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

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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 polyphenols, alkaloids, terpenoids, 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.

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 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-Mejia et al., 2021; Zubair et al., 2013).

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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. Lanceolatus***

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). Sifosterol, erythrodiol, betulin, betulinic acid, ursolic acid, and 2-hydroxursolic 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′-hydroxyisopropyl)-5,6-dihydroxy-7,4′-dimethoxy flavone, 2,3,4-trihydroxyphenethyl tetracontanoate, and 2,3,4,5-tetrahydroxyphenyl tetracontanoate-4-β-xylopyranoside were isolated (Nazreen et al., 2019). In the aerial parts of *C. lanceolatus*, 4′,5-dihydroxy-6,8-dimethyl-7-methoxyflavonone, eucalyptin, 8-demethyleucalyptin, sideroxylin, syzyalitin, 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-hydroxyalphtolic acid, alphitoic acid, lupenol, 3-acetoxy-olean-18-28-ene acid, betulinic acid, ursolic acid, betulinic acid 3-O-caffeate, morlic acid 3-O-caffeate, and ursolic acid 3-O-caffeate from *C. lanceolatus*. 2-Amino-2-ethylpropane-1,3-diydoleate 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-trifluoromethylenzoic 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-Triacsonol, n-eicosanoyl palmitate, n-heptadecanal arachidate, n-tricosanoyl palmitate, 4-hydroxyphenethyl carbocerate, 4-hydroxyphenethyl ghdetate, urs-12-en-3alpha-acetoxy-18beta-H-28-oc acid, and stigmast-5-en-3beta-ol-3beta-D-glucuronopyranoside were also identified from *C. lanceolatus* (Nazreen et al., 2020). Two neolignans such as callisignan 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 1,8-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 extract 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*.

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observed for cardiac glycosides and phytosterols. The partially purified components showed the maximum inhibitory effect against methillin-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 antifungal 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 B1 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

Callisignan A

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

Sideroxylin

1,8-Cineole
**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-picylhydrazyl (DPPH), superoxide, nitric oxide, and hydroxyl radicals. Methanol extracts from the leaves of *C. lanceolatus* revealed a considerable DPPH radical scavenging activity with an IC₅₀ 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 ghdette 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”-hydroxisopropyl)-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 alloxaan-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 alloxaan-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 alloxaan-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 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 fungim 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 *Biophalaria alexandrina*. The extract of *C. lanceolatus* showed antithrombin activity (80%) based on a chromogenic bioassay (Chistikokhodova *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).
CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

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