



Active Compounds of *Usnea* Lichen and Their Potential as Pharmaceutical Raw Materials: A Review of Phytochemistry and Pharmacological Activities

A Musdalifah *, Nurul Inaya Muhtar

Department of Pharmacy, Faculty of Medicine and Health Sciences, Universitas Muhammadiyah Kendari, Indonesia

*Email (corresponding author): amusdalifah47@gmail.com

Abstract. Lichens represent a unique symbiotic system and an important yet relatively underexplored source of bioactive natural products. Among them, the genus *Usnea* has attracted considerable scientific interest due to its chemically diverse secondary metabolites and wide range of pharmacological activities. However, current knowledge integrating phytochemical diversity, pharmacological mechanisms, and safety considerations remains fragmented. Therefore, this review aims to systematically summarize the major bioactive compounds identified in *Usnea* species and critically evaluate their pharmacological potential as pharmaceutical raw materials. Particular attention is given to polyketide-derived metabolites, including usnic acid, depsides, and depsidones, which exhibit diverse phenolic structures and contribute to antimicrobial, antioxidant, anti-inflammatory, and anticancer activities through mechanisms such as membrane disruption, free radical scavenging, modulation of inflammatory pathways, and apoptosis induction. Furthermore, toxicity concerns, especially hepatotoxicity associated with high-dose usnic acid, are discussed to highlight the need for improved safety evaluation and formulation strategies. The exploration of *Usnea*-derived natural products also supports global health initiatives, particularly the Sustainable Development Goals (SDGs), including SDG 3.4 (reducing premature mortality from non-communicable diseases) and SDG 3.b (promoting research and development of new medicines). Overall, *Usnea* represents a promising source of bioactive compounds for sustainable natural product-based pharmaceutical development.

Keywords: *Usnea*; Usnic acid; Depsidones; Phytochemistry; Pharmacological

1. Introduction

Natural products have long been a major source of therapeutic agents and have made significant contributions to the discovery and development of modern medicine. A substantial proportion of currently used drugs are either directly derived from natural sources or inspired by natural compounds. Among these sources, lichens represent a promising yet relatively underexplored group of organisms in natural product research. As unique symbiotic associations between fungi and photosynthetic partners, they are capable of producing structurally diverse secondary metabolites. Their adaptation to extreme and fluctuating environmental conditions has driven the biosynthesis of distinctive bioactive compounds, underscoring their significant pharmacological potential (Prado et al., 2025; Armstrong, 2017). In this context, the exploration of bioactive compounds from lichens may also contribute to global health initiatives, particularly the Sustainable Development Goals (SDGs). The discovery of novel therapeutic agents from natural resources supports SDG 3.4, which aims to reduce premature mortality from non-communicable diseases through prevention and

treatment, as well as SDG 3.b, which emphasizes the promotion of research and development of new medicines.

The genus *Usnea*, commonly referred to as “beard lichen,” represents one of the most widely distributed fruticose lichen genera in tropical and temperate regions worldwide, with a notable abundance in Indonesia. *Usnea* species are characterized by their shrubby morphology and the presence of a central elastic axis, as well as their rich content of phenolic secondary metabolites. Among these, usnic acid is the most prominent and extensively studied compound, accompanied by other important constituents such as depsides and depsidones. These active compounds have attracted increasing scientific attention due to their broad spectrum of reported biological activities (Gerlach et al., 2017; Ureña-Vacas et al., 2023).

Over the past decades, a growing body of literature has documented that secondary metabolites isolated from *Usnea* possess diverse pharmacological activities, including antimicrobial, antioxidant, anti-inflammatory, and anticancer properties. Collectively, these findings emphasize the considerable promise of *Usnea* as a strategic source of bioactive compounds for pharmaceutical raw materials and novel drug development. However, despite the growing body of research, information regarding the integration of phytochemical profiles with pharmacological evidence remains fragmented. In addition, concerns related to toxicity, standardization, and sustainable utilization continue to present challenges for its development into clinically applicable products (Manojlović et al., 2025).

Therefore, this review aims to comprehensively summarize the active compounds identified in *Usnea* species and critically discuss their phytochemical characteristics and pharmacological activities. Unlike previous reviews, this article provides an integrated analysis of pharmacological studies on *Usnea*, with particular emphasis on the relationship between the chemical structures of its secondary metabolites and their biological activities. Furthermore, this review highlights current perspectives on safety considerations and discusses potential strategies for the pharmaceutical development of *Usnea*-derived compounds.

2. Methods

This review article was prepared through a comprehensive and systematic literature search focusing on the active compounds of *Usnea* lichen and their pharmacological potential as pharmaceutical raw materials. Scientific publications were retrieved from reputable electronic databases, including Scopus, Web of Science, PubMed, and ScienceDirect. The search strategy employed combinations of keywords such as “*Usnea*,” “lichen secondary metabolites,” “usnic acid,” “depsides,” “depsidones,” “phytochemistry,” “pharmacological activity,” and “drug development.” Inclusion criteria comprised original research articles, review papers, and relevant book chapters reporting phytochemical identification and biological activity of *Usnea* metabolites. All selected references were screened based on titles, abstracts, and full texts to ensure relevance and scientific rigor. The collected studies were organized systematically to provide a coherent framework for analysis. This structured approach was intended to ensure comprehensive coverage of current scientific evidence related to *Usnea* and its bioactive constituents.

The collected literature was examined to synthesize current knowledge regarding the phytochemical diversity and pharmacological relevance of *Usnea* species. Comparative evaluation was conducted to identify consistencies, discrepancies, and emerging research trends within the available studies. Particular attention was given to findings that support the



development of *Usnea*-derived compounds as pharmaceutical raw materials, including reported biological efficacy and safety considerations. The synthesis of information was performed descriptively and analytically to integrate findings from different experimental approaches and study designs. Emphasis was placed on correlating chemical composition with biological activity to provide a clearer understanding of structure–activity relationships. This methodological framework ensures that the review presents a balanced, integrative, and up-to-date overview of the active compounds of *Usnea* and their pharmaceutical development prospects.

3. Results and Discussion

3.1. Characteristics of *Usnea* Lichen

Usnea is a genus of fruticose lichens in the large family Parmeliaceae. *Usnea* lichen is characterized by its hanging, grayish-green or yellowish fringed shape, which grows epiphytically on tree bark, especially in fresh air. Its main distinguishing feature is the presence of a strong and elastic central axis, which differentiates it from other fruticose lichens (Jannah et al., 2025). Anatomically, the thallus is composed of several layers, including the outer cortex, the photobiont layer (containing green algae such as *Trebouxia*), the medulla, and the central axis. This mutualistic symbiosis between the fungal partner (mycobiont), commonly belonging to the class Ascomycetes, and the photosynthetic partner enables *Usnea* to perform photosynthesis while benefiting from structural protection, thereby allowing it to survive under fluctuating and sometimes extreme environmental conditions, such as high ultraviolet radiation, low temperatures, and limited nutrient availability (D'Souza et al., 2023).

Geographically, *Usnea* is widely distributed across tropical and subtropical regions and is abundantly found in Indonesia, particularly in tropical rainforest ecosystems and mountainous areas characterized by high humidity and relatively good air quality. It predominantly grows epiphytically on tree trunks and branches, although some species may occur on rocky substrates. The distribution and abundance of *Usnea* are strongly influenced by environmental factors, including light intensity, humidity, altitude, and air pollution levels, making it a valuable bioindicator of air quality (Nadel & Clerc, 2022; Santos et al., 2022). In addition to its morphological traits, *Usnea* is notable for its diverse array of secondary metabolites, such as usnic acid, depsides, and depsidones, which play crucial roles in ecological defense mechanisms against environmental stressors and microbial attack. Its distinctive morpho-anatomical characteristics, ecological distribution patterns, and unique chemical profile underscore its importance in taxonomic, ecological, and natural product-based pharmaceutical research (Salgado et al., 2017).

3.2. Phytochemistry of *Usnea* Lichen

The genus *Usnea* is well recognized for its richness in secondary metabolites, most of which are derived from polyketide biosynthetic pathways. Phytochemical screening has consistently demonstrated that *Usnea* is particularly abundant in phenolic compounds produced by its fungal symbiont. Among the major identified metabolites, usnic acid is the most characteristic and extensively investigated compound (Bharti & Nayaka, 2022). Usnic acid is a dibenzofuran derivative that occurs as two enantiomeric forms, namely (+)-usnic acid and (–)-usnic acid. In addition, *Usnea* species contain depsides and depsidones, which contribute to a broad spectrum of phenolic constituents, such as barbatic acid and diffractaic acid (depsides), as well as salazinic acid and norstictic acid (depsidones). These compounds

are generally localized in the cortical and medullary layers of the thallus and play important biological and ecological roles within the genus. The qualitative and quantitative composition of these metabolites may vary depending on species, geographical origin, altitude, and environmental conditions (Deoli et al., 2025; Ślusarczyk et al., 2021).

Phytochemical investigations of *Usnea* are typically conducted through extraction using organic solvents such as methanol, ethanol, acetone, or ethyl acetate, followed by chromatographic separation to obtain pure compounds (isolates). Structural elucidation and purity assessment of the isolated compounds are performed using advanced spectroscopic and analytical techniques, including High-Performance Liquid Chromatography (HPLC), Liquid Chromatography–Mass Spectrometry (LC–MS), and Nuclear Magnetic Resonance (NMR) spectroscopy. The diversity of phenolic metabolites in *Usnea* not only supports its ecological adaptability but also underpins its significant pharmacological potential. Therefore, phytochemical studies of *Usnea* provide a crucial foundation for the exploration of bioactive compounds in the development of natural product-based pharmaceuticals (Maulidiyah et al., 2022; Adjeng et al., 2023).

3.3 Pharmacologically Active Compounds of *Usnea*

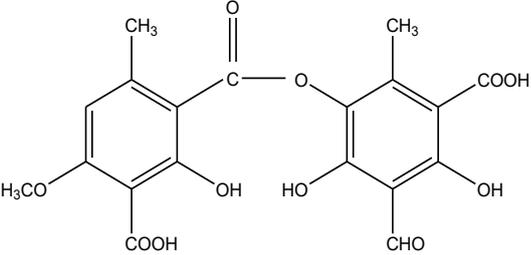
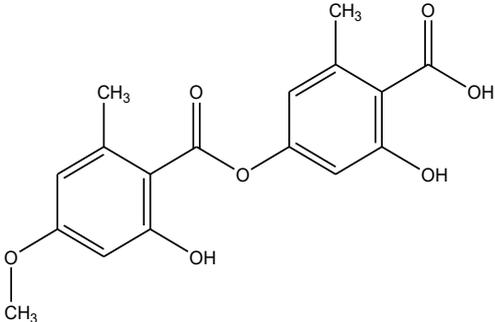
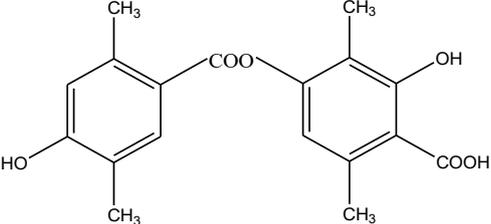
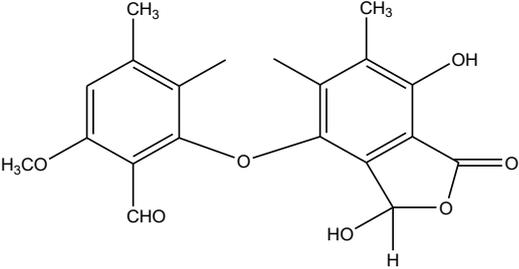
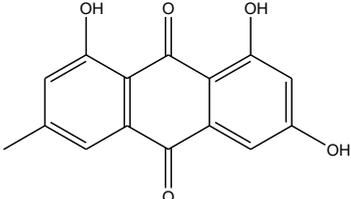
Usnea lichen has been extensively investigated due to its broad spectrum of pharmacological activities, which are primarily attributed to its secondary metabolites, particularly usnic acid, depsides, and depsidones. One of the most frequently reported activities is its antimicrobial effect, especially against Gram-positive bacteria such as *Staphylococcus aureus*, *Streptococcus* spp., and *Bacillus* spp. The mechanism of action of usnic acid has been reported to involve disruption of cell membrane function, inhibition of nucleic acid synthesis, and interference with cellular energy production. In addition, antifungal activity against *Candida albicans* and several dermatophyte species has been demonstrated, highlighting its potential for development as a natural product-based topical antimicrobial agent (Maulidiyah et al., 2022; Li et al., 2025).

Usnea also exhibits significant antioxidant and anti-inflammatory activities. The phenolic compounds present in *Usnea* function as free radical scavengers through proton or electron donation mechanisms, thereby reducing oxidative stress associated with various degenerative diseases. The anti-inflammatory activity of *Usnea* extracts has been linked to the inhibition of inflammatory mediators, including prostaglandins, nitric oxide (NO), and pro-inflammatory cytokines. These effects are generally associated with modulation of cellular signaling pathways, such as inhibition of cyclooxygenase (COX) enzymes and downregulation of transcription factors involved in inflammatory responses (Maulidiyah et al., 2021; Kocakaya et al., 2024).

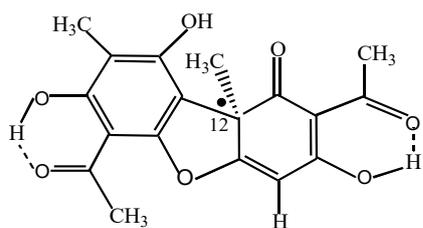
Furthermore, several *in vitro* and *in vivo* studies have demonstrated that bioactive compounds derived from *Usnea* exhibit cytotoxic and anticancer activities against various cancer cell lines. The proposed mechanisms include induction of apoptosis through activation of caspase pathways, increased production of reactive oxygen species (ROS), and disruption of mitochondrial function. The pharmacological activities of *Usnea* lichen metabolites reported in the literature are summarized and presented in Table 1. Although preliminary findings indicate promising therapeutic potential, toxicity concerns—particularly the risk of hepatotoxicity at high doses—remain a major challenge in its development. Therefore, further studies focusing on safety evaluation, extract standardization, and advanced drug delivery

systems are required to optimize the utilization of *Usnea* as a potential pharmaceutical raw material (Popovici et al., 2021).

Table 1. The pharmacological activities of *Usnea* lichen metabolites

Secondary Metabolites	<i>Usnea</i> Species	Pharmacological Activity	Ref.
 <p>Thamnic acid</p>	<i>Usnea florida</i>	Antibacterial	(Dieu et al., 2020)
 <p>Evernic acid</p>	<i>Usnea florida</i>	Antibacterial	(Dieu et al., 2020)
 <p>Barbatic acid</p>	<i>Usnea longissima</i> ; <i>Usnea lethariiformis</i>	Cytotoxic activity; Antibacterial	(Reddy et al., 2019) ; Piñeiro et al., 2025)
 <p>Stictic acid</p>	<i>Usnea ceratina</i> Arch	Cytotoxic activity	(Bui et al., 2022)
	<i>Usnea</i>	Cytotoxic activity	(Baczewska et al., 2024)

Emodin



Usnic acid

Usnea
aurantiaco-atra;

Usnea
longissima

Cytotoxic and
antioxidant;
antimicrobial and
cytotoxic activity

(Vega-Bello
et al., 2023) ;
Maulidiyah
et al., 2021)

3.4 Toxicology and Development Challenges

Toxicological aspects represent a critical consideration in the development of *Usnea* lichen as a pharmaceutical raw material. Although numerous studies have demonstrated its promising pharmacological potential, several reports indicate potential toxicity risks, particularly associated with usnic acid as the principal bioactive compound. Preclinical studies and case reports suggest that high doses or prolonged use of usnic acid may lead to hepatotoxicity, which is presumed to be related to mitochondrial dysfunction and increased oxidative stress in hepatic cells. Moreover, interindividual variability in biological responses and the limited availability of well-controlled clinical trials pose significant challenges in establishing a comprehensive safety profile. Therefore, thorough evaluations of acute, subchronic, and chronic toxicity are essential to determine safe dosage limits and its therapeutic index (Jha et al., 2017).

Beyond safety concerns, the development of *Usnea* as a pharmaceutical raw material also faces challenges related to raw material standardization, variability in metabolite content due to environmental factors, and sustainability of natural resources. The concentration of bioactive compounds may vary depending on species, geographical origin, altitude, and ecological conditions, thereby necessitating stringent quality control measures and extract standardization. Additionally, the relatively slow growth rate of *Usnea* raises sustainability concerns if large-scale exploitation is undertaken. Other challenges include improving the bioavailability of active compounds, developing appropriate drug delivery systems, and meeting regulatory requirements for safety and efficacy prior to clinical application. Through an integrated multidisciplinary approach, these challenges may be addressed to support the development of *Usnea* as a safe and effective pharmaceutical candidate (Alum et al., 2025).

Conclusions

This review emphasizes the considerable potential of *Usnea* lichen as a valuable source of bioactive secondary metabolites with promising applications in pharmaceutical development. Phytochemical studies have consistently demonstrated that *Usnea* species are rich in polyketide-derived compounds, particularly usnic acid, depsides, and depsidones, which exhibit structurally diverse phenolic frameworks. These compounds contribute significantly to a broad spectrum of pharmacological activities, including antimicrobial, antioxidant, anti-inflammatory, and anticancer effects. The growing body of evidence highlights a strong correlation between chemical composition and biological activity, underscoring the importance of comprehensive phytochemical characterization to support the development of natural product-based pharmaceutical raw materials.

Despite these promising findings, several challenges remain in translating *Usnea*-derived compounds into clinically applicable products. Safety concerns, especially hepatotoxicity associated with high doses of usnic acid, necessitate rigorous toxicological evaluations and careful dose optimization. In addition, issues related to standardization, variability in metabolite content due to environmental factors, sustainability of natural resources, and regulatory requirements must be systematically addressed. Future research focusing on structure–activity relationships, advanced formulation strategies to enhance bioavailability, and well-designed preclinical and clinical studies will be essential to fully realize the therapeutic and industrial potential of *Usnea* as a sustainable pharmaceutical resource.

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