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Industrial Crops & Products 132 (2019) 413–429

Contents lists available at ScienceDirect

Industrial Crops & Products

journal homepage: www.elsevier.com/locate/indcrop

Antimicrobial activity of *Eucalyptus camaldulensis* Dehn. plant extracts and essential oils: A review

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ARTICLE INFO

Keywords:
Antimicrobial activity
Plant extracts
Essential oils
Eucalyptus camaldulensis

ABSTRACT

Eucalyptus has become one of the world's most widely planted genera and *E. camaldulensis* (The River Red Gum) is a plantation species in many parts of the world. The plant traditional medical application indicates great antimicrobial properties, so *E. camaldulensis* essential oils and plant extracts have been widely examined. Essential oil of *E. camaldulensis* is active against many Gram positive (0.07–1.1%) and Gram negative bacteria (0.01–3.2%). The antibacterial effect is confirmed for bark and leaf extracts (conc. from 0.08 µg/mL to 200 mg/mL), with significant variations depending on extraction procedure. *Eucalyptus camaldulensis* essential oil and extracts are among the most active against bacteria when compared with those from other species of genus *Eucalyptus*. The most fungal model organisms are sensitive to 0.125–1.0% of *E. camaldulensis* essential oil. The extracts are active against *C. albicans* (0.2–200 mg/mL leaf extracts and 0.5 mg/mL bark extracts), and against various dermatophytes. Of particular importance is considerable the extracts' antiviral activity against animal and human viruses (0.1–50 µg/mL). Although the antiprotozoal activity of *E. camaldulensis* essential oil and extracts is in the order of magnitude of concentration several hundred mg/mL, it is considerable when taking into account current therapy cost, toxicity, and protozoal growing resistance. Some studies show that essential oils' and extracts' antimicrobial activity can be further potentiated in combinations with antibiotics (beta-lactams, fluorochinolones, aminoglycosides, polymyxins), antivirals (acyclovir), and extracts of other plants (*e.g. Annona senegalensis*; *Psidium guajava*). The present data confirm the river red gum considerable antimicrobial properties, which should be further examined with particular attention to the mechanisms of antimicrobial activity.

1. Introduction

The continuing increase in the degree of bacterial resistance to conventional antibiotics is a problem of global significance. The crisis of antimicrobial resistance has been ascribed to the misuse of these agents and today resistant strains are common, such as methicillin-resistant *Staphylococcus aureus,* vancomycin-resistant enterococci, drug resistant *Streptococcus pneumoniae* and *Mycobacterium tuberculosis*, carbapenem-resistant and extended-spectrum beta-lactamase producing enterobacteria, multidrug-resistant *Pseudomonas aeruginosa* and *Acientobacter baumannii etc.* It was estimated that the medical cost per patient with an antibiotic-resistant infection is up to $29,069 and infections are usually life treating (Ventola, 2018; Aslam et al., 2018). Similarly, fungi have become resistant to poliens, azoles and echinocandins, and the emergence of drug-resistant strains has been reported in all fungal species (Robbins et al., 2017). Beside the noticeable emergence of resistant protozoa and viruses, there is a problem with limited number of antiprotozoal and antiviral agents (El-Taweel, 2015; Irwin et al., 2016). This highlights the necessity for examination of new antimicrobial agents and treatment strategies of infections caused by the mentioned microorganisms.

The plant kingdom represents the source of various medicines. Indeed, since ancient times medicinal plants play an important role of health care population and could represent a significant source of new antimicrobial drugs for combating pan- and multi-drug resistant microorganisms. These new antimicrobial agents could be hidden in medicinal plant extracts and essential oils. One of the significant medicinal plants is *Eucalyptus camaldulensis*. Thus, this review represents the summary of previous researches data, regarding chemical composition, antimicrobial activity, and other significant effects of *Eucalyptus camaldulensis*.

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https://doi.org/10.1016/j.indcrop.2019.02.051
Received 12 November 2018; Received in revised form 20 February 2019; Accepted 24 February 2019
Available online 05 March 2019
0926-6690/

1.1. Eucalyptus camaldulensis Dehn. (1832)

The River Red Gum (*Eucalyptus camaldulensis* Dehn.) is a tree belonging to the genus *Eucalyptus* from Myrtaceae family. This family includes 140 genera and about 3800 species distributed in tropical and subtropical regions of the world (Ali et al., 2011). The genus *Eucalyptus* was described and named in 1788 by the French botanist l'Héritier. The name is generic, from the Greek words 'eu' (well) and 'kalyptos' (covered), because the flowers of various *Eucalyptus* species are protected by an operculum (Taoubi et al., 1997). The genus is indigenous to Australia and Tasmania, consists of over 800 species, spreading worldwide and successfully introducing due to its easy adaptability and fast growth (Coppen, 2002). As a consequence, *Eucalyptus* has become one of the world's most widely planted genera (Akin et al., 2010) and a plantation species in many parts of the world (Ames and Mathiews, 1968; Mubita et al., 2008).

Eucalyptus camaldulensis (formerly *Eucalyptus rostrata* Schl.), also known as long beak eucalyptus, murray red gum, red gum, river gum, and red river gum, is one of the most widely distributed *Eucalyptus* species. It is also considered one of the most widely planted trees in the world (*ca.* 5 000 000 ha planted) (N.A.S., 1980; Boland et al., 1984). *Eucalyptus camaldulensis* species is named for a private estate garden near the Camaldoli monastery near Naples (L'Hortus Camaldulensis di Napoli), from where the first specimen came to be described. Material from this tree was used by Frederick Dehnhardt, Chief Gardener at the Botanic Gardens in Naples, to describe this species in 1832 (Slee et al., 2006).

The habitus of the plant is very specific. Life form of *Eucalyptus camaldulensis* is a single-stemmed tree, with large trunk (Fig. 1). It is medium-sized to tall tree, average height 30 m (Bren and Gibbs, 1986), although some authors record trees to 45 m (Boland et al., 1984; Brooker et al., 2002). Leaves are grey-blue, alternate, drooping, 8–22 cm long, 1–2 cm wide, often curved or sickle shaped, tapering, and short pointed at base. Fruit is very small capsules at the end of thin stalks, 5–8 mm, valves 4, and containing minute seeds. *Eucalyptus camaldulensis* is an evergreen, perennial plant, and according to Jacobs (1955) it could reach ages of 500–1000 years. Commonly grows on riversides, whether of permanent or seasonal water (Brooker et al., 2002), generally dominate in the community, forming pure open forests or woodlands (Costermans, 1989).

The species *Eucalyptus camaldulensis* consists of two variations: *E. camaldulensis* var. *camaldulensis* and *E. camldulensis* var. *obtuse* Blakely, and one subspecies *Eucalyptus camaldulensis* subsp. *simulata* Brooker & Kleinig (Table 1), found in North Queensland, which has been recognised as a hybrid of *E. camldulensis* var. *obtusa* and *Eucalyptus tereticornis* Smith (Brooker and Kleinig, 1994). According to the Centre for Plant Biodiversity Research (EUCLID, 2006), the operculum shape in *E. camaldulensis* is highly variable (Table 1). In the past, this character has been used to break up the group into different varieties or subspecies. The entire complex is currently under revision and new varieties or subspecies may be described or extant ones rationalised. Until this work is completed, EUCLID (2006) decided to adopt a conservative view of *E. camaldulensis*.

1.2. Eucalyptus camaldulensis traditional and contemporary application

Used for centuries as a traditional Aboriginal herbal remedy, eucalyptus leaves and their essential oils have found various applications in everyday life due to their antiseptic, anti-inflammatory and antipyretic properties (Jeane et al., 2003; Kumar et al., 1988). Ancient Aboriginal society in Australia used *E. camaldulensis* plant in medicines to treat gastrointestinal symptoms (including colic, diarrhea, and dysentery), respiratory disease (colds, coughs, asthma, laryngalgia, laryngitis, pharyngitis, sore throat, trachalgia), arrest bleeding, open wounds, and cuts, as well as its decoctions for the relief of spasms, aches, and pains in muscles, but also pains in joints and even tooth (Duke and Wain, 1981).

As previously stated, *E. camaldulensis* plant is also known as red gum eucalyptus, murray red gum, and river red gum, because it produces red kino *i.e.* red gum, in significant amount. Thus besides different plant parts Aborigines used its secondary products as folk remedies. They made incisions in the tree trunks for obtaining the red kino and applied it directly to abrasions and cuts. Except fresh kino, the dried, dehydrated kino was prepared and used in the same way as fresh, but after softening in water (Williams, 2011; Clarke, 2014). Another significant folk remedy is young leaves which were used for smoke bath, where burning leaves smoke surrounds patient. The smoking medicine was used for fevers, colds, flu and general sickness (Williams, 2011; Pennacchio et al., 2010; Duke and Wain, 1981). Being useful for treating various health conditions, *E. camaldulensis* and its folk remedies then were transferred and introduced to other parts of the world, such as Africa. In Sudan the red kino was used for sore throat and diarrhea, while the smoke of burnt leaves was inhaled in case of respiratory problems. In Senegal for stomach-ache decoctions from leaves were prepared with sugar, while in Zimbabwe for cough, flu, and fever a decoction of *E. camaldulensis* leaves were combined with *Citrus limon* (L.) Burm. f. fruits and *Psidium guajava* L. leaves (Doran and Wongkaev, 2008; Maroyi, 2013). Further more, to prevent tooth decay and periodontitis in Nigeria teeth cleaning sticks were made from tree (Bukar et al., 2004), and in traditional medicine for healing wound infections, poultice of leaves containing eucalyptus oil have been used (Adeniyi et al., 2006).

Nowdays, *E. camaldulensis* has been the subject of numerous studies, to confirm plant's usefulness in traditional medicine for the treatment

Fig. 1. *Eucalyptus camaldulensis* (river red gum) on the Murchison River in Western Australia (by courtesy of Prof. Stephen D. Hopper).

Table 1
The main characters that distinguish *Eucalyptus camaldulensis* taxa.

Taxon	Bark		Leaves		Operculum	
E. camaldulensis var. *camaldulensis*	grey-white, rough at base bark		non-glaucous, green, narrowly lanceolate juvenile leaves		strongly beaked 0.3-0.7 cm long	
E. camaldulensis var. *obtusa*	essentially white, smooth and seasonally powdery bark		dull to slightly glossy green adult leaves with densely to very denselyreticulate venation		rounded or obtusely conical operculum 0.4-0.7 cm long at maturity and glaucous juvenile growth	
E. camadulensis subsp. *simulata*	grey-white, smooth to base bark		ovate or lanceolate juvenile leaves, adult leaves with dense reticulation		long horn-shaped operculum 0.9–1.6 cm long	

of various ailments (Coelho-de-Souza et al., 2005; Ghani, 2003; Ito et al., 2000). Its essential oils are reported to be anesthetic, antiseptic and astringent (Jeane et al., 2003; Kumar et al., 1988). In addition, a decoction of the leaves is reported to be a remedy for sore throat and other bacterial infections of the respiratory and urinary tracts (Bruneton, 1999). Due to numerous contemporary data regarding the antimicrobial activity of *E. camaldulensis*, this subject will be discussed in special section/chapter.

Except antimicrobial effects, *E. camaldulensis* plant extracts (PEx) and essential oils (EOs) and its constituents possess numerous other beneficial effects. One such effect is certainly gastrointestinal effect. In animal models, extracts of the leaves of *E. camaldulensis* and *E. torelliana* R. Muell are reported to decrease gastric acid production and thus appear useful for the treatment of gastric ulcers (Adeniyi et al., 2006). It has been proven that *E. camaldulensis* leaves methanol extracts possessed ulcer-healing promoting effect when investigated in acetic acid induced-ulcer in rat (*Rattus norvegicus domesticus*) (Lawal et al., 2014) (Table 2). Similarly, the poultice of the leaves is applied over wounds and ulcers (Gill, 1992).

The antioxidant effect represents one more useful *E. camaldulensis* characteristic. The free radical scavenging activities of the essential oils is assessed by measuring their scavenging abilities for 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals. The scavenging activity for the *Eucalyptus camaldulensis* was characterized as high (81.9%) (Ghaffar et al., 2015). The results of *E. camaldulensis* EO antioxidant effect evaluation indicated that the EO had high potent ferrous ions chelating and total antioxidant activities comparing to ascorbic acid and BHT (El-Baz et al., 2015). Also, the *E. camaldulensis* var. *brevirostris* leaves ethanol extract possessed antioxidant activity, where the prevailing antioxidants in the extract were gallic and ellagic acid (El-Ghorab et al., 2003). There are several more studies dealing with antioxidant activity of *E. camaldulensis* (Barra et al., 2010; Salem et al., 2015; Siramon and Ohtani, 2007; Olawore and Ololade, 2017), but it is interesting to mention here that *E. camaldulensis* flower EO inhibited melanogenesis through its antioxidant properties and by down-regulating both mitogen-activated protein kinases (MAPK) and protein kinase A (PKA) signaling pathways. This study indicated that the essential oil has the potential to be developed into a skin care product (Huang et al., 2015). Thus, except the medical application, *E. camaldulensis* extracts are also currently used in cosmetic formulations, and leaf extracts have been approved as food additives (Takahashi et al., 2004). Also, essential oils and their constituents have been used as flavoring agents in the formulation of different pharmaceutical products, cosmetics, and food industry (Cowan, 1999). Except this, *E. camaldulensis* PEx and EOs have the potential to be used as antibacterial and antifungal agents in cosmetic and pharmaceutical products. It is interesting to mention here the activity of *E. camaldulensis* EOs (2–8 mg/mL) on dental biofilm formation *in vivo* where detected inhibition was 14.5–39.2% after four weeks, comparing to chlorhexidine (2 mg/mL), which inhibited maximum 13.9% of dental biofilm formation (Rasooli et al., 2009). Extracts and essential oils of this aromatic plant can be used as food preservatives in order to reduce the dependency on synthetic chemicals in food preservation. In Australia, it is also used as sources of wild honey, providing bees with good quality pollens and heavy yields of nectar (Boland et al., 1984). Moreover, in industry, the wood of *E. camaldulensis* has been used for heavy construction, railway sleepers, flooring, framing, fencing, plywood, and veneer manufacture, wood turning, firewood, and charcoal production (Boland et al., 1984). Eucalyptus camaldulensis wood burns well and make a good fuel, also its dense wood and coppicing ability make it an excellent species for fuelwood production used in several countries such as Brazil (Jacobs, 1981; Eldridge et al., 1993). Furthermore, *Eucalyptus* biomass residues from agro-forest and pulping industries represent a valuable source of high-value compounds such as triterpenic compounds (Domingues et al., 2011; Ferreira et al., 2018).

Due to the diversity of *E. camaldulensis* beneficial effects, all effects reported in the literature are summarized in Table 2. Beside the beneficial effects, essential oils and plant extracts can exert potentially unfavorable effects as complex mixtures of different compounds. A risk assessment of their hazard is always necessary before commercialization, so the estimation of EOs toxicity has been already conducted resulting in human oral and dermal dose limit recommendations. For most EOs the recommended dose is in range 1–4%, but for cineole-rich *Eucalyptus* sp. EOs, including *E. camaldulensis*, the limit dose is 10%, indicating a generally low application risk (Lis-Balchin, 2006). The safe daily oral dose in human adults is 300–600 mg, while semisolid preparations for topical use may contain 5–20% of *Eucalyptus* oil (Blumenthal and Busse, 1998; Tisserand and Young, 2014). Similarly, *E. camaldulensis* bark methanolic extract LD50 value for Swiss albino mice (*Mus musculus*) is very high – 1120 mg/kg, indicating its low host toxic effects (Islam et al., 2014). The low toxicity and natural origin of *E. camaldulensis* essential oil and extracts, in contrast to synthetic antimicrobials, favor their application as antimicrobial agents.

2. Chemical composition

2.1. Eucalyptus camaldulensis plant chemical composition

Eucalyptus camaldulensis leaves contain 0.1–0.4% essential oil, of which 77% is 1,8-cineole. There is considerable amount of cuminal, phellandrene, aromadendren (or aromadendral), valerylaldehyde, geraniol, cymene, and phellandral (Council of Scientific and Industrial Research, 1948–1976Council of Scientific and Industrial Research (S.I.R, 1948Council of Scientific and Industrial Research, 1948–1976; Slee et al., 2006). Leaves contain 5–11% tannin. The kino (a class of wood exudates), contains 45% kinotannic acid as well as kino red, a

Table 2
Different significant effects of *Eucalyptus camaldulensis*.

Different *E. camaldulensis* effects	Model organism and/or cell line	Plant part extract, oil or compound	Effect of dosage and/or application mode	Reference
Gastrointestinal effect	Acetic acid induced-ulcer in rat	Leaves methanol extracts	Reduction the size from day 5 in animals treated with 500 mg/kg body weight of reconstituted extracts at 24 h interval	Lawal et al. (2014)
	Four ruminal fistulated buffaloes (*Syncerus caffer*), 4 years old with initial body weight 321 ± 20 kg	Leaves meal	Dietary treatments - different levels of leaf meal supplementation at 0, 40, 80, and 120 g/hd/d for 21 days. Protozoa count and proteolytic bacteria population were reduced ($p < 0.05$). Fungal spores, amylolytic, cellulolytic and total viable bacteria were unchanged.	Thao et al. (2015)
Anti-inflammatory and analgesic effect	Healthy albino rats (200 ± 30 g)	Seed essential oils of *E. camaldulensis* var. *nancy* and *E. camaldulensis* var. *petford*	Carrageenan induced paw oedema test model in rats, which received 1000 μg kg^{-1} body weight; 43.75-87.5% of anti-inflammatory activity	Olawore and Ololade (2017)
Anti-nociceptive activities	Healthy albino rats (200 ± 30 g)	Seed essential oils of *E. camaldulensis* var. *nancy* and *E. camaldulensis* var. *petford*	Rats treated with 1000 μg kg^{-1} body weight, measured neurogenic and inflammatory pain responses, 41.03-99.09% of inhibition	Olawore and Ololade (2017)
Cytotoxic effect	Two human breast cancer cell lines (MCF 7 and MDA-MB-231)	Leaves methanol, ethyl acetate, n-buthanol, and water extracts	Significant cytotoxic potential with IC50 values ranging from 3 to 250 μg/mL after 72h	Hrubik et al. (2012)
	L20B (a genetically engineered mouse cell line) and human rhabdomyo sarcoma cells	Crude methanol extracts	Moderate cytotoxicity	Adeniyi et al. (2015)
	Ehrlich's ascites carcinoma (EAC) in Swiss albino mice	Stem bark methanol extract	25, 50 and 100 mg/kg/day for 5 days; High LD50 value (1120 mg/kg)	Islam et al. (2014)
Anti-parasitic, insecticidal and repellent effects	*Trypanosoma brucei* infected mice	Leaves, stem and root barks extracts	200-600 mg/kg body weight/day of the hexane, ethyl acetate, methanol and water extracts for 21consecutive days	Kabiru et al. (2013)
	Promastigotes of *Leishmania major in vitro*	Methanol and aqueous extracts	IC50 values were 586.2 ± 47.6 and 1108.6 ± 51.9 μg/mL	Nosratabadi et al. (2015)
	Larvicidal activity against *Anopheles stephenssi*	Leaves extract and volatile oil	LC50 values of 89.85 and 397.75 ppm, respectively. Clear dose-response relationships, the highest dose of 320 ppm essential oil extract resulted almost in 100% mortality in the population after 24 h of exposure	Medhi et al. (2010)
	Mosquito larvicidal against two mosquito species, *Aedes aegypti* and *Aedes albopictus*	Leaves essential oils and their 12 constituents	400, 200, 100, 50, and 25 μg/mL of essential oil were tested and each compound was tested at 50, 25, 12.5, and 6.25 μg/mL; Mortality was recorded after 24 h; LC50 values 31.0-55.3 lg/mL, LC90 values 71.8-192.4 lg/mL.	Cheng et al. (2009)
	Aphis gossypii Glover (Hem: Aphididae)	Essential oil	LC_{50}values 2.28 μl L^{-1}air	Ebrahimi et al. (2013)
	Repellency against the adult females of *Culex pipiens*	Dried fruits essential oil	Two different treatment levels (5 and 10 μl) in six exposure times (15, 75, 135, 195, 255 and 315 s)	Erler et al. (2006)
Anti-diabetic effect	Albino rats	Leaves ethanol extract	Oral 500 mg/kg of body weight	Dawoud (2015)
	Alloxan-induced diabetic rats	Leaves ethanol extract	500 mg/kg of body weight in distilled water orally, *E. camaldulensis* leaves supplement incorporated into the diet 5 g/kg/day	Dawoud and Shayoub (2017)

glucoside, catechol, and pyrocatechol. Leaves and fruits test positive for flavonoids and sterols. The bark contains 2.5–16% tannin, the wood 2–14%, and the kino 46.2–76.7% (Watt and Breyer-Brandwijk, 1962). Some of the reported phytoconstituents of the tree included essential oils, sterols, alkaloids, glycosides, flavonoids, tannins, and phenols.

2.2. *Eucalyptus camaldulensis* essential oil chemical composition

A considerable variation in the yield of leaf essential oil from *E. camaldulensis* has been reported (Boland et al., 1984; Shieh, 1996; Moudachirou et al., 1999; Farah et al., 2002), depending on multiple biotope factors, and also genetic and/or epigenetic characteristics of the plant. The yields of *E. camaldulensis* leaves EO (0.90–0.98%) originating from Pakistan and Morocco were similar (Ashraf et al., 2010; Farah et al., 2002), while Moudachirou et al. (1999) reported a variable oil content of 0.6–1.4% from different locations of Benin. The oil yield of *E. camaldulensis* from Jerusalem was 0.5% (Chalchat et al., 2000) and significantly higher oil yield was reported for *E. camaldulensis* from Taiwan: 2.3–3.0% with respect to different seasons (Shieh, 1996). Similar EOs yield (0.77–2.53%) has been reported for *E. globulus*, as one of the economically important plants for essential oil production (Joshi, 2012; Selvakumar et al., 2012; Harkat-Madouri et al., 2015). The reported essential oil yield for other *Eucalyptus* species is slightly higher, ranging from 1.2% to 3% (w/w): the highest yield was obtained from *E. cinerea* F. Muell. ex Benth and *E. sideroxylon* A. Cunn. ex Woolls (3.0%), followed by *E. lehmannii* (Schauer) Benth. (2.8%), *E. bicostata* Maiden, Blakely & J.H.Simmonds (2.0%), *E. leucoxylon* F. Muell (1.6%), *E. maidenii* F.Muell. (1.5%), and *E. astringens* Maiden (1.2%) (Sebei et al., 2015).

All the *E. camaldulensis* essential oil single compounds belong to chemical class of hydrocarbons terpenes, further devided according to the number of isoprene units (C_5H_8) to monoterepenes ($C_{10}H_{16}$), sesquterepenes ($C_{15}H_{24}$), and longer chains of isoprene units. Oxygenated terpenes (oxygenated monoterepenes and oxygenated sesquterepenes) are called trepenoids. According to the literature, in *E. camaldulensis* EOs dominates 1,8-cineole (eucalyptol), *trans*-pinocarveol and terpinen-4-ol from chemical class of oxygenated monoterepenes. The oils also contain considerable amount of monoterpene hydrocarbons (β-pinene, α-thujene, γ-terpinene, p-cymene), while sesquterepene hydrocarbons and oxygenated sesquterepenes are detected in significantly lower amounts (Table 3).

When the composition of five *Eucalyptus* essential oils (*Eucalyptus camaldulensis*, *Eucalyptus astringens* Maiden, *Eucalyptus leucoxylon*, *Eucalyptus lehmannii* and *Eucalyptus rudis* Endl) are compared, a high percentage of monoterpenes, mainly oxygenated compounds, with lower quantities of sesquiterpenes were recorded throughout the four seasons (Ben Jemaa et al., 2012). In *E. camaldulensis* oil, monoterpenes were prevalent (34.6–56.3% for all seasons) while sesquiterpene hydrocarbons (6.6–16.5%) and oxygenated sesquiterpenes (2.1–11.1%) were present in less extent. *Eucalyptus astringens* oil had resembling chemical characteristic to *E. camaldulensis* oil, the abundant quantity of monoterpenes, which represented more than 50% of the total oil amounts for the all seasons (53.4–63.6 %). Similarlly, *E. leucoxylon* essential oil, contained mainly oxygenated monoterpenes with a prevalence of 1,8 cineole (13.1–17.6%), such as in *E. camaldulensis* oil (15.5–20.6%). The essential oil of *E. lehmannii* also was made up largely of monoterpenes (hydrocarbons 27.6–44.9% and oxygenated 30.9–62.8%), with smaller amounts of sesquiterpene hydrocarbons and absence of oxygenated sesquiterpenes, unlike the oils of other *Eucalyptus* species (Ben Jemaa et al., 2012).

The difference in the chemical composition of the *E. camaldulensis* EOs may be due to many reasons, which can generally be classified in five main groups: (1) the change in plant genes through generations and hybridizations (naturally and induced) may result in production a variety of volatile oils compared with those of different habitat; (2) nutrients of different soils and their accumulation in the leaves may result in different plant metabolism and consequently production of different bio-products and also EOs made of diverse compounds in variable amounts; (3) acclimation of species to the Australian environment in which it is growing in the past, compared with the introduced and/or worldwide planted trees on plantations; (4) different ecotypes of the *E. camaldulensis* and (5) differences may be due to plant part used for essential oils extraction and its stage of development (maturity). Knowing that these factors express significant effect on the percent compositions of some EO components for this species, *E. camaldulensis* can be grown in the corresponding areas and in specific conditions to enhance EO production.

The variations in the chemical composition of eucalyptus EOs with respect to seasons have also been reported (Tsiri et al., 2003), but the most commonly detected as major components in the eucalyptus essential oil are 1,8-cineole, β-pinene, γ-terpinene, and p-cymene. It is

Table 3
Classes of major *Euclyptus camaldulensis* essential oils compounds and their content in different plant parts.

Chemical classes	Chemical subclasses	Sublaclasses content in leaf and fruit (%)[a]	Major essential oils compounds	Major compounds content in oil[a,b]		
				L	Fr	Fl
Terpenes	Monoterpene hydrocarbons	5.7-52.2 L 18.7 Fr 18.5 Fl	α-Pinene	1.7-28.3	1.12-3	3.51
			β-Pinene	0.3-18.6	8.8	7.7-27.09
			α-Thujene	1.0-3.4	0.3	0.6-0.77
			β-Phellandrene	0.5-7.5	0.3	2.1-2.2
			p-Cymene	tr. -6.5	4.8	9.32
			γ-Terpinene	0.19-7.6	0.2	0.4-0.5
	Sesquiterpene hydrocarbons	1.8-3.6 L 6.1 Fr 1.2 F'l	Aromadendrene	0.1-11	0.2	0.21-0.24
			allo-Aromadendrene	0.2-1	3	0.2
			Bicyclogermacrene	0.3-1.8	2	0.09-0.4
			α-Copaene	0.9	tr.	–
Terpenoids	Oxygenated monoterpenes	40.8-87.42 L 14.1 Fr 50 Fl	1,8-Cineole	13.73-84.9	3.8	34.7-69.26
			trans-Pinocarveol	0.06-8.5	0.2	0.11-1.9
			Terpinen-4-ol	0.27-5.2	1.9	3.29-3.6
			Myrtenol	1.4-9.75	2.1	0.12
			Cuminal	0.09-3.2	1.3	0.94-1.01
	Oxygenated sesquiterpenes	4.9-39.6 L 23.2 Fr 12.7 Fl	Spathulenol	0.16-19.2	19	0.12-10.18
			Elemol	0.6-3	–	–
			β-Eudesmol	0.13-4.4	–	–
			cis-Farnesol	0.9-5	–	0.1

[a] L- leaf, Fr-fruit, Fl-flower.
[b] tr., traces (< 0.05%).

important to emphasize here that according to chemical composition the *Eucalyptus camaldulensis* EO generally can be divided in two different types. Type I is a cineole-rich essential oil containing 80–90% 1,8-cineole plus pinene, and Type II is a cineole-poor essential oil, containing significantly less cineol (Williams, 2011). Plant genotype is important factor influencing the final chemical composition of EO (Djilani and Dicko, 2012). Due to genetic and epigenetic factors same plant species can produce a similar EO, but with different chemical composition and therapeutic activities. Brophy and Southwell (2002) examined essential oils of two variations, *Eucalyptus camaledulensis* var. *camaldulensis* and *Eucalyptus camaledulensis* var. *obtuse*, and the main compounds of *Eucalyptus camaledulensis* var. *camaldulensis* were p-cymene (22%), cryptone (14%), and spathulenol (17%), while *Eucalyptus camaledulensis* var. *obtusa* had different main compounds: 1,8-cinole (52%), α-pinene (15%), and aromadendrene (3%), suggesting that these subspecies belong to different types of eucalyptus essential oils. The content of 1,8-cineole was also variable but in the same range for essential oils reported from Greece (25.3–44.2%) (Tsiri et al., 2003), Pakistan (34.4–40.0%) (Ashraf et al., 2010), Mozambique (37.1–40.0%) (Pegula et al., 2000), Nigeria (32.8–70.4%) (Oyedeji et al., 1999), and Taiwan (34.0–68.2%) (Shieh, 1996). Similarly, the major component of Eucalyptus camaldulensis oils originating form Burundi, Morocco, and Benin was 1,8-cineole ranging from 31.0 to 72.5% with no presence of cryptone (Dethier et al., 1994; Zrira and Benjilali, 1991; Zrira et al., 1992; Moudachirou et al., 1999). Cryptone has been shown to be present in low-cineole varieties of EOs from Australia (Bignell et al., 1996), Uruguay (Dellacassa et al., 1990) and South Florida (Pappas and Sheppard-Hanger, 2000). For example, the major constituents identified in the essential oil from South Florida included p-cymene (35.0%), cryptone (13.7%), terpinen-4-ol (5.7%), spathulenol (4.3%), and cuminaldehyde (3.7%), with a very low amount of 1,8-cineole (2.7%) (Pappas and Sheppard-Hanger, 2000).

It was proven that essential oils of different plant parts have different chemical composition (Table 3). Previous studies on the essential oil of *E. camaldulensis* flowers revealed the presence of 1,8-cineole, β-pinene, and spathulenol as the most abundant constituents (Giamakis et al., 2001). The essential oil of the leaves was found to contain *p*-cymene, γ-terpinene, α-pinene, 1,8-cineole, terpinen-4-ol, α-terpineol, carvacrol, and thymol as the major components (Siramon and Ohtani, 2007). The major components of the fruits essential oil were aromadendrene, α-pinene, drimenol, and cubenol (El-Ghorab et al., 2002).

Plant developmental stage and maturity of plant parts used for essential oil extraction also affect essential oil chemical composition. Giamakis et al. (2001) analyzed the immature flowers and calli grown in Athens (Greece), and they found that the main monoterpenes produced in *E. camaldulensis* calli, cultured in darkness and under light conditions, were 1,8-cineole, 62.70 and 69.26% as well as β-pinene, 27.09 and 25.31%, respectively. In lower amounts α-pinene (1.2 and 1.1%, respectively) and the terpenoids, camphene, myrcene, isocineole, myrtenol, bicyclogermacrene, spathulenol, and *trans*-pinocarveol were present (less than 1%). Apart from isocineole, these constituents were also determined in the essential oil from immature flowers. This is remarkable because Giamakis et al. (2001) showed that undifferentiated calli are capable of producing high amounts of monoterpenoid compounds (approx. one third of that produced by the explant). This makes immature flowers from *E. camaldulensis* an interesting candidate for the development of calli able to produce high percentages of these two important monoterpenes, 1,8-cineole and β-pinene (Giamakis et al., 2001). Also, the influence of light conditions on essential oil chemical composition showed that light conditions did not considerably affect the production of monoterpenes and sesquiterpenes compounds by calli developed from immature flowers (Giamakis et al., 2001).

Furthermore, plant culture conditions can influence the essential oil chemical composition. Soil salinity is a key ecological stress that severely influences plant productivity (Williams, 2011). Ashraf et al. (2010) showed that salinity had a considerable effect on the percent compositions of some components of *E. camaldulensis* leaves essential oil. The mean values of 1,8-cineole content of EO from saline and non-saline provenances of Pakistan were 34.42 and 40.05%, respectively (Ashraf et al., 2010). Therefore, they recommend stressing of this species by growing in the saline areas to enhance essential oil production for its various medicinal and pharmacological uses.

2.3. *Eucalyptus camaldulensis* extracts chemical composition

Extraction represents the primary step in obtaining the crude mixture of compounds from plants. Quality and quantity of the extracts dependent of the target compound structures, natural sources, and type of processes (Karacabey et al., 2013), explaining the different phenolic composition in the extracts obtained with different procedures. The most commonly plant extract have been obtained by conventional solvent extraction methods (infusion, decoction, digestion, maceration, and percolation) (Azwanida, 2015) using solvents such as water, ethanol, methanol, chloroform, dimethyl-sulfoxide *etc.* However, these techniques are demanding regarding the extraction process duration, organic solvent consumption, and lack of extraction automation. The potential and powerful alternative to conventional liquid solvent extraction methods are Ultrasonic-Assisted Extraction (UAE) and Microwave-Assisted Extraction (MAE), especially in the case of plant material (Hao et al., 2002; Eskilsson and Bjrklund, 2000). Interest in MAE has increased significantly over the past 5–10 years in particular medicinal plant research, as a result of its inherent advantages as special heating mechanism, moderate capital cost, and its good performance under atmospheric conditions (Ballard et al., 2010; Chan et al., 2011). In addition, MAE technique possesses many advantages compared with other methods for the extraction of compounds such as bioactive compounds (Sanchez-Aldana et al., 2013) saving in processing time and solvent, higher extraction rate, better products with lower cost, reduced energy consumption (up to 85-fold savings), and waste generation (Yan et al., 2010; Yemis and Mazza, 2012). This is confirmed for *E. camaldulensis* extraction of phenolic and flavonoid compounds, where the compounds were extracted with MAE for 5 min which was equivalent with UAE (60 min) and traditional extraction (24 h) methods (Gharekhani et al., 2012).

Many authors reported the chemical composition of *E. camaldulensis* extracts. The leaves of *E. camaldulensis* from the zoo-botanical garden in Giza (Egypt) yielded 4 major fractions (Singab et al., 2011). The major components of the first fraction (eluted with water) were identified as HHDP-glucopyranose, chlorogenic acid, and phloroglucinol derivatives. The second 30% methanol fraction was found to contain different galloyl-HHDP-glucopyranose positional isomers and pedunculagin as major components. The third 60% methanol fraction was predominantly composed of digalloyl-HHDP-glucopyranose (tellimagrandin I) α and β anomers, while the last 100% methanol fraction was composed of a mixture of ellagitannin dimers. The profiling of the obtained fractions by HPLC–PDA–ESI/MS/MS indicated that ellagitannins were the most predominant components of all three methanol fractions (Singab et al., 2011).

The secondary metabolites screening of *E. camaldulensis* leaf extracts from Nigeria confirmed presence of tannin, saponins, and cardiac glycosides (Ayepola and Adeniyi, 2008). Analyzed *n*-hexane, chloroform, and methanol extracts of *E. camaldulensis* stem bark and leaf also grown in Nigeria showed the presence of tannins and saponins in the stem bark and in the leaf of *E. camaldulensis* with absence of alkaloids in all extracts (Adeniyi et al., 2009). Furthermore, the crude methanol leaf extracts also from Nigeria contained in addition volatile oils and balsam (gum) (Babayi et al., 2004). Similarly, the phytochemical screening of ethanol, methanol, and petroleum ether leaf extracts from Nigeria contained in moderate to high amount secondary metabolites: alkaloids, saponins, tannins, flavonoids, steroid, carbohydrates, and cardiac glycosides, and not anthraquinones (Chuku et al., 2016). Crude

methanol leaf extracts of *E. camaldulensis* from Iran had saponins, tannins, volatile oils, and balsam (gum), while the components such as anthraquinones, hydrolysable tannin, flavonoid, alkaloid, and glycosides were not detected (Jouki and Khazaei, 2010); crude methanolic leaves extract of *E. camaldulensis* from India contained anthraquinones, flavonoids, saponins, and terpenoids, while alkaloids, cardiac glycosides, and tannins were not detected (Singh and Thakur, 2016). Phytochemical screening of the crude stem barks methanol extract of *E. camaldulensis* from Bangladesh indicated presence of saponins, flavonoids, tannins, and also volatile oils, while anthraquinones, hydrolysable tannins, alkaloids, and glycosides were not present (Islam et al., 2014). The polyphenolic composition (flavonoids and phenolic acids and aldehydes) also was studied in the soluble fractions of the methanolic extracts of *Eucalyptus camaldulensis* originating from two Spain provinces, Huelva and Pontevedra: gallic, protocatechuic, vanillic and ellagic acids, and protocatechic aldehyde were identified, along with eriodictyol, quercetin, naringenin, vanillin, naringin, quercitrin, luteolin, and kaempferol (Cadahia et al., 1997). *Eucalyptus camaldulensis* extracts are generally rich in tannins which vary qualitatively and quantitatively according to the origin of the samples, and consequently protoanthocyanidin levels were influenced by the geographical origin (Cadahia et al., 1997).

3. Antimicrobial effect of *Eucalyptus camaldulensis* extracts and essential oils

Antimicrobial activity of *E. camaldulensis* EO and extracts are well documented against many microorganisms listed in the Table 4. For easier comparison, all data commented here for EOs were re-calculated from microliter per milliliter or microgram/milligram per milliliter to percentage (v/v or w/v), using the equitations presented in Fig. 2. We considered here only minimal inhibitory and minimal bactericidal concentrations, while results obtained using disc or agar diffusion methods were not discussed. However, MIC/MBC results vary between several micrograms to several milligrams. Such high variation does not seem as real, even taking into account variation in oil composition, and are rather a consequence of erroneous equalization of one microliter and one microgram, or typographical errors. For instance, there are some nonsense MICs, such as 2000 µL/mL, that is practically impossible to obtain (Salem et al., 2015). In some manuscripts even a species was not precisely indicated (Harkenthal et al., 1999; Karpanen et al., 2008; Warnke et al., 2009; Tadtong et al., 2016) and these results were not considered in the present review.

3.1. Antibacterial effect

Eucalyptus camaldulensis plant extracts and EOs were tested against wide range of bacteria. The most frequently included Gram positive bacterium in screening is *S. aureus*. Minimal inhibitory concentrations in most studies were in range 0.07–0.5% indicating moderately high activity against this bacterium. Beside *S. aureus*, antibacterial effect was confirmed against *B. subtilis* (0.17–0.34%), *M. luteus* (0.2–0.4%), and *S. pyogenes* (0.4–1.1%) (Rasooli et al., 2009; Akin et al., 2010; Knezevic et al., 2016; Khubeiz et al., 2016; Reda et al., 2017; Ostad Asiaei et al., 2018). Activity of EOs was examined aginst L. *monocytogenes* in only one study and MIC was not obtained with the highest used concentration of 1.0%, and the same was reported for *Enterococcus durans* (Akin et al., 2010).

Activity against Gram negative bacteria has been documented in a greater extent and MICs for the most frequently used model organism *E. coli* was in range 0.15–3.2%. Sensitivity of other enterobacteria is similar, with MICs in range from 0.05 to 0.32% for *K. pneumoniae* (Khubeiz et al., 2016; Ostad Asiaei et al., 2018), 0.16–0.32% for *Salmonella enterica* subsp. *enterica* serovar Typhimurium (Khubeiz et al., 2016); 0.35–0.4% for serovars Typhi, Paratyphi, and 0.6% for *S.* Enteritis (Ostad Asiaei et al., 2018). Other enterobacteria are similarily sensitive: *Shigella soneii* was inhibited with 0.3% of EO (Ostad Asiaei et al., 2018), while *Proteus vilgaris* was sensitive in a broad range from 0.25% (Ostad Asiaei et al., 2018) to more than 1.28% (Khubeiz et al., 2016). The published data for *P. aeruginosa* are in the same range as for *P. vulgaris*, which is not surprising, as both species are generally highly resistant to antimicrobial agents. On the contrary, *A. baumannii* which is also known to be multi-drug resistant, showed sensitivity to EO in a range 0.05–0.1% (Knezevic et al., 2016). The lowest MIC among Gram negative bacteria was recorded for a gastrointestinal pathogen *V. parachaemoliticus* (0.01%) (Khubeiz et al., 2016).

Although the Gram positive bacteria are consider more sensitive to EOs in comparison to Gram negative, it cannot be applied for essential oils of *E. camaldulensis*, since the most sensitive bacteria are Gram negative – *A. baumannii* and *V. parahaemolyticus*. The minimal bactericidal concentrations for most bacteria are equal to, or rarely up to 4 times greater than MICs. This low range in MIC/MBC < 4 indicates that *E. camaldulensis* EOs act as bactericidal agents (Pankey and Sabath, 2004).

Antibacterial effects of *E. camaldulensis* extracts have been examined in a wider extent than essential oils. Inhibitory concentrations varied depending on extraction method, plant properties, and model organism, being in broad range from 0.08 µg/mL to 200 mg/mL. Crude aqueous leaf extracts show lower activity against various bacteria (range 25–50 mg/mL) (Abubakar, 2010), while bark aqueous extracts were more effective, with MIC from 0.1 mg/mL for *Propionobacterium acnes* to 4.0 mg/mL for *P. aeruginosa* (Mabona et al., 2013). The antimicrobial activity of methanol, ethanol or petroleum leaf extracts of *E. camaldulensis* showed significant variation; for instance, MICs against *B. subtilis* varied from 0.04 up to 200 mg/mL or against *S. aureus* 1.25–25 mg/mL (Chuku et al., 2016; Ayepola and Adeniyi, 2008). For most examined Gram negative bacteria MICs were in range 10–200 mg/mL, while *P. aeruginosa* was even more susceptible (MICs 10–100 mg/mL). Similar or better antibacterial effect showed acetone leaf extract, being active against examined bacteria in range 15–50 mg/mL. The highest activity was obtained with dichloromethen extracts, with MICs for *Staphylococcus* spp. in range 0.25–1.0 mg/mL, and even lower for *B. subtilis, P. acnes* and *B. agri* (MICs 0.10–0.79 mg/mL). Interestingly, generally highly resistant *M. tuberculosis* was sensitive to methanol, n-hexane or chloroform extract with MICs in range 0.004–0.064 mg/mL, while *M. bovis* was slightly less sensitive with MICs 0.01–0.05 mg/mL (Lawal et al., 2012; Gemechu et al., 2013).

The progresses made on the investigation of essential oils mode of action, especially against bacterial cell targets, gave new perspectives in this combat. The knowledge about the essential oils and their target(s) on bacterial cell is crucial to understand which parts of bacterial cell are affected. The essential oils antibacterial action is linked to oil hydrophobicity that increases cell permeability and consequent leakage of cell constituents (Dorman and Deans, 2000; Lambert et al., 2001; Helander et al., 1998; Turgis et al., 2009; Ultee et al., 2002; Faleiro, 2011). It is important to perceive that a disturbed cell structures may affect stability of other cellular structures in a cascade type of action (Carson et al., 2002). Essential oils have several target sites on bacterial cells; however it seems that all are directly or indirectly connected to the primary effect of essential oils on the bacterial envelopes. First of all, EOs may cause cell wall and membrane disturbance (Lambert et al., 2001; Oussalah et al., 2006), which further can lead to the significant loss of intracellular ATP (Oussalah et al., 2006; Turgis et al., 2009), induction the synthesis of heat shock proteins (Burt et al., 2007), pH disturbance (Turgis et al., 2009; Oussalah et al., 2006), and intracytoplasmic changes (*e.g.* coagulation, periplasmic space enlargement) (Becerril et al., 2007). Although the number of studies dealing with the EO mechanisms of action is increasing, there are still many questions to be answered before the precise mechanism is revealed. This is at the same time one of the main limitations for EOs and extracts wide usage as antimicrobials. Thus, the so far knowledge must be further improved enabling the combat bacterial pathogens and its resistance.

Table 4
Antimicrobial activity of *E. camaldulensis* essential oils and extracts.

E. camaldulensis		Microorganism	Activity[a]		Recalculated (%)		References
			MIC	MBC	MIC	MBC	
Essential oil	Leaves essential oil (%, v/v) from Northern Cyprus	*S. aureus*	0.5				Akin et al. (2010)
		L. monocytogenes, *E. durans*, *Salmonella* Typhi, *E. coli*, *B. subtilis*, *P. aeruginosa*	>1				
	Leaves essential oil (μg/mL) from Iran	*S. aureus*, *E. coli*	8		0.0008		Lima et al. (2013)
	Leaves essential oil (μg/mL) from Iran	*S. aureus*	3.9	3.9-7.8	0.00039	0.00039–0.00078	Panahi et al. (2011)
	Leaves essential oil (μL/mL) from Ethiopia	*Trichophyton* sp.	2.5–5.0		0.27–0.53		Nasir et al. (2015)
		Microsporum, *Candida* Rhodotorula	5.0		0.53		
		A. niger	2.5		0.27		
		E. coli, *Shigella* sp, *Bacillus* sp, streptococci	5.0		0.53		
	Essential oil (μg/mL) from Iran	*P. aeruginosa* ATCC 27853	64	128	0.0064	0.0128	Owlia et al. (2009)
	Leaves essential oil (%) from Iran	*S.aureus, A. baumannii*	0.1	0.2			Ostad Asiaei et al. (2018)
		E.coli	0.15	0.25			
		P. vulgaris	0.25	0.35			
		S. sonnei	0.30	0.45			
		P. aeruginosa	0.2	0.40			
		K. pneumonia	0.05	0.15			
		S. enetерica serovar. Typhi	0.4	0.6			
		S. enetерica serovar. Paratyphi	0.35	0.45			
		S. enetерica serovar. Enteritidis, Infantis	0.6	0.8			
	Leaves essential oil (mg mL^{-1}) from Iran	*Streptococcus mutans*, *S. pyogenes*	1	2	0.1	0.2	Rasooli et al. (2009)
	Leaves essential oil (mg mL^{-1}) from Thailand	*T. cucumeris*, *F. oxysporum*, *C. globosum*	5		0.5		Siramon et al. (2013)
		A. niger, *C. cladosporioides*, *F. palustris*, *P. citrinum*, *T. versicolor*	10		1		
		R. oryzae	>10		>1		
	Leaves essential oil (μl mL^{-1}) from Montenegro	Reference *Acinetobacter baumannii* and MDR clinical strains	0.5–1	0.7–4	0.05–0.1	0.07–0. 4	Knezevic et al. (2016)
		S. aureus ATCC 25923, *E. coli* ATCC 25922	1	1–2	0. 1	0.1–0.2	
	Leaves essential oil (μl/mL) from Kenya	*Fusarium sp.*	7–8	8–10	0.7–0.85	0.85–1	Gakuubi et al. (2017)
	Leaves essential oil (μl/mL) from Algeria	*F. graminearum*	2.5		0.27		Mehani et al. (2014)
		F. sporotrichioide	1.25		0.13		
	Leaves essential oil (μg mL^{-1}) from Brazil	*S. aureus*	1000		0.1		Chaves et al. (2018)
		E. coli	>1000		>0.1		
	Leaves essential oil from Egypt		% of reduction				El-Baz et al. (2015)
		Rotavirus Wa strain	50				
		Coxsackievirus B4	53.3				
		Herpes virus type 1	90				
		Adenovirus type 7	0				
	EOs in vegetable oil (mg/mL)	Trypanosoma brucei brucei and Trypanosoma evansi	100		10		Habila et al. (2010)
	Leaves essential oil (mg/mL) from Syria	*S. aureus*	0.2	0.8	0.02	0.8	Khubeiz et al. (2016)
		B. subtilis	1.6–3.2	1.6–3.2	0.16–0.32	0.16–0.32	
		M. luteus	0.2–0.4	0.4–1.6	0.02–0.04	0.04–0.16	
		S. pyogenes	0.4–0.8	0.8–1.6	0.04–0.08	0.08–0.16	
		K. pneumonia	1.6–3.2	3.2	0.16–0.32	0.32	
		V. parahaemolyticus	0.1	0.2	0.01	0.02	
		S. Typhimurium	1.6–3.2	3.2	0.16–0.32	0.32	
		E. coli	0.4–3.2	0.8–3.2	0.04–0.32	0.08–0.32	
		P. vulgaris, Ps. aeruginosa	>12.8	>12.8	>1.28	>1.28	
	Leaves essential oil from Iran		GI				Katooli et al. (2011)
		P. ultimum, R. solani, B. sorokiniana, C. gloeosporioides	100%				
		P. digitatum, A. flavus	0%				
Plant extract	Leaves acetone extract (mg/l) from Nigeria	MDR *Staphylococcus aureus*	20–50		0.002–0.005		Ibrahim et al. (2014)
	Leaves methanol extract (mg/mL) from Egypt	MDR *S. aureus*	0.78		0.078		Reda et al. (2017)
		MDR *P. aeruginosa*	3.12		0.312		
	Bark butanol extract (μg mL^{-1}) from Egypt	*Pectobacterium cartovorum*	16		0.0016		EL-Hefny et al. (2017)
		Ralstonia solanacearum	125		0.0125		
		Agrobacterium tumefaciens	250		0.025		
		Dickeya spp.	500		0.05		

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Table 4 (*continued*)

E. camaldulensis	Microorganism	Activity[a]		Recalculated (%)		References
		MIC	MBC	MIC	MBC	
Leaves methanol extracts (mg/mL) from India	*S. aureus, B. subtilis*	5		0.5		Potdara et al. (2015)
	P. aeruginosa, S. eneterica serovar. Paratyphi	10		1.0		
		P. vulgaris, K. pneumonia, 25		2.5		
		S. eneterica serovar. Typhi 50		5.0		
	E. coli	75	7.5			
Leaves crude methanolic extracts (μg mL^{-1}) from Egypt	*Dickeya solani, B. cereus*	0.08	0.16	0.000008	0.000016	Elansary et al. (2017)
	S. aureus	0.22	0.40	0.000022	0.00004	
Leaves methanol, ethanol, and petroleum ether extracts (mg mL^{-1}) from Nigeria	*P. aeruginosa*	100	200	10	20	Chuku et al. (2016)
	B. subtilis	50–200	200–400	5–20	20-40	
	E. coli	50–200	100–200	5–20	10–20	
	Penicillium expansum	50–100	50–400	5–10	5–40	
	C. albicans	50–200	50–200	5–20	5–20	
Leaves methanol–dichloromethane extracts (mg mL^{-1}) from Japan	*S. aureus*, methicillin-resistant *S. aureus*	0.063		0.0063		Takahashi et al. (2004)
	B. cereus, E. faecalis, Propionibacterium acnes, Trichophyton mentagrophytes	0.125		0.0125		
	E. coli, Pseudomonas putida, Alicyclobacillus acidoterrestris	>0.250		>0.0250		
Leaves crude methanol extracts (μg mL^{-1}) from Nigeria	*B. subtilis, C. albicans, S. aureus* (ATCC103207), *S. aureus* (clinical)	200		0.02		Babayi et al. (2004)
	E. coli (ATCC 10418), *P. aeruginosa* (ATCC 27853), *S.* Typhi	>200		>0.02		
Leaves methanol extract (mg mL^{-1}) from Nigeria	*Klebsiella spp, Salmonella* Typhi, *P. aeruginosa*	10		1.0		Ayepola and Adeniyi (2008)
Leaves dichloromethane fraction (mg mL^{-1}) from Nigeria	*S. aureus*	1.25		0.125		
	Yersinia enterocolitica	0.157		0.0157		
	B. subtilis	0.04		0.004		
	Klebsiella spp, Salmonella Typhi, *P. aeruginosa*	10		1.0		
	S. aureus, Yersinia enterocolitica	0.625		0.0625		
	B. subtilis	0.79		0.079		
Leaves crude n-hexane extracts; crude chloroform leaves and steam extracts (μg mL^{-1}) from Nigeria	*Helicobacter pylori* ATCC43504 and ATCC47619	<25		<0.0025		Adeniyi et al. (2009)
Steam crude n-hexane extracts (μg mL^{-1}) from Nigeria		<12.5		<0.00125		
Leaves and steam bark hexane, chloroform, methanol extracts (μg/mL) from Nigeria	*Mycobacterium tuberculosis* H37Rv	4–52.2		0.0004–0.0064		Lawal et al. (2012)
Leaves methanol extracts 80% (μg/mL) from Ethiopia	*M. tuberculosis*	6.25–50		0.000625–0.005		Gemechu et al. (2013)
	M. bovis	12.5–50		0.00125–0.005		
Leaves crude water extracts (mg/mL) from Nigeria	*E. coli, Salmonella* Typhi, *S. aureus*	50		5.0		Abubakar (2010)
Leaves crude ethanol extracts (mg/mL) from Nigeria	*Proteus mirabilis, Klebsiella pneumoniae*	25		2.5		
Leaves crude acetone extracts (mg/mL) from Nigeria	*E. coli,*	50		5.0		
	Salmonella Typhi, *S. aureus, Klebsiella pneumoniae*	25		2.5		
	Proteus mirabilis	15		1.5		
	E. coli, Klebsiella pneumoniae	25		2.5		
	Salmonella Typhi, *S. aureus, Proteus mirabilis*	15		1.5		
Leaves essential oil (mg/mL) from Egipt	*S. aureus*	0.7		0.07		Reda et al. (2017)
	P. aeruginosa	3.12		0.312		
Leaves DMSO extract (μg/mL) from Jordan	Newcastle Disease Virus (NDV)	50-500		0.005-0.05		Al-Hadid (2016)
Leaves methanol extract (μg/mL) from Israel		IC50		IC50		Abu-Jafar and Huleihel (2017)
	Herpes simplex virus -1	0.1 ± 0.08 0.3 ± 0.02		0.00001 ± 0.000008		
	Herpes simplex virus -2	1 ± 0.03		0.00003 ± 0.000002		
	Varicella-Zoster Virus			0.0001 ± 0.000003		

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Table 4 (*continued*)

E. camaldulensis		Microorganism	Activity[a]			Recalculated (%)			References
			MIC		MBC	MIC		MBC	
	Leaves methanol extracts from Nigeria	Poliovirus type I	neutralization index of one log and above						Adeniyi et al. (2015)
		Coxsackievirus B							
		Echovirus 6							
	Bark n-butanol extract (μg /mL) from Egypt	*P. carotovorum*	16			0.0016			El-Hefny et al. (2017)
		R. solanacearum	125			0.0125			
		A. tumefaciens	250			0.025			
		Dickeya spp.	500			0.05			
	Leaves methanol extracts (mg/mL) from Iran	*Microsporum canis*	0.8		6.4	0.08		0.64	Falahati et al. (2005)
		M. gypseum	1.6		3.2	0.16		0.32	
		Tricophyton rubrum	1.6		1.6	0.16		0.16	
		T. schoenleinii	0.4		0.8	0.04		0.08	
		T. mentagrophytes	0.2		0.8	0.02		0.08	
		Epedermophyton floccosum	0.2		0.8	0.02		0.08	
	Bark dichloromethane: methanol extract; aqueous extract (mg/mL) from South Africa		$MIC_{D:M}$	MIC_{AQ}		$MIC_{D:M}$	MIC_{AQ}		Mabona et al. (2013)
		S. aureus (3 strains, including MRSA)	0.25–1.0	0.5–0.63		0.025–0.1	0.05–0.0-63		
		S. epidermidis	0.5	2.0		0.05	0.2		
		P. aeruginosa	2.0	4.0		0.2	0.4		
		C. albicans	0.5	2.0		0.05	0.2		
		Brevibacillus agri	0.25	0.20		0.025	0.02		
		Propionobacterium acnes	0.10	2.0		0.01	0.2		
		Trichophyton mentagrophytes	1.0	1.0		0.1	0.1		
		M. canis	4.0	2.0		0.4	0.2		
	Leaves methanol and aqueous extracts (μg/mL) from Iran	*Leishmania major*	IC50 586.2-1108.6			IC50 0.05862–0.11086			Nosratabadi et al. (2015)
Leaves crude, diethyl ether, ethyl acetate, aqueous (mg/mL) from Iran	*Trichomonas vaginalis*	100% growth inhibition with 12.5–50; 24–72 h			100% growth inhibition with 1.25–5%; 24–72 h				Hassani et al. (2013)
Leaves wather and ethanolic extracts (μg/mL) from Iran	*Trichomonas vaginalis*	Dead for 72 h with 60-90			Dead for 72 h with 0.006–0.009%				Youse et al. (2012)
Leaves aqueous extract (mg/mL) from Iraq	*Trichomonas vaginalis*	Dead for 24 h with 500			Dead for 24 h with 50%				Mahdi et al. (2006)

[a] MIC – minimal inhibitory concentration, MBC – minimal bactericidal concentration, GI – growth inhibition, IC50 - 50% inhibitory concentration.

Contemporary research of EOs and extracts are also focused on mechanism that allows bacteria to regulate some physiological activities, such as virulence, competition amongst populations, motility, sporulation, conjugation, antibiotic production, and biofilm formation (Rodriguez-Garcia et al., 2014). This system of intercellular communication, quorum sensing (QS), is based on production of the signal molecules, called autoinducers (Abraham et al., 2011). This communication system is relative to cell density and some compounds interfere with the QS communication system and attenuating the bacterial pathogenicity, in the phenomenon known as anti-QS compounds (Abraham et al., 2011). There are reports of anti-QS activity of various plants species EOs from genus *Eucalyptus*, such as *Eucalyptus globulus* L. (Luís et al., 2016; Cervantes-Ceballos et al., 2015), *Eucalyptus radiata* D. (Luís et al., 2016), *Eucalyptus citriodora* Hook., *Eucalyptus smithii* R. T. Baker and *Eucalyptus staigeriana* F. Muell. ex Bailey (Luís et al., 2016). Unfortunately, there is still no data regarding *E. camaldulensis* anti-QS activity.

In one study, antibacterial and *in vivo* biofilm preventive efficacies of *E. camaldulensis* oil were significantly higher than that of *M. spicata* oil and chlorhexidine, suggesting that *E. camaldulensis* EO is capable of

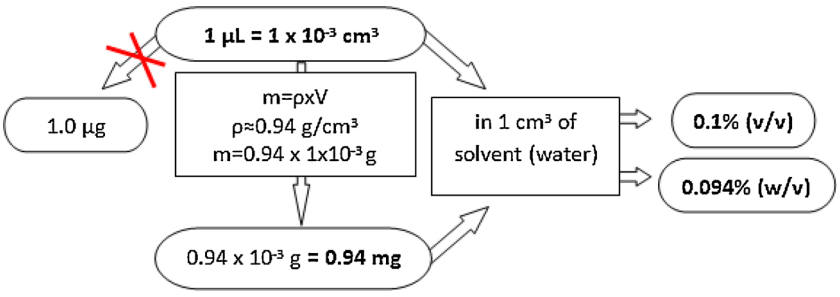

Fig. 2. Schematic diagram for re-calculation from microliter or milligram per milliliter to percentage (v/v or w/v).

affecting biofilm formation (Rasooli et al., 2009). Considering the anti-QS activity of above mentioned *Eucalyptus* species and also detected antimicrobial and anti-biofilm effect of *E. camaldulensis* it can be assumed that it possess similar or even higher anti-QS activity. However, future detailed studies of anti-QS and anti-biofilm *E. camaldulensis* activity are needed in order to confirm this assumption.

3.2. Antifungal effect

The *E. camaldulensis* leaves extracts and EOs have a potential as antifungal agents. They are able to act as a moderate antifungal agent against household molds, wood rot fungi (Siramon et al., 2013), and phytopathogenic fungi (Gakuubi et al., 2017; Mehani et al., 2014).

Eucalyptus camaldulensis EO has been studied for antifungal activity and was active in concentration 0.125–1.0% against most model organisms. The most sensitive seems to be *F. sporotrichioides* with MIC 0.125% (Mehani et al., 2014), while *R. oryzae* is the most resistant, as 1% of EO was ineffective against this fungus (Siramon et al., 2013). The best known human and animal pathogenic yeast *Candida* sp. showed considerable sensitivity to *E. camaldulensis* EO, with MIC approx. 0.5% (Siramon et al., 2013; Nasir et al., 2015). Most EOs from Sardinia inhibited growth of *A. niger* and *B. cinerea* in concentration of 20 μL/plate, while lower concentrations of the oils, such as 5 μL/plate were ineffective (Barra et al., 2010).

It is interesting to notice that liposomes containing *E. camaldulensis* EO were prepared (Moghimipour et al., 2012) for antifungal oil activity. The particle size varied from 40.5 to 298 nm for the different formulations, with approx. 95% of the essential oil entrapped. Inhibition of *Microsporum canis, M. gypseum, Trichophyton rubrum,* and *T. verrucosum* was achieved with 125 μL, and the liposomal gel formulation of the EO was proposed to improve antifungal activity.

Aqueous and organic extracts of *E. camaldulensis* have been reported to have antifungal activity (Table 4). Methanol leaves extracts showed inconsistent activity against *C. albicans*: in one study it was in range 50–200 mg/mL (Chuku et al., 2016), while in another it was 0.2 mg/mL (Babayi et al., 2004), indicating difference in active concentration of one thousand times. The bark methanole extract was active in concentration 0.5 mg/mL. Methanol leaf and bark extracts showed considerable activity against dermatophytes: 0.8–1.6 mg/mL against *Microsporum* spp, 0.125–1.6 mg/mL against *Trichophyton* spp., and 0.2 mg/mL against *Epidemophyton flocossum* (Takahashi et al., 2004; Falahati et al., 2005; Mabona et al., 2013).

Beside the antifungal activity of EOs and extracts of *E. camaldulensis*, it is worth noticing that this species, along with *E. blakelyi* M., *E. gomphocephala* A. DC, *E. rudis* Endl., and *E. tereticornis* Sm., is a reservoir of an emerging pathogenic fungus – *Cryptococcus gattii*. This fungus is usually related to tropic and subtropic regions, affecting the respiratory and nervous systems of the immunocompetent humans and domestic animals (Sorrell et al., 1996; Chakrabarti et al., 1997; Bielska and May, 2016; Roe et al., 2018). Similarily, *C. neoformans* var. *grubii* can be isolated from flowers and bark of *E. camaldulensis* (Gugnani et al., 2005). According to the literature, *E. camaldulensis* is natural reservoir of *Cryptococcus* and is considered responsible for occurring cryptococcosis worldwide. In this context, it is interesting to observe that *C. neoformans* is moderately sensitive to *E. citriodora* Hook EOs, with MIC90 0.5% (wt/v) (Pattnaik et al., 1996; Luqman et al., 2008) or *E. globulus* Labill. with MIC 0.13% (wt/v) (Suliman et al., 2010). Unfortunately, data on *Cryptococcus* sp. sensitivity to EOs and plant extracts of reservoir species of *Eucalyptus*, including *E. camaldulensis*, remains unknown.

Although there are no reports regarding *E. camaldulensis* mode of antifungal action, according to previous studies with other essential oils and fungi, the plasma membrane and the mitochondria are the probable antifungal targets of EOs. According to recent studies, the antifungal activity of EOs results from its ability to disrupt the permeability barrier of the plasma membrane and from the mitochondrial dysfunction-induced ROS accumulation in A. flavus and *C. albicans* (Tian et al., 2012; Chen et al., 2013). The exact mechanism of *E. camaldulensis* antifungal activity is unknown and should be elucidated in the future.

3.3. Antiviral effect

Infections caused by viruses are very common and sometimes life threatening, especially in immunocompromised patients and neonates (Snoeck, 2000; Khan et al., 2005). Despite the recent significant progress in antiviral drug development, viral infections are considered as one of the major causes of death worldwide (Müller et al., 2007; Meyers et al., 1982). Thus, novel natural antiviral agents need to be found urgently. Many natural products possess antiviral activity and some of them are already in use for treatment of human viral infections with both RNA and DNA viruses (*e.g.* myricetin against coronavirus, linalool, urosolic acid, and apigenin against coxsackievirus, quercetin and narasin against denge virus, curcumin against hepatitis B and C virus) (Lin et al., 2014; Kitazato et al., 2007). Numerous secondary plant metabolites such as essential oils, flavonoids, saponins, tannins, alkaloids, lignans, terpenes, and phenolic acids express significant antiviral activity against different viruses (Jassim and Naji, 2003; Chiang et al., 2003; Sanchez Palomino et al., 2002). Recently few studies confirmed the *E. camaldulensis* EOs and plant extracts antiviral activity (Table 4).

Eucalyptus camaldulensis EOs reduce coxackie B4 and rotavirus Wa multiplication for 50%, herpes simplex virus 1 for 90%, but have no effect on adenovirus 7 multiplication (El-Baz et al., 2015). Similarly, methanolic extracts showed 50% inhibition of HSV 1 and 2 in concentration 0.1–0.3 μg/mL, and against Varicella zoster virus at concentration 1.0 μL/ml (Abu-Jafar and Huleihel, 2017). Dimethyl sulfoxide (DMSO) extracts inhbit multiplication of animal New Castle virus in concentration range 50–500 μg/mL (Al-Hadid, 2016). Antiviral activity has been observed for *E. camaldulensis* methanolic extracts against polio virus, coxsackie B, and echovirus 6 (Adeniyi et al., 2015). The data on antiviral activity of *E. camaldulensis* EO and extracts, although scarce, indicate their great potential, and necessity for further studies in this context.

Despite the fact that many plant extracts and essential oils were previously reported for their antiviral activities, the mechanism of action still remains poorly understood. There are many factors that influencing the EOs mode of action, which should be taken in consideration when antiviral activity of plant antimicrobials is examined. One of such factors is the difference between enveloped and non-enveloped viruses, because the observed antiviral effect has usually been greater for enveloped viruses (Yamada et al., 2009; Siddiqui et al., 1996). In majority of the studies dealing with antiviral mode of action, the focus has been on either the inhibition of viral adsorption to host cells or examination of the plant antimicrobials effectiveness against intracellular virus multiplication (Gilling et al., 2014). So, most commonly described modes of antiviral actions are virus inactivation and the impaired virus adsorption to host cells, which is often difficult to distinguish. Like in other antimicrobial modes of action, antiviral mechanism is also dependent on EOs or extracts compounds activity. This is one more factor that should be considered, because it affects the final antiviral mechanism of action. For some compounds the potential mechanism is reported, *i.e.* carvacrol acts directly upon the virus capsid and subsequently the nucleic acid (Gilling et al., 2014). When EOs antiviral mechanism of action is considered, EOs may cause the loss of the viral capsid integrity, ultimately leading to exposure of the viral genome. In addition, some EOs subsequently act directly upon the viral nucleic acid (DNA or RNA). According to one study, *E. camaldulensis* EOs may be promising antiviral agent against RNA viruses with no effect against DNA virus (El-Baz et al., 2015). Also, with shorter periods of exposure to the antimicrobial, the virus is able to adsorb specifically to host cells; however, it may or may not be able to cause successful infection depending upon the integrity of the viral genome. On the other hand, after exposure to some EOs virus capsid and genome

remains intact. These antimicrobials appear to exert their antiviral effect by coating the capsid and thereby preventing specific adsorption of the virus to host cells (Gilling et al., 2014). Although, there are still no reports regarding *E. camaldulensis* EOs antiviral mode of action, there are some promising results about its antiviral effect (Table 4). These promising results represent foundation for further research and potential application of *E. camalulensis* EOs as potent antiviral agent.

3.4. Antiprotzoal effect

Among all deverse benefitial activities, *E. camaldulensis* expresess also an antiprotozoal effect as well. The reports regarding this effect are listed in Table 4. *Eucalyptus camaldulensis* methanolic and aqueous extracts were active against *Leishmania major* with IC50 values (50% inhibitory concentration) 586.2 ± 47.6 and 1108.6 ± 51.9 μg/mL, respectively (Nosratabadi et al., 2015). This was characterized as moderate leishmanicidal activity, but considering fact that present therapy consist antimony compounds which are expensive, toxic, and drug resistance is prevalent, *E. camaldulensis* plant extract derivatives represent safe, inexpensive, and promising alterantive solution.

There are also several reports regarding antiprotozoal activity against *Trichomonas vaginalis*, a causative agent of trichomoniasis which is the most prevalent nonviral sexual infection. The first report on *E. camaldulensis* aqueous extract anti-trichomonas activity showed that extract was active at concentration 500 mg/mL after 24 h (Mahdi et al., 2006). However, recent studies reported better effect of the *E. camaladulensis* extracts (Hassani et al., 2013; Youse et al., 2012). Five different *E. camaldulensis* leaves extracts including total extract, diethyl ether, chloroform, ethyl acetate, and water fractions were active in concentration range 12.5–50 mg/mL, with growth inhibiton achived after 24–72 h (Hassani et al., 2013). Ethyl acetate fraction showed the highest percentage of growth inhibition with the lowest concentration (12.5 mg/mL) after 24 and 48 h (Hassani et al., 2013). Even better anti-trichomonas activity was detedted for wather and ethanolic extracts, where concentration 60–90 μg/mL killed *Trichomonas vaginalis* for 72 h (Youse et al., 2012). The mainstay medication for trichomoniasis is metronidazole; however some resistant strains to this treatment have been detected making these results of *E. camaldulensis* anti-trichomonas activity very promising as antiprotozoal agent.

Except extracts, significant antiprotozoal activity was reported for *E. camaldulensis* EOs. The essential oils were found to possess anti-trypanosomal activity *in vitro* in a dose-dependent manner in a short time. The decrease of *Trypanosoma evansi* number over time was achieved in doses of 400 mg/mL for 3 min, 200 mg/mL for 4 min, and 100 mg/mL for 15 min. Against *Trypanosoma brucei brucei* EOs was more potent in the concentration of 400 mg/mL, decreasing the number of parasite for 3 min, 200 mg/mL for 4 min, and 100 mg/mL for 11 min (Habila et al., 2010). Such prompt decrease in parasite number in the *in vitro* tests for both *Trypanosoma brucei brucei* and *T. evansi*suggests that the EOs kill the parasites efficiently, but by an unknown mechanism. There are suggestions of some potential mechanisms of antiprotozoal EOs action. The activity of EOs could be due to the hydrophobic nature of the cyclic hydrocarbons, which allow EOs to interact with the protozoans causing conformational changes in the parasite membrane structure, resulting in the loss of membrane stability (Calsamiglia et al., 2007). The essential oils also can act by inhibiting some key enzymes in the parasite glycolytic pathway (Smith-Palmer et al., 2004). Furthermore, some EOs components inhibit acetylcholinesterase activity and act on other vulnerable sites, such as cytochrome p450 (Maciel et al., 2010). This multicomponent nature of plant EOs is an advantage for several target sites on protozoans, which is of great importance.

3.5. Antimicrobial activity of E. camaldulensis Dehn. vs. other species of genus Eucalyptus

It was shown that EOs of *E. camaldulensis* are more potent against *B. subtilis*, *S. aureus*, *E. coli*, *P. aeruginosa*, *S. lutea,* and *P. carotovorum* in comparison to EOs from *E. gomphocephala* DC., but not against *A. tumefaciens*. Furthermore, the *E. camaldulensis* var. *obtuse* showed even better effect than *E. camaldulensis* (Salem et al., 2015). Among seven examine essential oils of various *Eucalyptus* species, EO of *E. camaldulensis* was among the best against *B. subtilis*, *A. niger,* and *R. solani*, but not against *E. coli* and *S. aureus* (Ghaffar et al., 2015). Similar activity of *E. camaldulensis* and *E. torelliana* F. Muell. was recorded for extracts against six strains of *H. pylori* (Adeniyi et al., 2009).

It is worth to notice that among 132 extracts from 42 plants growing in southern Africa, *E. camaldulensis* bark extract showed considerable activity against bacteria and fungi, with an exception against *P. aeruginosa* and *M. canis* (Mabona et al., 2013). Finaly, in many studies regarding antimicrobial activity of various *Eucalyptus* species, *E. camaldulensis* was not always included (Ashour, 2008; Safaei-Ghomi and Ahd, 2010; Mulyaningsih et al., 2010; Elaissi et al., 2012; Sebei et al., 2015).

4. Interaction of *Eucalyptus camaldulensis* Dehn. EOs/extracts and other antimicrobial agents

Due to rapid emerging of microbial resistance to conventional drugs, the necessity for efficient solution(s) is rising. The main strategy represents finding new antimicrobial agents; however another strategy goes in the direction of reducing degree of bacterial resistance and/or bacterial re-sensitization to conventional antibiotics. This can be achieved using combined therapies. The most of the tested combinations are dual combinations, but the combinations of three, four or more agents also can be efficient (Lesjak et al., 2016). This is in line with antimicrobial efficiency and potential of EOs and plant extracts which are complex mixtures of numerous compounds. Combination strategy could be very promising regarding the diversity of agents that could be tested: (1) conventional non-antimicrobial agent (*e.g.* anti-inflammatory or anti-psychotic drug) + conventional antimicrobial agent (antibiotic); (2) conventional antimicrobial agent (antibiotic) + natural antimicrobial agent (essential oil, plant extract, bacteriophage, antimicrobial peptide ect.); (3) conventional antimicrobial agent (antibiotic) + single compound isolated from natural antimicrobial agent (with previously confirmed antimicrobial activity); (4) combination of two or more single compounds isolated from natural antimicrobial agents (with previously confirmed antimicrobial activity).

Being a plant with already detected and evaluated antimicrobial activity, it can be assumed that *E. camaldulensis* also have a potential in combined therapy. This assumption is confirmed in some studies *in vitro* and *in vivo* (Table 5). *Eucalyptus camaldulensis* EOs and extracts *in vitro* reduced resistance of MDR *A. baumannii* in combination with conventional antibiotics: β-lactams, ciprofloxacin, gentamicin, polymyxin B (Knezevic et al., 2016). Similarily, the increase of β-lactamase produing MRSA and *E. coli* sensitivity to cephalexin, cefuroxime, amoxicillin, and ampicillin has been obtained through combination with *E. camaldulensis* EOs (Chaves et al., 2018). Synergistic activity has been recorded between *E. camaldulensis* plant extracts and gentamicin or ceftriaxone against MDR *S. aureus* and *P. aeruginosa* (Reda et al., 2017; Ibrahim et al., 2014), as well as in combination with ampicillin against *S. aureus* (Ibrahim et al., 2014).

Furthermore, the combination of *E. camaldulensis* extract with another plant extract *Psidium guajava* L. was also efficient against MDR bacteria (Bala et al., 2014). Except antibacterial activity, other activities of *E. camaldulensis* extracts in combination were detected and characterized as efficient. Antiviral activity was confirmed for the combination of *E. camaldulensis* 80% methanol leaves extract and acyclovir against herpes simplex virus -1 and -2 and varicella-zoster virus (Abu-Jafar and Huleihel, 2017). Similaily, the combination of *Annona senegalensis* L. leaf methanol extract and *E. camaldulensis* extract efficiently cured *in vivo* albino mice infection with parasite *Trypanosoma brucei brucei* (Lafia strain) (Kabiru et al., 2012). All these data are very

Table 5
Effects of *Eucalyptus camaldulensis* and other antimicrobial agents in combination.

E. camaldulensis extract or essential oil	Antimicrobial agent(s) in combination	Test organism	Method	Effect of combination	Reference
Leaf essential oils from Montenegro	Ciprofloxacin, Gentamicin, Polymyxin B	Reference *Acinetobacter baumannii* and MDR clinical strains	Two-dimensional checkerboard method (Verma, 2007)	Synergism (FICI ≤ 0.5)	Knezevic et al. (2016)
Leaf essential oil from Brazil	Cephalexin	*Staphylococcus aureus* 29	The MIC of the antibiotics were determined in the presence and absence of sub-inhibitory concentrations (125 μg mL^{-1}) of the essential oil (Coutinho et al., 2010)	Combining the essential oil with β-lactams reduced the resistance of tested strains	Chaves et al. (2018)
	Cefuroxime	*S. aureus* 55 (MRSA) *E. coli* (all strains resistant to β-lactam antibiotics)			
	Amoxicillin				
	Ampicillin				
Leaf methanol extract (0.01 μg/mL) from Israel	Acyclovir (0.01 μg/mL)	*In vitro* infection of Vero cells with Herpes simplex virus -1 Herpes simplex virus -2 Varicella-Zoster Virus	Treating the cells with different combinations of the extract and acyclovir at the time and post-infection with the virus	Significant inhibition (˜75%) of the viral infection, comparing to single agent (10-20%)	Abu-Jafar and Huleihel (2017)
Leaf methanol extract from Nigeria	Leaf methanol extracts of *Annona senegalensis*	*In vivo* albino mice infection with *Trypanosoma brucei brucei* (Lafia strain)	200 mg/kg bodyweight/day (for 21 days) of crude methanol extracts of *A. senegalensis* and *E. camaldulensis* combinations in ratios 1:1, 1:2, and 2:1, respectively. Lajubutu et al. (1995)	Synergism (only the combination 1:1 resulted in the complete clearance of parasites from the circulation of animal)	Kabiru et al. (2012)
Leaf methanol extract from Egypt	Gentamicin, Ceftriaxone	MDR *S. aureus* MDR *P. aeruginosa*		Synergism	Reda et al. (2017)
Leaf acetone extract from Nigeria	Ampicillin	MDR S. aureus	Collins et al. (1995)	Synergism	Ibrahim et al. (2014)
	Ciprofloxacin				
Leaf ethanol extract from Nigeria	*Psidium guajava* ethanol extract	*E. coli* MDR *S. aureus*	Agar disc diffusion method was employed as described by Kirby and Bauer (1966), adopted by Yushau et al. (2009) and Bashir et al. (2011)	Synergism	Bala et al. (2014)

promising, but the methods used in different studies and results interpretation vary (Table 5). As a consequence, the data should be taken with precautions, as can not be compared and properly discussed. To avoid this problem, the testing combinations of different agents should be conducted using standardized methods, such as time-kill method (CLSI, 1999; Verma, 2007), checkerboard method (Verma, 2007; EUCAST, 2000), Chou-Talalay method (Chou, 2010) or Boik method (Boik, 2010). All these methods possess some shortfalls, such as time-consuming, labor-intensive, limitations regarding the number of the agents in combination, *etc.* Unfortunately, there is no one gold standard for synergy testing and prior the further application of different phytochemicals, this issue should be overcome.

5. Conclusion

Summarizing the available data on antimicrobial properties of *Eucalyptus camaldulensis* essential oil and extracts, it is obvious that this plant is a valuable source of phytotherapeutics. The essential oil, as well as leaf and bark extracts are particularly valuable as antibacterial, antiviral, and antifungal agents, and their antiprotozoal activity should not be neglected taking into account current therapy cost, toxicity, and protozoal growing resistance. Some *E. camaldulensis* plant characteristics such as easy cultivation, wide distribution by plantation, and rapid growth additionally support further examination of antimicrobial activity, in order to enhance the commercial production of *E. camaldulensis* based pharmaceuticals. The future studies should be focused on determination of the mechanisms of antimicrobial activity, paticularly potential anti-biofilm and anti-QS effects, as well as the activity enhancement in combination with other available agents.

Acknowledgments

This study was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia, grant OI 172058. The authors acknowledge Prof. Stephen D. Hopper (School of Agriculture and Environment, The University of Western Australia) for Eucalyptus *camaldulensis* image and Prof. Ljiljana Knezevic (Faculty of Sciences, University of Novi Sad) for the language revision.

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