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Review Article

Mechanistic Insights into the Xanthones Present in Mangosteen Fruit (*Garcinia mangostana*) and Their Applications in Diabetes and Related Complications

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Diabetes mellitus is one of the leading public health problems, affecting about 10% of the population. Chronic complications of diabetes cause several human sufferings, including kidney failure, blindness, amputations, stroke, and myocardial infarction. Xanthones from mangosteen fruit (*Garcinia mangostana*) and their physiological effects, such as antiobesity, antihyperglycemic, antidyslipidemia, antidiabetic, and anti-inflammatory effects have been demonstrated in experimental studies to have beneficial effects on obesity, diabetes, hyperglycemic, dyslipidemia, and inflammatory states. It is worthwhile to mention that, in this context, the PubMed, Scopus, and Google Scholar databases have been searched for articles containing the keywords of "*Garcinia mangostana,*" "Mangosteen," "α-mangostin," "diabetes mellitus," "diabetes complication," "hypoglycemic," "antihyperglycemic," "antidiabetic," and "without publication time limitation". This study aims to review the *in silico, in vitro, in vivo*, and clinical pharmacological effects of mangosteen fruit and its xanthones on diabetes mellitus and its complications as well as their molecular pathways related to them. Taking into account the findings of these studies, we can say that mangosteen fruit and its xanthones hold significant potential for designing human studies for controlling and even modifying diabetes mellitus and its related diseases.

1. Introduction

As the international diabetes federation (IDF) reported, the amount of individuals diagnosed with diabetes is estimated to rise from 285 million to 439 million by 2030 [1]. Diabetes mellitus (DM) is a chronic metabolic disorder correlated with glucose metabolism abnormalities. Mainly there are two reasons known for impaired glucose metabolism, either the insulin produced by the pancreas is not enough or the produced insulin cannot be effectively used in the body. This situation is followed by chronic high blood glucose levels, a characteristic of diabetes [2, 3]. Diabetes mellitus type 2 (DM2), which is much more common than diabetes mellitus type 1 (DM1), affects both children and the adult population [4, 5]. DM1 is caused by autoimmune β-cell destruction, which typically results in complete insulin shortage; DM2 is triggered by a progressive loss of adequate β-cell insulin secretion, which often occurs in the context of insulin resistance [6]. Diabetes includes gestational diabetes, diseases involving a pancreatic exocrine deficiency, drug or

chemically-induced diabetes, endocrinopathies, genetic defects of insulin action, β-cell function, maturity-onset diabetes of the young (MODY), and rare forms of autoimmune-mediated diabetes [7].

In the process of digestion of starch, the α-amylase enzyme hydrolyzes starch and produces dextrins and low molecular weight sugars. Therefore, the inhibition of α-amylase enzyme should be considered a valuable strategy in treating DM2, knowing that it retards the digestion of carbohydrates and decreases the glucose absorption rate and, as a result, reduces the post-prandial blood glucose level [8].

Over the centuries, people have widely used natural plant-derived substances studied, isolated, and converted into modern medicine to prevent or treat different diseases. Some natural substances and their derivatives may hold promise as therapeutic alternatives due to factors such as low cost, high compatibility with dietary consumption, and lack of destructive impacts on the human body [1, 3]. *Garcinia mangostana* Linn., also known as mangosteen, is available in South-East Asian countries and takes place in the family *Guttiferae*. The genus *Garcinia* contains more than 300 distinct species. As reported, each species can produce distinguished bioactive constituents such as xanthones, triterpenoids, benzophenones, and flavonoids [9]. As Karim et al. reported, the epicarp of the mangosteen fruit has 160 aromatic compounds, while its endocarp has 105 compounds [10].

HUPLC-MS/MS analysis of various xanthones and anthocyanins of mangosteen peel, using methanol as the optimal solvent for the extraction of xanthones and anthocyanins, exhibited that mangosteen fruit contained 74.496% α-mangostin, 2.200 β-mangostin, 16.195 γ-mangostin, 3.499% gartanin, 2.174% 8-deoxygartanin, 0.748% garcinone C, and 0.685% garcinone D [11]. Data obtained from different extraction techniques indicate that modern methods of extraction (microwave, ultrasonic, and supercritical fluid) offer greater quantitative and temporal efficacy in comparison to conventional extraction methods [12]. It also has other active constituents such as polyphenols, benzophenones, anthocyanins, and vitamins, which are shown in Figure 1 [13–15]. According to studies about plant-derived α-mangostin, this active compound has several pharmacological properties, such as anti-inflammatory, antidiabetic, cardioprotective, and antimicrobial actions [16]. In addition, mangosteen fruit can be helpful in treating arthritis, heart disease, cancer, diarrhea, tonsillitis, and dysentery. The pericarp extract of the mangosteen fruit also has benefits as an antihypertension and even antihuman immunodeficiency virus (HIV) [17]. An investigation done by Taher et al. exhibited which fruit rinds can be effective antifungal, antiallergy, antituberculosis, and immunomodulation [18]. Plant-derived xanthone-rich products have also shown potent antioxidant properties introducing them as a very effective dietary supplement [19]. *In vivo* studies have shown α-mangostin and related xanthones are well-tolerated and safe products [16]. According to Das et al., oral administration of crude and dried ethanolic extract of α-mangostin (45.2 μg/mL and 70.2 μg/mL) exhibited a noteworthy and dose-dependent inhibition of α-glucosidase in Wistar albino rats [20]. Hu et al. used *G. mangostana* ethanolic extract orally in Kunming mice. The result of a dose of 1.0 g/kg *G. mangostana* showed inhibition of protein tyrosine phosphatase 1B (PTP1B). Noteworthy, the PTP1B enzyme is a target for diabetic medicines. This study also revealed that the xanthones in mangosteen fruit possibly will hinder the action of PTP1B, and they found that Garcinone E is the most effective xanthone [21].

This review article aims to study the possible antidiabetic and antihyperglycemic impacts of α-mangostin and related xanthones derived from *G. mangostana*. The search was performed on PubMed, Scopus, databases, and Google Scholar search engine, from inception to March 23, 2022. As an outcome, all published documents reported in the English language were found and included in this review using the following keywords in the title and abstract: "*Garcinia mangostana,*" "Mangosteen," "α-mangostin," "diabetes mellitus," "diabetes complication," "hypoglycemic," "antihyperglycemic," and "antidiabetic." In addition, all *in silico*, *in vitro*, *in vivo,* and clinical trials were included (Figure 2).

2. *In Silico* Studies of Mangosteen Fruit and Its Xanthones

The promising antidiabetic effects of mangosteen fruit and its xanthones have been reported in different *in silico* studies (Table 1).

11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1) alters 11-dehydrocorticosterone to corticosterone in rodents (or cortisone to cortisol in humans). Glucocorticoids get activated by reducing 11-keto to 11-hydroxyl. Diabetes and obesity are linked to excess active glucocorticoids. Thus, treating these diseases requires targeting 11β-HSD1 [26]. Fructose 1,6-bisphosphatase (FBPase1), a well-known rate-controlling enzyme of gluconeogenesis, has developed as a molecular target to control glucose overproduction, and its inhibitors may fill an unmet medical need [27]. In Kumar et al.'s study, they docked α-mangostin with 11β-HSD and FBPase1 and noticed that there are some interactions between α-mangostin and these enzymes. They suggested that α-mangostin could inhibit them through these interactions [22].

α-Amylase is required for post-prandial glucose levels [28]. In addition, it was discovered that mangostana xanthone-VIIII has α-amylase inhibitory activity due to its interaction with active sites of enzymes in a molecular docking study [8].

According to an *in silico* study by Ibrahim et al. in 2019, methanol extract of *G. mangostana* dried pericarp extracts (garcixanthone A, garcimangostin A, gartanin, normangostin, and garcinone C) was used in α-amylase, which showed α-amylase repressing activity [23].

Furthermore, in 2022, Alhakamy et al. performed an *in silico* study by means of "protein preparation wizard" tool of the Schrödinger suite, LigPrep, and PROPKA [24]. They reported that garcimangophenones A and B and five

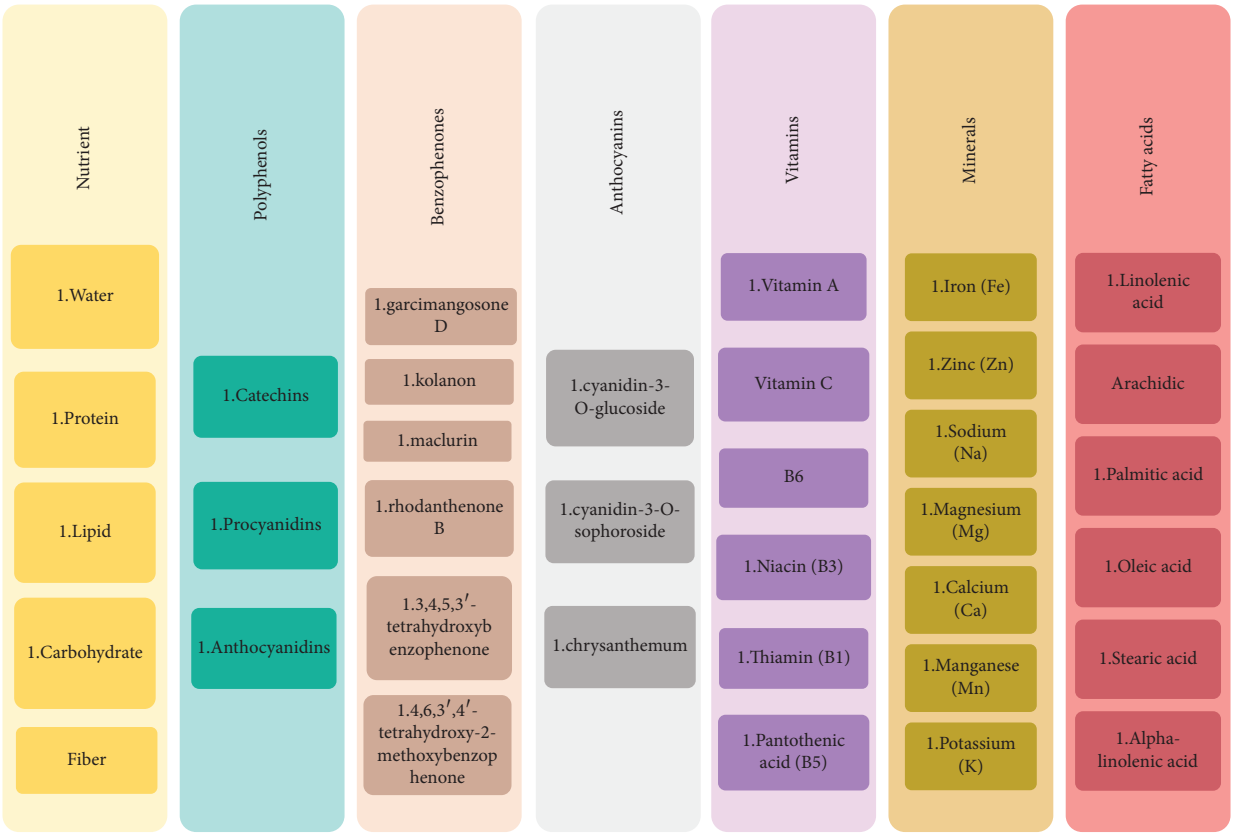


Figure 1: Active constituents of mangosteen fruit (*G. mangostana*).

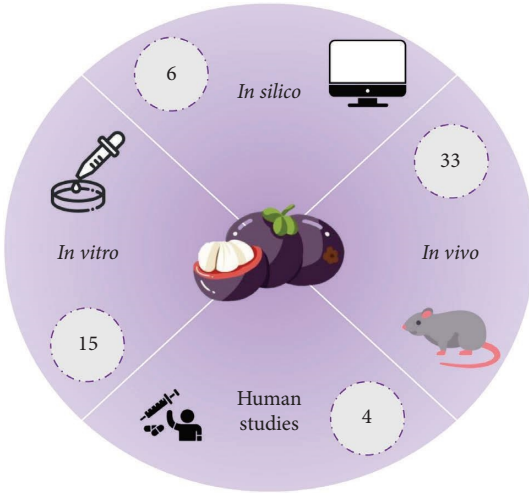


Figure 2: An overview of the current study (the number in a circle represents counts of studies).

metabolites purified from the pericarp extracts of *G. mangostana* have α-amylase inhibitory activities.

Xanthones from *G. mangostana* were used in molecular docking studies on α-amylase, α-glucosidase, and pancreatic lipase (PL) carried out by Cardozo-Muñoz et al. in 2022. Interestingly, they observed that xanthones could inhibit α-amylase, α-glucosidase, and PL [25].

In summary, mangosteen fruit comprises different xanthones (Figure 3), and each has its spatial conformation and, therefore, its own effects on the body [29].

3. Effects of Mangosteen Fruit and Its Xanthones on *In Vitro* Models of DM

The promising antidiabetic effects of mangosteen fruit have been reported in different *in vitro* models of DM (Table 2).

An *in vitro* study carried out by Lee et al. in 2018, using mangosteen fruit powder in rat insulinoma cell line (INS-1) (1, 2.5, 5, and 10 μM), caused recovery from a reduction in expression of P-IR, phosphoinositide protein 3-kinases (P-PI3K), phosphorylated Akt (P-Akt), phosphorylated extracellular regulated kinase (P-ERK), and pancreatic and duodenal homeobox 1 (PDX1) protein. Furthermore, there was an increase in glucose-stimulated insulin secretion (GSIS). Also, noteworthy enhancements in the atypical morphological variations related to apoptosis in streptozotocin (STZ)-treated cells were observed. These outcomes suggest that α-mangostin can improve insulin secretion in β-cells and defend cells from apoptotic impairment [30].

In Karim et al.'s study, the *in vitro* antidiabetic activity of xanthone was determined by means of a presented kit of pancreatic-α-amylase, using the kinetic method. The pancreatic-α-amylase substrate can catalyze and then hydrolyze via α-amylase and α-glucosidase enzymes that are existing in serum. This study inhibited pancreatic-

Table 1: *In silico* studies of antidiabetic effects of mangosteen fruit (*G. mangostana*).

Type of extracts or constituents	Software	Results	Ref.
α-Mangostin	Maestro	— 11β-Hydroxysteroid dehydrogenase (11β-HSD) inhibitory potential — Fructose 1,6-bisphosphatase (FBPase1) inhibitory potential	[22]
Garcinia mangostana ethanolic extract	SYBYL X	— α-Amylase inhibitory potential	[8]
Dried pericarp extracts of *Garcinia mangostana*	SYBYL_X	— α-Amylase inhibitory	[23]
Pure mangostin and its nanosponges and free nanosponges	Molecular operating environment (MOE)	— Antidiabetic response in plasma — Hypoglycemic response	[9]
Garcimangophenones A and B and five metabolites purified from the pericarp extracts of *Garcinia mangostana*	Schrödinger	— α-Amylase inhibitory	[24]
Xanthones from *Garcinia mangostana* ethanolic extract	AutoDock4, AutoDock Vina, and Glide (Mae)	— Inhibitors on α-amylase — Mixed inhibitors on α-glucosidase — Noncompetitive inhibitors on pancreatic lipase	[25]

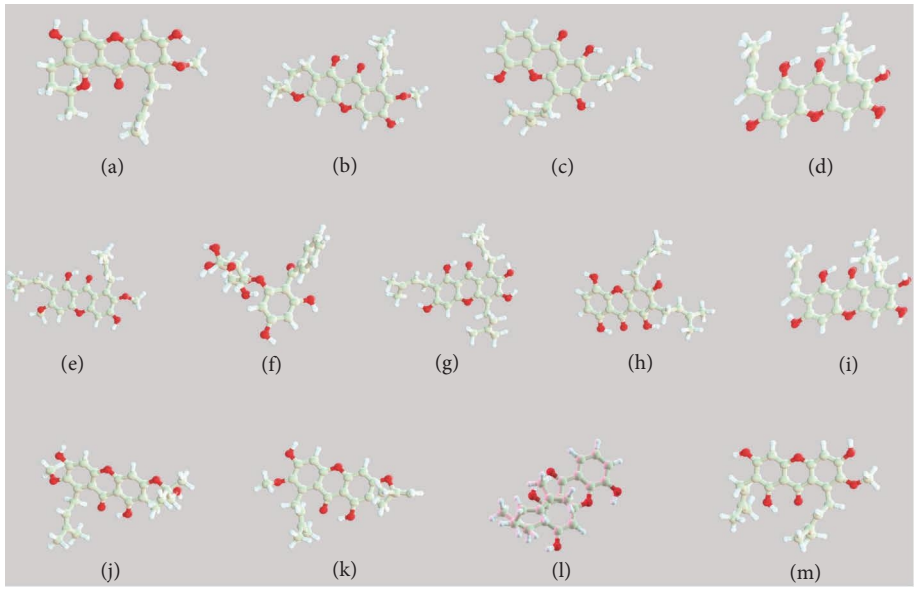


Figure 3: Configuration of some xanthones of mangosteen fruit. (a) 1-Isomangostin; (b) 3-isomangostin; (c) 8-deoxygartanine; (d) 11α-mangostin; (e) β-mangostin; (f) garcimangosone D; (g) garcinone E; (h) gartanine; (i) ɣ-mangostin; (j) mangostanol; (k) mangostenone F; (l) mangostinone; and (m) α-mangostin.

α-amylase activity using different xanthone concentrations (50–1000 μg/mL) [19].

In another investigation carried out by Djeujo et al. in 2022, the antiglycation activity was determined using the bovine serum albumin (BSA) assay, antioxidant capacity was detected with the oxygen radical absorbance capacity (ORAC) assay, and the inhibition of α-glucosidase action was considered with multispectroscopic approaches along with inhibitory kinetic analysis, α-mangostin at 5, 10, 25, 50, and 75 μM, reduced the creation of advanced glycation end-products (AGEs), α-glucosidase activity, and BSA glycation [33].

While these findings are promising, it is important to note that *in vitro* experiments may not always accurately reflect the effects of a substance on living organisms. Further research, including animal and human trials, will be necessary to approve these conclusions and determine the potential therapeutic applications of *G. mangostana* in preventing and treating diabetes.

4. Effects of Mangosteen Fruit and Its Xanthones on Animal Models of DM

The promising antidiabetic effects of mangosteen fruit and its xanthones have been reported in different animal models of DM (Table 3). Based on our study, we have three prevalent techniques used for inducing diabetes in laboratory animals: streptozotocin (STZ), alloxan, and high-fat diet (HFD) methods.

4.1. Protective Effects of Mangosteen Fruit against STZ-Induced DM. Streptozotocin (STZ) is a naturally occurring chemical that has been extensively used to induce experimental models of diabetes in animals. STZ targets explicitly and destroys insulin-producing β-cells in the pancreas, leading to reduced insulin secretion and hyperglycemia. STZ-induced diabetes is commonly used in animal studies to investigate the pathophysiology of diabetes and to evaluate new treatments for the disease. It is advantageous because it mimics some of the characteristics of human DM1 caused by the autoimmune destruction of β-cells. However, the severity and duration of STZ-induced diabetes can vary depending on the dose and mode of administration of the drug, as well as the species and strain of animal used. Typically, rats and mice are used for STZ-induced diabetes studies because they are small and easy to handle and reproduce quickly. Despite its widespread use, STZ-induced diabetes has some limitations as a model of diabetes. For example, it may not fully represent the complex metabolic abnormalities that occur in human diabetes, and it may not be suitable for studying the effects of specific therapies or interventions that target different aspects of the disease. Nonetheless, it remains a valuable tool for researchers studying diabetes and related conditions [49, 50].

When an ethanolic extract of *G. mangostana* was orally administered in STZ-induced rats (100 mg/kg), its pharmacological potential was demonstrated by a significant decrease of blood glucose levels. In addition, a series of isolated xanthones from mangosteen fruit exhibited α-glucosidase inhibition [34].

Kumar et al. propose several explanations for their findings and suggest potential mechanisms for α-mangostin action. Their results revealed that α-mangostin could increase the activity of pancreatic β-cells. It could promote the secretion of large quantities of insulin. Moreover, its action could reverse proteolysis, glycogenolysis, and gluconeogenesis. This xanthone may reduce glycation enzymes or increase endogenous antioxidant levels [22].

Table 2: The promising antidiabetic effects of mangosteen fruit (*G. mangostana*) against different *in vitro* models of DM.

Type of extract or constituent	Dose/concentration	Study model	Results	Ref.
Mangosteen fruit powder	1, 2.5, 5, and 10 μM	Streptozotocin (STZ)-induced damage on rat pancreatic insulinoma cell line (INS-1)	↓Expression levels P-IR, phosphoinositide protein 3-kinases (P-PI3K), phosphorylated Akt (P-Akt), and phosphorylated extracellular regulated kinase (P-ERK) ↓Phosphorylation of P38 and Jun N-terminal kinase (JNK) ↓Cleavage of caspase 3 ↓Pancreatic β-cell apoptosis — Glucose-stimulated insulin secretion (GSIS) — Stimulated insulin secretion — Expression level of phosphorylated insulin receptor substrate-1 (P-IRS-1) (serine (Ser) 1101) and pancreatic and duodenal homeobox 1 (PDX1), protective effects on the cell morphology	[30]
α-Mangostin and xanthone	0.78 μm, 1.56 μM, 3.125 μM, 6.25 μM, 12.5 μM, 25 μM, and 50 μM	Adipocyte cell culture	— Peroxisome proliferator-activated receptor gamma (PPAR-γ) expression	[31]
Xanthone from *Garcinia mangostana* extract	50–1000 μg/mL	Kit of pancreatic-α-amylase	— Inhibiting pancreatic-α-amylase activity	[19]
α-Mangostin	α-Mangostin (1.25 μM) for 6 days	Human umbilical vein endothelial cells (HUVEC)	— Reversed the toxic effects of high glucose in HUVECs	[32]
Pure α-mangostin and its nanosponges and free nanosponges	α-Mangostin (as free dispersion) and α-mangostin loaded nanosponges using the same dose	Yeast α-glucosidase	— Antidiabetic response in plasma — Hypoglycemic response	[9]
α-Mangostin	5, 10, 25, 50, and 75 μM	α-Glucosidase	↓Production of advanced glycation end-products (AGEs) ↓α-glucosidase activity — Bovine serum albumin (BSA) glycation	[33]

Table 3: Protective effects of mangosteen fruit (*G. mangostana*) against animal models of DM.

Type of extracts or constituents	Dose/concentration	Study model	Results	Ref
α-Mangostin	45.2 μg/mL and 70.2 μg/mL	Wistar albino rats	— α-Glucosidase inhibition	[20]
Garcinia mangostana ethanolic extract	100 mg/kg, orally	STZ-induced hypoglycemia rats	— α-Glucosidase inhibition ↓Blood glucose level	[34]
α-Mangostin (>98.0% of purity)	50 mg/kg	High fat diet (HFD)-induced obese mice	↓Body weight (BW) ↓Epidermal ↓Retroperitoneal fat ↓Mass accumulation ↓Cholesterol (CHOL) ↓High-density lipoprotein cholesterol (HDL-C) ↓Glucose ↓Total cholesterol (TC) — Fatty acid	[35]
α-Mangostin	200 mg/kg/day for 8 and 40 weeks	HFD and Low dose STZ-induced diabetes mellitus type 2 (DM2) rat	↓Serum insulin (40 weeks DM2) ↓Homeostatic model assessment for insulin resistance (HOMA-IR) (40 weeks DM2) ↓Fasting blood glucose FBG ↓Hemoglobin A1C (HbA1C) ↓Triglyceride (TG) ↓TC ↑Serum insulin (8 weeks DM2) ↑HOMA-IR (8 weeks DM2)	[36]

Table 3: Continued.

Type of extracts or constituents	Dose/concentration	Study model	Results	Ref
α-Mangostin	α-Mangostin (25, 50 and 100) mg/kg; orally for 56 days	STZ induced in Swiss albino (Wistar strain) rats	↓Oral glucose tolerance test (OGTT) ↓Blood glucose level ↓Glycated HbA1C ↓HOMA-IR ↓Glucose-6- phosphatase ↓Fructose-1-6- bisphosphatase ↓TC ↓TG ↓Low-density lipoprotein (LDL) ↓Very low-density lipoprotein (VLDL) ↓Atherogenic index ↓Coronary risk index ↓Serum glutamic-oxaloacetic transaminase (SGOT) ↓Serum glutamic pyruvic transaminase (SGPT) ↓Alkaline phosphatase (ALP) ↓Lipid peroxide (LPO) ↓Serum creatinine (CREA) ↓Blood urea nitrogen (BUN) ↑BW ↑Plasma insulin ↑Hemoglobin ↑Homeostasis model assessment of β-cell (HOMA-β) ↑Hexokinase ↑High-density lipoprotein (HDL) ↑Superoxide dismutase (SOD) ↑Catalase (CAT) ↑Glutathione (GSH) ↑Total protein	[22]

Table 3: Continued.

Type of extracts or constituents	Dose/concentration	Study model	Results	Ref
Crude, dried *Garcinia mangostana* ethanolic extract	50, 100, and 200 mg/kg; orally for 28 days	Normoglycemic and STZ-induced diabetic Sprague–Dawley (SD) rats. Multiple-dose study and single-dose study	↓Blood glucose level ↓TG ↓TC ↓LDL ↓VLDL ↓SGOT ↓SGPT ↓ALP ↓Urea ↓Serum CREA ↓Damaged islets of Langerhans ↓Presence of hyperplasia ↑BW ↑HDL ↑Total protein ↑Presence of evenly distributed β-cells in an increase number	[2]
Crude pericarp extracts of *Garcinia mangostana*	50, 100, and 200 mg/kg; orally for 14 days	STZ-induce DM2 in mice of strain BALB/c	↓Fasting blood CHOL ↑BW ↓Malondialdehyde (MDA)	[37]
Pericarp extracts of *Garcinia mangostana*	50, 100, and 200 mg/kg	STZ induced in male mice (*Mus musculus*) of the BALB/C strain	↓FBG ↑BW ↑Diameter of the islets of Langerhans ↑Fasting blood ↑Plasma insulin level — Improve cellular β-cells of the islets of Langerhans	[38]
Aqueous extract of xanthone derivative from *Garcinia mangostana*	100, 200, and 400 mg/kg; orally	HFD/STZ-induced DM2 in the Institute of Cancer Research (ICR) mice	↓BW ↓Plasma blood glucose level ↓Kidney hypertrophy (KI) ↓Plasma levels of BUN ↓CREA ↓Plasma MDA ↓Kidney tissue MDA	[39]

Table 3: Continued.

Type of extracts or constituents	Dose/concentration	Study model	Results	Ref
Mangosteen fruit vinegar rind (MVR)	100, 200 mg/kg; orally administered at 8.00–9.00 am for one week	HFD/STZ-induced DM2 in ICR adult male mice	↓Glucose levels ↓BW ↓Plasma TC ↓Plasma TG ↓LDL ↓Liver tissue TC ↓Liver tissue TG ↓Aspartate aminotransferase (AST) ↓Alanine transaminase (ALT) ↓Plasma MDA ↓Liver tissue MDA ↑Liver glycogen storage ↑Insulin sensitivity ↑HDL ↑Plasma bilirubin ↑Liver tissue SOD ↑Liver tissue CAT	[40]
α-Mangostin and xanthone (such as betta and gamma mangostin, garcinone E, 8-deoksigartanin and gartanin	5, 10, and 20 mg/kg for 10 days	10-day fatty emulsion in Wistar rats	↓Insulin resistance	[31]
Garcinia mangostana pericarp extract	50-100-200 mg/kg for 15 days	STZ-induced diabetic mice	↓FBG ↓HbA1C, Akt1, vascular endothelial growth factors (VEGF), erythroblastic oncogene B (ERBB2), and androgen receptor (AR) mRNA expression levels in pancreatic tissue	[41]
Pericarp extracts of *Garcinia mangostana*: nonpolar (NP), semipolar (SP), polar (P)	18 mg/kg NP, 80 mg/kg SP, and 50 mg/kg P For 14 days	STZ-induced diabetic mice	↓FBG ↓HbA1C	[42]
α-Mangostin and xanthone	5, 10, and 20 mg/kg for 21 days	Alloxan-induced diabetic mice	↑Plasma insulin	[43]
α-Mangostin	Injection of 150 mg/kg–1 alloxan and α-mangostin compound 10 mg/kg for 3 weeks	Induced DM2 in rats	↓MDA levels — Improvement in Langerhans β cells	[44]

Table 3: Continued.

Type of extracts or constituents	Dose/concentration	Study model	Results	Ref
Xanthone from *Garcinia mangostana* extract	100/200/400 mg/kg; orally	HFD and STZ-induced diabetes mellitus (DM) mice	↓Blood glucose and maltose level ↓TC ↓TG ↓Low-density lipoprotein cholesterol (LDL-C) ↓AST ↓ALT ↓Liver MDA ↓Cellular apoptosis of kidney and liver tissue ↑HDL-C ↑Liver tissue glycogen ↑Plasma insulin ↑HOMA-IR ↑Plasma bilirubin ↑Liver SOD ↑Liver CAT ↑Kidney SOD ↑Kidney CAT ↑Hepatocytes — Reformed the liver and kidney histological alterations	[19]
Γ-Mangostin	4 and 8 mg/kg of Γ-mangostin; orally	HFD-induced diabetic mice	↓FBG — Antihyperglycemic — Inhibition of α-amylase/α-glucosidase	[45]
Garcinia mangostana ethanolic extract	1.0 g/kg; orally for 15 min, 30 min, 1 h, 2 h, 4 h, 8 h and 12 h	Kunming mice	— Protein tyrosine phosphatase 1B (PTP1B) inhibitor	[21]
Mangosteen fruit rind	168 mg/kg/day α-mangostin for 8 weeks	Diet-induced metabolic syndrome rats	↓ BW ↓ Abdominal fat deposition ↓Abdominal circumference ↓Whole-body fat mass ↓Infiltration of inflammatory cells ↓Deposition of collagen in heart and liver ↓Adipocyte size in retroperitoneal adipose tissues — Improved liver structure and function — Improved blood pressure — Improved left ventricular stiffness — Improved endothelial function	[46]

Table 3: Continued.

Type of extracts or constituents	Dose/concentration	Study model	Results	Ref
Mangosteen fruit rind as an ointment	50 mg/kg ointment for 14 days	STZ-induced diabetic BALB/c mice	↓Wound width ↓Neutrophils ↑The number of fibrocytes, fibroblasts, and macrophages ↑Collagen densities	[47]
α-Mangostin	Oral administration of α-mangostin (as free dispersion) and α-mangostin loaded nanosponges using the same dose	STZ-induced diabetic wistar rats	↑Antidiabetic response in plasma — Hypoglycemic response	[9]
Pericarp extracts of *Garcinia mangostana*	20 and 40 mg/kg	HFD-induced SD rats	↓Blood glucose peak ↓Area under the curve (AUC) of glucose responses ↑Activity on α-amylase	[48]

Taher et al. performed single-dose and multiple-dose methods to determine the impact of *G. mangostana* pericarp ethanolic extract on blood glucose levels in nondiabetic and STZ-induced diabetic rats. *G. mangostana* pericarp ethanolic extract meaningfully (p value < 0.05) lowered blood glucose levels in nondiabetic rats and STZ-induced diabetic rats in comparison with control groups. In addition, histological analysis revealed a slight growth in the number of β-cells in diabetic rats. They claimed this result was related to antioxidant-rich catechins like epicatechin and xanthones like α-mangostin in *G. mangostana* pericarp ethanolic extract [2].

An investigation performed by Husen et al. showed that crude pericarp extracts of *G. mangostana* (50, 100, and 200 mg/kg; orally for 14 days) could reduce the serum concentration of malondialdehyde (MDA) in STZ-induced diabetic BALB/c mice. MDA may be considered an indicator of oxidative stress, so the lower the MDA level, the lower the oxidative stress. As a result, fewer β-cells were damaged, so insulin production and glucose uptake increased [37].

Husen et al. showed antihyperglycemic and antioxidant properties of pericarp extracts of *G. mangostana* by oral administration of 50, 100, and 200 mg/kg to STZ-induced BALB/c strain mice. The result showed that pericarp extracts of *G. mangostana* could increase the BW of mice, decrease fasting blood glucose (FBG), enhance the number of β-cells in Langerhans's islets, owing to a more extensive diameter of the islets of Langerhans, and increase fasting blood plasma insulin levels significantly [38].

In an *in vivo* study investigated by Ansori et al. in 2019, they measured the renoprotective effect of *G. mangostana* pericarp extract usage on plasma creatinine (CREA) and proximal renal tubules of 36 diabetic male BALB/c mice. The final results of oral administration of 50, 100, and 200 mg/kg for 14 days revealed a decrease in FBG, hemoglobin A1C (HbA1C), Akt1, vascular endothelial growth factors (VEGF), erythroblastic oncogene B (ERBB2), and androgen receptor (AR) mRNA expression levels in pancreatic tissue [41].

Husen et al. did an *in vivo* study to assess the antioxidant impact of various mangosteen fruit pericarp extract treatments on 3-4 months old male STZ-induced diabetic mice. They used 18, 80, and 50 mg/kg polar (P) on these mice, in which every fraction treatment dose equals 2.5 g/kg dry powdered pericarp extract. Eventually, the final result of 14-day monitoring of mice indicated that not only FBG but also HbA1C was reduced due to the treatment [42].

In an *in vivo* study by Wulandari et al. in 2021, they evaluated topical mangosteen fruit rind as an ointment (50 mg/kg for 14 days) on the wound in STZ-induced diabetic BALB/c mice. Their findings exhibited a reduction in wound width, neutrophil number, and increased fibrocytes and fibroblasts [47].

These studies suggest that mangosteen fruit may help protect against the damaging effects of STZ-induced diabetes, potentially by improving pancreatic function and reducing oxidative stress in the body.

4.2. Protective Effects of Mangosteen Fruit against Alloxan-Induced DM. Alloxan is a chemical compound often used to induce diabetes in laboratory animals. Alloxan is toxic to β-cells in the pancreas responsible for producing insulin. When alloxan is injected into an animal, it selectively accumulates in the β-cells and generates free radicals that cause oxidative stress and cellular damage. As a result, β-cells become dysfunctional or die. This leads to a decrease in both production and secretion of insulin. Finally, blood sugar levels increase, and diabetes symptoms appear. Besides its ability to induce diabetes, alloxan could have other effects. For example, alloxan has been shown to be a potent mutagen and carcinogen, capable of generating DNA damage and promoting tumorigenesis. In addition, alloxan has been reported to cause nephrotoxicity, hepatotoxicity, and other forms of tissue damage. Therefore, caution must be exercised while using alloxan in laboratory experiments [51].

According to Ratwita et al., in a 2018 study on Langerhans islet of alloxan-induced diabetic mice, oral administration of α-mangostin and xanthone (5, 10, and 20 mg/kg for 21 days) increased plasma insulin levels [43]. In 2020, a study by Wulandari et al. with the alloxan method showed a reduction in MDA levels, and β-cells in Langerhans islets were improved due to this research treatment [44]. These studies suggest that mangosteen fruit may help to protect these cells from damage and improve insulin sensitivity.

4.3. Protective Effects of Mangosteen Fruit against HFD-Induced DM. The high-fat diet (HFD) method is usually used to induce DM2 in laboratory animals. The principle behind this method is to feed the animals with a high-fat-content diet over an extended period, resulting in obesity and insulin resistance. The diet duration can vary but typically ranges 8–16 weeks, depending on the specific experimental protocol. The HFD method has been revealed to induce metabolic dysfunction in laboratory animals that closely mimic the pathophysiology of human DM2. In fact, it includes obesity, hyperinsulinemia, glucose intolerance, insulin resistance, and dyslipidemia. Overall, the HFD method is widely used for studying the mechanisms underlying the development of DM2 and testing potential therapeutic interventions [52–55].

In Mekseepralard et al.'s study, they investigated the effects of α-mangostin at 200 mg/kg body weight (BW)/day for 8 and 40 weeks on HFD-induced DM2 rats. At the end of the experiment period, levels of serum insulin (40-week DM2) and homeostatic model assessment for insulin resistance (HOMA-IR) (40-week DM2) decreased. However, a rise in the level of FBG, HbA1C, serum insulin (8-week DM2), and HOMA-IR (8-week DM2) was observed. Long-term α-mangostin supplementation has antihyperglycemic and antihyperlipidemic impacts and increases insulin sensitivity by refining β-cell functions in DM2 [36].

An *in vivo* investigation by Chaoi et al. stated the protective effects of α-mangostin supplement (50 mg/kg; PO) on HFD-induced obese mice. Compared to the control group, α-mangostin reduced body fat gain and epidermal

Table 4: Protective effects of mangosteen fruit (*G. mangostana*) against DM complications.

Type of extracts or constituents	Dose/concentration	Study model	Results	Ref
α-Mangostin and γ-mangostin	3 μM	Primary cultures of newly differentiated human adipocytes	↓Insulin resistance ↓Lipopolysaccharide (LPS)-mediated inflammation	[59]
α-Mangostin	200 mg/kg/day for 8 weeks	HFD and STZ-induced DM2 rat	↓HbA1C ↓Serum insulin ↓HOMA-IR ↓FBG ↓CHOL ↓TG ↓Mean arterial pressure ↓Leakage of blood-retinal barrier ↓Retinal MDA ↓Retinal AGEs ↓Retinal receptor for advanced glycation end-products (RAGE) ↓Retinal tumor necrosis factor α (TNF-α) ↓Retinal VEGF ↑Ocular blood flow	[60]
α-Mangostin and xanthone component isolated from the stem bark of *Garcinia mangostana*	50 μM, 25 μM	3T3-L1 cells	↓Intracellular fat ↑Free fatty acid (FFA) ↑Glucose uptake	[61]
Bioactive metabolites isolated from *Garcinia mangostana*	10–1000 μg/mL	Reaction mixture	↓Nonfluorescent AGE formation ↓Fluorescent AGE formation ↓Protein glycation	[62]
Dried and ground *Garcinia mangostana* ethanolic extract	200-500-21.6 mg/kg for 9 weeks	25 high-calorie diet male wistar rats	↓Fatty acid synthetase (FAS) — Preventing major BW gain	[63]

Table 4: Continued.

Type of extracts or constituents	Dose/concentration	Study model	Results	Ref
Garcinia mangostana ethanolic extract	50 or 200 mg/kg/day for 5 weeks	HFD in C57BL/6 mice	↓BW ↓Liver weight ↓Epididymal fat ↓Inguinal fat ↓Mesenteric fat ↓TG ↓TC ↓LDL ↓SGOT ↓SGPT ↓FFA ↓Glucose level ↓PPAR-γ levels ↓Lipogenesis in adipocyte differentiation ↓Activation of adenosine monophosphate-activated protein kinase (AMPK) and sirtuin 1 (SIRT1), carnitine palmitoyltransferase 1A (CPT1a)	[64]
Meratrim (extracts of *Sphaeranthus indicus* flower heads and *Garcinia mangostana* fruit rinds)	400 mg of Meratrim; twice daily or two identical placebo capsules for 16 weeks	Double-blind, placebo-controlled study in healthy overweight human	↓BW ↓Waist ↓Hip size ↓Body mass index (BMI) ↓LDL ↓TC ↓TG ↓SGOT ↓SGPT ↓BUN ↓CREA ↓VLDL ↓FBG ↓LHR ↓Visual analog scales (VAS)-appetite ↓Total mood disturbance (TMD) ↓Leptin ↓Ghrelin ↑HDL ↑Adiponectin ↑Insulin	[65]

Table 4: Continued.

Type of extracts or constituents	Dose/concentration	Study model	Results	Ref
Pericarp extracts of *Garcinia mangostana*	25 mg/day for 11 weeks	HFD-induced hepatic steatosis in SD rats	↓BW ↓FFA ↓TG ↓Thiobarbituric acid reactive substances (TBARS) ↓Total reactive oxygen species (tROS) ↓Mitoros ↓Ca^{2+} ↓Cytochrome c ↓Cytochrome complex (Cyt c) release from mitochondria ↓Caspases 9 and 3 activities ↓Mitochondrial membrane potential ↑Activity of SOD, GSH, glutathione peroxidase (GPx), glucose disappearance (GRd) and CAT ↑NADH cytochrome C reductase (NCCR) in liver tissue ↑Succinate cytochrome C reductase (SCCR) in liver tissue, mitochondrial membrane potential	[66]
Garcinia mangostana ethanolic extract	10, 100 and 1000 μg/mL	BSA glycation	↓AGEs ↓Dityrosine formation ↓N′-formylkynurenine	[67]
Γ-mangostin	1, 2, 4 mg/kg for 14 days	STZ-induced diabetic mice	↓Blood glucose level ↓BUN ↓CREA — Impaired renal proximal tubular cells	[68]
Mangosteen fruit peel extract	5, 20 μg/mL	Induced-glucose mesangial cells (SV40 MES 13 cell line)	↓Transforming growth factor beta 1 (TGF-β1) ↓Fibronectin level	[69]
MVR		Pancreatic α = amylase kit	— α-amylase inhibitory activity — Glucosidase inhibitory activity	[70]

Table 4: Continued.

Type of extracts or constituents	Dose/concentration	Study model	Results	Ref
MVR	100 and 200 mg/kg; orally	HFD and STZ-induced DM2 nephropathy of albino mice	↓Kidney cellular apoptosis ↓Blood glucose ↓Insulin resistance ↓KI ↓BUN ↓CREA ↓Kidney MDA ↑OGTT ↑Oral mixed-meal tolerance test (OMTT) ↑Insulin ↑HOMA-IR ↑Kidney SOD ↑ Kidney CAT — Significantly restored kidney histological alterations	[70]
α-Mangostin	1.25 μm for six days	High glucose-induced memory senescence in HUVECs	↓Reactive oxygen species (ROS) ↓Senescence-associated beta-galactosidase in HUVECs incubated in metabolic memory condition ↓SIRT1 proteins ↑Cell viability ↑P53 ↑Acetyl-P53	[71]
Pericarp extracts of *Garcinia mangostana*	Injected for 14 days by per-oral method	STZ-induced diabetic mice	↓ALT ↓AST ↓Necrosis and swollen cells injury	[72]
Pericarp extracts of *Garcinia mangostana*	4 weeks of Ya-Samarn-Phlae (YaSP) oil bandage) traditional Thai polyherbal preparation, and its constituents *Garcinia mangostana*, Oryza sativa, Curcuma longa, and Areca catechu)	DM2 patients	— Improvement of ulcers to varying degrees — Antibacterial activity against staphylococcus ↓Ulcer size	[73]
Mangosteen fruit peel extract	400 mg/kg/day	HFD-induced in albino Wistar rats	↓BMI ↓Blood glucose ↓BW ↓HDL-C/LDL-C ↓CHOL/HDL-C ↑CHOL ↑HDL-C ↓LDL-C	[74]

Table 4: Continued.

Type of extracts or constituents	Dose/concentration	Study model	Results	Ref
Pericarp extracts of *Garcinia mangostana*	100, 200 and 400 g/kg/day	Wistar rats with DM2 treated with HFD	↓BW ↓FBG ↓Glial nuclear factor kappa light chain enhancer of activated B cells (NF-κb) expression ↓Interleukin-6 (IL-6) expression ↓TNF-α expression ↑SOD generation	[75]
Garcinia mangostana leaves ethanolic extract		Diabetic ulcer specimens	— Inhibiting the growth of bacteria	[76]
Isolating α-mangostin	10, 30 and 50 mg/kg	High fructose-Induced adiposity in rats	— Significant difference in the examination of CREA levels — Normalizing damaged kidney tissue	[77]
Combination of *Sargassum duplicatum* and *Garcinia mangostana* extracts	50 mg/kg	STZ-induced in *Mus musculus* (BALB/c strain)	↓Wound width ↓Wound diameter ↓Neutrophils ↓Macrophage ↑Fibroblast ↑Fibrocyte ↑Collagen density ↑Re-epithelialization of the wounded area	[78]

and retroperitoneal fat mass accumulation, as well as the biochemical serum markers such as cholesterol (CHOL), glucose, triglyceride (TG), and fatty acid levels. These outcomes show that α-mangostin could have a part in regulating lipid metabolism [35].

According to an investigation performed by Ratwita et al, α-mangostin (5, 10, and 20 mg/kg for ten days) could reduce insulin resistance in diabetic Wistar rats. They believe this was due to the increased expression of gamma P21-activated kinase (PPAK-γ). In adipocytes, PPAK-γ regulates gene expression in insulin signaling and glucose metabolism [31].

Noteworthy, Karim et al.'s study used 100, 200, and 400 mg/kg oral doses of xanthone from *G. mangostana* extract on HFD and STZ-induced diabetic mice, meaningfully ameliorated HOMA-IR, enhanced plasma insulin level and decreased blood glucose and maltose level. Furthermore, it was shown in this study that xanthone from *G. mangostana* extract exerted hypoglycaemic action by reducing the levels of lipid profile, e.g., TC, TG, and low-density lipoprotein cholesterol (LDL-C) while increased high-density lipoprotein cholesterol (HDL-C). Furthermore, the treatment groups exhibited enhanced hepatic construction and meaningfully increased hepatocytes in this research. In addition, it reduced cellular apoptosis and reformed histological alterations in kidneys [19].

Another study on HFD-induced diabetic mice following the oral administration of 4 and 8 mg/kg of γ-mangostin exhibited that γ-mangostin applies antihyperglycemic action by promoting glucose uptake. Also, it could reduce saccharide digestion by inhibiting α-amylase/α-glucosidase with insulin sensitization [45].

The investigation of John et al. showed that oral administration of mangosteen fruit rind to rats with diet-induced metabolic syndrome gave a dose of 168 mg/kg/day α-mangostin, reduced BW, and whole-body fat mass. The study also showed diminished infiltration of inflammatory cells, reduced collagen deposition in both the liver and heart, and lessened mean adipocyte size in retroperitoneal adipose tissues, leading to enhanced liver construction, function, and cardiovascular parameters [46].

The study by Li et al. in 2022 showed 20 and 40 mg/kg of oral pericarp extracts of *G. mangostana* to HFD-induced Sprague–Dawley (SD) rats an inhibitory effect on α-amylase activity and significantly reduced post-prandial blood glucose [48].

These studies have demonstrated compounds found in mangosteen fruit may help regulate blood sugar levels and enhance insulin sensitivity.

5. Protective Effects of Mangosteen Fruit and Its Xanthones against Diabetes Complications

DM is a complex chronic disorder that may cause plenty of chronic complications, including retinopathy, neuropathy, cardiovascular diseases, hepatic failure [5], and fibrosis [56]. In this regard, DM is known as a silent killer [57, 58]. Interestingly, protective properties of mangosteen fruit against some DM complications have been reported (Table 4).

The accumulation of AGEs in tissues has an important part in the progression of diabetic complications [79, 80]. Abdallah et al. studied the inhibitory action of bioactive molecules isolated from *G. mangostana* fruit hulls on AGE creation. All of the compounds tested, including garcimangosone D (1), aromadendrin-8-C-glucopyranoside (2), epicatechin (3), and 2,31,4,51,6-pentahydroxybenzophenone (4), considerably inhibited the creation of fluorescent and nonfluorescent AGEs, with compound 3 (epicatechin) being the most effective [62].

5.1. Cardiovascular Diseases. In 2020, Tousian et al. conducted a study wherein α-mangostin was incubated at 1.25 μM for six days in human umbilical vein endothelial cells (HUVECs) induced with high glucose. The study showed a decrease in ROS, senescence-associated β-galactosidase, and SIRT1 proteins in HUVECs incubated in a metabolic memory state, along with an increase in cell viability, p53, and acetyl-P53. These results exhibit that α-mangostin defends endothelial cells against metabolic memory-induced senescence, which is likely via SIRT1 [71].

5.2. Adipocyte Tissue Disorders and Obesity. In an *in vitro* investigation by Bumrungpert et al., they evaluated 3 μmol/L of α-mangostin and γ-mangostin on primary cultures of recently differentiated human adipocytes. The result confirmed a reduction in lipopolysaccharide (LPS)-mediated inflammation and insulin resistance [59].

In an *in vitro* investigation by Taher et al., the α-mangostin and xanthone component, which were derived from the stem bark of *G. mangostana* (50 μM and 25 μM), showed a reduction in intracellular fat and a rise in glucose uptake and free fatty acid (FFA) in 3T3-L1 cells [61].

According to the result of an *in vivo* study by Abuzaid et al., using mangostana pericarp ethanolic extract causes major BW gain suppression and reduces fatty acid synthetase (FAS) in the adipose tissue and serum of monosodium glutamate, which has a significant impact on preventing obesity. In this study, researchers treated 25 male Wistar rats with a weight range of 90–110 g induced by a high-calorie diet aged four weeks old by administrating dried powder of the mangostana pericarp ethanolic extract for nine weeks. α-Mangostin and xanthone were used as marker compounds in this study [63].

In 2016, Chae et al. discovered that the mangosteen fruit ethanol extract (25.7% α-mangostin and 3.8% γ-mangostin) could have antiobesity effects. The proposed mechanism of the researchers in this study was that adenosine monophosphate-activated protein kinase (AMPK) and sirtuin 1 (SIRT1) could be activated, and this activation reduces the expression of peroxisome proliferator-activated receptor gamma (PPAR-γ) in the liver. Activation of PPAR-γ improves glucose metabolism and causes insulin sensitization [64, 81].

In a randomized, double-blind, placebo-controlled clinical trial performed from 2014 to 2015 by Kudiganti et al., it was concluded that Meretrim originally contains extracts of *Sphaeranthus indicus* flower heads and *G. mangostana* fruit rinds and can play a role in weight

management. Sixty volunteers with a body mass index (BMI) of 28.3 kg/m^2 participated in this study. In addition, they conducted an *in vitro* study to find a proposed mechanism. Their cellular study showed that the protein expression level of FAS decreased in 3T3-L1 adipocytes that received Meratrim. FAS protein is known for lipogenesis in the liver and fat cells. They also found that AMPK was activated in hepatocytes [65].

In a study on HFD-induced albino Wistar rats by Labban et al. in 2021, mangosteen fruit peel extract reduced BMI, blood glucose, BW, HDL-C/LDL-C, and CHOL/HDL-C and increased CHOL, HDL-C, and LDL-C when it was administered orally as 400 mg/kg/day [74].

In conclusion, adipocyte tissue disorders and obesity that DM causes can be improved with *G. mangostana* by reduction of FAS and insulin resistance and a rise in glucose uptake through AMPK and SIRT. These mechanisms reduce BMI and whole-body fat, therefore improving obesity.

5.3. Hepatic Failure. In an *in vivo* study by Tsai et al. in 2016, they aimed to explore the regulatory impact of α-mangostin on HFD-induced hepatic steatosis. 25 mg/day of pericarp extracts of *G. mangostana* was used orally in SD rats for 11 weeks. This study exhibited a reduction in BW, TG, FFA, thiobarbituric acid reactive substances (TBARS), mitoROS, Ca^{2+}, etc. It also showed an increase in the activity of superoxide dismutase (SOD), glutathione (GSH), glutathione peroxidase (GPx), glucose disappearance (GRd), catalase (CAT), and NADH cytochrome C reductase (NCCR) in liver tissue. With all said, α-mangostin attenuated hepatic steatosis in HFD rats with enhanced cellular antioxidant capacity, enhanced mitochondrial functions, and repressed apoptosis of hepatocytes [66].

According to Susilo et al. in 2020, when pericarp extracts of *G. mangostana* were injected for 14 days by per-oral method into STZ-induced diabetic mice, it decreased the levels of aspartate aminotransferase (AST) and alanine transaminase (ALT) and necrosis and swollen cell injury [72].

These results show that *G. mangostana* suppressed hepatic steatosis through different mechanisms, such as increased antioxidant capability, enhanced the functionalities of mitochondria, and repressed apoptosis associated with mitochondria. Hence, *G. mangostana* is a defensive agent for hepatosteatosis by regulating mitochondrial oxidative phosphorylation and apoptosis mechanisms.

5.4. Retinopathy. Diabetic retinopathy is one of the most common microvascular complications of DM1 and DM2, leading to visual damage and blindness. Furthermore, Jariyapongskul et al. studied the impacts of α-mangostin on the retinal microvasculature in a DM2 animal model. Using the ethanolic extract of *G. mangostana* with a dose of 200 mg/kg/day for eight weeks in HFD-induced diabetic rats exhibited an increase in ocular blood flow and reduction of mean arterial pressure and leakage of the blood-retinal barrier. Moreover, treatment with α-mangostin meaningfully decreased the levels of MDA, AGEs, RAGE, TNF-α, and VEGF in retinal tissue [60].

5.5. Renal Failure and Oxidative Stress. Husen and Ansori separated STZ-induced diabetic mice into three groups: diabetic control, diabetic mice treated with acarbose, and diabetic mice treated with γ-mangostin. The γ-mangostin group was divided into three groups based on 1, 2, and 4 mg/kg doses. Furthermore, γ-mangostin treatment significantly lowered plasma blood urea nitrogen (BUN) and CREA and improved the decreased renal proximal tubular cells. As a result, γ-mangostin has a high level of antioxidant activity [68].

In another study, Santoso et al. used 36 rats and separated them into six groups: negative control, positive control, standard medicine (glibenclamide), and α-mangostin with doses of 10, 30, and 50 mg/kg. The outcomes revealed a noteworthy reduction (p value < 0.05) in CREA levels but no important differences (p value > 0.05) in BUN or uric acid levels in each group. Compared to positive controls, renal histopathology analyses indicate that α-mangostin could normalize damaged kidney tissue. As a result, α-mangostin can be used to avoid additional impairment and repair damaged cells by inhibiting inflammation and oxidative stress [77].

Since DM2 nephropathy, a key cause of end-stage kidney disease, develops from oxidative stress. Natural polyphenols may defend the kidney from diabetic nephropathy by exerting antioxidant actions. Contextually, Karim et al. investigated MVR effects on HFD and STZ-induced DM2 nephropathy of albino mice. The result showed that using an oral dose of 100 and 200 mg/kg of MVR could reduce kidney tissue antioxidant markers (SOD and CAT) and elevate oxidative stress markers (MDA). Also, it can significantly modulate renal parameters (BUN and CREA) in comparison with the diabetic control group. Furthermore, based on the oral glucose tolerance test (OGTT)/oral mixed-meal tolerance test (OMTT), MVR treatment can reduce plasma glucose, insulin resistance, and HOMA-IR and improve plasma insulin levels. Furthermore, the impact of MVR on kidney morphology showed significant restoration of kidney histological alterations and considerable reduction of apoptosis cells. The *in vitro* antidiabetic activity of MVR in Karim et al.'s study was analyzed by pancreatic α-amylase kit protocol. The kit showed α-amylase and glucosidase inhibitory action of MVR [70].

An excessive quantity of extracellular glucose resulted in glucose uptake in mesangial cells, which initiates a number of metabolic signaling pathways that cause an increase in the creation of reactive oxygen species (ROS) and AGEs. Hence, pathways induce extracellular matrix (ECM) creation, such as fibronectin and critically transforming growth factor beta 1 (TGF-β1) synthesis. Yet, overexpression of TGF-β and fibronectin is closely connected to glomerulosclerosis. Moreover, Widowati et al.'s study evaluated the activity of mangosteen fruit peel extract, concentrations of 5, 20 μg/mL, as a protection agent on induced-glucose mesangial cells (SV40 MES 13 cell line). The result showed that mangosteen fruit peel extract could decrease the level of TGF-β1 and fibronectin. Furthermore, mangosteen fruit peel extract activity inhibits the diabetic glomerulosclerosis state and could rise mesangial cell proliferation [69].

Table 5: Clinical studies of the antidiabetic effects of mangosteen fruit (*G. mangostana*).

Type of extracts or constituents	Dose/concentration	Study model	Results	Ref
Capsule formulation	400 mg once daily for 26 weeks	Obese female patients (a prospective randomized controlled pilot study)	↓HOMA-IR ↓BW ↓Waist circumference ↓Glucose level ↓Insulin level ↓High-sensitivity C-reaction protein (hs-CRP) ↓Fibrinogen ↑HDL	[82]
Pericarp extracts of *Garcinia* mangostana	2520 mg/day for 90 days	High-risk cardiovascular patients (a randomized, single blind, placebo-controlled clinical trial)	↓Nitric oxide ↓Plasma IL-6 ↓Plasma Interleukin-1 (IL-1) ↓Plasma MDA ↓Plasma hs-CRP ↓TC ↓LDL ↓HbA1C	[78]

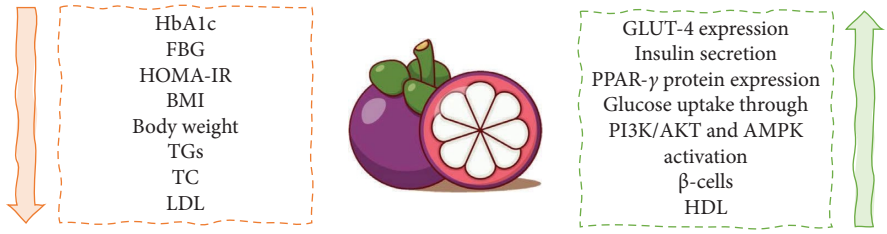


Figure 4: The antidiabetic mechanisms of mangosteen fruit (*G. mangostana*).

With a reduction of BUN, CREA, CAT, and SOD levels, an increase in MDA level, and modulation of renal parameters, it is evident that *G. mangostana* can improve renal function and be considered an antioxidant.

5.6. Diabetic Wounds. Winarni et al. meant to determine the topical administration impact of the combination of *Sargassum duplicatum* and *G. mangostana* extract at 50 mg/kg, to ameliorate diabetic open wounds on STZ-induced *Mus musculus*. Topical administration of combination extracts improved the re-epithelialization of the wounded area, fibroblasts, fibrocytes, and collagen synthesis and also decreased the number of neutrophils and macrophages, improving the open wound-healing procedure in diabetic mice [78].

Diabetic foot ulcers (DFUs) are mostly caused by diabetic neuropathy and peripheral vascular disorder. Bacterial infections in the area are accountable for the retarded healing process of DFUs. Sanpinit et al.'s investigation meant to study the antibacterial, antibiofilm, and wound-healing impacts of pericarp extracts of *G. mangostana* as a constituent of *Ya-Samarn-Phlae* (*YaSP*) oil, a traditional Thai polyherbal preparation, against infective bacteria in DFUs. Treatment using *YaSP* oil bandage on 14 DM2 patients for four weeks showed improvement of ulcers of varying degrees and antibacterial activity; *G. mangostana* has significant antibacterial effects against *Staphylococcus* [73].

Bacterial infections exacerbate diabetes-related complications and induce ulcers or sores on the feet, hands, knees, back, and other body regions. Rosalina et al. performed a study and discovered the impact of *G. mangostana* leaf ethanolic extract on *Escherichia* spp., *Klebsiella* spp., *Staphylococcus* spp., *Salmonella* spp., and *Shigella* spp. The disc diffusion technique was used to test antibacterial action, with 10% DMSO serving as a negative control. Antibacterial sensitivity methods were used to determine the positive control. Depending on the outcomes of this study, it is possible to say that the methanol extract of mangosteen fruit leaves at 100% concentration had the highest antibacterial action, with an inhibition zone of approximately 27.01 mm ± 0.1 [76].

5.7. Neuropathy. Pericarp extracts of *G. mangostana* were orally administered as 100, 200, and 400 g/kg/day to T2DM-induced Wistar rats treated with HFD. The result revealed the reduction in BW, FBG, glial nuclear factor kappa light chain enhancer of activated B cell (NF-κB) expression, interleukin-6 (IL-6) expression, and tumor necrosis factor α (TNF-α) expression and increased SOD generation, shown by Muniroh et al. in 2021 [75].

6. Clinical Investigations

Different clinical investigations have reported the promising antidiabetic effects of mangosteen fruit (*G. mangostana*) (Table 5).

A randomized, single-blind, and placebo-controlled clinical trial was performed by Handayani et al., on adults with high-risk cardiovascular disease. After 90 days of using *G. mangostana* extract, 2520 mg/day, the result showed a significant decrease in nitric oxide, plasma IL-6, interleukin-1 (IL-1), MDA, TC, low-density lipoprotein (LDL), HbA1C, and hs-CRP concentrations compared with placebo [83].

Watanabe et al. assessed the safety and efficiency of treatment with mangosteen fruit extract on insulin resistance, weight management, and inflammatory station in 22 obese female patients with insulin resistance. In this randomized, controlled, and parallel-group study, patients used a capsule formulation containing 400 mg of *G. mangostana*, titrated to 40% in α-mangostin and γ-mangostin. After 26 weeks, the reduced insulin levels in the treatment group were meaningfully higher than in the control group ($p = 0.004$). The same result was observed in HOMA-IR% reduction. Both results were proven even after weight loss and BMI changes correction over time. However, no important alteration was detected in blood glucose levels. After all, this study showed that this formulation had a perfect safety profile [82].

The main antidiabetic mechanisms and effects of mangosteen fruit (*G. mangostana*) are illustrated in Figure 4.

7. Conclusion

G. mangostana belongs to the Guttiferae family, genus *Garcinia*. The chief phytochemicals existing in this species are isoprenylated xanthones, a class of secondary metabolites with multiple reports of biological impacts, such as antioxidant, anti-inflammatory, hypoglycemic, and anti-obesity. Numerous *in silico*, *in vitro,* and *in vivo* documents have provided strong evidence for investigating mangosteen fruit efficacy against DM2. Data reported in this review show that mangosteen fruit has therapeutic potential to counteract diabetes and its complications. Its pericarp, rind, seed, stem bark, or leaves of ethanolic, aqueous, and vinegar extracts have revealed antidiabetic actions, such as lowering blood

glucose levels, insulin resistance, increasing plasma insulin levels, and reducing body weight and BMI. The mechanisms proposed for these effects are diverse. In particular, mangosteen fruit appears to be effective in inhibiting α-amylase and α-glycosidase and enzymes that hydrolyze starch and produce dextrins and low molecular weight sugars. Other mechanisms include inhibiting pancreatic lipase activity, stimulating the cell regeneration of the islets of Langerhans by increasing the size and density of the islets of Langerhans, increasing the expression of PPAK-γ and reducing the production of AGEs and BSA glycation and HBA1C levels. Mangosteen fruit can also help with DM2 complications, improving the liver structure and function and improving cardiovascular parameters, suppressing BW gain and preventing obesity, protecting the kidney from diabetic nephropathy, and improving the open wound-healing process. The dosing and frequency of which mangosteen fruit was used varied depending on the study model. In *in vitro* studies on different types of cells and enzymes, the mangosteen fruit concentration ranged from 0.78-75 μM, and in one study, these concentrations were loaded for six days. In animal studies, mangosteen fruit was orally administered, applied as an ointment or injected with a dosage range of 4–1000 mg/kg for 1–40 weeks. For investigating the effect of mangosteen fruit on diabetes complications, it was evaluated in animal and cell studies. In cells such as HUVECs, induced-glucose mesangial cells, and newly differentiated human adipocytes, the concentration varied from 1.25 to 50 μM. In HFD and STZ-induced DM2 rats, mangosteen fruit was administered 1–500 mg/kg for about 5–16 weeks. By evaluating the data in the scientific literature, it is hoped that more clinical investigations will be performed to assess the effects of mangosteen fruit and its specific dosage on glycemic outcomes.

Abbreviations

11β-HSD:	11β-Hydroxysteroid dehydrogenase
AGEs:	Advanced glycation end-products
ALP:	Alkaline phosphatase
ALT:	Alanine transaminase
AMPK:	Adenosine monophosphate-activated protein kinase
AR:	Androgen receptor
AST:	Aspartate aminotransferase
AUC:	Area under the curve
BMI:	Body mass index
BSA:	Bovine serum albumin
BUN:	Blood urea nitrogen
BW:	Body weight
CAT:	Catalase
CHOL:	Cholesterol
CPT1a:	Carnitine palmitoyltransferase 1A
CREA:	Creatinine
Cyt c:	Cytochrome complex
DFU:	Diabetic foot ulcers
DM:	Diabetes mellitus
DM1:	Diabetes mellitus type 1
DM2:	Diabetes mellitus type 2
DPPH:	2,2-Diphenyl-1-picryl-hydrazyl-hydrate
ECM:	Extracellular matrix
ERBB2:	Erythroblastic oncogene B
FAS:	Fatty acid synthetase
FBG:	Fasting blood glucose
FBPase1:	Fructose 1,6-bisphosphatase
FFA:	Free fatty acid
GPx:	Glutathione peroxidase
GRd:	Glucose disappearance
GSH:	Glutathione
GSIS:	Glucose-stimulated insulin secretion
HbA1C:	Hemoglobin A1C
HDL:	High-density lipoprotein
HDL-C:	High-density lipoprotein cholesterol
HFD:	High-fat diet
HOMA-IR:	Homeostatic model assessment for insulin resistance
HOMA-β:	Homeostasis model assessment of β-cell
HPLC:	High-performance liquid chromatography
hs-CRP:	High-sensitivity C-reactive protein
HUVEC:	Human umbilical vein endothelial cells
ICR:	Institute of cancer research
IDF:	International Diabetes Federation
IL-1:	Interleukin-1
IL-6:	Interleukin-6
INS-1:	Rat insulinoma cell line
JNK:	Jun N-terminal kinase
KI:	Kidney hypertrophy
LDL:	Low-density lipoprotein
LDL-C:	Low-density lipoprotein cholesterol
LPO:	Lipid peroxide
LPS:	Lipopolysaccharide
MDA:	Malondialdehyde
MODY:	Maturity-onset diabetes of the young
MVR:	Mangosteen fruit vinegar rind
NAFLD:	Nonalcoholic fatty liver disease
NCCR:	NADH cytochrome C reductase
NF-κb:	Nuclear factor kappa light chain enhancer of activated B cells
NP:	Nonpolar
OGTT:	Oral glucose tolerance test
OMTT:	Oral mixed-meal tolerance test
ORAC:	Oxygen radical absorbance capacity
P:	Polar
P-Akt:	Phosphorylated Akt
PDX1:	Pancreatic and duodenal homeobox 1
P-ERK:	Phosphorylated extracellular regulated kinase
P-IRS-1:	Phosphorylated insulin receptor substrate-1
PL:	Pancreatic lipase
PPAK-γ:	Gamma P21-activated kinase
PPAR-γ:	Peroxisome proliferator-activated receptor gamma
P-PI3K:	Phosphoinositide protein 3-kinases
PTP1B:	Protein tyrosine phosphatase 1B
RAGE:	Receptor for advanced glycation end-products
ROS:	Reactive oxygen species

SCCR: Succinate cytochrome C reductase
SD rat: Sprague–Dawley rat
Ser: Serine
SGOT: Serum glutamic-oxaloacetic transaminase
SGPT: Serum glutamic pyruvic transaminase
SIRT1: Sirtuin 1
SOD: Superoxide dismutase
SP: Semipolar
STZ: Streptozotocin
TBARS: Thiobarbituric acid reactive substances
TC: Total cholesterol
TG: Triglyceride
TGF-β1: Transforming growth factor beta 1
TMD: Total mood disturbance
TNF-α: Tumor necrosis factor α
tROS: Total reactive oxygen species
VAS: Visual analog scales
VEGF: Vascular endothelial growth factors
VLDL: Very low-density lipoprotein
YaSP: Ya-Samarn-Phlae.

Data Availability

No data were used to support the findings of this study.

Conflicts of Interest

The authors declare that they do not have any conflicts of interest.

Authors' Contributions

Rozhan Safaei, Katayoun Sakhaee, Mahsa Saberifar, and Mohammad Saleh Fadaei contributed equally to this work.

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