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Ellagitannins from *Eucalyptus camaldulensis* and their potential use in the food industry

Eliseo Sánchez-Loredo[1], Leonardo Sepúlveda[1], Jorge E. Wong-Paz[2], Lissethe Palomo-Ligas[1], Raúl Rodriguez-Herrera[1], Cristóbal N. Aguilar[1], Juan A. Ascacio-Valdés[1]*

[1]Food Research Department, School of Chemistry, Autonomous University of Coahuila, Saltillo, Coahuila 25280, Mexico
[2]Faculty of Professional Studies Zona Huasteca, Autonomous University of San Luis Potosí, Ciudad Valles, San Luis Potosí 79060, Mexico

***Correspondence:** Juan A. Ascacio-Valdés, Food Research Department, School of Chemistry, Autonomous University of Coahuila, Saltillo, Coahuila 25280, Mexico. alberto_ascaciovaldes@uadec.edu.mx
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Abstract

Plants play a key role in the treatment and prevention of diseases since ancient times. *Eucalyptus* has been traditionally used in the treatment of conditions related to the respiratory system, such as flu, colds, sore throats, bronchitis, as well as neuralgia, and stiffness. *Eucalyptus camaldulensis* has several phytoconstituents such as ellagitannins endowed with bioactivity, including antioxidant and inhibitory potential on various microorganisms causing foodborne diseases. Tellimagrandin I, pedunculagin, castalagin/vescalagin are among the most representative and have activity against pathogens such as *Staphylococcus aureus*, *Escherichia coli*, *Listeria monocytogenes*, and *Bacillus cereus*. These antioxidant ellagitannins may have potential application in the food, pharmaceutical, and cosmetic industries. The main industrial uses of *E. camaldulensis* are related to the production of wood, paper, and charcoal, with its leaves and branches considered by-products from these industrial activities. However, these plant by-products could be used to obtain bioactive compounds for the development of new and improved consumer goods. Therefore, the aim of this work was to review the main ellagitannins of *E. camaldulensis* and their antioxidant and antibacterial activities in foodborne microorganisms, as well as the relevance that these compounds may have in the food industry and related sectors.

Keywords

Antioxidants, ellagitannins, *Eucalyptus camaldulensis*, foodborne microorganisms, natural ingredients

Introduction

In human traditions, herbal medicine has played a role in treating and preventing ailments and diseases, bringing wellness to human beings [1]. One of the most widely used plants in traditional remedies is plants of the *Eucalyptus* genus. *Eucalyptus* has traditionally been used as a remedy for conditions related to the

respiratory system [2] as *Eucalyptus camaldulensis* to treat flu, common colds, and nasal infections, through decoctions. Also, *Eucalyptus globulus* for asthma, cold, cough, as decoction and extracts [3], and in Latin America, has also been used for nasal congestion, throat pain and inflammation, chest pain, airway clearance, removal of phlegm, pharyngitis and as a disinfectant and antiseptic, either as an infusion, ointment, ointment, tea, vaporization, and aromatic water [4]. *Eucalyptus* essential oils (EOs) are among the first oils marketed in the world besides, they have bioactivity that allows them to be used in traditional remedies for the treatment of gastrointestinal disorders and wound healing, as a herbicide, and against some pests, acaricide, nematicide, its use in perfumery, soap making, in addition as an antiseptic, antioxidant, against some fungi and bacteria that can be pathogenic [5].

Several species of the *Eucalyptus* genus have spread in many parts of the world due to its great qualities such as rapid growth rate and high biomass production, the ability to grow in various environments and soils, its short cellulose fiber, and the high quality of the wood, as well as its pulp for the paper industry, the timber industry for the production of plywood and solid wood [6] and production of EO in the cosmetic industry, since the oil of other eucalyptus species has been used in the cosmetic industry, some of the most used species were *E. globulus* [7–9] and *Eucalyptus citriodora* [5, 10]. *E. camaldulensis* is a plant source very rich in EO with bioactive properties, and phenolic compounds, that could be used in medicine and food preservation. Thus, in the Asian continent, *E. camaldulensis* is used in traditional medicine to mitigate various symptoms of respiratory diseases, such as cough, sore throat, and sinusitis [3, 11]. The EO of *E. camaldulensis* has shown a potential to inhibit malatogensis in the skin with mice and decrease intracellular oxygen reactant species, which makes its use as a skin care pharmaceutical product possible [12].

These EO are usually recovered from various parts of the plant, ranging from wood, leaves, roots, flowers, and fruits [13]. Different class of secondary metabolites can be found, among which terpene compounds stand out, especially monoterpenes, sesquiterpenes, alcohols, ketones, esters, aldehydes, and phenols [5].

Within the *Eucalyptus* genus, the most cultivated species in plantations are *Eucalyptus grandis*, *E. globulus*, *E. camaldulensis*, as well as the hybrids made from these species [6]. In addition, *E. camaldulensis* is a plant rich not only in EOs with bioactive properties, but also in the content of phenolic compounds as flavonoids and ellagitannins that can be used in medicine and food preservation [11]. The use of new sources of antioxidants and antimicrobials is necessary due to the potential use of these compounds and their multiple applications, avoiding the depletion of sources and taking advantage of by-products from agri-food industries. The aim of this work was to make a particular compilation about of the main ellagitannins of *E. camaldulensis*, and their antioxidant, antibacterial activities in food pathogenic microorganisms and the relevance that these may represent in food trends.

General information

E. camaldulensis is a plant native to Australia [11], known in the world as red gum, red gum Murray, red, and river gum [14]. It is employed industrially mainly in the paper industry (70–80%) [7], followed to that carbon (10–15%) and finally only 5% of the tree is used for pool construction; this type of industrial exploitation generates waste as leaves and branches that could whereas be a good potential source of bioactive compounds [11]. The botanic structure *E. camaldulensis* is composed of a bark that varies from white shades and smooth surface, dull green leaves in adulthood, narrow and pointed, the juvenile leaves are usually more oval. It has a strongly beaked operculum between 0.3–0.7 cm long at maturity and a long operculum of 0.9–1.6 cm long with curvature in some subspecies. In addition, it has a capsule that houses the seeds in its interior [14] (Figure 1). *E. camaldulensis* trees can generate tall forests and adapt to diverse climatic regions, from areas of high rainfall to semi-arid regions in high and low regions at sea level [6].

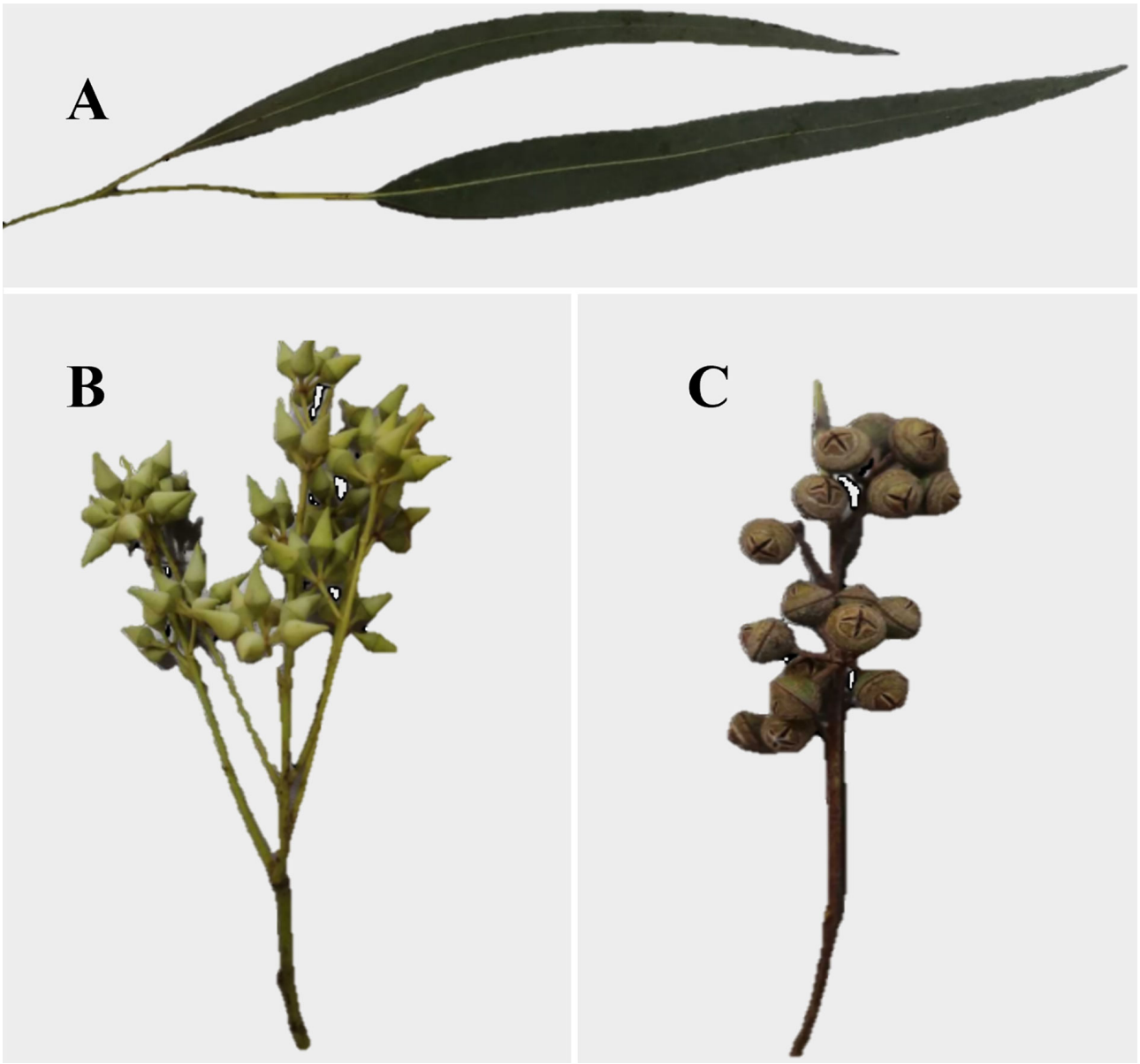

Figure 1. Upper parts from *E. camaldulensis*. A. Leaves; B. operculum; C. capsule from *E. camaldulensis*

Chemical composition

E. camaldulensis is a plant with a wide variety of chemical constituents among which stand out the terpenoids, alkaloids, flavonoids, tannins, saponins, and glucosides among others such as phenolic acids as seen in Table 1 [15], and the main compounds found is 1,8-cineole mainly in fresh leaves [16].

Moreover, other chemical constituents very important and high value reported for *E. camaldulensis* are phenolic compounds among which are flavonoids, and ellagitannins in more abundance. The total content of polyphenols in this species was estimated to be about 364.1 mg ± 8.2 mg, data reported in gallic acid equivalents, of which about 80.5 mg ± 0.9 mg appear to be flavonoids determined as quercetin equivalents [17].

Extraction is the most important step to obtain phenolic compounds from plant sources and this can be carried out by various extractions and solvents [18]. It has been possible to extract compounds from *E. camaldulensis* with different solvents. The use of different solvents varies in the type of compounds extracted as well as the amount, which makes the difference in obtaining these [17]. For example, flavonoids can be found in ether-soluble fractions of leaf extracts [10]. Whereas among the compounds found in aqueous fractions are flavones, different glycosides, and important phenolic compounds like

Table 1. Volatile and phenolic profile of *E. camaldulensis* extracts (expressed as % in the sample) [15, 17]

Class	Compound	EO (leaves, %)	Extract (leaves, %)
Monocyclic monoterpene	α-Pinene	14.68	-
Bicyclic monoterpene	Camphene	0.87	-
Monocyclic monoterpene	β-Pinene	6.66	-
Non-cyclic monoterpene	α-Pinene epoxide	0.27	-
Monocyclic monoterpene	γ-Terpinene	9.42	-
Monocyclic monoterpene	δ-Terpinene	1.11	-
Acyclic terpene	Isoamyl isovalerate	1.07	-
Monocyclic monoterpene	Fenchyl alcohol	0.79	-
Monocyclic monoterpene	α-Camphodenic aldehyde	0.66	-
Monocyclic monoterpene	Trans-pinocarveol	8.36	-
Monocyclic monoterpene	Mytenal	0.94	-
Monocyclic monoterpene	*Z*-Carveol	1.15	-
Monocyclic monoterpene	*d*-Carvone	0.51	-
Monocyclic monoterpene	*o*-Cymen-5-ol	0.46	-
Acyclic terpene	Benzyl valerate	0.14	-
Bicyclic monoterpene	α-Gurjunene	0.26	-
Bicyclic monoterpene	β-Gurjunene	0.22	-
Tricyclic monoterpene	Aromadendrene	2.63	-
Tricyclic monoterpene	Alloaromadendrene	0.89	-
Tricyclic monoterpene	Phenethyl isovalerate	0.90	-
Monocyclic monoterpene	Ledene	0.45	-
Monocyclic monoterpene	Epiglobulol	1.83	-
Monocyclic monoterpene	Ledol	7.42	-
Monocyclic monoterpene	Viridlorol	1.13	-
Monocyclic monoterpene	Eremophilene	1.13	-
Monocyclic monoterpene	γ-Cadinene	0.29	-
Sesquiterpenes	Camaldulin	P	-
Sesquiterpenes	Ursolic acid lactone	P	-
Sesquiterpenes	Betulinic acid	P	-
Sesquiterpenes	Oleanolic acid and ursolic acid	P	-
Cyclic monoterpene	Eucalyptol (1–8 cineol)	34.42	-
Hydrolyzable tannin	HHDP-glucopyranose	-	8.07
Hydrolyzable tannin	Galloylglucopyranose	-	4.11
Hydrolyzable tannin	Galloyl quinic acid	-	3.59
Hydrolyzable tannin	Galloyl shikimic acid	-	2.44
Phenolic acid	Phloroglucinol derivative	-	3.41
Phenolic acid	Chlorogenic acid	-	14.20
Hydrolyzable tannin	Digalloylglucopyranose	-	4.25
Flavonoid	Cypellocarpin B	-	8.08
Condensed tannin	Benzyl-galloylglucose	-	8.16
Flavonoid	Quercetin glucuronide	-	5.15
Flavonoid	Kaempferol glucuronide	-	3.36
Hydrolyzable tannin	Galloyl-HHDP-glucopyranose	-	13.38
Hydrolyzable tannin	Vescalagin	-	6.10
Hydrolyzable tannin	Galloyl-HHDP-glucopyranose	-	15.09
Hydrolyzable tannin	Pedunculagin isomer	-	9.40
Hydrolyzable tannin	Castalagin	-	1.10
Hydrolyzable tannin	Digalloylglucopyranose	-	2.28
Hydrolyzable tannin	Valoneoyl-HHDP-glucopyranose	-	1.40
Hydrolyzable tannin	Digalloylglucopyranose	-	2.28

Table 1. Volatile and phenolic profile of *E. camaldulensis* extracts (expressed as % in the sample) [15, 17] (*continued*)

Class	Compound	EO (leaves, %)	Extract (leaves, %)
Condensed tannin	pterocarinin A	-	0.56
Hydrolyzable tannin	Valoneic acid dilactone	-	1.65
Hydrolyzable tannin	Galloyl cypellocarpin B	-	2.59
Flavonoid	Quercetin pentoside	-	2.64
Hydrolyzable tannin	Ellagic acid derivative	-	2.08
Hydrolyzable tannin	Pedunculagin isomer	-	6.18
Hydrolyzable tannin	Ellagitannin dimer	-	6.75
Hydrolyzable tannin	Sanguiin H10-like ellagitannin dimer	-	9.79
Hydrolyzable tannin	Tellimagradin I	-	31.97
Hydrolyzable tannin	Galloyl-bis-HHDP-glucopyranose isomer	-	1.02
Hydrolyzable tannin	Valoneoyl-digalloyl-glucopyranose	-	1.45
Hydrolyzable tannin	Valoneic acid dilactone	-	2.70
Hydrolyzable tannin	Tetragalloylglucopyranose	-	1.79
Hydrolyzable tannin	Sanguiin H10-like ellagitannin dimer	-	0.47
Hydrolyzable tannin	Ellagitannin dimers	-	18.22
Hydrolyzable tannin	Trigalloyl-HHDP-glucopyranose	-	2.69

P: for only the compounds present without identifying the percentage; HHDP: hexahydroxy diphenic acid; -: not involving

phenolic acids, ellagitannins and their derivates, gallotannins and phloroglucinol derivatives [17]. It may also present other compounds such as alkaloids, caffeine derivatives, purine derivatives, and some acids [19].

Also, the extract in acetone was reported as rich in bioactive compounds as the ellagitannins pedunculagin and tellimagrandin I, flavonols, as well as terpenoids. Other fractions with 60% methanol have allowed the separating of ellagitannins, ellagitannins isomer, and ellagitannin dimers mainly among they are pedunculagin isomer and other compounds [17] as can be seen in Table 1.

Although *E. camaldulensis* has compounds that could be beneficial, it also has saponins, which could have a negative effect on health. On the other hand, it has also been reported that *E. camaldulensis* can retain trace elements such as zinc (Zn), copper (Cu), arsenic (As), magnesium (Mg), calcium (Ca), sulfur (S), iron (Fe), aluminum (Al), boron (B) [11, 19]. However, through conventional extractions for traditional treatments it has not been reported that dangerous quantities are extracted [20].

Ellagitannins in *E. camaldulensis*

In *E. camaldulensis* there are three main classes of bioactive compounds among are ellagitannins, flavonoids, and terpenes [17]. Flavonoids have been reported as one of the main compounds in *E. camaldulensis* [21], possessing antiviral, antioxidant, antibacterial and anticancer properties, as well as providing flavor to flowers, fruits, and seeds in plants [22]. Also, *E. camaldulensis* have terpenes and terpenoids [23] commonly present in EOs, which possess antimicrobial, antioxidant, anti-allergic and anticancer activities [24]. Apart from that, ellagitannins have only been found in parts such as leaves [17, 25, 26] in bark and wood [27, 28] as well as in seeds [29] but there have not been many recent reports where ellagitannins are present in *E. camaldulensis*. EOs have been recovered from bark, buds, flowers, fruits, leaves, husks, or roots, however, the yield of these is low and the use of solvents such as petroleum ether, ether, and hexane among others is necessary [24], unlike oils, ellagitannins can be recovered with ethanol, methanol, and aqueous mixtures. In addition, the bioactivity of ellagitannins has shown great variety due to their structure. Ellagitannins are an important group of phytochemicals, these compounds belong to the hydrolyzable tannins that have a high bioactivity value. Ellagitannins represent the defense in fruits and nuts, and they are phytochemicals with antioxidant powder, anticancer, and anti-atherosclerotic properties. Ellagitannins are hydrolyzable tannins with abased HHDP esterified to a polyol core. They can be found in plants as secondary metabolites, where one of their main roles is defense, and are found in flowers, leaves, stalks, peels, and fruits. They are localized in the cytoplasm and cell vacuoles [30, 31], and

among fruits that can contain ellagitannins are the berries, contributing to the health of the fruit itself due to the antioxidant properties of these compounds [32].

The use of different solvents varies in the type of compounds extracted as well as the amount, which makes the difference in obtaining these [33]. Solvents with water allow the extraction of different compounds like ellagitannins [34]. Been reported some ellagitannins in extracts from *E. camaldulensis* with acetone: water, highlighting HHDP-glucopyranose, as well as galloyl-HHDP-glucopyranose positional isomers, pedunculagin, tellimagrandin I, and ellagitannins dimers. Furthermore, other compounds are found in aqueous fractions such as HHDP-glucopyranose, and galloyl-HHDP-glucopyranose [17].

Acetone and ethanol have played an important role in the extraction of different compounds from *E. camaldulensis* that has allowed to recovery of these solvents. Has been reported to extract HHDP, which is an intermediary molecule in obtaining ellagic acid [35]. On the other hand, methanol has presented a role in the recovery of ellagitannins. Methanol allowed the recovery of ellagitannins, mainly pedunculagin isomers, ellagitannin dimer, sanguine H10 like ellagitannin dimer, tellimagrandin I, galloyl-bis-HHDP-glucopyranose isomer, and in fractions with methanol to 100% can be found dimers from ellagitannins in greater quantity as sanguiin H10-like ellagitannin dimer too, in addition to galloyl-HHDP-glucopyranose, vescalagin, galloyl-HHDP-glucopyranose, castalagin, digalloylglucopyranose, valoneoyl-HHDP-glucopyranose, pterocarinin A, valoneic acid dilactone, galloyl cypellocarpin B, quercetin pentoside, and ellagic acid derivative [17].

These compounds possess antibacterial, antifungal, antidiabetic, and antioxidant activity, antimutagenic, and antiproliferative activities [32]. Among all the compounds of *E. camaldulensis* leaves, ellagitannins such as telimagrandin I, pedunculagin, vescalagin and castalagin stand out for their structure [17, 27] (see Figure 2). However, there are not many reports mentioning the presence of ellagitannins in the plant.

Other species of *E. globulus* have reported the presence of ellagitannins such as pedunculaginm tellimagrandin I and II, hexahydroxydiphenoyl-β-*D*-glucose, as ellagic acid in leaves [36, 37] and wood [28]. nitens ellagic acid, HHDP-glucose, pedunculagin, tellimagrandin I and II, HHDP-digalloylglucose, casuarinin, casuarictin, Di-HHDP-galloylglucose, HHDP-trigalloylglucose in wood [38] as well as in *E. citriodora*, pedunculagin, vescalagin/castalagin, acustissimin A, pterocarinin A, tellimagrandin I, and casuarininin have also been found [39], however, there are reports in the literature on other *Eucalyptus* species.

E. camaldulensis and foodborne pathogens

Foodborne pathogens are disease-causing pathogens that come from contaminated food somewhere in the food chain [40]. These microorganisms are the cause of various diseases that not only affect health but also the economy of the people [41]. Foodborne pathogens have caused a cost in the treatment of foodborne illnesses of around $55.5 billion annually in the United States and are dangerous because of the population that is more susceptible to them, such as the elderly, immunocompromised people, infants, and pregnant women [42]. However, even with technology applied to food safety, the foodborne illness still represents a public health problem [43].

Among the most common microorganisms that cause foodborne illness are: *Staphylococcus aureus*, *Shigella* spp., *Salmonella* spp., *Yersinia enterocolitica*, *Escherichia coli*, *Listeria monocytogenes*, *Vibrio* spp., *Cronobacter sakazakii*, *Bacillus cereus*, *Campylobacter jejuni*, *Clostridium botulinum*, *Clostridium perfringens*, not to mention viruses and parasites such as viruses as hepatitis A and noroviruses as well as the parasites *Toxoplasma gondii*, *Cyclospora cayetanensis*, and *Trichinella spiralis* [41]. Besides, some of these microorganisms cause the deterioration of food in physical appearance, aroma, nutritional value and not only diseases [42].

Pathogenic microorganisms are a problem of great relevance and seriousness for health today, due to the resistance that these microorganisms have developed [44]. These microorganisms contaminate numerous food products, such as fruits, vegetables, water, seafood, cereals, and meat, dairy products, and during food processing the equipment and the human operator can be used to process food [42].

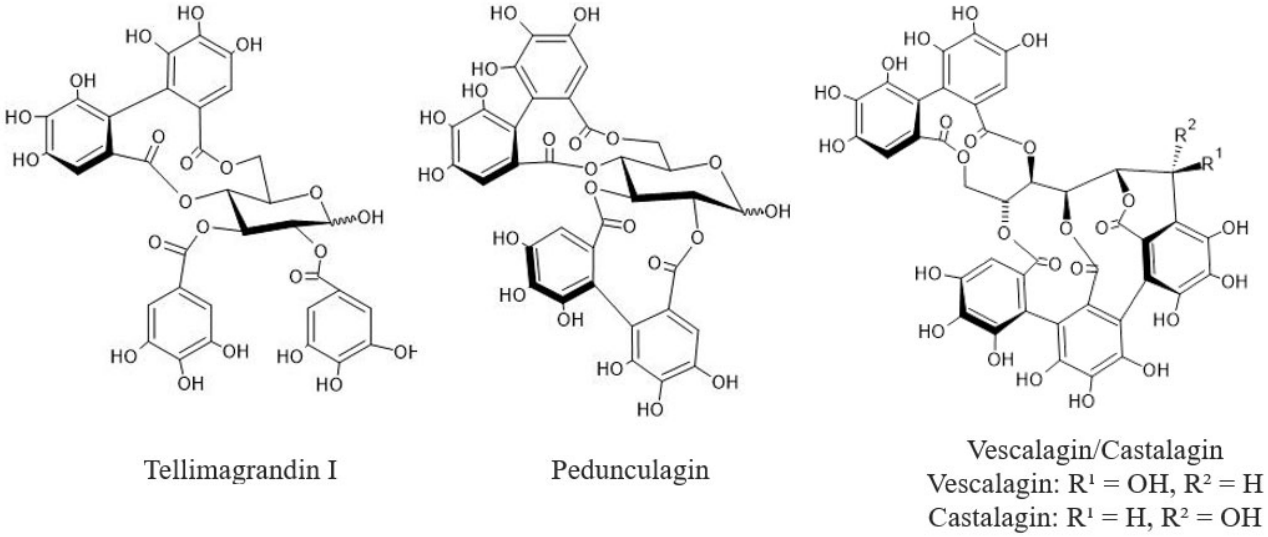

Figure 2. Chemical structures of tellimagrandin I, pedunculagin, and vescalagin/castalagin

The use of antimicrobial agents prevents the proliferation of microorganisms that cause food spoilage [11]. Some of secondary metabolites produced by various natural sources such as plants have antimicrobial potential against pathogenic microorganisms and can inhibit virulence factors [1]. These compounds with antibacterial properties have been used in food processing, acting as preservatives and preventing the deterioration of food products both in food pathogenic and non-pathogenic microorganisms [19], and have also been used antioxidant, and antitumor activities [44].

It has been reported that medicinal plant extracts such as *Eucalyptus* have shown activity against microorganisms, including *B. cereus*, *Alicyclobacillus acidoterrestris*, *Enterococcus faecalis*, and *E. coli*, *Propionibacterium acnes*, *S. aureus*, and methicillin-resistant *S. aureus* (MRSA), *Trichophyton mentagrophytes* [5].

Crude extracts of *E. camaldulensis* leaves have been reported to contain phenolic compounds with antimicrobial properties effective against *L. monocytogenes*, *S. aureus*, and *B. cereus* [11]. In addition, minimum inhibitory concentrations (MIC) of ethanol fraction have been reported between 16–64 μg/mL. As well as MIC of 158–316 μg/mL and minimum bactericidal concentrations (MBC) of 316–2,528 μg/mL of aqueous fraction of *E. camaldulensis* [11]. Also, *Eucalyptus* EOs have been tested on *E. coli* and *S. aureus*. Other reports have shown that EOs of *E. camaldulensis* have demonstrated inhibition on other microorganisms including *S. aureus*, *E. coli*, *Salmonella enteritidis*, *Bacillus subtilis*, and *Enterococcus faecalis* [16] (see Table 2).

On the other hand, *Eucalyptus* oil has shown antimicrobial activity, which has been mainly attributed to several compounds, among which terpenes such as 1,8-cineole, α-pinene, β-pinene, and limonene stand out [5]. *E. camaldulensis* oil has shown bioactivity on gram-positive bacteria that are more sensitive compared to gram-negative bacteria. This activity increased with increasing EO; however, at lower concentrations of 0.5 g/kg no activity was observed, and for gram-positive bacteria (*S. aureus* and *Streptococcus*). *E. camaldulensis* leaf EO showed activity at 1.0 g/kg and 5.0 g/kg, while for gram-negative bacteria such as *S. enteritidis*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, and *E. coli* it was 1 g/kg and 15 g/kg, respectively. In addition, the MBC against *S. aureus*, *Streptococcus aureus*, and *E. coli* was shown to be 5 g/kg, 10 g/kg, and 25 g/kg, respectively [5] as can be seen in Table 2.

Ellagitannins from *E. camaldulensis* and their potential in foodstuffs

Tellimagrandin I

One of the ellagitannin found in *E. camaldulensis* is tellimagrandin I that abound mainly in the young leaves in April and these after are replaced for casuarinin in July, that later change to pedunculagin. These compounds are the principal tannins that are found in the leaves from summer to fall [46]. Tellimagrandin

Table 2. *E. camaldulensis* inhibition of bacterial growth

Microorganism	MIC concentration	Type of extract	Part of the plant	Reference
B. cereus	16 µg/mL	Ethanol	Leaves	[11]
	158 µg/mL	Aqueous	Leaves	[11]
	31.36 µg/mL	EO	Leaves	[16]
L.monocytogenes	32–64 µg/mL	Ethanol	Leaves	[11]
	316 µg/mL	Aqueous	Leaves	[11]
S. aureus	32 µg/mL	Ethanol	Leaves	[11]
	158 µg/mL	Aqueous	Leaves	[11]
	100 µl/mL	EO	Leaves	[45]
	33.2 µg/mL	EO	leaves	[16]
E. coli	100 µl/mL	EO	Leaves	[45]
	85 µg/mL	EO	Leaves	[16]
Salmonella enteritis	51.36 µg/mL	EO	Leaves	[16]
Enterococcus faecalis	30.0 µg/mL	EO	Leaves	[16]

is made up of a molecule of HHDP and a *D*-glucopyranosyl with two galloyl units and this molecule has been widely used against bacterial and viral infections [47].

Effect of tellimagrandin I on pathogenic bacteria

Tellimagrandin I has been effective in the inhibition of *S. aureus* and *E. coli* [48, 49]. It has been reported that tellimagrandin I isolated from the rose extract was effective in reducing the MIC of oxacillin against methicillin-resistant *S. aureus*, acting together with tellimagrandin I and oxacillin. Reducing the MIC of oxacillin from 128 µg/mL to 1 µg/mL, when 50 µg/mL of tellimagrandin I was added to the medium [50]. On the other hand, tellimagrandin I also contributed to the reduction of the MIC of tetracycline in the MRSA strains *OM481*, *OM505*, *OM504*, and *OM506*. In addition, the MIC of other antibiotics such as benzylpenicillin and ampicillin was reduced with the addition of tellimagrandin I to MRSA [50].

S. aureus is one of the ten main microorganisms causing a food illness produced by bacteria and safety indicators. The foods most susceptible to contamination by *S. aureus* are all those that have had contact with animal skin, among which dairy meat and sausage products stand out [51, 52].

Also, the effect of isolated tellimagrandin I monomers was favorable against 32 strains of *Helicobacter pylori*. However, on *E. coli* only a MIC greater than 100 µg/mL could be obtained. In addition, the bactericidal effect of tellimagrandin I could be demonstrated according to time and dose against *H. pylori in vitro* showing that the effect is faster with 50 µg/mL [53]. Several extracts rich in tellimagrandin I extracts, and the pure compound isolated from *E. globulus*, has to be effective on bacteria such as *S. aureus* [54]. Its antimicrobial potential has also been proven by Boulekbache-Makhlouf et al. [55], who reported that extracts of *E. globulus* rich in tellimagrandin I inhibit *S. aureus* and *B. subtilis*.

It has been reported that tellimagrandin I on MRSA acts on penicillin-binding protein 2a (PBP2a) decreasing its production and inactivating it [56]. PBP is a protein enables resistance to β-lactam antibiotic drugs in MRSA, PBP2a is encoded by the *mecA* gene found in MRSA strains, which gives resistance to beta-lactam antibiotics due to its low affinity for them, and PBP2a provides transpeptidase activity to allow cell wall synthesis at concentrations that inhibit the sensitive PBPs normally produced by *S. aureus* [57]. Likewise, in E. coli, the characteristics of the free galloyl groups of the ellagitannins increase the hydrophobicity of the structure, promoting their interaction with bacterial lipid membranes [58], through inactivation of essential surface proteins, interaction with membrane lipids and causing membrane phase separation [59].

Pedunculagin

Among the important ellagitannins found in leaves of *E. camaldulensis* is pedunculagin [60]. Pedunculagin is a phenolic compound belonging to group of the ellagitannins which exhibit various antioxidant, anti-inflammatory, antitumor, gastroprotective, and hepaprotective activities [61].

Effect of pedunculagin on pathogenic bacteria

In phenolic compounds, antibacterial activity is one of the most sought-after due to its great capacity to inhibit pathogenic bacteria and the bactericidal effect that some of them have [62]. In antibacterial activity, pedunculagin has shown an anti-hemolytic effect on *S. aureus* [63] as well as in fractions of pedunculagin-rich extracts [64, 65], which is a bacterium commonly found in some foods causing food poisoning, being the main cause of food poisoning worldwide [51]. Anti-hemolytic effect is important due to the hemolysis produced by the alpha toxin of *S. aureus*. This hemolytic toxin causes the rupture of the red blood cell membrane. The α-hemolysin binds to the cell surface and facilitates the transport of molecules such as potassium ion (K^+) and Ca^{2+} ions, which causes necrotic death of the host cell [66], On the other hand, fractions obtained from *Clidemia hirta,* rich in pedunculagin have been effective to inhibit *E. coli* at concentrations greater than 100 µg/mL [64], as well as extracts of *Geum rivale* L. rich in pedunculagin were able to inhibit *E. coli* and *L. monocytogenes* at lower concentrations [65].

The individual activity of ellagitannins has not been extensively studied, but some of the mechanisms on which they act are the ability to interact with the cell wall and nucleic acids [67], however it has been proven that pedunculagin decreases the ability of *S. aureus* to cause hemolysis, as well as some phenolic groups cause enzymatic inactivity due to their hydroxyl groups, as well as affect the cell membrane by forming complexes with proteins and polysaccharides [63].

Effect of vescalagin and castalagin on pathogenic bacteria

It has been proven that ellagitannins such as vescalagin/castalagin isolate have bactericidal capacity on one of the main food pathogenic bacteria which is *S. aureus* [44].

In addition, extracts rich in vescalagin and castalagin have also shown antibacterial activity on several foodborne pathogens [68]. Extracts of *Myrciaria cauliflora* seeds with high values of vescalagin and castalagin (1,999 mg/100 g ± 24 mg/100 g and 1,872 mg/100 g ± 18 mg/100 g respectively) have shown inhibition against microorganisms such as *L. monocytogenes*, *Salmonella typhimurium*, *S. Enteritidis*, *B. cereus*, *E. coli*, *S. aureus* [69]. *Myrciaria dubia* extract has also reported activity against *S. typhimurium*, *E. coli*, *B. cereus*, *S. aureus*, and *L. monocytogenes* [70].

Fujita et al. [71] have also reported inhibition of *Myrciaria dubia* McVaugh rich in vescalagin and castalagin too, possess antibacterial activity on *S. aureus* at concentrations ranging 0.08–0.63 mg/ml. It has been demonstrated that vescalagin and castalagin have been able to inhibit microorganisms with extracts rich in these ellagitannins, as in the case of *Lythrum salicaria* L. acting on *E. coli*, *B. cereus*, *B. subtilis*, *Staphylococcus epidermidis*, *S. aureus*, *S. enteritidis*, *S. typhimurium* [72]. In addition, other microorganisms have been inhibited by vescalagin and castalagin, such as methicillin-resistant *S. epidermidis*, methicillin-resistant *S. aureus*, *Pseudomonas aeruginosa*, breaking and inhibiting the films by modulating the assembly of peptidoglycans on the bacterial surface, breaking the cell wall and bacterial death [44]. The inhibition concentrations of tellimagrandin I, pedunculagin, castalagin and vescalagin on food pathogenic bacteria are shown in Table 3.

The antibacterial activity of castalagin and vescalagin have also been shown to interact with PBP2a in MRSA, rendering the bacteria susceptible to lysis and its inhibition [46]. In addition, extracts with castalagin act on *H. pylori*, preventing adhesion to the gastric mucosa, as well as allowing the disintegration of the membrane of salmonella and *B. subtilis* [73].

Antioxidant activity

Antioxidant effect of tellimagrandin I

Tellimagrandin has been found in different extracts as *Cornus mas* L. These extracts have had antioxidant activity at 2,2-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS), ferric reducing antioxidant power assay (FRAP), and 2,2-diphenyl-1-picrylhydrazyl (DPPH) with a range of 255.9 mmol/100 g ± 8.48 mmol/100 g, 210.62 mmol/100 g ± 5.45 mmol/100 g, 191.00 mmol/100 g ± 0.04 mmol of Trolox (Tx)/100 g respectively [74]. In an essay on the antioxidant capacity of some ellagitannins performed by Moilanen et al.

Table 3. Antibacterial activity of tellimagrandin I, pedunculagin, and vescalagin/castalagin

Microorganism	Ellagitannins	Inhibition of microorganisms at MIC	Reference
E. coli	Tellimagrandin I	50 μg/mL	[53]
		500 ppm	[54]
	Pedunculagin	> 100 μg/mL	[64]
		15.6 μg/mL	[65]
	Vescalagin/Castalagin	9.04 mm ± 0.65 mm	[69]
		6.74 mm ± 0.80 mm	[70]
		2.5 mg/mL	[72]
S. aureus	Tellimagrandin I	50 μg/mL	[50]
		1,000 ppm	[54]
	Pedunculagin	< 100 ug/mL	[64]
		15.6 μg/mL	[65]
	Vescalagin/Castalagin	9.47 mm ± 1.86 mm	[69]
		9.70 mm ± 1.92 mm	[70]
		0.08–0.63 mg/mL	[71]
		0.625 mg/mL	[72]
H. pylori	Tellimagrandin I	12.5 μg/mL	[54]
L. monocytogenes	Pedunculagin	62.5 μg/mL	[65]
	Vescalagin/Castalagin	8.87 mm ± 0.49 mm	[69]
		8.58 mm ± 0.82 mm	[70]
B. cereus	Vescalagin/Castalagin	8.07 mm ± 0.96 mm	[69]
		9.04 mm ± 1.36 mm	[70]
		2.5 mg/mL	[72]

[75] with tellimagrandin showed radical scavenging antioxidant properties at concentrations of 3 mmol/L and 5 mmol/L, however, at fewer concentrations they exhibited prooxidant activity enhancing the degradation of 2-deoxyribose used in the assay.

Within the *Eucalyptus* genus, it has been mentioned that they are high in ellagitannins among they are tellimagrandin I, with high antioxidant potential, as is *E. globulus* with extracts, where the presence of ellagitannins is higher and gives it activity [76]. Furthermore, in extracts of *Plinia cauliflora*, showed a DPPH inhibitory concentration (IC_{50}) of 1.45 μg/mL ± 0.02 μg/mL, as well as a peroxidation inhibition greater than 70% [77].

Antioxidant effect of pedunculagin

Due to its antioxidant potential, pedunculagin has been one of the ellagitannins of great interest. Extracts from natural sources such as walnuts have been identified with the presence of pedunculagin, obtaining antioxidant potential by inhibiting lipid peroxidation in mice, as well as the ferric reducing antioxidant power [78]. However, the antioxidant capacity of *Eucalyptus* isolates has also provided antioxidant activity on DPPH and ABTS [79]. Other extracts, including *Geum rivale* L. extract with the presence of pedunculagin, have shown antioxidant potential with great inhibition against DPPH (about 90%) and ABTS [65].

Due to the number of compounds found in crude plant extracts or residues, chromatography is usually performed to allow the recovery of fractions with more specific compounds in each one. Oliveira et al. [80] in 3 feijoa fractions with the presence of pedunculagin reported antioxidant potential on ABTS.

In addition, pedunculagin from *Quercus mongolica in vitro* has been evaluated for inhibition of inflammatory cytokines [interleukin-6 (IL-6) and IL-8], as well as 5α-reductase inhibitory activity by western blotting, being pedunculagin were able to inhibit nitric oxide production, as well as decrease IL-6 and IL-8, and exhibited potent 5α-reductase type 1 inhibitory activity [81].

Antioxidant potential of vescalagin/castalagin

Interestingly, in antioxidant and prooxidant assays, castalagin/vescalagin has exhibited the opposite of antioxidant for 2-deoxyribose used in the assay, obtaining prooxidant results at concentrations from

1–5 mmol/L [75]. Other reports on isolated vescalagin have reported around 5 mg/L for DPPH inhibition, however, from the same extract castalagin contained slightly low values compared to that of castalagin [44]. Fidelis et al. [70] in extracts of *Myrciaria dubi*a have reported DPPH inhibition. *Myrciaria dubia*, among its main components, is mainly pedunculagin. Also, within the same genus *Myrciaria cauliflora* containing pedunculagin presented DPPH inhibition at higher values, as well as lipid peroxidation values, as well as lipid peroxidation values slightly greater than 80% inhibition [69]. Other important extracts of Jabuticaba extracts rich in vescalagin and castalagin vescalagin and castalagin showed a DPPH inhibition capacity of about 33.643 mmol ± 3.129 mmol of Tx/100 g fruit [82] (see Table 4).

Table 4. Antioxidant activity of tellimagrandin I, pedunculagin, and vescalagin/castalagin

Compound	ABTS	FRAP	DPPH	Lipoperoxidation	Reference
Tellimagrandin I	-	-	-	51.34% ± 0.72%	[76]
Tellimagrandin I	255.9 mmol/100 g ± 8.48 mmol/100 g	210.62 mmol/100 g ± 5.45 mmol/100 g	191.00 mmol ± 0.04 mmol of Tx/100 g	-	[74]
Tellimagradin I	-	-	1.45 µg/mL ± 0.02 µg/mL	71.47% ± 5.64%	[77]
Tellimagrandin I	54.5 µmol/L ± 0.6 µmol/L	-	73.5 µmol/L ± 2.5 µmol/L	-	[79]
Tellimagrandin I	73.6 µmol/L ± 3.2 µmol/L	-	65.8 µmol/L ± 1.2 µmol/L	-	[79]
Pedunculagin	83.69% ± 4.28% inhibition 0.111 mg/mL	-	0.139 mg/mL	-	[83]
Tellimagrandin I	0.03 µmol/L ± 0.02 µmol/L Tx equivalent/µg	-	94.65% ± 0.29%	-	[65]
Pedunculagin	10.8 µg/mL ± 0.7 µg/mL	-	-	-	[80]
Vescalagin	-	-	5 mg/mL	-	[44]
Castalagin	-	-	4 mg/mL	-	[44]
Vescalagin/ Castalagin	-	-	4,455 mg ± 15 mg AAE/ 100 g	86% ± 1%	[70]
Vescalagin/ Castalagin	-	-	33.643 mmol ± 3.129 mmol of Tx/100 g	-	[82]
Pedunculagin	-	-	1.55 µmol ± 0.12 µmol of Tx equivalent/µmol	-	[37]
Tellimagrandin I	-	-	1.33 µmol ± 0.03 µmol of Tx equivalent/µmol	-	[37]

AAE: ascorbic acid equivalent; -: not involving

Future trends

It is important to take into account that in plants of the *Eucalyptus* genus the use is oriented towards the use of EOs and compounds of these, but making use of extracts rich in ellagitannins allows them to be applied in various matrices, from supplements to functional foods for preservation or functional foods, in addition to the fact that they have provided coloration. Many of the extracts of phenolic compounds from natural sources have been mostly oriented to the pharmaceutical and cosmetic industry [84, 85]. There are several studies on the use of ellagitannins in the cosmetic industry [86, 87], showing their possible use in the pharmaceutical industry against cell oxidation, as well as in products aimed at cellular rejuvenation. Others have highlighted the potential use of ellagitannins in the pharmaceutical, food, and nutraceutical industries [36, 88] either for its prebiotic potential [89], as is pedunculagin from walnuts [90], and for the treatment of gastric ulcers, wounds, and ulceration [39].

However, the use of phenolic compounds such as hydrolyzable tannins, especially ellagitannins for the food industry, may be an option to solve problems such as lipid oxidation [91]. Pomegranate extracts with a high presence of ellagitannins have been investigated for the inhibition of lipid oxidation in sausage, where the peroxide value was decreased by the effect of pomegranate extract [92].

Well as for the conservation against pathogenic microorganisms in food, since several studies have shown the inhibition of microorganisms in food, extracts themselves as Mantzourani et al. [93] with extracts from *Vaccinium macrocarpon* and *Punica granatum* L., applied on pork meat to inhibit

Enterobacteriaceae, total mesophilic bacteria, yeasts/molds, *Staphylococcus* spp., *Pseudomonas* spp. and lactic acid bacteria and EOs for chicken meat preservation [91, 94]. As in the case of pomegranate extract films with the presence of ellagitannins including pedunculagin, for the inhibition of microorganisms such as *L. monocytogenes* and *E. coli* [95]. On the other hand, extracts with ellagitannins have been shown to improve the antioxidant and meat quality of broiler meat by supplementing it, which helped to improve the intestinal bacterial population in the chicken [83]. In addition, the use of ellagitannins is possible in the formation of materials with antibacterial potential, such as the case of vescalagin/castalagin that can be loaded into alginate hydrogels to generate antibacterial biomaterials [44]. This is a step in the development of products in the food area that can aid in the inhibition of oxidation, as well as the use of antibacterial agents for the inhibition of food pathogens.

Conclusions

E. camaldulensis is a plant commonly used in industries such as wood, paper, and oil production. However, the residues of its leaves and small branches are often left unused, presenting an opportunity for utilization. This review focuses on the potential of *E. camaldulensis* residues particularly the phenolic compounds they contain, including hydrolyzable tannins such ellagitannins. Ellagitannins are known for their antioxidant and antimicrobial proprieties, making them valuable for various applications, specifically in the food industry for inhibiting lipid oxidation in oils and meat products. It is worth noting that there is a limited number of studies that specifically isolate ellagitannins, with most research focusing on their presence in extracts. This lack of isolated compound studies makes it challenging to gather comprehensive information about ellagitannins. Therefore, this review aims to contribute essential knowledge about these compounds and their potential uses.

Abbreviations

ABTS: 2,2-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid)

DPPH: 2,2-diphenyl-1-picrylhydrazyl

EOs: essential oils

HHDP: hexahydroxy diphenic acid

IL-6: interleukin-6

MIC: minimum inhibitory concentrations

MRSA: methicillin-resistant *Staphylococcus aureus*

PBP2a: penicillin-binding protein 2a

Tx: Trolox

Declarations

Author contributions

ESL: Conceptualization, Visualization, Investigation, Writing—review & editing. LS: Validation, Resources, Writing—review & editing. JEWP: Validation, Supervision, Writing—review & editing. LPL: Validation, Writing—review & editing. RRH and CNA: Validation, Supervision, Writing—review & editing. JAAV: Conceptualization, Resources, Validation, Visualization, Writing—review & editing.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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