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Insights into *Eucalyptus* genus chemical constituents, biological activities and health-promoting effects

Bahare Salehi[a], Javad Sharifi-Rad[b,*], Cristina Quispe[c,**], Henrry Llaique[c], Michael Villalobos[c], Antonella Smeriglio[d], Domenico Trombetta[d], Shahira M. Ezzat[e,f,***], Mohamed A. Salem[g], Ahmed Zayed[h], Carla Marina Salgado Castillo[i], Simin Emamzadeh Yazdi[j], Surjit Sen[k,l], Krishnendu Acharya[k], Farukh Sharopov[m,****], Natália Martins[n,o,*****]

[a] *Student Research Committee, School of Medicine, Bam University of Medical Sciences, Bam, Iran*
[b] *Zabol Medicinal Plants Research Center, Zabol University of Medical Sciences, Zabol, Iran*
[c] *Instituto de EtnoFarmacología, Facultad de Ciencias de la Salud, Universidad Arturo Prat, Avda. Arturo Prat 2120, Iquique, 1110939, Chile*
[d] *Department of Chemical, Biological, Pharmaceutical and Environmental Sciences, University of Messina, Italy*
[e] *Department of Pharmacognosy, Faculty of Pharmacy, Cairo University, Kasr El-Aini Street, Cairo, 11562, Egypt*
[f] *Department of Pharmacognosy, Faculty of Pharmacy, October University for Modern Sciences and Arts (MSA), 6th October 12566, Egypt*
[g] *Department of Pharmacognosy, Faculty of Pharmacy, Menoufia University, Gamal Abd El Nasr st., Shibin Elkom, 32511, Menoufia, Egypt*
[h] *Department of Pharmacognosy, College of Pharmacy, Tanta University, Elguish Street, 31527, Tanta, Egypt*
[i] *Facultad de Medicina, Universidad del Azuay, Cuenca, Ecuador*
[j] *Department of Plant and Soil Sciences, University of Pretoria, Gauteng, 0002, South Africa*
[k] *Molecular and Applied Mycology and Plant Pathology Laboratory, Department of Botany, University of Calcutta, Kolkata, 700019, India*
[l] *Department of Botany, Fakir Chand College, Diamond Harbour, West Bengal, 743331, India*
[m] *Department of Pharmaceutical Technology, Avicenna Tajik State Medical University, Rudaki 139, 734003, Dushanbe, Tajikistan*
[n] *Faculty of Medicine, University of Porto, Alameda Prof. Hernâni Monteiro, 4200-319, Porto, Portugal*
[o] *Institute for Research and Innovation in Health (i3S), University of Porto, 4200-135, Porto, Portugal*

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ABSTRACT

Background: *Eucalyptus* genus members have received a great interest worldwide for their antibacterial, antiviral, antifungal, anti-inflammatory and insect-repellent properties for cosmetic, pharmaceutical, nutraceutical and furniture purposes. Indeed, the application of *Eucalyptus* essential oil in cosmetic and personal hygiene products is gradually increasing. Also, it has been widely used in the traditional medicine for centuries, in the treatment of respiratory diseases, common cold, influenza, and sinus congestion.

Scope and approach: This review addressed botanical and ethnopharmacological aspects of *Eucalyptus* plants, as also its *in vitro* and *in vivo* pharmacological activities, and current insights with regards to clinical efficacy and safety.

Key findings and conclusions: Eucalyptol (1,8-cineole) is the main component present in *Eucalyptus* oils. According to the previously reported uses of *Eucalyptus* oils and extracts, there is urgently required further *in vivo* studies with the distinct *Eucalyptus* constituents to reveal the secrets beyond the traditional uses for treatment of a wide spectrum of ailments. A great attention has also been given for its nanotechnological applications by food and pharmaceutical industries. Nanoemulsions containing *Eucalyptus globulus* oil have been recognized for its antimicrobial and antibiofilm effects against gram-negative bacteria and the major microorganism responsible for causing fungal infections worldwide (*Candida albicans*). Moreover, eucalyptol does not present genotoxicity or carcinogenicity. Subacute hepatotoxic and nephrotoxic effects in animal models have been stated after application of high doses, higher than the estimated LD_{50} (2400 mg/kg b.w. In rats). However, an in-deep risk assessment on further exposure and toxicity data is highly needed.

* Corresponding author.
** Corresponding author.
*** Corresponding author. Department of Pharmacognosy, Faculty of Pharmacy, Cairo University, Kasr El-Aini Street, Cairo 11562, Egypt.
**** Corresponding author.
***** Corresponding author. Faculty of Medicine, University of Porto, Alameda Prof. Hernâni Monteiro, 4200-319, Porto, Portugal.
E-mail addresses: javad.sharifirad@gmail.com (J. Sharifi-Rad), elencris@yahoo.com (C. Quispe), shahira.ezzat@pharma.cu.edu.eg (S.M. Ezzat), shfarukh@mail.ru (F. Sharopov), ncmartins@med.up.pt (N. Martins).

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1. Introduction

A special attention has been drawn worldwide to *Eucalyptus* plants in various fields of industry, among them perfumery, pharmaceuticals, nutraceuticals and furniture. Hence, they represent a fast-growing source of wood as well as a source of oil used for several purposes (Vecchio, Loganes, & Minto, 2016). Conceptually, the name *Eucalyptus* comes from the prefix "*Eu",* which means true and *calyptus* (kalypto) which means to cover; describing the flower bud formed by united calyx and corolla parts, which seal the flower till it blooms (Kantvilas, 1996; Naithani, 2014).

Specifically addressing its phytopharmacological potential, there has been is a growing number of studies assessing in an in-depth manner its biological potentialities. For instance, the oil from leaves, fruits, buds and bark possess a wide spectrum of antibacterial, antiseptic, antioxidant, anti-inflammatory, and anticancer effects, and for this reason is used traditionally in the treatment of respiratory diseases, common cold, influenza, and sinus congestion (Sebei, Sakouhi, Herchi, Khouja, & Boukhchina, 2015; Sharifi-Rad, Sureda, et al., 2017). In fact, the medicinal value of *Eucalyptus* oil has been owes, in a great extent, to its main constituent 1,8-cineole (cineole or eucalyptol) (Mohamed et al., 2015; Sebei et al., 2015). Interestingly, various studies showed that both essential oil yield and composition (e.g., α-pinene, cineol, citronellal, citronellol, and isopulegol) are largely influenced by seasonal variations and even diurnally depending on the environmental conditions (Barra, Coroneo, Dessi, Cabras, & Angioni, 2010; Ben Jemâa, Haouel, Bouaziz, & Khouja, 2012). In this sense, and considering the both multiple potentialities and the current demand given to *Eucalyptus* species, this review aims to address the botanical, chemical and ethnopharmacological aspects of *Eucalyptus* plants, and the different *in vitro* and *in vivo* pharmacological activities reported so far. Finally, and not least interesting, a special emphasis is given to clinical studies reporting its feasibility for upcoming drugs formulation.

2. Eucalyptus genus: from botany to ethnopharmacology

Genus *Eucalyptus* was first described and named by L' Heritier, a French botanist (Boland et al., 2006), and around 800 species were already identified throughout the globe. *Eucalyptus* are woody perennial, shrubs to tall trees, with a rapid growth to attain a gigantic size and mostly evergreen (I. Brooker, 2002). *Eucalyptus* species show leaf dimorphism, the juvenile and mature leaves. First leaves of seedlings or juvenile stage are opposite, oval to roundish, occasionally sessile and glaucous. Subsequent leaves are either opposite or alternate, covered by soft hairs of different forms, which are highly specific species. Mature leaves are alternate, entire, petiolate, lanceolate/elliptical/oblong/oval, often thick, stiff, highly cutinized and coriaceous (Hardel & Sahoo, 2011). Leaf venations are of pinniveined or spreading or oblique type. *Eucalyptus* bark is of various types, persistent or deciduous, rough or smooth or both. Bark fiber length, shedding pattern, hardness, thickness, color and the level of furrowing varies with the plant age. In *E. macrorhyncha* the bark consists of long fibers, loosely intertwined and pulled off easily (Stringybarks) or in *E. leptophleba* the bark consists of short fibers, more tightly adherent (Box). In some species, such as *E. crebra* and *E. jensenii* the bark is rough, non-fibrous, dark in color, hard and deeply furrowed (Iron barks). In *E. sheathiana*, *E. diversicolor*, *E. cosmophylla* and *E. cladocalyx* the bark is smooth and shed in form of large slabs, leaving a smooth colorfully mottled surface. Ribbon like bark with smooth at the top but rough at the basal part are found in *E. youngiana* and *E. viminalis*. Diverse types of inflorescence are observed within species of this genus, viz. solitary (only in *E. globulus*), axillary umbel, cymes, panicles and corymbs. In flowers, petals are joined together to form a cup like cover (operculum) and looks like a bud. Shape of the operculum are highly variable from species to species, e.g. conical (*E. rudis*), obtuse (*E. cladocalyx*), acute (*E. tereticornis*), horned (*E. occidentalis*), hemispherical (*E. maculata*), hemispherical apiculate (*E. diversicolor*), rostrate (*E. camaldulensis*), ovoid (*E. salubris*), among others. On maturity, the operculum is forced off by expanding stamens. Stamens are showy and colorful. Blakely used stamen characters for the classification of the genus into section and subsection (Blakely, 1934). Major characters of stamens, like tips of filament and anther, mouth of sac, gland and fertility are considered for classification. Fruits of *Eucalyptus* are woody capsule. The lower part of the fruit is covered by the receptacle and the shape varies from hemispherical, campanulate, globular, ovoid, conical, urceolate to cylindrical. Four distinct segments, i.e. calycine ring, stamina ring, disc and upper part of the ovary are present on the upper part of fruits (Naithani, 2014). All these characters along with the valve (shape and position) character are used for scientific description of the fruits. Seeds are > 1 mm to < 2 cm in size, spherical, cuboid, elliptical, etc. In shape, subulate to deeply pitted, winged to unwinged, yellow to black colored (Boland, Brooker, & Turnbull, 1980).

On the other hand, the genus has a debatable taxonomic history (Boland et al., 2006; Parra-O, Bayly, Udovicic, & Ladiges, 2006). Different taxonomists have classified this genus and proposed various taxonomic positions time to time. Bentham and Von Mueller classified *Eucalyptus* into five series based on their anther characteristic (Bentham & Von Mueller, 1866). Maiden worked on eucalypts and described all taxa with illustration found up to that time (Maiden, 1903). A comprehensive classification of the eucalypts was based on the extended Bentham's anthral classification, published in a book of three revised editions by Blakely (Blakely, 1934, 1955, 1965), comprising 606 species and 138 varieties. Pryor and Johnson combined the genus *Eucalyptus* with the closely related *Angophora* genus and divided into seven subgenus, viz. *Blakella*, *Corymbia*, *Eudesmia*, *Gaubaea*, *Idiogenes*, *Monocalyptus* and *Symphyomyrtus* (Pryor & Johnson, 1971). Hill and Johnson classified *Eucalyptus,* where the genus split into a new genus *Corymbia,* comprising two of the subgenera, viz. *Blakella* and *Corymbia* (K. D. Hill & Johnson, 1995). Traditionally eucalypts are classified into one of the two genera, i.e. *Angophora* Cav. and *Eucalyptus* L′ Her. (Ladiges, 1997). Brooker classified and combined eucalypts with *Angophora* Cav., *Corymbia* Hill & Johnson and *Eucalyptus* L'Hér., as a single genus, *Eucalyptus* and are divided into 13 subgenera, six of which are monotypic (M. I. H. Brooker, 2000). The synonymy of the three genera is rather confusing, however, a number of molecular studies and advanced phylogenetic analysis provide sufficient evidence to support both *Angophora* and *Corymbia,* being now recognized as separate genera (M. I. H. Brooker, Slee, Connors, & Duffy, 2006; Parra-O et al., 2006; Steane, McKinnon, Vaillancourt, & Potts, 1999; Udovicic & Ladiges, 1999; Udovicic, McFadden, & Ladiges, 1995). Nicolle, in an informal classification based on morphology and previous molecular phylogenies, classified eucalypts into three genera, *Angophora, Corymbia* and *Eucalyptus* (D. Nicolle, 2015). He divided the *Eucalyptus* genus into 3 polytypic (*Eudesmia*, *Symphomyrtus* and *Eucalyptus*) and 5 monotypic (*Acerosa, Cruciformes, Alveolata, Cuboidea and Idiogenes*) subgenera. Following this recent classification, around 730 species falls under *Eucalyptus* genus (D. Nicolle & Jones, 2018). Systematically the genus is placed under the Kingdom: Plantae; Class: Magnoliapsida; Order: Myrtales and Family: Myrtaceae and Genus: *Eucalyptus* (Sonker, Verma, & Gupta, 2017).

Most of *Eucalyptus* species are endemic to Australia, although they are actually are distributed throughout the world (Konoshima & Takasaki, 2002). The natural distribution of the *Eucalyptus* genus is chiefly restricted to the hypothetical line called 'Wallace's line'

extending from 9°N to 44°S in latitude, which separates the Indo-Malayan and Austro-Malayan life forms (William & Brooker, 1997). The line passes between Bali and Lombok through Indonesia, between Borneo to the west and Sulawesi on the east, then northeast through the Celebes sea, and Philippines at the southern part. Southwestern Australia are the main region of diversity. Native *Eucalyptus* species are abundant in the eastern part of Indonesia, such as *E .deglupta* from Celebes island, *E. pellita* from West Papua and *E. alba* from East Nusu Tenggara (Naithani, 2014). The *Eucalyptus* distribution and dominance within Australia means that the genus is of great ecological importance, but now the plant is cultivated in sub-tropical and temperate regions of the world, especially in countries, like Angola, Argentina, Brazil, Ethiopia, India, Kenya, South Africa, Tanzania, Uganda, Uruguay, Zambia and Zimbabwe (Orwa, Mutua, Kindt, Jamnadass, & Anthony, 2009).

3. Traditional uses of *Eucalyptus* plants in different human cultures

It is estimated that up to four billion people (representing 80% of the world's population) living in the developing world rely on traditional herbal medicines in health care. The main goal of ethnopharmacology is to identify novel compounds derived from plants and animals for use in indigenous medical systems. This knowledge can be used in the development of new drugs in pharmaceutical companies (Abubakar, 2010; Gómez-Estrada et al., 2011).

Although *Eucalyptus* species (Myrtaceae family) are originary from Australia and Tasmania, these plants now grow in almost all tropical and sub-tropical areas, and are cultivated in many other climates. It is the second largest genera after acacia. In ancient times, aboriginal people used eucalyptus plant for several purposes, mostly as medicine and as food. Nowadays, the plant is used in forestry to make timber, fuel, paper pulp, environmental planting as water and wind erosion control, as a source of essential oil for medicinal and perfumery industries and for arts and craft (Vecchio et al., 2016). As an ingredient in many products, it is used to reduce symptoms of cough, cold, and congestion. It also features in creams and ointments aimed at relieving muscle and joint pain. The best health benefits of *Eucalyptus* include its ability to boost respiratory health, strengthen the immune system, protect skin health, ease stress and anxiety, lower blood sugar, eliminate inflammation, and fight against bacterial infections. Traditionally it is also used to support the release of mucous in the respiratory tract. *Eucalyptus globulus*, also known as Blue Gum, is the main source of eucalyptus oil used globally (Nordqvist, 2017; Van Wyk & Wink, 2017). Not only native Australians, but also Chinese, Indian Ayurvedic, Greek, and other European styles of medicine have incorporated it into the treatment of a wide range of conditions for many years (Nordqvist, 2017). *Eucalyptus* spp. leaf extract is a well-known example of trees that have been used as anti-inflammatory, antibacterial and antioxidant agents (Qabaha, Abu Ras, Abbadi, & Al-Rimawi, 2016; Salari, Amine, Shirazi, Hafezi, & Mohammadypour, 2006).

Australian aboriginal tribes traditionally used *Eucalyptus* genus for medical purposes. In fact, traditional aboriginal society have used a wide range of Australian native plants as bush foods and medicines. Aborigines used several *Eucalyptus* species as tonics for gastro-intestinal symptom (Kluthe & Chen, 2017). Plants from *Eucalyptus* species have special importance for the Dharawal indigenous people of Australia and have been used for their anti-inflammatory activity along with other medicinal uses, as stated in the Dharawal pharmacopeia as well as for shelter and weapons (Akhtar, Raju, Beattie, Bodkin, & Münch, 2016).

Australian aborigines traditionally used *E. camaldulensis* Dehnh. as an herbal medicine for its antimicrobial properties. The red kino or red gum is obtained by making incisions in the tree trunks, and applied it directly to abrasions and cuts. Across Australia, dried gum was prepared by mixing fresh gum with water and subsequently dehydrated. The dried gum has been used in the same way as fresh, just it is softened in water before usage (Knezevic et al., 2016; Williams, 2011). Young leaves have been used to prepare smoke bath, with a patient sitting surrounded with smoke medicine from burning leaves and used to treat fevers, colds, flu and general sickness (Knezevic et al., 2016; Pennacchio, Jefferson, & Havens, 2010; Williams, 2011).

The medicinal usefulness of the red gum tree has been subject of numerous studies. Some of the reported phytoconstituents of tree include essential oils, sterols, alkaloids, glycosides, flavonoids, tannins and phenols. The tree is widely used in traditional medicine to treat a wide variety of clinical conditions, such as colds, asthma, coughs, diarrhea and dysentery, haemorrhage, laryngalgia, laryngitis, sore throat, spasm, trachagia and vermifuge (Adamu & Yushau, 2018). Traditional Aboriginal society in Australia used a wide range of *Eucalyptus* species to treat gastrointestinal symptoms, arrest bleeding, open wounds and cuts as well as drink the decoctions for the relief of aches and pains in muscles, joints and even tooth. In some cases, leaves are burnt and the smokes inhaled to treat fever. A plant decoction is used to treat enteric infections, including diarrhea and dysentery, constipations and other stomach problems, asthma, oral thrush, boils, sores, skin and wound infections, bronchitis, eczema and athletes foot (Abubakar, 2010; Adamu & Yushau, 2018; Bala, 2006). After established *E. camaldulensis* in Africa, this species was also used in folk medicine. Its gum was used for sore throat and diarrhea, while the smoke of burnt leaves was inhaled to treat respiratory problems in Sudan; decoctions from leaves were prepared with sugar for stomachache in Senegal. A combination decoction of *E. camaldulensis* leaves with *Citrus limon* (L.) Burm. f. fruits and *Psidium guajava* L. leaves were used for cough, flu and fever in Zimbabwe (Maroyi, 2013). In Nigeria the resinous exudates from *E. camaldulensis* trunk, commonly called “zaity”, is taken orally to cure bladder infections (Abubakar, 2010). The sticks of this species have been used as a teeth cleaner to prevent tooth decay and periodontitis (Bukar, Danfillo, Adeleke, & Ogunbodede, 2004) and poultice of leaves containing eucalyptus oil have been used in traditional medicines to heal wound infections. The genus *E. camaldulensis* and *E. torelliana* F. Muell. have been used to treat gastrointestinal disorders (B. A. Adeniyi, Odufowoke, & Olaleye, 2006; Knezevic et al., 2016). In addition, a decoction of *E. camaldulensis* leaves is reported to be a remedy for sore throat and other bacterial respiratory and urinary tracts infections. The poultice of the leaves is applied over wounds and ulcers. The leaves essential oils have been used in the treatment of lung diseases and were stated to have antitubercular effect (B. A. Adeniyi et al., 2006; C. B. A. Adeniyi, Lawal, & Mahady, 2009).

The essential oil extracted from *E. globulus* Labill leaves is known to be a rich source of traditional medicines with a variety of biological activities. It is widely used to treat common cold, pulmonary tuberculosis, diabetes, nasal congestion, bronchial disease, asthma and is also used as disinfectant, antioxidant, and antiseptic agent, especially in the treatment of upper respiratory tract infections (Song, Wang, & Liu, 2009). The oil is applied externally to relief rheumatism as a counter-irritant and for the certain skin diseases (Song et al., 2009; Van Wyk & Wink, 2017).

On the other hand, the introduction of *Eucalyptus* species to East Africa was driven by the need for a fast-growing wood source to fuel that expansion of the railroad system (Kluthe & Chen, 2017). Wood pulp is the main source of industrially used cellulose for conversion to manufactured textiles and fine paper. Most of the ‘dissolving pulp’ is derived from *E. grandis*, *E. smithii*, *E. nitens*, *E. dunnii, E. globulus* and *E. urophylla* (Lewington, 2003).

4. *Eucalyptus* species chemical composition

As referred above, there are more than 700 *Eucalyptus* species, mostly originating from the Australian continent, with a very small number found on the neighboring islands of Papua New Guinea, Indonesia, and Philippines (Yang et al., 2017). The chemical

Table 1
Phytochemicals present in *Eucalyptus* species leaves using hydro and steam (*) distillation.

Eucalyptus spp	Phytoconstituents	Reference
E. bicostata	α-pinene, limonene, 1,8-cineole, ρ-cymene, *trans*-pinocarveol, α-terpineol, globulol, viridiflorol	(A. Elaissi et al., 2011)
	α-pinene, camphene, β-pinene, limonene, γ-terpinenene, β-trans-ocimene, ρ-cymene, α-ρ-dimethylstyrene, 1,8-cineole, pinocarvone, fenchol, terpinene-4-ol, myrtenal, *trans*-pinocarveol, carvotanacetone, α-terpineol, borneol, phellandral, D-piperitone, carvone, myrtenol, *trans-p*-mentha-1(7),8-dien-2-ol, *trans*-carveol, ρ-cymen-8-ol, *cis-p*-mentha-1(7),8-dien-2-ol, thymol, carvacrol, δ-elemene, β-gurjunene, β-caryophyllene, aromadendrene, α-bulnesene, alloaromadendrene, α-humulene, δ-cadinene, palustrol, caryophyllene oxide, epiglobulol, ledol, globulol, viridiflorol, spathulenol, δ-cadinol, α-eudesmol, jacksone, β-phenyl propanoate, torquatone	(A. Elaissi et al., 2010)
E. bosistoana	α-pinene, α-phellandrene, ρ-cymene, limonene, 1,8-cineole, β-phellandrene, γ-terpinene, ρ-cymenene, *trans*-pinocarveol, pinocarvone, cryptone, ρ-cymene-8-ol, terpinen-4-ol, *cis*-pinocarveol, α-terpineol, *trans*-carveol, cuminaldehyde, piperitone, phellandral, ρ-cymene-7-ol, allo-aromandendrene, spathulenol, globulol, β-eudesmol	Bouzabata, Bighelli, Abed, Casanova, and Tomi (2014)
E. botryoides	α-pinene, α-Phellandrene, limonene, 1,8-cineole, ρ-cymene, benzaldehyde, *trans*-pinocarveol, cryptone, α-terpineol, caryophyllene oxide, globulol, viridiflorol, spathulenol, α-eudesmol, β-eudesmol	(A. Elaissi et al., 2011)
E. botryoides	α-pinene, limonene, 1,8-cineole, ρ-cymene, α-terpineol, borneol, caryophyllene oxide, globulol, viridiflorol, spathulenol, α-eudesmol, β-eudesmol	(A. Elaissi et al., 2011)
E. camaldulensis	1,8-cineole, ρ-cymene, β-phellandrene, limonene, γ-terpinene, α-pinene, myrtenol, myrtenal, α-phellandrene, β-pinene, m-cymene, α-cadinol, α-caryophyllene, carvacrol, linalool, spathulenol	(L. C. A. Barbosa, Filomeno, & Teixeira, 2016)
	6-methyl-5-hepten-2-one, 3-heptafluorobutyryl-delta-camphor, β-bisabolene, β-farnesol, α-farnesene, farnesyl acetone, α-limonene diepoxide, megastigma-3,7(Z),9-triene, dihydrocarveol acetate, *cis*-nerolidol, tricycle 5.1.0.02,4 octane-5-carboxylic acid 3,3,8,8,-tetramethyl-,methyl ester, 2-butanone,4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-, (-)-spathulenol, α-bisabolol	Abd El-Mageed, Osman, Tawfik, and Mohammed (2011)
E. cinerea	1,8-cineole, α-terpineol, α-pinene, α-terpinyl acetate, ρ-cymene	(L. C. A. Barbosa et al., 2016)
	α-pinene, limonene, 1,8-cineole, ρ-cymene, *trans*-pinocarveol, α-terpineol, globulol	(A. Elaissi et al., 2011)
	α-pinene, β-pinene, camphene, α- phellandrene, limonene, β-cis-ocimene, γ-terpinene, β-trans-ocimene, ρ-cymene, terpinolene, α-ρ-dimethylstyrene, 1,8-cineole, isoamyl isovalerate, *trans*-linalool oxide, pinocarvone, fenchol, terpinene-4-ol, *trans*-pinocarveol, *cis*-piperitol, mentha-1,8-dien-4-ol, α-terpineol, borneol, phellandral, carvone, cuminal, *trans-p*-mentha-1(7),8-dien-2-ol, *trans*-carveol, ρ-cymen-8-ol, *cis*-carveol, *cis-p*-mentha-1(7),8-dien-2-ol, eugenol, carvacrol, β-caryophyllene, aromadendrene, alloaromadendrene, α-humulene, bicyclogermacrene, calamenene, epiglobulol, globulol, viridiflorol, spahulenol, β-eudesmol, *cis*-jasmone	(A. Elaissi et al., 2010)
E. citriodora	citronellal, iso-isopulegol, citronellyl acetate, citronellol, isopulegol, trans caryophyllene, 1,8-cineole, neothujan-3-ol, neo-iso-3-thujanol, β-citronellal, (-)-isopulegol, menthol, β-citronellol, eugenol, β-pinene, terpinen-4-ol, α-pinene	(L. C. A. Barbosa et al., 2016)
	α-pinene, limonene, 1,8-cineole, ρ-cymene, *trans*-pinocarveol, α-terpineol, borneol	(A. Elaissi et al., 2011)
	citronellal, *cis*-geraniol, 2,6-octadien-1-ol-3,7-dimethyl-(Z)-, 3-hexen-1-ol, citronellol acetate, 3-hexenoic acid, butil ester, (Z), β-bisabolene, dihydrocarveol acetate,1,6,10-dodecatrien-3-ol,3,7,11-trimethyl-,S-(Z)-, pregn-5-en-20-one,3,17-dihydroxy-3,3-acetate, 5-hepten-1-ol,3,6-dimethyl.	Abd El-Mageed et al. (2011)
	α-pinene, sabinene, β-pinene, β-myrcene, δ-2-carene, ρ-cymene, limonene, 1,8-cineole, melonal, γ-terpinene, *cis*-rose oxide, *trans*-rose oxide, citronellal, α-terpineol, citronellol, citronellyl acetate, *cis*-jasmone, β-caryophyllene, α-humulene, bicyclogermacrene, caryophyllene oxide.	Benchaa, Hazzit, and Abdelkrim (2018)
	α-pinene, β-pinene, limonene, 1,8-cineole, *cis*-rose oxide, *trans*-rose oxide, isopulegol, citronellal, neolsoisopulegol, α-terpineol, citronellol, geranial, isopulegyl acetate, ρ-menthane-3,8-diol, citronellyl acetate, jasmone < (Z)- > , β-caryophyllene, α-humulene, bicyclogermacrene, spathulenol, caryophyllene oxide, 2,6-dimethyl-5-heptenal	Tolba et al. (2015)
	* α-pinene, 1,8-cineole, isopulegol, β-citronellal, β-citronellol	Maciel et al. (2010)
E. cladocalyx	α-pinene, limonene, 1,8-cineole, ρ-cymene, *trans*-pinocarveol, α-terpineol, borneol, globulol, spathulenol	(A. Elaissi et al., 2011)
E. diversicolor	α-pinene, α-phellandrene, limonene, 1,8-cineole, ρ-cymene, cryptone, α-terpineol, caryophyllene oxide, spathulenol, α-eudesmol	(A. Elaissi et al., 2011)
E. exserta	1,8-cineole, ρ-cymene, α-terpineol, D-piperitone, caryophyllene oxide, globulol, viridiflorol, spathulenol, α-eudesmol, β-eudesmol.	(A. Elaissi et al., 2011)
	α-pinene, α-thujene, β-pinene, α-phellandrene, limonene, β-phellandrene, ρ-cymene, α-ρ-dimethylstyrene, 1,8-cineole, *cis*-linalool oxide, α-campholenic aldehyde, linalool, *trans-p*-menth-2-en-1-ol, terpinene-4-ol, myrtenal, *trans*-pinocarveol, *cis*-piperitol, α-terpineol, borneol, phellandral, D-piperitone, carvone, *trans*-piperitol, citronellol, *trans-p*-mentha-1(7),8-dien-2-ol, *trans*-carveol, ρ-cymen-8-ol, *cis*-carveol, *cis-p*-mentha-1(7),8-dien-2-ol, perillyl alcohol, thymol, carvarol, carvacrol, isoledene, α-gurjunene, β-cubebene, aromadendrene, α-bulnesene, alloaromadendrene, α-humulene, α-amorphene, germacrene D, α-muurolene, σ-cadinene, γ-cadinene, α-clacorene, β-maaliene, palustrol, caryophyllene oxide, epiglobulol, ledol, *trans*-nerolidol, β-oplopenone, globulol, viridiflorol, spathulenol, γ-eudesmol, δ-cadinol, agarospirol, α-cadinol, T-muurolol, β-eudesmol, farnesyl acetate, jacksone, isobicyclogermacral, (E,E)-farnesol, β-phenyl propanoate, 4-methylacetophenone, pentacosane	(A. Elaissi et al., 2010)
E. fasciculosa	α-pinene, limonene, 1,8-cineole, ρ-cymene, cryptone, α-terpineol, bicyclogermacrene, caryophyllene oxide, globulol, viridiflorol, spathulenol	(A. Elaissi et al., 2011)
E. gigantea	α-pinene, limonene, 1,8-cineole, ρ-cymene, cryptone, α-terpineol, caryophyllene oxide, globulol, viridiflorol, Spathulenol, α-eudesmol, β-eudesmol	(A. Elaissi et al., 2011)
	α-pinene, α-thujene, myrcene, limonene, β-cis-ocimene, ρ-cymene, α-ρ-dimethylstyrene, 1,8-cineole, *cis*-linalool oxide, α-campholenic aldehyde, linalool, *trans-p*-menth-2-en-1-ol, fenchol, terpinene-4-ol, myrtenal, *trans*-pinocarveol, *cis*-piperitol, α-terpineol, borneol, verbenone, carvone, *trans*-piperitol, cuminal, *trans-p*-mentha-1(7),8-dien-2-ol, geraniol, ρ-cymen-8-ol, *cis*-carveol, *cis-p*-mentha-1(7),8-dien-2-ol, perillyl alcohol, thymol, carvarol, carvacrol, β-caryophyllene, aromadendrene, alloaromadendrene, α-humulene, viridiflorene, β-selinene, α-selinene, α-muurolene, δ-cadinene, σ-cadinene, γ-cadinene, cadina-1,4-diene, calamenene, α-clacorene, palustrol, caryophyllene oxide, epiglobulol, ledol, β-oplopenone, globulol, viridiflorol, spathulenol, γ-eudesmol, δ-cadinol, agarospirol, α-cadinol, T-muurolol, β-eudesmol, farnesyl acetate, jacksone, isobicyclogermacral, (E,E)-farnesol, lateriticone, amyl benzoate, β-phenyl propanoate, cryptone, 4-methylacetophenone, agglomerone, torquatone	(A. Elaissi et al., 2010)
E. globulus	1,8-cineole, spathulenol, α-terpineol, α-pinene, limonene, tricyclene, camphene, globulol, o-cimene, *cis*-ocymene, α-terpinyl acetate, ρ-cymene, β-myrcene, solanone, β-pinene	(L. C. A. Barbosa et al., 2016)

(*continued on next page*)

Table 1 (*continued*)

Eucalyptus spp	Phytoconstituents	Reference
	* α-pinene, o-cymene, limonene, 1,8-cineole	Maciel et al. (2010)
E. gomphocephala	ρ-cymene, β-phellandrene, eucalyptol, β-citronellal, 2,6-octadien-1-ol-3,7-dimethyl-, (E)-, terpinene-4-ol, α-hexylacrylonitrile, 4-(1-methylethyl)-benzaldehyde, citral (isomer 1) *cis-*,*trans-*, 3-octil acetate, β-bisabolene, dihydrocarveol acetate, megastigma-3,7(Z),9-triene, α-limonene diepoxide	Abd El-Mageed et al. (2011)
E. gracilis	α-pinene, ρ-cymene, limonene, 1,8-cineole, β-phellandrene, γ-terpinene, isoamyl isovalerate, fenchol, *trans*-pinocarveol, borneol, pinocarvone, ρ-cymen-8-ol, neral, pulegone, α-selinene, β–selinene, elemol, γ-eudesmol	Marzoug et al. (2010)
E. grandis	α-pinene, 1,8-cineole, ρ-cymene, γ-terpinene, o-cimene, β-pinene,α- terpinyl acetate	(L. C. A. Barbosa et al., 2016)
	α-pinene, α-phellandrene, limonene, 1,8-cineole, ρ-cymene, cryptone, α-terpineol, bicyclogermacrene, caryophyllene oxide, globulol, viridiflorol, spathulenol	(A. Elaissi et al., 2011)
E. gunni	α-pinene, α-phellandrene, 1,8-cineole, ρ-cymene, bicyclogermacrene, caryophyllene oxide, globulol, viridiflorol, spahulenol, β-eudesmol	(A. Elaissi et al., 2011)
	α-pinene, α-thujene, β-pinene, sabinene, α-phellandrene, α-terpinene, limonene, γ-terpinenene, ρ-cymene, terpinolene, 1,8-cineole, α-campholenic aldehyde, linalool, *trans-p*-menth-2-en-1-ol, terpinene-4-ol, 1-terpineol, *trans*-pinocarveol, D-piperitone, geranyl acetate, *trans-p*-mentha-1(7),8-dien-2-ol, geraniol, ρ-cymen-8-ol, *cis*-carveol, *cis-p*-mentha-1,8-dien-6-ol, *cis-p*-mentha-1(7),8-dien-2-ol, perillyl alcohol, thymol, carvacrol, isoledene, α-copaene, α-gurjunene, β-cubebene, β-elemene, β-caryophyllene, aromadendrene, α-bulnesene, alloaromadendrene, α-humulene, α-amorphene, ledene, β-selinene, α-muurolene, bicyclogermacrene, σ-cadinene, γ-cadinene, α-clacorene, β-maaliene, palustrol, caryophyllene oxide, epiglobulol, ledol, *trans*-nerolidol, β-oplopenone, globulol, viridiflorol, spathulenol, γ-eudesmol, δ-cadinol, agarospirol, α-cadinol, T-muurolol, isospathulenol, β-eudesmol, farnesyl acetate, jacksone, isobicyclogermacral, (E,E)-farnesol, lateriticone, β-phenyl propanoate, 6-methylhept-5-en-2-one, 2-nonanone, cryptone, geranyl acetone, β-ionone, torquatone	(A. Elaissi et al., 2010)
E. macarthurii	α-pinene, limonene, 1,8-cineole, ρ-cymene, *trans*-pinocarveol, cryptone, α-terpineol, globulol, viridiflorol, spathulenol	(A. Elaissi et al., 2011)
	α-pinene, camphene, β-pinene, myrcene, limonene, β-phellandrene, γ-terpinenene, β-trans-ocimene, ρ-cymene, α-ρ-dimethylstyrene, 1,8-cineole, isoamyl isovalerate, *trans*-linalool oxide, α-campholenic aldehyde, linalool, pinocarvone, fenchol, terpinene-4-ol, 1-terpineol, *trans*-pinocarveol, *cis*-piperitol, carvotanacetone, α-terpineol, borneol, phellandral, D-piperitone, carvone, geranyl acetate, cuminal, *trans-p*-mentha-1(7),8-dien-2-ol, *trans*-carveol, geraniol, ρ-cymen-8-ol, *cis-p*-mentha-1,8-dien-6-ol, *cis-p*-mentha-1(7),8-dien-2-ol, thymol, carvarol, carvacrol, α-gurjunene, β-gurjunene, aromadendrene, α-bulnesene, alloaromadendrene, α-humulene, α-selinene, α-clacorene, palustrol, caryophyllene oxide, epiglobulol, ledol, β-oplopenone, globulol, viridiflorol, spathulenol, γ-eudesmol, δ-cadinol, α-eudesmol, β-eudesmol, farnesyl acetate, isobicyclogermacral, β-phenyl propanoate, cryptone, torquatone, pentacosane, diphenyl oxide.	(A. Elaissi et al., 2010)
E. macroyncha	α-pinene, α-phellandrene, limonene, 1,8-cineole, ρ-cymene, cryptone, α-terpineol, d-piperitone, caryophyllene oxide, globulol, viridiflorol, spathulenol, α- eudesmol, β-eudesmol	(A. Elaissi et al., 2011)
	α-pinene, α-thujene, β-pinene, α-phellandrene, limonene, ρ-cymene, terpinolene, 1,8-cineole, linalool, *trans-p*-menth-2-en-1-ol, terpinene-4-ol, 1-terpineol, *trans*-pinocarveol, carvotanacetone, α-terpineol, D-piperitone, *trans*-piperitol, *trans-p*-mentha-1(7),8-dien-2-ol, *trans*-carveol, geraniol, ρ-cymen-8-ol, perillyl alcohol, eugenol, thymol, carvacrol, α-copaene, α-gurjunene, β-caryophyllene, aromadendrene, α-bulnesene, alloaromadendrene, α-humulene, β-selinene, α-selinene, γ-cadinene, α-clacorene, β-maaliene, palustrol, caryophyllene oxide, epiglobulol, ledol, β-oplopenone, globulol, viridiflorol, spathulenol, γ-eudesmol, δ-cadinol, agarospirol, T-muurolol, α-eudesmol, β-eudesmol, farnesyl acetate, jacksone, isobicyclogermacral, (E,E)-farnesol, β-phenyl propanoate, cryptone, *cis*-jasmone, tasmanonene	(A. Elaissi et al., 2010)
E. maidenii	α-pinene, limonene, 1,8-cineole, ρ-cymene, *trans*-pinocarveol, α-terpineol, globulol, viridiflorol, α- eudesmol, β-eudesmol	(A. Elaissi et al., 2011)
	α-pinene, β-pinene, camphene, α- phellandrene, limonene, β-cis-ocimene, γ-terpinene, β-trans-ocimene, ρ-cymene, terpinolene, α-ρ-dimethylstyrene, isoamyl isovalerate, 1,8-cineole, α-campholenic aldehyde, pinocarvone, fenchol, terpinene-4-ol, *trans*-pinocarveol, mytenal, mentha-1,8-dien-4-ol, α-terpineol, borneol, D-piperitone, carvone, mytenol, *trans-p*-mentha-1(7),8-dien-2-ol, *trans*-carveol, ρ-cymen-8-ol, *cis-p*-mentha-1(7),8-dien-2-ol, thymol, carvarol, carvacrol, β-gurjunene, β-caryophyllene, aromadendrene, α-bulnesene, alloaromadendrene, α-humulene, α-silenene, α-muurolene, palustrol, caryophyllene oxide, epiglobulol, ledol, globulol, viridiflorol, spathulenol, γ-eudesmol, agarospirol, α-cadinol, α-eudesmol, β-eudesmol, farnesyl acetate, jacksone, β-phenyl propanoate, torquatone	(A. Elaissi et al., 2010)
E. odorata	α-pinene, limonene, 1,8-cineole, ρ-cymene, *trans*-pinocarveol, cryptone, α-terpineol, d-piperitone, caryophyllene oxide, globulol, viridiflorol, spathulenol	(A. Elaissi et al., 2011)
	α-pinene, α-thujene, β-pinene, verbenene, α-phellandrene, α-terpinene, limonene, γ-terpinenene, ρ-cymene, terpinolene, α-ρ-dimethylstyrene, 1,8-cineole, β-thyjone, *trans*-linalool oxide, α-campholenic aldehyde, camphor, linalool, *trans-p*-menth-2-en-1-ol, pinocarvone, fenchol, terpinene-4-ol, myrtenal, 1-terpineol, *trans*-pinocarveol, carvotanacetone, α-terpineol, borneol, verbenone, phellandral, D-piperitone, carvone, geranial, *trans*-piperitol, cuminal, myrtenol, *trans-p*-mentha-1(7),8-dien-2-ol, *trans*-carveol, ρ-cymen-8-ol, *cis*-carveol, *cis-p*-mentha-1(7),8-dien-2-ol, perillyl alcohol, thymol, carvarol, carvacrol, isoledene, α-copaene, β-cubebene, β-elemene, aromadendrene, alloaromadendrene, α-humulene, α-selinene, δ-cadinene, σ-cadinene, γ-cadinene, cadina-1,4-diene, α-clacorene, palustrol, caryophyllene oxide, ledol, globulol, viridiflorol, spathulenol, γ-eudesmol, agarospirol, α-cadinol, T-muurolol, isospathulenol, β-eudesmol, farnesyl acetate, jacksone, isobicyclogermacral, (E,E)-farnesol, lateriticone, amyl benzoate, β-phenyl propanoate, cryptone, 4-methylacetophenone, torquatone	(A. Elaissi et al., 2010)
E. oleosa	α-pinene, sabinene, ρ-cymene, limonene, 1,8-cineole, β-phellandrene, γ-terpinene, isoamyl isovalerate, fenchol, *trans*-pinocarveol, borneol, pinocarvone, ρ-cymen-8-ol, verbenone, neral, pulegone, cuminaldehyde, ρ-cymen-7-ol, carvacrol, β-bourbonene, β-caryophyllene, α-himachalene, γ-muurolene, α-selinene, β–selinene, δ-cadinene, β-caryophyllene oxide, viridiflorol, γ-eudesmol, α-cadinol	Marzoug et al. (2010)
E. ovata	α-pinene, limonene, 1,8-cineole, ρ-cymene, *trans*-pinocarveol, α-terpineol, borneol, globulol, viridiflorol, spathulenol, α- eudesmol, β-eudesmol	(A. Elaissi et al., 2011)
E. pauciflora	1,8-cineole, ρ-cymene, α-terpineol, d-piperitone, globulol, viridiflorol, spathulenol, α- eudesmol, β-eudesmol	(A. Elaissi et al., 2011)
	α-pinene, α-thujene, α-phellandrene, limonene, ρ-cymene, 1,8-cineole linalool, *trans-p*-menth-2-en-1-ol, terpinene-4-ol, 1-terpineol, *trans*-pinocarveol, *cis*-piperitol, carvotanacetone, α-terpineol, borneol, D-piperitone, carvone, *trans-p*-mentha-1(7),8-dien-2-ol, ρ-cymen-8-ol, *cis*-carveol, *cis-p*-mentha-1(7),8-dien-2-ol, perillyl alcohol, eugenol, thymol, carvarol, carvacrol, α-gurjunene, β-elemene, β-caryophyllene, aromadendrene, α-	(A. Elaissi et al., 2010)

(*continued on next page*)

composition of the different eucalypt species has been described in several studies. In Tables 1 and 2, we can observe the most studied species of this genus, related to the type of extraction and plant part from which the compounds are extracted. Hydrodistilattion and steam distillation comprise the most commonly used extraction technique used, and leaves, followed by fruits, flowers and stems the most widely investigated plant part.

The main products obtained from *Eucalyptus* are essential oils (Small, 2013), mainly used for its antimicrobial (Bachir & Benali, 2012; Mulyaningsih, Sporer, Reichling, & Wink, 2011), antifungal (Gakuubi, Maina, & Wagacha, 2017), antiseptic, astringent (Marzoug et al., 2011), anti-inflammatory (J. Silva et al., 2003), wound healing, disinfectant (Valeriano et al., 2012) and expectorant properties (Horváth & Ács, 2015). Other products obtained from eucalyptus are gum, cellulose and wood, while the essential oil extracted from the leaves is widely employed for medicinal, cosmetic and food industries (S. M. Silva et al., 2011).

Eucalyptus contains high levels of volatile organic compounds (VOC), which comprise its essential-oil profile. Essential oils are a mixture of volatile compounds, mainly mono- and sesquiterpenoids,

Table 1 (*continued*)

Eucalyptus spp	Phytoconstituents	Reference
	bulnesene, alloaromadendrene, β-selinene, α-selinene, bicyclogermacrene, σ-cadinene, γ-cadinene, α-clacorene, β-maaliene, palustrol, caryophyllene oxide, epiglobulol, ledol, β-oplopenone, globulol, viridiflorol, spathulenol, γ-eudesmol, δ-cadinol, α-cadinol, α-eudesmol, isospathulenol, β-eudesmol, farnesyl acetate, jacksone, isobicyclogermacral, (E,E)-farnesol, β-phenyl propanoate, cryptone, tasmanonene, pentacosane, diphenyl oxide	
E. resinifera	9,12-octadecadienoic acid(Z,Z)-, phenyl methyl ester, eucalyptol, 9,12,15-octadecatrienal, α-terpineol, α-terpineol acetate, α-limonene diepoxide, dihydrocarveol acetate, 1,2,4,5-tetramethyl-3-(3-phenylpropyl)-benzene, α-farnesene, 3,7,11-trimethyl-2,6,10-dodecatrien-1-ol, 10-ethyl-19-norpregn-4-ene-3,20-dione, 1-ethyl-(16,α)-curan-17-ol, spathulenol, *trans*-nerolidol, benzenepropanoic acid, α-oxo-,β.,β.-bis(trimethylsilyl)-, androst-5-en-7-one, 3-(acetyloxy)-4,4-dimethyl-,(3.β.)-, undecane,1-(1-naphthyl)-	Abd El-Mageed et al. (2011)
E. saligna	1,8-cineole, limonene, ρ-cymene, γ-terpinene, α-pinene, α-terpineol, α- camphonellal, α-pinene oxide, ο-cimene, α-thujene	(L. C. A. Barbosa et al., 2016)
	2,4-dimethyl-3-pentanone, isovaleric acid, 2-methylbutanoic acid, (Z)-3-hexenol, (E)-2-hexen-1-ol, 1,2-dimethyl-1,4-cyclohexadiene, α-phellandrene, α-pinene, β-Fenchene, thuja-2,4(10)-diene, benzaldehyde, 3-methylbutyl propanoate, sabinene, (E)-dehydroxylinalool oxide, β-phellandrene, isoamyl isobutyrate, ο-cymene, 1,8-cineole, (Z)-β-ocimene, phenylactealdehyde, γ-terpinene, isopentyl isovalerate, *endo*-fenchol, α-campholenal, [1S-(1α,3α,5α)]-6,6-dimethyl-2-methylenebicyclo[3.1.1]heptan-3-ol, camphene hydrate, pinocarvone, borneol, terpinen-4-ol, α-terpineol, verbenone, terpinolene, piperitone, thymol, benzyl isobutanoate, 2,2,5,5-tetramethyl-3-cyclopenten-1-one, α-copaene, phenylethyl butyrate, (E)-jasmone, germacrene B, α-guaiene, viridiflorene, durohydroquinone, γ-gurjunene, pogostol, spathulenol, globulol, iso-leptospermone, β-gurjunene	Bett et al. (2015)
E. salmonophloia	α-pinene, α-fenchene, camphene, ρ-cymene, limonene, 1,8-cineole, β-phellandrene, γ-terpinene, isoamyl isovalerate, fenchol, *cis*-verbenol, *trans*-pinocarveol, camphor, borneol, pinocarvone, ρ-cymen-8-ol, myrtenal, verbenone, neral, pulegone, cuminaldehyde, β-bourbonene, β-gurjunene, α-himachalene, γ-muurolene, α-selinene, α-amorphene, β-caryophyllene oxide, γ-eudesmol, α-cadinol	Marzoug et al. (2010)
E. salubris	α-pinene, α-fenchene, sabinene, ρ-cymene, limonene, 1,8-cineole, β-phellandrene, γ-terpinene, isoamyl isovalerate, fenchol, *trans*-pinocarveol, borneol, pinocarvone, ρ-cymen-8-ol, verbenone, neral, pulegone, cuminaldehyde, piperitone, carvacrol, β-bourbonene, α-selinene, β –selinene, elemol, β-caryophyllene oxide, γ-eudesmol, α-cadinol	Marzoug et al. (2010)
E. sideroxylon	α-pinene, limonene, 1,8-cineole, ρ-cymene, *trans*-pinocarveol, α-terpineol, bicyclogermacrene, globulol, viridiflorol, spathulenol, β-eudesmol	(A. Elaissi et al., 2011)
	α-pinene, camphene, β-pinene, α-phellandrene, limonene, γ-terpinenene, β-trans-ocimene, ρ-cymene, 1,8-cineole, isoamyl isovalerate, pinocarvone, fenchol, terpinene-4-ol, myrtenal, *trans*-pinocarveol, mentha-1,8-dien-4-ol, carvotanacetone, α-terpineol, borneol, carvone, *trans-p*-mentha-1(7),8-dien-2-ol, *trans*-carveol, ρ-cymen-8-ol, *cis*-carveol, *cis-p*-mentha-1(7),8-dien-2-ol, thymol, carvacrol, α-gurjunene, β-caryophyllene, aromadendrene, α-bulnesene, alloaromadendrene, α-humulene, α-selinene, bicyclogermacrene, σ-cadinene, caryophyllene oxide, epiglobulol, ledol, globulol, viridiflorol, spathulenol, γ-eudesmol, agarospirol, α-eudesmol, β-eudesmol, (E,E)-farnesol, β-phenyl propanoate, 4-methylacetophenone	(A. Elaissi et al., 2010)
E. staigeriana	* α-pinene, ο-cymene, limonene, 1,8-cineole, α-terpinolene, isopulegol, β-citronellal, β-citronellol, Z-citral, *trans*-geraniol, E-citral, methyl geranate, geraniol acetate	Maciel et al. (2010)
E. tereticornis	α-pinene, limonene, 1,8-cineole, ρ-cymene, *trans*-pinocarveol, cryptone, α-terpineol, caryophyllene oxide, viridiflorol, spathulenol.	(A. Elaissi et al., 2011)
	α-pinene, α-thujene, β-pinene, thuja-2,4(10)-diene, α-phellandrene, limonene, γ-terpinenene, β-trans-ocimene, ρ-cymene, α-ρ-dimethylstyrene, 1,8-cineole, linalool, *trans*-sabinene hydrate, *trans-p*-menth-2-en-1-ol, pinocarvone, fenchol, terpinene-4-ol, myrtenal, 1-terpineol, *trans*-pinocarveol, carvotanacetone, α-terpineol, borneol, verbenone, phellandral, ᴅ-piperitone, carvone, geranial, *trans*-piperitol, cuminal, myrtenol, *trans-p*-mentha-1(7),8-dien-2-ol, *trans*-carveol, geraniol, ρ-cymen-8-ol, *cis*-carveol, *cis-p*-mentha-1(7),8-dien-2-ol, perillyl alcohol, thymol, carvarol, carvacrol, β-caryophyllene, aromadendrene, alloaromadendrene, α-humulene, δ-cadinene, cadina-1,4-diene, palustrol, caryophyllene oxide, epiglobulol, ledol, viridiflorol, spathulenol, γ-eudesmol, δ-cadinol, agarospirol, α-cadinol, α-eudesmol, isospathulenol, β-eudesmol, farnesyl acetate, isobicyclogermacral, (E,E)-farnesol, lateriticone, β-phenyl propanoate, cryptone, 4-methylacetophenone, agglomerone, torquatone	(A. Elaissi et al., 2010)
	1,8-cineole, ρ-cymene, γ-terpinene, β-phellandrene, α-phellandrene, caryophyllene oxide, spathulenol, cryptone, β-pinene, α-pinene.	(L. C. A. Barbosa et al., 2016)
E. viminalis	α-pinene, limonene, 1,8-cineole, ρ-cymene, *trans*-pinocarveol, α-terpineol, globulol, viridiflorol, spathulenol, β-eudesmol	(A. Elaissi et al., 2011)
	α-pinene, β-pinene, myrcene, limonene, ρ-cymene, 1,8-cineole, isoamyl isovalerate, bornyl acetate, fenchol, terpinene-4-ol, *trans*-pinocarveol, mentha-1,8-dien-4-ol, α-terpineol, borneol, ᴅ-piperitone, carvone, *trans-p*-mentha-1(7),8-dien-2-ol, *trans*-carveol, ρ-cymen-8-ol, *cis*-carveol, *cis-p*-mentha-1(7),8-dien-2-ol, perillyl alcohol, thymol, carvacrol, isoledene, β-gurjunene, β-caryophyllene, aromadendrene, α-bulnesene, alloaromadendrene, α-humulene, β-selinene, α-selinene, δ-cadinene, σ-cadinene, α-clacorene, palustrol, caryophyllene oxide, epiglobulol, ledol, globulol, viridiflorol, spathulenol, δ-cadinol, agarospirol, α-cadinol, α-eudesmol, β-eudesmol, jacksone, β-phenyl propanoate, torquatone, benzaldehyde	(A. Elaissi et al., 2010)

Table 2
Phytochemicals present in *Eucalyptus oleosa* stems, fruits and flowers using hydro distillation.

Phytoconstituents	References
Stems: α-pinene, α-fenchene, camphene, ρ-cymene, limonene, 1,8-cineole, β-phellandrene, γ-terpinene, α-terpinolene, *cis*-sabinol, *trans*-pinocarveol, borneol, pinocarvone, ρ-cymen-8-ol, myrtenal, myrtenol, verbenone, pulegone, cuminaldehyde, piperitone, bornyl acetate, ρ-cymen-7-ol, methyl geranate, exo-2-hydrixycineole acetate, β-bourbonene, methyl eugenol, γ-selinene, α-selinene, calamenene, sphatulenol, globulol, β-caryophyllene oxide, viridiflorol, guaiol, γ-eudesmol, α-cadinol, β-eudesmol	Marzoug et al. (2011)
Fruits: α-pinene, camphene, sabinene, ρ-cymene, limonene, 1,8-cineole, γ-terpinene, α-terpinolene, *endo*-fenchol, 4-acetyl-1-methylcyclohexene, *trans*-2-caren-4-ol, *cis*-sabinol, *trans*-pinocarveol, borneol, pinocarvone, ρ-cymen-8-ol, myrtenal, myrtenol, verbenone, *cis*-carveol, neral, pulegone, cuminaldehyde, piperitone, ρ-cymen-7-ol, carvacrol, methyl geranate, exo-2-hydrixycineole acetate, isoledene, α-copaene, β-bourbonene, α-gurjunene γ-selinene, γ-muurolene, β-selinene, viridiflorene, α-selinene, δ-cadiene, calamenene, ledol, sphatulenol, globulol, β-caryophyllene oxide, viridiflorol, γ-eudesmol, α-cadinol	Marzoug et al. (2011)
Flowers: α-pinene, α-fenchene, camphene, sabinene, ρ-cymene, limonene, 1,8-cineole, β-phellandrene, γ-terpinene, α-terpinolene, methyl benzoate, *endo*-fenchol, 4-acetyl-1-methylcyclohexene, *trans*-2-caren-4-ol, *cis*-sabinol, *trans*-pinocarveol, borneol, pinocarvone, ρ-cymen-8-ol, mytenal, mytenol, verbenone, *cis*-carveol, neral, pulegone, cuminaldehyde, piperitone, bornyl acetate, ρ-cymen-7-ol, carvacrol, methyl geranate, exo-2-hydrixycineole acetate, isoledene, α-copaene, β-bourbonene, methyl eugenol, α-gurjunene, γ-selinene, γ-muurolene, β-selinene, viridiflorene, α-selinene, δ-cadiene, calamenene, ledol, sphatulenol, globulol, β-caryophyllene oxide, viridiflorol, guaiol, (+)-spathulenol, γ-eudesmol, α-cadinol, β-eudesmol	Marzoug et al. (2011)

phenylpropanoids, etc., containing hundreds of individual chemical constituents, which may have biological activity. It has been found that 1,8-cineole, citronellal, *p*-cymene and benzaldehyde are the main phytochemical constituents in essential oils from species growing in Uruguay (Dellacassa, Menkndez, Moyna, & Soler, 1990). For medicinal purposes, the value of *Eucalyptus* oil is based largely on the content of a particular oil constituent: 1,8-cineole (cineole or eucalyptol). One of the widely studied *Eucalyptus* species is *G. globulus*. The main constituent of all the oils examined, except that produced from leaves of young branches, was 1,8-cineole. In overall, the 1,8-cineole content ranged from 4.1% from leaves of young branches (Spanishorigin) to 57.0% from bare branches (Montenegro origin). The major components in the oil from leaves of young branches were cryptone (17.8%), spathulenol (17.0%), terpinen-4-01 (6.0%), globulol (8.0%), and transpinocarveol (6.9%) (Chalchat, Chabard, Gorunovic, Djermanovic, & Bulatovic, 1995). *p*-cymene is the second most abundant component in *E. globulus* oils. This compound was found in high percentage only in Budva leaves (27.2%), flower buds (8.0%) and mature fruits (6.4%) oils (Chalchat et al., 1995). In other study, shade-dried samples produced the highest oil yield and 1,8-cineole content, but the highest percentage of 1,8-cineole was obtained using water and steam distillation methods (Fathi & Sefidkon, 2012).

Leaves together with fruits are the parts of *Eucalyptus* that have been mostly studied regarding their phytochemical components, as it can be seen in Tables 1–2. From the leaves of *E. citriodora* have been extracted 13 compounds, of which betulinic and corosolic acids showed a significant increase in GLUT-4 translocation activity (Wang et al., 2014). In the case of wood, terpenes have been isolated and type compounds flamyrin, erythrodiol, uvaol, acetyloleanolic, acetylbetulinic, acetylursolic, betulinic, ursolic, 23-hydroxyursolic and *trans-p*-methoxycinnamoyloxy-ursolic acids, in *E. globulus* (Santos et al., 1997).

With regards to the extraction techniques used, hydrodistillation has been the most commonly used for the extraction of the greatest amounts of chemical compounds in *Eucalyptus* species. This technique is

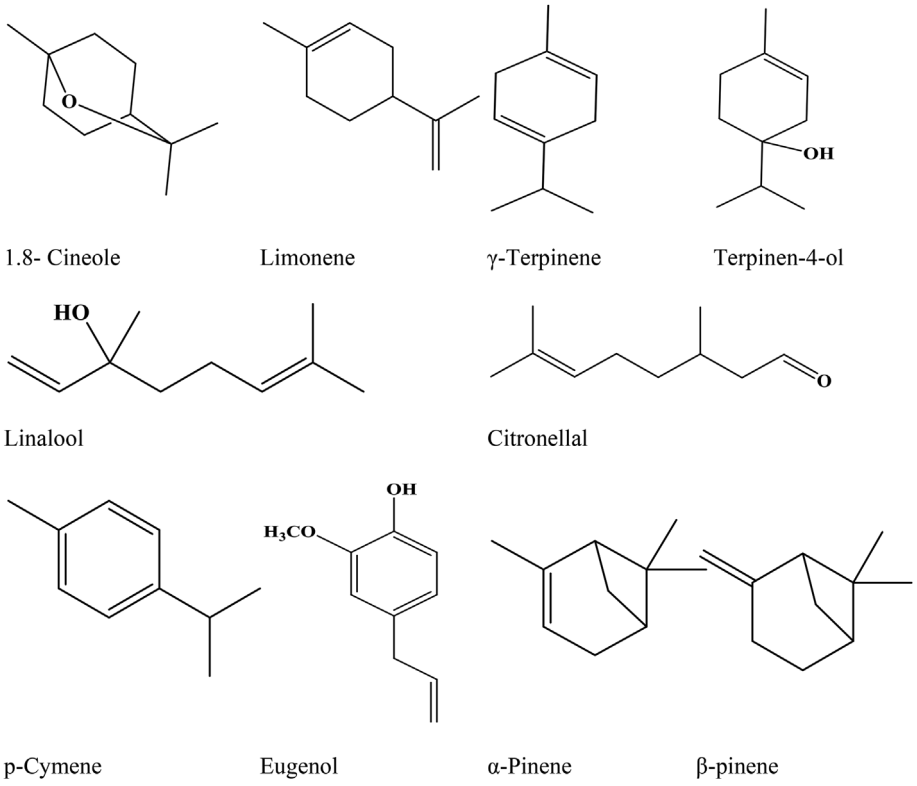

Fig. 1. Chemical structure of some volatile compounds in *Eucalyptus* essential oils.

a steam distillation variant and is the mostly used in obtaining phytochemicals compounds. In Tables 1–2 are shown the different compounds obtained using hydrodistillation and steam distillation technique, the chemical structure of some volatile compounds present in *Eucalyptus* essential oils are represented in Fig. 1.

As observed in Tables 1–2, the most abundant phytochemicals in the different *Eucalyptus* species correspond to terpenes, as are phenolic compounds. There are different reports demonstrating the high potential of *Eucalyptus* species as a source of bioactive phenolic compounds. Indeed, phenolic compounds are those which contribute significantly to the antioxidant activities of extracts. A study of the chemical components of *E. robusta* species indicates water as the most suitable solvent for the extraction of total phenolic content (TPC), total flavonoid content (TFC), proanthocyanidins, and antioxidants from *E. robusta*, using conventional extraction. For the same species, the acetone extract was proved to contain the highest amount of saponins. When comparing TPC, TFC and antioxidant content, proantocianidins and saponins from *E. robusta* with *E. saligna*, *E. microcorys* (fruit and leaves) and *E. globulus*, it was stated that the aqueous extract of *E. robusta* had the highest TPC, TFC, and antioxidant contents, whereas the proanthocyanidins content was on the same level as with *E. saligna* and *E. globulus*. By contrast, the aqueous extract of *E. microcorys* (leaf) had a significantly higher saponin content than the other *Eucalyptus* extracts tested (Bhuyan et al., 2016). The other uses of leaf extracts comprise as food additives. In Japan, the extract of *Eucalyptus* leaves appears on the List of Food Additives as an antioxidant. Meanwhile, in Europe the use of eucalyptus essences as aromatizers in foods has also received approval. The eucalyptus essential oil is regarded as safe and non-toxic by the United States Food and Drug Authority (FDA) (S. M. Silva et al., 2011).

5. *In vitro* pharmacological activities of *Eucalyptus* species

5.1. Antibacterial activity

The antibacterial activity of *Eucalyptus* essential oils and its selected components have been investigated against representatives from Gram-positive and Gram-negative bacteria, including multidrug-resistant bacterial pathogens. In a study of 2011, the hydrodistilled oils of the dried powder of *E. globulus* fruits, in addition to the *E. globulus*, *E. radiate*, and *E. citriodora* leaves, and 1,8-cineole were tested against different Gram-positive bacteria, as reference strain of methicyllin-resistant *Staphylococcus aureus* (MRSA) NCTC 10442, clinical isolates of MRSA, reference strain of VRE (ATCC 51299), and clinical isolates of VRE, and Gram negative bacteria, as *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853, *Klebsiella pneumoniae* ATCC 700603, and *Acinetobacter baumannii* ATCC BAA 747 (Mulyaningsih et al., 2011). The results of this study revealed some differences between the investigated *Eucalyptus* oils with regards to the chemical composition and consequently antibacterial activity against Gram-positive bacteria. However, all oils and their components were almost inactive against multi-drug resistant Gram-negative bacteria due to differences on cell wall sub-structures. Regarding oil constituents, aromadendrene was found to be the most active, followed by citronellol, citronellal and 1,8-cineole. To 1,8-cineole was attributed the most potent biological activity as reported with good antimicrobial activity (Sharifi-Rad, Salehi, et al., 2017; Sharopov, 2015). In another study, performed by Bachir Raho et al., the antibacterial activity of the essential oils from *E. globulus* leaves was investigated against *E. coli* and *S. aureus*. The plant was collected from Algeria, the oil was prepared by hydrodistillation, and the activity was measured using agar disc diffusion and dilution broth methods. This study showed both positive antibacterial activity of the oil against Gram-positive and Gram-negative representatives, *S. aureus* and *E. coli*, respectively (Bachir & Benali, 2012). In addition, the antibacterial activity of essential oils from leaves of two *Eucalyptus* species (*E. globulus* and *E. camaldulensis*) was determined against *S. aureus* and *E. coli* bacteria. The inhibiting activity was evaluated by three different assays: aromatogramme, microatmosphere and germs in suspension. The results demonstrated that the two species oils had an inhibitory effect on both bacteria, but with a less degree on *E. coli* (Ghalem & Mohamed, 2008). Thus, based on these reports, the antibacterial activity of *Eucalyptus* essential oil may indicate its potential usefulness as a microbiostatic, antiseptic or disinfectant agent, especially against Gram-positive bacteria.

5.2. Antifungal activity

5.2.1. Plant pathogens

In the last few decades, agricultural studies have focused on the biocontrol of plant diseases through the discovery and creation of new pollution-free biopesticides, especially from plant sources. These studies have included the screening of antifungal and germicidal compounds from plants, such as *Eucalyptus* species. The essential oil of *E. camaldulensis* Dehnh. leaves collected from Kenya was investigated against five plant pathogenic isolates of *Fusarium* species, namely *Fusarium oxysporum*, *Fusarium solani*, *Fusarium verticillioides*, *Fusarium proliferatum*, and *Fusarium subglutinans*. These fungal pathogens are associated with and responsible for maize crops deterioration and contamination due to production of several mycotoxins, such as fumonisins, trichothecenes, zearalenone T-2 toxin, and HT-2 toxin. The results of this experiment demonstrated an interesting fungicidal activity. The essential oil completely inhibited the mycelial growth of the five isolates tested, at a concentration ranging from 7 to 8 μL/mL after five days of incubation (Gakuubi et al., 2017). In addition, the fungicidal activity against rice blast fungi (e.g., *Setosphaeria turcica*, *Magnaporthe grisea*, *Botrytis cinerea*, *Fusarium graminearum* and others) was performed on leaves essential oil from *E. grandis* x *E. urophylla*, a fast-growing hybrid clone between *E. grandis* and *E. urophylla*, which is an economically important pulp tree, widely grown in many provinces of south China. The oil, with a final concentration of 2.5 mg/mL, showed a significant inhibitory activity in mycelium growth. The most interesting findings were variations in colony morphology and abnormal hypha growth, according to the scanning electron microscopy (SEM) observations. These effects may be due to interferences with genes expression involved in cellulose synthesis, respiration process and nucleic acid synthesis (Yuan et al., 2016).

5.2.2. Dermatophytes

The Algerian *E. citriodora* leaves essential oil was assessed as an antifungal candidate against four medically important dermatophytes. These clinical isolates were *Microsporum canis, Microsporum gypseum, Trichophyton mentagrophytes,* and *Trichophyton rubrum* using disc diffusion, disc volatilization, and agar dilution methods. The results showed that *E. citriodora* essential oil had a valuable antifungal potential against the tested microorganisms, except against the most resistant strain *M. gypseum*, with inhibition zone diameters varying from 12 to 90 mm and minimum inhibitory (MIC) minimum fungicidal (MFC) concentrations ranged from 0.6 to 5 and 1.25–5 mL/mL, respectively (Tolba, Moghrani, Benelmouffok, Kellou, & Maachi, 2015). With regards to its anti-*Candida* activity, the essential oils of *E. citriodora* and *E. globules* were investigated against numerous *Candida* species. Both tested oils showed inhibitory activity on *Candida* species cells, determined through microdilution technique (J. P. Barbosa, 2018).

5.3. Antiviral activity

The antiviral activity of *Eucalyptus* oil was tested against herpes simplex virus type 1 (HSV-1) strain KOS. In a dose-response assay (plaque reduction assay), the inhibition of the viral replication was measured. The oil has succeeded to suppress the viral multiplication and infectivity by more than 96%, while its major constituent 1,8-cineole was less active. It was shown that the inhibitory mechanism of HSV was much more prominent before the viral adsorption, indicating

the binding of essential oil components to viral proteins involved in host cell adsorption and penetration (Astani, Reichling, & Schnitzler, 2010). Thus, given the current insights, the development of an effective and less toxic an anti-influenza virus drug is urgently needed due to continual appearance of drug-resistant mutants. The essential oil from *E. globulus* have shown a significant virucidal activity against influenza virus following exposures to oil vapors over only 10 min. In addition, this activity was observed without measurable adverse effect on the epithelial cell monolayers (Vimalanathan & Hudson, 2014).

5.4. Cytotoxic and antitumor activity

Several reports have confirmed the cytotoxic and antitumor activity of a wide variety of *Eucalyptus* species extracts. The activity was most likely mediated through induction of apoptotic pathways and cell death against several cancerous cell lines, e.g., HeLa, non-lymphoma, BJAB and Raji lymphoma, MCF7, human colon cancer HCT116 and RKO, and human leukemia HL-60 cell lines. In more detail, the essential oils from young and adult leaves of *E. benthamii* collected from Brazil were assessed as *in vitro* cytotoxic agents on Jurkat, J774A.1 and HeLa cells lines. GC/MS analysis of the extracted oils showed that α-pinene, globulol, aromadendrene, and γ-terpinene were the oil main consituents. The results regarding the cytotoxic activity was based on MTT assay and showed that the essential oil had significant cytotoxic effect on Jurkat and HeLa cell lines. Moreover, the LDH activity and decrease in DNA content indicated that the cytotoxic activity against Jurkat cells probably involved cell death through apoptosis induction and cells proliferation inhibition, respectively (Döll-Boscardin et al., 2012).

In Jordan, six *Eucalyptus* species leaves, namely *E. woodwardi, E. stricklandii, E. salubris, E. sargentii, E. torquata* and *E. wandoo*, were hydrodistilled and investigated against nine human cancerous cell lines, such as the human breast adenocarcinoma MCF7 cell line, human ductal breast epithelial tumor cell line T47D, human clear cell renal cell carcinoma Caki cell line, human kidney carcinoma cell line A498, human prostate cancer PC3 cell line, human Burkitt's lymphoma Raji cell line, EBV-negative Burkitt's lymphoma BJAB cell line, human colon adenocarcinoma Caco-2 cell lines, and human epithelial carcinoma HeLa cell line. Based on MTT assay, the survival curves showed weak-to-moderate cytotoxicity of the investigated oils against non-lymphoma tumor cell lines, whereas potent cytotoxicity was evident against BJAB and Raji lymphoma tumor cell lines (Bardaweel, Hudaib, & Tawaha, 2014). Morevoer, the anticancer activity was assessed to the essential oil from the fresh leaves of *E. citriodora* Hook. via MTT assay using three human tumor cell lines, namely hepatocellular carcinoma (liver) HePG-2, mammary gland (breast) MCF-7 and colorectal carcinoma (colon) HCT-116. The essential oil exhibited a high anticancer activity against HCT-116, MCF-7 and HepG-2 with IC_{50} values of 4.75, 8.8, and 11.8 μg/mL, respectively (Ghareeb, Refahy, Saad, & Ahmed, 2016).

5.5. Others

Other pharmacological activities for *Eucalyptus* have been reported, as summarized in Table 3. Based on these previously reported uses of *Eucalyptus* essential oils and extracts, there is still urgently required further *in vivo* studies using various *Eucalyptus* constituents to reveal the secrets beyond their traditional uses for the treatment of a wide spectrum of ailments.

6. *In vivo* pharmacological activities of *Eucalyptus* species

So far, there have been conducted several studies assessing the *in vivo* pharmacological activities of *Eucalyptus* species (Table 4).

Toxoplasmosis is a worldwide disease caused by the protozoan parasite *Toxoplasma gondii*, which is most commonly treated by pyrimethamine and sulfadiazine. However, this treatment presents several adverse side effects. Thus, new drugs with lower toxicities are urgently

Table 3
Other reported pharmacological activities of *Eucalyptus* sp. oils and extracts.

Bioactivity	*Eucalyptus* species	Part used	Applied evaluation assay	Reference
Antioxidant	*E. camaldulensis* Dehnh.	Hydrodistilled oil of the aerial parts	DPPH radical	Barra et al. (2010)
	E. globulus	Leaves	DPPH and No radicals	Jha et al. (2013)
	E. globulus	Acetone extracts of leaves and fruits (phenolic contents)	DPPH and H_2O_2 scavenging	Remini and Mazauric (2016)
	E. globulus	Hydrodistillated extract of fruits	DPPH, reducing power and lipid peroxidation inhibition assays	Said et al. (2016)
Anti-inflammatory and analgesic	Unspecified *Eucalyptus* sp. (Palestine)	Leaves ethanolic extract (gallic acid and chlorogenic acid)	Determination of TNF-α and IL-6 by immunoassay ELISA test	Qabaha et al. (2016)
	E. citriodora, E. tereticornis, and *E. globulus*	Aerial parts essential oils	Inhibition of rat pawedema induced by carrageenan and dextran. Acetic acid induced writhes in mice and hot plate thermal stimulation in rats	(J. Silva et al., 2003)
Pesticide, insecticide and herbicide	*E. camaldulensis, E. astringens, E. leucoxylon, E. slehmannii and E. rudis* (Tunisia)	Hydrodistilled dried leaves	Fumigation activity against three stored-date moth pests: *Ephestia kuehniella, Ephestia cautella* and *Ectomyelois ceratoniae*.	Ben Jemâa et al. (2012)
	Several species of *Eucalyptus*	Leaves essential oils	Fumigation bioassays against several insects	Batish, Singh, Kohli, and Kaur (2008)

Table 4
In vivo studies of *Eucalyptus* species biological effects.

Extract	Dose	Model	Results	References
Toxoplasmosis				
97% Ethanol extract of *Eucalyptus* leaves	100 and 200 mg/kg/day	Female Balb/c mice IP inoculated with *T. gondii* (RH strain, 2 × 103 tachyzoites per mouse)	Reduction in the spleen index	Mirzaalizadeh et al. (2018)
Antihyperglycemic				
Alcoholic extract of *E. globulus* leaves	sole beverage for 15 days; each 150 g animal ingested the equivalent of 20 mg dry leaves/day	Alloxan-diabetic rats	Restored blood glucose to almost normal levels; increased SOD, CAT and GPX activities in liver and kidney	Ahlem et al. (2009)
Anticancer				
Euglobal-G1 isolated from the leaves of *E. grandis*	For pulmonary tumor: glycerol solution containing 0.0025% EG-1 (intake of EG-1 was 1.26 mg/mouse per week) as drinking solution for 25 weeks. For skin tumor: a topical application of EG-1 (250 nmol) 1 h before each promotion treatment	Specific pathogen-free female SENCAR (6 weeks old) mice Pulmonary tumor initiated by single subcutaneous injection of 0.3 mg of 4-NQO per mouse. Promotion was done by Glycerol (8%). Skin tumor was initiated topically by DMBA (100 mg, 390 nmol) and promoted by fumonisin B1 (36 mg, 50 nmol) application in cetone (0.1 ml) twice a week	> 60% inhibition in the total number of pulmonary tumors > 45% reduction in the percentage of mice with the tumors in the pulmonary lobe 42% reduction in the number of papillomas	Takasaki et al. (2000)
Analgesic				
Essential oils of *E. citriodora* (EC), *E.sTereticornis* (ET), and *E. globulus* (EG)	In mice: 0.1, 10, and 100 mg/kg subcutaneously 30 min prior to the injection of acetic acid. In rats: intraperitoneal injection at a dose of 10 or 100 mg/kg	Acetic acid-induced writhes in mice and hot plate thermal stimulation in rats	43–73% of inhibitory effect EC was the most effective followed by ET and EG. In hot plate model: prolongation of the reaction time at several time points 30 min post-treatment	(J. Silva et al., 2003)
Methanol and 50% ethanol of *E. camaladulensis*	800 mg/kg per os	Tail flick method in mice	50% ethanol extract seemed to be full of analgesic component; the highest effect of the methanol extract was seen in 180 min, whereas of the 50% ethanol extract at 60 and 90 min with the turn over time in around 90 min	Upreti et al. (2018)
Anti-inflammatory				
Essential oils of *E. citriodora*, *E. tereticornis*, and *E. globulus*	10 or 100 mg/kg subcutaneously	Paw edema was induced by a single 0.1 ml subplantar injection of carrageenan (200 μg/paw) or dextran (300 μg/paw), containing prostaglandin I2 (PGI2, 200 ng/paw)	Marked reduction of edema. Significant reduction of neutrophil migration. Significant reduction of vascular permeability	(J. Silva et al., 2003)
E. robusta leaves methanolic extract	25 mg/kg body weight	Experimental endometritis was induced in female adult Wistar rats using the mixed culture of clinical isolates (*E. coli* and *S. aureus*)	No cardinal inflammation signs. Significant decrease in secretion index, reduction in bacterial load and polymorphonuclear cells count in uterine discharge, decrease in levels of TLR-4 and TLR-9, and increase in COX-1 and decrease in COX-2, MPO, NO, iNOS, and in serum levels of IL-10 and serum amyloid A	Tiwari et al. (2018)
Methanol and 50% ethanol of *E. camaladulensis*	300 mg/kg per os	0.1 ml of 1% w/v Carrageenan suspension was injected subcutaneously into the planar surface of the right hind paw of rats	50% ethanol extract showed the highest protective ratio (54.58%) compared to 37.64% of methanol extract	Upreti et al. (2018)
Antiulcer				
Methanol and 50% ethanol of *E. camaladulensis*	300 mg/kg per os	Ulcer induced by 60% Ethanol and 37% HCl in the ratio of (8:2) was given to mice 1 h after treatment	Protective ratio of 44.44% and 41.67% was observed in methanol and 50% ethanol	Upreti et al. (2018)
Anti-diarrheal				
Methanol and 50% ethanol of *E. camaladulensis*	500 mg/kg per os	Gastrointestinal transit was measured using the charcoal propulsion test	Methanol and 50% ethanol extracts showed preventive indexes of 62.54% and 60.36%	Upreti et al. (2018)
Antiwrinkle				
50% ethanol extracts of *E. globulus*	Topical application of 1% and 5% extracts three times per week 1 h after UVB irradiation for four weeks	UV-induced photoaging in UVB-irradiated hairless mice	Decrease in erythema index, reduction in UVB-induced wrinkle formation; inhibition of the increased epidermis thickness Restored the collagen fibers, attenuated MMP-1 activation and increased the procollagen type 1, TGF-β1, and elastin abundance	Park et al. (2018)

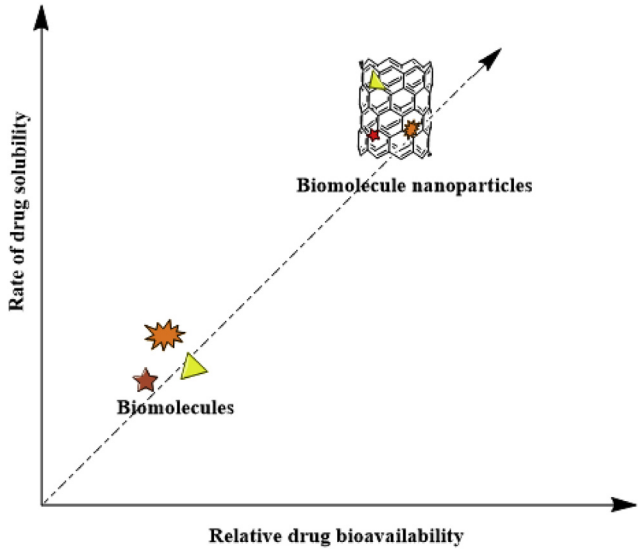

Fig. 2. Corelation between rate of solubility and bioavailability of biomolecules and their nanoparticles.

needed. *Eucalyptus* extracts have been evaluated *in vivo* by measuring the survival rates of mice infected with 2×10^3 tachyzoites of RH strain of *T. gondii* and, then, injected intraperitoneally with different concentrations of extracts for 4 days. The mice treated with *Eucalyptus* have revealed a better survival rate than others, at the same time that the increased weight of liver and spleen, triggered by infection, was reduced by this treatment (Mirzaalizadeh et al., 2018).

The antihyperglycemic activity of *E. globulus* was investigated in alloxan-diabetic rats. *E. globulus* extract significantly reduced the blood glucose levels in diabetic animals, but failed to restore the liver glycogen levels (Ahlem et al., 2009). The antihyperglycemic action of eucalyptus extract has been attributed to the enhancement of peripheral glucose uptake, at same time that it also exert antioxidant effects through increasing the activities of catalase, superoxide dismutase and gluthatione peroxidase in liver and kidney, while lowering lipids peroxidation (Ahlem et al., 2009).

Euglobal-G1 (EG-1) is a phlorogrucinol-monoterpene derivative isolated from *E. grandis* leaves. This compound exhibit a significant inhibitory effect on two-stage carcinogenesis test of mouse skin tumors induced by 7,12-dimethylbenz[a]anthracene (DMBA), as an initiator and fumonisin-B1, which has been known as one of mycotoxins produced by *Fusarium monifliforme*, as a promoter. Moreover, EG-1 exhibited potent anti-tumor promoting effects on two-stage carcinogenesis test of mouse pulmonary tumor using 4-nitroquinoline-N-oxide (4-NQO) as an initiator and glycerol as a promoter (Takasaki et al., 2000).

The essential oils of *E. citriodora*, *E. tereticornis*, and *E. globulus* have also proved to have analgesic effects in both acetic acid-induced writhes in mice and hot plate thermal stimulation in rats. Further, the essential oils from these three species has anti-inflammatory effects, as demonstrated by inhibition of dextran and carrageenan-induced rat paw edema, neutrophil migration into rat peritoneal cavities induced by carrageenan, and vascular permeability induced by carrageenan and histamine. The obtained data suggest that the essential oils of the three species had both central and peripheral analgesic effects, as well as neutrophil-dependent and independent anti-inflammatory effects (J. Silva et al., 2003).

E. robusta leaves extract display curative and protective effect against endometritis and the results are comparable to or even better than cefixime. Endometritis was induced using clinical isolates of *E. coli* and *S. aureus* from bovines (cows and buffaloes) (Tiwari et al., 2018).

On the other hand, Upreti et al. (2018) reported that the 50% ethanol extract of the leaves of *E. camaladulensis* Dehnh exhibited better anti-ulcer properties than its methanol extract. The anti-inflammatory activity was evaluated in carrageenan-induced edema in right paw of rats, where 50% extract treated rat group showed maximum inhibition of inflammation, significantly comparable to the standard drug aspirin. On the contrary, the methanol extract was found to act more quickly against inflammation than 50% ethanol extract. Both methanol and 50% ethanol extract of *E. camaladulensis* Dehnh decreased the propulsive movement in the charcoal meal study, though the decrease in movement of charcoal was found to be less than standard drug, loperamide. Tail-flick model was performed as thermal pain model to study the central mechanism of analgesic activity. The methanol and 50% ethanol extracts of *E. camaladulensis* Dehnh exhibited significant analgesic activity by increasing the reaction time of the rats to heat compared to control (D/W treated rats) at all-time points, except at 180 min. The highest effect of the methanol extract was seen in 180 min, being the results comparable with that of aspirin (Upreti et al., 2018). Not least interesting to higlight is that, Park et al. (2018) reported that the topical application of *E. globulus* extract on UVB-irradiated hairless mice reduced wrinkle formation and dryness by down-regulating MMP-1 and up-regulating expression of elastin, transforming growth factor beta 1 (TGF-β1), and procollagen type 1 (Park et al., 2018). Thus, taken together, these data suggest that *E. globulus* may be a useful agent in cosmetic products.

7. Incorporation of *Eucalyptus* in nanoparticles

In the last few years, a great attention has been given for nanotechnological applications in the field of food and pharmaceutical industries. In fact, nanoparticle-based delivery systems ensure an efficient encapsulation, improve the digestibility and increase bioavailability and targeted delivery of specific components (Fig. 2) (Gupta, Eral, Hatton, & Doyle, 2016; Karthik, Ezhilarasi, & Anandharamakrishnan, 2017; McClements, 2011; H. D.; Silva, Cerqueira, & Vicente, 2012). Indeed, nanoparticle-based delivery systems have unique characteristics, such as small size, increased surface area and less sensitivity to physical and chemical changes, making them ideal formulas for drug delivery (Karthik et al., 2017; McClements, 2011). In addition, the aforementioned advantages of nanoparticles over the conventional formulas increased their utility in pharmaceutical industry.

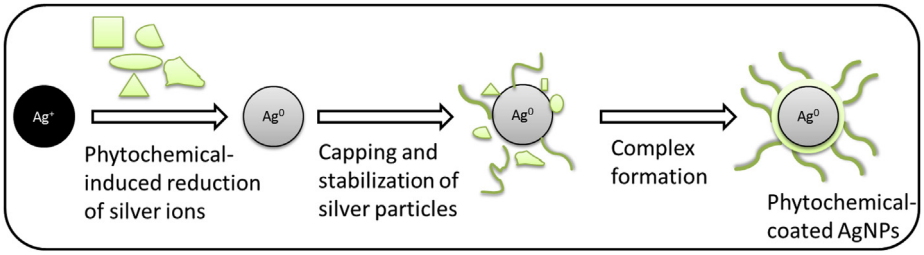

Fig. 3. Green synthesis of silver nanoparticles (AgNPs) by phytochemicals. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

7.1. Green synthesis of nanoparticles with inclusion of Eucalyptus

Metal nanoparticles (MNPs), such as gold, platinum and silver, have been extensively used in recent years as green chemistry approaches in numerous biotechnological applications owing to their unique chemical and biological properties. Plant extracts contain different constituents that are considered sustainable, economically efficient and safe for MNPs biosynthesis (Ashraf, Ansari, Khan, Alzohairy, & Choi, 2016). These phytoconstituents, such as vitamins, hemicelluloses, polyphenols, amino acids, polysaccharides and terpenoids have invaluable roles as reducing agents for metal ions, and as stabilizing agents in MNPs. Moreover, plant constituents improve the biological activity of MNPs (Raghunandan et al., 2011).

This process of bio-capping MNPs with phytoconstituents, generally called "green synthesis", ensures the control of stability, size, shape and surface area NPs. A previous study described the biosynthesis of silver nanoparticles (AgNPs) using pre-hydrolyzed liquor of *Eucalyptus* wood (Shivakumar et al., 2017). Both reduction and stabilization process of Ag^+ ions to AgNPs can be achieved via help of several metabolites (Fig. 3). The high content of phenolic compounds, hemicelluloses, as well as their derivatives in *Eucalyptus* pre-hydrolyzed liquor have contributed to its large use in AgNPs biosynthesis (Shivakumar et al., 2017). The biosynthesized AgNPs was found to have effective *in vitro* antimicrobial effects against a wide range of bacteria and fungi.

Silver nanoparticles synthesized with the ethanol leaf extract of *E. critriodora* have been reported as having a significant antibacterial activity against clinically multidrug-resistant (MDR) *Acinetobacter baumannii* isolated from pneumonia patients (Wintachai, Paosen, Yupanqui, & Voravuthikunchai, 2019). Indeed, *A. baumannii* is a Gram-negative bacteria (coccobacillus) causing nosocomial infections and has been linked to wound and urinary tract infections, pneumonia and septicemia. The production of silver nanoparticles (AgNPs) by using leaf extract of *E. camaldulensis* has also revaled promising cytotocic effects against Gram-negative (*P. aeruginosa* and *E. coli*) and Gram-positive (*S. aureus* and *Bacillus subtilis*) bacteria (Mohammed, 2015). Additionally, and not least interesting, Siripireddy and Mandal reported the biosynthesis of spherical zinc oxide nanoparticles (ZnONPs) mediated by *E. globulus* leaf extract (Siripireddy & Mandal, 2017). The resulted ZnONPs exhibited high photocatalytic and antioxidant activities (Siripireddy & Mandal, 2017).

7.2. Nanoemulsions-containing Eucalyptus essential oil

Microbial resistance is a current worldwide life threatening issue, and there is an increasing demand for screening new alternative naturally-derived antimicrobial agents. There are no doubts that plants provide a wide range of secondary metabolites with a broad spectrum antimicrobial effects. Among such metabolites, plant essential oils are considered a valuable source. In addition, microbial contamination is still considered a major concern in food industry, with the aim of inhibiting the growth of pathogenic microorganisms. In this field, there has been also an increasing demand to use plant-derived essential oils as natural alternative to synthetic preservatives in wide applications. Indeed, plant essential oils are sustainable, safe and economically efficient preservatives (Lim, 2011). However, the pure essential oils are insoluble in water, and impart their characteristic taste as well as odor the final product, aspects that is sometimes undesirable for some plant oils. Additionally, essential oils are volatile at ordinary temperatures, and to overcome the aforementioned challenges, a host molecule, β-cyclodextrin (β-CD), is often complexed with essential oils. Cyclodextrins comprise a family of cyclic oligosaccharides, consisting of a macrocyclic ring of glucose subunits joined by α-1,4-glycosidic linkage. β-CD (7 glucose units) has a lipophilic cavity to host the nonpolar molecules of essential oils (Aytac, Kusku, Durgun, & Uyar, 2016). Specifically, *Eucalyptus* essential oil is rich in hydrocarbons and oxygenated compounds that are reported to have broad spectrum antimicrobial effects. The major constituents of essential oil are 1,8-cineol, limonene, citronelal, isopulegol, citronellol, α- and β-pinene, cyclohexanol-5-methyl and *trans*-2-hexenal (Dias Antunes et al., 2017). The ultrafine fibers from zein-containing *Eucalyptus* essential oil/β-CD-IC was found to have promising antimicrobial effects for wide applications, such as food packaging (Fig. 4) (Dias Antunes et al., 2017). For instance, nanoemulsions containing *E. globulus* oil have been reported to possess antimicrobial and antibiofilm activities against the gram-negative bacterium commonly found in immunocompromised patients (*P. aeruginosa*) and the main responsible microorganisms for causing fungal infections worldwide (*C. albicans*) (Quatrin et al., 2017).

8. Health-promoting effects of *Eucalyptus*

8.1. Oral health

One of the most common uses of *Eucalyptus* is as a component of phenolic mouthrinses (Listerine®). Indeed, its effectiveness in the management of supragingival dental plaque and gingivitis has been widely established, compared to placebo and other mouthwashes. Over 24 studies have found an 18% and 25% mean reduction in gingivitis and plaque, respectively (J.C. Gunsolley, 2006; J. C. Gunsolley, 2010). Several studies have also assessed the efficacy of eucalyptus extract chewing gum in oral malodor and periodontal health. However, and despite the reported positive results, the amount of randomized controlled trials (RCTs) is small, and, thus, further studies are needed (Nagata et al., 2008; Tanaka et al., 2010).

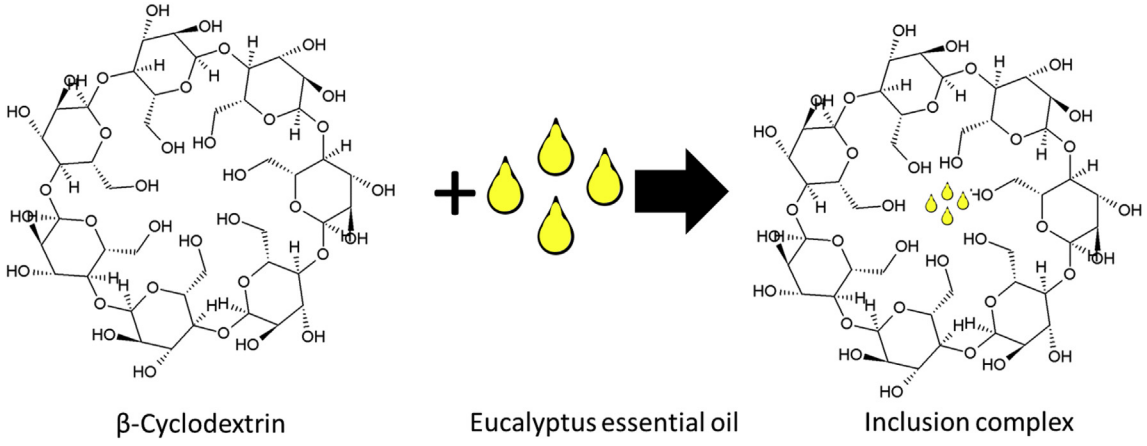

Fig. 4. *Eucalyptus* essential oil/β-cyclodextrin-inclusion complex (EEO/β-CD-IC).

8.2. Respiratory diseases

In the past 20 years, cineole capsules and Myrtol® standardized (GeloMyrtol®, GeloMyrtol forte®), a phytomedicine that includes cineole as one of its main components, have gained a huge attention due to its potential benefits in various respiratory conditions.

8.2.1. Sinusitis

8.2.1.1. Acute sinusitis. In a multicenter, randomized clinical trial, Myrtol® was found to alleviate uncomplicated sinusitis symptoms significantly, when compared to placebo. It has been also stated that antibiotics should not be considered as first-line treatment in this scenario. Anyway, similar results were obtained in an RCT that evaluated the efficacy and safety of cineole capsules (Federspil, Wulkow, & Zimmermann, 1997; Kehrl, Sonnemann, & Dethlefsen, 2004).

8.2.1.2. Chronic sinusitis. Myrtol® was evaluated in a multicenter, randomized, double-blind, placebo-controlled stuy for three months in search of radiological changes. After the follow-up period, the group under Myrtol® standardized treatment showed significant improvement in the computed tomography of the sinuses compared to the control group (De Mey & Riechelmann, 2008).

8.2.2. Bronchitis

8.2.2.1. Acute bronchitis. Two clinical trials assessed the efficacy and tolerability of Myrtol® compared to placebo, one of those compared it with cefuroxime or ambroxol in patients with acute bronchitis of recent onset. Myrtol® standardized and the other treatments were considered as safe as placebo, although significantly superior in terms of a more rapid and complete recovery (Matthys et al., 2000). Moreover, its efficacy was comparable to cefuroxime and ambroxol, making it a great alternative to antibiotic treatment, especially in patients without other respiratory illnesses, where bacterial infection is uncertain. Similar results are also observed in an RCT studying cineole capsules, where dyspnea, cough, secretions, and other symptoms were less frequent after four days after the first visit (Gillissen, Wittig, Ehmen, Krezdorn, & de Mey, 2013).

8.2.2.2. Chronic bronchitis. One RCT compared the efficacy and tolerability of Myrtol® standardized in the long-term treatment of patients with chronic bronchitis during winter-time. Compared to placebo, Myrtol® had significantly less acute exacerbations and shorter antibiotic regimens. Well-being and the overall therapeutic score was also higher for the treatment group (Meister, Wittig, Beuscher, & de Mey, 1999).

8.2.3. Chronic obstructive pulmonary disease (COPD)

A double-blind, multicenter, randomized control study assessed the efficacy of concomitant therapy with cineole for six months during the winter. Not only exacerbations decreased in both frequency and severity, but also dyspnea and overall quality of life. However, this study found no improvement in lung function. Other two randomized control studies have evaluated the role of Myrtol® as a supplemental treatment in COPD, compared to placebo. One study used Myrtol® and "Qi-invigorating", which is a Chinese tonic herb in the experimental group. Both studies found improvement in exacerbations, cough, sputum, and lung function parameters. However, the study with the Chinese herb did not allow authors to assess the Myrtol® activity, while the other had an insufficient sample size (Hua & Chang, 2013; Worth, Schacher, & Dethlefsen, 2009).

8.2.4. Asthma

A study evaluated the benefit of supplemental cineole therapy over six months. There was a statistical superiority in experimental group in the three following categories: lung function, symptoms, and quality of life (Worth & Dethlefsen, 2012).

8.3. Pre and postoperative management

A study conducted in Korea showed that the inhalation of cineole could help in reducing the preoperative anxiety, when compared to placebo, almond oil and eucalyptus oil (Kim, Seo, Min, Park, & Seol, 2014). As for postoperative pain, eucalyptus oil seemed to be more useful as an adjuvant pain therapy after total knee replacement surgery when compared to placebo (Jun et al., 2013). However, these studies are small and further research is still required.

8.4. Repellent

PMD, a repellent produced using lemon eucalyptus oil, is the only plant-based repellent approved by the CDC for use in malaria-endemic areas, as it has proven to be clinically useful for this disease (N. Hill, Lenglet, Arnéz, & Carneiro, 2007; Maia & Moore, 2011). In addition, lemon eucalyptus extract has shown potential benefits as repellent against tick bites (Gardulf, Wohlfart, & Gustafson, 2004).

9. Safety and adverse effects

As referred above, *Eucalyptus* genus has been widely used in traditional medicine over the world for centuries. Certainly, the most used remedy is its essential oil, with multiple applications due to its antibacterial, antiviral, antifungal, anti-inflammatory and insect-repellent properties (Higgins, Palmer, & Nixon, 2015); consequently, the most important concerns regarding this plant are linked to both safety and toxicity data.

The public perception of *Eucalyptus* essential oil as safe contrasts with the substantial risk, which arises whenever a pure essential oil is used. The most frequently observed adverse effect is the allergic contact dermatitis (ACD), due to the increasing use of this essential oil in cosmetic and personal hygiene products. Several publications reported ACD episodes after *Eucalyptus* essential oil application alone or in combination with other products. Recently, Higgins et al. (2015) retrospectively reviewed the patch-testing data at the Skin and Cancer Foundation over twenty years (1993-2013). Among the patch-tested patients, about the 7% was treated with 5% *Eucalyptus* essential oil conveyed in pet and only the 0.34% showed not well-established adverse effects (Higgins et al., 2015). These results are in accordance with the previous ones collected over 9 years (2000-2008) from the Information Network of Departments of Dermatology by Uter and coauthors, which showed a prevalence of 0.25% positive reactions after 2% *Eucalyptus* essential oil application (Uter et al., 2010). Furthermore, two prospective studies have shown that in fragrance-sensitive subjects, the onset of adverse effects is directly correlated with *Eucalyptus* essential oil exposure concentration, varying from 0.6% in subjects treated with 2% essential oil to 1.8% in subjects treated with 10% essential oil (Larsen et al., 2002; Wöhrl, Hemmer, Focke, Götz, & Jarisch, 2001). Moreover, several case reports related to adverse dermatological effects following occupational (florist and gardeners) or occasional exposure to *Eucalyptus* essential oil used in aromatherapy, in topical anti-inflammatory formulations or cross allergies with other essential oils with shared constituents such as tea tree oil, were reported (Higgins et al., 2015).

In light of these studies, it appears that, when applied topically, *Eucalyptus* essential oil is generally safe, although the use at non-standardized concentrations greatly limits the correct data interpretation and reproducibility. Furthermore, the adverse effects of *Eucalyptus* essential oil could also be underestimated compared to other essential oils due to its less commercial diffusion and use at lower concentrations (de Groot & Schmidt, 2015).

Regarding pure phytochemical constituents, the 1,8-cineole (eucalyptol), which represents 61.6–88.7% of *Eucaliptus* essential oil, is the

most investigated. Eucalyptol did not show genotoxicity or carcinogenicity, but it may be toxic to the reproductive system (Bhowal & Gopal, 2015). In addition, the subacute hepatotoxic and nephrotoxic effects in animal models have been observed after application of high doses, greater than the estimated LD_{50} of 2400 mg/kg b.w. In rats (Bhowal & Gopal, 2015). Eucalyptol has also a good pharmacokinetic profile, being easily absorbed orally, through the mucous membranes and topically, reaching the plasma peak, depending on the route of administration, within 1–3 h. In light of this, the use of concentrated extract or undiluted essential oil is not recommended (Dey & Mitra, 2013). The most frequent, and sometimes severe, side effects observed following its oral administration include other than the above mentioned allergic skin reactions, shock, tremor, ataxia, aphasia, vomiting, dizziness, diarrhea and epigastric pain. Because of its antinociceptive properties, which exert potential calmative and depressant action on the central nervous system, the co-administration with anti-depressant drugs should be avoided. The estimated lethal dose of Eucalyptol in humans ranged from 0.05 to 0.5 ml/kg, but due to the few safety data available on humans, its use during pregnancy and lactation is not recommended (Bhowal & Gopal, 2015; Dey & Mitra, 2013).

In short, the toxicological studies available so far are limited and inadequate to estimate an acceptable daily intake. Furthermore, it is necessary to underline that, even if eucalyptol was effectively responsible for the acute toxicity showed by *Eucalyptus* essential oil, the estimated daily intake of eucalyptol would be much lower than lethal dose. However, for an in-deep risk assessment, further exposure and toxicity data would be needed.

10. Conclusions and upcoming perspectives

For long time, *Eucalyptus* genus has been used in traditional medicine. Indeed, *Eucalyptus* plants possesses a broad spectrum of biological effects, such as antibacterial, antiseptic, antioxidant, anti-inflammatory, anticancer activities. Eucalyptol (1,8-cineole) is the mainly responsible component for the *Eucalyptus* oils medicinal value.

Anyway, considering the previously reported uses of *Eucalyptus* essential oils and extracts, there is still urgently required further *in vivo* studies using the various *Eucalyptus* constituents to reveal the secrets beyond its traditional uses in the treatment of a wide spectrum of ailments.

In the last years, a great attention has been given to its nanotechnological applications in the field of food and pharmaceutical industries. The application of essential oils nonoemultion, particulary of *Eucalyptus* essential oil in nanotechnology has great future perspectives. Indeed, nanoemulsions containing *E. globulus* oil has been widely recognized for its antimicrobial and antibiofilm effects both against gram-negative and gram-positive bacteria and even against the main responsible microorganisms for causing fungal infections worldwide (*C. albicans*).

Nonetheless, the public perception of *Eucalyptus* essential oil as a safe product contrasts with the substantial risk, which arises whenever a pure essential oil is used. Allergic contact dermatitis is the most frequently observed adverse effect, associated with an increasing use of *Eucalyptus* essential oil in cosmetic and personal hygiene products, although others may be also stated, specially when used at hig concentrations. Thus, regarding safety, a more in-depth risk assessment of *Eucalyptus* essential oil toxicity is needed.

Conflicts of interest

The authors declare no conflict of interests.

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