

Review

Effects of Essential Oils and Selected Compounds from *Lamiaceae* Family as Adjutants on the Treatment of Subjects with Periodontitis and Cardiovascular Risk

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Abstract: Essential oils from different plant species were found to contain different compounds exhibiting anti-inflammatory effects with the potential to be a valid alternative to conventional chemotherapy that is limited in long-term use due to its serious side effects. Generally, the first mechanism by which an organism counteracts injurious stimuli is inflammation, which is considered a part of the innate immune system. Periodontitis is an infectious and inflammatory disease caused by a dysbiosis in the subgingival microbiome that triggers an exacerbated immune response of the host. The immune-inflammatory component leads to the destruction of gingival and alveolar bone tissue. The main anti-inflammation strategies negatively modulate the inflammatory pathways and the involvement of inflammatory mediators by interfering with the gene's expression or on the activity of some enzymes and so affecting the release of proinflammatory cytokines. These effects are a possible target from an effective and safe approach, using plant-derived anti-inflammatory agents. The aim of the present review is to summarize the current evidence about the effects of essential oils from derived from plants of the *Lamiaceae* family as complementary agents for the treatment of subjects with periodontitis and their possible effect on the cardiovascular risk of these patients.

Keywords: periodontitis; inflammation; oils; volatile; heart disease risk factors

1. Periodontitis

Periodontal disease is classically defined as a chronic inflammatory lesion, and gingivitis and periodontitis are the most common diseases derived from periodontium involvement [1]. Periodontitis is a complex chronic inflammatory disease caused by Gram-negative anaerobic bacteria located in the subgingival biofilm [2], which can induce the production of inflammatory mediators, causing the destruction and loss of dental bone support [3]. Periodontitis is also described as an infectious disease which affects the tooth-supporting tissues and leads a numerous clinical, microbiological and immunological symptoms, associated with and, probably, induced by progressive interaction among infectious agents, host immune responses, hazardous environmental exposure and genetic predisposition [4].

Anaerobic bacteria are considered as periodontal pathogens, and the following have been highlighted: *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, *Prevotella*

intermedia, *Tannerella forsythia*, *Eikenella* spp. and *Capnocytophaga* spp. However, it is important to highlight that those bacteria are mandatory for the disease development but are not enough and do not account for all cases of periodontitis [5]. The results of one survey in the USA indicate that chronic periodontitis affects about 46% of the adult population, with a higher prevalence among the elderly population [6]. This prevalence refers to the cohort of young adults according to the World Health Organization (WHO), aged 35 to 44 years. Interestingly, forms of periodontitis that occur at younger ages (before the age of 30 years), have other characteristics in addition to age and are known as aggressive periodontitis, with the prevalence ranging from 0.2% in Caucasians to 2.6% in Afro-Americans [7]. It is known that oral microbiome is in equilibrium between these microorganisms and the host response, which has a crucial role in both health and disease development [8]. Unfavourable modifications in the composition of the microbiota are known as dysbiosis [9], which is seen in both cases, periodontitis and CVD. In case of periodontitis, antiseptics and antibiotics such as chlorhexidine or metronidazole are delivered locally in addition to scaling and root planning procedures in order to eradicate the subgingival microbes, therefore creating a healthy subgingival environment. However, the evidence in the literature is still inconclusive [10], and future clinical trials with strict methodological criteria that will allow a more precise evaluation of the efficacy of local antimicrobials in the treatment of chronic periodontitis are required.

In the initial phase, there are no clinical signs; thus, the presence of inflammation cannot be observed. However, when the lesion progresses, vasodilation occurs locally due to the action of bacterial metabolic products, including cytokines [11]. Such initial lesion continues to progress, and a leukocyte infiltrate (mostly lymphocytes and neutrophils) is produced towards the site of inflammation. Crevicular fluid increase occurs, and clinical signs of inflammation appear [12]. In the next phase, or established injury, an inflammatory infiltrate, consisting of T and B lymphocytes, plasma cells and neutrophils, appears, followed by an increase in collagenolytic activity and more collagen-producing fibroblasts. This stage corresponds to moderate to severe gingivitis [12]. The final phase or advanced lesion is distinguished by an unresolved process, fibrosis and an irreversible loss of bone structure, characterized by clinical and histological patterns [2]. In addition, a dense inflammatory infiltrate in connective tissues and predominantly neutrophils in the epithelium are noticed, while, on the other hand, an apical migration of plasma cells to the junctional epithelium occurs to try to defend or keep the epithelial barrier intact, and, consequently, there is a continuous loss of collagen and connective tissue. Finally, if the lesion extends deep, the osteoclasts cause a resorption that affects the alveolar bone [1].

It should be highlighted that periodontitis is a multifactorial disease that requires interdisciplinary treatment concepts and the selection of a therapy that affects the microbiological nature of the disease [13]. In this regard, the recently introduced classification of periodontal diseases [14] aims to identify well-defined clinical entities using clear criteria that are able to link diagnosis with prevention and treatment, thus moving towards precision and individualized dentistry [15].

The interest in the application of natural products has been increased in the last years [16]. Several natural products and herbs have suggested that they have better properties and less side effects compared to chemical agents for irrigation. Furthermore, the use of natural extracts and essential oils (EOs) as an irrigation agent for ultrasonic instrumentation has shown to benefit slight adjunctive effect compared to chlorhexidine or water [17]. Yet, the use of natural extract in subjects with a more severe degree of periodontitis was associated with a greater improvement compared with controls [18]. Natural products in forms of oral spray have shown to be efficient against common oral pathogens, but also safe, without significant cytotoxicity in an in vitro study [19]. Thus, nutraceuticals might have the potential to prevent the infections and may be used as an adjunctive treatment to conventional therapy, as they seem to have the same or even more anti-inflammatory and antimicrobial effect without adding any chemicals. However, still there is not enough scientific evidence on this topic [20,21].

2. Cardiovascular Diseases

Cardiovascular diseases (CVDs) such as coronary heart disease, myocardial infarction, and ischemic stroke are one of the main causes of death worldwide [22]. In 2012, CVDs accounted for around 17.5 million deaths, representing almost a 31% of the worldwide mortality [23]. Atherosclerosis represents one of the main underlying processes for CVDs. It is defined as a condition characterized by formation of an atheroma plaque in the intima layer of the arterial wall; it is composed by an accumulation of lipids, cells and extracellular matrix [24]. High LDL-cholesterol (LDL-C) levels have been traditionally considered as one of the major risk factors for coronary heart disease and, together with triglycerides, are the main risk factors for atherosclerosis [25]. The current approaches for atherosclerosis management focus on the prevention of plaque growth and its destabilization through risk factor control (hypertension, lipid profile, diabetes, smoking, etc.), using lifestyle interventions (diet, physical activity, smoking cessation, etc.) and pharmacological therapies [26]. Recent advances in the understanding of the atherosclerotic process revealed that cholesterol and lipid deposition is not the only causative factor of this disease [27]. Systemic and chronic inflammation plays critical roles in the initial phases, as well as atherosclerotic plaque progression [26,28,29]. During atherosclerotic plaque formation, monocytes are recruited from the blood flow to the arterial wall and differentiate into macrophages of inflammatory phenotype and lipid-containing foam cells. These cells drive the inflammatory process and stimulate plaque maturation and thrombosis [30,31]. Interleukin 10 (IL-10) is an immunoregulatory cytokine with reported anti-inflammatory properties [32]. IL-10 has shown to play a protective role against atherogenesis by inhibiting several inflammatory mediators from activated macrophages and dendritic cells [33–35]. Intramuscular injection of IL-10-encoding plasmid DNA in IL10 knockout mice caused an increase in the cytokine level and inhibited plaque formation by 60% [33]. These findings clearly suggest that IL-10 may be a promising therapeutic target for atherosclerosis management [27]. Inflammation plays a key role in atheroma plaque formation and progression [36]. Evidence has suggested that higher levels of circulating C reactive protein (CRP) have a greater risk of suffering an acute myocardial infarction or cerebrovascular event [37]. The main factors of atheroma plaque vulnerability are the composition of the plaque core, the inflammatory process and the formation of a fibrotic layer that covers the nuclei [38]. It has been reported that inflammation of the atheroma plaque interferes with the formation of the fibrous cape, causing apoptosis and degradation of the extracellular matrix by metalloproteinase activation and increasing the risk of plaque rupture and consequent thrombotic cardiovascular events [38,39]. In those situations, alternative therapeutic approaches, such as the use of dietary supplements and nutraceuticals, may be useful [40]. It is known that the main causes of mortality of subjects with non-alcoholic fatty liver disease (NAFLD) are CVDs. Although the available data are not numerous for a final conclusion and relatively few nutraceuticals have been adequately studied for their effects on NAFLD, several nutraceuticals have been shown to contribute to the improvement of lipid infiltration of the liver and of the related anthropometric and/or biochemical parameters [41]. However, such their positive effects are associated with well-chosen dose, supplementation for a medium-long period and lifestyle changes. There are growing data in the literature demonstrating the beneficial effects of nutraceuticals in metabolic diseases and showing significant impact on different cardiometabolic risk factors (including inflammatory markers) and CVD risk [42]. However, more randomized trials as well as observational studies with specific CVD endpoints are needed.

3. Periodontitis and Cardiovascular Risk

Numerous mechanisms have been proposed as links between periodontitis and atherosclerotic CVD, but the most important include systemic inflammation, molecular mimicry and direct plaque colonization by periodontal pathogens [38]. Several systematic reviews and meta-analyses have reported an association between periodontal disease and ischaemic heart disease [43–47]. Some authors have suggested that at clinical exploration

level, periodontitis and CVD have a weak association, and that, actually, systemic bacterial exposure from periodontitis could be a more plausible risk factor. In this context, Mustapha et al. [46] reported that periodontitis with increased markers of systemic bacterial exposure (periodontal bacterial burden, periodontitis-related specific serology and CRP) was associated with a greater risk of coronary heart disease compared with subjects without periodontitis [37]. It has also been shown that periodontitis patients present increased levels of inflammatory markers (tumour necrosis factor (TNF), interleukin (IL)-1, 6 and 8) [48]. Short-term adaptive response to inflammation is essential for a correct injury response and cell and tissue repair processes, while long-term consequences of a maintained inflammatory situation are often not beneficial [49]. It has also been reported that low-grade and chronic inflammation are characteristic in cardiometabolic diseases such as obesity, insulin resistance, type 2 diabetes and CVDs [50,51]. An atypical immune response has been referred in these situations, described as metabolically triggered inflammation or “metaflammation”, originated by metabolic surplus, which leads to the activation of different inflammatory molecules and signalling pathways [50]. It is worth mentioning that both metabolic and immune systems are regulated by the same cellular processes, through several hormones, cytokines and bioactive lipids that have a role in the metabolic and immune response. The activation of these “metaflammatory” pathways has been related to extracellular mediators such as cytokines and lipids, especially saturated fatty acids, and also by intracellular mediators such as endoplasmic reticulum stress and elevated production of mitochondria-derived reactive oxygen species. Fatty acid-binding proteins (FABPs), a family of lipid chaperones, have shown molecular and cellular links with “metaflammation”, particularly in cases of cardiometabolic diseases such as obesity, diabetes and atherosclerosis [49].

The most recent consensus document regarding association between periodontitis and CVDs was the results from the joint workshop of the European Federation of Periodontology (EFP) and the World Heart Federation (WHF) in February 2019 [52]. According to its recommendations, periodontitis was considered as an established, novel CV risk factor that influences the management of subjects suffering from CVD or at increased CVD. The management of traditional CV risk factors, such as hypertension, is also required in the presence of periodontitis, and a good periodontal health is of great relevance for achieving CV health [53]. However, it remains to be determined if periodontal treatment in subjects with hypertension would translate into a reduced CV risk. Again, inflammation still appears to be one of the main links between CVD and periodontitis [52]. It should be mentioned that the available evidence mainly comes from observational studies, assessing major CV outcomes such as myocardial infarction, stroke, heart failure or CVD death, but few studies have investigated preclinical markers of CVD in subjects with periodontitis. Very interestingly, some studies suggested that healthy subjects with periodontitis may present signs of early atherosclerosis, and thus, periodontitis may be considered as a risk factor in case of CV events that cannot be fully explained by the presence of other commonly used CV risk factors [37,52]. Future studies are needed to better understand the relationship between both diseases and to detect early stages of CVD or alterations in CV structure and function linked to periodontitis. The last published randomized controlled trials confirm a positive effect of periodontal treatment on surrogate CV measures, while its effect on the incidence of CVD events (myocardial infarction and stroke) have not been investigated in powered randomized controlled studies with adequate control of traditional CV risk factors [54,55].

Interestingly, it has been proposed that botanical products may provide a new perspective in stem cell-based periodontal regeneration thanks to their angiogenic properties that may be beneficial for bone formation and periodontal regeneration [56].

4. Plant-Derived Essential Oils

An essential oil (EO) is generally defined as a product obtained from a natural raw material of plant origin, usually by steam distillation or by mechanical processes [57].

These plant products are very complex natural mixtures of secondary volatile metabolites produced by aromatic plants, where they represent chemical defences against herbivores and pathogens such as bacteria, viruses and fungi [58]. They also exert a dual role in attracting pollinating insects and in repelling the harmful ones [59]. In plants, essential oils are synthesized by all tissues and are stored in secretory cells, epidermic cells or glandular trichomes; consequently, they can be extracted from any plant organs such as buds, stems, twigs, leaves, roots, wood, bark, flowers, fruits and seeds [59]. The particular composition of each EO depends not only on the plant species or plant tissue from which it is extracted but also on the climate, on the soil composition, on the vegetative cycle stage or age and even on the time of the harvest [60]. Moreover, the chemical profile is also affected by the extraction method carried out, thus highlighting the importance of specific extraction techniques over the steam distillation, such as solvent extraction, Soxhlet extraction, microwave-assisted hydro distillation, solvent flavour evaporation, etc., in compliance with the plant material characteristics [61]. Their peculiar chemical composition is mainly represented by various terpenoids and their oxygenated derivatives, along with aldehydes and ketones, esters and alcohols [60]. Generally, they are colourless volatile liquids soluble in organic solvents with a density lower than that of water. The most commercial EOs are extracted from various aromatic plants growing in temperate and warm regions of the Mediterranean and tropical areas, where they are historically used in traditional medicine against a wide variety of pathological conditions due to their numerous pharmacological activities including antimicrobial, antiviral, antioxidant and anti-inflammatory effects [59].

Chronic inflammation and oxidative stress are associated with most of the common chronic disorders and diseases [62,63]. It is known that the normal functions of biological molecules (such as proteins, lipids and DNA) are destabilized by oxidative stress sustained by free radicals (ROS, NRS), which also affects many inflammation-related signalling pathways, thus influencing the cellular and tissues homeostasis. On the other hand, chronic inflammation is characterized by the production of proinflammatory cytokines and chemokines, which leads to pain, redness and swelling of the involved tissue [64]. In traditional medicine, EOs have been used for the treatment of inflammatory processes [65], as they possess many beneficial properties due to the presence of several antioxidant and anti-inflammation compounds such as terpenes, the main class of compounds, and especially monoterpenes [61]. They are also present in numerous pharmaceutical products [66]. In recent studies, *Citrus bergamia* Risso and Poiteau juice (known as Bergamot) on cardiometabolic risk in dyslipidemic subjects was shown to significantly reduce plasma lipids and improve the atherogenic lipoproteins and subclinical atherosclerosis [67]. Other recent studies with chlorogenic acid and luteolin-based supplement from artichoke extract showed an improvement of two early atherosclerotic markers, carotid intima-media thickness and flow-mediated dilation, evidencing a clinical relevance, considering their beneficial nutraceutical properties, on vascular function and remodelling, including a beneficial cardiovascular and hepatoprotective effects [68].

It is widely known that EOs are recognized for their antimicrobial, antiviral and antifungal activity, but recent studies have also demonstrated potent antioxidant, anti-inflammatory and antidiabetic properties as well as cancer suppressor activity [69]. Thus, the potential of EOs as effective and safe phytotherapeutic agents should not be underestimated, although their efficacy in oral health is well documented [70]. The antibacterial activity of EOs as well as their isolated constituents and their potential applicability in novel dental formulations have been summarized in a systematic review [71], emphasizing the need for further nonclinical and clinical studies. Interestingly, in the last two decades, EOs have been extensively tested for their beneficial properties against a broad spectrum of bacterial species [72] that indicate their use in the files of dentistry and periodontal diseases. All these beneficial actions increase an interest in future investigation of these plants, including the field of periodontitis. Recent research suggests that oxygenated terpenoids found in the EOs diffuse within the bacterial cell membrane, irreversibly damaging it

and causing cell death. In this regard, recently Anusha D. et al. assessed the efficacy of mouthwash containing EOs and curcumin (MEC) as an adjunct to nonsurgical periodontal therapy on the disease activity of rheumatoid arthritis (RA) among RA subjects with chronic periodontitis. They also investigated epigenetic modifications including chemical alterations of DNA and associated proteins influencing the remodelling of the chromatin and gene malfunctions, which may be related to both periodontitis and RA. The results revealed that MEC as an adjunct to SRP as an effective approach in reducing the disease activity of both RA and chronic periodontitis [73].

5. Essential Oils from *Lamiaceae* Family

Based on recent literature data, the *Lamiaceae* family seems to be one of the richest sources of a wide variety of plants with biological and medical applications [74]. It is a large group with a cosmopolitan distribution that includes 236 genera and about 7000 species that occupy different natural ecosystems [75]. The most interesting members of this family are a variety of aromatic spices traditionally harvested from spontaneous or cultivated population for their culinary use and for their characteristic and unique EOs obtained from them [76]. Numerous *Lamiaceae* species are native of the Mediterranean area and are widely used in natural medicine, pharmacology, cosmetology and aromatherapy due to the multiple therapeutic effects exerted by the components of their EOs [74]. The volatile compounds most generally found as the main ingredients in EOs among plants of this family are caryophyllene, linalool, limonene, β -pinene, 1,8-cineole, carvacrol, α -pinene, p-cymene, γ -terpinene, thymol and terpineols [77]. Several EOs from the *Lamiaceae* species are often present in toothpastes and mouthwashes as flavourings and fragrances, and recently also as antibacterial, antifungal and anti-inflammatory agents [77].

It has been proposed that high doses of EOs are needed in order to exert pharmacological effects, but recent studies indicate that this matter can be avoided using the oil formulated as nanoemulsions to improve its bioavailability [78]; thus, more investigations are needed in the future to confirm this finding. Interestingly, in addition to antioxidant, anti-inflammatory, antimicrobial, spasmolytic, antinociceptive, antitumor activity, some EOs, such as those from *Thymus vulgaris* L. may enhance cognitive function, as shown in animal models [79]. In a recent study, Carbone et al. developed nanostructured lipid carriers (NLC) using EOs from Mediterranean species *Rosmarinus officinalis* L., *Lavandula x intermedia* "Sumian", *Origanum vulgare* L. subsp. *Hirtum* (Link) Ietswaart and *Thymus capitatus* (L.) Hoffmanns. & Link (syn. *Coridothymus capitatus* (L.) Reichenb. fil., *Thymbra capitata* (L.) Cav.) with the purpose of examining the antioxidant and anti-inflammatory effects. Their results demonstrated that EOs in these NLC induced a significant and dose-dependent anti-inflammatory effect in the following order from greater to less potency: *Lavandula* L. > *Rosmarinus* L. \geq *Origanum* L. It is worth noting that encapsulation of both *Lavandula* and *Rosmarinus* EOs in the NLC did not modify the anti-inflammatory activity of the EOs compared to the use of them as free compounds [80].

5.1. *Lavandula x intermedia* (Lavender)

The lavender EOs are generally composed mainly by camphor, terpinen-4-ol, linalool, linalyl acetate, beta-ocimene and 1,8-cineole [81]. Immunomodulatory and anti-inflammatory properties of compounds found in the lavender EOs have also been reported [82]. Many inflammatory processes are associated with leukotriene production catalysed by lipoxygenase (LOX), which can use molecular oxygen or hydrogen peroxide as oxidants. *L. x intermedia* EOs showed a moderate antioxidant activity, mainly attributed to the effect of linalool and linalyl acetate. These findings supported the use of EOs of *L. X intermedia* as natural ingredients useful for gastrointestinal disorders and for oxidative stress-related diseases [83].

5.2. *Rosmarinus officinalis* (Rosemary)

Characteristic EOs of *Rosmarinus officinalis* include 1,8-cineole, α -pinene, camphor, bornyl acetate, borneol, camphene, α -terpineol, limonene, β -pinene, β -caryophyllene and myrcene. In traditional medicine, it is used for the treatment of inflammation-related disorders [84]. Yet, this plant exerts antioxidant activity and prevents inflammatory ROS-related injury, stimulates smooth muscle relaxation and has low toxicity. Bustanji et al. performed a study to identify the effects of rosemary in blood glucose and lipid profile. They reported through an in vitro assay that rosemary extract (with the component gallic acid: IC₅₀ 14.5 μ g/mL) inhibited in a dose-dependent manner the activity of cyclic adenosine monophosphate of gluconeogenic genes, cytosolic phosphoenol-pyruvate carboxykinase and glucose-6-phosphatase. Rosemary extract showed hypoglycaemic and hypolipidemic effects by activation of signalling pathways including AMP-activated protein kinase (which induces glycolysis) and proliferator-activated receptor gamma (PPAR- γ). It upregulated the expression of LDL-C receptor (responsible of the endocytosis of LDL-C from blood plasma to liver hepatocytes), sirtuin-1 (increasing the oxidation of fatty acids) and PGC1 α (activates PPAR- γ) [85]. Neutrophils are rapidly mobilized, and they are one of the first and main cells to arrive at the inflammation site. Oral treatment with *R. officinalis* aqueous extract reduced the neutrophil influx, the release of cytokines and the oxidative stress on inflamed exudates [86]. The study of Borges et al. [87] showed that all nanoemulsions showed no toxicity and also showed the ability to potentiate the anti-inflammatory action of essential oils by exerting immunomodulatory activity by inhibiting the production of the proinflammatory mediator nitric oxide.

Plant extracts and their compounds have proven to be an alternative for treating periodontal diseases, since rosemary has shown antibacterial and anti-inflammatory activities in toothpaste presentation, which reduced biofilm formation and improved gingival bleeding [88]. Rasooli et al. also reported an in vivo reduction of biofilm by rosemary EO and suggested its potential use as an anticaries agent [89]. Bernardes et al. also confirmed this antimicrobial activity against oral bacteria in their study. These authors used common bacterial species from the oral cavity (*Streptococcus mutans*, *Streptococcus mitis*, *Streptococcus sanguinis*, *Streptococcus salivarius*, *Streptococcus sobrinus* and *Enterococcus faecalis*) in planktonic form, and the greatest antimicrobial activity of rosemary EO was shown against *Streptococcus mitis* [90]. The results of Smullen et al. have shown that rosemary and other plant-derived extracts inhibited growth and adhesion of oral bacteria to glass, inhibited both glucosyltransferase activity and glucan production by *S. mutans* and prevented plaque formation in vitro and on bovine teeth [91].

5.3. *Thymus capitatus* (Thyme)

The main single constituents of EOs from *Thymus* genus are thymol, carvacrol, linalool, α -terpineol, 1,8-cineole and borneol [92]. Iauk et al. [93] have investigated the hypoglycaemic activity of *T. capitatus* (L.) Hoffsgg. & Link via the inhibition of α -amylase and α -glucosidase, inhibitors that offer an attractive strategy to control postprandial hyperglycaemia for type 2 diabetes management. Manconi et al. [94] had suggested that formulations on *Thymus capitatus* EO in phospholipid vesicles might be used as an antibacterial-antioxidant mouthwash for the treatment of oral cavity diseases. Finally, Valerio et al. [95] indicated the potential use of thyme as biopreservative for bakery products due to its antimicrobial properties. The antioxidant activity of the formulations was evaluated as a protector of keratinocytes against the damage induced by hydrogen peroxide. They were capable of favouring wound repair in keratinocytes. The antibacterial activity of the EO was demonstrated against cariogenic *Streptococcus mutans*, *Lactobacillus acidophilus* and commensal *Streptococcus sanguinis* [94]. Alvarez-Echazú et al. used thymol-chitosan hydrogels to protect the dental biofilm from breakdown and treat inflammation [96]. *Thymus zygis* has been studied more extensively from an immunological point of view. In a cellular model with human macrophages the gene expression for IL-1 β , TNF α and IL-6 were significantly reduced, and anti-inflammatory cytokines such as IL-10 dose-dependently highly

increased [97]. *Thymus zygis* has also been tested in vitro as an antibacterial agent against *E. coli*, *S. enteritidis*, *S. essen* and other bacterial species [98]. Interestingly, in addition to antioxidant, anti-inflammatory, antimicrobial, spasmolytic, antinociceptive and antitumor activity, some EOs, such as those from *Thymus vulgaris* L. may enhance cognitive function, as shown in animal models [79].

5.4. Selected Compounds as Essential Oils from Lamiaceae Family

The following table presents a summary of the main compounds of EOs from the *Lamiaceae* family and their effects on inflammatory processes (Table 1).

Table 1. Anti-inflammatory effects of selected compounds of Essential Oils from *Lamiaceae* family.

Compound	Experimental Model	Effects	References
Terpineols	in vitro	↓ inflammatory mediators	Hart et al. 2000 [99]
	in vitro	↓ inflammatory cytokines	Nogueira et al. 2014 [100]
	in vivo	↓ inflammation	Zhang et al. 2018 [101]
Linalool	in vitro	↓ inflammatory mediators	Huo et al. 2013 [102]
	in vivo	↓ acute lung inflammation	Ma et al. 2015 [103]
Limonene	in vitro	↓ inflammatory mediators	Kummer et al. 2013 [104]
	in vitro	↓ inflammatory mediators	Yoon et al. 2010 [105]
	in vitro	↓ inflammatory mediators	Rufino et al. 2015 [106]
Carvacrol	in vivo	↓ inflammation, antibacterial	Botelho et al. 2008 [107]
	in vitro/in vivo	↓ inflammatory mediators	Guimaraes et al. 2012 [108]
	in vitro	↓ inflammatory mediators	Hotta et al. 2010 [109]
	in vitro	↓ inflammatory mediators	Landa et al. 2009 [110]
Eucalyptol	in vivo	↓ inflammation	Yalçin et al. 2007 [111]
	in vitro	↓ inflammatory mediators	Bastos et al. 2011 [112]
	in vitro	↓ inflammatory mediators	Kennedy-Feitosa et al. 2016 [113]
	in vitro	↓ inflammatory mediators	Juergens et al. 2004 [114]
	in vitro	↓ inflammatory mediators	Kim et al. 2015 [115]
Tymol	in vitro	↓ inflammatory mediators	Chauhan et al. 2014 [116]
	in vitro	↓ inflammatory mediators	Vigo et al. 2004 [117]
	in vitro	↓ inflammatory mediators	Marsik et al. 2005 [118]
	in vitro	↓ inflammatory mediators	Liang et al. 2014 [119]

↓: Decrease of levels.

Terpineols are isomers of monocyclic monoterpene alcohol naturally present in different plants, among which the most common are α -terpineol and terpinen-4-ol [120] (Figure 1). In particular, the latter has been shown in vitro to suppress inflammatory mediator production by activation of monocytes [99] and to inhibit inflammatory cytokine generation in LPS-stimulated human macrophages [100] but also in animal models to attenuate inflammation in dextran sulphate sodium-induced colitis [121], prevent LPS-induced acute lung injury by decreasing LPS-induced NF- κ B activation and trigger peroxisome PPAR- γ [122] (Figure 2).

Linalool (3,7-dimethyl-1,6-octadien-3-ol) is an acyclic monoterpene found in EOs of hundreds of plants widely spread worldwide and principally in *Lamiaceae* family [74] (Figure 3A). Several in vitro and in vivo studies demonstrated different anti-inflammatory effects of this monoterpene also interfering with the mediators of the inflammation pathways. In detail, in RAW 264.6 monocyte/macrophage-like cells linalool decreased the generation of lipopolysaccharide (LPS)-induced TNF- α and IL-6 and inhibited the activation of the nuclear factor- κ B (NF- κ B) and mitogen-activated protein kinase (MAPK) pathways [102]. In addition, in animal models, it has been shown that linalool attenuated acute lung inflammation by reducing TNF- α , IL-6, IL-8, IL-1 β and monocyte chemoattractant protein-1 (MCP-1) production [103], further supporting linalool as a promising tool to treat inflammatory related diseases.

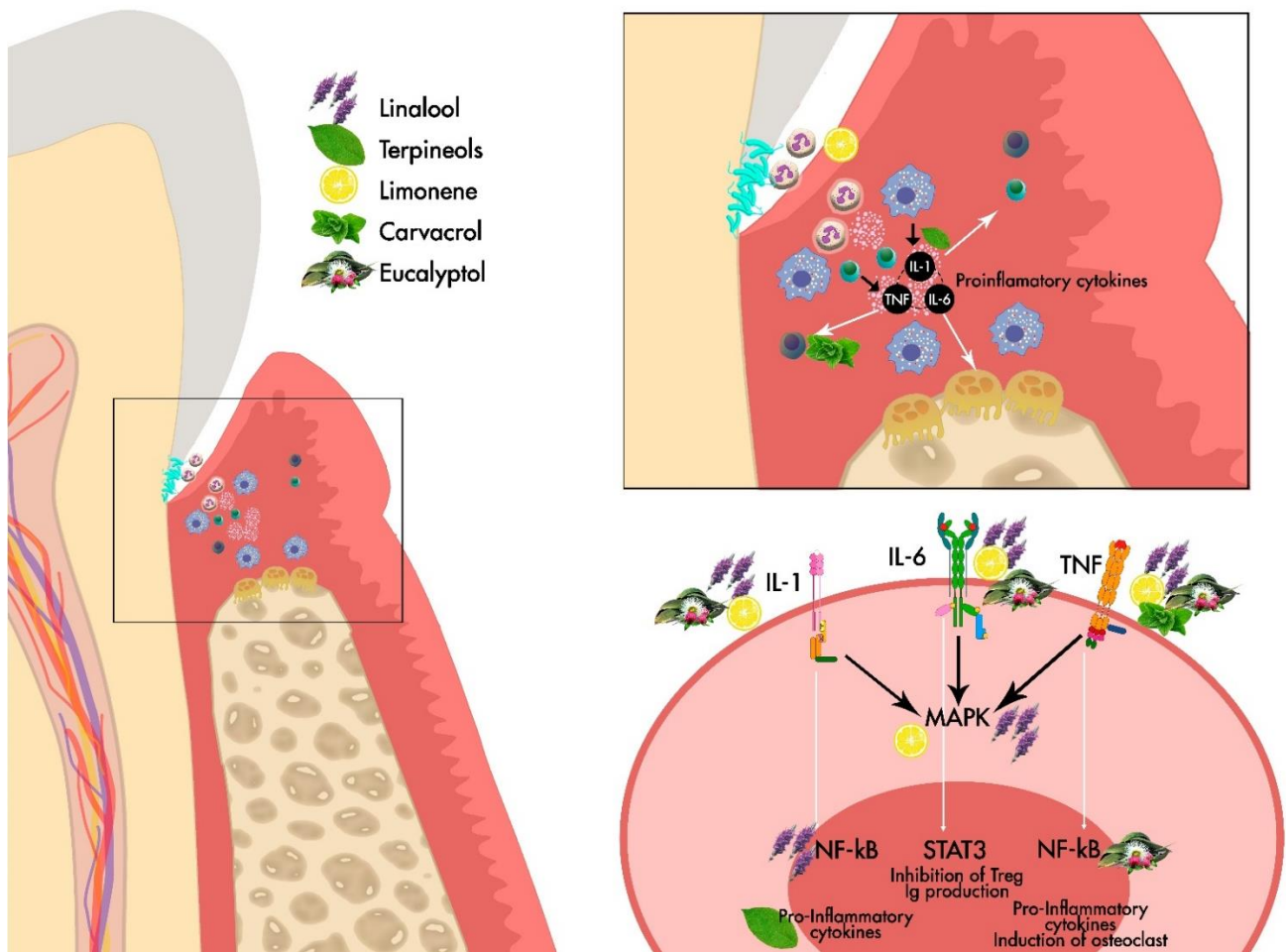


Figure 1. General Scheme of the effect of the main EO components on the periodontium.

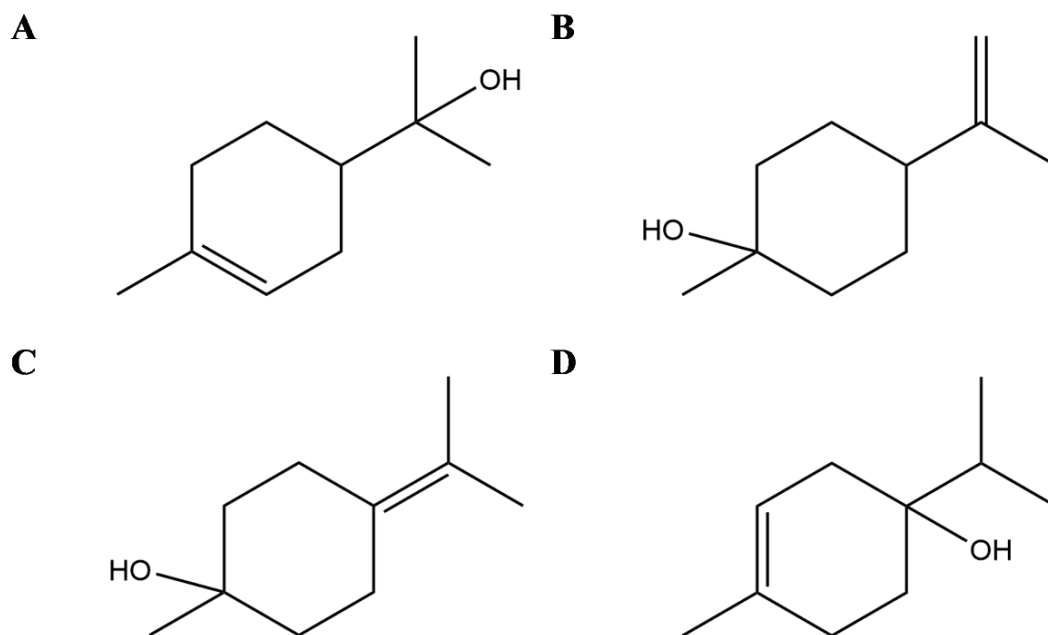


Figure 2. Selected compounds from Essential Oils from Lamiaceae family. Terpineols: α -terpineol (A), β -terpineol (B), γ -terpineol (C), and terpinen-4-ol (D).

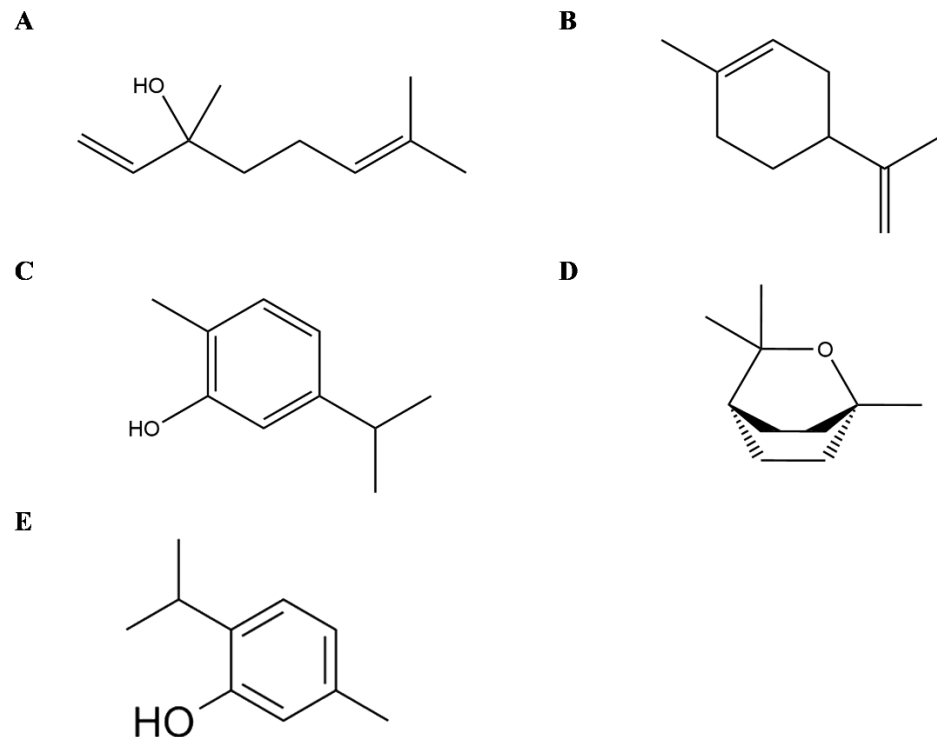


Figure 3. Selected compounds from Essential Oils from *Lamiaceae* family. Linalool (A), Limonene (B), Carvacrol (C), Eucalyptol (D), Thymol (E).

Limonene (1-Methyl-4-(prop-1-en-2-yl)cyclohex-1-ene) is a cyclic monoterpene and one of the most common terpenes in nature as well as the main constituent of citrus Eos (Figure 3B). Its anti-inflammatory effects are principally linked to the modulation of cytokines and the interference with the inflammatory-related pathways, as demonstrated by *in vitro* and *in vivo* assays. Limonene decreases leukocytes infiltration and neutrophils migration, as well as the levels of TNF- α in cell derived from the peritoneal cavity and in the peritoneal exudate of zymosan-induced peritonitis BALB/C mice [104]. In LPS inflammation-induced RAW 264.7 macrophages, limonene reduced in a dose-dependent manner the levels of proinflammatory cytokines TNF- α , IL-6 and IL-1 β , together with the expression of inducible nitric oxide synthase (iNOS), cyclooxygenase (COX) and prostaglandin E2 (PGE2) [105]. Similarly, *in vitro* model of osteoarthritis with IL-1 β -stimulated human chondrocytes, limonene negatively modulated nitric oxide (NO) production by decreasing iNOS, matrix metalloproteinase (MMP)-1 and MMP-13 expression, besides NF- κ B and p38 activation [106].

Carvacrol (5-isopropyl-2-methylphenol) is a cyclic monoterpene mainly present in the EO of plants from *Lamiaceae* family (Figure 3C). In an experimental rat model of periodontal disease, carvacrol maintained alveolar bone resorption and decreased tissue lesion at histopathology, with preservation of the gingival tissue also demonstrating anti-inflammatory and antibacterial activities [107]. In addition, *in vitro* in murine macrophages carvacrol (1, 10, and 100 μ g/mL) reduced the LPS-induced nitrite production as well as *in vivo* in a model of carrageenan-induced pleurisy with a pretreatment 50 or 100 mg/kg, i.e., carvacrol reduced the levels of TNF- α and suppressed leukocytes recruitment in pleural lavage [108]. In human macrophage-like U937 cells, carvacrol suppressed LPS-induced COX-2 expression, activating PPAR γ , indicating its anti-inflammatory properties [109] and having no selectivity for both COX-1 and COX-2 enzyme isoforms [110]. Furthermore, it has been shown that carvacrol induces Nav blockade in DRG neurons [123,124], and Gonçalves et al. also reported significant analgesic activity and dose-dependency of *T. capitatus* EO. It is suggest that it is the main active molecule behind the antinociceptive effects of *T. capitatus* through peripheral nervous excitability blockade [125]. Other study showed that

carvacrol and thymol have the most potent antimicrobial activity against *Escherichia coli*, *St. aureus*, *Str. epidermidis*, *Enterococcus faecalis*, *Yersinia enterocolitica*, *Candida albicans*, *Bacillus cereus*, *Listeria monocytogenes*, *Salmonella typhimurium* and *Saccharomyces cerevisiae*, with the exception of *Pseudomonas aeruginosa* [126]. Taking into account that *T. capitatus* fractions are characterized by the presence of carvacrol as dominant constituent, the antibacterial properties may be attributed to this oxygenated monoterpene.

Thymol (2-isopropyl-5-methylphenol), a monoterpene phenol, is a typical compound in EOs from thyme species (Figure 3E). Thymol also ameliorates inflammation in vitro in LPS-induced inflammation in murine macrophage cells [116] as well as in LPS- and interferon (IFN)- γ -induced macrophage inflammation, besides inhibition of the iNO RNA expression in J774A.1 cells [117]. Thymol may also modify prostaglandin catalysed biosynthesis by the inhibition of COX-1 and COX-2 isoforms [118]. Moreover, in mouse mammary epithelial cells, LPS-induced inflammatory response was decreased after thymol treatment (40 $\mu\text{g}/\text{mL}$) by the downregulation of MAPK and NF- κB signalling pathways [119]. Recently, Perrino et al. [127] have reported a high bioactivity also found in endemic wild species as *spinulosus* Ten., indicating its potential use in organic agriculture, since thymol may also serve as natural agent against phytopathogenic microorganisms.

Eucalyptol or 1,8-cineole (1,3,3-trimethyl-2-oxabicyclo[2.2.2]octane) is a bicyclic monoterpene isolated from EOs from numerous plants [111] (Figure 3D). Its anti-inflammatory properties have also been investigated in human and animal models of respiratory diseases such as asthma, Chronic Obstructive Pulmonary Disease and bronchitis [112,113,128]. In vitro studies on LPS-induced human lymphocytes and monocytes showed a reduced expression of cytokines including TNF α , IL-6 and IL-1 β accompanied with a decrease in NF κB activated form [114,115].

6. Conclusions

The available published evidence provides substantial data to consider several species of the *Lamiaceae* family (*Rosmarinus officinalis*, *Lavandula x intermedia*, *Thymus capitatus*) as potential agents for the treatment of inflammatory diseases. The studies reviewed support the use of EOs of these plants against inflammation-related diseases, and the mechanisms described here provided pathways that explain these anti-inflammatory effects. Furthermore, the wide variety of species of the *Lamiaceae* family should be considered. Different chemotypes can be found, even within the same species, depending on the region and the environment in which the species have been grown. These factors could affect the percentage of EOs. The phenological phase of the same individual can also change the chemical composition and therefore the EOs obtained from it. Several nutraceutical products based on EOs as an adjuvant therapeutic agent for periodontal treatment might have some additional beneficial effect on periodontitis variables, preventing progression of disease when used as an irrigation solution and/or mouthwash. The utilization of such agents may reduce the intake of the drugs and consequently minimize the risk of a possible appearance of drug resistance as well as other risk factors. The plant extracts may act beneficially on periodontitis possibly through the known anti-inflammatory effects of each compound that remain to be clarified by future studies. Therefore, EOs from the *Lamiaceae* family can be considered as potential therapeutic agents for the complementary treatment periodontitis, as well as for other immune-inflammatory diseases. The potential applications role of each specific EO needs to be further studied to allow a full understanding of the spectrum of potential applications.

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