Variations in Essential Oil Chemical Composition and Biological Activities of Cryptomeria japonica (Thunb. ex L.f.) D. Don from Different Geographical Origins—A Critical Review

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Abstract: The scientific community is paying increasing attention to plant waste valorization, and also to “greener” practices in the agriculture, food and cosmetic sectors. In this context, unused forest biomass (e.g., leaves, seed cones, branches/twigs, bark and sapwood) of Cryptomeria japonica, a commercially important tree throughout Asia and the Azores Archipelago (Portugal), is currently waste/by-products of wood processing that can be converted into eco-friendly and high added-value products, such as essential oils (EOs), with social, environmental and economic impacts. Plant-derived EOs are complex mixtures of metabolites, mostly terpenes and terpenoids, with valuable bioactivities (e.g., antioxidant, anti-inflammatory, anticancer, neuroprotective, antidepressant, antimicrobial, antiviral and pesticide), which can find applications in several industries, such as pharmaceutical, medical, aromatherapy, food, cosmetic, perfumery, household and agrochemical (e.g., biopesticides), with manifold approaches. The EOs components are also of value for taxonomic investigations. It is known that the variation in EOs chemical composition and, consequently, in their biological activities and commercial use, is due to different exogenous and endogenous factors that can lead to ecotypes or chemotypes in the same plant species. The present paper aims to provide an overview of the chemical composition, biological properties and proposals of valorization of C. japonica EO from several countries, and also to indicate gaps in the current knowledge.

Keywords: sustainability; circular economy; Cryptomeria japonica; waste/by-products valorization; plant secondary metabolites; essential oil; terpenes/terpenoids; chemotypes; bioactivities; crop pest control

1. Introduction

Numerous plant-derived essential oils (EOs), due to their valuable odoriferous and bioactivity properties, and GRAS (Generally Recognized as Safe) status, have applications in many fields, such as aromatherapy, cosmetic, cosmeceutical, food, beverage, household, pharmaceutical, phytomedicine and pest control. However, the bioactivity and potential commercial use of EOs depends on their complex mixture of organic compounds, produced through the secondary metabolic pathways of aromatic plants [1–4], such as the conifer Cupressaceae family [4].
Cryptomeria japonica (Thunb. ex L.f.) D. Don (Cupressaceae), commonly called a Japanese cedar or sugi, is a forest tree endemic to Japan, and widely distributed in warm and cool temperate climates. Cryptomeria is a monotypic genus that includes only one species with two recognized varieties: C. japonica var. japonica and C. japonica var. sinensis, the latter being native to China [5].

C. japonica is a very large, conical, evergreen monoecious tree that can reach up to 70 m (230 ft) in height with a trunk diameter of up to 4 m (13 ft). It is a fast growth tree that prefers moist, deep and well-drained soils [6]. The bark is reddish-brown, fibrous and peels off in vertical strips. The leaves are odorous due to the presence of EO and are 0.5–1 cm (0.20–0.39 in) long and needle-like in structure. The seed cones are globular up to 1–2 cm (0.39–0.79 in) in diameter with about 20–40 scales [7].

C. japonica is one of the main plantation forest tree species in Asian countries (Japan, Korea, Taiwan, India and China) and in the Azores Archipelago (Portugal). In Azores, forests account for 31% of the land area, where C. japonica occupies over 12,698 hectares and is the most commercially important tree species. It was introduced in Azores in the mid-19th century, where it developed very well due the similar pedological and climatic conditions to those of its original country. In Azores, C. japonica is often planted around farms to create shelter lines, which increase pasture productivity by creating favorable microclimates for crop and livestock [8].

The pollen of C. japonica causes pollinosis/hay fever, which is a serious health problem in Japan. Male-sterile C. japonica populations that release no pollen have recently gained interest as a potential measure to fight this problem [9].

The wood (heartwood) of C. japonica has different colors, including red, yellow and black, that also determines its economic value. This wood is traditionally used in house building and pulping, due to its “unique” characteristics, which include pleasant aroma, excellent durability, decay resistance and insect repellency properties [10–13].

Owing to the high industrial importance of C. japonica, their leaves, bark, twigs and sawdust are currently waste/by-products of worldwide wood processing. However, this large unused biomass could be converted into useful natural resources of bioactive compounds, such as EOs, in an economically and environmentally sustainable manner with zero competition for land areas. In fact, the production of plant-derived EOs has increased tremendously over the last few decades due the strong demand for natural products, which are less hazardous to the public health and environment than their synthetic equivalents [1,3,4,14].

Particularly, botanical pesticides, including EOs-based pesticides [3], are gaining popularity namely in organic farming, due to their efficiency, availability, safety, inexpensiveness, easily biodegradation (non-pollutant) and low toxicity to non-target organisms [15]. Therefore, they are suitable alternatives in crop pest management and in sustainable agriculture. Botanical pesticides could also be used in rotation with synthetic pesticides in order to minimize crop pest resistance [16,17]. However, EOs have high volatility, limited water solubility and are easily oxidized by ambient factors, such as temperature, light/sun and oxygen, which can have a negative impact on their activities as biopesticides [18]. In this context, nanotechnologies may be useful to overcome some of these limitations [19]. Alternatively to botanical pesticides, EO from C. japonica could be raw material for food preservatives or ecological health-related products, as discussed further below.

It should also be highlighted that deterpenation of EOs (i.e., separation of terpenes and terpenoids) to recover terpenoids is a flourishing issue [20]. Deterpenation also contributes to increase the concentration of trace compounds, enhancing EO bioactivity [18,20]. In fact, main bioactivities might also come from minor constituents [21,22].

Although the bioactivities of C. japonica EO are well documented in Asian countries, limitations, such as inconsistency in EO chemical profile between different regions, volatility, lipophilicity and effectivity of the EO under field conditions, must be reviewed. Therefore, the present review aims to update the current knowledge on the C. japonica EO,
its chemotypes, main reported biological activities and consequent industrial/commercial applications.

2. Data Analysis

The principal component analysis (PCA) and hierarchical cluster analysis (HCA) were performed by using SPSS version 27.0 software (SPSS Inc., Chicago, IL, USA) to show the relationship among the \textit{C. japonica} EO from different regions based on their percentage chemical composition. The PCA was achieved selecting the three highest principal components (PCs) obtained by the linear regressions operated on scaled data. For the statistical evaluation of the complete EO composition, the covariance data was a 19 × 14 matrix (19 EO samples × 14 chemical compounds = 266 data). The first three PCs (PC1, PC2 and PC3) explained 46.8%, 14.7% and 10.0% of the total variance, respectively, allowing the visualization of more than 70% of the information contained within the dataset. HCA was performed using Ward’s method and squared Euclidean distance.

3. Yield and Chemical Composition of \textit{C. japonica} EO

Plant-derived EOs are generally complex mixtures of low-molecular-weight metabolites, particularly monoterpenes (C10) and sesquiterpenes (C15) hydrocarbons, and their oxygenated derivatives, usually extracted from non-woody parts of the plant, such as foliage. However, to a lesser extent, it could also be extracted from other plant tissues (e.g., wood, seeds and bark). Hydrodistillation and steam distillation are the traditional extraction methods used to obtain EO from plants. Another less-used technique is the classic extraction with organic solvents [23], which is a non-eco-friendly process. In order to improve conventional extraction methods, other innovative and green techniques have been developed, such as supercritical fluid extraction [24–26].

Leaves of \textit{C. japonica} are by far the plant organ most used to obtain EO. \textit{C. japonica} leaf EO, typically obtained by hydrodistillation and chemotyped by gas chromatography and mass spectrometry analysis, is pale yellow in color and has a fresh aromatic odor [27–29]. Terpenes and terpenoids are the major components found in \textit{C. japonica} leaf EO, as illustrated in Figure 1.

![Figure 1. Some of the major components of Cryptomeria japonica leaf essential oil.](image-url)

Table 1 shows the yield and major components of \textit{C. japonica} leaf EO according to geographic region. The results revealed that \textit{C. japonica} leaf EO is often characterized by two or more major compounds, which may be present in similar amounts, and that
in most countries, namely in East Asia, ent-kaurene is the major *C. japonica* leaf EO constituent, followed by elemol. However, based on other geographical regions and using PCA (Figure 2), we can categorized the *C. japonica* leaf EO into three distinct chemotypes, regarding major constituents: (1) ent-kaurene chemotype (very frequent in Taiwan [10] and Korea [30]) (2) elemol plus ent-kaurene chemotype (more frequent in Japan [31], China [27] and Nepal [11]) and (3) α-pinene chemotype (found in Azores islands [32], Corsica island [33] and Japan [18]). The corresponding PCs data are found in Table 2.

### Table 1. Yield and major components of *Cryptomeria japonica* leaf EO from different geographical origins.

| Origin             | Major Components of *Cryptomeria japonica* Essential Oil | EOs Yield | Ref. |
|--------------------|---------------------------------------------------------|-----------|-----|
| Taiwan_1           | ent-kaurene (40.6%), valencene (19.9%), eudesma-3,7 (11)-diene (8.4%), α-ocimene (7.9%), β-eudesmol (5.9%), p-cymene (3.7%), elemol (18.2%), ent-kaurene (11.6%), 3-carene (9.7%), sabinene (9.4%), 4-terpineol (9.1%), limonene (5.3%) | 27.38 mL/kg | [10] |
| Taiwan_2           | ent-kaurene (20.4%), elemol (19.1%), α-β eudesmol (11.8%), sabine (10.2%), γ-eudesmol (6.3%), 4-terpineol (6.2%), α-pinene (4.8%) | 24.6 mL/kg | [34] |
| Taiwan_3           | ent-kaurene (21.7%), β-elemol (13.9%), 3-carene (13.1%), sabine (10.3%), α-pinene (6.5%), 4-terpineol (6.0%), γ-eudesmol (4.5%) | 2.37% (w/w) | [21] |
| Taiwan_4           | ent-kaurene (19.1%), α-pinene (16.5%), elemol (16.3%), 3-carene (9.5%), α-eudesmol (8.9%), γ-eudesmol (5.4%) | 39.3 mL/kg | [12] |
| Taiwan_5           | ent-kaurene (27.6%), sabine (11.9%), 4-terpineol (8.2%), β-elemol (7.1%), cedrol (6.8%), γ-terpinene (4.8%) | 2.14% (w/w) | [28] |
| Taiwan_6           | ent-kaurene (23.3%), β-elemol (18.3%), α-pinene (8.5%), γ-eudesmol (8.2%), limonene (6.8%), α-eudesmol (6.5%), β-eudesmol (4.8%), bornyl acetate (3.8%) | 1.6% (w/w) | [36] |
| South Korea_1      | elemol (11.2%), 4-terpineol (9.8%), sabine (8.9%), 10 (15)-cadinene-4-ol (7.2%), α-terpineol (6.1%), α-pinene (6.1%), γ-terpinene (4.7%) | 0.70% 2 | [37] |
| South Korea_2      | ent-kaurene (17.2%), elemol (10.9%), γ-eudesmol (9.4%), sabine (8.9%), α-eudesmol (5.3%), β-eudesmol (5.1%), 4-terpineol (4.1%) | 0.6% (w/w) 2 | [38] |
| South Korea_3      | ent-kaurene (26.3%), γ-eudesmol (19.0%), α-eudesmol (7.9%), elemol (6.9%), β-eudesmol (6.0%), sabine (5.1%), 4-terpineol (4.6%), α-pinene (3.0%) | 0.84% (w/w) | [30] |
| South Korea_4      | ent-Kaurene (19.4%), α-terpineol (13.4%), α-eudesmol (12.2%), elemol (10.9%), γ-eudesmol (10.6%), α-pinene (9.8%), 4-terpineol (5.7%) | 4.7% (w/w) | [39] |
| China_1            | β-elemol (20.1%), ent-kaurene (14.8%), α-pinene (8.0%), β-phellandrene (6.0%), β-elemene (5.9%), α-eudesmol (5.6%), γ-eudesmol (4.1%) | 1.15% (w/w) | [27] |
| China_2            | ent-kaurene (30.6%), α-eudesmol (12.5%), elemol (11.6%), β-eudesmol (11.4%), γ-eudesmol (11.3%), α-pinene (1.8%), 4-terpineol (1.7%) | 1.5% (w/w) | [40] |
| Japan_1            | α-pinene (17.0%), sabine (12.0%), elemol (9.6%), ent-kaurene (6.7%), γ-terpineol (6.1%), γ-eudesmol (4.9%) | — | [18] |
| Japan_2            | ent-kaurene (22.5%), elemol (22.4%), 4-terpineol (21.0%), γ-eudesmol (17.2%), β-eudesmol (8.0%), α-pinene (2.0%) | — | [31] |
| Japan_3            | α-pinene (13.1%), ent-kaurene (9.2%), thujopene (8.8%), β-pinene (8.2%), limonene (5.1%), camphene (3.6%), cedrol (3.3%) | 2.2 mL/kg | [41] |
| Nepal              | ent-kaurene (42.1%), elemol (20.3%), γ-eudesmol (7.0%), β-eudesmol (5.0%), α-eudesmol (4.7%), sabine (4.3%), α-pinene (4.2%) | 0.5% (w/w) | [11] |
| Portugal (Azores)  | α-pinene (9.6–9.5%), (+)-phyllocladene (3.5–26.5%), ent-kaurene (0.2–20.6%), sabine (0.5–19.9%), limonene (1.4–11.5%), elemol (0.2–12.7%), α-eudesmol (1.6–7.1%) | 0.5–1.9% (w/w) 2 | [32] |
| France (Corsica)   | sabine (19.6%), α-pinene (19.1%), β-elemol (10.7%), limonene (9.0%), ent-kaurene (6.5%), 4-terpineol (6.4%), myrcene (4.3%) | 0.61% (w/w) | [33] |

1. The compounds are listed according to their decreasing quantities. 2. Fresh leaves. (—-), not reported.
Figure 2. 3D loading plot of principal components PC1, PC2 and PC3 for Cryptomeria japonica essential oil, based on the major constituents (A) and 3D score plot of C. japonica essential oil setting by its geographical origin (B).

Table 2. Principal components data, based on 14 major compounds of Cryptomeria japonica essential oils.

| Principal Components | PC 1   | PC 2   | PC 3   |
|----------------------|--------|--------|--------|
| α-Pinene             | 0.481  | 0.837  | −0.182 |
| Sabinene             | 0.784  | 0.334  | −0.238 |
| β-Pinene             | −0.046 | 0.871  | −0.279 |
| β-Myrcene            | 0.750  | 0.579  | −0.179 |
| 3-Carene             | 0.641  | −0.421 | −0.358 |
| Limonene             | 0.694  | 0.577  | −0.058 |
| γ-Terpinene          | 0.816  | 0.098  | −0.251 |
| α-Terpineol          | 0.893  | 0.005  | −0.111 |
| Bornyl acetate       | 0.619  | 0.132  | −0.117 |
| Elemol               | −0.126 | −0.006 | 0.714  |
| α+β Eudesmol         | −0.277 | −0.378 | 0.651  |
| γ-Eudesmol           | −0.165 | −0.240 | 0.767  |
| Ent-kaurene          | −0.539 | −0.655 | −0.174 |
| Phyllocladene        | 0.034  | 0.613  | −0.178 |
| Eigenvalue           | 4.56   | 3.44   | 2.00   |
| % of variance        | 46.79  | 16.67  | 10.05  |
| Cumulative %         | 46.79  | 61.45  | 71.50  |

The results of the HCA are shown in Figure 3, revealing that three groups were also distinguished based on the dendrogram, which is in accordance with the PCA.

Alternatively, EO of C. japonica could be classified by the diterpene chemotype of the leaves, which contained ent-kaurene, phyllocladene or ent-sclarene as a main diterpene hydrocarbon or mixtures of these compounds [42]. It is believed that these diterpenes chemotypes are mainly genetically controlled [27,33,42]. Moreover, Yamashita et al. [31] had reported that the diterpene chemotype of the leaves has an impact on the biological activity of the EO, i.e., the ent-kaurene chemotype exhibited higher acaricidal activity than the other diterpene hydrocarbon chemotypes (phyllocladene or ent-sclarene), where the difference between ent-kaurene and phyllocladene was a diastereomer with the same planar structure. This study [31] highlights the importance of the stereostructure/stereochemistry of the compounds on their biological activities. In addition, Suzuki et al. [43] have achieved the same conclusions, regarding sesquiterpenoids from C. japonica extracts.
Ent-kaurene is a diterpene that, apart from its function in plant defense, is the precursor of gibberellins, which represent an important group of plant hormones involved in various physiological plant processes [44]. Although this diterpene is generally the major component of *C. japonica* leaf EO in East Asia, the oxygenated sesquiterpenes made up the higher contribution in this EO [12,45]. However, in α-pinene chemotype, the major EO fraction is normally composed by monoterpenic hydrocarbons [18].

In Azores Archipelago, Moitero et al. [32] reported that the *C. japonica* leaf EO chemotype is α-pinene type, and regarding diterpene hydrocarbon is an ent-kaurene-phyllocladene type. These authors found that ent-kaurene compound is higher in leaf EO of red heartwood-type than on black-type *C. japonica* populations [32]. Nevertheless, in our PCA (Figure 2), α-pinene chemotype was positively associated with phyllocladene but negatively correlated with ent-kaurene.

In addition, in China, Xie et al. [46] reported that elemol-rich leaf EO (elemol plus ent-kaurene chemotype) is usually poor in phyllocladene content. Moreover, this last chemotype is associated with high biological activities (see Sections 4 and 5).

Concerning the EO yield from *C. japonica*, leaves cultivated in different regions varied from 0.5% to 4.7% (w/w) of dry weight, with the highest value found in South Korea (Table 1). The yield of different parts of *C. japonica* in decreasing order is leaf > bark > heartwood > sapwood [10]. However, Garcia et al. [33] have reported that the EO yield from *C. japonica* cones growing in Corsica (France) is 2.7 fold higher than that of leaf EO. Moreover, these authors reported that the cone chemical profile is similar to that of the leaf EO. Further studies should explore this plant organ.
Oppositely to cones, the EO of other tissues of *C. japonica* (bark, heartwood and sapwood) exhibits a dissimilar chemical profile as compared to that of the leaf EO. Briefly, the major fraction in bark EO is usually composed by monoterpenes and monoterpenoids, where ferruginol is a main component [10,12,22,40]. In heartwood EO, the major fraction is composed by sesquiterpene hydrocarbons, mainly cadinene isomers [10,12,40]. Lastly, sapwood EO contains sesquiterpenes and sesquiterpenoids as main fractions, where ferruginol is also a major compound [12,40].

Overall, based on the data described above, a large chemical variability is observed among *C. japonica* EO. Such variation can be attributed to several factors, including exogenous (such as light, precipitation, growing region, nature of the soil and season) or/and endogenous factors (e.g., plant age, plant organ, developmental stage and genotype). Also, the EO yield can be influenced by these same parameters [27,46–48] along with the extraction method used. However, there are conflicting reports in the literature about the influence of environmental conditions on *C. japonica* EO chemotypes, with some studies reporting no effects [33] and others [27] indicating that environmental factors strongly influenced the EO chemical profile. Apart from these studies, it is reasonable to envisage that chemotype variation (within the same plant species) appearing as a plant adaptive process to the local ecologic conditions.

4. Antimicrobial Activity of *C. japonica* EO in Food Industry and Human Diseases

EOs are generally accepted as natural antimicrobials and antioxidants that can be used in the food industry as bio-preservatives to increase shelf life and quality of food products [49]. In addition, infections caused by fungi and bacteria represent a key issue due to the development of resistant species to current fungicides and antibiotics. Therefore, EOs could be an ecological and effective alternative to synthetic antimicrobial agents [49].

Table 3 shows the antimicrobial activity of *C. japonica* EO from different tissues and geographical origins, against several gram-positive and gram-negative bacterial strains, as well as against various fungal species. The minimal inhibitory concentrations (MICs) were determined by the broth dilution method.

Cha et al. [37] reported that EO from leaves of South Korean *C. japonica* has excellent antimicrobial activity against several oral bacteria, except *Escherichia coli*, with MICs ranging from 0.025 to 12.8 mg/mL (Table 3). According to the authors, this activity is mainly due to the presence of α-pinene, sabinene, α-terpineol and 4-terpineol compounds. In fact, the major chemical group of the studied EO is the monoterpene hydrocarbons (highly lipophilic), which possibly possess cytotoxicity by the disruption of bacteria membrane integrity. On the other hand, Lee et al. [50] showed that EO from needles and twigs of South Korean *C. japonica* had weak antibacterial activity, namely against gram-negative bacteria, with MICs greater than 10 mg/mL (Table 3). Similar findings have already been reported for heartwood components of *C. japonica* [51]. The observed discrepancy between the two referred studies can be attributed to the influence of the plant organ on the EO chemical composition. However, it is known that gram-negative bacteria have an outer membrane, rich in lipopolysaccharides, which acts as a permeability barrier against hydrophobic molecules, hence it is expected that EOs are less effective against gram-negative than gram-positive bacteria. Nevertheless, it is worth noting that EOs could also be cytotoxic to eukaryotic cell membranes [52]. Therefore, further studies are needed with respect to both target and non-target organisms.

Oppositely, in the Lee et al. [50] study, *C. japonica* EO (which is ent-kaurene type) exhibited antifungal activity against fungal strains that cause foot rot and other human diseases, namely against *Cryptococcus neoformans* (Table 3). Contrary to the leaves, twigs or heartwood are rich in sesquiterpene hydrocarbons, namely δ-cadinene, which is associated with superior antifungal activities [10,53]. In fact, Cheng et al. [10] showed that the heartwood EO of *C. japonica* from Taiwan, which is rich in sesquiterpene hydrocarbons, has the strongest antifungal activity against wood decay and tree pathogenic fungi, followed by leaf EO. This activity was associated mainly with δ-cadinene, the major compound in
the EO. Therefore, EO from C. japonica could also have applications in timber industry as natural wood preservatives. Moreover, in Takao et al. [53] study, the EO from the heartwood of Japanese C. japonica inhibited the growth of Trichophyton rubrum, while no antibacterial activity was observed with respect to Staphylococcus epidermidis (Table 3), possibly due to the lack of monoterpene hydrocarbons, as the authors stated. Contrary to heartwood EO, leaf EO of C. japonica, which is rich in monoterpene hydrocarbons, is highly active against this gram-positive strain [37,38] (Table 3). Furthermore, diterpenoids [54] and diterpenes in EO from C. japonica leaves can also affect microbes that cause skin [38] and human diseases, such as tuberculosis [32]. However, these last authors were more restrictive as considering EOs with MIC > 0.250 mg/mL as inactive (Table 3). Yet, C. japonica EO had shown weak antibacterial activity against Legionella pneumophila, with a minimal bactericidal concentration (MBC) value higher than 2 mg/mL [55]. Overall, components from C. japonica EO have strong antimicrobial effects that can inhibit food decay-related microbial growth and can be promising antibiotic therapeutic agents.

| Origin   | Plant Organ            | Target Species                                                                 | Efficiency                                                                 | Ref.  |
|----------|------------------------|-------------------------------------------------------------------------------|---------------------------------------------------------------------------|-------|
| Portugal | Leaves, heartwood, bark| Mycobacterium tuberculosis, Botrytis cinerea, Fusarium circinatum, Cryptocercia parasitica, Aspergillus niger, Trichoderma harzianum, Cladosporium cladosporioides, Cladosporium sp., Candida albicans, Candida tropicalis, Saccharomyces cerevisiae, Cryptococcus neoformans, Aspergillus fumigatus, Microsporum gypseum, Trichophyton rubrum, Trichophyton mentagrophytes | Effective against M. Tuberculosis, T. harzianum, B. cinerea, C. cladosporioides and Cladosporium sp., MICs range 0.025-0.25 mg/mL | [32]  |
| South Korea | Leaves plus twigs     | Candida albicans, Candida pseudotropicalis, Candida glabrata, Candida tropicalis, Candida krusei, Candida parapsilosis, Cryptococcus neoformans, Aspergillus fumigatus | Effective, MICs 2.18 mg/mL or higher                                      | [50]  |
| Taiwan   | Leaves, heartwood, sapwood, bark | Trametes versicolor, Lenzites betulina, Laetiporus sulphureus, Gloeophyllum trabeum, Fusarium oxysporum, Rhizoclonia solani, Canoderna austral, Fusarium solani, Pestalotiopsis funerale, Collectotrichum gloeosporioides | Highly effective, IC50 range 0.039 > 0.500 mg/mL, except bark EO          | [10]  |
| Japan    | Heartwood             | Staphylococcus epidermis, Trichophyton rubrum                                 | Effective, MIC = 0.313 mg/mL, except S. epidermis                        | [53]  |
| South Korea | Leaves                | Staphylococcus epidermis, Propionibacterium acne                              | Effective, MICs range 0.156–10 µL/mL                                     | [38]  |
| South Korea | Leaves                | Escherichia coli, Staphylococcus aureus, Staphylococcus epidermis, Streptococcus pyogenes, Streptococcus mutans, Streptococcus sanguinis, Streptococcus sobrinus, Streptococcus ratti, Streptococcus criceti, Streptococcus anginosus, Streptococcus gordonii, Actinobacillus actinomy cetemcomitans, Fusobacterium nucleatum, Prevotella intermedia, Porphyromonas gingivalis | Effective, MICs range 0.025–12.8 mg/mL, except E. coli                  | [37]  |
| South Korea | Leaves plus twigs     | Acinetobacter calcoaceticus, Staphylococcus aureus, Bacillus subtilis, Klebsiella oxytoca, Klebsiella pneumoniae, Pseudomonas aeruginosa, Serratia marscens | Ineffective, MICs > 21.8 mg/mL                                         | [50]  |
| Taiwan   | Leaves, heartwood, twigs, bark | Legionella pneumophila                                                         | Ineffective, MBC > 2 mg/mL                                               | [55]  |

MIC—minimal inhibitory concentration; MBC—minimal bactericidal concentration; IC50—half maximal inhibitory concentration.
Antimicrobial compounds are usually highly correlated with antioxidant effects [56]. In fact, besides microbial contamination, lipid peroxidation is a real problem related to food deterioration and the addition of antioxidants is an attractive strategy to retard or even stop oxidation processes. *C. japonica* extracts from different tissues are rich in phenolics, which are well-known natural antioxidants and antibacterial agents [43,57]. Contrary to *C. japonica* extracts, EO from various tissues of this plant exhibited weak antioxidant activities (in 2,2-diphenyl-1-picrylhydrazyl free radical scavenging assays), presenting the sapwood EO with the best value (IC$_{50}$ = 113 µg/mL), followed by twigs, heartwood, bark and lastly leaf EOs [12]. The effect of sapwood EO on the free radical scavenging assay is attributed to its hydrogen-donating ability, possibly due to the high content of ferruginol (an oxygenated diterpene). Thus, sapwood EO or ferruginol can also be used as natural food preservatives in food industry. In fact, it has already been reported that diterpenes show higher antioxidant and antimicrobial effects than monoterpenes [39].

As discussed earlier, it is noteworthy that enrichment of *C. japonica* EO fractions with specific compounds can be a useful strategy to pest/microbes management, where deterpenation with vacuum fractional distillation can be effective. Kusumoto and Shibutani [18] had submitted EO from *C. japonica* leaves to an open system mild heat treatment, which decreased the content of monoterpen hydrocarbons and increased the content of oxygenated sesquiterpenes and diterpenes. They found that the evaporation residue had higher antifungal activity than the crude EO. Also, Salha et al. [20] reported the same findings for *Origanum majorana* EO. Further studies should explore this issue.

5. Acaricidal and Insecticidal Activities of *C. japonica* EO

The EOs play a functional role in the plant chemical defense against phytopathogens and pests [2,15]. For that reason, they are a potentially good source of environmentally friendly pesticides or pest-control agents. Table 4 shows the insecticidal and acaricidal effects of *C. japonica* EO from different tissues.

Spider mites, such as *Tetranychus urticae* and *Tetranychus kanzawai*, are known as world pests of agricultural crops. However, since spider mites easily build up a tolerance to pesticides, EOs have been studied as alternative eco-pesticides. Yamashita et al. [31] found that EO from the leaves of *C. japonica* is a fruitful option to control these mites (Table 4). They mainly attributed this acaricidal activity to the ent-kaurene compound, followed by elemol.

Silverfish (*Lepisma saccharina*), another pest common in libraries and museums where paper books and labels are abundant, are insects that owe their survival to their secretive life in damp, cool places. As observed in a Wang et al. [34] study, this pest is also sensitive to *C. japonica* leaf EO, which highly repelled silverfish (>80% of repellency at 0.01 mg/cm$^3$ after 4 h) and killed it on contact assay (LD$_{50}$ value of 0.087 mg/cm$^3$ after 10 h) (Table 4). These authors assigned these toxic effects to volatiles (monoterpenes) and non-volatiles compounds (such as ent-kaurene and elemol), respectively.

Biodegradation of wood caused by termites is one of the most serious problems for wood utilization, and extracts from wood tissues can provide natural protection against harmful pests. Therefore, and as shown in Table 4, EO from *C. japonica* (namely from leaf and heartwood) can be a natural termicide. In particular, elemol plus ent-kaurene chemotype is associated with high antitermitic activity (by contact assay), which in the Cheng et al. [36] study was correlated with elemol and α-terpineol compounds.

In addition to pest control, EOs have been used since ancient times to repel insects, especially insect vectors of human diseases, such as yellow fever, dengue and malaria. Investigations on the insecticidal and repellent effects of *C. japonica* EO (elemol plus ent-kaurene chemotype) on *Aedes aegypti* and *A. albopictus* larvae and adults were carried out by Cheng’s research team [21,35,58]. When compared to other plant tissues, leaf EO showed superior larvicidal [58] and repellent activities against those mosquitoes (Table 4), and when the authors [35] assessed individual EO components, they found that 4-terpineol had the best repellent activity. Other monoterpenes, such as 3-carene, were also important
in larvicidal effects [21]. Apart from bark, leaves are the main plant tissue that have high concentrations of monoterpenoids (volatile compounds), which are usually associated with the best insect repellency [34,35].

It is interesting to note that EO from *C. japonica* leaves is more effective in larvicidal and repellent activities against *A. aegypti* and *A. albopictus* than their methanolic extracts [21,45]. However, methanolic extracts from other *C. japonica* tissues (such as sapwood) have also been stated as excellent mosquito larvicidal agents [45,59].

A further study [17] reported the larvicidal effects of *C. japonica* leaf EO on *Anopheles gambiae* (the main malaria vector), and revealed promising results in the laboratory (Table 4) and semi-field conditions.

**Table 4. Insecticidal and acaricidal activities of Cryptomeria japonica essential oil from different tissues.**

| Plant Organ | Pests | Bioassay | Efficiency | Ref |
|-------------|-------|----------|------------|-----|
| Leaves      | *Lepisma saccharina* | Contact assay (on treated filter papers) against the adult silverfish | Significant toxicity with LD$_{50}$ of 0.087 mg/cm$^3$ after 10 h More than 80% of repellency at 10 µg/cm$^3$ after 4 h | [34] |
| Leaves      | *Aedes aegypti* | Aqueous suspension of essential oil against the fourth-instar mosquito larvae | Significant larvicidal activity with LC$_{50}$ of 37.5 µg/mL after 24 h | [58] |
| Bark        | *Aedes aegypti* | Aqueous suspension of essential oil against the fourth-instar mosquito larvae | Significant larvicidal activity with LC$_{50}$ of 48.1 µg/mL after 24 h | [58] |
| Sapwood     | *Aedes aegypti* | Aqueous suspension of essential oil against the fourth-instar mosquito larvae | Significant larvicidal activity with LC$_{50}$ of 82.7 µg/mL after 24 h | [58] |
| Heartwood   | *Aedes aegypti* | Aqueous suspension of essential oil against the fourth-instar mosquito larvae | Significant larvicidal activity with LC$_{50}$ of 72.0 µg/mL after 24 h | [58] |
| Leaves      | *Aedes albopictus* | Aqueous suspension of essential oil against the fourth-instar mosquito larvae | Significant larvicidal activity with LC$_{50}$ range of 51.2–57.9 µg/mL after 24 h | [21] |
| Leaves      | *Aedes aegypti* | Repellent assay | 82% of repellency at 1.92 µg/cm$^3$ after 20 min More than 70% of repellency at 1.92 µg/cm$^3$ after 20 min About 70% of repellency at 1.92 µg/cm$^3$ after 20 min More than 50% of repellency at 1.92 µg/cm$^3$ after 20 min | [35] |
| Leaves      | *Aedes albopictus* | Repellent assay | 71% of repellency at 1.92 µg/cm$^3$ after 20 min More than 60% of repellency at 1.92 µg/cm$^3$ after 20 min More than 60% of repellency at 1.92 µg/cm$^3$ after 20 min More than 60% of repellency at 1.92 µg/cm$^3$ after 20 min | [35] |
| Leaves      | *Anopheles gambiae* | Aqueous suspension of essential oil against the third-instar mosquito larvae | Significant larvicidal activity with LC$_{50}$ of 40.9 µg/mL after 24 h | [17] |
| Leaves      | *Coptotermes formosanus* | Contact assay (on treated filter papers) against the adult termite | High mortality, with LD$_{50}$ of 1.57 mg/g after 7 days Inactive | [36] |
| Leaves      | *Reticulitermes chinensis* | Contact assay (on treated filter papers) against the adult termite | High mortality, with LC$_{50}$ of 0.9 µL/mL after 5 days LC$_{50}$ of 19.6 µL/mL after 5 days LC$_{50}$ of 158.3 µL/mL after 5 days | [40] |
| Leaves      | *Tetranychus urticae* | Contact assay (on treated leaf discs) against spider mites | Significant mortality, with LC$_{50}$ of 1109 µg/mL after 96 h | [31] |
| Leaves      | *Tetranychus urticae* | Contact assay (on treated leaf discs) against spider mites | Significant mortality, with LC$_{50}$ of 1150 µg/mL after 96 h | [31] |
| Leaves      | *Reticulitermes chinensis* | Contact assay (on treated filter papers) against the adult termite | High mortality, with LC$_{50}$ of 0.9 µL/mL after 5 days LC$_{50}$ of 19.6 µL/mL after 5 days LC$_{50}$ of 158.3 µL/mL after 5 days | [40] |
| Leaves      | *Tetranychus urticae* | Contact assay (on treated leaf discs) against spider mites | Significant mortality, with LC$_{50}$ of 1109 µg/mL after 96 h | [31] |
| Leaves      | *Tetranychus urticae* | Contact assay (on treated leaf discs) against spider mites | Significant mortality, with LC$_{50}$ of 1150 µg/mL after 96 h | [31] |
6. Other Biocidal Activities of C. japonica EO

Although studies regarding elemol plus ent-kaurene chemotype or ent-kaurene chemotype are the most reported in the literature, EO from leaves of C. japonica from Azores (α-pinene chemotype) has recently been reported to have high molluscicidal activity against Radix peregra (Lymnaeidae), a freshwater snail that hosts a number of significant parasites, such as Fasciola hepatica [61]. This parasite is the causing agent of fascioliasis, a well-known veterinary problem of vertebrate domestic livestock, which causes animal production losses and consequent economic costs [62]. The lethal concentrations (LC_{50}) of the EO varied between 33.3 and 61.8 ppm on an aqueous suspension assay [61]. Although the author has not assessed individual EO components for molluscicidal activity, it is worth pointing out that this EO has α-pinene as the major component. Moreover, this same EO chemotype exhibited inhibitory activities against Pseudaletia unipuncta (Lepidoptera: Noctuidae), an important pest of agricultural crops. Particularly, this leaf EO inhibited eggs hatching and thereafter exhibited lethal and sub-lethal effects. Additionally, it showed high repellency properties against adults [63].

More recently, some other C. japonica bioactivities have been described. For instance, Tanaka et al. [64] reported that chemical components of C. japonica leaves suppress the growth of invasive plants (Robinia pseudoacacia) and weeds (Trifolium repens), which are the largest competitor of agricultural crops, with negative impact on productivity. In addition, there are some studies on the growth inhibition activities of C. japonica chemical components (mainly from bark) against harmful marine [22] and freshwater [43] algae. The strong growth-inhibitory activity of the C. japonica bark EO against the bacillariophyceae Skeletonema costatum (commonly known as red tide plankton) was correlated with the presence of ferruginol [22], which has a strong antioxidant activity, as already mentioned. The results of this study [22] indicate the potential of a new use for components of C. japonica bark EO to control red tide plankton growth, a serious environmental problem in the world’s oceans, which can have an adverse impact on aquaculture. Further studies should explore this item, as the C. japonica bark is a promising waste that is available in large quantities.

7. Pharmacological Properties of C. japonica EO

Aromatic plants, such as C. japonica, synthesized and emitted complex mixtures of volatile organic compounds (VOCs) in order to facilitate their growth and survival [13,65]. The VOCs from C. japonica have already been reported to provide relaxing and stress-relieving effects on mice [66] and on humans [67]. In this way, C. japonica EO could be a useful tool in mental health management.

In addition, the most abundant VOCs emitted from C. japonica wood during the drying process, in the wood industry, are sesquiterpenes, such as δ-cadinene, α-muurolene and β-cadinene. These VOCs were assessed as having soothing effects in a human sensory evaluation [68]. Moreover, the main constituent of C. japonica heartwood EO is δ-cadinene [10,13]. It is believed that this compound and other VOCs of C. japonica suppress the sympathetic nervous system activity in humans, especially in women, stimulating relaxing and pleasurable emotions [69]. Furthermore, VOCs from C. japonica leaves display antitussive effects in guinea pigs [70] and increases the output of fluid in the respiratory tract [71]. However, further studies regarding the long-term effects of the inhalation of these volatiles are required.

On the other hand, different tissues of C. japonica also have bioactive compounds with benefits to the skin, which can have several skin health applications (inhibiting melanin production, skin ageing, antiseptic, etc.) [39,72,73]. In particular, phytochemicals from this heartwood have been reported to possess antifungal properties in vitro against Trichophyton rubrum, a major cause of Tinea pedis [53], as already seen in Section 4. Moreover, EO from C. japonica leaves also showed excellent anti-inflammatory and antibacterial activities in vitro, being an attractive acne-mitigating candidate [38]. Another recent study [54] also stated
that phytochemicals compounds from *C. japonica* by-products, namely diterpenoids, can be useful in skin health.

In addition, the EO from *C. japonica* leaves, namely its diterpenes, is a strong inhibitor of acetylcholinesterase activity, which could be an effective therapeutic agent for Alzheimer’s disease [74]. Alternatively, this EO can be explored in the preventive dentistry field, as an effective inhibitor of oral bacteria [37,75], or as an anticancer chemopreventive [76] and antiulcer [77] agent. The results of this last study, suggested that 4-terpineol could have gastroprotective activity.

Overall and according to the literature [76], various parts of *C. japonica* have been used in Asian folk medicine for a variety of indications, including liver ailments, and an antitussive, and for its antiulcer activities. Hence, more studies are warranted with respect to these health benefits, namely, the toxic effects.

8. Conclusions

In the last two decades, several investigations have been conducted on components of *C. japonica* EO, mainly on Asian chemotypes. However, all *C. japonica* EO chemotypes exhibited antimicrobial properties and hence can have applications as food preservatives and/or as antibiotic alternatives. Moreover, this EO can have applications in agrochemical (as repellent, larvical, insecticidal, acaricidal or termicidal) and cosmeceutical industries (as skin whitening agents or oral bacteria inhibitors). Nevertheless, future research should establish EO safe concentration prior any of these biological applications. Additionally, other *C. japonica* by-products (such as seed cones, bark and sawdust), as well as the enrichment of *C. japonica* EO fractions with specific compounds, should be exploited.

Thus, the interest in the *C. japonica* EO by the scientific community and the EOs market, quickly increases.

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