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Antidiabetic Effects of *Pterocarpus marsupium* (*Gammalu*)

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Author's contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

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Review Article

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ABSTRACT

Herbal medicines are considered to offer gentle means of managing chronic diseases at a lower cost. *Pterocarpus marsupium* Roxb. (PM) (*Gammalu* in Sinhala) heartwood and bark have been used as antidiabetic remedies in many cultures for thousands of years. The aim of this review is to address the existing evidence on antidiabetic effects of the *P. marsupium.* The hypoglycaemic effects, antidyslipidaemic effects, antioxidative effects and the safety of the PM heartwood and the bark have been scientifically validated using a multitude of *in vitro* and *in vivo* studies. Multiple mechanisms responsible for hypoglycaemic effects of PM including β-cell regeneration, insulin release and insulin-like actions of some compounds isolated were identified. (-)-Epicatechin, a flavonoid isolated from the bark has shown insulin-like effects, effects on β-cell regeneration and insulin release. Several compounds including pterostilbene and marsupsin isolated from the PM heartwood were identified as compounds with hypoglycaemic effects. The latex (gum) of the tree is a popular remedy used in Sri Lanka for diabetes even though the literature on PM does not discuss about the antidiabetic effects of the latex. Few investigations focused on the antidiabetic effects of PM latex have demonstrated strong inhibitory effects of the latex on α-amylase and α-glucosidase activities and on protein glycation. Investigations focusing on the antidiabetic effects and possible toxicity of the PM latex are essential to validate its efficacy and safety.

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Keywords: Pterocarpus marsupium; Gammalu; antidiabetic; latex.

1. INTRODUCTION

Humankind has a long history of using herbal remedies to treat diseases. Herbal medicines are considered to offer more gentle means of managing chronic diseases at a lower cost. Studies of traditional antidiabetic remedies around the world have identified more than 1,200 species of plants with hypoglycemic activity [1]. Due to their perceived effectiveness, fewer side effects in clinical experience and relatively low costs, herbal drugs are now being prescribed widely by many health practitioners [2]. Diabetes is characterized by hyperglycemia and absolute or relative deficiency of insulin action leading to the development of chronic diabetic complications [3]. These complications include retinopathy, nephropathy, neuropathy and cardiovascular diseases. The increase in the oxidative stress, dyslipidaemia and glycation of macromolecules are major mechanisms contributing to the development of diabetic complications. Therefore therapeutic agents which can normalize the metabolic alterations that occur in diabetes are invaluable in the treatment of diabetes. The aim of this review is to address the existing evidence on antidiabetic effects of the *P. marsupium.*

Published data were searched within the year range of 1950-2015. Main search words used were *Pterocarpus marsupium*, antidiabetic, diabetes, hypoglycaemic, antidyslipidaemic, antioxidant, antiglycation and toxicity. Key search engines employed were Google scholar and PubMed.

Pterocarpus marsupium Roxb. (PM) (*Gammalu* in Sinhala) is known as Indian kino and belongs to the family Fabaceae (Leguminoceae). PM is native to Sri Lanka, India and Nepal. It has a long history as a versatile medicinal plant with multiple pharmacological activities. PM is extensively used to treat diabetes mellitus for thousands of years [4-8]. Even the ancient renowned text, Charaka Samhita which is believed to be one of the oldest of the surviving ancient treatise of ayurveda recommended PM for treating diabetes mellitus [7,9]. PM grows as a medium to large tree with a height up to 30 meters. The outer bark of PM is rough and vertically cracked [9]. The inner heartwood is golden yellow in colour while the outer sapwood is light yellow. Leaves are compound and flowers are yellow. Fruits have a flat circular wing. Latex (gum), which looks like dried blood comes out through the bark when an incision is made up to the cambium [9].

Water kept overnight in the tumblers made out of the PM heartwood is a popular traditional remedy used to lower blood glucose concentration in diabetics [10-12]. Several commercial preparations which include PM as a therapeutic agent alone or in combinations are available to treat diabetes [13]. Even though the scientific evidence for the use of the PM latex as an antidiabetic agent is lacking, the latex obtained from PM is widely used to treat diabetes in Sri Lanka [14]. A dose of one tea spoon of gum daily is considered as the effective dose [15,16]. A patent was obtained for a Sri Lankan ayurvedic preparation made with five antidiabetic plants to treat diabetes in which the main ingredient is PM latex [17]. Latex contains 75% tannic acid, kino tannic acid (a non-glucosidal tannin), kinonin, kinored and small quantities of catechol, protocatechic acid, resin pectin and gallic acid [9].

Hypoglycaemic effects of the PM heartwood and bark are studied extensively. Many of these studies were conducted in diabetes induced rats and there are some reports on the clinical trials conducted with PM. Some of these studies have addressed the mechanism of action (Fig. 1) and toxicity of the extracts as well. Evidence for the β-cell regeneration in the pancreas [18,19], insulin release [20,21], insulin-like action [20-24], increased expression of glucose transporter [22], inhibition of digestive enzymes amylase and glucosidase (by the latex) [25,26] are some of the mechanisms identified. Furthermore, evidence on protective effects such as antioxidant effects [7,27], antidyslipidaemic effects [27-29] and evidence for antiglycation effects of the latex are available [30,31]. Several compounds responsible for the antidiabetic effects of PM have been revealed. Many investigations have focused on pterostilbene and (-)-epicatechin which were recognized as two major compounds responsible for the antidiabetic effects of heartwood and bark respectively.

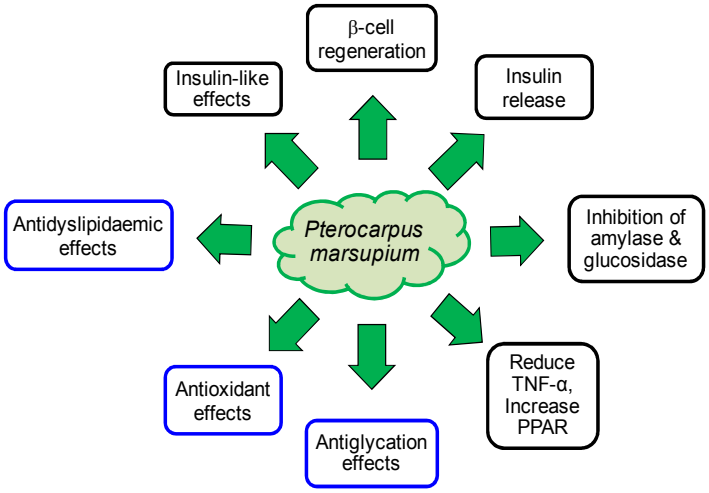


Fig. 1. Scientifically proven antidiabetic effects of *Pterocarpus marsupium*
Effects outlined in black are responsible for hypoglycaemic effects. Additional effects outlined in blue provide further protection in alleviating diabetic complications

2. EXPERIMENTAL EVIDENCE ON HYPOGLYCAEMIC EFFECTS

Experiments conducted *in vivo* in animal models and humans have validated the hypoglycaemic effects of PM heartwood and bark as well as various fractions and compounds isolated from them.

2.1 Hypoglycaemic Effect of PM Heartwood

Methanol, ethanol and aqueous extracts of PM heartwood and their sub fractions have shown hypoglycaemic effects in streptozotocin or alloxan- induced rats. More recent studies have used a daily dose of 100 to 300 mg/kg body weight for 7 to 28 days which were effective. However, others have used higher doses such 750 mg or 1 g/kg for 5 to 30 days. Several clinical trials have demonstrated the hypoglycaemic effects of PM heartwood with a flexible dose of 2 to 4 g/day for a period of 12 or 36 weeks.

Different extracts prepared from the heartwood of PM (crude powder, ethanolic extract and sub fractions of ethanol extract; aqueous, chloroform, hexane and n-butanol fractions) resulted an improvement in the oral glucose tolerance after a sucrose load in normal rats [21]. This study revealed that, after a sucrose load, all fractions other than the aqueous fraction improved the oral glucose tolerance in streptozotocin-induced diabetic rats as well. Ethanol extract (100 mg/kg/day) was found to be effective when given to diabetic rats for 10 consecutive days [21]. Similar effect was observed with ethanol extracts of PM heartwood (150 mg/kg) administered daily for a period of 14 days in alloxan-induced diabetic rats. It resulted in a reduction in blood glucose [27]. Aqueous extract of the PM heartwood (100 and 200 mg/ kg/day) given orally for 4 weeks decreased the fasting and postprandial blood glucose concentration in streptozotozin-induced diabetic rats [32]. Methanol extract of PM heartwood (300 mg/kg/day) given for 7 and 14 days caused a reduction in serum glucose in streptozotocin-induced diabetic rats [33]. When PM heartwood ethanol extract was given at 100, 200, 300 mg/kg/day for 12 days, it had shown a reduction in fasting blood glucose levels in streptozotocin-induced diabetic rats [34]. Aqueous extract of PM heartwood (250 mg/kg/day) has produced hypoglycemic effects in alloxan-induced diabetic rats [35]. Methanol extract of PM heartwood (750 mg/kg/day for 6 days) caused a reduction in blood glucose concentration in both normal and diabetic rats [7]. Aqueous extract of PM bark (1 g/kg/day) resulted in a decrease in blood glucose by 38% and 60% on 15th and 30th day in streptozotozin-induced diabetic rats [1]. Ethyl acetate fraction of ethanol extract of PM heartwood lowered the blood sugar concentration in alloxan-diabetic rats treated for 5 days [36].

Pterostilbene isolated from PM heartwood (10 mg/kg/ intravenous) has caused hypoglycemia in dogs [37]. Marsupsin and pterostilbene have lowered the blood glucose level in a manner comparable to that of metformin when marsupsin, pterosupin and pterostilbene from the PM heartwood were given to streptozotocin-induced diabetic rats [38].

Antidiabetic effects of PM heartwood were explicitly demonstrated in clinical trials conducted in India [12]. In one such study, PM lowered fasting and postprandial blood glucose concentrations in 69% of the patients by the 12th wk [39]. In this group a dose of 2 g/ day was sufficient to produce glycaemic control in 73% of the patients while rest of the patients received either 3 or 4 g/day [39]. A similar double-blind trial conducted using capsulated dried decoction of PM heartwood (2-4 g/day) showed glycaemic control in 86% of patients treated with PM for 36 weeks [4]. In another clinical study PM was found to be useful in treating non-obese diabetic patients [40].

2.2 Hypoglycaemic Effect of PM Bark

Ethanol and aqueous extracts of PM bark were investigated in several studies. In one study, ethanol extracts of PM bark (150 mg/kg) administered daily for a period of 14 days to alloxan-induced diabetic rats caused a reduction in blood glucose [27]. Another study revealed that various sub fractions of the alcohol extract of PM bark were effective as antidiabetic agents in alloxan-induced diabetic rats and the butanol subfraction was found to be most effective [29]. Aqueous extracts of PM bark (1 g/kg/day) given to rats fed with a fructose-rich diet for 30 days lowered the serum glucose concentration compared to the group which did not receive the extract [28]. Aqueous extract of PM bark lowered blood glucose and improved glucose tolerance with no side effects in alloxan-induced diabetic rats [41]. In another study conducted with alloxan-induced diabetic rats, hypoglycaemic effects of a 21 day dose of aqueous extract of the PM stem bark (1 g/kg) was demonstrated [42].

A compound responsible for the hypoglycaemic effects was identified from the PM stem bark. First it was recognized that a flavonoid fraction from the PM bark effectively reduces the blood glucose concentration in alloxan induced-diabetic rats [18]. Another study conducted by the same group determined the hypoglycaemic effects of the flavonoid (-)-epicatechin in alloxan-induced diabetic rats after administering 30 mg/kg/day for 4 to 5 days [19].

3. MECHANISM OF ACTION

3.1 β-cell Regeneration

There is evidence to suggest that (-)-epicatechin is effective in β-cell regeneration. Chakravarthy et al. [18] demonstrated the effectiveness of a flavonoid fraction from the PM bark in reversing the β-cell population of the pancreas in alloxan-induced diabetic rats. Later they showed that (-)-epicatechin given for 4 to 5 days resulted in regeneration of the β-cell population of the islets of pancreas which were previously necrosed due to alloxan in alloxan-induced diabetic rats [19]. Functional nature of the regenerated β-cells was identified based on the immune reactive insulin studies [19]. However, some other investigators could not confirm the effectiveness of epicatechin in β-cell regeneration [43].

3.2 Insulin Release

Studies have revealed that ethanol and aqueous extracts of PM heartwood, their sub fractions and (-)-epicatechin from PM bark increase insulin release. Ethanol extract of PM heartwood given for 10 days increased serum insulin concentration in streptozotocin-induced diabetic rats [21]. Antidiabetic constituents in the aqueous extract of PM heartwood were fractionated using bioassay-guided fractionation in a study and a high molecular weight fraction (>10 < 30 kDa) isolated has shown potent insulinotrophic and insulin-like properties [20]. The same study revealed that PM stimulated the insulin secretion from the mouse pancreas in a concentration-dependent manner *in vitro* [20]. Furthermore, the increase in glucose clearance observed after intra venous administration of glucose to normoglycaemic sheep was positively correlated with insulin secretion when water extract and the high molecular weight fraction of PM were administered [20]. In another investigation, ethyl acetate fraction of the ethanol extract of PM heartwood increased blood insulin concentration in alloxan-diabetic rats treated for 5 days [36]. The same study showed that (-)-epicatechin in the water extract of PM bark increased the cAMP content of the islets of pancreas in rats with an associated increase in insulin release and conversion of proinsulin to insulin [36]. Ethanol extracts of PM heartwood and bark administered daily for a period of 14 days increased

the plasma insulin concentration in diabetic rats [27].

3.3 Insulin-like Activities

3.3.1 Increase in glucose uptake

Increase in glucose uptake by peripheral tissues is a major event which lowers the blood glucose concentration during fed state. Skeletal muscle and adipose tissue are major tissues which respond to insulin mediated increase in glucose uptake. Mishra et al. [21] studied the effects of five phenolic compounds isolated from n-butanol fraction of the ethanolic extract of PM heartwood on 2-deoxy-glucose uptake by mouse skeletal muscle cells (C2C12). When incubated for 24 h of which the final 3 h prior of the assay were in serum free media, four phenolic compounds namely vijayoside, pteroside, marsuposide and pterosupol (10 μM/ml) increased the glucose uptake in basal and insulin-stimulated cells in a concentration-dependent manner [21]. The other phenolic compound 2,4, dihydroxy-phenyl glucopyranosyl-C-glycoside did not show an effect on glucose uptake [21]. In another study, a high molecular weight fraction of PM heartwood aqueous extract stimulated glucose uptake by mouse skeletal muscle in a dose-dependent manner *in vitro* [20]. They also suggested that PM and insulin share a common signaling pathway, as the PM mediated muscle glucose uptake did not improve in the presence of insulin [20]. PM methanolic extract and an isoflavone purified from the extract have increased glucose uptake in L6 myotubes with a parallel increase in the GLUT4 expression which was comparable with those of insulin and rosiglitazone [22]. In this study, the fraction showing maximum glucose uptake was purified and the active compound was identified as 7-O-α-L-rhamnopyranosyl-oxy-4′-methoxy-5-hydroxy isoflavone [22]. Evidence from the same study suggested the involvement of a PI3 kinase dependent pathway by PM methanol extract and a PI3 kinase independent pathway by 7-O-α-L-rhamnopyranosyl-oxy-4′-methoxy-5-hydroxy isoflavone in increasing glucose transport [22].

Evidence for the effect of (-)-epicatechin in increasing the glucose uptake in rat diaphragm in a dose-dependent manner is available [44].

3.3.2 Increase in glycogen synthesis

During the fed state excess glucose is channeled to synthesize glycogen with the action of insulin, resulting in lowering of blood glucose. Several investigations have looked in to the ability of PM in restoring glycogen synthesis. Aqueous extract of PM (1 g/kg/day) corrected the decline in glycogen content occurred in insulin dependent tissues such as liver and skeletal muscle of diabetic rats [1]. Oral administration of the aqueous extract of PM bark (300 and 500 mg/kg/day for 12 weeks) to diabetic rats restored the level of glycogen synthase [23]. (-)-Epicatechin increased the glycogen content in rat diaphragm in a dose-dependent manner [44]. Ahmad et al. revealed insulin-like activities of (-)-epicatechin and demonstrated that (-)-epicatechin does not share the plasma membrane receptor with insulin [44].

3.3.3 Increase in activity of oxidative enzymes

Glycolysis and tricarboxylic acid (TCA) cycle are central pathways which oxidize glucose and are important in the regulation of glucose homeostasis. Dysregulation of glycolysis occurs in diabetes due to reduction in the amount and/or activity of regulatory enzymes of glycolysis [45,46]. Reduction of TCA cycle flux in tissues such as skeletal muscle [24] and peripheral neurons [46] have been observed in diabetes. In diabetic rats the activities of glucokinase, hexokinase and phosphofructokinase were found to be reduced by 35%, 50% and 60% of the controls respectively [1]. Aqueous extract of PM (1 g/kg/day) has corrected this alteration completely in phosphofructokinase and partly in glucokinase and hexokinase of diabetic rats [1]. Oral administration of the aqueous extract of PM bark (300 and 500 mg/kg/day) to diabetic rats restored the levels of glucokinase, lactate dehydrogenase, succinate dehydrogenase and malate dehydrogenase at the end of 12th week [23]. Authors have suggested that the restoration of the enzyme levels after administration of PM might be due to stimulatory effects of the extract on insulin secretion [23]. In diabetic-induced rats, pterostilbene (40 mg/kg for 6 weeks) increased the activity of hexokinase. Furthermore, it decreased the activities of gluconeogenic enzymes glucose-6-phosphatase and fructose-1,6-bisphosphatase in the liver leading to a decrease in the release of glucose into the circulation [47].

3.4 α-amylase & α-glucosidase Inhibitory Effects

Antidiabetic drugs target at various biochemical mechanisms including digestion of

carbohydrates. α-Amylase and α-glucosidase are principle enzymes involved in digesting dietary carbohydrates into absorbable molecules. Inhibition of these enzymes is helpful in bringing down postprandial blood glucose spikes. Strong *in vitro* inhibitory effects of PM latex were observed on α-amylase and α-glucosidase with IC_{50} of 2.97 and 0.54 µg/ml respectively [26]. Aqueous extract of the PM latex had shown a marked α-glucosidase inhibitory activity [25].

3.5 Effects on TNF-α and Peroxisome Proliferator Activator Receptors (PPARs)

The inflammatory cytokine tumor necrosis factor TNF-α is elevated in type 2 diabetes and it is known to cause insulin resistance [48]. TNF-α has a direct inhibitory effect on insulin signaling [49] in addition to indirect effects leading to insulin resistance. Aqueous extract of PM heartwood (100 and 200 mg/kg/day) given orally for 4 weeks decreased TNF-α to the normal levels in diabetic rats [32]. TNF-α down regulates peroxisome proliferator activator receptors (PPARs) which are nuclear receptors that regulate metabolic events of cells [50]. Methanolic extract of PM and an isolated isoflavone 7-O-α-L-rhamnopyranosyl-oxy-4′-methoxy-5-hydroxy isoflavone induced the expression of PPAR-γ in L6 myotubes [22]. In the same study cycloheximide mediated inhibition of protein synthesis blocked the effect of the extract and the isoflavone suggested that new protein synthesis is required for these effects [22]. Furthermore, PI3 kinase was activated by the methanolic extract but not by the pure isoflavone suggesting the need of a PI3 kinase independent pathway for the effect of isoflavone [22]. It has been revealed that pterostilbene (100 µM) activates PPAR-α activity by 8 fold [51].

4. OTHER PROTECTIVE EFFECTS

4.1 Antidyslipidemic Effects

Diabetes leads to derangement in the lipid metabolism [52] which becomes an underlying cause for the increase in the risk of cardiovascular diseases in diabetes. Scientific evidence for antidyslipidaemic effects of PM is available. The ethanolic extract of PM (100 mg/kg) had demonstrated antidyslipidemic effects in hamsters that were on a high fat diet [21]. Lipid parameters (total cholesterol, LDL cholesterol, VLDL cholesterol, HDL cholesterol and triglycerides) were restored when ethanol extracts of PM heartwood and bark (150 mg/kg) were given to alloxan-induced diabetic rats for 14 days [27]. In another study, PM controlled the diabetes related metabolic alterations of cholesterol and triglycerides in diabetic rats [29]. Only PM extract had prevented the hypertriglyceridaemia when an aqueous extracts of PM bark (1 g/kg/day), *Ocimum sanctum* leaves and *Trigonella foenum-graecum* seeds were given to rats concurrently with a fructose-rich diet for 30 days [28]. However, in this study, all three extracts have lowered blood glucose concentrations [28]. Hypoglycaemic effects of *O. sanctum* leaves were revealed in a recent study as well [53]. Ethyl acetate extract of PM heartwood and its flavonoid constituents, marsupsin, pterosupin and liquiritigenin were orally administered to hyperlipidaemia-induced rats for 14 days [54]. Ethyl acetate extract was found to be effective in reducing serum triglyceride, total cholesterol, LDL cholesterol and VLDL cholesterol concentration without changing HDL cholesterol [54]. Liquiritigenin and pterosupin reduced the serum cholesterol, LDL cholesterol and atherogenic index while pterosupin lowered serum triglyceride too [54]. Pterostilbene (25 ppm) given to hypercholesterolaemic hamsters reduced LDL cholesterol and increased HDL cholesterol [51].

4.2 Antioxidant Effects

Persistent hyperglycemia induces the oxidative stress in diabetic patients as a result of increased free radical generation and impaired antioxidant defense system [52,55]. Increased oxidative stress contributes to diabetic complications [56]. The antioxidant defense system includes the enzymes superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase [57]. Reduced glutathione is a key endogenous non enzymatic antioxidant [57]. PM heartwood, bark and (-)-epicatechin from the bark have demonstrated protection against oxidative stress in diabetes.

Methanol extract of PM heartwood (750 mg/kg/day) administered for 6 days reversed the level of superoxide dismutase and catalase in streptozotocin-induced diabetic rats [7]. Antioxidant status was normalized when alloxan-induced diabetic rats were treated with ethanol extracts of PM heartwood and bark (150 mg/kg/day) for 14 days [27]. The same study demonstrated an improvement in the concentration of superoxide dismutase, catalase,

glutathione peroxidase, glutathione reductase and reduced glutathione [27].

Methanolic extract of PM bark showed antioxidant effects on H_2O_2 induced oxidative stress in isolated frog heart muscle as demonstrated by the time taken for cardiac arrest to occur [58]. Aqueous extract of PM stem bark showed a strong antioxidant activity in vitro as shown by measurements of DPPH scavenging and ferric reducing ability [59]. The study also demonstrated the normalization of the antioxidant status (superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase) in the liver slices [59].

Level of reduced glutathione was found to be decreased in type 2 diabetes [6]. Insulin caused an increase in the reduced glutathione level of normal and type-2 diabetic erythrocytes. (-)-Epicatechin is a member of catechins a group of compounds widely known for their antioxidant effect. A remarkable increase in the glutathione content of normal and type-2 diabetic erythrocytes was observed with 1 mM and 10 mM (-)- epicatechin [6]. In diabetic-induced rats, pterostilbene (40 mg/kg for 6 weeks) increased the activity of superoxide dismutase, catalase, glutathione peroxidase and reduced glutathione [60].

4.3 Glycation Inhibitory Effects

Advanced glycation end products (AGEs) are produced as a result of non enzymatic glycation of molecules. AGEs are key players of causation of chronic diabetic complications. Persistent elevation of blood glucose existing in diabetes leads to formation of AGEs at an enhanced rate. A reduction of the level of early glycation product, glycosylated hemoglobin (HbA1c) was revealed with the administration of PM. However, it is not clear whether the decline seen was a direct effect or an indirect effect of the hypoglycaemic effects of PM. Ethanol extracts of PM heartwood and bark (150 mg/kg/day for 14 days) has significantly reduced HbA1c in alloxan-induced diabetic rats [27]. Methanol extract of PM heartwood (300 mg/ kg/ day for 7 and 14 days) lowered the HbA1c concentration by 14.4 and 22.6% respectively in diabetic rats [33]. PM (2-4 g/day) produced a 4% decline in HbA1c at 12 wks in type 2 diabetic patients [39]. Two recent *in vitro* studies conducted have demonstrated strong glycation inhibitory effects [30] and glycation induced cross-link inhibitory effects [31] of PM latex in the presence of high concentration of fructose. These in vitro studies found evidence for the possible beneficial effects of PM latex in reducing diabetic complications [30,31]. (-)-Epicatechin was able to break preformed glycated human serum albumin *in vitro* [61]. Furthermore (-)-epicatechin (50 and 100 mg/kg for two weeks) reduced AGE accumulation in the retinas of rats injected with AGEs [61].

4.4 Anti-cataract Effects

Diabetes increases the risk of developing cataract. An aqueous extract of PM bark (1 g/kg), aqueous extract of *Ocimum sanctum* leaves and alcoholic extract of *Trigonella foenum-graecum* seeds were tested in alloxan-induced diabetic rats that have developed cataract. The best anti-cataract effects were observed with PM in this study [62].

5. COMPOUNDS WITH ANTIDIABETIC PROPERTIES

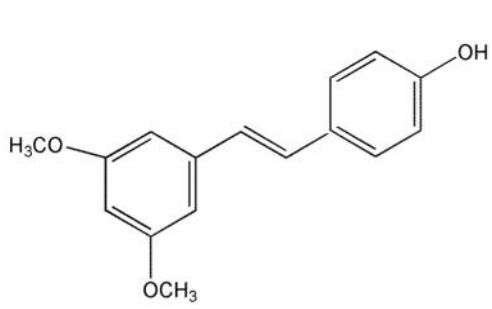
Several polyphenolics isolated from PM have showed antidiabetic effects. Pterostilbene, marsupsin, 7-O-α-L-rhamnopyranosyl-oxy-4′-methoxy-5-hydroxy isoflavone, marsuposide, pteroside, pterosupol, vijayoside, liquiritigenin and pterosupin isolated from PM heartwood and (-)-epicatechin isolated from PM bark are recognized as antidiabetic compounds (Table 1, Fig. 2). Concentration of pterostilbene was demonstrated to be several times higher than that of marsupsin [63]. A recovery of 17.5% epicatechin is evident in 50% methanol water extract of PM bark [64]. Furthermore, there is evidence for the presence of a high molecular weight antidiabetic compound (>10<30 kDa) in PM heartwood [20]. Accordingly, pterostilbene from heartwood and (-)-epicatechin from bark seem to be two major antidiabetic compounds of PM.

6. TOXICITY

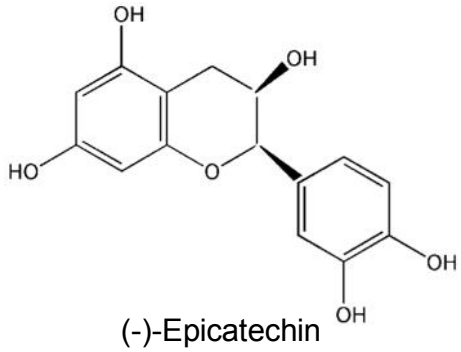
Commonly used herbal medicines which have been in use for thousands of years are less likely to cause significant toxic effects. There is scientific evidence to support the safety of PM heartwood, bark and pterostlibene demonstrating lack of hepatic and renal toxicity. Some studies have shown hepatoprotective effects of PM as well.

Evidence from a clinical trial revealed the lack of toxic effects in type 2 diabetic patients when a

dose of 2-4 g PM per day was given for 36 weeks [4]. The altered renal and hepatic function markers were normalized when ethanolic extract of PM heartwood (100 mg/kg) was given for 28 consecutive days to diabetic rats that were on a high fat diet [21]. Ethanol extract of PM heartwood (5, 50, 100 and 1000 mg/kg/day) did not show acute toxicity in alloxan-induced diabetic rats when administered using gastric intubations and observed for another 14 days [27]. Normalization of alanine transaminase, aspartate transaminase and alkaline phosphatase levels was observed in this study [27]. Methanol extract of PM heartwood did not

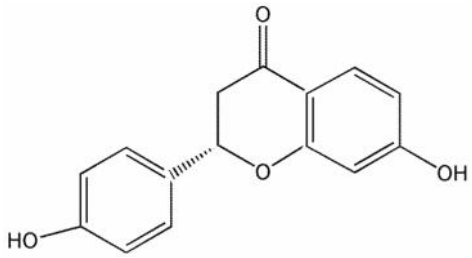


Pterostilbene

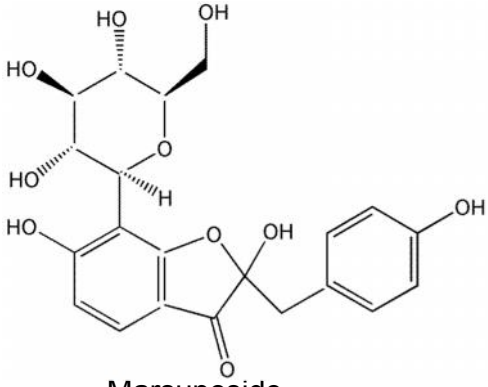


(-)-Epicatechin

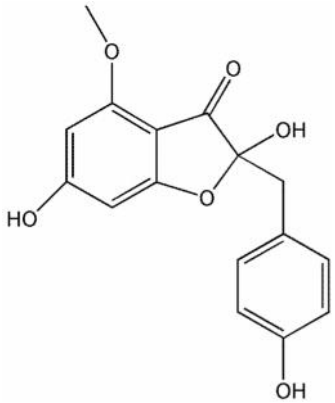
A



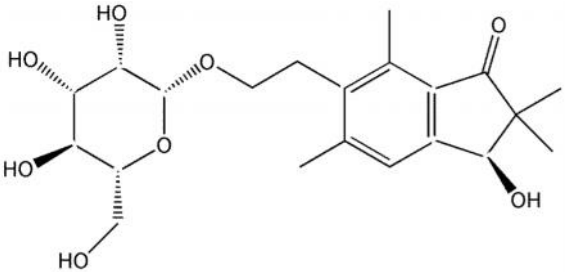
Liquiritigenin



Marsuposide



Marsupsin



Pteroside

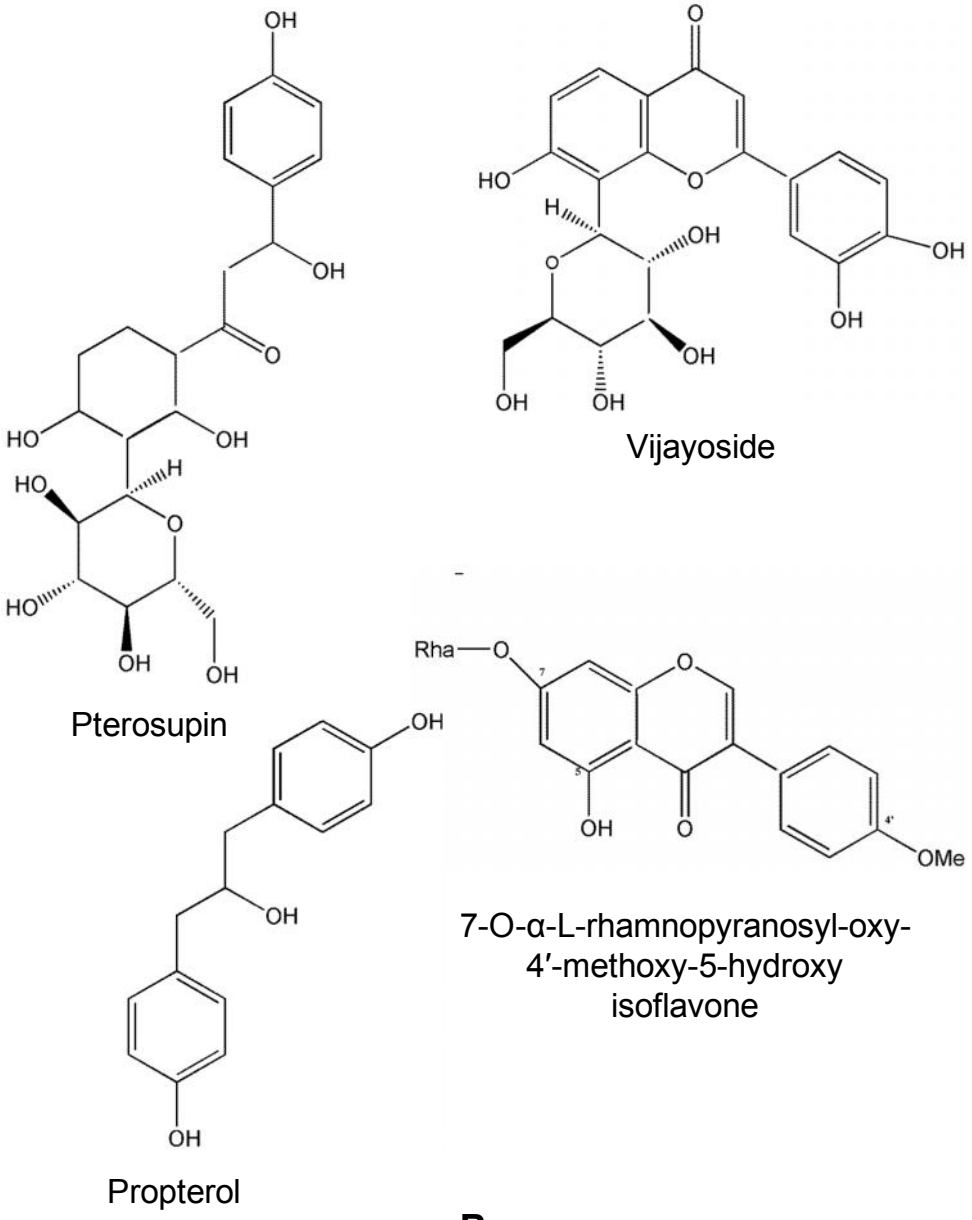


Fig. 2. Structures of antidiabetic compounds of PM

A: Two major compounds of PM with antidiabetic effects, B: Other antidiabetic compounds identified from PM. (Identity of propterol with pterosupol was revealed previously [65]. Structures were adapted from published data [66,67] except for 7-O-α-L-rhamnopyranosyl-oxy-4′-methoxy-5-hydroxy isoflavone)

show acute toxicity in mice after oral administration doses of 500, 1000, 2000, 4000 and 8000 mg/kg and no mortality was observed up to 7 day in mice [7]. Methanol and water extracts of heartwood had reversed the hepatotoxic effects of CCl_4 as shown by the normalization of serum bilirubin, transaminases and normal histology in liver [68]. Pterostlibene when given at a dose of 125 mg twice daily for 6-8 weeks to hypercholesterolaemic patients did not show signs of hepatic or renal toxicity [69].

Table 1. Antidiabetic compounds of PM heartwood and bark and their mechanisms

Source	Compound	Effect- mechanism
PM heartwood	Pterostilbene	PM Heartwood Hypoglycaemic [37,38]- Increase glucose oxidation [47], decrease gluconeogenesis [47], peroxisome proliferator activator receptor agonist [51], antidyslipidaemic [51], antioxidant [59]
	7-O-α-L-rhamnopyranosyl-oxy-4′-methoxy-5-hydroxy isoflavone	Hypoglycaemic- Increase glucose uptake [22], GLUT4 expression [22], peroxisome proliferator activator receptor expression [22]
	Marsuposide	Hypoglycaemic- Increase glucose uptake [21]
	Marsupsin	Hypoglycaemic [38]
	Pteroside	Hypoglycaemic- Increase glucose uptake [21]
	Pterosupol (Propterol) [65]	Hypoglycaemic- Increase glucose uptake [21]
	Vijayoside	Hypoglycaemic- Increase glucose uptake [21]
	Liquiritigenin	Antidyslipidaemic [54]
	Pterosupin	Antidyslipidaemic [54]
PM bark	(-)-Epicatechin	Hypoglycaemic [19]- β-cell regeneration [19], increase in insulin release [36], conversion of proinsulin to insulin [36], glucose uptake [44] and glycogen synthesis [44] Protective effects- antioxidant [6], antiglycation [60]

PM bark was also able to control the diabetes related increases in transaminases and alkaline phosphatase levels [29]. Methanol and aqueous extracts of PM stem bark (25 mg/kg/day for 14 days) showed a significant hepatoprotective activity against CCl_4 induced hepatotoxicity in rats with a more pronounced effect with the methanol extract [70]. The hepatic damage seen in streptozotocin-induced diabetic rats normalized with the treatment of PM stem bark methanol extract at a dose of 100 and 300 mg/Kg/day for 21 days, indicating hepatoprotective effects of PM [71].

7. CONCLUSION

Pterocarpus marsupium (*Gammalu* in Sinhala) heartwood and bark have been extensively used in the treatment of diabetes in many cultures for thousands of years. This review has focused on the scientific evidence available on antidiabetic effects of *P. marsupium* and is presented highlighting the existing evidence for antidiabetic effects under different cellular mechanisms. Existing evidence validates the use of *P. marsupium* to treat diabetes and demonstrated the hypoglycaemic effects, antidyslipidaemic effects, antioxidative effects and the safety of the *P. marsupium*. This review revealed that the investigations were focusing on the heartwood, bark and some compounds present in these two parts. It was identified that the scientific evidence on the antidiabetic effects of the latex of *P. marsupium* is meager even though it is a popular remedy used in Sri Lanka for diabetes. Hence it is necessary to scientifically validate the efficacy and the safety of the *P. marsupium* latex.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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