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EXPLORING THE THERAPEUTIC POTENTIAL AND BIOACTIVE PROPERTIES OF URSOLIC ACID FROM ROSEMARY (ROSMARINUS OFFICINALIS): A COMPREHENSIVE REVIEW

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ABSTRACT

Ursolic acid (UA), a natural pentacyclic triterpenoid present in various plant sources, has attracted considerable interest due to its wide-ranging pharmacological effects, which include anti-inflammatory, antioxidant, and anti-cancer properties. Although it is found in several plant species, Rosemary (Rosmarinus officinalis L.) stands out as a key and highly bioactive source of this compound.[1] This review consolidates findings from multiple scientific studies to assess the therapeutic potential of Ursolic acid derived from Rosemary for addressing complex medical issues. Existing research indicates that UA is crucial for metabolic health, as it promotes skeletal muscle growth and helps mitigate diet-related obesity and fatty liver disease.[2] In addition, its role in reproductive health, particularly in the management of Polycystic Ovary Syndrome (PCOS) through the regulation of insulin resistance, underscores its versatility.[3] The compound also demonstrates notable neuroprotective and cardiovascular advantages by influencing oxidative stress levels and enhancing endothelial function.[4]

Moreover, its antibacterial and cytotoxic properties against several malignant cell lines position it as a promising candidate in the development of phytopharmaceuticals.[5][7] Despite its strong bioactivity, the clinical use of UA is often constrained by its low solubility in water and inadequate bioavailability, highlighting the need for further investigation into advanced delivery methods.

KEYWORDS: Rosmarinus officinalis; Ursolic Acid; Pentacyclic Triterpenoid; Therapeutic Potential; Bioactive Properties; Phytochemicals.

I. INTRODUCTION

1. Background of Herbal Medicine and Natural Products

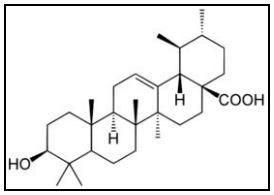
For thousands of years, medicinal plants have been integral to human healthcare and disease management. Various cultures have traditionally relied on the healing properties of botanical extracts to address both acute and chronic health issues. Current global health data indicates that about 80% of the population worldwide continues to use traditional herbal medicine as their primary source of healthcare. In contemporary pharmacology, natural products are gaining recognition as a valuable resource for discovering new bioactive compounds, including flavonoids, alkaloids, and triterpenoids.[6]

These plant-derived substances present notable advantages over synthetic medications, including their ability to target multiple biological pathways, reduced systemic toxicity, and improved patient adherence during long-term treatment.

2. Plant Profile: Rosmarinus officinalis L.

Rosemary, scientifically known as Rosmarinus officinalis L. and part of the Lamiaceae family, is a fragrant, evergreen herb native to the Mediterranean region. While it is commonly used in cooking as a spice and preservative, rosemary is also highly regarded in pharmacognosy for its diverse range of phytochemicals. It comprises a complex array of bioactive secondary metabolites, such as carnosic acid, rosmarinic acid, and the primary focus of this research, ursolic acid.[1]

3. The Target Compound: Ursolic Acid (UA)



Ursolic acid (UA) is a natural pentacyclic triterpenoid carboxylic acid with a thirty-carbon structure that allows interaction with various biological membranes and signaling pathways. It is a potent bioactive compound that influences lipid metabolism, boosts insulin sensitivity, and reduces oxidative stress.[7] Recent pharmacological studies show that UA can induce apoptosis in cancer cell lines, protect liver tissues from chemical damage, and promote skeletal muscle growth via the Akt signaling pathway.[2] [3] Rosemary leaves are a rich source of high-purity Ursolic acid.

4. Rationale of the Study

Despite its therapeutic potential, UA's clinical use is limited due to its lipophilic nature, leading to low solubility and bioavailability. This study aims to consolidate research on Rosemary-derived UA, focusing on its effects on conditions like Polycystic Ovary Syndrome (PCOS), Type 2 Diabetes, and cardiovascular diseases [4] The review seeks to connect traditional herbal remedies with modern pharmaceutical applications, highlighting UA's potential for drug development.

II. BOTANICAL AND TAXONOMICAL PROFILE

A. Taxonomical Hierarchy

Rosemary is classified within the Lamiaceae family, known for essential oils and bioactive triterpenoids like Ursolic acid.[6]

Table 1: Taxonomic Classification of Rosmarinus officinalis L.

Rank	Taxon
Kingdom	Planate
Division	Magnoliphyta
Class	Magnoliopsida
Order	Lamiales
Family	Lamiaceae
Genus	Rosmarinus
Species	Rosmarinus officinalis L.

B. Botanical Description

Rosmarinus officinalis L. is a perennial, evergreen shrub with a woody stem and aromatic qualities. Key characteristics include.[1][8]

I. **Stem**: Erect and multi-branched, usually 1.5 to 2 meters tall. Older stems have shredded bark, while younger shoots are square and hairy.

II. **Leaves**: Leathery, linear, and 2–4 cm long, with a shiny dark green upper surface and a white, hairy lower surface due to glandular trichomes.

III. **Flowers**: Small and borne in short axillary racemes, with pale blue or violet bilabiate corollas; white varieties exist. The calyx is bell-shaped.

IV. **Root System:** The plant features a robust, fibrous rooting structure that enables it to thrive in the dry, rocky soils characteristic of the Mediterranean region.

V. **Seeds:** The fruit contains four small, dry nutlets, each housing a single seed, located at the base of the persistent calyx.

VI. MORPHOLOGICAL CHARACTERISTICS (MACROSCOPY)

VII. The morphological analysis of Rosmarinus officinalis L. includes a thorough examination of its organoleptic properties. These traits are crucial for the initial identification and quality assessment of the crude plant material prior to the extraction of Ursolic acid. [1][6]

A. Organoleptic Evaluation:

i. **Color of Upper Surface:** The leaves' upper surface typically displays a dark green to grayish-green hue, exhibiting a smooth and shiny appearance.

i. **Color of Lower Surface:** The undersides of the leaves are notably silvery-white or pale gray, attributed to a dense coat of fine, woolly hairs.
ii. **Odor:** The plant emits a strong and distinctive aromatic scent with camphor-like notes that is refreshingly invigorating.
iii. **Taste:** Its flavor is sharp, mildly bitter, and leaves a cooling sensation on the palate.
iv. **Size:** Leaves typically range from 1.0 to 4.0 cm in length and about 2 to 4 mm in width.
v. **Shape:** The leaves are linear and possess a needle-like (acicular) morphology.

B. Detailed Morphological Features

Based on the macroscopic evaluation of Rosemary as a source of bioactive compounds, the following characteristics are noted[8][6]

i. **Phyllotaxy (Leaf Arrangement):** The leaves are arranged in an opposite and decussate pattern along the woody stems.
ii. **Surface Texture:** The upper surface is glabrous (devoid of hairs), while the lower surface is tomentose, covered with thick, white, felt-like hairs providing protection to the glandular trichomes.
iii. **Leaf Margin:** A key distinguishing feature is the strongly rolled-down (revolute) margins of the leaves, bending towards the midrib.
iv. **Apex and Base:** The leaf apex is obtuse or slightly rounded, and the base is sessile, attaching directly to the stem without a petiole.
v. **Venation:** The midrib is distinctly pronounced on the lower surface, although the lateral veins are often obscured by the dense hairy covering.
vi. **Fracture:** Upon drying, the leaves become brittle and fracture easily, releasing a balsamic scent when crushed.

III. GEOGRAPHICAL DISTRIBUTION

The distribution and natural growth of Rosmarinus officinalis L. are shaped by various climatic and soil conditions. As a resilient, drought-tolerant shrub, it is found across multiple continents, largely driven by its commercial potential for essential oils and bioactive triterpenoids, such as Ursolic acid.[6][8]

A. Native Habitat (Mediterranean Region)

Rosemary is native to the Mediterranean Basin, primarily found in coastal regions. It is widely grown across Southern Europe (including Spain, Italy, Greece, and France), Northern Africa (notably Tunisia, Morocco, and Algeria), and Western Asia (like Turkey). In its

original environment, it thrives in dry, sunny, and rocky calcareous soils, often located near the coast (the name Rosmarinus translates to "dew of the sea").[1]

B. Global Cultivation

Due to its adaptability and significant economic value in the pharmaceutical, cosmetic, and food sectors, Rosemary has been successfully cultivated in various parts of the world

i. **Europe:** It is extensively cultivated in the Balkan Peninsula, Portugal, and the United Kingdom.
ii. **Americas:** The plant is widely grown across the United States (especially in California and the Southern states), Mexico, and regions of South America, including Brazil and Argentina.
iii. **Africa:** Beyond the Mediterranean shoreline, it is cultivated in South Africa due to its superior phytochemical profile.
iv. **Asia:** Large-scale cultivation occurs in China, India, and Vietnam, where it is processed to extract antioxidant compounds.

C. Distribution in India

In India, Rosemary was introduced as both an ornamental and medicinal plant, cultivated mainly in areas that replicate its native temperate and Mediterranean climate:

i. **Himalayan Region:** Notable cultivation exists in the temperate hills of Uttarakhand, Himachal Pradesh, and Jammu & Kashmir.
ii. **Southern India:** It flourishes in the Nilgiri hills of Tamil Nadu and parts of Karnataka (near Bangalore), where the elevation provides the necessary cooler, drier conditions.
iii. **Maharashtra:** Some small-scale experimental and commercial farming is also practiced in plateau regions with well-draining soil.

D. Environmental Requirements

The growth of Rosemary is influenced by its preference for specific environmental factors

i. **Climate:** A warm, temperate climate with ample sunlight is necessary, along with a sensitivity to extreme frost and water saturation.
ii. **Soil:** Rosemary thrives in well-drained, sandy, or loamy soils with a neutral to slightly alkaline pH.
iii. **Altitude:** In the Mediterranean area, it grows at sea level, whereas in tropical countries like India, it is limited to higher altitudes (1000–2500 meters) to prevent exposure to excessive heat and humidity.[6]

IV. CULTIVATION AND POST-HARVEST PROCESSING

The yield of bioactive compounds such as Ursolic acid is significantly affected by the methods of cultivation, harvesting, and drying of the plant. Adopting appropriate agricultural practices is essential to achieve the highest concentration of secondary metabolites in the leaves.[6][1]

A. Propagation

Rosemary can be propagated using two primary methods, with vegetative propagation being favored for consistent commercial results.

i. **Stem Cuttings (Most Common):** Cuttings from healthy mother plants, specifically softwood or semi-hardwood cuttings measuring approximately 10–15 cm in length, are placed in a well-drained rooting medium. This method ensures that the new plants are genetically identical to the parent (cloning).

ii. **Seeds:** Seed propagation is challenging due to the low and slow germination rate of rosemary seeds, often falling below 30%. Consequently, this method is seldom utilized for large-scale cultivation.

iii. **Layering and Division:** Occasionally, branches that come into contact with the ground will develop roots naturally through a process known as layering, enabling the separation of these branches to create new plants.

B. Planting Season

The timing of planting is essential for the survival of young shrubs

i. **Ideal Time:** In temperate regions, the optimal planting period occurs in early spring (March–April), following the cessation of severe frost.

ii. **In India:** For tropical and sub-tropical areas like India, the ideal planting time is during the post-monsoon season (September–October) or early winter, allowing the plants to establish roots in cooler temperatures before the summer heat.

iii. **Environment:** It is recommended to space the plants approximately 60–90 cm apart to ensure adequate air circulation, which helps prevent fungal diseases.

C. Harvesting

Harvesting must be conducted carefully to preserve the health of the plant and enhance the yield of phytochemicals.[8]

i. **Timing:** To achieve the highest levels of Ursolic acid, harvesting is typically performed just before or during the flowering period.

ii. **Method:** Only the upper 10–15 cm of young, green, and tender shoots should be harvested, avoiding woody stems as they contain less bioactive material.

iii. **Frequency:** A well-established rosemary shrub can be harvested 2–3 times annually. However, it is important to avoid over-harvesting (removing more than 20% of the plant at one time) to minimize stress on the shrub.

iv. **Drying (Post-Harvest Stabilization)**

v. Drying is a vital step in preventing the degradation of antioxidants and essential oils:

vi. **Shade Drying:** Harvested shoots should be laid out in thin layers on trays or hung in bunches in a cool, dry, and well-ventilated setting, away from direct sunlight, which can cause essential oils to evaporate and reduce Ursolic acid levels.

vii. **Temperature:** When using mechanical dryers, it is crucial to keep the temperature below 40°C to 45°C, as higher temperatures can lead to a significant loss of bioactive volatile components.

viii. **Storage:** Once the leaves become brittle and exhibit a "short fracture," they should be stripped from the stems and stored in airtight, amber-colored glass containers or moisture-proof bags to shield them from light and humidity.[6]

V. MICROSCOPICAL CHARACTERISTICS (ANATOMY OF LEAF)

Microscopic analysis of the leaf of Rosmarinus officinalis L. reveals a characteristic dorsiventral structure. The anatomical features, as observed in the transverse section (T.S.) of the leaf, are elaborated below according to pharmacognostical standards.[6][8]

A. Epidermal Layers

i. **Upper Epidermis**: Comprising a single layer of rectangular, thin-walled cells, the upper epidermis is covered by a thick, smooth cuticle that minimizes water loss. Stomata are generally absent on this surface, indicating it is a hypostomatic leaf.

ii. **Lower Epidermis**: This layer consists of smaller cells densely populated with various types of trichomes and stomata, specifically of the diacytic type.

B. Trichomes

Rosemary features a high density of both glandular and non-glandular trichomes, which are crucial for storing Ursolic acid and essential oils:

i. **Glandular Trichomes**: These are represented by "Lamiaceous trichomes" featuring a short stalk and a substantial 8-celled head where essential oils are secreted.

ii. **Non-Glandular Trichomes:** These trichomes are branched, multicellular, and star-shaped, forming a dense protective layer on the lower leaf surface, contributing to its silvery-white macroscopic appearance.

C. Mesophyll Tissue

The tissue situated between the two epidermal layers is differentiated into:

i. **Palisade Parenchyma:** Located just beneath the upper epidermis, this layer contains 1–2 rows of elongated, closely packed cylindrical cells filled with numerous chloroplasts.

ii. **Spongy Parenchyma**: Found below the palisade layer, it consists of loosely arranged, irregular cells with large intercellular spaces, which accommodate the vascular traces.

D. Midrib Region

The transverse section through the midrib displays a noticeable convex projection on the lower side

i. **Vascular Bundle:** A prominent, large collateral vascular bundle is centered within the midrib, with the xylem (composed of vessels and tracheids) oriented toward the upper epidermis and the phloem (containing sieve tubes and companion cells) facing the lower epidermis.

ii. **Collenchyma:** In the midrib region, layers of collenchyma cells are found just beneath the upper epidermis and above the lower epidermis, providing mechanical support.

E. Secretory Structures

The leaf features numerous oil glands and glandular hairs, with ursolic acid commonly associated with the cuticular wax and located within the glandular structures of the leaf surface.

VI. PHYTOCHEMISTRY OF ROSMARINUS OFFICINALIS L.

The healing properties of rosemary are ascribed to its intricate array of secondary metabolites, which can be classified into two main groups: volatile oils (terpenoids) and non-volatile polyphenolic compounds. Ursolic acid (UA), a pentacyclic triterpenoid, is recognized as one of the most significant bioactive constituents present in the leaves. [6][8]

A. Major Chemical Constituents

According to the phytochemical analysis of rosemary leaves, several classes of compounds have been identified.

Triterpenoids (Primary Focus)

i. **Ursolic Acid (UA):** This review's primary emphasis, noted for its notable anti-cancer and anti-inflammatory effects.
ii. **Oleanolic Acid:** A structural isomer of ursolic acid typically found alongside it in the cuticular wax.
iii. **Betulinic Acid:** Another vital triterpenoid with considerable biological impact.
iv. **Diterpenes (Phenolic Diterpenes):**
v. **Carnosic Acid:** A strong antioxidant that provides protection to the plant against UV exposure.
vi. **Carnosol:** A stable degradation product of carnosic acid noted for its biological effectiveness.
vii. **Polyphenols (Phenolic Acids):**
viii. **Rosmarinic Acid:** A soluble ester of caffeic acid that contributes to the remarkable antioxidant and antimicrobial attributes of the aqueous extract.
ix. **Essential Oils (Volatile Fraction):** The volatile oil, comprising approximately 1-2.5%, contains monoterpenes, including 1,8-cineole (eucalyptol), camphor, alpha-pinene, camphene, and borneol, which give the plant its distinctive aroma.

B. Detailed Profile of Ursolic Acid (UA)

As the main focus of this study, Ursolic acid's chemical profile is outlined as follows.[7][3]

IUPAC Name: 3β-Hydroxyurs-12-en-28-oic acid

i. **Molecular Formula:** C30H48O3

ii. **Molecular Weight:** 456.7 g/mol

iii. **Chemical Nature:** A pentacyclic triterpenoid within the ursane family, characterized by five interconnected rings, a carboxylic acid group at position 28, and a hydroxyl group at position3.

i. **Solubility:** Predominantly lipophilic and nearly insoluble in water but dissolves in organic solvents such as ethanol, methanol, and chloroform.

ii. **Stability:** UA demonstrates relative stability under standard environmental conditions but may undergo structural changes to yield more soluble derivatives suitable for pharmaceutical applications.

C. Localization of Ursolic Acid in the Plant

Phytochemical mapping indicates that Ursolic acid is primarily concentrated in the cuticular wax of the leaves, as well as within glandular trichomes and epidermal cells. The concentration of UA can range from 1% to 4% of the leaf's dry weight, influenced by geographical location and harvesting time.[6]

VII. BIOLOGICAL ACTIVITIES OF URSOLIC ACID (UA)

Ursolic acid (UA) derived from Rosmarinus officinalis L. acts as a versatile therapeutic agent. Its unique pentacyclic structure enables interactions with various molecular pathways, making it beneficial for numerous chronic and acute conditions. The primary biological activities are summarized as follows.[8][3]

A. Anti-inflammatory and Antioxidant Activity

UA effectively inhibits oxidative stress and inflammation through.

Neutralizing ROS: It scavenges reactive oxygen species (ROS) directly while enhancing the activity of the body's natural antioxidant enzymes, such as Superoxide Dismutase (SOD) and Catalase.

Inhibiting Cytokines: By suppressing the NF-κB signaling pathway, UA reduces the production of pro-inflammatory cytokines like TNF-α and IL-6 [9] making it particularly effective in managing arthritis and skin inflammation.

B. Anti-Cancer and Cytotoxic Potential

Extensive research has focused on UA's cancer-fighting capabilities, operating through multiple mechanisms

Induction of Apoptosis: UA activates programmed cell death (apoptosis) in malignant cells while sparing healthy cells.[5]

Cell Cycle Arrest: It obstructs the growth of cancer cells during the G1/S phase.

Anti-Angiogenesis: UA inhibits the formation of new blood vessels supplying nutrients to tumors, thereby impeding metastasis in breast, colon, and prostate cancers. [10]

C. Role in Polycystic Ovary Syndrome (PCOS)

Recent predictive analyses and clinical investigations suggest UA's beneficial role in reproductive health, specifically in PCOS patients, where it assists by

Reducing Insulin Resistance: UA enhances glucose uptake and decreases hyperinsulinemia.

Hormonal Balance: It helps mitigate hyperandrogenism (excess male hormones), thereby facilitating regular menstrual cycles and enhancing fertility.[3]

D. Management of Obesity and Diabetes

UA distinctly influences energy metabolism:

Skeletal Muscle Hypertrophy: It stimulates the Akt/mTOR signaling pathway, resulting in increased muscle mass and strength.

Reduction of Fat: It heightens the activity of "brown fat," which is involved in calorie burning, leading to a reduction in diet-induced obesity and glucose intolerance.[2]

D. Neuroprotective Effects

In the nervous system, UA provides a protective effect against neurodegeneration:

Alzheimer’s Disease: UA prevents the formation of amyloid-beta plaques within the brain.

Memory Enhancement: By mitigating neuroinflammation, ursolic acid enhances cognitive abilities and shields neurons from oxidative damage.

E. Hepatoprotective and Cardiovascular Benefits

Liver Health: UA offers protection to hepatocytes from harmful substances and alcohol-related injuries, consequently preventing conditions like fatty liver disease and fibrosis.

Heart Health: It promotes endothelial function and lowers the risk of atherosclerosis by keeping lipid profiles healthy.[4]

F. Antibacterial Activity

Ursolic acid demonstrates a wide array of antibacterial properties against both Gram-positive and Gram-negative bacteria. Its mechanism involves disrupting bacterial cell membranes and inhibiting critical enzymes.[5]

Gram-Positive Bacteria: UA is especially effective against strains such as Staphylococcus aureus and Bacillus subtilis, compromising the integrity of the peptidoglycan layer and causing cell lysis.

Synergistic Effect: When combined with conventional antibiotics, UA has the potential to boost their effectiveness and mitigate bacterial resistance.

Biofilm Inhibition: Additionally, it inhibits the formation of bacterial biofilms, which are often linked to chronic infections and antibiotic resistance.[7]

G. Antifungal Activity

In addition to its antibacterial properties, UA acts as a powerful natural antifungal agent, targeting various pathogenic fungi impacting human health and agricultural crops.[5][6]

Mechanism of Action: UA hinders the synthesis of ergosterol, an essential component of the fungal cell membrane. The reduction of ergosterol escalates membrane permeability, ultimately leading to the death of the fungal cell.

Activity against Candida species: Studies underscore its efficacy against Candida albicans, a common culprit of opportunistic infections in humans. Agricultural Utility: With its low toxicity, rosemary-derived UA is being investigated as a natural fungicide to safeguard stored grains and crops from fungal spoilage.

VIII. CONCLUSION

This review of scientific literature substantiates that ursolic acid (UA), derived from Rosmarinus officinalis L., is a bioactive triterpenoid with considerable potential. Its diverse pharmacological profile—encompassing anti-inflammatory, antioxidant, and anti-cancer properties—positions it as a versatile therapeutic agent. Noteworthy evidence emphasizes its effectiveness in addressing Polycystic Ovary Syndrome (PCOS) and metabolic issues such as obesity and diabetes by improving insulin sensitivity and promoting muscle mass. Furthermore, its significant antibacterial and antifungal capabilities suggest it as a promising lead for the development of natural drugs. While low bioavailability is a challenge, rosemary-

derived ursolic acid shows promise as a candidate for future phytopharmaceuticals. Ongoing clinical research and innovative nano-formulation strategies are recommended to fully realize its therapeutic potential in global health management.

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