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The pharmacological and therapeutic importance of Eucalyptus species grown in Iraq

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Abstract:- Eucalyptus species grown in Iraq were included *Eucalyptus bicolor* (Syn: *Eucalyptus largiflorens*), *Eucalyptus griffithsii*, *Eucalyptus camaldulensis* (Syn: *Eucalyptus rostrata*) *Eucalyptus incrassate, Eucalyptus torquata* and *Eucalyptus microtheca* (Syn: *Eucalyptus coolabahs*). Eucalypts contained volatile oils which occurred in many parts of the plant, depending on the species, but in the leaves that oils were most plentiful. The main constituent of the volatile oil derived from fresh leaves of Eucalyptus species was 1,8-cineole. The reported content of 1,8-cineole varies for 54-95%. The most common constituents co-occurring with 1,8-cineole were limonene, α-terpineol, monoterpenes, sesquiterpenes, globulol and α , β and ϒ-eudesmol, and aromatic constituents. The pharmacological studies revealed that Eucalypts possessed gastrointestinal, antiinflammatory, analgesic, antidiabetic, antioxidant, anticancer, antimicrobial, antiparasitic, insecticidal, repellent, oral and dental, dermatological, nasal and many other effects. The current review highlights the chemical constituents and pharmacological and therapeutic activities of Eucalyptus species grown in Iraq.

Keywords: *Eucalyptus species, constituents, pharmacological, therapeutic*

I. INTRODUCTION:

In the last few decades there has been an exponential growth in the field of herbal medicine. It is getting popularized in developing and developed countries owing to its natural origin and lesser side effects. Plants are a valuable source of a wide range of secondary metabolites, which are used as pharmaceuticals, agrochemicals, flavours, fragrances, colours, biopesticides and food additives [1-50]. Eucalyptus species grown in Iraq were included *Eucalyptus bicolor* (Syn: *Eucalyptus largiflorens*), *Eucalyptus griffithsii*, *Eucalyptus camaldulensis* (Syn: *Eucalyptus rostrata*) *Eucalyptus incrassate, Eucalyptus torquata* and *Eucalyptus microtheca* (Syn: *Eucalyptus coolabahs*)[51-54]. Eucalypts contained volatile oils which occurred in many parts of the plant, depending on the species, but in the leaves that oils were most plentiful. The main constituent of the volatile oil derived from fresh leaves of Eucalyptus species was 1,8-cineole. The reported content of 1,8-cineole varies for 54-95%. The most common constituents co-occurring with 1,8-cineole were limonene, α-terpineol, monoterpenes, sesquiterpenes, globulol and α , β and ϒ-eudesmol, and aromatic constituents. The pharmacological studies revealed that Eucalypts possessed gastrointestinal, antiinflammatory, analgesic, antidiabetic, antioxidant, anticancer, antimicrobial, antiparasitic, insecticidal, repellent, oral and dental, dermatological, nasal and many other effects. The current review will highlight the chemical constituents and pharmacological and therapeutic activities of Eucalyptus species grown in Iraq.

Synonyms

Eucalyptus bicolor:*Eucalyptus largiflorens* F. Muell., *Eucalyptus parviflora* F. Muell. and *Eucalyptus pendula* [55].

Eucalyptus camaldulensis: *Eucalyptus acuminata* Hook, *Eucalyptus canalouensis* Dehnh, *Eucalyptus rostrata* Schltdl, *Eucalyptus longirostris* F. Muell. ex Miq, *Eucalyptus subulata* A. Gray, *Eucalyptus camaldulensis* subsp. camaldulensis, *Eucalyptus camaldulensis* subsp. obtusa (Blakely) Brooker & M.W. McDonald, *Eucalyptus camaldulensis* var. acuminata (Hook.) Blakely, *Eucalyptus camaldulensis* var. brevirostris (F. Muell. ex Miq.) Blakely, *Eucalyptus camaldulensis* var. camaldulensis, *Eucalyptus camaldulensis* var. obtusa Blakely, *Eucalyptus camaldulensis* var. pendula Blakely & Jacobs, *Eucalyptus camaldulensis* var. subcinerea Blakely, *Eucalyptus longirostris* f. brevirostris F.Muell. ex Miq, *Eucalyptus longirostris* forma longirostris Miq; *Eucalyptus rostrata* var. acuminata (Hook.) Maiden, *Eucalyptus rostrata* var. borealis R. T. Baker & H. G. Sm; *Eucalyptus rostrata* var. brevirostris Maiden and *Eucalyptus tereticornis* var. rostrata (Schldl.) Ewart [56].

***Eucalyptus griffithsii*:** *Eucalyptus griffithsii var. angustiuscula* [57].

Eucalyptus incrassata*: *Eucalyptus costata F. Muell., *Eucalyptus costata* subsp. *murrayana* L A S Johnson & K D Hill, *Eucalyptus incrassata* subsp *costata* F Muell and *Eucalyptus incrassata* subsp. *costata* (F Muell) F C Johnstone & Hallam [58].
Eucalyptus microtheca*: *Eucalyptus coolabah and *Eucalyptus raveretiana var. jerichoensis* [59-60].
***Eucalyptus rostrata*:** It is one of the synonyms of *Eucalyptus camaldulensis* [61].
Taxonomic classification:
Kingdom: Plantae, **Subkingdom:** Viridiplantae, **Infrakingdom**: Streptophyta, **Superdivision**: Embryophyta, **Division**: Tracheophyta, **Subdivision**: Spermatophytina, **Class**: Magnoliopsida, **Superorder:** Rosanae, **Order**: Myrtales, **Family**: Myrtaceae, **Genus**: *Eucalyptus* [62].

II. COMMON NAMES

Eucalyptus bicolor: **Arabic:** kalebtoz, kalmtoz; **English**: red box, goborro.
***Eucalyptus camaldulensis* (syn: *Eucalyptus rostrata*): Afrikaans**: rooibloekom; **Arabic:** eucalyptus, eucalyptus kamali, Kaffour, kena; **Chinese**:chi an; **English**: blue gum, Murray red gum, red gum, red river gum, river gum, river red gum; **French**: eucalyptus rouge; **German**: roter Eukalyptus; **Indonesian**: ekaliptus; **Italian**: eucalipto rostrato; **Spanish**: eucalipto-negro, eucalipto-rojo; **Swedish**: röd eucalyptus [63].

***Eucalyptus griffithsii*: English**: grey gum, Griffith's grey gum [64]**.**
***Eucalyptus incrassata*: English:** lerp mallee, mallee-box, ridge-fruit mallee, yellow mallee [64]**.**
***Eucalyptus microtheca* (Syn: *Eucalyptus coolabahs*): English:** coolabahs, coolibah, flooded-box, western coolibah [60, 63].

***Eucalyptus torquata*: Arabic:** Kalptos**, English:** christmas tree, coolgardie gum, coolgardie-rose, coral gum, coral-flower gum, goldfields red-flower gum, pink-flower gum [65].

III. DISTRIBUTION

Eucalyptus is a large genus 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. Now Eucalyptus genus is found in almost all parts of the world due to human introduction, particularly in sub-tropical and warm temperate regions [63-64, 66-67].

IV. DESCRIPTION

Eucalyptus bicolor:

Tree to 20 m high; bark persistent, grey to grey black, fibrous-flaky (box), throughout. Juvenile leaves disjunct, linear, dull grey-green to glaucous. Adult leaves disjunct, narrow-lanceolate to lanceolate, 9–18 cm long, 0.8–1.8 cm wide, grey-green, dull, concolorous. Conflorescence compound; umbellasters 7–11-flowered; peduncle terete, 3–11 mm long; pedicels terete, 1–5 mm long. Buds ovoid, 4–5 mm long, 2–3 mm diam., scar present; calyptra hemispherical or conical, shorter and narrower than hypanthium. All stamens fertile. Fruit hemispherical or ovoid-truncate, 3–6 mm long, 3–5 mm diam.; disc depressed; valves enclosed or rim-level [68-69].

Eucalyptus camaldulensis:

Eucalyptus camaldulensis commonly grows to 20 m tall, occasionally reaching 50 m, with a trunk diameter of 1 (max. 2) m; in open formations has a short, thick bole and a large, spreading crown; in plantations has a clear bole of 20 m with an erect, lightly branched crown; bark smooth, white, grey, yellow-green, grey-green or pinkish grey, shedding in strips or irregular flakes; rough bark occupies the 1st 1-2 m of the trunk. Leaves grey-blue, alternate, drooping, 8-22 cm long, 1-2 cm wide, often curved or sickle shaped, tapering, short pointed at base. Inflorescence axillary, solitary, 7-11 flowered; flower buds white, globularrostrate or ovoid-conical; operculum hemispherical, rostrate or conical, 4-6 x 3-6 mm, obtuse. Fruit very small capsules at the end of thin stalks, 5-8 mm, valves 4, containing minute seeds [70-71].

Eucalyptus griffithsii:

Bark: smooth throughout, white or grey or red-brown. Leaves: Intermediate leaves disjunct early, lanceolate to ovate, straight, entire, dull grey green, petiolate. Adult leaves disjunct, lanceolate, falcate, acute, basally tapered, glossy, green or grey-green, thick, concolorous; Petioles narrowly flattened or channelled. Lateral veins obscure, acute. Inflorescences: Conflorescence simple, axillary; Umbellasters 3-flowered. Peduncles narrowly flattened or angular (to 3mm wide). Flowers: Buds clavate, not glaucous or pruinose. Calyx calyptrate; shedding early. Calyptra hemispherical, 1 times as long as hypanthium, wider than hypanthium;

corrugated. Hypanthium ribbed. Flowers white. Fruits: campanulate. Disc depressed. Valves exserted. Chaff dimorphic, linear and cuboid [72-73].

***Eucalyptus incrassata*:**

Bark: smooth throughout, grey or grey-brown, shedding in long ribbons. Branchlets green. Leaves: Intermediate leaves disjunct early, elliptic to ovate, straight, entire, dull grey green to dull green, petiolate, 10 cm long, 5 mm wide. Adult leaves disjunct, lanceolate or broad lanceolate, not falcate, obtuse or apiculate, basally tapered, glossy or semi-glossy, grey-green, thick, concolorous, 6–11 cm long, 1.5–2.5 mm wide; Petioles narrowly flattened or channelled, Petioles 10–20 mm long. Lateral veins obscure, acute, moderately spaced. Inflorescences: Conflorescence simple, axillary; Umbellasters 3-flowered to 7-flowered, regular. Peduncles narrowly flattened or angular (to 3mm wide), 13–20 mm long. Pedicels terete, 3–5 mm long. Flowers: Buds cylindrical or fusiform, not glaucous or pruinose, 12–20 mm long, 6–8 mm diam. Calyx calyptrate; shedding early. Calyptra conical (often beaked), 2 times as long as hypanthium or 3 times as long as hypanthium, as wide as hypanthium; smooth, or ribbed. Hypanthium smooth, or ribbed. Flowers cream. Fruits: cylindrical or urceolate (slightly), pedicellate, 3–4 locular, 8–13 mm long, 7–11 mm diam. Disc depressed. Valves enclosed. Chaff dimorphic, linear and cuboid, chaff same colour as seed [74-75].

***Eucalyptus microtheca* (Syn: *Eucalyptus coolabah*)**

Bark: persistent throughout, fibrous-flaky with whitish patches (box), grey or grey-black, grey. Leaves: Intermediate leaves disjunct early, lanceolate to ovate, straight, entire, dull grey green, petiolate. Adult leaves disjunct, narrow lanceolate to broad lanceolate, not falcate, acute, basally tapered, dull, grey-green, thin, concolorous. Lateral veins obscure, acute. Inflorescences: Conflorescence compound, terminal or axillary; Umbellasters 3-flowered to 7-flowered. Peduncles terete. Flowers: Buds ovoid or obovoid, not glaucous or pruinose. Calyx calyptrate; shedding early. Calyptra hemispherical and rostrate, 1 times as long as hypanthium or 2 times as long as hypanthium, as wide as hypanthium; smooth. Hypanthium smooth. Flowers white, or cream. Fruits: hemispherical. Disc flat. Valves rim-level or exserted. Chaff dimorphic, linear and cuboid [76-77].

***Eucalyptus torquata*:**

Eucalyptus torquata is a small to medium-sized, spreading tree from 4 to 10 metres high with rough, persistent bark on the trunk and often also on the larger branches. The leaves are lanceolate, 90-120 mm long by 15-20 mm wide and greyish green in colour. The flower buds are distinctive, having a rough, corrugated base to both the bud itself and the cap (operculum), which tapers to a long point. The flowers are large (up to 35 mm in diameter) and normally coral-pink but white, cream and red flowered plants are known [78].

Traditional uses:

The oil was used traditionally for the treatment of cystitis, diabetes, gastritis, kidney disease, laryngitis, leukorrhoea, malaria, pimples, ringworm, wounds, ulcers of the skin, urethritis and vaginitis. It was also used as an expectorant for symptomatic treatment of mild inflammation of the respiratory tract, bronchitis, asthma, and inflammation of the throat [79-81]. In south Europe, oil was used for fever, neuralgic pain, asthma, lung tuberculosis and as an antiseptic agent [82]. It is used externally for wounds, acne, poorly healed ulcers, stomatitis, bleeding gums, rheumatism and neuralgia [83]. However, There were three broad categories of uses for Eucalyptus oil (medicinal, industrial and perfumery/flavouring) [84].

Medicinal parts:

The oil extracted from the fresh and dried leaves and branch tips were used medicinally [85].

Chemical constituents:

Eucalypts contained volatile oils which occurred in many parts of the plant, depending on the species, but in the leaves that oils were most plentiful. Eucalyptus oil was produced and stored in small glands, the leaves of different species contained from 0.1-7% of the fresh weight of the leaves [84].The main constituent of the volatile oil derived from fresh leaves of Eucalyptus species was 1,8-cineole. The reported content of 1,8-cineole varies for 54-95%. 1,8-cineole showed a great variations along the seasons, but mature leaves always have higher contents of 1,8-cineole. Beside 1,8-cineole, the oil contained monoterpenes such as cymene, α-pinene, β-pinene and limonene, geraniol and camphene. Aromadendrene, cuminaldehyde, globulol and pinocarveol were also isolated from the Eucalyptus oil [79, 86-90]. The most common constituents co-occurring with 1,8-cineole were limonene, α-terpineol (both of which can be derived from the menth-1-en-8-yl cation, the same

biogenetic precursor from which cineole is thought to be derived), monoterpenes (such as α-pinene), sesquiterpenes (such as aromadendrene), globulol and α , β and ϒ-eudesmol, and aromatic constituents (such as methyl cinnamate) [91-93].Beside the oil, the genus *Eucalyptus* also contained complex mixtures of plant secondary metabolites, including terpenoids, cyanogenic glycosides, hydrolysable and condensed tannins, flavonoids, long chain ketones, and formylated phloroglucinol compounds [94]. Twenty-six compounds were isolated from the oil of *Eucalyptus bicolor* (Syn*: Eucalyptus largiflorens*) with 1,8-cineole (37.5%), p-cymene (17.4%) and neoisoverbenol (9.1%) as main components [95].The preliminary phytochemical analysis of different parts of *Eucalyptus camaldulensis* revealed that the plant contained alkaloids, flavonoids, terpenoids, tannins, saponins, glycosides, steroids and anthraquinones [96].The constituents of the essential oil of *Eucalyptus camaldulensis* were predominately oxygenated monoterpenes (34.9%), followed by oxygenated sesquiterpenes (31.8%), monoterpene hydrocarbons (29.0%) and sesquiterpene hydrocarbons (4.3%) [97]. Essential oil from aerial parts of *Eucalyptus camaldulensis* growing wild in different localities of Sardinia-Italy, was extracted by steam distillation and analyzed by gas chromatography, FID and GC-ion trap mass spectrometry. The yields of essential oil (v/dry wt) ranged between 0.2-0.5%. Thirty-seven compounds, accounting for at least 97.7% of the total essential oils were identified, the major components being p-cymene (27.8-42.7%), 1,8-cineole (4.1-39.5%), beta-phellandrene (3.9-23.8%), spathulenol (2.1-15.5%) and cryptone (3.2-10.2%). The oils showed moderate amounts (1.4-4.7%) of two uncommon aldehydes, cuminal and phellandral [98].

Analysis of the *Eucalyptus camaldulensis* leaves essential oil revealed the presence of 24 and 27 compounds from the saline and non saline samples, respectively. The constituents of the essential oil from saline and non saline samples (%)resspectively were: α-Pinene 14.68 ± 0.42 and 12.43 ± 0.37, Camphene 0.87 ± 0.07 and 2.96 ± 0.12, β-Pinene 6.66 ± 0.17 and 2.33 ± 0.19, Eucalyptol 34.42 ± 1.21 and 40.05 ± 1.20, ϒ-Terpinene 9.42 ± 0.36 and 7.48 ± 0.29, δ-Terpinene 1.11 ± 0.06 and 1.17 ± 0.05,α-Iinene epoxide 0.27 ± 0.02 and 0.28 ± 0.02, Isoamyl isovalerate 1.07 ± 0.09 and 1.10 ± 0.07, Fenchyl alcohol 0.79 ± 0.03 and 0.89 ± 0.05,α-Camphdenic Aldehyde 0.66 ± 0.03 and 0.67 ± 0.02, *t*-Pinocarveol 8.36 ± 0.40 and 3.32 ± 0.11, Myrtenal 0.94 ± 0.03 and 0.97 ± 0.06, Z-Carveol 1.15 ± 0.04 and 1.25 ± 0.07, *d*-Carvone 0.51 ± 0.03 and 0.36 ± 0.02, *o*-Cymene 5-ol 0.46 ± 0.03 and 0.54 ± 0.02, Benzyl valerate – and 0.14 ± 0.01, α-Gurjunene – and 0.26 ± 0.02, b-gurjunene – and 0.22 ± 0.03, Aromadendrene 2.63 ± 0.16 and 2.78 ± 0.20, Alloaromadendrene 0.89 ± 0.05 and 0.97 ± 0.07, Phenethyl Isovalerate 0.90 ± 0.03 and 1.01 ± 0.06, Ledene 0.45 ± 0.05 and 0.52 ± 0.03, Epiglobulol 1.83 ± 0.09 and 1.96 ± 0.03, Ledol 7.42 ± 0.05 and 7.67 ± 0.08, Viridiflorol 1.13 ± 0.04 and 2.76 ± 0.06, Eremophilene 0.78 ± 0.03 and 0.85 ± 0.02 and g-Cadinene 0.29 ± 0.01 and 0.33 ± 0.02 [99]. The physicochemical characteristics of *Eucalyptus camaldulensis* leaves essential oil, saline and non saline samples were (respectively): oil content (% fresh matter basis) 0.98 ± 0.10 and 0.96 ± 0.12 0.83; refractive index (40 °C) 1.4620 ± 0.01 and 1.4580 ± 0.02 0.77; solubility (ml/5ml of 70 % ethanol) 0.93 ± 0.10 and 1.05 ± 0.16 0.33; density (25 °C) 0.938 ± 0.04 and 0.936 ± 0.04 0.95; specific gravity (25 °C) 0.920 ± 0.04 and 0.919 ± 0.04 0.97; physical appearance: colorless- dark yellow [99].New triterpenoid acids (eucalyptanoic acid) was isolated from the fresh uncrushed leaves of *Eucalyptus camaldulensis* var. obtusa along. Its structure has been established as 3β-hydroxyolean-9(11),12-dien-28-oic acid [100].A new triterpenoid camaldulin (3β-formyloxyurs-11-en-28,13β-olide) along with ursolic acid lactone acetate, ursolic acid lactone, betulinic acid and β-sitosterol 3-O-β-d-glucopyranoside were isolated from *Eucalyptus camaldulensis* var. *obtuse* leaves [101]. Triterpenoid amirinic acid (2alpha,3beta,7beta-trihydroxy-11alpha-methoxyurs -12-en-28-oic acid and 2alpha, 3beta, 7beta-trihydroxyurs-11-en-28,13beta –olide), ursolic acid lactone, betulinic acid, oleanolic acid and ursolic acid, were isolated from fresh, uncrushed leaves of *Ecalyptus camaldulensis* var. obtuse [102]. Total penolics in the *Eucalyptus camaldulensis* leaves was 364.1 ± 8.2 (mg gallic acid equivalent/ g) and total flavonoids was 80.5 ± 0.9 (mg quercetin equivalent/ g) *Eucalyptus camaldulensis* leaves contained many phenolic groups and compounds including ellagitannins, flavonoids, phloroglucinol derivatives and galloyl esters [103]. *Eucalyptus incrassata* leave sample yielded 2% w/w (dry leaves) of essential oils [104]. 1,8-cineole (30%), α-pinene (18%), aromadendrene (13%) were the main constituents of *Eucalyptus incrassate* leaves essential oils, however, the oils of *Eucalyptus incrassata* contained: 1,8-cineole; Allo-aromadendrene; Alpha-bulnesene; Alpha-campholenic-aldehyde; Alpha-copaene; Alpha-cubebene; Alpha-eudesmol; Alpha-fenchene; Alpha-gurjunene; Alpha-phellandrene; Alpha-pinene; Alpha-selinene; Alpha-terpineol; Aromadendrene; Beta-caryophyllene; Beta-cis-ocimene; Beta-cubebene; Beta-elemene; Beta-eudesmol; Beta-phellandrene; Beta-pinene; Beta-selinene; Beta-trans-ocimene; Bicycloelemene; Bicyclogermacrene; Cadina-1,4-diene; Calacorene; Calamenene; Caryophyllene-oxide; Cis-p-menth-1,8-dien-6-ol; Cryptone Leaf; Delta-cadinene; Delta-elemene; Fenchol; Gamma-eudesmol; Gamma-terpinene; Geraniol; Globulol; Isoamyl-isovalerate; Isobutyl-isovalerate; Limonene; Myrcene; P-cymen-8-ol; P-cymene; Palustrol; Pinocarvone; Sabinene; Spathulenol; Terpinolene; Torquatone; Trans-p-menth-1,8-dien-6-ol; Trans-p-menth-2-en-1-ol; Trans-p-mentha-1(7),8-dien-2-ol; Trans-pinocarveol, Trans-piperitol, Viridiflorene and Viridiflorol [105-106].

New euglobals, euglobal-In-1, euglobal-In-2, euglobal-III and euglobal –V having an acylphloroglucinol-sesquiterpene structure were isolated from the juvenile leaves of *Eucalyptus incrassate* [107].
The total amount of the oil in the leaves of the *Eucalyptus griffithsii* was 0.3% of the dry weight. The main constituents of the *Eucalyptus griffithsii* leaves essential oils were 1,8-cineole (26%), *trans* pinocarveol (11%) and α-pinene (8%) [105]. The Phytochemical analysis of *Eucalyptus microtheca* leaves extracts revealed the presence of essential oils, flavonoids, tannins and alkaloids [108]. The major components of *Eucalyptus microtheca* essential oils were 1,8-cineole (34.0%), p-cymene (12.4%), α-pinene (10.7%), β- pinene (10.5%) and virdiflorene (5.2%) [95].However, in the oil of *Eucalyptus microtheca* flowers, 88 compounds were identified including (%): α –thujene 0.504; α –pinene 16.246; α –fenchene 0.078; Comphene 0.271; Verbenene 0.051; β – pinene 11.082; β -myrcene 0.263; α –phellandrene 7.006; α –terpinene 0.367; o-cymene 13.522; Sabinene2.131; Limonene 2.713; cis-ocimene 0.149; γ –terpinene 0.868; Isopropenyltoluene-cymene 0.093; α –terpinolene 0.189; Linalool L 0.058; Appel oil 0.113; D-fenchyl alcohol 0.085; Hexadecane0.147; Trans-pinocarveol 0.365; Pinocarvone 0.303; 4-methyl-1,3-heptadiene (c,t) 0.088; 2, 4-hexadiene, 2, 5-dimethyl- 0.070; 4-terpineol 1.052; Myrtenal 0.202; α -terpineol0.425; Myrtenol 0.160; Dodecane 0.392; β –citronellol 0.365; Piperitone 0.167; Citrol 0.063; Citronellyl formate 0.115; Diglycol dimethacrylate 0.787; Carvacrol 0.494; 2-butylpyridine 0.129; soledene 0.170; Copaene 0.150; Tetradecane 0.063; β –elemene 0.063; α –gurjunene 0.542; Seychelene0.040; Trans-Caryophyllene 0.227; γ –selinene 0.122; Calarene 0.112; β – gurjunene 0.073; Aromadendrene7.444; α –humulene 0.080; Alloarmadendrene1.632; α -amorphene 0.400; β –selinene 0.311; α -guaiene 0.320; Ledene2.135; α –muurolene 0.318; γ –cadinene 0.667; Calamenene0.248; δ -cadinene1.040; Cadina-1, 4-diene 0.045; α –calacorene 0.070; Epiglobulol 0.975; β –maaliene 0.253; Plustrol 0.221; Spathlenol1.848; Globulol 5.419; Veridiflorol 1.044; Ledol 0.631; Hexadecane 0.212; α –ylangene 0.196; Isospathulenol 0.217 ; Tau-cadinol 0.791; α –cadinol 0.444; Cadalene 0.120; N-octadecane 0.246; Tetradecanamide 0.321; n-hexadecanoic acid 0.375; Ecosane 0.167; Hexaadecanamide0.918; Octadecanoic acid 0.425; Docosan 0.145; 9-octadecenamide 5.414; Di-[2-ethylhexyl] phthalate 0.584; 4- methylenespiro [2 ,4] heptane 0.055; (2-methylprop-1-enyl)-cyclohexa- 1, 3-diene 0.098; 1-(2′-hydroxy-3′,4′-dimethylphenyl) ethanone0.603; Trans-1,6-dimethyl bicycle (4.3.0) non-2-en-7-one 0.346; 7, 9-di-tert-butyl-1-oxaspiro [4.5] deca-6, 9- diene-2, 8-dione0.117; 1, 3- cyclohexadiene, 2-methyl-5-(1-methylethyl), monoepoxide 0.139 and 1H-cyclopropa[e]azulene, decahydro-1, 1, 7-trimethyl-4-methylene-,[1aR (1a.1alpha. 4a.beta. 7b.alpha)] - 7.alpha, 7a.beta 0.243. While, in the essential oil of *Eucalyptus microtheca* leaves, 101 compounds were identified included (%): α –thujene 0.742; α –pinene 6.752; comphene 0.079; β – pinene 5.006; β –myrcene 0.533; α –phellandrene 16.487; α –terpinene 0.832; p- cymene 5.251; β –phellandrene 2.194; Limonene 1.503; Cis-ocimene 1.655; β –ocimene Y 0.101; γ –terpinene 1.235; Cymene 0.024; α –terpinolene 0.425; Rosefuran 0.024; Cycloheptanmethanol 0.061; Linalool L 0.093; Isoamyl isovalerate 0.529; Isoamyl valerate 0.056; Fenchol 0.076; Trans-pinene hydrate 0.062; Allocimene 0.049; 1-terpineol 0.045; 1-methylnorcarane 0.051; Ethylbenzoate 0.124; 4-terpineol1.256; 1-(adamantly) cyclohexene 0.042; β –fenchol 0.203; cis-sabinol 0.224; Thiophene, 2-ethyl-5-methyl 0.120; Ascaridole 0.085; Dicyclobutylidene oxide 0.084; Divinyl dimethylsilane 0.114; Piperitone 0.196; 1-methoxyhept-1-yne 1.809; Citronellyl formate 0.029; Carvacrol 0.420; α –cubebene 0.160; Isoledene 0.278; Copaene 0.308; 2-pentene-1-ol, 2-methyl 0.215; α –gurjunene 1.897; Trans-caryophyllene 0.539; Aromadendrene 12.773; Epizonaren 0.067; α –humulene 0.142; Alloarmadendrene 2.520; γ –gurjunene 0.327; α –copaene 0.755; β –selinene 0.525; β –panasinsene 0.702; Ledene 5.665; α –muurolene 0.398; Geremacrene B 0.099; α –amorphene 1.666; cis-calamenene 0.207; δ -cadinene 2.663; Cadina-1, 4-diene 0.103; α –calacorene 0.087; α –cadinene 0.163; Ledane 0.092; Epiglobulol 1.167; β –maaliene 0.306; Palustrol 0.190; Spathlenol 1.915; Globulol 5.997; Veridiflorol 1.243; 1, 3-dimethyl-5-ethyladamantane 0.285; Ledol 0.753; γ- curcumene 0.391; Isospathulenol 0.300; Tau-muurolol 1.580; δ –cadinol 0.231; Guaia-3, 9-diene 0.292; α– cadinol 0.806; Vulgarol A 0.129; Hexadecanoic acid 0.093; 2-tridecanol 0.028; Hexadecanoic acid ethyl ester 0.025; Decyltetraglycol 0.025; Tricosane 0.012; Benzonitrile, m-phenethyl 0.032; Pentacosane 0.073; Pentaethoxylated pentadecyl alcohol 0.036; 1-cyclohexene-1-carboxaldehyde, 4-(1-methylethyl) 0.170; Cyclohexene, 3-methyl-6-(1-methylethyl) 0.108; 2- cyclohexene-1-ol, 2-methyl-5-(1-methylethenyl)-, trans- 0.059; 2, 3-dimethyl-cyclohexa-1, 3-diene 0.390; α –campholonic acid 0.049; Furan, 2, 3-dihydro-4-(1-methylpropyl) 0.458; (E)-3-isopropyl-6-oxo-2-heptenal 0.058; 1, 5, 5-trimethyl-6-methylene-cyclohexene 0.056; 2, 6, 10-trimethyl-2, 5:7, 10-dioxido- dodeca-3, 11-diene-5-ol 0.268; Tricyclo [6.3.0.1(2, 3)] undec-7-ene, 6, 10, 11, 11-tetramethyl 0.138; 1-methyl-4-isopropyl-cis-3- hydroxycyclohex-1-ene-6-one 0.230; 1H-cyclopropa[a]naphthalene, decahydro- 1,1,3 a-trimethyl-7-methylene-, [1as(1a.1alpha.,3a.alpha.,7a.beta.,7b.alpha.)] 0.235; Naphthalene, 1, 2, 3, 4, 4a, 7- hexahydro-1, 6- dimethyl-4-(1-methylethyl) 0.139; Bicyclo[3.1.0]hex-2-ene,2-methyl-5- (1-methylethyl) 0.026; +)-(1R, 2S, 4R, 7R)-7-isopropyl-5- methyl-5- bicycle [2.2.2] octen-2-ol 0.140 and 1, 6-dimethyl-2-cyano-3-ethyl-3- piperidine 0.612 [109].

Pharmacological effects:

Eucalyptus, with almost 900 species, is found worldwide, More than 300 species of this genus contain volatile oils in their leaves [110]. There were three broad categories of uses for Eucalyptus oil (medicinal, industrial and perfumery/flavouring). Medicinal oils were defined by the British Pharmacopoeia as containing not less than 70% cineole; industrial oils contain principally piperitone and phellandrene as main constituents, and perfumery and flavouring oils contain high percentages of citronella1 (a lemon scent) and geranyl acetate (a rose scent). Medicinal oils were used primarily as a decongestant agent and antiseptic in inhalants, sprays, embrocations, gargles and lozenges. It was also prepared as emulsions, ointments and other preparations. Industrial oils were used in the manufacture of disinfectants, deodorants, liquid soaps, germicides and in the manufacture of synthetic menthol and thymol. Perfumery and flavouring oils were used either directly as a scenting agent and food flavouring, or in the synthesis of other scents and flavor [84].Medicinal Eucalyptus oil was produced from *Eucalyptus globulus* in China, Portugal, Spain, India, Brazil Bolivia, Uruguay and Paraguay; and from *Eucalyptus smithii* in South Africa, Swaziland, and Zimbabwe; from *Eucalyptus polybractea*, *Eucalyptus viridis* and *Eucalyptus dives* in Australia; from *Eucalyptus radiata* in South Africa and Australia; and from *Eucalyptus camaldulensis* in Nepal. Perfumery Eucalyptus oil was produced from *Eucalyptus citriodora* in China, Brazil and India; and from *Eucalyptus staigeriana* in Brazil. Industrial Eucalyptus oil was produced from *Eucalyptus dives* in south Africa and Australia; and from *Eucalyptus campanulata in* Australia [111].

Gastrointestinal effects:

The ulcer-healing promoting effect of the methanol extracts of *Eucalyptus camaldulensis* leaves was investigated in acetic acid induced-ulcer in rat. The results showed that methanol extracts of *Eucalyptus camaldulensis* leaves reduced the size of the ulcer from day 5 in animals treated with 500mg/kg body weight of reconstituted extracts at 24 hours interval. At the end of the experiment (day 14) most of the ulcers has reduced by half the original size with 46.67 ±3.33 % decrease in diameter compared to the controls (distilled water and ranitidine) which afforded 21.67 ±1.05% and 59.17 ± 1.54% decrease in diameter respectively [112]. The *in vitro* anti- *Helicobacter pylori* of *Eucalyptus camaldulensis* was investigated in six strains of *Helicobacter pylori* (ATCC 4504, ATCC 47619, A2, TI8984, 019A, and A6). The minimum inhibitory concentrations of the crude extracts against all the tested strains ranged from 12.5 to 400 mµg/ml [113]. A new triterpenoid acid, eucalyptanoic acid isolated from the fresh uncrushed leaves of *Eucalyptus camaldulensis* var obtusa along. This compound and its acetyl and acetylmethyl derivatives were tested for spasmolytic activity. The acetylmethyl derivative was found to be the most active spasmolytic agent, its effect was mediated through blockade of calcium influx at 1 mg/ml [100]. The triterpenoid camaldulin (3β-formyloxyurs-11-en-28,13β-olide), ursolic acid lactone acetate and ursolic acid lactone isolated from *Eucalyptus camaldulensis* var. *obtuse*, showed spasmolytic activity and possessed calcium antagonist activity [101].

Antiinflammatory and analgesic effect:

1,8-Cineole (cineole) possessed an inhibitory effect on some types of experimental inflammation in rats, (paw oedema induced by carrageenan and cotton pellet-induced granuloma). Cineole also inhibited the acetic acid-induced increase in peritoneal capillary permeability and the chemical nociception induced by intraplantar formalin and intraperitoneal acetic acid in mice at an oral dose range of 100-400 mg/kg. In the formalin test, the antinociceptive effect of cineole was not reversed by pretreatment of mice with naloxone (1 mg/kg, sc), a mu-opioid receptor antagonist, suggesting the involvement of a non-opioid mechanism. Cineole demonstrated a significant inhibitory effect on locomotion and also potentiated the pentobarbital sleeping time in mice, indicating a depressant effect on the central nervous system [114].The effect of 1.8-cineole was evaluated on arachidonic acid (AA) metabolism in blood monocytes of patients with bronchial asthma. Production of the representative AA-metabolites LTB4 and PGE2 from isolated monocytes stimulated with the calcium ionophore A23187 were measured ex *vivo* before therapy with 1.8-cineole (3 x 200 mg/day), after three days of treatment (day 4) and four days after discontinuation of 1,8-cineole (day 8). The production of LTB4 and PGE2 from monocytes ex *vivo* was significantly inhibited on day 4 in patients with bronchial asthma (-40.3%, n = 10 and -31.3%, p = 0.1, n = 3 respectively) as well as in healthy volunteers (-57.9%, n = 12 and -42.7%, n = 8 respectively). In conclusion, 1,8-cineole was shown to inhibit LTB4 and PGE2, both pathways of AA-metabolism [115]. In studying the potential anti-inflammatory efficacy of 1,8-cineol (eucalyptol) in inhibiting polyclonal stimulated cytokine production by human unselected lymphocytes and LPS-stimulated monocytes, the therapeutic concentrations of 1,8-cineol (1.5 µg/ml=10−5 M) inhibited significantly (p=0.0001) cytokine production in lymphocytes of TNF-α, IL-1β, IL-4, IL-5 by 92, 84, 70, and 65%, respectively. Cytokine production in monocytes of TNF-α, IL-1β, IL-6, IL-8 was also significantly (P< 0.001) inhibited by 99, 84, 76, and 65%, respectively. In the presence of 1,8-cineol (0.15 µg/ml=10−6 M), the production of TNF-α and IL-1β by monocytes and lymphocytes was significantly inhibited by 77, 61 and 16, 36%, respectively [116]. The

effect of Eucalyptus essential oils (EO) was studied on the phagocytic ability of human monocyte derived macrophages (MDMs) *in vitro* and of rat peripheral blood monocytes/granulocytes *in vivo* in absence or in presence of immuno-suppression induced by the chemotherapeutic agent 5-fluorouracil (5-FU). Eessential oil was able to induce activation of MDMs and dramatically stimulating their phagocytic response. Implementation of innate cell-mediated immune response was also observed *in vivo* after essential oil administration, mainly involving the peripheral blood monocytes/granulocytes. The 5-FU/EO combined treatment inhibited the 5-FU induced myelotoxicity and raised the phagocytic activity of the granulocytic/ monocytic system, significantly decreased by the chemotherapic [117].The inhibitory effect of 1,8-cineole was studied on LPS-and IL1beta-stimulated mediator production by human monocytes *in vitro*. A dose-dependent and highly significant inhibition of production of tumor necrosis factor-alpha, interleukin-1beta, leukotriene B4 and thromboxane B2 were achieved by 1,8-cineole [118]. 1,8-cineole and beta-pinene, two monoterpenes isolated from the essential oil of *Eucalyptus camaldulensis* leaves were tested for antinociceptive properties. Tail-flick and hot-plate methods, reflecting the spinal and supraspinal levels, respectively, were used in mice and/or rats using morphine and naloxone for comparison. Cineole exhibited an antinociceptive activity comparable to that of morphine, in both algesic stimuli. A significant synergism between cineole and morphine was observed, but naloxone failed to antagonize the effect of cineole. Beta-pinene exerted supraspinal antinociceptive actions in rats only, and it reversed the antinociceptive effect of morphine in a degree equivalent to naloxone, probably acting as a partial agonist through the mu opioid receptors [119].
Eucalyptus camaldulentis possessed an anti-nociceptive effect against both acetic acid-induced writhing and hot plate-induced thermal stimulation in mice [120].

Antioxidant effect:

The effects of 1,8-cineole on systolic blood pressure (SBP) and oxidative stress was investigated in rats chronically exposed to nicotine. 0.1 mg/kg 1,8-cineole significantly reduced SBP, and 1 mg/kg 1,8-cineole significantly increased plasma nitrite concentrations, compared with rats chronically exposed to nicotine alone. Rats chronically exposed to nicotine showed a significant increase in lipid peroxidation levels, an elevation significantly antagonized by treatment with 0.01 and 0.1 mg/kg 1,8-cineole. Chronic exposure to nicotine also significantly increased plasma corticosterone levels, but this effect was not diminished by treatment with 1,8-cineole [121].The *in vitro* antioxidant activities of the essential oil and the subfractions of methanol extract from leaves of *Eucalyptus largiflorens* (*Eucalyptus bicolor*) were investigated using 2,2-diphenyl-1-picrylhydrazyl (DPPH) and β-carotene-linoleic acid assays. In DPPH, the IC_{50} of polar subfractions of the methanol extract was lower than that of non polar one, while in the case of the linoleic acid system; oxidation of the linoleic acid was effectively inhibited by the non polar subfraction of the methanol extract (92 - 94.5 %), which was comparable to the synthetic antioxidant BHT. In both evaluating methods, the oils were less effective. The amounts of total phenolics in the polar subfractions of each extracts were positively correlated with the antioxidant activity [122].The antioxidant activity of the essential oil and methanol extracts of *Eucalyptus largiflorens* (*Eucalyptus bicolor*) was studied *in vitro*. The extract showed better antioxidant activity than the essential oil. Also, the polar subfraction of methanol extract showed the highest radical-scavenging activity. The inhibition capacity (%) of the nonpolar subfraction was found to be the stronger one [123]. The free radical scavenging activities of the *Eucalyptus camaldulensis* essential oil were assessed by measuring their scavenging abilities for stable 2,21-diphenyl-1-picrylhydazyl DPPH radicals. The DPPH scavenging activity was high in *Eucalyptus camaldulensis* (81.9%) [124]. The results of evaluation of antioxidant effect of essential oil of *Eucalyptus camaldulensis* indicated that the essential oil had weak radical scavenging activity comparing with ascorbic acid and Butylated hydroxyanisole, while it had high potent ferrous ions chelating and total antioxidant activities comparing to ascorbic acid and BHT [125]. The leaves extract of *Eucalvptus camaldulensis* var. brevirostris, grown in Nile delta in Egypt, were examined for the antioxidant activity. The extracts obtained by ethanol digestion and by supercritical fluid extraction showed the most promising antioxidative activities. In order to identify the most active compounds, the contents of both extracts were separated by reversed-phase HPLC. Gallic and ellagic acid were found to be the prevailing antioxidants in the ethanolic extract [126]. The antioxidant activity of the essential oils of *Eucalyptus camaldulensis*, was assessed by DPPH-test and expressed as Trolox equivalent antioxidant capacity, they showed values ranging between 0.5 and 5.8 mmol/l [98].The antioxidant activities of *Eucalyptus camaldulensis*, *Eucalyptus camaldulensis* var. obtusa and *Eucalyptus gomphocephala* essential oils was studied (2,2'-diphenypicrylhydrazyl). The values of total antioxidant activity were 70 ± 3.13%, 50 ± 3.34% and 84 ± 4.64% for of *Eucalyptus camaldulensis*, *Eucalyptus camaldulensis* var. obtusa and *Eucalyptus gomphocephala*, respectively. The highest antioxidant activity value of 84 ± 4.64% could be attributed to the high amount of spathulenol (37.46%) [127].The effects of essential oil from *Eucalyptus camaldulensis* flowers oil on melanogenesis and the oil's antioxidant characteristics were investigated. Assays of mushroom and cellular tyrosinase activities and melanin content of mouse melanoma cells were performed spectrophotometrically, and

the expression of melanogenesis-related proteins was determined by Western blotting. The possible signaling pathways involved in essential oil-mediated depigmentation were also investigated using specific protein kinase inhibitors. *Eucalyptus camaldulensis* flower essential oil inhibited melanogenesis through its antioxidant properties and by down-regulating both mitogen-activated protein kinases (MAPK) and protein kinase A (PKA) signaling pathways. The study indicated that the essential oil has the potential to be developed into a skin care product [97].The free radical scavenging activities of the *Eucalyptus microtheca* essential oil were assessed by measuring their scavenging abilities for stable 2,21-diphenyl-1-picrylhydazyl DPPH radicals. The DPPH scavenging activity was high in *Eucalyptus microtheca* (81.8%) [124].

Cytotoxic effect:

The anti-proliferative effect of 1, 8-cineole was studied on human colon cancer cell lines HCT116 and RKO by WST-8 and BrdU assays. The cytotoxicity of 1, 8-cineole was investigated by LDH activity and TUNEL staining. The mechanism of apoptosis by 1, 8-cineole was determined by western blot analyses. In *in vivo* study, RKO cells were injected into the mice and the effect of 1, 8-cineole was investigated. Specific induction of apoptosis, not necrosis, was observed in human colon cancer cell lines HCT116 and RKO by 1, 8-cineole. The treatment with 1, 8-cineole was associated with inactivation of survivin and Akt and activation of p38. These molecules induced cleaved PARP and caspase-3, finally causing apoptosis. In xenotransplanted mice, 1, 8-cineole significantly inhibited tumor progression compared to the control group [128].14 plant species used in traditional medicine in Yemen were screened for cytotoxic activity against human ECV-304 cells. Extracts of *Eucalyptus camaldulensis* possessed a remarkable cytotoxic activity [129].*Eucalyptus camaldulensis* leaves essential oil demonstrated cytotoxic effects in three tested cancer cell lines; WEHI-3, HT-29 and HL-60. WEHI-3 was the most sensitive with IC_{50} =16.10µg/ml. The essential oil exhibited less cytotoxic effects in HT-29 and HL-60 cells (IC_{50}=50.5 and 42.10µg/ml, respectively). Essential oil also exhibited a weak cytotoxic effect in RAW 264.7 cells [130]. The cytotoxicity of the aqueous acetone extract was evaluated on MCF-7, Hep-2, HepG-2, HeLa, HCT-116 and Caco-2 cell lines. The extract reduced the viability of all cell lines in a dose-dependent manner, and was more active on MCF-7 and HCT-116 cell lines. IC_{50} ranged from 33.3 to 57.7 µg/ml [103]. The cytotoxic effects of essential oil of *Eucalyptus camaldulensis* was evaluated in different cancer and normal cell lines, the essential oil showed high potent cytotoxic effect on colon, prostate and breast cancer cell lines as well as moderate potency against liver and lung cell lines with IC_{50} 19.8, 31.5, 34.9, 51.7 and 64.0µg/ml respectively. In the same pattern, the oil showed high cytotoxic effect on normal epithelial retina cell line and moderate effect on normal skin fibroblast cell with IC_{50} 41.3 and 60.6µg/ml respectively [125].

In vitro cytotoxicity of methanol, ethyl acetate, *n*-buthanol, and water extracts of *Eucalyptus camaldulensis* leaves was examined against two human breast cancer cell lines (MCF 7 and MDA-MB-231) using MTT and SRB assays. The results showed that the extracts possessed significant cytotoxic potential with IC_{50} values ranging from 3 to 250 µg/ml [131]. Anticancer activities of *p*-menth-1-ene-4,7-diol (EC-1) isolated from *Eucalyptus camaldulensis* were studied on Ehrlich ascites carcinoma (EAC) cells. Anticancer activities also analyzed in EAC-bearing mice by assessment of cancer growth inhibition, changes in cancer volume, changes in life span, and hematological parameters. Apoptosis was analyzed by fluorescence microscope, DNA fragmentation assay, and flow cytometry. The expression of apoptosis-related genes, *Bcl-2*, *Bcl-X*, *PARP-1*, *p53*, and *Bax*, were analyzed using polymerase chain reaction (PCR). *p*-menth-1-ene-4,7-diol (EC-1) significantly inhibited proliferation of EAC cells *in vivo* and restored the altered hematological parameters of EAC-bearing mice. Cytological observation by fluorescence microscope showed apoptosis of EAC cells upon treatment with EC-1. Also, DNA fragmentation assay revealed EAC cells' apoptosis following EC-1 treatment. Increased mRNA expressions of *p53* and *Bax* genes and negative expressions of *Bcl-2* and *Bcl-X* were observed in cells treated with EC-1. MTT assay showed dose-dependent anticancer activity of EC-1 against EAC cell. Cell cycle analysis revealed that EC-1 treatment caused suppression of EAC cells at S phase [132]. The cytotoxic effect of the crude methanolic extracts of *Eucalyptus camaldulensis* was investigated against L20B (a genetically engineered mouse cell line) and human rhabdomyo sarcoma (RD) cells showed that the extract of *Eucalyptus camaldulensis* possessed moderate cytotoxicity [133]. The *in vivo* antitumor effect of *Eucalyptus camaldulensis* stem bark methanol extract was studied against Ehrlich's ascites carcinoma (EAC) in Swiss albino mice. *Eucalyptus camaldulensis* stem bark methanol extract showed 96% ($P < 0.001$) cell growth inhibition and reduced tumor burden significantly (81.4%; $P < 0.01$) when compared with control mice. It also increased the lifespan of EAC-bearing mice significantly (71.36%; $P< 0.01$). In addition, it also restored the altered hematological and biochemical parameters towards normal level. The high LD_{50} value (1120 mg/kg) of *Eucalyptus camaldulensis* stem bark methanol extract indicated its low host toxic effects. *Eucalyptus camaldulensis* stem bark methanol extract -treated EAC cells showed membrane blebbing, chromatin condensation, nuclear fragmentation (apoptotic features) in Hoechst 33342 staining under

fluorescence microscope. The DNA profile in agarose gel (1.5%) electrophoresis also confirmed that *Eucalyptus camaldulensis* stem bark methanol extract caused EAC cell death by apoptosis [134].

Antiparasitic, insecticidal and repellent effects

In studying anti- schistosomal effect of Eucalyptus essential oil, the scanning electron microscope observation showed that of essential oil produced sever damage in schistosoma worm's typography [135]. The effect of the leaves, stem and root barks extracts of *Eucalyptus camaldulensis* was investigated in *Trypanosoma brucei* infected mice. 200-600 mg/kg body weight/day of the hexane, ethyl acetate, methanol and water extracts for 21 consecutive days. One control group was treated with 3.5mg/kg bodyweight of berenil while the other control group was left untreated. The methanol extract of *Eucalyptus camaldulensis* (leaf) produced complete cure for the animals in the different dose groups and survived as long as those treated with the standard drug, berenil, although the clearance time was faster for the standard drug. Sub inoculation of healthy mice with the blood and cerebrospinal Fluid (CSF) of the cured mice did not result in infection, thus indicating a complete and permanent cure. Bioassay-guided fractionation of the crude methanol extract of *Eucalyptus camaldulensis* leaf gave 10 fractions, only fractions 8 and 9 exhibiting minimal antitrypanosomal activities that were not comparable to those of the crude extract and the standard drug ($p \leq 0.05$) [136]. The effect of methanolic and aqueous extracts of *Eucalyptus camaldulensis* was studied on the promastigotes of *Leishmania major*. The stationary phase promastigotes of *Leishmania major* was incubated in the methanolic and aqueous extractions *in vitro*. Tartar emetic was used as the positive control drug. After 72 h of incubation, the activity of the extracts was measured, using MTT method. The IC_{50} values were 586.2 ± 47.6 and $1,108.6 \pm 51.9$ μg/ml for methanolic and aqueous extracts, respectively, whereas it was 32.5 ± 6.8 μg/ml for tartar emetic [137]. The effect of different extracts of *Eucalyptus camaldulensis* (total extract, diethyl ether, chloroform, ethyl acetate, and water fractions) on *T. vaginalis* was investigated in culture medium. Crude extract of *Eucalyptus camaldulensis* showed 80% growth inhibition in a concentration of 12.5 mg/ml during 24 h. Diethyl ether extract in a concentration of 25 mg/ml showed 100% growth inhibition during 24 h. With ethyl acetate extract, 100% growth inhibition was detected with the minimum concentration of 12.5 mg/ml in the first 24 h. Water extract in a concentration of 50 mg/ml showed 80% and 100% growth inhibition after 48 and 72 h, respectively [138].Eucalyptus essential oil showed a wide biological activity against insects, nematodes, weeds and mites. The use of Eucalyptus oil as a natural pesticide was of immense significance in view of the environmental and toxicological implications of the indiscriminate use of synthetic pesticides and vercoming/reducing the problem of increasing pest resistance [139].The larvicidal activity of *Eucalyptus camaldulensis* was studied against *Anopheles stephensi*. The leaf extract and volatile oil exerted significant larvicidal activity with LC_{50} values of 89.85 and 397.75 ppm, respectively. Clear dose-response relationships were established, with the highest dose of 320 ppm essential oil extract resulted almost in 100% mortality in the population [140]. Vapors of essential oils extracted from *Eucalyptus camaldulensis* and its major components were found to be toxic to *Aedes aegypti* adults, the yellow fever mosquito. An aliquot of oil was placed in a cylindrical test chamber and the number of knocked-down mosquitoes was recorded as function of time. Knockdown time 50% was then calculated. A correlation was observed between the content of 1,8-cineole in the Eucalyptus essential oils and the corresponding toxic effect. The correlation between KT_{50} values and calculated vapor pressures of the essential oil components showed that the fumigant activity of simple organic compounds in insects was correlated with their volatility [141].The mosquito larvicidal activity of leaf essential oils of *Eucalyptus camaldulensis* and their constituents was investigated against two mosquito species, *Aedes aegypti* and *Aedes albopictus*, Essential oil of the leaves of *Eucalyptus camaldulensis* had an excellent inhibitory effect against both *Aedes aegypti* and *Aedes albopictus* larvae. The 12 pure constituents extracted from the Eucalyptus leaf essential oils were also tested individually against two mosquito larvae. Among the six effective constituents, alpha-terpinene exhibited the strongest larvicidal effect against both *Aedes aegypti* and *Aedes albopictus* larvae [142]. Eucalyptus essential oil can act directly as a natural insect repellent. Eucalyptus essential oil can protect plants against rice weevils, pine processionary moths and mushroom flies [139].Essential oils extracted from the dried fruits of *Eucalyptus camaldulensis*, and essential oils of many other plants were tested for their repellency against the adult females of *Culex pipiens*. The essential oils showed repellency in varying degrees, Eucalyptus, basil and anise being the most active [143].The insecticidal effects of hot and cold aqueous *Eucalyptus microtheca* leaves extracts were studied on mosquito *Culex pipiens*. Hot water extract was more effective on immature stages of insect. Eggs mortality rate of the hot and cold extracts was 51% and 47.3% respectively at a concentration of 20 mg/ml. Larval mortalities rate was significantly increased in hot and cold water extracts as compared with control. The hot and cold extracts caused 31.5 % and 28.6% pupal mortality at concentration of 20 mg/ml, respectively [144].The accumulative and non accumulative effects of aqueous and organic extracts of the leaves of *Eucalyptus microtheca* was investigated on larvae of *Culex quinqefasciatus*. The petroleum ether extract was the most effective, however, all extracts increased the duration of larval stage and caused morphological changes of larva [53].

Antimicrobial effect:

The antibacterial effect of Eucalyptus oil was investigated against *Klebsiella spp., Proteus spp., Pseudomonas spp., Escherichia coli,* and *Staphylococcus aureus.* The results showed that, *Escherichia coli* and *Klebsiella spp*. were sensitive to 5 µl, *Staphylococcus aureus* to 25 µl, while *Pseudomonas* and *Proteus spp*. required 50 µl of Eucalyptus oil. With an increasing dose of oil of Eucalyptus, the resulting diameter of the zone of inhibition increased for all the organisms [145]. The *in vitro* antimicrobial activity of the essential oil and methanol extracts of *Eucalyptus largiflorens* (*Eucalyptus bicolor*) was studied against *Aspergillus niger* ATCC 16404, *Candida albicans* ATCC 10231, *Pseudomonas aeruginosa* ATCC 27853, *Bacillus subtilis* ATCC 6633, *Staphylococcus aureus* ATCC 29737, *Escherichia coli* ATCC 10536, *Klebsiella pneumoniae* ATCC 10031, *Staphylococcus epidermidis* ATCC 12228, *Shigella dysenteriae* PTCC 1188, *Proteus vulgaris* PTCC 1182 and *Salmonella paratyphi*-A serotype ATCC 5702. The essential oil of *Eucalyptus largiflorens* exhibited moderate to high antimicrobial activity against all the bacteria, yeast and mold tested, except three microorganisms, *Pseudomonas aeruginosa*, *Escherichia coli* and *Shigella dysenteriae*. The evaluation of methanol fraction indicated that polar fraction showed strong activity against 7 out of 11 microorganisms while non-polar fractions did not posses any inhibitory action against the strains evaluated except *Escherichia coli* [123].The antimicrobial properties of essential oil, its major component, 1,8-cineole, and extracts of *Eucalyptus largiflorens* (*Eucalyptus bicolor*) were evaluated *in vitro*. Minimum inhibitory concentration of the extracts was calculated by broth dilution method and the zone of inhibition was studied by agar disk diffusion method. Gentamicin (10 µg/disk) and rifampin (5 µg/disk) were used as reference controls for antibacterial, and nystatin (100 µg/disk) for antifungal tests. The results of MIC study revealed that the essential oil has a stronger activity and broader spectrum than those of methanol extracts. The oil also had greater antimicrobial potential than 1,8-cineole [146].Disk diffusion method was used to determine the antimicrobial activity of aqueous extract and essential oils of *Eucalyptus incrassata* leaves against eight isolates of multidrug- resistant *Staphylococcus aureus*. It was found that aqueous extract and essential oils possessed variable antimicrobial activity (the inhibition zone diameter ranged from 7 to 14 mm respectively). Essential oils showed more antibacterial effect than aqueous extract [104]. The *in vitro* antimicrobial activity of acetone, methanol and water extracts of leaf, stem and bark of *Eucalyptus camaldulensis* was studied against six bacterial species *Bacillus megaterium, Bacillus subtilis, Staphylococcus epidermidis Staphylococcus aureus, Micrococcus luteus* and *E. coli* using the agar well diffusion method. The results showed that the extracts exhibited a dose-dependent inhibition of microorganisms. The acetone and methanol extracts of leaf and stem bark of *Eucalyptus camaldulensis* displayed maximum antibacterial activity against all the bacterial species. There was no significant difference in the antimicrobial activity of the extracts on Gram negative and Gram positive bacteria [147]. The antibacterial activity of the crude leaf extracts of *Eucalyptus camaldulensis* were studied against clinical isolates of *Escherichia coli, Staphylococcus aureus, Salmonella typhi, Proteus mirabilis* and *Klebsiella pneumoniae.* The growth of all the pathogenic bacteria was arrested at 50 mg/ml concentration of extracts. The least activity was possessed by aqueous extract against *E. coli* (7 mm), *K. pneumoniae* (9 mm), *P. mirabilis* (13 mm), *S. typhi* (12 mm) and *S. aureus* (12 mm), while the highest was recorded for the acetone extract, with a diameter of inhibition for *E. coli* (12 mm), *K. pneumonia* (13 mm), *S. typhyi* (14 mm), *P. mirabilis* (15 mm) and *S. aureus* (14 mm) [148]. The antibacterial activities of *Eucalyptus camaldulensis, Eucalyptus camaldulensis* var. obtusa and *Eucalyptus gomphocephala* essential oils were studied using agar disc diffusion and minimum inhibitory concentration methods. The essential oils from the leaves of Eucalyptus spp. exhibited considerable antibacterial activity against Gram positive and Gram negative bacteria [127].The antimicrobial and biofilm preventing activities of the oils of *Eucalyptus camaldulensis* were studied *in vitro* and *in vivo*. Minimal bactericidal concentrations (MBC) of the *Eucalyptus camaldulensis* oils were found to be 4 and 2 mg /ml, and those of chlorhexidine (2%) were 8 and 1 mg/ml for both *S. mutans* and *S. pyogenes* respectively. Decimal reduction time of *S. mutans* by *Eucalyptus camaldulensis* oils at their MBC levels was 2.8 min, while that of cholrhexidine was 12.8 min. D-value of *S. pyogenes* exposed to the MBC levels of *Eucalyptus camaldulensis* oils and of chlorhexidine were 3.6 and 2.8 min respectively. Antibacterial and *in vivo* biofilm preventive efficacies of all the concentrations of Eucalyptus oil were significantly ($P< 0.001$) higher than that of chlorhexidine [149].

The antimicrobial potential of two *Eucalyptus camaldulensis* essential oils was investigated against multi-drug resistant (MDR*) Acinetobacter baumannii* wound isolates, the possible interactions of essential oils with conventional antimicrobial agents was also studied. MIC values of essential oils against *Acinetobacter baumannii* strains were estimated by modified broth microdilution method. The components responsible for antimicrobial activity were detected by bioautographic analysis. The potential synergy between the essential oils and antibiotics (ciprofloxacin, gentamicin and polymyxin B) was examined by checkerboard method and time kill curve. The bioautographic assay confirmed antibacterial activity of polar terpene compounds. In combination with conventional antibiotics (ciprofloxacin, gentamicin and polymyxin B), the examined essential

oils showed synergistic antibacterial effect. The synergistic interaction was confirmed by time-kill curves for *Eucalyptus camaldulensis* essential oil and polymyxin B combination which reduced bacterial count under detection limit very fast, after 6h of incubation [150].The *in vitro* antimicrobial activities of the crude oil of *Eucalyptus camaldulensis* leave was investigated against *Escherichia coli* and *Staphylococcus aureus*. The diameter of zones of inhibition by the crude oil of leaf extracts of *Eucalyptus camaldulensis* was 10- 31mm and 10-26mm for *Escherichia coli* and *Staphylococcus aureus*. Gram positive, *Staphylococcus aureus* was more resistant than Gram negative, *Escherichia coli* [151]. The in vitro anti- *Helicobacter pylori* of *Eucalyptus camaldulensis* was investigated in six strains of *H. pylori* (ATCC 4504, ATCC 47619, A2, TI8984, 019A, and A6). The minimum inhibitory concentrations of the crude extracts against all the tested strains ranged from 12.5 to 400 mug/ml [113]. Hexane, chloroform, methanol extracts, and isolated compounds of *Eucalyptus camaldulensis* were screened for activity against *Mycobacterium tuberculosis* H37Rv (MtbH37Rv). The extracts inhibited the growth of *Mycobacterium tuberculosis* with MIC of 4-64 µg/ml. Spectroscopic characterization led to the identification of two compounds, hydroxymyristic acid methylester and a substituted pyrenyl ester, a sterol. These two compounds had MIC of 49.45 and 46.99 µg/ml; IC_{50} >100 and 38.21 µg/ml; selectivity index (SI) >2.02 and 0.81, respectively, and a minimum bactericidal concentration of 62.50 µg/ml [152].Essential oil of the leaves of *Eucalyptus camaldulensis* possessed high antibacterial effects against Gram positive and negative bacteria with inhibition zones ranged from 9.3 to 12.5 Mm. The same effect was observed against yeast (21% inhibition) and fungi (10% inhibition) [135]. The antibacterial effect of essential oil of *Eucalyptus camaldulensis* was evaluated against *L. monocytogenes, S. aureus, E. coli, K. pneumoniae, S. cerevisiae, C. albicans, M. ramamnianus and A. ochraceus*. Essential oil of *Eucalyptus camaldulensis* showed activity against *S. aureus* (21mm), *B. subtilis* (24mm) and *E. coli* (10mm). Significant anti fungal activity was also shown by essential oil of *Eucalyptus camaldulensis* against *A. niger* (28mm) and *R. solani* (12mm) [124]. Methanolic leaf extracts of *Eucalyptus camaldulensis* were investigated for *in vitro* antifungal activities against *Microsporum canis, Microsporum gypseum, Tricophyton rubrum, Tricophyton schoenleinii, Tricophyton mentagrophytes* and *Epedermophyton floccosum*. *Eucalyptus camaldulensis* showed antifungal activity against all the tested dermatophytes with MIC values ranging from 0.4 to 1.6 mg/ml [153].
The essential oils of *Eucalyptus camaldulensis* were screened for their antifungal activities against common phytopathogenic fungi using the paper disk diffusion method, they showed activity at low doses against the tested fungi [98]. The antiviral effect of the leaf essential oil of *Eucalyptus camaldulensis* was studied against many viruses. Rotavirus Wa strain, Coxsackievirus B4, and herpes virus type 1 were affected by essential oil with percentage of reduction 50%, 53.3%, and 90% respectively, but no effect was found against adenovirus type 7 [135]. The methanolic extracts of *Eucalyptus camaldulensis* was tested against human enteroviruses: Poliovirus type I, Coxsackievirus B and Echovirus 6. The virucidal tests showed that the crude extracts were active against the tested viruses. Poliovirus type 1, coxsackievirus B and echovirus 6 giving a neutralization index of one log and above [133]. The aqueous, ethanolic, chloroform and acetone extracts of *Eucalyptus microtheca* showed inhibitory effects against *Staphylococcus aureus* while benzene extract was not effective. The aqueous, ethanolic and acetone extracts also possessed inhibitory effects against *S. typhimurium*. The extracts also showed synergistic inhibitory activity when combined with antibiotics against both *Staph. aureus* but not against *S. typhimurium* [54].The antibacterial activity of *Eucalyptus microtheca* leaves crude (ethanolic, methanolic and aqueous) extracts were tested against *Pseudomonas aeruginosa* isolates. All crude extracts exhibited an *in vitro* antibacterial activity against all *Pseudomonas aeruginosa* isolates with a zone of inhibition ranged between 17-25mm for methanolic extract, 20-29mm for ethanolic extract at a concentration of 1 mg/ml, while the zone of inhibition for aqueous extract was 12-16mm [154].The antibacterial activity, MIC, and MBC of alcoholic extracts of *Eucalyptus microtheca* were studied against *Bacillus cereus*, *Staphylococcus aureus*, *Salmonella typhi*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, and *Proteus mirabilis* using standard disk diffusion method. The structural changes following the exposure to these extracts were also investigated in the tested bacteria. Significant antibacterial activity was found against Gram positive and Gram negative bacteria, among them, *Escherichia. Coli* and *Pseudomonas. aeruginosa* showed the most sensitivity and *Staphylococcus aureus* the least. The value of MIC and MBC for both extracts were 8 mg/ml for *E. coli*, 8 and 16 mg/ml for *Bacillus cereus*, respectively. MIC and MBC values of methanolic and ethanolic extracts against *P. aeruginosa* were 8 and 16 mg/ml respectively. Scanning electron microscopy revealed structural changes in the affected bacteria, which suggested that the cell wall was the main target site of active constituents [155]. The antibacterial effect of essential oil of *Eucalyptus microtheca* was evaluated against *L. monocytogenes, S. aureus, E. coli, K. pneumoniae, S. cerevisiae, C. albicans, M. ramamnianus* and *A. ochraceus*. Essential oil of *Eucalyptus microtheca* showed activity against *S. aureus* (16mm), *B. subtilis* (20mm) and *E. coli* (11mm). Significant antifungal activity was shown by essential oil of *Eucalyptus microtheca* against *A. niger* (21mm) and *R. solani* (17mm) [124]. The antifungal activity of the *Eucalyptus microtheca* leaves crude aqueous, ethanolic and methanolic extracts were tested *in vitro* by agar well diffusion method against *Penicillium digitatum* and *Aspergillus niger*. Alcoholic extracts significantly inhibited the

mycelial growth of *P. digitatum* and *A. niger* more than aqueous extracts. Methanolic extracts showed higher inhibition activity than ethanolic extracts [108].

Effects on oral and dental health:

The antimicrobial properties of aqueous and alcoholic extracts of Eucalyptus leaves was investigated against the most cariogenic bacteria in mouth (Mutans streptococci and Lactobacilli) and against *Candida albicans*. There was statistically highly significant difference ($P< 0.001$) between different concentrations of the aqueous and alcoholic extracts on the sensitivity of the isolates, whilst the alcoholic extract was more effective than aqueous extract just at low concentrations. At 100 and 150 mg/ml the alcoholic and the aqueous extracts showed more potent effect than 2mg/ml chlorhexidine against Mutans streptococci and *Candida albicans*. Minimum bactericidal concentration for the aqueous extract was 5-8mg/ml, 6-10mg/ml and 3-7mg/ml against Mutans streptococci, Lactobacilli and *Candida albicans* respectively while that of alcoholic extract was 4-8mg/ml, 6-10mg/ml and 2-6mg/ml against the same microorganisms respectively [156].The effect of chewing gum containing Eucalyptus extract on periodontal health was investigated in a double-masked, randomized, controlled trial. Healthy humans with gingivitis but not deep periodontal pockets were randomly assigned to the following groups: high-concentration group (n=32): use of 0.6% Eucalyptus extract chewing gum for 12 weeks (90 mg/day); low-concentration group (n=32): use of 0.4% Eucalyptus extract chewing gum for 12 weeks (60 mg/day); and placebo group (n=33): use of chewing gum without Eucalyptus extract for the same period. Plaque accumulation (PLA), gingival index (GI), bleeding on probing (BOP), periodontal probing depth (PD), and clinical attachment level (CAL) were measured at weeks 0, 4, 8, 12, and 14. The interaction between the effects of Eucalyptus extract chewing gum and the intake period was statistically significant for PLA, GI, BOP, and PD, but not for CAL. The low- and high-concentration groups exhibited statistically significant ($P< 0.05$) improvements compared to the placebo group for PLA, GI, BOP, and PD [157].

Dermatological effects:

A long-term usage of a scalp lotion containing Eucalyptus extract, was investigated to explore the change in physical properties of the hair fiber. Half-head or whole-head usage studies of a scalp lotion with Eucalyptus extract were carried out on the following groups: Japanese female, Japanese senior female, Japanese male, and Caucasian female panelists. The improvement in hair luster and bounce in the root part of the hair were recognized by the panelists after the long-term application of the scalp lotion with Eucalyptus extract. The results indicated that the recognition of panelists was based on an actual change in the hair fiber properties. The efficacy of Eucalyptus extract was expressed regardless of race, age, or gender, since similar results were confirmed in all panelist groups. To study the mechanism, the elasticity (Young's modulus) of the new-growth part of the cortex in Eucalyptus extract-treated hair and placebo hair were evaluated by the nano-indentation method of atomic force microscopy (AFM). The results suggested that the Young's modulus of the new-growth part of the cortex in Eucalyptus extract treated-hair was increased in comparison with placebo hair. The IR spectra of treated samples of hair showed changes that appear to confirm a decrease in the alpha-helix structure and an increase in the beta-sheet structure [158].

Nasal effect:

An ex *vivo* cultures of human nasal turbinate slices was established to investigate the effects of 1,8-cineol on mucus hypersecretion in experimentally induced rhinosinusitis. Treatment of nasal slice cultures with lipopolysaccharides mimicking bacterial infection led to a significantly increased number of mucin-filled goblet cells. The number of mucin-filled goblet cells was found to be significantly decreased after co-treatment with 1,8-cineol. On a molecular level, real time PCR-analysis further showed that 1,8-cineol significantly reduce the expression levels of the mucin genes MUC2 and MUC19 in close association with significantly attenuated NF-κB-activity [159].

Antidiabetic effect:

The anti-hyperglycemic activity of the ethanolic extract of *Eucalyptus camaldulensis* leaves was studied on oral glucose tolerance test on albino rats. The administration of the ethanolic extract at a dose of 500 mg/kg of body weight showed a highly significant reduction in blood glucose when compared with control ($P< 0.001$)[160].

Other effects:

The effect of Eucalyptus essential oil mixed with milk casein peptide food was studied on physiological relaxation in human. Fifteen male university students (21.2 ± 0.9 yr) were participated in the study. They were given one of two types of experimental drink (peptide + Eucalyptus flavor (Pep + EF), and peptide + grape fruit, orange flavor (Pep + G·O), each flavor contains natural essential oil). The change in

salivary cortisol concentration and profile of mood states (POMS) scores before and two hours after taking experimental drink was investigated. The concentration of salivary cortisol decreased significantly two hours after taking Pep + EF. There were no statistically significant differences in all POMS scores between before and after taking Pep + EF and Pep + G·O [161].

Side effects and toxicity:

An accidental ingestion of Eucalyptus oil by a 3-year-old boy caused profound central nervous system depression within 30 minutes, on examination he was deeply comatose and his breath smelt Eucalyptus odour. The pupils were constricted, muscle tone was markedly reduced, and his tendon reflexes could not be elicited. His respiration was shallow and irregular at a rate of 10/min. The pulse rate was 70 beats/min and the blood pressure 75/40 mmHg. However, he recovered rapidly after gastric lavage. 2 hours after admission his pulse, blood pressure, and respiration rate had gradually returned to normal. After 5 hours consciousness had gradually been regained, and by 24 hours physical examination was normal apart from a faint smell of Eucalyptus on the breath [162]. Callers to the Poison Information Centre reported that 251 children had ingested an essential oil or product of them, 50 children ingested Eucalyptus oil. The most common symptoms were cough, vomiting and cough associated with vomiting. Two children had seizures but recovered [163].A retrospective analysis, of infants and children admitted to the Royal Children's Hospital, Melbourne, between 1 January 1981 and 31 December 1992 with a diagnosis of Eucalyptus oil poisoning, was carried out. 109 children (mean age, 23.5 months; range, 0.5-10.7) were admitted; clinical effects were observed in 59%. Thirty-one (28%) had depression of conscious state; 27 were drowsy, three were unconscious after ingesting of known or estimated volumes of between 5 and 10 ml, and one was unconscious with hypoventilation after ingesting an estimated 75 ml. Vomiting occurred in 37%, ataxia in 15% and pulmonary disease in 11%. In 27 patients who ingested known doses of Eucalyptus oil, 10 had nil effects after a mean of 1.7 mL, 11 had minor poisoning after a mean of 2.0 ml, five had moderate poisoning after a mean of 2.5 ml and one had major poisoning after 7.5 ml. No treatment was given for 12%. Ipecac or oral activated charcoal was given for 21%, nasogastric charcoal for 57%, and gastric lavage without anaesthesia for 4% and under anaesthesia for 6%. All patients were recovered [164].

V. CONCLUSION:

The current review discussed the chemical constituents of different Eucalyptus species grown in Iraq and their pharmacological and therapeutic potentials to enhance their uses in medical practice as a results of their effectiveness and safety.

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