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Review Article

Antidiabetic Potential of *G. Mangostana* Extract and α-Mangostin Compounds from Mangosteen (*Garcinia mangostana* Linn.)

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Abstract: ***Background:*** Diabetes mellitus is a high prevalence disease that increases and requires continuous treatment. However, antidiabetic drugs can cause side effects in long-term use. Traditional medicine derived from natural sources such as mangosteen (*Garcinia mangostana* Linn.) is potential as one of the solutions as an antidiabetic drug. α-mangostin has an antidiabetic activity where this compound lowers blood glucose levels and normalize hyperglycemic conditions. This review summarized the antidiabetic activity of *G. mangostana* and α-mangostin compound in the mangosteen (*G.mangostana* Linn) plant. ***Method:*** We reviewed and compiled published articles search through several sites such as Google Scholar, NCBI, Pubmed, Research Gate, and Science Direct within the last ten years. ***Result:*** Several studies show an antidiabetic effect from *G. mangostana* and α-mangostin observed from several parameters, including blood glucose levels, plasma insulin, HOMA-IR values, histopathology examination, and others. ***Conclusion*****:** *G.mangostana* extract and α-mangostin are promising candidates for the treatment of diabetes.

Keywords: α -mangostin, diabetes, *Garcinia mangostana*.

INTRODUCTION

Diabetes Mellitus (DM) is a chronic disease caused by insufficient insulin production by the pancreas or impaired insulin sensitivity (World Health Organization, 2016). It is a non-communicable disease with various complications, a high mortality rate, and requires high costs for treatment (International Diabetes Federation, 2013; Saydah, 2016). The number of cases and the prevalence of DM has continued to increase over the last few decades (World Health Organization, 2016). The Middle East and North Africa region had the highest prevalence of diabetes in adults (10.9%), while the Western Pacific region had the highest number of adults diagnosed with diabetes and had the country with the highest diabetes prevalence (37.5%) (Kharroubi, 2015). International Diabetes Federation (IDF) estimates that 463 million adults aged 20-79 years have diabetes (9.3% of all adults in this age range). By gender, diabetes in women aged 20-79 years is slightly lower than in men. In adults age between 75–79 years, the prevalence of diabetes was 19.9% in 2019 and predicted to increase to 20.4% in 2030 and 20.5% in 2045. The total number of people with diabetes is expected to increase to 578 million in 2030 and 700 million in 2045 (International Diabetes Federation, 2019).

There are four types of DM: type 1 diabetes, type 2 diabetes, gestational diabetes, and specific types of diabetes due to other causes (American Diabetes Association, 2019). Type 2 diabetes is the most common diabetes resulting from dysfunction of pancreatic β-cell and insulin resistance, or both, that lead to relative insulin deficiency (Newman, 2014; World Health Organization, 2016). In individuals, this occurs due to modifiable lifestyle-related risk factors that interact with genetic risk factors (Newman, 2014). The general goal for DM management is improving the quality of life of people with DM. The long-term goals are preventing and inhibiting the progression of microangiopathy and macroangiopathy complications, and the ultimate goal of management is to reduce DM morbidity and mortality (PERKENI, 2019). The treatment for type 2 diabetes includes non-pharmacological and pharmacological treatment to lower and control glucose levels. Pharmacological intervention includes insulin, metformin, sulfonylureas, meglitinide, thiazolidinedione, DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT2 inhibitors (Jamwal, 2020). People with diabetes require long-term therapy

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(American Diabetes Association, 2018). However, these antidiabetic drugs can cause side effects in chronic use (Achmad *et al*., 2017).

Nowadays, research is carried out on various plants as antidiabetic to find alternatives for DM treatment and minimizing side effects (Wulandari, 2015). Many plants have antidiabetic activity, including mangosteen (*G.mangostana* Linn) (Darmawansyih, 2015; Maliangkay & Rumondor, 2018; Pasaribu *et al*., 2012; Yusni *et al*., 2017). Mangosteen (*G. mangostana* Linn) is a plant that is useful as traditional medicine. The rind use for abdominal pain, dysentery, wound infections, suppuration, and chronic ulcers (Cui *et al.*, 2010). Mangosteen (*G.mangostana* Linn) has various bioactivities beneficial for therapy, including antiproliferative (Moongkarndi *et al.*, 2004), antibacterial (Sakagami *et al.*, 2005), and antitumor (Doi *et al.*, 2009).

Mangosteen (*G.mangostana* Linn) extract also showed antidiabetic activity (Darmawansyih, 2015; Maliangkay & Rumondor, 2018; Pasaribu *et al*., 2012; Yusni *et al*., 2017), antioxidant (Jung *et al*., 2006; Supiyanti *et al.*, 2010), inhibition of human leukemia cell line HL60 growth (Matsumoto *et al.*, 2003), cytotoxic (Suksamrarn *et al*., 2006), and analgesic (Cui *et al*., 2010). The main component of *G.mangostana* rind is xanthones, which are polyphenolic compounds. One of them is α-mangostin (Aisha *et al*., 2012).

Fig-1: Mangosteen (*G. mangostana* Linn*)* fruit (www.klikdokter.com, n.d.).

G.mangostana fruit rinds contained high concentrations of α-mangostin (Aisha *et al*., 2012). This difference in α-mangostin is concentration in *G.mangostana* influence by temperature, humidity, soil, rainfall, and geographical location (Muchtaridi *et al*., 2016). α-mangostin shows many pharmacological effects such as antioxidant activity (P. Kumar *et al*., 2017), anti-inflammatory (Chen *et al.*, 2008; P. Kumar *et al*., 2017), antifungal (Kaomongkolgit *et al*., 2009), antimetastatic in the human prostate carcinoma cell line PC-3 (Hung *et al*., 2009) anticancer and anti-invasive in human skin cancer cell lines (Wang e*t al*., 2012), and strong cytotoxic effect against T47D cells (Dachriyanus *et al*., 2015). In addition, other studies have also shown that α-mangostin produces antimicrobial/antibacterial activity (Asasutjarit *et al*., 2019), is antidiabetic (Ersam & Wulandari, 2015; Husen *et al*., 2018; P. Kumar *et al.*, 2017) and effective as antiplasmodial (Larson *et al*., 2010).

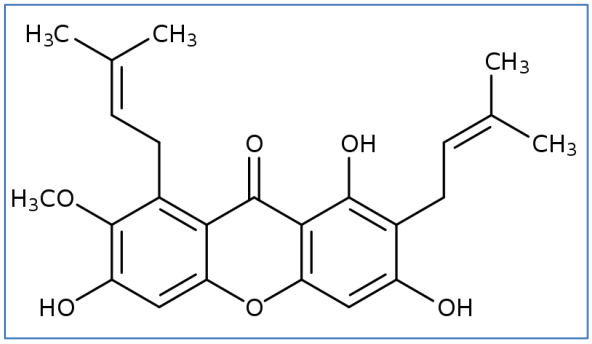

Fig-2: Structure of α-mangostin (Aisha *et al*., 2012).

We collected and reviewed the current knowledge on the antidiabetic potential of *G.mangostana* extract and α-mangostin from *G.mangostana* Linn. The aim is to explore the possibility of α-mangostin developed as an antidiabetic drug choice for type 2 diabetes.

METHOD OF COLLECTING DATA

We collect primary data from journals published from 2010-2020. The keywords used were "Alpha-mangostin" and "Antidiabetic" or "hypoglycemic" or "antihyperglycemic." We search through different websites such as Google Scholar (n = 42), NCBI (n = 316), Pubmed (n = 126), Research Gate (n = 100), Science Direct (n = 8). Article searches are

carried out in English and Bahasa. The articles were selected according to inclusion and exclusion criteria. We obtained 18 articles that matched our criteria and were included in this review.

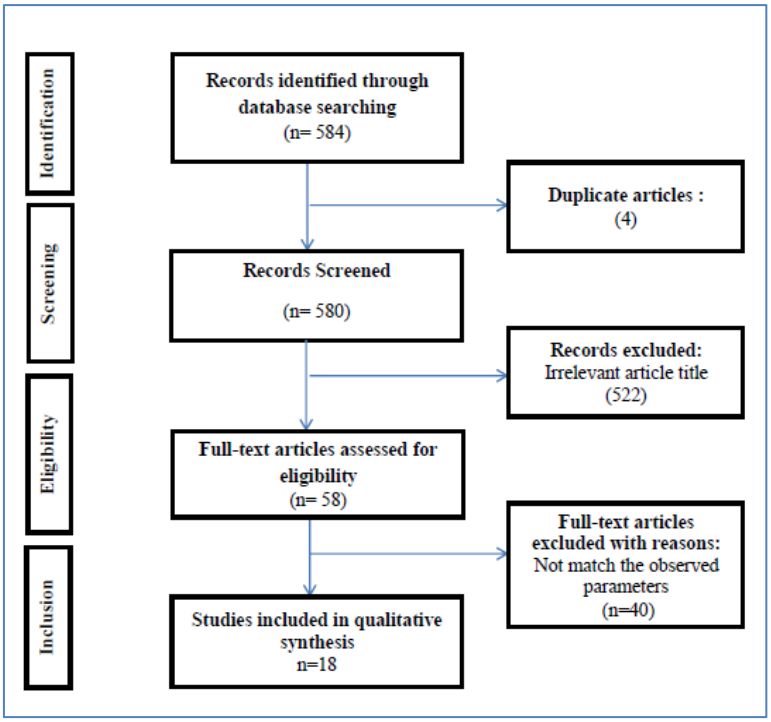

Fig-3: Flowchart of search and selection of articles

RESULTS AND DISCUSSION

From eighteen articles selected, thirteen were carried out in vivo testing, four in vitro tests, and one clinical trial article. The sample used in the article is *G.mangostana* extract and isolated α-mangostin or synthetic α-mangostin, with dose variation. In vivo test is carried out with male Wistar rats (*Rattus norvegicus*) or mice (*Mus musculus* L.). INS-1 cells, HUVECs, or both used in in vitro tests. Only one article was tested in humans, with the adult female patient as the subject.

In Vivo Test

The in vivo test on animals is divide into three based on diabetogenic agents, the Alloxan, Streptozotocin (STZ), and glucose tolerance test.

1. Alloxan Inductor

Alloxan is a diabetogenic substance, toxic, especially to pancreatic cells. Alloxan will accumulate in the islets of Langerhans of the pancreas and damage the cells, disrupted insulin production. Due to this, the pancreas cannot produce the insulin needed for glucose metabolism and cause a hyperglycemia state. This condition will trigger the production of reactive oxygen species (ROS) (Lenzen, 2008). Alloxan also induces diabetes by causing disturbances in intracellular calcium homeostasis. In addition to these two actions, the diabetogenic ability of alloxan was also supported by the role of alloxan in inhibiting glucokinase in energy metabolism processes (Gleichmann *et al*., 2002; Szkudelski, 2001). There are several doses of alloxan uses as a diabetes inducer in the study. For mice, 70 mg/kgBW (iv) (Ratwita *et al*., 2019), and rats 120 mg/kgBW, 90 mg/kgBW and 150 mg/kgBW (ip) (Ersam & Wulandari, 2015; Maliangkay & Rumondor, 2018; Yusni *et al*., 2017). The antidiabetic activity of several in vivo research was summarized in table 1.

There are variations in the dose of alloxan and also the duration of diabetes in test animals. The fastest confirmation of diabetes in animals is within two days with the administration of alloxan 150 mg/kg BW (Yusni *et al*., 2017). In another study, diabetes occurred on the third day with a dose range of 70-120 mg/kg BW (Ersam & Wulandari, 2015; Maliangkay & Rumondor, 2018; Ratwita *et al*., 2019), and the longest time is within seven days (unspecified dose) (Darmawansyih, 2015). One of the reasons for this difference in response is the difference in individual rats' resistance to alloxan administration so that the diabetes conditions that occur are not uniform (Suarsana *et al*., 2010).

Three studies tested the activity of *G.mangostana* extract from rind and peel, and two studies using α-mangostin in vivo. Two research using *G.mangostana* rind extract gives a decrease in blood glucose level. The first study showed that 100 mg/kg BW extract significantly decreased glucose levels compared to the control (Darmawansyih, 2015). In another study, administration of ethanol extract of *G.mangostana* rind also had activity to repair damage to pancreatic β-cells in alloxan-induced white rats. From two doses, the lower dose gave a better percentage

reduction in glucose levels. The theory put forward by the researchers is that compounds contained in the extract at high doses have an antagonistic effect in reducing glucose (Maliangkay & Rumondor, 2018). Combination of *G.mangostana* extract with other plants also showed antidiabetic activity. *G. mangostana* and tomato peel extract at a dose of 50 mg/kg BW each showed a significant decrease in the percentage of glucose levels (Yusni *et al*., 2017).

Table-1: In vivo test of antidiabetic activity of *G.mangostana* extracts and α-mangostin

No.	Sample	Method	Results	Reference
***Garcinia mangostana* Linn. Extracts**				
1.	Ethanol Extracts of *G. mangostana* rind	Mice were induced by alloxan. The treatment group: *G. mangostana* rind extract 100 mg/KgBW The negative control group: Na-CMC 1 % Comparison: Glibenclamide 0.03 mg/kgBW	↙ blood glucose levels significantly ($p < 0.05$) compared to the control group, but not significant compared to glibenclamide ($p > 0.05$)	(Darmawansyih, 2015)
2.	Ethanol Extracts of *G. mangostana* rind	White male Wistar rats were induced by alloxan 90 mg/kg BW (i.p). The treatment group: ethanol extract of *G. mangostana* rind 150 mg/kg BW and 300 mg/kg BW. Comparison: glibenclamide 5 mg/kg BW	↙ glucose levels 64.68% on the 7th day and 81.46% on the 14th day with a dose of 150 mg/kg BW ↙ glucose levels 35,77 % on the 7th day and 76,75 % on the 14th day with a dose of 300 mg/kg BW. ↙ glucose levels on the administration of glibenclamide 57.12% on the 7th day and 72.62% on the 14th day.	(Maliangkay & Rumondor, 2018)
3.	*G. mangostana* and tomato (*Lycopersicum esculentum Mill*) peel extract	White male Wistar rats were induced by alloxan 150 mg/kgBW (i.p). The treatment group: extracts of *G.mangostana* and tomatoes at a dose of 50 mg/kg BW/day each for seven days	↙ blood glucose levels by 56,67% significantly ($p=0,00$)	(Yusni et al., 2017)
α-mangostin				
4.	α-mangostin from pericarp	White male Wistar rats were induced by 120 mg/kg alloxan (i.p.). Experiment group: α-mangostin at a dose of 10 mg/kg, 30 mg/kg, 50 mg/kg. Normal control : saline (0.9%, w/v) Diabetic control : saline (0.9%, w/v) Comparison: glibenclamide 10 mg/kg.	↙ blood glucose in all α-mangostin group and comparison The 30 mg/kg dose group showed the best reduction in glucose levels (367.4±146.1 to 272±119.9,$p < 0.05$ compare to diabetic control)	(Ersam & Wulandari, 2015)
5.	***α-mangostin***	Male mice were induced by alloxan (70 mg/kg BW, i.v.) The treatment group: α-mangostin at a dose of 5, 10, and 20 mg/kg BW. The positive control group, which was diabetic and received vehicle only. Comparison: Glibenclamide 0.65 mg/kgBW Metformin 65 mg/kgBW	↙ fasting blood glucose after 21 days significant compared to positive control ($p <0.05$) ↗ plasma insulin significant after 21 days compared to positive control ($p<0.05$) Administration α-mangostin improve the langerhans area.	(Ratwita *et al.*, 2019)

The α-mangostin compound, a xanthone derivative compound found in *G. mangostana*, also shows a favorable antidiabetic effect in the experimental animal. The α-mangostin used was isolated from the pericarp of *G. mangostana* (Ersam & Wulandari, 2015) and synthetic α-mangostin (Ratwita *et*

al., 2019). Ersam and Wulandari used three doses of α-mangostin, 10 mg/kg, 30 mg/kg, 50 mg/kg. The three α-mangostin groups was comparable to control, and the 30 mg/kg group showed the most reduction of blood glucose level and significant compared to diabetic controls (Ersam & Wulandari, 2015).

Another study also used three doses, 5 mg/kg BW, 10 mg/kg BW, and 20 mg/kg BW of α-mangostin. The difference between doses used did not show a significant difference, although the greatest decrease in glucose levels occurred at a dose of 20 mg/kg BW. The α-mangostin 20 mg/kg BW group also significantly increased insulin levels compared to the control group. Histopathological examination showed alloxan causes shrunken in the islet of Langerhans without any degenerative changes and necrosis. Administration of α-mangostin improved the islet of Langerhans of alloxan-induced diabetic animals. The effect of α-mangostin seen from the test is due to the regeneration of β-cells that produce insulin and maintain and protect the integrity of β-cells (Ratwita *et al*., 2019).

2. Streptozotocin Inductor

Streptozotocin (STZ) inhibits insulin secretion and causes insulin-dependent diabetes mellitus (IDDM). These are attributed alkylation potential of STZ (Lenzen, 2008). STZ enters pancreatic β-cells via glucose transporter 2 (GLUT 2) and causes the alkylation of DNA. DNA damage induces activation of poly ADP-ribosylation, a process that is more important for the diabetogenicity of streptozotocin than DNA damage itself. Poly ADP-ribosylation leads to depletion of cellular NAD^+ and ATP. The enhancement of ATP dephosphorylation after streptozotocin treatment resulting in the formation of superoxide radicals. Consequently, this will also degenerate hydrogen peroxide and hydroxyl radicals. Furthermore, streptozotocin liberates toxic amounts of nitric oxide that inhibit aconitase activity and participates in DNA damage. As a result of the streptozotocin action, β-cells undergo destruction by necrosis (Szkudelski, 2001).

Seven in vivo studies used the extracts of *G.mangostana* and α-mangostin in STZ-induced diabetes experimental animals. Two studies used STZ at higher dose (50 mg/kg and 55 mg/kg) confirmed diabetes within 3-7 days. Five other studies used a low dose of STZ with a range of 30-35 mg/kg. Two studies using STZ at a 30 mg/kg dose for five consecutive days (Husen *et al.*, 2017, Husen *et al*., 2018). Two studies induced insulin resistance in diabetic animals with a combination of STZ 35 mg/kg and a High Fat/High Glucose diet (Lazarus *et al*., 2020; Soetikno *et al*., 2020).

Pericarp extract of *G.mangostana* at doses of 50 mg/kg, 100 mg/kg and 200 mg/kg showed a significant decrease in glucose levels ($p < 0.005$). In single-dose administration, the 200 mg/kg group showed a significant decrease in glucose levels starting from the 4th hour. In multiple doses administration, the decrease in glucose levels occurred gradually starting from the seventh day ($p<0.005$). Histopathological examination showed that different doses showed different effects on the islet of Langerhans (Taher *et al*., 2016). Another study also used 50 mg/kg, 100 mg/kg, and 200 mg/kg of *G.mangostana* pericarp extract. The extract not only decreases blood glucose but also increases insulin levels and the diameter of the islet of Langerhans (Husen *et al*., 2017).

Table-2: Antidiabetic activity of extracts of *G. mangostana* and α-mangostin in STZ-induced test animals.

No.	Sample	Method	Results	Reference
***Garcinia mangostana* Linn. Extracts**				
1.	Ethanol Extracts of *G. mangostana* pericarp (GME)	Adult male Sprague-Dawley rats were induced by STZ 50 mg/kg BW (i.p). Diabetic control received the only vehicle The treatment group: ethanol extract of *G. mangostana* with 50, 100, and 200 mg/kg BW doses. Comparison: glibenclamide 0.5 mg/kg BW	↙ blood glucose level of all doses of GME ($p < 0.05$) STZ-induced diabetic rats (single-dose) ($p < 0.05$) ↙ blood glucose level in GME at 200 mg/kg after 4h ↙ blood glucose level in glibenclamide group after 2h STZ-induced diabetic rats (multiple-dose) ↙ blood glucose level in all doses of GME ($p<0.05$) ↙ blood glucose level gradually in glibenclamide group ($p <0.05$) starting from day 7 Histopathological studies 50 mg/kg BW: restoration of normal cell population; reduce damaged islet and decrease hyperplasia 100 mg/kg BW: the presence of granulated islet of Langerhans with prominent hyperplasia 200 mg/kg BW: increase number of β-cell; the absence of damaged islet and hyperplasia	(Taher *et al*., 2016)

2.	Extract of *G. mangostana* pericarp	· STZ-induced male mice (30 mg/kg BW for five days). · The treatment group: *G. mangostana* extract at 50, 100, and 200 mg/kg BW doses. · Normal control: non-diabetic mice · Diabetic control: STZ-induced mice · Comparison: metformin 100 mg/kg BW	↙ fasting blood glucose significantly compared to diabetic group ↗ insulin production by repairing β-cell ↗ diameter of the islet of Langerhans significantly compared to diabetic group	(Husen *et al*., 2017)
α-mangostin				
3.	α-mangostin isolated from pericarp of G. mangostana	· Male Wistar rats were induced by STZ 55 mg/kg BW (i.p) · The treatment group: α-mangostin 25 and 50 mg/kg BW Diabetic control rats: STZ-induced rats · Comparison: gliclazide 1 mg/kg BW	↙ blood sugar levels from α-mangostin and gliclazide group compared with diabetic controls ($p < 0.01$)	(Nelli *et al*., 2013)
4.	α-mangostin	Male Wistar rats were induced by STZ 60 mg/kg BW (i.p). The treatment group: α-mangostin at a dose of 25 mg/kg, 50 mg/kg and 100 mg/kg. Comparison: glibenclamide 10 mg/kg body weight	↙ blood glucose levels significantly ($p < 0.001$) at all doses, the best result showed in 100 mg/kg BW group ↗ insulin level α-mangostin showed a protective effect against insulin resistance in an effective dose-dependent manner	(V. Kumar *et al*., 2016)
5.	***α-mangostin***	Male mice were induced by STZ 30 mg/kg BW for five days The treatment group: ***α***-mangostin at a dose of 2, 4, 8 mg/kg BW Comparison: metformin HCl 100 mg/kg BW	↙ fasting blood glucose levels ***α***-mangostin 2 mg/kg BW gives the highest response compared to other doses.	(Husen *et al*., 2018)
6.	***α-mangostin***	Male Wistar rats get high fat/high glucose (HF/HG) diet for 3 weeks, then induced by STZ 35 mg/kg BW (i.p). The diet continues until 8 weeks The treatment group: ***α***-mangostin with doses of 100 and 200 mg/kg/day Comparison: metformin 200 mg/kg BW/day	↗ insulin sensitivity ↙ HOMA-IR ↙ fasting plasma glucose levels were	(Soetikno *et al*., 2020)
7.	***α-mangostin***	IR-induced rats: high fat/high glucose (HF/HG) diet for 3 weeks, then induced by STZ 35 mg/kg (i.p). The diet continues until 11 weeks Experimental group: · IR-induced group treated with ***α***-mangostin (100 and 200 mg/kg) · Untreated IR-induced rats · The normal group served as control · Healthy rats + *α-mangostin 200 mg/kg*	↗ significant insulin sensitivity in both doses of *α-mangostin compared to untreated IR group* ↙ HOMA-IR index ↗ GLUT4 expression significantly	(Lazarus *et al*., 2020)

Studies with α-mangostin also showed a positive effect on diabetic-induced animals. At a dose of 2 mg/kg, 4 mg/ kg, 8 mg/kg**,** α-mangostin showed decreased fasing blood glucose with the 2 mg/kg group showing the best response. The higher dose of α-mangostin also significantly decreased blood glucose levels (Kumar *et al*., 2016; Nelli *et al*., 2013). In insulin-resistant diabetic rats, α-mangostin increase insulin sensitivity, evidenced *by a* significant decrease in HOMA-IR *(*Lazarus *et al.,* 2020; Soetikno *et al.,* 2020).

3. Glucose Tolerance Test Method

The glucose tolerance test method was carried out on normal male mice as a preliminary test to determine the ability of the test material (*G.mangostana* extract) to restore blood glucose levels after administration of glucose solution. The glucose tolerance test method begins with measuring the initial blood glucose level (T_0), then the test material is given (Susilawati *et al*., 2016).

Table-3: Antidiabetic activity of *G.mangostana* extract by glucose tolerance method

No	Sample	Method	Results	Reference
1.	Ethanol extracts of *G. mangostana* rind	Treatment Dosage of ethanol extract of *G. mangostana* rind: 50, 100, and 200 mg/kg BW. Control group: Mice were given 0.5% Na-CMC suspension Comparison: glibenclamide dose of 0.65 mg/kg BW Thirty minutes later, each group was given a 50% glucose solution (3 g/kg BW). Time of measurement: 30, 60, 90, and 120 min using a glucometer	↙ Blood glucose levels at 60 – 120 minutes were significantly compared to the control group and comparable to glibenclamide at a dose of 0.65 mg/kg BW.	(Pasaribu *et al*., 2012)
2.	***α-mangostin***	Treatment Dosage of ethanol extract of *G. mangostana* rind: 50, 100, and 200 mg/kg Control group: Mice were given 0.5% Na-CMC suspension Comparison: glibenclamide dose of 0.65 mg/kg BW Thirty minutes later, each group was given a 50% glucose solution (3 g/kg BW).	↙ blood glucose level by 13.58%, 24.07%, and 37.45% at the tested doses 50 mg/kg, 100 mg/kg and 200 mg/kg ($p < 0.001$)	(V. Kumar *et al*., 2016)

The analysis results showed that the administration of the ethanolic extract of *G. mangostana* rind and α-mangostin reduce blood glucose level significantly. In the first study, the best reduction showed in the 100 mg/kg group compared to 50 mg/kg and 200 mg/kg group. At a dose of 200 mg/kg, there was no increase in antidiabetic activity. The binding receptors have been saturated, and interactions occur with other chemical compounds in *G. mangostana*. If the receptor has been saturated, increasing the dose can not reach its maximum effect (Pasaribu *et al*., 2012). While in another study using α-mangostin, the reduction of blood glucose level is proportional to the dose (Kumar *et al*., 2016).

In Vitro Test

In vitro test is a preclinical test on isolated cell cultures or isolated organs (Priyambodo, 2014). The summary of the antidiabetic activity of *G. mangostana* extracts and α-mangostin performed in vitro test shows Table 4. Administration of α-mangostin can reduce cell apoptosis induced by high glucose induction in a concentration-dependent manner. The concentration of 15 μM α-mangostin showed significant results ($p < 0.05$) in reducing cell apoptosis. Apoptosis in cell cultures treated with 30 mM D-glucose + 15 μM α-mangostin was significantly lower than in cells cultured with 30 mM d-glucose alone. One of the important factors in diabetic angiopathy is abnormal ceramide accumulation that can induce cell apoptosis. Diabetic angiopathy occurs due to narrowing and blockage of blood vessels in DM patients. α-mangostin can inhibit the increase in ceramide concentration in HUVECs cultured at high glucose (Luo & Lei, 2017).

α-mangostin 1 μM, 2.5 μM and, 5 μM increased insulin secretion in INS-1 cells. α-mangostin stimulates insulin secretion in INS-1 cells by activating insulin receptors (IR), and also pancreas and duodenal homeobox 1 (Pdx1) followed by phosphorylation of phospho-phosphatidylinositol-3 kinase (PI3K), Akt, and extracellular signal-regulated kinase (ERK) and inhibits the phosphorylation of insulin receptor substrate (IRS-1). α-mangostin was also able to restore STZ-induced INS-1 cell viability that was decreased in a dose-dependent manner. INS-1 cells induced with 50 μM of STZ resulted in increased intracellular reactive oxygen species (ROS) levels. This oxidative stress was reduced by 5 μM α-mangostin treatment. Similarly, the marked increase in P38 phosphorylation, c-Jun N-terminal kinase (JNK), and caspase-3 cleavage by STZ decreased significantly with 5 μM α-mangostin treatment. These results indicate that α-mangostin can increase insulin secretion in pancreatic cells and protect cells from apoptotic damage (D. Lee *et al*., 2018).

High glucose (60 mM) significantly decreased cell viability and increased ROS and cell senescence. α-mangostin (1.25 μM) reversed the toxic effect of high glucose in these HUVECs. α-mangostin reduces oxidative stress and cell aging as indicated by decreased senescence-associated-beta-galactosidase (SA-β-GAL) activity. The protective effect of α-mangostin against HUVECs was similar to control (metformin 50 μM) (Tousian *et al*., 2020a). SA-β-GAL is the most widely used biomarker for senescent and aging cells *(*Lee *et al*., 2006).

Oxidative stress induces a hyperglycemic condition that results in DNA damage and exhibits endothelial cell senescence and angiopathy (Burton &

Faragher, 2018; Goligorsky, 2017). Administration of α-mangostin significantly increased cell viability, decreased ROS, and SA-β-GAL in HUVECs incubated under metabolic memory conditions (Tousian *et al*., 2020b). Metabolic memory is a history of high glucose conditions, even after returning to physiological conditions that cause permanent side effects (Zhang *et al*., 2015). These data suggest that α-mangostin is comparable to metformin in protecting endothelial cells against aging-induced by metabolic memory, most likely via Sirtuin1 (SIRT1) (Tousian *et al*., 2020b). SIRT1 is an enzyme that is a key metabolic sensor in various metabolic tissues and acts in the pathogenesis of chronic conditions such as diabetes (Iside *et al*., 2020).

Studies also showed α-mangostin decreases β-galactosidase activity, which hydrolyzes D-galactosyl residues of polymers, oligosaccharides, or secondary metabolites (Tousian *et al*., 2020a, 2020b). The enzyme β-galactosidase, better known as lactase, is a biocatalyst for the hydrolysis of lactose into glucose and galactose and the trans-galactosylation reaction (Husain, 2010). The inhibition of these enzymes will cause reduction in blood glucose levels.

Table-4: Antidiabetic activity of extracts of *G. mangostana* and α-mangostin in vitro

No.	Sample	Method	Results	Reference
	α-mangostin	HUVECs were divided into seven groups and assigned: (i) 5 mM D-glucose (ii) 30 mM D-glucose (iii) 30 mM D-glucose + 5 μM α-mangostin (iv) 30 mM D-glucose + 10 μM α-mangostin (v) 30 mM D-glucose + 15 μM α-mangostin (vi) 30 mM D-glucose + 2 μM desipramine (positive control) (vii) 30 mM L-glucose α-mangostin was added to the culture medium immediately after addition of glucose. The expression of the apoptosis-related proteins, were detected by Western blotting. The cell apoptosis rate was detected by flow cytometry after staining with annexin V/propidium iodide (PI). Ceramide concentration and acid sphingomyelinase (ASM) activity were assayed by HPLC.	↙ high glucose-induced apoptosis in a concentration-dependent manner High glucose-induced increase in ceramide levels was significantly attenuated by 15 μM α-mangostin (P <0,05) and 2 μM desipramine (P <0,01).	(Luo & Lei, 2017)
	α-mangostin	Rats pancreatic INS-1 cells were treated with a non-toxic dose of α-mangostin (1-10 μM) Insulin signaling was examined by Western blotting. The protective effect of α-mangostin against pancreatic cell apoptosis was verified by using β-cell toxin STZ. In the insulin secretion test, cells were given α-mangostin (1, 2.5, 5 μM) and gliclazide as a positive control.	α-mangostin stimulates insulin secretion in INS-1 cells. ↗ INS-1 cell viability ↙ Intracellular ROS ↙ P38, JNK, and caspase-3 phosphorylation	(D. Lee *et al*., 2018)
	α-mangostin	HUVECs were incubated with high glucose (10–60 mM) for 6 days, treated with metformin (50 μM) or α-mangostin (1.25 μM) for 6 days cell viability was measured by MTT assay, dichlorofluorescein diacetate assay to investigate the cellular ROS, percentage of senescent cells was evaluated using an SA-β-gal assay kit, secretory interleukin-6, and expression of SIRT1, AMK, p53, and p21 also measured.	↗ cellular viability ↗ SIRT1 protein levels and total AMPK ↙ ROS and cellular senescence ↙ β-galactosidase activity ↙ protein levels of p53, acetyl-p53, and p21 ↙ IL-6 secretion.	(Tousian *et al*., 2020a)
	α-mangostin	To induce the memory senescence model, HUVECs incubated for 3 days with high glucose were then incubated with normal glucose for the next 3 days. After 6 days, cells were given metformin (50 μM) or α-mangostin (1.25 μM). cell viability was measured by MTT assay, oxidative stress by fluorimetric assay, number of senescent cells by SA kit staining β-galactosidase, SIRT1, and Protein P53 were also evaluated by Western blotting.	↗ viability cell ↗ SIRT1 protein in HUVECs ↙ reactive oxygen species (ROS) ↙ β-galactosidase ↙ p53 and acetyl-p53	(Tousian *et al*., 2020b)

Clinical Trial

Clinical trials are research activities involving human subjects with the intervention of test products. The researcher can confirm any clinical, pharmacological effects, pharmacodynamic effects, or identify unwanted reactions of test products through clinical trials. They can also study the absorption, distribution, metabolism, and excretion of drugs. Using healthy or sick humans in experiments is justified in medical science because it will provide knowledge to understand the effects of drugs. This knowledge will lead to more confidence about their effectiveness and safety (Pradono *et al*., 2019).

Clinical trials on *G.mangostana* extracts are needed to confirm its anti-diabetic properties in humans. One clinical trial was conducted on 22 obese females aged between 18-65 years. The patients consumed a supplement containing the active substance *G.mangostana* 400 mg, titrated to 40% in α-mangostin and γ-mangostin at lunch once daily. Patient compliance was seen through the number of capsules brought at the next visit (monthly visits). Patients in the control group did not receive placebo treatment and only benefited from lifestyle interventions (Watanabe *et al*., 2018).

Table-5: Antidiabetic activity of *G.mangostana* extracts in clinical trials

Sample	Method	Results	Reference
G. mangostana fruit extract	Twenty-two female patients were divided into two groups. Group 1 (control): hypocaloric diet and physical activity. Group 2 (treatment): diet, physical activity, and *G.mangostana* extract 400 mg once a day. The study was observed for 26 weeks, conducted in a prospective randomized, controlled, and concurrent manner.	Insulin levels decreased significantly in the treatment group compared to the control at 26 weeks HOMA IR % change went in the same direction in favor of the mangosteen group that showed a frank improvement in insulin resistance	(Watanabe et al., 2018)

There is a widely recognized association between obesity, type 2 diabetes, and insulin resistance. Insulin sensitization treatments are effective in preventing diabetes and promote weight loss. The first intervention for obesity and type 2 diabetes is lifestyle changes, but in many patients is still not sufficient and required drug therapy. Mangosteen extract Supplement for 26 weeks led to improvements in glucose homeostasis in insulin-resistant obese female subjects independent of body mass index variation. The results of this study indicate that *G.mangostana* potential to treat obesity and its comorbidities (Watanabe *et al*., 2018).

Antidiabetic activity of *G.mangostana* extract and α-mangostin

The effect of extracts of *G. mangostana* and α-mangostin act as antidiabetic seen in several in-vivo, in vitro, and also clinical trials. The antidiabetic effect of the extracts of *G. mangostana* and α-mangostin is associated with their antioxidant properties that can reduce ROS. High ROS can damage pancreatic islets and cause disturbances in insulin production. Insulin is a hormone that helps the uptake of glucose in cells. Decreased insulin levels will cause high glucose levels (hyperglycemia). The administration of extracts of *G. mangostana* and α-mangostin was proven to reduce blood glucose levels. Other effects seen were increased GLUT4 expression, inhibition of α-amylase and β-glucosidase enzymes, decreased β-galactosidase activity, and provided a protective effect on apoptosis damage induced by high glucose levels. The histopathological examination shows that the extracts of *G.mangostana* and α-mangostin can repair damaged cells in the Langerhans area. After the treatment, there was an increase in the β-cell population due to improvement in the Langerhans area, thereby increasing plasma insulin production. Increased plasma insulin will increase glucose absorption into muscle cells and the liver so that glucose levels outside the cells were reduced because blood glucose levels decreased. Under conditions of insulin resistance, extracts of *G.mangostana* and α-mangostin increased insulin sensitivity as indicated by a decrease in the HOMA-IR index. The effect of decreasing blood glucose levels on the administration of *G.mangostana* and α- mangostin was due to antioxidants in the plant *G.mangostana*. *G. mangostana* extract contains xanthone compounds which are high levels of antioxidants (66.7%). Antioxidants are substances that can inhibit the negative effects of free radicals by acting as electron donors. Antioxidant compounds from *G.mangostana* were able to donate hydrogen atoms and stabilize free radicals. In addition to neutralizing free radicals, antioxidants were expected to reduce oxidative stress, especially in various cells that are affected by the worsening effects of prolonged hyperglycemic conditions, such as cells in the islet of Langerhans (Husen *et al*., 2017; Jung et al., 2006; Moongkarndi *et a*l., 2004). This condition will repair the islet of Langerhans and inhibit the remaining cell damage so that it still functions α-mangostin also regenerates cells so that the cell population increases through increased protein synthesis, accelerated detoxification, potentiation of antioxidant defenses, and neutralization of free radicals (Maliangkay & Rumondor, 2018; Ratwita *et al*., 2019).

CONCLUSION

Based on research using in vivo, in vitro, and clinical trials that have been summarized, it can be concluded that *G. mangostana* extract and ***α***-mangostin have been shown to have anti-diabetic effects. Although clinical trials need to be increased, it is are promising candidates for the treatment of diabetes.

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AUTHOR CONTRIBUTIONS

All the authors have contributed equally to the literature review, analysis, and interpretation part.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

- Achmad, A., Putra, R. J. S., & Rachma, H. (2017). Kejadian Efek Samping Potensial Terapi Obat Anti Diabetes Pasien Diabetes Melitus Berdasarkan Algoritma Naranjo. *Pharmaceutical Journal of Indonesia*, *2*(2), 45–50.
- Aisha, A. F. A., Abu-Salah, K. M., Siddiqui, M. J., Ismail, Z., & Majid, A. M. S. A. (2012). Quantification of α-,β- and γ-mangostin in *Garcinia mangostana* fruit rind extracts by reverse-phase high-performance liquid chromatography. *Journal of Medicinal Plants Research*, *6*(29), 4526–4534.
- American Diabetes Association. (2018). Standards of Medical Care in Diabetes — 2018. *The Journal of Clinical and Applied Research and Education*, *41*(1).
- American Diabetes Association. (2019). Standards of Medical Care in Diabetes-2019. *The Journal of Clinical and Applied Research and Education*, *42*(1).
- Asasutjarit, R., Meesomboon, T., Adulheem, P., Kittiwisut, S., Sookdee, P., Samosornsuk, W., & Fuongfuchat, A. (2019). Physicochemical properties of alpha-mangostin loaded nanoemulsions prepared by ultrasonication technique. *Heliyon*, *5*(9).
- Burton, D. G. A., & Faragher, R. G. A. (2018). Obesity and type-2 diabetes as inducers of premature cellular senescence and aging. *Biogerontology*, *19*(6), 447–459.
- Chen, L. G., Yang, L. L., & Wang, C. C. (2008). Anti-inflammatory activity of mangostins from *Garcinia mangostana*. *Food and Chemical Toxicology*, *46*(2), 688–693.
- Cui, J., Hu, W., Cai, Z., Liu, Y., Li, S., Tao, W., & Xiang, H. (2010). New medicinal properties of mangostins: Analgesic activity and pharmacological characterization of active ingredients from the fruit hull of *Garcinia mangostana* L. *Pharmacology Biochemistry and Behavior*, *95*(2), 166–172.
- Dachriyanus, Andayani, R., Wahyuni, F. S., & Wirasti, Y. (2015). Development and validation of RP-HPLC method for quantitative estimation of α-Mangostin in the rind extract and fractions of *Garcinia mangostana* L. and their cytotoxic activity on T47D breast cancer cell line. *International Journal of Pharmacy and Pharmaceutical Sciences*, *7*(2), 174–178.
- Darmawansyih. (2015). Preparasi kulit ekstrak kulit buah manggis untuk penangkal diabetes. *Prosding Seminal Nasional Mikrobiologi Kesehatan Dan Lingkungan*, 79–83.
- Doi, H., Shibata, M. A., Shibata, E., Morimoto, J., Akao, Y., Iinuma, M., Tanigawa, N., & Otsuki, Y. (2009). Panaxanthone isolated from pericarp of *Garcinia mangostana* L. suppresses tumor growth and metastasis of a mouse model of mammary cancer. *Anticancer Research*, *29*(7), 2485–2495.
- Ersam, T., & Wulandari, D. D. (2015). Study of α-Mangostin Compound And Antidiabetic Assay From Fruit Hull of *Garcinia mangostana* Linn. *International Seminar on Medicinal Chemistry*.
- Gleichmann, H., Walde, S. S. I., Dohle, C., & Schott-Ohly, P. (2002). Molecular target structures in alloxan-induced diabetes in mice. *Life Sciences*, *71*(14), 1681–1694.
- Goligorsky, M. S. (2017). Vascular endothelium in diabetes. *American Journal of Physiology - Renal Physiology*, *312*(2), F266–F275.
- Hung, S. H., Shen, K. H., Wu, C. H., Liu, C. L., & Shih, Y. W. (2009). α-Mangostin suppresses PC-3 human prostate carcinoma cell metastasis by inhibiting matrix metalloproteinase-2/9 and urokinase-plasminogen expression through the JNK signaling pathway. *Journal of Agricultural and Food Chemistry*, *57*(4), 1291–1298.
- Husain, Q. (2010). β Galactosidases and their potential applications: A review. *Critical Reviews in Biotechnology*, *30*(1), 41–62.
- Husen, S. A., Kalqutny, S. H., Nur, A., Ansori, M., Joko, R., Susilo, K., Alymahdy, A. D., & Winarni, D. (2017). Antioxidant and antidiabetic activity of *Garcinia mangostana* induced diabetic mice. *International Conference and Workshops on Basic and Applied Sciences*.
- Husen, S. A., Nur, A., Ansori, M., Joko, R., Susilo, K., Hayaza, S., & Winarni, D. (2018). The Effect of Alpha-mangostin in Glucose Level, Cholesterol Level, and Diameter of the Islets of Langerhans of STZ-induced Diabetic Mice. *International Conference Postgraduate School*, 561–566.
- International Diabetes Federation. (2013). IDF Diabetes Atlas Sixth edition. Retrieved March 10, 2021, from www.idf.org/diabetesatlas.

- International Diabetes Federation. (2019). IDF Diabetes Atlas Ninth edition. Retrieved March 10, 2021, from https://www.idf.org/e-library/welcome/copyright-permission.html.
- Iside, C., Scafuro, M., Nebbioso, A., & Altucci, L. (2020). SIRT1 Activation by Natural Phytochemicals: An Overview. *Frontiers in Pharmacology*, *11*(1225), 1–14.
- Jamwal, A. (2020). Systematic Review on Medicaments Used in Management of Diabetes Mellitus. *International Journal of Pharmacy and Pharmaceutical Sciences*, *12*(8), 21–29.
- Jung, H. A., Su, B. N., Keller, W. J., Mehta, R. G., & Kinghorn, A. D. (2006). Antioxidant xanthones from the pericarp of *Garcinia mangostana* (Mangosteen). *Journal of Agricultural and Food Chemistry*, *54*(6), 2077–2082.
- Kaomongkolgit, R., Jamdee, K., & Chaisomboon, N. (2009). Antifungal activity of alpha-mangostin against *Candida albicans*. *Journal of Oral Science*, *51*(3), 401–406.
- Kharroubi, A. T. (2015). Diabetes mellitus: The epidemic of the century. *World Journal of Diabetes*, *6*(6), 850.
- Kumar, P., Puranik, S., & Nandini, B. (2017). Evaluation of Alpha-Mangostin, Isolated and Purified from the Crude Extract of *Garcinia mangostana* for the Anti-Diabetic, Anti-Inflammatory, and Antioxidant Activity. *International Journal Of Pharmacy & Pharmaceutical Research Human Journals*, *8*(2), 76–95.
- Kumar, V., Bhatt, P. C., Kaithwas, G., Rashid, M., Khan, J. A. J., Anwar, F., & Verma, A. (2016). α-Mangostin Mediated Pharmacological Modulation of Hepatic Carbohydrate Metabolism in Diabetes Induced Wistar Rat. *Beni-Suef University Journal of Basic and Applied Sciences*, *5*(3), 255–276.
- Larson, R. T., Lorch, J. M., Pridgeon, J. W., Becnel, J. J., Clark, G. G., & Lan, Q. (2010). The biological activity of α-mangostin, a larvicidal botanic mosquito sterol carrier protein-2 inhibitor. *Journal of Medical Entomology*, *47*(2), 249–257.
- Lazarus, G., Alexander, S., Kusuma, G. O., Wijaya, K., & Soetikno, V. (2020). Antioxidative activities of alpha-mangostin in high-fat/high-glucose diet and streptozotocin-induced insulin-resistant rodents. *Journal of Applied Pharmaceutical Science*, *10*(11).
- Lee, B. Y., Han, J. A., Im, J. S., Morrone, A., Johung, K., Goodwin, E. C., Kleijer, W. J., DiMaio, D., & Hwang, E. S. (2006). Senescence-associated β-galactosidase is lysosomal β-galactosidase. *Aging Cell*, *5*(2), 187–195.
- Lee, D., Kim, Y. M., Jung, K., Chin, Y. W., & Kang, K. S. (2018). Alpha-mangostin improves insulin secretion and protects INS-1 cells from streptozotocin-induced damage. *International Journal of Molecular Sciences*, *19*(5), 1–13.
- Lenzen, S. (2008). The mechanisms of alloxan- and streptozotocin-induced diabetes. *Diabetologia*, *51*(2), 216–226.
- Luo, Y., & Lei, M. (2017). α-Mangostin protects against high-glucose-induced apoptosis of human umbilical vein endothelial cells. *Bioscience Reports*, *37*, 1–10.
- Maliangkay, H. P., & Rumondor, R. (2018). Uji Efektifitas Antidiabetes Ekstrak Etanol Kulit Buah Manggis (*Garcinia mangostana* L) Pada Tikus Putih (*Rattus norvegicus*) yang Diinduksi Aloksan. *Chemistry Progress*, *11*(1).
- Matsumoto, K., Akao, Y., Kobayashi, E., Ohguchi, K., Ito, T., Tanaka, T., Iinuma, M., & Nozawa, Y. (2003). Induction of apoptosis by xanthones from mangosteen in human leukemia cell lines. *Journal of Natural Products*, *66*(8), 1124–1127.
- Moongkarndi, P., Kosem, N., Kaslungka, S., Luanratana, O., Pongpan, N., & Neungton, N. (2004). Antiproliferation, antioxidation, and induction of apoptosis by *Garcinia mangostana* (mangosteen) on SKBR3 human breast cancer cell line. *Journal of Ethnopharmacology*, *90*(1), 161–166.
- Muchtaridi, M., Suryani, D., Qosim, W. A., & Saptarini, N. M. (2016). Quantitative analysis of A-mangostin in mangosteen (*Garcinia mangostana* L.) pericarp extract from four districts of West Java by HPLC method. *International Journal of Pharmacy and Pharmaceutical Sciences*, *8*(8), 232–236.
- Nelli, G. B., Solomon, A., & Kilari, E. K. (2013). Antidiabetic effect of α-mangostin and its protective role in sexual dysfunction of streptozotocin-induced diabetic male rats. *Systems Biology in Reproductive Medicine*, *59*, 319–328.
- Newman, R. (2014). General practice management of type 2 diabetes. In *The Royal Australian College of General Practitioners*.
- Pasaribu, F., Sitorus, P., & Bahri, S. (2012). Uji Ekstrak Etanol Kulit Buah Manggis (*Garcinia mangostana* L.) Terhadap Penurunan Kadar Glukosa Darah. *Journal of Pharmaceutics and Pharmacology*, *1*(1), 1–8.
- PERKENI. (2019). Pedoman Pengelolaan dan Pencegahan Diabetes Mellitus Tipe 2 Dewasa Di Indonesia. Jakarta: PB PERKENI.
- Pradono, J., Sampurno, O. D., Halim, F. X. S., Widowati, L., Imaningsih, N., Handayani, S., Isnawati, A., Delima, Lestari, C. W., Rooslamiati, I., Karyana, M., Raharni, Dewi, R. M., Lisdawati, V., & Setyawati, V. (2019). *Bunga Rampai Uji Klinik: Vols. 1(2-5)* (pp. 99–107). Badan Penelitian dan Pengembangan Kesehatan.
- Priyambodo, B. (2014). Jalan Panjang Penemuan Obat Baru. Retrieved September 4, 2021, from Bambang Priyambodo's Weblog. https://priyambodo1971.wordpress.com/2014/03/27/jalan-panjang-penemuan-obat-baru/

- Ratwita, W., Sukandar, E. Y., Adnyana, I. K., & Kurniati, N. F. (2019). Alpha mangostin and xanthone activity on fasting blood glucose, insulin, and Langerhans islet of Langerhans in alloxan-induced diabetic mice. *Pharmacognosy Journal*, *11*(1), 64–68.
- Sakagami, Y., Iinuma, M., Piyasena, K. G. N. P., & Dharmaratne, H. R. W. (2005). Antibacterial activity of α-mangostin against Vancomycin-Resistant Enterococci (VRE) and synergism with antibiotics. *Phytomedicine*, *12*(3), 203–208.
- Saydah, S. (2016). Socioeconomic Status and Risk of Diabetes-Related Mortality in the U.S. *Public Health Reports*, *125*(3), 377–388.
- Soetikno, V., Murwantara, A., Andini, P., Charlie, F., Lazarus, G., Louisa, M., & Arozal, W. (2020). Alpha-Mangostin Improves Cardiac Hypertrophy and Fibrosis and Associated Biochemical Parameters in High-Fat / High-Glucose Diet and Low-Dose Streptozotocin Injection-Induced Type 2 Diabetic Rats. *Journal of Experimental Pharmacology*, *12*, 27–38. https://doi.org/178.171.48.109
- Suarsana, I. N., Priosoeryanto, B. P., Bintang, M., & Wresdiyati, T. (2010). Profil Glukosa Darah dan Ultrastruktur Sel Beta Pankreas Tikus yang Diinduksi Senyawa Aloksan. *Jurnal Ilmu Ternak Dan Veteriner*, *15*(2), 118–123.
- Suksamrarn, S., Komutiban, O., Ratananukul, P., Chimnoi, N., Lartpornmatulee, N., & Suksamrarn, A. (2006). Cytotoxic Prenylated Xanthones from the Young Fruit of *Garcinia mangostana*. *ChemInform*, *37*(34).
- Supiyanti, W., Wulansari, E. D., & Kusmita, L. (2010). Uji Aktivitas Antioksidan dan Penentuan Kandungan Antosianin Total Kulit Buah Manggis (*Garcinia mangostana* L). *Majalah Obat Tradisional*, *15*(2), 64–70.
- Susilawati, E., Adnyana, I. K., & Fisheri, N. (2016). Studies on the Antidiabetic Activity of Ethanol Extract and its Fractions of Singawalang (*Petiveria alliacea* L.) Leaves in Mice. *Pharmacy*, *13*(02), 182–191.
- Szkudelski, T. (2001). The mechanism of alloxan and streptozotocin action in B cells of the rat pancreas. *Physiological Research*, *50*(6), 537–546.
- Taher, M., Tg Zakaria, T. M. F. S., Susanti, D., & Zakaria, Z. A. (2016). Hypoglycaemic activity of ethanolic extract of *Garcinia mangostana* Linn. in normoglycaemic and streptozotocin-induced diabetic rats. *BMC Complementary and Alternative Medicine*, *16*(1), 1–12.
- Tousian, H., Razavi, B. M., & Hosseinzadeh, H. (2020a). Alpha-mangostin decreased cellular senescence in human umbilical vein endothelial cells. *DARU Journal of Pharmaceutical Sciences*, *28*, 45–55.
- Tousian, H., Razavi, B. M., & Hosseinzadeh, H. (2020b). Effects of alpha-mangostin on memory senescence induced by high glucose in human umbilical vein endothelial cells. *Iranian Journal of Basic Medical Sciences*, *23*, 1–7.
- Wang, J. J., Sanderson, B. J. S., & Zhang, W. (2012). Significant anti-invasive activities of α-mangostin from the mangosteen pericarp on two human skin cancer cell lines. *Anticancer Research*, *32*(9), 3805–3816.
- Watanabe, M., Gangitano, E., Francomano, D., Addessi, E., Toscano, R., Costantini, D., Tuccinardi, D., Mariani, S., Basciani, S., Spera, G., Gnessi, L., & Id, C. L. (2018). Mangosteen extract Shows a Potent Insulin Sensitizing Effect in Obese Female Patients : A Prospective Randomized Controlled Pilot Study. *Nutrients*, *10*.
- World Health Organization. (2016). Executive Summary Global Report on Diabetes. Retrieved March 6, 2021, from www.who.int/diabetes/global-report
- Wulandari, H. I. (2015). Effectivity Mangosteen Rind (*Garcinia mangostana* L.) To Decrease Blood Glucose Level. *J Majority*, *4*(1), 28–32.
- www.klikdokter.com. (n.d.). 6 Manfaat Manggis Untuk Kesehatan Tubuh. Retrieved September 4, 2021, from https://www.klikdokter.com/info-sehat/read/3104203/6-manfaat-manggis-untuk-kesehatan-tubuh-anda
- Yusni, Akbar, I. B., Rezania, & Fahlevi, R. (2017). Blood Sugar Levels Reduction by Mangosteen (*Garcinia mangostana*) and Tomato (*Lycopersicum esculentum* Mill) in Diabetic Rats. *Journal Global Medical and Health Communication*, *5*(1), 57–63.
- Zhang, E., Guo, Q., Gao, H., Xu, R., Teng, S., & Wu, Y. (2015). Metformin and Resveratrol Inhibited High Glucose-Induced Metabolic Memory of Endothelial Senescence through SIRT1/p300/p53/p21 Pathway. *PLoS ONE*, *10*(12), 1–19.

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