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Therapeutic effects of rosemary (*Rosmarinus officinalis* L.) and its active constituents on nervous system disorders

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ABSTRACT

Rosemary (*Rosmarinus officinalis* L.) is an evergreen bushy shrub which grows along the Mediterranean Sea, and sub-Himalayan areas. In folk medicine, it has been used as an antispasmodic, mild analgesic, to cure intercostal neuralgia, headaches, migraine, insomnia emotional upset, and depression. Different investigations have highlighted rosemary neuropharmacological properties as their main topics. Rosemary has significant antimicrobial, anti-inflammatory, anti-oxidant, anti-apoptotic, anti-tumorigenic, antinociceptive, and neuroprotective properties. Furthermore, it shows important clinical effects on mood, learning, memory, pain, anxiety, and sleep. The aim of the current work is to review the potential neuropharmacological effects of different rosemary extracts and its active constituents on nervous system disorders, their relevant mechanisms and its preclinical application to recall the therapeutic potential of this herb and more directions of future research projects. The data were gathered by searching the English articles in PubMed, Scopus, Google Scholar, and Web of Science. The keywords used as search terms were '*Rosmarinus officinalis*', 'rosemary', 'nervous system', 'depression', 'memory', 'Alzheimer's disease' 'epilepsy', 'addiction', 'neuropathic pain', and 'disorders'. All kinds of related articles, abstracts and books were included. No time limitation was considered. Both *in vitro* and *in vivo* studies were subjected to this investigation. This review authenticates that rosemary has appeared as a worthy source for curing inflammation, analgesic, anti-anxiety, and memory boosting. It also arranges new perception for further investigations on isolated constituents, especially carnosic acid, rosmarinic acid, and essential oil to find exquisite therapeutics and support drug discovery with fewer side effects to help people suffering from nervous system disorders.

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Introduction

Nervous system disorders include abnormalities in either function or structure of the central or peripheral nervous system (1). These illnesses might be the result of trauma, metabolic dysfunction, infection or genetic conditions. A large number of scientific studies and discoveries aim to reduce the impacts and frequency of neurological disorders, mental health, and drug abuse.

Herbal medicines and natural products were used in ancient therapies (2). During the last decades, researchers focused more on herbs in drug discovery because of their limited side effects and fewer complications (3). According to the improving demand, the medicinal and pharmacological studies have been increasing worldwide (4).

Rosemary, *Rosmarinus officinalis* L. (Labiatae) has been used in folk medicine to alleviate several diseases including headache, dysmenorrhea, stomachache, epilepsy, rheumatic pain, spasms, nervous agitation, improvement of memory, hysteria, depression, as well as physical and mental fatigue (5, 6). Today, rosemary is grown worldwide but it is an evergreen perennial shrub native to southern Europe and Asia especially Mediterranean region (7). Recently, noticeable scientific interest is focused on the beneficial therapeutic properties of different kinds of rosemary extracts and its main constituents, such as carnosic acid, carnosol, rosmarinic acid, etc. A large number of studies either on animal models or cultured cells indicate the wide range medicinal properties of rosemary and its compounds such as anti-inflammatory (8, 9), anti-oxidant (10), antinociceptive (11), neuroprotective (12), antidepressant, anti-hysteric, ameliorative of memory and mental fatigue (13-15) (Figure 1). Moreover, the safety of rosemary has been displayed in various studies. The median lethal dose (LD_{50}) value of methanolic extract of rosemary leaves prescribed intraperitoneally to mice was 4.125 g/kg of their body weight (16). Rosemary has also been classified as "generally safe" or GRAS (CFR182.10; 182.20) by the FDA in America (17). Rosmarinic acid was observed to have very scarce toxicity with an LD_{50} of 561 mg/kg in mice (18). The oral LD_{50} of carnosic acid was 7100 mg/kg in the acute toxicity in mice (19).

Phytochemical studies revealed that rosemary contains terpenoids, essential oils, alkaloids and flavonoids (20-22). Chemical analysis of different kinds of rosemary extracts composition reveals that the most potent active components are triterpenes, phenolic diterpenes and phenolic acids including rosmarinic acid, carnosic acid, rosmanol, carnosol, ursolic acid and betulinic acid (23, 24) (Figure 2). According to the

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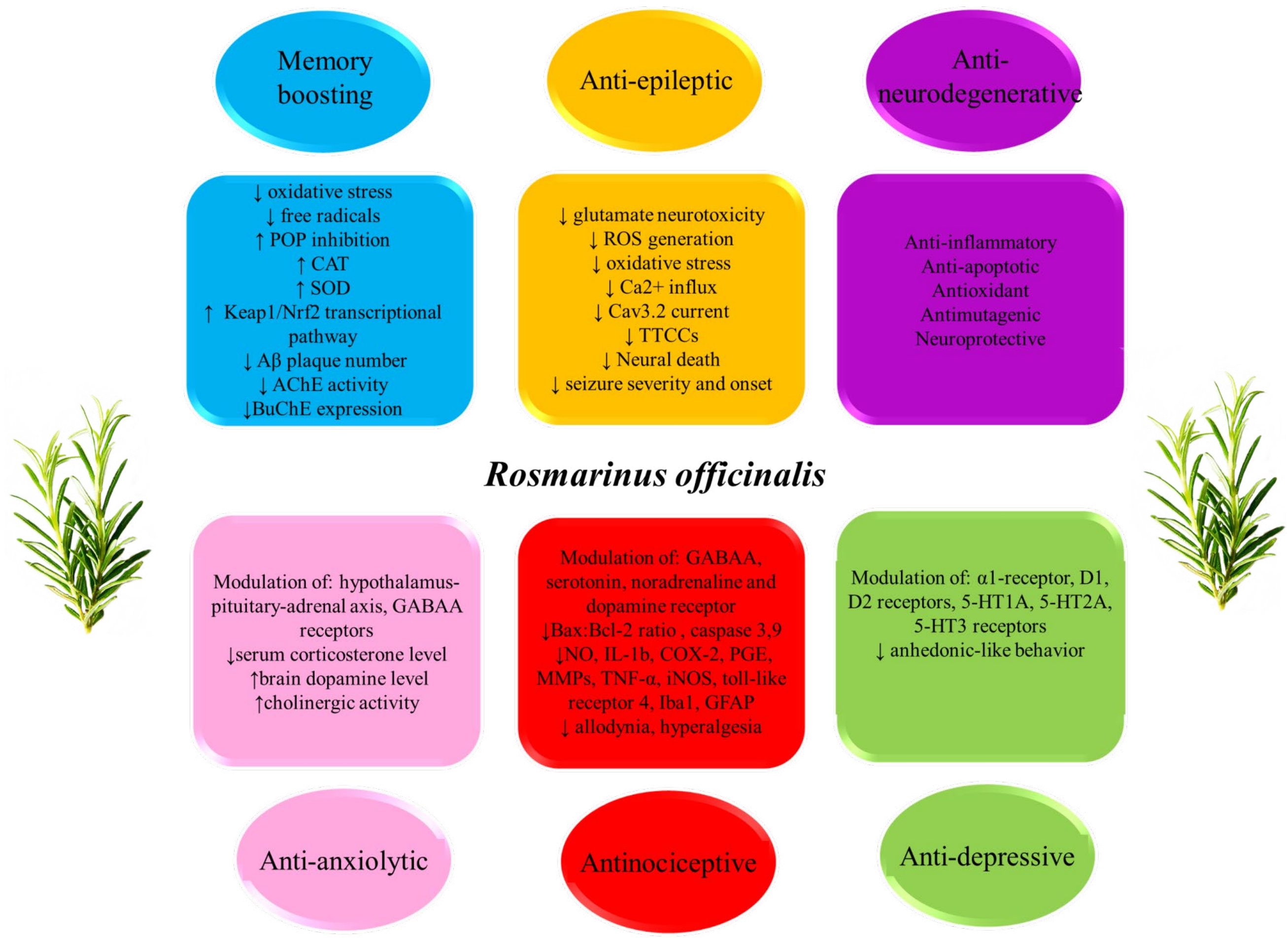

Figure 1. Neuropharmacological properties of rosemary on nervous system

documents, rosmarinic acid and carnosic acid possess the most medicinal effects among the mentioned phenolic compounds i.e. anti-inflammatory and anti-oxidants (25-28). Nowadays because of presence of many beneficial and un-useful constituents in medicinal plants it needs to focus on determination and effectiveness of the effective substances of extracts but not crude extracts.

Methods

The data were gathered by searching the English articles in PubMed, Scopus, Google Scholar, and Web of Science. The keywords used as search terms were '*Rosmarinus officinalis*', 'rosemary', 'nervous system', 'depression', 'memory', 'Alzheimer's disease' 'epilepsy', 'addiction', and 'neuropathic pain'. All kinds of related articles, abstracts and books were included. No time limitation was considered in this review. Both *in vitro* and *in vivo* studies were subjected to this investigation.

Therapeutic effects of rosemary constituents on nervous system disorders

Depression

Depression is a serious chronic psychiatric disease (29). Clinical and experimental studies have suggested several alterations occurred in neuronal noradrenergic and serotonergic function in the central nervous system (30). Another hypothesis focuses on the role of brain-derived neurotrophic factor (BDNF) in the brain (31). In addition, other studies point to the involvement of endogenous metabolites or inflammatory cytokines in the induction of depression (32).

The antidepressant-like effect of hydro-alcoholic extract of the leaves and stems of rosemary (100 mg/kg, PO) for 14 days was revealed in behavioral tests in mice and it was also shown that its antidepressant-like effect is dependent on its interaction with the noradrenergic (α 1-receptor), dopaminergic (D1 and D2 receptors) and serotonergic (5-HT1A, 5-HT2A and 5-HT3 receptors) systems (14). This research group also reported that chronic administration of the hydro-alcoholic extract of rosemary (10-300 mg/kg, PO) for 14 days similar to fluoxetine (10mg/kg, PO) could reduce anhedonic-like behavior and hyperactivity that were associated with hippocampal acetylcholinesterase (AChE) activity in olfactory bulbectomized mice (33). Although, more studies are necessary to determine which isolated compounds are responsible for the antidepressant-like effects of this extract. In fact, this is a major problem of using crude extracts in medicine.

In the extrapyramidal system of the brain, dopamine is a precursor to norepinephrine and epinephrine and it has an important role in behavior regulation (32). So, regulating the amount of dopamine and dopaminergic

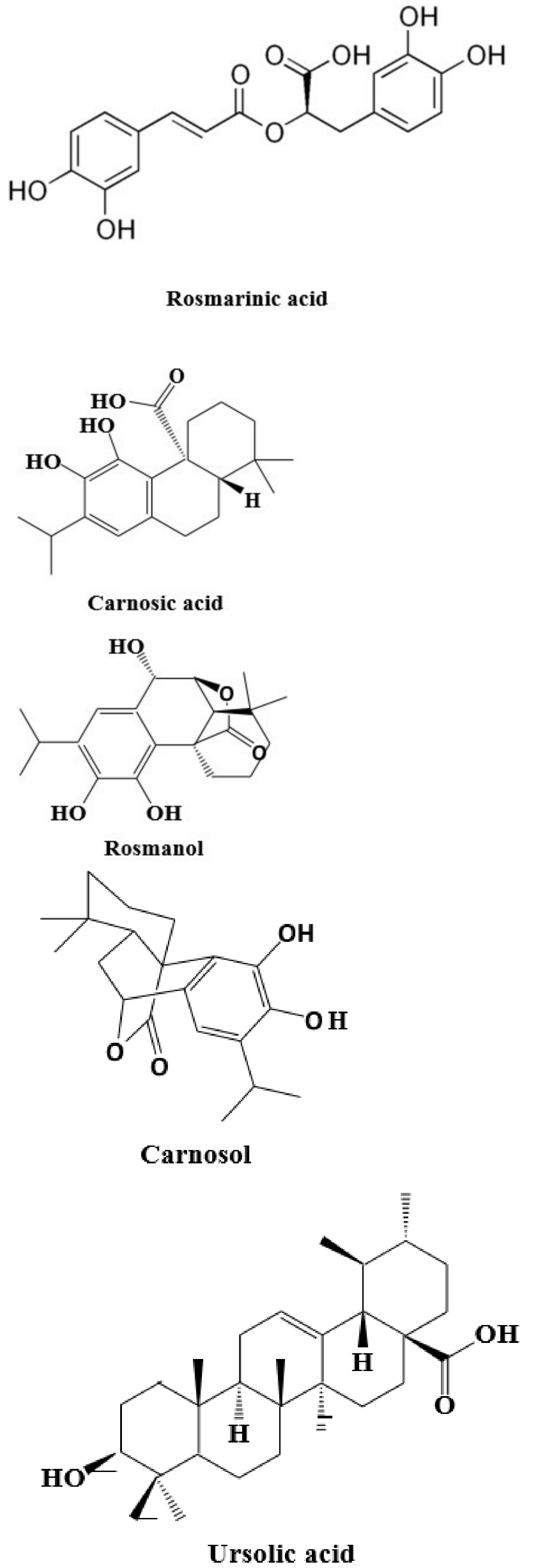

Figure 2. Chemical structures of some constituents of rosemary (*Rosmarinus officinalis* L.)

pathways is an important goal in controlling depression. It was also revealed that ursolic acid, a pentacyclic triterpenoid derived from rosemary could reduce the immobility time both in tail suspension test and forced swimming test in mice. Pretreatment with SCH23390 (0.05 mg/kg, SC, a dopamine D(1) receptor antagonist) and sulpiride (50 mg/kg, IP, a dopamine D(2) receptor antagonist) prevented the ursolic acid effects (0.001–10 mg/kg, PO) in the tail suspension test. Moreover, administrating the sub-effective dose of ursolic acid in addition to the sub-effective doses of SKF38393 (0.1 mg/kg, SC, a dopamine D(1) receptor agonist), apomorphine (0.5 μg/kg, IP, a preferential dopamine D(2) receptor agonist) or bupropion (1 mg/kg, IP, a dual dopamine/ noradrenaline reuptake inhibitor) decreased the immobility time in the tail suspension test compared with each of the drugs alone. These results show that the antidepressant effect of ursolic acid in the tail suspension test could be because of an interaction with the dopaminergic pathway and through activation of dopamine D_1 and D_2 receptors (34). This team also assessed the antidepressant-like property of different fractions of rosemary including, hexane (0.1-10 mg/kg, PO), ethanolic, ethyl acetate 1 and 2, and essential oil-free (0.1-100 mg/kg, PO), and some isolated compounds such as betulinic acid (10 mg/kg, PO), and carnosol (0.01-0.1 mg/kg, PO) in the tail suspension, a predictive test to investigate the antidepressant activity, in mice. Results showed that all of the fractions and prescribed constituents produced a significant antidepressant-like effect (35). This finding could be further evaluated by molecular and biochemical tests to determine the exact mechanisms involved in their antidepressant like properties.

By these documents, it may be suggested that antidepressant-like effect of rosemary could be, at least in part, because of carnosol, ursolic acid, betulinic acid and 1,8-cineole, the main compound in the essential oil of rosemary. A few of these studies are represented in Table 1.

Memory, learning, and Alzheimer's disease

The number of elderly adults, over 65 years old, worldwide is supposed to be doubled by the year 2030 and to help individuals stay in the workforce longer, the need to stay cognitively fit is improving. Thus, the development of natural interventions to slow or prevent cognitive decline naturally associated with aging is crucial. Herbal ingredients and nutrients have been studied as a probable solution to this developing concern. One of the important hallmarks of the aging process is oxidative damage (36). The neuronal dysfunction observed in disorders associated with aging such as Alzheimer's disease is mainly thought to be from oxidative stress. Free radicals are responsible for oxidative stress and aging (37). Aging and related diseases reveal when endogenous anti-oxidants are not able to counter free radicals damage to cells and cellular molecules (38). So, plant extracts with anti-oxidant ingredients might be a great help. In this regard a study by Farr *et al*. 2016, investigated the effects of rosemary extract contained 60% or 10% carnosic acid and spearmint extract contained 5% rosmarinic acid, anti-oxidant-based components of rosemary for 90 days, on

Table 1. Clinical studies of rosemary and the active constituents on depression, memory and learning

Subjects	Type of extract, constituents/ doses/ Time of exposure	Endpoints	Ref. No.
Mice	Hydroalcoholic extract; 10–300 mg/kg 14 days	- The hydroalcoholic extract drove back the olfactory bulbectomy -induced hyperactivity, amplified exploratory and anhedonic behavior. - It improved serum glucose level and decreased hippocampal AChE activity in bulbectomized mice	30
Mice	Ursolic acid; 0.01 and 0.1 mg/kg,	- Ursolic acid decreased the immobility period in the tail suspension test (0.01 and 0.1 mg/kg) and also in the forced swimming test (10 mg/kg) - The effect of ursolic acid (0.1 mg/kg) in the tail suspension test was prevented by the pretreatment of SCH23390 (0.05 mg/kg, a dopamine D 1 receptor antagonist) and sulpiride (50 mg/kg, a dopamine D 2 receptor antagonist)	31
Wistar rats	Extract (containing 40% carnosic acid); (50,100 and 200 mg/kg/day); 12 weeks	- The extract (100 mg/kg) recovered the spatial memory retrieval score. - SOD, GPx and CAT enzymes significantly elevated in comparison with the normal group	46
(hAPP)-J20 mice and (3xTg AD) mice	Carnosic acid; 3 months	- Carnosic acid treatment of hAPP-J20 mice alleviated memory and learning in the Morris water maze test - Carnosic acid increased dendritic and synaptic markers, and reduced astrogliosis, Aβ plaque number, and phospho-tau staining in the hippocampus	52

memory and learning in mice and their results showed the positive effects of these ingredients on memory improvement in a mouse model (39).

It is known that inhibition of prolyl oligopeptidase (POP) might be effective in memory-related function (40). Rosmarinic acid (1, 2, 4, or 8 mg/kg, PO) for acute (4 training days) or 2 or 3 weeks sub-chronic periods inhibited POP activity and therefore showed a cognitive- improving effect in mice (41). These cognitive-enhancing effects of rosmarinic acid might be beneficial to populations of advanced age.

Song and colleagues, 2016, also confirmed the effect of rosemary extract containing 20% carnosic acid on the improvement of cognitive deficits in rats and it might be mediated by anti-oxidative (decreased ROS and increased superoxide dismutase (SOD)) and anti-inflammatory (reduced protein level of TNF-α, IL-6, and IL-1β in hippocampus) properties of rosemary (42). However, the pharmacological mechanisms behind the improvement in cognitive deficits are not clear enough and further examinations are needed to find the exact relationship between different doses of rosemary extract and improvement in cognitive deficits.

The inhalation of rosemary oil in 144 healthy volunteers induced subjective effects on mood as well as objective effects on cognitive performance (43). In another study, the aroma of rosemary oil improved performance in exam students by enhancing free radical scavenging activity and decreasing cortisol levels (44). In a study by Pengelly *et al*. 2012, rosemary powder (750 mg), the dose nearest to the normal culinary consumption, showed positive influences on the speed of memory, the time taken to effectively regain information from both episodic and working memory, on 28 older adults (mean age, 75 years) which is a useful predictor of cognitive function during aging (45). These results point to the value of further studies on the effects of different doses of rosemary on memory and cognition over the longer period of time.

Hippocampus is a part of the brain which has an important role in learning and memory, mood regulation, cognition and response to stress (46). It is one of the most vulnerable brain parts to oxidative stress (47). There are plenty of enzymatic and non-enzymatic anti-oxidant defense systems in cells to protect them from damages of free radical reactions (48). Since the endogenous anti-oxidant protection systems are not 100% effective, we assume that nutritional anti-oxidants could have beneficial effects on the memory, neurogenesis, and activities of enzymatic oxidative in the brain. Rasoolijazi and colleagues, 2015, evaluated the effect of rosemary extract on memory and anti-oxidant status of the hippocampus in middle-aged rats. They reported that prescription of rosemary extract (50,100 and 200 mg/kg/day, containing 40% carnosic acid, o.p.) for 12 weeks in middle-aged rats increased spatial memory and the activity of SOD and chloramphenicol acetyltransferase (CAT) anti-oxidant enzymes (49).

Alzheimer's disease is a complicated disease which implicates interaction between genetic and environmental risk factors and it is characterized by tau tangles, amyloid plaques, loss of synapses and neuronal loss (50). The generation of nitrosative and oxidative stress partially damage neurons, because oligomeric amyloid-β (Aβ) peptide triggers generation of reactive oxygen/nitrogen species (ROS/RNS) (51, 52). Activation of the Kelch-like ECH-associated protein 1-nuclear factor (erythroid-derived 2)-like2 (Keap1/Nrf2) pathway increases the transcription of anti-inflammatory proteins and phase 2 anti-oxidant. Hence, it could be a promising therapeutic process in various neurodegenerative conditions. It has been shown that carnosic acid converts to its active form by oxidative stress and its active form stimulates the Keap1/Nrf2 transcriptional pathway and therefore, produces phase 2 anti-oxidant enzymes in both *in vitro* and *in vivo* models

(53, 54). In another research, the protective effects of carnosic acid were studied on primary neurons exposed to oligomeric Aβ in both *in vitro* and *in vivo* models. The histological results revealed that carnosic acid (10 mg/kg b.w., trans-nasally) expanded synaptic and dendritic markers, and decreased Aβ plaque number, astrogliosis, and phospho-tau staining in the hippocampus (55) (Table 1). Since carnosic acid is on the 'generally regarded as safe' (GRAS) list of FDA, same studies on the human for clinical approach will be useful.

It is also believed that prolong the existence of acetylcholine into the synaptic cleft might cause cholinergic function in Alzheimer's disease due to inhibition of acetylcholine hydrolysis (56). It is proposed that cholinergic neurons degenerate in the basal forebrain and it is associated with loss of cholinergic neurotransmission in the cerebral part of the cortex. This might be therapeutically important because the cholinergic system of basal forebrain is involved in the attention and cognitive processing of memory (57). There are two major forms of cholinesterases in the human brain: butyrylcholinesterase (BuChE) and acethylcholinesterase (AChE). In the human brain, both of them are found in neurons, oligodendrocytes, astrocytes, tangles in Alzheimer's disease and neuritic plaques (58). It is reported that AChE activity reduced in the cortex but BuChE activity increased or remained unchanged during Alzheimer's disease development (59). A group of researchers assessed the influence of sub- chronic administration of rosemary extract (200 mg/kg, PO) on cognitive activities and behavior of rats and to evaluated BuChE and AChE gene expression level and activity in frontal cortex and hippocampus. It was observed that rosemary extract alleviated long-term memory and inhibited the AChE activity. It also had a stimulatory effect on BuChE in both parts of the rat brain. In addition, it reduced BuChE expression in cortex and increased it in the hippocampus (60). By the data in hand, it could be concluded that rosemary extract could improve long-term memory by inhibiting AChE activity in rat brain.

In order to check the possible effects of stimulation through the sense of smell on cognitive function, another team applied aromatherapy treatment on Alzheimer patients and proposed that aromatherapy might improve cognitive function, especially in Alzheimer patients (61).

Epilepsy

Epilepsy is a neurological disease that causes periodic spontaneous seizures and memory and learning deficits (62). Seizures lead to neuronal death because of over-activating of glutamate receptors (63). Glutamate has an important role in cognitive actions including learning and memory and in synaptic plasticity as well, but the higher concentration of glutamate and over activation of its receptor leads to neurodegeneration in the central nervous system (64). According to previous studies, glutamate neurotoxicity is because of generating ROS damages to cellular organelles like mitochondria (65). Thus, substances which are able to neutralize ROS could protect neurons and prevent subsequent death. Anti-oxidant components of rosemary extract (250, 500 and 750 mg/kg) reduced lipid peroxidation and interact with the free radical chain reaction and donate hydrogen and finally neutralize harmful agents in cooking liver pâté (66). Another study showed that rosemary extract (100 mg/kg/day, containing 40% carnosic acid, PO, for 23 days) might improve working and spatial memory deficits and neuronal degeneration induced by the toxicity of kainic acid (9.5 mg/kg, IP) in the hippocampus of rats, which might be because of its anti-oxidant properties. Rosemary also significantly decreased both seizure severity and onset in rats. In addition, neuronal loss in the CA1 region reduced (67). Although, the mechanisms of this improving effects of rosemary has not been well understood and need to be further investigated.

Previous studies reported that oxidative stress increased Ca^{2+} influx from extracellular fluid into neurons (68, 69). Ca^{2+} driven by the endoplasmic reticulum might raise Ca^{2+} concentration as well. The increased Ca^{2+} concentration raises amount of Ca^{2+} in nuclei and mitochondria and finally leads to disrupting normal metabolism and neurodegeneration. T-type calcium channels (TTCCs) play important roles in neuroprotection, neuronal excitability, sleep, and sensory processes. They are also involved in pain and epilepsy. Diversity in the functional properties of T-type calcium channels is further supported by molecular investigations that have explained three genes encoding these channels: CaV3.1, CaV3.2, and CaV3.3 subunits (70, 71). In a research done by El Alaoui, 2017, essential oil and methanolic extract of rosemary, as well as rosmarinic acid, inhibit the Cav3.2 current in a concentration-dependent manner in HEK-293T cells. Furthermore, they induce a negative shift of the steady-state inactivation of CaV3.2 current with no change in the activation properties. These results suggest that the inhibition of TTCCs might contribute to the neuroprotective and anxiolytic effects of rosemary (72). Taken together, these findings support a pharmacological modulation of TTCCs by rosemary and suggest that TTCC inhibition might contribute to the anticonvulsant and neuroprotective properties of this medicinal plant. TTCCs might therefore, represent a novel molecular target for rosmarinic acid; although further studies are needed to investigate the efficacy of rosmarinic acid to possibly regulate other ion channels. Some performed studies on addiction are summarized in Table 2.

Addiction

Using opiates is a global epidemic and it continues to spread. Finding a non-addicting agent to prevent the addiction process is one of the main concerns of researchers in this field, however, it has not yet fully solved (73). Opioid withdrawal symptoms include nausea or vomiting, rhinorrhea, dysphoric mood, muscle aches, pupil dilation, lacrimation, sweating, piloerection, yawning, diarrhea, insomnia and fever (74). Previous studies conducted on lab animals have reported that *R. officinalis* could be effective in reducing symptoms of opioid withdrawal syndrome. It has been observed that analgesic properties of alcoholic (0.96 g/kg, IP, for 4 days) and aqueous (1.68 g/kg and 2.4 g/kg, IP, for 4 days) extracts of rosemary have been antagonized by naloxone (5 mg/kg, SC). Thus, it might reinforce the interaction of rosemary with opioid receptors (22,

Table 2. Clinical studies of rosemary and the active constituents on epilepsy and addiction

Subjects	Type of extract, constituents/ doses/ Time of exposure	Endpoints	Ref. No.
Rats	Extract (containing 40% carnosic acid); 100 mg/kg; 23 days	- Neuronal loss in CA1 decreased remarkably in the animals in Kainic Acid (9.5 mg/kg) + extract group - Spatial memory impairment reduced in the animals in Kainic Acid (9.5 mg/kg) + extract group - Shuttle box test showed that passive avoidance learning disability obviously, boosted in the animals in the mentioned group	64
HEK-293T cells	Methanolic and essential oil extracts	- Both the methanolic extract and essential oil of rosemary inhibit Cav3.2 current in a concentration-dependent manner - These extracts compel a negative shift of the balanced inactivation of CaV3.2 current with no alteration in the activation properties	69
Mice	Aqueous and ethanol extracts; (1.68, 2.4 g/kg) and (0.96 g/kg) respectively; 4 days	- Both extracts lessened the number of jumps after naloxone injection	18
Mice	Aqueous, methanolic-aqueous and chlorformic fractions; (0.96 g/kg and 1.68 g/kg), 4 days	- All fractions reduced the number of jumps when they were injected 1 h before the last dose of morphine	72

75) (Table 2). In another study, in 81 patients, it has been confirmed that rosemary (8-16 capsules/day, containing 300 mg dried leaves of rosemary) could be used as an herbal medicine for alleviating withdrawal syndrome symptoms during treatment strategies for opium addiction and likely addiction to other opioids. In this study, the effectiveness of rosemary in the reduction of insomnia, musculoskeletal pain in opium addicts and improvement of sleep was clearly demonstrated during 4 weeks (76). It is probable that the anticonvulsant effects observed in the former studies occur with the same mechanisms as rosemary's effects on reducing insomnia in this study. An investigation by Hosseinzadeh *et al*. 2006, showed that rosemary can decrease muscle jerks produced by morphine withdrawal syndrome (75). These beneficial properties of the plant might be attributed to psycho-stimulant and anti-inflammatory effects (8, 77). These documents revealed that rosemary might be used as an elective complementary compound to modify withdrawal syndrome through treatment procedure for opium addiction and likely addiction to other opioids.

Neuropathic pain

Neuropathic pain is known as pain caused by a disease or lesion of the central or peripheral nervous system by features like hyperalgesia and allodynia (78). Recently, it has been reported that pro-inflammatory cytokines including interleukin-1b (IL-1b) produced by immune cells, microglia, and astroglia, in the spinal cord have important roles in the pathogenesis of neuropathic pain (79). These agents can initiate a cascade of neuro-inflammation-related events that might keep up and worsen the original injury that finally leads to pain and chronicity (80). Moreover, inflammation induces cyclooxygenase-2 (COX-2) expression and results in the generation of prostaglandins (PGE) (81). PGE2 is a pain-inducing factor. It is able to sensitize primary sensory neurons and leads to central sensitization and also facilitate the release of pain-related neuropeptides (82). Metalloproteinases (MMPs) are mostly involved in tissue remodeling and inflammation associated with some neurodegenerative disorders (83). These agents have important roles in nociception and hyperalgesia in the chronic phase of neuropathic pain (84). Studies in these fields demonstrated that hydroalcoholic extract of rosemary (10-50 mg/kg, IP) and carnosol (0.5-2 mg/kg, IP) inhibit formalin-induced pain and inflammation in mice (88). In a previous study, it was reported that different triterpenes (micromeric, oleanolic, and ursolic acids) in *R. officinalis* revealed anti-inflammatory and antinociceptive properties in experimental models of pain including acetic acid-induced writhing test, formalin test, and a model of arthritic pain in mice. Moreover, each of the mentioned triterpenes revealed a similar capability to that observed with ketorolac (10 mg/kg, IP), a non-steroidal anti-inflammatory medicine and a typical clinic analgesic (86). González-Trujano and colleagues, 2007, studied the antinociceptive effect of ethanol extract of rosemary aerial parts. They compared the antinociceptive property of this herb with either tramadol (3.16-50 mg/kg, IP in mice, and 1.0-31.62 mg/kg, IP in rats) or acetylsalicylic acid (31.62-562.32 mg/kg, PO). The achieved data indicate that aerial parts of rosemary have antinociceptive and anti-inflammatory properties, and consolidate the use of it in folk medicine (11). In this regard, Ghasemzadeh *et al*. 2016, conducted a research to investigate the potential anti-inflammatory properties of ethanolic extract of *R. officinalis* (100, 200, and 400 mg/kg, IP) and rosmarinic acid (10, 20, and 40 mg/kg, IP) in a rat model of sciatic nerve chronic constriction injury (CCI)-induced neuropathic pain. In this study, the effects of 14 days, intraperitoneal prescription of ethanolic extract of rosemary and rosmarinic acid on the lumbar spinal cord expression of oxidative stress and inflammatory markers including PGE-2, IL-1b, COX2, NO, and MMP2 were assessed (87). Histological analysis of the sciatic nerve revealed that terpenoid-enriched rosemary extract prevented axon and myelin derangement, edema, and inflammatory infiltrate (88). The obtained data reinforced the traditional use of rosemary as an effective treatment for inflammatory disorders and pain relief. These data also suggest that the ethanolic extract of rosemary and rosmarinic acid might be potential candidates in treating neurological disorders accompanied by inflammation and neuropathic pain by modulating neuro-inflammation. According to the data, it could be suggested that the extract and rosmarinic acid might have an important role against oxidative and inflammatory markers including IL-1b, PGE-2, NO, COX-2, and MMP2.

As previous studies reported, the apoptosis process is activated in the dorsal horn of spinal cord after CCI surgery of sciatic nerve (89). However, the relation between neuronal apoptosis in the spinal cord and the occurrence of hyperalgesia and allodynia is not fully known yet. Apoptosis may cause structural changes in neurons, increase the sensitivity of the nociceptive system and finally induce hyperalgesia or allodynia (90). Astrocytes and microglia might have regulatory roles in neuropathic pain by releasing chemokines and cytokines. Microglia and astrocytes have different neuronal activity. However, sometimes their activities overlap in mediating CNS innate immune responses. Both of these cells are activated following nerve injury and might lead to inflammatory reactions and pathological impacts such as neuronal chronic inflammation, toxicity, and hyper-excitability (91). Thus, it could be concluded that anti-inflammatory and anti- apoptotic reactions may lead to the anti-hyperalgesic and anti-allodynic effects of rosemary after nerve injury. Some other research projects have been designed to investigate the underlying mechanisms of the alcoholic extract of rosemary and one of its main constituents, rosmarinic acid on neuropathic pain on rats. The results suggest that alcoholic extract of rosemary (100, 200, and 400 mg/kg, IP) and rosmarinic acid (10, 20, and 40 mg/kg, IP) reduced inflammatory responses by decreasing apoptosis-related mediators (Bax, cleaved caspase- 3, and 9), inflammatory factors (TNF-α, iNOS, toll-like receptor 4) and the protein levels of glial activation markers (Iba1, GFAP) in rats' spinal cords. Rosmarinic acid might be partially responsible for observed protective effects (92, 93). These studies might offer a new potent and promising therapy in alleviating neuropathic pain, however, more research into the antinociceptive mechanisms of rosemary and its components as well as clinical studies on patients suffering from chronic conditions of pain will be mandatory.

In another study analgesic effects of rosemary essential oil (10, 20 mg/kg, PO) and its pharmacodynamics interactions with paracetamol (acetaminophen) (60 mg/kg, IP) and codeine (30 mg/kg, IP) were investigated in mice. Their results support the use of rosemary in pain management and show a therapeutic potential of rosemary essential oil in combination with analgesic medicines (94). In line with this study, the data of another research showed that rosemary essential oil (70, 125, 250 mg/kg) had a significant antinociceptive influence in the acetic acid-induced abdominal writhing test (95). By the achieved data, it might be concluded that rosemary essential oil has anti-inflammatory and peripheral antinociceptive activity. A research examined the effect of the rosemary essential oil on analgesic effect and percutaneous absorption of diclofenac topical gel in mice and it was observed that rosemary essential oil (0.1, 0.5, and 1.0% w/w) enhanced diclofenac percutaneous absorption (96).

Abdelhalim and colleagues, 2015, studied the effects of non-volatile constituents of rosemary including cirsimaritin, rosmanol, and salvigenin (50-200 mg/kg) on the central nervous system function. These components show biphasic modulation of GABAA receptors and demonstrated CNS activity in mouse models of antinociception (97) (Table 3). But, further studies have to be done to find the probable antinociceptive mechanisms of these substances and to investigate the effect of these compounds on GABAA receptor subtypes.

Previous studies reported that 54% of hemodialysis patients suffer from pain (98). Furthermore, 64% of pain is due to musculoskeletal issues and reveals in the legs (99). The experience of chronic pain has negative effects on patients; the resulting immobility causes high prevalence of depression, irritability, inability to cope with stress, increased fatigue, and reduced the quality of life (100). The topical application of rosemary was able to alleviate the frequency and severity of recurrence of musculoskeletal pain in these patients (101). So, rosemary induces its analgesic properties by affecting different antinociceptive pathways. But further detailed investigations are essential to determine the exact involved mechanisms through which rosemary exhibits its antinociceptive activities such as the number of inflammatory cells, apoptotic and microglial activation markers or the probable direct effect of rosemary on muscles.

Diabetes mellitus could also cause neuronal tissue damage in the central and peripheral nervous system. A study have reported that more than one-half of diabetic patients suffer from diabetic neuropathy and pain due to diabetes neuropathy (102). In diabetic patients, hyperglycemia is reported to be the main underlying factor of injury to the nervous system (103). Some previous results have led to the proposal that diabetic neuropathy might occur because of constant production of reactive oxygen species through glucose auto-oxidation and development of glycation end-products, activation of nuclear enzyme Poly(ADP-ribose) polymerase (PARP), and reduction of anti-oxidant protection (104). Moreover, apoptosis has been reported to be another probable mechanism for the high glucose-induced neural disorder and cell death (105). The neuroprotective and anti-hyperalgesic effects of rosemary extract (100, 150, or 200 mg/kg, PO) in a rat model of streptozotocin-induced diabetes were studied for 21 days. It was observed that treating with rosemary extract improved hyperalgesia, hyperglycemia, and motor deficit, decreased caspase-3 activation and Bax: Bcl-2 ratio (106). In another study it was also concluded that different rosemary extracts and its main phenolic components exert advantageous properties against diabetes and metabolic syndrome through increasing insulin secretion and response, inhibition of advanced glycation end products generation, suppression of gluconeogenesis, anti-oxidant, anti-inflammatory, and anti- hyperlipidemic properties. These magnificent effects are systematically related to enzyme modulation, transcription factors, various vital signal transduction pathways, and important gene expressions (107). Although there are several documents which examined the neuroprotective and analgesic effects of rosemary extracts in animal studies and *in vitro* investigations, more clinical assessments are essential to support the safety and potency of the phenolic agents of rosemary in humans. Hence, it can be finalized that rosemary extract has anti-hyperalgesic and neuroprotective properties in

Table 3. Clinical studies of rosemary and the active constituents on neuropathic pain, stress and anxiety

Subjects	Type of extract, constituents/ doses/ Time of exposure	Endpoints	Ref. No.
Rats	Alcoholic extract; (100, 200, and 400 mg/kg); 14 days	- All three mentioned doses of rosemary extract reduced neuropathic behavioral changes as compared with CCI animals that received the vehicle - Rosemary extract, 400 mg/kg notably declined the levels of Bax, cleaved caspases 3 and 9, Iba1, TNF-α, iNOS and TLR4 in comparison with vehicle-treated CCI animals	84
Mice	Rosmanol, cirsimaritin and salvigenin; (50-200 mg/kg)	- They elicited anxiolytic, antinociceptive, and antidepressant properties - These compounds were indicated to possess biphasic modulation of $GABA_A$ receptors	95
Mice	essential oil	- Inhalation of rosemary essential oil considerably minified the immobility time of mice and serum corticosterone level, accompanied by increased brain dopamine level	121
Mice	Rosemary tea; (2% w/w); 4 weeks	- Cholinesterase isoforms activity was lowered in the brain of rosemary treated group	124

diabetes.

Generally, pain has a negative impact on quality of life. Considering the limited effectiveness of current medications, it is necessary to study the effects of different complementary therapies such as aromatherapy massage (Swedish massage therapy using massage herbal essential oils). After inhaling essential oil molecules or their absorbance through the skin, these molecules stimulate hippocampus and amygdala and initiate their impact on emotional, physical and mental health (108). The antinociceptive effects of aromatherapy could be related to the following mechanisms: 1. the complex mixture of volatile chemical agents might reach pleasure memory sites in the brain; 2. certain analgesic factors within essential oils that may affect some neurotransmitters including serotonin, noradrenaline and dopamine receptor sites in the brain; 3. the interaction of touch sense with sensory neurons in the skin; and 4. increased rate of essential oil absorption into the bloodstream (109). In this field, a study aimed to investigate the effects of rosemary essential oil in aromatherapy massage on the quality of life and severity of neuropathic pain in 46 patients with diabetes. They reported a reduction in scores of neuropathic pain significantly and an increase in scores of quality of life (110). Thus, essential oil of rosemary could be safely used in a clinical setting by nurses. However, experience and training are critical to gain positive results.

Stress and anxiety

Emotional disorders, such as anxiety, cause a huge burden on health all around the world. Documents suggest that stress might lead to the loss of neuronal cells, atrophy and reduce the volume of key structures in the brain. Long-term exposure to stress may induce neuronal degeneration, neuronal inflammation and brain microdamage (111). Chronic stress occurs because of high glucocorticoids level and hyperactivity of hypothalamus- pituitary-adrenal axis that triggers several physiological adaptive feedback regulatory mechanisms (112). Furthermore, some documents have displayed that stress stimulates ACh release in a brain region-specific method (113, 114). In previous research projects it has been claimed that *R. officinalis* contains polyphenols such as rosmarinic acid, luteolin, carnosic acid, and other components that possess several effects on psychiatric disorders or neurological functions such as anti- depressive and anti-anxiety properties and neuroprotective and cognitive effects (15,115,116). It has also been reported that rosemary essential oil exhibited improved mood and cognition in healthy adults (43). The inhalation of rosemary essential oil as an anti-stress (117, 118) and anxiolytic (117-121) therapy has fewer side effects (122). The detailed mechanisms and effectiveness of this essential oil on neurological and psychological function is not well-understood. In a recent study, the effect of inhalation of rosemary essential oil was evaluated on the molecular mechanism that reduces stress *in vitro* using PC12 cells and *in vivo* using mice. The results showed that inhalation of rosemary essential oil decreased stress by reducing serum corticosterone level and increased brain dopamine level *in vivo*. Thus, this essential oil might modulate the activities of the sympathetic nervous system and hypothalamic–pituitary–adrenal (HPA) axis. In addition, it has been reported that rosemary essential oil regulates brain neurotransmitter activity and demonstrates neurophysiological effect related to acetylcholine synthesis and release, as well as inducing neuronal differentiation in mice (123). Moreover, *R. officinalis* L. has been claimed to activate cholinergic activity (AChE activity) in PC12 cells via phosphorylation of ERK1/2 (124). More investigations might be useful to examine the validity of these results in clinical trials. The results also reinforce that rosemary essential oil has potential properties to be used as a safe alternative treatment method for stress-related mood disorders.

Liquid chromatography-mass spectrometry analysis of rosemary tea showed the presence of 16 compounds that are classified into the categories of flavonoids, diterpenes, and hydroxycinnamic derivatives; it was shown that rosmarinic acid was the major bioactive compound of the infusion, followed by a caffeic acid derivative and luteolin 7-O-glucuronide. Rosmarinic acid was also the major component of the water-soluble extract of rosemary leaf in the study of del Bano *et al.* 2003, but it was found only in trace amounts in methanol and acetone extracts (125). Rosemary tea (2% w/w) prescription employs anxiolytic and antidepressant properties on mice and inhibits ChE activity; its main phytochemicals might affect in a similar way as inhibitors (126) (Table 3). An *in vivo* study showed that when rosmarinic acid was intraperitoneally administered to adult male mice, it reduced significantly the immobility time during the forced swim test (127). Caffeic acid also demonstrated antidepressant effects. Moreover, a dose-dependent anxiolytic action of rosmarinic acid (1, 2, 4 or 8 mg/kg) was observed when it was administrated intraperitoneally to adult male mice (128). Rosemary (500 mg, twice daily, for a month) as a traditional herb might be used to enhance prospective and retrospective memory, reduce anxiety, depression, and promote sleep quality in university students (129). Herbal extracts are chemically complex mixtures containing several compounds with multiple potential targets and mechanisms. Hence, more investigations are necessary to explain the involved mechanisms, although the behavioral effects have been definitely demonstrated in several studies.

Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative illness that is caused by a loss of dopaminergic neurons in the substantia nigra. The clinical symptoms of PD are characterized by a combination of bradykinesia, resting tremor, rigidity, and postural instability (130). The brain in PD is more susceptible to oxidative damage because it is rich in polyunsaturated fatty acids and has high oxygen utilization. Recent studies have suggested that oxidative stress is implicated in the dopaminergic neuronal cell death in PD (131). In rotenone-induced neurotoxicity of cultured dopaminergic cells carnosol significantly increased the amount of tyrosine hydroxylase, an enzyme that is down-regulated in Parkinson's disease (132). Carnosic acid protected against 6-hydroxydopamine-induced neurotoxicity in a rat model of Parkinson's disease which is probably attributable to its anti-oxidative and anti- apoptotic properties. The present data might help to distinguish the possible mechanisms of rosemary in the neuroprotection of PD (133). Carnosic acid had the potential for neuroprotection both *in vivo* and *in vitro*. Carnosic acid protected against 6-hydroxydopamine-induced neurotoxicity by inducing anti-oxidant enzymes and inhibiting cell apoptosis. So, carnosic acid could be a potent candidate for protection against neurodegeneration in PD.

Conclusion

The present review demonstrates that the main ethnopharmacological uses (anti-spasm, analgesic, anti-inflammatory, anti-anxiety and memory-boosting) of rosemary have been validated by neuropharmacological investigations. By reviewing the previous literature, it is concluded that the most important components of rosemary which are medicinally and pharmacologically active are rosmarinic acid, carnosic acid, and the essential oil. These compounds can provide promising natural medicines in the treatment of the nervous system pathological conditions including anxiety, depression, Alzheimer's disease, epilepsy, Parkinson's disease, and withdrawal syndrome.

It is also noteworthy to mention that studies regarding herbal medicines should be taken into more consideration because the safety and efficacy of many herbal medicines are still unclear. Also, additional reliable trials are essential to evaluate the safety and efficacy of different constituents of rosemary in treating different nervous system disorders. Furthermore, the probable mechanisms of action and the potential antagonistic and synergistic properties of multi-component mixtures of rosemary need to be examined by the integration of physiological, pharmacological, bioavailability-centered, and pharmacokinetic methods. Prolonged and high dose usage of traditional formulations of rosemary and its active constituents should be avoided until more profound toxicity investigations become available. The new findings may expand the present therapeutic importance of rosemary and develop its future use in modern medicine.

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Non.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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Everything you need to know about rosemary

Rosemary is an ingredient that adds a fragrant, savory note to dishes. Some people claim that rosemary can help reduce muscle pain, boost the immune system, and improve memory. However, it can interact with some medications.

Rosemary is a fragrant evergreen herb native to the Mediterranean. It is used as a culinary condiment, an ingredient in perfumes, and for its potential health benefits. Like oregano, thyme, basil, and lavender, rosemary is a member of the mint family Lamiaceae.

People typically prepare it as a whole dried herb or a dried powdered extract or make teas from fresh or dried leaves.

The herb has been hailed since ancient times for its medicinal properties. Traditional uses of rosemary include helping alleviate muscle pain, improving memory, boosting the immune and circulatory system, and promoting hair growth.

Fast facts on rosemary:

- Rosemary is a perennial plant (it lives more than 2 years).
- The leaves are often used in cooking.
- Possible health benefits include improved concentration, digestion, and brain aging.
- Very high doses may cause vomiting, coma, and pulmonary edema.

This *Medical News Today* Knowledge Center feature is part of a collection of articles on the health benefits of popular foods.

Benefits of rosemary

Share on Pinterest

Rosemary has a range of possible health benefits.

The herb not only tastes good in culinary dishes, such as rosemary chicken and lamb, but it also contains iron, calcium, and vitamin B6.

Contains antioxidants and anti-inflammatory compounds

Rosemary is a rich source

Trusted Source

of antioxidants and anti-inflammatory compounds.

Antioxidants play an important role in neutralizing harmful particles called free radicals and preventing oxidative stress, both of which can contribute to preventing and alleviating chronic inflammatory conditions.

Boosts mood and aids mental health

Limited research suggests that rosemary may be beneficial for depression, stress, and emotional upset.

For example, a 2020 study

Trusted Source

of 42 Japanese men with mood disturbances concluded that taking rosemary extract for 4 weeks improved mental energy and sleep quality.

The researchers concluded that rosemary extract may have beneficial effects on mood and cognitive function.

Additionally, a 2020 review

Trusted Source

examined the antidepressant effects of rosemary in animal studies and concluded that rosemary may help regulate dopamine in the brain.

Enhances memory and concentration

According to the same 2020 review

Trusted Source

, rosemary may have beneficial effects on cognition, including memory and learning.

Additionally, a 2018 randomized controlled trial showed that university students who took rosemary supplements for 1 month had significantly improved memory performance.

Another 2021 review

Trusted Source

of animal research found that rosemary may help enhance cognition in animals, increasing their memory and learning abilities.

Neurological protection

Rosemary could also be good for the brain. Rosemary contains an ingredient called carnosic acid, which can fight off damage by free radicals in the brain.

Some studies mentioned in the 2020 review

Trusted Source

also posited that rosemary can, in theory, have beneficial effects on Alzheimer's.

It may have a protective effect against the progression of the disease, and rosemary aromatherapy might improve cognitive function in people with Alzheimer's. However, this theory is based on test tube and animal study results.

An animal study

Trusted Source

in the review also found that rosemary significantly decreased seizure severity and onset in rats. They propose that rosemary may be beneficial for epilepsy in humans.

Good for skin health

A 2023 review

Trusted Source

proposes that rosemary may have beneficial effects on the skin and that its anti-inflammatory properties could help with some inflammatory skin conditions.

They also detail studies that found that rosemary has anti-aging effects on the skin due to it containing carnosic acid. Carnosic acid may help protect the skin from damage caused by UV rays, which may support graceful aging.

May prevent and treat cancer

According to a 2020 review

Trusted Source

, rosemary could theoretically be beneficial for preventing and treating cancer.

Many test tube and animal studies in the review found that rosemary stops the activation of carcinogens, increases antioxidant enzyme activity, reduces tumor-stimulating inflammation, and suppresses tumor growth.

The researchers recommend more research into the possible cancer-fighting properties of rosemary.

Relieves pain

One of the traditional uses of rosemary is as a mild analgesic or pain reliever.

A 2020 review

Trusted Source

noted that rosemary might help treat neuropathic pain, a type of pain that occurs due to damage or dysfunction in the nervous system. However, more research is needed.

Rosemary also has antibacterial properties

Trusted Source

. In one 2019 animal study

Trusted Source

, rosemary essential oil helped infected wounds heal quicker.

However, a person should not put undiluted essential oil directly on the skin or into an open wound. A person should consult a doctor if they wish to use rosemary for pain and healing.

Safety

The US Food and Drug Administration (FDA) has labeled rosemary extracts as Generally Recognized as Safe (GRAS), and rosemary is safe to take in low doses.

Experts consider safe doses to be around 400 milligrams per kilogram

Trusted Source

(mg/kg) of rosemary herb.

A person should consult a doctor before starting any new natural supplement and purchase supplements from a trusted source.

How to use rosemary

There are a few different ways to use rosemary. A person can use the herb in cooking or make rosemary tea by steeping the herb in hot water and then drinking it.

Rosemary essential oil can also be used by inhaling it, also known as aromatherapy, or applying it topically to the skin. To inhale, a person can put a few drops of the oil into an oil dispenser or a bowl of hot water before inhaling the steam.

Essential oils are highly concentrated, so it is best to dilute a few drops with a carrier oil, such as coconut or almond oil, before applying it to the skin. A person should never ingest essential oils.

While research suggests there are health benefits, the FDA doesn't monitor or regulate the purity or quality of essential oils. It's important to talk with a healthcare professional before using essential oils and research the quality of a brand's products. Always do a patch test before trying a new essential oil.

Summary

Rosemary is a safe herb with minimal side effects and may benefit cognition, mental health, skin, and more.

Rosemary may interact with some medications, so it is important to consult a doctor before using it for medicinal purposes.

antioxidants

MDPI

Review

Rosmarinus officinalis and Skin: Antioxidant Activity and Possible Therapeutical Role in Cutaneous Diseases

Federica Li Pomi [1,†], Vincenzo Papa [2,†], Francesco Borgia [1,*], Mario Vaccaro [1], Alessandro Allegra [3], Nicola Cicero [4,‡] and Sebastiano Gangemi [2,‡]

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Abstract: The rosemary plant, Rosmarinus officinalis L., one of the main members of the Lamiaceae family, is currently one of the most promising herbal medicines due to its pharmaceutical properties. This research aimed to evaluate the antioxidant role of Rosmarinus officinalis and its bioactive compounds on the skin, with a focus on the newly emerging molecular mechanisms involved, providing extensive scientific evidence of its anti-inflammatory, antimicrobial, wound-healing and anticancer activity in dermatological practice. The search was conducted on articles concerning in vitro and in vivo studies in both animals and humans. The results obtained confirm the antioxidant role of R. officinalis. This assumption derives the possibility of using R. officinalis or its bioactive elements for the treatment of inflammatory and infectious skin pathologies. However, although the use of rosemary in the treatment of skin diseases represents a fascinating line of research, future perspectives still require large and controlled clinical trials in order to definitively elucidate the real impact of this plant and its components in clinical practice.

Keywords: *Rosmarinus officinalis*; rosemary; skin; cutaneous disease; oxidative stress; ROS; carnosol; skin cancer; anti-aging; lymphoma

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1. Introduction

Phytotherapy, to take its most classic meaning, is the branch of medicine that uses plants in their entirety or their components for medical purposes to treat or prevent a plethora of diseases. A cornerstone of various medical traditions over the centuries, above all Ayurvedic medicine, traditional Chinese medicine, allopathic and naturopathic medicine [1], it is, more than ever, a current and much-investigated discipline, even in extraordinary scenarios such as the most recent pandemic period [2–5]. Considering its growth as a field worthy of scientific interest [6–9], the need to introduce guidelines for a better understanding of clinical indications, efficacy and safety profiles is arising [1,10,11]. Among the many plants and their active constituents studied in this unconventional setting [12–16], the rosemary plant, *Rosmarinus officinalis L.*, one of the main members of the Lamiaceae family, cultivated in the Mediterranean basin for culinary use [17], is listed as one of the most promising. This is due to its increasingly established clinical utility [18] supported by the development of breakthrough methods for the targeted extraction of its bioactive metabolites [19]. Rosemary extracts are commercially available in Europe and the USA for use as natural antioxidants in the food industry. They have received Generally Recognized as Safe (GRAS) status from the US Food and Drug Administration. Among these extracts, the most notable, being of scientific interest, are rosmarinic acid, a derivative of caffeic acid [20,21]; phenolic diterpenes, of which carnosic acid and carnosol are the most medically relevant [22–24]; flavonoids such as diosmin [25]; and rosemary essential oil (EO), consisting of more than a hundred chemical compounds, the main molecules of which include 1,8-cineole, α-pinene, α-terpineol, verbenone, limonene, bornyl acetate, terpinolene and camphor [26,27]. Rosmarinic acid, beyond its anti-infectious, antioxidant, anti-inflammatory and immunomodulatory properties, has been extensively investigated in recent years for its anti-cancer activity on various apparently functionally disconnected molecular targets leading to various types of cancer. This has justified the increasing efforts of nanomedicine in the development of therapeutic delivery systems to improve its bioavailability [28]. The EO of *Rosmarinus officinalis* owes its clinical notoriety to its anti-inflammatory potential [26], as well as its antioxidant action, elicited mainly at the hepatic level [29]. Carnosic acid and carnosol, in addition to their antioxidant and anti-inflammatory potential, are clinically relevant for their lipid and glucose metabolism regulatory activity, which would justify their use in the treatment of diabetes mellitus and its complications [30,31]. An interesting and reasonably recent line of research has narrowed the field of interest to the phenolic compounds of *Rosmarinus officinalis*, investigating their therapeutic potential in various neurological disorders, including neurodegenerative diseases [32,33], prion diseases [34], cerebral ischemia [35], neuropathic pain [36] and encephalomyelitis [37]. Along the lines of what has already been widely discussed, the purpose of our review is to provide a detailed overview of the potential beneficial effects of *Rosmarinus officinalis L.* and, more specifically, of the wide range of its bioactive constituents on various dermatological diseases, with a special focus on its promising antioxidant role and the ambitious attempts to elucidate the pathogenetic molecular pathways involved.

2. Results and Discussion

2.1. Rosmarinus Officinalis and Antioxidant Action

Oxidative stress is the pathogenic primum movens of most cutaneous disorders, as the skin is the organ most widely and severely exposed to oxidative stress, despite the extensive endogenous and exogenous antioxidant system at its disposal [38]. For descriptive purposes, the causative agents of skin oxidative stress can be divided into exogenous and endogenous, including intracellular metabolic processes. The main exogenous pro-oxidant agents include ultraviolet (UV) light, environmental pollution and chronic psychological stress. The synergistic action of these factors accelerates the processes of pigmentation and skin aging [39]. The latter recognizes oxidative stress secondary to UV irradiation as the primary causal agent; hence, the need to coin the term photoaging. A greater contribution is made by UVA, since UVB, while participating in the damage, has limited penetration capacity into the epidermis and its cells, including keratinocytes and melanocytes above all [40]. The UV-induced oxidative damage of assorted intracellular structures can be direct or indirect. UVB, for the most part absorbed in the stratum corneum, is essentially accountable for the direct damage that sees DNA as its biologically most crucial molecular target [41]. Over the last two decades, the antioxidant potential of *Rosmarinus officinalis* and its bioactive constituents has been extensively investigated in both in vitro and in vivo studies, especially for its promising therapeutic effects on UV-induced photoaging, atopic dermatitis (AD) and pollution-induced skin aging. Relative to the aforementioned time frame, one of the first in vitro studies on this topic highlighted the interesting proportionality between protein glycation-inhibiting activity and antioxidant activity [42]. This functional synergy is said to be largely attributable to the polyphenolic compounds of various plant extracts, including *Rosmarinus officinalis*, paving the way for their prospective therapeutic use in diabetic complications and aging. Further confirmation of the antioxidant potential of this plant came from Ezzat et al., who emphasized the anti-wrinkle action of the defatted rosemary extract (DER), an effect attributable largely to rosmarinic acid, the main phenolic compound, but also to the diterpenes carnosic acid, carnosol and rosmanol [43]. Furthermore, the encapsulation of this extract in transferomes improves its skin penetrability. The most recent and relevant confirmation of the antioxidant action of rosemary's phenolic compounds comes from an in vitro study evaluating the radical-scavenging and anti-aging activity of aqueous and ethanoic extracts of five phenolic-rich selected herbs, including *Rosmarinus officinalis*, which showed both the highest antioxidant activity and the most pronounced anti-elastase, anti-tyrosinase and anti-collagenase activity [44].

Very recent is the interest in the curative potential of rosemary in skin oxidative damage from pollution. In a randomized, double-blind, placebo-controlled study, Nobile et al. evaluated the antioxidant efficacy of the oral supplementation of four phenol-rich plants, including R. officinalis, in one hundred Caucasian and Asian women living in the polluted urban area of Milan [45]. It was found that long-term supplementation improved all clinical–biochemical parameters monitored, including increased skin elasticity, reinforced skin barrier function and a reduction in wrinkle depth and black spots in the enrolled patients [45]. Hoskin et al. demonstrated, for the first time, the effective action of the topical application of a gel based on hydroalcoholic rosemary extract complexed with algae proteins on pollution-induced oxidative skin damage [46]. The emerging molecular mechanisms through which rosemary phenolic diterpenes acts are the inhibition of the increasing levels of active metalloproteinase-9 (MMP-9), the reduction of protein adducts formation and the reduction of filaggrin loss, which are induced by dermal exposure to diesel engine exhausts (DEE). The pharmacological basis of the anti-inflammatory action of carnosol and carnosic acid from *Rosmarinus officinalis* was first investigated in vivo by Mengoni et al., who evaluated how these bio-active compounds could modify the expression of the inflammation-associated genes cyclooxygenase-1/2 (COX-1, COX-2), interleukin 1β (IL-1β), intercellular adhesion molecule 1 (ICAM-1), tumor necrosis factor-α (TNF-α) and fibronectin, thus revealing a downregulation of IL-1β and TNF-α, leucocyte migration reduction and, most interestingly, selective COX-2 inhibitory activity [47]. Regarding the potential use of *Rosmarinus officinalis* in atopic dermatitis, beyond the first study that more generally attributed an ameliorative role in skin lesions to nerve growth factor (NGF) inhibition, a more recent and detailed molecular characterization of carnosol's intracellular action partially recalled the already known molecular targets and brought to light new ones involved in the implementation of its antiphlogistic action [48]. The most interesting aspect that emerged was the interaction of carnosol with the signal transducer and activator of transcription 3 (STAT3) pathway, which promotes skin inflammation via the upregulation of inducible nitric oxide synthase (iNOS) and COX-2. The carnosol–STAT3 interaction blocks lipopolysaccharide (LPS)-induced STAT3 phosphorylation. On the other hand, carnosol also showed a direct downregulation of the LPS-induced expression of iNOS, COX-2 and nitric oxide (NO). Such synergistic effects of this phenol explain its curative potential in AD [49]. Further confirmation of these molecular mechanisms comes from an in vivo study conducted by Yeo et al., highlighting the anti-inflammatory role of carnosol in UVB-induced skin damage in AD-affected mice. The topical application of carnosol reduced epidermal thickness, erythema, edema and erosion, and dramatically decreased serum levels of the pro-inflammatory cytokines TNF-α and IL-1β, together with a significant reduction in UVB-induced serum IgE [50].

A much more widely represented topic in the literature is the photoprotective role of *Rosmarinus officinalis* and its bioactive elements in UVR-induced skin aging. Martin et al. identified the photoprotective role of a water-soluble extract of *Rosmarinus officinalis* which downregulates both the basal levels of matrix metalloproteinase-1 (MMP-1) and the transcription of UVA/UVB-induced MMP-1 in dermal fibroblasts. Moreover, in a reconstructed skin model, the MMP-1 downregulatory action was also demonstrated further upstream, through the decrease in the UV-induced cytokines IL1- α and IL-6 [51].

In the wake of the above-mentioned work, Park et al. deeply evaluated the molecular mechanisms underlying the anti-photoaging activity of carnosic acid, identifying its ability to downregulate the UV-induced expression of MMP-1, MMP-3 and MMP-9 in human fibroblasts and keratinocytes. In addition, its UVB-induced MMP expression inhibitory activity would recognize the carnosic acid-mediated suppression of MEK/ERK/AP-1 pathways as an upstream causative agent [52]. The photoprotective action on the skin is not only a prerogative of the active bioelements of *Rosmarinus officinalis*, but also involves compounds from other plants, such as citrus flavonoids, in a synergic action that is even stronger than the therapeutic efficacy of the plants taken individually. To this end, Pérez-Sánchez et al., in their clinical trial, highlighted the advantageous effects of combinations of these extracts in human HaCaT keratinocytes, a spontaneously transformed aneuploid immortal keratinocyte cell line from adult human skin, and in human volunteers after oral supplementation. A consistent reduction in the UVB-induced formation of ROS and prevention of DNA damage was demonstrated in HaCaT cells, with consequent higher survival. In human volunteers taking 250 mg of combined citrus and rosemary extracts daily, a significant and progressive increase in minimal erythema dose (MED) was detected, thus suggesting that oral supplementation could improve UVB protection [53]. Further confirmation of the synergistic photoprotective, anti-inflammatory and anti-aging efficacy of these plants came a few years later from Nobile et al., who showed both in a human cell model and in a pilot study beneficial effects such as reduced UVR-induced erythema, diminished skin lipoperoxides (LPO), decreased wrinkle depth and improved elasticity following long-term oral supplementation of combined extracts of *Rosmarinus officinalis* and *Citrus paradisi*. These effects are probably attributable to the inhibition of UVR-induced ROS formation, as well as proinflammatory cytokines, coupled with the downregulatory action of intracellular matrix metalloproteinase-activating pathways [54].

The recent literature is teeming with works confirming the photoprotective role of various plant extracts, of which rosemary, with its bioactive elements, is an increasingly consistent member. Hyuck Auh et al. pioneered the investigation of the anti-photoaging potential of combined extracts of marigold and rosemary, finding in a mouse model that the oral supplementation of these extracts suppressed UV-induced dermal–epidermal thickening in a dose-dependent manner; this histological finding was supported by reductions in various photoaging-related biomarkers observed in the lab [55]. A new molecular photoprotection mechanism was recently highlighted by Calniquer et al., who studied the phytotherapeutic efficacy of a combination of tomato and rosemary extracts. They found an interesting functional synergy of polyphenols (mainly represented by carnosic acid and carnosol in the rosemary extract) and carotenoids (mainly represented by lycopene, phytoene and phytofluene in the tomato extract) in activating the antioxidant response element/Nrf2 (ARE/Nrf2) transcription system, the main cellular antioxidant defense mechanism, in parallel with the inhibition of the UVB-induced pro-inflammatory nuclear factor kappa B (NFκB) pathway in keratinocytes and dermal fibroblasts, resulting in a decreased release of IL-6 and TNF-α and consequently a lowered activation of MMPs [56]. Additionally, for photoprotective purposes, the most recent strand of cosmetic research is working on the development of topical gel formulations containing *Rosmarinus officinalis* extract. The antioxidant, antiaging and healing potential of rosemary hexane extract was evaluated both in vitro and in a UVB-irradiated mouse model. Ibrahim et al. demonstrated the photoprotective potential of rosemary extract, the permeability and bioavailability of which improved when topically conveyed into lipid nanocapsule-based gel [57]. In the wake of the aforementioned work, Takayama et al. evaluated the in vitro antioxidant potential of rosemary hydroethanolic extract together with an evaluation, in vivo, of its anti-UVB photoprotective role if topically conveyed by an emulgel formulation [58]. The main findings regarding the role of *Rosmarinus officinalis* and its antioxidant functions are summarized in Table 1. The main antioxidant properties of *Rosmarinus officinalis* against UV-induced and pollution-induced skin aging and against cutaneous inflammation are shown in Figure 1.

Table 1. The role of *Rosmarinus officinalis* against oxidative stress.

Authors and Year	Topic	Model	Extraction Procedure	Study Characteristics
Takayama et al. [58], 2022	Antioxidants and UVB protection	In vivo/in vitro	Exhaustive maceration	An in vitro and in vivo study on the properties of R. officinalis demonstrated its protective role for the skin against tissue damage caused by UVB radiation.
Nobile et al. [54], 2016	Antioxidants and UVR protection	In vivo	Drying	The antioxidant, photoprotective and antiaging efficacy of the combination of *Rosmarinus officinalis* and *Citrus paradisi* extracts was demonstrated.
Ibrahim et al. [57], 2022	Antioxidants and anti-aging	In vivo/in vitro	Not specified	The photoprotective potential of rosemary extract, whose permeability and bioavailability improved when topically conveyed into lipid nanocapsule-based gel, was assessed.
Nobile et al. [45], 2021	Antioxidants and pollution	In vivo	Not specified	A double-blind randomized study demonstrated that oxidative stress-induced skin damage in both Asian and Caucasian women living in a polluted urban is reduced by oral supplementation with the following herbal extracts: *Olea europaea* leaf, *Lippia citriodora*, *Rosmarinus officinalis*, and *Sophora japonica*.
Mengoni et al. [47], 2011	Antioxidants, inflammation and AD	In vivo/in vitro	Drying	In a mouse model, the expression of IL-1β and TNF-α, markers of inflammation-associated genes in skin, were reduced by carnosic acid and carnosol.
Calniquer et al. [56], 2021	Antioxidants and UVB protection	In vitro	Not specified	An in vitro study demonstrated that the combination of carotenoids and polyphenols produces protective effects against UV-induced damage to skin cells, inhibiting UVB-induced NFκB activity and IL-6 release.
Sanchez et al. [53], 2014	Antioxidants and UVB protection	In vivo/in vitro	Drying and water dissolution	In HaCaT keratinocytes and in human volunteers, the oral intake of rosemary and citrus bioflavonoid extracts reduced UVB-induced ROS, thus preventing cellular DNA damage.
Kim et al. [42], 2003	Antioxidants	In vitro	Ethanol/water (50:50, *v*/*v*)	The protein glycation inhibitory activity of aqueous ethanolic extracts of various plants, including *Rosmarinus officinalis*, closely correlated with the antioxidant activity of the extracts.
Salem et al. [44], 2020	Antioxidants	In vitro	Drying, maceration, water distillation, boiling, filtration, lyophilization	An in vitro study evaluated the radical-scavenging and anti-aging activity of aqueous and ethanoic extracts of phenolic-rich selected herbs, including *Rosmarinus officinalis*, which showed the highest antioxidant activity and the most pronounced anti-elastase, anti-tyrosinase and anti-collagenase activity.
Ezzat et al. [43], 2016	Antioxidants	In vivo/in vitro	Drying, pulverization, defatting, percolation with 70% ethanol, evaporation	The anti-wrinkle activity of DER, which was optimized by encapsulation in transferosomes, was assessed in an in vitro study.
Yeo et al. [50], 2019	Antioxidants and atopic dermatitis	In vivo	Not specified	The anti-inflammation effect of the topical application of carnosol on UVB-induced skin inflammation in HR1 mice inhibited erythema, epidermal thickness and inflammatory responses.

Table 1. *Cont.*

Authors and Year	Topic	Model	Extraction Procedure	Study Characteristics
Lee et al. [49], 2019	Antioxidants and atopic dermatitis	In vivo/in vitro	Not specified	Carnosol inhibited LPS-induced nitric oxide generation and the expression of inflammatory marker proteins, including iNOS and COX-2 in RAW 264.7 cells. STAT3 phosphorylation and DNA-binding activity in RAW 264.7 cells were reduced.
Takano et al. [48], 2011	Antioxidant and atopic dermatitis	In vivo/in vitro	Ethanol	In an atopic dermatitis mouse model, the application of four herbal extracts, including *Rosmarinus officinalis*, reduced atopic lesions, thus inhibiting the effect of NGF on neuritic outgrowths in lesional skin.
Martin et al. [51], 2008	Anti UV	In vitro	Solubilization	IL1-α and IL-6, which play a role in the up-regulation of UV-induced MMP-1, could be suppressed by the *Rosmarinus officinalis* water-soluble extract.
Park et al. [52], 2013	Anti UV	In vitro	Not specified	The antiaging activity of carnosic acid downregulated the UV-induced expression of MMP-1, MMP-3 and MMP-9 in human fibroblasts and keratinocytes.
Hoskin et al. [46], 2021	Antioxidants and pollution	Ex vivo	Hydroalcoholization	The topical application of a gel based on hydroalcoholic rosemary extract complexed with algae proteins against pollution-induced oxidative skin damage was demonstrated.
Hyuck Auh et al. [55], 2021	Anti UV	In vivo	Ethanol at 72 °C for 3 h, evaporation	A mixture of marigold and rosemary extracts demonstrated anti-aging activity in a UV-induced mouse model of photoaging, with reduced expression of matrix metalloproteinase, interleukins, TNF-α, procollagen type I, superoxide dismutase, glutathione peroxidase and catalase

2.2. Rosmarinus Officinalis and Antimicrobial Action

In recent times, the scientific literature has provided ever-increasing knowledge on the antimicrobial activities of essential oils, which are finding use in both medical and cosmetic fields. Secondary plant metabolites have a pharmacological effect on the treatment of skin disorders, for which they are used within topical formulations. In this regard, rosemary extract has shown antimicrobial activity in several cases [59–62]. Starting from the assumption that EOs possess antimicrobial activity, De Macedo et al. reported the first attempt to produce an oil-in-water emulsion containing only natural excipients and rosemary extract, demonstrating that higher quantities of extracted phenolic compounds, flavonoids and tannins corresponded to greater antioxidant and antimicrobial activity, especially against *Staphylococcus aureus*, *Streptococcus oralis* and *Pseudomonas aeruginosa*. De Macedo et al. concluded by asserting that this topical formulation based on *Rosmarinus officinalis* could be a natural therapeutic novelty against microorganisms, which are becoming increasingly resistant to conventional drugs [63]. Another field of research is the treatment of Candida species, which are developing increasing resistance to traditional drugs [64,65], including azoles and polyenes [66,67], thus representing a great challenge for the medical field in the treatment of such common skin infections. Furthermore, conventional antifungal drugs often exhibit toxic side effects for human cells, including hepatotoxic effects. Hence, there is growing scientific interest in EOs, natural compounds that are proving to be promising for their various antibacterial, antifungal and antiviral properties [68,69]. Their action against a wide variety of microorganisms is believed to be due to their ability to alter the membrane and the microorganisms' cell wall, resulting in the extracellular loss of cytoplasmic material [70]. The pharmacological properties of EOs, mainly related to their complex chemical makeup and high levels of phenols, make these compounds a promising tool for the treatment and prevention of candidiasis [71]. However, the low solubility in water, high volatility and high instability of EOs represent the main limitations of their use in the pharmaceutical and cosmetic fields. To overcome this problem, the encapsulation of EOs has proven to be a useful solution. Starting from the knowledge that *Rosmarinus officinalis* can be successfully used as a matrix component and active ingredient of nanostructured lipid carriers (NLCs), it was subsequently demonstrated that the nanoparticles ensured a prolonged in vitro release of clotrimazole, thus increasing the antifungal activity. This confirmed that NLCs containing Mediterranean EOs represent a promising strategy to improve efficacy against topical candidiasis [71]. Specifically, an in vitro test highlighted that leaves from *Rosmarinus officinalis* and *Tetradenia riparia* contain antifungal bioactive compounds. Hydro-alcoholic extracts from these leaves seem to be effective against dermatophytes, including *Trichophyton rubrum, Trichophyton mentagrophytes* and *Microsporum gypseum*, with fungal growth inhibition and morphological alterations in the hyphae [72]. Moreover, it has been proven that the aryl hydrocarbon receptor (AhR), when activated by microbial metabolites, is implicated in a number of skin diseases. Starting from this assumption, Kallimanis et al. attempted to identify natural compounds potentially capable of inhibiting AhR activation by microbial ligands. In this regard, five different dry extracts of *Rosmarinus officinalis* were analyzed to evaluate its ability to inhibit AhR, confirming its dose-dependent antimicrobial activity against *Malassezia furfur* [73]. Another study conducted by Weckesser et al. evaluated the antimicrobial capacity of six extracts, including *Rosmarinus officinalis*, and plant extracts, including carnosol and carnosic acid, showing that *Rosmarinus officinalis* extract inhibited the growth of both aerobic and anaerobic bacteria and yeasts. Furthermore, the Rosmarinus extract was able to inhibit both Candida strains, further showing its antifungal action [74]. Sporotrichosis is a subcutaneous fungal infection caused by fungi of the genus *Sporothrix*, increasingly affecting humans and cats [75]. Despite the limited experimental data on the effects of rosemary essential oil on the treatment of sporotrichosis, studies in the current literature confirm its antifungal activity against *Sporothrix schenckii* [76] and itraconazole-resistant *Sporothrix brasiliensis* [76,77]. The first attempt to assess the effectiveness of rosemary essential oil against cutaneous sporotrichosis in vivo was conducted by Waller et al. Itraconazole-resistant *Sporothrix brasiliensis* was inoculated into 30 Wistar mice, which were randomly treated with itraconazole, rosemary oil or saline as the control population. In mice treated with rosemary oil, the remission of skin lesions was noted, with mild to absent yeast cells. Furthermore, rosemary oil has also shown a protective effect on systemic organs, such as the liver and spleen, delaying the spread of infection [78]. Finally, rosemary has been evaluated for its antibacterial functions. It is known that bacterial pathogens have numerous virulent mechanisms allowing them to enter, replicate and persist at host sites, but with only a few common mechanisms. Among the possible alternatives to overcoming the issue of the constant increase in antibiotic resistance, inhibiting the virulence factors, which are responsible for the damage caused to the host tissue, is increasingly gaining ground as a new line of research [79]. By specifically inhibiting bacterial virulence mechanisms, the pathogenicity of bacteria could be controlled, thus avoiding the increasing ability of bacteria to develop antimicrobial resistance. Furthermore, selectively inhibiting virulence mechanisms reduces the risk of altering the composition of commensal microorganisms, which also play a beneficial role within and on the host. Quorum sensing, as a virulence mechanism, is a cell-density-dependent transcriptional regulatory system, used by bacteria to communicate and to adapt to the environment [80]. *Staphylococcus aureus*, a common cause of skin and soft tissue infection (SSTI), has generated increasing concern due to drug resistance. *Staphylococcus aureus* is an opportunistic Gram-positive bacterium, whose virulence mechanisms involve the activation of the quorum-sensing accessor gene regulator (agr) operon. The diterpene carnosic acid and carnosol, found in *Rosmarinus officinalis L.* leaves, have been demonstrated to have a specific inhibitory effect on *Staphylococcus aureus* agr expression, thus suppressing the cell–cell communication system and, consequently, its pathogenicity [80]. Finally, the activity of basil and rosemary essential oils has also been demonstrated against multi-resistant clinical strains of *Escherichia coli*. The results show that both essential oils tested were active against all clinical strains of *Escherichia coli*, including broad-spectrum β-lactamase-positive bacteria [81]. All of this evidence supports the idea that *Rosmarinus officinalis* can be used both as an important therapeutic tool and as an adjuvant within cosmetological formulations for its broad-spectrum antioxidant and antimicrobial capacities. Table 2 summarizes the main findings about the antimicrobial activity of *Rosmarinus officinalis*.

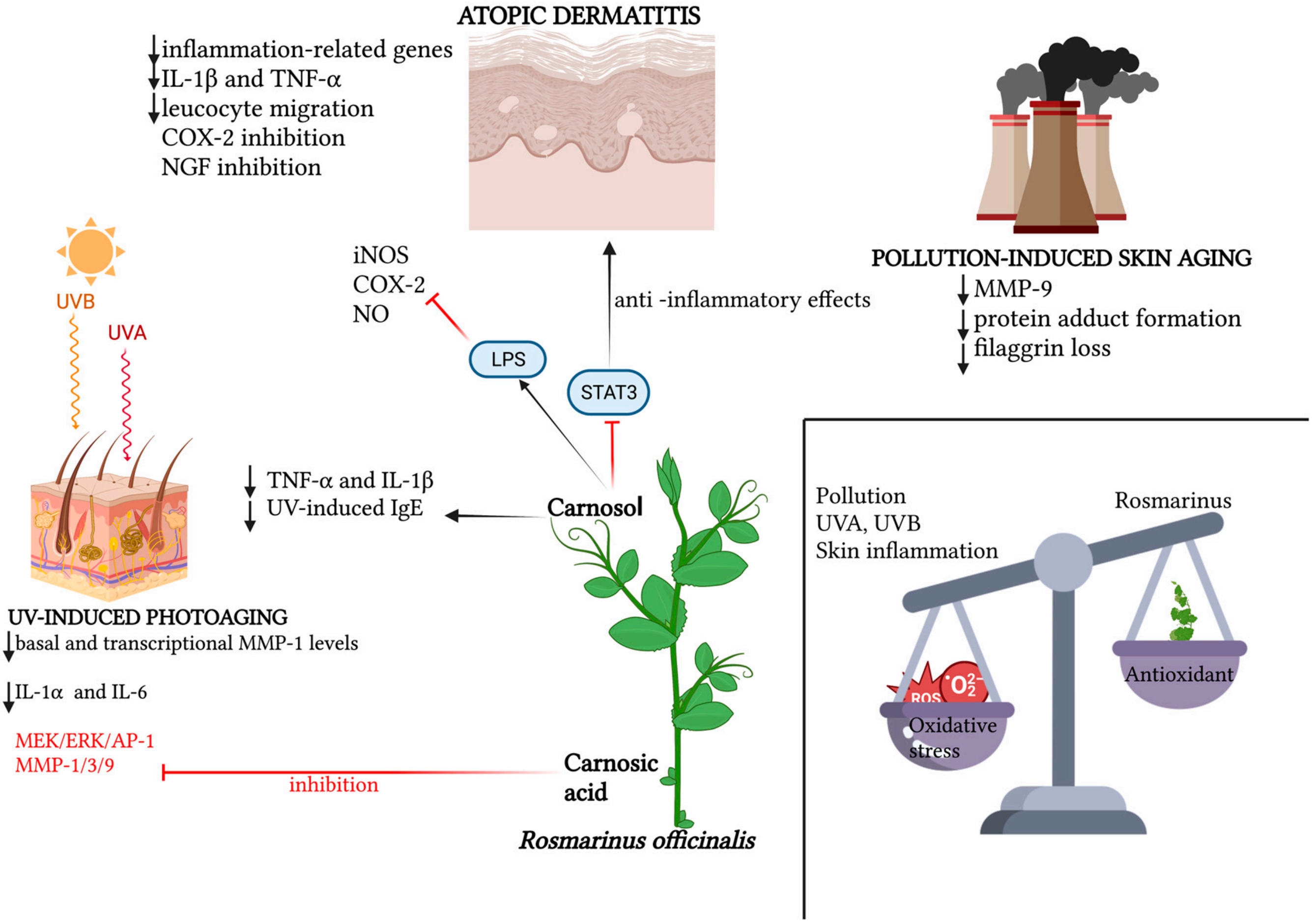

Figure 1. Schematic representation of the relevant molecular patterns involved in the promising antioxidant effects of *Rosmarinus officinalis* and its main bioactive compounds on three dermatological conditions: atopic dermatitis, UV-induced photoaging and pollution-induced skin aging. In atopic dermatitis, beyond the synergic action of carnosol and carnosic acid in downregulating inflammation-related genes, and therefore pro-inflammatory cytokines, leucocyte migration and NGF inhibition promotion, the specific action of carnosol on the STAT3 pathway is emphasized, for which the LPS-induced phosphorylation lock results in anti-inflammatory effects, together with carnosol's direct inhibition of iNOS, NO and COX-2 activation. In UV-induced photoaging, the action of *Rosmarinus officinalis* in downregulating basal and transcriptional levels of MMP-1, as well as the inflammatory cytokines IL-6 and IL-1α, is highlighted. Also portrayed is the specific action of carnosol in downregulating TNF-α, IL-1β and serum levels of UV-induced IgE, and the inhibitory action of rosmarinic acid both on the MEK/ERK/AP-1 pathway and on MMP-1, MMP-3 and MMP-9. In pollution-induced skin aging, the downregulatory action of the two main phenolic diterpenes of *Rosmarinus officinalis* is mainly demonstrated on MMP-9, protein adduct formation and the loss of filaggrin. Created with BioRender.com.

Table 2. The antimicrobial activity of R. officinalis.

Authors and Year	Topic	Model	Extraction Procedure	Study Characteristics
Kallimanis et al. [73], 2022	Anti-microbial activity	In vitro	After drying, the leaf was treated with each solvent in a 1:10 ratio, and then separated from the liquid part by filtration.	Five different dry ROEs were assayed for their activities as antagonists of AhR ligand, which in turn inhibited *Malassezia furfur* yeasts.
De Macedo et al. [63], 2022	Anti-microbial activity	In vitro	Maceration, infusion, Soxhlet and ultrasound	A topical formulation with R. officinalis extract demonstrated antimicrobial activity against *S. aureus*, *S. oralis*, and *P. aeruginosa*
Endo et al. [72], 2015	Anti-microbial activity	In vitro	Leaf were dried in a circulating-air oven at 40 °C. Subsequently, they were soaked in 90/10% (*v*/*v*) ethanol–water for 48 h at 25 °C, protected from light.	Hydroalcoholic extracts from R. officinalis and T. riparia in vitro was demonstrated to have antifungal activity against strains of *Trichophyton rubrum*, *Trichophyton mentagrophytes* and *Microsporum gypseum*
Nakagawa et al. [80], 2020	Anti-microbial	In vitro	Not specified.	Diterpene carnosic acid and carnosol, present in *Rosmarinus officinalis L.* leaves, had specific effect on S. aureus agr expression.
Waller et al. [76], 2021	Anti-microbial activity	In vitro	Distillation by steam dragging in Clevenger equipment for 4 h	The study demonstrated rosemary oil as a promising antifungal to treat sporotrichosis, thus postponing systemic fungal spreading.
Weckesser et al. [74], 2007	Anti-microbial activity	In vitro	The solvent used was Carbon dioxide/isopropyl alcohol.	Rosmarinus extract inhibited the growth of *Candida* strains
Sienkiewicz et al. [81], 2013	Anti-microbial activity	In vitro	Not specified.	Basil and *Rosmarinus officinalis* essential oils played a role against resistant *Escherichia coli* clinical strains, and also against extended-spectrum β-lactamase positive bacteria.
Carbone et al. [71], 2013	Anti-microbial activity	In vitro	Not specified.	Nanostructured lipid carrier systems containing EOs, including *Rosmarinus officinalis*, could improve Clotrimazole effectiveness against candidiasis.

2.3. Rosmarinus Officinalis and Wound Healing

In the past decade, a new and interesting strand of phytotherapeutic research has become increasingly popular, which aims to evaluate the curative potential of *Rosmarinus officinalis* in wound healing, as well as in promoting the survival of skin flaps. Concerning the wound-healing process, beyond some in vivo evidence of the regenerative potential of *Rosmarinus officinalis* in the treatment of acute wounds, especially burn wounds, much of the scientific evidence instead concerns the therapeutic potential of rosemary in chronic wounds, primarily diabetic wounds [82,83].

First, Abu-Al-Basal, in an in vivo study conducted on BALB/c mice, demonstrated the efficacy of both aqueous extract and essential oil of *Rosmarinus officinalis* in healing diabetic wounds by pointing out the greater healing efficacy of the essential oil over the aqueous extract [84]. In the wake of this phytotherapeutic interest, Sivamani et al. evaluated the wound-healing role of EO components from various plants, identifying as a potential molecular therapeutic mechanism their ability to inhibit elastases produced by skin, neutrophils and germs, including Pseudomonas aeruginosa [85]. Additionally, Pérez-Recalde et al. confirmed the therapeutic potential of EOs of various plants, including rosemary, especially in chronic wounds. In rodent wounds, improved collagen deposition associated with increased fibroblastic proliferation and a faster wound closure rate has been observed, even highlighting the promising role in wound healing of the incorporation of EOs into resorbable polymeric scaffolds [86]. Similarly, Labib et al. highlighted in vivo the wound-healing potential of a combination of rosemary and tea tree essential oils incorporated into chitosan-based preparations. In the excision wound model in rats, their topical application resulted histologically in complete re-epithelialization associated with follicular activation, together with a significant increase in the rate of wound contraction. In addition, a marked reduction in oxidative stress in the wound area was highlighted, probably attributable to the antioxidant capacity of oxygenated monoterpenes, well-represented in both essential oils examined [87]. The most recent in vivo evidence on the wound-healing potential of rosemary highlights the anti-fungal role that bioactive compounds in its EO such as α-pinene might play, thereby speeding up the healing process [88].

Regarding the potential use of *Rosmarinus officinalis* in improving skin flap survival in relatively recent times, Ince et al. topically tested this ability in vivo with encouraging results [89]. These last were soon confirmed by the same author in another in vivo study that highlighted the vasodilatory effect of orally administered *Rosmarinus officinalis* oil. The resulting increased blood flow to the flap averted the dreaded necrotic complication, suggesting a systemic use of rosemary, especially in patients with circulatory disorders such as chronic obliterative artery disease [90]. In line with the future goals of the aforementioned work, in their latest in vivo study, Ince et al. identified two bioactive compounds from the essential oil of *Rosmarinus officinalis*, alpha-pinene and cineole, as the main systemic contributors to the increased flap survival [91]. Table 3 summarizes the main findings regarding the role of *Rosmarinus officinalis* in wound healing and skin flap survival.

Table 3. The role of R. officinalis in wound healing and skin flap survival.

Author	Topic	Model	Extraction Procedure	Study Characteristics
Labib et al. [87], 2019	Wound Healing	In vivo	Not specified	The wound-healing potential of a combination of rosemary and tea tree essential oils incorporated into chitosan-based preparations was highlighted.
Abu-Al-Basal et al. [84], 2010	Wound healing	In vivo	Steam distillation	An in vivo study conducted on BALB/c mice demonstrated the efficacy of both aqueous extract and essential oil of *Rosmarinus officinalis* in healing diabetic wounds.
Mekkaoui et al. [83], 2021	Wound healing	In vivo	Not specified	A honey mixture with selected essential oils on chemical and thermal wound models in rabbits has healing effects.
Sivamani et al. [85], 2012	Wound healing	In silico	Not specified	Rosmarinus, among other essential oils, inhibited the deleterious activities of elastase, thus ameliorating wound healing.
Sakhawy et al. [88], 2023	Wound healing	In vivo	Not specified	Topical application of a mixture of essential oils, including *Rosmarinus officinalis*, had potential in healing wounds infected with *Candida albicans*.
Farhan et al. [82], 2021	Wound healing	In vivo	Methanol extraction	In vitro, the antifungal activities of *Rosmarinus officinalis* in wounds infected with *Candida albicans* was demonstrated.
Ince et a [90], 2016	Increasing skin flap survival	In vivo	Not specified	The vasodilatory effects of *Rosmarinus officinalis* contributed to increasing skin flap survival.
Ince et al. [89], 2015	Increasing skin flap survival	In vivo	Not specified.	*Rosmarinus officinalis* increased skin flap survival in a mouse model.
Ince et al. [91], 2018	Increasing skin flap survival	In vivo	Not specified	Alpha-pinene and cineole were the components of *Rosmarinus officinalis* responsible for increased flap survival.

2.4. Rosmarinus Officinalis and Cutaneous Diseases

Rosemary has been shown to have not only antioxidant and antimicrobial properties, but also a beneficial role in the treatment of various skin diseases.

In the treatment of alopecia aerate, an autoimmune disease affecting the follicles with subsequent hair loss, the essential oil of *Rosmarinus officinalis* managed to improve microcirculation surrounding the hair follicle [92]. Moreover, a clinical study compared the efficacy of rosemary essential oil to minoxidil 2% solution for the treatment of androgenetic alopecia. Patients used either minoxidil 2% solution or rosemary essential oil, with a dramatic increase in hair count reported for both treatments and without significant differences between the two study groups, which confirmed the therapeutic effectiveness of *Rosmarinus* *officinalis*. Moreover, scalp irritation was more frequent in the minoxidil 2% solution group, confirming the relatively few side effects of natural compound therapies [93]. Among the possible therapeutical approaches, increasing attention has been paid to platelet-rich plasma (PRP) to increase hair density and regrowth. The effect of PRP in combination with herbal extracts has been evaluated to identify the factors stimulating hair growth [94]. Combined herbal extracts and PRP promoted the proliferation of human dermal papilla cells via the regulation of extracellular signal-regulated kinase (ERK) and protein kinase B (Akt) proteins, shedding light on the possible future development of herbal extracts and PRP combination therapies in order to enhance hair growth. The role of *Rosmarinus officinalis* has also been evaluated in systemic sclerosis-related Raynaud's. Additionally, in this connective tissue disorder, the high levels of ROS contribute to the development of fibrotic processes and closely correlate with the severity of skin fibrosis [95,96]. In an open-label pilot study, Vagedes et al. enrolled twelve patients, each of whom received an application of olive oil on both hands as a control and three hours later an application of 10% essential oil of *Rosmarinus officinalis L.*, highlighting that warmth perception in patients with Raynaud's phenomenon was ameliorated by topical rosemary EO application [97]. The potential role of rosemary has also been evaluated from an aesthetic perspective, specifically in the treatment of cellulite, a condition characterized by localized adiposity and inflammation, with subsequent alteration of the microcirculation, mostly affecting women. On this topic, in 3T3-L1 cells (a mouse cell line with an adipocyte-like phenotype), a composition of extracts, including those from *Rosmarinus officinalis*, was shown to reduce lipid accumulation, platelet aggregation and inflammation, thus ameliorating microcirculation through a dose-dependent inhibition of free radical formation. This evidence suggests the potential topical use of rosemary, combined with other extracts, and also in the aesthetic field, taking advantage of its anti-inflammatory and antioxidant properties [98]. As already discussed, overexposure to UVB rays causes oxidative stress and DNA damage, resulting in an increased likelihood of developing different types of cutaneous cancer, including non-melanoma skin cancer and malignant melanoma [99,100]. ROS plays a pivotal role in oncogenesis and mutagenesis, especially in tumor promotion. ROS induces lipid peroxidation and DNA strand breaks by modulating different biochemical pathways and gene expression [101]. In recent years, increased scientific attention has been paid to identifying and characterizing natural compounds with chemopreventive properties against the formation of UVB-induced skin cancer [102].

On this topic, the potential role of carnosol in the chemoprevention of UVB light-induced non-melanoma skin cancer has been evaluated in an HaCat cell study, highlighting that carnosol leads to a partial reduction in UVB-induced ROS and subsequently in a reduction in DNA damage. This ability consists of the absorption of UVB radiation, which in turn could decrease the UVB-induced formation of cyclobutane pyrimidine dimers (CDP) in keratinocytes, further inhibiting the UVB-induced activation of NFκB and UVB-induced mutation [103].

In a mouse model, the modulatory effects of *Rosmarinus officinalis* were studied by *evaluating* the *skin tumor mean latency period*, incidence, burden, yield, weight and diameter. Mouse skin carcinogenesis, evaluated by the formation of papillomas, was induced by topical application on the dorsal skin of 7,12-dimethlybenz(a)anthracene (DMBA) and promoted by croton oil. The results of the study conducted by Sancheti et al. suggest that *Rosmarinus officinalis* leaf extract could postpone the onset of papillomas and their latency period. Furthermore, confirming its antioxidant action, it was observed that serum levels of lipid peroxidation, an index of cellular oxidation, were significantly reduced in mice treated with *Rosmarinus officinalis* [104].

A growing body of evidence indicates that specific compounds of rosemary, including carnosol, carnosic acid and rosmarinic acid, exert antiproliferative activity in several cancer cell lines [105–108]. In colorectal cancer cells, rosmarinic acid causes apoptosis [109], downregulating the mitogen-activated protein kinase (MAPK)/ERK pathway, while in hepatocellular carcinoma cells, rosemary essential oil reduced bcl-2 gene expression and upregulated bax gene expression [110]. In vivo, the anticancer properties of rosemary were proven in mice with acute myeloid leukemia, in which the increase in the administration of crude extracts of rosemary or carnosol, in combination with 1α-25 dihydroxy vitamin D3, led to an intense cytoprotective effect [111]. Thus, in vitro and in vivo data also indicated that crude extracts or purified components of rosemary exerted chemoprotective effects, inhibiting the early stages of tumor development [112,113], probably through the inhibition of enzymes of stage I carcinogenesis. Among the tumors with a rapidly increasing incidence rate, melanoma is a malignant tumor induced by the transformation of melanocytes [114]. When metastatic, the prognosis of melanoma becomes very bad, especially due to the poor response to the currently approved therapies. Hence, the growing interest in EOs is justified. On this topic, Huang et al. demonstrated in vitro that carnosol inhibited the migration of metastatic B16/F10 mouse melanoma cells through the suppression of MMP-9 expression. Furthermore, carnosol was shown to inhibit ERK1/2, AKT, p38 and c-Jun N-terminal kinases (JNK), and led to the activation of the transcription factors NFκB and c-Jun. From this assumption, the authors concluded that the invasive capacity of B16/F10 mouse melanoma cells could be limited by carnosol, through the downregulation of the above-mentioned pathways [115]. Finally, Cattaneo et al. highlighted that the proliferation of human melanoma cell line A375 was reduced by the hydroalcoholic extract of *Rosmarinus officinalis*, in a dose- and time-proportional way through cytotoxic and cytostatic effects on the cell cycle. Through the compositional characterization, the individual pure components of the extract were tested. The observations led researchers to hypothesize that the antiproliferative activity was a property of the entire extract, most likely deriving from multifactorial effects involving the majority of its elements [116]. All of these data agree in stating the potential role of rosemary in the therapy of various skin pathologies, first of all among skin cancer. From the analyzed studies, it emerges that the anti-cancer action derives in the first instance from its antioxidant action, which in its turn inhibits the genesis and progression of the tumor. Table 4 summarizes the main findings regarding the role of R. officinalis in cutaneous diseases.

Table 4. The main findings regarding the role of *Rosmarinus officinalis* in cutaneous diseases.

Author and Year	Topic	Model	Extraction Procedure	Study Characteristics
Panahi et al. [93], 2019	Alopecia			*Rosmarinus officinalis* improved microcirculation surrounding the follicle, with comparable results to topical Minoxidil 2% in hair regrowth in patients affected by androgenetic alopecia.
Rastegar et al. [94], 2013	Alopecia	In vitro	The herbs were dried, crushed, and passed through 80-mesh stainless-steel sieves and water was used as a base.	Herbal extract with *Rosmarinus officinalis* and PRP had a positive effect on hair regrowth, promoting the proliferation of human dermal papilla.
Vagedes et al. [97], 2022	Raynaud's phenomenon	In vivo	Not specified.	In an open-label pilot study, warmth perception in patients with systemic sclerosis-related Raynaud's phenomenon was increased by the application of topical rosemary essential oil.
Yimam et al. [98], 2017	Cellulite	In vitro	Dried rosemary leaf was extracted with an approximately 10-fold volume of 95% ethyl alcohol at 40 °C.	A composition of extracts, including those from *Rosmarinus officinalis*, reduced lipid accumulation, platelet aggregation and inflammation, thus ameliorating microcirculation through antioxidant activity
Tong et al. [103], 2018	Non-Melanoma skin cancer	In vitro	Not specified.	Carnosol inhibits the UVB-induced activation of NF-κB, thus reducing keratinocyte carcinogenesis in vitro

Table 4. *Cont.*

Author and Year	Topic	Model	Extraction Procedure	Study Characteristics
Sancheti et al. [104], 2006	Skin cancer	In vivo	Extraction in a Soxhlet apparatus with double-distilled water by refluxing for 36 h at 50–60 °C.	A mouse model demonstrated the protective role of *Rosmarinus officinalis* against skin tumorigenesis
Huang et al. [115], 2005	Melanoma	In vivo	Extraction with hexane, solvent evaporation, dissolving the dried material with methanol, and then filtrating and evaporating the solvent again.	Carnosol inhibited the migration of metastatic B16/F10 mouse melanoma cells in vitro by suppressing the expression of MMP-9
Cattaneo et al. [116], 2015	Melanoma	In vitro	Grinding into fine powder and suspension at 330 g/L in a solution of 65% (*w*/*w*) ethanol/water for 21 days. The extract was then filtered and stored at −20 °C until use.	In vitro, extract of *Rosmarinus officinalis L.* inhibited human melanoma A375 cell line proliferation in a dose- and time-proportional way

2.5. Rosmarinus Officinalis and Cutaneous Lymphoma

Other skin disorders, including lymphomas, may benefit from the antioxidant properties of rosemary. A rare and frequently severe T-cell lymphoma, which can develop in the blood, lymph nodes or skin, is known as adult T-cell leukemia/lymphoma (ATLL). Human T-cell lymphotropic virus type 1 (HTLV-1) infection has been related to ATLL onset; however, less than 5% of HTLV-1 infected-patients develop ATLL. The Caribbean, some regions of South and Central America, and some portions of Africa are the areas where the HTLV-1 virus is most prevalent. To date, we are unable to predict which infected patients will develop ATLL. Through their crucial functions in accelerating cell proliferation and preventing cell death, the viral genes tax and HTLV-1 bZIP factor (HBZ) supports the growth of infected cells. An ATL clone emerged as a result of the persistence of infected clones in vivo and the accumulation of genetic mutations and abnormal epigenetic alterations in host genes [117]. According to a study, the viral oncoproteins Tax and HBZ generate oxidative stress, mitochondrial damage and cytotoxicity, which are countered by the TP53-induced glycolysis and apoptosis regulator (TIGAR), which in turn is induced by the HTLV-1 latency-maintenance factor p30II. In colony transformation and foci formation assays, the p30II protein works in concert with Tax and HBZ to increase their oncogenic potential [118]. Additionally, in an in vivo xenograft model of HTLV-1-induced T-cell lymphoma, the authors demonstrated that TIGAR is substantially expressed in HTLV-1-induced tumors linked to oncogene deregulation and enhanced angiogenesis. These results show that the key oncoproteins Tax and HBZ likely work together as cofactors during retroviral carcinogenesis [119]. Therefore, reducing oxidative stress could alter the proliferative dynamics in ATLL patients. An experimental study revealed that carnosol caused ATL cell apoptosis through the inhibition of cell proliferation. The authors then used mass spectrometry and proteome analysis with fluorescent two-dimensional differential gel electrophoresis to look into the apoptosis-inducing mechanism of carnosol. According to the proteome study, carnosol-treated cells expressed more reductases, glycolytic pathway enzymes and enzymes in the pentose phosphate pathway than untreated cells did. These findings suggest that carnosol had an impact on the cell redox state. Additionally, the quantitative examination of glutathione, which is crucial for maintaining the intracellular redox state, revealed that carnosol was the reason for the decreased glutathione levels in cells. Furthermore, N-acetyl-L-cysteine, which is the precursor of glutathione, reduced carnosol efficiency. From these findings, it was suggested that the apoptosis-inducing activity of carnosol in ATL cells was provoked by the depletion of glutathione [120]. Although the results in the literature on the relationship between *Rosmarinus officinalis* and cutaneous lymphomas are rather limited, in vitro studies would seem to confirm the antineoplastic activity of this substance. Visanji et al. studied the antiproliferative effects of carnosol and carnosic acid on Caco-2 cells, demonstrating that after incubation with these components, the cells increased their doubling time, i.e., the time required to double their population.

This was estimated to be due to G2/M phase cell cycle arrest. Furthermore, carnosic acid and carnosol were observed to arrest the cell cycle at different times. While carnosic acid arrested cells before prometaphase by reducing cyclin A levels, carnosol exerted its major impact on the cell cycle after prometaphase [121]. All of these data could provide the basis not only for an investigation of the potential chemopreventive role of Rosmarinus through cell cycle arrest, but also for an evaluation of the existence of the possible synergistic action of rosemary with traditional chemotherapeutic drugs, to assess the possibility that it can reduce the evolution of viral infection to neoplastic disease.

3. Materials and Methods

This research was carried out on the PubMed database, using the keywords "Rosmarinus officinalis" and "skin". The preliminary research excluded previous reviews and systematic reviews, along with articles not in the English language. The results were screened and selected in the following order: title, abstract and content. Double results were screened and removed from the final article count. Tables 1–4 report the articles that were included and reviewed, divided into sections by topic.

4. Conclusions and Future Perspectives

Ever-increasing scientific attention is being paid to phytotherapeutics, plants with potential therapeutic activities. Among these, *Rosmarinus officinalis L.*, a medicinal plant native to the Mediterranean region, already well-known and thoroughly investigated for its anti-cancer potential, is increasingly showing promising results for its antioxidant and anti-inflammatory activity due to the interaction between the bioactive elements of the plant and the molecular pathways governing inflammatory processes, as well as the pro-oxidative/antioxidant balance. Among the organs that would benefit from such healing effects, according to the evidence, the skin stands out. In light of the promising and well-documented in vitro effects and in vivo results in animals, the future goals of phytotherapeutic research should be geared towards an expansion of clinical trials, especially aimed at investigating in more depth the single bioactive elements of the plant and characterizing new ones, as well as assessing their therapeutic efficacy when combined with other plant extracts. Another pursuable goal, with a view to systemic use, concerns the need for more studies to establish therapeutic dosages of this plant or its bioactive elements. For the latter, the development of innovative technologies directed at their targeted extraction should be encouraged in order to meet the growing future demand for phytotherapy. A further critical issue to be investigated considering the increasingly confirmed recognition of phytodermatitis as a clinical entity [122] is the need for a more in-depth assessment of the risk–benefit balance linked to the topical use of the plant. From what has been said so far, although the use of rosemary in the treatment of skin diseases represents a fascinating line of research, future perspectives still require large and controlled clinical trials in order to definitively elucidate the real impact of this plant and its components in clinical practice.

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antioxidants

MDPI

Review

Rosmarinus officinalis and Skin: Antioxidant Activity and Possible Therapeutical Role in Cutaneous Diseases

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Abstract: The rosemary plant, Rosmarinus officinalis L., one of the main members of the Lamiaceae family, is currently one of the most promising herbal medicines due to its pharmaceutical properties. This research aimed to evaluate the antioxidant role of Rosmarinus officinalis and its bioactive compounds on the skin, with a focus on the newly emerging molecular mechanisms involved, providing extensive scientific evidence of its anti-inflammatory, antimicrobial, wound-healing and anticancer activity in dermatological practice. The search was conducted on articles concerning in vitro and in vivo studies in both animals and humans. The results obtained confirm the antioxidant role of R. officinalis. This assumption derives the possibility of using R. officinalis or its bioactive elements for the treatment of inflammatory and infectious skin pathologies. However, although the use of rosemary in the treatment of skin diseases represents a fascinating line of research, future perspectives still require large and controlled clinical trials in order to definitively elucidate the real impact of this plant and its components in clinical practice.

Keywords: *Rosmarinus officinalis*; rosemary; skin; cutaneous disease; oxidative stress; ROS; carnosol; skin cancer; anti-aging; lymphoma

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1. Introduction

Phytotherapy, to take its most classic meaning, is the branch of medicine that uses plants in their entirety or their components for medical purposes to treat or prevent a plethora of diseases. A cornerstone of various medical traditions over the centuries, above all Ayurvedic medicine, traditional Chinese medicine, allopathic and naturopathic medicine [1], it is, more than ever, a current and much-investigated discipline, even in extraordinary scenarios such as the most recent pandemic period [2–5]. Considering its growth as a field worthy of scientific interest [6–9], the need to introduce guidelines for a better understanding of clinical indications, efficacy and safety profiles is arising [1,10,11]. Among the many plants and their active constituents studied in this unconventional setting [12–16], the rosemary plant, *Rosmarinus officinalis L.*, one of the main members of the Lamiaceae family, cultivated in the Mediterranean basin for culinary use [17], is listed as one of the most promising. This is due to its increasingly established clinical utility [18] supported by the development of breakthrough methods for the targeted extraction of its bioactive metabolites [19]. Rosemary extracts are commercially available in Europe and the USA for use as natural antioxidants in the food industry. They have received Generally Recognized as Safe (GRAS) status from the US Food and Drug Administration. Among these extracts, the most notable, being of scientific interest, are rosmarinic acid, a derivative of caffeic acid [20,21]; phenolic diterpenes, of which carnosic acid and carnosol are the most medically relevant [22–24]; flavonoids such as diosmin [25]; and rosemary essential oil (EO), consisting of more than a hundred chemical compounds, the main molecules of which include 1,8-cineole, α-pinene, α-terpineol, verbenone, limonene, bornyl acetate, terpinolene and camphor [26,27]. Rosmarinic acid, beyond its anti-infectious, antioxidant, anti-inflammatory and immunomodulatory properties, has been extensively investigated in recent years for its anti-cancer activity on various apparently functionally disconnected molecular targets leading to various types of cancer. This has justified the increasing efforts of nanomedicine in the development of therapeutic delivery systems to improve its bioavailability [28]. The EO of *Rosmarinus officinalis* owes its clinical notoriety to its anti-inflammatory potential [26], as well as its antioxidant action, elicited mainly at the hepatic level [29]. Carnosic acid and carnosol, in addition to their antioxidant and anti-inflammatory potential, are clinically relevant for their lipid and glucose metabolism regulatory activity, which would justify their use in the treatment of diabetes mellitus and its complications [30,31]. An interesting and reasonably recent line of research has narrowed the field of interest to the phenolic compounds of *Rosmarinus officinalis*, investigating their therapeutic potential in various neurological disorders, including neurodegenerative diseases [32,33], prion diseases [34], cerebral ischemia [35], neuropathic pain [36] and encephalomyelitis [37]. Along the lines of what has already been widely discussed, the purpose of our review is to provide a detailed overview of the potential beneficial effects of *Rosmarinus officinalis L.* and, more specifically, of the wide range of its bioactive constituents on various dermatological diseases, with a special focus on its promising antioxidant role and the ambitious attempts to elucidate the pathogenetic molecular pathways involved.

2. Results and Discussion

2.1. Rosmarinus Officinalis and Antioxidant Action

Oxidative stress is the pathogenic primum movens of most cutaneous disorders, as the skin is the organ most widely and severely exposed to oxidative stress, despite the extensive endogenous and exogenous antioxidant system at its disposal [38]. For descriptive purposes, the causative agents of skin oxidative stress can be divided into exogenous and endogenous, including intracellular metabolic processes. The main exogenous pro-oxidant agents include ultraviolet (UV) light, environmental pollution and chronic psychological stress. The synergistic action of these factors accelerates the processes of pigmentation and skin aging [39]. The latter recognizes oxidative stress secondary to UV irradiation as the primary causal agent; hence, the need to coin the term photoaging. A greater contribution is made by UVA, since UVB, while participating in the damage, has limited penetration capacity into the epidermis and its cells, including keratinocytes and melanocytes above all [40]. The UV-induced oxidative damage of assorted intracellular structures can be direct or indirect. UVB, for the most part absorbed in the stratum corneum, is essentially accountable for the direct damage that sees DNA as its biologically most crucial molecular target [41]. Over the last two decades, the antioxidant potential of *Rosmarinus officinalis* and its bioactive constituents has been extensively investigated in both in vitro and in vivo studies, especially for its promising therapeutic effects on UV-induced photoaging, atopic dermatitis (AD) and pollution-induced skin aging. Relative to the aforementioned time frame, one of the first in vitro studies on this topic highlighted the interesting proportionality between protein glycation-inhibiting activity and antioxidant activity [42]. This functional synergy is said to be largely attributable to the polyphenolic compounds of various plant extracts, including *Rosmarinus officinalis*, paving the way for their prospective therapeutic use in diabetic complications and aging. Further confirmation of the antioxidant potential of this plant came from Ezzat et al., who emphasized the anti-wrinkle action of the defatted rosemary extract (DER), an effect attributable largely to rosmarinic acid, the main phenolic compound, but also to the diterpenes carnosic acid, carnosol and rosmanol [43]. Furthermore, the encapsulation of this extract in transferomes improves its skin penetrability. The most recent and relevant confirmation of the antioxidant action of rosemary's phenolic compounds comes from an in vitro study evaluating the radical-scavenging and anti-aging activity of aqueous and ethanoic extracts of five phenolic-rich selected herbs, including *Rosmarinus officinalis*, which showed both the highest antioxidant activity and the most pronounced anti-elastase, anti-tyrosinase and anti-collagenase activity [44].

Very recent is the interest in the curative potential of rosemary in skin oxidative damage from pollution. In a randomized, double-blind, placebo-controlled study, Nobile et al. evaluated the antioxidant efficacy of the oral supplementation of four phenol-rich plants, including R. officinalis, in one hundred Caucasian and Asian women living in the polluted urban area of Milan [45]. It was found that long-term supplementation improved all clinical–biochemical parameters monitored, including increased skin elasticity, reinforced skin barrier function and a reduction in wrinkle depth and black spots in the enrolled patients [45]. Hoskin et al. demonstrated, for the first time, the effective action of the topical application of a gel based on hydroalcoholic rosemary extract complexed with algae proteins on pollution-induced oxidative skin damage [46]. The emerging molecular mechanisms through which rosemary phenolic diterpenes acts are the inhibition of the increasing levels of active metalloproteinase-9 (MMP-9), the reduction of protein adducts formation and the reduction of filaggrin loss, which are induced by dermal exposure to diesel engine exhausts (DEE). The pharmacological basis of the anti-inflammatory action of carnosol and carnosic acid from *Rosmarinus officinalis* was first investigated in vivo by Mengoni et al., who evaluated how these bio-active compounds could modify the expression of the inflammation-associated genes cyclooxygenase-1/2 (COX-1, COX-2), interleukin 1β (IL-1β), intercellular adhesion molecule 1 (ICAM-1), tumor necrosis factor-α (TNF-α) and fibronectin, thus revealing a downregulation of IL-1β and TNF-α, leucocyte migration reduction and, most interestingly, selective COX-2 inhibitory activity [47]. Regarding the potential use of *Rosmarinus officinalis* in atopic dermatitis, beyond the first study that more generally attributed an ameliorative role in skin lesions to nerve growth factor (NGF) inhibition, a more recent and detailed molecular characterization of carnosol's intracellular action partially recalled the already known molecular targets and brought to light new ones involved in the implementation of its antiphlogistic action [48]. The most interesting aspect that emerged was the interaction of carnosol with the signal transducer and activator of transcription 3 (STAT3) pathway, which promotes skin inflammation via the upregulation of inducible nitric oxide synthase (iNOS) and COX-2. The carnosol–STAT3 interaction blocks lipopolysaccharide (LPS)-induced STAT3 phosphorylation. On the other hand, carnosol also showed a direct downregulation of the LPS-induced expression of iNOS, COX-2 and nitric oxide (NO). Such synergistic effects of this phenol explain its curative potential in AD [49]. Further confirmation of these molecular mechanisms comes from an in vivo study conducted by Yeo et al., highlighting the anti-inflammatory role of carnosol in UVB-induced skin damage in AD-affected mice. The topical application of carnosol reduced epidermal thickness, erythema, edema and erosion, and dramatically decreased serum levels of the pro-inflammatory cytokines TNF-α and IL-1β, together with a significant reduction in UVB-induced serum IgE [50].

A much more widely represented topic in the literature is the photoprotective role of *Rosmarinus officinalis* and its bioactive elements in UVR-induced skin aging. Martin et al. identified the photoprotective role of a water-soluble extract of *Rosmarinus officinalis* which downregulates both the basal levels of matrix metalloproteinase-1 (MMP-1) and the transcription of UVA/UVB-induced MMP-1 in dermal fibroblasts. Moreover, in a reconstructed skin model, the MMP-1 downregulatory action was also demonstrated further upstream, through the decrease in the UV-induced cytokines IL1- α and IL-6 [51].

In the wake of the above-mentioned work, Park et al. deeply evaluated the molecular mechanisms underlying the anti-photoaging activity of carnosic acid, identifying its ability to downregulate the UV-induced expression of MMP-1, MMP-3 and MMP-9 in human fibroblasts and keratinocytes. In addition, its UVB-induced MMP expression inhibitory activity would recognize the carnosic acid-mediated suppression of MEK/ERK/AP-1 pathways as an upstream causative agent [52]. The photoprotective action on the skin is not only a prerogative of the active bioelements of *Rosmarinus officinalis*, but also involves compounds from other plants, such as citrus flavonoids, in a synergic action that is even stronger than the therapeutic efficacy of the plants taken individually. To this end, Pérez-Sánchez et al., in their clinical trial, highlighted the advantageous effects of combinations of these extracts in human HaCaT keratinocytes, a spontaneously transformed aneuploid immortal keratinocyte cell line from adult human skin, and in human volunteers after oral supplementation. A consistent reduction in the UVB-induced formation of ROS and prevention of DNA damage was demonstrated in HaCaT cells, with consequent higher survival. In human volunteers taking 250 mg of combined citrus and rosemary extracts daily, a significant and progressive increase in minimal erythema dose (MED) was detected, thus suggesting that oral supplementation could improve UVB protection [53]. Further confirmation of the synergistic photoprotective, anti-inflammatory and anti-aging efficacy of these plants came a few years later from Nobile et al., who showed both in a human cell model and in a pilot study beneficial effects such as reduced UVR-induced erythema, diminished skin lipoperoxides (LPO), decreased wrinkle depth and improved elasticity following long-term oral supplementation of combined extracts of *Rosmarinus officinalis* and *Citrus paradisi*. These effects are probably attributable to the inhibition of UVR-induced ROS formation, as well as proinflammatory cytokines, coupled with the downregulatory action of intracellular matrix metalloproteinase-activating pathways [54].

The recent literature is teeming with works confirming the photoprotective role of various plant extracts, of which rosemary, with its bioactive elements, is an increasingly consistent member. Hyuck Auh et al. pioneered the investigation of the anti-photoaging potential of combined extracts of marigold and rosemary, finding in a mouse model that the oral supplementation of these extracts suppressed UV-induced dermal–epidermal thickening in a dose-dependent manner; this histological finding was supported by reductions in various photoaging-related biomarkers observed in the lab [55]. A new molecular photoprotection mechanism was recently highlighted by Calniquer et al., who studied the phytotherapeutic efficacy of a combination of tomato and rosemary extracts. They found an interesting functional synergy of polyphenols (mainly represented by carnosic acid and carnosol in the rosemary extract) and carotenoids (mainly represented by lycopene, phytoene and phytofluene in the tomato extract) in activating the antioxidant response element/Nrf2 (ARE/Nrf2) transcription system, the main cellular antioxidant defense mechanism, in parallel with the inhibition of the UVB-induced pro-inflammatory nuclear factor kappa B (NFκB) pathway in keratinocytes and dermal fibroblasts, resulting in a decreased release of IL-6 and TNF-α and consequently a lowered activation of MMPs [56]. Additionally, for photoprotective purposes, the most recent strand of cosmetic research is working on the development of topical gel formulations containing *Rosmarinus officinalis* extract. The antioxidant, antiaging and healing potential of rosemary hexane extract was evaluated both in vitro and in a UVB-irradiated mouse model. Ibrahim et al. demonstrated the photoprotective potential of rosemary extract, the permeability and bioavailability of which improved when topically conveyed into lipid nanocapsule-based gel [57]. In the wake of the aforementioned work, Takayama et al. evaluated the in vitro antioxidant potential of rosemary hydroethanolic extract together with an evaluation, in vivo, of its anti-UVB photoprotective role if topically conveyed by an emulgel formulation [58]. The main findings regarding the role of *Rosmarinus officinalis* and its antioxidant functions are summarized in Table 1. The main antioxidant properties of *Rosmarinus officinalis* against UV-induced and pollution-induced skin aging and against cutaneous inflammation are shown in Figure 1.

Table 1. The role of *Rosmarinus officinalis* against oxidative stress.

Authors and Year	Topic	Model	Extraction Procedure	Study Characteristics
Takayama et al. [58], 2022	Antioxidants and UVB protection	In vivo/in vitro	Exhaustive maceration	An in vitro and in vivo study on the properties of R. officinalis demonstrated its protective role for the skin against tissue damage caused by UVB radiation.
Nobile et al. [54], 2016	Antioxidants and UVR protection	In vivo	Drying	The antioxidant, photoprotective and antiaging efficacy of the combination of *Rosmarinus officinalis* and *Citrus paradisi* extracts was demonstrated.
Ibrahim et al. [57], 2022	Antioxidants and anti-aging	In vivo/in vitro	Not specified	The photoprotective potential of rosemary extract, whose permeability and bioavailability improved when topically conveyed into lipid nanocapsule-based gel, was assessed.
Nobile et al. [45], 2021	Antioxidants and pollution	In vivo	Not specified	A double-blind randomized study demonstrated that oxidative stress-induced skin damage in both Asian and Caucasian women living in a polluted urban is reduced by oral supplementation with the following herbal extracts: *Olea europaea* leaf, *Lippia citriodora*, *Rosmarinus officinalis*, and *Sophora japonica*.
Mengoni et al. [47], 2011	Antioxidants, inflammation and AD	In vivo/in vitro	Drying	In a mouse model, the expression of IL-1β and TNF-α, markers of inflammation-associated genes in skin, were reduced by carnosic acid and carnosol.
Calniquer et al. [56], 2021	Antioxidants and UVB protection	In vitro	Not specified	An in vitro study demonstrated that the combination of carotenoids and polyphenols produces protective effects against UV-induced damage to skin cells, inhibiting UVB-induced NFκB activity and IL-6 release.
Sanchez et al. [53], 2014	Antioxidants and UVB protection	In vivo/in vitro	Drying and water dissolution	In HaCaT keratinocytes and in human volunteers, the oral intake of rosemary and citrus bioflavonoid extracts reduced UVB-induced ROS, thus preventing cellular DNA damage.
Kim et al. [42], 2003	Antioxidants	In vitro	Ethanol/water (50:50, *v*/*v*)	The protein glycation inhibitory activity of aqueous ethanolic extracts of various plants, including *Rosmarinus officinalis*, closely correlated with the antioxidant activity of the extracts.
Salem et al. [44], 2020	Antioxidants	In vitro	Drying, maceration, water distillation, boiling, filtration, lyophilization	An in vitro study evaluated the radical-scavenging and anti-aging activity of aqueous and ethanoic extracts of phenolic-rich selected herbs, including *Rosmarinus officinalis*, which showed the highest antioxidant activity and the most pronounced anti-elastase, anti-tyrosinase and anti-collagenase activity.
Ezzat et al. [43], 2016	Antioxidants	In vivo/in vitro	Drying, pulverization, defatting, percolation with 70% ethanol, evaporation	The anti-wrinkle activity of DER, which was optimized by encapsulation in transferosomes, was assessed in an in vitro study.
Yeo et al. [50], 2019	Antioxidants and atopic dermatitis	In vivo	Not specified	The anti-inflammation effect of the topical application of carnosol on UVB-induced skin inflammation in HR1 mice inhibited erythema, epidermal thickness and inflammatory responses.

Table 1. *Cont.*

Authors and Year	Topic	Model	Extraction Procedure	Study Characteristics
Lee et al. [49], 2019	Antioxidants and atopic dermatitis	In vivo/in vitro	Not specified	Carnosol inhibited LPS-induced nitric oxide generation and the expression of inflammatory marker proteins, including iNOS and COX-2 in RAW 264.7 cells. STAT3 phosphorylation and DNA-binding activity in RAW 264.7 cells were reduced.
Takano et al. [48], 2011	Antioxidant and atopic dermatitis	In vivo/in vitro	Ethanol	In an atopic dermatitis mouse model, the application of four herbal extracts, including *Rosmarinus officinalis*, reduced atopic lesions, thus inhibiting the effect of NGF on neuritic outgrowths in lesional skin.
Martin et al. [51], 2008	Anti UV	In vitro	Solubilization	IL1-α and IL-6, which play a role in the up-regulation of UV-induced MMP-1, could be suppressed by the *Rosmarinus officinalis* water-soluble extract.
Park et al. [52], 2013	Anti UV	In vitro	Not specified	The antiaging activity of carnosic acid downregulated the UV-induced expression of MMP-1, MMP-3 and MMP-9 in human fibroblasts and keratinocytes.
Hoskin et al. [46], 2021	Antioxidants and pollution	Ex vivo	Hydroalcoholization	The topical application of a gel based on hydroalcoholic rosemary extract complexed with algae proteins against pollution-induced oxidative skin damage was demonstrated.
Hyuck Auh et al. [55], 2021	Anti UV	In vivo	Ethanol at 72 °C for 3 h, evaporation	A mixture of marigold and rosemary extracts demonstrated anti-aging activity in a UV-induced mouse model of photoaging, with reduced expression of matrix metalloproteinase, interleukins, TNF-α, procollagen type I, superoxide dismutase, glutathione peroxidase and catalase

2.2. Rosmarinus Officinalis and Antimicrobial Action

In recent times, the scientific literature has provided ever-increasing knowledge on the antimicrobial activities of essential oils, which are finding use in both medical and cosmetic fields. Secondary plant metabolites have a pharmacological effect on the treatment of skin disorders, for which they are used within topical formulations. In this regard, rosemary extract has shown antimicrobial activity in several cases [59–62]. Starting from the assumption that EOs possess antimicrobial activity, De Macedo et al. reported the first attempt to produce an oil-in-water emulsion containing only natural excipients and rosemary extract, demonstrating that higher quantities of extracted phenolic compounds, flavonoids and tannins corresponded to greater antioxidant and antimicrobial activity, especially against *Staphylococcus aureus*, *Streptococcus oralis* and *Pseudomonas aeruginosa*. De Macedo et al. concluded by asserting that this topical formulation based on *Rosmarinus officinalis* could be a natural therapeutic novelty against microorganisms, which are becoming increasingly resistant to conventional drugs [63]. Another field of research is the treatment of Candida species, which are developing increasing resistance to traditional drugs [64,65], including azoles and polyenes [66,67], thus representing a great challenge for the medical field in the treatment of such common skin infections. Furthermore, conventional antifungal drugs often exhibit toxic side effects for human cells, including hepatotoxic effects. Hence, there is growing scientific interest in EOs, natural compounds that are proving to be promising for their various antibacterial, antifungal and antiviral properties [68,69]. Their action against a wide variety of microorganisms is believed to be due to their ability to alter the membrane and the microorganisms' cell wall, resulting in the extracellular loss of cytoplasmic material [70]. The pharmacological properties of EOs, mainly related to their complex chemical makeup and high levels of phenols, make these compounds a promising tool for the treatment and prevention of candidiasis [71]. However, the low solubility in water, high volatility and high instability of EOs represent the main limitations of their use in the pharmaceutical and cosmetic fields. To overcome this problem, the encapsulation of EOs has proven to be a useful solution. Starting from the knowledge that *Rosmarinus officinalis* can be successfully used as a matrix component and active ingredient of nanostructured lipid carriers (NLCs), it was subsequently demonstrated that the nanoparticles ensured a prolonged in vitro release of clotrimazole, thus increasing the antifungal activity. This confirmed that NLCs containing Mediterranean EOs represent a promising strategy to improve efficacy against topical candidiasis [71]. Specifically, an in vitro test highlighted that leaves from *Rosmarinus officinalis* and *Tetradenia riparia* contain antifungal bioactive compounds. Hydro-alcoholic extracts from these leaves seem to be effective against dermatophytes, including *Trichophyton rubrum, Trichophyton mentagrophytes* and *Microsporum gypseum*, with fungal growth inhibition and morphological alterations in the hyphae [72]. Moreover, it has been proven that the aryl hydrocarbon receptor (AhR), when activated by microbial metabolites, is implicated in a number of skin diseases. Starting from this assumption, Kallimanis et al. attempted to identify natural compounds potentially capable of inhibiting AhR activation by microbial ligands. In this regard, five different dry extracts of *Rosmarinus officinalis* were analyzed to evaluate its ability to inhibit AhR, confirming its dose-dependent antimicrobial activity against *Malassezia furfur* [73]. Another study conducted by Weckesser et al. evaluated the antimicrobial capacity of six extracts, including *Rosmarinus officinalis*, and plant extracts, including carnosol and carnosic acid, showing that *Rosmarinus officinalis* extract inhibited the growth of both aerobic and anaerobic bacteria and yeasts. Furthermore, the Rosmarinus extract was able to inhibit both Candida strains, further showing its antifungal action [74]. Sporotrichosis is a subcutaneous fungal infection caused by fungi of the genus *Sporothrix*, increasingly affecting humans and cats [75]. Despite the limited experimental data on the effects of rosemary essential oil on the treatment of sporotrichosis, studies in the current literature confirm its antifungal activity against *Sporothrix schenckii* [76] and itraconazole-resistant *Sporothrix brasiliensis* [76,77]. The first attempt to assess the effectiveness of rosemary essential oil against cutaneous sporotrichosis in vivo was conducted by Waller et al. Itraconazole-resistant *Sporothrix brasiliensis* was inoculated into 30 Wistar mice, which were randomly treated with itraconazole, rosemary oil or saline as the control population. In mice treated with rosemary oil, the remission of skin lesions was noted, with mild to absent yeast cells. Furthermore, rosemary oil has also shown a protective effect on systemic organs, such as the liver and spleen, delaying the spread of infection [78]. Finally, rosemary has been evaluated for its antibacterial functions. It is known that bacterial pathogens have numerous virulent mechanisms allowing them to enter, replicate and persist at host sites, but with only a few common mechanisms. Among the possible alternatives to overcoming the issue of the constant increase in antibiotic resistance, inhibiting the virulence factors, which are responsible for the damage caused to the host tissue, is increasingly gaining ground as a new line of research [79]. By specifically inhibiting bacterial virulence mechanisms, the pathogenicity of bacteria could be controlled, thus avoiding the increasing ability of bacteria to develop antimicrobial resistance. Furthermore, selectively inhibiting virulence mechanisms reduces the risk of altering the composition of commensal microorganisms, which also play a beneficial role within and on the host. Quorum sensing, as a virulence mechanism, is a cell-density-dependent transcriptional regulatory system, used by bacteria to communicate and to adapt to the environment [80]. *Staphylococcus aureus*, a common cause of skin and soft tissue infection (SSTI), has generated increasing concern due to drug resistance. *Staphylococcus aureus* is an opportunistic Gram-positive bacterium, whose virulence mechanisms involve the activation of the quorum-sensing accessor gene regulator (agr) operon. The diterpene carnosic acid and carnosol, found in *Rosmarinus officinalis L.* leaves, have been demonstrated to have a specific inhibitory effect on *Staphylococcus aureus* agr expression, thus suppressing the cell–cell communication system and, consequently, its pathogenicity [80]. Finally, the activity of basil and rosemary essential oils has also been demonstrated against multi-resistant clinical strains of *Escherichia coli*. The results show that both essential oils tested were active against all clinical strains of *Escherichia coli*, including broad-spectrum β-lactamase-positive bacteria [81]. All of this evidence supports the idea that *Rosmarinus officinalis* can be used both as an important therapeutic tool and as an adjuvant within cosmetological formulations for its broad-spectrum antioxidant and antimicrobial capacities. Table 2 summarizes the main findings about the antimicrobial activity of *Rosmarinus officinalis*.

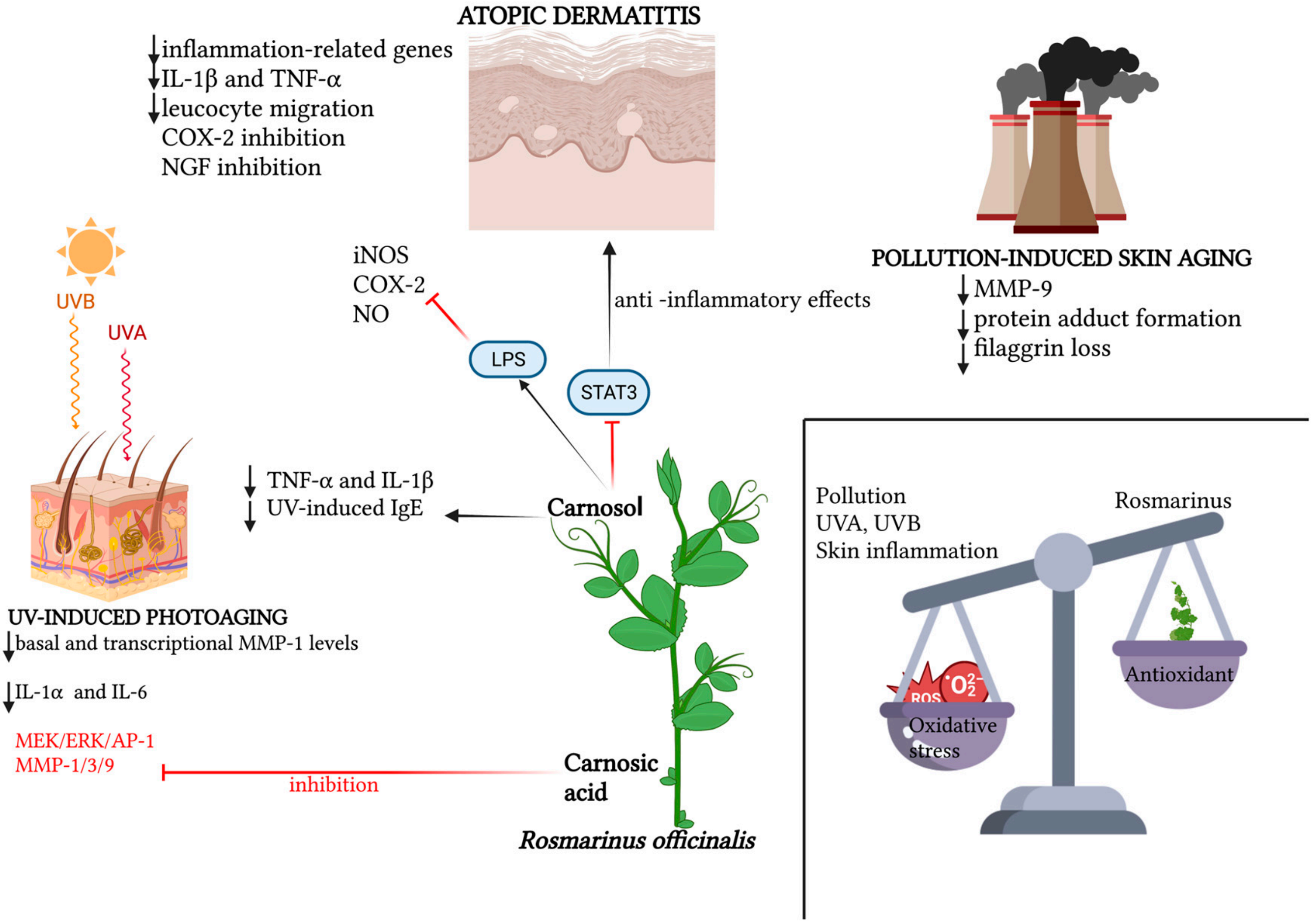

Figure 1. Schematic representation of the relevant molecular patterns involved in the promising antioxidant effects of *Rosmarinus officinalis* and its main bioactive compounds on three dermatological conditions: atopic dermatitis, UV-induced photoaging and pollution-induced skin aging. In atopic dermatitis, beyond the synergic action of carnosol and carnosic acid in downregulating inflammation-related genes, and therefore pro-inflammatory cytokines, leucocyte migration and NGF inhibition promotion, the specific action of carnosol on the STAT3 pathway is emphasized, for which the LPS-induced phosphorylation lock results in anti-inflammatory effects, together with carnosol's direct inhibition of iNOS, NO and COX-2 activation. In UV-induced photoaging, the action of *Rosmarinus officinalis* in downregulating basal and transcriptional levels of MMP-1, as well as the inflammatory cytokines IL-6 and IL-1α, is highlighted. Also portrayed is the specific action of carnosol in downregulating TNF-α, IL-1β and serum levels of UV-induced IgE, and the inhibitory action of rosmarinic acid both on the MEK/ERK/AP-1 pathway and on MMP-1, MMP-3 and MMP-9. In pollution-induced skin aging, the downregulatory action of the two main phenolic diterpenes of *Rosmarinus officinalis* is mainly demonstrated on MMP-9, protein adduct formation and the loss of filaggrin. Created with BioRender.com.

Table 2. The antimicrobial activity of R. officinalis.

Authors and Year	Topic	Model	Extraction Procedure	Study Characteristics
Kallimanis et al. [73], 2022	Anti-microbial activity	In vitro	After drying, the leaf was treated with each solvent in a 1:10 ratio, and then separated from the liquid part by filtration.	Five different dry ROEs were assayed for their activities as antagonists of AhR ligand, which in turn inhibited *Malassezia furfur* yeasts.
De Macedo et al. [63], 2022	Anti-microbial activity	In vitro	Maceration, infusion, Soxhlet and ultrasound	A topical formulation with R. officinalis extract demonstrated antimicrobial activity against *S. aureus*, *S. oralis*, and *P. aeruginosa*
Endo et al. [72], 2015	Anti-microbial activity	In vitro	Leaf were dried in a circulating-air oven at 40 °C. Subsequently, they were soaked in 90/10% (v/v) ethanol–water for 48 h at 25 °C, protected from light.	Hydroalcoholic extracts from R. officinalis and T. riparia in vitro was demonstrated to have antifungal activity against strains of *Trichophyton rubrum*, *Trichophyton mentagrophytes* and *Microsporum gypseum*
Nakagawa et al. [80], 2020	Anti-microbial	In vitro	Not specified.	Diterpene carnosic acid and carnosol, present in *Rosmarinus officinalis L.* leaves, had specific effect on S. aureus agr expression.
Waller et al. [76], 2021	Anti-microbial activity	In vitro	Distillation by steam dragging in Clevenger equipment for 4 h	The study demonstrated rosemary oil as a promising antifungal to treat sporotrichosis, thus postponing systemic fungal spreading.
Weckesser et al. [74], 2007	Anti-microbial activity	In vitro	The solvent used was Carbon dioxide/isopropyl alcohol.	Rosmarinus extract inhibited the growth of *Candida* strains
Sienkiewicz et al. [81], 2013	Anti-microbial activity	In vitro	Not specified.	Basil and *Rosmarinus officinalis* essential oils played a role against resistant *Escherichia coli* clinical strains, and also against extended-spectrum β-lactamase positive bacteria.
Carbone et al. [71], 2013	Anti-microbial activity	In vitro	Not specified.	Nanostructured lipid carrier systems containing EOs, including *Rosmarinus officinalis*, could improve Clotrimazole effectiveness against candidiasis.

2.3. Rosmarinus Officinalis and Wound Healing

In the past decade, a new and interesting strand of phytotherapeutic research has become increasingly popular, which aims to evaluate the curative potential of *Rosmarinus officinalis* in wound healing, as well as in promoting the survival of skin flaps. Concerning the wound-healing process, beyond some in vivo evidence of the regenerative potential of *Rosmarinus officinalis* in the treatment of acute wounds, especially burn wounds, much of the scientific evidence instead concerns the therapeutic potential of rosemary in chronic wounds, primarily diabetic wounds [82,83].

First, Abu-Al-Basal, in an in vivo study conducted on BALB/c mice, demonstrated the efficacy of both aqueous extract and essential oil of *Rosmarinus officinalis* in healing diabetic wounds by pointing out the greater healing efficacy of the essential oil over the aqueous extract [84]. In the wake of this phytotherapeutic interest, Sivamani et al. evaluated the wound-healing role of EO components from various plants, identifying as a potential molecular therapeutic mechanism their ability to inhibit elastases produced by skin, neutrophils and germs, including Pseudomonas aeruginosa [85]. Additionally, Pérez-Recalde et al. confirmed the therapeutic potential of EOs of various plants, including rosemary, especially in chronic wounds. In rodent wounds, improved collagen deposition associated with increased fibroblastic proliferation and a faster wound closure rate has been observed, even highlighting the promising role in wound healing of the incorporation of EOs into resorbable polymeric scaffolds [86]. Similarly, Labib et al. highlighted in vivo the wound-healing potential of a combination of rosemary and tea tree essential oils incorporated into chitosan-based preparations. In the excision wound model in rats, their topical application resulted histologically in complete re-epithelialization associated with follicular activation, together with a significant increase in the rate of wound contraction. In addition, a marked reduction in oxidative stress in the wound area was highlighted, probably attributable to the antioxidant capacity of oxygenated monoterpenes, well-represented in both essential oils examined [87]. The most recent in vivo evidence on the wound-healing potential of rosemary highlights the anti-fungal role that bioactive compounds in its EO such as α-pinene might play, thereby speeding up the healing process [88].

Regarding the potential use of *Rosmarinus officinalis* in improving skin flap survival in relatively recent times, Ince et al. topically tested this ability in vivo with encouraging results [89]. These last were soon confirmed by the same author in another in vivo study that highlighted the vasodilatory effect of orally administered *Rosmarinus officinalis* oil. The resulting increased blood flow to the flap averted the dreaded necrotic complication, suggesting a systemic use of rosemary, especially in patients with circulatory disorders such as chronic obliterative artery disease [90]. In line with the future goals of the aforementioned work, in their latest in vivo study, Ince et al. identified two bioactive compounds from the essential oil of *Rosmarinus officinalis*, alpha-pinene and cineole, as the main systemic contributors to the increased flap survival [91]. Table 3 summarizes the main findings regarding the role of *Rosmarinus officinalis* in wound healing and skin flap survival.

Table 3. The role of R. officinalis in wound healing and skin flap survival.

Author	Topic	Model	Extraction Procedure	Study Characteristics
Labib et al. [87], 2019	Wound Healing	In vivo	Not specified	The wound-healing potential of a combination of rosemary and tea tree essential oils incorporated into chitosan-based preparations was highlighted.
Abu-Al-Basal et al. [84], 2010	Wound healing	In vivo	Steam distillation	An in vivo study conducted on BALB/c mice demonstrated the efficacy of both aqueous extract and essential oil of *Rosmarinus officinalis* in healing diabetic wounds.
Mekkaoui et al. [83], 2021	Wound healing	In vivo	Not specified	A honey mixture with selected essential oils on chemical and thermal wound models in rabbits has healing effects.
Sivamani et al. [85], 2012	Wound healing	In silico	Not specified	Rosmarinus, among other essential oils, inhibited the deleterious activities of elastase, thus ameliorating wound healing.
Sakhawy et al. [88], 2023	Wound healing	In vivo	Not specified	Topical application of a mixture of essential oils, including *Rosmarinus officinalis*, had potential in healing wounds infected with *Candida albicans*.
Farhan et al. [82], 2021	Wound healing	In vivo	Methanol extraction	In vitro, the antifungal activities of *Rosmarinus officinalis* in wounds infected with *Candida albicans* was demonstrated.
Ince et a [90], 2016	Increasing skin flap survival	In vivo	Not specified	The vasodilatory effects of *Rosmarinus officinalis* contributed to increasing skin flap survival.
Ince et al. [89], 2015	Increasing skin flap survival	In vivo	Not specified.	*Rosmarinus officinalis* increased skin flap survival in a mouse model.
Ince et al. [91], 2018	Increasing skin flap survival	In vivo	Not specified	Alpha-pinene and cineole were the components of *Rosmarinus officinalis* responsible for increased flap survival.

2.4. Rosmarinus Officinalis and Cutaneous Diseases

Rosemary has been shown to have not only antioxidant and antimicrobial properties, but also a beneficial role in the treatment of various skin diseases.

In the treatment of alopecia aerate, an autoimmune disease affecting the follicles with subsequent hair loss, the essential oil of *Rosmarinus officinalis* managed to improve microcirculation surrounding the hair follicle [92]. Moreover, a clinical study compared the efficacy of rosemary essential oil to minoxidil 2% solution for the treatment of androgenetic alopecia. Patients used either minoxidil 2% solution or rosemary essential oil, with a dramatic increase in hair count reported for both treatments and without significant differences between the two study groups, which confirmed the therapeutic effectiveness of *Rosmarinus* *officinalis*. Moreover, scalp irritation was more frequent in the minoxidil 2% solution group, confirming the relatively few side effects of natural compound therapies [93]. Among the possible therapeutical approaches, increasing attention has been paid to platelet-rich plasma (PRP) to increase hair density and regrowth. The effect of PRP in combination with herbal extracts has been evaluated to identify the factors stimulating hair growth [94]. Combined herbal extracts and PRP promoted the proliferation of human dermal papilla cells via the regulation of extracellular signal-regulated kinase (ERK) and protein kinase B (Akt) proteins, shedding light on the possible future development of herbal extracts and PRP combination therapies in order to enhance hair growth. The role of *Rosmarinus officinalis* has also been evaluated in systemic sclerosis-related Raynaud's. Additionally, in this connective tissue disorder, the high levels of ROS contribute to the development of fibrotic processes and closely correlate with the severity of skin fibrosis [95,96]. In an open-label pilot study, Vagedes et al. enrolled twelve patients, each of whom received an application of olive oil on both hands as a control and three hours later an application of 10% essential oil of *Rosmarinus officinalis L.*, highlighting that warmth perception in patients with Raynaud's phenomenon was ameliorated by topical rosemary EO application [97]. The potential role of rosemary has also been evaluated from an aesthetic perspective, specifically in the treatment of cellulite, a condition characterized by localized adiposity and inflammation, with subsequent alteration of the microcirculation, mostly affecting women. On this topic, in 3T3-L1 cells (a mouse cell line with an adipocyte-like phenotype), a composition of extracts, including those from *Rosmarinus officinalis*, was shown to reduce lipid accumulation, platelet aggregation and inflammation, thus ameliorating microcirculation through a dose-dependent inhibition of free radical formation. This evidence suggests the potential topical use of rosemary, combined with other extracts, and also in the aesthetic field, taking advantage of its anti-inflammatory and antioxidant properties [98]. As already discussed, overexposure to UVB rays causes oxidative stress and DNA damage, resulting in an increased likelihood of developing different types of cutaneous cancer, including non-melanoma skin cancer and malignant melanoma [99,100]. ROS plays a pivotal role in oncogenesis and mutagenesis, especially in tumor promotion. ROS induces lipid peroxidation and DNA strand breaks by modulating different biochemical pathways and gene expression [101]. In recent years, increased scientific attention has been paid to identifying and characterizing natural compounds with chemopreventive properties against the formation of UVB-induced skin cancer [102].

On this topic, the potential role of carnosol in the chemoprevention of UVB light-induced non-melanoma skin cancer has been evaluated in an HaCat cell study, highlighting that carnosol leads to a partial reduction in UVB-induced ROS and subsequently in a reduction in DNA damage. This ability consists of the absorption of UVB radiation, which in turn could decrease the UVB-induced formation of cyclobutane pyrimidine dimers (CDP) in keratinocytes, further inhibiting the UVB-induced activation of NFκB and UVB-induced mutation [103].

In a mouse model, the modulatory effects of *Rosmarinus officinalis* were studied by *evaluating* the *skin tumor mean latency period*, incidence, burden, yield, weight and diameter. Mouse skin carcinogenesis, evaluated by the formation of papillomas, was induced by topical application on the dorsal skin of 7,12-dimethlybenz(a)anthracene (DMBA) and promoted by croton oil. The results of the study conducted by Sancheti et al. suggest that *Rosmarinus officinalis* leaf extract could postpone the onset of papillomas and their latency period. Furthermore, confirming its antioxidant action, it was observed that serum levels of lipid peroxidation, an index of cellular oxidation, were significantly reduced in mice treated with *Rosmarinus officinalis* [104].

A growing body of evidence indicates that specific compounds of rosemary, including carnosol, carnosic acid and rosmarinic acid, exert antiproliferative activity in several cancer cell lines [105–108]. In colorectal cancer cells, rosmarinic acid causes apoptosis [109], downregulating the mitogen-activated protein kinase (MAPK)/ERK pathway, while in hepatocellular carcinoma cells, rosemary essential oil reduced bcl-2 gene expression and upregulated bax gene expression [110]. In vivo, the anticancer properties of rosemary were proven in mice with acute myeloid leukemia, in which the increase in the administration of crude extracts of rosemary or carnosol, in combination with 1α-25 dihydroxy vitamin D3, led to an intense cytoprotective effect [111]. Thus, in vitro and in vivo data also indicated that crude extracts or purified components of rosemary exerted chemoprotective effects, inhibiting the early stages of tumor development [112,113], probably through the inhibition of enzymes of stage I carcinogenesis. Among the tumors with a rapidly increasing incidence rate, melanoma is a malignant tumor induced by the transformation of melanocytes [114]. When metastatic, the prognosis of melanoma becomes very bad, especially due to the poor response to the currently approved therapies. Hence, the growing interest in EOs is justified. On this topic, Huang et al. demonstrated in vitro that carnosol inhibited the migration of metastatic B16/F10 mouse melanoma cells through the suppression of MMP-9 expression. Furthermore, carnosol was shown to inhibit ERK1/2, AKT, p38 and c-Jun N-terminal kinases (JNK), and led to the activation of the transcription factors NFκB and c-Jun. From this assumption, the authors concluded that the invasive capacity of B16/F10 mouse melanoma cells could be limited by carnosol, through the downregulation of the above-mentioned pathways [115]. Finally, Cattaneo et al. highlighted that the proliferation of human melanoma cell line A375 was reduced by the hydroalcoholic extract of *Rosmarinus officinalis*, in a dose- and time-proportional way through cytotoxic and cytostatic effects on the cell cycle. Through the compositional characterization, the individual pure components of the extract were tested. The observations led researchers to hypothesize that the antiproliferative activity was a property of the entire extract, most likely deriving from multifactorial effects involving the majority of its elements [116]. All of these data agree in stating the potential role of rosemary in the therapy of various skin pathologies, first of all among skin cancer. From the analyzed studies, it emerges that the anti-cancer action derives in the first instance from its antioxidant action, which in its turn inhibits the genesis and progression of the tumor. Table 4 summarizes the main findings regarding the role of R. officinalis in cutaneous diseases.

Table 4. The main findings regarding the role of *Rosmarinus officinalis* in cutaneous diseases.

Author and Year	Topic	Model	Extraction Procedure	Study Characteristics
Panahi et al. [93], 2019	Alopecia			*Rosmarinus officinalis* improved microcirculation surrounding the follicle, with comparable results to topical Minoxidil 2% in hair regrowth in patients affected by androgenetic alopecia.
Rastegar et al. [94], 2013	Alopecia	In vitro	The herbs were dried, crushed, and passed through 80-mesh stainless-steel sieves and water was used as a base.	Herbal extract with *Rosmarinus officinalis* and PRP had a positive effect on hair regrowth, promoting the proliferation of human dermal papilla.
Vagedes et al. [97], 2022	Raynaud's phenomenon	In vivo	Not specified.	In an open-label pilot study, warmth perception in patients with systemic sclerosis-related Raynaud's phenomenon was increased by the application of topical rosemary essential oil.
Yimam et al. [98], 2017	Cellulite	In vitro	Dried rosemary leaf was extracted with an approximately 10-fold volume of 95% ethyl alcohol at 40 °C.	A composition of extracts, including those from *Rosmarinus officinalis*, reduced lipid accumulation, platelet aggregation and inflammation, thus ameliorating microcirculation through antioxidant activity
Tong et al. [103], 2018	Non-Melanoma skin cancer	In vitro	Not specified.	Carnosol inhibits the UVB-induced activation of NF-κB, thus reducing keratinocyte carcinogenesis in vitro

Table 4. *Cont.*

Author and Year	Topic	Model	Extraction Procedure	Study Characteristics
Sancheti et al. [104], 2006	Skin cancer	In vivo	Extraction in a Soxhlet apparatus with double-distilled water by refluxing for 36 h at 50–60 °C.	A mouse model demonstrated the protective role of *Rosmarinus officinalis* against skin tumorigenesis
Huang et al. [115], 2005	Melanoma	In vivo	Extraction with hexane, solvent evaporation, dissolving the dried material with methanol, and then filtrating and evaporating the solvent again.	Carnosol inhibited the migration of metastatic B16/F10 mouse melanoma cells in vitro by suppressing the expression of MMP-9
Cattaneo et al. [116], 2015	Melanoma	In vitro	Grinding into fine powder and suspension at 330 g/L in a solution of 65% (*w*/*w*) ethanol/water for 21 days. The extract was then filtered and stored at −20 °C until use.	In vitro, extract of *Rosmarinus officinalis L.* inhibited human melanoma A375 cell line proliferation in a dose- and time-proportional way

2.5. *Rosmarinus Officinalis and Cutaneous Lymphoma*

Other skin disorders, including lymphomas, may benefit from the antioxidant properties of rosemary. A rare and frequently severe T-cell lymphoma, which can develop in the blood, lymph nodes or skin, is known as adult T-cell leukemia/lymphoma (ATLL). Human T-cell lymphotropic virus type 1 (HTLV-1) infection has been related to ATLL onset; however, less than 5% of HTLV-1 infected-patients develop ATLL. The Caribbean, some regions of South and Central America, and some portions of Africa are the areas where the HTLV-1 virus is most prevalent. To date, we are unable to predict which infected patients will develop ATLL. Through their crucial functions in accelerating cell proliferation and preventing cell death, the viral genes tax and HTLV-1 bZIP factor (HBZ) supports the growth of infected cells. An ATL clone emerged as a result of the persistence of infected clones in vivo and the accumulation of genetic mutations and abnormal epigenetic alterations in host genes [117]. According to a study, the viral oncoproteins Tax and HBZ generate oxidative stress, mitochondrial damage and cytotoxicity, which are countered by the TP53-induced glycolysis and apoptosis regulator (TIGAR), which in turn is induced by the HTLV-1 latency-maintenance factor p30II. In colony transformation and foci formation assays, the p30II protein works in concert with Tax and HBZ to increase their oncogenic potential [118]. Additionally, in an in vivo xenograft model of HTLV-1-induced T-cell lymphoma, the authors demonstrated that TIGAR is substantially expressed in HTLV-1-induced tumors linked to oncogene deregulation and enhanced angiogenesis. These results show that the key oncoproteins Tax and HBZ likely work together as cofactors during retroviral carcinogenesis [119]. Therefore, reducing oxidative stress could alter the proliferative dynamics in ATLL patients. An experimental study revealed that carnosol caused ATL cell apoptosis through the inhibition of cell proliferation. The authors then used mass spectrometry and proteome analysis with fluorescent two-dimensional differential gel electrophoresis to look into the apoptosis-inducing mechanism of carnosol. According to the proteome study, carnosol-treated cells expressed more reductases, glycolytic pathway enzymes and enzymes in the pentose phosphate pathway than untreated cells did. These findings suggest that carnosol had an impact on the cell redox state. Additionally, the quantitative examination of glutathione, which is crucial for maintaining the intracellular redox state, revealed that carnosol was the reason for the decreased glutathione levels in cells. Furthermore, N-acetyl-L-cysteine, which is the precursor of glutathione, reduced carnosol efficiency. From these findings, it was suggested that the apoptosis-inducing activity of carnosol in ATL cells was provoked by the depletion of glutathione [120]. Although the results in the literature on the relationship between *Rosmarinus officinalis* and cutaneous lymphomas are rather limited, in vitro studies would seem to confirm the antineoplastic activity of this substance. Visanji et al. studied the antiproliferative effects of carnosol and carnosic acid on Caco-2 cells, demonstrating that after incubation with these components, the cells increased their doubling time, i.e., the time required to double their population.

This was estimated to be due to G2/M phase cell cycle arrest. Furthermore, carnosic acid and carnosol were observed to arrest the cell cycle at different times. While carnosic acid arrested cells before prometaphase by reducing cyclin A levels, carnosol exerted its major impact on the cell cycle after prometaphase [121]. All of these data could provide the basis not only for an investigation of the potential chemopreventive role of Rosmarinus through cell cycle arrest, but also for an evaluation of the existence of the possible synergistic action of rosemary with traditional chemotherapeutic drugs, to assess the possibility that it can reduce the evolution of viral infection to neoplastic disease.

3. Materials and Methods

This research was carried out on the PubMed database, using the keywords "Rosmarinus officinalis" and "skin". The preliminary research excluded previous reviews and systematic reviews, along with articles not in the English language. The results were screened and selected in the following order: title, abstract and content. Double results were screened and removed from the final article count. Tables 1–4 report the articles that were included and reviewed, divided into sections by topic.

4. Conclusions and Future Perspectives

Ever-increasing scientific attention is being paid to phytotherapeutics, plants with potential therapeutic activities. Among these, *Rosmarinus officinalis L.*, a medicinal plant native to the Mediterranean region, already well-known and thoroughly investigated for its anti-cancer potential, is increasingly showing promising results for its antioxidant and anti-inflammatory activity due to the interaction between the bioactive elements of the plant and the molecular pathways governing inflammatory processes, as well as the pro-oxidative/antioxidant balance. Among the organs that would benefit from such healing effects, according to the evidence, the skin stands out. In light of the promising and well-documented in vitro effects and in vivo results in animals, the future goals of phytotherapeutic research should be geared towards an expansion of clinical trials, especially aimed at investigating in more depth the single bioactive elements of the plant and characterizing new ones, as well as assessing their therapeutic efficacy when combined with other plant extracts. Another pursuable goal, with a view to systemic use, concerns the need for more studies to establish therapeutic dosages of this plant or its bioactive elements. For the latter, the development of innovative technologies directed at their targeted extraction should be encouraged in order to meet the growing future demand for phytotherapy. A further critical issue to be investigated considering the increasingly confirmed recognition of phytodermatitis as a clinical entity [122] is the need for a more in-depth assessment of the risk–benefit balance linked to the topical use of the plant. From what has been said so far, although the use of rosemary in the treatment of skin diseases represents a fascinating line of research, future perspectives still require large and controlled clinical trials in order to definitively elucidate the real impact of this plant and its components in clinical practice.

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