SYSTEMATIC REVIEW

Antidiabetic Effect of *Piper Sarmentosum*: A Systematic Review

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ABSTRACT

Introduction: Diabetes mellitus (DM) is an endocrine, metabolic syndrome and has reached pandemic proportions worldwide. The multifactorial pathology results in the patient to including lifelong drug therapy for treatment. Alternative medicines such as traditional remedies using plant herbs to treat various diseases are common in most countries. *Piper sarmentosum* extracts have been as a traditional medicine to treat various diseases. The plant has abundant phytochemical properties such as alkaloids and flavonoids exhibiting pharmacological activities such as antidiabetic effects, antioxidant, anti-inflammatory, and anticancer. This paper aims to appraise the data into a comprehensive systematic review on the antidiabetic effect of *P. sarmentosum* and it's potential in managing DM. **Methods:** This systematic review used the PRISMA method with searches in three electronic databases such as SCOPUS, PUBMED and WEB OF SCIENCE in November 2021. Six articles were included based on the inclusion criteria. **Results:** The results showed a hypoglycaemic effect in induced diabetic models. *Piper sarmentosum* extracts significantly reduces fasting blood glucose and reduces the risk of diabetes complications related to renal and cardiovascular system. In summary, a promising result regarding antidiabetic activity was found. **Conclusion:** This finding suggests that this plant has the potential to be used as an alternative therapy or pair along with other medications to treat DM.
Malaysian Journal of Medicine and Health Sciences (2022) 18(SUPP15): 341-348. doi:10.47836/mjmhs18.s15.46

Keywords: *Piper sarmentosum*, Type 2 diabetes mellitus, Antidiabetic effect, Hypoglycaemic effect, Traditional medicine

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INTRODUCTION

Herbal treatments have played an incredibly significant part in maintaining human health throughout history (1). For decades, herbal drugs and supplements derived from them have been utilised as a part of integrated complementary therapy to treat diabetes mellitus (2). People are drawn to herbal medicines because of their innate nature, ease of use, and minimal risk of adverse effects (3). *Piper sarmentosum* Roxb. (Piperaceae), also known as Daun Kaduk locally; is described as a creeping tropical herb that grows approximately 20 cm tall. The morphology of the leaves is dark green, varied in shape and size. Typically, the leaves shape is a heart-shaped and cordate with 2-8 cm long petiole (4). The plant is famously known for its antibacterial, antiprotozoal, antioxidant, anti-malaria, and hypoglycaemic effects (5). In Southern Thailand, locals consume a concoction of *P. sarmentosum* as a traditional medicine to manage diabetes (6). The plant is widely used in Southeast Asia as a potent antidiabetic medication (7). Extensive research has been undertaken over the years to examine the biological effects of *P. sarmentosum* and its potential for treating oxidative stress-related disorders such as hypertension and diabetes, which has offered more support for its traditional usage (8–10).

Given the traditional use of this plant and the presence of chemical constituents that point to *P. sarmentosum* antidiabetic potential, the objectives of this paper was to properly assess the literature through a systematic review, collecting existing data about the use of this natural product and highlighting its antidiabetic potential.

METHODOLOGY

Search strategy

The systematic review was performed on the basis of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) used in the study selection process (11). The search strategies and keywords used were based on the review questions developed using PICO. A thorough literature search was conducted to identify the potential value and antidiabetic effects from animal studies following the administration of

P. sarmentosum. The research papers were identified by searching three databases without applying date or language filters: PubMed, Scopus, and Web of Science. The search methodology comprised combinations of the following keywords, ['antidiabetic' OR 'hypoglycaemic effect'] including various ['Piper sarmentosum'] names for the three databases. The literature search was conducted in November 2021 and included studies from 1998 until 2020. The author conducted each procedure individually before reaching an agreement, and two reviewers addressed conflicts.

Inclusion and exclusion criteria

Studies were included in this review if they were in vivo experimental studies on antidiabetic activity of *P. sarmentosum* and if they were articles published in English. Only articles focused on phytochemistry and the antidiabetic activity of *P. sarmentosum* extracts were included. Studies were excluded if the article used combined preparation of *P. sarmentosum* with other herbs. Books, book chapters, conference papers, editorial comments, case studies, and duplicate articles were removed.

Data extraction and quality assessment

Primary searches resulted in PubMed, Web of Science and Scopus. Forty-six different studies were found in several databases. Six studies were selected in this review; the study selection flowchart is shown in Figure 1. Six papers selected were appointed to a rigorous, independent appraisal by two reviewers before inclusion in the review using SYRCLE's RoB tool (12). The risk of bias in the animal research included in this systematic review was evaluated as presented in Figure 2. The following elements were reviewed to assess the possibility of bias: selection bias, performance bias, detection bias, attrition bias, and reporting bias.

Critical Appraisal

Relevant details from the included papers were carefully extracted, including the article's baseline information (authors' names, year of publication, and country), type of extract, biological activity, study methodology, and findings. The SYRCLE's RoB tool was used to assess the risk of bias in the animal research included in this systematic review, as presented in Table I. The following aspects were analysed to identify the risk of bias: selection bias, performance bias, detection bias, attrition bias, and reporting bias. There are nine components: sequence generation, baseline characteristics, allocation concealment, random housing, blinding, random outcome assessment, blinding, incomplete outcome data, and selective outcome reporting.

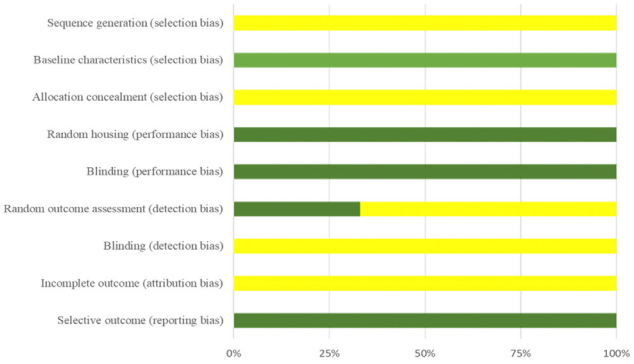

Figure 2: Risk of bias graph animal intervention studies

To determine whether each component described in the tool has a low, high, or unclear bias, the tool included a list of signalling questions that will help assist the decision-making process. This review assessed the included studies by discussing and adapting to the list provided. A "yes" verdict signifies a low risk of bias; a "no" verdict represents a high risk of prejudice, and the verdict will be "unclear" if inadequate facts are presented to assess the risk of bias fully. The author advised using the risk bias tool, at least two independent reviewers should conduct the evaluations, and any disputes should be handled by prevailing opinion discourse or

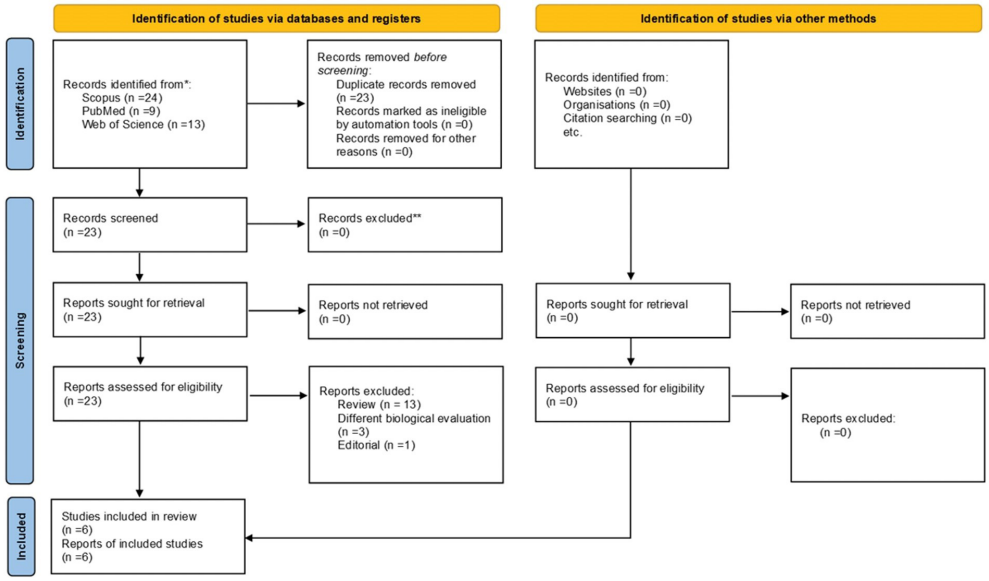

Figure 1: Flowchart of search and selection of published articles using PRISMA flow-chart (2020)

Table II: Summary of results of consensus risk of bias assessments using SYRCLE's risk of bias tool

Authors	Sequence generation (selection bias)	Baseline characteristics (selection bias)	Allocation concealment (selection bias)	Random housing (performance bias)	Blinding (performance bias)	Random outcome assessment (detection bias)	Blinding (detection bias)	Incomplete outcome (attribution bias)	Selective outcome (reporting bias)
13	?	+	?	+	?	?	?	?	+
15	?	+	?	+	?	+	?	?	+
30	?	+	?	+	?	+	?	?	+
7	?	+	?	+	?	?	?	?	+
16	?	+	?	+	?	?	?	?	+
18	?	+	?	+	?	?	?	?	+

by consulting a third party (12).

RESULTS

Table II is the summary characteristic of the six selected studies in which all the papers study designs used experimental in vivo antidiabetic models. In these studies, the researchers prepared the extract using the maceration technique, while one study prepared the extract using the fractionation technique. The most common solvent used in the experiments was water which included five studies; another study used methanol as the solvent. Among the six eligible studies, three used reference drugs such as glibenclamide and glycyrrhizic acid to investigate the hypoglycaemic effect of *P. sarmentosum*. Five studies used the leaves of *P. sarmentosum*, and one study used the whole plant of *P. sarmentosum*. The doses of extract administered to the animals are varied from 0.125 g per day to 1 g per day.

The studies showed that *P. sarmentosum* showed a decrement in blood glucose and improved fasting blood glucose level. Studies also reported a significant elevation in insulin levels, adiponectin level and bodyweight. A few studies that examined the histology of heart tissue and found less connective tissue deposited; there was a significant reduction in the thickness of the tunica intima and tunica media (four were from Malaysia and two from Thailand).

The sequence generation, allocation concealment, blinding and incomplete outcome were not described in any of the experimental investigations included, which could be a high risk of bias. Additionally, neither of the investigations found appropriate blinding (performance bias) of animal caretakers and researchers. The allocation of groups in the included studies considers the assessment of similarity in baseline characteristics (selection bias) between the experimental and control

Table II: Summary of characteristics of included studies

Author	Country	Part of Plant	Study Design	Type of Extraction	Solvent	Dose Extract	Reference Drug	Outcome
13	Thailand	Whole plant	Experimental Male Wistar rats (n=18)	Fractionation	Methanol	0.125 g/kg 0.25 g/kg	Glibenclamide (5 mg/kg) Insulin (5 IU/kg)	OGTT Blood glucose lowered at 90 min and 120 min after glucose administration
15	Malaysia	Leaves	Experimental Female Sprague-Dawley rats (n=28)	Maceration	Water	1.25 mg/kg	Glycyrrhizic acid (1.20 mg/kg)	Blood glucose reduced in 3 and 5 months. Adiponectin plasma level increase in 3 and 5 months
30	Malaysia	Leaves	Experimental Male Sprague-Dawley rats (n=32)	Maceration	Water	0.125 g/kg	None	Increased in body weight 231 g Fasting blood glucose level reduced to 23.2 mmol/L in 28 days
7	Malaysia	Leaves	Experimental	Maceration	Water	0.125 g/kg	None	Less severe histological changes in cardiac tissues, less connective tissue deposits, a significant decrease in TI: TM ratio and less damage on aortic tissues
16	Malaysia	Leaves	Experimental Male Sprague-Dawley rats (n=18)	Maceration	Water	0.125 g/kg	None	Fasting blood sugar is decreased from 26.58 to 23.33 mol/L. Mild inflammatory cells infiltration and decrease in size of urinary space
18	Thailand	Leaves	Experimental Male mice (n=44)	Maceration	Water	60 mg/100 g 100 mg/100 g	Glibenclamide (1 mg/100 g)	Fasting blood glucose at day 22 reduced to 47.56 mg/dl and 120.96 mg/dl Increase in insulin level to 21.16 IU/L

groups; there is a low risk of bias in this area. In six studies, the housing conditions (performance bias) of animals in various treatment groups were identical.

DISCUSSION

Hypoglycaemic effect

P. sarmentosum showed a hypoglycaemia effect on diabetic induced rats administered with aqueous extract of *P. sarmentosum* at two different doses, 0.125 g/kg and 0.25 g/kg decreasing plasma glucose levels substantially at 90 minutes and 120 minutes after oral glucose tolerance (OGTT) (13). Methanol soluble fraction of the P.sarmentosum water extract at 0.075 g/kg reduced blood glucose levels significantly in normal rats (13). In another study, aqueous and methanolic extracts demonstrated significant hypoglycemic effects in diabetic rats, however, during the dose-dependent experiment, the water extract produced the most significant antihyperglycemic effect in diabetic rats (14). Blood glucose level in ovariectomised rats administered with *P. sarmentosum* aqueous extract by oral gavage at a dose of 1.25 mg/kg, demonstrated a significant decline after 3- and 5-months of treatment compared with other groups of ovariectomised rats receiving glycyrrhizic acid (GCA) (15). GCA is derived from food known as liquorice that is widely used in the commercial food industry as an artificial sweetener. Prolonged intake of GCA may increase blood glucose levels (15).

Two studies used diabetic male Sprague-Dawley induced with streptozotocin (STZ) injection and evaluated the fasting blood glucose (FBG) (7,16). Thent et al, 2021 (7) administered *P. sarmentosum* for 28 days (four weeks), but Hussan et al. (16) only administered the plant extract treatment orally on day 11. The diabetic rats that received *P. sarmentosum* treatment for four weeks, had a significant reduction in FBG urine glucose (7). However, Hussan et al. (16) reported an insignificant reduction in blood glucose in their study . STZ impaired glucose oxidation and decreased insulin biosynthesis and secretion, causing irreversible damage to the pancreas beta-cell responsible for insulin production. This occurrence causes a reduction of insulin secretion and increases the blood glucose level (17). This condition results in the rats presenting DM symptoms hyperglycaemia and glycosuria. Although there was a difference in the length of administration of the *P. sarmentosum* in both studies, that may have led to the difference in the results, however, Hussan et al (16), had raised an argument that the effect of the leaves of the *P. sarmentosum*, possessed less potent hypoglycaemic activity than the whole plant.

The hypoglycaemic effect of *P. sarmentosum* leaf extract on STZ induced diabetic male mice, the diabetic mice treated *P. sarmentosum* extract at dose 60 mg/100 gBW, and 100 mg/100 gBW significantly reduced 65.11 mg/dl and 47.56 mg/dl respectively in FBG compared with untreated diabetic mice (18). The efficiency of hypoglycaemic activity of this plant is 73.04% and 120.96%. In contrast, histological investigations of pancreatic islets revealed that the cells improved cell size and reduced dead cells (18).

P. sarmentosum contains phytochemicals that help in blood glucose reduction. Phytochemicals such as tannins found in *P. sarmentosum* leaves, is an active antioxidants that decreases the blood glucose level. It contains an enzyme related to the benzoic acid molecule which inhibit insulinase preventing insulin degradation and promoting insulin secretion (19). In addition, Quercetin find in this plant, has potent superoxide scavenging activity effect on DM rats which helped to decrease blood glucose levels by enhancing the regeneration of pancreatic islets and promoting insulin production (20). Naringenin found in the leaves of *P. sarmentosum*, contained potent antioxidants with 75.7% of superoxide scavenging activity (21). Thus, it inhibits glucose absorption by inhibiting rat intestinal glucosidase activity dose-dependent (22).

P. sarmentosum ability in managing DM and its complication

Diabetes involves a direct influence on the development of cardiomyopathy (23). People with diabetes have more cardiac mass, which might be due to increased adipocyte secretion of cytokines, including leptin and resistin, which have hypertrophic implications on cardiomyocytes (24-27). Additionally, interstitial fibrosis with higher collagen deposition has been seen in diabetes, contributing to the decreased heart function (28). Although established cardiovascular risk factors could explain part of the variance, DM also directly modifies the heart structure and function by increasing hypertrophy and fibrosis (29).

Thent et al. (30) further investigated the histological changes in the heart of diabetic rats and linked DM to the progression of cardiovascular events and atherosclerosis since metabolic dysfunction in diabetes induces biochemical and structural modifications in the heart. It showed less disruption and uneven arrays of myofibrils inside cardiac sarcomeres. The size, disorganisation, and irregular patches of cytoplasmic space in heart tissue mitochondria were significantly decreased (30).
P. sarmentosum leaves extract could minimise cardiac dysfunction and early symptoms of atherosclerosis in STZ diabetic mice by preventing deterioration of the myocardial and aortic tissues. There seem to be a few considerations to contemplate. However, To validate the activity of *P. sarmentosum*, none of the in vitro investigations used a reference drug on antioxidant or anti-inflammatory as a positive control. Simvastatin did not lower c-reactive protein (CRP); it did lower vascular cell adhesion molecule (VCAM) and intercellular adhesion molecule (ICAM) more effective than the *P. sarmentosum* (31).

The degree of hyperglycaemia is the most critical factor leading to organ damage. Initial morphological markers of renal injury include nephromegaly and a modified Doppler, although proteinuria and glomerular filtration rate (GFR) is the most vital indicators of severe renal damage (32). Within the first 10 to 20 years following diabetes initiation, the mean incidence of diabetic nephropathy is substantial, 3% per year (33). It is anticipated that more than 20% of T2DM patients and perhaps up to 40% may develop chronic kidney disease (CKD) (34,35).

Only one study in this review reported the effect of *P. sarmentosum* on the kidney of diabetic rats (16). The study, showed that, the kidneys of STZ-induced DM rats have increased inflammatory cell infiltration, Bowman's capsule size, and glomerular membrane thickness. *P. sarmentosum* aqueous leaves extract 0.125 g/kg decreased these degenerative renal alterations in STZ-induced DM rats, indicating that the plant extract might prevent renal failure caused by DM (16).

A meta-analysis found that waist circumference and waist-to-height ratio were more significantly associated with diabetes than BMI (36). The excessive visceral fat build-up creates an imbalance in endocrine function leading to the production of pro-inflammatory substances, which can enhance the progression of IR and T2DM (37,38). This finding was comparable with another study that stated adiponectin level is positively interrelated with insulin sensitivity (39).

P.sarmentosum treated diabetic rats group had significantly higher ($P < 0.05$) body weight (231±13.52g) in comparison to untreated diabetic rats (178±0.91g) (7). Diabetic results in a reduction in body weight due to calorie deprivation. This leads to protein degradation and reduction in protein synthesis in a more extended DM state (40). However, the treated group benefited from the P.sarmentosum extract, due to the key minerals and vitamins content that resist weight loss (7).

Phytochemicals of *P. sarmentosum* related to the antidiabetic effect

Phytochemical compounds in *P. sarmentosum* contain various active compounds such as alkaloids, amides, flavonoids, and phenylpropanoids. These might be attributed to the antidiabetic effect discussed above. *P. sarmentosum* contains high amounts of potent antioxidant chemicals, which may regulate oxidative stress caused by diseases such as DM (6). Its leaves contain many flavonoids such as myricetin, quercetin, apigenin and naringenin. Naringenin is a powerful antioxidant showing 75.7% of superoxide scavenging activity and decreased oxidative stress (21,8). Likewise, it inhibits alpha-glucosidase activity in the gut, prolonging carbohydrate assimilation in diabetic mice and reducing postprandial blood glucose levels (22). Flavonoid substances such as quercetin have been shown to alleviate endothelial dysfunction, while naringenin has been shown to have outstanding superoxide scavenging capability (20). Henceforth, quercetin has an antioxidant effect in *P. sarmentosum* would be beneficial in managing glucose transport, as well as the comparable in the magnitude of mitochondrial ROS are connected to hyperglycaemia (41).

In a previous study, flavonoids were discovered to have antidiabetic efficacy via modulatory effects on molecular targets in multiple organs. Flavonoids interact with glucose transporters facilitated by phosphatidylinositol 3-kinase (PI3K)/protein kinase B (also known as Akt) and AMP-activated protein kinase (AMPK) pathways (42). Neurons in the brain could not synthesise or store glucose. Consequently, they rely on transporting glucose via the brain-blood barrier providing glucose to the cells facilitated by GLUTs (43). Another study assessed how quercetin and naringenin influenced changes in brain glucose transporters and essential parts in the insulin signalling pathway in experimental induced-diabetic rats (44). They determined that quercetin significantly modulated the expression of GLUT 1, GLUT 2, GLUT 3, and GLUT 4 primary insulin signalling components. Quercetin and naringenin were seen in Djungarian hamsters and C57BL/6JRj mice related to the brain insulin signalling pathway (45). Similarly, naringenin decreases IR in the liver of mice who consume a high-fat diet via an AMPK-dependent pathway and by activating insulin receptor substance 1 (IRS-1) (46). The structures of quercetin and its mechanism in skeletal muscle (L6 myotubes) cells increased glucose absorption via AMPK pathway regulation (47). Similarly, in a skeletal muscle cell line, quercetin increased GLUT4 transcription and translocation (47).

The naringenin effect on induced-diabetic hyperalgesia and allodynia, considering oxidative stress and inflammation are also present in renal diabetes, it discovered that naringenin treatment accelerated the activity of superoxide dismutase (SOD), an endogenous enzyme that is strongly linked to oxidative stress in DM (48). This suggests that administering naringenin to STZ-induced diabetic rats restored blood glucose level, lipid level, enhanced GLUT4 translocation in adipose tissue, reduced diabetic nephropathy, anti-inflammatory and antioxidant characteristics (48).

Quercetin is thought to dissipate the glucose by enhancing glucose absorption through insulin-mediated, whereas bioactive naringenin may improve insulin-independent glucose uptake (44). As a result, quercetin exerts antidiabetic efficacy by initiating several therapeutic targets to alleviate insulin resistance by traversing distinct metabolic pathways (49).

SYRCLE's risk of bias tool

A systematic review is a widespread method for making evidence-based healthcare recommendations in clinical

settings. A few parts of the systematic review procedure must be adjusted to account for the unique characteristics of animal intervention research. The Systematic Review Centre for Laboratory animal Experimentation (SYRCLE) presents the RoB tool for animal intervention studies adapted from the Cochrane Collaboration RoB Tool (50). This tool attempts to measure methodological quality and has been tailored to biases that occur in animal experiments. A few studies used this risk of bias tool to assess the quality of the evidence obtained from the studies in their interest (51–53).

CONCLUSION

DM is a progressive disease that affects millions of people around the world. DM management includes lifestyle modification, a change to an appropriate diabetic diet, and medication treatments for their entire life. This systematic review, suggest that *P. sarmentosum* may help in treating and managing secondary risk related to DM. It demonstrated an equal glycaemic level reduction compared to reference drugs such as glibenclamide and GCA in animal-induced diabetics. However, although *P. sarmentosum* has proven hypoglycaemic efficacy, its phytochemical compound and actions were not clearly explained. Thus, it is recommended that the hypoglycaemic properties of *P. sarmentosum* should be studied further in clinical settings to draw a more conclusive result.

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