Usnic acid and its Uses: A Review

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ABSTRACT

Usnic acid (UA) is a yellowish solid, found in lichens like Usnea and it was isolated from lichen metabolite, various studies were performed on it and now it became easily available in the market. It is well known for its anti-bacterial, anti-fungal, anti-cancer, wound healing activites. Its wide availability in different lichen species, being isolated easily, and high purity of the isolated product makes it an excellent base for producing new pharmaceuticals. In this review the various usage of UA was highlighted. It was used as an antioxidant, anti-proliferative, antimicrobial, antiprotozoal, larvicidal and insecticidal, antifungal, antiviral, anti-inflammatory, pain-relieving and antipyretic agent. Severalside effects were associated with using usnic acid, especially at higher doses, which includes hepatotoxicity, genotoxicity, allergenicity, side effects on the cardiovascular system and adipocytes of fatty tissue. This review highlighted the updated biological activities, effectiveness and safety as well as usage of usnic acid.

Keywords: Anti-inflammatory,Cytotoxicity, Human, Hepatotoxicity, Lichen, Nephrotoxicity, Neurotoxicity, Usnic Acid, Wound healing.

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Introduction

Lichens are composite organisms formed by a symbiotic relationship between a fungus (mycobiont) and an alga or cyanobacterium. In this symbiosis, the algae or cyanobacteria provide the fungus with organic metabolites, while the fungus supplies water and dissolved mineral salts. Lichens can survive under extreme conditions, thriving in environments such as air, rainfall, dew, fog, and soil.

It is estimated that lichens cover about **8% of the Earth's surface**, with over **17,000 species** and more than **800 known lichen products**. Researchers have shown great interest in lichen-derived compounds, including polysaccharides, proteins, and secondary metabolites like **usnic acid (UA)**. Usnic acid was first isolated from lichens in **1844**, and since then, extensive studies have been conducted, leading to its commercial availability.

Usnic acid is found in various lichen species and is valued for its easy isolation and high purity. This makes it an excellent candidate for pharmaceutical development. UA exhibits a range of biological and physiological properties, including **anti-inflammatory, analgesic, healing, antioxidant, antimicrobial, antiprotozoal, antiviral, larvicidal, and UV-protective effects**.

However, some studies have reported potential side effects such as **liver toxicity and contact allergies**. This review aims to summarize the effectiveness and safety of usnic acid based on research conducted over the past decades. [1]

Historical Use of Usnic Acid (UA):

- Used as an antibacterial agent in many countries before penicillin discovery.
- Applied for pulmonary tuberculosis, pain, fever, wounds, athlete's foot, deodorants, and herbal tinctures.
- Known by various names regionally: "Monogram" (Germany), "Rosalina Thrust" (Finland), "Barba del la Piedra" (Argentina).

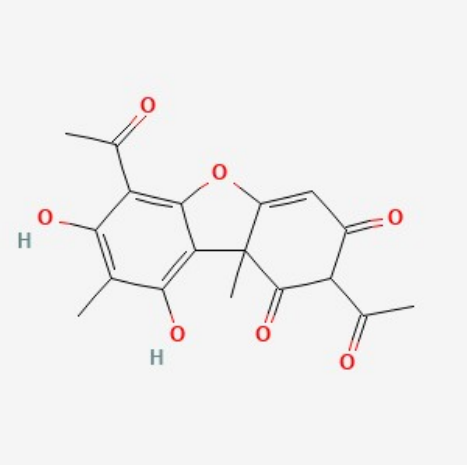
- Interest declined after penicillin but revived in the 1980s due to antibiotic resistance issues.

Nature and Source:

- Producedby lichens from genera such as *Cladonia*, *Usnea*, *Lecanora*, *Ramalina*, *Evernia*, *Parmelia*, and *Alectoria*.
- First isolated from *Ramalina* in 1843; chemical structure determined about 90 years later.

Chemical Structure:

- Yellow crystalline compound, scientifically named 2,6-diacetyl-7,9-dihydroxy-8,9b-dimethyl-dibenzofuran-1,3(2H,9bH)-Dione.
- Exists as two enantiomers: (+) D-usnic acid and (−) L-usnic acid, each with different biological activities.
- Also two natural isomers: (+) and (−) isousnic acids.
- Can be chemically synthesized from methylphloroacetophenone.[2]



Biological Activities:

- **Antioxidant and Pro-oxidant:**
  - Scavenges peroxyl and hydroxyl radicals, decreases nitrite synthesis.
  - Can increase intracellular reactive oxygen species (ROS).
- **Antimicrobial and Antiprotozoal:**
  - Active against Gram-positive bacteria and mycobacteria.
  - Re-emerged as antibiotic interest due to resistant strains.
- **Antiviral:**
  - Inhibits replication of Epstein–Barr virus, herpes simplex type I, and polio type 1 viruses.
- **Anti-inflammatory:**
  - Comparable to ibuprofen in reducing inflammation in rat models.
  - Reduces expression of pro-inflammatory cytokines such as TNF-α, IL-6, IL-8, and MIP-2.[3]

Adverse Effects and Safety Concerns:

- **Hepatotoxicity:**
  - Liver toxicity observed when used as a weight-loss supplement.
- **Genotoxicity:**
  - Some in vitro studies show DNA damage at higher doses.
- **Allergenicity:**
  - Can cause allergic reactions; both enantiomers may trigger allergies.[4]

Traditional Use:

- Used in Traditional Chinese Medicine since 101 B.C. as an antimicrobial and for liver cleansing, malaria, wound healing, and snake bites.

Wound Healing:

- (+)-Usnic acid promotes skin cell migration and wound closure in cell models.
- Combined with gyrophoric acid, it enhances wound healing synergistically.[5]

Photoprotective Activity:

- Absorbs UV light, protecting lichens and potentially skin from UV damage.

Conclusion and Current Challenges

- Although promising, clinical use is limited by:
  - Hepatotoxicity risks with oral use.
  - Poor water solubility and limited bioavailability data.
  - Insufficient human trials and regulatory hurdles.
- Topical nanocarrier formulations may reduce systemic toxicity but require more animal and human studies to confirm safety and efficacy.[6]

Although UA is used in some cosmetic products, a number of clinical translation barriers still exist for its medicinal use. These include the stated hepatotoxicity upon oral administration, poor solubility in water, scarce data on its bioavailability (especially in terms of skin penetration), and a lack of results of human trials to support the potential use, or some regulatory hurdles. As highlighted in the recent literature, topical nanocarriers restrict the action of UA to the target dermal layers, thereby mitigating the risk of systemic absorption and hepatotoxic side effects, but there are still a lot of animal and human trials needed to clearly indicate the effectiveness and safety of UA.[7,8,9] Therefore, further researchers should consider the *in vivo* safety studies: performing rigorous,

extended *in vivo* toxicity studies in animal models to foundaccurate safe dosage thresholds for topical application.[10.11,12]

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