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PHYTOCHEMICAL AND PHARMACOLOGICAL ASPECTS OF EUCALYPTUS GENUS

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ABSTRACT

Eucalyptus is a diverse genus of flowering trees and shrubs in the myrtle family, Myrtaceae. Different chemical constituents such as Sideroxylonal C, (+)-oleuropeic acid, cypellocarpins A, B and C, cypellogins A, B and C, Leptospermone, Isoleptospermone, grandinol, various essential oils and many others have been isolated from plants of eucalyptus genus. Various eucalyptus species have been reported to possess potent pharmacological actions against diabetes, hepatotoxicity, inflammation, cancer etc. This review article is presented to compile all the updated information on phytochemical and pharmacological activities of Eucalyptus species which have been performed by widely different methods.

INTRODUCTION: Eucalyptus is a large genus of evergreen aromatic tress, rarely shrubs (mallees), indigenous to Australia, Tasmania, New Guinea and the neighboring islands, where they constitute a large portion of the forest vegetation and giving it a characteristic appearance. Various species of *Eucalyptus* are cultivated, particularly in sub-tropical and warm temperate regions, on account of their economic value [1].

Eucalyptus species (Family- Myrtaceae) are remarkable for their rapid growth. Some species of them, in their natural habitat, attain gigantic sizes and are among the tallest trees of the world. Most of the species are popularly called "gum trees" although the exudation from them is not a gum, but an astringent; a tanniferous substance called "kino".

Major species: There are over 500 species of *Eucalyptus. Amygdalina*, *australiana*, *botryoides*, *calophylla*, *camaldulensis*, *citriodora, cladocalyx*, *consideniana*, *cypellocarpa, dives*, *gigantea*, *globulus*, *gomphocephala*, *grandis*, *gunnii*, *incrassate*, *kino*, *largeflorens*, *lesouefii*, *macrocarpa*, *macrorhyncha*, *maculata*, *marginata*, *melanophloia*, *melliodora*, *microtheca*, *nitens*, *ovata*, *pauciflora*, *perriniana*, *pilularis*, *polyanthemos*, *polybractea*, *populnea*, *radiata*, *regnans*, *risdonni*, *robusta*, *rossi*, *Ostrata*, *saligna*, *sideroxylon*, *sieberiana*, *smithii*, *tereticornis*, *tetrodonta*, *umbra*, *urophylla*, *viminalis*, *wandoo* are the major species of *Eucalyptus* genus.

Taxonomical Classification:

Kingdom	:	Plantae
Subkingdom	:	Tracheobionta
Super division	:	Spermatophyta
Division	:	Magnoliophyta
Class	:	Magnoliopsida
Subclass	:	Rosidae
Order	:	Myrtales
Family	:	Myrtaceae
Genus	:	*Eucalyptus*

PHYTOCHEMICAL AND PHARMACOLOGICAL ASPECTS:

1. *Eucalyptus albens*:

Chemical Constituents: Sideroxylonal C, isolated from the flowers of *Eucalyptus albens* is the major chemical constituent of *E. albens.*

Pharmacological Activity: Sideroxylonal C inhibits human plasminogen activator inhibitor type-1 without any significant effect on human tissue plasminogen activator [2].

2. *Eucalyptus amplifolia*

Chemical Constituents: Euglobal-Am-II, Euglobal-Am-IVb and Euglobal-Am-VII (acylphloroglucinol-monoterpenes) are the main chemical constituent.

Pharmacological Activity: Euglobal-Am-II isolated from leaves of Eucalyptus *amplifolia*, exhibit significant inhibitory effects on Epstein-Barr virus (EBV) [3].

3. *Eucalyptus camaldulensis:*

Chemical Constituents: Essential oil (Aromandendrene Myrtenal, Borneol, Camphene, Carvacrol Citronellal Citronellyl acetate, Cryptone- α- Terpenyl acetate.) [4], Flavonoids (Apigenin, Chrysin, Flavone, Luteolin, Eriodictyol, Hesperetin, Naringenin, Pinocem-brin), [5] Triterpenoids (Oleanolic Acid, Maslinic Acid, Camaldulic Acid, Camaldulensic Acid) are the main constituents present in *E. camaldulensis* [6-10].

Pharmacological Activity:

Antimicrobial: Bark of *Eucalyptus camaldulensis* is commonly used a chewing stick. Bark extract of *Eucalyptus camaldulensis* shows inhibition zones of comparable magnitude with those of the standard antimicrobial agents [11].

Anti-Nociceptive: *Eucalyptus camaldulensis*, possesses an anti-nociceptive effect against both acetic acid-induced writhing and hot plate-induced thermal stimulation [12].

Antioxidative: The extracts obtained by ethanol digestion and by supercritical fluid extraction (SFE; CO_2 with 15% ethanol) of leaves from *Eucalvptus camaldulensis* var. *brevirostris* trees show the most promising antioxidative activities. The main two compounds of the SFE extract with antioxidative activity are 5-hydroxy-7, 4'-dimethoxy flavone and 5-hydroxy-7, 4'-dimethoxy-8-methyl flavone. Gallic and ellagic acid are found to be the prevailing antioxidants in the ethanolic extract [13].

Cytotoxic: Extracts obtained from *Eucalyptus camaldulensis* has significant cytotoxic activity against human ECV-304 cells [14].

4. *Eucalyptus citriodora:*

Chemical Constituents: Essential oils (Cineole, Citronellal, Citronellic Acid) [15], Sterols (9β-Sitosterol) are mainly present in this species [16].

Pharmacological Activity:

Analgesic: Using acetic acid-induced writhes in mice and hot plate thermal stimulation in rats, it has been prooved that the essential oil of *Eucalyptus citriodora* induced analgesic effects in both models, suggesting peripheral and central actions.

Antifungal activity: The volatile oil extracted from the leaves of *Eucalyptus citriodora* showed a wide spectrum of antifungal activity. *Eucalyptus* oil, camphor and menthol and thymol oil are the most efficacious component against the fungal pathogens such as *Tricophyton rubru,, Trichophyton mentagrophytes*, *Microsporum canis*, *Epidermophyton floccosum* and *Epidermophyton stockdale* [17].

Anti-inflammatory: Essential oil from the *Eucalyptus citriodora* produced anti-inflammatory effects, Anti inflammatory activity of *Eucalyptus citriodora* demonstrated by inhibition of rat paw edema induced by carrageenan and dextran, neutrophil migration into rat peritoneal cavities induced by carrageenan, and vascular permeability induced by carrageenan and histamine.

Bone Resorption Inhibition: *Eucalyptus* essential oil and monoterpenes are efficient inhibitors of bone resorption in the rat [18].

Natural repellent: A lemon *Eucalyptus* extract (Citriodiol) has been shown to be a natural repellent against mosquitoes, stable flies, and midges [19]. It kill the *Ixodes ricinus* which can transmit several microorganisms, out of which *Borrelia burgdorferi* and tick-borne encephalitis (TBE) virus are the most important pathogens in humans.

5. *Eucalyptus cladocalyx:*

Chemical Constituents: triterpene named cladocalol isolated from the leaves, ursulolactone acetate, ursolic acid, 3- beta- acetate-12, 20 (29)-lupadien- 28- oic acid, beta- sitosterol and eucalyptine are the major chemical constituents of this species [20].

Pharmacological Activity: Cladocalol and its derivatives induce cytotoxic effect on the myeloid leukemia cell line HL-60.

6. *Eucalyptus cypellocarpa:*

Chemical Constituents: Acylated flavonol glycosides, cypellogins A, B and C are the major chemical constituents, present in leaves of *Eucalyptus cypellocarpa* [21].

Pharmacological Activity: Cypellogins A, B and C showed potent in vitro antitumor-promoting

activity. These compounds also suppressed an in vivo two-stage carcinogenesis induced with nitric oxide and TPA (12- O- tetradecanoyl phorbol 13-acetate) on mouse skin [22].

7. *Eucalyptus globules:*

Chemical Constituents: Euglobals, Essential oil (1, 8-Cineole, Carvone, Citral, Citronellal, Geranyl acetate, α-Pinene, α-Pinocarvone, β-Pinene) [23-25] Hydrocarbons (4-Hydroxytritriacontane-16, 18-dione, 16-Hydroxy Btritriacontanone, n-Tritriacontane 16, 18-dione), Macrocarpals H, I, J [26] are main chemical constituents.

Pharmacological Activity:

Antibacterial: A 50% EtOH extract of *Eucalyptus globulus* leaves have antibacterial activity against oral pathogenic microorganisms with MIC values ranging from 0.20 micrograms/mL to 6.25 micrograms/mL. A 50% EtOH-soluble material was extracted from the dried leaves of *E. globules* shows appreciable antibacterial activity against *S. mutans* Ingbritt and *P. gingivalis* ATCC 33277 (causes dental caries and periodontal disorders) with MICs values 12.5 and 6.25 μg/ml [27].

Dried residue of methalonic extract of *Eucalyptus globulus* leaves showed antimicrobial activity against *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa* and *Candida albicans* with minimum inhibitory concentration of 5.0, 10.0, 10.0, 1.25 mg/ml respectively [28]. Phloroglucinol- sesquiterpene coupled compounds, macrocarpals H, I, and J showed potent antibacterial activity and inhibitory effect of glucosyltransferase [29]. Ethanolic extract of *Eucalyptus globulus* also active against the reference strains of *Staphylococcus aureus*, *Saturia hortensis L., Teucrium polium L* [30]. Most concentrations of the extracts of the *Eucalyptus globulus* showed a high antibacterial activity against *Pseudomonas aerugenosa* [31].

Methanol-dichloromethane extract of *Eucalyptus globulus*, significantly inhibited the growth of six Gram-positive bacteria (*Staphylococcus aureus*, *MRSA*, *Bacillus cereus*, *Enterococcus faecalis*, *Alicyclobacillus acidoterrestris*, *Propionibacterium acnes*), and a fungus (*Trichophyton mentagrophytes*). Periodontopathic bacterial strains tested were killed completely by exposure for 30 seconds to 0.2% oil of *Eucalyptus globules* [32]. The antibacterial activity of *Eucalyptus globulus* leaf extract has been determined against *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus pneumoniae* and *Haemophilus influenzae* obtained from 200 clinical specimens of patients with respiratory tract disorders [33].

Antidiabetic: *Eucalyptus globulus* is used as a traditional treatment for diabetes. Incorporation of *Eucalyptus globulus* in the diet (62.5 g/kg) and drinking water (2.5 g/L) reduced the hyperglycemia and associated weight loss of streptozotocin-treated mice. An aqueous extract of *Eucalyptus globolus* (AEE) (0.5 g/L) enhanced 2-deoxy-glucose transport by 50%, glucose oxidation by 60% and incorporation of glucose into glycogen by 90% in abdominal muscle of mice. In acute, 20 min incubation, 0.25-0.5 g AEE/L evoked a stepwise 70-160% enhancement of insulin secretion from the clonal pancreatic beta-cell line (BRIN-BD11). These data indicate that *Eucalyptus globulus* represents an effective antihyperglycemic dietary adjunct for the treatment of diabetes and a potential source for discovery of new orally active agent(s) for future therapy [34.]

Antiplaque: *Eucalyptus globulus* may be useful in inhibiting dental plaque formation [35].

Antitumor: Antitumor-promoting activity of Euglobals Ia_1, Ia_2, Ib, Ic, IIa, IIb, IIc, III, IVa, IVb, and V and VIII has been tested *in vitro* on 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced Epstein-Barr virus early antigen (EBV-EA)

activation test system. Euglobal-III showed strong inhibitory activity, followed by euglobals Ib, IIa, Ic, Ia1, Ia2 [36.] *Eucalyptus globulus* oil inhibits the nuclear translocation of NF-kappa B induced by LPS in THP-1 cells [37].

Antiviral: Twelve euglobals from *Eucalyptus globulus* and their twenty-six related compounds were examined for their inhibitory effects on Epstein-Barr virus activation by a short-term in vitro assay. The results showed that most of the euglobals having monoterpene structures, and euglobal-III had strong inhibitory activity [38]. *Eucalyptus* globulus oil has antiviral activity against herpes simplex virus (herpes simplex virus-1 and -2) [39].

Antifungal: Freshly prepared camphor oil from *Eucalyptus globulus* with or without glycerol dilutions gave complete cure of human facial demodicidosis with concentrations of 100%, 75% and 50% [40]. *Eucalyptus globulus* leaf extracts and oil showed antifungal property as they progressively inhibited the growth of *Malassezia furfur* on Sabouraud's destrose agar medium [41].

Antihistaminic: Hexane extract of leaves, ethanol extract of fruits and leaves of *Eucalyptus globulus* inhibited IgE dependent histamine release from RBL-2H3 cells [42].

Anti-inflammatory: 1,8-cineole, major constituent present in volatile oil of *Eucalyptus globulus* is a strong inhibitor of cytokines, that might be suitable for long term treatment of airway inflammation in bronchial asthma and other steroid-sensitive disorders [43]. Using acetic acid-induced writhes in mice and hot plate thermal stimulation in rats, it has proved that the essential oil of *Eucalyptus globulus* induced analgesic effects in both models, suggesting peripheral and central actions. In addition, essential oil extracts from the *Eucalyptus globulus* produced anti-inflammatory effects, as demonstrated by inhibition of rat paw edema induced by carrageenan and dextran, neutrophil migration into rat peritoneal cavities induced by carrageenan, and vascular permeability induced by carrageenan and histamine [44].

E. *globulus* oil has the anti-inflammatory effect on chronic bronchitis induced by lipopolysaccharide in rats and the inhibition effect on hypersecretion of airway mucins [45]. E. *globulus* extracts significantly inhibited the enhanced production of NO induced by LPS and IFN-gamma in a dose-dependent manner. It is well known that nitric oxide (NO) plays an important role in the pathogenesis of inflammatory diseases. *Eucalyptus globulus* have been used in traditional medicine in the treatment of bronchitis, asthma and other respiratory diseases [46].

Cutaneous application of essential oils of *Eucalyptus globulus* to mice suppressed the cellular inflammation of skin. This suggests that essential oils using in aromatherapy massage may suppresses the inflammatory symptoms related with neotrophil accumulation and edema [47].

Antimalarial: *Eucalyptus globulus* oil significant action against plasmodium species. It is popularly used anti-malarial plants in Brazil [48.]

Antioxidant: The methanol extracts of *Eucalyptus globulus* showed efficiency in preventing the oxidation process.

Cytochrome p450 enzymes inhibitor: *Eucalyptus* oil (*Eucalyptus globulus*), is identified as inhibitor of the six major cytochrome P450 enzymes with IC(50) values between 20 and 1000 µg/Ml [49].

Intestinal Fructose Absorption Inhibition: *Eucalyptus globulus* leaf extract inhibits intestinal fructose absorption, and suppresses adiposity due to dietary sucrose in rats [50].

Larvicidal: *Eucalyptus globulus* leaves has potent action against *Culex quinquefasciatus* and *Culex tritaeniorhynchus* [51].

Nerve Blocker: Terpineol, a relatively nontoxic, volatile monoterpenoid alcohol, is a major component of the essential oil of *Eucalyptus globulus* (*Eucalyptus*), is widely used in folk medicine and aromatherapy. Terpineol induced a dose-dependent blockade of the compound action potential (CAP) of rat sciatic nerve [52].

8. *Eucalyptus grandis:*

Chemical Constituents: Volatile oil from *E. grandis* contains cyclic ketones i.e. Flavesone, Leptospermone, Isoleptospermone, grandinol [53], euglobals G8--G12, together with a known euglobal-IIc present in leaves of *Eucalyptus grandis* [54]. Other volatile oils present in *E. grandis* are α-pinene (44.7%), camphene (0.8%), β-pinene (30.5%), limonene (5.6%), β-phellandrene (0.2%), 1,8-cineole (2.7%), γ-terpinene (0.3%), terpinolene (0.8%), α-fenchyl alcohol (0.6%), terpinen-4-ol (0.9%) and α-terpineol (5.4%)

Pharmacological Activity:

Anticancer: Euglobal-G1 (EG-1) is an active constituent, inhibited the promotion stages on two-stage carcinogenesis induced by both TPA-type and non TPA-type promoter (fumonisin B1). It inhibited the pulmonary tumor genesis induced by 4-NQO and glycerol. Therefore, EG-1 might be valuable as a chemo protective agent in chemical carcinogenesis.

Antiviral: Euglobal- G1, -G2, and -G3 strongly inhibited the Epstein-Barr virus activation [55]. Euglobal-G1--G5 isolated from leaves of *Eucalyptus grandis* exhibited significant inhibitory effects on Epstein-Barr virus (EBV) activation induced by TPA.

9. *Eucalyptus macrocarpa:*

Chemical Constituents: Phloroglucinol dialdehyde diterpene derivatives (macrocarpals B, C, D, E, F, G) are the main constituents of leaves of *Eucalyptus macrocarpa* [56].

Pharmacological Activity: macrocarpals A, B, D, and G have inhibitory activity against porcine lens ALR2 (Aldose reductase) [57].

10. *Eucalyptus occidentalis:*

Chemical Constituents: 6, 8- di- *C*-methyl-kaempferol 3, 4'- dimethyl ether, 6, 8- di-*C*-methylkaempferol 3- methyl ether, oleanolic acid, and 2α, 3*β* dihydroxyurs- 12- en- 28- oic acid are the main constituents present in aerial parts of *Eucalyptus occidentalis*.

Pharmacological Activity: Flavonoids (6, 8-di-*C*-methylkaempferol 3, 4'-dimethyl ether and 6, 8-di-*C*-methylkaempferol 3-methyl ether) have been used for study the biological activities of the human promyelocytic leukemia cell line, HL-60. These compounds induce morphological changes and inter nucleosomal DNA fragmentation characteristic of apoptotic cell death, which is mediated by caspase-8/caspase-3 activation and cytochrome *c* release [58].

11. *Eucalyptus radiata*

Chemical Constituents: 1, 8-cineole (74.2%) followed by alpha-terpineol (11.6%) and limonene (4.5%) are the major component of essential oil of *Eucalyptus radiate* [59].

Pharmacological Activity: Volatile oil is effective against 20 species of *Listeria* monocytogenes [60].

12. *Eucalyptus robusta:*

Chemical Constituents: Robustadial A and B are the major constituents of *Eucalyptus robusta* leaves [61].

Pharmacological Activity: Decoction of the leaves and bark is used to treat fever and to wash skin diseases [62]. Leaves are used in China for the treatment of dysentery, malaria and bacterial diseases [63].

13. *Eucalyptus viminalis:*

Chemical Constituents: Euvimal-1 and euvimal-2 are the main constituents of leaf of *Eucalyptus viminalis*.

Pharmacological Activity:

Antibacterial: Methanol-Dichloromethane extract of *Eucalyptus viminalis* leaves significantly inhibited the growth of six Gram-positive bacteria (*Staphylococcus aureus, MRSA, Bacillus cereus, Enterococcus faecalis, Alicyclobacillus acidoterrestris, Propionibacterium acnes*), and of a fungus (*Trichophyton mentagrophytes*), but they did not show strong antibacterial activity against Gram-negative bacteria (*Escherichia coli, Pseudomonas putida*) [64].

14. *Eucalyptus tereticornis:*

Chemical Constituents: Essential oil (1, 8-Cineole, Camphene, Carvone, Citral. Citronellal, Geranyl acetate, Limonene, Linalool oxide), Phloroglucinol monoterpene derivatives (Euglobal-T1, Euglobal IIc), urosolic acid [65] and Triterpene esters (Tereticornate A and B) [66] are the main constituents of *E. tereticornis*.

Pharmacological Activity:

Anti-Hyperglycemic: *Eucalyptus tereticornis* exhibited anti-hyperglycemic activities when fed simultaneously with glucose [67].

Hepatoprotective: Ursolic acid isolated from the leaves of *Eucalyptus* hybrid *E. tereticomis* showed a dose dependent (5-20 mg/kg) hepatoprotective activity (21-l00%) in rats against thioacetamide, galactosamine and carbon tetrachloride induced hepatotoxicity [68].

Myorelaxant: Essential Oil of *Eucalyptus tereticornis* produces myorelaxant effects on guinea-pig isolated trachea [69].

CONCLUSION: The extensive survey of literature revealed that Eucalyptus species is an important source of many pharmacologically and medicinally important chemicals, such as Essential oils, terpenoids which have been use in aromatherapy. Various Eucalyptus species have also been widely studied for their various pharmacological activities like analgesic, antifungal, anti-inflammatory, antibacterial, antidiabetic, antioxidative, Antiviral, Antitumor, antihistaminic, anticancer cytochrome p450 inhibitor and hepatoprotective properties. Although aromatherapy is pleasant, inexpensive, and has little side effects (except for rare allergies), there is little evidence that it is effective in patients undergoing medical interventions.

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