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A SPECIAL EMPHASIS ON EUCALYPTUS GLOBULUS HAVING PHYTOCONSTITUENTS ALONG WITH IN-VIVO AND IN- VITRO PHARMACOLOGICAL ACTIVITY: A REVIEW

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Abstract
Eucalyptus globulus, a well-known species, has a wealth of therapeutic potential. The Eucalyptus globulus species, sometimes known as blue gum, thrives well in the Nilgiris, Annamalai, Palani, and Shimla hills. It has a high concentration of phytochemical elements like as flavonoids, alkaloids, tannin, and propanoid, which are found in the plant's leaves, steam, and root. Eucalyptus is extensively planted for pulp, plywood, solid wood production but its leaf aromatic oil has astounding wide spread biological activities including antimicrobial, antiseptic, antioxidant, chemotherapy agent, anticancer Cytochrome p450, Hepatoprotective effect, respiratory and gastrointestinal disorders treatment, wound healing, and insecticidal insect repellent, herbicidal, acaricidal, nematocidal, and perfumes, soap making and grease remover. In this study, we attempted to compile the biological components of leaf essential oil, leaf oil as a natural medicine, and the pharmacological and toxicological properties of several Eucalyptus species from around the world. The elements of Eucalyptus will disclose secrets beyond the traditional benefits for treating a wide range of diseases.

Keyword: - Cytochrome P450, Antioxidant, Acaricidal, Nematocidal.

Introduction

Plants and their parts have been employed in traditional medicine since antiquity. All plants are thought to have medicinal powers in Indian traditions. "Jagatyevamanoushadham na kinchit vidyate dravyam vasatnanartha yoga Yoh" Jivaka. It refers to the fact that "there is no plant in the world which is non-medicinal or which cannot be used as medicine" Eucalyptus plants have received special attention around the world in a variety of industries, including perfumes, medicines, nutraceuticals, and furniture. As a result, they are a rapidly developing source of wood as well as a source of oil utilized for a variety of uses (1). The name Eucalyptus is derived from the word "Eu" which means true and calyptus (kalypto) which means to cover; describing the flower bud created by combined calyx and corolla parts, which seal the flower until it blooms (2). For example, the oil derived from the leaves, fruits, buds, and bark has a broad spectrum of antibacterial, antiseptic, antioxidant, anti-inflammatory, and anticancer properties, and is thus traditionally used in the treatment of respiratory disorders, the common cold, influenza, and sinus congestion. (3, 4). Indeed,

the medicinal effect of Eucalyptus oil is owed to its primary ingredient, 1, 8-cineole (cineole or eucalyptol) (3, 5). Interestingly, several studies have shown that seasonal variations and even diurnal variations in essential oil yield and composition (e.g., -pinene, cineol, citronellal, citronellol, and isoeugenol) are heavily influenced by environmental circumstances (6, 7). In this regard, and in light of the numerous potentialities and current demand for Eucalyptus species, this review aims to address the botanical, chemical, and ethnopharmacological aspects of Eucalyptus plants, as well as the various in vitro and in vivo pharmacological activities reported thus far. Finally, and perhaps most intriguingly, a special emphasis is placed on clinical trials that report its feasibility for impending drug formulation.

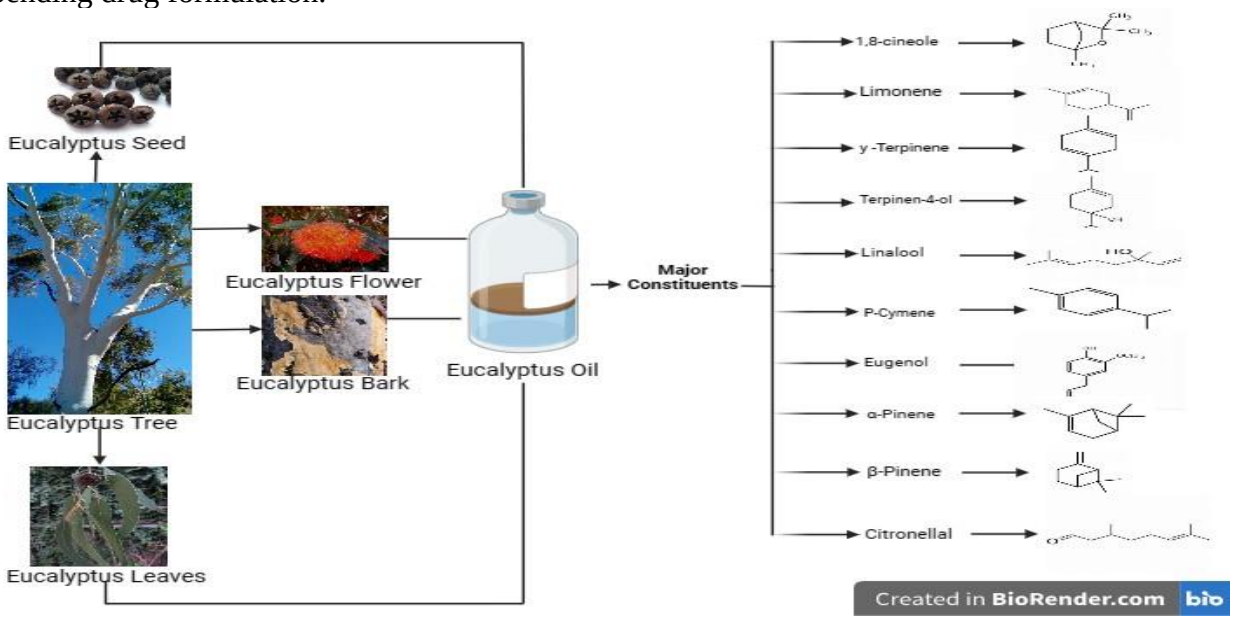


Figure 1: Parts of Eucalyptus Plants and Some Chemical Constituents

Traditional use of Eucalyptus

It is estimated that up to four billion people (80% of the world's population) rely on traditional herbal remedies for health treatment in the developing countries. The primary purpose of ethnopharmacology is to discover new chemicals originating from plants and animals that can be used in traditional medicine systems. This knowledge can be applied in pharmaceutical corporations to the development of new medications. (8, 9). Aborigines used the eucalyptus shrub for a variety of reasons, most notably medicine and food. Nowadays, the plant is utilized in forestry to produce lumber, fuel, paper pulp, environmental planting to manage water and wind erosion, as a source of essential oil for the pharmaceutical and perfumery industries, and for arts and crafts. (1). It is used as a component in many medicines to relieve cough, cold, and congestion symptoms. It is also found in lotions and ointments used to treat muscle and joint pain. Eucalyptus has the capacity to improve lung health, enhance the immune system, protect skin health, relieve stress and anxiety, lower blood sugar, eliminate inflammation, and fight bacterial infections. It is also traditionally used to promote mucus discharge in the respiratory tract. The largest source of eucalyptus oil utilized internationally is Eucalyptus globulus, popularly known as Blue Gum (10, 11). For many years, not only aboriginal Australians, but also Chinese, Indian Ayurvedic, Greek, and other European forms of medicine have used it to treat a wide range of ailments (11). The leaf extract of Eucalyptus spp. is a well-known example of a tree that has been utilized as an anti-inflammatory, antibacterial, and antioxidant agent (12, 13). Aboriginal communities in Australia have always employed the Eucalyptus genus for medicinal purposes. Indeed, previous aboriginal societies used a diverse range of Australian wild plants as bush meals and medicines. Several Eucalyptus species were employed as tonics by Aboriginals to treat gastro-intestinal symptoms (14). Red kino, often known as red gum, is obtained by creating incisions in tree trunks and applying it directly to abrasions and injuries. Throughout

Australia, dried gum was made by combining fresh gum with water and then dehydrating it. Young leaves have been used to make smoke baths, in which a patient sits surrounded by smoke medicine made from burning leaves and used to cure fevers, colds, flu, and general illness (15, 16, 17). Numerous studies have been conducted to investigate the therapeutic value of the red gum tree. Tree phytoconstituents have been documented to include essential oils, sterols, alkaloids, glycosides, flavonoids, tannins, and phenols. Colds, asthma, coughs, diarrhoea and dysentery, haemorrhage, laryngoplegia, laryngitis, sore throat, spasm, trachagia, and vermifuge are all common clinical diseases treated by the tree in traditional medicine (18). The essential oil derived from the leaves of E. globulus Labill is known to be a rich source of traditional remedies with a wide range of biological properties The introduction of Eucalyptus species to East Africa, on the other hand, was motivated by the necessity for a fast-growing wood source to fuel the train system's expansion (14). Wood pulp is the primary source of cellulose used in the manufacturing of textiles and fine paper. The majority of the 'dissolving pulp' comes from E. grandis, E. smithii, E. nitens, E. dunnii, E. globulus, and E. urophylla. (19).

Eucalyptus species Chemical Composition

There are about 700 Eucalyptus species, the most of which are native to Australia, with a small number also present on the neighbouring islands of Papua New Guinea, Indonesia, and the Philippines. Several studies have described the chemical composition of several eucalypt species.

Sr. No	Eucalyptus Sapp.	Phytoconstituents	Reference
1.	E. bicostata	α-pinene, limonene, 1,8-cineole, ρ-cymene, trans-pinocarveol, α-terpineol, globulol, viridiflorol α-pinene, camphene, β-pinene, limonene, γ-terpinenene, β-trans-ocimene,ρ-cymene, α-ρ-dimethylstyrene, pinocarvone, fenchol.	20
2.	E. bosistoana	α-pinene, α-phellandrene, ρ-cymene, limonene, β-phellandrene, γ-terpinene, ρ-cymenene.	21
3.	E. botryoides	E. botryoides α-pinene, limonene, 1,8-cineole, ρ-cymene, α-terpineol, borneol, caryophyllene oxide, globulol.	20
4.	E. camaldulensis	1,8-cineole, ρ-cymene, β-phellandrene, limonene, γ-terpinene.	22
5.	E. cinerea	α-terpineol, α-pinene, α-terpinyl acetate, ρ-cymene.	23
6.	E. citriodora	citronellal, iso-isopulegol, citronellol, isopulegol, trans caryophyllene.	22
7.	E. cladocalyx	α-pinene, limonene,ρ-cymene, trans-pinocarveol, α-terpineol, borneol, globulol, spathulenol.	20
8.	E. diversicolor	α-pinene, α-phellandrene, ρ-cymene, cryptone, α-terpineol, caryophyllene oxide,	20
9.	E. exserta	ρ-cymene, α-terpineol, D-piperitone, caryophyllene oxide, globulol, viridiflorol, spathulenol,	20
10.	E. fasciculosa	α-pinene, limonene, 1,8-cineole, ρ-cymene, cryptone, α-terpineol, bicyclogermacrene, caryophyllene oxide,viridiflorol, spathulenol.	20
11.	E. gigantea	α-pinene,ρ-cymene, cryptone, α-terpineol, caryophyllene oxide	20
12.	E. globulus	spathulenol, α-terpineol, α-pinene, limonene, tricyclene, camphene.	22
13.	E. gomphocephala	ρ-cymene, β-phellandrene, eucalyptol, 4-(1-methylethyl)-benzaldehyde, citral (isomer 1) cis-,trans-, 3-octil acetate, β-bisabolene, dihydrocarveol acetate, megastigma-3,7(Z),9-triene, α-limonene diepoxide	23
14.	E. gracilis	α-pinene, ρ-cymene, limonene, β-phellandrene, γ-	24

		terpinene, isoamyl isovalerate, fenchol,	
15.	E. grandis	γ-terpinene, o-cimene, β-pinene,α- terpinyl acetate.	22
16.	E. gunni	α-phellandrene, 1,8-cineole, ρ-cymene, bicyclogermacrene.	20
17.	E. macarthurii	trans-pinocarveol, cryptone, α-terpineol, α-pinene, camphene, β-pinene, myrcene, limonene, β-phellandrene	20
18.	E. macroyncha	β-eudesmol, farnesyl acetate, jacksone, isobicyclogermacral, (E,E)-farnesol, β-phenyl propanoate, cis-jasmone.	20
19.	E. maidenii	α-cadinol, α-eudesmol, β-eudesmol, farnesyl acetate,	20
20.	E. odorata	limonene, 1,8-cineole, ρ-cymene, trans-pinocarveol, cryptone, α-terpineol, d-piperitone, spathulenol	20
21.	E. oleosa	α-pinene, sabinene, ρ-cymene, limonene, β-phellandrene, γ-terpinene, isoamyl isovalerate, fenchol.	24
22.	E. ovata	α-pinene, limonene, trans-pinocarveol, α-terpineol, borneol, globulol, viridiflorol, spathulenol, α-eudesmol, β-eudesmol.	20
23.	E. pauciflora	alcohol, eugenol, thymol, carvarol, carvacrol, α-gurjunene, β-elemene, β-caryophyllene, aromadendrene.	21
24.	E. resinifera	9,12-octadecadienoic acid(Z,Z)-, phenyl methyl ester, eucalyptol, 9,12,15-octadecatrienal, α-terpineol	23
25.	E. saligna	limonene, ρ-cymene, γ-terpinene, α-pinene, α-terpineol, α- camphonellal, α-pinene oxide, o-cimene.	22
26.	E. salmonophloia	α-pinene, camphene, ρ-cymene, limonene, 1,8-cineole, β-phellandrene, γ-terpinene, isoamyl isovalerate, fenchol, cis-verbenol.	24
27.	E. salubris	α-fenchene, sabinene, ρ-cymene, limonene, β-phellandrene, isoamyl isovalerate, fenchol, trans-pinocarveol, borneol	24
28.	E. sideroxylon	ρ-cymene, trans-pinocarveol, α-terpineol, bicyclogermacrene.	20
29.	E. staigeriana	α-terpinolene, isopulegol, β-citronellal, β-citronellol, Z-citral, transgeraniol, methyl geranate, geraniol acetate	25
30.	E. tereticornis	δ-cadinol, agarospirol, α-cadinol, α-eudesmol, isospathulenol, β-eudesmol, farnesyl acetate, (E,E)-farnesol, lateriticone, β-phenyl propanoate.	20
31.	E. viminalis	myrcene, isoamyl isovalerate, bornyl acetate, fenchol, terpinene-4-ol, mentha-1,8-dien-4-ol.	20

Table1: Phytochemicals present in Eucalyptus species leaves using hydro and steam (*) distillation

Phytochemical Stem (26).

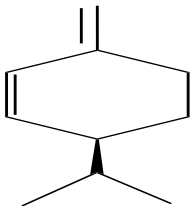
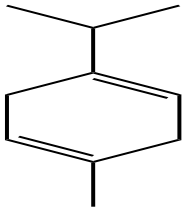
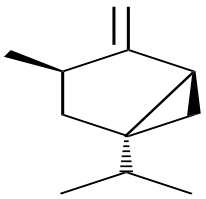
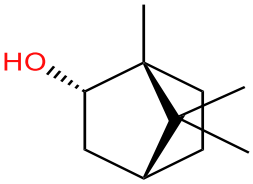
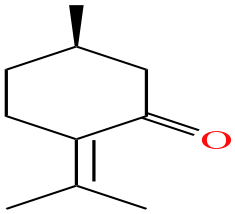
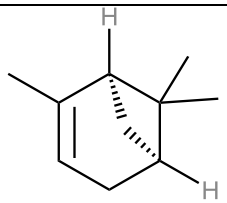
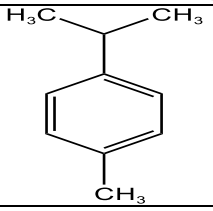
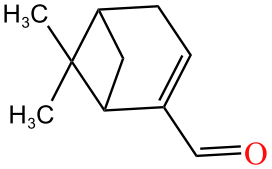
Sr. No	Phytoconstituents	Structure
1	β-phellandrene	
2.	γ-terpinene	
3.	cis-sabinol	
4.	Borneol	
5.	Pulegone	

Table 2: Phytoconstituents Stem and Chemical Structures

Phytochemical Fruits (27).

Sr. No	Phytoconstituents	Structures
1.	α-pinene	
2.	ρ-cymene	
3.	Myrtenal	

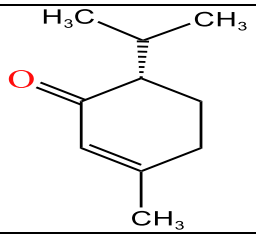
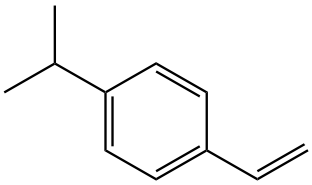
4.	Piperitone	
5.	Cuminaldehyde	

Table 3: Phytoconstituents Fruit and Chemical Structures

Phytochemical Flowers (27).

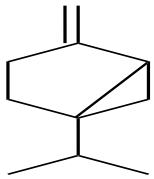
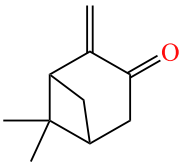
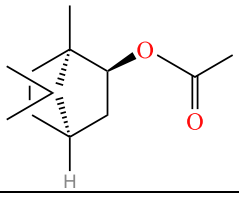
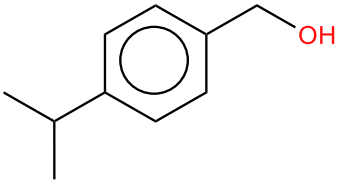
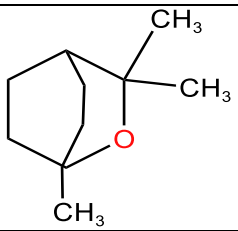
Sr. No	Phytoconstituents	Structures
1.	Sabinene	
2.	Pinocarvone	
3.	Bornyl acetate	
4.	ρ-cymen-7-ol	
5.	1,8-cineole	

Table 4: Phytoconstituents Flower and Chemical Structures

In Vitro Pharmacological Activities of Eucalyptus species

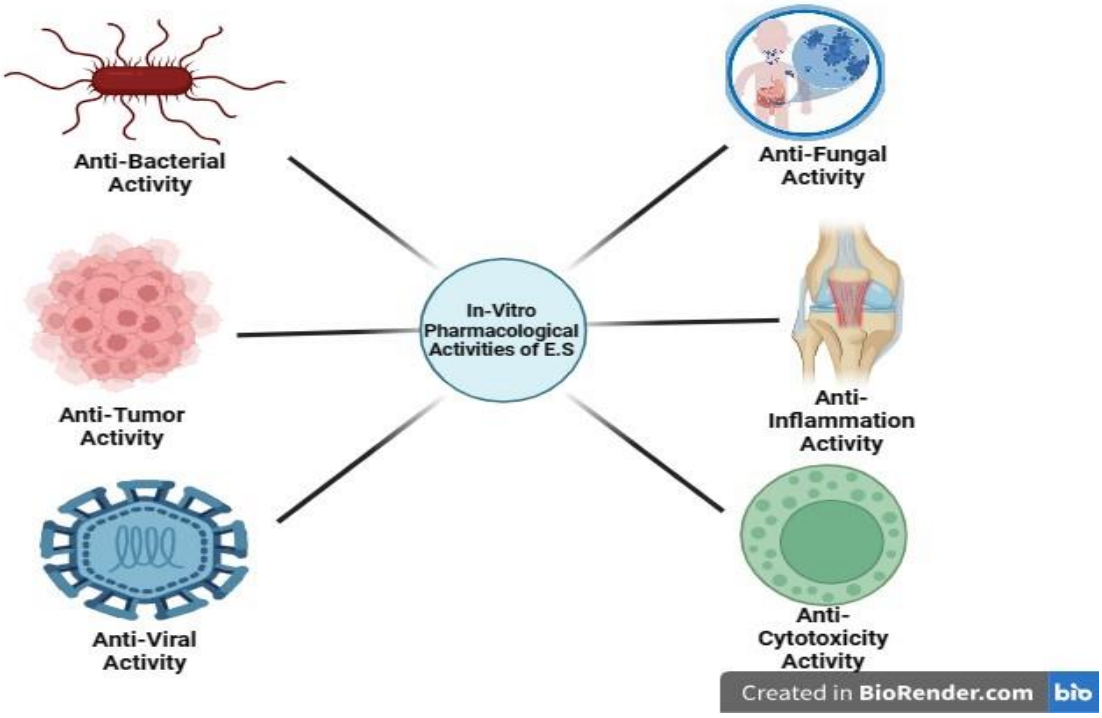


Figure 2: 'Eucalyptus species' In vitro Pharmacological Activities

1. Anti-bacterial activity: - The antibacterial activity of Eucalyptus essential oils and selected components against Gram-positive and Gram-negative bacteria, including multidrug-resistant bacterium pathogens, has been studied. The plant was gathered in Algeria, the oil was extracted via hydrodistillation, and the activity was determined using agar disc diffusion and dilution broth techniques. The oil was found to have antibacterial action against Gram-positive and Gram-negative bacteria, S. aureus and E. coli, in this study. (27). Furthermore, the antibacterial activity of essential oils extracted from the leaves of two Eucalyptus species (E. globulus and E. camaldulensis) against S. aureus and E. coli bacteria was determined. Three distinct assays were used to determine the inhibitory activity aromatogramme, micro atmosphere, and germs in suspension. The results showed that the two species oils inhibited both bacteria, but only to a lesser extent E. coli. (28). Based on these findings, Eucalyptus essential oil's antibacterial activity may indicate its potential utility as a micro biostatic, antiseptic, or disinfectant agent, particularly against Gram-positive bacteria.

2. Antifungal activity: - After five days of incubation, the essential oil totally suppressed the mycelia growth of the five isolates tested at concentrations ranging from 7 to 8 L/ml. (29). Furthermore, the fungicidal activity of leaves essential oil from E. grandis x E. urophylla, a fast-growing hybrid clone between E. grandis and E. urophylla, was tested against rice blast fungi (e.g., Setosphaeria turcica, Magnaporthe grisea, Botrytis cinerea, Fusarium graminearum, and others). With a final concentration of 2.5 mg/ml, the oil inhibited mycelium development significantly.

3. Antiviral activity: - Following a 10-minute exposure to oil vapours the essential oil of E. globulus demonstrated substantial veridical activity against influenza virus. Furthermore, this activity was found with no discernible negative effect on the epithelial cell monolayers. (30).

4. Cytotoxicity and antitumor activity: -The essential oils extracted from juvenile and adult leaves of E. benthamii collected in Brazil were tested for cytotoxicity on Jurkat, J774A.1, and HeLa cell lines. GC/MS examination of the extracted oils revealed that the primary constituents of the oil were -pinene, globulus, aromadendrene, and -terpinene. The cytotoxic activity was determined using the MTT assay, which revealed that the essential oil had a considerable cytotoxic effect on Jurkat and HeLa cell lines. Furthermore, the LDH activity and decrease in DNA content revealed that the

cytotoxic activity against Jurkat cells most likely involves cell death via induction of apoptosis and inhibition of cell growth, respectively. (31).

Sr. No	Bioactivity	Eucalyptus Species	Part used	Applied evaluation assay	Reference
1.	Antioxidant	E.camaldulensis Dehnh.	Hydro distilled oil of the aerial parts leaves	DPPH radical	6
2.	Anti-inflammatory and analgesic	Unspecified Eucalyptus sp. (Palestine)	Leaves ethanolic extract (gallic acid and chlorogenic acid)	Determination of TNF-α and IL-6 by immunoassay ELISA test	12
3.	Pesticide, insecticide and herbicide	E.camaldulensis, E. astringens, E. leucoxylon, E. slehmannii and E. rudis (Tunisia)	Hydrodistilled dried leaves	Fumigation activity against three stored-date moth pests: Ephestiakuehniella, Ephestiacautella and Ectomyeloisceratoniae.	7

Table 6: Other Pharmacological Activities for Eucalyptus have been reported, as summarized.

In -Vivo Pharmacological Activities of Eucalyptus Species

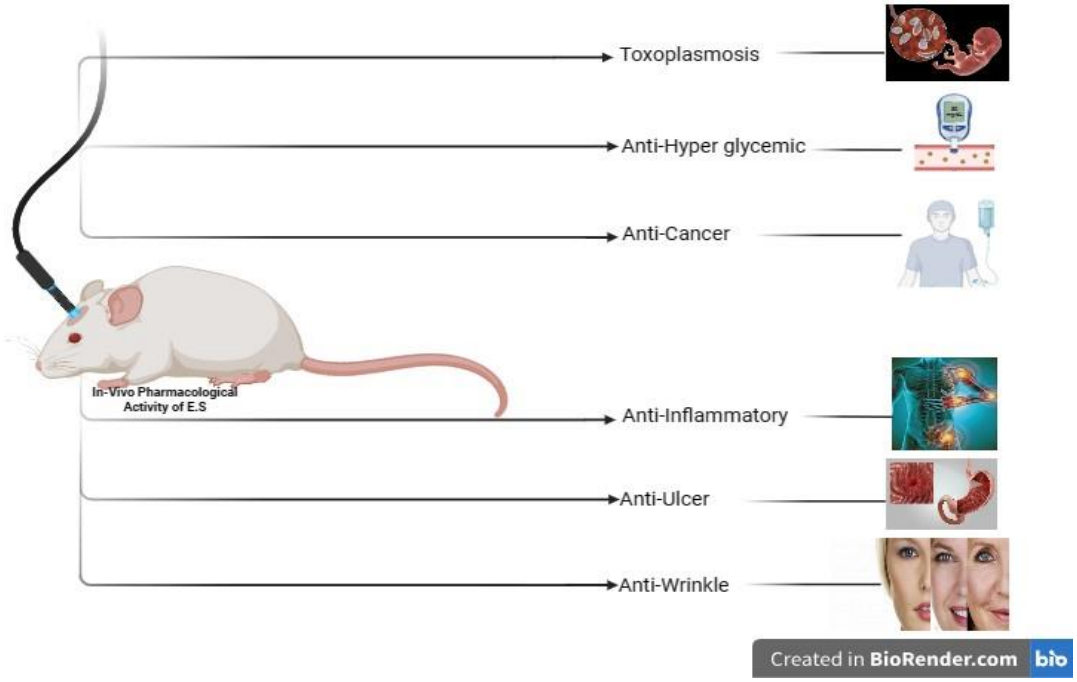


Figure 3: 'Eucalyptus species' In vitro Pharmacological Activities

Sr. No	Extract	Dose	Model	Result	Reference
1.	Toxoplasmosis 97% Ethanol extract of Eucalyptus leaves	100 and 200 mg/kg/day	Female Balb/c mice IP inoculated with T. gondii (RH strain, 2×103 tachyzoites per mouse)	Reduction in the spleen index	32
2.	Antihyperglycemic Alcoholic extract of E. globulus leaves	sole beverage for 15 days; each 150 g animal ingested the equivalent of 20 mg dry leaves/day	Alloxan-diabetic rats	Restored blood glucose to almost normal levels; increased SOD, CAT and GPX activities in liver and kidney	33

3.	Anticancer Euglobal-G1 isolated from the leaves of E. grandis	For pulmonary tumor: glycerol solution containing 0.0025% EG-1 (intake of EG-1 was 1.26 mg/mouse per week) as drinking solution for 25 weeks. For skin tumor: a topical application of EG-1 (250 mol) 1 h before each promotion treatment	Specific pathogen-free female SENCAR (6 weeks old) mice Pulmonary tumor initiated by single subcutaneous injection of 0.3 mg of 4-NQO per mouse. Promotion was done by Glycerol (8%). Skin tumor was initiated topically by DMBA (100 mg, 390 mol) and promoted by .fumonisin B1 (36 mg, 50 mol) application in acetone (0.1 ml) twice a we	> 60% inhibition in the total number of pulmonary tumor> 45% reduction in the percentage of mice with the tumours' in the pulmonary lobe 42% reduction in the number of papillomas	34
4.	Analgesic Essential oils of E. citriodora (EC), E.STereticornis (ET), and E. globulus (EG)	In mice: 0.1, 10, and 100 mg/kg subcutaneously 30 min prior to the injection of acetic acid. In rats: Intraperitoneal injection at a dose of 10 or 100 mg/kg	Acetic acid-induced writhes in mice and hot plate thermal stimulation in rats	43–73% of inhibitory effect EC was the most effective followed by ET and EG. In hot plate model: prolongation of the reaction time at several time points 30 min post treatment	35
5	Methanol and 50% ethanol of E. camaldulensis	800 mg/kg per os	Tail flick method in mice	50% ethanol extract seemed to be full of analgesic component; the highest effect of the methanol extract was seen in 180 min, whereas of the 50% ethanol extract at 60 and 90 min with the turn over time in around 90 mi	36
6	Anti-inflammatory Essential oils of E. citriodora, E. tereticornis, and E. globulus	10 or 100 mg/kg subcutaneously	Paw edema was induced by a single 0.1 ml sub plantar injection of Carrageenan (200 µg/paw) or dextran (300 µg/paw), containing prostaglandin I2 (PGI2, 200 mg/ paw)	Marked reduction of edema. Significant reduction of neutrophils migration. Significant reduction of vascular permeability	35
7	E. robusta leaves methanolic extract	25 mg/kg body weight	Experimental endometritis was induced in female adult Wistar rats using the mixed culture of clinical	No cardinal inflammation signs. Significant decrease in secretion index, reduction in bacterial load and polymorph nuclear cells	37

			isolates (E. coli and S. aureus	count in uterine discharge, decrease in levels of TLR-4 and TLR-9, and increase in COX1 and decrease in COX-2, MPO, NO, iNOS, and in serum levels of IL-10 and serum amyloid A	
8	Methanol and 50% ethanol of E. camaldulensis	300 mg/kg per	0.1 ml of 1% w/v Carrageenan suspension was injected subcutaneously into the planar surface of the right hind paw of rats	50% ethanol extract showed the highest protective ratio (54.58%) compared to 37.64% of methanol extract	36
9	Antiulcer Methanol and 50% ethanol of E. camaldulensis	300 mg/kg per	Ulcer induced by 60% Ethanol and 37% HCl in the ratio of (8:2) was given to mice 1 h after treatment	Protective ratio of 44.44% and 41.67% was observed in methanol and 50% ethanol	36
10.	Anti-diarrheal Methanol and 50% ethanol of E. camaldulensis	500 mg/kg per	Gastrointestinal transit was measured using the charcoal propulsion test	Methanol and 50% ethanol extracts showed preventive indexes of 62.54% and 60.36%	36
11	Antiwrinkle 50% ethanol extracts of E. globulus	Topical application of 1% and 5% extracts three times per week 1 h after UVB irradiation for four weeks	UV-induced photoaging in UVB-irradiated hairless mice	Decrease in erythema index, reduction in UVB-induced wrinkle formation; inhibition of the increased epidermis thickness Restored the collagen fibres, attenuated MMP-1 activation and increased the precollege type 1, TGF-β1, and elastin abundance	38

Table 7: In Vivo Pharmacological Activities of Eucalyptus Species

Conclusion

The Eucalyptus genus has long been employed in traditional medicine. Indeed, Eucalyptus plants have a wide range of biological benefits, including antibacterial, antiseptic, antioxidant, anti-inflammatory, and anticancer properties. Eucalyptol (1,8-cineole) is the primary component responsible for the therapeutic efficacy of Eucalyptus oil. The use of essential oils, particularly Eucalyptus essential oil, in nanotechnology has promising future prospects. Indeed, Nano-emulsions containing E. globulus oil have been extensively recognized for their antibacterial and antibiofilm properties against gram-negative and gram-positive bacteria, as well as the principal pathogen responsible for causing fungal infections globally (C. albicans). Nonetheless, the public's impression of Eucalyptus essential oil as a safe product contrasts with the significant risk that occurs when a pure essential oil is utilized. Allergic contact dermatitis is the most commonly seen adverse impact connected with the increased use of Eucalyptus essential oil in cosmetic and personal hygiene products, but others have been reported, particularly when used at high concentrations. As a result, a more thorough risk assessment of Eucalyptus essential oil toxicity is required.

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