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Review Article

A Comprehensive Review on Phytochemical, Pharmacological and Future Prospective of Dietary Medicinal Plant *Cinnamomum osmophloeum* Kanehira

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Abstract

Background: The plants belonging to the genus *Cinnamomum* traditionally used as an ethnomedicine in Asia, Europe, and North America. *Cinnamomum osmophloeum* Kanehira, is an endemic and economic medicinal plant of Taiwan. It is traditionally used as an antibacterial, antifungal, anti-termite, antidiabetic, anti-hyperuricemia, antiinflammatory, and antioxidant agent. Despite these attributes, *C. osmophloeum* is not enough explored scientifically. This review updated the essential oils and other secondary metabolites, and the pharmacological activities of *C. osmophloeum*, as well as its other economic benefits. **Methods:** The information in the review is extracted from the major scientific databases, such as PubMed, BioMed Central, Google scholar, Elsevier, ACS publications, MDPI, Taylor and Francis, Wiley Online Library, Scopus, Springer, and Web of Science, using journals, dissertations, books and/or chapters, and conference proceedings. **Results**: Various secondary metabolites including essential oil components, flavonoids, lignans, and benzenoids are reported from the extracts of *C. osmophloeum*. The review established a wide range of pharmacological properties including, antibacterial, antidiabetic, anti-fungal, anti-inflammatory, antioxidant, antitermitic, anti-tyrosinase, anti-xanthine oxidase, anxiolytic, cytotoxic, hepatoprotective, and mosquito larvicidal properties of extracts, as well as essential oils and other secondary metabolites of *C. osmophloeum*. **Conclusions**: The present review provides a scientific basis for future studies and necessary information for the development of *C. osmophloeum* based therapeutic agents.

Keywords: *Cinnamomum osmophloeum*; Current Research; Complementary & Alternative Medicine; Essential oils; Non-essential oil metabolites; Biological activities; Analyses

Introduction

The genus *Cinnamomum* belongs to the plant family of Lauraceae. It comprises about 250 species, which are distributed in tropical and subtropical Asia, Australia, Pacific islands [1]. The inner bark of the *Cinnamomum* trees is known as cinnamon [1]. Commercial cinnamons are obtained from various *Cinnamomum* species, such as Ceylon cinnamon and Cassia cinnamon. The Ceylon cinnamon usually refers to the dried bark of *C. verum* Berchthold and Presl. (*syn C. zeylanicum*), and it is indigenous to Sri Lanka and southern India [1]. Cassia cinnamons are differ from Ceylon cinnamon, which are usually known as Chinese cassia (*C. cassia* (L.) Berchthold and Presl.), Saigon cassia (*C. loureiroi* Nees, Vietnamese cinnamon), and Indonesian cassia (*C. burmannii*) [1]. The species of *Cinnamomum* are cultivated as landscape plants and

sidewalk trees, and used in traditional medicine, timber, as well as edible fruits. Importantly, cinnamon is commonly used as a spice in food to give aroma taste and flavor, and to act as a preservative [1]. Other folk uses of cinnamon include applying its essential oil as a fragrance in cosmetics, perfumes, and cigarettes [1].

Although people used cinnamon for quite a long time, however, the hepatotoxic compound, coumarin is found in cinnamon in various amounts [2]. Coumarin is a natural flavoring molecule used as an ingredient in foods, alcoholic beverages, tobaccos, toothpastes, and detergents. In this connection, it is interesting to note that the coumarin contents of Cassia cinnamons are generally higher (~40–12180 mg/kg), than that of Ceylon cinnamon (~0−486 mg/kg) [3,4]. However, the use of coumarin as a food flavoring agent is prohibited in the 1950s due to its hepatotoxicity. In this connection, it is necessary to found the alternative source for the safer cinnamons with low coumarin content, which can be beneficial to the global spice market.

Cinnamomum osmophloeum Kanehira is a native tree species in Taiwan, commonly known as pseudo cinnamomum or indigenous cinnamon [5]. Eight of 14 *Cinnamomum* species in Taiwan are endemic, including *C. osmophloeum* [5]. It is a small evergreen tree that grows in the mountainous area of Po-Li, Taiwan [6]. The plant *C. osmophloeum* grows to 12 m in height and about 40 cm in diameter, and normally inhabits in Taiwan's natural hardwood forests at elevations between 400 and 1500 m [6]. The leaves of *C. osmophloeum* are traditionally used in Taiwanese folk medicines as an antibacterial, antifungal, antitermite, antidiabetic, antihyperuricemia, antiinflammatory, and antioxidant agent [5]. Additionally, *C. osmophloeum* leaves are used in food, flavoring agent, spices, beverages, medical products, and perfumes. The leaves of *C. osmophloeum* has nine chemotypes with various secondary metabolite profiles, which are discussed later of this review. It is interesting to note that the leaf essential oil of *C. osmophloeum* is similar to those of commercial *C. cassia* bark essential oil [2]. However, the Cassia cinnamon bark samples contain higher level of coumarin, whereas the *C. osmophloeum* leaf samples comparatively contains the lower levels of coumarin [2]. Taste-wise, *C. osmophloeum* leaves are milder than ceylon cinnamon, and less heavy on the spicy notes with wafts of vanilla. The plant *C. osmophloeum* is cultivated in the large areas in Taiwan. A recent review reported that the potential use of *C. osmophloeum* in the alleviation of oral mucositis [7]. However, the chemical structures of the compounds and their complete pharmacological activities are not fully displayed. Therefore, the present review reported the phytochemical constituents and their potential pharmacological activities, analyses methods, as well as other economic benefits of *C. osmophloeum*.

Literature Methodology

Relevant information about *C. osmophloeum* is obtained from ancient books, records, doctoral and master's theses, and scientific search engines including, PubMed, SciFinder, Web of Science, Science Direct, Google Scholar, and so on. The literature search is carried out to gather all relevant information about the traditional uses, phytochemicals and pharmacological activities, and underlying mechanism of action, toxicological and safety considerations of *C. osmophloeum*. All chemical structures were drawn using ChemDraw 17.0 software.

Specific Identification of *C. osmophloeum*

Many *Cinnamomum* plants are morphologically similar [1]. The hepatotoxic adulterant *Cinnamomum* species, such as *C. burmannii*, *C. loureiroi*, and *C. cassia*, are easily confused with that of non-hepatotoxic *C. osmophloeum*. Therefore, specific differentiation of *C. osmophloeum* is critical to avoid toxic issues associated with fraudulent adulteration. In this connection, it is reported that the genetic variation and taxonomic relationship of *C. osmophloeum*, *C. macrostemon* and *C. insulari* [8]. The linalool synthase (LIS) genes are isolated from different provenances of *C. osmophloeum* [9], and the cinnamaldehyde is increased in 4-coumarate: coenzyme A ligase 1 and 4 (*Co4CL1* and *Co4CL4*), and cinnamoyl-CoA reductase (*CoCCR*) transgenic plants [10]. Further, the *Cinnamomum* species, *C. burmannii* (Nees & T. Nees) Blume, and *C. insularimontanum* Hayata are morphologically similar with *C. osmophloeum* [11,12]. However, the leaves of *C. burmannii* and *C. insularimontanum* contains lower amount of cinnamaldehyde as compared with the leaves of *C. osmophloeum* [12]. Therefore, quantitative determination of cinnamaldehyde is an optional method for the identification of *C. osmophloeum* from *C. burmannii* and *C. insularimontanum* [12]. On the other hand, a novel method using leaf images and deep convolutional neural networks (CNN), is reported for the distinction of *C. burmannii*, *C. insularimontanum* and *C. osmophloeum* [12]. To continue, a novel DNA sequence comparisons of internal transcribed spacer 2 (ITS2) method is also reported for the identification of gene resources, genetic diversity, and nucleotide sequence polymorphisms for 73 geographical strains of *C. osmophloeum* [13]. Recently, Yang et al., developed a polymerase chain reaction based restriction fragment length polymorphism (PCR-RFLP) method for rapid identification *C. osmophloeum* from adulterant *Cinnamomum* species by DNA polymorphism analysis [14].

Chemical Constituents of *C. osmophloeum*

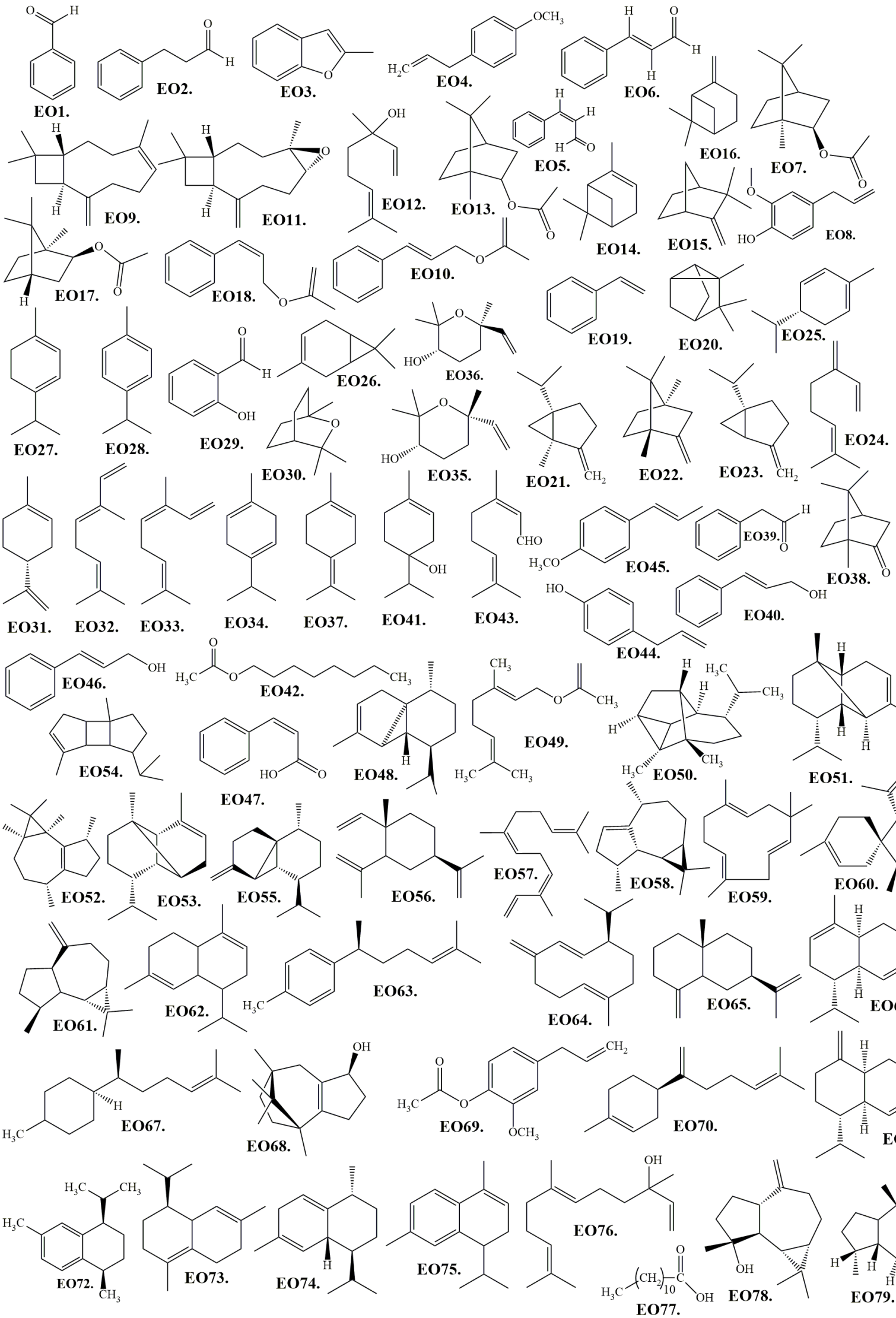
Essential oil components

Essential oils (EOs) are colorless volatile liquids with a characteristic feature of strong odor. Hence, they are widely used in aromatherapy and cosmetics industry [15]. The EOs comprising the aromatic and volatile compounds naturally present in all parts of the plants including seeds, flowers, peel, stem, bark and whole plants [15]. EOs are freely soluble in various solvents such

as alcohol, ether, and fixed oils, but insoluble in water [15]. In general, EOs display similar chemical composition and biological activities when obtained from a single plant species grown under similar climate, edaphic conditions and common harvest season. However, the quality and quantity of EOs are vary depends on plant organ, age of trees, chemotypes, growing season, methods of preparation, soil type and climatic conditions [15]. The GC and GC/MS analyses methods are widely used to identify the leaf EO components of *C. osmophloeum*. The chemical components of leaf EOs are different from various *C. osmophloeum* clones found in different regions in Taiwan [16-20]. It is interesting to note that the chemical constituents of *C. osmophloeum* leaf EOs are similar to those of *C. cassia* bark oil with cinnamaldehyde as the major component [21]. *C. cassia* bark oil has commercial value, and generally used in food and beverages.

Hu et al., (1985) [22], established an indigenous cinnamon clonal orchard with cuttings of trees from 13 natural populations from central, eastern and southern regions of Taiwan, and analyzed the composition of the EOs of *C. osmophloeum* leaves [22]. They found that *C. osmophloeum* leaves from certain provenances contain cinnamaldehyde as the major constituent, whereas linalool is a major compound in some other provenances. Based on the abundances of each individual constituent, it is classified the *C. osmophloeum* leaf EOs into nine types: cassia type, cinnamaldehyde type, coumarin type, linalool type, eugenol type, camphor type, 4-terpineol type, linalool/terpineol type, and mixed type [22]. The GC/MS analysis of volatile oil obtained from the steam distillation of *C. osmophloeum* leaves, resulted in the identification of EOs components, such as α-pinene (**EO14**), camphene (**EO15**), benzaldehyde (**EO1**), etc. (Figure 1, Table, 1) [22]. Fang et al., (1989) [24] reported that the quantitative analysis of EO components from the bark and leaves of *C. osmophloeum* (Table 1) [24]. They identified that the component, *trans*-cinnamaldehyde (**EO6**), as a major constituents in the EO of the both the bark and leaves (~85%) [24]. Furthermore, the five years old plantation trees gives the EOs with an yield of 0.88%, and 0.16% from the leaves and bark, respectively [24]. It is reported that EOs of clones A and B are different, where A belongs to the mixed type, whereas B belongs to the cinnamaldehyde type [25,26]. Further, Cheng et al., (2004) [19] classified the *C. osmophloeum* leaf EOs of eight provenances into five chemotypes namely, cinnamaldehyde type, linalool type, camphor type, cinnamaldehyde/cinnamyl acetate type, and mixed type [19]. To continue, based on the abundance the leaf EOs are classified into six chemotypes namely, cinnamaldehyde type, cinnamaldehyde/cinnamyl acetate type, cinnamyl acetate type, linalool type, camphor type, and mixed type [27,28]. It is identified that the EOs and key constituents from the leaves of two *C. osmophloeum* clones are belongs to two different chemotypes, which are classified as the cinnamaldehyde type and camphor type [29]. Cheng et al. (2012) [30], reported that the content of linalool (**EO12**) varied from 28.8 to 35.1 mg/g, in the EOs of *C. osmophloeum* ct. linalool leaves collected from various plants and seasons [30]. Lee et al., identified the chemotype of major *C. osmophloeum* leaf EOs are linalool type (40.24%), followed by *trans*-cinnamyl acetate (**EO10**, 11.71%), camphor (**EO38**, 9.38%), cinnamaldehyde (**EO6**, 6.87%), etc. (Figure 1, Table 1) [31]. This chemotype, contains relatively small amount of cinnamaldehyde as compared with linalool (6.87% *vs* 40.24%) [31]. To continue, *C. osmophloeum* leaf EOs are obtained by hydrodistillation, and the GC-MS analysis indicates that the *trans*-cinnamaldehyde (70.20%) as a the major one, while the caryophyllene oxide (**EO11,** 0.08%) is the least abundant [32]. These above previous reports indicates that the leaf EOs of *C. osmophloeum* contains numerous volatile compounds, including monoterpenes, sesquiterpenes, and their oxygenated derivatives and, alcohols, phenols, aldehydes, ketones, esters, acids, and other miscellaneous compounds (Figure 1, Table 1). It is also observed that the major components of *C. osmophloeum* leaf EOs are, *trans*-cinnamaldehyde, cinnamyl acetate, linalool and eugenol (Table 1).

On the other hand, EOs from the twigs of *C. osmophloeum* constituents various components including *trans*-cinnamaldehyde (**EO6**) (Table 1) [41]. The thermal stability results of *C. osmophloeum* leaf EOs indicated that *trans*-cinnamaldehyde content in eugenol-free EO is affected by high temperatures, however, the stability of EO improved by adding appropriate amounts of eugenol [33]. The identified chemical structures of the EOs from the *C. osmophloeum* are presented as in Figure 1, and the components names are listed in Table 1.


EO1.
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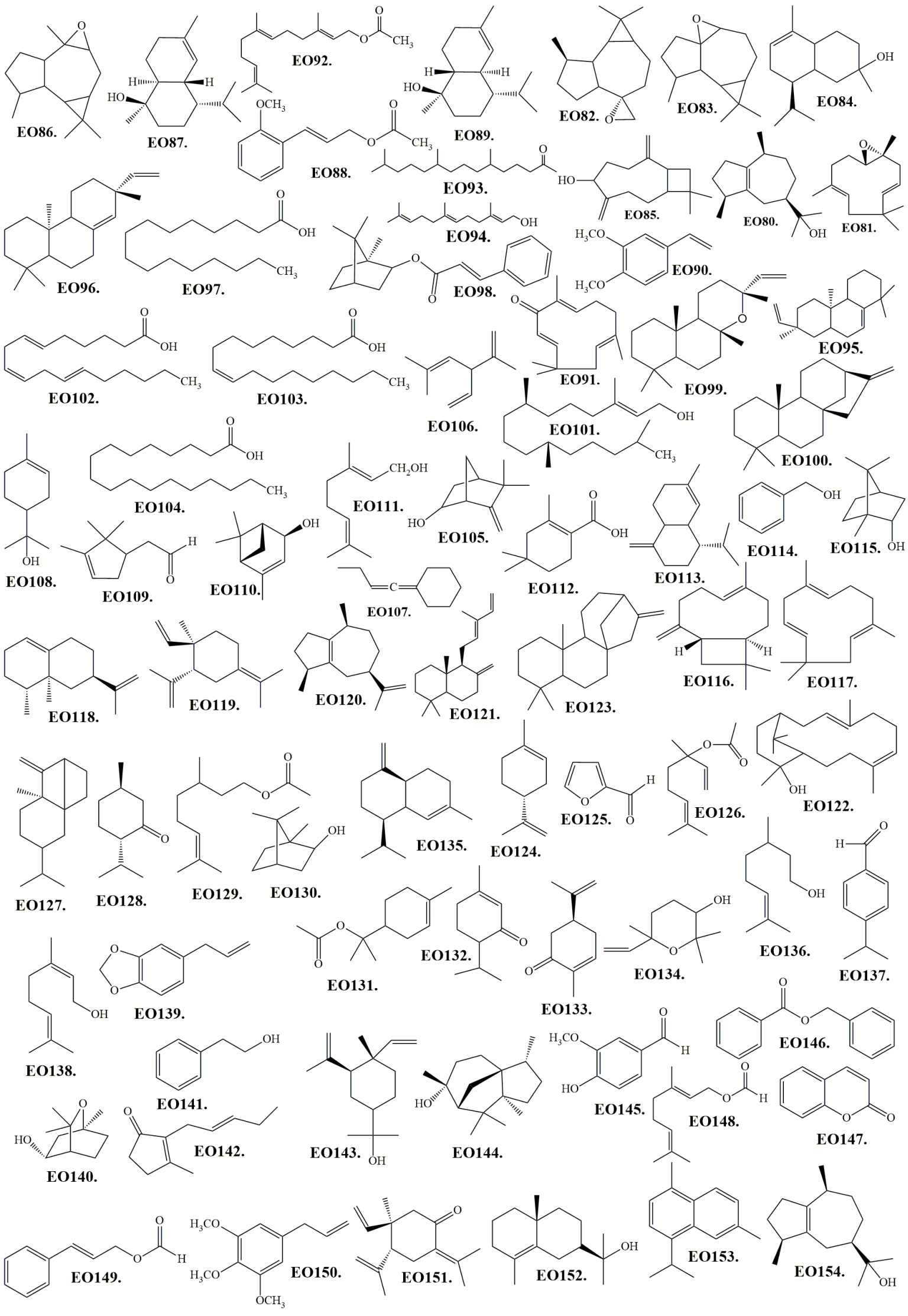

Figure 1: Chemical structures of essential oil components from *C. osmophloeum*.

NO.	Name	Ref.	NO.	Name	Ref.
	From Leaves		**EO116**	*β*-Caryophyllene	[19],[24],[34]
EO1	Benzaldehyde	[19], [23–26], [31], [32], [34–37]	**EO117**	*α*-Caryophyllene	[19]
EO2	Benzenepropanal	[29], [32], [34], [37]	**EO118**	Valencene	[19]
EO3	2-methyl benzofuran	[32], [35], [36]	**EO119**	γ-elemene	[19], [36]
EO4	*p*-allylanisole, Estragole	[19], [23], [24], [29], [31], [32[, [34–36]	**EO120**	*α*-guaiene	[19]
EO5	*cis*-cinnamaldehyde	[19], [24], [26], [31], [32], [34–37]	**EO121**	Labda-8(20),12,14-triene	[19]
EO6	*trans*-cinnamaldehyde	[19], [23–26], [29], [31], [32], [35–37]	**EO122**	Verticiol	[19], [36]
EO7	L-bornyl acetate	[29], [32], [34], [35]	**EO123**	Kaur-16-ene	[19]
EO8	Eugenol	[19], [23–26], [31], [32], [34–37]	**EO124**	Limonene	[23], [24]
EO9	*trans*-β-caryophyllene	[29], [31], [32], [36]	**EO125**	Furfural, 2-Furaldehyde	[24]
EO10	*trans*-cinnamyl acetate	[24–26], [29], [31], [32], [34], [35], [38]	**EO126**	Linalool acetate, Bergamiol	[24]
EO11	Caryophyllene oxide	[19], [24], [29], [31], [32], [35],[36],[39]	**EO127**	Copacamphene	[24]
EO12	Linalool	[19], [24–26], [31], [35], [36], [40]	**EO128**	Menthone	[24]
EO13	Bornyl acetate	[19], [24], [31], [36], [40]	**EO129**	Citronellyl acetate	[24]
EO14	*α*-pinene	[23], [24], [31], [35], [37]	**EO130**	Isoborneol, Isocamphol	[24]
EO15	Camphene	[19], [23], [24], [31], [35], [36], [37]	**EO131**	α-terpinyl acetate	[24]
EO16	*β*-pinene	[19], [23], [24], [31], [36], [37]	**EO132**	Piperitone, 3-Carvomenthenone	[24]

EO17	Isobornylacetate	[37]	**EO133**	*d*-carvone, (*S*)-(+)-Carvone	[24]
EO18	*cis*-Cinnamyl acetate	[19], [26], [34], [35], [36], [37]	**EO134**	2,2,6-trimethyl-6vinyltetrahydropyran-3-ol	[24]
EO19	Ethenylbenzene, Styrene	[31]	**EO135**	γ-cadinene	[24], [36]
EO20	Tricyclene	[31]	**EO136**	Citronellol, or dihydrogeraniol	[24]
EO21	*α*-thujene	[31]	**EO137**	Cuminaldehyde	[24]
EO22	α-fenchene	[19], [31], [36]	**EO138**	Nerol	[24], [35]
EO23	Sabinene	[31], [39]	**EO139**	Safrole, Safrol, Shikimole	[24]
EO24	*β*-myrcene	[24], [31], [35]	**EO140**	2-hydroxy-1,8-cineol	[24]
EO25	α-phellandrene	[31]	**EO141**	2-Phenylethanol	[24]
EO26	3-carene	[31]	**EO142**	*cis*-jasmone	[24]
EO27	*α*-terpinene	[19], [24], [31]	**EO143**	Elemol	[24]
EO28	*p*-cymene	[19], [23], [24], [31], [36]	**EO144**	Cedrol	[24]
EO29	Salicylaldehyde	[19], [31], [35], [36]	**EO145**	Vanillin	[24]
EO30	1,8-cineole	[24–26], [31], [35], [39]	**EO146**	Ascabiol, benzyl benzoate	[24]
EO31	Limonene	[19], [31], [35]	**EO147**	Coumarin	[19], [24–26], [29], [35], [36]
EO32	*trans*-*α*-ocimene	[31]	**EO148**	Geranyl formate	[35]
EO33	*β*-ocimene	[24], [31]	**EO149**	Cinnamyl formate	[35]
EO34	*γ*-terpinene	[31]			

EO35	*cis*-linalool oxide	[19], [24], [31], [35], [39]		***From Bark***	
EO36	*trans*-linalool oxide	[24], [31], [35], [39]	**EO1**	Benzaldehyde	[24]
EO37	Terpinolene	[24], [31]	**EO4**	Estragole, *p*-allylanisole	[24]
EO38	Camphor	[19], [29], [31], [35], [36]	**EO5**	*cis*-cinnamaldehyde	[24]
EO39	Benzylacetaldehyde	[19], [23], [31], [35], [36]	**EO6**	*trans*-cinnamaldehyde	[24]
EO40	Cinnamyl alcohol	[24], [31], [35]	**EO8**	Eugenol	[24]
EO41	4-terpineol	[19], [23], [24], [31], [35], [36]	**EO10**	*trans*-cinnamyl acetate	[24]
EO42	Octyl acetate	[31]	**EO11**	Caryophyllene oxide	[24]
EO43	*cis*-citral, Neral	[19], [24–26], [31], [36], [39]	**EO12**	Linalool	[24]
EO44	Chavicol, or 4-allyphenol	[19], [31]	**EO13**	Bornyl acetate	[24]
EO45	*trans*-anethol	[19], [31], [36]	**EO14**	α-pinene	[24]
EO46	Cinnamyl alcohol	[19], [31]	**EO15**	Camphene	[24]
EO47	*cis*-cinnamic acid	[24], [31]	**EO16**	β-pinene	[24]
EO48	α-cubebene	[19], [31], [34], [36]	**EO24**	β-myrcene	[24]
EO49	Geranyl acetate	[24–26], [31], [35], [36], [39]	**EO27**	α-terpinene	[24]
EO50	(+)-cyclosativene	[19], [31]	**EO28**	*p*-cymene	[24]
EO51	α-ylangene	[31]	**EO30**	1,8-cineole	[24]
EO52	Isoledene	[19], [31], [36]	**EO33**	β-ocimene	[24]

EO53	Copaene	[19], [31]	**EO36**	*trans*-linalool oxide	[24]
EO54	*α*-bourbonene	[31]	**EO37**	Terpinolene	[24]
EO55	*β*-cubebene	[31], [38]	**EO40**	Cinnamyl alcohol	[24]
EO56	*β*-elemene	[31]	**EO41**	4-terpineol	[24]
EO57	(*cis*,*trans*)-*α*-farnesene	[31]	**EO43**	*cis*-citral, Neral	[24]
EO58	Aromadendrene	[31], [36]	**EO47**	*cis*-cinnamic acid	[24]
EO59	*α*-humulene	[19], [24], [31]	**EO49**	Geranyl acetate	[24]
EO60	*α*-acoradiene	[31]	**EO59**	*α*-humulene	[24]
EO61	Alloaromadendrene	[19], [31]	**EO71**	*γ*-murrolene	[24]
EO62	*α*-amorphene	[31]	**EO75**	*α*-calacorene	[24]
EO63	*α*-curcumene	[31]	**EO78**	(+) spathulenol	[24]
EO64	Germacrene-d	[31], [39]	**EO87**	*τ*-cadinol	[24]
EO65	*β*-selinene	[31]	**EO90**	Methyl eugenol	[24]
EO66	*α*-murrolene	[19], [31]	**EO101**	Phytol	[24]
EO67	*α*-zingibirene	[31]	**EO108**	α-terpineol	[24]
EO68	*β*-patchoulene	[31]	**EO111**	*cis*-geraniol	[24]
EO69	Acetyleugenol	[31]	**EO117**	*β*-Caryophyllene	[24]
EO70	*β*-bisabolene	[31]	**EO125**	Limonene	[24]

EO71	*γ*-murrolene	[19], [24], [31], [39]	**EO126**	Furfural	[24]
EO72	1*S*, *cis*-calamenene	[31]	**EO127**	Linalool acetate, Bergamiol	[24]
EO73	*δ*-cadinene	[19], [31], [35], [36], [39]	**EO128**	Copacamphene	[24]
EO74	Cadina-1,4-diene	[31]	**EO129**	Menthone	[24]
EO75	*α*-calacorene	[24], [31]	**EO130**	Citronellyl acetate	[24]
EO76	(+)-nerolidol	[31]	**EO131**	Isoborneol, Isocamphol	[24]
EO77	Lauric acid	[31]	**EO132**	α-terpinyl acetate	[24]
EO78	(+) spathulenol	[24], [31], [35], [39]	**EO133**	Piperitone, 3- Carvomenthenone	[24]
EO79	(+)-ledol	[31]	**EO134**	d-carvone, (*S*)-(+)-Carvone	[24]
EO80	Guaiol	[19], [31]	**EO135**	2,2,6-trimethyl-6-vinyltetrahydro-2H-pyran-3-ol	[24]
EO81	Humulene oxide II	[31]	**EO136**	γ-cadinene	[24]
EO82	Alloaramadendrene oxide (I)	[31]	**EO137**	Citronellol, or dihydrogeraniol	[24]
EO83	Ledene oxide (II)	[31]	**EO138**	Cuminaldehyde	[24]
EO84	6-cadinol	[19], [31], [39]	**EO139**	Nerol	[24]
EO85	10,10-dimethyl-2,6-dimethylenebicyclo[7.2.0]undecan-5-ol	[31]	**EO140**	Safrole, Safrol, Shikimole	[24]
EO86	Isoaromadendrene epoxide	[31]	**EO141**	2-hydroxy-1,8-cineol	[24]
EO87	*τ*-cadinol	[24], [29], [31], [35], [36], [39]	**EO142**	2-Phenylethanol	[24]
EO88	*O*-methoxy cinnamyl acetate	[31]	**EO143**	*cis*-jasmone	[24]

EO89	*α*-cadinol	[19], [31], [35], [36], [39]	**EO144**	elemol	[24]
EO90	Methyl eugenol	[24], [31]	**EO145**	Cedrol	[24]
EO91	Zerumbone	[31]	**EO146**	Vanillin	[24]
EO92	Farnesyl acetate	[31]	**EO147**	Ascabiol, benzyl benzoate	[24]
EO93	6,10,14-trimethylpentadecan-2-one	[31]			
EO94	Farnesol	[31]		***From twigs***	
EO95	Rimuene	[19], [31], [36]	**EO4**	4-allylanisole, or *p*-allylanisole	[41]
EO96	*ent*-pimara-8(14),15-diene	[31]	**EO6**	*trans*-cinnamaldehyde	[41]
EO97	Hexadecanoic acid	[31]	**EO8**	Eugenol	[41]
EO98	Bornyl cinnamate 1	[31]	**EO10**	*trans*-cinnamyl acetate	[41]
EO99	Manoyl oxide	[31]	**EO11**	Caryophyllene oxide	[41]
EO100	(−)-kaurene	[31]	**EO13**	Bornyl acetate	[41]
EO101	Phytol	[24], [31]	**EO53**	Copaene	[41]
EO102	Linolenic acid	[31]	**EO63**	*α*-curcumene	[41]
EO103	Oleic acid	[31]	**EO73**	*δ*-cadinene	[41]
EO104	Octadecanoic acid	[31]	**EO75**	*α*-calacorene	[41]
EO105	6-camphenol	39	**EO76**	(+)-nerolidol	[41]
EO106	Santolina triene	39	**EO78**	(+) spathulenol	[41]
EO107	1-butenylidene-cyclohexane	39	**EO87**	*τ*-cadinol	[41]
EO108	α-terpineol	[19],[24–26], [29], [35], [36], [39]	**EO108**	α-terpineol	[41]

EO109	α-campholenal	[39]	**EO115**	(+)-Borneol	[41]
EO110	*trans*-verbenol	[39]	**EO117**	*β*-Caryophyllene	[41]
EO111	*cis*-geraniol	[19], [24–26], [35], [36], [39]	**EO150**	Elemicin, 3,4,5 Trimethoxyallylbenzene	[41]
EO112	2,4,4-trimethylcyclohex-1enecarboxylic acid	[39]	**EO151**	*trans*-*β*-Elemenone	[41]
EO113	*τ*-cadinene	[39]	**EO152**	γ-Eudesmol, Selinenol, Uncineol	[41]
EO114	Benzyl alcohol, phenylmethanol	[19]	**EO153**	Cadalin	[41]
EO115	(+)-Borneol	[19], [25], [26], [35]	**EO154**	Guaiol acetate	[41]

Table 1: The essential oil components of *C. osmophloeum*

Cinnamon (*C. cassia*) is a common spice with sweet, spicy, and special flavor. It has been widely used in bakeries, drinks, desserts, and cuisines. The main constituent of essential oil from cinnamon bark is *trans*cinnamaldehyde (**EO06**). The leaf EOs of indigenous cinnamon (*C. osmophloeum*) contains higher amount of **EO06** as compared with Cinnamon (*C. cassia*) [2]. In particular, the *C. osmophloeum* leaf EOs contains ~80% (w/w) of *trans*-cinnamaldehyde (**EO06**), and these values ranged from 769 to 809 g/kg of EOs, which correspond to about 8.9−26.1 g/kg of sample [2]. Additionally, the cinnamaldehyde content of the cinnamon bark EOs is ~325 g/kg, which is much lower than the cinnamaldehyde contents of the *C. osmophloeum* leaf EOs (769 to 809 g/kg). Therefore, *C. osmophloeum* leaves can be considered a good quality and has a potential cinnamon substitute source to replace commercial bark cinnamons [2]. Further, a recent report indicates that the relative content of *trans*cinnamaldehyde in the leaves of *C. osmophloeum* ct. cinnamaldehyde has the seasonal variation, which is relatively lower (32.2%) in the month of May as compared with the rest of the months (>76.3%) [42]. On the other hand, the leaf EOs of *C. osmophloeum* contains comparatively lower level of coumarin (0.29−13.99 mg/kg), as compared with the EOs of Cassia cinnamon (26.8−97.4 mg/kg) [2]. Therefore, it is reasonable to suggest that the *C. osmophloeum* as a safer spice substitute for *C. cassia*.

Other (Non-essential oil) metabolites of *C. osmophloeum*

Flavonoids are a class of secondary metabolites that consist of more than 7000 structures with fifteen carbon atoms. This class of compound have a wide-range of bioactive properties, including antioxidant, protective against inflammatory processes, hypertension, arthritis and AIDS, and so on. The flavonoid glycosides compounds, kaempferitrin (**F1**) and kaempferol-7-*O*-*α*-rhamnoside (**F10**) along with coumarin, fumaric acid are reported from the leaves of *C. osmophloeum* (Figure 2, Table 2) [43]. Chemical examination of the 80% methanolic extract from *C. osmophloeum* leaves, resulted in the isolation of highly sweet constituent, *trans*-cinnamaldehyde (in 1.03% yield, w/w) [23]. Phytochemical investigation on the n-butanol fraction of methanol extract from *C. osmophloeum* leaves, resulted in the isolation of four kaempferol glycosides (**F1 – F4**), including a novel one, kaempferol 3-*O*-*β*-Dglucopyranosyl-(1→4)-α-L-rhamnopyranosyl-7-O-α-L-rhamnopyranoside (**F2**) (Figure 2, Table 2) [44]. It is interesting to mention that the compound kaempferitrin (**F1**) is obtained in an appreciable quantity of 0.2428% (w/w) from the leaves of *C. osmophloeum* [44]. The hot water extract of leaves of *C. osmophloeum* resulted in the identification of **F1** and **F3** [37]. The ethanolic extract of twigs from *C. osmophloeum* led to the isolation of kaempferol glycosides, **F1 – F3**, and **F5 – F10** (Figure

2, Table 2) [45]. Chemical examination of water extract of *C. osmophloeum* leaves resulted in the isolation of kaempferol glycosides **F1** and **F10** (Figure 2, Table 2) [46]. To continue, chemical investigations of the $CHCl_3$- and *n*-BuOH-soluble layer of the methanolic extract of the stems of *C. osmophloeum* resulted in the isolation of flavonoids, lignans, and benzenoids (Figure 2, Table 2) [47].

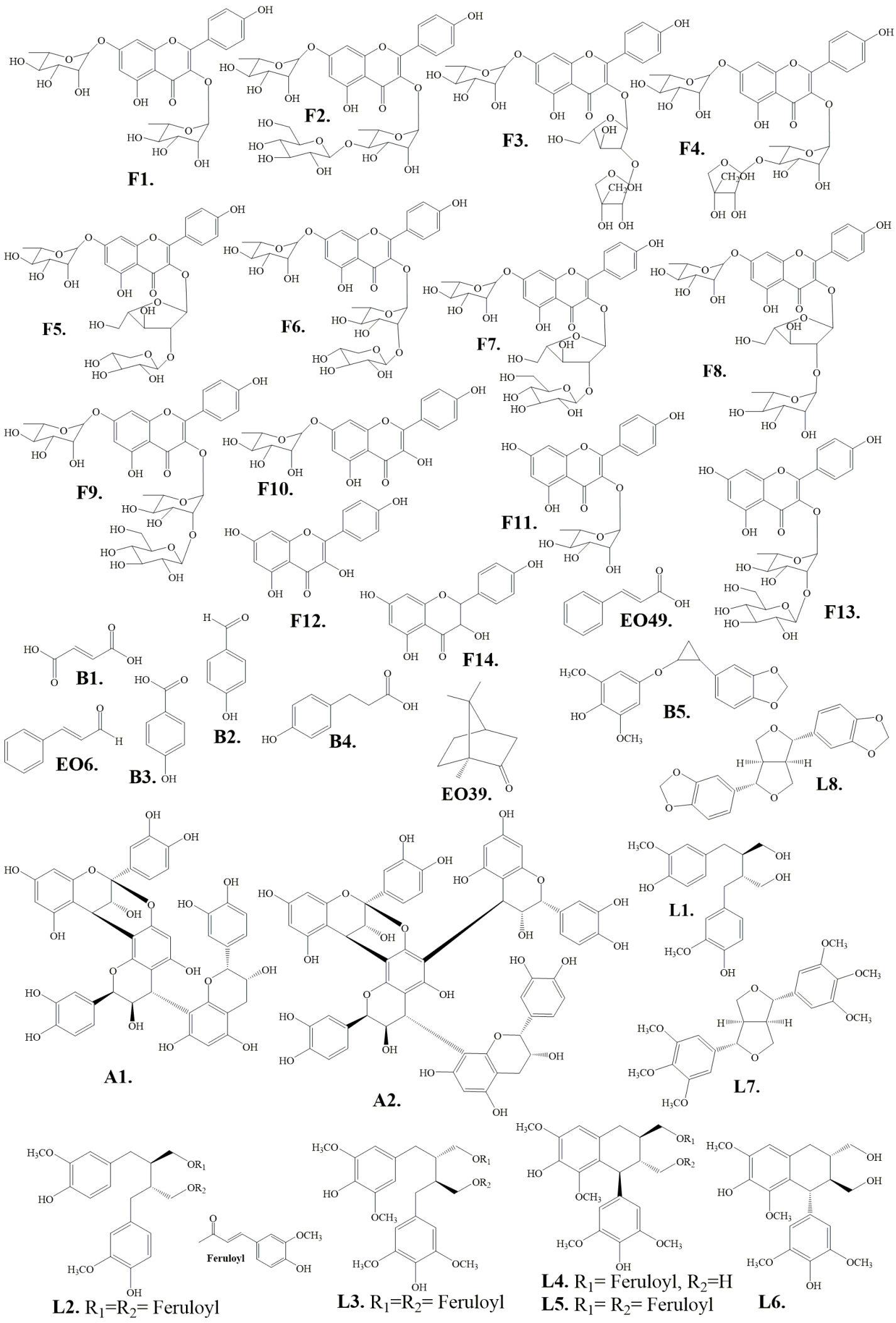

Figure 2: Chemical structures of non-essential oil metabolites from *C. osmophloeum*

On the other hand, lignans are an important part of the secondary metabolites of *Cinnamomum* species, which have high content and abundant structural types. The phytochemical investigations of the ethanol extracts of *C. osmophloeum* heartwood and roots, resulted in the isolation of various lignans including three novel structurally related lignan esters, one secolignan ester (**L3**) and two cyclolignan (or aryltetralin lignan) esters (**L4** and **L5**) (Figure 2, Table 2) [48]. Chemical examination of the *n*-butanol soluble fraction of 70% acetone extract from *C. osmophloeum* twig extracts, resulted in the isolation and structure identification of proanthocyanidins, cinnamtannin B1 (**A1**) and parameritannin A1 (**A2**) (Figure 2, Table 2) [49]. Recently, a novel cyclopropanoid, 4(2-(benzo[d][1,3] dioxol-5-yl)cyclopropoxy)-2,6-dimethoxyphenol (**B5**) is reported from the stems of *C. osmophloeum* (Figure 2, Table 2) [50].

No.	Name	Source / Extraction method	Ref.
	Flavonoids		
F1	Kaempferol 3,7-dirhamnoside or Kaempferitrin	Leaves / n-butanol fraction of methanol extract	[43–45]
		Leaves / Water extract	[46]
		Leaves / hot water extract	[71]
		Stems / $CHCl_3$- and *n*-BuOH fractions of methanolic extract	[47]
F2	Kaempferol 3-O-*β*-D-glucopyranosyl(1→4)-*α*-L-rhamnopyranosyl-7-O-*α*-Lrhamnopyranoside	Leaves / n-butanol fraction of methanol extract	[44], [45]
F3	Kaempferol 3-O-*β*-D-apiofuranosyl(1→2)-*α*-L-arabinofuranosyl-7-O-*α*-Lrhamnopyranoside	Leaves / n-butanol fraction of methanol extract	[44], [45]
		Leaves / hot water extract	[71]
F4	Kaempferol 3-O-*β*-D-apiofuranosy(1→4)-*α*-L-rhamnopyranosyl-7-O-α-Lrhamnopyranoside	Leaves / n-butanol fraction of methanol extract	[44]
F5	Kaempferol 3-O-*β*-D-xylopyranosyl(1→2)-*α*-L-arabinofuranosyl-7-O-*α*-Lrhamnopyranoside	Twigs / 70% ethanol	[45]
F6	Kaempferol 3-O-*β*-D-xylopyranosyl(1→2)-*α*-L-rhamnopyranosyl-7-O-*α*-Lrhamnopyranoside	Twigs / 70% ethanol	[45]
F7	Kaempferol 3-O-*β*-D-glucopyranosyl(1→2)-*α*-L-arabinofuranosyl-7-O-*α*-Lrhamnopyranoside	Twigs / 70% ethanol	[45]
F8	Kaempferol 3-O-α-Lrhamnopyranosyl-(1→2)-α-Larabinofuranosyl-7-O-α-Lrhamnopyranoside	Twigs / 70% ethanol	[45]
F9	Kaempferol 3-O-*β*-D-glucopyranosyl(1→2)-*α*-L-rhamnopyranosyl-7-O-*α*-Lrhamnopyranoside	Twigs / 70% ethanol	[45]
F10	Kaempferol 7-O-*α*-L- rhamnopyranoside	Twigs/ ethanol	[43], [81]
		Stems / $CHCl_3$- and *n*-BuOH fractions of methanolic extract	[47]
		Leaves/ water extract	[46]
F11	Kaempferol 3-O-*α*-L-rhamnopyranoside	Stems / $CHCl_3$- and *n*-BuOH fractions of methanolic extract	[47]
F12	Kaempferol	Stems / $CHCl_3$- and *n*-BuOH fractions of methanolic extract	[47]

F13	Kaempferol 3-*O*-*α*-Lrhamnopyranosyl-(1→2)-*α*-Lrhamnopyranoside	Stems / $CHCl_3$- and *n*-BuOH fractions of methanolic extract	[47]
F14	Dihydrokaempferol	Stems / $CHCl_3$- and *n*-BuOH fractions of methanolic extract	[47]
	Proanthocyanidins		
A1	Cinnamtannin B1	Twigs / n-butanol fraction of 70% acetone extract	[49]
A2	Parameritannin A1	Twigs / n-butanol fraction of 70% acetone extract	[49]
	Benzenoids		
B1	Fumaric acid	Stems / CHCl3- and n-BuOH fractions of methanolic extract	[43], [47]
B2	*p-hydroxybenzadehyde*	Stems / CHCl3- and n-BuOH fractions of methanolic extract	[47]
B3	*p*-hydroxybenzoic acid	Stems / CHCl3- and n-BuOH fractions of methanolic extract	[47]
EO49	Cinnamic acid	Stems / CHCl3- and n-BuOH fractions of methanolic extract	[47]
EO150	Coumarin	Stems / CHCl3- and n-BuOH fractions of methanolic extract	[47]
B4	*p*-dihydrocoumaric acid	Stems / CHCl3- and n-BuOH fractions of methanolic extract	[47]
EO6	*trans*-cinnamaldehyde	Stems / CHCl3- and n-BuOH fractions of methanolic extract	[47]
B5	4-(2-(benzo[d][1,3]dioxol-5yl)cyclopropoxy)-2,6dimethoxyphenol	Stems	[50]
	Lignans		
L1	Secoisolariciresinol	Heartwood and roots/ethanol	[48]
L2	9,9′-di-O-feruloyl secoisolariciresinol	Heartwood and roots/ethanol	[48]
L3	9,9′-di-O-feruloyl-(+)-5,5′-dimethoxy secoisolariciresinol	Heartwood and roots/ethanol	[48]
L4	(7′*S*,8′*R*,8*R*)-lyoniresinol-9-O-(*E*)feruloyl ester	Heartwood and roots/ethanol	[48]
L5	(7′*S*,8′*R*,8*R*)-lyoniresinol-9,9′-di-O-(*E*)- feruloyl ester	Heartwood and roots/ethanol	[48]
L6	(−)-lyoniresinol	Heartwood and roots/ethanol	[48]
L7	(+)-yangambin	Stems/ $CHCl_3$- and *n*-BuOH fractions of methanolic extract	[47]
L8	(+)-sesamin *Terpenoids*	Stems/ $CHCl_3$- and *n*-BuOH fractions of methanolic extract	[47]
EO39	Camphor	Leaves	[40]

Table 2: The reported non-essential oil metabolites of *C. osmophloeum*

Pharmacological Activities of *C. osmophloeum* Extracts and Compounds

Pharmacological potential of essential oils (EOs)/components

Most of the chemical components in EOs of *C. osmophloeum* are low-molecular weight compounds, which can easily diffuse across cell membranes to induce biological reactions [7]. A couple of studies have proposed cinnamaldehyde to be a major functional compound for the antidiabetic activity of cinnamon [1]. The antibacterial activities of the EOs from leaves of two *C. osmophloeum* clones (A and B) were examined against nine strains of bacteria. The results showed that the MICs (minimum inhibitory concentrations) of the B leaf oil were 500 μg/ml against both *Klebsiella pneumoniae* and *Salmonella* sp. and 250 μg/ml against the other 7 strains of bacteria (Table 3) [25]. The MICs of cinnamaldehyde against the *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Staphylococcus aureus*, *S. epidermidis*, MRSA, *K. pneumoniae*, *Salmonella sp*., and *Vibrio parahemolyticus* are 500, 1000, 250, 250, 250, 250, 1000, 500, and 250 μg/ml, respectively (Table 3) [25]. The compound *trans*cinnamaldehyde showed potent inhibitory activity against Jurkat (IC_{50}=0.057μM) and U937 (IC_{50}=0.076μM) cell viability, without affecting the viability of primary purified T cells and macrophages (Table 3) [51]. The leaf EOs from various geographical provenances showed potential antifungal effect against tree pathogens *Rhizoctonia solani*, *Collectotrichum gloeosporioides*, *Ganoderma australe* and *Fusarium solani* [36], and inhibit the expression of pro-IL-1β, IL-1β and IL-6 in endotoxin-induced J774A.1 macrophages [39]. The leaf EOs of 92 cutting clones from a clonal orchard of *C. osmophloeum* showed antioxidant activity [38]. The EOs of *C. osmophloeum* leaves showed potential xanthine oxidase (XOD) inhibition and anti-hyperuricemia effect in mice [37], and the major component in it **EO06** showed inhibitory effect in controlling the red imported fire ant [34]. The mosquito larvicidal activity of leaf EOs and their constituents from six chemotypes of *C. osmophloeum* is examined against the three mosquito species, and the results demonstrated that the cinnamaldehyde type and cinnamaldehyde/cinnamyl acetate type showed superior inhibitory effect against *Aedes albopictus* larvae [35]. The compounds, *trans*-cinnamaldehyde, *T*-cadinol, and *α*-cadinol are the major components of leaf EOs to the observed anti-inflammatory activity of *C. osmophloeum* in the endotoxin-treated RAW 264.7 macrophages [52]. The leaf EO components showed *in vivo* hepatoprotective effects through reduction in serum levels of AST, ALT, TNF-α, and IL-6, as well as hepatic inflammation and, necrotic and apoptotic tissue injury in lipopolysaccharide/ Dgalactosamine (LPS/D-GalN)-treated mice [53]. The compound *trans*-cinnamaldehyde (**EO6**, 1 mg/kg) showed *in vivo* cytokine modulatory effects through increased serum concentrations of IL‐2, IL‐4 and IL‐10, but not IFN‐γ in ovalbumin (OVA)‐primed balb/c mice [54]. The EOs from *C. osmophloeum* leaves exert *in vivo* antioxidant [29], and *in vivo* anti-diabetic effect through improved insulin secretion [31]. The linalool chemotype leaf EOs from *C. osmophloeum* showed, *in vivo* protective effect in the endotoxin-induced systemic inflammatory response through suppression of the TLR4 and NLRP3 signaling pathways [55]. The leaf EOs (13 mg/kg body weight) of *C. osmophloeum* reduced the endotoxin-induced systemic inflammation through the inhibition of the expression of molecules in both TLR4 and NLRP3 signaling pathways [40]. Additionally, it is confirmed that both cinnamaldehyde (**EO06**) and linalool (**EO12**) are the responsible active compounds for the observed biological activity [40]. The thermos-stability of cinnamaldehyde-chemotype *C. osmophloeum* leaf EOs is stabilized by microencapsulation with β-cyclodextrin, and the microencapsulated oil showed superior xanthine oxidase inhibitory activity [56]. The *C. osmophloeum* ct. linalool leaf oil showed *in vivo* antidepressant and motor coordination activities in a rodent animal model [57]. Additionally, the thermal degradation of linalool-chemotype *C. osmophloeum* leaf EOs is stabilized by its microencapsulation with β-cyclodextrin [58]. On the other hand, twigs EOs and its major constituents from the twigs of *C. osmophloeum* showed anti-inflammatory activity through reduced nitric oxide (NO) and prostaglandin E2 (PGE2) production in activated RAW 264.7 macrophages [41]. The reported pharmacological activities of *C. osmophloeum* EOs and their major constituents are presented as in Table 3.

Comp. NO or Tested Sample	Reported activity	Ref.
EO1 (benzaldehyde)	Mosquito larvicidal activity against *Aedes albopictus*, LC_{50}=47.0µg/ml, LC_{90}=85.5µg/ml	[35]
EO6 (*trans*-cinnamaldehyde)	Antibacterial against *E. coli*, *P. aeruginosa*, *E. faecalis*, *S. aureus*, *S. epidermidis*, MRSA, *K. pneumoniae*, *Salmonella sp*., and *V. parahemolyticus*	[25]
	Cytotoxic effect against Jurkat (IC_{50}=0.057µM) and U937 (IC_{50}=0.076µM) cell viability, without affecting the viability of primary purified T cells and macrophages (Fang et al., 2004).	[51]
	Mosquito larvicidal activity (LC_{50}=29ppm, LC_{90}=48ppm)	[19]
	Antioxidant activity determined using DPPH assay. IC_{50}=11 µg/ml	[38]
	Cytotoxicity against human leukemia K562 cells, induce apoptosis through ROS production, glutathione depletion, and caspase activation	[59]
	Inhibit xanthine oxidase (XOD) activity (IC_{50}= 8.4 µg/ml). *In vivo*- 150 mg/kg, oral administration reduced the serum uric acid by 84.48% as compared to the hyperuricemic control mice.	[37]
	Inhibits proinflammatory cytokines secretion from activated macrophages through suppression of intracellular signaling	[60]
	Inhibitory effect in controlling the red imported fire ant. LT_{50} = 32.2 min	[34]
	Mosquito larvicidal activity against *Aedes albopictus*, LC_{50}=48.1µg/ml, LC_{90}=89.1µg/ml	[35]
	Antipathogenic against plant pathogenic fungus *Rhizoctonia solani* IC_{50}=56.4µg/mL	[61]
	In vivo 100 µmol/kg, hepatoprotective effect, attenuated LPS/D-GalN-induced liver injury, reduced the serum AST, ALT, TNF-α, IL-6	[53]
	In vivo 1 mg/kg, cytokine modulatory effect	[54]
	In vivo anti-inflammatory through reduced TLR4 and/or NLRP3 signaling pathways	[40]

	Antifungal activity against wood-decay fungi. Antifungal action attributed to fumigation instead of direct contact	[62]
EO8 (Eugenol)	Mosquito larvicidal activity against *Aedes albopictus*, LC_{50}=67.4μg/ml.	[35]
	Antipathogenic against plant pathogenic fungus *Rhizoctonia solani* IC_{50}=47.8 μg/mL	[61]
EO10 (*trans*-cinnamyl acetate)	Antioxidant activity determined using DPPH assay. IC_{50}=10.4 μg/ml	[38]
	Mosquito larvicidal activity against *Aedes albopictus*, LC_{50}=52.7μg/ml, LC_{90}=99.3μg/ml	[35]
EO11 (Caryophyllene oxide)	Mosquito larvicidal activity against *Aedes albopictus*, LC_{50}=65.6μg/ml.	[35]
EO12 (Linalool)	Antioxidant activity determined using DPPH assay. IC_{50}=29.7 μg/ml	[38]
EO45 (*cis*-citral, Neral)	Mosquito larvicidal activity against *Aedes albopictus*, LC_{50}=70.7μg/ml.	[35]
EO57 (*β*-cubebene)	Antioxidant activity determined using DPPH assay. IC_{50}=19.3 μg/ml	[38]
EO60 (Aromadendrene)	*In vivo* 100 μmol/kg, hepatoprotective effect, attenuated LPS/D-GalN-induced liver injury, reduced the serum AST, ALT, TNF-α, IL-6	[53]
EO90 (*τ*-cadinol)	*In vivo* 100 μmol/kg, hepatoprotective effect, attenuated LPS/D-GalN-induced liver injury, reduced the serum AST, ALT, TNF-α, IL-6	[53]
EO92 (*α*-cadinol)	*In vivo* 100 μmol/kg, hepatoprotective effect, attenuated LPS/D-GalN-induced liver injury, reduced the serum AST, ALT, TNF-α, IL-6	[53]
Leaf essential oils	Antibacterial against *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Staphylococcus aureus*, *S. epidermidis*, methicillinresistant *S. aureus* (MRSA), *Klebsiella pneumoniae*, *Salmonella* sp., and *Vibrio parahemolyticus*.	[25]
Leaf essential oils	Antitermitic activity against *Coptotermes formosanus*	[26]
Leaf essential oils	Antimite activity	[63]

Leaf essential oils	Antifungal activities against tree pathogenic fungi, *Rhizoctonia solani*, *Collectotrichum gloeosporioides*, *Ganoderma australe* and *Fusarium solani*.	[36]
Leaf essential oil	Mosquito larvicidal activity against larvae of *Aedes aegypti*. LC_{50} for cinnamaldehyde type and cinnamaldehyde/cinnamyl acetate type in 24 h were 36 ppm (LC_{90}=79 ppm) and 44 ppm (LC_{90}=85ppm), respectively.	[19]
Leaf essential oil	Anti-inflammatory- 60 µg/mL, inhibited IL-1β and IL-6 but not for TNF-α in LPS-treated J774A.1 murine macrophage	[39]
Leaf essential oils of 92 cutting clones from a clonal orchard	Antioxidant activities determined using DPPH assay	[38]
Leaf essential oils	*In vitro* xanthine oxidase inhibition (IC_{50}=16.3 µg/ml)	[37]
Leaf essential oils	Inhibitory effect in controlling the red imported fire ant. LT_{50} of 2% leaf essential oil is 105.0 min	[34]
6 chemo types of leaf essential oil	Mosquito larvicidal activities against *Aedes albopictus*, *Culex quinquefasciatus*, and *Armigeres subalbatus* larvae. The LC_{50} of cinnamaldehyde and cinnamaldehyde/cinnamyl acetate type against *A albopictus* larvae are 40.8 µg/ml (LC_{90} = 81.7 µg/ml) and 46.5 µg/ml (LC_{90} = 83.3 µg/ml), respectively	[35]
Leaf essential oil	Anti-inflammatory activity in endotoxin-treated RAW 264.7 macrophages	[52]
Leaf essential oil	Antipathogenic against plant pathogenic fungus *Rhizoctonia solani* IC_{50}=79.3µg/mL	[61]
Leaf essential oil	*In vivo* antioxidant activity against juglone-induced oxidative stress in *Caenorhabditis elegans*. Enhanced of antioxidant-genes, SOD-3, GST-4	[29]
Leaf essential oil	*In vivo* antidiabetic activity in STZ-induced rats. 12.5 mg/(kg bw)- reduced fasting blood glucose, fructosamine and, elevated plasma and pancreatic insulin levels. However, 25 and 50 mg/(kg bw) shown to be less effective than that of 12.5 mg/(kg bw). Ameliorated oxidative stress and proinflammatory environment in the pancreas.	[31]
Leaf essential oils	Larvicidal activity against *An. gambiae* s.s. Dose and time dependent. The LC_{50} = 22.18 to 58.15 µg/ml (in laboratory), 11.91 to 63.63 µg/ml (in semi-field environments).	[32]
Essential oil alloaromadendrene from mixed-type leaves	*In vivo* antioxidant activities against juglone-induced oxidative stress on *Caenorhabditis elegans*. Prolongs the Lifespan in *C. elegans*	[64]
trans-cinnamaldehyde chemotype leaf essential oils	Anti-inflammatory, inhibit *H. pylori* growth and postinfectiously inhibit IL-8 mRNA and protein expression in *H. pylori*- and IL-1β-pretreated AGS cells	[65]
Linalool chemotype leaf essential oils	6.5, 13, or 26 mg/kg, *in vivo* protective effect in endotoxin-induced systemic inflammatory response through suppression of the TLR4 and NLRP3 signaling pathways	[55]
S-(+)-linalool and essential oil from leaves	*In vivo* leaf essential oil-250, 500 mg/kg, S-(+)-linalool (500 mg/kg), R-(−)-linalool (500 mg/kg). anxiolytic properties- reduced serotonin, dopamine, and norepinephrine in mice brain	[66]

S-(+)-linalool and essential oil from leaves	*In vivo* hypolipidemic effects- inhibited lipid accumulation through down-regulation of 3T3-L1 adipocyte differentiation	[67]
Leaf essential oils	*In vivo* anti-inflammatory, 13 mg/kg body weight- reduced endotoxin-induced systemic inflammation through inhibition of expression of molecules in both TLR4 and NLRP3 pathways	[40]
Cinnamaldehyde-chemotype leaf essential oil	Thermostability stabilized by its microencapsulation with β-cyclodextrin, and microencapsulated oil showed superior xanthine oxidase inhibitory activity	[56]
Leaf essential oils	Antifungal activity against brown root rot disease fungus *Phellinus noxius*	[68]
Twigs essential oil	Anti-inflammatory, reduced NO and PGE2 in activated RAW 264.7 macrophages	[41]
Linalool leaf essential oil	*In vivo* motor coordination and antidepressant activities in rodent animal model	[57]
Linalool-chemotype leaf essential oil	Thermal degradation is stabilized by its microencapsulation with β-cyclodextrin	[58]

Table 3: The biological activities of *C. osmophloeum* essential oil / components.

Pharmacological activities of *C. osmophloeum* crude extracts

Studies are reported that *C. osmophloeum* crude extracts showed various pharmacological activities such as antioxidant, anti-inflammatory, anti-tyrosinase, anti-obesity, and anti-diabetic, and wound-healing effects. Diabetes mellitus (DM) is a chronic disease that affects about 7% of the world's people and it is expected to increase by 5.5% in 2025 [69]. DM type 2 (T2DM) accounts for 85–90% of all diagnosed diabetic patients with high medical and social costs [69]. Cinnamon also has a long history of therapeutic use for various health problems including diabetes [1]. However, it was not until the past decade that the possible antidiabetic role of cinnamon in humans and in experimental animals has been investigated scientifically [1]. The results of the antidiabetic effect of cinnamon are inconsistent [1]. Although several clinical studies and a few meta-analyses have confirmed the usefulness of cinnamon as an antidiabetic agent, the results of other clinical studies and meta-analysis have shown cinnamon to be ineffective in oral glucose tolerance, insulin sensitivity, fasting blood glucose, glycated hemoglobin, lipid profile, or peripheral insulin levels in type 2 diabetes patients [1].

Rao et al., (2007) [70] reported that the chloroform and methanol extracts of *C. osmophloeum* bark showed anti-inflammatory and anti-cancer properties through the reduced inflammatory mediators (NO, TNF-α and IL12) production in activated macrophages, and tumor cells proliferation, respectively [70]. Oral administration of *C. osmophloeum* leaves hot‐water extracts, reduced the total cholesterol (TC), triglyceride (TG) and low‐density lipoprotein (LDL‐C) levels in hyperlipidemic hamsters [71]. The phenolic content of *C. osmophloeum* water extracts is 160.9 mg/g, which showed a potential antioxidant activity with an IC_{50} values of 10.3 and 16.9 μg/mL, for DPPH and superoxide radical scavenging assays, respectively (Table 4) [46]. The ethanolic extract of *C. osmophloeum* leaves, dose-dependently (10, 25, 50, 100, and 200 μg/mL) reduced the cell viability, tyrosinase activity and melanin content in melanoma B16-F10 cells (Table 4) [72]. Additionally, the ethanolic extract also showed *in vivo* wound-healing activity [72]. To continue, the ethanolic extract from the leaves showed skinwhitening and protective properties through decreased tyrosinase activity and melanin content in IBMX-induced B16-F10 cells [73]. The proanthocyanidin-rich *n*-butanol soluble fractions of 70% acetone extract from *C. osmophloeum* twig extracts, showed anti-hyperglycemic effects through reduced *α*-glucosidase, *α*-amylase and protein tyrosine phosphatase 1B [49,74]. Additionally, the twig extracts showed better α-glucosidase and αamylase activities than leaf, 2-cm branch and 5-cm branch extracts [74]. Furthermore, the proanthocyanidin-rich *n*-butanol soluble fractions of 70% acetone extract also showed antihyperglycemic activity in high-fat diet and streptozotocin-induced hyperglycemic rats [75]. The ethanolic

extract from the *C. osmophloeum* leaves showed liver protective property through induced the *ghrelin* gene variant 1 but not variant 3, mRNA and ghrelin hormone expression in D-ribose-treated HepG2 cells [76]. Recently, the water extract of *C. osmophloeum* (COK) leaves are confirmed to be useful to treat hair loss [77]. The *in vitro* bioassays suggested that COK water extract significantly promoted the proliferation of human hair dermal papilla cells (hDPCs) via up-regulating mRNA levels of some hair growth-related factors covering vascular endothelial growth factor, keratinocyte growth factor (KGF) and transforming growth factor-β2 [77]. Besides, the *in vivo* assays showed that COK leaf extract promoted the anagen phase in the hair growth cycle in hair removal C57BL/6 mouse model [77]. The hydrosol obtained from the steam distillation of *C. osmophloeum* leaves, reduced oxidative stress and melanogenesis in B16F10 melanoma cells and protect against DNA damage [78]. A recent *in vivo* study indicated that 95% ethanolic extract from *C. osmophloeum* leaves had a therapeutic effect against 5-fluororacil-induced oral mucositis in rats [79]. On the other hand, the water-soluble fractions from ground wood of *C. osmophloeum*, enhanced the cultured mycelia of *Antrodia camphorata* and its anti-inflammatory potential through reduced ROS production in human leukocytes [80]. The reported pharmacological activities of *C. osmophloeum* crude extracts are presented as in Table 4.

Tested Sample / Extract	Reported Activity	Ref.
Water-soluble fractions from ground wood	Enhanced the cultured mycelia of *Antrodia camphorata* and its anti-inflammatory potential through reduced ROS production in human leukocytes	[80]
Bark/ hexane, ethyl acetate and methanol extracts	*In vitro*-reduced inflammatory mediators NO, iNOS, TNF-α and IL-12 in LPS/IFN-γ activated murine peritoneal macrophages, and tumor cells proliferation	[70]
Twigs / ethanolic extract	Antioxidant- DPPH, NBT, reducing power, lipid peroxidation	[81]
Leaves / water extract	Antioxidant- DPPH, reducing power	[46]
leaf powder (CoLP)/	Larvicidal activity against *An. gambiae* s.s. Dose and time dependent. The LC_{50} = 22.18 to 58.15 µg/ml (in laboratory), 11.91 to 63.63 µg/ml (in semi-field environments).	[32]
Leaves / ethanolic extract	*In vitro* anti-tyrosinase activity, antioxidant. *In vivo* wound-healing activity	[72]
Leaves / ethanolic extract	Skin-whitening and protective properties through decreased tyrosinase activity and melanin content in IBMX-induced B16-F10 cells	[73]
Twigs/ n-butanol fractions of 70% acetone extract	*In vitro* anti-hyperglycemic effects through reduced α-glucosidase, α-amylase and protein tyrosine phosphatase 1B	[49]
Leaves/ ethanolic extract	Liver protective property through induced *ghrelin* gene variant 1 but not variant 3, mRNA and ghrelin hormone expression in D-ribose-treated HepG2 cells	[76]
Twig extracts/ n-butanol fractions of 70% acetone ext.	*In vivo* (30, 150 mg/kg bw), antihyperglycemic- improved glucose tolerance, decreased weight of visceral fats and lower atherogenic index, weight gain	[75]

Leaves / water extract	Promote hair growth *in vitro* and *in vivo* C57BL/6 mice. Hair growth-related factors- vascular endothelial growth factor, keratinocyte growth factor (KGF), and transforming growth factor-β2 increased in the cultured human hair dermal papilla cells (hDPCs)	[77]
Leaves/ hydrosol	from Decreased melanin synthesis in B16-F10 melanoma cells, antioxidant, anti-tyrosinase, steam distillation anti-melanogenesis, and DNA protective activities.	[78]
Leaves/ 95% ethanol	*In vivo* anti-inflammatory against 5-FU-induced oral mucositis in rats. 100 mg/ mL, inhibit major proinflammatory cytokines	[79]

Table 4: The reported biological activities of *C. osmophloeum* crude extracts.

Pharmacological activities of non-essential oil secondary metabolites

Lignan esters (**L3**, **L4**, **L5**) showed cytotoxicities against human liver carcinoma cells HepG2, Hep3B, and Ca9-22 cancer cells [48] (Table 5). It is reported that kaempferitrin (**F1**) showed anti-inflammatory activity through reduced pro-inflammatory mediators such as nitric oxide, TNF-α and IL-12 in activated-macrophages [44] (Table 5). Diabetes mellitus is characterized by an altered metabolism (of carbohydrates, lipids, and lipoproteins) and chronic hyperglycemia resulting from pancreatic β-cell dysfunction, insulin production deficiency, insulin resistance in key target tissues and impaired glycemic index control [69]. These alterations cause severe complications in the functioning of the cardiovascular system, as well as hypertension and dyslipidemia that are risk factors for stroke and myocardial infarction [69]. The major constituent of *C. osmophloeum* leaves, kaempferitrin activates the insulin signaling pathway and stimulates secretion of adiponectin in 3T3-L1 adipocytes [82] (Table 5). The compounds **F2** and **F3** showed insulin-like anti-diabetic activity in mouse 3T3-L1 adipocytes, through enhanced adiponectin secretion, activation of insulin signaling pathway, GLUT4 translocation activity, phosphorylation of IR and activation of phosphatidylinositol-3 kinase (PI3K) [83] (Table 5).

NO.	Reported activity[a]	Ref.
Flavonoids		
F1	Anti-inflammatory against LPS/IFN-γ-stimulated peritoneal macrophages. Inhibit NO (IC_{50}= 40μM), TNF-α, IL-12	[44]
	Anti-diabetic activity. Activates the insulin signaling pathway and stimulates secretion of adiponectin.	[82]
F2	Insulin-like anti-diabetic activity in mouse 3T3-L1 adipocytes. At 5μM, increase adiponectin secretion, phosphorylation of IR*β*, GLUT4 translocation	[83]
F3	Anti-inflammatory against LPS/IFN-γ-stimulated peritoneal macrophages. Inhibit NO (IC_{50}= 15μM), TNF-α, IL-12	[44]
	Insulin-like anti-diabetic activity in mouse 3T3-L1 adipocytes	[83]
F4	Anti-inflammatory against LPS/IFN-γ-stimulated peritoneal macrophages. Inhibit NO (IC_{50}= 20μM), TNF-α, IL-12	[44]
K10	Anti-inflammatory against LPS-stimulated NO generation in RAW 264.7 macrophages. Inhibit NO (IC_{50}= 41.2 μM). At 50 μM, decreased PGE_2 production by 26%.	[45]
Lignans		
L3	Cytotoxicity in HepG2, Hep3B, Ca9-22 (IC_{50}= > 20 μg/mL in all cells)	[48]
L4	Cytotoxicity in HepG2 (IC_{50}=16.64 μg/mL), Hep3B (IC_{50}=14.49 μg/mL), Ca9-22 (IC_{50}=8.51 μg/mL)	[48]
L5	Cytotoxicity in HepG2 (IC_{50}=7.87 μg/mL), Hep3B (IC_{50}=4.31 μg/mL), Ca9-22 (IC_{50}=2.51 μg/mL)	[48]

Table 5: The reported biological activities of non-essential oil compounds of *C. osmophloeum*. NO: nitric oxide; TNF-α: tumor necrosis factor-α; IL-12: interleukin-12

Analyses of Secondary Metabolites, and Formulations of *C. osmophloeum*

A simple and accurate reversed-phase high-performance liquid chromatographic (RP-HPLC) separation method is developed for the determination of bioactive flavonol glycosides, namely kaempferol-3,7-O-*α*-Ldirhamnoside (kaempferitrin, **F1**), and kaempferol 3-O-β-D-glucopyranosyl-(1→4)-α-L-rhamnopyranosyl-7-O-αL-rhamnopyranoside (**F2**), from the leaves of *C. osmophloeum* [84]. Separation of these two compounds is achieved with a Hypersil BDS C18 column by gradient elution using acetonitrile-water (30:70, v/v) containing 0.1% trifluroacetic acid as a mobile phase. The flow rate and detection wavelength was set at 0.8 ml/min and 265 nm, respectively [84]. A HPLC method is used for the identification of **F1** and kaempferol 3 - O - *β* - D - apiofuranosyl(1→2) - *α* - L - arabinofuranosyl - 7 - *O* - *α* - L - rhamnopyranoside (**F3**), from the hot - water extracts of *C. osmophloeum* leaves [74]. A simple HPLC separation method is reported for the quantitative determination *trans*cinnamaldehyde (**EO06**) from the leaves of *C. osmophloeum* [51,54]. On the other hand, a recent study reported an ultrasound-assisted microextraction method for the rapid determination of essential oil, *S*-(+)-linalool (**EO12**) from the leaves of *C. osmophloeum* ct. linalool [85]. The secondary metabolites of *C. osmophloeum* leaves, kaempferol glycosides are transformed into aglycone kaempferol during the 8 week ensilaged storage at 37°C [86]. A formulation developed by using the hot water extract of *C. osmophloeum* and the ethanolic extract from the solidstate cultured *Antrodia cinnamomea* mycelia, attenuated the metabolic syndrome through improved the abnormal blood glucose and balance the gut microbiota in high-fat diet-induced mouse model [87].

Conclusions/Future Prospects

The major compounds of *C. osmophloeum* are essential oils, and flavonoids. Based on a recent report, *Cinnamomum* essential oil containing cinnamaldehyde might be useful as a food preservative [88]. The self-life of *C. osmophloeum* essential oil is comparatively longer than that of *C. cassia* bark oil due to the existence of both eugenol and cinnamaldehyde in *C. osmophloeum*. Therefore, *C. osmophloeum* essential oil might useful as a natural food products preservative. The different clones (cultivars) may provide different amount of essential oil and flavonoids as well as the biological activities. Thus, the cultivars of *C. osmophloeum* need to take into account for the future medical and pharmaceutical research studies. It is interesting to mention that the *C. osmophloeum* leaves are rich source for the flavonoid compound, kaempferitrin (kaempferol 3,7-dirhamnoside, 0.2428%, w/w) [44]. Kaempferitrin (**F1**) has various interesting biological activities such as insulin-mimetic in glucose homeostasis, anti-inflammatory, anti-convulsant, anti-depressant, anthelmintic, and osteoporosis [89]. Kaempferitrin also improves the meat quality of broiler chickens [89]. On the other hand, the *C. osmophloeum* leaves compounds, kaempferol 3-*O*-*β*-D-glucopyranosyl-(1→4)-α-L-rhamnopyranosyl-7-O-α-Lrhamnopyranoside (**F2**) and kaempferol 3-O-*β*-D-apiofuranosyl-(1→2)-*α*-L-arabinofuranosyl-7-O-*α*-Lrhamnopyranoside (**F3**) had an important role on the insulin signaling pathway through insulin-mimetic potential, stimulate the glucose transporter-4 (GLUT4), phosphorylation of IRβ, and activation of PI3-K, which are important for the treatment of diabetes and insulin resistance [89]. Therefore, *C. osmophloeum* extract enriched these compounds has the potential to be used as a new drug, or as a lead to develop novel therapeutic antidiabetic drugs. Although, various pharmacological activities are reported from the *C. osmophloeum* leaves, however, little is known about the specific active substances and their pharmacological action mechanisms. Therefore, systematic *in vivo* studies of can be done to better interpret the traditional usage of *C. osmophloeum* for diabetes, and to develop as a dietary supplement. Additionally, further *in vivo* studies are need to investigate the bioavailability, distribution and metabolism of *C. osmophloeum*.

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