

REVIEW

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# Rosemary bioactive phytochemicals as a strategy for the management of age related conditions

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## Abstract

Research on plant-derived bioactive metabolites has earned growing interest in pharmaceutical applications. Rosemary (*Rosmarinus officinalis* L., Lamiaceae family) is one of the most used aromatic food ingredients due to a plethora of specialized metabolites with beneficial health effects. Several rosemary components, including phenolic compounds (flavonoids and phenolic acids) and terpenoids (triterpenes, phenolic diterpenes, and volatile monoterpenes), have demonstrated various biological activities, such as antioxidant, anti-inflammatory, and beneficial effects against neurological, metabolic, and age-related disorders. This review critically examines the scientific evidence supporting the use of rosemary bioactives in managing both systemic age-related diseases (e.g., neurodegenerative disorders) and dermatological aging conditions (e.g., photoaging, loss of elasticity). Additionally, recent scientific evidence related to its use in skin-aging ingredients, functional foods, and applications in aromatherapy has been detailed and critically discussed, including possible bioactive metabolites and safety concerns.

## Significance statement

This review examines the latest scientific evidence on rosemary's utilization in age-related disease, skin-aging, functional foods, and aromatherapy, emphasizing potential bioactive metabolites and safety considerations.

**Keywords** Rosemary, Foods, Aging, Carnosic acid, Skin-aging

## 1 Introduction

Aging is a complex, multifactorial biological process associated with a progressive decline in physiological function and an increased risk of various disorders. These include systemic conditions such as neurodegenerative (e.g., Alzheimer's disease), and inflammatory diseases, as well as tissue-specific manifestations like age-related skin deterioration [94]. The search for natural, multi-target strategies to mitigate age-related decline has intensified, with medicinal plants offering a rich source of bioactive compounds [19, 41, 94].



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*Rosmarinus officinalis* L. (Lamiaceae family), commonly known as rosemary, is one of the most popular aromatic plants, commonly used as a spice and flavoring agent [103].

Rosemary has also been traditionally used in folk medicine, particularly in the rural areas of the western Mediterranean region as an antispasmodic, carminative, antirheumatic, diuretic, antiepileptic, and expectorant [32].

A plethora of rosemary specialized metabolites provides its beneficial health effects such as antimicrobial, anti-inflammatory, chemopreventive, and antidiabetic, as well as the management of several metabolic and neurological disorders [49, 53]. Several rosemary components such as phenolic compounds (e.g. rosmarinic acid, carnosic acid, and carnosol) and essential oil components (e.g.  $\alpha$ -pinene, 1,8-cineole, borneol, and camphor) demonstrated its different biological activities [48]. Plants like ginseng (*Panax ginseng*), turmeric (*Curcuma longa*), ginkgo (*Ginkgo biloba* L.), sage (*Salvia officinalis*), lavender (*Lavandula angustifolia*), and rosemary (*R. officinalis*) have been reported to exert promising activities in the management of age-related diseases [19, 41, 94].

Previous reviews on rosemary have largely focused on individual compound classes or specific biological activities, lacking a comprehensive integration of its phytochemical diversity with the full spectrum of age-related applications. This review addresses this gap by providing a holistic synthesis that connects the major chemical classes of rosemary—specifically terpenoids and phenolic compounds—with their fundamental mechanisms of action and their translational potential in both systemic and dermatological aging. By critically evaluating recent evidence across multiple application areas (pharmacotherapy, functional foods, cosmeceuticals, and aromatherapy), this work advances current knowledge through an integrated framework that emphasizes the relationship between chemical classification, bioavailability considerations, and therapeutic outcomes. Special emphasis is given to bioactive metabolites, safety profiles, and emerging formulation strategies to enhance clinical efficacy.

## 2 Review methodology

A comprehensive literature search was conducted to identify relevant studies on the bioactive phytochemicals of *R. officinalis* (rosemary) and their potential roles in the prevention and management of age-related diseases. The review followed a structured approach as outlined below:

### 2.1 Databases searched

The electronic databases PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar were systematically searched.

### 2.2 Search terms and MeSH keywords

The search strategy included a combination of the following Medical Subject Headings (MeSH) and free-text terms:

- "*Rosmarinus officinalis*" OR "rosemary"
- "phytochemicals" OR "bioactive compounds" OR "secondary metabolites"
- "age-related diseases" OR "neurodegenerative diseases" OR "inflammation" OR "oxidative stress" OR "skin-aging" OR "photoaging" OR "wrinkles" OR "functional food" OR "aromatherapy" OR "safety" OR "bioavailability"
- "anti-inflammatory", "antioxidant", "neuroprotective", "anticancer"

Boolean operators (AND/OR) were used to combine terms appropriately. A snowballing technique (checking reference lists of key articles) was employed to identify additional relevant studies.

### 2.3 Search period

Literature published between **January 2000 and May 2025** was considered, with an emphasis on recent advances over the past 10 years (2015–2025).

### 2.4 Inclusion criteria

- Peer-reviewed articles and reviews written in English
- Studies that investigated the phytochemical composition of *R. officinalis*
- Studies reporting on the pharmacological or therapeutic effects of rosemary phytochemicals in the context of age-related diseases (in vitro, in vivo, or clinical), including dermatological aging, functional food applications, or aromatherapy
- Articles providing mechanistic insights or molecular pathways
- Studies on the safety, pharmacokinetics, or bioavailability of rosemary preparations

### 2.5 Exclusion criteria

- Articles not in English
- Studies lacking sufficient methodological details or relevance to age-related conditions
- Reports focusing solely on rosemary as a culinary herb without exploring health-related aspects
- Editorials, commentaries, abstracts, and non-peer-reviewed sources

### 2.6 Study selection and data extraction

All identified articles were screened by title and abstract. Full texts of potentially relevant studies were then reviewed to confirm eligibility. Key data extracted included study design, phytochemical(s) investigated, biological targets, disease models, and outcomes.

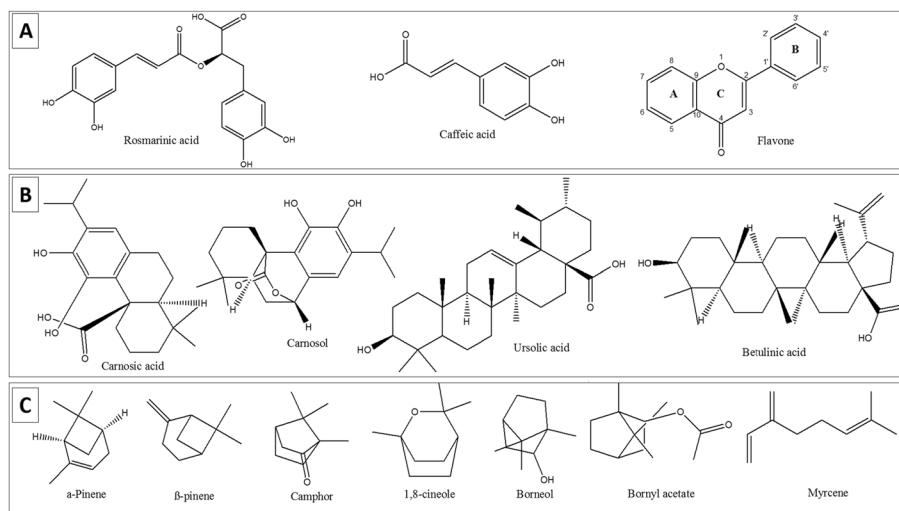
This methodological framework ensured a focused and evidence-based review of how rosemary's phytochemicals contribute to the management of aging and associated pathologies.

## 3 Phytochemical overview

The diverse pharmacological activities of rosemary are attributed to its complex mixture of secondary metabolites, which can be systematically classified into two major groups based on their biosynthetic origin: phenolic compounds and terpenoids. The phenolic fraction comprises phenolic acids and flavonoids, which contribute significantly to the plant's antioxidant properties. The terpenoid fraction includes volatile monoterpenes (the primary constituents of rosemary essential oil), along with non-volatile diterpenes and triterpenes [20, 21, 61, 71, 90] (Fig. 1).

### 3.1 Phenolic compounds

Phenolic compounds from *R. officinalis* are major contributors to the antioxidant and anti-inflammatory properties of the plant and are classified into two main subgroups:



**Fig. 1** Chemical structures of major bioactive compounds in *R. officinalis*. **A** Phenolic compounds: phenolic acids and flavonoids. **B** Terpenoids: non-volatile diterpenes and triterpenes. **C** Terpenoids: volatile monoterpenes (major constituents of the essential oil)

phenolic acids and flavonoids. The most common phenolic acids are rosmarinic acid and caffeic acid. The most common flavonoids are mostly flavones (apigenin, luteolin, diosmin, genkwanin, apigenin-7-O-glucoronide, and luteolin-7-O-rutinoside) [77].

### 3.1.1 Flavonoids

Different studies revealed the potency of different flavones in re-establishing the redox balance of transcription factors as well as signaling cascades for cell survival [29, 62, 64]. The structural assortment of flavones identifies their efficacy as essential for diverse biological activities [30]. For instance, the in vitro scavenging activity of free radicals of flavones is related to the arrangement of the different functional groups on their core structure; the configuration as well as the whole number of hydroxyl groups are important. Accordingly, the antioxidant influence is associated with the dihydroxy ortho substitution of the B-ring, the unsaturation of the 2–3 bond, and the 4-carbonyl in the C-ring [9]. As well, their efficacy as chelators for metal ions was related to the presence of dihydroxy ortho substitution in the B-ring, 5-hydroxy substitution, and the 4-carbonyl in the C-ring [78]. Regarding the neurotherapeutic potential of flavones, a study performed by Echeverry et al. [38] examined the structure–activity relationship of different flavones against oxidative stress in neuronal cells. They revealed that the 5 and 7 hydroxy ortho substitution is important for neuroprotection potential, anti-apoptotic possession, and inhibition of xanthine oxidase, signifying that the structural supplies for neuronal protection are diverse from those of the antioxidant potential [38].

Furthermore, free 3', 4', and 7 hydroxyls (coplanar flavone) are significant factors in inhibiting different signal transduction enzymes [9]. However, this flavone coplanarity is not an element issue for neuroprotection [38].

### 3.1.2 Phenolic acids

Different studies revealed the efficacy of rosmarinic acid in the scavenging of the peroxynitrite as well as reactive oxygen and nitrogen species (ROS and RNS) [27, 95]. In this order, rosmarinic acid was shown to be the most potent compound as a DPPH scavenger

(IC<sub>50</sub>: 0.49  $\mu$ M) among other compounds isolated from *R. officinalis* such as carnosol and ursolic acid [74]. Rosmarinic acid (10  $\mu$ M) could reduce the production of NO in glial cells to protect dopaminergic neurons, but to a lesser extent than carnosol showed a reduction in NO production up to 50% [74]. As well, rosmarinic acid significantly proved to regain the memory loss initiated with the aggregation of  $\beta$  amyloid in both models of AD and ALS [7, 111]. Further, rosmarinic acid could inhibit the activity of AChE and BChE activity in vitro and in vivo [51, 84].

In addition, caffeic acid an important phenolic acid in *R. officinalis*, showed a potent inhibitory activity against some oxidative stress implications and age-related enzymes. Caffeic acid showed a potent DPPH scavenging activity with IC<sub>50</sub>: 8.72  $\mu$ g/ml, H<sub>2</sub>O<sub>2</sub> scavenging activity with IC<sub>50</sub>: 15.23  $\mu$ g/ml, and ABTS-reducing activity with IC<sub>50</sub>: 6.23  $\mu$ g/ml. Caffeic acid also showed to inhibit collagenase enzyme (IC<sub>50</sub>: 74.42  $\mu$ g/ml) elastase enzyme (IC<sub>50</sub>: 76.95  $\mu$ g/ml), tyrosinase enzyme (IC<sub>50</sub>: 145.91  $\mu$ g/ml), and hyaluronidase enzyme (IC<sub>50</sub>: 244.45  $\mu$ g/mL) [47]. As well, many studies revealed the potent antioxidant and anti-inflammatory effects of caffeic acid [35, 57, 85, 123]. Furthermore, caffeic acid proved to be a potent neurotherapeutic agent in many age-related diseases [5]. In this order, caffeic acid could reduce the oxidative stress in pilocarpine-induced seizures in rat hippocampus [37]. Caffeic acid also could protect mouse brains against aluminum-induced injury [113] and  $\beta$  amyloid-induced neurotoxicity through hindering calcium influx and tau phosphorylation [52]. As well, it decreased the inflammatory damage that occurred in MPTP-intoxified striatum of mice [45].

Furthermore, chlorogenic acid also proved to have potent cognitive and neurotherapeutic effects [55].

### 3.2 Terpenoids

#### 3.2.1 Monoterpenes (volatile components—essential oil constituents)

The essential oil of *R. officinalis* is derived from the leaves, its color is very faint yellow and has a characteristic camphor aroma [21]. The hallmark constituents of the essential oil are  $\alpha$ -pinene (9–35%), camphor (16–28%), 1,8-cineole (5–24%), borneol (4–10%), bornyl acetate (1–14%), camphene (5–9%),  $\beta$ -pinene (2–8%), myrcene (3–6%), and  $\beta$ -phellandrene (4–7%) [69] (Fig. 1). This composition may vary according to the vegetation stage as well as ecological and physiological situations [109].

These terpenes proved their efficacy against different age-related diseases by being anti-inflammatory or as an inhibitor for specific related enzymes. For instance, 1,8-cineole revealed a strong antinociceptive and anti-inflammatory effect by reducing the capillary permeability in vivo [104]. Furthermore,  $\alpha$ -pinene and 1,8-cineole proved to be more potent AChE uncompetitive reversible inhibitors with IC<sub>50</sub> values of 0.63 mM and 0.67 mM, respectively, than camphor (IC<sub>50</sub> = > 10 mM) [92]. In addition, rats administered 100 and 200 mg/kg of  $\alpha$ -pinene enhanced their movement disorder, improved memory, and reduced MDA levels in both brain tissues and blood [50].

#### 3.2.2 Diterpenes (non-volatile components)

Another important class from *R. officinalis* is phenolic diterpenes such as carnosol, carnosic acid, rosmadial, and epi/rosmanol (Fig. 1), which can control the different signaling pathways responsible for oxidative stress as well as neuronal functions [116].

For instance, carnosic acid displayed the facility to cross the blood–brain barrier in mammals and was detected in the brain tissues of animals, representing their likely neuroprotective effect against different age-related diseases [101, 107, 108]. In this order, carnosic acid (5–10  $\mu$ M) has been indicated to protect the SN4741 cell line from the neurotoxin dieldrin through the enhancement of the brain-derived neurotrophic factor (BDNF) and the control of the apoptotic cascade of the dopaminergic neurons [87]. Further, carnosic acid (1 mg/kg) significantly decreased the infarct volume (by 52%) in the cortex of animal models exposed to cerebral ischemia [56]. Also, carnosic acid (10 and 20  $\mu$ M) significantly sheltered the whole integrity of cerebellar granule neurons (CGNs) against 5 K-mediated apoptosis by targeting the PI3K pathway [116]. Furthermore, carnosic acid (10 mg/kg) declined the death of motor neurons in AD mice [18]. In addition, carnosic acid (20 mg/kg) could reduce the ROS level in 6-hydroxydopamine (6-OHDA)-induced activation of JNK1/2 and p38 in dopaminergic neurons in PD brains of Wistar rats [34, 60]. Carnosic acid (0.1–1.0  $\mu$ M) also proved to protect PC12 cells from hypoxia-mediated cell injury, reduce dehydrogenase (LDH) and MDA levels, preserve SOD activity, ameliorate ROS, and increase cell viability [56]. Furthermore, several studies have established that carnosic acid could restrain the production of nitric oxide (NO) in LPS-mediated inflammation in MG6 cells in a concentration-dependent manner [125]. As well, carnosic acid (0.1 to 1  $\mu$ M) could reduce 6-OHDA-induced apoptosis in SH-SY5Y cell lines by inducing the synthesis of GSH [26].

On the other hand, pretreatment of PC12 cells with carnosol (10  $\mu$ m) protected the cortical neurons against N-methyl-D-aspartate (NMDA)-induced excitotoxicity by enabling the Nrf2/ARE pathway [75]. As well, carnosol up-regulated HO-1 expression via the activation of the PI3K/Akt/Nrf2 pathway in C6 cell lines [114]. However, studies proved that carnosic acid is a better neuroprotective mediator than carnosol by preventing the oxidative glutamate toxicity in HT22 cells [107, 108, 118]. Carnosic acid also could bind to Kelch-like ECH-associated protein 1 (Keap1) in the PC12h dopaminergic cell line and activate the antioxidant response element (ARE) [34]. Although rosmarinic acid and carnosol displayed similar antioxidant effects, some studies revealed that carnosol might be more active than rosmarinic acid and this can suggest that aspects other than the antioxidant ability may be accountable for its efficacy [90].

Carnosic acid also could block A $\beta$ 42 and A $\beta$ 43 peptide production through increasing  $\alpha$ -secretase TACE expression in U373MG cell lines. However, carnosic acid could reduce A $\beta$ 40 and A $\beta$ 42 production in hypoxia situations but didn't show any alter in the expression of  $\alpha$ -secretase TACE,  $\beta$ -secretase BACE, and  $\gamma$ -secretase PS1. In this order, the down-regulation of A- $\beta$  peptide production can consequently amend the redox status in the neuronal cells and so prevent the cell death [127].

### 3.2.3 Triterpenes (non-volatile components)

The most potent triterpenes from *R. officinalis* are ursolic acid and betulinic acid [120]. Further, five novel terpenoids (A1, A2, B, C and D) were also isolated from the ethanolic extract of *R. officinalis* [128]. Ursolic acid and betulinic acid along with carnosic acid and carnosol proved to be potent anti-inflammatory agents. They could reduce the levels of leukocytes, interleukin-1 beta (IL-1 $\beta$ ), and tumor necrosis factor-alpha (TNF- $\alpha$ ), as well as the activity of myeloperoxidase activity (MPO), and the production of nitrite/nitrate (NO $_x$ ) [22].

4 Pharmacological activities relevant to aging

4.1 Antioxidant activity

Antioxidants have an important role in guarding against diseases that are linked to oxidative stress damage, such as cancer and neurodegenerative disorders. Organisms spontaneously produce reactive oxygen species such as (hydrogen peroxide  $H_2O_2$ ), and free radicals such as superoxide anion ( $O_2^{\cdot-}$ ) and hydroxyl radical ( $HO^{\cdot}$ ), which are gained as a result of internal metabolism or from an external source. Repeated exposure to free radicals over a long time may lead to aging, cell damage, and even death [11].

Rosemary is particularly rich in antioxidants, including phenolic diterpenes (carnosic acid and carnosol) and phenolic acids (rosmarinic acid), which are essential for mitigating the harmful effects of free radicals and are believed to enhance immune function and promote better blood circulation [66].

The antioxidant activity of rosemary is mediated through a multifaceted and synergistic set of mechanisms. Its bioactive constituents, particularly in extracts and essential oils, function as potent scavengers, directly neutralizing harmful free radicals such as superoxide anions and hydroxyl radicals. Furthermore, rosemary compounds effectively inhibit lipid peroxidation, a destructive chain reaction that damages cell membranes and contributes to cellular dysfunction under oxidative stress. Beyond these direct actions, rosemary modulates the body's endogenous defense systems by upregulating the activity of key antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). Simultaneously, it helps reduce the overall burden of reactive oxygen and nitrogen species. This coordinated approach—combining direct radical quenching, protection of cellular structures, and enhancement of natural antioxidant capacity—collectively bolsters the organism's resilience against oxidative damage, which is a central pillar of its anti-aging and therapeutic effects [66].

Rosemary's antioxidant effect is the base of most of its therapeutic effect [66]. Many studies were performed to evaluate the antioxidant effect of rosemary that contributed to its antiaging, memory-enhancing and photo-protective effects [16, 58, 97] (Tables 1 and 2). For instance, rosemary hexane extract shows dose-dependent inhibition of skin-aging enzymes like elastase ( $IC_{50}$  57.6  $\mu$ g/mL) [58], while its major diterpenes, such as

**Table 1** In vitro studies demonstrating key anti-aging and neuroprotective activities of rosemary extracts and compounds

| Extract/Compound                                | Key Activity Assessed                                        | Model/Assay                                       | Major Outcome(s)                                                                                                                                                                                   | References |
|-------------------------------------------------|--------------------------------------------------------------|---------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Rosemary hexane extract                         | Anti-elastase, anti-collagenase, anti-hyaluronidase activity | Enzymatic inhibition assays                       | Showed dose-dependent inhibition of elastase ( $IC_{50}$ : 57.6 $\mu$ g/mL), collagenase ( $IC_{50}$ : 520.2 $\mu$ g/mL), and hyaluronidase ( $IC_{50}$ : 448.1 $\mu$ g/mL)                        | [58]       |
| Hydroethanolic extract of <i>R. officinalis</i> | Sun protection factor (SPF) determination                    | UV-visible spectrophotometry (Mansur equation)    | SPF value calculated as 7.56, indicating satisfactory sunscreen activity at 0.2 $\mu$ g/mL                                                                                                         | [117]      |
| Rosemary ethanolic and aqueous extracts         | Anti-tyrosinase, anti-elastase, anti-collagenase activity    | Comparative study with other medicinal plants     | Rosemary extracts showed superior inhibition of tyrosinase ( $IC_{50}$ : 55.03–65.03 $\mu$ g/mL), elastase ( $IC_{50}$ : 45.11–58.22 $\mu$ g/mL), and collagenase ( $IC_{50}$ : 100.32 $\mu$ g/mL) | [102]      |
| Carnosic acid                                   | Neuroprotective effects against A $\beta$ toxicity           | Primary neurons exposed to A $\beta$ 42 oligomers | Inhibited dendritic spine loss in neurons exposed to oligomeric A $\beta$                                                                                                                          | [72]       |

**Table 2** In vivo and clinical studies on rosemary's effects in aging models

| Study Design/Model                             | Key Intervention                                   | Major Findings                                                                                                             | References |
|------------------------------------------------|----------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|------------|
| Randomized controlled trial in elderly         | Rosemary leaf powder (750–6000 mg)                 | 750 mg dose improved speed of memory and alertness; higher doses showed impairment in some cognitive measures              | [89]       |
| Quasi-experimental study in secondary students | Rosemary essential oil inhalation                  | Significant improvement in short-term image memory compared to control                                                     | [44]       |
| UVB-induced skin-aging in rats                 | Rosemary hexane extract and nanocapsule gel        | Restored antioxidant enzymes (SOD, CAT, GPx), reduced inflammatory markers, decreased wrinkling markers (MMP1, elastase)   | [58]       |
| Middle-aged rats                               | Rosemary extract (40% carnosic acid, 50–200 mg/kg) | Enhanced hippocampal antioxidant enzymes (SOD, GPx, CAT) and memory scores in dose-dependent manner                        | [97]       |
| UVB-induced skin inflammation in mice          | Hydroethanolic extract-loaded emulgel              | Protected skin against UVB damage via antioxidant and anti-inflammatory effects of carnosol, carnosic and rosmarinic acids | [117]      |
| UV-induced photoaging in mice                  | Rosemary-marigold extract combination              | Dose-dependent reduction in MMPs (MMP-1, -3, -10, -13) and inflammatory cytokines; increased type I procollagen            | [16]       |
| Randomized trial in university students        | Oral rosemary powder                               | Improved anxiety, depression, sleep quality, and memory performance after 1 month                                          | [83]       |
| Quasi-experimental study in elderly            | Rosemary aromatherapy                              | Significant improvement in short-term memory scores after inhalation                                                       | [115]      |
| SAMP8 accelerated aging mice                   | Rosemary extracts (10–60% carnosic acid)           | Enhanced learning/memory in behavioral tests; reduced hippocampal protein carbonyls                                        | [42]       |
| Transgenic Alzheimer's mouse models            | Carnosic acid treatment                            | Improved spatial learning/memory; reduced A $\beta$ plaques, phospho-tau, and astrogliosis                                 | [72]       |

carnosic acid, exhibit direct neuroprotective effects against amyloid- $\beta$  oligomers in neuronal models [72].

#### 4.2 Anti-inflammatory activity

Rosemary has potent anti-inflammatory properties [24], as it was reported that rosemary extract and essential oils can hinder the migration of leukocytes in vivo, and reduce the number of white blood cells at the inflammation site, so it gives strong anti-inflammatory effect [33]. Furthermore, rosemary extract has been observed to inhibit the production of other proinflammatory substances, including nitric oxide and inflammation-related genes. Carnosic acid and carnosol play an important role in its anti-inflammatory effect, often synergizing with other rosemary components [54].

#### 4.3 Neuroprotective and cognitive-enhancing activity

Rosemary has shown remarkable potential in protecting the brain from neurodegenerative illnesses such as Alzheimer's disease and dementia. A key mechanism involves the inhibition of enzymes that break down acetylcholine. Rosemary contains compounds, including rosmarinic acid and certain terpenes (e.g.,  $\alpha$ -pinene, 1,8-cineole), that inhibit acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) activity. By increasing acetylcholine levels in synaptic clefts, rosemary may help mitigate memory loss and cognitive decline associated with aging and Alzheimer's disease [66].

In vivo studies support these neuroprotective claims (Table 2). For example, administration of a rosemary extract containing 40% carnosic acid to middle-aged rats enhanced

spatial memory and increased hippocampal antioxidant enzyme activities (SOD, CAT, GPx) in a dose-dependent manner [97]. The usage of rosemary leaf hydro-alcoholic extract (RHE) resulted in significant progress in cerebral damage and neurological assessments, in addition to effectively reducing BBB permeability, thereby reducing brain edema. As a result, RHE can protect against acute ischemic injury-induced BBB disruption by reducing brain edema, and intracranial pressure, and improving cerebral hemodynamics [110].

Regarding age-related macular degeneration (AMD), the main compound of rosemary, carnosic acid, could have clinical significance in treating diseases that impact the outer retina, such as AMD and retinitis pigmentosa, where oxidative stress is believed to play a role in disease progress [63]. The proposed mechanism involves carnosic acid's activation of the Nrf2 antioxidant pathway in retinal pigment epithelial cells, countering oxidative stress central to AMD pathogenesis [99].

The neuroprotective mechanisms extend to cognitive enhancement. The main active compounds in rosemary, including 1,8-cineole and rosmarinic acid, have been found to have neuroprotective effects and may help to prevent age-related cognitive decline [96]. Rosemary essential oil has been shown to improve cognitive function and memory by increasing blood flow to the brain and stimulating the nervous system [17]. Furthermore, rosmarinic acid significantly proved to regain the memory loss initiated with the aggregation of  $\beta$  amyloid in both models of AD and ALS [7, 111].

## 5 Applications in age-related conditions

### 5.1 Dermatological applications: targeting skin-aging

Rosemary extracts were pursued as potential topical therapy in literature and have been incorporated into numerous drug delivery systems to enhance their targeting efficacy, absorption, and bioavailability [6]. Montenegro et al. [79, 80] found that encapsulating rosemary extract in nanostructured lipid carriers (NLCs) significantly improved its topical efficacy for skin hydration and elasticity. The NLC formulation enhanced skin penetration, outperforming the essential oil alone [79, 80]. Angourani et al. [12] aimed to preserve the rosemary oils stability and prevent evaporation by developing zein nanoparticles between 70 and 200 nm in size and entrapment efficiency (EE) of 71% [12]. This encapsulation enhances the chemical stability of the oil, prevents its rapid evaporation, and can facilitate sustained release and deeper skin penetration, thereby improving topical efficacy. Casanova et al. [25] improved skin permeation of rosmarinic acid by incorporating it in chitosan microparticles and modified chitosan microparticles (4.2  $\mu$ m and 7.7  $\mu$ m in size, respectively) [25]. The anti-wrinkle activity of rosemary extract was enhanced by Ezzat et al. [39], through encapsulation in transfersomes with enhanced permeation compared to free extract as well as significant inhibition of MMP-2 and MMP-9 expression, enhanced anti-wrinkling scores, and reduced the thickness of the epidermis without pigmentation [39]. Rosemary oil nanoemulsions were also utilized in addition to *Centella asiatica* (CA) transfersomes in an effort to counteract the antiaging effects of ultraviolet (UVB) rays namely epidermal hyperplasia, wrinkle formation, and collagen fiber arrangement. The prepared nanoemulsions significantly decreased such effects by reducing the malondialdehyde (MDA) expression and collagen destruction by inhibiting the expression of matrix metalloproteinase-9 (MMP-9) in addition to

upregulation of type I collagen through transforming growth factor- $\beta$  (TGF- $\beta$ )/Smad pathway activation, leading to recovery of the collagen fiber density [67, 68].

Dryness, wrinkles, and irregular pigmentation are the main observed signs of aging skin accompanied by some histological alterations such as a noticeable loss of skin elasticity, and atrophy of the skin connective tissue [59]. The efficacy of rosemary essential oil was clinically proved in free state preparation versus rosemary essential oil-loaded NLCs both incorporated in a gel formula on cutaneous changes such as skin hydration and elasticity [79, 80].

Aging also has a substantial influence on the skin's healing properties as it extends the inflammatory stage and increases reactive oxygen species (ROS) production. This will lead to more protein degradation, which will result in chronic wound healing with complications [65]. The efficacy of rosemary essential oil in wound healing was evaluated in an in vivo infected wound model in rats. The oil, either in its free form or encapsulated within nanostructured lipid carriers (NLCs), was compared to the topical antibiotic Mupirocin®. Both rosemary formulations significantly reduced tissue infection (assessed by measuring bacterial colonization), enhanced cell regeneration, increased fibroblast infiltration, and stimulated collagen production [70].

As well, an antibacterial assessment showed that the rosemary essential oil and silver nanoparticle-loaded fiber mats created significant inhibition zones against *Staphylococcus aureus* and *Escherichia coli*, with larger zones against *E. coli* ( $13.83 \pm 0.05$  mm) than *S. aureus* ( $9.96 \pm 0.11$  mm) at the highest concentration (7 wt%) [98]. The cell viability and attachment assay indicated that the composite fibers supported robust cell growth and adhesion, reflecting their enhanced hydrophilicity and biocompatibility, which are favorable for wound bed integration [98]. Using a rat model with *Candida albicans*-infected wounds, topical application of a 2.4% rosemary essential oil ointment significantly accelerated wound contraction in a dose-dependent manner. Histological analysis showed improved re-epithelialization and higher collagen density, while microbiological assessment confirmed reduced fungal load [82]. These findings were consistent with that of Saporito et al. [105] that proved the efficacy of rosemary essential oil in the acceleration of the initial stages of healing, reduction of inflammation, increasing angiogenesis, collagen fibers density, and wound contraction [105]. The healing efficacy of both aqueous extract and essential oil of the aerial parts was tested on an alloxan-induced diabetic BALB/c mice. It was noticed that rosemary essential oil positively impacted the diabetic wound healing process by reducing inflammation and increasing wound contraction, re-epithelialization, regeneration of granulation tissue, angiogenesis, and collagen deposition were detected in the treated wounds [1].

Medical devices such as nanoparticle-loaded fibrous mats or hydrogel dressings were created that can be used in wound healing acceleration by developing nanoparticles loaded with (75 mg) rosemary oil and was in vitro tested for the enhancement of cell proliferation. The device also has proven its antimicrobial activity against *Staphylococcus aureus* and other *Streptococcus pyogenes*; on in vivo rat burnt model [105].

Rosemary essential oil was also assessed as a healing agent in the treatment of skin lesions induced in mice. The rosemary essential oil-treated groups exhibited a satisfactory healing process [31].

Ultraviolet B (UVB) radiation induces physiological and morphological photoaging of the skin resulting in wrinkles, and loss of elasticity. Rosemary essential oil was

incorporated in a nano-emulsion with lipid nanocarriers with *Centella asiatica* (CA) transfersomes where it proved its in vivo activity in protection against UVB radiation, accompanied by ameliorative and anti-aging properties in a BALB/c hairless mouse model owing to its anti-matrix metalloproteinase-9 (MMP-9) expression and the up-regulation of type I collagen [67, 68]. It was also proved that 70% acetone rosemary extract possessed antioxidant effects in the DPPH test, great absorption power for UVA and UVB radiation, and anti-microbial test against *Staphylococcus aureus* [48].

Rosemary extract was tested alone and in combination with citrus extract for in vivo and in vitro protection against UV irradiation, using the MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide) assay on keratinocytes (HaCaT cells). Both extracts increased the *viability* of the keratinocytes and oral administration of the combined citrus and rosemary extracts over the course of 8 weeks increased the UV dose required to induce erythema in the skin [91]. An in vivo study using a UV-induced photoaged mouse model (Table 2) found that an ethanolic rosemary extract, combined with marigold, significantly reduced the expression of MMPs (MMP-1, -3, -10, -13) and inflammatory cytokines (IL-1, IL-6, TNF- $\alpha$ , COX-2), while restoring type I procollagen and boosting antioxidant enzymes (SOD, GPx, CAT) in a dose-dependent manner, with effects comparable to hyaluronic acid [16].

Cellulite has a high prevalence rate in post-adolescent women, it starts with alterations in the skin with the appearance of dimples presented as dimpled or furrowed skin whose management is very difficult, so the prospect of a combination management is favored, hence; natural products are being explored for such purpose [32]. Rosemary extract exhibited anti-platelet aggregation, radical scavenging activity, and nitric oxide inhibition effect which may help in cellulite control [126].

Aging is a skin process that occurs owing to intrinsic and extrinsic factors. Rosemary was tested in comparison to other plants (*Lavandula officinalis*, *Matricaria chamomilla*, *Camellia sinensis*, and *Pelargonium graveolens*) for its in vitro anti-aging activity [86]. The inhibitory action of the plants' ethanolic extracts on tyrosinase, elastase, and collagenase enzymes was explored with rosemary extracts coming up as the most potent of all extracts [102]. It also proved the anti-elastase activity of rosemary extract by testing it on human leukocyte elastase [119]. As well, a comprehensive in vivo study (Table 2) evaluated a rosemary hexane extract-loaded lipid nanocapsule gel against UVB-induced photoaging in rats. The formulation effectively restored antioxidant levels (GSH, SOD, CAT), reduced inflammatory markers, and decreased levels of wrinkling mediators (GM-CSF, MMP1, elastase), demonstrating superior photo-protection compared to the free extract [58].

Hair graying and hair loss are two typical aging signs that highly affect patients' quality of life and represent a challenge for dermatologists. The hair is subject to intrinsic and extrinsic factors that influence hair follicle changes and clinically result in hair alterations such as graying and hair loss, which are commonly described in elderly patients [122].

Rosemary essential oil (10% in an oleogel) demonstrated hair growth promotion comparable to 2% minoxidil in a rat model, increasing hair follicle count and density after 4 weeks of treatment [121]. These findings were similar to the results obtained when rosemary oil was clinically tested on patients having different types of alopecia, proving that rosemary oil was as effective as minoxidil (2%) in reducing hair loss and stimulating

hair growth [124]. It was reported that the anti-hair loss ability of rosemary essential oil is due to the improvement of blood circulation in the scalp [36].

## 5.2 Systemic conditions: osteoarthritis

Osteoarthritis is the most common disease of the joints among humans, and knee osteoarthritis is the largest cause of disability among the elderly in the most developed countries. The main pathological feature of osteoarthritis is the progressive destruction of articular cartilage, in addition, synovial joints and all associated tissues such as synovium and subchondral bone are also involved [23, 46]

Rosemary and lavender essential oils were incorporated in a hydrophilic ointment and tested on 15 patients with knee osteoarthritis for 3 months. The results were assessed using WOMAC (the Western Ontario and McMaster Universities Arthritis Index) and Lequesne indices and were evaluated by the Wilcoxon statistical test. The WOMAC questionnaire denotative survey also showed that the pain and physical function at the 4th, 8th, and 12th weeks were significantly less than the first week of admission ( $p \leq 0.05$ ) [46]. The observed reduction in pain and improvement in function is likely due to the combined anti-inflammatory and analgesic properties of both essential oils, as evidenced by studies on their individual components [40, 112].

## 6 Rosemary as a functional food

Rosemary is considered an aromatic herb that has been used for centuries as a culinary spice, medicinal herb, and fragrance ingredient. Rosemary has gained increasing attention in recent times due to its potential health benefits as a functional food and its therapeutic effects in aromatherapy [53].

Rosemary contains bioactive materials such as rosmarinic acid, carnolic acid, and essential oils that have been shown to possess antioxidant, anti-inflammatory, antimicrobial, and anticancer properties. These properties make rosemary a promising ingredient for functional foods that can promote health and prevent disease [11].

Beyond its use as a spice, rosemary extracts are employed as natural antioxidants to preserve foods like meats and oils. More significantly, dietary intervention studies suggest potential health benefits. For instance, dietary supplementation with rosemary extract has been shown to improve plasma antioxidant status in humans. In animal models, incorporation of rosemary into the diet attenuated age-related cognitive decline and improved metabolic parameters. Its use as a natural preservative in food matrices (e.g., cheese) adds bioactive compounds to the diet while enhancing shelf-life [15, 100].

## 7 Rosemary applications in aromatherapy

Aromatherapy is a complementary therapy that utilizes essential oils to enhance physical and mental well-being [4]. Rosemary essential oil is a commonly used oil in aromatherapy due to its therapeutic effects. It has been demonstrated that rosemary essential oil can improve cognitive function and mood in elderly patients, making it a popular choice in the field of aromatherapy [81]. The proposed mechanisms for these benefits include the inhalation of active monoterpenes (e.g., 1,8-cineole), which may influence the limbic system, modulate neurotransmitter levels, and increase cerebral blood flow, leading to improved alertness, memory, and mood [8].

Rosemary essential oil has been found to have potential benefits for age-related diseases when used in aromatherapy, rosemary oil is employed to invigorate the central nervous system and enhance blood circulation, thus easing muscle soreness [106].

Inhaling rosemary essential oil or using it in a massage oil may help to improve mental clarity and focus, promote relaxation, and reduce feelings of stress and anxiety. Rosemary essential oil has a calming effect on the nervous system and may help to reduce stress and anxiety [73]. Finally, depression is a common issue among older adults, and rosemary essential oil may help improve mood and alleviate symptoms of depression [76].

Rosemary essential oil has analgesic properties and may be useful for relieving pain associated with arthritis in old age people, or other types of pain. The main active compounds in rosemary essential oil, including camphor and 1,8-cineole, have been found to have analgesic effects. Using rosemary essential oil in a massage oil or applying it topically may help to relieve pain and inflammation, alleviate pain, and enhance the ability to function, resulting in an improved quality of life [88].

## 8 Rosemary safety and bioavailability

Safe use of rosemary extracts in foods and drinks has been established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), which set a limit of limit of 0–0.3 mg/kg body weight as an acceptable daily intake (ADI) for rosemary extract, identified as carnosic acid and carnosol, in 2016. Additionally, the European Food Safety Agency (EFSA) Panel on Food Additives and Nutrient Sources added to Food (ANS) in 2008 established safe limits of use on the refined exposure of extracts of rosemary as a food additive. The EFSA Panel likewise concluded that the no observed adverse effect level (NOAEL) for rosemary acetone extract can be regarded as 5000 mg/kg (equal to 316 or 401 mg/kg body weight/day for males and females, respectively daily) [93].

Nonetheless, rosemary extracts in different solvents have been proven safe through a plethora of studies, Christopoulou et al. [28] proved the safety of both rosemary alcoholic extract (38%, v/v) and the essential oil through genotoxicity determination (AMES test) against TA98 and TA100 cell lines at 5% and 90% dilutions, which are commonly used in the drinks industry [28]. Anadon et al. [10] conducted a safety study on oral rosemary extracts at a single dose of 2000 mg/kg body weight in Wistar rats. Results showed that rosemary extracts were safe, and showed no adverse effects, histopathological or behavioral changes, or mortality during the study period of 2 weeks [10].

Attempts to study rosemary extract pharmacokinetics, absorption, and metabolism have been made to better understand its bioavailability in the body. Achour et al. [2] conducted a study to assess the bioavailability and pharmacokinetics of phenolic compounds in *R. officinalis* in healthy humans. The study identified forty-eight compounds in plasma and urine. It was shown that the polyphenols in rosemary are metabolized into phase II conjugates, with quick appearance and clearance in plasma linked to small intestine absorption. Phase II derivatives of caffeic acid demonstrated kinetics that matched rosmarinic acid's intestinal and colonic hydrolysis [2]. The same research team used rosemary infusion, rosmarinic acid and caffeic acid standards, and ferulic acid in a study to evaluate the bioactivity, absorption, and metabolism of rosmarinic acid and caffeic acid in human Caco-2 and HepG2 cells, which represented small intestine and liver models, respectively. Both caco-2 and hepg2 cells partially absorbed and metabolized

the test substances, albeit hepg2 did so to a greater extent. The best-absorbed compounds were ferulic acid, rosmarinic acid, and caffeic acid, with metabolite percentages of 34.3%, 10.3%, and 3.2% in hepg2 cells and 30.4%, 11.8%, and 4.4% in caco-2 cells, respectively [3]. To explore the absorption and metabolism of phenolic components in rosemary extract, Fernandez-Ochoa et al. [43] performed an in-situ perfusion experiment, which revealed that both flavonoids and diterpenes absorption was higher than triterpenes. Additionally, several diterpenes and their metabolites were detectable in plasma, compared to phenolic substances [43].

To enhance rosemary extract bioavailability and pharmacokinetics, Arranz et al. [14] studied two oppositely charged rosemary supercritical fluid extracts enclosed in an oil-in-water emulsion prepared with 2% whey protein isolate or lactoferrin and 7% of canola oil. The results demonstrated that protein type did not affect the bioavailability of carnosic acid and carnosol in the Caco-2 cell line. However, when lactoferrin emulsions led to a larger retention of carnosic acid in the apical layer of co-cultures of HT-29 MTX [13]. Additionally, Arranz et al. [14] attempted to increase the bioavailability of carnosic acid and carnosol through loading in oil emulsion droplets and casein micelles, which significantly reduced the rosemary extract's ability to degrade during digestion and resulted in 81 and 97% recovery of carnosic acid, respectively leading to enhanced bioavailability in the Caco-2 cell line [14].

## 9 Conclusion and future directions

Bioactive metabolites derived from *R. officinalis* have garnered increasing attention due to their broad spectrum of pharmacological activities and promising applications in the food, pharmaceutical, and cosmetic industries. Recent evidence supports their potential role in the prevention and management of age-related diseases, including neurodegenerative, metabolic, and inflammatory disorders, as well as dermatological conditions associated with aging.

Despite the compelling preclinical data, significant research gaps remain. Clinical studies are urgently needed to validate the efficacy, bioavailability, and pharmacokinetics of rosemary-derived phytochemicals in human populations. Moreover, deeper mechanistic insights into their molecular targets and signaling pathways in aging-related pathologies are essential to support translational applications.

From a formulation perspective, the interaction of rosemary constituents with other bioactive compounds in functional foods and cosmeceuticals remains poorly understood and warrants systematic investigation. Furthermore, nanotechnology-based delivery systems present a novel and promising avenue for enhancing the stability, targeted delivery, and therapeutic efficacy of rosemary bioactives in both food and pharmaceutical matrices.

In conclusion, *R. officinalis* holds substantial potential as a multipurpose bioactive source, yet realizing its full therapeutic and commercial value requires interdisciplinary research integrating phytochemistry, pharmacology, clinical sciences, and formulation technologies.

### Author contributions

S.M.E conceptualization, writing the draft and revising the final version. R.M.M. collected and analyzed the data, and wrote the manuscript. B.R. collected and analyzed the data, and wrote the manuscript. N.M.E. collected and analyzed the data, and wrote the manuscript. O.M.A. collected and analyzed the data, and wrote the manuscript. M.A.S. collected and analyzed the data, and wrote the manuscript. All authors read and approved the manuscript.

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