



## REVIEW

# $\alpha$ -Mangostin from *Garcinia mangostana* Linn: An updated review of its pharmacological properties



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## KEYWORDS

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**Abstract** Over the past decades, various studies have highlighted the pure natural compound,  $\alpha$ -mangostin as their main topic. The compound's pre-clinical and pharmacological properties have been recognized and defined in these studies.  $\alpha$ -Mangostin shows strong pharmacological effects in *in vitro* and *in vivo* model systems by targeting a number of vital cellular factors through various mechanisms of action. Despite its important molecular versatility, the  $\alpha$ -mangostin still has limited clinical application. In order to optimize the conditions of this compound as a chemotherapeutic and chemopreventive agent, for instance in diseases such as cancer, obesity, diabetes as well as

**Abbreviations:** CAT, catalase; CD, concentration required to double QR induction activity; CNS, central nervous system; COX, cyclooxygenase; CPK, creatine phosphokinase; LD50, lethal dose 50%; DMH, 1,2-dimethylhydrazine; GSH, reduced glutathione; GML, *Garcinia mangostana* Linn; H<sub>2</sub>O<sub>2</sub>, hydrogen peroxide; GPx, glutathione peroxidase; GPT, glutamate pyruvate transaminase; GST, glutathione-S-transferase; HIV-1, human immunodeficiency virus; IC<sub>50</sub>, inhibitory concentration at 50%; LDH, lactate dehydrogenase; LDL, low density lipoprotein; LOX, lipoxygenase; LPS, lipopolysaccharide; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide; NO, nitric oxide; iNOS, inducible nitric oxide synthase; ONOO<sup>-</sup>, superoxide anion; PGE<sub>2</sub>, prostaglandin-E<sub>2</sub>; PML, polymorphonuclear leucocyte; QR, quinone reductase; ROS, reactive oxygen species; SOD, superoxide dismutase; TBARS, thiobarbituric reactive substances; VRE, *Vancomycin Resistant Enterococci*; HPLC/MS, high performance liquid chromatography–mass spectrometry; LC–MS/MS, liquid chromatography–mass spectrometry

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inflammatory disorders, the recent tendency is to limit the range of its pharmacological properties. The present work reviews recent studies on the central and potential pharmacological principles as well as the preclinical applications of the  $\alpha$ -mangostin.

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## 1. Introduction

In recent times, the focus on plant research around the world has increased; numerous lines of evidence have been gathered to demonstrate the enormous potential of medicinal plants. By means of modern scientific approaches, different types of medicinal plants have been recognized and studied. The results reveal these medicinal plants as having a promising potential, particularly in pharmacology (Fiala et al., 1985; Tapsell et al., 2006; Triggiani et al., 2006).

A number of human diseases have been associated with oxidative stress; these include diabetes, cardiovascular diseases, neurodegenerative disorders and especially carcinogenesis (Nakabeppu et al., 2006; Triggiani et al., 2006). As a result, a lot of interest is given toward researching naturally occurring protective antioxidants as well as their mechanisms of action. In accordance with this, it has been revealed that a number of plant extracts or their secondary metabolites demonstrate powerful antioxidant activity and the ability to protect from oxidant-induced damages (Collins, 2005; Hayatsu et al., 1988; Loo, 2003; Triggiani et al., 2006). Consequently, it was observed in the last decade that a lot of plant extracts have exhibited potent cancer chemopreventive properties (Ames, 1998; Ames and Gold, 1998; Beckman and Ames,

1998; Borek, 2004; Cassady et al., 1990). For most of these extracts, their effects are known to be achieved via antioxidant mechanisms that either quench reactive oxygen species, stimulate cellular antioxidant defense systems or prevent lipid peroxidation (Carilli and Yun, 2000; Valko et al., 2007). Mangosteen (*Garcinia mangostana*) Linn is a type of fruit that grows in the Asian region such as Malaysia, Myanmar, Thailand, Philippines, Sri Lanka and India. Mangosteen is also referred to as the "queen of fruits" due to its unique and delectable tropical taste. The fruit is dark purple or reddish in color and contains soft and juicy edible white pulps inside. The flavor is slightly acidic and sweet and it has a delightful smell (Jung et al., 2006). The pericarps of this fruit have been used for many years as traditional medicine in treating sicknesses such as trauma, skin infection, abdominal pain, dysentery and wounds (Peres et al., 2000). Moreover, mangosteen has been proven to contain various secondary metabolites (e.g. prenylated and oxygenated xanthenes) (Govindachari et al., 1971; Peres et al., 2000). In 1855,  $\alpha$ -mangostin (Fig. 1) was found among the major xanthenes taken from the pericarps of the mangosteen fruit (Schmid, 1855). The compound is a yellowish coloring matter which can be obtained from the other parts of the plant as well, such as the dried sap and the bark (Dragendorff, 1930). Subsequently, the structure of this xanthone was construed by Dragendorff (1930) and Murakami (1932). The molecular formula, type and position of the substituent groups of  $\alpha$ -mangostin were then determined by Yates and Stout (1958). This compound has been discovered to possess a wide range of biological activities, with anti-inflammatory, anti-tumor, cardioprotective, antidiabetic, antibacterial, antifungal, antiparasitic, antioxidant and anti-obesity agents. In this paper, we review the main pharmacological effects of this pure compound.

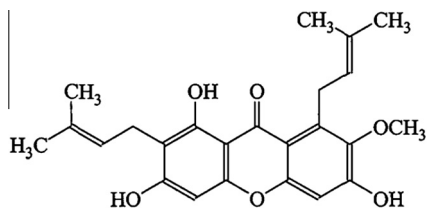


Figure 1 Chemical structure of  $\alpha$ -mangostin.

**Table 1** Antioxidant properties of  $\alpha$ -mangostin.

Effect	Reference
$\alpha$ -Mangostin showed antioxidant properties using the ferric thiocyanate method	Fan and Su (1997) and Yoshikawa et al. (1994)
$\alpha$ -Mangostin is acting as a free radical scavenger to protect the LDL from oxidative damage	Williams et al. (1995)
Structural modification of $\alpha$ -mangostin can inhibit the oxidation of LDL	Mahabusarakam et al. (2000)
$\alpha$ -Mangostin showed antioxidant activities using authentic and morphosydnonimine-derived roxynitrite methods	Jung et al. (2006)
$\alpha$ -Mangostin has a protective effect on lipid peroxidation and antioxidant tissue defense system during ISO-induced myocardial infarction in rats	Devi Sampath and Vijayaraghavan (2007)
$\alpha$ -Mangostins inhibited nitric oxide (NO) from lipopolysaccharide (LPS)-stimulated RAW 264.7 cells	Chen et al. (2008)
$\alpha$ -Mangostin can be an effective cardiotoxic preventative against $\beta$ -adrenergic catecholamine induced myocardial toxicity and associated oxidative stress	Devi Sampath and Vijayaraghavan (2007)
$\alpha$ -Mangostin attenuated renal dysfunction, structural damage, oxidative/nitrosative stress and decreased the catalase expression in rats	Pérez-Rojas et al. (2009)
$\alpha$ -Mangostin has the ability to scavenge several ROS and has a neuroprotective effect against 3-NP in primary cultures of CGNs, which is associated with its ability to ameliorate 3-NP-induced ROS production	Pérez-Rojas et al. (2009)
$\alpha$ -Mangostin protects renal tubular cells by blocking CDDP-induced apoptosis through ROS generation and p53 signaling	Sánchez-Pérez et al. (2010)
$\alpha$ -Mangostin induces a protective effect in postischemic heart associated with the prevention of oxidative stress secondary to reperfusion injury	Buelna-Chontal et al. (2011)

## 2. Extraction and isolation of $\alpha$ -mangostin

Mangosteen pericarps collected were dried, ground and extracted separately in water and 50% ethanol. The 50% ethanol extract was freeze-dried and subsequently, the dried powder resulting from the freeze-drying process was suspended in water that was partitioned with ethyl acetate. Then, the ethyl acetate extract was purified by chromatography on silica gel with the *n*-hexane–ethyl acetate system and recrystallized to achieve >98% purity of the compound (Mahabusarakam et al., 1987; Parveen et al., 1991).

## 3. Main pharmacological properties of $\alpha$ -mangostin

### 3.1. Antioxidant properties

The antioxidant properties of  $\alpha$ -mangostin which have been studied are summarized in Table 1. These antioxidant properties were demonstrated through the ferric thiocyanate method (Fan and Su, 1997; Yoshikawa et al., 1994). (Williams et al., 1995) discovered that  $\alpha$ -mangostin reduces copper- or peroxy radicals-induced oxidation of the human low density lipoproteins (LDL). They also found that  $\alpha$ -mangostin: (i) dose-dependently prolonged the lag time of conjugated dienes at 234 nm; (ii) decreases the production of thiobarbituric reactive substances (TBARS); and (iii) diminishes the consumption of  $\alpha$ -tocopherol that is induced by LDL oxidation. In fact, this consumption is also decreased by the synthetic derivatives of  $\alpha$ -mangostin. These authors also discovered that the antioxidant activity of the  $\alpha$ -mangostin could be modified by its structural modifications. For instance, substituting C-3 and C-6 with aminoethyl derivatives caused the antioxidant activity to be enhanced, whereas substituting them with methyl, propanediol, acetate or nitrile resulted in a decrease of antioxidant activity (Mahabusarakam et al., 2000). Furthermore, the IC<sub>50</sub> ( $\mu$ M)

value for ONOO<sup>-</sup> scavenging on a 7,12-dimethylbenz[ $\alpha$ ]anthracene-induced mouse mammary organ culture assay for different xanthenes was determined by Jung et al. (2006).  $\alpha$ -Mangostin is one of the compounds that possesses the highest capacity to scavenge ONOO<sup>-</sup> with 12.2  $\mu$ M as opposed to 3.1  $\mu$ M for the positive control of DL-penicillamine.

The impact of  $\alpha$ -mangostin on the antioxidant defense system as well as on lipid peroxidation during myocardial infarction in rats induced by isoproterenol was evaluated by Devi Sampath and Vijayaraghavan (2007). Results of this evaluation revealed that there was a significant decrease in the antioxidant enzymes glutathione-S-transferase (GST), glutathione peroxidase (GPx), catalase (CAT), superoxide dismutase (SOD) and reduced glutathione (GSH) following the treatment with isoproterenol (150 mg/kg for 2 days). On the contrary, there was a remarkable increase in serum enzymes, including creatine phosphokinase (CPK), lactate dehydrogenase (LDH), glutamate pyruvate transaminase (GPT), glutamate oxaloacetate transaminase (GOT) and lipid peroxides. After being histopathologically examined, rats treated with isoproterenol exhibited necrotic alterations in the tissue, along with intense neutrophil infiltration. These alterations were reduced significantly by a 6-day prior pretreatment with  $\alpha$ -mangostin (200 mg/kg) and 2 days concurrently with isoproterenol administration. The protective effect of this xanthone against lipid peroxidation and toward the antioxidant defense system throughout injury-induced myocardial infarction in rats was shown. In addition, nitric oxide (NO) was also significantly inhibited from lipopolysaccharide (LPS)-stimulated RAW 264.7 cells, and the inhibition showed an IC<sub>50</sub> value of 12.4  $\mu$ M (Chen et al., 2008).

The wholesome effect of exogenously administered  $\alpha$ -mangostin against  $\beta$ -adrenergic catecholamine-induced cardiovascular toxicity, especially with regard to membrane ATPases, lysosomal hydrolases and inflammatory mediators TNF- $\alpha$  and cyclooxygenase-2 (COX-2) expressions in albino rats was explored by Devi Sampath and Vijayaraghavan

(2007). The result of a 2-day induction of rats with isoproterenol (150 mg/kg body wt, i.p.) showed increasing serum and cardiac lysosomal hydrolase ( $\beta$ -d-glucuronidase,  $\beta$ -d-galactosidase,  $\beta$ -d-N-acetylglucosaminidase, acid phosphatase and cathepsin-D) activities. Moreover, in the hearts of ISO-administered rats, the cardiac levels of sodium and calcium showed a significant increase, along with a decrease in the level of potassium and abnormal activities of membrane-bound phosphatases ( $\text{Na}^+ - \text{K}^+$  ATPase,  $\text{Ca}^{2+}$  ATPase and  $\text{Mg}^{2+}$  ATPase). Expressions of Cardiac TNF- $\alpha$  and COX-2 that were evaluated using Western blotting showed a significant elevation in ISO-intoxicated rats. An 8-day oral pre-co-treatment with  $\alpha$ -mangostin (200 mg/kg body wt) mitigated these abnormalities significantly and restored the levels to near normalcy as opposed to the ISO-intoxicated group of rats. The preservation of myocardial membrane integrity as well as the extenuation of inconsistent TNF- $\alpha$  and COX-2 expressions by  $\alpha$ -mangostin are made possible by effectively mitigating ISO-induced oxidative stress and cellular damage. The cytoprotective role of  $\alpha$ -mangostin is proven by the restoration of cellular normalcy.

The renoprotective effect of  $\alpha$ -mangostin on cisplatin (CDDP)-induced nephrotoxicity in rats was evaluated by Pérez-Rojas et al. (2009). 12.5 mg/kg/day, i.g. of  $\alpha$ -mangostin was administered for 10 days (7 days prior to and 3 days following CDDP injection). On the 7th day, the rats were treated with a single injection of CDDP (7.5 mg/kg, i.p.). After 3 days, the rats were killed. Effects of  $\alpha$ -mangostin include the attenuation of renal dysfunction, oxidative/nitrosative stress and structural damage. The compound also abated the decrease in catalase expression and increases in mRNA levels of tumor necrosis factor alpha as well as transformed growth factor beta. In a nutshell, the attenuation in oxidative/nitrosative stress, inflammatory and fibrotic markers as well as preservation of catalase activity are inherent in the renoprotective effect of  $\alpha$ -mangostin on CDDP-induced nephrotoxicity.

Pérez-Rojas et al. (2009) discovered the ability of  $\alpha$ -mangostin to scavenge singlet oxygen, superoxide anion and peroxynitrite anion in a concentration-dependent manner. On the contrary, the compound was unable to scavenge hydroxyl radicals and hydrogen peroxide.  $\alpha$ -Mangostin was also able to improve the neuronal death induced by 3-nitropropionic acid (3-NP) in a concentration-dependent manner. This protective effect of the  $\alpha$ -mangostin was related to the amelioration of 3-NP-induced reactive oxygen species formation.

In a study conducted by Sánchez-Pérez et al. (2010) to evaluate the ability of  $\alpha$ -mangostin in protecting proximal tubule renal epithelial cells (LLC-PK1) from cisplatin CDDP-induced apoptotic death, cells were co-incubated with 5  $\mu\text{M}$   $\alpha$ -M and 100  $\mu\text{M}$  CDDP for a 24-h period. Results revealed that the following alterations were attenuated by  $\alpha$ -mangostin: apoptotic cell death, glutathione depletion, as well as increase in reactive oxygen species and p53 expression induced by CDDP. The preventive effect of  $\alpha$ -mangostin on CDDP-induced apoptotic death is attributable to the inhibition of p53 expression and ROS generation.

The protective effect of  $\alpha$ -mangostin on cardiac reperfusion damage was investigated by Buelna-Chontal et al. (2011). The findings indicate that  $\alpha$ -mangostin preserves the mechanical work of the cardiac, reduces the area of infarct as well as prohibits the decrease in cardiac ATP and phosphocreatine levels in the reperfused myocardium. This particular protective effect

of the xanthone was affiliated with the reduction of oxidative stress. Moreover, treatment with  $\alpha$ -mangostin was found to prevent the following: reperfusion injury-induced protein oxidation (i.e. protein carbonyl content), diminution of glutathione content and lipid peroxidation (i.e. malondialdehyde and 4-hydroxynonenal content).

### 3.2. Anticancer and cytotoxic properties

As shown in Table 2, the anticancer and cytotoxic properties of  $\alpha$ -mangostin that is isolated from the pericarp of the mangosteen fruit have been explored through a number of studies.

In a study conducted by Matsumoto et al. (2003), the inhibitory effects of  $\alpha$ -mangostin and 5 other xanthones on the cell growth of the human leukemia cell line HL60 were explored. The cytotoxic effects were examined 72 h following cell incubation with  $\alpha$ -mangostin at 5 or 40  $\mu\text{M}$ .  $\alpha$ -Mangostin was found to be especially effective from 10  $\mu\text{M}$  and displayed the highest inhibitory activity ( $\text{IC}_{50}$  10  $\mu\text{M}$ ) compared to other xanthones, although they also exhibited significant suppression effect. Afterwards, other leukemia cell lines (K562, NB4 and U937) showed the  $\alpha$ -mangostin effect as well.  $\alpha$ -Mangostin inhibited the cell growth of the abovementioned leukemic cell lines at 5–10  $\mu\text{M}$ .

The ability of  $\alpha$ -mangostin administered in the diet to exert short-term chemopreventive effects on 1,2-dimethylhydrazine (DMH)-induced putative preneoplastic lesions in rat colon carcinogenesis through subcutaneous injection (40 mg/kg body wt, administered once a week for 2 weeks) was examined by Nabandith et al. (2004). The findings showed that administering  $\alpha$ -mangostin in the diet could significantly inhibit the release of biomarkers for DMH-induced short term colon carcinogenesis (such as dysplastic foci, aberrant crypt foci and  $\beta$ -catenin accumulated crypt).

Sato et al. (2004) conducted a study to examine the cell death effects of eight xanthones on PC12 rat pheochromocytoma cells. It was discovered that  $\alpha$ -mangostin obtained from the fruit hull of *G. mangostana* L. had the most potent effect among the eight compounds, with the  $\text{EC}_{50}$  value of 4  $\mu\text{M}$ . PC12 cells treated with  $\alpha$ -mangostin displayed typical apoptotic DNA fragmentation and caspase-3 cleavage (equivalent to activation). The time- and concentration-dependent manners of the apoptosis induced by  $\alpha$ -mangostin were indicated by the flow cytometric analysis.  $\alpha$ -Mangostin also exhibited features of the mitochondrial apoptotic pathway, including mitochondrial membrane depolarization and cytochrome c release. Moreover,  $\alpha$ -mangostin remarkably inhibited the sarco/endoplasmic reticulum  $\text{Ca}^{2+}$ -ATPase. The  $\text{Ca}^{2+}$ -ATPase inhibitory effects and the apoptotic effects of the xanthone derivatives showed a correlation with each other. On the contrary,  $\alpha$ -mangostin treatment caused one of the signaling molecules of endoplasmic reticulum (ER) stress, c-Jun NH2-terminal kinase (JNK/SAPK), to be activated. These findings imply that  $\alpha$ -mangostin inhibits  $\text{Ca}^{2+}$ -ATPase to bring about apoptosis through the mitochondrial pathway.

The antiproliferative effect of  $\alpha$ -mangostin along with 3 other prenylated xanthones in DLD-1 human colon cancer cells was studied by Matsumoto et al. (2005). It was found that  $\alpha$ -mangostin strongly suppressed cell growth at 20  $\mu$  and its antiproliferative efficacy was associated with the number of

**Table 2** Anticancer and cytotoxic properties of  $\alpha$ -mangostin.

Effect	Reference
$\alpha$ -Mangostin showed complete inhibition at 10 $\mu$ M through the induction of apoptosis on human leukemia cell line HL60	Matsumoto et al. (2003)
Crude $\alpha$ -mangostin has a potent chemopreventive effect in short-term colon carcinogenesis in rats	Nabandith et al. (2004)
$\alpha$ -Mangostin Induces $Ca^{2+}$ -ATPase-dependent apoptosis via mitochondrial pathway in PC12 cells	Sato et al. (2004)
$\alpha$ -Mangostin induces cell-cycle arrest and apoptosis in human colon cancer DLD-1 cells	Matsumoto et al. (2005)
$\alpha$ -Mangostin has cytotoxic effect against breast cancer (BC-1) and epidermoid carcinoma of the mouth (KB) cells	Suksamrarn et al. (2006)
$\alpha$ -Mangostin-induced cell death: caspase-independent apoptosis with release of endonuclease-G from mitochondria and increased miR-143 expression in human colorectal cancer DLD-1 cells	Nakagawa et al. (2007)
$\alpha$ -Mangostin suppresses Pc-3 human prostate carcinoma cell metastasis by Inhibiting Matrix Metalloproteinase-2/9 and urokinase-plasminogen expression through the JNK signaling pathway	Hung et al. (2009)
$\alpha$ -Mangostin suppresses phorbol 12-myristate 13-acetate-induced MMP-2/MMP-9 expressions via $\alpha$ v $\beta$ 3 Integrin/FAK/ERK and NF- $\kappa$ B signaling pathway in human lung adenocarcinoma A549 cells	Shih et al. (2010)
$\alpha$ -Mangostin suppresses TPA-Mediated MMP-2 and MMP-9 expressions through the ERK signaling pathway in MCF-7 human breast adenocarcinoma cells	Lee et al. (2010)
$\alpha$ -Mangostin has cytotoxic properties against head and neck squamous cell carcinoma (HNSCC) cell lines	Kaomongkolgit et al. (2011)
$\alpha$ -Mangostin has potential cytotoxic effect against human melanoma SK-MEL-28 cell line	Wang et al. (2011)
$\alpha$ -Mangostin Inhibits the proliferation of colon cancer cells via $\beta$ catenin gene regulation in Wnt/cGMP signaling pathway	(Yoo et al., 2011)
$\alpha$ -Mangostin reduces tumor growth and lymph node metastasis in an immunocompetent xenograft model of metastatic mammary cancer carrying a p53 mutation	Shibata et al. (2011)
$\alpha$ -Mangostin induced apoptotic cell death against canine osteosarcoma D-17 cells	Krajarng et al. (2012)
$\alpha$ -Mangostin showed potent effects against HCT 116 colorectal carcinoma in an <i>in vitro</i> and <i>in vivo</i>	Aisha et al. (2012)

hydroxyl groups. The antiproliferative effect of  $\alpha$ -mangostin was attributable to cell-cycle arrest by affecting the cyclins, cdc2 and p27 expression.

A study conducted by Suksamrarn et al. (2006) revealed that  $\alpha$ -mangostin exerted potent effect on breast cancer (BC-1) cells at a lower  $IC_{50}$  value (0.92  $\mu$ g/mL) compared to that of the standard drug ellipticine ( $IC_{50}$  = 1.46  $\mu$ g/mL). The compound also exerted cytotoxic effects against epidermoid carcinoma of the mouth (KB) cells ( $IC_{50}$  = 2.08  $\mu$ g/mL).

Nakagawa et al., 2007 evaluated  $\alpha$ -mangostin for *in vitro* cytotoxicity against DLD-1 human colon cancer cells. They found that treatment with 20  $\mu$ M of  $\alpha$ -mangostin reduced the number of viable cells consistently. As implied by morphological findings, the cytotoxic effect of 20  $\mu$ M  $\alpha$ -mangostin was discovered to be largely due to apoptosis. Although no signs of activation of any of the caspases tested were shown through Western blotting, the results of an apoptosis inhibition assay using caspase inhibitors and the examination of caspase activity, the release of endonuclease-G from mitochondria with the decreased mitochondrial membrane potential were shown. In the early phase, there was an increase in the levels of phospho-Erk1/2 until 1 h following the beginning of treatment; the levels subsequently decreased and then increased again in the late phase. However, the level of phospho-Akt showed a sharp decline with the process of apoptosis following 6 h of treatment. One interesting finding is that the level

of microRNA-143, which negatively regulates Erk5 at translation, increased gradually until 24 h after the treatment. The synergistic growth suppression in DLD-1 cells was also examined by treating the cells with a combination of  $\alpha$ -mangostin and 5-FU, a chemotherapeutic agent that is deemed as one of the most effective against colorectal adenocarcinoma. At 2.5  $\mu$ M each, the co-treatment with  $\alpha$ -mangostin and 5-FU enhanced growth inhibition as opposed to solely treating the cells with 5  $\mu$ M of  $\alpha$ -mangostin or 5  $\mu$ M 5-FU individually. These findings show the distinctive  $\alpha$ -mangostin-induced apoptosis mechanisms and its action as an effective chemosensitizer. The researchers found that treatment with 20  $\mu$ M  $\alpha$ -mangostin reduced the number of viable cells.

The antimetastatic effects of  $\alpha$ -mangostin against human prostate carcinoma cell line PC-3 was found in a study by Hung et al. (2009). In addition, treatment with  $\alpha$ -mangostin could decrease the expressions of the following enzymes in a concentration-dependent manner: matrix metalloproteinase-2 (MMP-2), matrix metalloproteinase-9 (MMP-9) and urokinase-plasminogen activator (u-PA).  $\alpha$ -Mangostin also demonstrated an inhibitory effect against the phosphorylation of c-Jun N-terminal kinase 1 and 2 (JNK1/2) as well as inhibited the activation of nuclear factor kappa B (NF- $\kappa$ B), c-Fos, and c-Jun. Furthermore, the treatment with JNK-specific inhibitor (SP600125) could reduce MMP-2, MMP-9 and u-PA expression in PC-3 cells. These results demonstrated the ability

of  $\alpha$ -mangostin to mediate PC-3 cells metastasis through the reduction of MMP-2, MMP-9 and u-PA expression, which is done by suppressing the JNK1/2 signaling pathway and inhibiting NF- $\kappa$ B and AP-1 binding activity.

Lee et al. (2010) discovered the effectiveness of  $\alpha$ -mangostin as an antimetastatic agent against the expressions of 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9) in human breast adenocarcinoma cells, MCF-7. Moreover,  $\alpha$ -mangostin inhibited the activation of extracellular signal-regulated kinase 1 and 2 (ERK1/2) that takes place in the down-regulation of TPA-induced enzyme activities, protein, and MMP-2 and MMP-9 messenger RNA levels, as well as TPA-induced degradation of inhibitor of kappaB $\alpha$  (I $\kappa$ B $\alpha$ ) and the nuclear levels of nuclear factor kappa B (NF- $\kappa$ B), c-Fos, and c-Jun. In addition,  $\alpha$ -mangostin treatment also resulted in a dose-dependent inhibition of the binding abilities of NF- $\kappa$ B and activator protein-1 (AP-1). Furthermore, MCF-7 cells treated with the specific inhibitor for ERK (U0126) could inhibit TPA-induced MMP-2 and MMP-9 expressions as well as cell invasion and migration. Results revealed the effectiveness of  $\alpha$ -mangostin as a novel and effective antimetastatic agent that acts through the down-regulation of MMP-2 and MMP-9 gene expressions.

Shih et al. (2010) investigated the anti-metastatic effect possessed by  $\alpha$ -mangostin that is exerted on phorbol 12-myristate 13-acetate (PMA)-induced matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9) expressions in A549 human lung adenocarcinoma cells.  $\alpha$ -Mangostin was found to inhibit PMA-induced adhesion, invasion and migration. Moreover,  $\alpha$ -mangostin could inhibit  $\alpha$ v $\beta$ 3 integrin, focal adhesion kinase (FAK) and extracellular signal-regulated kinase1/2 (ERK1/2) activation involved in the down-regulation of the PMA-induced enzyme activities, protein and messenger RNA levels of MMP-2 and MMP-9.  $\alpha$ -Mangostin also strongly inhibited the degradation of inhibitor of kappaB $\alpha$  (I $\kappa$ B $\alpha$ ) and the nuclear levels of nuclear factor kappa B (NF- $\kappa$ B) induced by PMA. It was also observed that  $\alpha$ -mangostin treatment resulted in a dose-dependent inhibition on the binding abilities of NF- $\kappa$ B. The effect of  $\alpha$ -mangostin is further potentiated in the reduction of FAK or ERK1/2 phosphorylation by FAK small interfering RNA (FAK siRNA). Finally, in a concomitant manner, MMP-2 and MMP-9 expressions were significantly down-regulated through the transient transfection of ERK siRNA, with considerable inhibition of cell invasion and migration.

Kaomongkolgit et al. (2011) examined the apoptotic effect exerted by  $\alpha$ -mangostin in the human head and neck squamous carcinoma cells (HNSCC) HN-22, HN-30 and HN-31. The results showed that  $\alpha$ -mangostin had exceptional apoptotic effects on HNSCC cell lines, which induced the down-regulation of bcl-2, while on the other hand caused an up-regulation of bax and p53 in HN-22, HN-30 and HN-31.

In a study by Wang et al. (2011), the cytotoxic effect of xanthone compounds ( $\alpha$ -mangostin,  $\gamma$ -mangostin, and 8-deoxygartanin) obtained from the pericarp of mangosteen was examined using the human melanoma SK-MEL-28 cell line. All of the tested compounds were found to induce apoptosis; especially  $\alpha$ -mangostin which induced 59.6% early apoptosis at 7.5  $\mu$ g/mL, compared to merely 1.7% in untreated cells. This apoptotic effect was due to caspase activation and mitochondrial membrane pathway disruption as shown by a

25-fold increase in caspase-3 activity and 9-fold decrease in mitochondrial membrane potential when compared to untreated cells.

Yoo et al. (2011) found that  $\alpha$ -mangostin has a potential inhibitory effect against the Wnt/b-catenin signaling pathway.  $\alpha$ -mangostin inhibited TCF/ $\beta$ -catenin transcriptional activity and  $\beta$ -catenin protein expression in colon cancer cells. However, instead of being dependent on  $\beta$ -catenin phosphorylation and degradation, the inhibition  $\beta$ -catenin resulted from its gene regulation, as indicated by increased cGMP and cGMP-dependent kinase levels.

(Shibata et al., 2011) discovered the effect of  $\alpha$ -mangostin in reducing tumor growth and lymph node metastasis. The study was conducted using an immunocompetent xenograft model of mouse metastatic mammary cancer which carried a p53 mutation that induces a metastatic spectrum similar to the one observed in human breast cancers. Prior to treatment, mammary tumors were induced by inoculating BALB/c mice syngeneic with metastatic BJMC3879luc2 cells. Treatment with  $\alpha$ -mangostin was performed at 0, 10 and 20 mg/kg/day by means of mini-osmotic pumps and tumors were then histopathologically examined. Furthermore, *in vitro* studies were conducted to investigate the antitumor mechanisms of  $\alpha$ -mangostin. The results showed that besides having a significantly higher *in vivo* survival rates compared to controls, the 20 mg/kg/day  $\alpha$ -mangostin group also showed suppression of tumor volume and the multiplicity of lymph node metastases. Mammary tumors of mice that were given 20 mg/kg/day demonstrated a significant increase in apoptotic levels due to increased active caspase-3 and -9 expression. It was observed that this particular dose level also produced other considerable effects such as decreased micro vessel density and lesser numbers of dilated lymphatic vessels with intraluminal tumor cells in mammary carcinoma tissues. Mitochondria-mediated apoptosis, G1-phase arrest and S-phase suppression in the cell cycle were induced by  $\alpha$ -mangostin *in vitro*. Considering the vital role of the activation by Akt phosphorylation in various oncogenic processes such as cell proliferation, anti-apoptotic cell death, angiogenesis and metastasis, *in vitro* and *in vivo* investigations of the alterations in Akt phosphorylation induced by  $\alpha$ -mangostin treatment were also conducted. Based on quantitative analysis and immunochemistry,  $\alpha$ -mangostin was shown to significantly decrease phospho-Akt-threonine 308 (Thr308) levels in mammary carcinoma cell cultures and mammary carcinoma tissues *in vitro*, whereas this is not the case for serine 473 (Ser473).

(Krajarnng et al., 2012) examined the antiproliferative effect of  $\alpha$ -mangostin in D-17 canine osteosarcoma cells. According to the results, antiproliferation induced by  $\alpha$ -mangostin showed an IC<sub>50</sub> value of 15  $\mu$ g/ml. Nuclear condensation and fragmentation, normally observed in apoptosis, were also induced by  $\alpha$ -mangostin, as revealed through Hoechst 33,342 nuclear staining and nucleosomal DNA-gel electrophoresis.  $\alpha$ -Mangostin was also able to induce sub-G1 peak as demonstrated by cell-cycle analysis, as well as membrane flipping of the phosphatidylserine and the loss of mitochondrial membrane potential in D-17 cells.

The anti-colon cancer effects (including cytotoxicity, apoptosis, anti-tumorigenicity as well as effects on cell signaling pathways) of 81%  $\alpha$ -mangostin and 16%  $\gamma$ -mangostin xanthones extract on HCT 116 human colorectal carcinoma cells were examined by (Aisha et al., 2012). Investigation of the

**Table 3** Anti-inflammatory, antiallergy and analgesic properties of  $\alpha$ -mangostin.

Effect	Reference
CNS depression (ptosis, sedation, decreased motor activity, potentiation of pentobarbital sleeping time, ether anesthesia) in mice and rats	Shankaranarayan et al. (1979)
Significant antiulcer effect in rats	Shankaranarayan et al. (1979)
Prohibition of systemic anaphylaxis, immunocytoadherence in guinea pigs and rats, and inhibition of the primary and secondary responses of adjuvant-induced arthritis in rats	Gopalakrishnan et al. (1980)
Histaminergic and a serotonergic receptor blocking agent	Chairungrilerd et al. (1996)
$\alpha$ -Mangostin suppressed histamine-induced contractions in rabbit thoracic aorta and guinea-pig trachea in a dose of dependent manner.	Chairungrilerd et al. (1996)
Inhibition of 12-human lipoxygenase (12-LOX)	Deschamps et al. (2007)
$\alpha$ -Mangostin suppressed the degranulation in Ag-mediated activation of IgE receptors in rat basophilic leukemia RBL-2H3 cells through SYK/PLC $\gamma$ s/PKC pathway	Itoh et al. (2008)
Anti-inflammatory activity by inhibition of inducible NO synthase and cytotoxicity to mouse leukemic monocyte macrophage cell line (RAW 264.7 cells)	Chen et al. (2008)
Analgesic and antinociceptive activity	Cui et al. (2010)
$\alpha$ -Mangostin inhibits allergic mediators in bone marrow-derived mast cell	Chae et al. (2012)

*in vivo* anti-colon cancer activity was also conducted on subcutaneous tumors formed in nude mice. The xanthenes extract demonstrated strong cytotoxicity through induction of the mitochondrial apoptosis pathway, with a median inhibitory concentration of  $6.5 \pm 1.0$   $\mu$ g/ml. In addition, the extract was found to inhibit cell migration, invasion and clonogenicity, which are three main steps in tumor metastasis. MAPK/ERK, c-Myc/Max, and p53 cell signaling pathways were also up-regulated. The xanthenes extract also inhibited the growth of subcutaneous tumor of HCT 116 colorectal carcinoma cells significantly when fed to the nude mice. In summary, all of the above results indicate that  $\alpha$ -mangostin would be a suitable candidate for preventive and therapeutic applications in cancer treatment.

### 3.3. 3Anti-inflammatory, anti-allergy analgesic properties

In Table 3, the anti-inflammatory and anti-allergy properties of  $\alpha$ -mangostin that have been studied are summarized.

(Shankaranarayan et al., 1979) studied the diverse pharmacological effects of  $\alpha$ -mangostin and its derivatives [namely 3-O-methyl mangostin, 3,6-di-O-methyl mangostin, 1-isomangostin (IM), mangostin triacetate (MT), mangostin 3,6-di-O-(tetra acetyl) glucoside (MTG) and mangostin-6,6-di-O-glucoside (MOG)] in experimental animals.  $\alpha$ -mangostin was found to produce CNS depression in mice and rats; characteristics of this depression include sedation, ptosis, decreased motor activity, potentiation of pentobarbital sleeping time and ether anesthesia. Moreover, based on the results of carrageenan-induced hind paw edema, cotton pellet implantation and granuloma pouch techniques,  $\alpha$ -mangostin produced prominent anti-inflammatory activity in rats, via both intraperitoneal and oral routes. In fact, this anti-inflammatory activity was present in bilaterally adrenalectomized rats as well. No mast cell membrane stabilizing effect was produced by the compound, and it did not prevent the degranulation effects of polymyxin B, diazoxide and Triton X-100 on rat peritoneal mast cells *in vitro*. The prothrombin time of albino rats was also not altered. Finally, administration of  $\alpha$ -mangostin in rats revealed considerable antiulcer activity of the compound.

The effect of  $\alpha$ -mangostin in prohibiting systemic anaphylaxis and immunocytoadherence in guinea pigs and rats was demonstrated in a study by (Gopalakrishnan et al., 1980). The study also found that this compound, isolated from the rinds of the mangosteen, could also inhibit primary and secondary responses of adjuvant-induced arthritis in rats.

(Chairungrilerd et al., 1996) showed the ability of the methanolic extract of mangosteen-fruit pericarp to inhibit histamine- and serotonin-induced contractions of isolated rabbit thoracic aorta. The authors suggested that  $\alpha$ -mangostin is a histaminergic receptor blocking agent, whereas  $\gamma$ -mangostin is a serotonergic receptor blocking agent. The same research group evaluated the effect of  $\alpha$ -mangostin on the contractions of rabbit thoracic aorta and guinea-pig trachea induced by histamine. Results revealed that either with or without cimetidine (the H<sub>2</sub>-histamine receptor antagonist),  $\alpha$ -mangostin could dose-dependently suppress contractions induced by histamine. Contractions that are mediated by the histamine H<sub>1</sub> receptor were also prohibited. In addition, a specific histamine H<sub>1</sub> receptor antagonist binding to rat aortic smooth muscle cells, [3H] mepyramine, was also suppressed competitively by  $\alpha$ -mangostin.

(Deschamps et al., 2007) showed the ability of  $\alpha$ -mangostin to inhibit 12-human lipoxygenase (12-LOX) at an IC<sub>50</sub> value of 0.58  $\mu$ M. The intracellular signal transductions activated by the IgE receptor caused the inflammatory signal mediators such as histamine to be released, which is a primary event in a number of allergic responses. This information became the basis for (Itoh et al., 2008) to demonstrate that the degranulation in Ag-mediated activation of IgE receptors was suppressed by  $\alpha$ -mangostin in rat basophilic leukemia RBL-2H3 cells. The authors suggested that suppression of the SYK/PLC $\gamma$ s/PKC pathway played the main role in the inhibitory mechanism of degranulation by  $\alpha$ -mangostin.

In addition, Chen et al. (2008) demonstrated the significant effect of  $\alpha$ -mangostin in the inhibition of lipopolysaccharide-stimulated NO<sup>-</sup> production and cytotoxicity in mouse leukemic monocyte macrophage cell line (RAW 264.7 cells). At 3–25  $\mu$ M  $\alpha$ -mangostin, the amount of

**Table 4** Antibacterial, antifungal and antiviral properties of  $\alpha$ -mangostin.

Effect	Reference
$\alpha$ -Mangostin and four of its derivatives have antibacterial effect against <i>S. aureus</i> , <i>P. aeruginosa</i> , <i>Salmonella typhimurium</i> and <i>Bacillus subtilis</i> , <i>Klebsiella</i> sp. and <i>Escherichia coli</i>	Sundaram et al. (1983)
$\alpha$ -Mangostin and four of its derivatives has antibacterial effect against <i>Epidermophyton floccosum</i> , <i>Alternaria solani</i> , <i>Mucor</i> sp., <i>Rhizopus</i> sp., <i>Cunninghamella echinulata</i> , <i>Trichophyton mentagrophytes</i> , <i>Microsporium canis</i> , <i>Aspergillus niger</i> , <i>Aspergillus flavus</i> , <i>Penicillium</i> sp., <i>Fusarium roseum</i> and <i>Curvularia lunata</i>	Sundaram et al. (1983)
$\alpha$ -Mangostin showed high efficacy against the growth of methicillin-resistant <i>S. aureus</i> (MRSA)	Iinuma et al. (1996))
$\alpha$ -Mangostins inhibits HIV-1 protease	Chen et al. (1996)
$\alpha$ -Mangostin-derivatives have antifungal properties against three phytopathogenic fungi ( <i>Fusarium oxysporum vasinfectum</i> , <i>Alternaria tenuis</i> and <i>Dreschlera oryzae</i> )	Gopalakrishnan et al. (1997)
Inhibiting role in the replication cycle of HIV virus	Vlietinck et al. (1998)
Potent inhibitory effect against <i>Mycobacterium tuberculosis</i>	Suksamrarn et al. (2003)
$\alpha$ -Mangostin have inhibitory activity against vancomycin resistant <i>Enterococci</i> (VRE) and Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)	Sakagami et al. (2005)
Antibacterial activity against Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)	Chin and Kinghorn (2008))
$\alpha$ -Mangostin has effective antifungal properties against <i>Candida albicans</i>	Kaomongkolgit et al. (2009)
$\alpha$ -Mangostin metabolized by two fungi, <i>Colletotrichum gloeosporioides</i> (EYL131) and <i>Neosartorya spathulata</i> (EYR042)	Arunrattiyakorn et al. (2011)

NO<sup>-</sup> production was measured continuously and the IC<sub>50</sub> value was 12.4. The production of PGE<sub>2</sub> in lipopolysaccharide-activated RAW 264.7 cells was also significantly reduced by  $\alpha$ -mangostin, with IC<sub>50</sub> value of 11.08  $\mu$ M. To probe the effect of this xanthone, the induction of inducible nitric oxide synthase as well as COX enzyme expressions was measured.  $\alpha$ -Mangostin concentration was found to reduce iNOS induction in a dependent manner. 1  $\mu$ g/mL lipopolysaccharide was used to activate the RAW 264.7 cells for 12 h and iNOS activity in the activated RAW 264.7 macrophages was observed to be weakly inhibited following a 24-h treatment with 5  $\mu$ g/mL  $\alpha$ -mangostin. Carrageenan-induced paw edema in mice was used to evaluate the anti-inflammatory effect of  $\alpha$ -mangostin. Both  $\alpha$ -mangostin and sulindac (reference compound) potently inhibited paw edema. However,  $\alpha$ -mangostin acted more rapidly, showing potent inhibition at 3 h of treatment compared to 5 h of treatment with sulindac.

Cui et al. (2010) showed that 25 mg/kg intragastric (i.g.)  $\alpha$ -mangostin exhibited analgesic effects in the hot-plate. Moreover, the results demonstrate the potent peripheral and central antinociceptive effects exerted by  $\alpha$ -mangostin in mice.

Chae et al. (2012) investigated the effect of  $\alpha$ -mangostin on the bone marrow-derived mast cell (BMMC) mediated allergy mechanism induced by phorbol 12-myristate 13-acetate (PMA) plus A23187.  $\alpha$ -Mangostin was shown to inhibit the production of Interleukin (IL)-6, prostaglandin D2 (PGD2) and leukotriene C4 (LTC4) as well as degranulation in BMMC induced by PMA plus A23187. Another effect of  $\alpha$ -mangostin that was observed was the repression of cyclooxygenase (COX)-2 expression. These results reflect the potential usefulness of  $\alpha$ -mangostin in alleviating allergic inflammatory responses mediated by the mast cell.

The above data indicate that the anti-inflammatory, antiallergic and analgesic properties possessed by  $\alpha$ -mangostin isolated from the mangosteen fruit make it a novel and promising compound.

### 3.4. Antimicrobial properties

Table 4 shows a number of studies which have demonstrated the antibacterial, antifungal and antiviral properties of  $\alpha$ -mangostin.

A study by Sundaram et al., 1983 on the antibacterial and antifungal properties of  $\alpha$ -mangostin as well as four of its derivatives found that the following bacteria were highly susceptible to xanthenes: *S. aureus*, *P. aeruginosa*, *Salmonella typhimurium* and *Bacillus subtilis*. *Klebsiella* sp., *Proteus* sp., *Klebsiella* sp. and *Escherichia coli* showed moderate susceptibility. Fungi that were found to be highly susceptible to xanthenes include *Epidermophyton floccosum*, *Alternaria solani*, *Mucor* sp., *Rhizopus* sp. and *Cunninghamella echinulata*, whereas those found to be moderately susceptible were *Trichophyton mentagrophytes*, *Microsporium canis*, *Aspergillus niger*, *Aspergillus flavus*, *Penicillium* sp., *Fusarium roseum* and *Curvularia lunata*. The minimum inhibitory concentration, which is the lowest concentration of an antimicrobial required to inhibit the visible growth of a microorganism following overnight incubation, of  $\alpha$ -mangostin was between 12.5 and 50  $\mu$ g/mL and between 1 and 5  $\mu$ g/mL for bacteria and fungi, respectively. The following is the order of the antibacterial and antifungal efficiency:  $\alpha$ -mangostin > isomangostin > 3-O-methyl mangostin > 3, 6-di-O-methyl mangostin. On the other hand, mangostin triacetate did not demonstrate any activity.

(Iinuma et al., 1996) evaluated a few xanthenes isolated from the pericarp of mangosteen fruit for their inhibitory effect against methicillin-resistant *S. aureus* (MRSA) growth. Findings showed the high efficacy of  $\alpha$ -mangostin, with MIC values ranging between 1.57 and 12.5  $\mu$ g/mL.

(Chen et al., 1996; Iinuma et al., 1996) demonstrated the effective inhibition of HIV-1 protease by the ethanolic extract. Using Pepstatin A as a positive control at an IC<sub>50</sub> value of 76  $\pm$  5.5 nM,  $\alpha$ -mangostin displayed an IC<sub>50</sub> value of 5.12  $\pm$  0.41  $\mu$ M.



A study by Gopalakrishnan et al., 1997 showed high inhibitory activities of  $\alpha$ -mangostin-derivatives against three phytopathogenic fungi, namely *Fusarium oxysporum vasinfectum*, *Alternaria tenuis* and *Drechslera oryzae*, by using 1, 10, 100 and 1000 ppm in the culture medium. Modification in the bioactivities of the compounds was observed following substitution in A and C rings.

Vlietinck et al., 1998 discovered the role of  $\alpha$ -mangostin as a non-competitive inhibitor of HIV-1 protease by inhibiting the HIV virus replication cycle.

Suksamrarn et al., 2003 conducted a study on prenylated xanthenes obtained from the pericarp of the mangosteen fruit to examine the anti-tuberculosis potential. Results showed that at an MIC value of 6.25  $\mu\text{g}/\text{mL}$ ,  $\alpha$ -mangostin demonstrated potent inhibitory effect against *Mycobacterium tuberculosis*.

(Sakagami et al., 2005) discovered the inhibitory activity of  $\alpha$ -mangostin against *vancomycin resistant Enterococci* (VRE) with an MIC value of 6.25 as well as against *Methicillin-resistant Staphylococcus aureus* (MRSA) with an MIC value of 12.5  $\mu\text{g}/\text{mL}$ .

In addition, (Chin and Kinghorn, 2008) demonstrated the high efficacy of  $\alpha$ -mangostin in terms of its antibacterial activity against *Methicillin-resistant Staphylococcus aureus* (MRSA) with MIC value of 1.95  $\mu\text{g}/\text{mL}$  and MBC value of 3.91  $\mu\text{g}/\text{mL}$ .

The activity of  $\alpha$ -mangostin against the most important microorganism implicated in oral candidiasis, namely *Candida albican*, in comparison with Clotrimazole and Nystatin was examined by Kaomongkolgit et al., 2009.  $\alpha$ -Mangostin showed to be effective at a minimum inhibitory concentration of 1,000  $\mu\text{g}/\text{ml}$  and minimum fungicidal concentration (MFC) of 2,000  $\mu\text{g}/\text{ml}$ , exhibiting higher efficiency compared to Clotrimazole and Nystatin. In determining its cytotoxicity, it was revealed that at 4,000  $\mu\text{g}/\text{ml}$ ,  $\alpha$ -mangostin was not toxic to human gingival fibroblast for 480 min. Hence,  $\alpha$ -mangostin can be a promising agent in treating oral candidiasis due its low toxicity and strong antifungal activity.

(Arunrattiyakorn et al., 2011) studied the microbial metabolism of  $\alpha$ -mangostin isolated from *G. mangostana* L on fungus and found that two fungi metabolized  $\alpha$ -mangostin; they are *Colletotrichum gloeosporioides* (EYL131) and *Neosartorya spathulata* (EYR042). The following four metabolites were produced as a result of incubating  $\alpha$ -mangostin with *C. gloeosporioides* (EYL131): mangostin 3-sulfate (2), mangostanin 6-sulfate (3), 17, 18-dihydroxymangostanin 6-sulfate (4) and isomangostanin 3-sulfate (5). Spectroscopic data analysis was used to elucidate structures of the isolated compounds.

### 3.5. Anti parasitic and anthelmintic properties

As shown in Table 5, Taylor and Mangostin, 2006 found that  $\alpha$ -mangostin showed moderate *in vitro* antiplasmodial activity against *Plasmodium falciparum* with an  $\text{IC}_{50}$  value of 17  $\mu\text{M}$ .

Bullangpoti et al., 2007 evaluated the extracts of mangosteen pericarp (*Garcinia mangostana* L.) for their efficiency as an alternative control of Brown Plant Hopper (BPH) Thailand strain. Toxicity was determined by topical spraying at different nymphal and adult BPH stages. Compared to the other solvents (hexane, acetone and dichloromethane), ethanol extract of the mangosteen pericarp exhibited the best control of BPH with  $\text{LC}_{50}$  value of 4.5% w/v ( $r^2 = 0.95$ ) and 3rd instar

BPH nymphs. The  $\text{LC}_{50}$  value of the active compound,  $\alpha$ -mangostin, was 5.44% w/v ( $r^2 = 0.88$ ). Compared to Imidacloprid ( $\text{LC}_{50}$  of 0.0042% w/v ( $r^2 = 0.99$ )), this extract had less toxicity. In determining toxicity to non-target organisms, it was found that the extract demonstrated toxicity to the following: guppies ( $\text{LC}_{50} = 2.53$  ppm for females and 4.27 ppm for males;  $r^2 = 0.97$  and 0.97, respectively), bees ( $\text{LC}_{50} = 4.38\%$  w/v,  $r^2 = 0.95$ ) and mice (no oral acute toxicity and dermal inflammation, only eye irritation which occurred in 1 day and returned to normal within 3 days). *in vitro* detoxification enzyme activities from BPH, namely carboxylesterase, acetylcholinesterase and glutathione-S-transferase, were observed following a 24-h exposure. Stronger activity was exhibited by carboxylesterase compared to other enzymes. In each generation, there was an increase of toxicity in terms of  $\text{LC}_{50}$  values for treatments with both the extract and imidacloprid. Following sequential spraying, each generation showed LC values of 4.22–6.67. The ethanol extract was kept at different temperatures (4 °C, room temperature and 55 °C) for 3 months and it was found that at 55°, the quantity of  $\alpha$ -mangostin and the BPH control efficiency was lower. The above results indicate that besides causing minimal environmental problems, the mangosteen pericarp extract possesses high efficiency and causes less resistance in BPH, making it a potential alternative insecticide for BPH control.

A study by Larson et al. (2010) to investigate the larvicidal activity of  $\alpha$ -mangostin against third instar larvae of six mosquito species found that the values of median lethal concentration range from 0.84 to 2.90 ppm. Subsequent to putting  $\alpha$ -mangostin under semi field conditions to examine its residual larvicidal activity,  $\alpha$ -mangostin was found to be photolytic with a half-life of 53 min in water under full exposure to sunlight. Based on the results,  $\alpha$ -mangostin significantly elevated P450 and glutathione S-transferase activities in larvae, but on the contrary, esterase activity was suppressed. Following a study on its toxicity against young rats,  $\alpha$ -mangostin did not demonstrate any adverse effects even at a high dosage of 80 mg/kg.

The activities of  $\alpha$ -mangostin and mangostin diacetate, the synthetic derivative, were studied by Keiser et al. (2012). Lack of activity was observed for both  $\alpha$ -mangostin and mangostin diacetate against the following nematodes: *Heligmosomoides polygyrus* (third-stage larvae (L3)), *Ancylostoma ceylanicum* L3, and *Trichuris muris* adults. A low activity level was observed against *A. ceylanicum* adults ( $\text{IC}_{50}$ s of 91  $\mu\text{g}/\text{ml}$ ) *in vitro*, while promising activities were demonstrated by  $\alpha$ -mangostin against trematodes: *Schistosoma mansoni*, *Echinostoma caproni*, and *Fasciola hepatica in vitro*, with  $\text{IC}_{50}$  value of 2.9–15.6  $\mu\text{g}/\text{mL}$ . Worm burden reductions, ranging from 0% to 38% (against *S. mansoni*) and 11–54% (against *E. caproni*) were achieved by single oral doses of the drugs (400 mg/kg and 800 mg/kg) *in vivo*.

### 3.6. Anti-obesity properties

Table 5 displays the *in vitro* cytotoxicity of  $\alpha$ -mangostin against 3T3-L1 cells and its inhibitory effect on fatty acid synthase (FAS, EC 2.3.1.85) as discovered by Quan et al. (2012)). Based on the research,  $\alpha$ -mangostin with an  $\text{IC}_{50}$  value of 20  $\mu\text{M}$  had uncomplicated cytotoxicity in apoptotic events such as increase of cell membrane permeability, mitochondrial

**Table 5** Anti-parasitic, anthelmintic and anti-obesity properties of  $\alpha$ -mangostin.

Effect	Reference
Moderate activity in an <i>in vitro</i> anti-plasmodial against <i>Plasmodium falciparum</i>	Taylor and Mangostin (2006)
$\alpha$ -Mangostin can be an alternative insecticide for the control of Brown Plant Hopper (BPH)	Bullangpoti et al. (2007)
$\alpha$ -Mangostin has a larvicidal effect on botanic mosquito sterol carrier protein-2 inhibitor	Larson et al. (2010)
$\alpha$ -Mangostin has promising activities against the trematodes <i>Schistosoma mansoni</i> , <i>Echinostoma caproni</i> , and <i>Fasciola hepatica in vitro</i> (IC <sub>50</sub> of 2.9–15.6 $\mu$ g/mL)	Keiser et al. (2012)
$\alpha$ -Mangostin has <i>in vitro</i> cytotoxicity against 3T3-L1 cells as well as inhibiting fatty acid synthase (FAS, EC 2.3.1.85)	Quan et al. (2012)

**Table 6** Pharmacokinetic studies of  $\alpha$ -mangostin.

Assay	Reference
A HPLC/MS assay has been established for the determination of $\alpha$ -mangostin in rat plasma after oral and intravenous (i.v) injection. Non-compartmental analysis was performed	Li et al. (2010)
An LC-MS/MS assay has been established for the determination of $\alpha$ -mangostin in rat plasma after intravenous (i.v) and oral administration. Both non-compartmental and compartmental analyses were performed	Li et al. (2011)

membrane potential ( $\Delta\psi_m$ ) loss and nuclear chromatin condensation. A decline of FAS activity in cells also occurred along with this cytotoxicity, which could be rescued by 50  $\mu$ M or 100  $\mu$ M exogenous palmitic acids. This suggested that  $\alpha$ -mangostin induced the apoptosis of 3T3-L1 preadipocytes by inhibiting FAS.  $\alpha$ -Mangostin also showed its ability to suppress intracellular lipid accumulation in differentiating adipocytes and stimulated lipolysis in mature adipocytes; this was associated to its inhibition of FAS as well. It was also found that the susceptibility of 3T3-L1 preadipocytes toward the cytotoxic effect of  $\alpha$ -mangostin is higher compared to that of the mature adipocytes. Further studies demonstrated that inhibition of FAS by  $\alpha$ -mangostin was probably due to stronger action on the ketoacyl synthase domain and weaker action on the acetyl/malonyl transferase domain. These findings suggested the usefulness of  $\alpha$ -mangostin in treating or preventing obesity.

### 3.7. Treatment of Alzheimer's disease (AD)

Wang et al. (2012) discovered that  $\alpha$ -mangostin attenuated the neurotoxicity induced by A $\beta$ -(1-40) or A $\beta$ -(1-42) oligomers, with EC<sub>50</sub> values of 3.89 nM and 4.14 nM respectively, through decreased cell viability and impaired neurite outgrowth in primary rat cerebral cortical neurons in a concentration-dependent manner. The potential of  $\alpha$ -mangostin to bind to A $\beta$  and stabilize  $\alpha$ -helical conformation was demonstrated through molecular docking and dynamics simulations.

It was found that  $\alpha$ -mangostin could dissociate A $\beta$ -(1-40) and A $\beta$ -(1-42) oligomers directly via blotting with oligomer-specific antibodies. Furthermore, the ability of  $\alpha$ -mangostin to block the fibril formation and disturb the pre-formed fibrils was observed through ThioflavinT fluorescence assay and electron microscopy imaging. All in all, these results point out the capability of  $\alpha$ -mangostin to inhibit and dissociate the A $\beta$  aggregation, which could play a role in its effect of attenuating

A $\beta$  oligomers-induced neurotoxicity. This suggests the great potential of  $\alpha$ -mangostin to be a candidate for AD treatment.

### 3.8. Pharmacokinetics Studies

Table 6 shows that in order to determine  $\alpha$ -mangostin in rat plasma, HPLC-MS assay was established, with bergamottin as internal standard. The recovery percentage of  $\alpha$ -mangostin from the plasma samples was 93.19%. A linear calibration curve, over the range of 20–2000 ng/ml was observed. Total run time was 8 min, and the intra- and inter-assay variability was less than 9.32% and 9.87%, respectively.  $\alpha$ -Mangostin showed within +15% accuracies when determined at the concentrations of 70, 850 and 1800 ng/mL. Following oral and intravenous (i.v) injection, pharmacokinetic studies in rats were supported successfully using the rapid, simple and precise validated method. Non-compartmental and compartmental analyses were performed, where the two-compartment body model fits well with the (i.v) data. Non-compartmental analysis suggested a short half-life of 4 min and a low oral bioavailability of only 4.24% for  $\alpha$ -mangostin (Li et al., 2010). Subsequent to (i.v) administration,  $\alpha$ -mangostin exhibited biphasic disposition in rat plasma, which is subdivided into two phases: fast distribution and slow elimination. The half-life of the distribution phase was 3 min, and that of the terminal elimination phase 3.5 h, indicating a high tissue binding. However, for oral administration, the bioavailability was so low that it was not possible to obtain a full concentration–time profile (Li et al., 2011).

## 4. Conclusion

The quest of discovering various pharmacological properties and applications of  $\alpha$ -mangostin is an endeavor that continues to develop and progress rapidly. This is evident through the

numerous studies reviewed above as well as others that are continuously being reported. Nevertheless, the extensive clinical use of  $\alpha$ -mangostin to treat various human diseases is confronted with the pharmacokinetic constraints of this particular compound. Despite that, this predicament is addressed through an exceptional amount of work that is being conducted by means of unique delivery systems and chemical modifications. Another manner in which this work can be advantageous to the realm of  $\alpha$ -mangostin study is through generating patentable drug constructs that could influence major development and production of  $\alpha$ -mangostin as a drug by the prominent and affluent pharmaceutical companies around the world. The studies that are reviewed above illustrate the promising qualities and extensive potential preclinical application of  $\alpha$ -mangostin which are largely due to its diverse pharmacological effects on nearly all major organ systems in the animal models. These effects, accompanied by an equally enormous amount of molecular targets and mechanisms of action demonstrated in a large host of cell types both *in vitro* and *in vivo*, further substantiated the strong potential of the  $\alpha$ -mangostin. In addition, preliminary studies have suggested the safety of this natural compound for human administration, therefore making  $\alpha$ -mangostin a reliable agent that can be used in the prevention and treatment of a wide array of human pathological conditions, especially inflammatory-based processes or even cancer. In implying the powerful effect of  $\alpha$ -mangostin for treating patients, we can perhaps relate to a quote by Dr. Carl C. Pfeiffer, the author of *Pfeiffer's Law* who stated that "For every drug that benefits a patient, there is a natural substance that can achieve the same effect."

## 5. Conflict of interest

The authors declare that there are no conflicts of interest.

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