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REVIEW ARTICLE

Revisiting Bungur (*Lagerstroemia speciosa*) from Indonesia as an Antidiabetic Agent, Its Mode of Action, and Phylogenetic Position

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ABSTRACT

Worldwide, the diabetes epidemic is rapidly increasing and has become a growing health threat over the past few decades. The continuous investigation into the development of antidiabetic agents and treatments is crucial because current synthetic antidiabetic drugs cause adverse side effect and are often ineffective. Indonesia is blessed with a mega-biodiversity of medicinal plants. Having an abundance of medicinal plant species has caused several problems, like the adulteration of medicinal plants when used as herbal products, and serious overharvesting resulting in the disappearance of the plants from nature. The DNA barcoding technique is a promising tool to authenticate the identity and phylogenetic position of a medicinal plant. Using DNA barcoding, a close genetic relationship of Bungur from Riau, Sumatra to related taxa from other areas is confirmed; it represents *Lagerstroemia speciosa* (*Lythraceae*). Moreover, the active secondary metabolites of Bungur are summarized and most importantly, the mechanism of action as an antidiabetic agent is described. Some of them are well-known principles, and some are known as new mechanisms with the potential to be revisited. This report indicates that *L. speciosa* may have anti-diabetic properties that might be useful in therapy of diabetes. More research is needed to determine possible side effects, and to identify its relevant chemical components.

Key words: Antidiabetic, Bungur, *Lagerstroemia speciosa*, *Lythraceae*, Riau

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disease characterized by elevated blood glucose levels, known as hyperglycemia.[1] Comprehensive studies suggest that there are two types of diabetes, namely, type 1 diabetes in which the pancreas is not able to produce enough insulin, and type 2 diabetes when there is an insulin resistance or the body does not produce enough insulin. According to global preview, the diabetes epidemic has become a worldwide health threat. A 2015 report from the International Diabetes Federation indicated that 415 million people worldwide, or one in 11 adults, have diabetes, and this number will probably continue to rise to 642 million by 2040.[2] According to the same report, the Western Pacific area, including Indonesia, has the highest incidence of people with diabetes.[2] Currently, there are a number of antidiabetic drugs and treatments, such as alpha-glucosidase inhibitors, biguanides (metformin), meglitinides, thiazolidinediones (glitazones), incretin mimetics, dipeptidyl peptidase-4 inhibitors, sulfonylureas, and combination treatments. Some of them have various adverse side effects and are not fully effective in reducing blood glucose.

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Diabetes causes economic instability, especially for those who are living in developing countries due to the lack of access to medical services and health insurance. Moreover, people with diabetes are at a high risk of occurring other health problems, such as cardiovascular disease,[3] retinopathy,[4] nephropathy,[5] neuropathy,[6] and foot disorders.[7] In addition, improper treatment of diabetes can cause severe complications. Due to the various side effects of antidiabetic drugs, many scientists are currently developing alternative antidiabetic drugs from natural sources, such as medicinal plants which produce a high diversity of bioactive secondary metabolites.[8,9] Before the administration of nutraceuticals or antidiabetic drugs from natural sources, it is important to understand their mechanisms of action so that they work efficiently when compared to synthetic antidiabetic drugs.

Natural products are re-emerging as alternatives to pharmaceutical drugs due to their abundance and chemical diversity. Indonesian traditional medicine has been used since ancient times to treat several diseases, including diabetes. Currently, data mining, screening, and computer modeling are possible approaches for drug discovery, in addition to local wisdom of the traditional uses of medicinal plants. This review will explore the chemical diversity of the *Lagerstroemia* species (Lythraceae), which has a potential as anti-diabetic agents. The mechanism of action will be also described to raise awareness of possible side effects.

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MOLECULAR PHYLOGENY ANALYSIS OF *LAGERSTROEMIA* FROM RIAU-INDONESIA, KNOWN AS BUNGUR

The evolutionary history was inferred using the maximum likelihood method based on the General Time Reversible model.[10] The tree with the highest log likelihood (−1590,8817) is shown. The percentage of trees in which the associated taxa clustered together is shown next to the branches. Initial tree (s) for the heuristic search were obtained automatically by applying Neighbor-Join and BioNJ algorithms to a matrix of pair-wise distances estimated using the Maximum Composite Likelihood MCL approach, and then, selecting the topology with superior log-likelihood value. A discrete Gamma distribution was used to model evolutionary rate differences among sites (5 categories (+*G*, parameter = 0,4876)). The rate variation model allowed for some sites to be evolutionarily invariable ([+I], 28,8251% sites). The tree is drawn to scale, with branch lengths measured in the number of substitutions per site. The analysis involved 13 nucleotide sequences. Codon positions included were 1^{st} +2^{nd} +3^{rd}. There were a total of 593 positions in the final dataset. Evolutionary analyses were conducted in MEGA 7.[11]

Figure 1 shows the amplification of Internal Transcribed Species ITS sequences of *Lagerstroemia* for DNA barcoding and thus shows the genetic relationship with other *Lagerstroemia* species distributed outside Indonesia (our unpublished work). The phylogenetic analyses are based on a representative sampling of the genus Lagerstroemia, which includes 13 GenBank accessions. Another *Lytheraceae*, *Lawsonia inermis* serves as an outgroup for the phylogeny reconstruction. As shown in Figure 1, the phylogeny reconstruction reveals two major clades, supported with high bootstrap *P* values. *Lagerstroemia* from Riau clusters together with *L. speciosa* in a clade of *L. parviflora*, *L. indica*, and *L. villosa* as a sister group with high bootstrap support [Figure 1]. This is the first report showing that Bungur from Riau, Indonesia, represents *L. speciosa* and identical to *L. speciosa* that grows in other countries. Based on that, we can conclude that the other populations also have similar chemical components as Bungur. However, the chemical components between species that grow in different countries could vary due to chemotypes, climate and other geographic factors.

MORPHOLOGY AND TAXONOMY OF *LAGERSTROEMIA SPECIOSA*

- Kingdom: Plantae
- Subkingdom: Tracheobinata
- Superdivision: Spermatophyta
- Division: Magnoliophyta
- Class: Magnoliopsida
- Subclass: Rosidae
- Order: Myrtales
- Family: Lythraceae
- Genus: Lagerstroemia L
- Species: *Lagerstroemia speciosa* L.

L. speciosa is famous for its attractive and colorful flowers as shown in Figure 2. The origin of this plant is in South and Southeast Asia. It has several local names[12] as summarized in Table 1. *L. speciosa* can be categorized as a small-to-medium-sized deciduous or semi-deciduous shrub but can also include large trees that grow up to 40-45 m in height. The bole is fairly straight to crooked, has a diameter of 100–150 cm, and is branchless for up to 18 m. It is often fluted and sometimes has small buttresses. The simple leaf form is obovate, opposite, and distichous. The stipules are minute or absent. The bark surface is smooth or exhibits small, papery flakes with a color of grey-to-light fawn-brown in a mottled pattern. The inside bark is fibrous with a grey-fawn to yellow color, which turns to dirty mauve or purple after some exposure. The crown is usually bushy and broad.[12]

The flowers are found in an axillary or terminal panicle and are large, bell-shaped, and showy. The calyx has 6–9 lobes and is funnel or bell-shaped. It often has 6 petals inserted near the mouth of the calyx tube. The flowers have wrinkled petals and are white to pink or purple in color. There are many yellow stamens in several rows. The ovary is superior, with 3–6 locules, and many ovules in each cell. Each flower contains 1 style. The fruits are large woody capsules with a persistent calyx. The seeds have an apical wing. The plant can easily be found as an ornamental tree on roadsides or in gardens and parks.[13]

Table 1: Local names of *Lagerstroemia speciosa*[12]

Origin	Local name
India	Arjuna, Bondaro, Challa, Ajhar, Jarul, Varagogu, Moto-bhandaro
Indonesia	Bungur
Java (Indonesia)	Ketangi
Malaysia	Bongor biru
Thailand	Ta-Bak, Tabaek dam, Chuangmuu
Phillipines	Banaba
Burma	Gawkng-uchyamang
English speak countries	Queen's flower, Queen of flowers, Queen crape myrtle, Pride of India
Vietnam	b[awf]ng l[aw]ng n[uw][ows]c

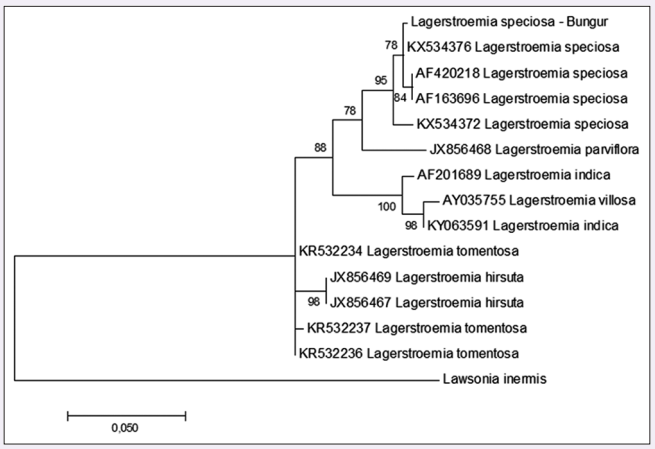

Figure 1: Molecular phylogenetic analysis of Bungur as compared to related *Lagerstroemia* species by maximum likelihood method

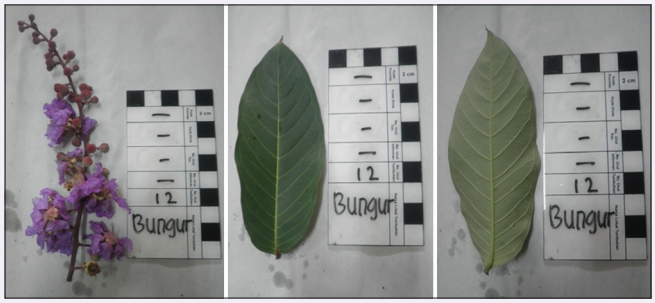

Figure 2: Morphological characters of *Lagerstroemia speciosa* grown in Riau, Sumatra (age of over 7 years old)

PHYTOCHEMISTRY OF *LAGERSTROEMIA*

Several secondary metabolites SM from *Lagerstroemia* with specific potential as antidiabetic drugs are summarized in Table 2 and Figure 3. Other SM from *L. speciosa* include the class of ellagic acids: ellagic acid, 3-*O*-methyl ellagic acid, 3,3'-di-*O*-methyl ellagic acid, 3,3', 4-tri-*O*-methyl ellagic acid; gallic acid, 4-hydroxybenzoic acid, 3-*O*-methyl protocatechuic acid, caffeic acid, p-coumaric acid, kaempferol, quercetin, isoquercetin, cyanidin 3-*O*-glucoside, virgatic acid, ursolic acid, β-sitosterol glucoside, valoneic acid dilactone, flosin A, dimeric ellagitannins: reginin B, reginin C, and reginin D.[14-16]

PHARMACOLOGY OF *LAGERSTROEMIA SPECIOSA*

As a traditional medicinal plant, all part of *L. speciosa* has been used in folk medicine as a remedy for several diseases. For instance, the leaves part is commonly used as a diuretic, decongestant, and antidiabetes. Whereas, the roots part are used for treating mouth ulcers, and the bark as a stimulant, a febrifuge, and for abdominal pains.[13] Several studies have also examined *L. speciosa* for their numerous pharmacological activities, such as antioxidant and anti-obesity properties and most importantly, for their antidiabetic properties.[22-50]

Antioxidant activity

Waterleaf extract of *L. speciosa* exhibits scavenging activity against free radicals which have been observed in several assay such as, DPPH, superoxide radicals, and lipid peroxidation inhibition.[22] *Lagerstroemia* with purple flowers possesses a higher antioxidant activity as compared to the *Lagerstroemia* with pink flowers.[13] Several studies demonstrated that the antioxidant activity of *L. speciosa* tea is comparable to green tea and superior to oolong and black tea (*Camellia sinensis*).[23]

The pathogenesis of DM involves oxidative stress. Therefore, antioxidants appear to be useful for therapy of diabetes, in its prevention and treatment of complication.[24-27] Many studies have shown that medicinal plants with anti-diabetic properties possess antioxidant activity. In the case of *Lagerstroemia*, it has been confirmed that plants (leaves or fruit) are more effective when compared to synthetic antioxidants and are able to decrease the risk of DM.[28-30] A growing body of evidence suggests that supplementation with a single antioxidant may not be beneficial and that diets high in antioxidants (medicinal plants containing antioxidant, fruits, and vegetables) are mostly useful. The possible reason is that the mixture of compounds possessing antioxidant activity is working in a synergistic fashion to improve therapeutic effect, while supplementation usually uses only one or two substances. Furthermore, the resorption of polar antioxidants can be facilitated by terpenoids (such as saponins) which are often present in plants. Because of synergistic effects plant extracts appear to have stronger antioxidant activity than a single supplement.[32-35] Moreover, if the antioxidant supplement is not stabilized by other compounds after scavenging free radicals, it can turn into a pro-oxidant and cause damage to cells.[31-34] Therefore, consumption of vegetable and fruits as well as medicinal plants with high antioxidant content is often recommended.[31-36]

The 1:1 herbal mixture comprised of *Allium sativum* and *L. speciosa* exhibit synergistic effect in scavenging reactive oxygen species (ROS) and also inhibiting the enzyme alpha-glucosidase, known as the enzyme that breaks down starch and disaccharides to glucose. The inhibitory activity of herbal mixture is greater as compared to its individual extracts. The synergistic effects may be due to the presence of the antioxidant-rich flavonoids, phenols, and tannins present in *L. speciosa* and *Allium sativum*.[37] Recently, Tiwary *et al.* also suggested that flower extract of *L. speciosa* not only exhibit strong antioxidant activity through the reduction in lipid peroxidation and restoration of catalase activity but also that flower extract do not affect growth and survivability of murine splenocytes and cancerous cell lines, MCF7 and HepG2. Flower of *L. speciosa* is also capable of reversing the damage induced by CCl_4-intoxication, though this finding needs further investigation.[38] Moreover, other findings suggest that *L. speciosa* that

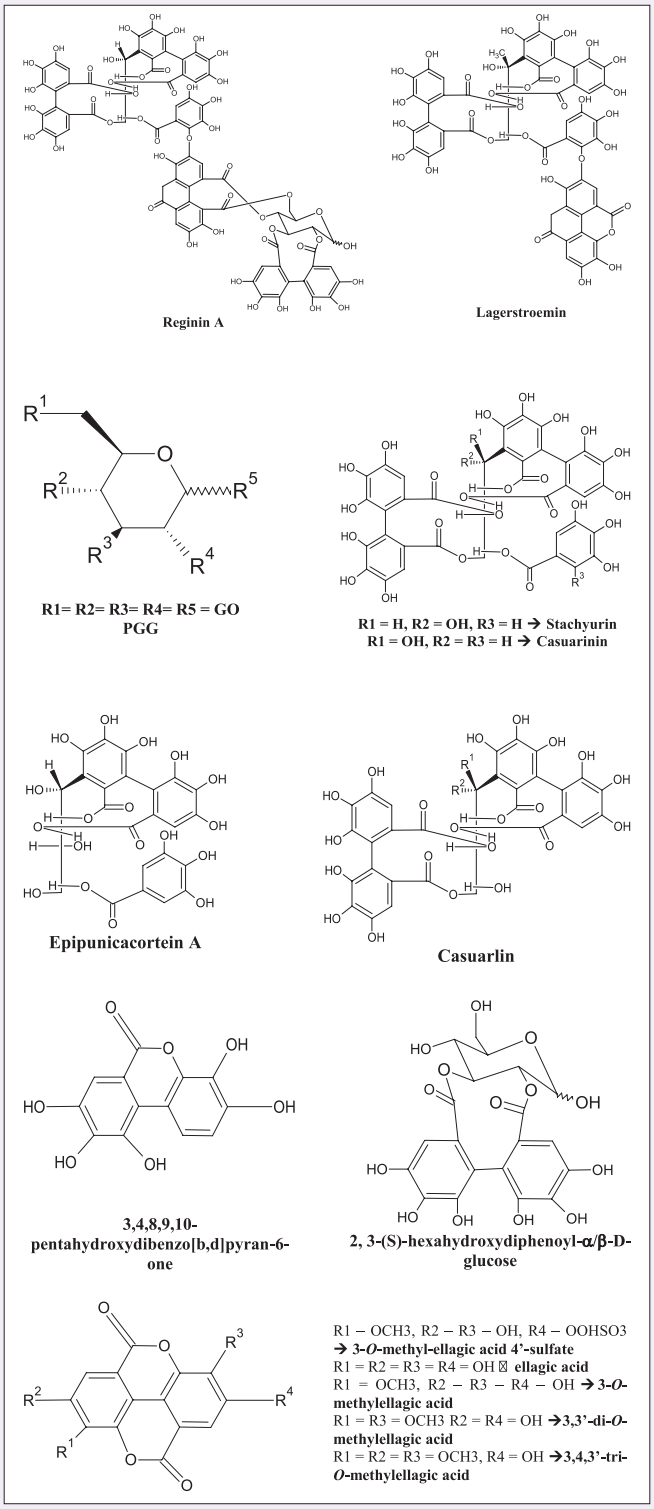

Figure 3: Chemical structures of secondary metabolites from *Lagerstroemia speciosa*

Table 2: Secondary metabolites from *Lagerstroemia* with potential antidiabetic properties

Compound	Mode of action	References
Flosin B	Stimulation of insulin-like glucose uptake; increased glucose uptake of adipocytes; and lowering blood glucose level	[11-15]
Reginin A Lagerstannins A Lagerstannins B Lagerstannins C	Increased glucose uptake of adipocytes and lowering blood glucose level	[11-13,15]
Lagerstroemin	Stimulation of insulin-like glucose uptake, inhibition of adipocyte differentiation	[14-15]
Casuarinin		[14]
Stachyurin Casuariin 2, 3-(S)-hexahydroxydiphenoyl-R/-D-glucose	Stimulation of insulin-like glucose uptake	[14]
Corosolic acid	Decrease of blood sugar levels within 60 min in human subjects, α-glucosidase inhibitory activity	[14,16-17]
3-O-methylellagic acid 3,3′-di-O-methylellagic acid 3,4,3′-tri-O-methylellagic acid 3,4,8,9,10-pentahydroxydibenzo[b, d] pyran-6-one	Inhibition of glucose transport	[14]

antidiabetic drugs belong to the hypoglycemic dipeptidyl peptidase–4 inhibitors (DPP-4i) class, and antineuropathic drugs induce prolonged activation of the nuclear factor E2–related factor 2 (NRF2)–mediated antioxidant response. This property results in the degradation of NRF2 and upregulated expression of the metastasis-associated proteins, cancer cell migration, and promotion of metastasis. This phenomenon has been observed in xenograft mouse models. Deactivation of NRF2 attenuated naturally occurring and DPP-4i–induced tumor metastasis, whereas NRF2 activation can accelerate metastasis. It was also observed in human liver cancer tissue samples that increasing NRF2 expression correlated with metastasis.[39] We do not know whether the antioxidant activity of *L. speciosa* activates NRF2 signaling. Further investigations are required.

Anti-obesity activity

Obesity is associated with the occurrence of low-level chronic inflammation, indicating a connection to metabolism and immunity.[40-41] Fat cells known as adipocytes vigorously secrete a mixture of hormones that are associated with obesity and diabetes. Suzuki *et al*. identified a significant reduction of body weight and parametrial adipose tissue weight in obese female KK-A^{Y} mice when fed a hot water extract of *L. speciosa* leaf. Triglycerides in the liver were also reduced, indicating the anti-obesity activity of *L. speciosa*. It was shown that the anti-obesity activity was associated with the antidiabetic activity.[42]

Antidiabetic activity

As an antidiabetic agent, *L. speciosa* has several modes of action. It has a hypoglycemic effect and acts as a glucose transport enhancer. It also exhibits insulin-mimetic (peptide analogs) activity, stimulates insulin receptors, activates GLUT4, and is an alpha-amylase and alpha-glucosidase inhibitor.[43-53]

The hypoglycemic effects

The effect of hypoglycemic from *L. speciosa* has been studied using hereditary diabetic mice (Type II, KK-AY/Ta JcI). The administration of a hot water extract of *L. speciosa* can suppress the elevation of blood plasma glucose level in noninsulin-dependent diabetic mice fed a cellulose diet as a control. It was also observed that water intake increased gradually in the group fed either cellulose diet or a partial fraction of hot water extract. However, the mice fed either a hot water extract or partial fraction of *L. speciosa* had a lower intake of water. Other parameters, such as serum insulin levels, urinary glucose excretion, and total plasma cholesterol also decreased in mice fed with water extract of *L. speciosa*. The hot water extract reduced the levels of plasma glucose and insulin and improved diabetic symptoms in noninsulin-dependent diabetic mice. In addition, the plant extract also reduced total plasma cholesterol levels.[43] Another study also revealed that *L. speciosa* possesses beneficial antihyperglycemic activity by controlling glucose levels in alloxan-induced diabetic mice.[44]

Glucose transport enhancers

The antidiabetic properties of *L. speciosa* have been widely investigated from *in vitro* to human studies. Kakuda *et al*., (1996) has identified the reduction of level of plasma glucose and insulin in hereditary type 2 diabetic mice. In addition, the plasma cholesterol levels in treated mice were significantly reduced, indicating that *L. speciosa* leaf extracts restrained or delayed cholesterol absorption in the intestine.[43] In another study, it was shown in 3T3-L1 adipocytes, the water extract of *L. speciosa* stimulated glucose uptake. In addition, the benefit of this plant is that unlike insulin, *L. speciosa* has the ability to reduce the side effects of weight gain in the treatment of type 2 diabetes because the plant extract does not regulate lipid biosynthesis in adipocytes, and the plant can inhibit the differentiation of adipocyte. Another study has revealed several active components such as ellagitannins, lagerstroemin, flosin B, and reginin that contribute to its antidiabetic activity. These components have been isolated from the leaf of the plant and have been shown to increase glucose uptake and lower glucose levels in rats. Lagerstroemin produced dose-dependent glucose transport activity from concentrations of 0.02-0.30 mM. This result suggests activity similar to insulin and was reported to decrease blood glucose levels in patients with diabetes.[18]

Several studies mention that compounds belong to the group of tannins are the key players of the antidiabetic and anti-obesity properties of *L. speciosa* because they exhibit insulin-like glucose transport stimulatory activity.[45] Among tannins, gallotannins are more efficient than ellagitannins in the activity as insulin receptor binding, insulin receptor activation, and glucose transport induction. Derivatives of methyl ellagic acid showed an inhibitory effect on glucose transport. Thus, it has been also confirmed by several studies that derivatives of methyl ellagic acid is one the active constituents responsible for its antidiabetic properties. Another mechanism of action is the blocking of the activity of NF-kB by TNF in dose- and time-dependent manners. This indicates that *L. speciosa* can inhibit the DNA-binding of NF-kB through the inhibition of diabetes-induced cardiomyocyte hypertrophy. Common to ellagitannins and gallotannins are a large number of phenolic hydroxyl groups, which can partly dissociate to negative charged O-groups. These

hydroxyl groups can form multiple hydrogen bonds and ionic bonds to all proteins and can thus modify their activity.[46,47] As Bungur is rich of such SM, the broad activity against several proteins involved in diabetes would be plausible.

Insulin-mimetic (peptide analogs) activity

Small components identified in *Lagerstroemia* as alpha- and beta-pentagalloylglucose (PGG) (α- and β-PGG) showed insulin-mimetic activities. α-PGG is more potent than β-PGG. α-PGG also stimulates translocation of GLUT4,[48] inhibits differentiation of preadipocytes, and targets insulin receptors.

Stimulation of insulin receptors

Stimulation of insulin receptors can cause phosphorylation of several proteins on tyrosine residues. Hattori *et al*.[49] found that a *L. speciosa* compound called lagerstroemin induces tyrosine-phosphorylation of IR (insulin receptor). This study suggested that lagerstroemin can act as an antidiabetic drug, such as metformin, by activating insulin receptors.

GLUT4 activation

GLUT4 is a protein in muscle and adipose cells. This protein transports glucose across the plasma membrane, allowing cells to gain energy and maintain healthy blood sugar levels. When the transporters are in the plasma membrane, glucose enters into the cytoplasm and is converted to glucose-6-phosphate (G6P) by hexokinase HK, thus promoting the glycogen synthesis. Physical exercise is widely known to maintain healthy glucose metabolism because it enhances GLUT 4 levels in muscle. Miura *et al*.(2004) reported that corosolic acid can cause GLUT4 translocation into the plasma membrane and induce uptake of glucose into the cells, lowering glucose levels in the blood.[50] The mechanism of action of corosolic acid is that it stimulates glucose uptake by enhancing insulin receptor phosphorylation, similar to the function of pioglitazone (Actos) and rosiglitazone (Avandia).[51]

Fructose-2,6-bisphosphate (F-2,6-BP) plays a role in liver gluconeogenesis and glycolysis, which effects glucose production. Corosolic acid acts as an inhibitor of gluconeogenesis by increasing the level of F-2,6-BP and inhibiting PKA activity in isolated hepatocytes. The activity on hepatic glucose metabolism may underlie the antidiabetic activity of corosolic acid.[52] Rosiglitazone (Avandia), pioglitazone (Actos), and metformin (Glucophage) can decrease glucose production, whereas *L. speciosa* does not. Thus, *L. speciosa* showed better efficacy compared to those drugs.

Alpha-amylase and alpha-glucosidase inhibitors

In one study, *L. speciosa* tea caused a 38% reduction of alpha-amylase activity. Another study suggested methanol and water extracts of *L. speciosa* reduces alpha-amylase and alpha-glucosidase activity. Both enzymes are involved in the digestion of carbohydrates, which increases glucose levels. Inhibiting these enzymes causes a delay of carbohydrate absorption, therefore decreasing blood sugar levels.[20,53]

CLINICAL STUDIES

Research suggests that Glucosol™ which contains standardized leaf extract of *L. speciosa* and 1% corosolic acid, demonstrated antidiabetic activity in a clinical study involving type 2 diabetes patients.[54] A blood glucose reduction was observed at a daily concentration of 32 mg and 48 mg of Glucosol™ administrated for 2 weeks. Gel capsule form had better bioavailability than hard gelatin capsules, and reductions of 30% and 20% of blood glucose levels, was observed, respectively.

In addition to its hypoglycemic effect (glucose transport enhancement, insulin mimetic activity, GLUT4 activation, α-amylase, and α-glucosidase inhibition), antioxidant activity was also observed in a number of animal models and clinical studies.[53] These antioxidants can exhibit antidiabetic activity. The active compounds of *L. speciosa*, such as corosolic acid and tannins, including lagerstroemin, act like insulin and lower blood sugar levels in the body. Corosolic acid is a triterpenoid glycoside with insulin-like activity, stimulating the cellular uptake of glucose.[55] It also activates the insulin receptor tyrosine kinase by inhibiting tyrosine phosphatase and lowering blood sugar.

Through several studies, *L. speciosa* extract has demonstrated the properties of antidiabetic drugs, such as lowering or maintain blood sugar levels through different mechanism by increasing insulin activity and GLUT4 translocation, improving hyperglycemia, and lowering liver enzymes, and triglycerides.

CONSIDERATION TO THE POSSIBLE SIDE EFFECT

All sulfonylurea drugs may cause hypoglycemia. The overuse of these drugs can lead to drug resistance over time and may require dose adjustments. The oral administration of these drugs is also associated with increased cardiovascular mortality as compared with diet treatment. Alpha-glucosidase inhibitors are better tolerated and do not cause hypoglycemia; however, they cause gastrointestinal problems such as flatulence, diarrhea, and abdominal pain. Metformin causes gastrointestinal (stomach and digestive) reactions.[53] Thiazolidinediones are associated with liver function problems.

Antioxidant therapy for DM needs to be investigated further because antioxidant agents influence several mechanisms of actions that can modulate molecular signaling. For instance, the results from clinical trials on the beneficial effects of Vitamin E and C have been disappointing.[31,33] A meta-analysis of clinical trials of Vitamin E therapy suggests that the use of high-dose Vitamin E (greater than 400 IU/day) may actually increase mortality.[31,32] Moreover, zinc and melatonin, in combination with metformin, have exhibited different results in reducing fasting glucose and glycated hemoglobin levels in patients with type 2 diabetes.[31-33] The differences are probably caused by a variety of factors, such as patient diversity and zinc speciation.

In relation to the antioxidant activity, the results from a study suggest that antidiabetic antioxidants that activate NRF2 signaling may require caution when administered to diabetic patients with cancer.[39] The question as to whether the antioxidant activity of *L. speciosa* activates NRF2 signaling needs further investigation.

CONCLUSION

Lagerstroemia, known as Bungur in Indonesia, belongs to *L. speciosa*, indicating that the chemical diversity and pharmacological activity of Bungur are probably similar to that of *L. speciosa* grown outside Indonesia. Extracts from Bungur, which are rich in ellagitannins and other polyphenols exhibit antioxidant and antidiabetic properties. The antidiabetic properties have been demonstrated in animal and a few human studies. Several modes of actions have been explored. These studies indicate that Bungur is an interesting candidate for the development of an antidiabetic remedy. More clinical studies are however required.

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Conflicts of interest

There are no conflicts of interest.

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