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*Review Article*

# An Overview of the Phenolic Constituents and Pharmacological Properties of Extracts and Compounds from *Lagerstroemia speciosa* Leaves

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ABSTRACT

*Lagerstroemia speciosa* is a semi-deciduous tree bearing attractive pink or purple flowers with wrinkled petals and yellow stamens. It is a common ornamental tree planted along roadsides, and in gardens and parks. Major types of compounds isolated from *L. speciosa* leaves include ellagitannins, triterpenes, terpenes, flavonoids, phenolic acids and sterols. Leaf extracts possess properties such as anti-diabetic, anti-cancer, anti-obesity, antioxidant, antibacterial, anti-inflammatory, analgesic, anti-hepatic steatosis, anti-ulcerative colitis, anti-cariogenic and anti-human immunodeficiency virus (anti-HIV). In this article, the phenolic constituents and pharmacological properties of extracts and bioactive compounds from *Lagerstroemia speciosa* leaves were reviewed. The phenolic compounds of *L. speciosa* leaves were compiled for the first time. Sources of information were from Google Scholar, PubMed, Science Direct, J-Stage and PubChem. The criteria used for the selection of articles were based on topics rather than on the period of coverage, although recent references were accorded higher priority. Among the ellagitannins, lagerstroemin possesses anti-diabetic properties, valoneic acid dilactone displays potent inhibitory effect on xanthine oxidase and ellagic acid inhibits the growth of HIV and human rhinoviruses (HRVs). Among the triterpenes, corosolic acid (CA) has anti-diabetic, anti-cancer, hepatoprotective and osteoblast differentiation properties. In conclusion, the anti-diabetic properties of ellagitannins and CA, in comparison with gallotannins, are worthy of further studies. The development of anti-diabetic drugs from *L. speciosa* leaves presents promising prospects for commercialization following clinical trials. Other topics worthy of further research include the toxicity, pharmacokinetics and metabolism of *L. speciosa*. The bioactivity of compounds and their structure-activity relationships need more in-depth studies.

***Keywords***: Ellagitannins, Gallotannins, Lagerstroemin, Ellagic Acid, Corosolic Acid.

## Introduction

*Lagerstroemia* is a genus of the family Lythraceae and consists of ~60 tropical and sub-tropical tree species, distributed from South to East Asia and from Southeast Asia to North Australia. Species are deciduous or semi-deciduous, small to medium-sized trees, and have boles that are often fluted with smooth or papery bark. Leaves are simple and opposite. Flowers are large and showy with clawed and wrinkled petals that are pink or purple in color. Some *Lagerstroemia* species such as *L. speciosa*, *L. floribunda* and *L. indica* are commonly planted as ornamental trees in gardens and along roadsides.[1,2] The phenolic constituents reported in the leaves of *Lagerstroemia* species include ellagitannins, triterpenes, flavonoids and phenolic acids.[3,4] Tannins are a major group of plant polyphenols that have attracted a lot of attention because of their multi-functional properties, beneficial to human health.[5] They are divided into two main groups, namely, hydrolysable and condensed tannins. Hydrolysable tannins comprise mainly of ellagitannins.

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Ellagitannins are a complex class of polyphenols characterized by having one or more hexahydroxydiphenoyl (HHDP) moieties esterified to a glucose core.[6] In *Lagerstroemia* species, ellagitannins are of the *C*-glycosidic and oligomer types.[5] Triterpenes are a group of terpenes, often having pentacyclic or tetracyclic structures. Pentacyclic triterpenes, with five isoprene units, can be classified into lupane, oleanane and ursane types.[7,8] Flavonoids are the largest family of phenolic metabolites, found in almost all herbs, fruits and vegetables.[9,10] Flavonoids consist of two benzene rings that are joined by a heterocyclic pyran ring forming the benzo-pyrone (C6–C3–C6) moiety. They are divided into classes such as flavones, flavonols, flavanones and flavanols.[11–13] Phenolic acids are phenolic compounds having one carboxylic acid functionality with hydroxycinnamic acids (C6–C3) and hydroxybenzoic acids (C6–C1) as the two main groups.[14] In this overview, the phenolic constituents and pharmacological properties of extracts and bioactive compounds from the leaves of *Lagerstroemia speciosa* were reviewed. The phenolic compounds of *L. speciosa* leaves were compiled for the first time. Highlighted under pharmacological properties were the anti-diabetic effects and mechanisms of leaf extracts and bioactive compounds.

## Methodology

Sources of information were from Google Scholar, PubMed, Science Direct, J-Stage, and PubChem. The criteria used for the selection of articles were based on topics rather than on the period of coverage, although recent references were accorded higher priority.

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## Results

*Botany and Uses*

*Lagerstroemia speciosa* (L.) Pers. (synonyms: *Lagerstroemia flos-reginae*, *L. reginae* and *L. major*) of the family Lythraceae, has common names such as Queen's Flower, Queen of Flowers, Crepe Myrtle, and Pride of India, that reflect its attractive and colorful flowers.[15] The species is locally known as Arjuna in India, Bungur in Malaysia and Indonesia, Tabak 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 simple, opposite, broadly ovate to oblong, and somewhat leathery, with prominent abaxial veins.[15] Young leaves are glossy red, before gradually becoming green, and old leaves turn orange-red before shedding (Figure 1). Borne on large, axillary or terminal panicles, the attractive pink or purple flowers of *L. speciosa* 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. The species is a common ornamental tree planted along roadsides, and in gardens and parks.[15]

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.[16] In recent years, herbal products such as Banabamin and Glucosol™ have been developed from leaves of *L. speciosa* for use as anti-diabetic drugs, with preliminary clinical trials conducted.[17]

*Phenolic Constituents*

From the leaves of *L. speciosa*, ellagitannins (29), triterpenes (10), terpenes (7), flavonoids (11), phenolic acids (7), sterols (5), anthocyanins (3), coumarin (1) and neolignan (1) have been isolated and identified (Table 1).

Among the ellagitannins, methyl ellagic acid derivatives are fairly common (Table 1). They include 3-*O*-methyl ellagic acid, 3,3′-di-*O*-methyl ellagic acid, 3,3′,4-tri-*O*-methylellagic acid, 3′-*O*-methyl-3,4-methylenedioxy ellagic acid, 3,4,3′-tri-*O*-methyl flavellagic acid, 3,4,3′,4′-tetra-*O*-methyl flavellagic acid and 3′,4′-di-*O*-methyl-3,4-methylenedioxy flavellagic acid (Figure 2). Flavellagic acid is an ellagic acid derivative, with a hydroxyl group substituent at C50 of ellagic acid, but the compound has never been isolated from *Lagerstroemia* species.[21]

**Figure 1:** Mature Leaves (top left), Old Leaves (bottom left), Purple Flowers (top right) and Pink Flowers (bottom right) of *Lagerstroemia speciosa*

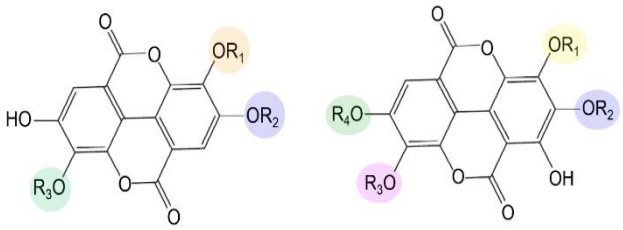


**Figure 2** Chemical Structures of Ellagic Acid, Flavellagic acid and some Derivatives

Ellagic acid ($R_1$ = H, $R_2$ = H, $R_3$= H), 3-*O*-methyl ellagic acid ($R_1$ = $CH_3$, $R_2$ = H, $R_3$= H), 3,3′-di-*O*-methyl ellagic acid ($R_1$ = $CH_3$, $R_2$ = H, $R_3$= $CH_3$), 3,3′,4-tri-*O*-methyl ellagic acid ($R_1$ = $CH_3$, $R_2$ = $CH_3$, $R_3$= $CH_3$) (left); flavellagic acid ($R_1$ = H, $R_2$ = H, $R_3$ = H, $R_4$ = H), 3,4,3′-tri-*O*-methyl flavellagic acid ($R_1$ = $CH_3$, $R_2$ = $CH_3$, $R_3$ = $CH_3$, $R_4$ = H), 3,4,3′,4′-tetra-*O*-methyl flavellagic acid ($R_1$ = $CH_3$, $R_2$ = $CH_3$, $R_3$ = $CH_3$, $R_4$ = $CH_3$) (right).

**Table 1:** Phenolic Constituents of Leaves of *Lagerstroemia speciosa*

| No. | Compound type | Compound name | Reference |
|---|---|---|---|
| 1 | Ellagitannins | Banasulin | 18 |
| 2 | | Brevifolin carboxylic acid | 19 |
| 3 | | Castalagin | 19 |
| 4 | | Casuariin | 18–20 |
| 5 | | Casuarinin | 18–20 |
| 6 | | 5-Desgalloyl stachyurin | 19 |
| 7 | | Ellagic acid | 18,20–23 |
| 8 | | Epipunicacortein A | 18,20 |
| 9 | | Flosins A & B | 18−20,24,25 |
| 10 | | Gentisic acid 5-*O*-*β*-glucopyranoside | 19 |
| 11 | | 2,3-(*S*)-Hexahydroxydiphenoyl-α/*β*-D-glucose | 18,20 |
| 12 | | Lagerstannins A–C | 22,26 |
| 13 | | Lagerstroemin | 18–20,24,25,27 |
| 14 | | 3-*O*-Methyl ellagic acid | 18,20,21,28,29 |
| 15 | | 3,3′-di-*O*-Methyl ellagic acid | 18,20,21,29 |
| 16 | | 3,4,3′-tri-*O*-Methyl ellagic acid | 18,20,21 |
| 17 | | 3-*O*-Methyl ellagic acid 4′-sulfate | 18,20,28 |

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|---|---|---|---|
| 18 | | 3′-*O*-Methyl-3,4-methylenedioxy ellagic acid * | 21 |
| 19 | | 3′,4′-di-*O*-Methyl-3,4-methylenedioxy flavellagic acid + | 21 |
| 20 | | 3,4,3′,4′-tetra-*O*-Methyl flavellagic acid + | 21 |
| 21 | | 3,4,3′-tri-*O*-Methyl flavellagic acid + | 21 |
| 22 | | 3,4,8,9,10-Pentahydroxydibenzopyran-6-one | 18,20 |
| 23 | | Penduculagin | 19 |
| 24 | | Punicacortein A | 19 |
| 25 | | Reginins A–D | 19,24,25 |
| 26 | | Stachyurin | 18–20,24 |
| 27 | | Valoneic acid | 19 |
| 28 | | Valoneic acid dilactone | 23,30 |
| 29 | | Vescalagin | 19 |
| 30 | Triterpenes | Alphitolic acid | 21 |
| 31 | | Arjunolic acid | 31 |
| 32 | | Asiatic acid | 21,31,32 |
| 33 | | orosolic acid | 18,20,21,31–34 |
| 34 | | 3*β*,23-Dihydroxy-1-oxo-olean-12-en-28-oic acid ● | 34 |
| 35 | | 23-Hydroxyursolic acid | 31 |
| 36 | | Maslinic acid | 31 |
| 37 | | Oleanolic acid | 31 |
| 38 | | Ursolic acid | 21,34 |
| 39 | | Virgatic acid | 34 |
| 40 | Terpenes | Cycloeucalenol acetate | 35 |
| 41 | | Lageracetal | 36 |
| 42 | | Largerenol acetate | 35 |
| 43 | | 24-Methylenecycloartanol acetate | 35 |
| 44 | | 31-Norlargerenol acetate ● | 35 |
| 45 | | Tinotufolins C & D | 35 |
| 46 | Flavonoids | 1-*O*-Benzyl-6-*O*-*E*-caffeoyl-*β*-D-glucopyranoside ● | 28 |
| 47 | | Benzyl-6'-*O*-galloyl-*β*-D-glucopyranoside ○ | 28 |
| 48 | | 1-*O*-*E*-Caffeoyl-*β*-D-glucopyranoside ○ | 28 |
| 49 | | 1,6-di-*O*-*E*-Caffeoyl-*β*-D-glucopyranoside ○ | 28 |
| 50 | | Dihydrosyringin ○ | 28 |
| 51 | | 1-*O*-Guaiacylglycerol-(6-*O*-*E*-caffeoyl)-*β*-D-glucopyranoside ● | 28 |
| 52 | | Isoquercitrin | 20 |
| 53 | | Kaempferol | 20 |
| 54 | | Quercetin | 18,20 |
| 55 | | Quercetin-3-*O*-(6"-*O*-*E*-caffeoyl)-*β*-D-galactopyranoside ○ | 28 |
| 56 | | Quercetin-3-*O*-*β*-D-galactopyranoside ○ | 28 |
| 57 | Phenolic acids | Caffeic acid | 20 |
| 58 | | Chlorogenic acid (3-*O*-Caffeoylquinic acid) | 19,28 |
| 59 | | *p*-Coumaric acid | 20 |
| 60 | | Cryptochlorogenic acid (4-*O*-Caffeoylquinic acid) ○ | 28 |
| 61 | | Gallic acid | 20 |
| 62 | | 4-Hydroxybenzoic acid | 20 |
| 63 | | 3-*O*-Methyl protocatechuic acid | 20 |
| 64 | Sterols | Campesterol | 22 |

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|---|---|---|---|
| 65 | | *β*-Sitosterol | 22,32,35 |
| 66 | | *β*-Sitosterol acetate | 35 |
| 67 | | *β*-Sitosterolglucoside | 34 |
| 68 | | Stigmasterol | 22 |
| 69 | Anthocyanins | Cyanidin 3-*O*-glucoside | 37 |
| 70 | | Malvidin 3-*O*-glucoside | 37 |
| 71 | | Malvidin 3,5-di-*O*-glucoside | 37 |
| 72 | Coumarin | 6,7-Dihydroxycoumarin +* | 21 |
| 73 | Neolignan | Dihydrodehydrodiconiferyl alcohol 9′-*O*-sulfate +* | 21 |

● New to science, + new to the family, * new to the genus, ○ new to the species

Studies on the phenolic constituents of leaves of *L. speciosa* have isolated and identified compounds that are new to science, new to the family, new to the genus, and new to the species (Table 1). New to science include 1-*O*-benzyl-6-*O*-*E*-caffeoyl-*β*-D-glucopyranoside,[28] 1-*O*-guaiacylglycerol-(6-*O*-*E*-caffeoyl)-*β*-D-glucopyranoside,[28] 3*β*,23-dihydroxy-1-oxo-olean-12-en-28-oic acid[34] and 31-norlargerenol acetate.[35] 3′-*O*-Methyl-3,4-methylenedioxy ellagic acid, 3′,4′-di-*O*-methyl-3,4-methylenedioxy flavellagic acid, 3,4,3′,4′-tetra-*O*-methyl flavellagic acid and 3,4,3′-tri-*O*-methyl flavellagic acid are new to the family.[21] New to the genus are 3′-*O*-methyl-3,4-methylenedioxy ellagic acid and dihydrodehydrodiconiferyl alcohol 9′-*O*-sulfate.[21] Novel to the genus and family are dihydrodehydrodiconiferyl alcohol 9′-*O*-sulfate and 6,7-dihydroxycoumarin.[21] Quercetin-3-*O*-(6"-*O*-*E*-caffeoyl)-*β*-D-galactopyranoside, quercetin-3-*O*-*β*-D-galactopyranoside,1,6-di-*O*-*E*-caffeoyl-*β*-D-glucopyranoside, 1-*O*-*E*-caffeoyl-*β*-D-glucopyranoside, benzyl-6'-*O*-galloyl-*β*-D-glucopyranoside, cryptochlorogenic acid and dihydrosyringin are new to the species.[28]

In Table 1, compounds that are most often isolated from leaves of *L. speciosa* are ellagic acid, lagerstroemin, 3-*O*-methyl ellagic acid and corosolic acid (CA). Lagerstroemin is an ellagitannin and has a chemical structure similar to flosin B with a HHDP group at C4 and at C6.[19,27] CA or 2α-hydroxyursolic acid is an ursane-type pentacyclic triterpene with a molecular formula of $C_{30}H_{48}O_4$ and molecular weight of 473 g/mol.[38,39] The 30-carbon skeleton comprises five six-membered rings (A−E). It has an –OH group at C3 and a –COOH group at C27 (Figure 3). Structurally, CA is similar to ursolic acid, asiatic acid and 23-hydroxyursolic acid, all of which are found in leaves of *L. speciosa* (Table 1). Ursolic acid has an –OH group at C3 and a –COOH group at C27.[40] The difference between CA and ursolic acid is R = OH and R = H at C2, respectively (Figure 3).

Phytochemical studies showed that the aqueous leaf extract of *L. speciosa* contained total phenol (0.03%), ellagitannin (0.01%), gallotannin (0.02%), and condensed tannin (0.02%).[41] Earlier, freeze-dried leaves of *L. speciosa* have been reported to contain 36.8% of tannin.[42]

Several studies have reported on the content of CA in *L. speciosa* leaves. In Thailand, the content ranged from 0.01−0.75% w/w.[43] In India, the CA content in the leaves of *L. speciosa* was found to be 12.9 µg/mg.[44] Higher content of CA in *L. speciosa* leaves was reported in old red leaves than mature green leaves (Figure 1), and other plant parts such as petals, roots, and seeds.[37] Red leaves contain 58.5 µg/g of CA or almost two times that of green leaves. Leaf redness was due to anthocyanin (cyanidin 3-*O*-glucoside), identified in the species for the first time. There was a strong correlation between the content of CA and cyanidin 3-*O*-glucoside. Two other anthocyanins isolated from the leaves of *L. speciosa* were malvidin 3-*O*-glucoside and malvidin 3,5-di-*O*-glucoside.[37] In the Western Ghat of India, the content of CA in *L. speciosa* was reported to be the highest in mature leaves (0.85%) but made no mention of leaf age or color.[45] The highest extraction yield of CA (9.4 mg/g) was obtained by batch extraction and three phase partitioning.[46]

*Pharmacological properties of leaf extracts*

The dominant bioactivity of leaf extracts of *L. speciosa* is anti-diabetic property (Table 2). Other pharmacological properties include anti-cancer, anti-obesity, antioxidant, antibacterial, anti-inflammatory, analgesic, anti-hepatic steatosis, anti-ulcerative colitis and anti-cariogenic effects.

A randomized, double-blind, and placebo-controlled clinical trial, conducted from 2015−2017 at the University of Guadalajara in Mexico, yielded clinical evidence on the anti-diabetic effects of banaba leaf extract.[72] Twelve patients received banaba extract in capsules (500 mg) twice a day for 12 weeks. The remaining 12 patients received placebo at the same dosage. Results showed that banaba administration resulted in the remission of metabolic syndrome, and a significant decrease in systolic blood pressure, fasting plasma glucose, triglyceride, very low-density lipoprotein, area under the curve of insulin and total insulin secretion.[72]

*Pharmacological Properties of Leaf Compounds*

*Ellagitannins*

Ellagitannins isolated from the leaves of *L. speciosa* exhibited strong activities in stimulating insulin-like glucose uptake (lagerstroemin, flosin B, stachyurin, casuarinin, casuariin and 2,3-(*S*)-hexahydroxydiphenoyl-α/*β*-D-glucose), and in inhibiting adipocyte differentiation (lagerstroemin and casuarinin) in 3T3-L1 cells.[20] In addition, ellagic acid derivatives (3-*O*-methylellagic acid, 3,3′-di-*O*-methylellagic acid, 3,4,3′-tri-*O*-methylellagicacid and 3,4,8,9,10-pentahydroxydibenzopyran-6-one showed inhibitory effect using the glucose transport assay. Lagerstroemin increased glucose transport in rat adipocytes at $IC_{50}$ of 0.08 mM.[25] Other ellagitannins with the ability to increase glucose transport are flosin B and reginin A. Lagerstroemin activated insulin receptors and its insulin-like mechanism differed from that of insulin.[27]

Other bioactive ellagitannins are valoneic acid dilactone and ellagic acid (Figure 4). Valoneic acid dilactone displayed potent inhibitory effect on xanthine oxidase, suggesting its potential for the prevention and treatment of hyperuricemia.[23] Ellagic acid inhibited human immunodeficiency virus (HIV) infection through suppression of protease activity,[71]and inhibited the growth of human rhinoviruses (HRVs) with $IC_{50}$ values of 29–38 µg/mL.[73]

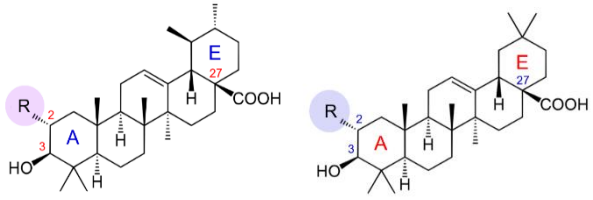


**Figure 3:** Comparative Chemical Structures of Corosolic Acid (R = OH) and Ursolic Acid (R = H) (left), and of Oleanolic Acid (R = H) and Masnilic Acid (R = OH) (right)

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**Table 2:** Effects and Mechanisms of Bioactivities of Leaf Extracts of *Lagerstroemia speciosa*

| Bioactivity | Effect and Mechanism | Reference |
|---|---|---|
| Anti-diabetic | Extracts produced by different manufacturing processes exerted significantly different anti-diabetic effects on alloxan-induced diabetic mice. | 18 |
| | Hot-water extract lowered plasma glucose in KK-$A^Y$ hereditary diabetic mice. | 47 |
| | Hot-water extract had insulin-like glucose uptake stimulation activity in 3T3-L1 cells. | 48 |
| | In a clinical trial, a standardized extract (Glucose$^{TM}$) lowered the blood sugar of subjects, with soft gel capsules more effective than hard gelatin capsules. | 49 |
| | Aqueous extract exhibited anti-diabetic activity *via* hypoglycemic and hypolipidemic effects in alloxan-induced diabetic mice. | 41 |
| | When tested with alloxan-treated diabetic mice, the effects of non-irradiated and irradiated extracts (25% and 50%, respectively) were comparable to the hypoglycemic effect of insulin. | 50 |
| | Non-diabetic subjects administered with an extract standardized to 18% corosolic acid showed a decrease in fasting as well as postprandial blood glucose levels after 2 weeks. | 51,52 |
| | Hot-water extract had hypoglycemic effect on STZ-induced diabetic rats. | 53,54 |
| | Hot-water extract had hypoglycemic effect on alloxan-induced diabetic mice. | 55 |
| | Aqueous extract inhibited DNA-binding of NF-κB and this may explain its possible inhibition of diabetes-induced caridomyocyte hypertrophy. | 56 |
| | Aqueous extract decreased the level of blood glucose in STZ-induced diabetic mice. | 57 |
| | Extract ameliorated oxidative stress in rats with diabetic nephropathy by inhibiting AGEs formation. | 58 |
| Anti-cancer | Ethanol extract reduced lung tumorigenesis *via* alleviation of oxidative stress, inflammation and apoptosis. | 59 |
| | Ethanol extract triggered apoptosis and cell cycle arrest *via* intrinsic mitochondrial pathway in HepG2 cells. | 60,61 |
| Anti-obesity | Hot-water extract stimulated insulin-like glucose uptake and adipocyte differentiation inhibitory activity in 3T3-L1 cells. | 48 |
| | Hot-water extract reduced body weight, adipose tissue weight and total hepatic lipid content in female KK-$A^Y$ mice | 62 |
| Antioxidant | Aqueous methanol extracts of trees with purple flowers had significantly higher antioxidant values than those of trees with pink flowers. | 4 |
| | Out of the antioxidant properties of 12 types of herbal teas, banaba tea ranked number one. | 63 |
| | Antioxidant properties of aqueous methanol extracts of leaves dried using thermal methods were generally lower than those of fresh leaves, with the exception of freeze-drying. | 64 |
| Antibacterial | Aqueous and ethanol extracts inhibited Gram-positive and Gram-negative bacteria. | 65 |
| Anti-inflammatory | Ethanol extract attenuated dapsone-induced liver inflammation in rats. | 44 |
| | Ethyl acetate extract exerted significant anti-inflammatory effects using the paw edema of mice. | 66 |
| | Aqueous ethanol extract displayed anti-inflammatory effects using the paw edema of rats. | 67 |
| Analgesic | Aqueous ethanol extract exhibited analgesic effects using standard chemical and thermal models. | 67 |
| Anti-hepatic steatosis | A bioactive fraction ameliorated hepatic lipid accumulation in HepG2 cells. | 68 |
| Anti-ulcerative colitis | Methanol extract protected DSS-induced ulcerative colitis in C57BL/6 mice. | 69 |
| Anti-cariogenic | Methanol extract displayed significant inhibitory activity against cariogenic isolates. | 70 |
| Anti-HIV | Aqueous and ethanol extracts inhibited TZM-bl cells with $IC_{50}$ values of 1.1 and 1.2 µg/mL, respectively. | 71 |

Abbreviations: AGES = advanced glycation end products, DNA = deoxyribonucleic acid, DSS = dextran sulfate sodium, HIV = human immunodeficiency virus, $IC_{50}$ = half-maximal inhibitory concentration, NF-κB = nuclear factor kappa B and STZ = streptozotocin.

It was reported that a hot-water leaf extract of *L. speciosa* possessed the ability to stimulate insulin-like glucose uptake and inhibit adipocyte differentiation in 3T3-L1 cells, suggesting that the extract may be useful for prevention and treatment of hyperglycemia and obesity in type II diabetics.[48] In a follow-up study, the extract with tannin removed was devoid of the two bioactivities. Tannic acid, a major component of tannin, purchased from Sigma, was tested and showed to have similar activities. The anti-diabetic property of tannic acid was therefore a serendipitous discovery. Results of the study showed that tannic acid stimulated insulin-like glucose uptake and adipocyte differentiation inhibitory activities in 3T3-L1 cells.[74] Tannic acid stimulated glucose transport with a profile similar to that of insulin. 3T3-L1 cells remained undifferentiated after treatment with tannic acid. Inhibitors of the insulin-mediated pathway also blocked tannic acid-induced glucose transport. Tannic acid did not induce glucose transport in insulin receptor-deficient cells. Tannic acid

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stimulated phosphorylation of protein factors in the insulin-mediated glucose transport pathway and induced glucose transporter type 4 (GLUT 4) translocation. Finally, tannic acid inhibited adipocyte differentiation and affected key genes involved in adipogenesis.

Tannic acid or 1,2,3,4,6-penta-*O*-galloyl-D-glucopyranose ($C_{76}H_{52}O_{46}$) is a naturally occurring polyphenol ester of gallic acid with a glucose core, i.e., a gallotannin.[75] The compound is a deca-galloyl glucose. Its chemical structure has a central glucose molecule esterified at all five hydroxyl moieties, each with two gallic acid molecules.[76]

Gallotannins are likely to be more efficient than ellagitannins in insulin receptor binding, insulin receptor activation and glucose transport induction.[74] 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.[77]

*Corosolic Acid*

Two recent reviews on the bioactivities and underlying mechanisms of CA have included antioxidant, anti-metabolic syndrome, anti-diabetic, anti-cancer, anti-neoplastic, tumour inhibition, cellular protection and anti-inflammatory properties.[78,79] Studies have affirmed the anti-diabetic properties of CA. An *in vitro* study on CA reported strong α-glucosidase inhibitory activity with $IC_{50}$ value of 3.53 µg/mL.[80] $IC_{50}$ values of oleanolic acid and maslinic acid (Figure 3) were 6.29 and 5.52 µg/mL, respectively. *In vivo* studies using diabetic mice showed that CA significantly reduced blood glucose and induced GLUT-4 translocation.[81,82] CA ameliorated alloxan-induced diabetic nephropathy in mice,[83] and significantly decreased blood cholesterol and liver cholesterol content.[84] A clinical trial conducted in Japan, showed for the first time that CA had a lowering effect on post-challenge plasma glucose levels in humans.[85] CA treated subjects displayed lower glucose levels from 60−120 min, reaching statistical significance of $P < 0.05$ at 90 min. From the literature, there is ample evidence affirming that CA is cytotoxic to cervical, colorectal, renal, lung, brain, mouth, and liver cancer cells. The cancer cell lines, and the effects and mechanisms of CA are shown in Table 3. Five out of the eight studies were published in 2021, suggesting that the anti-cancer properties of CA are still actively studied. Other pharmacological properties of CA included cellular protection and anti-inflammation. CA protected against liver injury by modulation of mitogen-activated protein (MAP) kinase signaling and autophagy activation,[94] promoted osteoblast differentiation of mouse osteoblastic cells by activating transcription factors and MAP kinases,[95] and protected against doxorubicin-induced cardiotoxicity by restoring autophagic flux and improving mitochondrial function.[96] Studies have found that acute inflammation was improved by CA through suppression of phosphorylation and transcription of IL-1 receptor-associated kinase (IRAK-1) in mouse macrophages.[97] An earlier study reported that CA prevented oxidative stress and reduced inflammation in rats with metabolic syndrome.[98] CA administered at 0.07% for 14 weeks attenuated hypertension, regulated hyperlipidemia, prevented oxidative stress and ameliorated inflammation. CA from banaba was also found to improve the erectile function in metabolic syndromerats.[99] Rats were treated with CA daily by oral gavage for 4 weeks and erectile function parameters were determined using the apomorphine test. Results showed that CA improved erectile function in rats by reducing the level of reactive oxygen species, increasing nitric oxide bioavailability and ameliorating endothelial dysfunction.

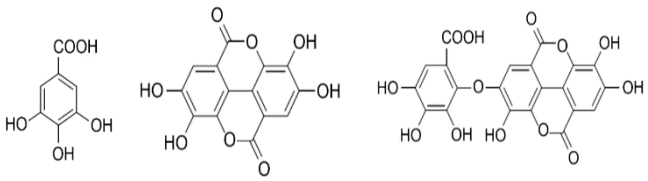

**Figure 4** Chemical structures of gallic acid (left), ellagic acid (middle) and valoneic acid dilactone (right)

**Table 3:** Effects and Mechanisms of Anti-cancer Properties of Corosolic Acid

| Cancer Cell Line | Effect and Mechanism | Reference |
|---|---|---|
| HeLa cervical | Induced apoptosis of cells through the mitochondrial pathway and activation of caspase-8, -9 and -3. | 86 |
| HCT116 colorectal | Induced apoptotic cell death through a caspase-dependent pathway involving the activation of caspase-8, -9 and -3. | 87 |
| HCT116 & SW480 colorectal | Inhibited cell growth by suppressing HER2/3 heterodimerization and by inhibiting mitochondrial fission. | 88 |
| Caki renal | Induced non-apoptotic cell death through LPI and ROS production. | 89 |
| A549 & PC9 lung | Reduced cell proliferation, invasion, and chemoresistance by inducing mitochondrial and liposomal oxidative stress. | 90 |
| GBM8401 brain | Exerted anti-metastatic effect on cells and attenuated their invasiveness by targeting the AXL/CHIP/GAS6 axis. | 91 |
| HSC3 & SAS mouth | Inhibited cell growth by suppressing the ERK1/2 pathway and by inhibiting MMP1 expression. | 92 |
| HCC liver | Inhibited tumour growth and cancer progression by inactivating the CDK19/YAP/O-GlcNAcylation pathway. | 93 |

Abbreviations: CDK = cyclin dependent kinase, CHIP = carboxyterminus of Hsc70-interacting protein, ERK = extracellular signal-regulated protein kinase, GAS = growth arrest specific, HER = human epidermal growth-factor receptor, LPI = lipid peroxidation inhibition, MMP = matrix metalloproteinase, ROS= reactive oxygen species and YAP = yes associated protein.

## Conclusion

Further phytochemical studies on the leaves of *L. speciosa* have good prospects of yielding compounds that are new to science, new to the family, new to the genus and new to the species. Studies on the phytochemistry and pharmacology of flowers of *L. speciosa*, and leaves of other *Lagerstroemia* species such as *L. floribunda* and *L. indica* are meagre, providing opportunities for further research. The anti-diabetic properties of ellagitannins and CA from leaves of *L. speciosa* warrant more detailed studies. In addition, studies comparing the anti-diabetic properties of ellagitannins and gallotannins would provide scientific explanations between these two groups of tannins. Studies have shown that gallotannins are likely to be more efficient than ellagitannins in insulin receptor binding, insulin receptor activation and glucose transport induction. If indeed gallotannins have stronger anti-diabetic properties than ellagitannins, research should then proceed to determine the anti-diabetic properties and plant

sources of gallotannins. The development of anti-diabetic drugs from leaves of *L. speciosa* presents promising prospects for commercialization following clinical trials. Other topics worthy of further research include the toxicity, pharmacokinetics and metabolism of *L. speciosa*. The bioactivity of compounds and their structure-activity relationships need more in-depth studies.

## Conflict of Interest

The authors declare no conflict of interest.

## Authors' Declaration

The authors hereby declare that this short review is original and that any liability for claims relating to the contents will be borne by them.

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