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The role of *Swietenia* seed extract in ameliorating blood glucose level for potential treatment of gestational diabetes mellitus: A literature review

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Abstract

Gestational diabetes mellitus (GDM) can be defined as glucose intolerance identified for the first time during pregnancy. The number of diabetes occur in pregnancy about 1 of 10 cases, but the use of pharmacological drug needs to be considered. So, there is non-pharmacological treatment for alternative such as of using mahogany seeds that have potential hypoglycemia activity. The aim of this study to provide a comprehensive understanding the roles of *Swietenia* seeds extract in ameliorating blood glucose level for potential treatment of gestational diabetes mellitus condition. This study uses a systematic literature Review based on PRISMA-P. To identify the analyzed literature, we used five databases [including Google Scholar, PubMed, ProQuest, Science direct, and Springer] with relevant keywords using Boolean. Selected articles should discuss about mahogany seeds (*Swietenia macrophylla* and *Swietenia mahogany*) as an antidiabetic candidate. The search from 5 databases yielded 12 eligible articles to analyze. 7 articles discuss about *Swietenia macrophylla* King and 5 articles about *Swietenia mahogani* (L.) Jacq that related as an antidiabetic effect. Both of *Swietenia macrophylla* and *Swietenia mahogani* have potential role as antidiabetic agent to reduce blood glucose level and can be potential treatment option in patients with GDM.

Keywords: Antidiabetic; Gestational diabetes mellitus; Hyperglycemia; Phytochemistry; *Swietenia* seed

1. Introduction

Pregnancy is a phase where metabolic changes occur in the form of mild insulin resistance which is temporary as a form of physiological adaptation to fetal growth [1]. In normal pregnancies, insulin sensitivity of maternal is decreases due to an increase in pregnancy hormones produced by placental [1,2]. The mechanism of compensation for this condition is mediated by expansion of pancreatic β-cell mass, increased production and secretion of insulin [3]. When the adaptation process cannot keep up with the increased insulin demand, the mother's blood glucose levels will increase, resulting in the development of gestational diabetes mellitus (GDM).

GDM can be defined as glucose intolerance with varying degrees of severity and identified for the first time during pregnancy, it commonly happens on 24 to 28 weeks of gestation, which may lead to adverse health consequences [4,5]. This condition is due to increased insulin resistance and decreased function of pancreatic β cells [6,7]. In world, 1 of 10 cases of diabetes occur in pregnancy. The global prevalence of diabetes in pregnancy was 21.1 million in 2021, out of which 80.3% was GDM, and 9.1% were other types of diabetes that discovered during pregnancy while 10.6% were discovered before pregnancy [5].

The main feature of GDM is identification of spontaneous hyperglycemia during pregnancy [8]. GDM is affected by an increase in pregnancy hormones, especially human placental lactogen [HPL], estrogen, and progesterone produced by

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placental syncytiotrophoblast cells [1,2]. The presence of HPL hormone increases insulin resistance, which results in increased plasma glucose levels in maternal blood. This is a normal physiological process during pregnancy to increase maternal blood glucose level to be available in sufficient quantities to be transferred to the fetus [9]. There is also the influence of other hormones and adipokines, including leptin, cortisol, placental growth hormone, tumor necrosis factor alpha (TNF-α), which can cause insulin resistance in pregnancy [1]. To compensate for this insulin resistance during pregnancy, the pancreas increases insulin secretion. GDM occurs when the β-cell of pancreas is unable to secrete enough insulin to compensate for metabolic stress [10,11]. Additionally, increased caloric intake, increased deposition of maternal adipose, and decreased physical activity, also contribute to a state of glucose intolerance, leading to hyperglycemia during pregnancy [10].

Undiagnosed or inadequately treated GDM can lead to significant health impact in the mother and fetus, both short- or long-term complications. Hence, this condition requires good health management. The components of GDM management according to Perkumpulan Endokrinologi Indonesia (2021), consist of medical nutrition therapy, physical activity training, self-monitoring of blood glucose levels, monitoring and controlling maternal weight, and pharmacological therapy if needed. Pharmacological therapies that can be given in pregnancy (such as insulin or metformin) require monitoring by an internal medicine specialist or endocrine and metabolic consultant [12]. The use of pharmacological drug needs to be considered because both therapies can cross the placenta [13].

The alternative methods are given in the form of non-pharmacological therapies for diabetes by using herbal. This method has several advantages, including fewer side effects, relatively low cost and minimal toxic effects, resulting in good long-term acceptance. *Swietenia* seeds is one of many herbals that have potential hypoglycemia activity [14]. In Indonesia, the *Swietenia* seeds have been used as traditional medicine such as diabetic, hypertension, malaria, and diarrhea [15–17]. Therefore, the aim of this study to provide a comprehensive understanding the roles of *Swietenia* seeds extract in ameliorating blood glucose level for potential treatment of GDM condition.

2. Material and methods

The research method's type is a systematic literature review. The source of data is derived from the previous research studies obtained online (secondary data). This literature source was obtained from 5 databases, including Google Scholar, PubMed, ProQuest, Science direct, and Springer. The keywords used are related to the variables "antidiabetic", "gestational diabetes mellitus", "hyperglycemia", "phytochemical", and "*Swietenia* seed". The following keyword pairs connected by using Boolean ''OR" or "AND".

The inclusion criteria used in this systematic review include, (a) Journals published in the range of 2013-2023; [b] Geographically from all countries; (c) The language of the article used is English; (d) Articles must be available in full text and open access; (e) Indexed Sinta 1-2 or Scopus Q1-4; (f) The type of scientific article is an original article; (g) The article discusses mahogany seeds (*Swietenia macrophylla* and *Swietenia mahogany*) as an antidiabetic candidate. While the exclusion criteria used in this systematic review were, (a) The research method of the article uses review; (b) The article does not provide full text; (c) The content of the article is not relevant to the topic area discussed.

Literature screening and eligibility assessment for writing this article using PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) guideline as an approach. The stages carried out include, (1) determining the topic; (2) determining the formulation of the problem (research question); (3) determining keywords; (4) determining the criteria of inclusion and exclusion study; (5) searching for literature from the database based on keywords; (6) screening literature starting from journal titles, abstracts and keywords; (7) searching for full text that relevant to the topic; and (8) performing the article synthesis stage.

3. Results and discussion

The search results from 5 databases yielded 12 eligible articles to analyze based on inclusion and exclusion criteria. This study contains of 7 topics about *Swietenia macrophylla* King and 5 topics about *Swietenia mahogani* (L.) Jacq that related as an antidiabetic. The PRISMA-P flowchart of the article search process can be seen in Figure 1. Then, the article characteristics are summarized in Table 1 and listed in the discussion for more detailed explanation.

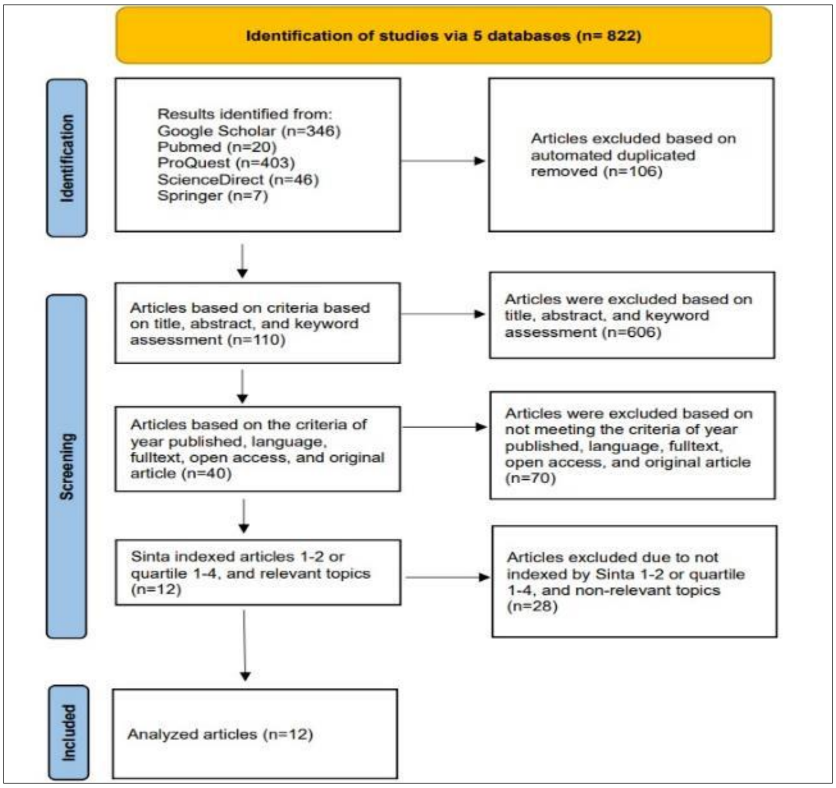

Figure 1 PRISMA-P Diagram of Article Search Process

Swietenia commonly known as sky fruit. There are two species most widely known of *Swietenia spp.* based on geographical differences and its leaf, namely *Swietenia macrophylla* King and *Swietenia mahagoni* (L.) Jacq. The different between this type of mahogany are *S. macrophylla* (broad-leaf mahogany) and *S. mahagoni* (narrow-leaf mahogany) [18].

Table 1 Result of Data Synthesis Based on Characteristics Studies

First author, year	**Type of sampel**	**Diabetes Induction Method**	**Intervention**	**Time of interven-tion**	**Outcomes measurement**
Hashim et al, 2013 [19]	Male Sprague–Dawley rats	60 mg/kg BW streptozotocin [STZ] by intraperitoneal injection	1000 mg/kg of petroleum ether extract, chloroform extract, and methanol extract	14 days	Primary compound Blood glucose Glucose uptake and absorption
Shiming et al, 2021[20]	Wistar rats of either sex	50 mg/kg BW STZ by intraperitoneal injection	Swietenine doses: 10, 20 and 40 mg/kg.	4 weeks	The biochemical parameters: glucose, total cholesterol, triglycerides, HDL, LDL, urea, creatinine, ALP, ALT, AST, GSH, MDA and TAC. Histology of pancreas

First author, year	Type of sampel	Diabetes Induction Method	Intervention	Time of interven-tion	Outcomes measurement
Dutta et al., 2013 [21]	Wister rats	65 mg/kg STZ by intraperitoneal injection	*S. macrophylla* seeds 2 g/kg BW and 1 g/kg BW plus peptide 1 g/kg BW.	30 days	The biochemical parameters: HbA1c, plasma glucose, TC, TG, total protein, SGPT, SGOT, ALP, and BUN. Hematological parameter: Hb, Hct, reticulocyte, platelet, and leucocytes.
Basy et al., 2015 [22]	Male Wistar strain rats	60 mg/kg BW STZ by intraperitoneal injection	50, 100, and 200 mg/kg BW of ethanolic extract *S. macrophylla* seeds.	21 days	The level of blood glucose, serum creatinine and MDA.
Lau et al., 2015 [23]	3T3-L1 and C2C12 cells	NA	Insulin, DMSO, TZD, and the 3 natural compounds isolated from *S. macrophylla*.	GLUT4 translocation assay: for 15, 30, 60 and 120 min Glucose uptake assay: for 60 min	Gene expression of adiponectin, adipsin, GLUT4 and PPARγ. Glucose uptake
Bakar et al., 2020 [24]	Sample Human Skin Fibroblast 1184	NA	α-glucosidase enzyme inhibition assay: sample (0-100 μg/mL), 1-Deoxynojirimycin (control +) α-amylase enzyme inhibition assay: sample with 1 μg/mL acarbose (control +) MTT assay: the crude extracts at doses 10, 1, 0.1, 0.01, 0.001, 0.0001 mg/mL.	NA	Antioxidant activity The α-glucosidase and α-amylase inhibition activity Toxicity
Prasetyastuti et al., 2016 [25]	Male Wistar rats	Intraperitoneal injection of 65 mg/kg BW STZ + injection of 230 mg/kg BW nicotinamide.	The main intervention by given metformin, and 7-hydroxy-2-(4-hydroxy-3-methoxy-phenly)-chroman-4-one isolate at doses 10, 30 and 90 mg/200 gramBW.	4 weeks	Biochemical analysis: plasma glucose, serum insulin, and HOMA-IR. Expression gene: PEPCK and RBP-4
Wresdiyati et al., 2015 [26]	Male Sprague-Dawley rats	Orally administrated 1 mL 90% sucrose	100, 200, 300, 400, 500 mg/kg BW of ethanol extract of *S. mahagoni* seed. Also, 4.5 mg/kg BW of acarbose.	The treatment given once at 0 minutes after fasting for 10 hours.	Phytochemical compounds The α-glucosidase inhibition activity Blood glucose level

First author, year	Type of sampel	Diabetes Induction Method	Intervention	Time of interven-tion	Outcomes measurement
Smmma et al., 2013 [27]	Long Evans rats of either sex	Alloxan 120 mg/kg BW by intraperitoneal	Ethanol extract of *S. mahagoni* seeds 1000 mg/kg.	10 days	Blood glucose level Histological of islet pancreas
Fiorenza et al., 2022 [28]	Male *Rattus norvegicus*	Alloxan 120 mg/kg BW	Ethanol extract of *S. mahogani* seeds 250, 500, 1000 mg/kg BW.	14 days	Blood glucose level Histological of pancreas
Norodin et al., 2018 [29]	*S. mahogany* seeds	NA	α-glucosidase and α-amylase inhibition assay: 10 μL of sample (0-100 μg/ml), DMSO and acarbose	NA	The α-glucosidase inhibition activity The α-amylase inhibition activity
Asmara, 2018 [30]	*S. Mahagoni* L. Jacq. seeds	NA	α-glucosidase inhibition assay: 10 μL of each isolate or acarbose, at different concentrations.	NA	Phytochemical screening The α-glucosidase inhibition activity

*NA: Not available or described

3.1. Taxonomy and botanical view of *Swietenia* spp.

Swietenia macrophylla King is a semi-deciduous or deciduous, mainly tropical mahogany tree species [31]. *S. macrophylla* is widely found in several Asian countries used for slope protection, water catchment, and road planting. *S. macrophylla* is a tree that has umbrella-shaped crown, often reaching heights of more than 30 meters and diameters about 1.5 meters. The fruit of mahogany is capsule-shaped, oval, light grey to brown in color, and has 4-5 valves. Each fruit contains about 22-71 developed seeds (Figure 2). The seeds are cryptoid, about 7-12 cm long and 2-2.5 cm wide [32].

Meanwhile, *Swietenia mahagoni* Jacq. is a deciduous tree with height up to 30 meters, diameter up to 1 meter, and in spherical crown. Its flowers have greenish-yellow color and its unisexual. The seed capsules are green to reddish brown varies, it is about 6–10 cm of long, 4-5 cm of diameter, and produced about 20 flat brown seeds [17,33].

The taxonomic position of *Swietenia* is as follows according to the Integrated Taxonomic Information System [2022]:

Kingdom : Plantae
Division : Magnoliophyta
Class : Magnoliopsida
Order : Sapindales
Family : Meliaceae
Genus : *Swietenia*
Spesies : (1) *Swietenia macrophylla* King
(2) *Swietenia mahagoni* (L.) Jacq.

Figure 2 Fruit and seed of *Swietenia* [32]

3.2. Etnomedical of *Swietenia* spp.

Swietenia seed extract known to have many medical properties for treatment in various diseases such as hypertension, malaria, chest pain, constipation, cancer, and diabetes [35]. *S. macrophylla* has been widely used in many countries, especially in Asia, to treat of various diseases due to its antimicrobial, anti-inflammatory, antioxidant, antimutagenic, anticancer, antitumor and antidiabetic properties [14]. *S. mahogani* have beneficial in several disease including malaria, diabetes, hypertension, diarrhea, as antipyretic, astringent and bitter tonic [16,17,36].

According to a study by La Basy et al [22], the alcoholic extract of mahogany seeds stimulates the glucokinase enzyme in lowering blood glucose levels. The aqueous extract of *S. macrophylla* seeds was found to have the ability to lower blood glucose levels, improve lipid profile, and restore β-cell function without altering the histopathology of kidney and liver tissues in diabetic rats [37]. In addition, a study showed that the administration of *S. mahogani* seeds extract, especially at a dose of 500 mg/kg BW, was able to prevent the process of pancreatic cell damage due to alloxan based on the average number of Langerhans islet cells [28].

Swietenia seeds is contain swietenine known as agonist of peroxisome proliferator-activated receptor γ (PPARγ) [28,38]. PPARγ promotes blood glucose clearance by improving uptake of glucose and insulin sensitivity [39]. The expression of PPARγ is reduced in maternal adipose tissue and placental cells from women with GDM. The downregulated expression of PPARγ in GDM cases may worsen glucose intolerance [40,41]. Besides, PPAR-γ has been shown to prevent lipotoxicity, an important mechanism for the development of insulin resistance in insulin target tissues that causes β-cell dysfunction in type 2 diabetes and GDM [42,43]. Lipotoxicity refers to the deleterious effects of high lipid concentrations and derivatives on cells [44]. Lipotoxicity's contribution to the onset of insulin resistance is linked to its involvement in diminishing mitochondrial oxidative capacity, prompting mitochondrial dysregulation, and generating oxidative stress [40,43,45,46]. Several compounds in *Swietenia* exhibits the potential to serve as high-affinity ligands for PPARγ that can stimulate glucose uptake and reduce the risk of obesity [23]. Therefore, mahogany seed extract provides a hypoglycemic effect so that it can act as an antidiabetic.

3.3. Phytochemistry of *Swietenia* seeds with antidiabetic activity

There are similarities in the phytochemistry of these two *Swietenia* species. Phytochemical studies have revealed that the primary bioactive compounds in *Swietenia* seeds are limonoids, specifically swietenine and its derivatives [14,20,30,47]. Limonoids are triterpene derivatives that have lost of four carbon atoms, so the side chain becomes a furan ring [30]. The presence of swietenine is known to have a role as a hypoglycemic agent [48]. Swietenine and metformin is synergistic as antidiabetic, and the combination of that compound as a treatment (40 mg/kg Swietenine+50 mg/kg Metformin) brings several biomarkers to normal levels including glucose, total cholesterol, triglycerides, HDL, and LDL [20].

Additionally, there were three compounds isolated from *S. macrophylla* seeds, including 6-O-acetylswietenolide (6OA), swietenine (Sw), and diacetyl swietenolide (DS) that have roles for diabetes by promoting the translocation of GLUT4 from intracellular compartments to the plasma membrane in C2C12 muscle cells [23]. These compounds can potentially serve high-affinity PPARγ ligands in stimulating cellular uptake of glucose until five-to six-fold after treatment. In addition, the 6OA, DS and Sw shown increasing in the expression levels of the adipogenic markers although at lower levels, so this activity known as well as rosiglitazone [23].

Other phytochemical contents both of *S. macrophylla* and *S. mahogany* seeds include polyphenols, terpenoids, anthraquinones, hidroquinones, glycosides, steroids, fatty acid esters, flavonoids, alkaloids, saponins, and tannins [26,35,49,50]. The contents known to have a role as antidiabetic activity such as flavonoids and saponins [20,25,30,51]. During the administration of *S. mahogany* seeds extract, it was found that flavonoids can increase the proliferation of pancreatic β-cell islets because one of its functions is to protect β-cells and maintain insulin signaling [28]. Prasetyastuti et al [25] showed that 90 mg/200 grams BW dose of flavonoid compounds 7-hydroxy-2-(4-hydroxy-3-methoxy-phenyl)-chroman-4-one can reducing blood glucose levels like activity of metformin. The 7-hydroxy-2-(4-hydroxy-3-methoxy-phenyl)-chroman-4-one also decreased significantly the HOMA-IR value that was in accordance with PEPCK expression [25].

Meanwhile, the potential of saponins as antidiabetic from *S. mahogany* seeds can reduce plasma blood glucose levels, inhibit gluconeogenesis, improve insulin signaling, inhibit α-glucosidase activity, and increase GLUT-4 expression [28]. According to research by Muthmainah et al [51], mahogany seeds isolate containing 1,4-bis-3,4,5-trimethoxy-phenyl-tetrahydro-furo[3,4-c]-furan from saponin that can lower the level of blood glucose and MDA in diabetic rats. *S. macrophylla* seed isolate 1,4-bis-(3,4,5-trimethoxy-phenyl)-tetrahydro-furo(3,4-c) furan is thought to have strong hypoglycemic activity due to its low binding energy about -97.29 kcal/mol to bind to PPARγ [51].

Another compound found in *Swietenia* is β-sitosterol from bioactive phytosterol [19,29]. The function of β-sitosterol is being a potent antioxidant, reduced blood glucose level, increased the expression of PPARγ and GLUT4 to improved insulin sensitivity [52,53].

3.4. Extract preparation that commonly used for *Swietenia* seed extract

There were several methods could be applied for *Swietenia* seeds extraction. The selection method of extraction is point crucial to ensure high purity, richness in components and non-toxic. Several studies using ethanol for extraction including Asmara [30], Basy et al [22], Fiorenza et al [28], Hasan et al [38], and Wresdiyati et al [26]. Ethanol macerated extract has greatest potential as an antidiabetic agent contain with the highest flavonoid compound. Ethanol extract has proven antioxidant activity that can protect the function of kidney from oxidative stress by insulinotropic effect [22].

The ethanolic maceration extract of *S. mahagoni* seeds by in vitro experiment showed the greatest α-glucosidase inhibitory activity compared to other that can be correlate with alkaloid, flavonoid, and triterpenoid levels [26]. The inhibition of carbohydrate hydrolyzing enzymes, specifically α-glucosidase and α-amylase, is an effective method for diabetes mellitus by reducing postprandial hyperglycemia by slowing glucose absorption and delaying the release of D-glucose from carbohydrates in the digestive organs [26,29,54,55]. The therapeutic approach by inhibiting the activity of these two enzymes can reduced the risk of developing diabetes [56].

Another extraction method is by using supercritical carbon dioxide (SC-CO_2) that applied on Bakar et al [24] and Norodin et al [29]. SC-CO_2 extraction is cost-effective, non-flammable, non-toxic, and leaves no residual solvent. These method uses a lower volume of solvent (CO_2) compared to soxhlet extraction which uses 80.0% ethanol concentration. *S. macrophylla* seeds oil produced from SC-CO_2 possesses an elevated level of antioxidants based on DPPH radical scavenging activity by inhibiting 45.95±0.3% radical capture activity compared to the oil extract from soxhlet extraction with 34.68±0.2%. Based on enzyme activity, S. *macrophylla* seeds extract using SC-CO_2 method shows more potential in inhibiting α-amylase compared to α-glucosidase [24]. The study showed that *S. macrophylla* seed exhibits a higher percentage inhibition of α-amylase, reaching 100.0±0.3% and lower percentage of inhibition of α-glucosidase with the value of 4.1±2.0% by using SC-CO_2 [24].

In contrast with study by Norodin [29], *S. mahagoni* seed extract showed strong α-glucosidase activity with moderate α-amylase activity. The stronger α-glucosidase inhibition activity, make lower the IC_{50}. Then, the result of strong α-glucosidase inhibition with moderate α-amylase inhibition may offer a therapeutic strategy by slowing down the availability of dietary carbohydrate substrates for production of glucose [29].

3.5. Molecular mechanism of *Swietenia* seeds overcoming diabetes cases

Diabetes is a chronic, intricate metabolic disorder marked by elevated blood glucose levels, and instability in metabolism of carbohydrate [56,57]. This condition can be divided into four types: type 1 diabetes mellitus, type 2 diabetes mellitus, GDM, and other specific types of diabetes [58]. According to several world organizations, such as WHO, ADA, and FIGO, diabetes in pregnancy can be classified as pre-gestational diabetes (women with history of type 1 or 2 diabetes) and GDM [1,59].

There are various phases of metabolic adaptation that correspond to the varying nutritional requirements of both the mother and fetus during pregnancy [60]. GDM could be seen as an inability to compensate for the insulin resistance in the context of these metabolic and β-cell changes throughout pregnancy, leading to glucose intolerance and hyperglycemia [42]. The diagnostic criteria for diabetes mellitus and GDM involve a fasting blood glucose level is >126 mg/dL and >92 mg/dL, respectively [61–63].

Based on study of Shiming [20], the treatment of type 2 diabetic rats induced by streptozotocin with Swietenine from *S. macrophylla* at 20 and 40 mg/kg BW for four weeks reduced the level of glucose to 234.18 mg/dL and 160.2 mg/dL, respectively. The levels of blood glucose in diabetic rats induced by STZ after treatment four weeks with 7-hydroxy-2-[4-hydroxy-3-metoxy-phenyl]-chroman-4-one from *S. macrophylla* seeds at 10, 30, and 90 mg/200 g BW concentration decreased with 53.8%, 37.5%, 44.5% and 52.7%, respectively ($p<0.05$). The 90 mg/200 g BW dose of that isolate demonstrated comparable efficacy to metformin in lowering blood glucose levels [25]. In study by Hasan et al [38], the effect of ethanolic extract of *S. mahagoni* seeds at 1000mg/kg for 10 days in diabetic rats induced by alloxan shown that the blood glucose levels were 5.80±0.64 mmol/L, 15.05±3.45 mmol/L and 8.03±2.04 mmol/L on day 1 (pre-alloxan), day 4 (post-alloxan) and day 15 (post-alloxan), respectively. The percentage change of this treatment was 41.50% [27].

Moreover, the hyperglycemia condition causes excessive production of free radicals, which is the main factor causing the development of pathogenesis complications in diabetes [22,25]. Excessive production of free radical can lead increasing reactive oxygen species (ROS), acting as mediator in elevating oxidative stress conditions and contributing to tissue damage [9]. The oxidative stress, mitochondrial dysfunction and endoplasmic reticulum stress are observed in insulin-resistant peripheral tissues in GDM [42]. Therefore, there was a significant relationship between high levels of oxidative stress and poor treatment outcomes, high requirement of insulin treatment, and demand for other treatment in pregnancy [9].

Malondialdehyde (MDA) is a byproduct of lipid peroxidation due to the rise in ROS level, it can be a marker of oxidative stress conditions [22]. In diabetic condition, plasma MDA level was increased and antioxidant level was decreased [22]. Swietenine has the ability to increase the total antioxidant capacity to repair oxidative stress, so it can reduce MDA levels [20]. After administration ethanolic extract from *S. macrophylla* seeds at a dose of 50, 100, and 200 mg/kg BW for a period of 21 days, a notable reduction in the serum MDA level was observed significant in diabetic rats [22]. The level of oxidative stress was found to correspond to the level of HbA1c (hemoglobin A1c or glycated hemoglobin or glycosylated hemoglobin) [9]. Study by Dutta et al showed that there was a significant reduction in HbA1c levels in diabetic rats given the extract *S. macrophylla* seeds (2 g/kg BW) and extract *S. macrophylla* seeds (1 g/kg BW) with peptide after 30 days of treatment [21].

Hyperglycemia in diabetic condition also might be caused by excess expression of phosphoenolpyruvate carboxykinase (PEPCK), the key enzyme of gluconeogenesis through oxidative stress [64]. The group that was treated with 7-hydroxy-2-(4-hydroxy-3-methoxy-phenyl)-chroman-4-one from *S. macrophylla* at dose 90 mg/200 g BW showed the highest capability to inhibit expression of PEPCK in the liver, approximately 4.25±0.15. In addition, treatment with 7-hydroxy-2-(4-hydroxy-3-methoxy-phenyl)-chroman-4-one from flavonoid isolate compound at doses of 10, 30 and 90 mg/200 g BW reduced expression of RBP4 more effectively than metformin [25]. Flavonoid, functioning as antioxidants, possess the capacity to inhibit oxidative stress, consequently lowering levels of RBP-4 to improve insulin sensitivity, and decreasing level of PEPCK [25]. Despite of mahogany seeds can increase insulin sensitivity, stimulate pancreatic β-cell regeneration, and prevent kidney function decline due to a decrease in creatinine and urine levels on the 21st day after treatment [22].

Moreover, mechanisms by which increased oxidative stress and hyperglycemia can activation of advanced glycation end products (AGE) formation and protein kinase C (PKC) [21]. AGEs play a role in diabetes progression by further increasing oxidative stress and activating AGE receptor (RAGE) [65]. AGEs mediate the effects of inflammation through the nuclear factor kappa B (NF-kB) and protein kinase signaling pathways in human pregnancy tissues [66]. The interaction between AGE-RAGE and downstream signaling pathways implicated for development of diabetes complications [67]. The short-term complications in GDM cases include an increased risk of pregnancy complications such as preeclampsia, eclampsia, premature labor, and cesarean section. In addition, short-term complications can also result in increased labor complications such as large for gestational age, macrosomia, shoulder dystocia, neonatal hypoglycemia, and hypoxia [12,68]. Meanwhile, the long-term impact for GDM is the increased risk of developing type 2 diabetes mellitus and cardiovascular disease for the maternal, also obesity and diabetes mellitus in her offspring [10].

Diabetes also associated with hyperlipidemia condition. The β-cells destruction leads to depletion of plasma insulin. The significant level of plasma lipid control indicates that mahogany extract can help increasing insulin secretion [69]. In study by Shiming et al [20], the result showed that after treatment Swietenine from *S. macrophylla* isolate at doses 20 and 40 mg/kg BW resulted in decreaded cholesterol level (to 125.6 and 107.4 mg/dL) in diabetic rats, triglyceride (to 112.2 and 91.98 mg/dL), and LDL (to 26.64 and 22.56 mg/dL). Based on this study, the treatment of Swietenine dose-dependently that given during four weeks can reversed these elevated biomarkers of lipid serum in diabetic rats [20].

Another mechanism that related to pathophysiology GDM involves alterations in the expression and phosphorylation of insulin signaling components, including insulin receptor substrate (IRS)-1, phosphatidylinositol 3-kinase (PI3K), and glucose transporter type 4 (GLUT4) [1]. The expression of GLUT4 also directly regulated by PPARγ for glucose uptake [70]. In study by Lau et al [2015], the C2C12 muscle cells given treatment with 2 μM of S. macrophylla compounds including 6-O-acetylswietenolide, diacetyl swietenolide and swietenine promoted the translocation of GLUT4 from intracellular compartments to the plasma membrane. Additionally, this treatment produced a significant enhancement in glucose uptake that the result from glucose homeostasis in downstream regulation of PPARγ [23].

Weight factor is also associated with diabetes. Obesity or overweight leads to an increased number of macrophages in adipose tissue, which secrete proinflammatory cytokines that can impair insulin signaling and inhibit insulin release from pancreatic β cells. These factors can induce insulin resistance through decreased insulin receptor tyrosine kinase activity, increased IRS-1 serine phosphorylation, or the STAT3-SOCS3 pathway. Circulating concentrations of pro-inflammatory cytokines (such as TNF-α, IL-6, IL-1β) are known to be increased in DMG [71]. Based on study by Hashim et al, treatment with 500 mg/kg or 1000 mg/kg petroleum ether extract of *S. macrophylla* seed for 14 days led to a significant decrease in body weight of diabetic rats induced by STZ. This result showed that treatment with *S. macrophylla* seeds can improvement of body weight [19].

3.6. Safety of *Swietenia* seeds as diabetes alternatives therapy

Insulin is the first-line therapy that commonly used to treat diabetes mellitus and other therapies with OADs, such as metformin [10,12]. The administration of metformin can reduce blood glucose levels, but there is an increase in serum SGOT levels, leukocytosis and neutrophilia, indicating the possibility of side effects in the form of hepatotoxicity [21]. In addition, the use of metformin during pregnancy needs monitoring as they are classified as category B drugs [13]. Other side effects that may be given during the use of metformin, such as maternal weight gain and pregnancy-induced hypertension [72].

Due to the safety factor of the side effects of pharmacological therapy, the use of non-pharmacological therapy with herbs was developed. The use of herbs as a form of pharmaceutical product development certainly requires comprehensive investigations to know biological and phytochemical activities [14,73]. To evaluate the effects of herbal materials before administered for systemic use, the toxicity test must be conducted to determine the dose was safe for human consumption and evaluate the potential side effects that could arise [73].

The following studies conducted some toxicity tests of *Swietenia* administration, both in vitro and in vivo. Based on study in vitro by Lau *et al* [23], the concentration of *S. macrophylla* isolated compounds, including 6OA, SW, and DS, did not induced cytotoxic effects on C2C12 and 3T3-L1 cell lines with IC_{50} values of >100 µM. IC_{50} is the half-maximal inhibitory concentration that used to indicate the amount of drug required to inhibit half of the biological process for efficacy in pharmacological studies [74]. *S. macrophylla* seeds oil extract is non-toxicity at concentration of 0.01, 0.1, and 1 mg/mL. This extract was reported to enhance cell growth or cell viability compared to the control group [23]. In line with study by Bakar *et al* [24],showed that extract *S. macrophylla* seeds using SC-CO_2 was non-toxic at concentrations 10, 1, 0.1, 0.01, 0.001 and 0.0001 mg/mL [24]. On another study by Shiming et al found that oral administration of Swietenine from *S. macrophylla* (doses 10, 20, 40 mg/kg BW) did not show any toxicity signs such as no rising in several marker of liver toxicity (levels of ALT, AST, and ALP) and renal toxicity (levels of urea and creatinine) in normal rats [20]. Also, the treatment with Swietenine at doses 20 and 40 mg/kg BW for diabetic rats, slightly improved the number of islets β-cell [20]. The increased islet cell mass would result in an elevation in insulin secretion, peripheral utilization and uptake of glucose [75].

Additionally, regarding the herbal-drug interactions, some natural products have been reported to produce synergistic effects when combined with antidiabetic agents [76]. So, there was synergistic activity between antihyperglycemic of Swietenine with Metformin based on increasing in the islet size and function to near normal values [20]. In line with the previous in vivo study, Balijepalli et al [73] prove that there were no signs of toxicity observed during the study period indicate that the treatment is relatively safe. In humans, the recommended safe dosege for S. *macrophylla* seeds is below 325 mg/kg BW, corresponding to 2000 mg/kg BW in rats [73]. However, no clinical studies have been conducted based on extraction of this literature study, so the further side effects and toxicity in human are still unknown.

4. Conclusion

The study conducted has found that several compounds of *Swetenia* seed extracts from both *S. macrophylla* and *S. mahogani* can act as antidiabetic agents. Our report suggests that *Swietenia* seed extracts has the potential as alternative treatment in patients with diabetes based on the ability to ameliorate blood glucose levels and safety from toxicity test results. Ameliorating of blood glucose levels under *Swietenia* extract treatment may be related to increased peripheral glucose utilization, increased insulin sensitivity, protection from oxidative stress, and improved β-cell function. However, developmental research especially in gestational diabetes mellitus cases is needed to further investigate the effect of *Swietenia* seed extract during pregnancy. Also, further research needs to determine the best *Swietenia* genus for the treatment of diabetes.

Compliance with ethical standards

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Disclosure of Conflict of interest

The authors report no conflicts of interest to declare.

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