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Review article

Exploring the antioxidant and protective effects of usnic acid: Opportunities and challenges

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Abstract

Lichens are symbiotic organisms that produce a variety of secondary metabolites, including the well-known usnic acid ($C_{18}H_{16}O_7$), which has garnered attention for its diverse biological activities and potential applications. Usnic acid, primarily found in lichen species such as *Usnea* and *Cladonia*, is a yellowish-green compound with notable antimicrobial, antiviral, and anti-inflammatory properties. Its antioxidant activity is particularly significant, with the ability to neutralize free radicals, inhibit lipid peroxidation, and stabilize cell membranes. Usnic acid, a secondary metabolite found in various lichen species, is recognized for its potent antioxidant properties. Its structure, characterized by a dibenzofuran backbone and phenolic hydroxyl groups, allows it to neutralize free radicals and inhibit lipid peroxidation, protecting cells from oxidative stress. Usnic acid can also chelate metal ions like iron and copper, preventing them from catalyzing reactions that produce harmful reactive oxygen species. This antioxidant capacity is of interest in both pharmaceutical and cosmetic fields. Usnic acid's ability to reduce oxidative damage makes it a promising ingredient in sunscreens and anti-aging products, where it protects the skin from ultraviolet (UV) radiation and environmental pollutants. Additionally, its potential to modulate antioxidant enzymes like superoxide dismutase (SOD) and catalase may further enhance its protective effects against oxidative stress-related damage, including inflammation and cell aging. Usnic acid effectively neutralizes free radicals, and its ability to prevent lipid peroxidation is comparable to that of vitamin E. However, this may vary depending on specific conditions. Vitamin C is particularly potent against ROS types in aqueous environments, but its ability to directly prevent lipid peroxidation is more limited compared to vitamin E or usnic acid. However, the practical use of usnic acid is limited by its potential hepatotoxicity at high concentrations, particularly in systemic applications. Despite these challenges, usnic acid remains a valuable compound for ongoing research, especially for topical products aimed at combating oxidative stress and protecting against skin damage.

Keywords: *Antioxidant properties; free radicals; inflammation; lichens; oxidative stress; pharmaceutical applications; usnic acid*

1. Introduction

Lichens are fascinating organisms that result from a symbiotic relationship between fungi and either algae or cyanobacteria. They are unique because they are not just one organism, but a combination of two or sometimes three different types of organisms living together (Morillas et al., 2022). Lichens consist of a fungal component (called the mycobiont) and a photosynthetic partner, either algae or cyanobacteria (called the photobiont). The fungus provides structure and protection, while the algae or cyanobacteria produce food through photosynthesis (Honegger, 2009). There are three main types based on their growth forms. Crustose lichens form flat, crust-like structures that are tightly attached to the surface. Foliose lichens are leaf-like lichens that have a flat, leafy appearance and are attached to the surface loosely. Fruticose lichens have a bushy or hair-like appearance and are often three-dimensional, standing out from the surface they grow on

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(Armstrong and Bradwell, 2010; Grube, 2024).

Lichens can grow in a wide variety of environments, from tree bark and rocks to extreme locations like deserts and the Arctic. They are very resilient and can survive in harsh conditions where many other organisms cannot. Lichens play several important roles in ecosystems. They help break down rocks into soil, provide food for some animals, and are indicators of air quality since they are sensitive to pollution (Asplund and Wardle, 2017; Toksoz, 2023). Lichens grow slowly, often just a few millimeters per year, but they can live for a long time, sometimes hundreds or even thousands of years. Lichens reproduce in two main ways: by producing spores (from the fungal part) or by fragmenting and dispersing pieces that contain both the fungal and photosynthetic partners (Garrido-Benavent and Pérez-Ortega, 2017).

Lichens produce a wide range of secondary metabolites, many of which are unique to them. These metabolites serve various functions, including protection against environmental stressors, herbivores, and microbial infections (Yildirim et al., 2012a). Some of these compounds are also valuable in pharmaceutical and industrial applications (Yildirim et al., 2012b; Emsen et al., 2013; Gokalsin et al., 2020). Lichen metabolites can be broadly classified into two categories. Primary metabolites are essential for the growth and survival of the lichen and include basic compounds like carbohydrates, proteins, and lipids. Secondary metabolites are not directly involved in growth but play important ecological roles. The majority of lichen metabolites fall into this category and include various unique compounds (Boustie and Grube, 2005). Lichens often grow in exposed environments where they receive high levels of sunlight. Metabolites and certain phenolic compounds help absorb UV light and protect the lichen's cells from damage. Lichen metabolites have strong antimicrobial properties, helping lichens fend off bacteria, fungi, and viruses (Shah et al., 2024). Some lichen compounds are toxic or unpalatable to herbivores, providing protection from being eaten. Some lichens release chemicals into the environment that inhibit the growth of other plants or organisms nearby, allowing them to reduce competition for resources (Yildirim et al., 2012b; Emsen et al., 2015; 2016; Bhagarathi et al., 2023).

Many lichen metabolites are being studied for their potential therapeutic effects. They have shown promise in treating infections, inflammation, and even cancer (Aslan Engin et al., 2023). Some lichen compounds are used in skincare products for their antioxidant and anti-inflammatory properties (Turkez et al., 2014; Emsen et al., 2017). Historically, some lichen metabolites were used as natural dyes, especially in traditional textile industries (Rather et al., 2018).

The primary aim of our study is to explore the unique biology, ecological roles, and chemical properties of lichens, emphasizing their symbiotic structure, environmental resilience, and the significance of their metabolites in ecological, pharmaceutical, and industrial applications.

2. Main classes of lichen secondary metabolites

Many lichen species produce phenolic acids, which provide protection against UV radiation and oxidative stress (Xu et al., 2016; Furmanek et al., 2024). Depsides and depsidones are large groups of compounds, such as atranorin and gyrophoric acid, known for t heir antioxidant and antimicrobial properties (Ureña-Vacas et al., 2023). The most abundant and structurally diverse class of lichen compounds are polyketides. Many of these have antibiotic, antiviral, and anti-inflammatory properties. Usnic acid inside polyketides ($C_{18}H_{16}O_7$) is one of the most studied lichen metabolites, with strong antimicrobial, antiviral, and anti-inflammatory activities (Piska et al., 2018; Antonenko et al., 2019; Bangalore et al., 2019; Tripathi et al., 2021).

3. General information about usnic acid

Usnic acid is one of the most well-known and widely studied secondary metabolites produced by lichens. It is a yellowish-green compound that has attracted attention due to its diverse biological activities and potential applications in various fields, particularly in pharmaceuticals and cosmetics. Usnic acid ($C_{18}H_{16}O_7$) is a dibenzofuran derivative with two phenolic hydroxyl groups (Nie et al., 2024). This structure contributes to its strong antioxidant and antimicrobial properties. Usnic acid exists in two enantiomeric forms, (+)-usnic acid and (−)-usnic acid. Both forms are commonly found in lichens but may have different biological activities. (Cocchietto et al., 2002; Luzina and Salakhutdinov, 2018).

Usnic acid is found in a variety of lichen species, including genera such as *Usnea*, *Cladonia*, *Evernia*, *Lecanora*, and *Ramalina* (Elkhateeb et al., 2022). It serves as a photoprotective compound in these lichens, helping them survive in exposed and extreme environments. The content of usnic acid can vary significantly among species and environmental conditions. For example, lichens growing in high-altitude or high-UV environments often have higher concentrations of this compound (Rojas et al., 2016; Salian et al., 2021).

Usnic acid possesses a range of biological activities, making it an attractive compound for medical and cosmetic research. Usnic acid has potent antibacterial and antifungal properties. It is particularly effective against Gram-positive bacteria like *Staphylococcus aureus* and *Bacillus subtilis*. It also shows activity against several fungi and yeasts, including *Candida* species (Cansaran et al., 2006; Bangalore et al., 2019).

Preliminary studies suggest that usnic acid may have antiviral effects, particularly against some viruses like the Herpes Simplex Virus (HSV). Usnic acid has demonstrated anti-inflammatory properties, making it a candidate for treating skin conditions and inflammatory diseases (Hassan et al., 2019). Usnic acid has shown cytotoxic effects against certain cancer cell lines, including breast cancer, melanoma, and leukemia cells. Its ability to induce apoptosis (programmed cell death) in cancer cells is of particular interest in oncology research (Galanty et al., 2017; Emsen et al., 2018; Ozben and Cansaran-Duman, 2020).

4. Antioxidant properties of usnic acid

Usnic acid exhibits significant antioxidant activity, which makes it a compound of interest in both pharmaceutical and cosmetic fields (Luzina and Salakhutdinov, 2018). Its antioxidant properties stem from its ability to neutralize free radicals, prevent oxidative damage to cells, and inhibit lipid peroxidation. These actions are vital for protecting biological systems from oxidative stress, which is implicated in aging, cancer, and various chronic diseases (Martin-Cordero et al., 2012).

Usnic acid's antioxidant activities can be attributed to several mechanisms (Araújo et al., 2015). Usnic acid has a structure rich in phenolic groups, which allows it to donate hydrogen atoms or electrons to free radicals, neutralizing their reactivity. This helps in preventing cellular damage caused by reactive oxygen species (ROS) such as superoxide anions, hydroxyl radicals, and peroxyl radicals (Ingólfsdóttir, 2002; Araújo et al., 2015).

Lipid peroxidation refers to the oxidative degradation of lipids, particularly in cell membranes, which can lead to cell damage or death (Gaschler and Stockwell, 2017; Recknagel et al., 2020). Usnic acid helps inhibit this process by neutralizing the free radicals that initiate and propagate lipid peroxidation, protecting cellular membranes (Kwong and Wang, 2020; Gulcin and Alwasel, 2023).

Usnic acid may chelate metal ions like iron and copper, which catalyze the formation of free radicals through Fenton reactions (Kováčik et al., 2018). By binding these metal ions, usnic acid reduces the generation of free radicals. Some studies suggest that usnic acid may influence the activity of endogenous antioxidant enzymes such as SOD, catalase, and glutathione peroxidase. These enzymes play critical roles in detoxifying reactive oxygen species within the body (White et al., 2014; Fernández-Moriano et al., 2017). SOD converts superoxide radicals into less reactive hydrogen peroxide (H_2O_2).

Usnic acid, with its phenolic hydroxyl groups, may directly scavenge superoxide radicals or inhibit the generation of ROS. This could reduce the burden on SOD by lowering the superoxide levels in the cellular environment (Mittal et al., 2021). Catalase breaks down hydrogen peroxide into water and oxygen. By scavenging ROS and reducing oxidative stress, usnic acid may indirectly decrease H_2O_2 levels, affecting catalase activity. Alternatively, it may assist catalase by preventing the accumulation of toxic hydrogen peroxide (Beckett et al., 2021). GPx neutralizes lipid peroxides and hydrogen peroxide using glutathione. Usnic acid might reduce lipid peroxidation, thereby lowering the substrate levels for GPx. However, its direct interaction with the glutathione system remains unclear (Fernández-Moriano et al., 2017).

5. Antioxidant capacity measurement

Various experimental assays are used to measure the antioxidant capacity of usnic acid. Some of the most common methods include: 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay measures the ability of usnic acid to scavenge the DPPH radical (Popovici et al., 2018). Usnic acid shows significant activity in reducing DPPH radicals, reflecting its hydrogen-donating ability. Similar to the DPPH assay, this method uses 2,2′-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) radicals to evaluate antioxidant potential. Usnic acid can effectively neutralize ABTS radicals, showing its capacity to quench reactive radicals (Verma et al., 2012; Cakmak and Gulcin, 2019).

Ferric reducing antioxidant power (FRAP) method assesses the ability of antioxidants to reduce ferric ions (Fe^{3+}) to ferrous ions (Fe^{2+}) (Ananthi et al., 2015). Usnic acid demonstrates reducing power in this assay, indicating its electron-donating capacity. Lipid peroxidation inhibition assay measures the ability of usnic acid to prevent the oxidation of lipids. It shows strong inhibition of lipid peroxidation in various biological and artificial membranes, which is crucial for maintaining cell integrity (Suwalsky et al., 2015).

The antioxidant activity of usnic acid is closely related to its chemical structure, particularly its phenolic hydroxyl groups. These groups are capable of donating hydrogen atoms to neutralize free radicals (Kocer et al., 2014). The dibenzofuran backbone of usnic acid enhances its stability after donating hydrogen atoms, making it an effective antioxidant. The presence of hydroxyl groups in the structure allows usnic acid to act as a hydrogen donor, neutralizing radicals (Millot et al., 2016). The dibenzofuran core structure contributes to the delocalization of electrons, which helps stabilize the radical form of usnic acid after it donates a hydrogen atom (Yousuf and Choudhary, 2014).

Usnic acid has been compared to other well-known antioxidants such as vitamin C, vitamin E, and synthetic antioxidants like butylated hydroxytoluene. While its antioxidant capacity is notable, its activity may vary depending on the experimental conditions and the specific assay used (Balanco et al., 2019; Ayusman et al., 2020).

In some studies, usnic acid has shown antioxidant activity comparable to that of vitamin C and vitamin E, particularly in lipid peroxidation inhibition (Thakur et al., 2023). However, its radical scavenging ability may be lower than these vitamins in some assays. Nonetheless, the unique combination of antimicrobial and antioxidant properties makes usnic acid an attractive compound for skin care, where oxidative stress and microbial infections are common issues (Shcherbakova et al., 2021; Kocovic et al., 2022).

6. Biological and pharmaceutical significance

The antioxidant properties of usnic acid have significant implications across various fields of study. Due to its ability to neutralize free radicals and prevent oxidative damage, usnic acid is a potential ingredient in sunscreens and anti-aging products. Its antioxidant activity helps protect the skin from damage caused by UV radiation and environmental pollutants (Galanty et al., 2021).

Oxidative stress is closely linked to inflammation. By reducing oxidative damage, usnic acid may also reduce inflammatory responses in tissues, contributing to its potential as an anti-inflammatory agent (Su et al., 2014). Oxidative stress plays a key role in neurodegenerative diseases such as Alzheimer's and Parkinson's. Some studies have suggested that usnic acid's antioxidant properties could be harnessed to protect neurons from oxidative damage (Fernández-Moriano et al., 2017). Since oxidative stress is involved in cancer progression, the antioxidant properties of usnic acid have sparked interest in its potential role in cancer prevention or treatment. Its ability to induce apoptosis in cancer cells, combined with its antioxidant activity, makes it a compound of interest for future research in oncology (Kumar et al., 2020; Azhamuthu et al., 2024).

While usnic acid has potent antioxidant properties, there are some challenges and concerns regarding its use. Usnic acid can be hepatotoxic at high concentrations, especially when taken orally (Gao et al., 2024). This limits its use in systemic antioxidant therapies and highlights the need for careful dosing in topical applications. Animal studies have demonstrated that high doses of usnic acid can induce liver damage, characterized by elevated liver enzymes (ALT and AST), oxidative stress, and histopathological changes such as hepatocyte necrosis and inflammation (Kwong and Wang, 2020). Cases of liver toxicity in humans have been reported, particularly in individuals using dietary supplements containing usnic acid for weight loss. Symptoms include jaundice, fatigue, and in severe cases, acute liver failure requiring transplantation (Sanchez et al., 2006). These findings underscore the need for stricter regulations and comprehensive safety evaluations of usnic acid-containing products. The proposed mechanism involves mitochondrial dysfunction, where usnic acid disrupts oxidative phosphorylation, leading to excessive ROS generation and ATP depletion. Usnic acid's stability can be affected by environmental factors such as light and temperature, which may reduce its effectiveness in some formulations. Encapsulation techniques or combining it with stabilizing agents might be necessary to maintain its antioxidant efficacy in cosmetic and pharmaceutical products (Brugnoli et al., 2024; Fadhila et al., 2024).

At higher concentrations, usnic acid can exhibit pro-oxidant behavior, generating excessive ROS and exacerbating oxidative stress. This paradoxical effect may contribute to cellular damage, including lipid peroxidation, protein modification, and DNA fragmentation (Popovici et al., 2021). High doses of usnic acid can impair mitochondrial function by disrupting oxidative phosphorylation. This results in ATP depletion, increased ROS production, and apoptosis or necrosis, particularly in hepatocytes, leading to liver toxicity (Croce et al., 2022). Systematic investigations into the concentration-dependent effects of usnic acid in different cell types and animal models are essential. These studies should focus on defining the thresholds for beneficial vs. harmful effects (Araújo et al., 2015).

Usnic acid is used in products designed to combat oxidative stress and protect the skin from premature aging. Its antioxidant properties are particularly beneficial in sunscreens, moisturizers, and anti-aging creams (Ramaraj and Narayan, 2024). While not widely used yet due to safety concerns, usnic acid is being studied for its antioxidant potential in treating conditions related to oxidative stress, such as chronic inflammation and neurodegenerative diseases (Cazarin et al., 2021; Al Rihani et al., 2024).

7. Anticancer properties and cosmetic usage

Usnic acid inhibits the proliferation of cancer cells and induces apoptosis (programmed cell death), which is a key mechanism in preventing cancer cell survival. Usnic acid has been shown to trigger apoptosis in cancer cells by increasing cellular stress and DNA damage (Singh et al., 2013). This process leads to cancer cell death. Usnic acid facilitates apoptosis by altering the expression of pro-apoptotic and anti-apoptotic proteins, promoting the death of cancer cells. Usnic acid can affect the expression of proteins from the Bcl-2 family, such as Bcl-2 and Bax, which regulate cell death. By altering the balance of these proteins, usnic acid promotes the apoptosis of cancer cells (Erdogan et al., 2023).

Usnic acid influences the regulation of the cell cycle, which is critical for cancer cell division and proliferation. It inhibits the progression of cancer cells through the cell cycle, thus preventing cell division. Usnic acid can arrest cancer cells in the G1 phase of the cell cycle, preventing them from proceeding to DNA replication and cell division. This effectively halts cancer cell growth. Usnic acid may reduce the expression of key proteins involved in cell cycle regulation, such as Cyclin D1 and Cyclin-Dependent Kinases (CDK). This disruption inhibits cancer cell growth and proliferation (Gimła and Herman-Antosiewicz, 2024).

Another crucial anticancer property of usnic acid is its ability to inhibit metastasis—the spread of cancer to other parts of the body. Usnic acid can inhibit Matrix Metalloproteinases (MMPs), enzymes that play a key role in the invasion of cancer cells into surrounding tissues. By blocking MMP activity, usnic acid helps prevent cancer cells from spreading and metastasizing. Usnic acid reduces the ability of cancer cells to invade adjacent tissues, a crucial step in metastasis. This anti-invasive effect can limit the spread of cancer (Wu et al., 2022).

Usnic acid also exhibits anti-inflammatory and antioxidant properties, which contribute to its anticancer activity. Chronic inflammation is often associated with cancer progression. Usnic acid can reduce the production of pro-inflammatory cytokines such as TNF-α and IL-6, which are involved in cancer development. By modulating these inflammatory signals, usnic acid can limit tumor progression (Paździora et al., 2023). Usnic acid can exert influence on genetic and epigenetic processes, which are crucial in cancer development. It has been shown to help repair DNA damage in cancer cells. DNA damage is a hallmark of cancer cell proliferation. By promoting DNA repair mechanisms, usnic acid may help to reduce the likelihood of mutations that drive cancer progression (Shukla et al., 2023). Usnic acid may affect DNA methylation and histone modification processes, which can regulate gene expression. These epigenetic changes can result in the silencing of oncogenes and activation of tumor suppressor genes, ultimately limiting cancer cell growth (Reddy et al., 2016). Usnic acid may also interact with hormonal and neurogenic pathways in certain types of cancer. Some studies suggest that usnic acid can influence estrogen receptors, which are important in the growth of estrogen-related cancers (e.g., breast cancer). This interaction could be beneficial in managing these types of cancers (Unver et al., 2019).

Usnic acid is has been studied for its various potential applications in cosmetics due to its beneficial properties for skin care. Usnic acid has strong antimicrobial properties, making it useful in treating skin conditions caused by bacteria and fungi. Due to its antibacterial properties, usnic acid can help reduce acne by inhibiting the growth of Propionibacterium acnes, the bacteria responsible for acne breakouts. Usnic acid can help in treating fungal skin infections, such as ringworm or athlete's foot, by preventing the growth of harmful fungi (Sepahvand et al., 2021). By reducing oxidative stress, usnic acid helps protect the skin from premature aging, fine lines, and wrinkles. Its antioxidant effects can promote skin regeneration and improve the overall appearance of the skin (Ramakrishnan et al., 2020).

8. Usnic Acid's safety profile and potential toxicity

Usnic acid has been most notably associated with hepatotoxicity (liver damage) when consumed orally, particularly in dietary supplements marketed for weight loss, detoxification, or fat burning. Several cases of liver toxicity have been reported, leading to liver failure and, in some cases, requiring liver transplantation (Gao et al., 2024). The mechanism behind this toxicity is believed to involve mitochondrial dysfunction, as usnic acid can inhibit mitochondrial respiration, leading to oxidative stress and cellular damage (Demir et al., 2025). There have been documented cases where individuals experienced symptoms such as fatigue, jaundice, abdominal pain, and elevated liver enzymes after taking products containing usnic acid. While such severe cases are rare, they underscore the potential risks associated with prolonged or excessive use (Pandit et al., 2024).

Although studies on the bioaccumulation of usnic acid are limited, it is known that topical products containing usnic acid can lead to gradual accumulation in the skin. This may increase the likelihood of sensitization or allergic reactions with prolonged use, especially if the skin is exposed to usnic acid regularly or in large amounts. This is why proper usage and adherence to recommended guidelines are important (de Souza et al., 2024).

9. Conclusion

In conclusion, usnic acid stands out as a remarkable bioactive compound produced by lichens, offering immense potential across diverse fields such as dermatology, anti-aging treatments, neuroprotection, and cancer therapies. Its potent antioxidant properties, along with its antimicrobial and anti-inflammatory activities, make it a versatile agent with significant implications for both pharmaceutical and cosmetic applications. However, the practical application of usnic acid is not without challenges. Notably, issues such as its toxicity, formulation stability, and the need for optimized delivery systems represent critical hurdles that must be addressed to fully harness its potential.

This review underscores the importance of bridging the gaps in current knowledge regarding usnic acid's mechanisms of action and safety profile. While its efficacy in addressing oxidative stress and microbial infections is well-documented, further investigations are essential to ensure its safe and effective use. For instance, studies focusing on dose optimization, long-term safety evaluations, and innovative formulation approaches could pave the way for its broader adoption in clinical and commercial settings. Additionally, the exploration of usnic acid's role in combating oxidative stress-related conditions highlights its relevance in addressing pressing health challenges. By mitigating cellular damage caused by free radicals, usnic acid holds promise in advancing therapeutic strategies for chronic inflammatory diseases, skin health, and neurodegenerative disorders. Similarly, its application in cosmetic products, particularly in anti-aging and skin protection formulations, aligns with the growing demand for natural and effective solutions in the industry.

The review also emphasizes the dual nature of usnic acid's impact, balancing its substantial benefits with the necessity to manage potential risks. Addressing its toxicity and enhancing formulation stability are pivotal for realizing its full potential. Future research should prioritize innovative delivery systems, such as encapsulation techniques, to minimize adverse effects and improve bioavailability.

In summary, usnic acid represents a compelling avenue for future exploration, with promising applications that extend beyond its current scope. By addressing key challenges through targeted research and development, its potential can be maximized, contributing to advancements in medicine and industry. This review provides a foundation for guiding future studies and underscores the need for interdisciplinary collaboration to unlock the full spectrum of benefits that usnic acid offers.

Conflict of interest: The author declares that she has no conflict of interests.

Informed consent: The author declares that this manuscript did not involve human or animal participants and informed consent was not collected.

References

Al Rihani, S. B., Elfakhri, K. H., Ebrahim, H. Y., Al-Ghraiybah, N. F., Alkhalifa, A. E., El Sayed, K. A., & Kaddoumi, A. (2024). The usnic acid analogue 4-FPBUA enhances the blood-brain barrier function and ınduces autophagy in Alzheimer's disease mouse models. *ACS Chemical Neuroscience*, *15*(17), 3152-3167.

Ananthi, R., Tinabaye, A., & Selvaraj, G. (2015). Antioxidant study of usnic acid and its derivative usnic acid diacetate. *International Journal of Research in Engineering and Technology*, *4*(2), 356-366.

Antonenko, Y. N., Khailova, L. S., Rokitskaya, T. I., Nosikova, E. S., Nazarov, P. A., Luzina, O. A., Salakhutdinov, N. F., & Kotova, E. A. (2019). Mechanism of action of an old antibiotic revisited: Role of calcium ions in protonophoric activity of usnic acid. *Biochimica et Biophysica Acta - Bioenergetics*, *1860*(4), 310-316.

Araújo, A. A. S., de Melo, M. G. D., Rabelo, T. K., Nunes, P. S., Santos, S. L., Serafini, M. R., Santos, M. R. V., Quintans-Júnior, L. J., & Gelain, D. P. (2015). Review of the biological properties and toxicity of usnic acid. *Natural Product Research*, *29*(23), 2167-2180.

Armstrong, R., & Bradwell, T. (2010). Growth of crustose lichens: a review. *Geografiska Annaler: Series A, Physical Geography*, *92*(1), 3-17.

Aslan Engin, T., Emsen, B., Yilmaz Ozturk, R., Cakir Koc, R., Inan, B., & Ozcimen, D. (2023). Cytotoxicity of *Usnea longissima* Ach. extracts and its secondary metabolite, usnic acid on different cells. *Anatolian Journal of Botany*, *7*(2), 140-145.

Asplund, J., & Wardle, D. A. (2017). How lichens impact on terrestrial community and ecosystem properties. *Biological Reviews*, *92*(3), 1720-1738.

Ayusman, S., Duraivadivel, P., Gowtham, H. G., Sharma, S., & Hariprasad, P. (2020). Bioactive constituents, vitamin analysis, antioxidant capacity and α-glucosidase inhibition of *Canna indica* L. rhizome extracts. *Food Bioscience*, *35*, 100544.

Azhamuthu, T., Kathiresan, S., Senkuttuvan, I., Asath, N. A. A., Ravichandran, P., & Vasu, R. (2024). Usnic acid alleviates inflammatory responses and induces apoptotic signaling through inhibiting NF-κB expressions in human oral carcinoma cells. *Cell Biochemistry and Function*, *42*(4), e4074.

Balanco, J. M. F., Sussmann, R. A. C., Verdaguer, I. B., Gabriel, H. B., Kimura, E. A., & Katzin, A. M. (2019). Tocopherol biosynthesis in *Leishmania* (L.) amazonensis promastigotes. *FEBS Open Bio*, *9*(4), 743-754.

Bangalore, P. K., Vagolu, S. K., Bollikanda, R. K., Veeragoni, D. K., Choudante, P. C., Misra, S., ... & Kantevari, S. (2019). Usnic acid enaminone-coupled 1, 2, 3-triazoles as antibacterial and antitubercular agents. *Journal of Natural Products*, *83*(1), 26-35.

Beckett, R. P., Minibayeva, F., Solhaug, K. A., & Roach, T. (2021). Photoprotection in lichens: adaptations of photobionts to high light. *The Lichenologist*, *53*(1), 21-33.

Bhagarathi, L. K., DaSilva, P. N. B., Subramanian, G., Maharaj, G., Kalika-Singh, S., Pestano, F., Phillips-Henry, Z., & Cossiah, C. (2023). An integrative review of the biology and chemistry of lichens and their ecological, ethnopharmacological, pharmaceutical and therapeutic potential. *GSC Biological and Pharmaceutical Sciences*, *23*(3), 92-119.

Boustie, J., & Grube, M. (2005). Lichens-a promising source of bioactive secondary metabolites. *Plant Genetic Resources*, *3*(2), 273-287.

Brugnoli, B., Perna, G., Alfano, S., Piozzi, A., Galantini, L., Axioti, E., Taresco, V., Mariano, A., Scotto d'Abusco, A., & Vecchio Ciprioti, S. (2024). Nanostructured poly-l-lactide and polyglycerol adipate carriers for the encapsulation of usnic acid: a promising approach for hepatoprotection. *Polymers*, *16*(3), 427.

Cakmak, K. C., & Gulcin, I. (2019). Anticholinergic and antioxidant activities of usnic acid-an activity-structure insight. *Toxicology Reports*, *6*, 1273-1280.

Cansaran, D., Kahya, D., Yurdakulol, E., & Atakol, O. (2006). Identification and quantitation of usnic acid from the lichen *Usnea* species of Anatolia and antimicrobial activity. *Zeitschrift Für Naturforschung C*, *61*(11-12), 773-776.

Cazarin, C. A., Dalmagro, A. P., Gonçalves, A. E., Boeing, T., da Silva, L. M., Corrêa, R., Klein-Júnior, L. C., Pinto, B. C., Lorenzett, T. S., & da Costa Sobrinho, T. U. (2021). Usnic acid enantiomers restore cognitive deficits and neurochemical alterations induced by Aβ1-42 in mice. *Behavioural Brain Research*, *397*, 112945.

Cocchietto, M., Skert, N., Nimis, P., & Sava, G. (2002). A review on usnic acid, an interesting natural compound. *Naturwissenschaften*, *89*, 137-146.

Croce, N., Pitaro, M., Gallo, V., & Antonini, G. (2022). Toxicity of usnic acid: A narrative review. *Journal of Toxicology*, *2022*(1), 8244340.

de Souza, J. B., de Lacerda Coriolano, D., dos Santos Silva, R. C., da Costa Júnior, S. D., de Almeida Campos, L. A., Cavalcanti, I. D. L., ... & Cavalcanti, I. M. F. (2024). Ceftazidime and Usnic acid encapsulated in chitosan-coated liposomes for oral administration against colorectal cancer-inducing Escherichia coli. *Pharmaceuticals*, *17*(6), 802.

Demir, S., Alemdar, N. T., Yulug, E., Demir, E. A., Durmus, T. B., Mentese, A., & Aliyazicioglu, Y. (2025). Usnic acid suppresses inflammation and endoplasmic reticulum stress in a methotrexate-induced pulmonary toxicity model via modulating Nrf2 pathway. *South African Journal of Botany*, *177*, 572-578.

Elkhateeb, W. A., El-Ghwas, D. E., & Daba, G. M. (2022). Lichens uses surprising uses of lichens that improve human life. *Journal of Biomedical Research and Environmental Sciences*, *3*(2), 189-194.

Emsen, B., Aslan, A., Togar, B., & Turkez, H. (2016). In vitro antitumor activities of the lichen compounds olivetoric, physodic and psoromic acid in rat neuron and glioblastoma cells. *Pharmaceutical Biology*, *54*(9), 1748-1762.

Emsen, B., Aslan, A., Turkez, H., Taghizadehghalehjoughi, A., & Kaya, A. (2018). The anti-cancer efficacies of diffractaic, lobaric, and usnic acid: in vitro inhibition of glioma. *Journal of Cancer Research and Therapeutics*, *14*(5), 941-951.

Emsen, B., Aslan, A., Yildirim, E., & Ercisli, S. (2013). Toxicity effects of some lichen species extracts against the Colorado potato beetle, *Leptinotarsa decemlineata* Say (Coleoptera: Chrysomelidae). *Egyptian Journal of Biological Pest Control*, *23*(2), 193-199.

Emsen, B., Turkez, H., Togar, B., & Aslan, A. (2017). Evaluation of antioxidant and cytotoxic effects of olivetoric and physodic acid in cultured human amnion fibroblasts. *Human and Experimental Toxicology*, *36*(4), 376-385.

Emsen, B., Yildirim, E., & Aslan, A. (2015). Insecticidal activities of extracts of three lichen species on *Sitophilus granarius* (L.) (Coleoptera: Curculionidae). *Plant Protection Science*, *51*(3), 156-161.

Erdogan, O., Abas, B. I., & Cevik, O. (2023). Usnic Acid Exerts Antiproliferative and Apoptotic Effects by Suppressing NF-B p50 in DU145 Cells. *European Journal of Biology*, *82*(2), 251-257.

Fadhila, M., Effendy, S., & Siregar, S. H. (2024). Inclusion complexation of usnic acid-hydroxypropyl-β-cyclodextrin: physicochemical characterization and dissolution rate studies. *Research Journal of Pharmacy and Technology*, *17*(5), 2206-2212.

Fernández-Moriano, C., Divakar, P. K., Crespo, A., & Gómez-Serranillos, M. P. (2017). Protective effects of lichen metabolites evernic and usnic acids against redox impairment-mediated cytotoxicity in central nervous system-like cells. *Food and Chemical Toxicology*, *105*, 262-277. https://doi.org/10.1016/j.fct.2017.04.030

Furmanek, Ł., Czarnota, P., Tekiela, A., Kapusta, I., & Seaward, M. R. D. (2024). A spectrophotometric analysis of extracted water-soluble phenolic metabolites of lichens. *Planta*, *260*(2), 40.

Galanty, A., Koczurkiewicz, P., Wnuk, D., Paw, M., Karnas, E., Podolak, I., Węgrzyn, M., Borusiewicz, M., Madeja, Z., Czyż, J., & Michalik, M. (2017). Usnic acid and atranorin exert selective cytostatic and anti-invasive effects on human prostate and melanoma cancer cells. *Toxicology In Vitro*, *40*, 161-169.

Galanty, A., Popiół, J., Paczkowska-Walendowska, M., Studzińska-Sroka, E., Paśko, P., Cielecka-Piontek, J., Pękala, E., & Podolak, I. (2021). (+)-Usnic acid as a promising candidate for a safe and stable topical photoprotective agent. *Molecules*, *26*(17), 5224.

Gao, X., Campasino, K., Yourick, M. R., Cao, Y., Yourick, J. J., & Sprando, R. L. (2024). Oxidative DNA damage contributes to usnic acid-induced toxicity in human induced pluripotent stem cell-derived hepatocytes. *Journal of Applied Toxicology*, *44*(9), 1329-1346.

Garrido-Benavent, I., & Pérez-Ortega, S. (2017). Past, present, and future research in bipolar lichen-forming fungi and their photobionts. *American Journal of Botany*, *104*(11), 1660-1674.

Gaschler, M. M., & Stockwell, B. R. (2017). Lipid peroxidation in cell death. *Biochemical and Biophysical Research Communications*, *482*(3), 419-425.

Gimła, M., & Herman-Antosiewicz, A. (2024). Multifaceted properties of usnic acid in disrupting cancer hallmarks. *Biomedicines*, *12*(10), 2199.

Gokalsin, B., Berber, D., Hur, J. S., & Sesal, N. C. (2020). Quorum sensing inhibition properties of lichen forming fungi extracts from Cetrelia species against *Pseudomonas aeruginosa*. *Frontiers in Life Sciences and Related Technologies*, *1*(1), 22-27.

Grube, M. (2024). Lichens. In *Fungal Associations* (pp. 145-179). Springer.

Gulcin, İ., & Alwasel, S. H. (2023). DPPH radical scavenging assay. *Processes*, *11*(8), 2248.

Hassan, S. T. S., Šudomová, M., Berchová-Bímová, K., Šmejkal, K., & Echeverría, J. (2019). Psoromic acid, a lichen-derived molecule, inhibits the replication of HSV-1 and HSV-2, and inactivates HSV-1 DNA polymerase: shedding light on antiherpetic properties. *Molecules*, *24*(16), 2912.

Honegger, R. (2009). Lichen-forming fungi and their photobionts. In *Plant Relationships* (pp. 307-333). Springer.

Ingólfsdóttir, K. (2002). Usnic acid. *Phytochemistry*, *61*(7), 729-736.

Kocer, S., Urus, S., Cakir, A., Gulluce, M., Dıgrak, M., Alan, Y., Aslan, A., Tumer, M., Karadayı, M., Kazaz, C., & Dal, H. (2014). The synthesis, characterization, antimicrobial and antimutagenic activities of hydroxyphenylimino ligands and their metal complexes of usnic acid isolated from *Usnea longissima*. *Dalton Transactions*, *43*(16), 6148-6164.

Kocovic, A., Jeremic, J., Bradic, J., Sovrlic, M., Tomovic, J., Vasiljevic, P., Andjic, M., Draginic, N., Grujovic, M., Mladenovic, K., Jakovljevic, V., & Manojlovic, N. (2022). Phytochemical analysis, antioxidant, antimicrobial, and cytotoxic activity of different extracts of *Xanthoparmelia stenophylla* lichen from Stara Planina, Serbia. *Plants*, *11*(13), 1624.

Kováčik, J., Dresler, S., Peterková, V., and Babula, P. (2018). Metal-induced oxidative stress in terrestrial macrolichens. *Chemosphere*, *203*, 402-409.

Kumar, K., Mishra, J. P. N., & Singh, R. P. (2020). Usnic acid induces apoptosis in human gastric cancer cells through ROS generation and DNA damage and causes up-regulation of DNA-PKcs and γ-H2A.X phosphorylation. *Chemico-Biological Interactions*, *315*, 108898.

Kwong, S. P., & Wang, C. (2020). Usnic acid-induced hepatotoxicity and cell death. *Environmental Toxicology and Pharmacology*, *80*, 103493.

Luzina, O. A., & Salakhutdinov, N. F. (2018). Usnic acid and its derivatives for pharmaceutical use: a patent review (2000-2017). *Expert Opinion on Therapeutic Patents*, *28*(6), 477-491.

Martin-Cordero, C., Jose Leon-Gonzalez, A., Manuel Calderon-Montano, J., Burgos-Moron, E., & Lopez-Lazaro, M. (2012). Pro-oxidant natural products as anticancer agents. *Current Drug Targets*, *13*(8), 1006-1028.

Millot, M., Dieu, A., & Tomasi, S. (2016). Dibenzofurans and derivatives from lichens and ascomycetes. *Natural Product Reports*, *33*(6), 801-811.

Mittal, S., Ashhar, M. U., Ahuja, A., Ali, J., & Baboota, S. (2021). Role of natural bioactives and their nanocarriers for overcoming oxidative stress induced cancer. *Current Medicinal Chemistry*, *28*(36), 7477-7512.

Morillas, L., Roales, J., Cruz, C., & Munzi, S. (2022). Lichen as multipartner symbiotic relationships. *Encyclopedia*, *2*(3), 1421-1431.

Nie, W. Z., Shen, Q. K., Quan, Z. S., Guo, H. Y., & Li, Y. M. (2024). Bioactivities and Structure-Activity Relationships of Usnic Acid Derivatives: A Review. *Mini Reviews in Medicinal Chemistry*, *24*(14), 1368-1384.

Ozben, R., & Cansaran-Duman, D. (2020). The expression profiles of apoptosis-related genes induced usnic acid in SK-BR-3 breast cancer cell. *Human and Experimental Toxicology*.

Pandit, S., Kim, M.-A., Jung, J.-E., Choi, H.-M., & Jeon, J.-G. (2024). Usnic acid brief exposure suppresses cariogenic properties and complexity of Streptococcus mutans biofilms. *Biofilm*, *8*, 100241.

Paździora, W., Podolak, I., Grudzińska, M., Paśko, P., Grabowska, K., & Galanty, A. (2023). Critical assessment of the anti-Inflammatory potential of usnic acid and its derivatives—A review. *Life*, *13*(4), 1046.

Piska, K., Galanty, A., Koczurkiewicz, P., Żmudzki, P., Potaczek, J., Podolak, I., & Pękala, E. (2018). Usnic acid reactive metabolites formation in human, rat, and mice microsomes. Implication for hepatotoxicity. *Food and Chemical Toxicology*, *120*, 112-118.

Popovici, V., Bucur, L., Popescu, A., Caraiane, A., & Badea, V. (2018). Determination of the content in usnic acid and polyphenols from the extracts of *Usnea barbata* L. and the evaluation of their antioxidant activity. *Farmacia*, *66*(2), 337-341.

Popovici, V., Matei, E., Cozaru, G. C., Aschie, M., Bucur, L., Rambu, D., Costache, T., Cucolea, I. E., Vochita, G., & Gherghel, D. (2021). Usnic acid and *Usnea barbata* (L.) FH wigg. dry extracts promote apoptosis and DNA damage in human blood cells through enhancing ROS levels. *Antioxidants*, *10*(8), 1171.

Ramakrishnan, V., Aiswarya, P. S., Pallavi, K., Husain, R. S. A., & Ahmed, S. S. S. J. (2020). Photoaging and anti-photoaging activity of compounds derived from marine origin. *Encyclopedia of Marine Biotechnology*, *3*, 1641-1657.

Ramaraj, J. A., & Narayan, S. (2024). Anti-aging strategies and topical delivery of biopolymer-based nanocarriers for skin cancer treatment. *Current Aging Science*, *17*(1), 31-48.

Rather, L. J., Jameel, S., Ganie, S. A., & Bhat, K. A. (2018). Lichen derived natural colorants: history, extraction, and applications. *Handbook of Renewable Materials for Coloration and Finishing*, *1*, 103-114.

Recknagel, R. O., Glende, E. A., & Britton, R. S. (2020). Free radical damage and lipid peroxidation. In *Hepatotoxicology* (pp. 401-436). CRC press.

Reddy, R. G., Veeraval, L., Maitra, S., Chollet-Krugler, M., Tomasi, S., Dévéhat, F. L. Le, Boustie, J., & Chakravarty, S. (2016). Lichen-derived compounds show potential for central nervous system therapeutics. *Phytomedicine*, *23*(12), 1527-1534.

Rojas, J., Londoño, C., & Ciro, Y. (2016). The health benefits of natural skin UVA photoprotective compounds found in botanical sources. *International Journal of Pharmacy and Pharmaceutical Sciences*, *8*(3), 13-23.

Salian, A., Dutta, S., & Mandal, S. (2021). A roadmap to UV-protective natural resources: classification, characteristics, and applications. *Materials Chemistry Frontiers*, *5*(21), 7696-7723.

Sanchez, W., Maple, J. T., Burgart, L. J., & Kamath, P. S. (2006). Severe hepatotoxicity associated with use of a dietary supplement containing usnic acid. *Mayo Clinic Proceedings*, *81*(4), 541-544.

Sepahvand, A., Studzińska-Sroka, E., Ramak, P., & Karimian, V. (2021). Usnea sp.: Antimicrobial potential, bioactive compounds, ethnopharmacological uses and other pharmacological properties; a review article. *Journal of Ethnopharmacology*, *268*, 113656.

Shah, A. A., Badshah, L., Muhammad, M., Basit, A., Ullah, I., Mohamed, H. I., & Khan, A. (2024). Secondary metabolites of lichens and their application. In *Fungal Secondary Metabolites* (pp. 91-115). Elsevier.

Shcherbakova, A., Strömstedt, A. A., Göransson, U., Gnezdilov, O., Turanov, A., Boldbaatar, D., Kochkin, D., Ulrich-Merzenich, G., & Koptina, A. (2021). Antimicrobial and antioxidant activity of *Evernia prunastri* extracts and their isolates. *World Journal of Microbiology and Biotechnology*, *37*(8), 129.

Shukla, A. K., Yadav, V. K., Mishra, R. K., Kumar, M., Sharma, M., Dev, S. K., & Maurya, R. (2023). Role of Usnic acid and its derivatives in the management of cancer. *Asian Journal of Pharmacy and Pharmacology*, *9*(1), 6-12.

Singh, N., Nambiar, D., Kale, R. K., & Singh, R. P. (2013). Usnic acid inhibits growth and induces cell cycle arrest and apoptosis in human lung carcinoma A549 cells. *Nutrition and Cancer*, *65*(sup1), 36-43.

Su, Z. Q., Mo, Z. Z., Liao, J. Bin, Feng, X. X., Liang, Y. Z., Zhang, X., Liu, Y. H., Chen, X. Y., Chen, Z. W., Su, Z. R., & Lai, X. P. (2014). Usnic acid protects LPS-induced acute lung injury in mice through attenuating inflammatory responses and oxidative stress. *International Immunopharmacology*, *22*(2), 371-378.

Suwalsky, M., Jemiola-Rzeminska, M., Astudillo, C., Gallardo, M. J., Staforelli, J. P., Villena, F., & Strzalka, K. (2015). An in vitro study on the antioxidant capacity of usnic acid on human erythrocytes and molecular models of its membrane. *Biochimica et Biophysica Acta-Biomembranes*, *1848*(11), 2829-2838.

Thakur, M., Kasi, I. K., Islary, P., & Bhatti, S. K. (2023). Nutritional and health-promoting effects of lichens used in food applications. *Current Nutrition Reports*, *12*(4), 555-566.

Toksoz, O. (2023). Geçmişten günümüze potansiyel hammadde kaynağı: Likenler. *Frontiers in Life Sciences and Related Technologies*, *4*(SI), 38-44.

Tripathi, A. H., Negi, N., Gahtori, R., Kumari, A., Joshi, P., Tewari, L. M., Joshi, Y., Bajpai, R., Upreti, D. K., & Upadhyay, S. K. (2021). A review of anti-cancer and related properties of lichen-extracts and metabolites. *Anti-Cancer Agents in Medicinal Chemistry*, *22*(1), 115-142.

Turkez, H., Aydin, E., & Aslan, A. (2014). Role of aqueous *Bryoria capillaris* (Ach.) extract as a genoprotective agent on imazalil-induced genotoxicity *in vitro*. *Toxicology and Industrial Health*, *30*(1), 33-39.

Unver, H., Berber, B., Demirel, R., & Koparal, A. T. (2019). Design, synthesis, anti-proliferative, anti-microbial, anti-angiogenic activity and in silico analysis of novel hydrazone derivatives. *Anti-Cancer Agents in Medicinal Chemistry*, *19*(13), 1658-1669.

Ureña-Vacas, I., González-Burgos, E., Divakar, P. K., & Gómez-Serranillos, M. P. (2023). Lichen depsides and tridepsides: progress in pharmacological approaches. *Journal of Fungi*, *9*(1), 116.

Verma, N., Behera, B. C., & Sharma, B. O. (2012). Glucosidase inhibitory and radical scavenging properties of lichen metabolites salazinic acid, sekikaic acid and usnic acid. *Hacettepe Journal of Biology and Chemistry*, *40*(1), 7-21.

White, P. A. S., Oliveira, R. C. M., Oliveira, A. P., Serafini, M. R., Araújo, A. A. S., Gelain, D. P., Moreira, J. C. F., Almeida, J. R. G. S., Quintans, J. S. S., & Quintans-Junior, L. J. (2014). Antioxidant activity and mechanisms of action of natural compounds isolated from lichens: a systematic review. *Molecules*, *19*(9), 14496-14527.

Wu, Y., Gan, D., Leng, X., He, W., Zhang, X., Li, C., Gu, X., Hu, Y., Du, S., & Han, Y. (2022). Anti-ageing and anti-lung carcinoma effects of vulpinic acid and usnic acid compounds and biological investigations with molecular modeling study. *Journal of Oleo Science*, *71*(2), 247-255.

Xu, M., Heidmarsson, S., Olafsdottir, E. S., Buonfiglio, R., Kogej, T., & Omarsdottir, S. (2016). Secondary metabolites from cetrarioid lichens: chemotaxonomy, biological activities and pharmaceutical potential. *Phytomedicine*, *23*(5), 441-459.

Yildirim, E., Aslan, A., Emsen, B., Cakir, A., & Ercisli, S. (2012b). Insecticidal effect of *Usnea longissima* (Parmeliaceae) extract against *Sitophilus granarius* (Coleoptera: Curculionidae). *International Journal of Agriculture and Biology*, *14*(2), 303-306.

Yildirim, E., Emsen, B., Aslan, A., Bulak, Y., & Ercisli, S. (2012a). Insecticidal activity of lichens against the maize weevil, *Sitophilus zeamais* Motschulsky (Coleoptera: Curculionidae). *Egyptian Journal of Biological Pest Control*, *22*(2), 151-156.

Yousuf, S., & Choudhary, M. I. (2014). Lichens: chemistry and biological activities. *Studies in Natural Products Chemistryroducts Chemistry*, *43*, 223-259.

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