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Antioxidant potential and other medicinal properties of edible mushrooms naturally grown in Iran.

Sharareh Rezaeian[1], Sara Saadatmand[1*], Taher Nejad Sattari[1], Amin Mirshamsi[2]

[1]Department of Biology, Science and Research Branch, Islamic Azad University, Tehran, Iran.

[2]Department of Biotechnology, Faculty of Agriculture, Ferdowsi University of Mashhad, Mashhad, Iran.

Abstract

Wild edible mushrooms have been collected and consumed by people from many countries for thousands of years, having been known to possess various pharmacological benefits. There is a great variety of wild populations of mushrooms in different climate and geographical regions in the world. However, there is inadequate data in the literature regarding identity and medicinal and biochemical properties of Iranian wild mushrooms. The focus of this mini-review is largely on identification of Iranian wild mushrooms and their antioxidant potential. In addition, it tries to outline achievements in investigation of other pharmacological activities of these wild mushrooms. This review may encourage more research into biochemical properties and chemical analysis in a range of edible mushrooms growing wild in various climatic regions of the country. It might also be helpful for researchers from other countries that have a significant resource of wild mushrooms but have not yet launched research programs on collection, identification, recovery, and assessment of wild edible mushrooms.

Keywords: Iranian wild mushrooms; Antioxidant activity; Medicinal properties; Molecular identification.

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Introduction

Over decades, edible mushrooms have been considered one of the most prominent functional foods. They have earned this reputation based on a body of information demonstrating that edible mushrooms are excellent sources of fiber, essential oils, protein (including all the essential amino acids), vitamins, minerals, lectins, and bioactive compounds [1]. However, the current cultivated mushrooms are a very small proportion of the total wild mushrooms, as many of wild mushrooms have not yet been standardized for cultivation [2]. Thus, it is not surprising that the interest in exploring nutritional and medicinal capabilities of wild mushrooms has been increasing.

At least, three review articles have exclusively focused on a specific area of medicinal properties of mushrooms, including antioxidant [3], anticancer [4], and antibacterial activities [5]. In addition, a number of other review articles have covered a wider range of pharmacological and medicinal properties of edible mushrooms, including antimicrobial, anticancer, antioxidant, antiviral, immunomodulatory, immunosuppressive, anti-allergic, anti-inflammatory, and anti-cholesterol activities [6]. Among other medicinal properties, the antioxidant activity of edible mushrooms could be directly applicable to daily life, as it may associate to natural prevention of oxidative stress that itself is largely influenced by lifestyle habits [7].

Over the past decade, advances have been made in research on antioxidant properties of Iranian wild mushrooms. Therefore, in order to update the existing knowledge, this review will outline efforts on collection, identification and study of medicinal properties of edible mushrooms growing wild in Iran. The main focus of this mini-review is on antioxidant activity, though other important medicinal properties have been mentioned. It may also encourage researchers from other countries (similar to Iran) to develop protocols for collection and cultivation of well-identified wild mushrooms and explore their pharmaceutical properties.

Oxidative Stress and Natural Antioxidants

Oxidative stress is a well-known phenomenon caused by an imbalance between formation and removal of reactive micro-molecules such as reactive oxygen species (ROS). In a broad spectrum, the term of ROS may refer to both the oxygen-centered radicals and non-radical derivatives of O2 (such as hydrogen peroxide, singlet oxygen, and hypochlorous acid) [8]. These reactive molecules may be produced in all mammalian cells in response to exogenous stimuli through normal cellular metabolism or activation of membrane-bound enzymes [8, 9]. Oxidative stress has the potential to damage cells and may eventually lead to cancer, cardiovascular diseases, diabetes, aging, and a vast number of other illnesses and disorders [10]. The human body's defense system responds to oxidative stress generally through scavenging or lessening ROS formation

using endogenous and/or diet-derived molecules [9]. However, the antioxidant defense system needs to be assisted by consumption of antioxidant-containing supplements. Due to carcinogenic risks associated with consuming synthetic antioxidants, there has been increasing interest to replace synthetic antioxidants by natural sources of antioxidants, namely vegetables, herbs, fruits and mushrooms [11].

Wild Edible Mushrooms as Sources of Antioxidants

Up to the present, only around 40 mushroom species have been commercially cultivated. Although recent efforts have been made to standardize cultivation of wild edible mushrooms, the number of cultivated mushrooms is still a very small proportion of the total number of wild mushrooms, as it has been estimated that the number of wild mushrooms could reach around 140,000 [2].

A number of studies have reported antioxidant capability of wild or cultivated edible mushroom species, extensively reviewed by Ferreira et al., 2009 [3]. Most of these studies have measured antioxidant activity through in vitro assays including DPPH inhibition, reducing power, ferric chelating, and biochemical assays including lipid peroxidation inhibition. In addition, a number of compounds related to antioxidant activity have been identified, including polyphenols (phenolic acids, phenylpropanoids, lignin, melanins, tannins, and flavonoids), β-caroten, and ascorbic acid [12].

In recent years, there has also been increasing research on testing antioxidant activity of mushrooms in animal model systems. The findings of a study demonstrated that polysaccharides of the spent compost of *Ganoderma lucidum* lowered lipid peroxidation and increased catalase levels in vivo [13]. Another study reported that polysaccharides of a Chinese wild strain of *Agaricus bisporus* exhibited anti-hypoxic activity and prolonged the survival time. It also decreased the blood urea nitrogen and lactic acid contents and increased the liver glycogen significantly. The findings were compared with the blank control and the commercialized product Hongjingtian [14].

Current Status of Research on Wild Mushrooms in Iran and Other Countries

Cultivation of mushrooms and their use in folk medicine in regions such as East Asia dates back to thousand years. In fact, local people in East Asian countries had been using wild edible mushrooms for nutritional and medical purposes, long before commercial mushroom growing was standardized [1]. Thus, it is not surprising that therapeutic properties of wild mushrooms such as *G. lucidum* have been indicated in ancient pharmacopoeia of countries like China [15]. Nevertheless, there is no recorded history of wild mushrooms in many other countries in which the importance of wild mushrooms has largely been ignored.

Thus far, at least one review article has outlined studies undertaken on antioxidant activities and phenolic composition of wild mushrooms in different countries; including: India, Taiwan, Turkey, Spain, China, Korea, Portugal, Finland, and Brazil [3]. Moreover, the literature shows that research on nutritional composition, antimicrobial and anticancer activities of wild mushrooms have also been performed mostly in the afore-mentioned countries [5,12].

There are several more recent research articles reporting antioxidant activity, biochemical analysis and nutritional composition of wild mushrooms from many other countries or regions that could be added to the existing knowledge, including African countries such as Nigeria [16], Ghana [17], Kenya [18], and Tanzania [19], Australia [20], the middle-east [21], Pakistan [22], Europe [23] and Mexico [24].

As opposed to a great history of medicinal use of herbs and plants in Iran [25], medicinal properties of wild mushrooms do not have any significant place in the folk medicine. Over decades, mushroom technology has significantly advanced in the country and has found a commendable place in the market. However, what is currently more known about mushrooms is their protein content, whilst their other significant medicinal or nutritional properties are largely overlooked. Therefore, there is apparently a low public awareness on specific medical properties of mushrooms.

During the past years, several research programs have been launched to collect and identify Iranian wild mushrooms [26-29]. Antioxidant activity and some other pharmacological benefits of these wild mushrooms have also been investigated (Table 1). However, most of these studies have been limited to the North of Iran (along the Caspian Sea), while various geographical and climatic zones could be found in Iran that has a total land area of 1,648,195 square kilometers. It is believed that Iran would be a center for accessing valuable and scarce medicinal plant species [30]. Furthermore, it has been estimated that there might be around 3500 fungi species in the country [31].

Table 1: *Summary of reports on Iranian wild mushrooms collected and studied for pharmacological activities.*

Species	Location of collection	Method of authentication	Type of assay	Reference
Ganoderma spp.	Northern Iran (Mazandaran and Guilan provinces)	Morphological identification	Antibacterial activity and chemical analysis	43,44,47
Agaricus bisporus	North-Eastern Iran (Khorasan Razavi province)	ITS molecular analysis	In vitro antioxidant activity and antibacterial activity	29,45
Agaricus spp and *Pleurotus* spp.	North-Eastern Iran (Khorasan Razavi province)	ITS molecular analysis	In vitro antioxidant activity	42

Several mushroom species: *Morchella* spp., *Cantharellus cibarius*, *Pleurotus ostreatus*, and *Russula paludosa*	Northern Iran (Guilan province)	Morphological identification	Chemical analysis without further biological assays	28
Phellinus torulosus	Northern Iran	Morphological identification	*In vitro* antioxidant activity	35
Cantharellus cibarius	Northern Iran	Morphological identification	*In vitro* antioxidant activity	36
Laetiporus sulphureus	Northern Iran	Morphological identification	*In vitro* antioxidant activity	32

Antioxidant activity

The previous findings of our research group with the ethanolic extract of the wild mushroom *Laetiporus sulphureus* (collected from Mazandaran in the north of Iran) showed a considerable antioxidant activity for this mushroom. The inhibition of linoleic acid by *L. sulphureus* extract, BHA and α-tocopherol at 160 µg/ml was found to be 79.2%, 92.3%, and 96.2%, respectively. In addition, the extract at 800 µg/ml inhibited 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radicals by 82%, whereas its total phenol content was 58.8 ± 0.23 µg/ml (pyrocatechol equivalent) [32]. *L. sulphureus* is considered as a wood-rotting basidiomycete that grows on several tree species. Various medicinal properties have been reported for this mushroom, including antioxidant, antibacterial, antifungal, and anti-proliferative activities [33]. On the contrary, it has been demonstrated that this mushroom produces a type of a toxic lectin (similar to bacterial toxins) which has haemolytic and haemagglutination activities [34]. Cultivation of this mushroom has not yet been reported in Iran.

In vitro antioxidant activity of Iranian medicinal mushroom *Phellinus torulosus* has been reported [35]. The total methanol extract of *P. torulosus* showed a significant antioxidant activity, but its butanol fraction had a stronger activity than the total methanolic extract [35].

Recently, another research group has reported antioxidant activity of a medicinal edible mushroom *Cantharellus cibarius* collected from Northern Iran [36]. Various fractions of the methanolic extract including n-hexane, chloroform, ethyl acetate, n-butanol, and water, were evaluated for antioxidant activity. The n-hexane fraction had the highest amounts of flavonoids contents (40.01 ± 1.30 mg quercetin equivalent per gram of extract), nitric oxide scavenging activity (77.21 ± 1.48%), and total phenols (40.97 ± 0.99 mg gallic acid equivalent per gram of extract). However, it was the ethyl acetate fraction that showed the highest DPPH scavenging activity (33.43 ± 1.30%), although the aqueous fraction displayed higher reducing power [36].

Our research team has collected over 100 samples of wild mushrooms belonging to various genera from east-northern Iran (Khorasan Razavi Province) during the year 2012, including *Agaricus* spp., *Pleurotus* spp., *Lentinus* spp., and *Flammulina* spp. The collected mushroom specimens were then authenticated by Internal Transcribed Spacer (ITS) sequencing analysis [29]. Mycelia of the mushroom strains are periodically cultured in order to maintain their viability. Antioxidant activities of crude methanolic extracts of four wild strains of the button mushroom, *A. bisporus*, was then evaluated in comparison with four cultivated strains. The results showed that wild strains possessed significantly greater antioxidant activity, and higher levels of phenol, flavonoid and anthocyanin content, as compared to the cultivated strains [29].

Among the tested mushrooms, a brown wild isolate of *A. bisporus* considerably exhibited the greatest antioxidant activity as well as the highest level of phenolic content (9.6 mg GAEs/g dry weight). This amount of phenol was higher than those of wild *A. bisporus* reported from Turkey [37], Portugal [12] and China [38] with the phenol amounts of 4.02 4.49 and 6.18 mg GAEs/g, respectively. But it was lower than that of another Turkish wild *A. bisporus* with 13 mg GAEs/g [39]. The selected Iranian wild *A. bisporus* was further subjected to mycelia growth characterization [40] and standardization of cultivation [41]. Therefore, it was possible to maintain mycelia and fruiting bodies of the collected wild specimens and facilitate reproducibility of further pharmacological bioassays.

These studies were further broadened by assessing antioxidant activities of methanol-dichloromethane (1:1) extracts of a range of *Agaricus* and *Pleurotus* species, using various chemical and biochemical assays. In this study, for the first time, we also reported the cultivation of two wild species of *Agaricus*; *A. devoniensis* and *A. gennadii*. These two species proved to be potent antioxidants among the others, having high levels of phenols, efficient scavenging activities on DPPH radicals, high chelating abilities, and an apparent high reducing power [42].

So far, no report of cultivation or medicinal properties of *A. devoniensis* and *A. gennadii* has been found in the literature. Thus, it was not possible to compare their antioxidant competency with those of other countries. As compared to *A. bisporus*, the phenol content observed in the Iranian wild *A. devoniensis* (5.8 mg GAEs/g) and *A. gennadii* (4.9 mg GAEs/g) was lower than that of wild *A. bisporus* reported in Turkey [39] and China [38]. This amount of phenol, however, was higher than those reported in another Turkish study [37] and Portugal [12], respectively.

Antibacterial activity

Few studies have been conducted to investigate antibacterial activities of mushrooms from Iran. The antibacterial activity of a chloroform extract from an Iranian wild strain of *G. lucidum* (collected from Northern Iran) was evaluated. Different concentrations of the crude extract were tested against Gram-positive bacteria (*Bacillus subtilis*, *Staphylococcus aureus*, and *Enterococcus faecalis*) and Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeroginosa*). The minimum inhibitory concentration (MIC) as well as minimum

bactericidal concentration (MBC) for *S. aureus* were 8 mg/ml, while for *B. subtillis*, they were 8 and 16 mg/ml, respectively. Further biochemical methods revealed that a variety of lipid derivatives, including sterols and triterpenoid acids, were present in the chloroform extract [43].

A more recent study on another Iranian wild strain of *G. lucidum* (collected from Northern Iran) demonstrated that the hexane fraction had the following constituents: ergosta-7,22-dien-3β-yl acetate, ergosta-5,7,22-trien-3β-yl acetate (isopyrocalciferol acetate), ergosta-7,22-dien-3-one, ergosta-7,22-dien-3β-ol, and ergosta-5,7,22-trien-3β-ol (ergostrol). In addition, the structure of ganodermadiol was shown after purification from the chloroform fraction. The fractions inhibited Gram-positive bacteria and yeast, with minimum inhibitory concentration values of 6.25 mg/ml, but were ineffective against Gram-negative bacteria in the tested concentrations. It was suggested that the antimicrobial effect of crude fractions was the consequence of mixing triterpenoid and steroid compounds [44].

Our recent findings on antibacterial activities of Iranian *Agaricus* spp. revealed significant differences between the wild and cultivated strains. In this study, we tested the antibacterial activity of methanol-dichloromethane (1:1) extracts of several wild and cultivated species of *Agaricus* using a colorimetric micro-dilution method. *A. devoniensis* and *A. gennadii* exhibited slight inhibitory effects against only *Staphylococcus aureus*, though the cultivated *A. bisporus* showed quantifiable inhibition towards all the Gram-positive bacteria. Two different fractions eluted from the crude extract of cultivated *A. bisporus* exerted quantifiable antibacterial activities, against both the Gram-positive and the Gram-negative bacteria particularly *E.coli* at 8 mg/ml [45]. Further chemical analysis is underway to discover myco-constituents present in these fractions that are responsible for the antibacterial activity.

Cytotoxic effect

As far as our investigations are concerned, there are very limited studies undertaken on cytotoxic activity of Iranian wild mushrooms. In a study, we investigated cytotoxic properties of methanol-dichloromethane (1:1) extracts of several Iranian *Agaricus* spp. against two cancerous cell lines (PC3 and MCF-7). Our findings revealed that the Iranian wild strains, including *A. devoniensis*, *A. gennadii* and a wild brown isolate of *A. bisporus* could not significantly prevent proliferation of the cells. By contrast, the extract of commercially cultivated *A. bisporus* and its ethyl acetate-petroleum ether fraction exhibited potent anti-proliferative activities, as well as cytotoxicity against PC3 and MCF-7 cells [46].

Chemical and biochemical composition of Iranian wild mushrooms

There is little known about nutritional and chemical composition of Iranian wild mushrooms. Limited studies have been conducted on mineral and biochemical analysis of mushrooms growing wild in the country. In some cases, these studies have been performed on cultivated strains of mushrooms and thus were excluded in this review.

Chemical analysis of several Iranian wild mushroom species from Guilan province (one of the Iran's Northern provinces) was reported. The mushroom species included *Morchella* spp., *Cantharellus cibarius*, *Pleurotus ostreatus*, *Amanita caesarea*, and *Russula paludosa*. Macro-minerals including P, K, Na, Ca, and Mg were measured. The highest amounts of P (8.5 mg/g), Ca (1.4 mg/ml), and Mg (1.8 mg/ml) were found in *M. procera*, while K (34.5 mg/ml) and Na (1.4 mg/ml) were found to be the maximum in *C. cibarius,* and *A. caesarea*, respectively [28].

Chemical composition of medicinal mushroom *G. lucidum* grown in Iran was compared to a Chinese strain of the mushroom. Using a reversed phase HPLC combined with UV and electrospray ionisation-mass spectrometry, it was found that the intensity of ganoderic acid C2 peak in the chromatogram of the Iranian sample was relatively low. By contrast, three high intensity peaks were attributed to ganoderic acids including ganoderic acids T, Me and H in the Chinese strain. These differences may encourage more studies on bioactive molecules in different strains grown in a variety of climatic conditions [47].

Molecular Identification of Wild Mushrooms and their Clinical and Research Implications

With the progress in molecular genetics, conventional approaches and non-PCR molecular techniques (such as isozymes and restriction fragment length polymorphism (RFLP)) for fungi identification have evolved to reliable and effective DNA-based methods [48]. In addition, the 1990's PCR-based methods such as random amplified polymorphic DNA (RAPD), amplified fragment length polymorphisms (AFLP), simple sequence repeat (SSR), and inter-simple sequence repeats (ISSR) markers have been replaced with DNA barcoding methods. DNA barcoding is defined as 500- to 800-bp sequences to identify species of all eukaryotic kingdoms using primers that are applicable for a broad taxonomic group. A DNA barcode sequence is ideally constant and unique to one species [49].

Currently, ribosomal DNA barcodes are universally accepted as efficient tools for fungi taxonomy. The eukaryotic nuclear rRNA cistron include the 18S, 5.8S, and 28S rRNA genes that are further split through posttranscriptional processes, removing two internal transcribed spacers (ITS). These two spacers, including the 5.8Sgene, are usually referred to as the ITS regions. Among the regions of the ribosomal cistron, ITS has the highest probability of successful identification for the broadest range of fungi. The 18S nuclear ribosomal small subunit rRNA gene (SSU) has fewer hypervariable domains in fungi, while the 28S nuclear ribosomal large subunit rRNA gene (LSU) has been used to distinguish species particularly for yeasts [49].

In addition to ribosomal DNA barcodes, recently protein-coding genes are widely used for phylogenetic analysis of

fungi. Several protein-coding genes may have potential as a fungal barcode, including translation elongation factor 1-α (for *Fusarium*), β-tubulin (for *Penicillium*), the largest subunits of RNA polymerase II (RPB1) (for *Basidiomycota*, *Zygomycota*, and *Microsporidia*), and a gene encoding a minichromosome maintenance protein (for *Ascomycota*). Moreover, the mitochondrial cytochrome oxidase I (COXI) locus has been used for DNA barcode for fungal taxonomy (particularly for *Penicillium*) [50].

ITS markers have also been commonly used for identification of wild mushrooms [51]. A study reported the comparison of SSU, ITS, RPB1 and RPB2 markers, showing ITS was more reliable barcode for identifying wild edible mushrooms [52]. However, there are several reports showing the potential of other barcodes for mushroom identification. COXI was shown to be more effective than ITS in several mushroom species of *Ascomycota* and *Basidiomycota*, particularly in *A. bisporus* [50, 53]. Controversially, the findings of another study showed that COXI and ITS performed similarly as a barcode among the small proportion of *Agaricomycotina*. However, in a closely related taxa, COXI was less different than ITS and failed to distinguish all samples [54]. Working on Iranian wild *Agaricus* spp, our laboratory has also demonstrated that ITS and intergenic spacer (IGS) regions were identical between genotypes of one species but different among species. On the contrary, ISSR markers were powerful enough for detection of polymorphism among closely related genotypes of one species of *Agaricus* [55]. Another study reported that an integration of IGS1 and ITS sequences gave better genetic differentiation among and within species of *Pleurotus* [56].

Despite the importance of accurate identification of wild mushrooms, still there are many articles reporting biological activity of wild mushrooms without proper authentication. In some cases, only a trivial morphological identification has been given. The lack of accurate identification and authentication of wild mushrooms might make the findings of a study unreliable [57].

Accurate characterization of wild mushrooms may also have implications for safe consumption of mushrooms and lowering the risk of mushroom poisoning. Although only around 3% of the total mushroom species might be poisonous, mushroom poisoning is a serious health risk in rural areas and mainly occurs as a result of misidentification of wild mushrooms [58]. Some of the mushroom toxins such as amatoxins seriously affect liver and account for 90% of fatal mushroom poisonings. Fatal cases due to ingestion of poisonous mushrooms are mainly reported from Western Europe, while other countries such as the US, Africa, Asia, Australia, and Central and South America have also been mentioned [58].

Currently, there is very limited local knowledge on identification of wild edible mushrooms in Iran [28]. As such, several retrospective studies have reported mushroom poisoning in patients admitted to hospitals in the country [59-61]. Clinical symptoms of mushroom poisoning reported in these studies varied from mild gastrointestinal symptoms to organ failure and death. These investigations have revealed a high rate of incidence of mushroom poisoning in Iran; 0.05% as compared to 0.005% of The US [61]. Similar situations have been reported from some other countries, such as Poland [62], where the importance of molecular identification of wild mushrooms has been described in accordance with the increasing risk of mushroom poisoning.

Conclusion and Further Research

As compared to medicinal plants, no considerable attention is paid to research programs on wild mushrooms in Iran. However, efforts have been made to collect and identify Iranian wild mushrooms. In addition, several wild mushroom species or isolates have been reported to possess promising pharmacological potentials. In this regard, wild strains of *A. bisporus*, *A. devoniensis* and *A. gennadii* have been reported to remarkably exhibit high levels of antioxidant activities and high amounts of total phenols. These strains have also successfully been adapted to be cultivated on synthetic compost. Wild strains of *G. lucidum* have also been reported to possess significant antibacterial activities. Their main compounds have been elucidated to be lipid derivatives, including sterols and triterpenoid acids. Furthermore, n-hexane and ethyl acetate fractions of a wild strain of *C. cibarius* have been reported to possess antioxidant activity and have high amounts of total phenols and flavonoids.

Despite the studies conducted to collect Iranian wild mushrooms and evaluate their medicinal properties, still there are drawbacks and limitations that should be taken into account. Firstly, collection of the wild mushrooms has been limited to the Northern regions, while their identification has largely been dependent on conventional methods. In addition, many of the collected mushroom isolates are not accessible for utilization by other researchers. Therefore, establishment of a germplasm bank of well-authenticated Iranian wild mushrooms is essential in order to study, conserve, and characterize genetic diversity of wild mushrooms. This bio-bank should be able to supply a reliable source of mushroom strains for researchers. Finally, still little is known about nutritional and pharmacologically active constituents of mushrooms growing wild in Iran that warrant further investigations.

Considering the high prevalence and incidence of cancers in the country, natural antioxidants prepared from wild mushrooms could have a place in the future. Thus, further research studies on various pharmacological aspects of wild mushrooms are warranted. Wild mushrooms might also be directly used in the daily diet, if accurate identification, nutritional analysis and allergic reactions tests are performed.

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Correspondence to:

Sara Saadatmand Department of Biology
Science and Research Branch
Islamic Azad University
Tehran
Iran