The metabolic and molecular mechanisms of α-mangostin in cardiometabolic disorders (Review)

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Abstract. α-mangostin is a xanthone predominantly encountered in *Garcinia mangostana*. Extensive research has been carried out concerning the effects of this compound on various diseases, including obesity, cancer and metabolic disorders. The present review suggests that α-mangostin exerts promising anti-obesity, hepatoprotective, antidiabetic, cardioprotective, antioxidant and anti-inflammatory effects on various pathways in cardiometabolic diseases. The anti-obesity effects of α-mangostin include the reduction of body weight and adipose tissue size, the increase in fatty acid oxidation, the activation of hepatic AMP-activated protein kinase and Sirtuin-1, and the reduction of peroxisome proliferator-activated receptor γ expression. Hepatoprotective effects have been revealed, due to reduced fibrosis through transforming growth factor-β 1 pathways, reduced apoptosis and steatosis through reduced sterol regulatory-element binding proteins expression. The antidiabetic effects include decreased fasting blood glucose levels, improved insulin sensitivity and the increased expression of GLUT transporters in various tissues. Cardioprotection is exhibited through the restoration of cardiac functions and structure, improved mitochondrial functions, the promotion of M2 macrophage populations, reduced endothelial and cardiomyocyte apoptosis and fibrosis, and reduced acid sphingomyelinase activity and ceramide depositions. The antioxidant effects of α-mangostin are mainly related to the modulation of antioxidant enzymes, the reduction of oxidative stress markers, the reduction of oxidative damage through a reduction in Sirtuin 3 expression mediated by phosphoinositide 3-kinase/protein kinase B/peroxisome proliferator-activated receptor-γ coactivator-1α signaling pathways, and to the increase in Nuclear factor-erythroid factor 2-related factor 2 and heme oxygenase-1 expression levels. The anti-inflammatory effects of α-mangostin include its modulation of nuclear factor-κB related pathways, the suppression of mitogen-activated protein kinase activation, increased macrophage polarization to M2, reduced inflammasome occurrence, increased Sirtuin 1 and 3 expression, the reduced expression of inducible nitric oxide synthase, the production of nitric oxide and prostaglandin E2, the reduced expression of Toll-like receptors and reduced proinflammatory cytokine levels. These effects demonstrate that α-mangostin may possess the properties required for a suitable candidate compound for the management of cardiometabolic diseases.

Contents

1. Introduction
2. Anti-obesity effects of α-mangostin
3. Antidiabetic effects of α-mangostin
4. Anti-steatotic and hepatoprotective effects of α-mangostin
5. Cardioprotective and anti-atherogenic effects of α-mangostin
6. Antioxidant effects of α-mangostin
7. Anti-inflammatory effects of α-mangostin
8. Toxicity and bioavailability of α-mangostin
9. Future perspectives
10. Conclusions

1. Introduction

Metabolic syndrome is a combination of symptoms, including abdominal obesity, atherogenic dyslipidemia, hypertension, insulin resistance characterized by hyperglycemia, proinflammatory state and prothrombotic state [National Cholesterol Education Programs Adult Treatment Panel III report (ATP III)] (1). The comorbidities associated with the metabolic syndrome include cardiovascular disease, type 2 diabetes and other diseases including polycystic ovary syndrome, fatty liver, asthma, cholesterol gallstones, sleep disturbances and several cancers (1-3).

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Abdominal obesity is characterized by a waist circumference of >102 cm in men and >88 cm in women (1). Obesity is often caused by excessive food intake and a lack of physical activity, resulting in an energy imbalance, where energy intake is greater than energy expenditure, leading to an elevated body mass index (BMI >30 kg/m^2) and increased body fat mass (4,5). It has been linked to increased proinflammatory states due to chronic adipose tissue inflammation, leading to the development of insulin resistance and type 2 diabetes (6). Atherogenic dyslipidemia is manifested by increased plasma triglyceride levels, a high concentration of plasma low-density lipoprotein (LDL)-cholesterol (LDL-C) and low level of high-density lipoprotein (HDL) cholesterol (HDL-C), increasing the risk of cardiovascular disease (1). Hypertension is caused by a high blood pressure where systolic blood pressure of is >130 mm Hg and diastolic >85 mm Hg (1). Insulin resistance occurs when fasting blood glucose level is ≥110 mg/dl (1). The World Health Organization criteria for metabolic syndrome is the presence of insulin resistance accompanied with any two of the other symptoms of metabolic syndrome including increased waist/hip ratio and increased urinary albumin excretion rate (7).

Currently, there are several pharmacological drugs available for obesity treatment, including orlistat (Xenical) and sibutramine; however, these drugs have several undesirable side effects including mood changes, and gastrointestinal or cardiovascular complications (8). Plant-derived natural compounds have been revealed to demonstrate positive effects on obesity, diabetes, renal and cardiovascular disease (9). Thus, natural products from plants have been suggested as a better alternative for treating obesity and cardiometabolic syndrome (10).

α-mangostin is a xanthone by chemical structure (Fig. 1), and one of the significant phytochemical constituents in the tropical fruit *Garcinia mangostana* (11-13). It has also been found in other *Garcinia* (*G.*) species, including *G. dulcis* (14), *G. staudtii* (15) *G. merguensis* (16) and *G. cowa* (17), and in the perennial tropical trees *Cratoxylum cochinchinense* (18), *Cratoxylum arborescens* (19), *Cratoxylum formosum* (20) and *Pentadesma butyracea* (21). In *G. mangostana*, α-mangostin is mainly found in the fruit pericarp (12,22) which has been traditionally used to treat several health conditions, including abdominal pain, diarrhea, dysentery, wound infections, suppuration, and chronic ulcers (23).

Previous reports have demonstrated that α-mangostin exerts numerous health-promoting effects including anti-obesity (24), antidiabetic (25), antioxidant (26), anti-inflammatory (27), antiallergic (28), anticancer (29), neuroprotective (30), hepatoprotective (31), cardioprotective (32), antimicrobial (33) and antifungal (34) properties. Although previous reviews have summarized the health properties of α-mangostin (30,35-40), limited information is available on its molecular mechanisms in cardiometabolic disease. Hence, the present review aimed to elucidate the potential molecular effects of α-mangostin on metabolic syndrome parameters, observed in biological models of cardiometabolic syndrome and other related models.

2. Anti-obesity effects of α-mangostin

The anti-obesity effects of α-mangostin and α-mangostin-rich materials have been extensively studied. Various doses of purified α-mangostin compound have been revealed to reduce body weight in animal models (mice and rats) even when treated with *G. mangostana* fruit pericarp/rind/peel or flesh (12,41-46).

Kim *et al* (25) suggested that the treatment of high fat-fed C57BL/6 mice with 50 mg/kg of α-mangostin per day reduced, their body weight, cholesterol levels, serum triglycerides, and increased adiponectin levels, also noting that the treatment reduced epididymal adipose tissue size and reduced the crown like structures in adipocytes. Choi *et al* (24) also stated that an α-mangostin dose of 50 mg/kg per day in C57BL/6 mice reduced body weight, total cholesterol (TC), LDL-C and free fatty acids in mice fed a high-fat diet. Furthermore, they found that α-mangostin increased the expression of hepatic peroxisome proliferator-activated receptor γ (PPARγ), sirtuin (SIRT) 1, AMP-activated protein kinase (AMPK) and retinoid-X-receptor alpha, suggesting that the anti-obesity and hepatoprotective effects of α-mangostin are mediated via the SIRT1-AMPK and PPARγ pathways in mice with obesity induced by a high fat diet. Li *et al* (42) treated aged mice with an α-mangostin dose of 25 and 50 mg/kg per day and observed a reduction in body weight, epididymal and inguinal white adipose tissue, serum concentrations of triglycerides, LDL-C and TC. The treatment increased phosphorylated (p-) protein kinase B (p-AKT) expression in epididymal white adipose tissue (42).

The hallmark of dyslipidemia in obesity includes increased triglycerides and free fatty acids, low HDL-C or slightly increased LDL-C (47). John *et al* (12) demonstrated that the administration of an α-mangostin dose of 168 mg/kg per day from *G. mangostana* rind to rats on a high fat/carbohydrate diet decreased their body weight gain and visceral fat accumulation accompanied by reduced adipocyte size and plasma triglycerides. In a monosodium glutamate, high-calorie diet-induced male Wistar rat model, Abuzaid *et al* (41) noted that the administration of 200 and 500 mg/kg *G. mangostana* extract per day, equivalent to a dose of 60 and 150 mg/kg α-mangostin per day, respectively, caused a reduction in body weight gain, which was associated with a reduction in fatty acid synthase activity in adipose tissue and serum. In the study by Mohamed *et al* (46), the treatment of Balb/c mice with high-fat non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) with 50 mg/kg α-mangostin per day also reduced body weight gain and free fatty acid levels.

Chae *et al* (45) examined the effect of the 50 and 200 mg/kg dose of *G. mangostana* extract per day, equivalent to a dose of ~12.5 mg/kg and 50 mg/kg α-mangostin per day, respectively, in C57BL/6 mice fed a high-fat diet. The treatment decreased body weight and visceral fat (epididymal, inguinal and mesenteric), although not retroperitoneal fat. The treatment also improved lipid metabolism by reducing triglycerides, LDL-C, TC at both concentrations. Protein expression analysis revealed that α-mangostin activated the AMPK and SIRT-1 pathways, aiding in body weight reduction. In the 200 mg/kg per day group, the PPARγ levels decreased, suggesting a reduction of lipogenesis in adipocyte differentiation and an increase in carnitine palmitoyl transferase 1a (CPT1a), which in turn promotes fatty oxidation (45). In the study by Tsai *et al* (43) rats fed a high

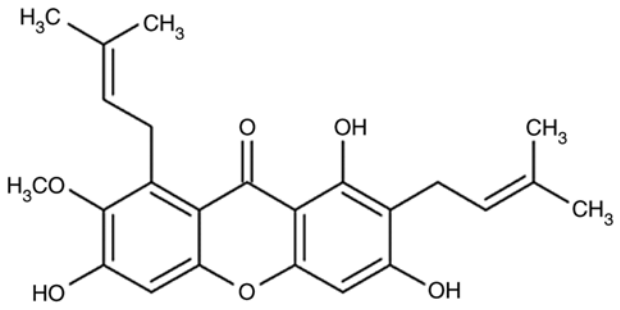

Figure 1. Chemical structure of α-mangostin.

fat-diet were treated with 25 mg/day of mangosteen pericarp extract for 11 weeks. A decrease in body weight gain, plasma free fatty acids and hepatic triglyceride accumulation was observed. In another study, Sprague-Dawley rats fed a high-fat diet were treated with dried *G. mangostana* flesh doses of 200, 400, 600 mg/kg per day and exhibited a reduced body weight, food intake, plasma cholesterol and TC levels (44). However, in that study, the amount of α-mangostin was not quantified (44).

In vitro studies using α-mangostin have demonstrated similar conclusions as *in vivo* studies. The treatment of breast cancer cell lines with α-mangostin (1-4 μM) led to the inhibition of fatty acid synthase (FAS) expression and activity (29). In another study, 3T3-L1 pre-adipocytes treated with α-mangostin exhibited a concentration-dependent reduction in intracellular fat accumulation up to 44.4% relative to methylisobutylxanthine, dexamethasone, insulin (MDI)-treated control cells at a 50 μM concentration. PPARγ expression and pre-adipocyte differentiation were suppressed by α-mangostin (48). Additionally, the use of α-mangostin resulted in leptin production increase (48) and exerted potent inhibitory effects against pancreatic lipase (49).

The treatment with *G. mangostana* pericarp, rich in α-mangostin, demonstrated similar effects across studies. John *et al* (12), Li *et al* (42) and Chae *et al* (45) observed reduced white adipose tissue deposition, TC, free fatty acids, triglyceride, and visceral fat accumulation. Li *et al* (42) and Chae *et al* (45) additionally observed reduced LDL-C with pericarp treatment. The treatment has also been previously reported to increase hepatic AMPK and SIRT1 (24) and reduce PPARγ expression (45). AMPK activity maintains cellular energy storage by activating catabolic pathways that generate ATP, primarily by increasing oxidative metabolism and mitochondrial biogenesis, while 'switching off' anabolic pathways that utilize ATP (50).

In principle, the reduction of body weight by α-mangostin is associated with a decrease in adipose tissue size and accumulation, decreased fatty acid synthase activity, decreased intracellular fat accumulation, increased adiponectin expression, increased fatty acid oxidation via an increased CPT1a expression, the increased activation of the SIRT1-AMPK, and reduced PPARγ pathways (Fig. 2 and Table I). This may suggest that the main methods of action in obesity reduction by α-mangostin occur through fatty acid metabolism and adipose tissue biology as the major depot for fatty acids, requiring further elucidation.

3. Antidiabetic effects of α-mangostin

Diabetes is characterized by insulin resistance and hyperglycemia, and is associated with hyperlipidemia. The main hallmarks of diabetes include insulin resistance and pancreatic β-cell dysfunctions (51). In animal studies, treating high fat-fed mice with a dose of 50 mg/kg α-mangostin per day has been reported to improve glucose tolerance, increase insulin sensitivity as evaluated by the homeostatic model assessment for insulin resistance (HOMA-IR), increase adiponectin levels and increase the phosphorylation levels of insulin receptor substrate 1 (IRS-1) and AKT in both liver and adipose tissues (25). This indicates that α-mangostin affects insulin signaling in both tissues.

By using rat pancreatic INS-1 cells, Lee *et al* (52) revealed that the use of α-mangostin at a concentration between 1-10 μM increased insulin secretion in a concentration-dependent manner in cells grown under high glucose conditions (16.7 mM glucose) without inducing cytotoxicity, which was maintained for 48 h. Additionally, it was further demonstrated that high glucose levels reduced the phosphorylated or active insulin receptor (p-IR), phosphoinositide 3-kinases (PI3K), p-AKT, protein kinase R-like endoplasmic reticulum kinase and pancreatic and duodenal homeobox 1 (Pdx1) protein levels, but increased the expression of IRS-1 phosphorylated at Ser 1101 (p-IRS-1Ser1101) in INS-1 cells (52).

Reduced p-IR levels indicate a response to the increased serine phosphorylation of IRS-1 proteins (53). The phosphorylation of IRS proteins on serine residues negatively regulates IRS signaling (54,55). IRS-1 acting downstream of pIR, recruits p85, a regulatory subunit of PI3K, and activates the PI3K/AKT pathway (56). This pathway activates PDK kinases, which phosphorylate AKT and permit its translocation to the nucleus, activating genes involved in glucose intake and blocking FOXO genes, inducing gluconeogenesis (57). High glucose levels essentially shut down insulin signaling by altering IR phosphorylation. This shutdown mechanism is attributed to the increased proteasome degradation of IRS proteins, the failure to recruit p85 to IRS proteins, thereby not activating the PI3K/AKT signaling pathway (54).

Treatment with a 5 μM concentration of α-mangostin, has been reported to protect against these effects, by reducing the inhibitory pIRS-1Ser1101, and restoring IR signaling as evidenced by increased PI3K, AKT and Pdx1 proteins (52). The loss of Pdx1 has been revealed to be associated with a decrease in b cell mass. It should be noted that hyperinsulinemia lowers the expression of IRS1 family of proteins in both cultured cells and mouse tissues, which has been linked to insulin resistance in animal models. The mechanism has been largely attributed to increased degradation (by ubiquitination) and decreased synthesis of IRS proteins (54,55).

Streptozotocin (STZ) is commonly used to induce type 1 diabetes in animal models, which induces oxidative stress in pancreatic β-cells, resulting in the increased activation of p38 MAPKs, JNK proteins and cleaved caspase-3 protease which causes hyperglycemia, the increased generation of reactive oxygen species (ROS), osmotic stress, proinflammatory cytokine secretion and apoptosis (52,58). However, co-treatment with α-mangostin (5 μM) has been found to reduce caspase-3 protease levels, reduce the apoptosis of the cells, and increase

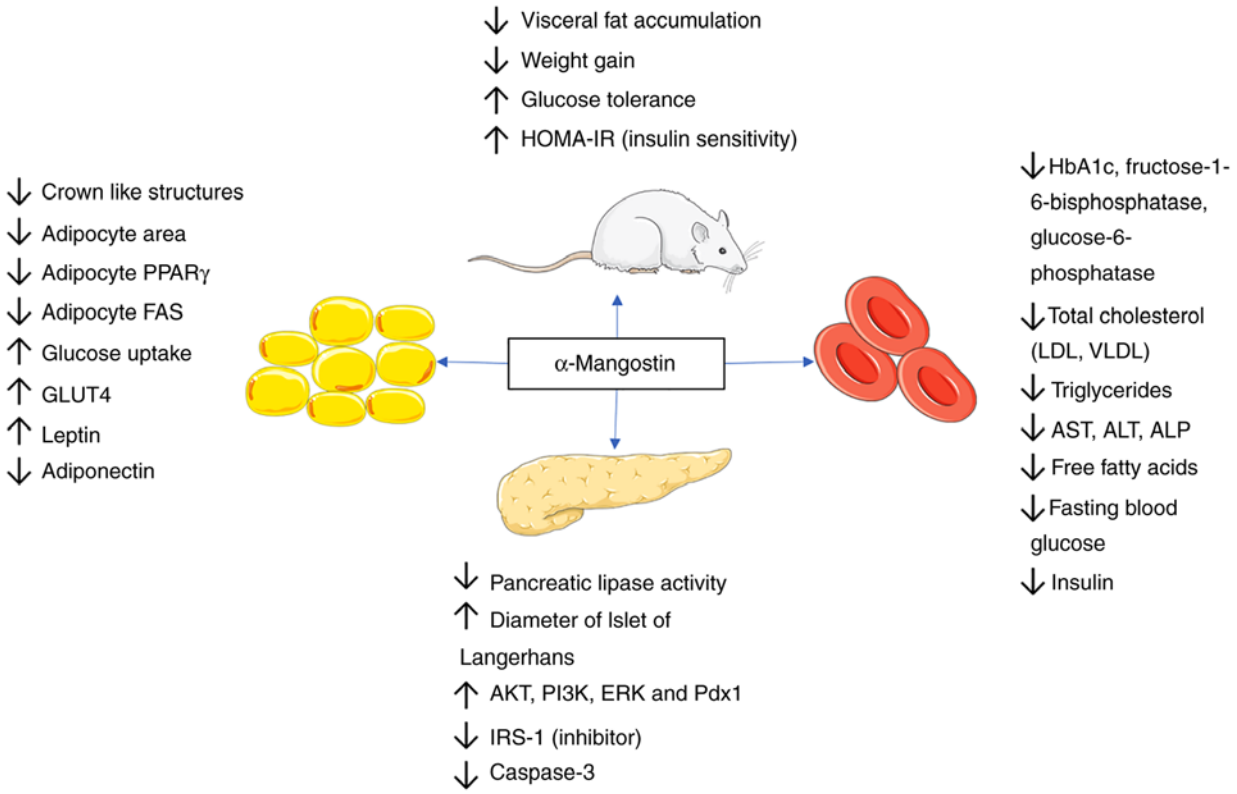

Figure 2. Anti-obesity and antidiabetic effects of α-mangostin. The anti-obesity effects of α-mangostin are mediated via the modulation of adipose tissue biology, reduction in visceral fat accumulation and inhibition of fatty acid synthase. Its antidiabetic effects are mediated through an improvement in insulin sensitivity and glucose tolerance, increased pancreatic lipase activity, increased glucose transporter activity, the increased stimulation of insulin receptor and the increased phosphorylation of the PI3K, AKT and ERK signaling cascades. PPARγ, peroxisome proliferator-activated receptor γ; GLUT4, glucose transporter 4; HOMA-IR, homeostatic model assessment for insulin resistance; Pdx1, pancreatic and duodenal homeobox 1; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase.

p-PI3K-AKT levels, demonstrating the protective effect of this compound in the presence of STZ (52). The antiapoptotic properties of α-mangostin could be attributed to its anti-oxidant properties, as described in a following section. The effects of α-mangostin in reducing pro-apoptotic proteins levels, particularly caspase-3 levels have been also observed in a previous study in human umbilical vein endothelial cultured cells (59), where α-mangostin led to an increase in Bcl-2, an antiapoptotic protein, and a reduction in Bax, a pro-apoptotic protein, in a concentration-dependent manner (59).

Hyperglycemia also induces ROS generation via a series of complex processes involving diacylglycerol, protein kinase C and NADPH-oxidase (60). ROS production eventually leads to tissue damage, which decreases insulin production as pancreatic β-cells are damaged over time, leading to hyperglycemia. These effects are attenuated by α-mangostin, which protects the pancreatic β-cells from damage and restores damaged pancreatic cells to allow for optimal insulin release (59,61,62).

In another *in vivo* study, histological samples of mice with STZ-induced diabetes treated with α-mangostin exhibited a restored diameter of islets of Langerhans (61), thereby improving insulin secretion. Jariyapongskul *et al* (63), who studied the effects of α-mangostin on hyperglycemia induced ocular hypoperfusion retinal leakage in rats, revealed that α-mangostin treatment significantly improved ocular flow and reduced leakage in rats, by reducing malondialdehyde (MDA) levels and lipid peroxidation in the retina. Hyperglycemic tissues have been shown to exhibit increased levels of MDA and advanced glycation end-products (AGEs). MDA is an end product of lipid peroxidation prevalent in hyperglycemia due to increased free radicals (63). AGEs are involved in the pathogenesis of diabetes-related complications, including cardiomyopathy, retinopathy and nephropathy (64). At a 25 μM concentration, α-mangostin was found to reduce the production of AGEs (65). In another study, the treatment of mice with STZ-induced diabetes with α-mangostin resulted in decreased glycated hemoglobin levels and reduced key gluconeogenic enzymes fructose-1-6-bisphosphatase and glucose-6-phosphatase lowering glucose production (66).

A pilot study previously investigated the effects of mangosteen supplement (400 mg, once per day) in obese female patients with insulin resistance (67). In that study, Watanabe *et al* (67) revealed that the treatment significantly improved insulin sensitivity (HOMA-IR) along with a reduction in insulin levels, improved HDL-C and lowered high-sensitivity C-reactive protein levels.

In general, treatment with α-mangostin or a diet rich in α-mangostin in various obese and diabetic rat models, *In vitro* studies and human studies has revealed that the compound can improve the markers of diabetes by lowering fasting blood glucose concentration, lowering insulinemia, increasing glucose tolerance and increasing insulin sensitivity, as measured by HOMA-IR, and increasing glucose uptake. The treatment with α-mangostin promotes glucose uptake by

Table I. Anti-obesity effects of a-mangostin.

Authors	Source of α-mangostin	Model: *in vitro*/*in vivo*	Dosage and duration of treatment	Mechanisms of action of anti-obesity effects	(Refs.)
John *et al*	*G. mangostana* rind	Wistar rats (High carbohydrate, high fat)	168 mg/kg per day 8 weeks	• ↓Weight gain • ↓Visceral fat accumulation • ↓Adipocyte area • ↓Plasma triglyceride • ↓FFA	(12)
Taher *et al*	*G. malaccencis*	3T3-L1 preadipocytes	10, 25, and 50 μM of α-mangostin 2 days	• ↓Intracellular fat accumulation • ↓PPARγ expression	(48)
Chae *et al*	*G. mangostana*	In vitro pancreatic lipase assay model	IC_{50}=5.0 μM	• ↓Pancreatic lipase activity	(49)
Abuzaid *et al*	*G. mangostana* pericarp	Wistar rats	200 mg/kg body weight per day 500 mg/kg body weight per day (~60 mg/kg per day and 150 mg/kg α-mangostin per day) 9 weeks	• ↓Body weight • ↓Fatty acid synthase (adipose tissue/serum)	(41)
Chang *et al*	Mangosteen concentrate drink	Sprague-Dawley rats	13 mg/day 6 weeks	• ↓Fasting plasma triglyceride • ↓Total cholesterol • ↓Hepatic CAT	(107)
Tsai *et al*	Mangosteen pericarp extract	Sprague-Dawley rats; rat primary hepatocytes	25 mg/day-rat 11 weeks 10-30 μM-rat hepatocytes 24 h	• ↓Plasma FFA • ↓Weight gain	(43)
Muhamad Adyab *et al*	*G. mangostana* flesh	Sprague-Dawley rats	200-600 mg/kg (α-mangostin concentration not detailed) 7 weeks	• ↓Weight gain • ↓Plasma LDL-C • ↓Total cholesterol	(44)
Chae *et al*	*G. mangostana* peel	Male C57BL/ 6 mice	50 and 200 mg/kg per day (~12.5 and 50 mg/kg of α-mangostin per day) 45 days	• ↓Weight gain • ↓AST and ALT • ↓LDL cholesterol • ↓Total cholesterol • ↓Triglyceride • ↓FFA, ↓glucose • ↓Visceral fat accumulation • ↓PPARγ • ↑Hepatic SIRT1 and AMPK	(45)
Mohamed *et al*	*G. mangostana* extract	Balb/c mice	Group III-50 mg/kg of α-mangostin per day 16 weeks	• ↓Weight gain • ↓FFA	(46)
Kim *et al*	Purified α-mangostin	C57BL/6 mice RAW264.7 macrophages	50 mg/kg per day 12 weeks 25 μM/ml	• ↓Body weight • ↓Cholesterol • ↓Serum triglyceride	(25)

Table I. Continued.

Authors	Source of α-mangostin	Model: *in vitro*/*in vivo*	Dosage and duration of treatment	Mechanisms of action of anti-obesity effects	(Refs.)
		Mesenteric adipose tissue culture		• ↑Adiponectin • ↓Serum ALT • ↓Crown-like structures (adipocytes) • ↓Epididymal adipose tissue size	
Li *et al*	Purified α-mangostin	MCF-7, estrogen receptor-positive cells, MDA-MB-231, estrogen receptor-negative cells	1, 2, 3, 4 μM 24 h	• ↓FAS expression • ↓Intracellular FAS activity	(29)
Li *et al*	Purified α-mangostin	Mouse derived RAW264.7 macrophage 3T3-L1 preadipocytes Male C57BL/6J	10 mg/kg per day (inflammation mice) 5 days 25 and 50 mg/kg per day 8 weeks (aged mice)	• ↓Weight, indexes eWAT and iWAT • ↑Insulin sensitivity (HOMA-IR), p-AKT level • ↓Total cholesterol, triglyceride, LDL-cholesterol • ↑HDL-C	(42)
Choi *et al*	Purified α-mangostin	Male CB57L/6 mice	50 mg/kg per day 6 weeks	• ↓Weight gain • ↓FFA • ↓Total cholesterol • ↓LDL-C • ↑Hepatic PPARγ, SIRT1, AMPK and RXRα	(24)

Upward arrows (↑) indicate an increase, and downward arrows (↓) indicate a decrease. *G. mangostana, Garcinia mangostana*; FFA, free fatty acid; PPARγ, peroxisome proliferator-activated receptor γ; CAT, catalase; LDL-C, low-density lipoprotein-cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; SIRT1, sirtuin 1; FAS, fatty acid synthase; eWAT, epididymal white adipose tissue; iWAT, inguinal white adipose tissue; HOMA-IR, homeostatic model assessment for insulin resistance; HDL-C, high-density lipoprotein cholesterol; RXRα, retinoid-X-receptor α.

increasing the expression of glucose transporters in tissues, including glucose transporter (GLUT)4 in adipose tissues, adipocytes, cardiac tissues, and skeletal muscles and GLUT2 in hepatic tissues (25,68). Furthermore, α-mangostin may stimulate insulin release in the pancreatic, liver and adipose tissues by activating IRs and increasing the phosphorylation of PI3K, AKT and ERK signaling cascades (25,52). These observations could explain the increased glucose uptake and plasma glucose level reduction in cells or animals treated with α-mangostin. A summary of the mechanism of α-mangostin is presented in Fig. 2 and Table II.

4. Anti-steatotic and hepatoprotective effects of α-mangostin

The use of α-mangostin and products rich in α-mangostin from *G. mangostana* peel have been extensively studied in both cell culture and rodent models of hepatic diseases. *G. mangostana* peel has been revealed to decrease hepatic fat vacuole accumulation (12) and reduce hepatic triglyceride accumulation (43). The infusion of *G. mangostana* peel decreases hepatic structural damage induced by hydrogen peroxide (H_2O_2) (69). The ability of *G. mangostana* peel to improve liver morphology has also been reported by Hassan *et al* (70), John *et al* (12), Yan *et al* (71), and Fu *et al* (72) in various hepatic disease models.

The improvement in hepatic structure has been associated with improved liver function tests indicated by reduced levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) (70,72,73). The reduction in liver fibrosis has also been observed following treatment with *G. mangostana* peel (12,73). Mangosteen peel extract (doses of 250 and 500 mg/kg per day) administration in a thioacetamide-induced hepatoxicity rat model, prevented the development of liver changes, decreased fibrosis through reduced expression of

Table II. Antidiabetic effects of a-mangostin.

Authors	Source of α-mangostin	Model *In vitro/in vivo*	Dosage and duration	Mechanisms of action of anti-diabetic effects	(Refs.)
Kim *et al*	Purified α-mangostin	C57BL/6 mice RAW264.7 macrophages Mesenteric adiposetissue culture	50 mg/kg per day 12 weeks 25 μM/ml 24 h	• ↑Gucose tolerance • ↑HOMA-IR (insulin sensitivity) • ↑p-AKT • ↑p-IRS-1 • ↑GLUT4 (adipose) • ↑GLUT2 (liver)	(25)
Taher *et al*	*G. malaccencis*	3T3-L1 preadipocytes	10, 25 and 50 μM of α-mangostin 2 days	• ↑Glucose uptake (1, 25 μM only) • ↑GLUT4 (adipocyte) • ↑Leptin	(48)
Jiang *et al*	Purified α-mangostin	C57BL/KsJ diabetic (db/db) mice Primary aortic endothelial cells	10 mg/kg/d, i.p.; mice 12 weeks 15 μM α-mangostin; cell culture 24 and 48 h	• ↓Fasting blood glucose • ↓Insulin • ↓Ceramide and aSMase signaling and accumulation	(79)
John *et al*	*G. mangostana* rind	Wistar rats	168 mg/kg per day 8 weeks	• ↑Glucose tolerance	(12)
Lazarus *et al*	α-mangostin compound	Wistar rats	100, 200 mg/kg per day 8 weeks	• ↑Insulin sensitivity (HOMA-IR) • ↑GLUT4 (skeletal muscle) expression • ↓STZ-induced weight loss	(108)
Ratwita *et al*	α-mangostin compound	Wistar rats adipocytes (WAT)	5, 10, 20 mg/kg day 21 days 3.125 mM; 6.25 and 25 mM (cell culture)/48 h	• ↑Glucose tolerance • ↑GLUT4 (adipocytes) • ↑GLUT4 (cardiac)	(68)
Luo and Lei	α-mangostin	Human umbilical vein endothelial cells	5, 10, and 15 μM of α-mangostin Effects noted at 15 μM 24 h	• ↓Glucose induced cell apoptosis • ↓Pro-apoptotic proteins • ↑Anti-apoptotic proteins	(59)
Soetikno *et al*	α-mangostin	Male Wistar rats	100 and 200 mg/kg, 8 weeks	• ↑Insulin sensitivity • ↓Lipid profiles (LDH) • ↓Fasting blood glucose	(98)
Jariyapongskul *et al*	Purified, extracted α-mangostin	Male Sprague-Dawley rats	200 mg/kg 8 weeks	• ↑Insulin sensitivity • ↓Fasting blood glucose • ↓Blood cholesterol and triglycerides • ↓TNF-α • Re-establishes ocular blood flow and reduces retinal blood leakage	(63)
Husen *et al*	α-mangostin	Male BALB/C mice	2, 4 and 8 mg/kg per day 14 days	• ↓Fasting blood glucose • ↓Blood cholesterol • ↑Diameter of Islet of Langerhans	(61)

Table II. Continued.

Authors	Source of α-mangostin	Model *In vitro/in vivo*	Dosage and duration	Mechanisms of action of anti-diabetic effects	(Refs.)
Lee *et al*	α-mangostin extracted and purified	Rat insulinoma, INS-1 cells (store and secrete insulin)	1, 2.5 and 5 μM 1 h	• ↑Insulin secretion after glucose stimulation • ↑Active insulin receptor • ↑AKT, PI3K, ERK and Pdx1 • ↓IRS-1 (inhibitor) • ↑Protection of INS-1 cells in presence of damaging chemicals • ↓Pro-apoptotic caspase 3	(52)
Kumar *et al*	α-mangostin compound	Streptozotozin-induced diabetes in Wistar rat	25, 50 and 100 mg/kg 56 days Toxicity test up to 1,250 mg/kg; 48 h	• ↓Blood glucose • ↓Glycated hemoglobin, fructose-1-6-bisphosphatase, glucose-6-phosphatase • ↓Total cholesterol (LDL, VLDL) • ↓Triglycerides • ↓AST, ALT, ALP • ↓Structural renal and hepatic damage • ↓IL-6, CRP, TNF-α concentrations	(66)
Usman *et al*	α-mangostin	Male Sprague-Dawley rats	Determined IC_{50}	• ↑Potential to lengthen α-mangostin release • ↓Hyperglycemia	(158)
Watanabe *et al*	*G. mangostana* extract	Obese female patients with insulin resistance	400 mg/day 26-week	• ↓Insulin levels • ↓HOMA-IR • ↓HsCRP • ↑HDL-C	(67)

Upward arrows (↑) indicate an increase, and downward arrows (↓) indicate a decrease. *G. mangostana*, *Garcinia mangostana*; HOMA-IR, homeostatic model assessment for insulin resistance; IRS-1, insulin receptor substrate 1; GLUT, glucose transporter; aSMase, acid sphingomyelinase; LDH, lactate dehydrogenase; Pdx1, pancreatic and duodenal homeobox 1; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein; HsCRP, high-sensitivity C-reactive protein; HDL-C, high-density lipoprotein cholesterol; STZ, streptozotocin.

α smooth muscle actin (α-SMA) and transforming growth factor β1 (TGF-β1) genes (73). Acute and chronic liver injury activate TGF-β1 from the extracellular matrix, activating hepatic stellate cells to transdifferentiate into myofibroblasts expressing a large amount of α-SMA (74). Additionally, treatment with *G. mangostana* peel also increases hepatic PPARγ, AMPK and SIRT1 activation, which are linked to its anti-obesity effect (45).

In an acute acetaminophen-induced liver injury study by Yan *et al* (71), α-mangostin from *G. mangostana* peel presented with hepatoprotective benefits by increasing antioxidant markers, glutathione (GSH) and MDA, and reducing inflammatory cytokines, including tumor necrosis factor α (TNF-α) and interleukin (IL)-1β. α-mangostin also inhibited the expression of autophagy-related microtubule-associated protein light chain 3 (LC3) and Bcl-2/adenovirus E1B protein-interacting protein 3. Western blot analysis further indicated that α-mangostin partially hindered the activation of apoptotic signaling pathways by increasing Bcl-2 expression, concurrently reducing Bax and cleaved caspase 3 proteins. α-mangostin also increased the expression of p62, phosphorylated mammalian target of rapamycin (mTOR), phosphorylated AKT and

reduced LC3 II/LC3 I ratio in autophagy signaling pathways in mouse liver. This indicates that the effect of α-mangostin on this model may be related to alteration in the AKT/mTOR pathway (71).

NAFLD is caused by multiple factors, including hepatic oxidative stress, lipotoxicity, and mitochondrial dysfunction. Obesity is among the risk factors for NAFLD alongside type 2 diabetes mellitus and hyperlipidemia. In NAFLD and NASH models of high fat diet-induced liver disease, treatment with an α-mangostin concentration of 50 mg/kg per day was shown to reduce the liver weight coefficient, AST and ALT levels, reduce hepatic fibrosis and reduce plasma cholesterol, triglyceride and LDL-C cholesterol levels. The treatment also improved hepatic structure and function, and increased glycogen storage, as shown by PAS staining (46). Additionally, α-mangostin reduced the levels of caspase-3, a marker of apoptosis, increased autophagy process and reduced CD68-positive macrophages, and reduced sequestosome-1 (SQSTM1)/p62, LC3 and α-SMA expression levels (46).

The accretion of lipids in non-adipose tissues, including the liver, promotes free fatty acid accumulation in the hepatocytes and increases apoptosis through production of ROS, lysosomal pathway and death receptor mediated pathway (75). In high-fat diet models, the significant increase in SQSTM1/P62 and LC3 expression in the obese group signifies marked autophagy suppression (46,76), possibly suggesting that a lack of lysosomal activity may affect autophagic processes and may cause SQSTM1/P62 and LC3 accumulation (77). Yang *et al* (76) revealed that hepatic autophagy was suppressed in dietary and genetic obesity models, due to the decreased expression of key autophagy molecules such as Atg7. Hepatic autophagy activation has been reported to promote fatty acid β-oxidation; thus, autophagy suppression has been suggested to reduce fatty acid α-oxidation in both *in vivo* and *in vitro* models (78). The reduced expression of SQSTM1/P62 and LC3 in α-mangostin groups may occur due to the upregulation of autophagy by inducing pre-autophagosomal structure expression levels and reducing SQSTM1/p62 and LC3 within hepatocytes (46,47). This is coupled with the downregulation of the apoptosis process by improved cellular antioxidant and antioxidant enzymatic capacity and reduced lipid peroxidation, due to reduced oxidative stress (43).

The treatment of rats with 25 mg/kg body weight mangosteen extract a day has been reported to increase hepatic antioxidant enzyme activities and reduce ROS in rat liver tissue (43). Treated rats and mice have demonstrated reduced plasma free fatty acid and hepatic thiobarbituric acid reactive substances levels, while antioxidant enzymes and the activities of NADH-cytochrome c reductase, and succinate-cytochrome c reductase (SCCR) were increased (43,79). *In vitro* research also demonstrated showed that α-mangostin also increased membrane potential, cellular oxygen rate, decreased total ROS and mitochondrial ROS levels, and reduced calcium and cytochrome c release from the mitochondria, which reduced caspase-9 and -3 activities linked to the apoptotic processes (43).

There are numerous reports on the hepatoprotective effects of α-mangostin as an individual compound. Kim *et al* (25) reported the reduction of hepatic lipid droplet, tissue weight, hepatic triglyceride in obese mice treated with α-mangostin. They further reported that the changes were associated with reduced expression of sterol regulatory element-binding transcription factor 1, sterol regulatory element-binding transcription factor (SREBP)-2, SREBP-1c, lipoprotein lipase (LPL) and stearoyl-CoA desaturase-1 (SCD1) (25). Li *et al* (42) also examined the effects of α-mangostin on aged mice and noted that the treatment reduced liver injury, AST and ALT levels, and reduced the expression of microRNA (miRNA/miR)-155 from epididymal white adipose tissue and macrophage/monocyte-like (RAW264.7) cells and bone marrow-derived macrophages. miRNA-155 is a crucial mediator in liver steatosis and fibrosis and its expression is increased during inflammatory responses in macrophages (42). α-mangostin also reduced hepatic steatosis by reducing hepatic triglyceride and fat accumulation and reducing AST and ALT (24).

Following the administration of α-mangostin at a dose of 5 mg/kg per day in a thioacetamide induced hepatic fibrosis rat model, it was noted that the expression of TGF-β1, α-SMA, tissue inhibitor of metalloproteinases 1 (TIMP-1) was downregulated (31). In another study by Rahmaniah *et al* (80), α-mangostin was observed to decrease the ratio of pSmad/Smad and pAKT/AKT in TGF-β-induced liver fibrosis model using human hepatic stellate (LX-2) cells. They also noted that this treatment reduced the expression of antigen Ki-67, collagen type I alpha 1 chain (COL1A1), TIMP-1, plasminogen activator inhibitor-1, α-SMA and phosphorylated Smad3 (p-Smad3) (80).

In another study, the levels of the hepatic enzymes, fatty acid transporter and β-hydroxy β-methylglutaryl-CoA (HMG-CoA) synthase, were significantly suppressed in apolipoprotein E (Apoe)-deficient mice treated with α-mangostin. However, HMG-CoA reductase levels increased, and this may be attributed to compensatory mechanisms triggered by the decrease in HMG-CoA synthase. Histologically, the treatment also reduced hepatic lipid accumulation and fibrosis and could be linked to the reduction of TC due to HMG-CoA synthase inhibition and a reduction of fatty acid transporter gene expression (81).

In a STZ diabetic mouse model, α-mangostin treatment (doses of 25, 50 and 100 mg/kg per day) increased plasma insulin levels, increased superoxide dismutase (SOD), catalase (CAT) and GSH and reduced TC, triglycerides, LDL-C, very low-density lipoprotein cholesterol (VLDL-C), AST, ALT, alkaline phosphatase (ALP) and lipid peroxidation. The treatment also improved hepatic damage induced by streptozotocin (66).

Another study reported that α-mangostin (10 and 20 μM) inhibited acetaldehyde-induced hepatic stellate (LX-2) cell proliferation through the downregulation of Ki-67; and activation through the reduced expression of α-SMA (82). The treatment also reduced the hepatic stellate cell (HSC) migration markers: Matrix metallopeptidase (MMP)-2 and -9 as well as expression and concentration of TGF-β1. The phosphorylation of ERK1/2 and the expression levels of the fibrogenic markers, COL1A1, TIMP-1 and TIMP-3, were also reduced. In addition, α-mangostin upregulated the expression of the antioxidant defenses manganese superoxide dismutase and glutathione peroxidase (GPx), and reduced intracellular ROS levels (82). Overall, α-mangostin reduced

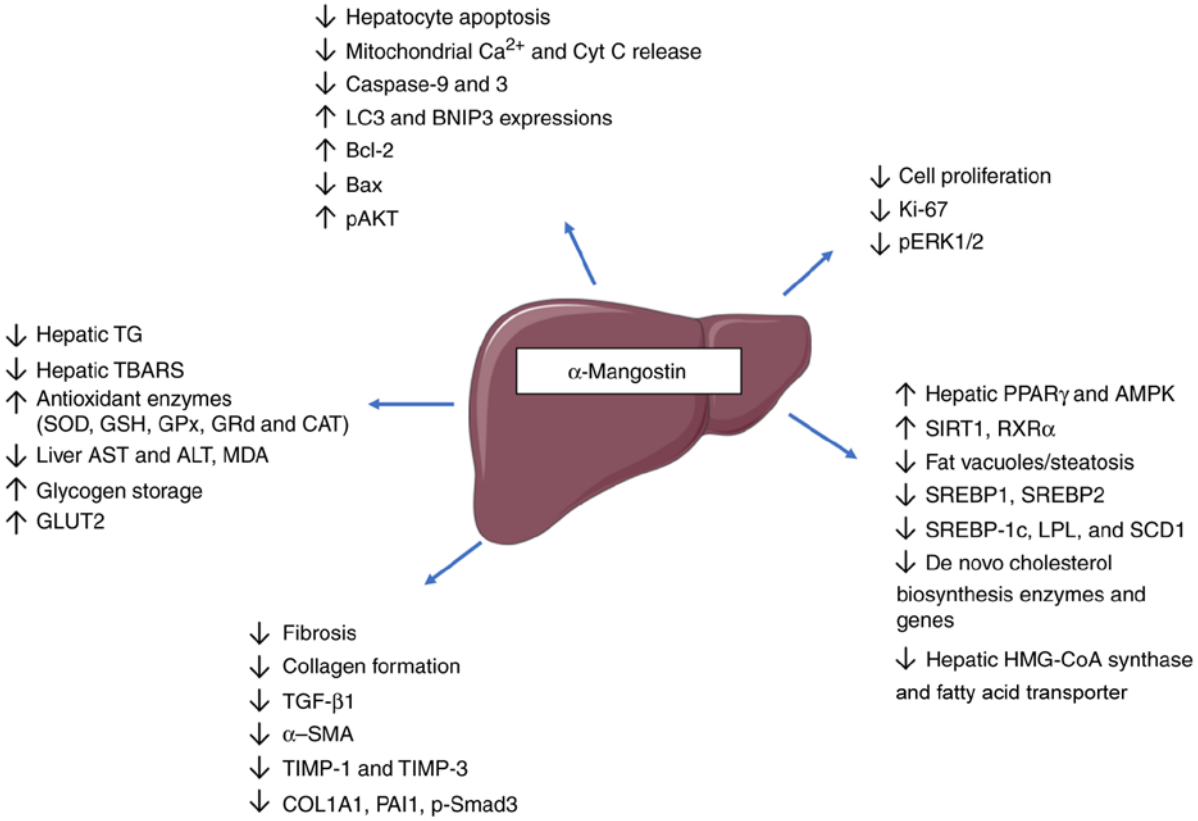

Figure 3. Anti-steatotic and hepatoprotective effects of α-mangostin. The improvement in hepatic structure and function by α-mangostin is mediated through decreased collagen deposition and fibrosis, affecting related genes/proteins (TGF-β1, Smad3, TIMP-3, TIMP-1, PAI1, COL1A1, miRNA-155-5p and α-SMA). α-mangostin also prevents the apoptosis of hepatic tissues, regulates hepatic lipid and carbohydrate homeostasis via AMPK, PPARγ, SIRT1 and RXRα, reduces steatosis, improves liver function, prevents inflammation and oxidative stress and upregulates hepatic autophagy. TIMP, tissue inhibitor of metalloproteinases; PAI1, plasminogen activator inhibitor-1; COL1A1, collagen type I alpha 1 chain; α-SMA, α-smooth muscle actin; TG, triglyceride; TBARS, thiobarbituric acid reactive substances; SOD, superoxide dismutase; GSH, glutathione; GPx, glutathione peroxidase; GRd, glutathione reductase; CAT, catalase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; MDA, malondialdehyde; GLUT, glucose transporter; PPARγ, peroxisome proliferator-activated receptor γ; SIRT1, sirtuin 1; RXRα, retinoid-X-receptor α; SREBP, sterol regulatory element-binding transcription factor; LPL, lipoprotein lipase; SCD1, stearoyl-CoA desaturase-1; HMG-CoA, β-hydroxy β-methylglutaryl-CoA.

acetaldehyde-induced HSC proliferation and activation via the TGF-β and ERK 1/2 pathways (82).

A sophisticated transcriptomic study conducted by Chae *et al* (83), revealed several novel pathways in lipid and cholesterol metabolism when HepG2 and Huh7 cells were treated with α-mangostin (10 and 20 μM) for 24 h. The compound decreased the expression levels of several cholesterol biosynthetic genes, including SQLE, HMGCR, LSS and DHCR7, and controlled the specific cholesterol trafficking-associated genes, ABCA1, SOAT1 and PCSK9. α-mangostin also reduced SREBP2 expression, indicating that SREBP2 is an essential transcriptional factor in lipid or cholesterol metabolism, as observed by the decreased amount of SREBP2-SCAP complex. When exogenous cholesterol was added, α-mangostin reduced SREBP2 expression and the synthesis of PCSK9 which could increase cholesterol uptake in cells and provide a feasible explanation of the cholesterol-reducing properties of α-mangostin (83). Overall, α-mangostin treatment in HepG2 cells, controlled cholesterol homeostasis through a reduction in the expression of SREBP2 and its downstream target genes in cholesterol synthesis (SQLE and IDI1) and cholesterol trafficking (ABCA1 and PCSK9) (83). α-mangostin also downregulated the expression levels of FADS1, FADS2 and ACAT2 involved in the lipid metabolic pathway.

Overall, the molecular effects of α-mangostin in hepatic tissue are multifaceted and complex, reflecting the key functions of the liver in metabolism. The improvement in hepatic structure is associated with decreased collagen deposition and fibrosis observed by several researchers associated with the modulation of genes or proteins involved in fibrosis, including TGF-β1, smad3, TIMP-3, TIMP-1, PAI1, COL1A1, miRNA-155-5p and α-SMA. α-mangostin also prevents the apoptosis of hepatic tissues, as demonstrated by the decrease in cleaved caspase-3 and 9-activity levels in liver cells, regulating hepatic lipid and carbohydrate homeostasis, reducing fat vacuoles or steatosis, improving liver function, and preventing hepatic inflammation and oxidative stress, as well as upregulating hepatic autophagy. The molecular mechanisms of α-mangostin in hepatoprotective effects are summarized in Fig. 3 and Table III.

5. Cardioprotective and anti-atherogenic effects of α-mangostin

Garcinia mangostana pericarp extract has been previously suggested to counteract the effects of NG-nitro-L-arginine methyl ester in a hypertensive rat model (84). The administration of *G. mangostana* extract at a concentration of

Table III. Anti-steatotic and hepatoprotective effects of a-mangostin.

Authors	Source of α-mangostin	Model *in-vitro/in vivo*	Dosage and duration	Mechanisms of action of hepatoprotective effects	(Refs.)
Tsai *et al*	Mangosteen pericarp extract	Sprague-Dawley; Rat primary hepatocytes	25 mg/day; rat 11 weeks 10-30 μM; rat hepatocytes 24 h	• ↓Hepatic TG • ↓Hepatic TBARS • ↑Antioxidant enzymes (SOD, GSH, GPx, GRd and CAT) • ↑NCCR and SCCR activities in liver tissue Cell study • ↑OCR • ↓tROS and mitoROS • ↓Mitochondrial Ca^{2+} and cytochrome *c* release • ↓Caspase-9 and -3	(43)
Chae *et al*	*G. mangostana* peel	Male C57BL/6 mice	200 mg/kg per day 45 days	• ↑Hepatic PPARγ, AMPK, SIRT1	(45)
John *et al*	*G. mangostana* rind	Wistar rats	168 mg/kg per day 8 weeks	• ↓Hepatic fat vacuoles and inflammatory cells • ↓Collagen formation	(12)
Mohamed *et al*	*G. mangostana* extract	Balb/c mice	Group III, 50 mg/kg of α-mangostin per day for 16 weeks Group IV, 50 mg/kg of α-mangostin per day for the last 2 weeks	• ↓Liver weight coefficient • ↓Liver AST and ALT • ↓Plasma cholesterol, triglycerides and LDL-C, ↑HDL-C • ↑Hepatic structure and function • ↓Hepatic fibrosis • ↑Glycogen storage • ↑Autophagy process • ↓Hepatocyte apoptosis (caspase 3) • ↓CD68-positive macrophages • ↓p62 expression • ↓LC3 expression • ↓α-SMA expression	(46)
Muhamad Adyab *et al*	*G. mangostana* flesh	Sprague Dawley rats	200-600 mg/kg (α mangostin concentration not detailed) 7 weeks	• ↓Hepatic lipid accumulation	(44)
Rusman *et al*	*G. mangostana* peel infusion	Wistar rats	0.25-2% 1 month	• ↓Hepatic structural damage induced by H_2O_2	(69)
Fu *et al*	*G. mangostana* fruit rind	lipopolysaccharide/ d-galactosamine (LPS/D-GalN)-induced acuteliver failure mice model	12.5, 25 mg/kg 7 days	• ↑Liver morphology • ↓Hepatic MDA, ALT and AST	(72)
Abood *et al*	*G. mangostana* peel	Sprague-Dawley rats	250 mg/kg per day and 500 mg/kg per day	• ↓Liver index • ↓Hepatocyte proliferation (PCNA staining)	(73)

Table III. Continued.

Authors	Source of α-mangostin	Model *in-vitro/in vivo*	Dosage and duration	Mechanisms of action of hepatoprotective effects	(Refs.)
			8 weeks	• ↓Hepatic fibrosis • ↓α-SMA, TGF-β1 • ↓Serum bilirubin • ↓Total protein, albumin and liver enzymes (ALP, ALT and AST)	
Hassan *et al*	*G. mangostana* fruit rind	Wistar rats	500 mg/kg per day for 30 days after irradiation	• ↑Liver function test • ↑Liver morphology	(70)
Yan *et al*	Purified α-mangostin	ICR mice exposed to acetaminophen, acute liver injury model	100 and 200 mg/kg 7 days	• ↑Liver morphology • ↓Expression of LC3, BNIP3 • ↑expression Bcl-2 • ↓Bax and cleaved caspase 3 • ↑p-mTOR, ↑ p-AKT • ↓LC3 II/LC3 I ratio in autophagy signaling pathways in mouse liver • ↓Degradation of p62/SQSTM1 protein	(71)
Rodniem *et al*	Purified α-mangostin	Thioacetamide-induced hepatic fibrosis rat model	5 mg/kg (twice a week) 8 weeks	• ↓TGF-β1, α-SMA, TIMP-1	(31)
Rahmaniah *et al*	Purified α-mangostin	Human hepatic stellate cells, LX-2	(5 or 10 μM) 24 h	• ↓TGF-β concentration • ↓Ki-67 and p-Akt expression • ↓Expression of COL1A1, TIMP1, PAI1, α-SMA • ↓p-Smad3 as fibrogenic markers	(80)
Lestari *et al*	Purified α-mangostin	Acetaldehyde induced human hepatic stellate cells (HSC), LX-2	(10 μM) 24 h	• ↓proliferation and migration of HSC • ↓Ki-67 • ↓pERK1/2 • ↓TGF-β • ↓COL1A1 • ↓TIMP1 and TIMP3 • ↑Expression MnSOD and GPx • ↓α-SMA • ↓ROS	(82)
Kim *et al*	Purified α-mangostin	C57BL/6 mice RAW264.7 macrophages Mesenteric adipose tissue culture	50 mg/kg per day 12 weeks 25 μM/ml 24 h	• ↓Lipid droplets • ↓Liver tissue weight • ↓Liver triglyceride • ↓SREBP1, SREBP2 • ↓Expression of hepatic SREBP-1c, LPL and SCD1 • ↑Liver functions (AST and ALT)	(25)
Li *et al*	Purified α-mangostin	Mouse derived RAW264.7 macrophage 3T3-L1 preadipocytes Male C57BL/6J	25 and 50 mg/kg per day 8 weeks (old mice)	• ↓MicroRNA-155-5p from macrophages, eWAT and serum • ↓AST, ALT • ↑p-AKT • ↓Liver injury	(42)

Table III. Continued.

Authors	Source of α-mangostin	Model *in-vitro/in vivo*	Dosage and duration	Mechanisms of action of hepatoprotective effects	(Refs.)
Choi *et al*	Purified α-mangostin	Male CB57L/6 mice	50 mg/kg per day 6 weeks	• ↓Hepatic TG • ↓Hepatic fat accumulation • ↓Serum AST and ALT	(24)
Chae *et al*	Purified α-mangostin from *G. mangostana*	HepG2 cell lines Hur7 cells	0.8, 1, 10, 20 μM 24 h	• ↓FDFT1, SQLE, LSS, CYP51A1, MSMO1, HSD17B7 and DHCR7 (*de novo* cholesterol biosynthesis) • ↓PCSK9, SQLE, HMGCR and LSS (enzyme-encoding metabolic genes) • ↓DHCR7, FDFT1, FDPS, HMGCR, IDI1, PCSK9, SQLE and SREBP2 (cholesterol biosynthesis) • ↓SCAP-SREBP2 complexes formation in endoplasmic reticulum and Golgi • ↑Cholesterol and LDL-C uptake • ↓FADS1, FADS2 and ACAT2 expression	(83)
Shibata *et al*	*G. mangostana* extract rich in α-mangostin	Male Apoe$^{-/-}$ mice	0, 0.3, 0.4% of α-mangostin 17 weeks	• ↓Body weight • ↓Hepatic HMG-CoA synthase and fatty acid transporter • ↓Hepatic steatosis • ↑Serum lipoprotein lipase	(81)
Ibrahim *et al*	α-mangostin (*Cratoxylum arborescens*)	ICR female and male mice Human Normal hepatic cells (WRL-68)	100, 500 and 1,000 mg/kg body weight IC_{50}, 65 mg/ml	• No toxicity	(19)

Upward arrows (↑) indicate an increase, and downward arrows (↓) indicate a decrease. *G. mangostana*, *Garcinia mangostana*; TG, triglyceride; TBARS, thiobarbituric acid reactive substances; SOD, superoxide dismutase; GSH, glutathione; GPx, glutathione peroxidase; GRd, glutathione reductase; CAT, catalase; NCCR, NADH-cytochrome c reductases; SCCR, succinate cytochrome c reductase; OCR, oxygen consumption rate; tROS, total reactive oxygen species; mitoROS, mitochondrial reactive oxygen species; PPARγ, peroxisome proliferator-activated receptor γ; SIRT1, sirtuin 1; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein cholesterol; MDA, malondialdehyde; LC3, light chain 3; BNIP3, BCL2 interacting protein 3; α-SMA, α-smooth muscle actin; TIMP, tissue inhibitor of metalloproteinases; PAI1, plasminogen activator inhibitor-1; COL1A1, collagen type I alpha 1 chain; SREBP, sterol regulatory element-binding transcription factor; LPL, lipoprotein lipase; LPL, lipoprotein lipase; eWAT, epididymal white adipose tissue; FDFT1, farnesyl-diphosphate farnesyltransferase 1; SQLE, squalene epoxidase; LSS, lanosterol synthase; CYP51A1, (cytochrome P450 family 51 subfamily A member 1; MSMO1, methylsterol monooxygenase 1; HSD17B7, hydroxysteroid 17-beta dehydrogenase 7; DHCR7, 7-dehydrocholesterol reductase; FDPS, farnesyl diphosphate synthase; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; IDI1, isopentenyl-diphosphate delta-isomerase; PCSK9, proprotein convertase subtilisin/kexin type 9; FADS, fatty acid desaturase; ACAT2, acetyl-coenzyme A acetyltransferase 2.

200 mg/kg per day partially attenuated the effects of the drug by reducing hypertension, arterial wall thickness, and cardiovascular remodeling. The treatment also attenuated oxidative stress activity induced by the drug by decreasing plasma MDA, increasing plasma nitric oxide (NO) metabolites and reducing $_{p}47^{phox}$NADPH oxidase subunit and inducible nitric oxide synthase (iNOS) protein expression in aortic tissues (84). The addition of *G. mangostana* rind in powder to the diet of obese rats (daily intake equivalent to α-mangostin concentration of 168 mg/kg per day) resulted in improved cardiovascular structures by reducing fibrosis and collagen deposition. Cardiac structure improvement was accompanied by a reduction in cardiac stiffness, as measured by Langendorff's isolated heart contraction assessment. The treatment also improved aortic endothelial tissue activity, while lowering blood pressure (12).

Pre-treatment with α-mangostin (200 mg/kg per body weight per day) for 8 days in Wistar rats significantly reduced cardiac TNF-α and cyclooxygenase (COX)-2 expression induced by Isoproterenol (ISO). α-mangostin also reduced lysosomal hydrolases in both serum and cardiac tissues, preserved myocardial membrane integrity through restoring membrane-bound phosphatases function, and reduced ISO-induced oxidative stress and cellular damage (32). In another study, pre-treatment with α-mangostin (200 mg/kg/day) for 8 days in Wistar rats decreased the functional abnormalities and mitochondrial function disturbance induced by ISO (72). Treatment with α-mangostin improved cardiac endothelial NOS (eNOS) expression and NO concentration. The administration of α-mangostin also increased cardiac mitochondrial cytochrome *c*, c1, b and aa3 levels, and improved NADH dehydrogenase and cytochrome c oxidase activity. The reduction of lipid peroxides in the treatment group was associated with enhanced antioxidant enzyme activity. The findings have suggested that α-mangostin may present with cardioprotective effects in myocardial cells by upregulating oxidative mitochondrial enzymes (85).

In an *Apoe*-deficient mouse model, α-mangostin (0.3 and 0.4%) reduced TC, triglycerides (0.4%) and VLDL-C (81). The treatment also reduced the risk of atherosclerosis by decreasing the deposition of cholesterol in the aortic arch, aortic hiatus and renal artery bifurcation area, and improved hepatic lipid droplets. The level of lipoprotein lipase enzyme was significantly increased in the 0.4%-concentration group; however, no changes were observed in the serum level of the proatherogenic indicator, soluble lectin-like oxidized LDL receptor-1. Macrophages analysis revealed that the expression of *Cd163* gene (M2 macrophage marker) was increased, whereas CD68 levels (pan-macrophage marker) and Nos1 (M1 macrophage marker) were not significantly altered. The M2 macrophage populations were more frequent in atherosclerotic lesions exposed with 0.4% treatment. Inflammatory cytokine levels (IFN-γ, TNF-α and IL-1β) exhibited a decreasing trend, while the IL-13 (M2 polarizing cytokine) was increased (81). The accumulation of M1 is a hallmark for atherosclerosis progression, however, the M2 type is predominant in atherosclerosis recession. Plausibly, α-mangostin has been suggested to induce the microenvironment for M2 polarization observed in the treatment group and subsequently reduce the development of atherosclerotic lesions (81).

A previous study using human umbilical vein endothelial cells (HUVECs) grown in a high glucose environment treated with α-mangostin has revealed the treatment decreased high glucose-induced ROS formation and high glucose-induced apoptosis. Further analysis then revealed that α-mangostin reduced apoptosis through the suppression of JNK and p38-MAPK pathway via the inhibition of JNK and p38-MAPK phosphorylation (86). Another study using HUVECs grown in high glucose (60 mM) significantly reduced cellular viability and increased reactive oxygen species and cellular senescence through the reduction of senescence-associated β-galactosidase activity (87). A high glucose environment also elevated p53, acetyl-p53 and p21 protein levels and IL-6 secretions; however, it reduced SIRT1 and total AMPK protein levels. Of note, α-mangostin (1.25 μM) reversed the toxic effects of high glucose in HUVECs by reducing apoptosis, ROS, IL-6 secretion, p53 expression while increasing SIRT1 expression. These results demonstrated that in high-glucose conditions, α-mangostin has demonstrated beneficial effects in endothelial cells, suggesting protective effects on the vasculature, and anti-senescence effects, most likely due to its antioxidant activity through the SIRT1 pathway. Thus, α-mangostin may act as a natural agent to protect against high glucose-induced vascular damage in diabetic patients (87).

In another study, the use of α-mangostin to treat $CoCl_2$-induced hypoxic injury in H9C2 cardiomyocytes demonstrated increased cell viability in the treatment group, with the concentration of 0.06 mM being the most effective concentration (88). Additionally, the treatment also reduced ROS and MDA, while increasing SOD levels. α-mangostin treatment reduced the number of apoptotic cells treated with $CoCl_2$. RT-qPCR analysis further revealed that the treatment also increased expression of Bcl-2, while reducing gene expression of Bax, caspase-3 and-9, involved in apoptosis. This finding was in accordance with the reduction of protein levels of Bax, caspase-3 and caspase-9, and revealed that α-mangostin exerted cardioprotective effects by reducing apoptotic genes and oxidative stress (88).

Hyperglycemia affects the vascular system, leading to vascular complications, which are the leading causes of mortality among individuals with diabetes. The damage to the endothelial stems from an aberrant accumulation of ceramide (59), occurs when NO production is impaired (79). NO is a natural molecule produced by endothelial cells that controls the vascular tone in a paracrine manner (89). Hyperglycemia activates the acid sphingomyelinase (aSMase)/ceramide pathway. The activation of this pathway leads to ROS generation, inhibiting NO production in endothelial cells (90) and affecting the vascular tone. Ceramide accumulation and its metabolites exert damaging effects on insulin sensitivity, pancreatic β-cell function, vascular reactivity and mitochondrial metabolism (91).

In a previous study, diabetic mice treated with α-mangostin (10 mg/kg) for 12 weeks presented with limited aSMase activity and ceramide deposition in the aortas and partially improved vascular dysfunction (79). The endothelial vascular dysfunction was also improved through eNOS/NO pathway as α-mangostin increased the expression of phosphorylated eNOS in diabetic mouse aortas. In isolated aortas, α-mangostin was also reported to prevent the activation of aSMase/ceramide pathway induced

by high glucose. Following a testing of the compound in high glucose environment endothelial cell culture, α-mangostin reversed the upregulation of aSMase/ceramide pathway. That study suggested that α-mangostin may improve endothelial dysfunction, by affecting the aSMase/ceramide pathway (79). α-mangostin could exert this effect as it has been revealed to be a competitive inhibitor of the aSMase enzyme (92). The restoration of the vascular function resulted from increased NO generation and eNOS phosphorylation. α-mangostin has also been proposed to reduce endothelial vasoconstrictor, endothelin-1 (ET-1) (63). ET-1 is overexpressed due to hyperglycemia-induced oxidative stress and the generation of free radicals, and enhances vascular resistance (93,94).

In a previous study using a rat model of doxorubicin-induced cardiotoxicity, treatment with α-mangostin (100 and 200 mg/kg) was suggested to improve electrocardiograph recordings, heart/body weight ratio and histological structures, increase systolic blood pressure, decrease MDA levels, improved the GSH level and normalize creatine kinase-MB (CK-MB) levels and lactate dehydrogenase (LDH) compared to doxorubicin-treated (DOX) rats (95). CK-MB detection in serum is a sensitive indicator in the early stages of cardiac damage, whereas LDH levels will increase when further cardiac damage occurs (96,97). As previously demonstrated, α-mangostin (100 mg/kg) reduced the ratio of Bax/Bcl-2 as compared to DOX in heart tissues. It also decreased apoptotic protein caspase-9 and-3 levels, and myocardial IL-1β and TNF-α expression levels (95). Similarly, Soetikno *et al* (98) revealed that treatment with α-mangostin (100 and 200 mg) decreased CK-MB, LDH, blood pressure and cardiac proinflammatory cytokine levels (TNFα, MCP-1, IL-6 and IL-1β), by inhibiting the infiltration of cardiac tissue with immune cells, and decreasing cardiac hypertrophy and fibrosis in rats with STZ-induced diabetes.

In a prospective cohort study, patients with high-risk Framingham Score treated with 2,520 mg of *G. mangostana* extract daily for 90 days, exhibited reduced MDA levels and increased SOD levels, as compared to the placebo group (99). The excessive formation of ROS can trigger the production of MDA, as a result of lipid peroxidation, endogenous antioxidants combined with exogenous antioxidant compounds could counteract MDA formation. The anti-atherogenic effects observed in that study could most possibly be attributed to the antioxidant properties of xanthones from *G. mangostana*, resulting in the inhibition of LDL oxidization and MDA formation (99).

In an animal model fed a high-cholesterol diet, the administration of 400 and 800 mg/kg ethanolic extract of mangosteen pericarp, rich in α- and γ-mangostin, significantly counteracted the effects of the high-cholesterol diet by reducing H_2O_2 plasma concentration, increasing CAT activity and inhibited the formation of foam cells in the aorta (100). The reduction of plasma H_2O_2 could possibly be attributed to the increased conversion of this compound into oxygen and water. However, it could also be potentiated by the antioxidant activities of phytocompounds in the pericarp extract (100). Another study using an animal model similar to the aforementioned one demonstrated that daily treatment with a 400 and 800 mg/kg body weight dose of ethanolic extract of mangosteen pericarp, reduced NF-κB and iNOS levels, while maintaining eNOS activity in treated rats (101).

Furthermore, Wistar rats fed a high-fat diet and treated with 200, 400 and 800 mg/kg body weight of ethanolic extract for 8 weeks exhibited a decreased thickness of aortic perivascular adipose tissue and reduced thickening of tunica intima-media compared to control high fat group (102). Smooth muscle vascular cell adhesion protein 1 expression was significantly decreased in treated rats, according to the evaluation by double-staining immunofluorescence. Additionally, HDL-C levels were increased and LDL-C levels were reduced in treated rats, along with the reduction of TG and TC, particularly in the 400 and 800 mg/kg groups (102).

In summary, α-mangostin exhibits cardioprotective activities through various mechanisms, including: i) Blood pressure, arterial wall thickness and cardiovascular remodeling reduction; ii) improvement of cardiovascular structures by reducing fibrosis and collagen deposition and cardiac stiffness; iii) reduction of lysosomal hydrolases in both serum and cardiac tissues; iv) preservation of myocardial membrane integrity by restoring membrane-bound phosphatases function; v) restoration of mitochondrial functions; vi) reduction of atherosclerosis risk by increasing M2 macrophage populations in atherosclerotic lesions; vii) reduction of cardiac and endothelial cell apoptosis through pathways including suppression of JNK and p38-MAPK pathway; viii) reduction of endothelial cell senescence through activation of SIRT1; ix) reduction of aortic aSMase and ceramide deposition; x) improvement of cardiac and aortic eNOS expression and NO concentration and reduction of iNOS and NFκB expressions while maintaining eNOS expression; xi) reduction of CK-MB and lactate dehydrogenase; xii) reduction of aortic perivascular adipose tissue and tunica intima-media thickening; and xiii) reduction of inflammation and oxidative stress. The molecular mechanisms of the cardioprotective and anti-atherogenic effects of α-mangostin are summarized in Fig. 4 and Table IV.

6. Antioxidant effects of α-mangostin

Antioxidants are of physiological importance as they reduce ROS generation, and are linked to tissue damage, aging and chronic inflammation (103). The human body has an antioxidant system involving SOD, GPx and CAT. These enzymes function together with SOD, converting the superoxide anion (O_2-) to H_2O_2, which GPx and CAT convert in turn to water. Another antioxidant protein is GSH, that reduces ROS accumulation (104). According to a previous study, α-mangostin was reported to exert protective effects against oxidative stress by modulating the production of SOD, GPx, GSH and CAT, via the nuclear factor-erythroid 2-related factor 2 (Nrf2) transcription factor which targets genes involved in antioxidant, detoxification, metabolism and inflammatory pathways (104).

Fang *et al* (105) used a mouse light damage model to induce retinal death via the production of H_2O_2. H_2O_2 produces oxidative stress, acting as ROS and activates caspase 3, leading to apoptotic reactions. Treatment with α-mangostin (30 mg/kg) increased Nrf2 translocation to the nucleus following light exposure to, inducing the expression of antioxidant genes, reducing cleaved caspase-3 expression and retinal damage. The interaction of α-mangostin with Nrf2 is a common mechanism, inducing antioxidant expression, leading to resistance

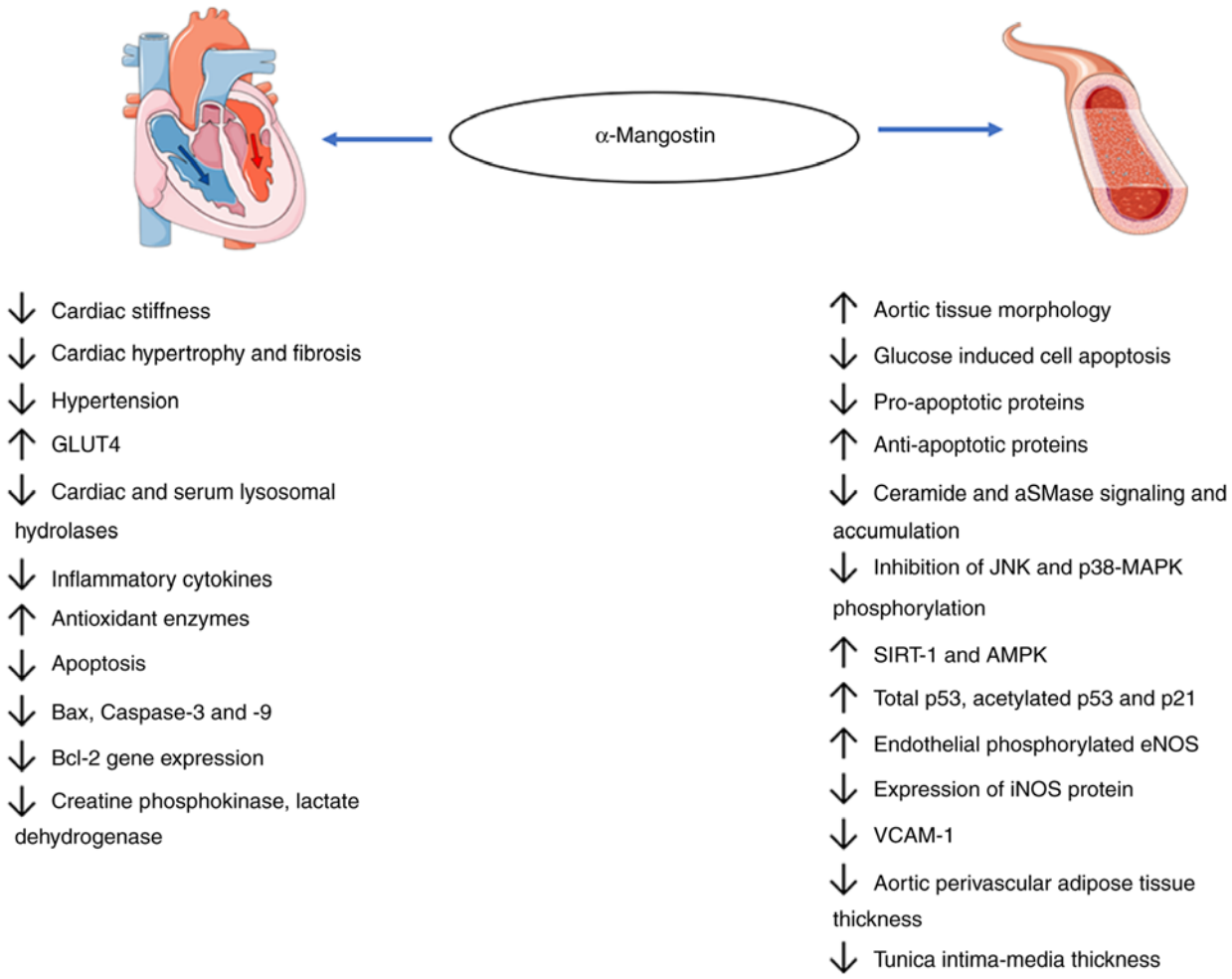

Figure 4. Cardioprotective and anti-atherogenic effects of α-mangostin. α-mangostin protects the heart and blood vessels against several stressors, including reactive oxygen species, drug-induced stressors, lipids, aSMase activity, hyperglycemia and various potentially harmful signaling pathways. It lowers the levels of inflammatory cytokines and proapoptotic proteins, such as Bax and caspase-3 and-9, leading to tissue death, lactate accumulation and aSMase/ceramide signaling. α-mangostin increases the levels of anti-apoptotic proteins (p53) and antioxidant enzymes. It restores the heart and blood vessel morphology by reducing creatine kinase-MB and lactate dehydrogenase, reducing aortic perivascular adipose tissue deposition and reducing VCAM-1 expression, tunica intima-media thickening. aSMase, acid sphingomyelinase; VCAM-1, vascular cell adhesion molecule 1; GLUT, glucose transporter; SIRT1, sirtuin 1.

to oxidant stress. In the same mouse experiment, treatment with α-mangostin restored the levels of SOD, GPx and GSH. In the same study, retinal pigment epithelia 19 (ARPE-19) cells exposed to H_2O_2 were used to induce cytotoxicity. Pre-treatment with α-mangostin led to a reduced apoptosis in a dose-dependent manner (4-12 μM), with an apoptotic rate of 5.85% observed at 12 μM. α-mangostin reduced ROS production, as observed by DCF fluorescence in flow cytometry. A similar effect was observed in cultured cells in terms of restoring levels of SOD, GPx, GSH, and increasing heme oxygenase 1 (HO-1) expression, revealing the robustness of this molecule (105).

In a previous study by Fu *et al* (72) in a mouse model of lipopolysaccharide (LPS)/d-galactosamine (D-GalN)-induced acute liver failure, α-mangostin also interacted with Nrf2. In that study, treatment with α-mangostin resulted in an increased expression of Nrf2, heme oxygenase 1 (HO-1) hepatic GSH, SOD and CAT with a reduction in hepatic MDA levels (72). This suggests that α-mangostin either positively interacts with Nrf2 or negatively with Kelch-like ECH-associated protein 1 (KEAP1). KEAP1 is a negative regulator of Nrf2, as it ubiquitinates Nrf2, targeting it for degradation (106). Further research has revealed that α-mangostin stimulation induces the dissociation of KEAP1 from Nrf2 in the cytosol and *in vivo*, supporting the notion that α-mangostin could dissociate Nrf2 from KEAP1, permitting Nrf2 protein accumulation and nuclear translocation (105).

α-mangostin also has anti-oxidant activity by inhibiting the aSMase enzyme (79). A high-fat/carbohydrate diet decreases SOD and GPx levels, favors the accumulation of glucose-induced ROS, and results in increased levels of the pro-inflammatory markers, TNF-α and IL-6 (44,79). Increased ROS generation aggravates the system by activating the aSMase/ceramide pathway, leading to ceramide-induced cell death. By using primary endothelial cells and a db/db diabetic mice, Jiang *et al* (79) revealed that α-mangostin reversed the high glucose-induced ROS production and aSMase/ceramide pathway activation by inhibiting the aSMase enzyme, as α-mangostin is a competitive inhibitor of the aSMase enzyme according to another study (92). This results in an upregulation of eNOS/NO pathway in aortas from diabetic mice, reducing ROS levels and restoring their structure and function (79).

Table IV. Cardioprotective and anti-atherogenic effects of a-mangostin.

Authors	Source of α-mangostin	Model *in-vitro/in-vivo*	Dosage and duration	Mechanism of action on cardioprotective effects	(Refs.)
Sampath and Vijayaragavan	Purified α-mangostin	Isoproterenol induced-myocardial necrosis Wistar rats	200 mg/kg/body weight 8 days	• ↓TNF-α and COX-2 • ↓Activities of membrane-bound phosphatases • ↓Cardiac and serum lysosomal hydrolases	(32)
Sampath and Kannan	Purified α-mangostin	Isoproterenol induced-myocardial necrosis; Wistar rats	200 mg/kg/body weight (pre-treatment) 8 days	• ↑Cytochrome *c*, c1, aa3 and b levels • ↑NADH dehydrogenase and cytochrome *c* oxidase activities • ↑Antioxidant enzymes (GSH, GPx, GST, SOD, CAT) • ↓Lipid peroxides • ↑Cardiac eNOS	(85)
Jittiporn *et al*	α-mangostin extracted from *G. mangostana* peel	Human umbilical vein endothelial cells	10-100 nM 72 h	• ↓ROS, ↓ apoptosis • ↓Inhibition of JNK and p38-MAPK phosphorylation	(86)
Fang *et al*	Purified α-mangostin	CoCl2-induced apoptotic damage H9C2 cardiomyoblasts	0.012, 0.06, 0.3, 0.6 or 1.2 mM 24 h	• ↓ROS, MDA • ↑SOD • ↓Apoptosis • ↓Bax, caspase-9 and caspase-3 gene expression and protein • ↓Bcl-2 gene expression	(88)
Tousian *et al*	Purified α-mangostin	Human umbilical vein endothelial cells	1.25 μM (non-toxic xconcentration) 6 days	• ↑Total p53, acetylated p53 and p21 • ↓SA-β-GAL • ↑SIRT-1 and AMPK	(87)
Jiang *et al*	Purified α-mangostin	Primary aortic endothelial cells C57BL/KsJ; diabetic (db/db) mice	10 mg/kg/day, i.p.; mice 12 weeks 15 μM α-mangostin; cell culture 24 and 48 h	• ↓Serum aSMase and ceramide • ↓Aortic aSMase and ceramide • ↑Endothelial cell NO production • ↑Endothelial phosphorylated eNOS	(79)
Eisvand *et al*	Purified α-mangostin	Doxorubicin-induced cardiotoxicity rat model Heart cells MC7 cells	50, 100, 200 mg/kg per day 19 days	• ↓MDA, caspase-3 and -9 • ↓Inflammatory markers • ↑Heart weight • ↓Creatine phosphokinase, lactate dehydrogenase • ↓IL-1β and TNF-α	(95)

Table IV. Continued.

Authors	Source of α-mangostin	Model *in-vitro*/*in-vivo*	Dosage and duration	Mechanism of action on cardioprotective effects	(Refs.)
Soetikno *et al*	Purified α-mangostin	Wistar rat	100, 200 mg/kg per day 8 weeks	• ↓CK-MB, LDH • ↓Prevent weight loss in diabetic rats • ↓Blood pressure • ↓AST and ALT • ↓Total cholesterol and triglyceride • ↓Cardiac pro-inflammatory levels (TNFα, MCP-1, IL-6, IL-1β) • ↓Cardiac hypertrophy and fibrosis	(98)
Shibata *et al*	*G. mangostana* extract rich in α-mangostin	Male Apoe$^{-/-}$ mice	0%, 0.3%, 0.4% of α-mangostin; 17 weeks	• ↑Aortic tissue morphology • ↓Total cholesterol (VLDL) • ↓Triglyceride • ↑Serum lipoprotein lipase • ↑CD163 • ↑IL-13 • ↑M2 polarization • ↓IFN-γ, TNF-α and IL-1β	(81)
John *et al*	*G. mangostana* rind rich in α-mangostin	Wistar rats (high carbohydrate, high fat)	168 mg/kg per day 8 weeks	• ↓Systolic blood pressure • ↓Cardiac stiffness • ↓Cardiac hypertrophy and fibrosis • ↑Endothelial tissue activity	(12)
Boonprom *et al*	*G. mangostana* pericarp extract	Sprague-Dawley rats (L-Name induced hypertension)	200 mg/kg per day (extract) concentration (extract) concentration of α-mangostin; not detailed; 5 weeks	• ↓Hypertension and cardiovascular remodeling • ↓Oxidative stress (MDA) and inflammation (TNF-α) • ↓Expression of $_{p}47^{phox}$NADPH oxidase subunit • ↓Expression of iNOS protein in aortic tissues • ↓Arterial wall thickness • ↑Plasma NO metabolites	(84)

Table IV. Continued.

Authors	Source of α-mangostin	Model *in-vitro/in-vivo*	Dosage and duration	Mechanism of action on cardioprotective effects	(Refs.)
Ismail *et al*	*G. mangstana* Pericarp extract	Patients with high-risk Framingham score	2,520 mg/day (extract) Concentration of α-mangostin; not detailed; 90 days	• ↑Plasma SOD • ↓Plasma MDA • ↓Atherosclerosis risk	(99)
Adiputro *et al*	*G. mangostana* Ethanolic pericarp extract	Wistar rats (High-cholesterol diet)	200, 400, 800 mg/kg per day (containing 0.064% α-mangostin and 6.144% of γ-mangostin) (Treatment duration not stated)	• ↓Plasma H_2O_2 • ↑Plasma CAT • ↓Foam cells	(100)
Wihastuti *et al*	*G. mangostana* Ethanolic pericarp extract	Wistar rats (High-cholesterol diet)	200, 400, 800 mg/kg per day 3 months	• ↓NF-κB • ↓iNOS • Maintain eNOS	(101)
Wihastuti *et al*	*G. mangostana* Ethanolic pericarp extract	Wistar rats (High-cholesterol diet)	200, 400, 800 mg/kg per day 2 months	• ↓Aortic perivascular adipose tissue thickness • ↓Tunica intima-media thickness • ↓VCAM-1 expression	(102)

Upward arrows (↑) indicate an increase, and downward arrows (↓) indicate a decrease. *G. mangostana*, *Garcinia mangostana*; GSH, glutathione; GPx, glutathione peroxidase; CAT, catalase; eNOS, endothelial nitric oxide synthase; ROS, reactive oxygen species; MDA, malondialdehyde; SIRT1, sirtuin 1; aSMase, acid sphingomyelinase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; NO, nitric oxide; iNOS, intracellular nitric oxide synthase.

Muhamad Adyab *et al* (44), using an obese rat model, demonstrated that rats fed a high-fat/carbohydrate diet supplemented with a 200-600 mg/kg dose of mangosteen flesh extract improved SOD and GPx levels (44).

α-mangostin can counteract the effects of lactate-induced ROS production via MDA generation, and liver damage due to ionizing radiation and thioacetamide. In a previous study by Chang *et al* (107), rats subjected to high rates of exhaustive exercise accumulated high levels of lactate in both liver and muscle tissues, which was rapidly cleared in rats given α-mangostin. Levels of MDA also diminished in both tissues (5-fold in liver and 10-fold in muscle) and levels of CAT and GPx increased in both tissues. Thioacetamide- and radiation-induced liver damage, as measured by ALT, AST and ALP liver biomarkers, has been also reported to be reversed in α-mangostin-treated mice (70,73). Hassan *et al* (70) previously exposed rats to ionizing radiation, in order to mimic the situations in which the liver is damaged due to radiotherapy treatment or accidental exposure. Radiation caused alterations in liver protein homeostasis and increased plasma liver markers like ALT, AST and ALP, indicating liver damage. SOD and CAT levels were significantly reduced after radiation; however, their levels were restored by treatment with α-mangostin at the 500 mg/kg equivalent dose per day. MDA and NO levels in the radiated liver doubled compared to the control; however, this was reduced to normal levels by α-mangostin treatment.

Abood *et al* (73) examined the effects of in thioacetamide-induced liver cirrhosis in rats. Thioacetamide increased liver markers, AST, ALP and ALT, increased MDA levels, and reduced SOD and CAT enzymes, while α-mangostin (250 and 500 mg/kg), significantly reduced the effects of thioacetamide treatment and conserved the liver, heart and kidney from thioacetamide damage. In a previously reported experiment by Lazarus *et al* (108), SOD levels increased significantly in

the heart with an α-mangostin dose of 100 mg/kg. However, a significant improvement was observed with 200 mg/kg treatment in the kidneys. GSH also increased in both tissues, and α-mangostin reversed MDA levels in the liver, kidneys, and heart tissues. Further study is still required, in order to finalize the ideal concentration at which beneficial effects are seen.

Harliansyah *et al* (109) also reported on the potential tissue-specific potency of α-mangostin. By using HepG2 and WRL-68 cells, it was observed that when they were exposed to ROS stimulating chemicals, α-mangostin reduced ROS levels in both cell lines at comparable levels in a concentration-dependent manner (5-1,000 μg/ml). However, when assessing MDA levels, α-mangostin led to a more significant MDA reduction in the HepG2 cancer line, possibly due to the increased oxidative stress in comparison with the WRL-68 cell line. Notably, when compared to WRL-68, a normal human hepatic cell line, HepG2 cell line presented with a more notable reduction of MDA (109). It is possible that HepG2 presented with more reduced MDA because of the effects of both ROS that stabilizes Nrf2, and oncogenic signaling via KRAS and BRAF that has been revealed to induce Nrf2 stabilization (110), leading to enhanced production of antioxidant proteins. They also analyzed protein carbonyl levels, evaluating the amount of ROS oxidized protein, and observed that α-mangostin-treated cells demonstrated decreased ROS levels. The effect was more intense in the WRL-68 cell line, indicating that this cell line was more responsive, highlighting the potential anticancer properties of α-mangostin.

Mitochondria are essential organelles involved in energetic homeostasis and the production of reactive oxygen species. In a previous study, treatment of proximal tubule Lilly laboratory culture porcine kidney (LLC-PK1) cells with Cis-dichlorodiammineplatinum II (CDDP)-induced damage with α-mangostin (4 μM) demonstrated that the compound preserved mitochondrial function and mass (111). α-mangostin inhibited the CDDP-induced decrease in cell respiratory states, in the maximum capacity of the electron transfer system and the respiration associated with oxidative phosphorylation protein, preventing changes in mitochondrial bioenergetics alterations. It also prevented mitochondrial mass reduction and fragmentation through the preservation of the mitofusin 2 fusion marker, reducing induction of autophagy by CDDP (111), and revealing that α-mangostin can modulate the ROS production at the organelle level.

In another study, in a model of sodium iodate-induced ROS-dependent toxicity using ARPE-19 cells, α-mangostin (3.75, 7.5 and 15 μM) prevented cell death, although not at the 20 μM dose. α-mangostin also prevented mitochondrial damage as revealed by JC-1 staining, reduced intracellular ROS levels and the extracellular H_2O_2 concentration, increased CAT and GSH levels, and decreased SOD levels (112). This treatment also prevented cell apoptosis through the regulation of apoptosis-related proteins. α-mangostin treatment protected ARPE cells against sodium iodate-induced oxidative damage by reducing SIRT-3 expression, mediated by the PI3K/AKT/PGC-1α signaling pathway. Treatment with α-mangostin in this mouse model revealed that it could prevent retinal degradation and apoptosis induced by sodium iodate (112). The proposed mechanism was that α-mangostin modulated the SIRT-3 pathway (113). SIRT-3, a member of the sirtuin family, is a mitochondrial enzyme that modulates deacetylation and acetylation of mitochondrial enzymes and is known to prevent ROS and the development of cancerous cells or apoptosis (114). As previously explained, α-mangostin treatment reduced caspase-3 protease levels, reduced cell apoptosis, and increased p-PI3K-AKT levels, demonstrating the protective effects of this compound in the presence of STZ (52,58) and high glucose (59).

In summary, the antioxidant effects of α-mangostin are exerted primarily through the stabilization of cytoplasmic Nrf2, the increase in heme oxygenase 1 (HO-1) expression, the modulation of the aSMase/ceramide pathway, kinase signaling pathways (p38 MAPKs and JNK kinases) and the acetylation activity of SIRT-3 enzymes. The mechanisms through which α-mangostin affects these enzymes remain unknown. However, a recent study investigating α-mangostin and α-glucosidase suggested, that in the presence of α-mangostin, α-glucosidase has a more α-helical secondary structure, making it more compact and decreasing its catalytic activity (65). Acting via these mechanisms, antioxidant enzymes including SOD, GPx, CAT, GSH are increased and oxidative stress markers including MDA and ROS are reduced. There is also a mechanism controlling the apoptotic pathways, protecting cells from ROS induced caspase 3 cell damage. α-mangostin also protects the mitochondria via the preservation of mitochondrial respiratory processes, leading to reduced ROS production and improvement in cell homeostasis. The antioxidant effects of α-mangostin are summarized in Fig. 5 and Table V.

7. Anti-inflammatory effects of α-mangostin

The increased expression of pro-inflammatory cytokines has been reported in obesity (115). This has been linked to the changes in adipose tissue biology in the excess nutrient environment of obesity, by undergoing hypertrophy and hyperplasia (116). Adipocyte hypertrophy reduces blood supply to adipocytes and promotes hypoxia (117). Hypoxia leads to necrosis and macrophage migration into adipose tissues, enhancing the production of proinflammatory chemokines, including TNF-α and IL-6 resulting in systemic inflammation (118,119). Chronic low-grade inflammation has been associated with the development of insulin resistance and type 2 diabetes in obese subjects (6). Excluding obesity, various factors have been suggested to induce inflammation, including pathogens, damaged cells and toxic compounds (120). The anti-inflammatory effects of α-mangostin have been extensively investigated and reviewed, underlining the importance of this compound as an anti-inflammatory agent.

In a previous study, in a mouse model fed a high-fat diet, treatment with-mangostin (50 mg/kg per day) reduced macrophage infiltration in white adipose tissue as tested using F4/80 macrophage marker. Obese mice treated with α-mangostin also presented with reduced levels of M1 macrophage marker, CD11c, diminished collagen staining, and increased levels of the M2 macrophage marker, CD206 (25). α-mangostin-treatment in obese mice reduced macrophage genes F4/80 and CD11c, in both the white adipose tissue and liver tissue. α-mangostin-treatment also reduced proinflammatory genes MCP-1 and IL-6 in white tissue and reduced TNFα, MCP-1 and C-C chemokine receptor type 2 (CCR2)

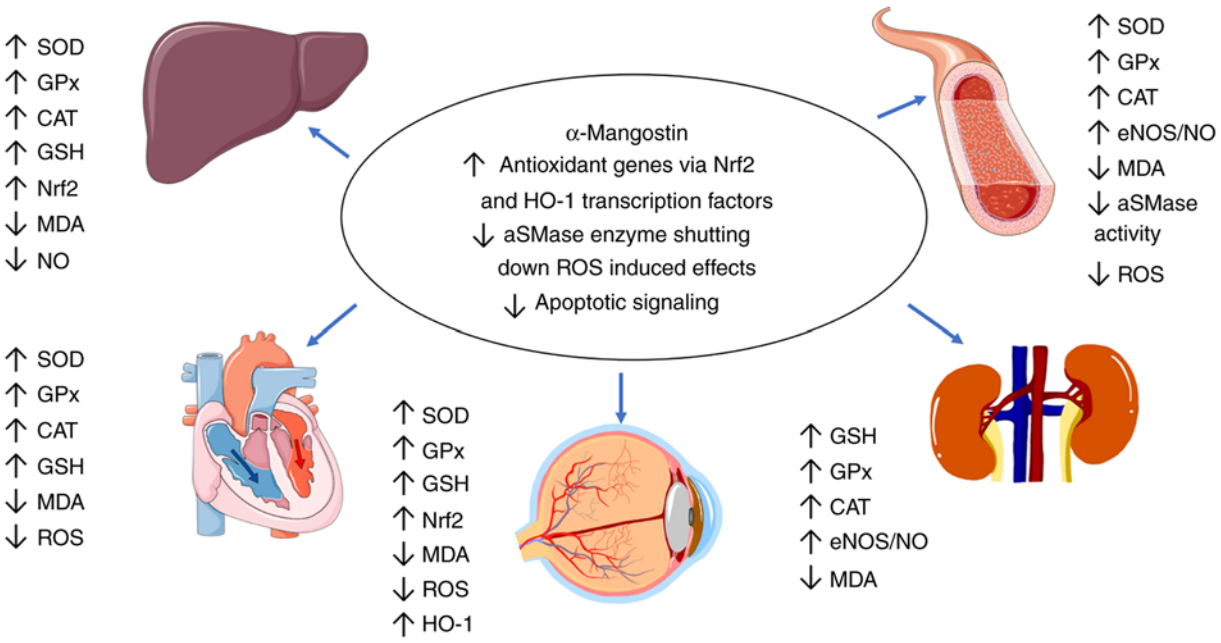

Figure 5. Antioxidant mechanisms of α-mangostin. α-mangostin exhibits antioxidant activity via three main mechanisms as demonstrated in the present review. It stabilizes Nrf2, which is a transcription factor that leads to the production of antioxidant proteins. It inhibits aSMase activity and modulates various signaling pathways. These actions in turn increase production of SOD, GPx, CAT and GSH in various tissues, leading to a decrease in ROS and MDA levels. aSMase, acid sphingomyelinase; ROS, reactive oxygen species; SOD, superoxide dismutase; GSH, glutathione; GPx, glutathione peroxidase; CAT, catalase; MDA, malondialdehyde; NO, nitric oxide; Nrf2, nuclear factor-erythroid 2-related factor 2; HO-1, heme oxygenase 1; eNOS, endothelial nitrix oxide synthase.

in the liver. The levels of the anti-inflammatory genes, IL-10 and M2, and the macrophage marker, CD206, increased (25). Kim *et al* (25) also demonstrated that α-mangostin reversed hepatic steatosis, delayed the movement of macrophages in tissues, and reduced the expression of proinflammatory cytokines (TNFα, MCP-1, CCR2 and IL-6).

In another study, in mice exposed to LPS, the serum concentrations of IL-6, TNFα, and MCP1 were reduced in the α-mangostin group, and their expression was downregulated in epididymal white adipose tissue (eWAT) (42). Gene expression analysis on eWAT revealed a reduced expression of the chemokines, MCP-1, macrophage inflammatory protein-1α (Mip-1α) and the CXCL10, CCL11, CX3CL1 and CCL5. Pre-treatment with α-mangostin also reduced the gene expression in eWAT of macrophage-specific markers, F4/80 and Cd68. This reduced expression indicates a decreased macrophage content in eWAT. Moreover, the M1 macrophage marker, Cd11c, was suppressed; however, the levels of M2 macrophage markers, Cd206 and Arginase-1, were increased in treated mice. Additionally, α-mangostin reduced iNOS expression, increased SIRT3 expression, reduced the activation of the MAPK and NF-κB pathways in eWAT, and reduced Iκ activation in macrophages. These findings were consistent with those obtained with RAW264.7 macrophages and demonstrated that α-mangostin reduced inflammation by suppressing MAPK and NF-κB activation, while promoting SIRT3 expression (42). Similarly, in the study by Li *et al* (42) in aged mice, it was also revealed that α-mangostin alleviated aging-related adipose tissue inflammation by significantly reducing the adipocyte size and the amount of F4/80$^+$ macrophages in eWAT in aged mice. A Transwell chemotaxis assay revealed that the pre-treatment of RAW264.7 macrophages with α-mangostin reduced macrophage migration towards the adipocyte cellular matrix, revealing that α-mangostin promoted a shift towards anti-inflammatory macrophage polarization. In comparison to LPS-exposed mice, similar effects of α-mangostin in aged mice were also observed, with the reduced expression of the chemokines, Mcp-1, Mip-1α, Cx3cl1 and Ccl5, and reduced adipose tissue inflammation through the inhibition of iNOS, TNF-α, IL-1β and COX-2 expression levels, while increasing SIRT3 expression. Furthermore, α-mangostin protected aged mice from liver injury by inhibiting macrophage release of miR-155-5p (42).

Using the LPS-induced inflammation IEC-6 cell line model, Yin *et al* (121) demonstrated that the expression levels of the NLRP3 inflammasome and caspase-1, proteins that initiate inflammation and trigger the release of the proinflammatory cytokines, IL-1β and IL-18, were significantly reduced following the administration of α-mangostin, as indicated by RT-qPCR, western blotting and immunohistochemistry. Whole-genome transcriptomic analysis in the IEC-6 lines revealed that α-mangostin upregulated 175 genes and downregulated 324 genes. Gene Ontology (GO) analysis suggested that two groups of differentially expressed genes affected by either LPS or α-mangostin are mainly linked with inflammation and oxidative stress. The Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis revealed that pre-treatment with α-mangostin affected the TNF, JAK-STAT, p53 and MAPK signaling pathway cytokine-cytokine receptor interaction (121). α-mangostin also normalized the intestinal villus morphology of mitochondria and nucleus and improved the swelling of the villi in an LPS-induced inflammatory rat model. The tips of the intestinal villi were relatively intact, the damage to the lamina propria was reduced, congestion was clearly improved and bleeding was significantly reduced (121). In

Table V. Antioxidant effects of a-mangostin.

Authors	Source of α-mangostin	Model *In vitro*/*in vivo*	Dosage and duration	Mechanisms of action of antioxidant effects	(Refs.)
Chang *et al*	Mangosteen concentrate drink	Sprague-Dawley rats	13 mg/day 6 weeks	• ↓Hepatic MDA • ↓Hepatic and muscular GPx • ↓Hepatic and muscular SOD • ↓Hepatic and muscular CAT	(107)
Jiang *et al*	Purified α-mangostin	C57BL/KsJ; diabetic (db/db) mice primary aortic endothelial cells	10 mg/kg/day; i.p.; mice 12 weeks 15 μM α-mangostin; cell culture 24 and 48 h	• ↓Hepatic TBARS • ↑Hepatic antioxidant enzymes (GSH, GPx, GRd, SOD, CAT) • ↓Primary hepatocytes (TBARS, tROS, mitoROS, cytocrhome *c*) • ↑Primary hepatocytes mitochondrial function (NCCR mito complex I and III) and SCCR (mito complex II and III) • ↑Primary hepatocytes mitochondrial oxygen consumption rate	(79)
Abood *et al*	*G. mangostana* peel extract	Sprague-Dawley rats	250 and 500 mg/kg per day (α-mangostin concentration not detailed) 8 weeks	• ↓Hepatic MDA • ↑Hepatic SOD and CAT	(73)
Hassan *et al*	*G. mangostana* fruit rind	Wistar rats	500 mg/kg per day for 30 days after irradiation	• ↓Hepatic MDA, NO, SOD and CAT	(70)
Yan *et al*	*G. mangostana* fruit hull	ICR mice induced by acetaminophen, acute liver injury model	100 and 200 mg/kg 7 days	• ↑Serum AST, GSH • ↓Serum MDA	(71)
Fu *et al*	*G. mangostana* fruit rind	Lipopolysaccharide/ d-galactosamine (LPS/D-GalN)-induced acute liver failure mouse model	12.5, 25 mg/kg 7 days	• ↓Hepatic MDA • ↑Hepatic GSH, SOD, CAT • ↑Expression of Nrf2 and HO-1	(72)
Fang *et al*	α-mangostin powder	Hydrogen peroxide (H_2O_2)-stressed RPE cells, human retinal pigment epithelial cell line, light-damaged mice model	10 and 30 mg/kg; mice; 7 days 10 μM; cell culture 24 h	• ↓MDA • ↑SOD, GPx, Gsh • ↑Expression Nrf2 and HO-1 • ↑Expression PKC-δ • ↓Expression of MAPK, ERK1/2, JNK, P38	(105)
Harliansyah *et al*	α-mangostin powder	HepG2 Cells and WRL-68 cells	5-1,000 μg/ml 24 h	• ↓MDA • ↓Protein carbonyl • ↓ROS	(109)

Table V. Continued.

Authors	Source of α-mangostin	Model *In vitro/in vivo*	Dosage and duration	Mechanisms of action of antioxidant effects	(Refs.)
Lazarus *et al*	α-mangostin compound	Wistar rats	100, 200 mg/kg per day 8 weeks	• ↓MDA (hepatic, heart, kidney) • ↑SOD, GSH	(108)
Tousian *et al*	Purified α-mangostin	Human umbilical vein endothelial cells	1.25 μM 6 days	• ↓ROS	(87)
Reyes-Fermín *et al*	Purified α-mangostin	CDDP-induced damage in proximal tubule Lilly laboratory culture porcine kidney (LLC-PK1) cells	4 μM 24 h	• ↓CDDP-induced cell death • ↓Respiratory states alterations • ↑MFN2 fusion marker • ↓Mitochondrial mass reduction and fragmentation • ↓Mitochondrial biogenesis alterations and induction of mitophagy.	(111)
Chuang *et al*	Purified α-mangostin	$NaIO_3$-induced reactive oxygen species (ROS)-dependent toxicity in ARPE-19 cells BABL/c mice	3.75, 7.5, and 15 μM 24 h 20 mg/kg Administered before injection of $NaIO_3$	• ↑Cell viability and intracellular antioxidant enzymes • ↓Apoptosis • ↓Bax, cleaved PARP-1, cleaved caspase-3 expression • ↑Bcl-2 protein • ↓Intracellular ROS and extracellular H_2O_2 • ↓CAT • ↓PI3K-AKT-PGC-1α-STRT-3 signaling • ↑Retinal structure and thickness	(112)
Muhamad Adyab *et al*	*G. mangostana* flesh	Sprague-Dawley rats	200-600 mg/kg (No α-mangostin concentration) 7 weeks	• ↑Plasma GPx • ↑Antioxidant capacity	(44)

Upward arrows (↑) indicate an increase, and downward arrows (↓) indicate a decrease. *G. mangostana*, *Garcinia mangostana*; MDA, malondialdehyde; GSH, glutathione; GPx, glutathione peroxidase; GRd, glutathione reductase; CAT, catalase; TBARS, thiobarbituric acid reactive substances; tROS, total reactive oxygen species; mitoROS, mitochondrial reactive oxygen species; NCCR, NADH-cytochrome c reductases; SCCR, succinate cytochrome c reductase; CDDP, Cis-dichlorodiammineplatinum II.

addition, pre-treatment with α-mangostin (2.5, 5 and 10 μM) in LPS-stimulated IEC-6 cells strongly decreased the phosphorylation of NF-κB subunits IB and p65, as well as their upstream proteins, transforming growth factor β-activated kinase 1 and Iκκ. This notably inhibited the degradation of NF-κB inhibitor IB, according to Zou *et al* (122).

COX-2 expression increases when there is an inflammatory reaction and results in prostaglandin 2 (PGE-2) and NO production via NF-κB, which localizes to the nucleus and promotes the expression of inflammatory genes (123). Previous research has indicated that α-mangostin can inhibit the NF-κB signaling pathway. RAW 264.7 cells treated with

LPS culminated in inflammatory cytokine level increase, including PGE-2, TNF-α, IL-6 and increased NO production and iNOS. A high NO concentration is toxic and proinflammatory (124), and TNF-α is a potent inflammatory cytokine. In a previous study, α-mangostin reversed such effects in a concentration-dependent manner by reducing the translocation of NF-κB into the nucleus compared to LPS only treated cells (123). Using a mouse peritonitis model, Mohan *et al* (123) also demonstrated that α-mangostin inhibited the infiltration of mononuclear immune cells and neutrophils in inflamed tissue in a dose-dependent manner. Inhibiting the infiltration of immune cells into tissues is particularly important as immune cells, such as neutrophils, release proinflammatory cytokines. A decreased tissue infiltration is associated with the reduced presence of TNF-α and IL-1β (123). Widowati *et al* (125) reported that the concentrations of inflammatory mediators (COX-2, IL-6 and IL-1β) and NO in treated LPS-exposed RAW 264.7 cells were reduced by α-mangostin and γ-mangostin. An *in silico* analysis of α-mangostin demonstrated that it preferentially binds to COX-2 rather than COX-1 (123). This is important as it shows that α-mangostin could acts as an anti-inflammatory agent via COX-2, suggesting that it can be a potential alternative lead compound, since current anti-inflammatory drugs target COX-1, a physiologically important enzyme with adverse effects when blocked.

Franceschelli *et al* (126) examined the effects of α-mangostin on LPS-treated U937 cells; LPS is an inducer of inflammation. α-mangostin (10 μM) inhibited LPS-induced NO production by 40%. Furthermore, α-mangostin markedly increased SIRT-1 expression, blocking the p65 acetylation, suggesting that the anti-inflammatory action of α-mangostin involves NF-κB pathway inhibition. This is supported by the reduced expression of iNOS and COX-2. An experiment using EX-527, an inhibitor of SIRT1, confirmed that α-mangostin inhibits proinflammatory NF-κB signaling through SIRT1 induction. α-mangostin also reduced the expression of IL-1β and TNFα but increased the anti-inflammatory IL-10. Similarly, the effect of α-mangostin on LPS-induced human monocytes demonstrated similar anti-inflammatory action through the modulation of SIRT-1/NF-κB signaling (126).

Additionally, according to Sugiyanto *et al* (127), the treatment with α-mangostin (5, 10 and 20 μM) reduced the expression of both TNF-α and IFN-γ in human peripheral blood mononuclear cells (PBMCs) in a concentration-dependent manner (P=0.01) following both a 24- and a 48-h post-infection. In another previous *in vivo* study, similar findings were reported on the role of α-mangostin in inhibiting the NF-κB signaling pathway (128). Yin *et al* (128) revealed that the ability of rat PBMCs, obtained from rats with collagen-induced arthritis treated with mangostin, to promote the production of cytokines (TNF-α and IL-1β) was lost.

Moreover, Tarasuk *et al* (129) demonstrated that various concentrations (10, 15 and 20 μM) of α-mangostin significantly reduced cytokine/chemokine transcription in Dengue virus (DENV-2)-infected cells. The percentage reduction of cytokines (IL-6 and TNF-α), and chemokine macrophage inflammatory protein 1β (MIP-1β), regulated upon activation, normally T-expressed, and presumably secreted (RANTES) and interferon gamma-induced protein 10 (IP-10) transcription was 94, 95, 92, 87 and 95%, respectively, as measured using RT-qPCR. At 48 h after treatment, α-mangostin considerably reduced TNF-α, MIP-1, and RANTES transcription, whereas IL-6 and IP-10 transcription was reduced, although not significantly, in comparison to the untreated control. Following 72 h, the effects on all parameters were diminished. Yongpitakwattana *et al* (130) observed that the inhibitory effects of α-mangostin (25 μM) on the expression levels of the genes, TNF-α, CCL4, CCL5, CXCL10 and IFN-α, gene involved in the vascular leakage and immunopathogenesis of DENV2-infected immature monocyte-derived dendritic cells were significantly reduced. However, it was noted that the levels of the anti-inflammatory cytokine, IL-10, were also reduced in that study, contrary to other studies reporting an increase in the levels of this cytokine following α-mangostin treatment (20,126).

In an arthritic animal model, Herrera-Aco *et al* (131) revealed that both doses of α-mangostin (10 and 40 mg/kg) significantly reduced the production of the chemokines, LIX/CXCL5, IP-10/CXCL10, MIG/CXCL9, RANTES/CCL5, IL-6 and IL-33. Furthermore, at a dose of 40 mg/kg, α-mangostin reduced the development of anti-collagen II IgG2a antibodies in DBA/1J mice in which arthritis was induced by collagen. This could indicate that one of the mechanisms through which α-mangostin exerts anti-inflammatory effects in mice with collage-induced arthritis is by altering the humoral response, which is reflected in decreased autoantibody synthesis and, most likely, immune complex development (131). In rats with adjuvant-induced arthritis, Zuo *et al* (132) found that α-mangostin reduced paw swelling, inflammatory cell infiltration and TNF-α and IL-1β release in joint serum. Additionally, Zuo *et al* (132) demonstrated that treatment with α-mangostin at 10 μg/ml suppressed the expression and phosphorylation of key proteins implicated in NF-κB pathway, and inhibited the nuclear translocation of p65 using human fibroblast-like synoviocytes/rheumatoid arthritis cells.

In rat chondrocytes treated with IL-1β, Pan *et al* (27) discovered that α-mangostin suppressed the expression of MMP-13 and ADAMTs-5, and promoted the expression of SOX-9 (27). They also observed that α-mangostin inhibited the expression of pro-apoptotic proteins, including Bax, cytochrome c and caspase-3, while increasing the anti-apoptotic protein, Bcl-2. In the same model, the treatment of α-mangostin also reduced NO and PGE2 production, and reduced the expression of iNOS, COX-2, MMP-3, MMP-9 and MMP-13, and also attenuated the degradation of collagen II and aggrecan (27,133). Moreover, α-mangostin has been demonstrated to inhibit the NF-κB signaling pathway by suppressing IL-1β-induced p65 nuclear translocation (27,133). *In vivo*, α-mangostin has been also observed to suppress the development of osteoarthritis in rat models underlined by decreased cartilage degeneration, most likely due to the downregulation of inflammation through the NF-κB pathway (27). Xu *et al* (134) observed similar findings on the reduction of the expression of IL-6 and TNF-α serum proteins and the downregulation of the NF-κB pathway in the paw tissue of male Wistar rats with adjuvant-induced arthritis treated with α-mangostin.

Under diabetic conditions, increased lipolysis leads to the increased formation of unsaturated fats. In turn, unsaturated fats activate immune cells to produce inflammatory proteins.

One protein included in this category is IL-1β, which deactivates the insulin response in tissues and organs, including the liver, muscle and adipose tissues (135), leading to insulin resistance and type 2 diabetes symptoms (136). Soetikno *et al* (98) demonstrated that α-mangostin specifically reduced IL-1β levels in a dose-dependent manner, as well as the levels of other proinflammatory proteins, including MCP-1, IL-6 and TNF-α using rats with STZ-induced diabetes fed a high-fat diet. Jariyapongskul *et al* (63) revealed that treating type 2 diabetic rats with α-mangostin treatment reduced the expression levels of AGE, receptor for AGEs, TNF-α and VEGF to 63.2, 40.9, 27.8, 65.6 and 22.3%, respectively, implying a possible mechanism by which α-mangostin suppresses inflammation and proinflammatory cytokine production.

A study investigating the anti-inflammatory effects of α-mangostin in neuroinflammation demonstrated that this compound decreased brain endothelial cell activation induced by peripheral LPS administration (137). The study by Nava Catorce *et al* (137) demonstated that α-mangostin inhibited the generation of the proinflammatory cytokines, IL-6, COX-2 and 18-kDa translocator protein (TSPO), in the brains of LPS-treated mice. The decline in COX-2 levels observed in that study was attributable to a decrease in IL-6 levels, which binds to its receptor on brain endothelial cells. Furthermore, immunofluorescence labelling revealed a decrease in TSPO-positive cells across the entire brain in mice supplied with α-mangostin (137). These findings suggest that α-mangostin could be further evaluated as an adjuvant therapy for the prevention or treatment of neurodegenerative diseases in pre-clinical models.

An interesting observation was made by Yang *et al* (138), revealing a novel anti-inflammatory mechanism of α-mangostin, involving cholinergic anti-inflammatory pathway (CAP) control, which markedly lowered IL-1β and TNF-α levels in the serum of rats with LPS-induced acute lung injury (ALI). These findings may support the hypothesis that the activation of the CAP through raising peripheral acetylcholine, upregulating α7nAchR expression, which leads to NF-κB inhibition, is involved in the therapeutic effects of α-mangostin on ALI.

In mice using a tape-stripping model, Tatiya-Aphiradee *et al* (139) revealed that formulations of *G. mangostana* pericarp ethanolic extract (GME) and α-mangostin (equivalent to -mangostin in 10% GME) decreased TNF-α, IL-6, IL-1β and TLR-2 gene mRNA expression levels in methicillin-resistant Staphylococcus aureus-induced superficial skin infection. Lim *et al* (140) reported that α-mangostin inhibited the production of IL-6, IL-8 and PGE2 in *P. gingivalis* KCOM 2804-immortalized human gingival fibroblast cells.

Based on the study by Fu *et al* (72), pre-treatment with α-mangostin (12.5 and 25 mg/kg) significantly decreased LPS/D-GalN-induced liver inflammation in mice. Furthermore, α-mangostin inhibited the LPS/D-GalN-induced upregulation of Toll-like receptor 4 (TLR4), and simultaneously phosphorylated NF-κB p65 and IκB, indicating that α-mangostin inhibited cytokine production by inhibiting TLR4-mediated NF-κB activation. In an acute acetaminophen-induced liver injury study, α-mangostin from *G. mangostana* peels reduced the levels of inflammatory cytokines, including TNF-α and IL-1β (71).

In a placebo-controlled clinical trial involving 60 healthy adults (30 females and 30 males), Xie *et al* (141) demonstrated significantly decreased C-reactive protein (CRP) levels from 2.9 mg/l on day 1 to 1.6 mg/l on 30 days following the consumption of the mangosteen product. The considerable reduction in CRP indicated that the daily consumption of the mangosteen product may help individuals reduce their inflammatory condition, although the amount of α-mangostin taken was not stated in that study. CRP reduction was also observed, along with the reduced infiltration of inflammatory cells in liver and heart tissues of obese rats treated with *G. mangostana* pericarp rich in α-mangostin (12). In the study by Hassan *et al* (70), α-mangostin reduced IL-6 and TNF-α levels in liver tissues, reduced CRP, and inhibited NF-κB/TGF-β1 signaling in Wistar rats exposed to γ-irradiation.

In summary, α-mangostin possesses exceptional anti-inflammatory properties, as demonstrated by numerous studies, as described above in this section. This compound exerts its anti-inflammatory effects by modulating the TNF-α, JAK-STAT, SIRT1/NF-κB, TLR4/NF-κB and NF-κB/TGF-β1 pathways, suppressing MAPK activation, increasing macrophage polarization to anti-inflammatory M2, reducing proinflammatory cytokine level (IL-6, MCP-1, TNF-α, IL-1β, IL-18, IFN-γ and COX-2), NLRP3 inflammasome and chemokine expression levels (MIP-1α, MIP-1β, CXCL10, CCL11, CX3CL1, CCL5, RANTES, IP-10), increasing SIRT3 and SIRT2 expression, reducing iNOS expression, and NO and PGE2 production, as well as the expression of TLR-2 and TLR-4 genes, and increasing anti-inflammatory cytokine expression levels (IL-10). The molecular mechanisms of the anti-inflammatory effects of α-mangostin are summarized in Fig. 6 and Table VI. Collectively, these findings demonstrate that α-mangostin has great potential for use as an anti-inflammatory agent.

8. Toxicity and bioavailability of α-mangostin

It has been reported that the consumption of a semi-purified diet with 845 mg/kg α-mangostin does not result in adverse effect in mice (142). The treatment of ICR mice with a 1,000 mg/kg α-mangostin dose did not lead to any detrimental effects on the mice (19). In another study, toxicity tests using α-mangostin at up to 1,250 mg/kg body weight did not significantly affect mice with STZ-induced diabetes (66). In an acute toxicity study on the effects of α-mangostin in rats, there were no toxic symptoms or mortality observed with treatment at up to 2,000 mg/kg administered orally at up to 48 h post-administration (143). However, in another study, the intraperitoneal administration of α-mangostin for 72 h caused mortality with the median lethal dose of 150 mg/kg, indicating that the route of administration could affect the bioavailability of this compound (144). In that study, the mortality observed could be most likely attributed to key organ damage, including liver, stomach, spleen, kidney, lung, heart and brain tissues, as demonstrated in the tissue distribution study following the intravenous administration of α-mangostin (144). Another study on the effects of the addition of α-mangostin in E3 medium on zebrafish (*Danio rerio*) embryos for 72 h, revealed that it could induce mortality and abnormal development with an LC_{50} value of 5.75 μmol/l (145). That study also demonstrated

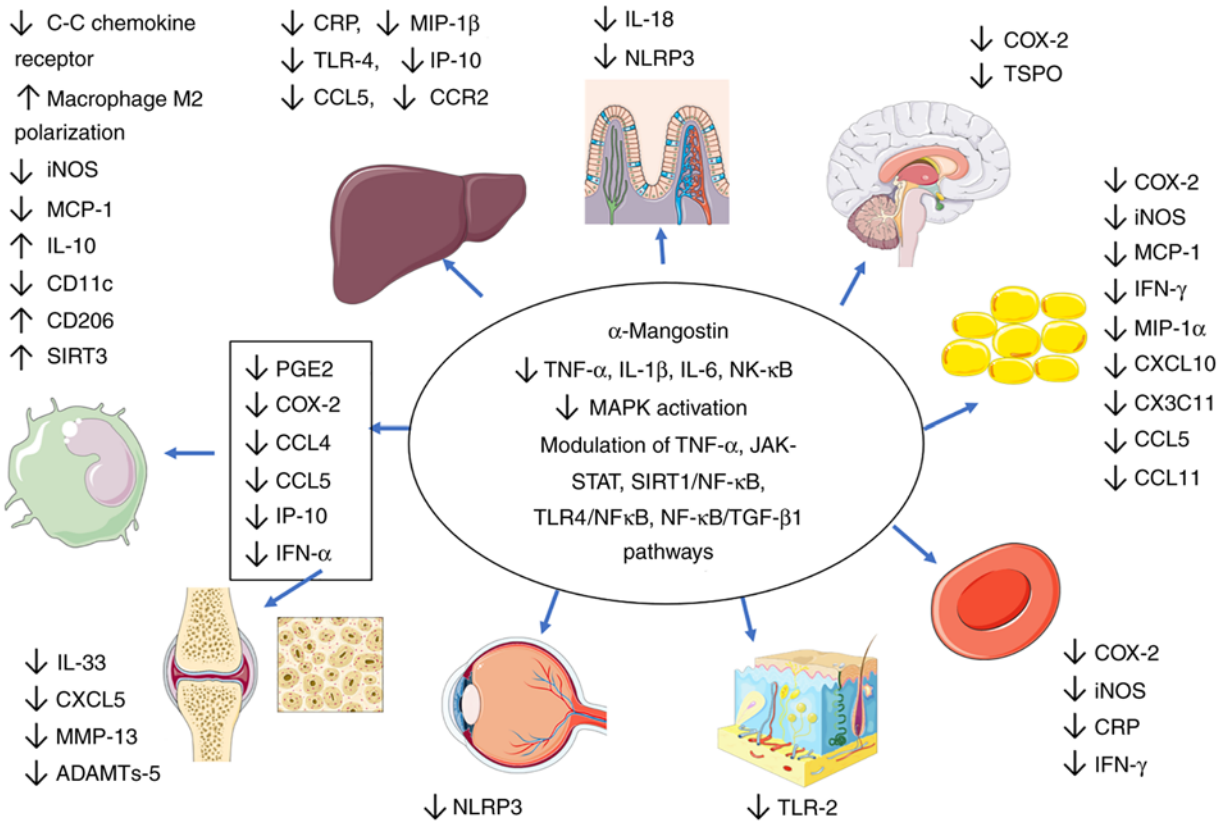

Figure 6. Anti-inflammatory effects of α-mangostin. Prolonged inflammatory responses lead to tissue damage. α-mangostin exerts anti-inflammatory effects and the effects are observed throughout the body. It modulates signaling pathways (JAK-STAT, TGF-β1, TLR4 and SIRT1 pathways) that terminate with NF-κB translocating into the nucleus. NF-κB activates inflammatory cytokines, such as TNF-α, IL-6 and IL-1β, which are released mainly through white blood cells. α-mangostin also reduces COX-2 signaling, suppresses MAPK activation, increases macrophage polarization to anti-inflammatory M2, reduces proinflammatory cytokine levels, reduces NLRP3 inflammasome levels, reduces chemokine expression (MIP-1α, MIP-1β, CXCL10, CCL11, CX3CL1, CCL5, RANTES, IP-10), increases SIRT3 and SIRT2 expression, reduces iNOS expression, reduces NO and PGE2 production, reduces the expression of TLR-2 and TLR-4 genes and increases anti-inflammatory cytokine levels (IL-10). TLR, Toll-like receptor; SIRT1, sirtuin 1; COX-2, cyclooxygenase 2; MIP, macrophage inflammatory protein; RANTES, regulated on activation, normal t cell expressed and secreted; IP-10, interferon gamma-induced protein 10; NO, nitric oxide; PGE2, prostaglandin 2; iNOS, intracellular nitric oxide synthase; CRP, C-reactive protein; TSPO, translocator protein.

that α-mangostin was potentially teratogenic and affected the embryonic ROS balance and erythropoiesis (145). Due to the variabilities among species, it is worth noting that the effects of α-mangostin may differ between species, suggesting that further studies are required to analyze the toxicity of this compound in human subjects.

As a xanthone, α-mangostin is a hydrophobic molecule affecting its solubility in aqueous environments, and is also known to have high permeation (146). The low solubility affects the bioavailability of the compound thus affecting final dose (147). A number of factors affect the solubility of compounds, including the solvent, particle size, molecular structure and nature of compound (148). In addition, α-mangostin and other cytotoxic drugs have several limitations that influence their effectiveness, including a first pass metabolism reaction, efflux reactions induced by intercellular transporters, a non-specific target site and fast drug release (149).

The bioavailability of α-mangostin has been previously studied, demonstrating different responses when pure α-mangostin compound and mangosteen extract rich in α-mangostin were administered to mice. Previously, pharmacokinetic analysis of the intravenous administration of α-mangostin or mangosteen extract revealed that the area under curve (AUC) of the compound mean arterial plasma concentration was higher in the extract group compared to α-mangostin group (144). This corresponds to the higher total body clearance of α-mangostin provided as an individual compound compared to extract formulation, suggesting that α-mangostin was mainly removed via a non-renal route, also reported by other studies (150,151). Previously, it has been reported that α-mangostin is metabolized through the hepatic microsomal cytochrome p450 (CYP) 1A2 and/or glucuronide/sulfate conjugates (151), therefore suggesting that other constituents or metabolites in mangosteen extract could interfere with glucuronide and/or sulfate conjugation of α-mangostin (144).

When orally administered, the peak plasma concentration (Cmax) of α-mangostin was higher in the extract group (0.0865 μg/ml) compared to α-mangostin group (0.0408 μg/ml); however, the time required to reach Cmax was shorter in the α-mangostin group (15 min) compared to the extract group (60 min) (144). The tissue distributions in the groups orally administered α-mangostin exhibited a higher concentration present in tissues (liver, stomach, small intestine, mesentery, spleen, kidney, muscle, lung and heart) at 45 min in the group treated with mangostin extract compared to the group treated with the pure compound (144). Notably, the concentration of α-mangostin was higher in the fat tissues

Table VI. Anti-inflammatory effects of a-mangostin.

Authors	Source of α-mangostin	Model *In vitro/in vivo*	Dosage and duration	Mechanisms of action of anti-inflammatory effects	(Refs.)
Kim *et al*	Purified α-mangostin	C57BL/6 mice RAW264.7 macrophages Mesenteric adipose tissue culture	50 mg/kg per day 12 weeks 25 μM/ml 24 h	• ↓Pro-inflammatory cytokine levels (TNF-α, IL-6, MCP1, IL-1β, CCR2) • ↑Anti-inflammatory cytokines (IL-10) • ↓C-C chemokine receptor (reduces infiltration of immune cells in tissues) • ↓M1 macrophage marker CD11c • ↑M2 macrophage marker CD206	(25)
Li *et al*	Purified α-mangostin	Mouse derived RAW264.7 macrophage 3T3-L1 preadipocytes Male C57BL/6J (LPS-induced acute inflammation and aged mice)	RAW264.7 macrophages; 1 h 10 mg/kg per day (inflammation mice) 5 days 25 and 50 mg/kg per day 8 weeks (aged mice)	• LPS group • ↓Il-6, TNF-α and MCP-1-serum and eWAT • ↓Chemokines in eWAT-MCP-1, Mip-1α and the Cxcl10, Ccl11, Cx3cl1, and Ccl5 • ↓Gene expression of F4/80 and Cd68 which are macrophage-specific markers • ↓Cd11c • ↑Cd206 and Arg-1 • ↓iNOS and IKK and ↑ SIRT3 • ↑MAPK • ↓NF-κB activation-adipose Aged mice • ↓The adipocyte size and the amount of F4/80^{+} macrophages in eWAT • ↓Expression of F4/80 and Cd68 in eWAT • ↓Cd11c, ↑ Cd206 • ↓Mcp-1, Mip-1α, Cx3cl1, and Ccl5 • ↓Reduced macrophage migration towards adipocytes • ↓MicroRNA-155-5p from macrophages, eWAT and serum and LPS stimulated RAW264.7 macrophages and bone marrow derived macrophages (BMDM)	(42)

Table VI. Continued.

Authors	Source of α-mangostin	Model *In vitro/in vivo*	Dosage and duration	Mechanisms of action of anti-inflammatory effects	(Refs.)
Yin *et al*	Purified α-mangostin	LPS-induced inflammation; intestinal epithelial cells, IEC-6 cell line (CRL21592) Sprague-Dawley rats (LPS-induced enteritis model)	10 μM; 1 h 50 mg/kg 5 days (intragastric)	• α-mangostin regulates 475 genes mainly related to inflammation and oxidative stress (151 genes up-regulated, 324 genes downregulated) in IEC-6 sample • ↓Reduced intestinal villus congestion and hemorrhage Preserve epithelial nuclei and mitochondrial morphology • ↓Expression of inflammatory genes in LPS induced cells (IL-18 and IL-1β) • ↓Production of NLRP3 inflammasomes • ↓Caspase 1	(121)
Zou *et al*	Purified α-mangostin	IEC-6 cells	2.5, 5, and 10 μM 1-h pre-treatment + 24 h LPS exposure	• ↓Production of inflammatory factors • ↓Activation of TAK1–NF-κB signaling pathway-related proteins, and the entry of p65 into the nucleus	(122)
Mohan *et al*	Pericarp of *Garcinia mangostana*	RAW 264.7 cells Male ICR mice	24 h 1 to 25 mg/kg 60 min or 30 min before carrageenan injection	• ↓Production of PGE_2, nitric oxide, iNOS protein expression. • ↓TNF-α and IL-6 Inhibit the translocation of NFkB and suppressing the COX-2 enzymes • ↓Total leukocyte migration • ↓TNFα and IL-1β in the peritoneal fluids	(123)
Widowati *et al*	Purified α-mangostin *Garcinia mangostana* peel extract (GMPE)	RAW264.7 cells	α-mangostin: 75, 50, 25 μM 24 h with LPS GMPE: 20, 10, 5 μg/ml 24 h with LPS	• ↓COX-2, IL-6, IL-1β, and NO production	(125)

Table VI. Continued.

Authors	Source of α-mangostin	Model *In vitro/in vivo*	Dosage and duration	Mechanisms of action of anti-inflammatory effects	(Refs.)
Franceschelli *et al*	Purified α-mangostin	LPS treated human myeloid leukemia cell (U937 cell line) Human peripheral blood monocytes	*Garcinia mangostana* extract (50, 100, 500 ng/ml, 1, 5, 10, 50, 100, 500, 1 mg/ml) for 24 h (1, 5, 10, 50, and 100 mM) for 24 h	• ↓NF-κB subunit p65 acetylation and pro-inflammatory gene products as COX-2, iNOS • ↑SIRT1 activation • ↓NO production, IL-1β, TNFα • ↑Anti-inflammatory IL-10	(126)
Sugiyanto *et al*	Purified α-mangostin from *G. mangostana*	Human peripheral blood mononuclear cells	5, 10, and 20 μM 24- and 48-h post infection	• ↓TNF-α and IFN-γ cytokines expression at 24- and 48-h post infection.	(127)
Yin *et al*	Purified α-mangostin	Collagen induced-arthritic rats Human and rat peripheral blood mononuclear cells	40 mg/kg 45 days 2.5, 5, and 10 μg/ml (AChE activity) 2 h	• ↓Secretion of TNF-α and IL-1β • ↓PBMCs potential to stimulate NF-κB activation and proinflammatory cytokine production	(128)
YP *et al*	Purified α-mangostin	Monocytes of healthy individuals infected with dengue virus	25 μM 24 h	• ↓TNF-α, CCL4, CCL5, CXCL10, IL-6, IL1β, IL10, and IFN-α transcription	(130)
Tarasuk *et al*	Purified α-mangostin	Dengue virus (DENV) infected HepG2 cells	20 μM 24, 48, and 72 h	• ↓IL-6 and TNF-α cytokines transcription • ↓RANTES, MIP-1β, and IP-10 cytokines transcription	(129)
Herrera-Aco *et al*	Pericarp of *Garcinia mangostana*	DBA/1J mice	10 and 40 mg/kg per day 33 days	• Affect the humoral response • ↓PGE_2 in joints • Block the production of pleiotropic cytokine IL-6 • ↓ IL-33 • ↓LIX/CXCL5 • ↓IP-10/CXCL10 • ↓RANTES/CCL5	(131)
Zuo *et al*	Purified α-mangostin	HFLS-RA cells Male Sprague-Dawley rats	6, 8, 10, 12 and 14 μg/ml 24 h 40 mg/kg per day 35 days	• ↓Inflammatory cells infiltration and secretion of TNF-α and IL-1β • ↓NF-κB induced by αMN by reducing the expression of p-p65 and VEGF	(132)

Table VI. Continued.

Authors	Source of α-mangostin	Model *In vitro/in vivo*	Dosage and duration	Mechanisms of action of anti-inflammatory effects	(Refs.)
Pan *et al*	Purified α-mangostin	Rat chondrocytes Male Sprague-Dawley rats	0, 3, 6, and 12 μM 24 h 10 mg/kg Every two days for 8 weeks	• ↓Expression of MMP-13 and ADAMTs-5 • ↑Expression of SOX-9 in rat chondrocytes stimulated with interleukin-1β (IL-1β) • ↓Expression of pro-apoptotic proteins including Bax, Cyto-c, and C-caspase3 • ↑Expression of the anti-apoptotic protein Bcl-2 • ↓IL-1β-induced activation of the NF-kB signaling pathway.	(27)
Pan *et al*	Purified α-mangostin	Rat chondrocytes Male Sprague-Dawley rats	0, 1.25, 2.5, and 5.0 μg/ml 24 h 10 mg/kg Every two days for 8 weeks	• ↓Production of NO and PGE2 • ↓Expression of INOS, COX-2, MMP-3, MMP-9, and MMP-13 • ↓Phosphorylation of the NF-κB signaling pathway • ↓IL-1β-induced p65 nuclear translocation • ↓Cartilage degeneration	(133)
Xu *et al*	Purified α-mangostin	Male Wistar rats (paw tissue)	100 mg/kg 21 days	• ↓TNF-α, IL-6 and NF-κB mRNA expression	(134)
Soetikno *et al*	Purified α-mangostin	Wistar rat	100, 200 mg/kg per day 8 weeks	• ↓Cardiac pro-inflammatory levels (TNFα, MCP-1, IL-6, IL-1β)	(98)
Jariyapongskul *et al*	Pericarp of *Garcinia mangostana*	Male Sprague-Dawley rats	200 mg/kg per day 8 weeks	• ↓MDA, AGE, RAGE, TNF-α, and VEGF	(63)
Nava Catorce *et al*	Pericarp of *Garcinia mangostana*	Young (2-month-old) female C57BL/6J mice	40 mg/kg 14 days	• ↓Brain levels of proinflammatory cytokine of cyclooxygenase-2 (COX-2) • ↓Brain levels of proinflammatory cytokinetranslocator protein (TSPO) • ↓IL-6	(137)

Table VI. Continued.

Authors	Source of α-mangostin	Model *In vitro/in vivo*	Dosage and duration	Mechanisms of action of anti-inflammatory effects	(Refs.)
Yang *et al*	Purified α-mangostin	Acute lung injury model male Sprague-Dawley rats	40 mg/kg 3 days	• ↓Nucleus translocation of p65 subunit, and secretion of TNF-α and IL-1β	(138)
Tatiya-Aphiradee *et al*	Pericarp of *Garcinia mangostana* Purified α-mangostin	Methicillin-resistant Staphylococcus aureus-induced superficial skin infection in mice (tape stripping model)	10% GME, 1.32% α-MG in 10% ethanol (equivalent to α-MG in 10% GME) 10 days	• ↓TNF-α, IL-6, IL-1β, and TLR-2 genes.	(139)
Fu *et al*	Purified α-mangostin	Lipopolysaccharide/ d-galactosamine (LPS/D-GalN)-induced acute liver failure mice model	12.5, 25 mg/kg 7 days	• ↓TLR-4 expression, p-NF-κB p65 and p-IκB activation • ↓Expression of TNF-α, IL-6, IL-1β	(72)
Yan *et al*	*G. mangostana* fruit hull	ICR mice induced by acetaminophen, acute liver injury model	100 and 200 mg/kg 7 days	• ↓TNFα and IL-1β	(71)
Lim *et al*	Pericarp of *Garcinia mangostana*	Immortalized human gingival fibroblasts (hTERT-hNOF) cells	1 μg/ml 24 h	• ↓Expression levels of IL-6, IL-8, and PGE2	(140)
Xie *et al*	Mangosteen juice and mangosteen extract	Healthy adults	245 ml 30 days	• ↓CRP protein level by 46%	(141)
John *et al*	*G. mangostana* rind	Wistar rat (obese)	168 mg/kg per day 8 weeks	• ↓CRP proteins • ↓Inflammatory cells (liver, heart)	(12)
Hassan *et al*	*G. mangostana* fruit rind	*W*istar rats (irradiation model)	500 mg/kg per day for 30 days after irradiation	• ↓TNF-α, CRP and IL-6 • ↓Transcription of NF-κB/TGF-β1 signaling pathways	(70)

YP, Yongpitakwattana P; CCR2, C-C chemokine receptor type 2; LPS, lipopolysaccharide; eWAT, epididymal white adipose tissue; iNOS, intracellular nitric oxide synthase; AGE, advanced glycation end products; RAGE, receptor for advanced glycation end products; PGE2, prostaglandin E2; CRP, C-reactive protein.

of the pure compound group administered the agent either orally or intravenously, demonstrating the lipophilic property of this compound and its potential in causing prolonged biological effects on this tissue. *In vitro* metabolism analyses using tissue homogenates demonstrated that α-mangostin was rapidly metabolized in the liver and small intestine which may also explain its *in vivo* metabolism. The oral administration of extract and pure compound both improved the bioavailability of α-mangostin due to decreased hepatic metabolism; however, it is still limited by increased intestinal metabolism (144).

Rigorous clinical trials using this product will further explain its potential toxicity and prove its credibility as a drug candidate for various conditions, including cardiometabolic diseases in human. For instance, a clinical study using

xanthone-rich mangosteen juice in human volunteers reported increased antioxidant capacity measured as oxygen radical absorbance capacity. It was hypothesized that other constituents in the extract could have had synergistic effects with the xanthone (152). In another study investigating the efficacy and safety of herbal medicines it was revealed that they were safe and had advantages over common medication: The comparison between the turmeric extract and paracetamol against knee pain, revealed the efficacy and safety of the extract, which also reduced the levels of CRP and TNF-α more effectively than paracetamol after 6 weeks (153).

9. Future perspectives

The application of α-mangostin, particularly in cardiometabolic diseases, has been steadily investigated over the years. Investigations have been performed using *in vitro* cellular models, *in vivo* animal models and human volunteer intervention, with the majority of studies demonstrating promising results. Although numerous studies have assessed the effects of *G. mangostana* products rich in α-mangostin, the interest of the impact of this single compound is increasing, as reflected in the literature. Although several studies have reported the *in vitro* digestion products, the exact metabolites of this compound in biological *in vivo* models remain to be further elucidated (154-156). The methods with which to increase the bioavailability of this compound also warrant further attention, due to the low solubility of α-mangostin in aqueous solution. The pharmaceutical industry has been trying to discover means with which to increase solubility by manipulating the different factors affecting solubility. Increasing solubility would help achieve therapeutic plasma level concentrations, as this therapeutic can be absorbed in the gastrointestinal tract. The nanotechnology approach has demonstrated improved success, as it reduces molecule size, increases the surface area, interaction with the solvent, and solubility and bioavailability (157). In a previous study, α-mangostin-loaded polymeric nanosponges made from hyper crosslinked ethyl cellulose polymers, were administered to rats at a predetermined minimum IC_{50}. When compared to rats administered pure α-mangostin, the loaded nanoparticles slowly released α-mangostin over time, requiring lower doses and prolonging the antidiabetic response in the rats (158), suggesting that nanotechnology could enhance the delivery of α-mangostin.

Nanoparticle technology also permits specific targeting of therapeutics. The study by Sodalee *et al* (159) using emulsion nanoparticles (nanoemulsion) revealed that this method increased the solubility and dissolution rates of α-mangostin. Nanoemulsion encourages self-microemulsion (160). Sodalee *et al* (159) observed greater distribution in lymphatic organs and increased digestive tract absorption. Increased bioavailability has the potential for clinical drug efficacy (159). There are numerous effects of α-mangostin in biological models on various diseases and studies have reported its molecular docking mechanisms (161,162); however, comprehensive reports on other receptors are still required.

In addition, as obesity forms the main comorbidity in metabolic syndrome involving the excessive accumulation of adipose tissue, it is of utmost importance to further explore the mechanisms of action of α-mangostin in adipose tissue. The upregulation of uncoupling protein 1 (UCP-1) in white adipose tissue promotes thermogenesis, energy metabolism and differentiation into a beige or brown phenotype (163). Phytochemicals, including quercetin and resveratrol have been demonstrated to enhance UCP-1 expression, implying increased white adipose tissue browning through the activation of the AMPK/PPARγ (164) and AMPKα1 pathways (165), respectively. This is one among numerous mechanisms through which α-mangostin could affect adipose tissue biology, including but not limited to, its effects on the secretion of adipocytokines, which are not yet widely reported. It is also unclear whether the actions of α-mangostin can be potentiated, synergized or antagonized by other phytochemical compounds or synthetic drugs; thus, further investigations are warranted in this matter. As the present review only aimed to discuss the potential mechanisms of α-mangostin in modulating the comorbidities of metabolic syndrome, the interrelations of the biological and molecular effects discussed herein with other diseases including, but not limited to, cancer, infection and neurodegenerative diseases, were not discussed and thus deserve further exploration.

10. Conclusions

α-mangostin, as a medicinal compound, has gained increasing attention, since the research community gradually delves into naturally-sourced bioactive compounds. The present review discussed the metabolic and molecular mechanisms through which α-mangostin functions to exert positive effects on metabolic syndrome parameters, including anti-obesity, antidiabetic, hepatoprotective and anti-steatotic, cardioprotective and anti-atherogenic, antioxidant and anti-inflammatory effects, without any severe adverse effects. Novel drug delivery systems are promising approaches in overcoming the low α-mangostin solubility and increasing the targeted delivery of α-mangostin to specific organs. When this system is optimized, dosage studies on humans can be thoroughly conducted. Importantly, rigorous clinical trials using products rich in α-mangostin may further demonstrate its potential toxicity and prove its credibility as a drug candidate for various conditions, including cardiometabolic diseases.

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Authors' contributions

ODJ designed the overall manuscript. ODJ, ATM and RMG participated in the writing process, reviewed the literature and

shared the writing drafts. ODJ and NS performed the final review of the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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