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Phytochemistry and Pharmacology of *Lagerstroemia speciosa*: A Natural Remedy for Diabetes

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Abstract
Lagerstroemia speciosa (Lythraceae) has several common names, which reflect its attractive and colourful pink or purple flowers. Native to South and Southeast Asia, *L. speciosa* is a common ornamental tree planted along roadsides, and in gardens and parks. The species has been traditionally used in folk medicine as remedy for illnesses and ailments, particularly for lowering blood sugar level, reducing body weight, and as a remedy for diabetes. The current knowledge on the phytochemistry and pharmacology of *L. speciosa* is reviewed since the species has been regarded as a natural product for anti-diabetic drugs. Triterpenes, tannins, ellagic acids, glycosides and flavones have been isolated from the leaves. Pharmacological properties of the species include antioxidant, antibacterial, antiviral, anti-inflammatory, antinociceptive, anti-diarrhoeal, cytotoxic, xanthine oxidase inhibition, anti-obesity and anti-fibrotic activities. A more exhaustive review is accorded to its anti-diabetic properties, which have generated much research involving in vitro, animal and human studies.

Keywords: Banaba, ellagitannins, corosolic acid, anti-diabetic

1. Introduction
Lagerstroemia speciosa (L.) Pers. (Lythraceae) has common names such as queen's flower, queen of flowers, crepe myrtle and pride of India [1], which reflect its attractive and colourful flowers. Synonyms are *L. reginae*, *L. flos-reginae* and *L. loudoni*. The species is locally known as arjuna in India, bungur in Malaysia and Indonesia, ta-bak in Thailand and banaba in the Philippines.

Native to South and Southeast Asia, *L. speciosa* is a semi-deciduous small- to medium-sized tree with fluted bole, small buttress and slightly flaky bark. Leaves are obovate, simple and opposite. Borne on large, axillary or terminal panicles, the attractive pink or purple flowers are clawed with wrinkled petals and yellow stamens (Figure 1). Fruits are large woody capsules with a persistent calyx and seeds have an apical wing. *L. speciosa* is a common ornamental tree planted along roadsides, and in gardens and parks.

Fig 1: *Lagerstroemia speciosa* with pink (left) and purple (right) flowers.

Traditionally, leaves, roots and bark of *L. speciosa* have been used in folk medicine as remedy for various illnesses and ailments [2]. Leaves serve as a diuretic and decongestant, and have been used to treat diabetes mellitus. Roots are applied for treating mouth ulcers. The bark is used as a stimulant, febrifuge, and for relief of abdominal pains.

In the Philippines, *L. speciosa* leaves are consumed as herbal tea for lowering blood sugar level and reducing body weight, while in India, they are used as a remedy for diabetes [3]. The edible flowers are used for garnishing dishes or as ingredients in salads, soups, desserts and drinks [4].

In recent years, herbal products such as Banabamin and Glucosol TM have been developed from *L. speciosa* for use as anti-diabetic drugs, with preliminary clinical trials conducted [5]. In general, herbal products need to be standardised, be of consistent quality and have their chemical constituents well defined, before reliable clinical trials can be conducted to derive consistent and maximum beneficial therapeutic effects [6].

2. Phytochemistry

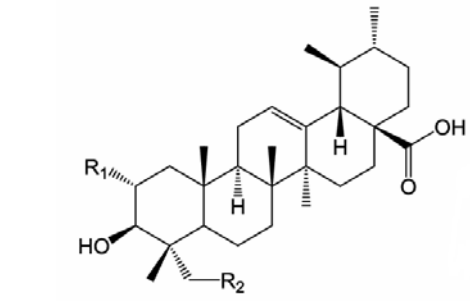
From the aqueous acetone leaf extract of *L. speciosa*, six new monomeric and dimeric ellagitannins (flosin A and B, and reginin A, B, C and D), and three new ellagitannins (lagerstannins A, B and C) were isolated and identified [7-9]. Further extraction of *L. speciosa* leaves with aqueous acetone led to the isolation of seven ellagitannins, ellagic acid, ellagic acid sulphate and four methyl ellagic acid derivatives, including corosolic acid, gallic acid, 4-hydroxybenzoic acid, 3-*O*-methyl protocatechuic acid, caffeic acid, *p*-coumaric acid, kaempferol, quercetin and isoquercitrin [10].

Ellagitannins are polyphenols that are abundant in some fruits, nuts and seeds such as pomegranates, raspberries, strawberries, walnuts and almonds [11]. They are derivatives of ellagic acid with biological properties such as antioxidant, anticancer, anti-atherosclerotic, anti-inflammatory, anti-hepatotoxic, antibacterial and anti-HIV replication.

Corosolic acid has been reported to decrease blood sugar levels within 60 min in human subjects [5]. The compound also exhibits antihyperlipidemic, antioxidant, antiinflammatory, antifungal, antiviral, antineoplastic and osteoblastic activities. The content of corosolic acid in *L. speciosa* leaves in Thailand ranged widely from 0.01−0.75% w/w, depending on the sampling location and season **[12]**. Corosolic acid content in *L. speciosa* indicated that the red leaves contained more corosolic acid than the green leaves and other plant parts such as petals, roots and seeds [13]. The leaf redness was due to cyanidin 3-*O*-glucoside, identified in the species for the first time. There was a strong correlation between the contents of corosolic acid and cyanidin 3-*O*-glucoside.

From leaves of *L. speciosa*, a new triterpenoid was isolated along with four known compounds of virgatic acid, corosolic acid, ursolic acid and β-sitosterol glucoside [14]. Both triterpenoids share similar skeleton structure aside for one hydroxyl methyl group. Using bioassay-guided fractionation, valoneic acid dilactone and ellagic acid was isolated from the aqueous *L. speciosa* leaf extract [15]. Six pentacyclic triterpenes (oleanolic acid, arjunolic acid, asiatic acid, maslinic acid, corosolic acid and 2, 3-hydroxyursolic acid) were isolated from *L. speciosa* leaves [16].

To date, more than 40 compounds including triterpenes, tannins, ellagic acids, glycosides and flavones have been identified from the leaves of *L. speciosa*. Recent isolation work reported four triterpenes (ursolic acid, corosolic acid, asiatic acid and alphitolic acid), eight ellagic acids, one coumarin and one neolignan [17]. Of the 14 compounds identified, four are new to the genus and family, and one new to the species. Some triterpenes and ellagic acids isolated from *L. speciosa* leaves are shown in Figure 2.

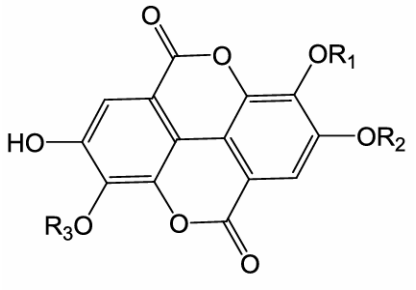


Triterpenes

R_1 = H, R_2 = H (ursolic acid)

R_1 = OH, R_2 = H (corosolic acid)

R_1 = OH, R_2 = OH (asiatic acid)



Ellagic acids

R_1 = H, R_2 = H, R_3 = H (ellagic acid)

R_1 = CH_3, R_2 = H, R_3 = H (3-*O*-methyl ellagic acid)

R_1 = CH_3, R_2 = H, R_3 = CH_3 (3,3'-di-*O*-methyl ellagic acid)

R_1 = CH_3, R_2 = CH_3, R_3 = CH_3 (3,3',4-tri-*O*-methyl ellagic acid)

Fig 2: Some triterpenes and ellagic acids isolated from leaves of *Lagerstroemia speciosa*.

3. Pharmacology

3.1 Antioxidant properties

With a tannin content of 37%, the hot water leaf extract of *L. speciosa* was found to have potent radical scavenging against DPPH and superoxide radicals, and lipid peroxidation inhibition [18]. The antioxidant activities of *L. speciosa* leaves extracted with four different solvents was studied by examining the superoxide and hydroxyl ion scavenging, and lipid peroxidation [19]. It was reported that ethyl acetate and ethanol extracts possessed stronger antioxidant activities than

methanol and water extracts. The radical scavenging activity of aqueous leaf extract of *L. speciosa* based on DPPH and hydrogen peroxide was found to be significantly stronger than rutin [20].

Based on total phenolic content (TPC), free radical scavenging (FRS), ferric reducing power (FRP) and ferrous ion chelating (FIC), aqueous methanol leaf extracts of *L. speciosa* trees with purple flowers had significantly higher values than those with pink flowers [21]. For flower extracts, a reversed trend was observed. Pink flowers had higher TPC, FRS and FRP values than purple flowers, but FIC values were comparable. Overall, flowers had stronger TPC, FRS and FRP than leaves, but not for FIC. The antioxidant activities of *L. speciosa* tea were comparable to green tea, and superior than oolong and black teas of *Camellia sinensis* (Table 1) [22, 23]. The FIC of *L. speciosa* tea surpassed all *C. sinensis* teas.

Table 1: Antioxidant properties of *Lagerstroemia speciosa* tea in comparison with those of green, oolong and black teas of *Camellia sinensis*.

Type of tea	TPC (mg GAE/100 g)	FRS (mg AA/100 g)	FRP (mg GAE/100 g)	FIC (mg/ml)
Green 1	14 120 ± 1810	25 000 ± 2780	14 300 ± 1100	1.8 ± 0.3
Green 2	11 370 ± 1480	18 460 ± 1740	8400 ± 1100	1.4 ± 0.1
L. speciosa	10 300 ± 260	17 890 ± 170	7840 ± 140	0.3 ± 0.0
Oolong 1	9090 ± 460	16 170 ± 2480	6900 ± 420	1.9 ± 0.2
Black 1	8490 ± 800	11 550 ± 1150	5300 ± 300	1.7 ± 0.1
Oolong 2	7500 ± 460	14 450 ± 3050	5900 ± 230	1.8 ± 0.5
Black 2	7410 ± 120	10 300 ± 560	5300 ± 300	1.0 ± 0.2

Data on phenolic content and antioxidant activity in dry weight are means ± standard deviations. Abbreviations and units: TPC = total phenolic content, FRS = free radical scavenging expressed as ascorbic acid equivalent antioxidant capacity (AEAC), FRP = ferric reducing power, FIC = ferrous ion chelating based on 50% chelating efficiency concentration (CEC_{50}), GAE = gallic acid equivalent and AA = ascorbic acid. Lower chelating values indicate stronger FIC ability

3.2 Antibacterial activity

The antibacterial activity of leaves of *L. speciosa* has been reported. *L. speciosa* leaf powder extracts were tested against *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Escherichia coli* with ampicillin as standard [24]. Based on the zone of inhibition, the water extract was more effective than the ethanol extract. The inhibitory efficacy of methanol extract of *L. speciosa* leaves was tested against 12 oral isolates of *Streptococcus mutans* using the agar well diffusion method [25]. Results showed significant inhibitory activity against cariogenic isolates with zones ranging from 0.0−0.9 cm, 0.8−2.1 cm and 1.0−2.6 cm for extract concentrations of 10, 25 and 50 mg/ml, respectively. Flowers of *L. speciosa* have also been reported to possess antibacterial activity. Methanol extract of flower was tested against *S. mutans* and *S. aureus* using the agar well diffusion assay [4]. The flower extract at 100 µl per well and 20 mg/ml concentration inhibited the bacteria with zones of inhibition ranging from 1.8−2.5 cm and 2.3−2.8 cm, respectively.

3.3 Antiviral activity

When tested for anti-human rhinovirus (HRV) activity in HeLa cells, orobol 7-*O*-D-glucoside (O7G) isolated from *L. speciosa* leaves showed broad-spectrum anti-HRV activity towards HRV of groups A and B [26]. The inhibitory concentration (IC_{50}) of O7G ranged from 0.58−8.80 µg/ml and the cytotoxic concentration (CC_{50}) was more than 100 µg/ml. The compound has great potentials to be developed into a potent anti-human rhinovirus agent.

3.4 Anti-inflammatory activity

The anti-inflammatory activity of ethyl acetate and ethanol leaf extracts of *L. speciosa* had been examined using the carrageenan-induced acute inflammation and formalin-induced chronic paw oedema assays [19]. For both the acute and chronic inflammatory models, the ethyl acetate extract significantly reduced inflammation in a dose-dependent manner, which was not observed in the ethanol extract.

3.5 Antinociceptive activity

At doses of 250 and 500 mg/kg body weight, the ethanol *L. speciosa* fruit extract produced 46% and 70% writhing inhibition in young Swiss-albino mice, respectively [27]. The antinociceptive activity of the extract was found to be comparable to the standard drug of diclofenac sodium, which had 84% inhibition at 25 mg/kg body weight.

3.6 Anti-diarrhoeal activity

The anti-diarrhoeal activity was tested on young Swiss-albino mice with castor oil-induced diarrhoea [27]. The ethanol fruit extract of *L. speciosa* at 500 mg/kg body weight delayed the diarrhoea from one to two hours. The anti-diarrhoeal activity was comparable to the standard drug of loperamide at 50 mg/kg of body weight with latent period of two hours. At 500 mg/kg body weight, the extract was also found to decrease the frequency of defecation.

3.7 Cytotoxic activity

Using the brine shrimp (*Artemia salina*) lethality bioassay, the ethanol fruit extract of *L. speciosa* showed prominent cytotoxic activity [27]. Lethal concentration (LC_{50}) was 60 µg/ml and LC_{90} was 100 µg/ml.

3.8 Xanthine oxidase inhibition

Valoneic acid dilactone isolated from aqueous leaf extract of *L. speciosa* was reported to have potent inhibitory effect on xanthine oxidase (XOD), suggesting its potential in preventing and treating hyperuricemia [15, 28]. The inhibitory effect was non-competitive and stronger than that of allopurinol, a clinical drug. XOD is the key enzyme in hyperuricemia as it catalyses the oxidation of hypoxanthine to xanthine and subsequently uric acid.

3.9 Anti-obesity activity
Significant reduction of body weight and parametrial adipose tissue weight was observed in obese female KK-A^Y mice when fed with a hot water *L. speciosa* leaf extract [29]. Although blood glucose levels and serum lipids were comparable between the control diet and test diet groups, the triglyceride content in the liver was reduced, confirming the anti-obesity activity of *L. speciosa*.

3.10 Anti-fibrotic activity
The effect of ethanol leaf extract of *L. speciosa* on male albino Wistar rats with liver fibrosis induced by carbon tetrachloride (CCl_4) was studied [30]. Liver fibrosis was induced twice weekly by administration of CCl_4 at a dose of 1 ml/kg body weight, mixed with an equal volume of corn oil. The extent of liver fibrosis was assessed by hydroxyproline content in the liver, level of aspartate transaminase, alanine transaminase, alkaline phosphatase and bilirubin in the serum, and by histological studies. Oral administration of the extract at 100 mg/kg body weight reduced the hydroxyproline content in the liver, serum enzyme levels and total bilirubin. The liver deranged by CCl_4 showed improvement following administration of the extract, confirming its potent anti-fibrotic effect.

3.11 Anti-diabetic properties
The anti-diabetic properties of *L. speciosa* leaves have generated much research interest, involving in vitro, animal and human studies. Among the earlier studies, the anti-diabetic effects of *L. speciosa* leaf extracts had reduced the levels of plasma glucose and insulin in hereditary type II diabetic mice [31]. One interesting finding was that the plasma cholesterol level in treated mice was significantly reduced, but not the plasma triglyceride level, suggesting that *L. speciosa* leaf extracts restrained or delayed cholesterol absorption in the intestine.

Another study reported the effectiveness of *L. speciosa* in the prevention and treatment of hyperglycaemia and obesity in type II diabetes **[32]**. The effect of hot water leaf extract was compared with that of insulin in stimulating glucose uptake in 3T3-L1 adipocytes. Results showed that the extract stimulated glucose uptake and inhibited adipocyte differentiation. Unlike insulin, which regulates both glucose transport and lipid biosynthesis in adipocytes, *L. speciosa* has the ability to reduce the side effect of weight gain in the treatment of type II diabetes. Ellagitannins, lagerstroemin, flosin B and reginin a isolated from aqueous acetone leaf extract of *L. speciosa* increased glucose uptake of rat adipocytes, and could be responsible for lowering the blood glucose level [33].

The anti-diabetic activity of a standardised leaf extract of *L. speciosa* (Glucosol™) with 1% corosolic acid was demonstrated in a randomized clinical trial involving Type II diabetics [34]. At daily doses of 32 mg and 48 mg of Glucosol™ for 2 weeks, subjects showed a significant reduction in the blood glucose levels. The extract in soft gel capsules had better bioavailability than that in hard gelatin capsules with declines of 30% and 20% of blood glucose levels, respectively.

The hypoglycemic activities of irradiated and non-irradiated ethanol leaf extracts of *L. speciosa* were tested on alloxan-treated diabetic mice [35]. Results showed that both types of extract at 25% and 50% had hypoglycemic effects comparable to that of insulin. The decline in blood glucose levels was evident 1.5 hours after administration.

A review of the anti-diabetic and anti-obesity properties of *L. speciosa* concluded that tannins are responsible for the insulin-like glucose transport stimulatory activity [36]. Gallotannins appeared to be more efficient than ellagitannins in insulin receptor binding, insulin receptor activation and glucose transport induction. Such activities were not observed in corosolic acid. Ellagitannins isolated from aqueous acetone leaf extract of *L. speciosa* were found to exhibit strong insulin-like glucose uptake and adipocyte differentiation inhibition in 3T3-L1 cells [10]. Derivatives of methyl ellagic acid had an inhibitory effect on glucose transport. The findings confirmed that these derivatives are among the active constituents responsible for the anti-diabetic properties of *L. speciosa*.

The effect of hot water leaf extract of *L. speciosa* on the activation of NF-kB as a key mediator of cardiomyocyte hypertrophy was investigated in rat cardiomyocyte H9c2 cells **[37]**. Results showed that the activation of NF-kB by TNF was completely blocked by the extract in a dose- and time-dependent manner. The study concluded that *L. speciosa* can inhibit DNA-binding of NF-kB, possibly through the inhibition of diabetes-induced cardiomyocyte hypertrophy.

Aqueous leaf extract of *L. speciosa* effectively decreased the blood glucose in streptozotocin (STZ)-induced diabetic mice two weeks after administration [38]. Further, the extract effectively inhibited lipid peroxidation and scavenged free radicals of superoxide, hydrogen peroxide and nitric oxide. At 150 mg/kg bodyweight, the extract reduced STZ-generated reactive intermediates and free radicals by regulating normal levels of enzymatic and non-enzymatic antioxidants.

The blood sugar lowering activity of *L. speciosa* leaf extracts has been demonstrated in a number of animal models and clinical studies **[3]**. Hypoglycemic effects of extracts have also been shown in clinical trials involving subjects with type II diabetes. Like anti-diabetic drugs, mechanisms of lowering blood glucose levels of extracts and corosolic acid involved glucose transport enhancement, insulin-mimetic (peptide analogs) activity, GLUT4 activation, and α-amylase and α-glucosidase inhibition.

4. Conclusion
Studies on the phytochemistry of *L. speciosa* have been focused on its leaves with more than 40 compounds of triterpenes, tannins, ellagic acids, glycosides and flavones identified. Pharmacological properties reported include antioxidant, antibacterial, antiviral, anti-inflammatory, antinociceptive, anti-diarrhoeal, cytotoxic, xanthine oxidase inhibition, anti-obesity and anti-fibrotic activities. The anti-diabetic properties of leaf extracts of *L. speciosa* and its compounds such as ellagitannins and corosolic acid have generated much research involving in vitro, animal and human studies. It is timely that the other plant parts of *L. speciosa* such as flowers and fruits be studied for comparison.

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