Botanical, Phytochemicals and Anti-cancer Properties of the *Eucalyptus* Species

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Abstract

The genus *Eucalyptus* (Myrtaceae) is native to Australia, however some species now distributed globally. *Eucalyptus* has been used in indigenous Australian medicines for the treatment of a range of aliments including colds, flu, fever, muscular aches, sores, internal pains, and inflammation. *Eucalyptus* oils containing volatile compounds have been widely used in the pharmaceutical and cosmetics industries for a multitude of purposes. In addition, *Eucalyptus* extracts containing non-volatile compounds are also an important source of key bioactive compounds, and several studies have linked *Eucalyptus* extracts with anti-cancer properties. With the increasing research interest in *Eucalyptus* and its health properties, this paper briefly outlines the botanical features of *Eucalyptus*, discusses the traditional use of *Eucalyptus* as medicines and comprehensively reviews its phytochemical and anti-cancer properties, and finally proposes the trend for future studies

Keywords: *Eucalyptus*, Myrtaceae, phytochemicals, anti-cancer.

Contents

1. Introduction. - The genus *Eucalyptus* belongs to Myrtaceae family (Figure 1) is an Australian native tree that is now distributed around the world [1]. Approximately 800 species of *Eucalyptus* have been identified. Within Australia, *Eucalyptus* is mainly cultivated for timber and paper production [1, 2]. Different parts of the plant such as leaves, bark and stems have been used to produce essential oils, which contain a variety of volatile compounds that have been widely utilised in the pharmaceutical and cosmetics industries [1]. Numerous non-volatile compounds including triterpenoids, flavonoids and tannins have also been identified [3] which are associated with a range of health benefits including cancer prevention [4, 5]

Eucalyptus is used in a numerous herbal preparations to treat a range of ailments including colds, flu, fever, aching, sore, internal pain, and inflammation [3, 6]. The effectiveness of these formulations has however, yet to be supported by experimental or clinical data. The widespread use of *Eucalyptus* within indigenous communities does however suggest the presence of key bioactive compounds with the potential to impart health benefits. While *Eucalyptus* is known to be a rich resource of antioxidants such as flavonoids, phloroglucinol derivatives, and tannins [3], studies to date have identified only a limited number of bioactive compounds.

Cancer remains a burdensome disease for many countries around the world, particularly in first world economies, where ageing populations dominate the population profile. Despite some success, the development of effective therapeutic agents remains elusive for many forms of cancer [7].

In the last 30 years, approximately 45% of all new anticancer drugs have been derived directly or indirectly from plant-based natural products [8]. While computer aided drug design has made significant inroads as a tool in drug discovery, the screening of plant extracts remains a useful and effective strategy for development of new,

effective anti-cancer therapies [9].

Preliminary studies on the extracts of several *Eucalyptus* species such as *globulus, camaldulensis, citriodora, maiden and torquate* have identified anti-cancer activity against a range of cancers cell lines both *in vitro* and *in vivo*. These studies comprise only a tiny fraction of the more than 750 identified *Eucalyptus* species, thus there is enormous untapped potential for the discovery of new anti-cancer compounds from these plants. In this review, we briefly describe *Eucalyptus*, highlight the traditional medicinal uses of *Eucalyptus* to emphasise their potential as herbal therapies. We also discuss the bioactive compounds identified from *Eucalyptus* to date and summarise the techniques associated with the extraction and isolation of *Eucalyptus* phytochemicals and suggest possibilities for yield improvement. Finally, we review links between *Eucalyptus* extracts and anti-cancer activity and propose the directions for future studies.

2. Botany. - The natural distribution of the genus *Eucalyptus* (Myrtaceae) is predominantly confined to the Southern Hemisphere, ranging from 9°N to 44°S in latitude [10]. The genus includes more than 660 species, the majority of which are endemic to Australia, with a small number of species found in the neighbouring South East Asian countries such as Indonesia, the Philippines, Timor and Papua New Guinea [10, 11]. *Eucalyptus* species possess diverse physical structure, occurring as trees, mallees (i.e. multi-stemmed dwarf form) or shrubs. Individuals of some species can reach 400-500 years in age [10].

The distribution and dominance of *Eucalyptus* within Australia means the genus is of great ecological importance, providing essential food and habitat resources for a diverse range of fauna. Within Australia, *Eucalyptus* dominate the natural forests and

woodlands of non-arid climates, but are notably absent from rainforests [12]. The mallee form covers vast areas in the drier regions to of southern Australia, but *Eucalyptus* is largely absent from the arid inland zones of the continent [12]. The genus is economically important, providing hardwood timber, nectar resources for honey, shelter in pastoral regions, fuel and essential oils [12].

The genus *Eucalyptus* was named in 1788 by the French botanist, Charles-Louis L'Héritier de Brutelle [12]. *Eucalyptus* means 'well covered' and refers to the operculum (or calyptra) - a distinguishing characteristic of the genus that completely covers and protects the many stamens and single style of eucalyptus flowers in bud [13].

Although hybridisation of reproductively compatible *Eucalyptus* species is relatively restricted (occurring in 15% of geographically adjacent pairs), the resulting intermediate forms can make species identification difficult [13]. The genus has a long and controversial taxonomic history [11, 12], with some species remaining undescribed [13]. There is general agreement about what constitutes the group broadly known as 'eucalypts', but there is controversy around different generic level classifications and especially the recognition of the genus *Corymbia* [11].

Eucalypts have been traditionally classified into one of two genera: *Angophora* Cav. and *Eucalyptus* L'Her. [13]. The debate over the reclassification of a group of *Eucalyptus* species, colloquially known as ghost-gums and bloodwoods, to the genus *Corymbia* is well documented [10, 14]. However, a number of molecular studies now provide convincing evidence to support both *Angophora* and *Corymbia* being recognised as separate genera [11].

The genus *Angophora* consists of nine species, all confined to mainland eastern Australia [11]. There are 113 species of *Corymbia* (K.D. Hill & L.A.S. Johnson), all of

which occur in either Australia or New Guinea [11]. Four other small genera of rainforest trees are also included in the eucalypt group [11], but are only represented by one or two species.

The practical implications for phytochemical research is that different interpretations of *Eucalyptus* taxonomy may result in the names of *Corymbia* and *Eucalyptus* being inconsistently applied in the literature leading to confusion amongst researchers and scholars. Further, it is important to note that the close evolutionary relationship between the sister eucalypt taxa of *Angophora*, *Corymbia* and *Eucalyptus* means they most likely a similar phytochemical profile.

3. Ethnopharmacology. - In Australia and some other parts of the world, *Eucalyptus* has historically been used to treat a variety of ailments. Although, there is no strong scientific evidence to elucidate the mechanism of action in many of these cases, many treatments are still considered to be effective, finding favour to the present, suggesting that *Eucalyptus* may contain health-promoting bioactives.

There is no information in the current literature highlighting the use *Eucalyptus* extracts as a traditional cancer treatment. However, the use of extracts to treat a range of ailments does suggest clinical potential and is further supported by recent *in vitro* and *in vivo* research findings.

3.1 Flu, colds and fever. *Eucalyptus* leaves and inner bark are traditionally brewed in water and the decoctions used as a wash to treat colds, flu and fever. Small amounts of decoction can also be ingested to further aid treatment [15, 16]. Smoke generated by placing red or young *Eucalyptus* leaves in a pit over hot coals is also used to relieve cold, flu and fever. The user stands, sits or leans over the smoke source inhaling the

smoke. This treatment is considered to be a very effective and is still commonly used today in lieu of western medicines [6].

3.2 Aching, sore, internal pain and headache. *Eucalyptus* extracts from leaves, stem and bark have been traditionally employed to alleviate aching, internal pain, headache. The strained liquids are also used as an antiseptic wash to sterilize sores, cuts and any skin infections [15]. Extracts are also used as a warm body wash to relieve internal pain associated with influenza, fever or rheumatism and to reduce the effects of chronic joint pain of the hips, knees, and ankles. It is also effective for relieving chest pain [6]. The strained liquid from leaves can also be taken internally in small quantity to alleviate nasal congestion and headache [15].

Juice extracted directly from freshly crushed young *Eucalyptus* leaves can be applied directly to infected skin to heal the sores and cuts [15]. In addition, an astringent viscous exudate (resin) known as *Eucalyptus* kino found on the trunk and branches of many *Eucalyptus* trees after pathological or mechanical wounding of the wood is also used for treatment of sores and cuts. Kino can be applied directly onto infected skin lesions and rubbed gently, or dissolved in cold or hot water and used as a wash on cuts and open sores. A fine powder of ground, crystalline kino can also applied directly to open sores as a healing agent [17].

3.3 Toothache and oral infection. *Eucalyptus* has been used as a traditional treatment for toothache and oral infection. An aqueous extract prepared by infusing fresh inner bark stripped from trees is commonly used as a mouthwash for mouth sores and tongue inflammation [6]. Solutions prepared by mixing ground kino and water have also been utilised as a general tonic for rinsing the mouth to alleviate the symptoms of toothache.

Kino can also plugged directly into a tooth cavity to act as an analgesic [18], or is used as tooth cleanser [17].

***3.4 Childbirth*.** A number of indigenous communities in Australia employ *Eucalyptus* leaves as a relaxant during childbirth, with fresh-cut leaves and stems placed on a bed of hot coals. The smoke and vapours released in this process are then inhaled by the mother and newborn [6].

Extracts from freshly macerated leaves were then rubbed over the mother's breasts to stimulate milk release. The liquid was also fed to the newborn to treat thrush of the mouth when required [6].

***3.5 Other ailments*.** Eucalyptus leaves can be used to relieve the symptoms of chest and respiratory tract infection by inhaling the vapours from an infusion of freshly picked leaves dispersed in boiling water [19]. Leaves have also been used to alleviate joint and muscle pain by heating them over a small flame, then holding them in contact with the affected body part [15].

Kino mixed with campfire ash is documented as being applied to wounds during male initiation ceremonies to accentuate decorative scarring on the chest and arms. Small amounts of the resin boiled in water have also been used to relieve eye soreness by and then splashing the resulting infusion around the eyes [6, 18].

4. Phytochemicals: volatile and non-volatile compounds in *Eucalyptus*

4.1 Volatile compounds in Eucalyptus. *Eucalyptus* contains high levels of volatile organic compounds (VOC), which comprise its essential oil profile. Both the bark and leaves of *Eucalyptus* have been utilised for extracting essential oil by steam distillation. The oil contains various VOC, many of which possess antiseptic properties, making it

a valuable element in both perfumery and medicinal preparations [1]. The major component found in *Eucalyptus* oil is the monoterpene ether 1,8-cineole (**1**) (otherwise known as eucalyptol), (Figure 2), which accounts for more than 70 per cent of oil mass and accounts for its camphor like smell. It has been widely applied in the pharmacopoeias of many countries, such as Britain, France, Germany, Belgium, Netherlands, USA, Australia, Japan and China [1]. 1,8-cineole's biological activity is linked to anti-bacterial, anti-inflammatory and anti-cancer effects [20].

Other principal constituents present in *Eucalyptus* oil (Figure 2) include limonene (**2**) and (+) - α-terpineol (**3**), which are derived from the menth-1-en-8-yl cation, the same biogenetic precursor from which cineole is derived [21].

The VOC present in *Eucalyptus* oil have been extensively profiled using gas chromatography (GC) gas chromatography-mass spectrometry (GC-MS). GC-MS is a more convenient and useful analytical tool, as individual compounds separated on the GC column can be immediately identified by comparing the resulting MS spectrum against an *in silico* reference library [21].

Extraction yields of essential oils and VOC - especially 1,8-cineole is dependent upon the eucalypt source, with oil content varying widely by species. E. *bakeri, E. kochii, E. camaldulensis, E. sparsa* and *E. polybractea* have higher levels of essential oil than that of *E. globulus, E. sturgissiana and E. smithii*. Within species, 1,8-cineole levels were shown to be present in lower concentration in *E. globulus* relative to *E. polybractea* and some other species. Somewhat paradoxically however, *E. globulus* is recognised as a major source of 1,8-cineole because of its worldwide availability for use in wood and for pulp production [21]. Other VOC such as α-terpineol (**3**), D-piperitone (**4**) and cuminal (**5**) (Figure 2) also vary in concentration between *Eucalypt* species [22].

Harvesting time, seasonal factors (sunlight, temperature) and habitat conditions (water availability, nutrient levels) all affect oil composition and yield [23, 24]. For example, the *Eucalyptus* species grown in Western Australia contain higher concentrations of VOC than similar species growing in Eastern Australia [25]. Oil extracted from *E. camaldulensis* trees grown in Kenya contain higher concentrations of 1,8-cineole compared with plants of the same species growing in Ethiopia. In contrast, the Ethiopian plantations are reported to contain high levels of the terpene derivatives p-cymene (**6**) and cryptone (**7**) (Figure 2) [26].

As with the extraction of oils from other plants, extraction yields of *Eucalyptus* oil and VOC is affected by variables such as extraction temperature, time, agitation rates, solvent to sample ratios and the physicochemical properties of the extraction solvent [27]. Steam distillation is the primary commercial extraction method for obtaining *Eucalyptus* essential oils [28]. Other methods utilised include hydro-distillation, solvent extraction, soxhlet extraction and thermal desorption [29, 30]. However, these methods are generally considered to be low yielding, more time consuming and resulting in the production of an inferior quality product, due to the degradation of key components, including unsaturated hydrocarbons and esters. More recently, research has explored the use of more passive technologies such as supercritical fluid extraction (SFE), microwave assisted extraction (MAE) and ultrasonic assisted extraction (UAE) in the hope of improving the quality and quantity of oil recovered. These protocols however require high capital outlay in comparison to steam distillation and are often limited in the quantity of material that they can process in a single event [29, 31].

Eucalyptus VOC not only contribute to fragrance, but also exhibit pharmaceutical properties such as stimulation of the mucous-secreting cells in the nose, throat and lungs

and antiseptic effects [32]. As a consequence, *Eucalyptus* oil is utilised in numerous commercial preparations, encompassing multi-purpose applications including insect repellents, aromatherapy, personal hygiene products, oral health care, cleaning products, and medicines [32]. It is therefore important to consider all factors, affecting the extraction yield of essential oil and VOC and their impact on quantity, quality and cost-effectiveness in producing oil for commercial purposes.

4.2 Non-volatile compounds in Eucalyptus. Phenolic compounds have been reported as the major non-volatile compounds in *Eucalyptus* and they have been found as a major contributor to antioxidant activities of *Eucalyptus* extracts (Table 1). Total Phenolic Content (TPC) is a commonly estimated using Folin–Ciocalteu reagent assay, while general antioxidant capacity (encompassing a broader range of antioxidant compounds) is estimated using a range of chemical techniques including DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging assay, ABTS (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) assay, FRAP (Ferric reducing ability of plasma) assay, deoxyribose assay and superoxide anion scavenging assay [33]. Phenolic compounds have been reported to be abundant in *Eucalyptus* extracts, comprising approximately 39 % of extracts prepared from *E. gomphocephala* leaf [33] and 31 % of the extract prepared from *E. globulus* leaf [34]. *Eucalyptus* extracts therefore represent a potentially important source of phenolics for value adding to food and pharmaceutical products.

More than 20 individual non-volatile compounds have been isolated from various *Eucalyptus* species (Table 2) using GC and HPLC, either alone, or in combination with an auxiliary spectroscopic technique such as mass spectrometry (MS) or nuclear magnetic resonance spectroscopy (NMR). Phenolic compounds shown in Figure 2 such as phenolic acids: gallic acid (**8**), protocatechuic acid (**9**), ellagic acid (**10**), ellagic acid

have been isolated from *Eucalyptus* extracts [33, 35], together with other phenolic compounds such as quercetin (**11**), quercetin glycoside (**12**), naringenin (**13**), catechin (**14**), epicatechin (**15**), rutin (**16**), quercitrin (**17**), apigenin (**18**), and myricetin (**19**) [33, 35]. Monoterpenes, cyanogenic glycosides, and the triterpene cladocalol have also been identified [2].

Many of these compounds are associated with health benefits including strengthening of the immune system, reducing the risk of diabetes, obesity, and cardiovascular disease [36-39].

Links between *Eucalyptus* bioactives and anti-cancer activity have been reported (Table 3), however the number of studies undertaken to date is limited. This fact, together with the relatively small number of phytochemical studies undertaken on eucalypt species suggests that untapped potential remains for the further characterization bioactive compounds from this plant species.

Extraction efficiency of bioactive compounds from source materials can be influenced by a variety of factors including plant species, growing location, seasonality, sample preparation method and extraction conditions [40]. As with the extraction of essential oils from *Eucalyptus*, both conventional and advanced techniques have been applied to capture bioactive compounds from *Eucalyptus* (Table 2). Advanced extraction techniques SFE, MAE and UAE have all proven effective in extracting high levels of bioactives [41-44]. Information on the effect of the aforementioned variables on bioactive yield remains limited and requires further study. Optimisation of preparation methods including drying techniques and drying times, storage methods and sample preparation techniques needs to be fully investigated to establish quality control parameters for the efficient extraction of bioactives.

5. Anti-cancer activities of Eucalyptus extracts. - Limited information has been published on the link between the *Eucalyptus* oils or extracts and cancer in human clinical trials, however, numerous *in vitro* and several *in vivo* studies have been conducted to assess the anti-cancer activity properties of extracts taken from different plant parts of *Eucalyptus* (Table 4). Anti-proliferative and cytotoxic studies Eucalyptus oils and extracts have been undertaken, revealing positive effects against several cancer cell lines. Essential oils extracted from *E. globulus, E. torquata, E. sideroxylon* and *E. benthamii* have been shown to inhibit the nuclear translocation of NF-kappa B induced by LPS in leukemic monotype THP-1 cells. These same extracts also exhibit cytotoxic effects on human breast adenocarcinoma cell line (MCF7), Jurkat (J774A.1), and HeLa cell lines [45-47]. The level of cytotoxic activity differed depending the part of the plant from which the extract was sourced [45]. Therefore, examination of extracts from all parts of *Eucalyptus* plants is necessary to effectively screen for bioactive compounds.

Both aqueous and organic solvent crude extracts from different *Eucalyptus* species have been reported to exhibit cytotoxic and anti-proliferative effects *in vitro*. Extracts from *E. citriodora, E. globulus*, *E. maiden* and *E. camaldulensis* were found to inhibit growth of colon (SW-620, SW480), liver (HEP-2), ovary (OVCAR-5, A2780), prostate (PC-3), cervix (HeLa), neuroblastoma (IMR-32), lung (HOP-62, A-549), breast (MCF7, MDA-MB-231), and gastric (BGC-823, KE-97) [27, 48, 49]. Crude extracts from *E. citriodora* was also shown to supress the growth of Ehrlich ascites carcinoma [27]. It is of interest to note that cytotoxic and anti-proliferative effects of the extracts also varied according to both the extraction method and extracting solvent used. For example, ethyl acetate extract was found to exhibit higher inhibition on cancer cell lines than other organic solvents such as methanol, ethanol [27]. Differences in inhibition can be explained by relative compatibilities between the

solvent and bioactive compound physicochemical properties. Optimisation of extraction conditions (including sequential extraction using solvents of varying polarity) is important to ensure compete capture of potential bioactives.

Several individual volatile compounds such as 1,8-cineole, α-pinene, terpinen-4-ol, and γ-terpinene have been isolated and tested against several cancer cell lines, showing favourable results in studies [20, 46]. In addition, several non-volatile compounds such as euglobal-G1 from *E. grandis*, and resveratrol, piceatannol and macrocapal G from *E. maiden* have been shown to inhibit the growth of several cancer cell lines *in vitro* [4, 5]. Other non-volatiles such as cypellocarpins and chromene glucoside (isolated from E. cypellocarp) were found to reduce the tumor growth *in vivo* [50].

To fully explore *Eucalyptus* for potential health benefits (especially for anti-cancer properties), a clear pathway for future research is required. Future studies need to screen key volatile and non-volatile compounds from various *Eucalyptus* species and then develop the optimum extraction and isolation conditions to prepare the crude extracts with high bioactive compounds. To achieve maximum efficiency, the crude extracts must be tested for their anti-cancer properties in order to formally identify the most potent extracts, which can then be purified to isolate and identify individual compounds and to elucidate their anti-cancer mechanisms. These compounds will then serve as the starting point for synthetic studies to develop analogues exhibiting greater potency and specificity as therapeutic agents.

6. Conclusions. - The available data from literature has revealed that although studies limited on several *Eucalyptus* species, preliminary results indicated that the genus *Eucalyptus* is an abundant source of phytochemicals, which possessed potent antioxidant capacity and exhibited anti-proliferative and cytotoxic effects against

different types of cancers. With numerous species have yet been studied, the opportunities for investigation of the key bioactive components for anti-cancer are enormous. Future studies are needed to screen, extract, purify and identify the key bioactive compounds from the most potential genus *Eucalyptus*, and then tested their anti-cancer properties *in vitro*, *in vivo* and clinical trails to develop novel therapeutic agents for prevention and/or treatment of cancers.

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Figure Legends

Figure 1. Selected common *Eucalyptus* species.

Figure 2. Chemical structures of major volatile and non-volatile compounds.

Figure 1. Selected common *Eucalyptus* species.

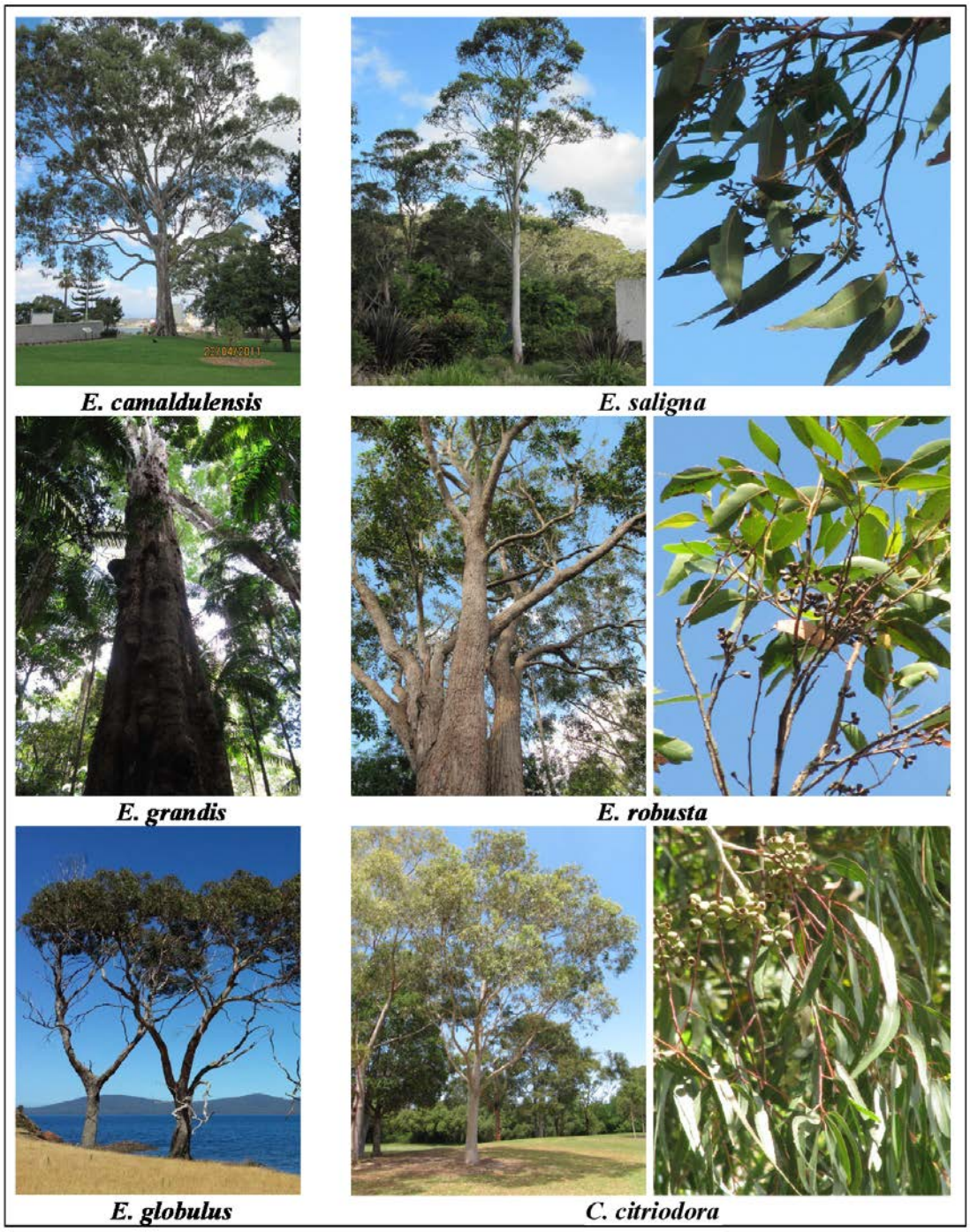

Figure 2. Chemical structures of volatile and non-volatile compounds.

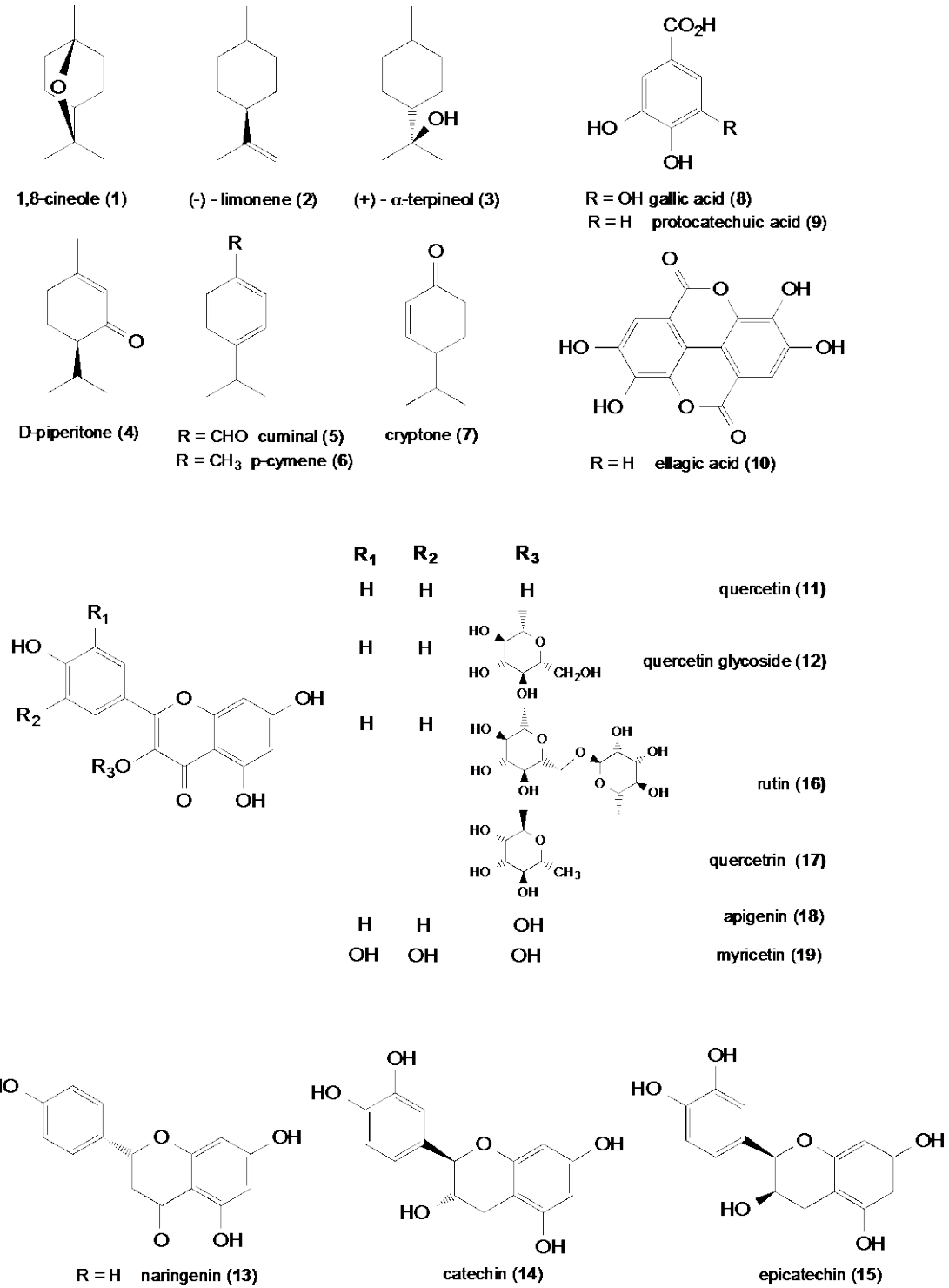

Table 1. Phenolic content and antioxidant properties of Eucalyptus

Plant name/ parts used	Extraction conditions	Phenolic compounds (mg GAE/ g)	Antioxidant capacity	References
E. globulus/ bark	EtOH:H_2O (50:50 v/v)	22.30	FRAP: 2146 nmol AAE/mg	[51]
E. robusta/ fruit	Tetrahydrofuran, then methanol:acetic acid:water (50:3.7:46.3, v/v)	54.80	FRAP: 502 µmol Fe(II)/g	[52]
E. globulus/ bark	52% ethanol, 264 min, 82.5°C	30.40	FRAP: 2.16 mmol AAE/g	[48]
E. globulus/ bark	Water, 60min, 100°C	25.8	0.119 mmol AAE/g	[35]
E. globulus/ leaf	Water, 10 minutes, 40°C	311.0*	DPPH IC50 (µg/mL): 12.0	[34]
E. gomphocephala/ leaf	70% aqueous acetone	389.05*	DPPH IC50 (µg/mL): 15.42	[33]
E. globulus/ bark	SFE: (70 °C, 20% ethanol, 10 g of CO_2/ min)	57.22	49.74 mg AAE/ g	[44]
E. camaldulensis/ leaf	MAE: (50% EtOH, 20:1mL/g, 5min, 600W)	77	ND	[43]
	UAE: (50% EtOH, 20:1mL/g, 30-40 ºC, 1h)	82	ND	
	CE: (50% EtOH, 20:1mL/g, 25 ºC, 24h)	82	ND	

ND: Not detection; AAE, ascorbic acid equivalent; GAE, gallic acid equivalent. (*) mg per g of dried extract; EtOH: Ethanol.
SFE: Supercritical fluid extraction; MAE: Microwave assisted extraction; UAE: Ultrasound-assisted extraction; CE: Conventional extraction.

Table 2. Extraction and identification of non-volatile compounds derived from *Eucalyptus*.

Plant name/ parts used	Extraction methods	Determination methods	Volatile and non-volatile compounds	References
E. globulus/ bark	SFE: (70 °C, 20% ethanol, and 10 g of CO_2 /min)	HPLC–UV	Gallic acid, protocatechuic acid, ellagic acid, quercetin, and naringenin	[44]
E. globulus/ bark	SFE: (160 bar, 40 °C, 8% ethanol). Soxhlet extraction with dichloromethane	GC-MS	β-sitosterol, β-amyrin, betulonic acid, oleanolic acid, betulinic acid, ursolic acid, 3-acetyloleanolic acid, 3-acetylursolic acid	[53]
E. globulus/fruit	95% EtOH	^{1}H NMR spectrum	Eucalyptals D and E	[54]
E. globulus/ bark	52% EtOH, 264 min, 82.5°C	GC-MS	Galacturonic acid, 4-O-methylglucuronic acid, gallic acid	[55]
E. globulus/ bark	Water, 60min, 100°C	HPLC	Catechin, epicatechin, ellagic acid, quercetin-3-o-rhamnoside, isorhamnetin	[35]
E. globulus/ leaf	Water, 10 minutes, 40°C	HPLC	Chlorogenic acid, flavonol glycoside, rutin, ellagic acid, quercitrin	[34]
E. globulus/ leaf	MAE: (60 sec, 1000W, 10:1mL/g)	GC	Cineole, α-pinene, camphene, cymene, limonene and γ - terpinene	[56]
E. gomphocephala/ leaf	70% aqueous acetone	LC–PDA–ESI/MS/MS	Chlorogenic acid, cypellocarpin B, ellagic acid hexoside, apigenin glucuronide, gallic acid, globuluside, myricetin hexoside, quercetin hexoside, galloyl cypellocarpin B, quercetin glycoside, catechin or epicatechin.	[33]
E. camaldulensis/ fruit	Direct thermal desorption	GC-MS	Aromadendrene, eucalyptol, gamma-gurjunene, terpinolen, spathulenol, alpha-pinene, ledene, and longifonene.	[57]

E. citriodora/ leaf	Steam distillation and solvent-ether extraction	GC-MS	Citronellal, citronellol, citronellyl acetate, cis-p-Menthane-3, 8-diol and trans-p-menthane-3, 8-diol.	[58]
E. citriodora/ leaf	Microwave-assisted headspace solid-phase microextraction	GC-FID and GC-MS	Polydimethylsiloxane, polydimethylsiloxane, and carboxen/polydimethylsiloxane.	[59]
E. citriodora/ leaf	Hydrodistillation.	GC-MS	Citronellal, isopulegol and 3,8-terpinolhydrat, citronellol, citronellic Acid.	[60]
E. citriodora/ leaf	Hydrodistillation and SFE	GC-MS	Citronellal and citronellol, isopulegol, α-terpinene, neoisopulegol, p-mentha-1(7),8-diene, 3,8-p-menthadiene, sabinene, α-phellandrene.	[61]
E. dunnii, *E. citriodora*, and *E. saligna*/ leaf	Headspace solid-phase microextraction (HS-SPME)	GC-ITMS	(E)-4,8-dimethyl-1,3,7-nonatriene (DMNT), (E,E)-4,8,12-trimethyl-1,3,7,11-tridecatetraene (TMNT), (E,E)-alpha-farnesene, (E,E,E)-3,7,11,15-tetramethyl-1,3,6,10,14-hexadecapentaene (TMHP), beta-caryophyllene, alpha-humulene, germacrene D, and beta-cubebene.	[62]
E. dunnii, *E. citriodora*, and *E. saligna*/ leaf	Headspace solid-phase microextraction (HS-SPME)	GC-ITMS	The biogenic volatile organic compounds (BVOC): (E)-β-Ocimene, β –Caryophyllene, α -pinene, p-cymene, limonene, 1,8-cineole, campholenal, α-terpineol, γ-terpinene, campholenal, α-terpineol, trans-carveol, rose oxide.	[63]
E. jensenii/ leaf	Acetone	RP-HPLC	Quercetin 3-O-b-D-glucopyranoside, sideroxylin, 4-O-demethyl miniatone, grandinol, jensenone, miniatone, euglobal G1, G2, G3 and G4.	[64]
E. hybrid/ leaf	MAE with organic solvents	HPTLC	Gallic acid	[65]

E. hybrida Maiden/ leaf	MAE with organic solvents	HPLC	Ursolic acid (UA)	[41]
E. spathulata, E. salubris, E. brockwayii and *E. dundasii/* leaf	Steam-distillation: Aqueous volatile fractions (AVFs)	GC-MS	1,8-cineole, pinocarvone, *trans*-pinocarveol, *alpha*-terpineol, globulol and isomenthol.	[66]
E. cinerea and *E. camaldulensis*/ leaf	Hydrodistillation and SFE	GC-MS	1,8-cineole, p-menth-1-en-8-ol, terpinen-4-ol, and alpha-pinene, 8,14- cedranoxide, terpinene-4-ol, p-cymene, limonene, myrtanal and caryophyllene alcohol.	[67]
E. camaldulensis/ leaf	SFE	HPLC	Gallic, ellagic acid, 5-hydroxy-7,4'-dimethoxy flavone and 5-hydroxy-7,4'-dimethoxy-8-methyl flavone	[68]
E. camaldulensis and *E. radiate*/ leaf	Hydrodistillation and SFE	GC-MS	1,8-cineole, alpha-pinene, beta-pinene, p-cymene, terpinen-4-ol, R-terpineol and globulol.	[69]

SFE: Supercritical fluid extraction; MAE: Microwave assisted extraction; UAE: Ultrasound-assisted extraction
Note: the currently accepted name of *Eucalyptus citriodora* is *Corymbia citriodora*

Table 3. Selected bioactive compounds identified in *Eucalyptus* and their link with anti-cancer activities.

Compounds identified	Anti-cancer activities and/ or mechanism of action of pure compounds	References
Globulusin A and Eucaglobulin	Concentration-dependent suppression of inflammatory cytokine production, tumor-necrosis factor-α and interleukin-1β in cultured human myeloma THP-1 cells co-stimulated with phorbol myristate acetate. Inhibition of melanogenesis in cultured murine melanoma B16F1 cells, without any significant cytotoxicity.	[2]
Euglobal III, Ib, IIa, Ic, Ia1 and Ia2.	Euglobal III exhibited a strong antitumor-promoting activity *in vitro* on 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced Epstein-Barr virus early antigen (EBV-EA) followed by euglobals Ib, IIa, Ic, Ia1 and Ia2.	[70]
Euglobals -G1--G5, -Am-2 and -III	Euglobal-G1--G5, -Am-2 and -III exhibited significant inhibitory effects on Epstein-Barr virus (EBV) activation induced by the tumor promoter, 12-O-tetradecanoylphorbol-13-acetate (TPA). Euglobal-G1 and –III also exhibited strong inhibition on the effect of the cell cycle induced by TPA. In addition, these two compounds showed remarkable anti-tumor-promoting effects on mouse skin tumor promotion in an *in vivo* two-stage carcinogenesis test.	[71]
Euglobal -1	EG-1 exhibited the remarkable 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. Further, EG-1 exhibited potent anti-tumor-promoting activity on two-stage carcinogenesis test of mouse pulmonary tumor using 4-nitroquinoline-N-oxide (4-NQO) as an initiator and glycerol as a promoter.	[4]
Apigenin	Inhibition of a glycogen synthatase kinase 3β (GSK-3β). This leads to decreased cancer cell proliferation and survival by abrogating nuclear factor κB (NFκB) activity and hence it suppresses the growth of pancreatic tumors.	[72]
3b-acetoxy-urs-11,13(18)-dien-28-oic acid; 3b-hydroxy-urs-11-en-28,13b-olide; 3b-	All the tested triterpenoids showed moderate activity (IC50 9.5-38.5 mg/mL) against A2780 human ovarian cancer cell lines and ursolic and oleanolic acids exhibited the highest activity with IC50 value of 9.5 and 10.7 mg/mL, respectively.	[73]

acetoxy-urs-11-en-28,13b-olide; 3-acetylbetulinic acid; Oleanolic acid; Ursolic acid and b-amyrin acetate		
Cladocalol and its derivatives	These three tested compounds exhibited cytotoxic activities on human tumor cell line HL-60 as revealed by the MTT assay.	[74]
28-nor-urs-12-ene-3b, 17b-diol and 28-nor-urs-12-ene-3b, 17b-diol		
Terpinen-4-ol	This compound exhibited a cytotoxic effect against Jurkat J774A.1 cell line similar to that observed for volatile oils.	[46]
Cypellocarpins A, B, and C; Chromene; and glucoside	These compound exhibited potent *in vitro* antitumor-promoting activity in a short-term bioassay evaluating the inhibitory effect on Epstein-Barr virus early antigen activation induced by 12-O-tetradecanoyl phorbol 13-acetate (TPA). These compounds also suppressed an in vivo two-stage carcinogenesis induced with nitric oxide and TPA on mouse skin.	[50]

Table 4. Anti-cancer activities of oils and extracts from *Eucalyptus*.

Plant name/ parts used	Type of extracts	Cell lines in vitro/ Administration in vivo	Effects and/or related mechanisms	References
E. citriodora/ leaf	Organic solvent and water crude extracts	In vitro: Colon (SW-620); liver (HEP-2), ovary (OVCAR-5), prostate (PC-3), Cervix (HeLa), Neuroblastoma (IMR-32), and lung (HOP-62). In vivo: Ehrlich ascites carcinoma	Growth inhibition and suppression	[27]
E. globulus/ bark	Ethanol crude extract	Breast cancer cell line (MDAMB-231)	Anti-proliferative effects	[48]
E. globulus/ fruit	Aromadendrene, cadinene, and a spirosesquiterpene	Human BGC-823 and KE-97 gastric, Huh-7 hepatocarcinoma, and Jurkat T lymphoma cancer cell lines	Cytotoxic effects	[54]
E. globulus/ leaf	Essential oil	Leukemic monocyte THP-1 cells	Inhibition of nuclear translocation of NF-kappa B induced by LPS in THP-1 cells	[75]
E. maiden/branches	Resveratrol, piceatannol, gallic acid, and macrocapal G	Breast cancer (MCH-7), hepatocellular carcinoma (SMMC-7721), human myeloid heukemia (HL-60), colon cancer (SW480), and lung cancer (A-549) cells	These compounds had moderate inhibitory effects on HL-60 cell line and only macrocapal G had inhibitory effect on SMMC-7721 cell.	[5]
E. camaldulensis	Petroleum ether extract	Ehrlich ascites carcinoma (EAC) cells	Reduced tumor growth rate and enhanced the life span of EAC bearing mice remarkably. Toxic effect of the extract is minimum and mostly reversible with time.	[49]

E. camaldulensis/ leaf	Ethyl acetate and n-butanol	Breast cancer cells (MCF7, MDA-MB-231)	Cytotoxic effects (IC50: 5-41 µg/mL)	[76]
E. camaldulensis/ leaf	Aqueous acetone	Breast cancer cell (MCF7)	Growth inhibitory effect (IC50: 36.5 µg/mL)	[77]
E. camaldulensis/ leaf and fruit	Methylene, hexane, and dichloromethane	Ovarian cancer cell line A2780	Anti-proliferative effects (Fruit extracts (IC50: 17.5 and 17.2mg/mL) > leaf extracts (IC50: 19.3 µg/mL))	[73]
E. camaldulensis/ resin	Methanolic extract	Human bladder carcinoma cell line with endothelial properties ECV-304	Cytotoxic effects (IC50 = 20.7 µg/mL)	[78]
E. torquate/ stem and leaf	Essential oils	Human breast adenocarcinoma cell line (MCF7)	Cytotoxic effects (stem extract (IC50 1.34 □g/mL) > leaf extract (IC50 5.22 □g/mL))	[45]
E. sideroxylon/ leaf	Essential oils	Human breast adenocarcinoma cell line (MCF7)	Cytotoxic effects (IC50: 6.76 □g/mL)	[45]
E. cladocalyx/ leaf	Cladocalol (1), 28-nor-urs-12-ene-3b, 17b-diol (2) and 28-nor-urs-12-ene-3b, 17b-diol (3)	Human tumor cell line HL-60	Cytotoxic effects. Compounds 1 ,2 and 3 (IC50:42, 51 and 83, respectively).	[74]
E. benthamii/ leaf	Essential oils and some related terpenes (α-pinene, terpinen-4-ol, and γ-terpinene)	Jurkat, J774A.1 and HeLa cells lines	Cytotoxic effects (essential oils > α-pinene and γ-terpinene). Cytotoxic activity probably involved cell death by apoptosis.	[46]
E. cypellocarpa/ leaf	Cypellocarpins A (1), B (2), and C (3), and chromene glucoside (7)	Raji cells	Reduced percentage of tumor-carrying mice to 30% after 10 weeks at a concentration of 50 mol ratio/TPA	[50]
E. grandis/ leaf	Euglobal-G1 (EG-1),	Mouse skin tumors and mouse pulmonary tumor	Inhibition of the two-stage carcinogenesis	[4]

Note – the currently accepted name of *Eucalyptus citriodora* is *Corymbia citriodora*; the currently accepted name of *Eucalyptus maideni* is *Eucalyptus globulus* subsp. *maideni*