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A Review on Ganoderic Acid, Cordycepin and Usnic Acid, an interesting Natural Compounds from Mushrooms and Lichens

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Review Article

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Abstract

Mushrooms and lichens are generous source of nutritional and medicinal compounds, and medicinal uses of the mushrooms and lichens still need to be worked out for their biological activities. This review aims to put ganoderic acid, cordycepin and usnic acid under light spot through representing their important as biological activities exerted by ever one. Further studies and investigations are fortified in order to find more about these interesting natural products.

Keywords: Medicinal Mushrooms; Ganoderic Acid, Cordycepin; Usnic Acid; Biological Activities

Introduction

Mushrooms are used from ancient times and have a long history as nutritious tasty food items with low fattening values and high in proteins, vitamins, iron, zinc, selenium, sodium, chitin, fibres, minerals and other important nutrients [1-5]. Besides high nutritional value mushrooms have well known medicinal usefulness due to well recognized therapeutic potential. Fruit bodies and mycelium of medicinal mushrooms are reported to contain important bioactive compounds (Such as ganoderic acid, cordycepin) with high antioxidant potential, Anticancer, Antiviral, Anti-inflammatory, Antidiabetic, anti-cholesterol and other [6,7]. Extracts from the wild mushroom fruiting body are considered as important medicines for the prevention and cure of many diseases in several parts of the world [8-11]. Wild edible mushrooms have a high nutritional property that has been consumed by people from different parts of the world, producing a wide variety of bioactive compounds such as polysaccharides, peptides, glycoproteins, triterpenoids, lipids, and their derivatives [12-14]. In the world, multidrug-resistant pathogens have been increasing extremely, and it is very urgent to search for alternative solutions to fight against multidrug-resistant pathogens. Moreover, unhealthy foods, ultraviolet radiation, as well as other environmental effects, are responsible for generating free radicals, oxidative stress, and numerous health diseases [15-20]. Hence, the wild edible mushroom could be an alternative source of new antimicrobial potential and possesses antioxidant properties that can play significant roles in preventing various health diseases. In this review, we focus on investigating the antimicrobial, antioxidant, anticancer, antiviral, anti-inflammatory, anti-diabetic, anti-cholesterol and others potential of wild edible mushrooms and their bioactive compound production [21-24].

Biologically active compounds from species of the phylum Basidiomycota and Ascomycota have been shown a wide range of pharmacological activities and provide a massive reservoir of potential innovational drugs. The aim of this review is to discuss some mechanisms of action involved in antioxidant, anti-inflammatory, cytotoxic/anticancer and other bioactivities attributed to the most common important bioactive compounds like Ganoderic acid and Cordycepin,

from the genera *Ganoderma* species and *Cordyceps* species belonging to the phylum Basidiomycota and Ascomycota. We show that isolated ganoderic acid and cordycepin from *Ganoderma* species and *Cordyceps* species fruit bodies, and other secondary metabolites like polysaccharides that presented antioxidant properties and other bioactivities. Investigating the mechanisms of action of biologically active compounds (Ganoderic acid and cordycepin) extracted form medicinal mushrooms (*Ganoderma* species and *Cordyceps* species) and other medicinal edible mushrooms will facilitate further efforts to accelerate the discovery of novel therapeutic strategies [25-26].

Lichens are unique structures formed by an association between fungi and algae or cyanobacteria, by developing a unique morphological form that is separate from either component organism [27-29]. They have been used by humans for centuries as food and as a source of dye, and for their therapeutic properties in traditional medicine [30]. An exhaustive collection of papers on these topics is Sylvia Sharnoff's database on human uses of lichens. The introduction of the innovative analytical techniques, TLC and HPLC, in the 1960s represented a significant contribution to the identification of a large number of lichen substances. In this often-mutualistic relationship, the fungus and the algae are referred as mycobiont and the phycobiont, respectively [31]. The mycobiont component most commonly belongs to the Ascomycetes, however, some may be Basidiomycetes and may even form mushroom-like spore bearing structures. The Phycobiont component belongs to the divisions Chlorophyta and Cyanophyta [32]. Lichens can grow on a range of surfaces from rocks to existing as epiphytes on trees or leaves [33]. The vegetative component of lichen is called the thallus and this can be subdivided into four main categories. Foliose: A leaf-like thallus, attached to the substrate at various points. Crustose: A thallus which is flattened against the substrate and its lower surface is entirely attached. Fruticose: the thallus is mainly composed of pendulous or, less commonly, upright branches and is attached at a single point. Squamulose: In which the thallus begins like a foliose lichen, but subsequently develops erect branches named podetia [34,35].

The lichen has different functional layers and each functional layer accumulates specific secondary metabolites such as upper cortex which is mycobiont layer (accumulates atranorin, parietin, usnic acid, fungal melanins), medullary layer (accumulates physodic acid, physodalic acid, protocetraric acid), and an algal layer which is having photobionts [36]. Most of the lichen secondary metabolites exhibit significant biological activities. For example, Usnic acid exhibits several biological properties such as antimicrobial, larvicidal, anticancer, and UV absorption etc. Lichens play an important role in many ecosystems and exist as a symbiotic association between fungi and algae or cyanobacteria. This symbiosis results in the production of unique secondary metabolites known as lichen substances, which arise within the thalli and are typically in crystal form on the surface of the fungal hyphae. Recently, lichens and their secondary metabolites have been receiving increased attention due to their nutritional value and pharmaceutical potential, [27-29,37,38]. This review aims to highlight on the importance of common lichen secondary metabolites usnic acid and summarises the most relevant studies, and focusing on a number of biological activities in different fields.

Ganoderic Acids

Mushrooms are rich sources of biologically active compounds and cosmetic ingredients [39]. *Ganoderma lucidum*, a traditional medicinal mushroom, has been used to treat and prevent various diseases for two millennia in Asian countries [40]. Ganoderic acids (GAs), a type of tetracyclic triterpenoid, are one of the major ingredients of *Ganoderma lucidum* and have diverse pharmacological activities, including antitumor, anti-metastasis, anti-HIV, antiviral, hepatoprotective, hypocholesterolemic antioxidant, and antiaging effects [41].

Ganoderma lucidum is a mushroom that has a long history of medicinal use in the Far East countries as this mushroom is revered for its supposed miracle cures and life improving properties. Recently, this mushroom has come under scientific scrutiny to examine the possibility of finding biologically active compounds that may have an impact on human physiology. The main category of biologically active compounds produced in the *Ganoderma lucidum*, are the triterpenoids, which are known as Ganoderic Acids [42]. *Ganoderma lucidum* contains a wide variety of bioactive compounds, such as, terpenoids, steroids, phenols, and nucleotides and their derivatives, glycoproteins, and polysaccharides. The biologically active molecules that may have a particular interest in the clinical setting are the terpenes and more specifically ganoderic Acids. Terpenes are a class of compounds produced by the *Ganoderma lucidum* which are carbon structures composed of one or more isoprene C5 units. Ganoderic acids (Figure 1) are classified as Triterpenes, a subtype of triterpenoids, as they are composed of six isoprene units [43].

In spite of their important biological functions, the low production of Ganoderic acids is a bottleneck for clinical trials and commercial applications [44,45]. At present, Ganoderic acids is mainly obtained from fruiting bodies and mycelia of *Ganoderma lucidum.* Compared to fruiting body cultures, a submerged culture is a promising alternative for the production of triterpenoids, as it is easy to control the product quality and is cost effective. Many efforts, such as by

operating fermentation conditions, developing bioprocessing and elicitor strategies, and metabolic engineering, have been conducted to increase the production of Gas by fermentation of mycelia. *Ganoderma lucidum*, common name Ling-Zhi in Chinese and Reishi in Japanese, has been used as a traditional medication for prevention and treatment of various human diseases for several thousand years in Asia [46,47]. Also, according to different functional groups and side-chain types, structural skeleton of Ganoderic acids can be classified into three categories [47]. The great extent of oxidative modification (with hydroxyl, oxo, acetoxyl group), especially at C-3, C-7, C-15, and C-22 positions. Until now, GAs is mainly extracted from the solid cultivated fruiting bodies of *Ganoderma lucidum* [48].

Ganoderic Acid-DM may be a potential therapeutic candidate to treat an assortment of cancers as well as other diseases. His compound is capable of inducing apoptosis in cancer cells while exhibiting minimal toxicity to healthy cells. Ganoderic Acid-DM is also capable of stimulating an immune response in the tumor environment to potentially provide long-term protection from the malignant tumors [43]. More studies provide great support for utilizing Ganoderic Acid-DM as an alternative or supplemental therapy for various types of cancers, and more research is required to better understand the full scope of molecular targets Ganoderic Acid-DM [43]. Li and Wang described ganoderic acid extracted from *Ganoderma lucidum* as an anti-hepatitis B agent since it inhibited virus replication [49]. Zhang, et al. recorded the significant anti-viral activity of *Ganoderma lucidum* against enterovirus, which is the major cause of hand, foot and mouth diseases [50]. Li, et al. and Yuen & Gohel reported that Ganoderic acid X produced by *Ganoderma amboinense* and *Ganoderma lucidum* have significant Anti-cancer activity [51,52]. Also Sliva, et al. and Zhang, et al. mentioned that Ganoderic acids from *Ganoderma lucidum* has Anti-oxidant activity and Anti- Microbial Activity [53,54].

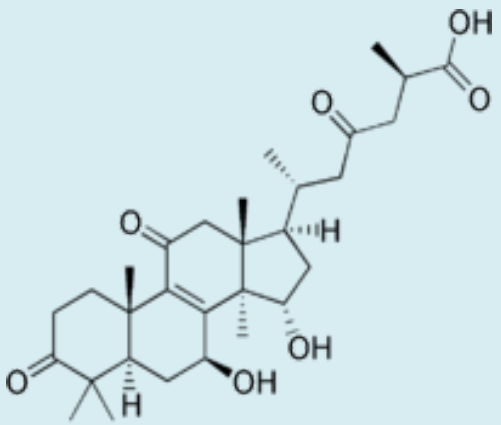

Figure 1: Structure of Ganoderic acids A.

Cordycepin

Cordyceps is a type of Ascomycetes which parasitizes insect larvae, grows and gradually changes into a fruit body [55]. In the early 1980s, many scientific institutes began to study the cultivation of *Cordyceps sinensis*. Previous work, over the course of a decade, was mainly focused on the anamorphic fungi related to *Cordyceps sinensis*. The Sichuan TCM Institute also achieved the artificial cultivation of *Cordyceps sinensis*, although commercial production has not been carried out because of the high cost and low stability [56,57]. *Cordyceps militaris* and *Cordyceps sinensis*, are a macro fungus of biomedical importance, contains a number of bioactive components. Many of them are biological response modifiers which activate our immune systems for a multitude of defensive functions. The immunomodulating effects are associated with its antitumour and other different biological activities. Cordycepin (Figure 2) was first isolated from *Cordyceps militaris* and its structural formula was confirmed as 3'-deoxyadenosine but it is only found in natural *Cordyceps militaris* with very low content and cannot be detected in the cultured ones [58]. Cordycepin is the most considerable adenosine analogue from some *Cordyceps*, which is a derivative of the nucleoside adenosine differing from the latter by the absence of oxygen in the 3' position of its ribose entity [59]. Cordycepin is a category of compounds that exhibits significant therapeutic potential and has many intracellular targets, including nucleic acid, apoptosis, and cell cycle. Cordycepin can participate in various molecular processes in cells because of its similarity with adenosine [60,61]. Cordycepin, a metabolite of *Cordyceps militaris,* cordycepin has been investigated previously for its pharmacological potential, particularly in connection with the use of *Cordyceps militaris* fruiting bodies as a traditional herbal medicine. It has been reported to have anti-inflammatory as well as anti-tumour and anti-angiogenic properties [50,62-64].

Up to now, in fact, the artificial cultivation of this valuable fungus has not been successfully achieved; only a product made using a *Cordyceps sinensis* anamorph has been made by fermentation methods. Modern experimental methods in biochemistry have proved that *Cordyceps sinensis* consists of active constituents such as crude fats, proteins, fibre, carbohydrate, cordycepin, cordycepic acid, polysaccharide, a series of vitamins, mannitol, nucleosides, ergosterol, aminophenol and trace elements [16,65]. It has a broad medical effect, and its function of immunity regulation plays an important role in antitumour effects, organ transplantation and the prevention of kidney, liver and heart disease [66,67].

On the other hand, *Cordyceps sinensis* is a complex of larva and parasitic fungus, many species in this genus are

valuable medicinal fungi with broad development potential. The parasitic complex of the fungus and caterpillar, well known as 'DCXC', is only found in the prairie soil at an elevation of 3500–5000 m. It is mostly distributed in Tibet, Qinghai, Sichuan, Yunnan and Gansu province in China. While complexes consisting of other species of fungi and insects are called 'ChongCao', not 'DCXC' [68].

Although the pharmacologically active components of *Cordyceps sinensis* are still unresolved, at least two chemical constituents, cordycepin and cordycepic acid, have been identified and proposed as important active constituents. It is now believed that cordycepic acid is, in fact, D-mannitol, and that cordycepin is 3'-deoxyadenosine (3'-dA), a purine alkaloid, a derivative of the nucleoside adenosine, differing from the latter by the absence of oxygen in the 3' position of its ribose part [16].

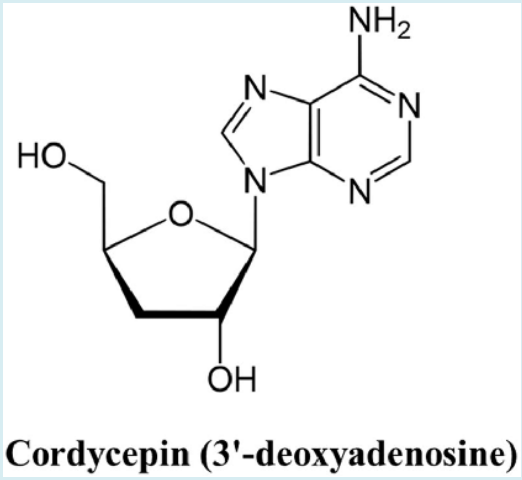

Figure 2: Structure of Cordycepin (3'-deoxyadenosine).

Usnic Acid

Lichen substances are derived for defence against most of the pathogens in nature. There are several interesting examples found reported in literature. Atranorin isolated from *Physcia aipolia*, fumarprotocetraric acid isolated from *Cladonia furcata*, gyrophoric acid isolated from *Umbilicaria polyphylla*, lecanoric acid isolated from *Ochrolechia androgyna*, physodic acid isolated from *Hypogymnia physodes*), protocetraric acid isolated from *Parmelia caperata*, stictic acid isolated from *Parmelia conspersa* and the most important lichen substances is usnic acid isolated from *Flavoparmelia caperata*, *Pseudocyphellaria glabra*, *Pseudocyphellaria homoeophylla*, *Usnea campestris, Usnea diffracta, Usnea longissima*, *Usnea misaminensis* and other exhibited potential antimicrobial effects against six types of bacteria and ten types of fungi, including human, animal, plant pathogens, mycotoxin producers and food-spoilage organisms [69]. Usnic acid (Figure 3) is a yellowish pigment produced by several lichen species. It is a product of the secondary metabolism of the fungal partner and it exists in two enantiomers which differ in the orientation of the methyl group located in position 9b.

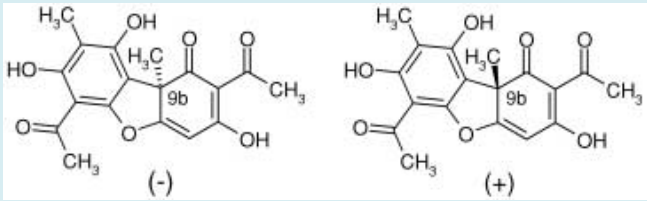

Figure 3: Structure of (–)-usnic acid and (+)-usnic acid enantiomers.

Usnic acid seems to play many biological roles such as: antibiotic, antimycotic, antifeedant, phytotoxic, photobiont regulator, UV filter. The difficulty of culturing whole lichen thalli in controlled conditions for an appropriate length of time clearly represents a limitation for research. Usnic acid probably does not have a single main biological role, but can play different, species-specific roles, also depending on habitat factors. Further investigations are necessary in order to test these hypotheses [70]. Usnic acid seems to be an exclusive lichen product. No synthetic derivatives more effective than the natural form are known. On the other hand, both the (+) and (–) enantiomers of usnic acid are effective against a large variety of Gram-positive (G+) bacterial strains. The (+)-usnic acid enantiomer appears to be selective against *Streptococcus mutans* without inducing perturbing side effects on the oral saprophyte flora. Furthermore, the (–) usnic acid enantiomer is a selective natural herbicide because of its blocking action against a specific key plant enzyme [70].

Usnic acid has significant biological profile against pathogenic gram +ve organisms and anaerobic bacteria [71]. In addition, usnic acid has also been used in topical preparations, toothpastes and mouth washes. Lichen compounds significantly inhibit bacterial growth at lower concentration, while comparing with other antibiotics [36]. Usnic acid is class of dibenzofuran functional group and it has multiple biological activities. It shows antitumor activity against Lewis Lung carcinoma and P388 leukaemia through the mechanism of mitosis inhibition and apoptotic induction [71,72]. Usnic acid was found to be a good antimicrobial agent when compared to streptomycin [73]. (+)-usnic acid produced by *Cladonia arbuscula* (Have antimycobacterial activity), and (–) usnic acid produced by *Cladonia leptoclada* (Have anti-tumour activity) [74,75]. Also Odimegwu, et al. and Bhattacharjya, et al. reported that, usnic acid produced by *Pseudocyphellaria glabra* and *Pseudocyphellaria*

homoeophylla have antiviral, antimicrobial and cytotoxic activities [76,77]. *Usnea campestris, Usnea diffracta, Usnea longissima* and *Usnea misaminensis* can produced usnic acid which have different biological activities (Antimicrobial and anti-inflammatory) [78,79].

Moura et al., and Gylfason, mentioned that, usnic acid produced by *Cladonia* spp. and *Alectoria ochroleuca*, have antibiotic activity and antifungal. *Protousnea poeppigii* produced usnic acid, Isodivaricatic acid, 5-propylresorcinol and divaricaticacid have different biological activities like Antiprotozoal, antifungal [73,80,81]. D-Usnic acid, evernic acid and atranorin produced by *Pseudoevernia furfuracea* have significant anti-Allergy activity [82]. *Parmotrema dilatatum, Parmotrema tinctorum* and *Pseudoparmelia sphaerospora* all can produce usnic acid, orsellinic acid esters and salazinic acid, all have significant anti-*Mycobacterium tuberculosis* [83]. Usnic acid isolated from *Ramalina terebrata* and *Parmelia caperata* inhibits the growth of *Bacillus subtilis, Staphyrococcus aurens, Escherichia coli* and *Pseudomonas aeruginosa* [84]. (-)-Usnic acid isolated from *Cladonia stellaris* and *Alectoria sarmentosa*, active against *Staphylococcus aureus* [85-88].

Also, more research is needed to make possible intensive lichen culture, in order to produce large quantities of lichen usnic acid and other substances for pharmaceutical, cosmetic and agricultural purposes. Some biological aspects, i.e. the possible biological roles of usnic acid, need to be investigated and discussed.

Conclusion

Studies with mushrooms and lichens have been developed recently and it is figured out that potent property of secondary metabolites from different wild mushroom and lichens species showed great biological activities. There is a growing interest in active metabolites that are obtained from these natural sources as an alternative to synthetic drugs like ganoderic acid and cordycepin from wild mushrooms and usnic acid from lichens.

Several compounds are responsible for the therapeutic activities of many medicinal mushrooms and lichens genera, the main groups of these compounds are polysaccharides, terpenes, phenolic compounds, and essential amino acids, as well as minerals. Ganoderic acid and cordycepin from wild mushrooms and usnic acid from lichens are showing the most potent therapeutic activities.

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