrease with the apoptotic process. The amount of microRNA-143, which negatively regulated ERK5 during translation, increased gradually up to 24 hrs after treatment. The growth inhibition on DLD-1 cells was also examined. Cells were treated with a combination of α-mangostin and 5-FU, a chemotherapy agent considered most effective against colorectal adenocarcinoma. The combination treatment of α-mangostin and 5-FU at a concentration of 2.5 μM resulted in increased inhibition of growth compared to treating cells with only 5 μM α-mangostin or 5 μM 5-FU individually [23].

The administration of α-mangostin in food inhibited significantly of biomarkers for 1,2-dimethylhydrazine (DMH)-induced short-term colon carcinogenesis release. To provide short-term chemopreventive effects on DMH in rat colon carcinogenesis, α-mangostin was administered in food for 2 weeks by subcutaneous injection (40 mg/kg body weight, given once a week) and examined [77]. Colorectal cancer causes about 500,000 deaths annually [68]. Putative precursor lesions of colon carcinogenesis or aberrant crypt foci considered as useful preneoplastic biomarkers [69-71]. In the colon carcinogenesis model systems, adenomatosis polyposis coli/β-catenin pathway plays an important role [72-73]. Accumulate β-catenin protein in the cytoplasm shown in azoxymethane-induced rat colon carcinomas have [74] and thought to be useful as preneoplastic biomarkers [75,76].

α-mangostin showed Ca^{2+}-ATPase inhibition in apoptosis through mitochondrial path. Mitochondrial pathway and death receptor pathway are two major signaling of apoptosis. Cytochrome c involves in mitochondrial pathway and induces caspase-9 activation [78,79]. Death ligands such as TNF-related apoptosis-inducing ligand [80] or Fas ligand [81] trigger death receptor pathway and caspase-8 activation are detected typically [82].

In the study, the effects of eight xanthones on cell death in pyromocytoma cells PC12 were studied. The results showed α-mangostin value of effective concentration or EC_{50} (4 μM) and the most potent effect among the eight compounds. PC12 cell treatment with α-mangostin showed typical apoptotic DNA fragmentation and caspase-3 cleavage. Cytometric flow analysis shows the time and apoptotic behavior caused by α-mangostin. α-mangostin also exhibited apoptotic characteristics of mitochondrial pathways, including depolarization of mitochondrial membranes and cytochrome c release. α-mangostin also inhibited sarcoendoplasmic Ca^{2+}-ATPase reticulum. Correlations of each other were seen in the inhibitory effects of Ca^{2+}-ATPase and apoptotic effects of xanthone derivatives. In contrast, the use of α-mangostin caused activation of one of the signaling molecules of endoplasmic reticulum, c-Jun NH2 terminal kinase (JNK/SAPK) [83]. The results of the various studies from the source data review that show anticancer and cytotoxic properties of α-mangostin can be seen in Table 2.

Pharmacokinetic properties of α-mangostin

Percentage recovery of α-mangostin in rat plasma and bergamottin as internal standard showed 93.19%. The range of 20-2000 ng/ml linear calibration curve was observed with total running time of 8 minutes. Non-compartment analysis results showed a half-life of 4 minutes and oral bioavailability of 4.24% for α-mangostin. The high tissue binding indicated by the distribution phase half-life was 3 minutes and 3.5 hrs of the terminal elimination phase. The biphasic properties were divided into two phases: Rapid distribution and slow elimination. The slow elimination of rat plasma was shown after administration (i.v). However, oral administration of α-mangostin bioavailability was very low [84].

Based on Syamsudin's study, at 12 hrs, there was α-mangostin in intact form in urine of 0.0199 and was not found again after 24 hrs. Most of α-mangostin turned into its metabolites or underwent fecal excretion. On oral administration, there was no cumulative effect of α-mangostin. The highest levels of α-mangostin were present in the heart (9.12 μg/g). The intestine had the smallest levels α-mangostin (2.23 μg/g).[84].

PROSPECT AND FUTURE

α-mangostin has a high antiproliferative activity with IC_{50} values almost equal to 5-FU. With these properties, α-mangostin can be used as one of the chemotherapy agents or complementary therapies to accomplish increased therapeutic efficacy and reduce chemotherapy-induced toxicity. α-mangostin also has low toxicity. However, despite the numerous *in vitro* and *in vivo* studies, as a potent chemotherapy and chemopreventive agent, further research must be conducted for further safety and efficacy of α-mangostin. Long-term epidemiological studies and clinical trials are also needed to determine the efficacy of

Table 2: α-mangostin mechanism of anticancer and cytotoxic

Effect	Reference
Perfect inhibition of HL60 leukemia cell line in humans by α-mangostin through induction of apoptosis	Matsumoto *et al.* (2003) [89]
Carcinogenesis in rat colon was inhibited by chemopreventive effect of α-mangostin	Nabandith *et al.* (2004) [78]
In PC12 cells, Ca-ATPase-dependent apoptosis induced by α-mangostin through mitochondrial pathways	Sato *et al.* (2004) [27]
Cytotoxic effects on breast cancer cells (BC-1) and epidermoid cells of mouth carcinoma (KB)	Suksamrarn *et al.* (2006) [84]
Proliferation of colon cancer cells is inhibited by inhibition of β-catenin gene regulation in the Wnt/cGMP pathway by α-mangostin	Yoo *et al.* (2011) [90]
Apoptosis in SLJJ-1 cells of human colon cancer is induced by α-mangostin	Matsumoto *et al.* (2005) [23]
Increased of miR-143 expression in colorectal cancer DLD-1 cells and cell death through caspase-independent apoptosis induced α-mangostin with release of G-endonuclease from mitochondria	Nakagawa *et al.* (2007) [65]
In an *in vitro* and *in vivo*, α-mangostin has a strong effect on colorectal HCT116 carcinoma	Aisha *et al.* (2012) [91]
Potential cytotoxic effects of α-mangostin in cell line SK-MEL-28 melanoma cell	Wang *et al.* (2011) [47]
Induction of D-17 canine-osteosarcoma cell death with apoptosis by α-mangostin	Krajarng *et al.* (2012) [92]
α-mangostin cytotoxicity in squamous cell lines on neck and head carcinoma (HNSCC)	Kaomongkolgit *et al.* (2011) [22]
Pc-3 human prostate carcinoma cell metastasize is inhibited by inhibition of matrix expression of metalloproteinase-2/9 and urokinase-plasminogen through JNK signaling pathway by α-mangostin	Hung *et al.* (2009) [62]

α-mangostin alone or with the other anticancer agents before it can be suggested for the purposes of treatment and cancer prevention.

CONCLUSION

The quest to discover various pharmacological activities and α-mangostin applications continues to grow rapidly. The studies mentioned above illustrate the promising anticancer and cytotoxic properties of α-mangostin, in animal models and large numbers of cells, both *in vitro* and *in vivo*. The development of α-mangostin is useful as complementary or alternative medicine and a chemopreventive tool against cancer development.

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