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Review article

THE POTENTIAL BENEFITS OF SOME COMMONLY USED LAMIACEAE HERBS FOR NEUROINFLAMMATION

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ABSTRACT

Purpose. This review aims to present recent data from contemporary scientific literature on the anti-neuroinflammatory effects of selected herbs from the Lamiaceae family.

Material and methods. A literature search was conducted to obtain current information on the role of phenolic compounds from Lamiaceae species in neuroinflammation. The Lamiaceae family, widely represented across Europe by genera such as *Salvia, Mentha, Melissa, Origanum, Ocimum, Thymus,* and *Satureja*, is a rich source of bioactive phenolic compounds with antioxidant, anti-inflammatory, and emerging neuroprotective potential.

Results. Species belonging to the Lamiaceae family, including rosemary, sage, mint, thyme, oregano, and others, are rich in phenolic compounds, particularly phenolic acids and flavonoids. These herbs demonstrate promising anti-neuroinflammatory and neuroprotective properties, largely attributed to their phenolic content.

Conclusion. Phenolic compounds from Lamiaceae plants modulate key neuroinflammatory pathways by suppressing microglial activation, downregulating pro-inflammatory mediators, and activating antioxidant defences. Through these mechanisms, they mitigate oxidative stress and promote neuronal survival, thereby exerting protective effects in experimental models of neuroinflammation and neurodegenerative disorders. Thus, phenolic compounds from Lamiaceae species represent promising multifunctional agents for targeting neuroinflammation and potentially slowing the progression of neurodegenerative diseases.

Keywords: neuroinflammation, Lamiaceae, phenolic compounds, phenolic acids, flavonoids, microglia.

INTRODUCTION

Neuroinflammation is an inflammatory process in the central nervous system (CNS), triggered by trauma, infection, autoimmune reaction, involving activation of glial cells. Microglia and astrocytes are key regulators of inflammatory responses in the CNS. In cases of acute impact, their activation has a neuroprotective effect. However, in chronic inflammation, the excessive secretion of pro-inflammatory cytokines, increased formation of reactive oxygen species, and disruption of the blood-brain barrier initiate processes that lead to impaired neurotransmission, neuronal damage, and cell death. Neuroinflammation is believed to contribute to the development of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, and others. The aging process and the accompanying cognitive decline are associated with a number of morphological, functional, and biochemical changes in the brain, including neuroinflammation. Targeting neuroinflammatory pathways offers a promising approach for neuroprotection, helping to preserve cognitive function and slow the progression of neurodegenerative disorders.

The Lamiaceae family includes over 7,000 aromatic and herbaceous plants, divided into about 230 genera, mainly found in the Mediterranean region but also thriving in other parts of Europe, Southwest Asia, South America, and Australia. Some of these herbs, such as rosemary, sage, peppemint, spearmint, lemon balm, oregano, basil, thyme and savory are rich sources of phenolic compounds with known antioxidant and anti-inflammatory activities.

The Lamiaceae family is among the most widely used and extensively researched plant families owing to the diverse phytochemicals present in its species.

This mini review highlights the potential role of some Lamiaceae herbs in modulating neuroinflammation by summarizing current knowledge of their anti-inflammatory, antioxidative, and neuroprotective activities. Specifically, it focuses on their polyphenolic content and experimental data for beneficial effects on neuroinflammation.

MATERIALS AND METHODS

A search was conducted to obtain current information on the role of phenolic compounds from Lamiaceae species (common in Europe and Bulgaria) in neuroinflammation. The following keywords were used for the search of relevant articles: neuroinflammation, Lamiaceae, phenolic compounds, phenolic acids, flavonoids, and microglia. Articles published mainly over the past 5 years and indexed in the Web of Science, Scopus, and PubMed databases were reviewed and analyzed.

RESULTS

Species belonging to the Lamiaceae family, such as rosemary, sage, mint, thyme, oregano, and others, are rich in phenolic compounds, particularly phenolic acids and flavonoids. These molecules demonstrate consistent anti-inflammatory and neuroprotective effects in experimental models of neuroinflammation and neurodegenerative disorders.

DISCUSSION

Phenolic compounds of the Lamiaceae family

Plants of the Lamiaceae family are rich in phenolic compounds, which confer antioxidant, anti-inflammatory, and antimicrobial properties. [1] Our focus is on nine Lamiaceae herbs that are widely distributed across several continents, including Europe and Bulgaria. These herbs are traditionally used both as culinary flavorings and for medicinal purposes, owing to their diverse phytochemical composition.

Polyphenols are a large subclass of phenolic compounds and include molecules that have multiple phenolic groups. They are secondary metabolites synthesized by plants as a defense response to stress factors and are present in all parts of the plant – root, stem, leaves, flowers, seeds, fruits. Polyphenol compounds are divided into two main groups: flavonoids (flavones, flavonols, flavanols, flavanones, isoflavones, anthocyanins) and non-flavonoids (phenolic acids, stilbenes, and lignans). When exposed to various types of abiotic stress (e.g., UV light, drought, heavy metals), plants increase the production of reactive oxygen species (ROS) and consequently produce more phenolic compounds to protect themselves from the damaging effects. During a pathogen attack, plants accumulate phenolics to enhance resistance to the pathogen. The polyphenol content in plants depends on various environmental factors (such as soil mineral composition, moisture, sunlight exposure, pests, etc.), as well as storage conditions, extraction methods, and more. Sunlight and drought exposure are important environmental factors. Sun intensity influences the activity of enzymes involved in phenolic biosynthesis, while moderate drought acts as a form of stress, stimulating plant defense mechanisms through increased polyphenol production. The conditions under which the plants are harvested (e.g., developmental stage), stored (e.g., drying method, light and heat exposure), and processed (extraction method) also significantly affect the phenolic content.

A comprehensive Phenol-Explorer database was used to present the polyphenol content of nine Lamiaceae herbs (rosemary, sage, peppemint, spearmint, lemon balm, oregano, basil, thyme and summer savory), originating from different geographical regions. As shown, the listed Lamiaceae species exhibit high phenolic content, and the polyphenol composition varies depending on whether the plant is fresh or dried. The main phenolic compounds identified in plant extracts include mostly polyphenols (phenolic acids, flavones, and flavonoids), but also phenolic diterpenes. (Table 1).

Table 1. Phenolic compounds (polyphenols and phenolic terpenes) of some commonly used herbs of the Lamiaceae family.

Common name	Scientific name (genus)	Polyphenols in fresh herb (mg/100 g FW) and major phenolic compounds[a]	Polyphenols in dry herb (mg/100 g FW) and major phenolic compounds[a]	Phenolic compounds
Rosemary	Rosmarinus officinalis L. (Salvia Rosmarinus L.) (Salvia)	*Phenolic acid:* Rosmarinic acid - 123.90 *Phenolic terpenes*: Carnosic acid - 672.30 Rosmanol -124.10 Carnosol – 53.00	*Phenolic acid*: Rosmarinic acid - 987.20	*Phenolic acids* (rosmarinic acid, caffeic acid); *flavonoids* (apigenin, luteolin); *flavones* (mostly as glucosides), *phenolic diterpenes* (carnosic acid, carnosol) [2]
Sage	Salvia officinalis L. (Salvia)	*Phenolic acid:* Rosmarinic acid -117.80; *Flavones:* Luteolin -33.40	Caffeic acid - 26.40 5-Caffeoylquinic acid -19.85 Ferulic acid - 5.80 *Phenolic terpenes*: Carnosic acid - 525.86	*Phenolic acids* (mainly rosmarinic acid, also caffeic and chlorogenic acids) [3]
Peppermint	Mentha piperita L. (Mentha)	*Polyphenols:* 980.36	*Flavanones:* Eriocitrin - 8051.58 Eriodictyol7-O-glucoside -80.25 Hesperidin - 480.65	*Phenolic acids* (mainly rosmarinic acid, also cinnamic and caffeic acids); *flavonoids* (luteolin glycosides, hesperidin, eriocitrin) [4]

			Narirutin - 127.50 *Flavones:* Luteolin 7-O-rutinoside - 1170.35 Isorhoifolin - 125.05 Diosmin - 95.50 Pebrellin - 43.03	
Spearmint	Mentha spicata L. (Mentha)	*Polyphenols:* 246.90	*Phenolic acids*: Rosmarinic acid - 900.67 5-Caffeoylquinic acid - 31.00 Caffeic acid - 25.00	*Phenolic acids* (rosmarinic acid, caffeic acid); *flavonoids* (rutin, hesperidin, eriocitrin) [5]
Lemon balm	Melissa oficinalis L. *(*Melissa*)*	*Polyphenols:* 899.71	*Phenolic acids*: Ferulic acid - 48.00 Caffeic acid - 13,80	*Phenolic acids* (mainly rosmarinic acid); *flavonoids* (luteolin and its glycosides) [2]
Oregano	Origanum vulgare L. (Origanum)	*Flavones:* Apigenin - 3.00	*Phenolic acids:* Rosmarinic acid - 599.00 5-Caffeoylquinic acid -28.70 Caffeic acid - 10.70 Vanillic acid – 6.00	*Phenolic acids* (mainly rosmarinic acid); *flavonoids* (apigenin, luteolin, quercetin, and their glycosides) [2]
Basil	Ocimum basilicum L.(Ocimum)	Polyphenols: 231.80	*Phenolic acids:* Rosmarinic acid-308.00 Vanillic acid – 14.00	*Phenolic acids* (mainly rosmarinic); *flavonoids* **(**luteolin, kaempherol, rutin). [5]
Thyme	Thymus vulgaris L. (Thymus)	*Phenolic acids:* Rosmarinic acid- 91.80 Caffeic acid – 11.70 *Flavones:* Luteolin -39.50 Hesperidin - 20.80	*Phenolic acids:* Rosmarinic acid - 829.00 Caffeic acid - 21.28 Syringic acid - 11.70V anillic acid - 6.10 Ferulic acisilvad - 5.65	*Phenolic acids* (mainly rosmarinic acid, also caffeic, ferulic, syringic, p-coumaric); *flavonoids* (luteolin, apigenin[3]
Summer savory	Satureja hortensis L. (Satureja)	*Polyphenols:* 201.20	Polyphenols: 4512.00	*Phenolic acids* (mainly rosmarinic acid, also caffeic, isoferulic, syringic acids); *flavonoids* (catechin, rutin, hesperidin) [3]

[a] Data collected from Database on polyphenol content in foods (Phenol-explorer version 3.6, June 2015, http://phenol-explorer.eu/) [6]

A study evaluating the phenolic profile of extracts from five Lamiaceae spices (rosemary, oregano, sage, basil, and thyme) identified 38 phenolic compounds, divided as follows: Phenolic acids: hydroxycinnamic acid derivatives (caffeic acid, chlorogenic acid, p-coumaric acid, rosmarinic acid, and ferulic acid); hydroxybenzoic acid derivatives (gallic acid, syringic acid, vanillic acid, etc.); Flavonoids: (apigenin, luteolin and their glucosides, gallocatechin, quercetin, and rutin); Phenolic terpenes: carnosol and carnosic acid [7, Table 1].

A comparison of the phenolic content in medicinal plants from the Lamiaceae, Apiaceae, and Asteraceae families revealed that spices from the Lamiaceae family are richer in phenolic compounds and demonstrate stronger antioxidant activity compared to Apiaceae plants [8]. No significant differences were observed in total phenolic content, flavonoid content, or antioxidant activity among Lamiaceae species (oregano, thyme, and rosemary), and a clear correlation was established between their phenolic content and antioxidant activity. However, another study comparing four Lamiaceae species (rosemary, thyme, oregano, and basil) reported significant differences in total phenolic content, with the highest values for: rosemary: 50.51 mg gallic acid equivalents (GAE)/g dry weight (DW); thyme: 41.91 mg GAE/g DW; oregano: 32.62 mg GAE/g DW; basil: 24.24 mg GAE/g DW [9]. A screening of 20 Lamiaceae species found that several Salvia spp., among which Salvia officinalis had the highest total phenolic and flavonoid content as well as the greatest antioxidant activity [10].

Beneficial effects of Lamiaceae phenolic compounds on neuroinflammation

Microglia and astrocytes are the two principal glial cell types involved in neuroinflammation, a complex immune

response within the CNS [11]. Although both cell types play critical roles in maintaining neural homeostasis under normal conditions, their activation during injury, infection, or disease can be both protective and detrimental, depending on the context and duration of the response. Microglia are the immune cells of the CNS. Under normal conditions, they are involved in synaptic pruning, pathogen and debris clearance, and homeostasis maintenance. Upon sensing pathogens, damaged neurons, or misfolded proteins, microglia become activated and adopt two distinct phenotypes. The pro-inflammatory type releases cytokines (TNF-α, IL-1β, and IL-6, etc.) and generates reactive oxygen/nitrogen species (ROS/RNS), contributing to pathogen defense but also potentially causing neuronal injury. The anti-inflammatory (repair-oriented) type produces IL-10, TGF-β, and neurotrophic factors, promoting tissue repair and resolution of inflammation. Upon chronic activation, the pro-inflammatory type microglia contribute to neurodegeneration seen in disorders such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis. Astrocytes support neurons by maintaining ion and neurotransmitter balance, providing metabolic support, and contributing to the integrity of the blood-brain barrier. In response to CNS injury or inflammation, they undergo reactive astrogliosis, characterized by the release of pro-inflammatory cytokines. While the neuroprotective type secretes growth factors, promotes neuronal survival, and limits the spread of inflammation, the neurotoxic type induced by microglial cytokines (e.g., IL-1α, TNF, C1q), releases molecules toxic to neurons and oligodendrocytes. Neuroinflammation is largely driven by the activation of glial cells via pathways such as NF-κB, MAPKs, TLR4/MyD88, and Nrf2 [12]. Several phenolic compounds from the Lamiaceae family have demonstrated anti-neuroinflammatory and neuroprotective effects by modulating these pathways [13].

Long-term research has confirmed the antioxidant and anti-inflammatory properties of polyphenols, which contribute to their beneficial effects on a range of chronic diseases, including infectious, cardiovascular, metabolic, cancerous, and neurological conditions. Phenolic compounds exert anti-neuroinflammatory and neuroprotective effects through several mechanisms, namely: 1) Inhibition of microglia produced pro-inflammatory cytokines (IL-6, IL-1β, TNF-α); 2) Decrease of the activity of reactive astrocytes and microglia by modulation of key signaling pathways (e.g., NF-κB, MAPK); 3) Antioxidant activity: scavenging ROS and enhancing the endogenous antioxidant enzymes.

Phenolic acids and flavonoids are the most abundant polyphenols in the extracts from the selected Lamiaceae species (Table 1). Among the phenolic acids, hydroxycinnamic acid derivatives, particularly rosmarinic acid, caffeic acid, ferulic acid, and p-coumaric acid, are abundant in Lamiaceae plants. Their anti-neuroinflammatory effects have been demonstrated in numerous in vitro and in vivo experiments [13, 14,15]. Rosmarinic acid (RA), an ester of caffeic acid, is a bioactive phenolic compound that is synthesized by aromatic plants, primarily from the Lamiaceae and Boraginaceae families. It is the major polyphenol found in all nine Lamiaceae species (Table 1). The biological activities of this compound are well known, including anti-inflammatory, neuroprotective, cardioprotective, and antidiabetic properties [16, 17]. A standardized leaf extract from Salvia officinalis and its main constituent, RA, protected cultured rat pheochromocytoma cells against amyloid-beta-peptide-induced neurotoxicity. RA reduced ROS formation, lipid peroxidation, DNA fragmentation, caspase-3 activation, tau protein hyperphosphorylation, and inhibited phosphorylated p38 MAPK [18]. RA also protected neurons in a rat model of oxaliplatin-induced peripheral neuropathy by reducing oxidative stress, improving mitochondrial function, inhibiting spinal glial cell activation, and decreasing expression of inflammatory markers [19]. A standardized extract of Melissa officinalis L., with the main polyphenol RA, demonstrated anti-inflammatory and neuroprotective activity in two cell models of neuroinflammation. Both the extract and RA reduced pro-inflammatory factors (NF-κB, HDAC, IL-1в) in lipopolysaccharide (LPS)-stimulated microglial cells and protected neuronal cells from the toxic effects of activated microglia [20]. Similarly, in a model of hyperglycemia-induced neuroinflammation in BV2 cells, both the extract and RA attenuated microglia-mediated oxidative imbalance and neuroinflammation, including NF-κB pathway activation, iNOS expression, enhanced ERK1/2 phosphorylation, and increased IL-6 expression [21].

A recent study demonstrated that the hydroethanolic leaf extract of Salvia officinalis improved memory and cognitive performance in LPS-induced neuroinflammation in mice. Histological analysis revealed reduced neuronal damage, gliosis, and inflammation, suggesting a neuroprotective potential through antioxidant and anti-inflammatory mechanisms [22].

Given that inflammatory mechanisms contribute to the development of neuropathic pain; phenolic compounds offer promising therapeutic potential. Rosmarinic acid (RA) and the ethanolic extract of *Rosmarinus officinalis* have been shown to reduce inflammatory markers (COX-2, PGE-2, IL-1β, MMP-2, and NO) in a rat model of neuropathic pain [23].

Lamiaceae plants contain variable amounts of flavonoids, including flavones (e.g., apigenin and luteolin and their derivatives), flavonols (e.g., quercetin, kaempferol, rutin), and flavanones (e.g., hesperidin, eriocitrin), with well-known anti-inflammatory and antioxidant activities [24, Table 1]. Many in vivo and in vitro experimental studies confirm the anti-neuroinflammatory activity of flavonoids, which involves the inhibition of activated microglia and astrocytes, leading to a reduction in pro-inflammatory cytokines (such as TNF-α, IL-1β, and IL-6), suppression

of NF-κB, JNK, and STAT signaling pathways, and attenuation of oxidative stress and neuronal apoptosis, thereby providing neuroprotection and improving cognitive function. [25, 26, 27, 28].

The flavones luteolin and apigenin, along with their glycosides, are the predominant flavonoids in all nine Lamiaceae species mentioned, and among these, *Origanum vulgare* L. is particularly rich in luteolin. [29, 30]. The apigenin and luteolin have been shown to suppress key inflammatory pathways (such as NF-κB and MAPK), and to modulate redox signaling pathways (NF-κB, Nrf2, PI3K/Akt), thereby reducing the secretion of pro-inflammatory cytokines, inhibiting oxidative enzymes, and enhancing antioxidant defense mechanisms [31, 32, 33].

Carnosic acid and carnosol are phenolic diterpenes present in Lamiaceae plants such as Rosmarinus officinalis and Salvia officinalis [7]. These substances have been a subject of intensive research regarding their antioxidant, anti-inflammatory, and neuroprotective potential [34, 35]. A recent study confirmed the anti-inflammatory effect of rosemary extract on LPS-induced inflammatory responses in immune cells. Both the extract and rosemary diterpenes, carnosic acid (CA) and carnosol (CS), reduced LPS-induced levels of TNF-α, IL-1β, and IL-6, and increased oxidized glutathione in BV-2 microglial cells. Since the extract was more effective than the isolated diterpenes, a synergistic effect of the phenolic compounds was suggested [36]. The application of rosemary extract in a mouse model of repetitive mild traumatic brain injury reduced the injury-induced inflammatory response and cytokine production (IL-1β, IL-6, and TNF-α), decreased oxidative stress, and enhanced antioxidant defense. The extract's anti-inflammatory and antioxidant properties, driven largely by its high carnosic acid content, contributed to reduced astrogliosis and neuroprotection [37]. Studies conducted in vitro (cerebrocortical cultures) and in vivo (middle cerebral artery ischemia/reperfusion models) have shown that CA, derived from rosemary, exerts neuroprotective effects through activation of the Nrf2/ARE pathway - a key defense mechanism against oxidative stress [38]. CA and CS were also effective in a model of inflammatory pain. Maione [39] reported anti-inflammatory and anti-nociceptive effects of diterpenes in a carrageenan-induced mouse hyperalgesia model, involving inhibition of key enzymes in eicosanoid biosynthesis, such as microsomal prostaglandin E2 synthase-1 and 5-lipoxygenase. Rosemary extract, containing 10% CA, reduced oxidative markers in brain tissue (4-hydroxynonenal in the cortex and protein carbonyls in the hippocampus) in a SAMP8 mouse model of accelerated aging, and improved learning and memory as well [40].

The phenolic compounds present in Lamiaceae herbs (such as rosmarinic acid, caffeic acid derivatives, flavonoids, etc.) are generally regarded as safe when consumed as part of foods or traditional herbal preparations. However, safety in culinary use does not necessarily translate to safety at pharmacological doses. Experimental studies suggest that high-dose exposure to phenolic-rich extracts may affect liver and kidney function, as well as reproductive parameters in animal models, highlighting the importance of dose considerations. In general, many phenolic constituents, such as rosmarinic acid, exhibit comparatively low hematotoxicity and good safety profiles in vitro, but comprehensive toxicological evaluations and controlled clinical studies are still limited. Therefore, although these phytochemicals show promising neuroprotective and anti-inflammatory activities, careful assessment of dosage, bioavailability, and long-term safety is necessary when considering therapeutic applications.

Recent patent activity reflects growing interest in phenolic compounds derived from Lamiaceae plants for neurological and neuroinflammatory conditions. Several patents describe the use of polyphenol-based compositions or metabolites for the prevention or treatment of neuroinflammation and neurodegenerative disorders such as Alzheimer's and Parkinson's diseases (EP4230201A1). Patents have been filed on phenolic diterpenes such as carnosic acid, found in species of the genus Salvia (e.g., Salvia rosmarinus*),* for their ability to modulate neuroinflammatory pathways and oxidative stress involved in neurodegeneration (WO2023055733A1). These inventions typically claim specific compounds, enriched extracts, or pharmaceutical formulations rather than the plants themselves. Overall, current patent trends indicate increasing translational interest in Lamiaceae-derived phenolic compounds as potential agents for the management of neuroinflammation and related neurological disorders.

CONCLUSION

The Lamiaceae herbs exhibit promising anti-neuroinflammatory and neuroprotective properties, largely attributed to their phenolic content. Their traditional culinary and medicinal use, combined with accumulating experimental evidence, highlights their potential as complementary therapeutic agents for managing neuroinflammation and supporting brain health. Further in vivo studies and clinical trials are warranted to establish their efficacy and optimal use in neuroprotective interventions.

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