COURSE #98210 — 3 CONTACT HOURS/CREDITS Release Date: 10/01/24 Expiration Date: 09/30/27

Medicinal Mushroom Supplements

HOW TO RECEIVE CREDIT

- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a physician or Florida nurse, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
- Receive your Certificate(s) of Completion by mail, fax, or email.

Faculty

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Faculty Disclosure

Contributing faculty, Natalie Yates, PharmD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Division Planners/Director Disclosure

The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for healthcare professionals in any practice setting whose patients may be taking mushrooms for potentially medicinal uses.

Accreditations & Approvals

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A complete Works Cited list begins on page 19.

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NetCE designates this continuing education activity for 3 ANCC contact hours.

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Special Approvals

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About the Sponsor

The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

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Disclosure Statement

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Course Objective

The purpose of this course is to help healthcare professionals in all practice settings increase their knowledge base on medicinal mushrooms.

Learning Objectives

Upon completion of this course, you should be able to:

1. Name the main bioactive compounds found in medicinal mushrooms.
2. Discuss which medicinal mushrooms should be used cautiously with certain disease states.
3. Recognize which medicinal mushrooms have the potential to cause severe adverse effects.
4. Identify interactions between specific medicinal mushrooms and drugs, herbs, and supplements.
5. Describe which conditions specific medicinal mushrooms have evidence to support their use.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION AND BACKGROUND

In 1991, a Neolithic corpse called the "Ice Man" was discovered in an Alpine glacial field near the Austrian-Italian border who, according to radiocarbon dating, lived between 3350 and 3100 B.C.E. Among the Ice Man's belongings were three fungal objects. There is still speculation about whether the intended use of the mushrooms was medicinal, spiritual, or utilitarian, but this discovery suggests that humans and mushrooms share a long history [1].

Humans have used medicinal mushrooms for thousands of years for their culinary, nutritional, and medicinal value. Recently, there is increased public interest in medicinal mushrooms due to possible anticancer, antidiabetic, antimicrobial, antioxidant, anti-obesity, and immunomodulatory effects [2]. However, the therapeutic properties and mechanisms of action are still not well understood. In vitro and animal research is used to elucidate the pharmacological activity of medicinal mushrooms, but studies in humans on the safety and efficacy of medicinal mushrooms are lacking [3]. This course reviews the properties of certain medicinal mushrooms and the current evidence for their safety and use as medicine.

WHAT ARE MUSHROOMS?

Mushrooms are part of the Eukarya domain, which includes all organisms that have a nucleus. Mushrooms are members of the Fungi kingdom, which also includes yeast. Mushrooms are mostly multicellular, but there are some types that are unicellular. The general structure of the most commonly known mushrooms, sporophores, is the fruiting bodies made up of the cap and the stalk, which stem from an underground network of strands called mycelium [4]. Mushroom mycelia can live for hundreds of years, so long as there is a food supply available and temperature and moisture levels are adequate [4]. Less recognizable mushrooms, called polyphores, are heterogeneous in form but usually include fruiting bodies with pores on the underside and grow on dead or living trees, sometimes as pathogenic organisms [4].

By fresh weight, most commercially available mushrooms are approximately 90% water, 3% protein, 5% carbohydrates, 1% fat, and 1% minerals and vitamins [4]. The most important bioactive compound with potential use for prevention and treatment of human disease are polysaccharides, which are structural components of the fungal cell wall [3]. It is theorized that polysaccharides are responsible for immunomodulatory effects of medicinal mushrooms by binding to certain cell wall receptors and stimulating specific immune responses [3]. Polysaccharides are also thought to contribute to antitumor, antioxidant, anti-inflammatory, antimicrobial, and antidiabetic effects of medicinal mushrooms [3]. Another important bioactive compound in medicinal mushrooms are terpenes, which modulate the immune system by stimulating the expression of genes implicated in immune responses [3]. They are also thought to have anti-inflammatory, antioxidant, and antitumor properties [3]. Other bioactive constituents of medicinal mushrooms thought to contribute to their medicinal value are proteins, phenolic compounds, antioxidants, copper-containing oxidases, and fatty acids [3].

MEDICINAL MUSHROOMS

Medicinal mushrooms are used to enhance health or treat certain medical conditions and do not cause people to hallucinate. ***Table 1*** provides a summary of the medicinal mushrooms discussed in this course, including details on their effectiveness, adverse effects, and potential interactions. Psychedelic mushrooms contain psychoactive compounds, such as psilocybin and ibotenic acid, that can cause hallucinations during which people see, hear, and feel things that are not there. However, the lines between medicinal and psychedelic mushrooms are becoming increasingly blurred as research has ramped up on the possible health benefits of psychedelic mushrooms, particularly for mood disorders, substance misuse, and pain.

SUMMARY OF MEDICINAL MUSHROOMS EFFICACY AND SAFETY				
Mushroom	**Description**	**Adverse Effects**	**Effectiveness**	**Interactions**
Agaricus blazei	Small brownish cap mushroom from Brazil	Gastrointestinal Hepatotoxicity	None known	Hypoglycemic agents Liver disease 5-S-Cysteinyldopa lab test
Black hoof	Orange mushroom grows on mulberry trees	None known	None known	CYP1A1, 1A2, 2E1 Immunosuppressants Benign prostatic hyperplasia (BPH)
Chaga	Parasitic fungus that forms "conks" on birch tree trunks	Acute oxalate nephropathy	None known	Anticoagulants and antiplatelets Hypoglycemic agents Immunosuppressants
Cordyceps	Fungus that grows on moth caterpillar larvae	Gastrointestinal	CKD, diabetic nephropathy	Anticoagulants and antiplatelets Immunosuppressants Testosterone
Fly agaric	Red cap mushroom with white spots	Poisonous Gastrointestinal, hallucinations, coma, cardiac arrest	None known	None known
Lion's mane	Long, dangling fleshy spines grows on hardwood trunks	Gastrointestinal, skin rash	None known	Anticoagulants and antiplatelets Hypoglycemic agents Immunosuppressants
Maitake	Mushroom clumps on stumps or trunks of trees	Gastrointestinal	None known	Hypoglycemic agents Hypotensive agents Warfarin
Poria	Sclerotium that grows on pine tree roots	None, other than rare mild allergic reactions	None known	Anticholinergics Cholinergics CNS depressants
Reishi	Shiny, woody flesh with bitter taste	Gastrointestinal Allergic reactions Hepatitis	None known	Anticoagulants and antiplatelets Hypoglycemic agents Hypotensive agents
Shiitake	Umbrella-shaped caps	Gastrointestinal Shiitake dermatitis	None known	CYP2D6 Immunosuppressants Hypereosinophilic Syndrome
Turkey tail	Grows in clusters of leathery brackets	None known	Cancer	Hypoglycemic agents Cyclophosphamide

Source: Compiled by Author *Table 1*

MEDICINAL MUSHROOMS WITH INSUFFICIENT EVIDENCE TO SUPPORT USE FOR CERTAIN INDICATIONS

The majority of medicinal mushrooms have insufficient evidence to support their use for certain indications. However, many of them are still consumed and have important safety concerns and potential interactions.

AGARICUS BLAZEI MUSHROOM

The *Agaricus blazei* mushroom, also called the Brazil mushroom, is native to the mountains of Piedade in Brazil [5]. It was first discovered by a Japanese researcher in 1965 who sent it to be studied in Japan and later identified by a Belgian botanist [5; 6]. *Agaricus blazei* is now cultivated in Brazil, China, Japan, and the United States for use in food, tea, and medicine.

Safety and Dosing

Agaricus blazei mushrooms are generally well-tolerated and have been used safely in doses up to 1,500 mg daily, usually administered as *Agaricus* mushroom extract 500 mg three times daily for up to 12 months [5]. There is no information about the use of *Agaricus* mushrooms in people who are pregnant or lactating, so avoid use in those populations [5].

Adverse Effects

One clinical study reported mild gastrointestinal side effects, such as nausea, diarrhea, and abdominal discomfort [5]. In individual case reports, *Agaricus* mushroom has been associated with allergic reactions including hives and allergic contact dermatitis on the lips (cheilitis), both of which resolved upon discontinuation of the *Agaricus* mushroom product [5]. In another case report, a patient developed interstitial lung disease [5].

There are also three case reports of severe hepatotoxicity in females receiving chemotherapy for ovarian or breast cancer who also took *Agaricus* mushroom supplements [5]. Two of the patients developed elevated liver function tests which progressed to fatal, fulminant hepatitis within days of starting *Agaricus* mushroom supplements [5]. The third patient turned out to be a carrier of hepatitis B virus, but her liver function tests improved upon discontinuation of *Agaricus* mushroom [5].

Uses and Benefit

There is interest in using *Agaricus* mushrooms for a variety of purposes including diabetes, hepatitis B, hyperlipidemia, inflammatory bowel disease, osteoporosis, and peptic ulcers, but there is no good evidence to support the use of *Agaricus* mushrooms for these conditions [5].

Drug, Herb, Supplement, and Disease Interactions

Hypoglycemic Agents

Theoretically, *Agaricus* mushroom might increase the risk of hypoglycemia when taken with antidiabetes drugs [5]. One clinical study in patients with type 2 diabetes on oral antidiabetes agents reported hypoglycemia in three subjects who were also taking *Agaricus* mushroom extract 500 mg three times daily [5]. Due to the risk of hypoglycemia, use caution when combining *Agaricus* mushroom with antidiabetes drugs and herbs and supplements with hypoglycemic potential, such as cinnamon, fenugreek, and bitter melon [5; 7]. Additionally, perioperative control of blood glucose levels is associated with improved surgical outcomes [8]. Since *Agaricus* mushroom could theoretically lead to hypoglycemia, advise patients to discontinue *Agaricus* mushroom at least two weeks prior to surgical procedures [5].

Liver Disease

There is some concern that *Agaricus* mushroom might cause or exacerbate liver disease; therefore, it should be avoided in people with liver disease. As discussed, three cases of severe hepatotoxicity have been reported in adults with ovarian or breast cancer receiving chemotherapy who also took *Agaricus* mushroom supplements [5].

Interactions with Lab Tests

5-S-Cysteinyldopa

Agaricus mushroom use may lead to false-positive results on tests that use serum 5-S-cysteinyldopa (5-S-CD) as a marker of tumor growth or recurrence [5]. Elevated serum 5-S-CD levels have been reported in patients taking *Agaricus* mushroom extracts [5].

BLACK HOOF MUSHROOM

Black hoof mushroom (*Phellinus linteus*) is an orange polyphore mushroom that grows on mulberry trees [9]. It has been used as medicine for centuries in China, Japan, Korea, and Taiwan where it is known as the sanghuang mushroom [10]. The earliest recorded medicinal use of black hoof mushroom appears in the oldest known Chinese medical book *Shennong's Compendium of Materia Medica*, which was written about 2,000 years ago [10]. Black hoof mushroom is also referenced in written form dating back to the Tang Dynasty in 630 C.E. and in the world's earliest known pharmacopoeia issued in China in 659 C.E. [10].

Despite a long history of human use, particularly in Asia, there is very little research into the safety and efficacy of this type of mushroom. In traditional Asian medicine, black hoof mushroom is used for allergies, arthritis, cancer, diabetes, and gastrointestinal disorders [9]. Animal and in vitro research suggests that black hoof mushroom could have anti-allergy, antimicrobial, anti-inflammatory, antihyperlipidemic, anticancer, immunostimulatory, and gastroprotective effects [9]. There has also been interest in using black hoof mushroom to treat COVID-19, but there is no good evidence to support the use of black hoof mushroom for this purpose.

Dosing and Safety

Currently available research suggests that black hoof mushroom extract has been used safely when taken orally in doses of 1 or 2 grams daily for up to 12 weeks [9]. There is no safety information currently available on the use of black hoof mushroom in adults who are pregnant or lactating, so advise patients in these special groups to avoid using black hoof mushroom until more information is available.

Black hoof mushroom seems to be well-tolerated, and no adverse effects have been reported, although a thorough evaluation of safety outcomes has not been conducted to date.

Drug, Herb, Supplement, and Disease Interactions

Cytochrome P450 (CYP) Substrates

Despite apparent safety in human research, in vitro evidence suggests that polysaccharides in black hoof mushroom inhibit CYP1A1, 1A2, and 2E1 activity, potentially leading to increased levels and clinical effects of other drugs metabolized by these CYP enzymes [9]. Although these effects have not been reported in humans, patients should be advised to use caution when taking black hoof mushroom in combination with substrates of CYP1A1, 1A2, and 2E1. Examples of CYP1A1, CYP1A2, and CYP2E1 substrates include [11; 12; 13; 14]:

- CYP1A1: Theophylline, tobacco
- CYP1A2: Clozapine, theophylline
- CYP2E1: Acetaminophen, nicotine

Immunosuppressants

In vitro and animal research suggest that polysaccharides in black hoof mushroom could stimulate immune responses, theoretically reducing the effects of immunosuppressant drugs and exacerbating autoimmune diseases, such as multiple sclerosis (MS), systemic lupus erythematosus (SLE), or rheumatoid arthritis (RA) [9]. Due to potential immunostimulant effects, people on immunosuppressant medications or those with autoimmune diseases should either avoid or use black hoof mushroom with caution.

Benign Prostatic Hyperplasia (BPH)

In an animal model of BPH, black hoof mushroom extract enlarged the prostate, particularly in the stroma region [9]. Even though this has not been shown in humans, patients with BPH should avoid using black hoof mushroom.

CHAGA MUSHROOM

Chaga (*Inonotus obliquus*), sometimes also referred to as birch mushroom, is a pathogenic parasitic fungus that grows on and destroys birch tree trunks throughout cool, humid climates in Europe, Russia, Korea, China, United States, and Canada [15; 16]. Chaga produces a woody growth on the tree surface referred to as a conk or canker, which is the part of chaga that is harvested and used for medicinal purposes [15]. The woody growth is supported by root-like mycelium structures that grow inside the tree, extracting nutrients and degrading the tree while producing decay known as white rot [16]. The canker that grows on the exterior of the tree releases spores, which are spread to other birch trees to continue chaga's parasitic life cycle [16].

Safety and Adverse Effects

There is no current reliable information on the dosing, safety, or adverse effects of chaga mushroom in children or adults. Additionally, there is no information available on the use of chaga in pregnant adults or those who are lactating, so advise patients in these groups to avoid using chaga.

Overdose and Toxicity

Due to its high oxalate content, excessive ingestion of chaga mushroom can result in acute oxalate nephropathy caused by the deposition of calcium oxalate crystals in the renal tubules [17]. There are two case reports of kidney failure and one case report of acute oxalate nephropathy in patients taking chaga mushroom powder doses of 3–22 grams daily for six months to five years [15]. Renal biopsies showed tubular atrophy, interstitial fibrosis, and the presence of oxalate crystals [15]. In all of these cases, the kidney damage was attributed to the high oxalate content in chaga mushroom [15].

Uses and Benefits

Traditionally, chaga mushroom is used to stimulate the immune system, prevent cancer, and treat certain conditions including gastritis, liver disease, and tuberculosis [15]. Recently, there has been interest in using chaga for cardiovascular disease, COVID-19, and diabetes [15]. However, there is currently no sufficient evidence to support the use of chaga for any of these conditions. There are in vitro and animal research that shows chaga mushroom could have anticancer, antidiabetes, anti-inflammatory, antioxidant, antihyperlipidemic, radioprotective, and immunostimulatory effects [15].

Drug, Supplement, and Disease Interactions

Anticoagulant and Antiplatelet Agents

In vitro and animal research suggests that chaga mushroom extract might inhibit platelet aggregation [15]. Therefore, chaga should be used with caution in combination with drugs or supplements with antiplatelet or anticoagulant effects due to an increased risk of bleeding. Additionally, people with bleeding disorders should use caution when taking chaga mushroom due to an increased risk of bleeding. However, this risk is theoretical and has not been shown in human research.

Hypoglycemic Agents

Animal research suggests that chaga mushroom might decrease blood glucose levels and increase insulin levels. Exercise caution when chaga mushroom is used in combination with antidiabetes drugs and herbs or supplements with hypoglycemic potential due to the additive risk of hypoglycemia [15]. However, this risk is theoretical and has not been shown in human research.

Surgery

Since chaga mushroom could increase the risk of bleeding and interfere with blood glucose control, advise patients to discontinue chaga mushroom at least two weeks prior to elective surgical procedures [15].

Immunosuppressants

In vitro research suggests that certain constituents of chaga mushroom could stimulate immune function [15]. Even though this interaction has not been reported in humans, it could theoretically reduce the effectiveness of immunosuppressive therapy, so use caution in patients on immunosuppressants. Also exercise caution in people with autoimmune diseases, such as MS, SLE, or RA, since immune system stimulation by chaga mushroom could worsen these conditions [15].

FLY AGARIC MUSHROOM

Fly agaric mushroom (*Amanita muscaria*), also known by the common name red toadstool, is a beautiful, distinctive, and very recognizable mushroom with a red or orange cap covered with small white plaques [18]. The applicable part of fly agaric mushroom is the fruiting body, and the levels of bioactive and chemical compounds vary considerably throughout the seasons and depend on the freshness of the mushroom [18]. The fly agaric mushroom got its name because it was once used as a fly poison. The cap was broken and sprinkled into saucers of milk. The ibotenic acid in fly agaric mushroom attracts and kills flies.

Due to its distinctive appearance, accidental ingestion is rare. However, it is a common cause of mushroom poisoning, especially when it is accidentally consumed by children or people seeking hallucinogenic experiences [19]. Historically, fly agaric mushroom was used by Buddhist monks in the 2nd and 9th centuries to achieve enlightenment [18]. Since boiling or other processing methods eliminates most of the water-soluble toxic compounds in fly agaric mushrooms, some traditional recipes have used it as a homeopathic remedy for neuropathy, fever, and joint pain [20; 21].

Additionally, there are reports of people consuming fly agaric mushroom as a means of suicide, or more recently, for its psychedelic effects [20]. Despite historical use for various spiritual and physical human conditions, there is no current recommended use for fly agaric mushroom for any medical or psychological conditions [18]. No information is currently available about drug, herb, supplement, or disease-state interactions with fly agaric mushroom. When consumed orally, fly agaric mushroom is highly poisonous and is not safe for anyone to consume [18].

Accidental fly agaric mushroom poisoning is rare because of its distinctive appearance. However, heavy rains can wash away the white spots, causing it to be mistaken for a different, edible species of mushroom, *Amanita caesarea*.

Toxicity and Overdose

Most cases of fly agaric mushroom overdose are associated with suicide attempts or people seeking a hallucinogenic experience [18]. Death due to fly agaric mushroom is rare but can occur in up to 5% of users [18]. Toxic symptoms have been observed after consuming just one mushroom, mind-altering effects are seen after consuming 2 to 4 mushrooms, and survival has been reported with consumption of as many as 20 large fly agaric mushrooms [18]. The mind-altering effects of fly agaric mushroom are thought to be due to the presence of ibotenic acid, muscimol, muscazone, and muscarine [18].

There are three stages of fly agaric mushroom poisoning [18; 19]:

- Stage 1: 15 to 90 minutes after ingestion
  - Gastrointestinal symptoms: Nausea, vomiting, diarrhea, and abdominal pain
- Stage 2: Peak effects occur two to three hours after ingestion and usually last for about 12 hours
  - Psychiatric symptoms: Hallucinations, mania, confusion, agitation, and suicide attempts
  - Neurological symptoms: Sedation and drowsiness
- Stage 3: Resolution of symptoms, usually takes about 12 hours but can take up to 5 days

There are two case reports of prolonged coma after fly agaric mushroom ingestion [18]. These patients were treated with gastric lavage, activated charcoal, and supportive care [18]. In both cases, the patients recovered within a few days [18]. In another case report, a 44-year-old male went into cardiac arrest several hours after ingesting 6 to 10 dried fly agaric mushrooms [18].

LION'S MANE MUSHROOM

Lion's mane mushroom (*Hericium erinaceus*) is an edible white mushroom that grows as singular long dangling fleshy spines on the dead trunks of hardwood trees (e.g., oak, beech, Japanese walnut) in East Asian countries, such as Japan and China [22; 23].

Other common names for lion's mane mushroom include bearded tooth, hedgehog fungus, monkey head, pom pom, tree hedgehog, and yamabushitake [22]. The fruiting body of lion's mane mushroom has been used in East Asian traditional medicine since ancient times. The fruiting bodies and mycelium are the parts of lion's mane mushroom that are consumed as medicine [22].

Safety and Adverse Effects

Lion's mane mushroom has been used with apparent safety in doses up to 1 gram daily for up to 16 weeks [22]. It is generally well-tolerated, but gastrointestinal discomfort, nausea, and skin rash have been reported [22]. Avoid using lion's mane mushroom in adults who are pregnant or lactating because there is no information available about safety in these special populations.

Uses and Benefits

Historically, lion's mane mushroom was thought to have antioxidant, antimicrobial, and anticancer effects [23]. More recently, there has been heightened interest in the neuroprotective, neuroregenerative, and mood-enhancing properties of lion's mane mushroom [23]. In vitro and animal research suggests that lion's mane mushroom might have anticancer, antidiabetic, anti-obesity, antioxidant, antihyperlipidemic, gastroprotective, hepatoprotective, and neuroprotective effects [22]. Despite interest and limited research, there is currently not enough information to recommend lion's mane mushroom for specific indications.

Neurological and Cognitive Function

There is interest in using lion's mane mushroom for neurological and cognitive benefit for Alzheimer disease, normal cognitive function, mild cognitive impairment, dementia, memory, and Parkinson disease, but there is insufficient reliable information about the clinical effects of lion's mane mushrooms for these conditions.

A small clinical study in older adults with mild Alzheimer disease shows that taking 1,050 mg of lion's mane mushroom mycelia daily for 49 weeks improves some activities of daily living when compared with placebo and some measures of cognitive impairment when compared to baseline [22]. Another study in older Japanese patients with mild cognitive impairment shows that taking lion's mane mushroom powder 3 grams daily for 16 weeks increases cognitive function when compared with placebo, but this benefit did not endure beyond 4 weeks after treatment termination [22].

There is no evidence that lion's mane mushroom is beneficial in people with normal cognitive function. A small clinical trial shows that middle aged to older adults taking lion's mane mushroom 3.2 grams daily for 12 weeks does not improve most measures of cognitive function when compared with placebo [22]. Another small clinical study in younger adults shows that taking a lion's mane mushroom product that was 50% dried mushroom and 50% mushroom extract 10 grams daily for 4 weeks does not improve measures of cognition during a period of exercise-induced fatigue when compared with taking placebo [22]. More human research and larger trials are needed to determine whether lion's mane mushroom is beneficial for neurological conditions and cognitive function.

Drug, Supplement, and Disease Interactions

Anticoagulants and Antiplatelets

In vitro research suggests that lion's mane mushroom might inhibit platelet aggregation [22]. Therefore, lion's mane mushroom should be used with caution in combination with drugs, herbs, or supplements with antiplatelet or anticoagulant effects and in people with bleeding disorders due to an increased risk of bleeding.

Hypoglycemic Agents

Animal research suggests that an aqueous extract of lion's mane mushroom might decrease serum blood glucose levels and increase serum insulin levels [22]. Lion's mane mushroom should be used cautiously when taken in combination with antidiabetes drugs or herbs and supplements with hypoglycemic potential due to the additive risk of hypoglycemia.

Surgery

Since lion's mane mushroom could increase the risk of bleeding and might interfere with blood glucose control perioperatively, lion's mane mushroom should be discontinued at least two weeks prior to elective surgical procedures.

Immunosuppressants

Animal and in vitro research suggest that polysaccharides in lion's mane mushroom might stimulate the immune system [22]. Therefore, caution should be used when taking lion's mane mushroom with immunosuppressant drugs due to the theoretical possibility of reduced immunosuppressant drug efficacy. Also exercise caution in people with autoimmune diseases, such as MS, SLE, or RA, because lion's mane mushroom could theoretically stimulate autoimmune disease activity.

MAITAKE MUSHROOM

Maitake mushroom (*Grifola frondosa*), also widely known as hen-of-the-woods, is an edible mushroom that grows in large clumps at the base of stumps or trunks or broadleaf trees in the temperate forests of Asia, Europe, and the eastern United States [24]. The medicinally useful parts of maitake mushroom are the fruiting body and mycelium [24]. Active constituents are polysaccharides, specifically beta-glucan constituents referred to as "D-fraction" and "SX-fraction" [24].

Formulations and Dosing

Maitake mushroom extract has been used with apparent safety at a dose of 3 mg/kg twice daily for up to 12 weeks and 5 mg/kg twice daily for up to 3 weeks [24]. Some clinical trials have used products standardized for certain constituents, including polysaccharides. A concentrated formulation of maitake mushroom polysaccharides (MMP) 1–1.5 grams daily has also been used with apparent safety for up to two years [24].

Adverse Effects

Maitake mushroom is generally well-tolerated when taken orally. The most commonly reported adverse effects are gastrointestinal side effects, such as diarrhea, epigastric pain, and nausea [24]. There are also individual case reports of rash with pruritis and joint swelling after taking MPP extract and hypersensitivity pneumonitis after taking maitake mushroom spores [24]. There is no sufficient reliable information on safety or adverse effects of maitake mushroom in people who are pregnant or lactating, so avoid use in these populations.

Uses and Benefits

Cancer

There is interest in using maitake mushrooms for treating cancer and side effects related to chemotherapy treatment. However, the currently available evidence is insufficient to conclude that maitake mushrooms are beneficial for these conditions.

One clinical study in patients with advanced laryngeal and pharyngeal cancer undergoing chemoradiation shows that taking MPP 1 gram three times daily prevents a decline in quality of life, reduces the incidence of some adverse effects associated with cancer treatment, and modestly increases five-year survival when compared with placebo [24].

Drug, Herb, Supplement, and Disease Interactions

Hypoglycemic Agents

A study in humans with type 2 diabetes shows that taking MPP might lower blood glucose levels [24]. Use caution in patients taking maitake mushrooms in combination with antidiabetes drugs or herbs and supplements with hypoglycemic effects due to the potential additive risk of hypoglycemia.

Hypotensive Agents

Animal research suggests that maitake mushroom can lower blood pressure [24]. Therefore, use caution in patients taking antihypertensive drugs or herbs and supplements with hypotensive effects due to the increased risk of additive hypotension.

Warfarin

There is a case report of a patient previously stabilized on warfarin developing an elevated international normalized ratio (INR) of 5.1 after taking a specific liquid maitake mushroom product at a dose of 1 drop/kg daily for a week [24]. The elevated INR resolved after holding warfarin for two days, followed by an 11% dose reduction [24]. While the evidence is limited to a single case report, this suggests that maitake mushroom could increase the anticoagulant effects of warfarin. Exercise caution in patients taking this combination.

Surgery

Due to potential hypoglycemic effects, maitake mushroom might interfere with perioperative blood glucose control. Advise patients to stop taking maitake mushroom at least two weeks prior to elective surgical procedures.

PORIA MUSHROOM

Poria mushroom (*Wolfiporia cocos*) is an edible medicinal mushroom of which the sclerotium, or resting spore, is the portion used as medicine [25]. The sclerotium of poria mushroom grows around the roots of certain pine trees in China and other East Asian countries. The availability of the appropriate pine tree species limits the availability of poria mushroom sclerotium. Poria mushroom has been used for more than 2,000 years in traditional Chinese medicine for anxiety, cough, diabetes, insomnia, memory, and vertigo [26]. The main bioactive component of poria mushroom is poria cocos polysaccharide (PCP), which accounts for 84% by weight of all constituents in the dried sclerotium [26].

Safety and Side Effects

There is currently no information about the safety of poria mushroom in children, adults, and special populations, such as those who are pregnant or lactating. However, animal research suggests that poria mushroom has low toxicity [26]. There is also no research on the long-term risks associated with taking poria mushroom. Poria mushroom seems to be well-tolerated, but a thorough evaluation of safety outcomes has not been conducted. In rare cases, there have been reports of mild allergic reactions, such as allergic rhinitis and allergic asthma, after taking poria mushroom [25].

Uses and Benefits

There is currently no evidence that poria mushroom is effective for any human conditions. However, animal and in vitro research show that poria mushroom might inhibit tumor growth, enhance immune function, and exhibit antioxidant activity [26].

Drug, Supplement, and Disease Interactions

Anticholinergic and Cholinergic Agents

Animal research suggests that poria mushroom essential oil reduces acetylcholinesterase activity [25]. Theoretically, taking poria mushroom could decrease the effectiveness of anticholinergic drugs [25]. Conversely, poria mushroom taken in combination with cholinergic drugs could have additive effects and increase the risk of adverse effects or toxicity [25]. Although this interaction has not been shown in humans, use caution in patients taking anticholinergic or cholinergic drugs with poria mushroom.

CNS Depressants

Animal research suggests that poria mushroom extract might have sedative properties, which could enhance therapeutic and adverse effects of other medications, herbs, or supplements with sedative effects [25]. Although this interaction has not been shown in humans, use caution in patients who are taking poria mushroom with CNS depressants, such as alcohol, opioids, or benzodiazepines. Additionally, due to the risk of CNS depression perioperatively, tell patients to discontinue poria mushroom extract at least two weeks prior to elective surgical procedures.

REISHI MUSHROOM

Reishi mushroom (*Ganoderma lucidum*) is a type of fungus with shiny, tough, woody flesh and a bitter taste that is black, orange, red, or other colors depending on the growing conditions [27; 28]. Reishi mushroom thrives in hot, humid, subtropical conditions but is rarely found in the wild. Reishi

mushroom is now commercially cultivated and is available in a wide range of formulations containing the fruiting bodies, mycelia, and spore powder [28].

Long referred to as the "mushroom of immortality," the reishi mushroom has been used in traditional Asian medicine for more than 2,000 years for promoting health, longevity, and spiritual potency [3; 28]. Before reishi mushroom cultivation, reishi mushroom was so rarely found in the wild that only the nobility could afford it as medicine [28]. As a result, it is unclear whether reishi mushroom is highly prized for its actual effects or due to is rarity and use only by the privileged members of ancient Chinese society [28].

Safety and Standardization

Reishi mushrooms are commercially available as extracts and powders. Extracts of reishi mushroom have been used safely in adults in doses of 6 mg daily for up to one year [27]. Powdered reishi mushroom has been used in doses of 1,400–5,400 mg daily for up to 16 weeks [27]. There is no sufficient reliable information on the use of reishi mushroom in children or adults who are pregnant or lactating, so avoid use in those populations.

There is some concern about the standardization and consistency of reishi mushroom products available in the United States. One study analyzed 19 reishi mushroom products and found that only 26% contained the labeled amount of reishi mushroom and 68% of tested reishi mushroom products contained polysaccharide fillers in place of active ingredients [27]. Therefore, advise patients to use caution when selecting products and to stick to high quality formulations that have been independently tested.

Adverse Effects

Orally, reishi mushroom is generally well-tolerated, but there have been some reports of mild immunologic, gastrointestinal, and other adverse effects [27]. There have been reports of allergic reactions resulting in dermatologic itching, rash, and other skin reactions and reishi mushroom spores have caused respiratory allergies characterized by sore throat and runny nose [27]. Reishi mushroom could also cause dryness of the mouth, throat, or nasal cavity and can lead to gastrointestinal adverse effects, such as nausea, diarrhea, and stomach upset [27].

There have also been serious hepatic adverse effects associated with reishi mushroom use, but the causation is not certain [27]. There are two case reports of hepatotoxicity in patients who took a specific reishi mushroom powder for one to two months, with one of the cases resulting in fatal fulminant hepatitis [27]. In another case report, a patient developed hypereosinophilic syndrome associated with hepatic nodules after using a reishi mushroom powder product for two months, which resolved after discontinuation [27].

Uses and Benefits

The pharmacological properties of reishi mushroom are mainly due to the presence of triterpenes and polysaccharides [3]. But there is currently no conclusive evidence that reishi mushroom benefits any human health conditions. However, there is in vitro and animal data to support anticancer, immunomodulatory, antihypertensive, cytotoxic, antidiabetic, antioxidant, antihyperlipidemic, antimutagenic, antiaging, antimicrobial, hepatoprotective, and gastroprotective properties, and many others [3].

There is interest in using reishi mushroom for hyperlipidemia and diabetes, but current research in humans shows that reishi mushroom is not beneficial for either of these conditions. However, there may be some benefits in cancer and lower urinary tract symptoms with various etiologies. Most human research is small, low-quality, and conflicting. No currently available evidence is strong enough to conclusively recommend reishi mushroom for a specific condition.

Drug, Supplement, and Disease Interactions

Anticoagulant and Antiplatelet Agents

Human research shows that reishi mushroom does not inhibit platelet aggregation at lower doses of 1.5 grams daily, but does inhibit platelet aggregation at a higher doses of 3 grams daily [27]. Therefore, reishi mushroom at high doses should be used

with caution in combination with drugs, herbs, or supplements with antiplatelet or anticoagulant effects and in people with bleeding disorders due to an increased risk of bleeding.

Hypoglycemic Agents

Animal research suggests that reishi mushroom decreases serum blood glucose levels [27]. However, research in humans with type 2 diabetes shows that reishi mushroom does not reduce fasting blood glucose levels and the effects on HbA1c are unclear [27]. Until more evidence of the effects of reishi mushroom on blood glucose levels is available, reishi mushroom should be used cautiously when taken in combination with drugs, herbs, or supplements with hypoglycemic potential due to the additive risk of hypoglycemia.

Surgery

Since reishi mushroom could increase the risk of bleeding and might interfere with blood glucose control, it should be discontinued at least two weeks prior to elective surgical procedures.

Hypotensive Agents

Animal research suggests that reishi mushroom can lower blood pressure [27]. Research in humans suggests that reishi mushroom reduces blood pressure in some, but not all, patients with hypertension [27]. Therefore, use caution in patients taking antihypertensive drugs or herbs and supplements with hypotensive effects due to the increased risk of hypotension.

SHIITAKE MUSHROOM

Shiitake mushroom is a type of edible fungus and is the second most commonly eaten mushroom in the world [29]. This type of mushroom is native to Japan and China, where it has a long history of use in traditional medicine [29]. Most clinical research is on the standardized oligosaccharide-rich shiitake mushroom mycelial extract called AHCC.

Safety and Adverse Effects

Shiitake mushroom is likely safe and well-tolerated when cooked and consumed in typical food amounts [29]. The shiitake mushroom extract AHCC is also likely safe and has been used in clinical trials and in population-based research in doses ranging from 3–6 grams daily for up to nine years [29]. There is no information available on the safety of shiitake mushroom consumption greater than food amounts in adults who are pregnant or lactating, so avoid use in these populations.

While shiitake mushrooms as part of the diet are generally well-tolerated, there are some adverse effects associated with their use. Discussed further below, the most common adverse effects are gastrointestinal, while the most serious adverse effect, which occurs rarely, is shiitake dermatitis. There are also individual reports of eosinophilia, allergic contact dermatitis, general allergic symptoms, joint stiffness, and hypersensitivity pneumonitis in people who have consumed shiitake mushrooms [29].

Gastrointestinal

Orally, shiitake mushrooms can cause abdominal discomfort, including bloating, nausea, pain, vomiting, and diarrhea [29]. Consumption of large pieces of shiitake mushroom with inadequate chewing can cause abdominal obstruction that has resulted in death in one case and surgical intervention in two others [29]. In another case, parenteral nutrition was used exclusively until the shiitake mushroom pieces were passed [29]. When used as an oral rinse for gum disease or gingivitis, shiitake mushroom extract is associated with teeth sensitivity, teeth staining, and burning in the mouth [29].

Shiitake Dermatitis

The cell wall of shiitake mushrooms contains a thermolabile compound called lentinan, which is toxic when consumed raw but safe to eat when heated. As a result, consuming raw shiitake mushroom can cause shiitake dermatitis, a skin eruption resembling whiplash marks which can be accompanied by systemic symptoms [29]. Shiitake dermatitis usually occurs on the trunk and limbs and can look like whiplash marks, small purple spots, skin plaques,

burns, blanching, and pustules [29]. In rare cases, the rash looks like measles [29]. Other symptoms associated with shiitake dermatitis include fever, aching, malaise, eosinophilia, diarrhea, prickling in the hands, trouble swallowing, conjunctivitis, and pustules with small ulcers in the mouth [29]. Symptom onset is usually within hours to days and can persist for 3 to 4 weeks before resolving on its own [29]. In some cases, treatment with steroids alone or in combination with antihistamines might reduce the duration of the rash [29].

Shiitake dermatitis is thought to be a delayed type hypersensitivity reaction to lentinan or other compounds found normally in uncooked or inadequately cooked shiitake mushroom [29]. Cooking shiitake mushroom generally prevents shiitake dermatitis, although there are reports of some cases in people who have consumed cooked sources [29]. It appears that to inactivate lentinan, cooking temperatures of at least 266°F (130°C) are needed [29].

Uses and Benefits

There is currently no evidence that shiitake mushroom is effective for any human conditions. However, animal and in vitro research show that poria mushroom might inhibit tumor growth, enhance immune function, and exhibit antioxidant, anti-inflammatory, and antimicrobial activity [29].

Drug, Supplement, and Disease Interactions

CYP2D6 Substrates

In vitro studies suggest that AHCC might induce CYP2D6, theoretically increasing the levels of other drugs metabolized by CYP2D6 [29]. Use caution in patients taking shiitake mushroom and CYP2D6 substrates.

Immunosuppressants

Data from human, animal, and in vitro studies suggests that shiitake mushroom extracts stimulate immune function [29]. Therefore, patients should use caution when taking shiitake mushroom extract with immunosuppressant drugs due to the theoretical possibility of reduced immunosuppressant drug efficacy. Also exercise caution in people with autoimmune diseases, such as MS, SLE, or RA, because shiitake mushroom could theoretically stimulate autoimmune disease activity.

Hypereosinophilic Syndrome

Shiitake mushroom can cause eosinophilia, which may exacerbate hypereosinophilic syndrome, a group of blood disorders characterized by persistently elevated eosinophils which can damage tissues and organs over time [29]. Avoid shiitake mushroom use in patients with this condition.

MEDICINAL MUSHROOMS WITH POSSIBLE EFFICACY FOR CERTAIN INDICATIONS

CORDYCEPS

The cordyceps species *Ophiocordyceps unilateralis*, also known as the zombie-ant fungus, achieved fame after playing a starring role in the post-apocalyptic video game and television series *The Last of Us*. In the story, rising temperatures cause zombie-ant fungus to evolve and mutate to infect humans instead of ants. The zombie-ant fungus parasitized human brains and turned them into zombies. Fortunately, there is no evidence that cordyceps can transition from usings insects to humans as hosts, and it is highly unlikely due to our sophisticated immune systems and high body temperatures.

Cordyceps is a genus containing more than 400 different species of fungus that grow on insect larvae [30]. Although many *Cordyceps* species have been identified around the world, *Cordyceps sinensis* is the primary species currently used as an herbal medicine and will be henceforth referred to as cordyceps for the purposes of this course [30].

Cordyceps is parasitic fungus that grows on the larvae of the moth *Hepialus armoricanus Oberthur* in China at high elevations [31]. Due to habitat destruction and overharvesting, the supply of natural cordyceps is extremely limited [30]. However, cultured cordyceps mycelial cells are available commercially through large-scale fermentation of natural

cordyceps strains [30; 32].The commercially available propagated form of cordyceps that is consumed as an herbal medicine usually contains only mycelial cells, not the fruiting body [32].

Dosing and Formulation

Cordyceps is available as capsules, powders, and liquid extracts [31]. Most studies use oral cordyceps doses of 3–6 grams daily for up to one year [32]. Most research is on two specific cordyceps products, Bailing (Cs-C-Q80) and Jinshuibao (Cs-4), which are fermented cordyceps mycelial products [32].

Safety and Adverse Effects

Cordyceps has been taken with apparent safety and seems to be well-tolerated in doses of 3–6 grams daily for up to one year [32]. However, there is no reliable information about the safety of cordyceps in people who are pregnant or lactating, so avoid use in these populations.

When cordyceps is taken orally, gastrointestinal side effects are the most common and include constipation, diarrhea, abdominal discomfort, dry mouth, and throat discomfort [32]. There have also been individual reports of lead poisoning and hepatitis, but it is suspected that these effects were due to contaminated cordyceps products [32].

Uses and Benefits

Cordyceps is used in traditional Chinese medicine for many conditions including fatigue, sexual dysfunction, cough, and immune stimulation [30]. Preclinical in vitro and animal research suggests that cordyceps has anticancer, anti-inflammatory, antitumor, radioprotective, antiplatelet, antidiabetic, and immune enhancing properties [30]. Research in humans shows that cordyceps does not improve athletic performance, but it might benefit certain types of kidney disease [32].

Athletic Performance

Although cordyceps is sometimes taken to increase strength and stamina, the currently available evidence shows that cordyceps does not improve athletic performance in adults [32]. One small clinical study in endurance-trained cyclists shows that taking a specific mycelial fermentation product of cordyceps 3.15 grams daily for five weeks does not improve endurance time trials or aerobic capacity when compared with placebo [32]. Another small study in healthy elderly adults shows that taking the same cordyceps preparation 3 grams daily for 12 weeks does not improve exercise performance when compared with placebo [32]. Despite these findings, cordyceps is still heavily marketed to trained and recreational athletes with claims that it enhances athletic performance, increases stamina, and fights muscle fatigue. Further research is needed to elucidate the effect of cordyceps on athletic performance.

Kidney Function

Chronic Kidney Disease (CKD)

Some clinical studies show that oral cordyceps modestly improves renal function in some patients. A meta-analysis of clinical studies conducted in China in patients with CKD shows that taking cordyceps 0.6–2 grams three times daily in addition to standard treatment decreases serum creatinine by 0.6 mg/dL and increases creatinine clearance by 9.2 mL/min when compared with standard treatment alone [32]. However, a meta-analysis of small clinical studies conducted in China in patients on hemodialysis suggests that taking cordyceps in addition to standard treatment does not seem to improve serum creatinine levels when compared with placebo.

Contrast-Induced Nephropathy

The currently available evidence is conflicting on whether cordyceps protects against contrast-induced nephropathy. A preliminary clinical study in patients with diabetic nephropathy shows that taking a specific oral cordyceps mycelial product 2–3 grams three times daily for three days before and after angiography reduces the risk of contrast-induced nephropathy by 48% to 66% when compared with standard treatment [32]. However, other preliminary clinical research in patients with stable angina pectoris shows that taking the same cordyceps product 3 grams orally three times daily for three days before and after angioplasty does not decrease the prevalence of contrast-induced nephropathy when compared with standard therapy [32]. Reasons for

these discrepancies are unclear, but it is possible that cordyceps is protective against contrast-induced nephropathy in people with kidney damage at baseline, but not in people with normal kidney function at baseline.

Diabetic Nephropathy

Most research suggests that oral cordyceps modestly improves kidney function in patients with diabetic nephropathy, or diabetic kidney disease. A meta-analysis conducted in China in patients with diabetic kidney disease shows that taking cordyceps 0.5–2 grams three times daily with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) decreases blood urea nitrogen by 2 mg/dL and decreases serum creatinine levels by 0.1 mg/dL when compared with ACE inhibitor or ARB treatment alone [32]. Another meta-analysis of clinical studies in patients with diabetic kidney disease shows that taking cordyceps as adjunctive therapy to an ACE inhibitor or ARB for 2 to 24 weeks modestly improves markers of kidney function, such as serum creatinine, urea nitrogen, urinary albumin, and total protein, when compared to these medications alone [32].

Kidney Transplant

Small clinical studies suggest that oral cordyceps is not better than standard treatment at reducing transplant rejection, improving survival, or enhancing kidney function in patients with kidney transplant. A meta-analysis of four heterogeneous clinical trials evaluating patients in China immediately post-kidney transplant or patients with complications post-kidney transplant suggests that adding cordyceps to standard therapy with cyclosporine and steroids is not superior to adding azathioprine 50–150 mg for improving overall survival or graft survival or reducing rejection risk [32]. A higher quality systematic review suggests that adding oral cordyceps 3–6 grams to standard therapy daily is no better than azathioprine or cyclosporine for preventing organ rejection or improving kidney function or survival in patients after kidney transplant [32].

Drug, Supplement, and Disease Interactions

Anticoagulant and Antiplatelet Agents

In vitro and animal research suggests that cordyceps might inhibit platelet aggregation, so cordyceps should be used with caution in people with bleeding disorders and when taken in combination with drugs, herbs, or supplements with antiplatelet or anticoagulant effects due to an increased risk of bleeding [32]. Because of the theoretical risk of bleeding, patients should stop taking cordyceps at least two weeks prior to elective surgical procedures.

Immunosuppressants

Research is conflicting on how cordyceps impacts the immune system. A review of five clinical studies in kidney transplant recipients suggests that taking cordyceps with immunosuppressive therapy could reduce transplant rejection [32]. However, animal and in vitro research suggests that cordyceps could stimulate immune function [32]. Whether it stimulates or suppresses immune function, taking cordyceps could alter the effectiveness of immunosuppressive therapy, so use caution in patients taking immunosuppressants. Also exercise caution in people with autoimmune diseases, such as MS, SLE, or RA, since immune system stimulation by cordyceps could worsen these conditions [15].

Testosterone

In vitro and animal research suggests that cordyceps can increase testosterone levels, but the clinical significance of this finding is unclear. Theoretically, cordyceps could have additive effects when taken with testosterone. However, this interaction is minor considering that it has not been shown in humans and the extent and clinical significance of increased testosterone is not clear and requires further research.

TURKEY TAIL MUSHROOM

Turkey tail mushroom (*Coriolus versicolor*) is a common mushroom that grows on the stumps and other decomposing wood of broad-leaved trees [33]. In traditional Chinese medicine, it is used for enhancing immune function, removing toxins, promoting good health, and as treatment for cancer, hepatitis, and infections [3; 33].

Two main bioactive polysaccharides of turkey tail mushroom, polysaccharide krestin (PSK) and polysaccharide peptide (PSP), are isolated and used medicinally [3]. They are among the most studied compounds in medicinal mushrooms, but their mechanisms of action are still not fully understood [3]. In adults, oral PSK is most commonly taken at a dose of 3 grams daily for up to 36 months [33]. When oral whole turkey tail mushroom is used, it has been studied at a dose of 2.4 grams daily for up to 12 weeks [33].

Safety and Adverse Effects

Turkey tail mushroom and its constituents PSK and PSP are likely safe when used orally and appropriately [33]. There is currently no safety information about other routes of administration. Additionally, there is no research available in people who are pregnant or lactating, so it is best to avoid the use of turkey tail mushroom and its constituents in these special populations.

Orally, turkey tail mushroom and its PSK component are generally well-tolerated. There have been reports of erythema, gastrointestinal side effects, hematological abnormalities, liver dysfunction, and palpitations, but these are in patients who received PSK in addition to standard chemotherapy [33]. It is not known if these are due to PSK, chemotherapy, or both.

Uses and Benefits

Cancer

Turkey tail mushroom constituents PSP and PSK have been officially approved for decades in routine clinical practice in Japan and China as an adjunct to chemotherapy and radiotherapy in doses ranging from 1–3.6 grams daily [3; 33]. It has been studied for many different types of cancer, including breast, colorectal, esophageal, gastric, hepatic, leukemia, lung, and nasopharyngeal [33]. Most studies show that taking PSK as an adjunct to standard cancer therapy may improve response rates and survival in some patients with cancer [33]. However, it is unclear whether whole turkey tail mushroom or its constituent PSP is beneficial for patients with cancer [33].

A meta-analysis of 13 clinical trials including over 2,500 patients with esophageal, gastric, colon, rectal, breast, or nasopharyngeal cancer shows that taking PSK in addition to conventional cancer therapy reduces five-year mortality by 9% when compared with conventional therapy alone [33]. When individual cancer types are considered, the benefit of PSK is most evident in patients with breast, gastric, colon, or rectal cancer [33]. Another meta-analysis of 14 clinical trials shows that taking PSK, PSP, or whole turkey tail mushroom in combination with chemotherapy is associated with a 17% lower risk of mortality in some, but not all, types of cancer when compared with chemotherapy alone [33]. However, overall there was no difference in relapse-free survival or total clinical efficacy. The reliability and relevance of these meta-analyses is unclear since there was significant heterogeneity in cancer types, dose and duration of turkey tail mushroom therapy, and type of turkey tail mushroom used. Furthermore, all the included studies were conducted in China or other Asian countries, limiting the generalizability of the results to other populations.

According to the National Cancer Institute, clinical studies of polysaccharide-K derived from turkey tail mushroom in colorectal cancer have shown reduction in recurrence and improvement in overall survival with adjuvant use.

(https://www.cancer.gov/about-cancer/treatment/cam/hp/mushrooms-pdq. Last accessed October 1, 2024.)

Level of Evidence: Expert Opinion/Consensus Statement

Research on the use of whole turkey tail mushroom rather than its isolated constituents for treating cancer is limited. A small clinical study in 15 patients with inoperable hepatocellular carcinoma shows that taking turkey tail mushroom 2.4 grams daily for 6 to 12 weeks does not improve time to progression, progression-free survival, overall survival, or quality of life when compared with placebo [33].

Drug and Supplement Interactions

Hypoglycemic Agents

Animal research suggests that turkey tail mushroom constituents might have hypoglycemic effects [33]. Turkey tail mushroom should be used cautiously when taken in combination with antidiabetes drugs or herbs and supplements with hypoglycemic potential due to the additive risk of hypoglycemia. Since turkey tail mushroom could interfere with blood glucose control, it should be discontinued at least two weeks prior to elective surgery.

Cyclophosphamide

Animal research suggests that turkey tail constituent PSP can increase the area under the concentration-time curve (AUC) of cyclophosphamide by 44% to 50% and the half-life by 34% to 43% [33]. Theoretically, this interaction could increase the effects and adverse effects of cyclophosphamide. However, it is unclear whether PSP changes the levels of active metabolites of cyclophosphamide, which are responsible for its clinical activity. Due to this theoretical interaction, use caution in patients taking cyclophosphamide and turkey tail mushroom.

Tamoxifen

Animal research suggests that PSP increases the time to reach maximum concentration of a single dose of tamoxifen by about 9.5 hours, or 228% [33]. When repeated doses of tamoxifen were given, the time to reach maximum concentration of tamoxifen was increased by 5.6 hours or 93% [33]. However, PSP did not change the maximum concentration or the AUC of tamoxifen [33]. While this has not been shown in humans, PSP could theoretically interfere with the absorption of tamoxifen and caution should be used in patients taking this combination.

CYP2C9 Substrates

In vitro research suggests that PSP inhibits cytochrome P450 2C9 (CYP2C9) enzymes in a dose-dependent manner [33]. Theoretically, taking PSP with other drugs metabolized by CYP2C9 could increase drug levels and the risk of adverse effects. Even though this interaction has not been reported in humans, remain watchful when turkey tail mushroom is combined with CYP2C9 substrates.

SUMMARY

Interest in using medicinal mushrooms for various conditions is rapidly growing. Healthcare providers need to be aware if their patients are using these mushrooms, as they can cause adverse effects or interact with conventional medications, supplements, or existing medical conditions.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

Works Cited

1. Poder, R. The Ice Man's Fungi: Facts and Mysteries. *International Journal of Medicinal Mushrooms.* 2005;7(3)357-359.
2. Łysakowska P, Sobota A, Wirkijowska A. Medicinal mushrooms: their bioactive components, nutritional value and application in functional food production: a review. *Molecules.* 2023;28(14):5393.
3. Venturella G, Ferraro V, Cirlincione F, Gargano ML. Medicinal mushrooms: bioactive compounds, use, and clinical trials. *Int J Mol Sci.* 2021;22(2):634.
4. Encyclopaedia Britannica. Mushroom. Available at https://www.britannica.com/science/mushroom. Last accessed May 31, 2024.
5. TRC Healthcare NatMed. *Agaricus* Mushroom. Available at https://naturalmedicines.therapeuticresearch.com/databases/food,-herbs-supplements/professional.aspx?productid=1165. Last accessed May 3, 2024.
6. Firenzuoli F, Gori L, Lombardo G. The medicinal mushroom *Agaricus blazei Murrill*: review of literature and pharmacotoxicological problems. *Evid Based Complement Alternat Med.* 2008;5(1):3-15.
7. Deng R. A review of the hypoglycemic effects of five commonly used herbal food supplements. *Recent Pat Food Nutr Agric.* 2012;4(1):50-60.
8. Kang ZQ, Huo JL, Zhai XJ. Effects of perioperative tight glycemic control on postoperative outcomes: a meta-analysis. *Endocr Connect.* 2018;7(12):R316-R327.
9. TRC Healthcare NatMed. Black Hoof Mushroom. Available at https://naturalmedicines.therapeuticresearch.com/databases/food,-herbs-supplements/professional.aspx?productid=1510. Last accessed May 6, 2024.
10. Shenghua W, Yu-cheng D, Hattori T, TuWen Y, et al. Species clarification for the medicinally valuable 'sanghuang' mushroom. *Botanical Studies.* 2012;53:135-149.
11. Munro AW. Cytochrome P450 1A1 opens up to new substrates. *J Biol Chem.* 2018;293(50):19211-19212.
12. Walsh AA, Szklarz GD, Scott EE. Human cytochrome P450 1A1 structure and utility in understanding drug and xenobiotic metabolism. *J Biol Chem.* 2013;288(18):12932-12943.
13. U.S. Food and Drug Administration. For Healthcare Professionals: FDA's Examples of Drugs that Interact with CYP Enzymes and Transporter Systems. Available at https://www.fda.gov/drugs/drug-interactions-labeling/healthcare-professionals-fdas-examples-drugs-interact-cyp-enzymes-and-transporter-systems. Last accessed May 28, 2024.
14. García-Suástegui WA, Ramos-Chávez LA, Rubio-Osornio M, Calvillo-Velasco M, Atzin-Méndez JA, Guevara J, Silva-Adaya D. The role of CYP2E1 in the drug metabolism or bioactivation in the brain. *Oxid Med Cell Longev.* 2017;2017:4680732.
15. TRC Healthcare NatMed. Chaga. Available at https://naturalmedicines.therapeuticresearch.com/databases/food,-herbs-supplements/professional.aspx?productid=1474. Last accessed May 6, 2024.
16. Fordjour E, Manful CF, Javed R, Galagedara LW, Cuss CW, Cheema M, Thomas R. Chaga mushroom: a super-fungus with countless facets and untapped potential. *Front Pharmacol.* 2023;14:1273786.
17. Kwon O, Kim Y, Paek JH, Park WY, Han S, Sin H, Jin K. Chaga mushroom-induced oxalate nephropathy that clinically manifested as nephrotic syndrome: a case report. *Medicine (Baltimore).* 2022;101(10):e28997.
18. TRC Healthcare NatMed. Fly Agaric Mushroom. Available at https://naturalmedicines.therapeuticresearch.com/databases/food,-herbs-supplements/professional.aspx?productid=190. Last accessed May 6, 2024.
19. Encyclopaedia Britannica. Fly agaric. Available at https://www.britannica.com/science/fly-agaric. Last accessed May 31, 2024.
20. Rampolli FI, Kamler P, Carnevale Carlino C, Bedussi F. The deceptive mushroom: accidental *Amanita muscaria* poisoning. *Eur J Case Rep Intern Med.* 2021;8(3):002212.
21. Carboué Q, Lopez M. *Amanita muscaria*: ecology, chemistry, myths. *Encyclopedia.* 2021;1(3):905-914.
22. TRC Healthcare NatMed. Lion's Mane Mushroom. Available at https://naturalmedicines.therapeuticresearch.com/databases/food,-herbs- supplements/professional.aspx?productid=1536. Last accessed May 7, 2024.
23. Docherty S, Doughty FL, Smith EF. The acute and chronic effects of lion's mane mushroom supplementation on cognitive function, stress and mood in young adults: a double-blind, parallel groups, pilot study. *Nutrients.* 2023;15(22):4842.
24. TRC Healthcare NatMed. Maitake Mushroom. Available at https://naturalmedicines.therapeuticresearch.com/databases/food,-herbs-supplements/professional.aspx?productid=560. Last accessed May 8, 2024.
25. TRC Healthcare NatMed. Poria Mushroom. Available at https://naturalmedicines.therapeuticresearch.com/databases/food,-herbs-supplements/professional.aspx?productid=246. Last accessed May 8, 2024.
26. Li X, He Y, Zeng P, Liu Y, Zhang M, Hao C, Wang H, Lv Z, Zhang L. Molecular basis for Poria cocos mushroom polysaccharide used as an antitumour drug in China. *J Cell Mol Med.* 2019;23(1):4-20.
27. TRC Healthcare NatMed. Reishi Mushroom. Available at https://naturalmedicines.therapeuticresearch.com/databases/food,-herbs-supplements/professional.aspx?productid=905. Last accessed May 9, 2024.
28. Wachtel-Galor S, Yuen J, Buswell JA, et al. *Ganoderma lucidum* (lingzhi or reishi): a medicinal mushroom. In: Benzie IFF, Wachtel-Galor S (eds). *Herbal Medicine: Biomolecular and Clinical Aspects.* 2nd ed. Boca Raton, FL: CRC Press/Taylor & Francis; 2011.

29. TRC Healthcare NatMed. Shiitake Mushroom. Available at: https://naturalmedicines.therapeuticresearch.com/databases/food,-herbs-supplements/professional.aspx?productid=680. Last accessed May 23, 2024.
30. Lin B, Li S. Cordyceps as an herbal drug. In: Benzie IFF, Wachtel-Galor S (eds). *Herbal Medicine: Biomolecular and Clinical Aspects*. 2nd ed. Boca Raton, FL: CRC Press/Taylor & Francis; 2011.
31. Memorial Sloan Kettering Cancer Center. Cordyceps. Available at https://www.mskcc.org/cancer-care/integrative-medicine/herbs/cordyceps#msk_professional. Last accessed May 29, 2024.
32. TRC Healthcare NatMed. Cordyceps. Available at https://naturalmedicines.therapeuticresearch.com/databases/food,-herbs-supplements/professional.aspx?productid=602. Last accessed May 6, 2024.
33. TRC Healthcare NatMed. Turkey Tail Mushroom. Available at https://naturalmedicines.therapeuticresearch.com/databases/food,-herbs-supplements/professional.aspx?productid=648. Last accessed May 23, 2024.

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National Cancer Institute. Medicinal Mushrooms: Health Professional Version. Available at https://www.cancer.gov/about-cancer/treatment/cam/hp/mushrooms-pdq. Last accessed October 1, 2024.