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Pharmacological Insights into Salvia Rosmarinus: A Natural Remedy with Diverse Therapeutic Potential

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Abstract

Rosmarinus officinalis, commonly known as rosemary, is an aromatic herb originating from the Mediterranean region, primarily processed in Murcia, Southeast Spain. It is highly valued in the United States and Europe for its antioxidant properties. Rosemary extracts are renowned for their diverse therapeutic applications, such as liver protection, Alzheimer's disease treatment, and inhibiting the growth of new blood vessels. These extracts also play a vital role in food preservation by preventing oxidation and microbial contamination, offering a natural alternative to synthetic antioxidants. In medicinal use, rosemary helps treat conditions like renal colic, menstrual pain, respiratory disorders, and general pain relief. It aids digestion and bile flow due to its carminative and cholagogue properties and has diuretic effects that enhance urine production. Moreover, rosemary exhibits antiepileptic effects and may benefit fertility. The plant's biosynthetic pathways produce phenolic compounds, including caffeic acid (CA) and dihydroxy-phenyl-lactic acid (DOPL). Shikimic acid is crucial in synthesizing amino acids like phenylalanine, tyrosine, and tryptophan. The process involves converting phenylalanine into cinnamic acid, leading to the formation of Rosmarinus acid (RA), which is an ester of DOPL and has traditionally been used for its liver-protective and bile-stimulating properties, with Rosemary studies confirming its effectiveness in increasing bile flow and protecting against liver toxicity. Rosemary extracts also reduce the formation of malonaldehyde and the release of enzymes in isolated rat liver cells, confirming their hepatoprotective effects. Rosemary also holds promise in cancer prevention, as its dietary non-nutrients effectively inhibit carcinogenesis. RA, absorbed through oral and parenteral routes, has a half-life of 1.8 hours and is detectable in various tissues, especially in the lungs. The herb's antioxidants, including vitamins C and E, and beta carotene, help mitigate oxidative stress, a major factor in many diseases and aging. These antioxidants prevent DNA damage, protein harm, and uncontrolled lipid peroxidation, which are crucial in disease development.

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Introduction

Due to growing concerns about synthetic chemicals in food, there's a rising demand for "clean label products." This has led to an increasing interest in natural extracts as substitutes for synthetic additives [1]. These natural extracts are preferred because they (a) work well with other preservation methods, (b) are considered safe, and (c) have specific properties like antioxidant, antidiabetic, antimutagenic, antioxygenic, and antibacterial effects. Typically, herbs and plants are abundant in antioxidant compounds such as vitamins E and C, glutathione, enzymes, and phenolic compounds [2]. Many spice extracts have proven effective in preventing the autoxidation of unsaturated triacylglycerols. In particular, natural extracts from the Liliaceae family, including thyme, sage, and rosemary, have been recognized in several studies for their antioxidative activity**.**

Rosmarinus officinalis, commonly known as rosemary, is an aromatic herb native to the Mediterranean and belongs to the Liliaceae family [3]. The province of Murcia in Southeast Spain is a leading region for the processing and import of rosemary. In both the United States and Europe, rosemary is uniquely available as a commercial antioxidant. Rosemary extracts have been used in treating various diseases due to their hepatoprotective properties, potential therapeutic effects for Alzheimer's disease, and antiangiogenic properties. Additionally, rosemary extracts are valuable in food preservation, as they prevent oxidation and microbial contamination [4]. Thus, rosemary extract serves as an effective alternative to synthetic antioxidants in foods, offering numerous technological benefits and advantages for consumers.

fig,3 Rosemary oil

Due to concerns about the harmful effects of synthetic chemicals in food, there is a rising demand for "clean label products." This has led to increased interest in using natural extracts as alternatives to synthetic additives because they: [5]

- Synergize with other preservation methods,
- Are considered safe,
- Possess properties like antioxidant, antidiabetic, antimutagenic, antioxygenic, and antibacterial activities.

Herbs and plants are rich in compounds with antioxidant properties, such as vitamins E and C, glutathione, enzymes, and phenolic compounds. Several spice extracts have demonstrated their ability to prevent the autoxidation of unsaturated triacylglycerols. Specifically, natural extracts from the Liliaceae family (such as thyme, sage, and rosemary) have been recognized for their antioxidative activity.

Rosmarinus officinalis (rosemary), native to the Mediterranean region, is an aromatic plant from the Liliaceae family. Murcia in Southeast Spain is a major processor and importer of rosemary [6]. In the U.S. and Europe, rosemary is uniquely used as an antioxidant. Its extracts have been utilized for treating diseases due to their hepatoprotective potential, therapeutic potential for Alzheimer’s disease, and antiangiogenic effects. Rosemary extracts also serve in food preservation, preventing oxidation and microbial contamination [7]. Thus, rosemary extract can replace or reduce synthetic antioxidants in foods, offering various technological advantages and consumer benefits.

The European Food Safety Authority (EFSA) has reviewed the safety of rosemary extracts. [8] They concluded that high intake estimates range from 0.09 mg/kg per day (in the elderly) to 0.81 mg/kg per day (in children) of carnosol and carnosol acid [9]. Currently, in the European Union, rosemary extracts are added to food and beverages at levels up to 400 mg/kg (as the sum of carnosol acid and carnosol).

Rosemary (Rosmarinus officinalis Linn.), part of the Labiatae family, is an evergreen shrub that can grow up to one meter tall [10]. It has upright stems, whitish-blue flowers, and small, dark green leaves with edges that curl backward, hiding glands containing aromatic oils. This plant grows wild along the Mediterranean coasts and in sub-Himalayan areas [11]. It has been cultivated since ancient times in countries such as England, Germany, France, Denmark, other Scandinavian nations, Central America, Venezuela, and the Philippines.

Rosemary has a long history associated with cultural rituals related to love, marriage, birth, and death. In England and Germany, it is a symbol of remembrance and is often included in bridal bouquets. A sprig of rosemary is sometimes placed in a newborn's cradle to protect against evil influences and forces. Additionally, it is used to protect books and clothing from moths and to impart a pleasant fragrance [12]. The plant is mentioned in classic literature, including "Hamlet" and "Don Quixote."

The name "Rosmarinus" derives from Latin, meaning "Dew of the Sea" (Ros=Dew; Marinus=Sea), reflecting its historical and cultural significance [13]. This aromatic plant has been valued for its versatile uses and symbolic meanings across different cultures and centuries.

Traditional use of Rosmery

Rosemary (Rosmarinus officinalis Linn.), from the Labiatae family, is an evergreen shrub valued for its aromatic oil, known as "rosemary oil." This oil is obtained by steam distillation of the plant's fresh leaves and flowering tops [14]. It is widely used as an ingredient in products like Eau-de-cologne, hair tonics, lotions, and cold creams. The leaves of rosemary also serve as a condiment to flavor foods. Historically, rosemary has had extensive use in folk medicine for a variety of ailments and conditions [15].

Rosemary has been utilized as an antispasmodic to treat conditions like renal colic and dysmenorrhea. It is also beneficial in easing respiratory disorders, acting as an analgesic to relieve pain, and serving as an antirheumatic [16]. Additionally, it has carminative properties, aiding in digestion, and functions as a cholagogue, promoting the flow of bile. Its diuretic properties help increase urine production, and it acts as an expectorant, aiding in the expulsion of mucus from the respiratory tract. Rosemary is also noted for its antiepileptic effects and its potential impact on human fertility [17].

Beyond these uses, rosemary serves as a general tonic for those engaged in excessive physical or intellectual work and is beneficial in treating heart diseases. It also functions as an insecticide and herbicide [18]. Externally, rosemary oil is used as a rubefacient, which stimulates blood flow to the skin. This property makes it useful in promoting hair growth and treating conditions like scalp eczema, boils, and wounds.

The diverse applications of rosemary have generated significant interest, leading to numerous pharmacological investigations into its volatile oil, plant extracts, and isolated constituents. [19] These studies aim to understand and validate the traditional uses of rosemary and explore its potential in modern medicine and wellness practices [20].

Rosemary's broad range of medicinal and practical uses highlights its importance in various fields, from culinary arts to herbal medicine. Its aromatic and therapeutic properties have been cherished across cultures for centuries [21]. The plant's versatility is reflected in its incorporation into everyday products, medical treatments, and traditional rituals, underscoring its enduring value and significance.

Preparation of Antioxidants from Rosemary

When testing a new rosemary extract, the extraction method and type of solvent are crucial, as they significantly impact its antioxidant properties [22]. Scientific studies have detailed various methods for extracting rosemary leaves. These include solvent extraction with vegetable oil or animal fat, mechanical pressing, the use of water at an alkaline pH, and a range of organic solvents like hexane, ethyl ether, chloroform, ethanol, methanol, dioxane, and ethylene dichloride.[23]

Older extraction techniques have become outdated and are rarely used in the industry. It has been demonstrated that active fractions of rosemary extract can be separated using molecular distillation. One extraction process involves using ethyl ether under reflux conditions, followed by washing the crude material with water, removing the solvent, dissolving it in methanol, and activating it with carbon at 60°C for 15 minutes [24]. Another process involves reducing the particle size to 600 µL and suspending it in peanut oil. The finely divided antioxidant components, which have a lower molecular weight than the triglycerides in peanut oil, can be separated through molecular distillation using either a fall-film or centrifugal system [25].

Nowadays, rosemary extracts are commonly prepared from dried rosemary leaves. Modern methods typically include partial deodorization and/or decolorization steps [26]. Depending on the raw material, the yield of rosemary extract reported by various authors generally ranges from 2% to 26%. [27]

Chemistry of Rosmery

When the aqueous extract of rosemary was analyzed to determine its active components, researchers identified numerous substances with demonstrated antioxidant and anti-lipoperoxidation activities [28]. These include Rosmarinus acid (RA), caffeic acid (CA), chlorogenic acid, carnosol acid, Romano, carnosol, and various diterpenes. [29] Additionally, the extract contains compounds like rosemary-diphenol, semiquinone, unsolid acid, glycolic acid, and the alkaloid romaine.

Rosemary oil, derived through the steam distillation of the plant's fresh leaves and flowering tops, contains esters (2-6%) such as borneol, cineole’s, and several terpenes, including alpha-pinene and camphene [30].

Among these identified compounds, caffeic acid (CA) and Rosmarinus acid (RA) have attracted significant research interest due to their potential therapeutic properties. These acids are found in a wide variety of plant species, including rosemary, and are noted for their health benefits [31].

This extensive chemical profile has prompted numerous pharmacological investigations into the potential uses of rosemary and its extracts, aiming to validate its traditional applications and explore new therapeutic possibilities.

Chemistry of Rosmarinus acid

The biosynthetic pathways of phenolic compounds such as caffeic acid (CA) and dihydroxy-phenyl-lactic acid (DOPL) are intricate and vital for plant biosynthesis. Shikimic acid, a widely present compound in plants, plays a crucial role in synthesizing aromatic essential amino acids, namely phenylalanine, tyrosine, and tryptophan [32]. The synthesis of cinnamic acid originates from phenylalanine through an enzymatic process that eliminates ammonia (catalyzed by phenylalanine ammonia lyase), followed by aromatic hydroxylation to yield CA. Rosmarinus acid (RA) is an ester of DOPL and CA, with the C6-C3 units deriving from phenylalanine for the A ring and tyrosine for the B ring [33].

Key enzymes involved in the biosynthetic pathway of RA have been identified, purified, and their activities have been studied to enhance or inhibit them. Prephenate aminotransferase (PAT) from RA-producing cell cultures of Anchusa officinalis has been purified to apparent homogeneity using techniques like high-performance anion-exchange and gel filtration chromatography [34]. The purified PAT exhibits a high affinity for prephenate and is not subject to feedback inhibition from L-phenylalanine or tyrosine, although its activity is affected by the RA metabolite, 3,4-dihydroxyphenyl-lactic acid.

Another crucial enzyme, tyrosine aminotransferase (TAT), was purified from the cell cultures of Anchusa officinalis and subsequently characterized into TAT-1, TAT-2, and TAT-3. These enzymes show a marked preference for L-tyrosine over other aromatic amino acids and are inhibited by the tyrosine metabolite, 3,4-dihydroxyphenyl-lactate [35].

In plants, phenolic acids like CA and RA form esters with tannins, which contain hydroxyl (OH) groups, creating a bond known as a depside bond. A new analytical method has been developed to separate and determine aqueous depsides efficiently.

The biosynthesis of these phenolic compounds begins with shikimic acid, which serves as a precursor for the essential amino phenylalanine, tyrosine, and tryptophan. Phenylalanine undergoes an enzymatic process involving phenylalanine ammonia lyase, which removes ammonia and forms cinnamic acid. This cinnamic acid is then hydroxylated to produce caffeic acid (CA) [36]. Rosmarinus acid (RA), a prominent phenolic compound in rosemary, is formed by the esterification of CA with dihydroxy-phenyl-lactic acid (DOPL). The A ring of RA is derived from phenylalanine, while the B ring comes from tyrosine.

Significant enzymes in the RA biosynthetic pathway, such as prephenate aminotransferase (PAT) and tyrosine aminotransferase (TAT), play crucial roles in this process. PAT, isolated from Anchusa officinalis cell cultures, has shown a high affinity for prephenate and is unaffected by L-phenylalanine or tyrosine but is influenced by 3,4-dihydroxyphenyl-lactic acid, a metabolite of RA [37]. TAT, also isolated from Anchusa officinalis, has been divided into three variants: TAT-1, TAT-2, and TAT-3, all of which prefer L-tyrosine over other aromatic amino acids and are inhibited by the metabolite 3,4-dihydroxyphenyl-lactate.

Phenolic acids in plants often form esters with tannins through depside bonds. Recent advancements have led to the development of new analytical methods for the separation and determination of these aqueous depsides, enhancing our understanding of their chemical properties and biological functions [38].

Production of Rosmarinus acid by plant cell culture

Plant cell culture techniques offer significant potential for the large-scale production of natural products. In particular, the production of Rosmarinus acid (RA) has been extensively studied using cell suspension cultures of Coleus blame Benth. These cultures can accumulate RA in concentrations ranging from 8-11% of their dry weight [39].

During active growth, these cultures can convert more than 20% of externally supplied phenylalanine and tyrosine into caffeoyl esters. This high rate of synthesis is associated with increased specific activity of the enzyme phenylalanine ammonia-lyase, which plays a crucial role in the biosynthesis pathway.

Pharmacological actions of rosemary

- **Effects on the Central Nervous System**
  Administering rosemary oil through inhalation or orally has been shown to stimulate the central nervous system (CNS), respiratory functions, and physical activities in mice. [40] This indicates a direct effect from one or more of its constituents. An alcoholic extract of Rosmarinus officinalis demonstrated antidepressant effects in mice when tested using the forced swimming test.
- **Effects on Circulation**
  Baths containing rosemary oil are reported to stimulate the skin, enhance circulation, and improve hemodynamics in conditions involving occlusive arterial diseases.
- **Effects on Smooth Muscle**
  Rosemary's volatile oil has been found to inhibit the contraction of tracheal smooth muscle in rabbits and guinea pigs induced by acetylcholine and histamine, both in the presence and absence of calcium. It also inhibits contractions caused by high potassium solutions.[41] Additionally, an aqueous extract of rosemary leaves was shown to inhibit spontaneous contractions of rabbit jejunum and those induced by acetylcholine, histamine, and barium chloride.
- **Choleretic and Hepatoprotective Effects**
  Traditionally, rosemary has been used as a choleretic and hepatoprotective agent. Experimental studies using lyophilized ethanol and aqueous extracts of young rosemary sprouts confirmed these effects, demonstrating choleretic activity and protection against carbon tetrachloride-induced liver toxicity in rats. This was evidenced by increased bile flow and reduced plasma liver enzyme levels when the extracts were given as a pretreatment.

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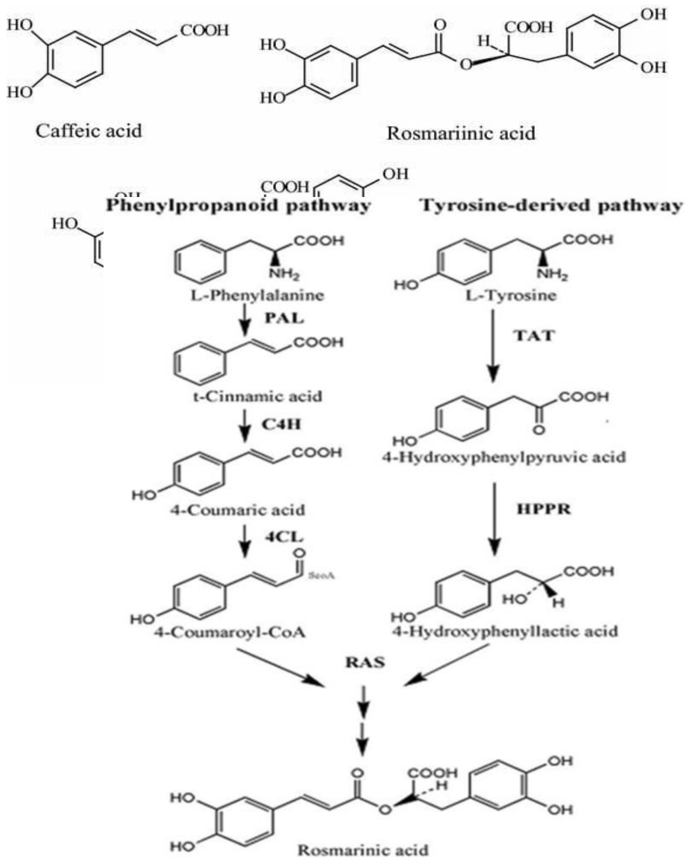
However, no protective effect was observed when extracts were administered post-exposure to carbon tetrachloride. Studies using tert-butyl-hydroperoxide to induce liver injury in isolated rat hepatocytes showed that the aqueous extract of young rosemary sprouts exhibited activity by significantly reducing malonaldehyde formation and decreasing the release of lactate dehydrogenase (LDH) and aspartate aminotransferase (ASAT), confirming its antihepatotoxic properties.

- **Antitumorigenic Effects**
  Rosemary has shown potential in cancer prevention. The incidence of cancer is influenced by multiple factors, including diet and nutritional status. Certain minor dietary constituents, which are non-nutrients, have been found to effectively inhibit experimental carcinogenesis [42].

These inhibitors have demonstrated strong antioxidant activity. Extracts from the leaves of Rosmarinus officinalis are widely used as antioxidants in the food industry and have been shown to be safe, not causing acute toxicity in animal tests. Moreover, these extracts exhibit inhibitory effects on KB cells, a common assay for identifying natural anticancer agents.

Research has also investigated rosemary extract's potential to prevent chemically-induced mammary tumors in female rats and the formation of carcinogen-DNA adducts in mammary epithelial cells. In these studies, a diet containing 1% (w/w) rosemary extract significantly reduced mammary tumor incidence by 47% and decreased the binding of 7,12-dimethylbenz(a)anthracene (DMBA) to mammary cell DNA by 42%.



Pharmacology of Rosmarinus acid

Absorption and Distribution

Rosmarinus acid (RA) can be absorbed through both oral and parenteral routes, with a half-life of about 1.8 hours. Within 30 minutes of intravenous administration, RA is detectable in various tissues, including the brain, heart, liver, lungs, muscles, spleen, and bones, with the highest concentration in lung tissue, which is 13 times higher than in the blood. When applied topically as an ointment on the hind limb, RA has a bioavailability of about 60%, peaking at 4.5 hours, and is measurable in the blood, skin, muscles, and bones. Alcohol enhances the topical absorption of RA [43].

Anti-inflammatory Properties

RA is a naturally occurring non-steroidal anti-inflammatory agent with several unique properties:

1. **Effects on Cell Mediators**: RA significantly inhibits the formation of 5-hydroxy-eicosatetraenoic acid (5-HETE) and leukotriene B4 in human polymorphonuclear leukocytes, while caffeic acid (CA) and several of its derivatives, including RA, enhance the formation of prostaglandin E2.
2. **Free Radical Scavenging Activity**: Hydroalcoholic extracts of medicinal plants with high hydroxycinnamic derivative content (with RA making up more than 3-6% of the dry weight) have shown significant antioxidative activities, particularly through free radical scavenging effects. This antioxidative activity is partly attributed to the high RA content in these plants [44]. Another study using spin trapping methods reported that rosemary extract has a scavenging effect on active oxygen free radicals in stimulated polymorphonuclear leukocyte systems.
3. **Effect on the Complement System**: The complement system can contribute to inflammation by increasing vascular permeability, forming edema, stimulating leukocyte chemotaxis, enhancing platelet activation and aggregation, promoting prostaglandin synthesis in macrophages, and releasing lysosomal enzymes. RA has been shown to inhibit complement activation in several in vivo models [45]. For example, RA inhibited passive cutaneous anaphylaxis for egg ovalbumin in rats at doses of 1-100 mg/kg orally. It also impaired the activation of mouse macrophages by heat-killed C [46]. perfringens at a dose of 10 mg/kg intramuscularly and reduced paw edema induced by cobra venom factor (CVF) in rats at doses of 0.316-3.16 mg/kg intramuscularly. The selectivity of RA for complement-dependent processes was demonstrated by its lack of effect on t-butyl-hydroperoxide-induced paw edema in rats [47].

In in vitro immunophenotypic tests using antibody-coated sheep red blood cells and guinea pig serum, RA caused a 70% inhibition of hemolysis at concentrations as low as 5-10 µmol/L by acting on the C3 convertase of the classical complement pathway. RA also inhibited the chemiluminescence of porcine and human polymorphonuclear leukocytes stimulated by pre-opsonized zymosan or phorbol myristate acetate [48]. Furthermore, RA inhibited the killing of E. coli at a concentration of 2 mM, but not Staphylococcus aureus, due to impaired opsonization resulting from RA's influence on complement activation. RA did not directly affect the killing mechanisms of polymorphonuclear leukocytes.

Conclusion and future prospects

Significant therapeutic potential has been demonstrated by the development and testing of arthritis oil boosted with rosemary extracts. The study's main conclusions stress how well the oil works to manage arthritis symptoms, especially pain and inflammation, because rosemary has anti-inflammatory and antioxidant effects. Delaying lipid oxidation in biological systems is a critical function of the antioxidant chemicals identified in essential oils and rosemary extracts, which may improve joint health. Additionally, the oil's effectiveness as a whole is enhanced by rosemary's antiseptic property, that lowers the probability of skin infections**.**

Increased creation of oxygen free radicals is known to cause tissue damage as well as degeneration, which could contribute to the development of a number of diseases and hasten the aging process. High amounts of antioxidants, including vitamin C, vitamin E, beta carotene, and specific food ingredients, have been scientifically linked to a lower risk of developing cancer as well as cardiovascular disease, revealed to research. A basically essential feature of disease is oxidative stress, which is caused by phagocyte activation and elevated activity of enzymes that produce radicals who are such as xanthine oxidase, and may be a factor in the pathophysiology of the disease. Only oxidants like vitamin E (tocopherol) can stop this "chain reaction" that is caused by free radicals. DNA adduction, protein damage, and unregulated lipid peroxidation can happen in the absence adequate antioxidants.

There is information that rosemary is an important antioxidant that is frequently used in many different kinds of traditional pharmaceuticals and drinks. It stops the breakdown of carcinogen-DNA adducts and suppresses lipid peroxidation. Adding this plant to food for flavoring or swallowing it as a beverage is a simple way to extend its use, as it has been confirmed to be safe in experimental toxicological research as well as effective as an antioxidant.

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