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Antimicrobial applications of lichens: secondary metabolites and green synthesis of silver nanoparticles: A review

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ABSTRACT

Lichens produce a variety of unique extracellular secondary metabolites because these organisms are a life form comprising a complex symbiotic relationship between fungi and algae, which occur in many ecosystems. These compounds are present within the thallus and form crystals on the surface of the fungal hyphae. More than 800 different secondary metabolites, such as usnic acid, norstictic acid, atranorin, salazinic acid, stictic acid, atranorin, and chloroatranorin have been identified in lichens, most of which are found exclusively in lichen species. In recent years, lichens have received much attention for pharmaceutical and phytochemical applications. Lichens and their secondary metabolites have been investigated for various pharmacological activity, including antimicrobial, antioxidant, antiviral, anticancer, antigenotoxic, anti-inflammatory, antipyretic, and analgesic effects. This review discusses recent progress and challenges related to the antimicrobial activity of lichens, focusing on secondary metabolites of the leading medical species of lichen and the green synthesis of silver nanoparticles and nanocomposites.

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1. Introduction

Bacterial infections caused by multidrug-resistant (MDR) and extensively drug-resistant (EDR) bacteria are a significant problem in world healthcare [1, 2]. For example, methicillin-resistant *Staphylococcus aureus* (MRSA) is an essential cause of hospital-acquired infections, and is resistant to many antibiotics, including methicillin, macrolides, aminoglycosides, and vancomycin. Several antibiotic resistance mechanisms have been identified so far. These include mutations in genes coding for antibiotic target proteins, inactivation of antibiotics by specific enzymes, sequestration of antibiotics, thickening of the cell wall preventing antibiotic entry, acquisition of transposons or plasmids coding for resistance genes, and up-regulation of multidrug efflux pumps which pump out antibiotics [3]. Nanomaterials, such as nanoparticles (NPs), nanotubes, or nanoplates synthesized from organic or inorganic materials, have been investigated as efficient antimicrobial agents against bacterial, viral, and fungal pathogens [4-6]. The large surface area to volume ratio and the high level of reactivity of these NPs in colloidal suspension are due to the smaller size (in the range of 1-100 nm) of these particles compared to bulk materials [7, 8]. In particular, silver (Ag) NPs are a type of metal NPs that have shown good antibacterial activity both in vitro and in vivo. For nanotubes, nanowires, nanorods, nanoneedle, and thorn-like NPs, the aspect ratio (length/diameter ratio) is a critical factor governing the antibacterial activity. For instance, a sol-gel preparation of ZnONPs showed higher bacterial inactivation of *Bacillus subtilis*, when the preparation was carried out with stirring at 2000 rpm compared to 500 rpm (Figure 1) [9].

Biosynthesis of metal or metal oxide NPs by the extracts of plants, bacteria, and lichens can lead to

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increased antimicrobial activity and biocompatibility [10]. Lichens having different secondary metabolites such as usnic acid, norstictic acid, atranorin, salazinic acid, stictic acid, atranorin, and chloroatranorin may be employed as the main biosource to reducing of metal ions and stabilizing metal or metal oxide NPs [11].

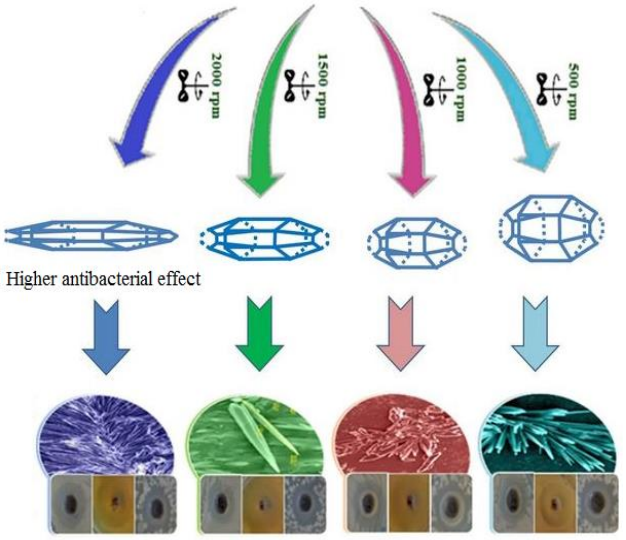

Fig. 1. Preparation of thorn-like ZnONPs under different stirring conditions (500, 1000, 1500, and 2000 rpm) resulted in different degrees of antibacterial activity (permission and adoption from [9]).

2. Antimicrobial activity of AgNPs

Release of Ag^+ ions from AgNPs in the bacterial medium can produce reactive oxygen species (ROS) such as singlet oxygen ($^1O_2$*), hydroxyl radical ($^*OH$), superoxide ($^*O_2^-$), and peroxides ($^*O_2^{-2}$) [12]. This can be followed by the intracellular production of reactive nitrogen species (RNS) such as nitric oxide (NO^*) and peroxynitrite ($ONOO^-$) damaging the bacterial structure and related biological macromolecules [12]. As shown in Figure 2, the minimum inhibition concentration (MIC) of each ROS with related toxicity on biological macromolecules is presented, wherein superoxide has demonstrated an ideal therapeutic effect at 10 nM concentration [13]. Physiological properties of AgNPs including size, shape, and charge, should be considered by controlling the conditions of synthesis to obtain effective antibacterial and antifungal activities *in vivo* and *in vitro*. For instance, positively charged AgNPs can interact electrostatically with a negative charge of the bacterial cell wall (teichoic acids bound to the peptidoglycan and plasma membrane) and membrane (phospholipids and lipopolysaccharides) [14].

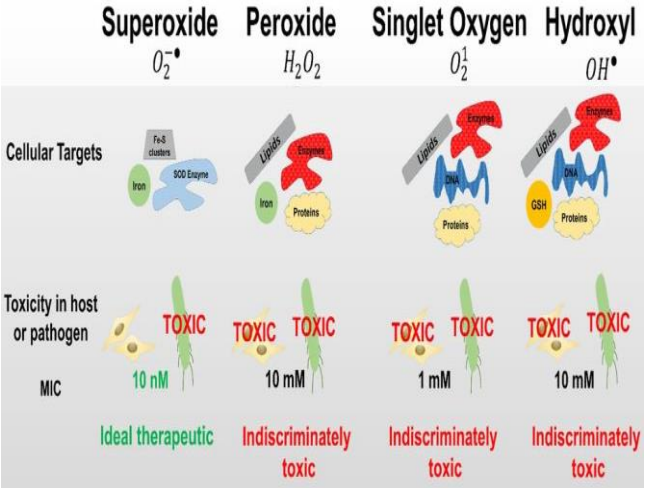

Fig. 2. MIC values of different ROS and their cellular targets (Reproduced with permission from [13].

3. Secondary metabolites from lichens with antimicrobial activity

Lichens have been classified into 18,500 different species worldwide. The lichen life cycle involves a mutualistic relationship between the fungal part (mycobiont) and the algal part or cyanobacteria acting as a photoautotroph (photobiont). Because the mycobiont part is predominant in this relationship, lichens are sometimes considered as types of fungi [15]. Roughly 21% of all fungal species can contribute as mycobionts in lichen symbiosis, with 98% found in the genus *Ascomycota*. In contrast, 40 genera including 25 algae and 15 cyanobacteria can participate as the photobiont in the lichen symbiosis [16]. Many secondary metabolites can be isolated from plants and herbs, and many have therapeutic effects, such as curcumin [17]. Various secondary metabolites have also been found in lichens, algae, and fungi, which many of these possess antimicrobial activity. Depending on their environment, lichens can produce many metabolites that have been designed by evolution to provide adequate protection against physical and chemical stresses. Metabolites synthesized by lichens are divided into two categories: primary metabolites and secondary metabolites [18, 19]. Primary (intracellular) metabolites include proteins, amino acids, carbohydrates, polysaccharides, and vitamins.

These metabolites are soluble in water and can be easily separated from lichens by extraction in boiling water. The primary metabolites produced by fungi and algae may be similar or different, and nonspecific compounds may be present in fungi, free algae, and higher plants [19-21]. Most organic compounds with therapeutic effects that have been discovered in lichens, are secondary metabolites (Table 1). These compounds may amount to between 0.1-30% of the dry weight of lichens [19]. Secondary metabolites in lichens are generally derived from the fungal component and can take the form of crystals on the surface of the hyphae. Due to their very low solubility in water, organic solvents must be employed to extract them [22]. The geography and morphology of the species and genus of lichens can affect the production of stable secondary metabolites. In contrast to primary metabolites, secondary metabolites are not critical for the growth of lichens. However these compounds protect the thallus against pathogens, high levels of UV radiation, and competitors for nutrients [23]. The antimicrobial activity of extracts of lichens, in aqueous, acetone, chloroform, or methanol solution, has been reported to be both bacteriostatic and bactericidal. For example, an acetone extract of *Bulbothrix setschwanensis* disrupted and deformed the bacterial and fungal cell walls with the minimum inhibitory concentrations (MIC) of 6.25 and 1.56 mg/mL for *Cryptococcus neoformans* and *S. aureus*, respectively [24].

Table 1. Antimicrobial activity of important secondary metabolites isolated from various lichen species.

Secondary metabolites	Lichen species	Antimicrobial activity	Ref.
Aspergyllone	*Parmotrema ravum*	Antifungal activity against *Candida parapsilosis*	[25]
(+) Montagnetol	*Roccella montagnei*	Inactivation of *Pseudomonas aeruginosa* and C*andida albicans*	[26]
Norstictic acid, usnic acid, and atranorin	*Parmelia conspersa*	Antibacterial effects against *Escherichia coli, Proteus mirabilis;* antifungal activity against *C. albicans* and *Aspergillus niger*	[27]
Salazinic acid, stictic acid, atranorin, and chloroatranorin	*Parmelia perlata*	Antifungal activity against *C. albicans* and *A. niger;* Antibacterial activity against *E. coli and P. mirabilis*	[27]
Divaricatic acid	*Evernia mesomorpha* and *Protousnea magellanica*	Active against MRSA, *Staphylococcus epidermidis*, *Enterococcus faecium*, *E. coli*, and *C albicans*	[28] [29]
Lecanoric acid and 2,4-dihydroxyl-6-pentylbenzoate	*Parmelia cetrata* Ach	Antibacterial effects against *Aliivibrio fischeri*	[30]
Perlatolic acid	*Stereocaulon* sp.	Growth inhibition of *E. coli*	[29]
Sphaerophorin	*Sphaerophorus globosus*	Antibacterial activity against *E. coli*	[29]
Alpha-collatolic acid	*Lecanora atra*	Inactivation of *E. coli*	[29]
Lobaric acid	*Stereocaulon alpinum*	Antibacterial activity against *E. coli*, *B. subtilis* and *S. aureus*	[29, 31]
Lichesterinic acid	*Cetraria chlorophylla* and *Cetraria islandica*	Antifungal activity against *C. albicans;* antibacterial activity against *S. aureus*, *Bacillus cereus*, *B. subtilis*, and *E. coli*	[29, 32]

Protolichesterinic acid	*Cornicularia aculeate* and *Usnea albopunctata*	Inactivation of *Trichophyton rubrum;* antibacterial activity against *Klebsiella. pneumonia, Vibrio cholerae* and *E. coli*	[29, 33]
Epiphorellic acid	*Cornicularia epiphorella*	Growth inhibition of *E. coli*	[29]
2,3-Bis(2-methylpentanoyloxy)propyl 2-methylpentanoate	*B. setschwanensis*	Disruption of cellular envelope of *S. aureus* and *C. neoformans* fungus	[24]
3,9-Dimethyltricyclo[4.2.1.1(2,5)]-dec-3-en-9-ol; 8S,14-Cedrandiol; usnic acid;	*Protoparmeliopsis muralis*	Antibacterial activity against *E. coli*, *P. aeruginosa*, *B. megaterium*, *S. epidermidis*, *S. aureus*, and *S. sonnei*	[34]
3-[2,4-Dichlorophenyl]-1-hydroxy-9,10-anthracenedione; 3-[5-(2-Chloro-5-nitro-phenyl)-furan-2-yl]-2-cyano-acrylic acid	*Fulgensia fulgens*	Antibacterial activity against *E. coli*, *P. aeruginosa*, *B. megaterium*, *S. epidermidis*, *S. aureus*, and *S. sonnei*	[34]

Continuation of Table 1

4. Use of lichens for biosynthesis of AgNPs with antimicrobial activity

The green synthesis of metal or metal oxide NPs involves the use of plants, microorganisms, or natural extracts for the bioreduction of metal ions into their elemental form to produce NPs [21]. Traditional physical and chemical methods of preparing metal NPs require high energy consumption, and may have low yields, high costs, and cause environmental damage by harsh reducing agents [35]. The biological synthesis methods can involve using microorganisms (bacteria, fungi, yeast, algae, etc.) or plants [20, 36, 37]. Lichens can contribute to the bio-fabrication of metal or metal oxide NPs, by either intracellular or extracellular processes. In addition, secondary metabolites of these organisms may be used to reducing or stabilizing agents in the preparation of metal or metal oxide NPs. In this respect, as a comparative study, secondary metabolites including usnic acid and thymol related to *P. muralis* lichen and *Artemisia haussknechtii* plant species were employed to synthesize Ag and copper (Cu) NPs. According to the results, more antibacterial activities were observed for usnic acid, usnic acid-Cu NPs, and thymol-Cu NPs by MIC/MBC amounts of 20, 40, and 40 ppm, respectively, compared to thymol-Ag NPs and usnic acid-Ag NPs toward MRSA bacteria [38]. Several mechanisms have been found for the antibacterial activity of lichen-produced metal or metal oxide NPs, including targeting bacterial cell walls, oxidative stress by production of ROS, interference in cell signaling processes, disturbance in transcription and translation processes, and damage to enzymes and nucleic acids [39]. A few studies are confirming the antifungal activity of metal or metal oxide NPs biosynthesized by lichens. The antifungal activity of metal or metal oxide NPs biosynthesized by lichens may be different depending on the type of pathogenic fungi and the NPs [40].

In one report, $ZnO@TiO_2@SiO_2$ and $Fe_3O_4@SiO_2$ nanocomposites were synthesized by the lichen *Lecanora muralis* [41]. *Candida* spp. were more susceptible to these NPs compared to *Aspergillus terrus*, *A. flavus*, and *A. niger* species. In the case of lichen-fabricated AgNPs providing rod-shaped particles with a mean size of <50 nm, there was one study showing the antifungal activity of these NPs. AgNPs prepared by *Parmelia perlata* lichen provided a 14 mm inhibition zone diameter against *Aspergillus terreus* fungus growing on agar plates [42].

5. Conclusions

Lichens consist of fungi and algae, which produce unique extracellular secondary metabolites (more than 800 different compounds such as usnic acid, norstictic acid, atranorin, and chloroatranorin), some of which show antimicrobial activity. One of the

main antibacterial mechanisms for lichen extracts against Gram-positive bacteria such as *S. aureus* may be cell wall disruption. Lichens can also be used to synthesize metal and metal oxide NPs. The reduction of the metal ions and the stabilization of the resulting NPs can be carried out by both primary and secondary metabolites via intracellular or extracellular pathways. The appropriate choice of lichen species can lead to the production of NPs with desirable sizes and shapes. In addition, the antimicrobial activity of metal or metal oxide NPs, such as AgNPs and ZnONPs, may be increased by the biosynthesis process and the combination of NPs with lichen, fungal or algal extracts. Controlling the size and shape is critical to obtain suitable antimicrobial activity of new formulations in physiological conditions. In this respect, more comprehensive studies are required to address these issues.

Study Highlights

- Lichens produce unique extracellular secondary metabolites such as usnic acid with antimicrobial activity.
- One of the main antibacterial mechanisms for lichen extracts against Gram-positive bacteria is cell wall disruption.
- The reduction of the metal ions and the stabilization of the resulting NPs can be carried out by both primary and secondary metabolites of lichens.
- The suitable choice of lichen species can lead to the production of NPs with appropriate physicochemical properties.
- The antimicrobial activity of metal or metal oxide NPs may be increased by the biosynthesis process.
- Controlling the size and shape is critical to obtain effective antimicrobial activity of new formulations in physiological conditions.

Abbreviations

MDR: Multidrug-resistant
EDR: Extensively drug-resistant
MRSA: Methicillin-resistant *Staphylococcus aureus*
NPs: Nanoparticles
ROS: Reactive oxygen species
$^1O_2$*: Singlet oxygen
$^*OH$: Hydroxyl radical
$^*O_2^-$: Superoxide
$^*O_2^{-2}$: Peroxides
RNS: Reactive nitrogen species
NO*: Nitric oxide
$ONOO^-$ or NO_3^-: Peroxynitrite
MIC: Minimum inhibitory concentration

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Conflict of interest
The authors declare that they have no conflict of interest.

Ethical approval
This article does not contain any studies with animals or human participants performed by any of the authors.

Authors' contribution
MA: conceptualization and preparing the first draft; MRH and JFK: revising the manuscript.

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