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A review of the chemical composition and biological activities of *Callistemon lanceolatus* (Sm.) Sweet

Kandhasamy Sowndhararajan[1], Ponnuvel Deepa[2], Songmun Kim[2]*

[1]Department of Botany, Kongunadu Arts and Science College, Coimbatore, India.
[2]School of Natural Resources and Environmental Science, Kangwon National University, Chuncheon, Republic of Korea.

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ABSTRACT

The genus *Callistemon* belongs to the family Myrtaceae that comprises approximately 50 shrub species. These species are mainly found in the east and southeast of Australia. Among them, *Callistemon lanceolatus* (Sm.) Sweet (common name: lemon bottlebrush) is an important medicinal plant and is traditionally used to treat various disorders. *C. lanceolatus* is widely distributed in tropical and subtropical regions. This plant contains a wide variety of chemical components such as triterpenoids, flavonoids, fatty acids, and phenolic compounds. In the present review, the chemical composition and biological activities of *C. lanceolatus* were summarized. In this regard, a literature search was carried out to retrieve information concerning the chemical composition and biological activities of *C. lanceolatus* from PubMed, Science Direct, Taylor and Francis, BMC, Wiley, Springer, ACS, Google Scholar, and other literature databases. The isolated compounds and extracts of *C. lanceolatus* were reported for a variety of biological properties, including antimicrobial, antioxidant, anti-inflammatory, antidiabetic, antiproliferative, and insecticidal activities. In this review, we attempt to combine the literature regarding phytochemical composition and biological activities of *C. lanceolatus*.

INTRODUCTION

Traditionally, numerous plant species have been extensively used to treat various ailments by ethnic people throughout the world. In general, plants contain a wide variety of biologically active components, including phenolic acids, flavonoids, alkaloids, terpenoids, phytosterols, saponins, tannins, and lignins (Clardy and Walsh, 2004; Goyal *et al*., 2012; Shanmugam *et al*., 2021). The genus *Callistemon* (Myrtaceae) contains about 50 species with immense medicinal importance. *Callistemon* species are mainly found in the eastern and southeastern regions of Australia (Sharma *et al*., 2021). The general characteristics of this genus are lanceolate leaves, flower spikes like bottlebrushes, and red stamens (Gad *et al*., 2019). Previous studies reported the isolation and identification of different chemical groups from *Callistemon* species, including polyphenols and terpenoids (Shehabeldine *et al*., 2020). The leaves of this plant possess a pleasant fragrance due to the presence of essential oil. Different species of *Callistemon* are cultivated for the purposes of essential oils, farm trees, land reclamation, and ornamental horticulture besides other applications (Lopez-Mejía *et al*., 2021; Zubair *et al*., 2013).

Callistemon lanceolatus (Sm.) Sweet is a medium-sized tree, native to Australia, and is widely found in subtropical and tropical zones. This plant is commonly known as lemon bottlebrush due to its cylindrical brush-like red flowers (Singh *et al*., 2020). It is also widely cultivated as an ornamental plant throughout the world. Aerial parts of *C. lanceolatus* are known to possess various biological activities, including antimicrobial (Nazreen *et al*., 2020), antioxidant, antidiabetic (Ahmad *et al*., 2018; Kumar *et al*., 2011a), anti-inflammatory (Kumar *et al*., 2011b), and antiproliferative (Park *et al*., 2018) activities. In particular, essential oils from the leaves of *C. lanceolatus* have antimicrobial and anti-inflammatory properties (Shukla *et al*., 2012; Sudhakar *et al*., 2004). This plant is a versatile source of

*Corresponding Author
Songmun Kim, School of Natural Resources and Environmental Science, Kangwon National University, Chuncheon, Republic of Korea.
E-mail: perfume @ kangwon.ac.kr

bioactive components. The leaves have been used as the best tea substitute owing to their refreshing flavor. In Egypt, essential oil from this plant is used to treat cough and bronchitis in addition to insecticidal properties (Das and Singh, 2012; Shinde *et al*., 2012).

Based on the highly acclaimed biological properties of *C. lanceolatus*, this review aimed to summarize the chemical composition and biological properties of crude extracts and isolated compounds from *C. lanceolatus* (Table 1).

METHODOLOGY

Published articles in connection with *C. lanceolatus* were retrieved from PubMed, Science Direct, Taylor and Francis, BMC, Wiley Online Library, Springer Link, ACS, Google Scholar, and other literature databases. In addition, some articles were found by tracking citations from other publications. The search keywords used were *C. lanceolatus* and lemon bottlebrush. The collection of literature was restricted to publications in English language. The search was carried out until August 2021. Chemical names were authenticated from PubChem website and chemical structures were made using ChemDraw Ultra 12.0. In this review, we briefly discussed recent scientific findings regarding the biological activities of *C. lanceolatus* and suggested some fields where further study is required.

Chemical Compositions of *C. Lanseolatus*

Phytochemicals are very important in pharmaceutical and medicinal fields owing to their biological properties. Numerous methods have been employed to isolate and characterize chemical components from different parts of *C. lanceolatus* (Fig. 1A and B). Sitosterol, erythrodiol, betulin, betulinic acid, ursolic acid, and 2-hydroxyursolic acid were isolated from this plant by Varma and Parthasarathy (1975). Phloroglucinol derivatives from the leaves of *C. lanceolatus* were identified by Lounasmaa *et al*. (1977). Rattanaburi *et al*. (2013) isolated callistenones A–E (acylphloroglucinols) from *C. lanceolatus* leaves.

The flavones are an important class of flavonoids, which can act as strong antioxidants. 3-Methyltetradec-2-en-7-ol, 5-hydroxy-7,4′-dimethoxy-6,8-dimethylflavone, and 5-hydroxy-7,4′-dimethoxy-6-methylflavone were characterized from the leaves of *C. lanceolatus* (Huq and Misra, 1997) and 5,7-dihydroxy-6,8-dimethyl-4′-methoxy flavone and 8-(2-hydroxypropan-2-yl)-5-hydroxy-7-methoxy-6-methyl-4′-methoxy flavone from the aerial parts of *C. lanceolatus* (Nazreen *et al*., 2012). In addition, 8-(1″-hydroxyisopranyl)-5,6-dihydroxy-7,4′-dimethoxy flavone, 2,3,4-trihydroxyphenethyl tetracontanoate, and 2,3,4-trihydroxyphenethyl tetracontanoate-4-β-xylopyranoside were isolated (Nazreen *et al*., 2019). In the aerial parts of *C. lanceolatus*, 4′,5-dihydroxy-6,8-dimethyl-7-methoxyflavanone, eucalyptin, 8-demethyleucalyptin, sideroxylin, syzalterin, and quercetin were also isolated (Park *et al*., 2010; 2018).

In the flowers and leaves of *C. lanceolatus*, Marzouk (2008) employed HPLC-ESI/MS followed by one- and two-dimensional nuclear magnetic resonance for characterizing quercetin 3-*O*-β-*D*-glucuronopyranoside *n*-butyl ester and *n*-butylgallate 4-*O*-(2′,6′-di-*O*-galloyl)-β-*D*-glucopyranoside from the aqueous methanol extracts. The leaves of *C. lanceolatus* also contain flavonol glycosides such as kaempferol 3-*O*-beta-*D*-galacturonopyranoside and quercetin 3-*O*-(2″-*O*-galloyl)-beta-*D*-glucoronopyranoside, in addition to 18 known polyphenols (phenolic acids, flavonoids, and 3 tannins) (Mahmoud *et al*., 2002).

Jeong *et al*. (2009) isolated triterpenoids such as 30-hydroxyalphitolic acid, alphitolic acid, lupenol, 3-acetoxy-olean-18-en-28-oic acid, betulinic acid, ursolic acid, betulinic acid 3-*O*-caffeate, morolic acid 3-*O*-caffeate, and ursolic acid 3-*O*-caffeate from *C. lanceolatus*. 2-Amino-2-ethylpropane-1,3-diyl dioleate and ursolic acid 3-*O*-acetate were identified from the ethanol extract of *C. lanceolatus* stems (Kim *et al*., 2012). Ahmad *et al*. (2018) reported the presence of 4-fluoro-2-trifluoromethylbenzoic acid, neopentyl ester, fumaric acid, di(pent-4-en-2-yl) ester, 2,3-dihydro-3,5-dihydroxy-6-methyl-4H-pyran-4-one, and 2-furancarboxaldehyde,5-(hydroxymethyl). 1-Triacosanol, *n*-eicosanyl palmitate, *n*-heptadecanyl arachidate, *n*-tricosanyl palmitate, 4-hydroxyphenethyl carbocerate, 4-hydroxyphenethyl gheddate, urs-12-en-3alpha-acetoxy-18beta-H-28-oic acid, and stigmast-5-en-3beta-ol-3beta-*D*-glucuronopyranoside were also identified from *C. lanceolatus* (Nazreen *et al*., 2020). Two neolignans such as callislignan A and B along with a lignan, C-methyl-flavonoids, and pentacyclic triterpenoid esters were identified from *C. lanceolatus* leaves (Rattanaburi *et al*., 2012).

The aerial parts also contain an appreciable amount of essential oils. Misra *et al*. (1997) investigated the essential oil composition of the leaves, flowers, and fruits of *C. lanceolatus*. The authors reported that 1,8-cineole and α-pinene were major components in the leaves. The flower contained a higher amount of β-pinene and 1,8-cineole, whereas l,8-cineole and α-terpineol were the major components in fruits. In the essential oils of *C. lanceolatus* leaves, the most abundant components were 1,8-cineole and α-pinene, followed by α-phellandrene, limonene, and α-terpineol (Sharma *et al*., 2006).

Biological Activities of *C. Lanceolatus*

The biological activities of crude extracts and compounds isolated from *C. lanceolatus* are presented in Table 1.

Antimicrobial activity

New eco-friendly approaches are required to prevent the growth of microbial pathogens in food products due to the adverse effects of synthetic preservatives. In recent times, numerous researchers evaluated the possible utilization of plant natural products as effective preservatives. Pandey *et al*. (1982) screened the inhibitory activity of 20 plant species from 12 families against *Fusarium oxysporum* and the authors found that only *C. lanceolatus* leaves exhibited absolute toxicity. The methanol extract from the leaves of *C. lanceolatus* exhibited maximum inhibitory activity against *Staphylococcus aureus* and minimum inhibitory activity against *Candida albicans* (Paluri *et al*., 2012). Kavitha and Satish (2013) investigated the antibacterial effect of different extracts (petroleum ether, chloroform, ethyl acetate, and methanol) of *C. lanceolatus* leaves against various human and plant pathogenic bacteria. The minimum inhibitory concentration (MIC) of different extracts ranged between 0.156 and 5 mg/ml.

Nim and Arora (2018) found that ethyl acetate extract from the leaves of *C. lanceolatus* exhibited strong inhibitory activity against different microbial pathogens with the zone of inhibition ranging from 15 to 27 mm. Among various pathogens, the ethyl acetate extracts effectively control the growth of *S. aureus* and *Klebsiella pneumonia*. Maximum antimicrobial activity was

Table 1. Biological activities of extracts and isolated compounds from *C. lanceolatus*.

S. No.	Extracts/compounds	Biological activity	Model	References
			Seed	
1.	Petroleum ether, chloroform, ethyl acetate, and methanol extracts	Antibacterial	Uropathogenic bacteria: *Acinetobacter baumannii*, *Citrobacter freundii*, *Enterobacter aerogenes*, *Enterococcus faecalis*, *E. coli*, *Klebsiella pneumoniae*, methicillin-resistant *S. aureus*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Serratia marcescens*, and *S. aureus*	Kavitha and Satish, 2014
2.	Aqueous extract	Antimicrobial	*E. faecalis*, *S. aureus*, *S. epidermidis*, *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *Salmonella typhimurium*, *Shigella flexneri*, *C. albicans*, and *Candida tropicalis*	Arora *et al*., 2016
			Stem	
3.	Methanol and water extracts	Antioxidant and antihyperglycemic	Metal ion chelating, free radical scavenging, and reducing power assays alloxan-induced diabetic rats	Kumar *et al*., 2020
			Leaves	
4.	Methanol extract	Anti-inflammatory	Carrageenan-induced paw edema in rats	Kumar *et al*., 2011c
5.	Callislignan A and B	Antibacterial	*Staphylococcus aureus* and methicillin-resistant *S. aureus*	Rattanaburi *et al*., 2012
6.	Methylene chloride and methanol extracts	Antithrombin activity	Chromogenic bioassay	Chistokhodova *et al*., 2002
7.	Ethyl acetate and methanol extracts	Antioxidant and apoptotic	DPPH, superoxide, hydrogen peroxide, nitric oxide radical scavenging assays, and reducing power assay.	Ahmad *et al*., 2018
			HepG2, MCF7, and HEK 293 cell lines.	
8.	Methanol extract	Antioxidant	DPPH radical scavenging activity	Kumar *et al*., 2015
			Plasmid nicking assay	
9.	Methanol extract	Antibacterial	*Staphylococcus aureus* and *S. epidermidis*	Srishti *et al*., 2017
10.	Ethanol extract	Cardioprotective	Doxorubicin-induced cardiomyopathy in rats	Firoz *et al*., 2011
11.	Methanol extract	Insecticidal	*Helicoverpa armigera*	Halder *et al*., 2009
12.	Methanolic extract	Antimicrobial	*Pseudomonas aeruginosa*, *K. pneumoniae*, *E. coli*, *S. aureus*, *Micrococcus luteus*, *Salmonella typhi*, *C. albicans*, and *C. tropicalis*	Paluri *et al*., 2012
13.	Methanol extract	Antidiabetic, hypolipidemic, and antioxidant	Streptozotocin-induced diabetic rats	Kumar *et al*., 2011a
			DPPH, superoxide, nitric oxide, and hydroxyl radical scavenging assays	
14.	Methanol extract	Hepatoprotective	Carbon tetrachloride-induced hepatic damage in rats	Jain *et al*., 2007
15.	Acylphloroglucinols, named callistenones A–E		*Staphylococcus aureus*, methicillin-resistant *S. aureus*, *E. coli*, and *P. aeruginosa*	Rattanaburi *et al*., 2013
16.	Methanol extract ethyl acetate fraction	Antihyperglycemic and antihyperlipidemic	Alloxan-induced diabetic rats	Kumar *et al*., 2011b
17.	Dried powder	Molluscicidal	*Biomphalaria alexandrina*	El-Ansary *et al*., 2001
18.	Petroleum ether, chloroform, ethyl acetate, and methanol extracts	Antibacterial	*Bacillus cereus*, *Bacillus subtilis*, *E. coli*, *Listeria monocytogenes*, *P. aeruginosa*, *Proteus mirabilis*, *S. aureus*, *Shigella flexineri*, and *Vibrio parahaemolyticus.*	Kavitha and Satish, 2013
			Agrobacterium tumefaciens, *Erwinia carotovora*, *Pseudomonas syringae*, *Ralstonia solanacearum*, *Xanthomonas axonopodis pv. malvacearum*, *Xanthomonas campestris pv. vesicatoria*, and *Xanthomonas oryzae pv. oryzae.*	
19.	Ethyl acetate extract	Antimicrobial and anticancer	*Staphylococcus aureus* and *K. pneumoniae*	Nim and Arora, 2018
			HeLa cell lines	
20.	Essential oil	Antifungal	Essential oil-loaded chitosan nanoparticles	Singh *et al*., 2020
			A. flavus	
21.	Essential oil	Fungitoxic	*Fusarium oxysporum*	Pandey *et al*., 1982

Continued

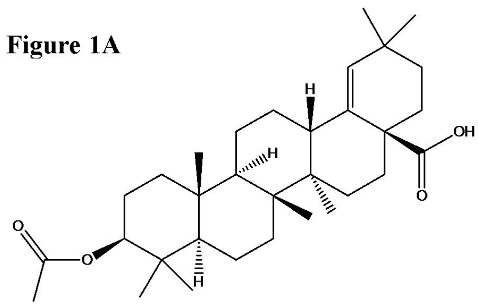
S. No.	Extracts/compounds	Biological activity	Model	References
22.	Essential oil	Antinociceptive and anti-inflammatory	Tail flick latent test in rats Hot plate reaction time in mice Analgesymeter-induced pain in mice Acetic acid-induced writhing response in mice Carrageenan-induced paw edema in rats	Sudhakar *et al*., 2004
23.	Essential oil	Allelopathic	*Echinochloa crus-galli*	Bunkoed *et al*., 2017
24.	Essential oil	Anticandidial	*Candida albicans*	Dutta *et al*., 2007
25.	Essential oil	Antifungal	*Trichophyton tonsurans*	Anita and Misra, 2012
26.	Essential oil and its major component 1,8-cineole	Insecticidal	Pulse beetle, *C. chinensis*	Shukla *et al*., 2011
27.	Essential oil and its major component 1,8-cineole	Antifungal, aflatoxin inhibition and antioxidant	*Aspergillus flavus* DPPH radical scavenging assay β-carotene/linoleic acid assay	Shukla *et al*., 2012
			Aerial parts	
28.	5,7-dihydroxy-6,8-dimethyl-4′ -methoxy flavone and 8-(2-hydroxypropan-2-yl)-5-hydroxy-7-methoxy-6-methyl-4′-methoxy flavone	Antidiabetic	Streptozotocin-induced diabetic rats	Nazreen *et al*., 2012
29.	8-(1″-hydroxyisopranyl)-5,6-dihydroxy-7,4′-dimethoxy flavone	Antidiabetic	Streptozotocin-induced diabetic rats *In vitro* PPAR-γ transactivation activity	Nazreen *et al*., 2019
30.	1-triacosanol, n-eicosanyl palmitate, n-heptadecanyl arachidate, n-tricosanyl palmitate, 4-hydroxyphenethyl carbocerate, 4-hydroxyphenethyl gheddate, urs-12-en-3a-acetoxy-18b- H-28-oic acid and stigmast-5-en-3b-ol-3b-D-glucuronopyranoside	Antimicrobial antioxidant	*Staphylococcus aureus*, *E.coli*, and *K. pneumoniae* DPPH radical scavenging activity	Nazreen *et al*., 2020
31.	Betulinic acid 3-O-caffeate	Inhibition of nitric oxide production	LPS-induced nitric oxide production in RAW264.7 cells	Jeong *et al*., 2009
32.	Sideroxylin	Anticancer	Ovarian cancer cells (ES2 and OV90 cells) Cell proliferation assay Mitochondrial membrane potential assay Cellular ROS and LIPID peroxidation assays	Park *et al*., 2018
33.	4′,5-dihydroxy-6,8-dimethyl-7-methoxyflavanone	Neuroprotective	Aβ-induced toxicity in PC12 cells	Park *et al*., 2010

observed for cardiac glycosides and phytosterols. The partially purified components showed the maximum inhibitory effect against methicillin-resistant *S. aureus* (MRSA), *Staphylococcus epidermidis*, and *S. aureus*. The ethyl acetate extract and partially purified constituents indicated a lower MIC (0.5–7 μg/ml). The methanol extract of *C. lanceolatus* showed appreciable antibacterial activity against *S. aureus* and *S. epidermidis* (Srishti *et al*., 2017).

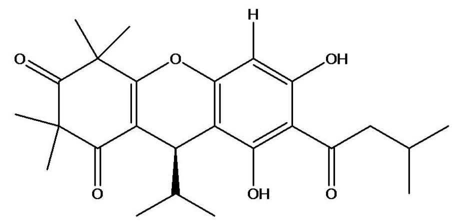
The essential oil of *C. lanceolatus* also showed a potent anticandidal activity (Dutta *et al*., 2007). Shukla *et al*. (2012) studied the antifungal activity of essential oil and its major component, 1,8-cineole, against fungal pathogens isolated from chickpea. The essential oil and 1,8-cineole exhibited significant antifungal activity against all the tested fungal isolates. Furthermore, the essential oil and 1,8-cineole strongly inhibited the production of aflatoxin B_1 by the isolate of *Aspergillus flavus* with lower fungistatic concentration. Kavitha and Satish (2014) evaluated the antibacterial activity of different solvent extracts from the seed of *C. lanceolatus* against 11 uropathogenic bacteria. Different extracts showed least to moderate inhibitory activity against these uropathogenic bacteria. The aqueous extract of *C. lanceolatus* seeds revealed a broad-spectrum antimicrobial activity against different microbial pathogens with MIC values ranging from 1 to 5 mg/ml (Arora *et al*., 2016).

The isolated compounds, callislignan (A and B) as well as callistenones (A–C), showed antibacterial activity against *S.*

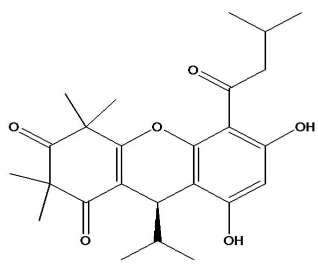
Figure 1A



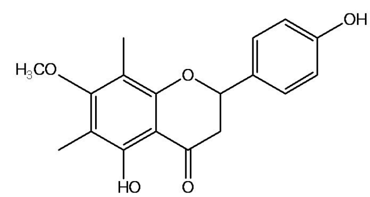
3-Acetoxy-olean-18-en-28-oic acid



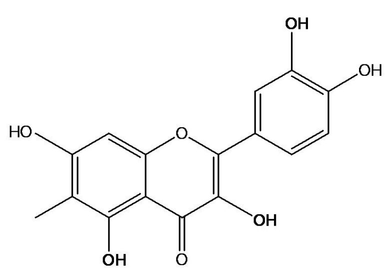
Callistenone A



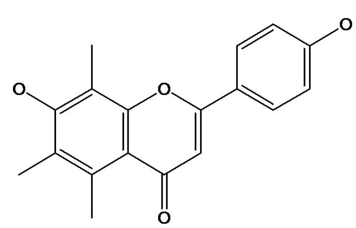
Callistenone B



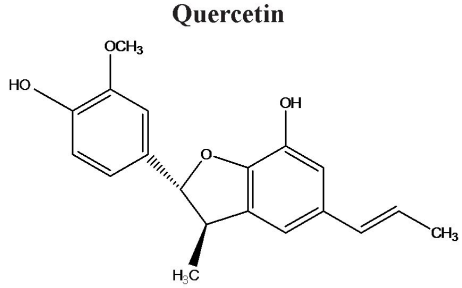
4′,5-Dihydroxy-6,8-dimethyl-7-methoxyflavanone



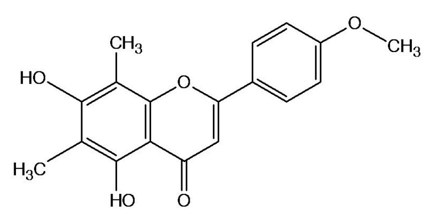
Quercetin



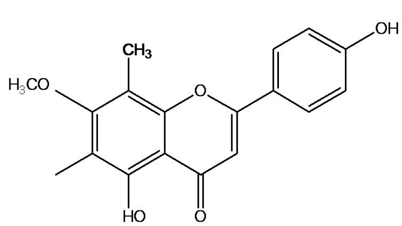
5-Hydroxy-7,4'-dimethoxy-6-methylflavone



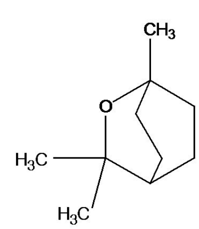
Callislignan A



5,7-Dihydroxy-6,8-dimethyl- 4′ -methoxyflavone



Sideroxylin



1,8-Cineole

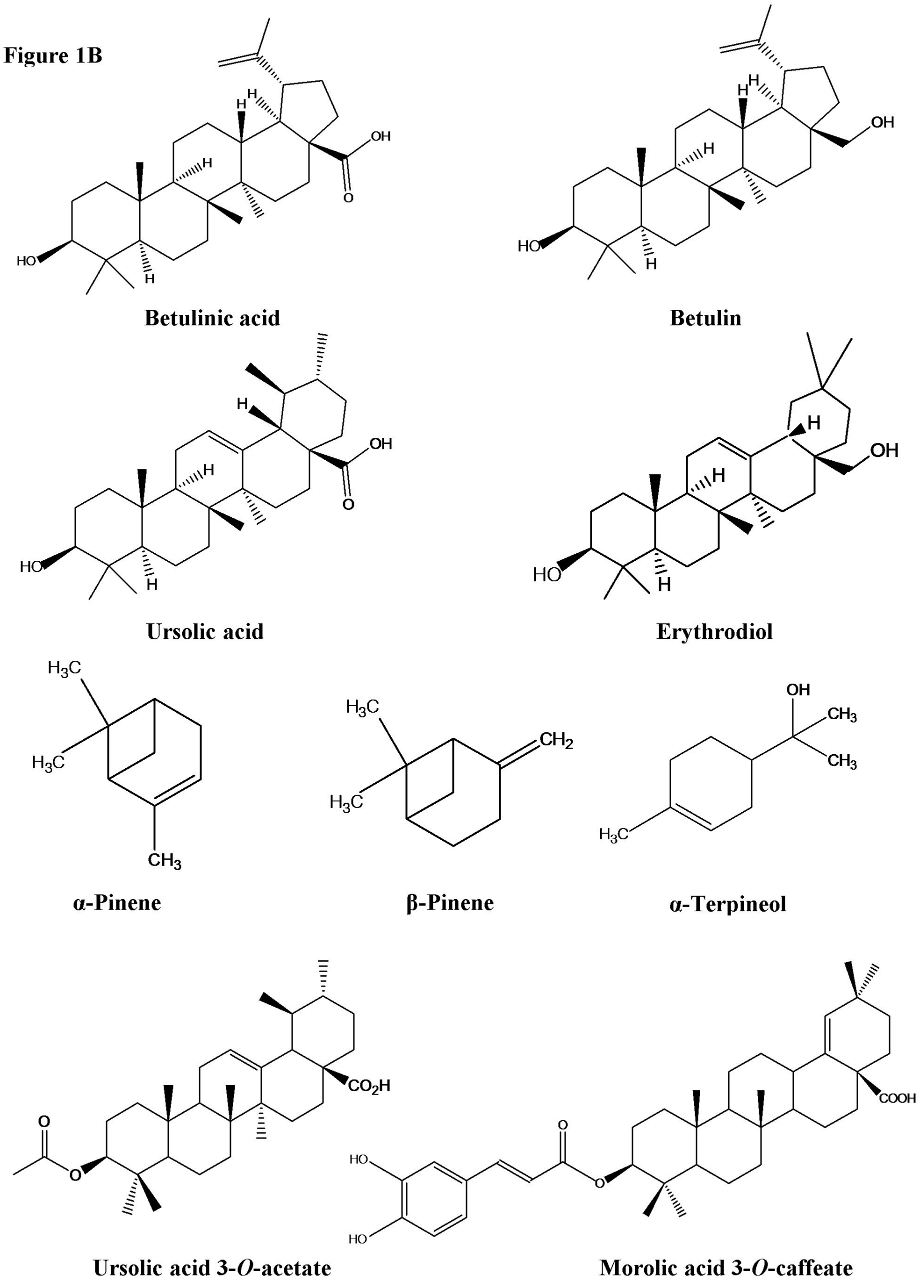


Figure 1(A and B). The chemical structure of some important compounds isolated from *C. lanceolatus*.

aureus and MRSA (Rattanaburi *et al*., 2012; 2013). Urs-12-en-3alpha-acetoxy-18beta-H-28-oic acid isolated from *C. lanceolatus* effectively inhibited the growth of *Escherichia coli* with the MIC value of 32 mg/ml (Nazreen *et al*., 2020). A recent study indicated that *C. lanceolatus* essential oil-loaded chitosan nanoparticles exhibited a strong inhibitory effect on aflatoxin B_1 production by *A. flavus* when compared to *C. lanceolatus* essential oil alone (Singh *et al*., 2020).

Antioxidant activity

Antioxidant substances such as phenolic acids, flavonoids, and tannins possess various biological properties, including anti-inflammatory, anticancer, and antidiabetic effects due to their antioxidant potential. Kumar *et al*. (2011a) studied the antioxidant potential of methanol extracts of *C. lanceolatus* and found that the extract showed antioxidant effect by scavenging 2,2-diphenyl-1-picrylhydrazyl (DPPH), superoxide, nitric oxide, and hydroxyl radicals. Methanol extracts from the leaves of *C. lanceolatus* revealed a considerable DPPH radical scavenging activity with an IC_{50} value of 155 µg/ml in addition to protecting ability against pBR322 plasmid DNA (Kumar *et al*., 2015). The ethyl acetate and methanol extracts from the leaves of *C. lanceolatus* showed a potent antioxidant activity under various *in vitro* assays such as DPPH, superoxide, hydrogen peroxide, nitric oxide radical scavenging assays, and reducing power assay (Ahmad *et al*., 2018).

The methanol extract from the stem of *C. lanceolatus* also showed potent antioxidant activity in terms of antioxidant assays such as ion chelating, free radical scavenging, and reducing power (Kumar *et al*., 2020). Furthermore, the fatty acid esters from *C. lanceolatus* such as 4-hydroxyphenethyl carbocerate and 4-hydroxyphenethyl gheddate DPPH radical scavenging activity (Nazreen *et al*., 2020).

Antidiabetic activity

Diabetes mellitus is one of the important metabolic diseases and is a major health concern today around the world due to increased mortality. Nowadays, medicinal plants play a major role in replacing synthetic antidiabetic drugs due to unavoidable side effects. In streptozotocin-induced diabetic rats, 8-(1″-hydroxyisopranyl)-5,6-dihydroxy-7,4′-dimethoxy flavone isolated from the chloroform fraction of the ethanol extract of *C. lanceolatus* aerial parts significantly reduced the blood glucose level. The isolated compound also exhibited a moderate PPAR-γ transactivation activity *in vitro* (Nazreen *et al*., 2019). Nazreen *et al*. (2012) reported that 5,7-dihydroxy-6,8-dimethyl-4′-methoxy flavone and 8-(2-hydroxypropan-2-yl)-5-hydroxy-7-methoxy-6-methyl-4′-methoxy flavone isolated from *C. lanceolatus* aerial parts effectively reduced the blood glucose level in streptozotocin-induced diabetic rats.

Kumar *et al*. (2011a) studied the antidiabetic potential of methanol extract from the leaves of *C. lanceolatus* in streptozotocin-induced diabetic rats. Oral administration of the methanol extract for 21 days markedly decreased the level of blood glucose level in glucose-loaded as well as streptozotocin-induced diabetic rats. When compared with the diabetic control group, there were decreases in blood glucose, serum cholesterol, and triglycerides levels and increases in the levels of high-density lipoprotein (HDL) cholesterol and serum insulin in the methanol extract-treated group. Oral administration of ethyl acetate fraction from the methanol extract of *C. lanceolatus* leaves markedly decreased the level of blood glucose and improved the functions of kidney and liver functions in alloxan-diabetic rats. Furthermore, the ethyl acetate fraction enhanced body weight, liver, and renal profiles in addition to total lipid levels (Kumar *et al*., 2011b). Recently, Kumar *et al*. (2020) investigated the antidiabetic potential of methanol extract from the stem of *C. lanceolatus* methanolic in alloxan-induced diabetic rats. The authors reported that the methanol extract-treated group for 28 days significantly reduced blood glucose level and serum markers accompanied by improving body weight and HDL level in alloxan-induced diabetic rats.

Anti-inflammatory activity

Uncontrolled production of inflammatory mediators is the major cause of various diseases, including allergies, cardiovascular dysfunctions, diabetes, cancer, and immune-mediated disorders. Extracts and secondary metabolites from plants have been increasingly used for the treatment of inflammatory-mediated diseases (Ghasemian *et al*., 2016). Sudhakar *et al*. (2004) studied the antinociceptive and anti-inflammatory activities of essential oil from *C. lanceolatus* leaves under *in vivo* animal models. Oral administration of *C. lanceolatus* essential oil showed antinociceptive activity in terms of a tail flick latent test in rats, hot plate reaction time, analgesymeter-induced mechanical pain, and acetic acid-induced writhing in mice. *C. lanceolatus* essential oil also decreased paw edema volume in the carrageenan-induced paw edema in rats. In a carrageenan-induced paw edema rat model, oral administration of the methanol extract of *C. lanceolatus* leaves showed appreciable anti-inflammatory activity at the concentration of 200 and 400 mg/kg bw (Kumar *et al*., 2011c). Another study revealed that betulinic acid 3-*O*-caffeate 7 moderately inhibited the production of nitric oxide in lipopolysaccharide- induced RAW264.7 cells with the IC_{50} value of 15.4 μM (Jeong *et al*., 2009).

Antiproliferative activity

The continuing search for novel and effective drugs from medicinal plants is a promising strategy for the prevention of cancer. The ethyl acetate and methanol extracts of *C. lanceolatus* leaves showed a potent antiproliferative effect against liver cancer cells HepG2 cells by reducing the cell growth, reactive oxygen species generation, and cell migration as well as inhibiting the metastatic activity. Furthermore, pretreated HepG2 cells with both extracts significantly suppressed signal transducer and activator of transcription 3 expression and upregulated p53 and inhibited cdk2 and cyclin A activities (Ahmad *et al*., 2018). The ethyl acetate extract and partially purified constituents from the leaves of *C. lanceolatus* showed promising antiproliferative activity against HeLa cell lines (Nim and Arora, 2018). A C-methylated flavone, sideroxylin, isolated from *C. lanceolatus* effectively decreased the proliferation of cells and increased apoptosis in ovarian cancer cells such as ES2 and OV90 cells by inducing mitochondrial dysfunction and activating phosphoinositide 3-kinase and mitogen-activated protein kinase signal transduction (Park *et al*., 2018).

Insecticidal activity

In Asia and Africa, *Callosobruchus chinensis* L. (Pulse beetle) is the most devastating insect pest in the stored pulses. The essential oil of *C. lanceolatus* and its major component, 1,8-cineole, registered 100% and 74.7% repellency of pulse beetle, respectively, in a Y-shaped olfactometer at the concentration of 150 μl. The essential oil and 1,8-cineole afforded 100% insect mortality at the concentration of 0.1 μl/ml. At the concentration of 0.1 μl/ml, the essential oil was found to be the most effective fumigant in terms of oviposition deterrent (96.03%) and antifeedant activity (100%). Furthermore, *C. lanceolatus* essential oil exhibited promising safety profiles when recorded on mice with the LD_{50} of 14,626.3 μl/kg (Shukla *et al*., 2011).

El-Ansary *et al*. (2001) demonstrated that the dry powdered *C. lanceolatus* exhibited molluscicidal activity against *Biomphalaria alexandrina*. The extract of *C. lanceolatus* showed antithrombin activity (80%) based on a chromogenic bioassay (Chistokhodova *et al*., 2002). The extracts from the leaves of *Vinca rosea* and *C. lanceolatus* alone and their mixtures effectively reduced the growth, increased larval toxicity, and inhibited normal adult emergence of *Helicoverpa armigera* (Halder *et al*., 2009).

Miscellaneous activities

A study reported that the methanol extract of *C. lanceolatus* leaves exhibited protective activity against carbon tetrachloride (CCl_4)-induced hepatic damage in rats by attenuating the increased serum level of enzymes (Jain *et al*., 2000). The ethanol extract from the leaves of *C. lanceolatus* (100 and 200 mg/kg bw) showed protective activity in doxorubicin-induced cardiomyopathy in rats (Firoz *et al*., 2011).

The essential oil of *C. lanceolatus* exhibited 100% toxicity against the test dermatophyte, *Trichophyton tonsurans* (Anita and Misra, 2012). A study indicated that the essential oil of *C. lanceolatus* showed an inhibitory effect on seed germination and seedling growth of *Echinochloa crus-galli* (L.) Beauv. at a concentration of 25 µl/plate (Bunkoed *et al*., 2017).

A higher amount of beta-amyloid (Aβ) production and its aggregation play a major role in Alzheimer's disease. Hence, reducing the accumulation of Aβ neuronal cells could provide an appropriate way of prevention of Alzheimer's disease. A flavanone, 4′,5-dihydroxy-6,8-dimethyl-7-methoxyflavanone isolated from *C. lanceolatus* aerial parts showed a potent neuroprotective effect against beta-amyloid (Aβ)-induced toxicity in PC12 cells (ED_{50} value: −6.7 µM). This compound significantly decreased Aβ-induced apoptotic cell death by decreasing the activation of caspase-3 and increasing the ratio of Bcl-2/ Bax (Park *et al*., 2010).

Nanoparticle Synthesis

In recent years, the biosynthesis of nanoparticles has gained considerable attention because of its eco-friendly approach, biocompatibility, extended half-life of drugs, cost-effectiveness, and no toxicity. Ravichandran *et al*. (2016) used the aqueous extract obtained from the leaves of *C. lanceolatus* to synthesis silver oxide nanoparticles. The biosynthesized silver oxide nanoparticles exhibited significant antioxidant activity in a concentration dependent-manner under various *in vitro* chemical assays and time-dependent cytotoxic activity against brine shrimp nauplii. *C. lanceolatus* was utilized to synthesis gold nanoparticles (Kowsalya *et al*., 2021).

CONCLUSION AND FUTURE PERSPECTIVES

The leaves of *C. lanceolatus* contain various compounds, including flavones, acylphloroglucinols, C-methyl-flavonoids, and most importantly essential oils. According to previous reports, crude extracts and isolated compounds from *C. lanceolatus* showed significant antimicrobial, antioxidant, antidiabetic, anti-inflammatory, and insecticidal activities. In particular, the essential oil and its major component, 1,8-cineole, exhibited remarkable antimicrobial activity with special reference to an inhibitory effect on aflatoxin production. The leaves of *C. lanceolatus* may be a potential candidate for the development of antimicrobial and antidiabetic agents. However, further studies are warranted in relation to mechanisms of antimicrobial and antidiabetic properties, toxicity profiles, and other animal model investigations. This review will provide a scientific basis for future studies in connection with the isolation of biologically active components from *C. lanceolatus* for the development of novel drugs.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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