Mechanism of Biological Activity and Species Resources of Usnic Acid: A Research Overview (Postprint)

Authors: Niu Dongling, Hu Lifang, Ma Qian, crystal, Bai Mingsheng, Niu Dongling

Date: 2018-05-14T00:00:00+00:00

Abstract

Usnic acid is one of the most widely distributed and abundant lichen acids in lichens, renowned worldwide for its early use as an antibiotic. Over the past two decades, continuous new breakthroughs have been made in elucidating the mechanisms of action underlying its antimicrobial, antiviral, and antitumor activities. Research has revealed that usnic acid primarily exerts its inhibitory effects on bacteria and viruses by interfering with bacterial biofilm formation and suppressing the synthesis of bacterial and viral RNA and DNA. It achieves tumor cell killing through pathways such as inducing programmed apoptosis in tumor cells and inhibiting tumor cell DNA synthesis, and additionally possesses the capability to suppress tumor cell migration. Concurrently, the capacity of usnic acid to cause hepatocellular mitochondrial dysfunction and subsequent liver injury when used as a weight-loss nutritional supplement has increasingly garnered attention within the scientific community. To better guide the direction of research and development of usnic acid resources, this article provides a comprehensive review and analysis of studies from the past two decades concerning the mechanisms of usnic acid' s antimicrobial, antiviral, and antitumor activities, as well as its hepatotoxicity. To date, usnic acid has been reported in species across 35 genera, predominantly fruticose lichens, followed by foliose lichens, with only occasional presence in crustose lichens. This article also systematically reviews the currently reported genera and species containing usnic acid and research on environmental factors influencing its content, aiming to provide theoretical support for the discovery of superior germplasm resources rich in usnic acid and for addressing germplasm resource challenges in future studies on its biological activities.

Full Text

Preamble

DOI: 10.11931/guihaia.gxzw201801035
Title: Review on the Bioactivity Mechanism and Species Resources of Usnic Acid
Authors: NIU Dongling*, HU Lifang, MA Qian, SHI Jing, BAI Mingsheng
Affiliation: School of Life Sciences, Ningxia University, Yinchuan 750021, Ningxia, China

Abstract

Usnic acid is one of the most widely distributed and abundant lichen acids, historically renowned for its antibiotic properties. Over the past two decades, significant breakthroughs have been made in elucidating its mechanisms of action in antibacterial, antiviral, and antitumor activities. Research has revealed that usnic acid primarily inhibits bacteria and viruses by disrupting biofilm formation and suppressing RNA and DNA synthesis. Its antitumor effects are achieved through inducing programmed apoptosis, inhibiting tumor cell DNA synthesis, and suppressing tumor cell migration. However, concurrent with these therapeutic developments, concerns have emerged regarding its hepatotoxicity when used as a weight-loss supplement, as it can trigger mitochondrial dysfunction in liver cells. To better guide future research and development of usnic acid resources, this review systematically analyzes studies from the last twenty years on its mechanisms of action and hepatotoxic effects.

To date, usnic acid has been reported in species across 35 genera, predominantly in fruticose lichens, followed by foliose lichens, with only occasional occurrence in crustose lichens. This review comprehensively catalogs the reported genera and species containing usnic acid and summarizes research on environmental factors affecting its content, providing a theoretical foundation for identifying high-yield germplasm resources and addressing raw material challenges in future bioactivity studies.

Keywords: anticancer activity, liver toxicity, active mechanism, lichen, usnic acid resources

Introduction

Lichens represent stable mutualistic symbioses between mycobionts (ascomycetes or basidiomycetes) and photobionts (algae or cyanobacteria), functioning as complex miniature ecosystems (Lumbsch, 1998). The mycobiont plays a dominant role, synthesizing unique depsidone and depside compounds that accumulate in specific cortical or medullary layers and serve important ecological functions (Nybakken & Gauslaa, 2007). While the precise ecological roles of these secondary metabolites in lichen survival and growth remain poorly understood, extensive experimental evidence demonstrates

their diverse biological activities and physiological effects on other organisms, leading to widespread applications in consumer products, natural dyes, health supplements, and pharmaceuticals (Molnar & Farkas, 2010).

Among these compounds, usnic acid has been particularly well-studied and widely utilized. This dibenzofuran derivative was first isolated by German scientist W. Knop in 1844 and later synthesized between 1933-1937 (Alahmadi, 2017). Naturally occurring as two enantiomers, usnic acid is chemically stable, highly soluble in chloroform, and poorly soluble in hot ethanol and water. It crystallizes in different forms depending on the solvent: yellow orthorhombic prisms in acetone, and needle-like crystals in chloroform-ethanol mixtures or benzene. Although generally considered exclusive to lichens as a mycobiont-derived secondary metabolite, usnic acid has also been isolated from phytopathogenic fungi and non-lichenized ascomycetes (Bondarenko et al., 1969; Sassa & Igarashi, 2014). Its broad distribution in lichens and ease of isolation have facilitated extensive investigations into its biological activities, revealing significant antioxidant, antiproliferative, cytotoxic, antibacterial, antiviral, and anti-inflammatory properties (Alahmadi, 2017). Since the 21st century, international research has increasingly focused on mechanism-of-action studies, while domestic research has traditionally emphasized activity screening, with mechanistic investigations only gaining attention in recent years. As development and applications have progressed, resource acquisition and production challenges have emerged. This review systematically examines the past two decades of research on the mechanisms of usnic acid' s major bioactivities and its species resources to inform future domestic research directions.

2. Mechanisms of Usnic Acid Biological Activity

2.1 Antibacterial Mechanism

The antibacterial properties of usnic acid have long been recognized, with widespread application as an antibiotic during World War I. In the 21st century, research has continued to focus on its antibacterial activity while elucidating underlying mechanisms. Safak et al. (2009) demonstrated that usnic acid isolated from *Usnea dasypoga* inhibits *Helicobacter pylori*, the bacterium causing gastric ulcers, with dose-dependent efficacy and synergistic effects when combined with clarithromycin. Studies have shown that usnic acid suppresses Gram-positive bacteria primarily by inhibiting RNA and DNA synthesis (Maciąg-Dorszyńska et al., 2014). Against *Candida albicans*, usnic acid reduces polysaccharide accumulation on fungal membranes and decreases biofilm thickness, thereby inhibiting biofilm formation (Nithyanand et al., 2015). L-(-)-usnic acid from *Usnea subfloridana* disrupts *Staphylococcus aureus* biofilms and exhibits no hepatotoxicity in mice at doses below 1000 mg/kg body weight (Gupta et al., 2012). Further research indicates that usnic acid multi-targetedly inhibits *S. aureus* biofilm formation and prevents binding to host matrix proteins, suggesting its potential as a lead compound for treating cystic fibrosis infections (Pompilio et al., 2016).

2.2 Antiviral Mechanism

Mechanistic studies demonstrate that usnic acid potentially inhibits mouse polyomavirus proliferation by suppressing RNA transcription, which indirectly blocks viral DNA replication (Campanella et al., 2002). Research also reveals enantiomeric differences in activity against influenza A(H1N1)pdm09, with (-)-usnic acid showing higher antiviral activity than (+)-usnic acid. However, chemical structure modification reverses this activity profile, with modified (+)-usnic acid exhibiting superior antiviral effects compared to modified (-)-usnic acid, though the underlying mechanism for this reversal requires further investigation (Sokolov et al., 2012).

2.3 Antitumor Mechanism

Recent studies have increasingly uncovered usnic acid's potential against various cancer cell lines and its antitumor mechanisms. Building upon previous comprehensive reviews (Hao et al., 2015), this section incorporates new research findings. Studies show that usnic acid significantly inhibits H22 tumor cell growth and angiogenesis by suppressing vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) expression while inhibiting human umbilical vein endothelial cell (HUVEC) proliferation (Hao et al., 2016). In breast cancer cells, usnic acid induces apoptosis specifically through ROS-mediated mitochondrial pathways (Zuo, 2016). Against lung cancer A549 cells, usnic acid causes G0/G1 cell cycle arrest and induces apoptosis through mitochondrial membrane depolarization (Singh et al., 2013). Both enantiomers isolated from *Ramalina farinacea* and *Cladonia foliacea* exhibit significant cytotoxicity and apoptosis induction in Chinese hamster lung fibroblast V79 cells, human lung epithelial A549 cells, and human lymphocytes (Koparal et al., 2006). In leukemia studies, HL-60 cells show greater sensitivity than K562 cells, with usnic acid markedly inhibiting growth and inducing apoptosis through downregulation of anti-apoptotic protein Mcl-1. Usnic acid also suppresses Mnk1/eIF4E and Pim-1/4E-BP1 signaling pathways, suggesting potential as a Pim-1 inhibitor (Fan et al., 2016). In prostate cancer PC-3M cells, usnic acid interferes with DNA synthesis to inhibit proliferation (Dong et al., 2007). Notably, usnic acid also inhibits migration of prostate cancer and melanoma cells, suggesting potential for targeting metastatic cascades (Galanty et al., 2017). Collectively, usnic acid' s anticancer mechanisms involve inhibiting tumor angiogenesis, inducing programmed apoptosis, suppressing DNA synthesis, and preventing tumor cell migration.

2.4 Anti-inflammatory and Antioxidant Mechanism

Usnea longissima has been used traditionally in Anatolia, Turkey, to treat gastric ulcers. Bioactivity-guided fractionation identified usnic acid as the protective component, attributed to its reduction of oxidative tissue damage and neutrophil infiltration. Current research indicates that usnic acid' s anti-inflammatory effects involve NF- B inhibition, increased production of anti-inflammatory cy-

tokine IL-10 and mediator HO-1, and downregulation of TNF- , iNOS, COX-2, IL-1 , and IL-6 expression (Huang et al., 2011; Huang et al., 2014; Jin et al., 2008). Interestingly, usnic acid from *Xanthoparmelia farinosa* exhibits dual pro-oxidant and antioxidant activities in UVB-irradiated human lymphocytes, with the opposing effects activated depending on UVB dose and usnic acid concentration (Kohlhardt-Floehr et al., 2010).

2.5 Hepatotoxicity

In the United States, crude extracts and pure usnic acid have been marketed extensively as weight-loss dietary supplements. However, accumulating evidence identifies usnic acid as a potent hepatotoxin that triggers oxidative stress and mitochondrial dysfunction in hepatocytes, disrupting normal metabolic processes and causing hepatotoxicity and acute liver failure in patients (Durazo et al., 2004; Joseph et al., 2009; Pramyothin et al., 2004; Yokouchi et al., 2015). Consequently, its continued use as a weight-loss supplement has been widely questioned, and the safe dosage range for clinical applications requires further investigation.

3. Research on Usnic Acid Species Resources

Usnic acid was first isolated in 1843 from *Ramalina* and *Usnea* species. Known usnic acid-containing genera currently include *Cladonia*, *Usnea*, *Lecanora*, *Ramalina*, *Evernia*, *Xanthoparmelia*, *Parmelia*, *Alectoria*, *Haematomma*, and *Cetraria*, with particularly high concentrations in *Cladonia* and *Usnea*. Usnic acid serves as a diagnostic characteristic for these genera, though they are phylogenetically distant and usnic acid exhibits evolutionary instability, frequently appearing and disappearing during species divergence. This pattern suggests that usnic acid confers significant ecological advantages for lichen survival and growth, leading to its selective retention throughout evolutionary history.

Literature surveys reveal usnic acid distribution in additional genera including *Dimelaena*, *Everniopsis*, *Flavoparmelia*, *Flavopunctelia*, *Halecania*, *Hypotrachyna*, *Leprocaulon*, *Psiloparmelia*, and *Relicina*, as well as in numerous species such as *Arctoparmelia centrifuga*, *Biatora pallens*, *Canoparmelia* species, *Caloplaca* species, *Cetraria nivalis*, *Cladina uncialis*, *Flavocetraria nivalis*, *Haematomma ochroleucum*, *Hypotrachyna sinuosa*, *Karoowia saxeti*, *Rhizoplaca melanophthalma*, *Melanelixia* species, *Megalospora* species, *Neuropogon* sp., *Parmotrema delicatulum*, and *Psora rubiformis* (Blanco et al., 2006; Eifler-lima et al., 2015; Grube & Winka, 2002; Leavitt et al., 2011; Mcevoy et al., 2006; Miadlikowska et al., 2014; Zhang et al., 2016; Liu et al., 2014). Usnic acid occurs across diverse growth forms, including fruticose, foliose, and crustose lichens, representing a rich species resource. However, high concentrations are concentrated primarily in fruticose lichens, followed by foliose species, with only sporadic occurrence in crustose lichens. The underlying determinants of this distribution pattern warrant further investigation.

Usnic acid content varies significantly among species and geographic regions. Studies of Turkish Anatolian lichens report concentrations up to 6.49% of dry weight, with *Rhizoplaca* species containing approximately 4% and *Ramalina* species about 3.23% (Duman et al., 2008). *Usnea longissima* from Linzhi, Tibet, contains 5.66% usnic acid (Yang et al., 2007). Notably, *Ramalina sinensis* and *Cladonia cornutu* from the Tianshan Mountains in Xinjiang have yielded exceptionally high concentrations of 18.32% and 26.95%, respectively (Tugunay et al., 2010; Reyim et al., 2010). Beyond taxonomic factors, usnic acid content correlates with seasonal changes, altitude, precipitation, and temperature. In the Patagonian heathland, *Flavocetraria nivalis* reaches peak usnic acid concentrations of approximately 8% dry weight in late spring and early summer, declining in autumn and winter. This seasonal variation correlates strongly with environmental factors, particularly UV-B radiation, which is maximal during spring and summer (Bjerke et al., 2005). UV exposure induces usnic acid synthesis and accumulation in cortical layers of *Cladonia* spp. and *Xanthoparmelia stenophylla*, and usnic acid' s UV-B absorption capacity suggests a photoprotective function (BeGora & Fahselt, 2001; Bjerke et al., 2002; McEvoy et al., 2006). In Nepal's Kaski district, *Parmelia flexilis* shows a negative correlation between usnic acid content and altitude, with precipitation also influencing concentrations (Neupane et al., 2017). Climate warming may affect carbon metabolism-related secondary metabolites; simulated warming experiments show a 31% increase in usnic acid content in *Cladonia stellaris* when temperature is elevated by 4°C (Asplund et al., 2017). Such changes could subsequently impact the species' ecological functions.

Since its post-WWII discovery, usnic acid has continued to demonstrate significant research potential and developmental promise as a natural lead compound. However, hepatotoxic side effects necessitate deeper mechanistic studies to establish safe usage parameters and guide development of highly effective, low-toxicity usnic acid-based therapeutics. As new lichen species are discovered and characterized, additional usnic acid resources continue to be identified, with many already developed into crude extracts or pure compounds for health products and pharmaceuticals. Nevertheless, the slow growth rate of lichens and low natural yields of secondary metabolites limit commercial-scale extraction from wild sources. Therefore, future development requires two complementary approaches: comprehensive investigation of factors influencing usnic acid content across diverse species and environments, and exploration of biotechnological methods to optimize production from selected high-yield strains under controlled conditions.

References

ALAHMADI AA, 2017. Usnic acid biological activity: history, evaluation and usage[J]. Int J Basic Clin Pharmacol, 6 (12): 2752-2759.

ASPLUND J, SIEGENTHALER A, GAUSLAA Y, 2017. Simulated global warming increases usnic acid but reduces perlatolic acid in the mat-forming terricolous lichen Cladonia stellaris[J]. Lichenologist, 49 (3): 269-273.

BEGORA MD & FAHSELT D, 2001. Usnic acid and atranorin concentrations in lichens in relation to bands of UV irradiance[J]. Bryologist, 104(1): 134-140.

BJERKE JW, ELVEBAKK A, DOMINGUEZ E, et al, 2005. Seasonal trends in usnic acid concentrations of Arctic, alpine and Patagonian populations of the lichen Flavocetraria nivalis[J]. Phytochemistry, 66(3): 337-343.

BJERKE JW, LERFALL K, ELVEBAKK A, 2002. Effects of ultraviolet radiation and PAR on the content of usnic and divaricatic acids in two arctic-alpine lichens[J]. Photochem Photobiol Sci, 1(9): 678-685.

BLANCO O, CRESPO A, REE RH, et al, 2006. Major clades of parmelioid lichens (Parmeliaceae, Ascomycota) and the evolution of their morphological and chemical diversity[J]. Mol Phylogenet Evol, 39(1): 52-69.

BONDARENKO BN, LYSENKO ZA, ROGOZHINA AP, et al, 1969. Isolation of usnic acid from the actinomycete C-2167[J]. Mikrobiologija, 620-623.

CAMPANELLA L, DELFINA M, ERCOLE P, et al, 2002. Molecular characterization and action of usnic acid: a drug that inhibits proliferation of mouse polyomavirus in vitro and whose main target is RNA transcription[J]. Biochimie, 84: 329-334.

DONG Y, YU N, WANG HJ, et al, 2007. Biological effects of usnic acid on the proliferation of prostate cancer PC-30M cells[J], Shenyang Army Med, 20(1): 7-9.

DUMAN DC, ARAS S, ATAKOL O, 2008. Determination of usnic acid content in some lichen species found in Anatolia[J]. Journal of Applied Biological Sciences, 2(3): 41-44.

DURAZA FA, LASSMAN C, HAN SH, et al, 2004. Fulminant liver failure due to usnic acid for weight loss[J]. Am J Gastroenterol, 99(5): 950-952.

EIFLER-LIMA V, SPERRY A, SINBANDHIT S, et al, 2015. NMR spectral data of salazinic acid isolated from some species of Parmotrema[J]. Magn Reson in Chem, 38(6): 472-474.

FAN Y, HUANG M, CAO Y, et al, 2016. Usnic acid is a novel Pim-1 inhibitor with the abilities of inhibiting growth and inducing apoptosis in human myeloid leukemia cells[J]. Rsc Adv, 6(29): 24091-24096.

GALANTY A, KOCZURKIEWICZ P, WNUK D, et al, 2017. Usnic acid and atranorin exert selective cytostatic and anti-invasive effects on human prostate and melanoma cancer cells[J]. Toxicol in Vitro, 40: 161-169.

GRUBE M & WINKA K, 2002. Progress in understanding the evolution and classification of lichenized ascomycetes[J]. Mycologist, 16(2): 67-76.

GUPTA VK, VERMA S, GUPTA S, 2012. Membrane-damaging potential of natural L-(−)-usnic acid in Staphylococcus aureus[J]. Eur J Clin Microbiol, 31(12): 3375-3383.

HAO KH, HAN T, HU PB, 2016. Growth inhibitory effect of usnic acid on H22 tumor cells on mice and underlying mechanism[J]. China Pharmacist, 19(1): 29-32.

HAO KH, HAN T, HU PB, 2015. Research progress of anticancer mechanism of usnic acid[J]. Mod Oncol, 23(23): 3535-3537.

HUANG ZJ, TAO JY, RUAN JL, et al, 2014. Anti-inflammatory effects and mechanisms of usnic acid, a compound firstly isolated from lichen Parmelia saxatilis[J]. J Med Plant Res, 8(4): 197-207.

HUANG ZJ, ZHENG GH, TAO JY, et al, 2011. Anti-inflammatory effects and mechanisms of usnic acid[J]. J Wuhan Univ Technol, 26(5): 955-959.

JIN JQ, LI CQ, HE LC, 2008. Down-regulatory effect of usnic acid on nuclear factor-kappaB-dependent tumor necrosis factor-alpha and inducible nitric oxide synthase expression in lipopolysaccharide-stimulated macrophages RAW 264.7[J]. Phytother Res, 22(12): 1605-1609.

JOSEPH A, LEE T, MOLAND CL, et al, 2009. Effect of (+)-usnic acid on mitochondrial functions as measured by mitochondria-specific oligonucleotide microarray in liver of B6C3F1 mice[J]. Mitochondrion, 9(2): 149-158.

KOHLHARDT-FLOEHR C, BOEHM F, TROPPENS S, et al, 2010. Prooxidant and antioxidant behaviour of usnic acid from lichens under UVB-light irradiation –Studies on human cells[J]. J Photochem Photobiol B, 101(1): 97-102.

KOPARAL AT, TUYLU BA, TURK H, 2006. In vitro cytotoxic activities of (+)-usnic acid and (-)-usnic acid on V79, A549, and human lymphocyte cells and their non-genotoxicity on human lymphocytes[J]. Natl Prod Res, 20(14): 1300-1307.

LEAVITT SD, FANKHAUSER JD, LEAVITT DH, et al, 2011. Complex patterns of speciation in cosmopolitan 'rock posy' lichens –Discovering and delimiting cryptic fungal species in the lichen-forming Rhizoplaca melanophthalma species-complex (Lecanoraceae, Ascomycota) [J]. Mol Phylogenet Evol, 59(3): 587-602.

LIU D, WANG XY, LI JW, et al, 2014. Contributions to the lichen flora of the Hengduan Mountains, China (6): revisional study of the Genus Canoparmelia (Lichenized Ascomycota, Parmeliacaea) [J]. Plant diver Resour, 36(6): 781-787.

LUMBSCH HT, 1998. Taxonomic use of metabolic data in lichen-forming fungi. In: Chemical Fungal Taxonomy (Frisvad J. C., Bridge P. D., and Arora D. K., eds.) [M]. New York: Marcel Dekker Inc., 345-387.

MACIAG-DORSZYNSKA M, WEZGRZYN G & GUZOW-KRZEMINSKA B, 2014. Antibacterial activity of lichen secondary metabolite usnic acid is primarily caused by inhibition of RNA and DNA synthesis[J]. Fems Microbiol Lett, 353(1): 57–62.

MCEVOY M, NYBAKKEN L, SOLHAUG KA, et al, 2006. UV triggers the synthesis of the widely distributed secondary lichen compound usnic acid[J]. Mycol Prog, 5(4): 221-229.

MIADLIKOWSKA J, KAUFF F, HOGNABBA F, et al, 2014. A multigene phylogenetic synthesis for the class Lecanoromycetes (Ascomycota): 1307 fungi representing 1139 infrageneric taxa, 317 genera and 66 families[J]. Mol Phylogenet Evol, 79(1): 132-168.

MOLNAR K & FARKAS E, 2010. Current results on biological activities of lichen secondary metabolites: a review[J]. Z Naturforsch, 65(3-4): 157-173.

NEUPANE BP, MALLA KP, GAUTAM A, et al, 2017. Elevational trends in usnic acid concentration of lichen Parmelia flexilis in relation to temperature and precipitation[J]. Climate, 5(4): 221-229.

NITHYANAND P, SHAFREEN RMB, MUTHAMIL S, et al, 2015. Usnic acid inhibits biofilm formation and virulent morphological traits of Candida albicans[J]. Microbiol Res, 179: 20–28.

NYBAKKEN L & GAUSLAA Y, 2007. Difference in secondary compounds and chlorophylls between fibrils and main stems in the lichen Usnea longissima suggests different functional roles[J]. Lichenologist, 39(5): 491-495.

POMPILIO A, RIVIELLA A, CROCETTA V, et al, 2016. Evaluation of antibacterial and antibiofilm mechanisms by usnic acid against methicillin-resistant Staphylococcus aureus[J]. Future Microbiol, 11(10): 1315-1338.

PRAMYOTHIN P, JANTHASOOT W, PONGNIMITPRASERT N, et al, 2004. Hepatotoxic effect of (+)-usnic acid from Usnea siamensis Wainio in rats, isolated rat hepatocytes and isolated rat liver mitochondria[J]. J Ethnopharmacol, 90(2-3): 381-387.

REYIM M, ADILJAN, ABDULLA A, 2010. Extraction technology of usnic acid from Cladonia cornuta(L.) Hoffm and content determination[J], China Brewing, 224(11): 121-124.

SAFAK B, CIFTCI IH, OZDEMIR M, et al, 2009. In vitro anti-Helicobacter pylori activity of usnic acid[J]. Phytother Res, 23(7): 955-957.

SASSA T & IGARASHI M, 2014. Structure of (−)-mycousnine, (+)-oxymycousnine, new usnic acid derivatives from phytopathogenic Mycosphaerella nawae[J]. Agri Biolog Chem, 54(9): 2231-2237.

SINGH N, NAMBIAR D, KALE RK, et al, 2013. Usnic acid inhibits growth and induces cell cycle arrest and apoptosis in human lung carcinoma A549 cells[J]. Nutr Cancer, 65(sup1): 36-43.

SOKOLOV DN, ZARUBAEV VV, SHTRO AA, et al, 2012. Anti-viral activity of (−)-and (+)-usnic acids and their derivatives against influenza virus A(H1N1)2009[J]. Bioorg Med Chem Lett, 22(23): 7060-7064.

TUGUNAY T, REYIM M, ADILIJIANG, et al, 2010. Content determination and antioxidant activity evaluation of usnic acid in Ramalina sinesis Jatta[J]. Food Sci, 31(19): 150-152.

YANG DS, SU YQ, PENG F, et al, 2007. Measurement on content of usnic acid in several Usnea and the activity of the extractives scavenging DPPH free radical, J Northwest For Univ, 22(4): 135-138.

YOKOUCHI Y, IMAOKA M, NIINO N, et al, 2015. (+)-Usnic Acid-induced Myocardial Toxicity in Rats[J]. Toxicol Pathol, 43(3): 424-434.

ZHANG YY, WANG XY, LIU D, 2016. The genus Bulbothrix (Parmeliaceae) in China. Lichenologist, 48(2): 121-129.

ZUO ST, 2016. The research on usnic acid induces apoptosis via an ROS-dependent mitochondrial pathway[D], Changchun: Jinlin University.

Note: Figure translations are in progress. See original paper for figures.