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Myco-Polysaccharides

DESCRIPTION

Some mushrooms and other fungal entities have possible immunomodulatory activities and possible other health benefits. It is thought these health benefits are mainly due to polysaccharides and polysaccharide-protein complexes, which comprise the cell walls of these organisms. The principal bioactive substances are believed to be the beta-D-glucans. Beta-D-glucans, usually called beta-glucans, are nondigestible polysaccharides found in nature in such sources as cereal grains, including oats and barley, as well as in yeast, bacteria, algae and mushrooms.

It is likely that the activities of the various myco-beta-D-glucans depend on such chemical characteristics as their molecular weight, their branching patterns, their solubility in water and their tertiary structure. The most studied mushroom beta-glucans, all of which are available in Japan for use as biological response modifiers, are lentinan from *Lentinus edodes*; grifolan (also called GRN and grifolan LE) from *Grifola frondosa*; schizophyllan (also called SPG, sonifilan, sizofiran and sizofilan) from *Schizophyllum commune*; SSG from *Sclerotinia sclerotiorum*; PSK (also called krestin) from *Coriolus versicolor*; and PSP (polysaccharide peptide), also from *Coriolus versicolor.*

The beta-glucan lentinan is comprised of a beta-(1→3)-D-glucan backbone with beta-(1→ 6)-glucan side chains. The molecular weight of lentinan is approximately $5x10^5$ daltons, the degree of branching is 2/5, and the tertiary structure of lentinan is a triple helix. Grifolan is also comprised of a beta-(1→3)-D-glucan backbone with beta-(1→6)-glucan side chains. The molecular weight of grifolan is approximately $5x10^5$ daltons, the degree of branching is 1/3, and its tertiary structure is a triple helix. Both schizophyllan and SSG also contain beta-(1→3)-D-glucan backbones and beta-(1→6)-glucan side chains; they have triple helix tertiary structures. The degree of branching in schizophyllan is 1/3; in SSG, it is 1/3. PSK and PSP are glycoproteins containing beta-glucans.

ACTIONS AND PHARMACOLOGY

ACTIONS

Myco-polysaccharides may have immunomodulatory, antitumor, antimicrobial, lipid-lowering and glucose-regulating activities.

MECHANISM OF ACTION

The best studied of the mushroom beta-glucans is lentinan. Lentinan is typically used parenterally and appears to have little antitumor activity when administered orally. Parenterally administered lentinan has been demonstrated to have immunomodulatory activity. Lentinan appears to stimulate such cells as macrophages, monocytes, neutrophils, NK (natural killer) cells and LAK (lymphokine-activated killer) cells. Stimulation of these cells by lentinan may release a number of different cytokines, including TNF (tumor necrosis factor)-alpha, IL (interleukin)-1, IL-2 and IL-6; lentinan may also stimulate the production of nitric oxide (NO) in macrophages. These effects may result in antimicrobial and tumoricidal activities. Grifolan, schizophyllan and SSG have been shown to have similar effects when used parenterally.

The possible immunomodulatory effects of oral mushroom beta-glucans remain unclear. They may have immunological activity by virtue of their interaction with gut-associated lymphoid tissue (GALT). Immune cells associated with GALT, activated by contact with mushroom or other myco-beta-glucans in the gut, may migrate to other tissues where they might exert immunomodulatory effects. Further, there may be some digestion of myco-beta-glucans in the large intestine, via bacterial beta-glucosidases, to produce some oligosaccharides, which may be absorbed and may have immunomodulatory activity. However, this is unclear. There also may be substances in mushrooms other than beta-glucans that have immunomodulatory activity.

The possible antitumor and antimicrobial activities of the myco-beta-glucans are thought to be accounted for, in large part, by their possible immunomodulatory activities.

The mechanism of the possible cholesterol-lowering activity of the myco-beta-glucans is unclear. The myco-beta-glucans are somewhat similar in structure to oat beta-glucan. It is thought that the cholesterol-lowering effect of oat beta-glucan may be accounted for, in large part, by promoting the excretion of bile acids. Myco-beta-glucans may also promote the excretion of bile acids.

The mechanism of the possible glucose-regulatory activity of myco-beta-glucans is poorly understood.

PHARMACOKINETICS

Following ingestion, there is virtually no digestion of myco-beta-glucans in the small intestine. There are no beta-glucosidases among the digestive enzymes. Some digestion of myco-beta-glucans does take place in the large intestine via the action of bacterial beta-glucosidases. Some oligosaccharides (up to molecular weights of 20,000 daltons) that are produced via the bacterial beta-glucosidases may get absorbed. A large percentage of the ingested myco-beta-glucans is excreted in the feces.

INDICATIONS AND USAGE

The myco-polysaccharides may have anticarcinogenic, immune-modulating, antimicrobial, anti-inflammatory, cardioprotective, hepatoprotective, nephroprotective, hypoglycemic and anticaries effects.

RESEARCH SUMMARY

Many myco-polysaccharides, particularly those derived from *Lentinus edodes* (the shiitake mushroom), *Grifold frondosa* (the maitake mushroom), *Sclerotinia sclerotiorum* and *Schizophyllum commune*, have demonstrated anticarcinogenic effects in both animals and humans. The beta-glucan constituents of these polysaccharides are believed to be their most active anticancer components. These beta-glucans are lentinan from *Lentinus edodes*, GRN from *Grifola frondosa*, SPG from *Schizophyllum commune* and SSG from *Sclerotinia sclerotiorum*.

In *in vitro* studies, lentinan demonstrated anticancer effects by significantly boosting the cytotoxic capabilities of macrophages, enhancing production of macrophage tumor necrosis factor-alpha. It also increased production of interleukin (IL)-1. GRN also produced macrophage-stimulating activity in mouse macrophages, as did (though to lesser extents) SPG and SSG.

In animal experiments, these beta-glucans have shown varying activity against sarcomas, mammary cancer, some chemically induced cancers, adenocarcinoma, colon cancer and some leukemias, among others.

In humans, lentinan and SPG are approved for clinical use in Japan. Injected lentinan has reportedly increased survival time in patients with gastric and colorectal cancers, while SPG has shown clinical activity against cervical cancer, prolonging survival time and time to recurrence in stage II, but not stage III, cervical cancer patients. Its efficacy against gastric cancer is low.

Lentinan, combined with some other anticancer agents, prolonged survival times in some patients with advanced cancers of different types, including gastric cancer. SPG similarly enhanced the efficacy of several cancer treatments, including surgery and radiotherapy. Combining these treatments with SPG resulted in significantly longer survival times. In one recently concluded multi-center prospective study of lentinan's use in advanced gastric cancer patients, the combination of lentinan, tegafur and cisplatin resulted in

median survival of 297 days versus 199 days for those controls receiving the two cancer drugs without lentinan.

Some substances, other than the beta-glucans identified above, have been isolated from these mushrooms, which also show anticancer activity in *in vitro* and animal experiments. Research continues.

The non-specific (macrophage-activating) immune-enhancing effects of the myco-polysaccharides most likely account for much of their reported anti-inflammatory and antimicrobial activities. Preliminary trials of intravenous lentinan have not produced significant results in HIV-positive subjects. One recent study found that lentinan significantly stimulated expression of IL-2 receptors on peripheral blood mononuclear cells in patients with chronic hepatitis B.

Another recent study identified three antibacterial substances in shiitake mushrooms. They showed efficient activity against *Streptococcus spp.* and *Actinomyces spp.*, among others. They were far less effective against *Enterococcus spp.*, *Staphylococcus spp.* and some others.

Cordyceps sinensis has enhanced cellular immune function in subjects with chronic renal failure and has boosted natural killer activity in cells from both healthy individuals and some with leukemia. NK activities were also boosted by an extract of *Cordyceps sinensis* in mice with lung melanoma.

Ganoderma lucidum has immunologically active polysaccharides. Some of these have shown some activity against HIV-1 *in vitro* but not *in vivo*. Various extracts of the mushroom have exhibited some antibacterial activity *in vitro*, especially against *Micrococcus luteus*, and have been shown to have microbial additive effects with some antibiotics and antagonistic effects with others. Clearly, more research is needed before ganoderma preparations can be recommended for use with antibiotic drugs.

Recently, two patients with postherpetic neuralgia that had not yielded to other therapies and two patients with severe pain due to herpes zoster infection were said to receive dramatic pain relief upon administration of hot water soluble extracts of *Ganoderma lucidum* (36 to 72 grams dry weight per day). More recently still, various ganoderma polysaccharides have been isolated that show significant antiherpetic activity *in vitro* against both HSV-1 and HSV-2. Research is ongoing.

Various constituents of shiitake have shown effects that could be cardioprotective. Inhibition of platelet aggregation and some hypocholesterolemic effects have been noted *in vitro*. Dietary shiitake significantly lowered plasma-free cholesterol, triglycerides and phospholipids in spontaneously hypertensive rats, compared with controls. Shiitake, however, did not reduce blood pressure in these animals. Maitake, on the other hand, significantly lowered blood pressure but had no significant effect on lipids in this study. In some other animal studies, however, maitake did have favorable lipid effects.

A constituent of *Cordyceps sinensis* has been shown to have hypotensive and vasorelaxant effects in animal studies. Another extract has reportedly counteracted chemically induced arrhythmias in rats.

Ganoderma lucidum was said to significantly inhibit platelet aggregation in 15 healthy volunteers and 33 subjects with atherosclerotic disease.

Cordyceps sinensis protected animals from the nephrotoxic effects of cyclosporin A in one experiment. *Ganoderma lucidum* was hepatoprotective in another animal model.

Maitake and some of its constituents have shown some antidiabetic activity in animals. Blood glucose reductions were observed in genetically diabetic mice given these substances, compared with controls in which blood glucose levels rose with age. In an animal model of NIDDM, maitake again produced significant reductions in blood glucose levels, compared with controls. Researchers in this study concluded that maitake does not inhibit glucose absorption at the enteron but, rather, inhibits the metabolism of absorbed glucose.

Cordyceps sinensis extracts have also shown some ability to lower plasma glucose levels in animal models of diabetes. A *cordyceps sinensis* polysaccharide was said to have potent hypoglycemic effects, via intraperitoneal administration, in genetic diabetic mice.

Finally, a polysaccharide constituent of shiitake has been reported to have an anticaries effect. A significantly lower caries score was seen in shiitake-supplemented rats fed a cariogenic diet, compared with controls on the same diet but without shiitake extract.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Myco-beta-glucans and myco-polysaccharides are contraindicated in those who are hypersensitive to mushrooms, to mushroom extracts and to any component in a mushroom-containing supplement, a mushroom extract-containing supplement, a mushroom polysaccharide-containing supplement or a mushroom beta-glucan-containing supplements.

PRECAUTIONS

Pregnant women and nursing mothers should avoid supplementation with mushroom extracts and should avoid mushroom polysaccharide-containing supplements and mushroom beta-glucan-containing supplements.

Those with cancer, immune deficiencies and other medical problems should only use mushroom supplementation, mushroom polysaccharide or mushroom beta-glucan supplements under medical supervision.

ADVERSE REACTIONS

The most commonly reported adverse reactions from the use of the various beta-glucan-containing fungal products are gastrointestinal, including nausea and epigastric distress. Eosinophilia has been reported in subjects taking 4 grams daily of shiitake mushroom powder. Contact dermatitis has also been reported in some cases, from the handling of shiitake mushrooms.

INTERACTIONS

DRUGS

Antibiotics and chemotherapeutic agents: In vitro studies, animal studies and parenteral use of the mushroom beta-glucans suggest that they may enhance the efficacy of various chemotherapeutic agents, as well as antibiotics. However, it is unclear if oral use of these substances, either in concentrated forms or in the form of mushrooms, would produce similar interactions.

Antiplatelet drugs: Ganoderma may enhance the effect of antiplatelet drugs.

OVERDOSAGE

There are no reports of overdosage of any of the products mentioned in this monograph.

DOSAGE AND ADMINISTRATION

The beta-glucans lentinan, grifolan, schizophyllan and SSG are available in Japan. Lentinan and schizophyllan are approved in Japan as drugs for the treatment of cancer. Edible mushrooms rich in beta-glucans include the shiitake mushroom (*Lentinus edodes*), the maitake mushroom (*Grifola frondosa*), the himematsutake mushroom (*Agaricus blazei*), the button mushrooms (*Schizophyllum commune* and *Sclerotina sclerotiorium*), the wood ear mushroom (*Auricularia auricula*), the tremella mushroom (*Tremella fuciformis*), the poria mushroom (*Wolfporia cocos*) and the enoki mushroom (*Flammulina velutipes*). Huitlacoche (*Ustilago maydis*) is not a true mushroom, but it is an edible fungus and also rich in beta-glucans. Non-edible mushrooms that are rich in beta-glucans include the reishi mushroom (*Ganoderma lucidum*) and the coriolus mushroom (*Coriolus versicolor*). *Cordyceps sinensis* is a fungus, not a mushroom.

Nutritional supplements containing extracts of the above edible and non-edible mushrooms are available and are typically marketed with emphasis on their beta-glucan content.

One supplement contains a mixture of reishi, maitake, shiitake, hericium, cordyceps, coriolus, wood ear, tremella, poria and umbellatus/polyporus (*Grifola umbellatus*). There is no typical dose of this supplement.

A beta-glucan-enriched maitake supplement, called the maitake D fraction, is available. The maitake D fraction comprises a mixed beta-D-glucan fraction prepared from the maitake mushroom. The supplement is available in solid and liquid form. Maitake in the form of a crude dried mushroom is also available. Crude dried reishi mushrooms, reishi powders and reishi tinctures are available, as are crude dried shiitake mushrooms and shiitake powders. *Cordyceps sinensis* is available in powdered form. No specific doses of these products can be recommended at this time.

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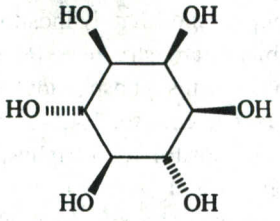
Myo-Inositol

DESCRIPTION

Myo-inositol, the major nutritionally active form of inositol, is vital to many biological processes of the body, participating in a diverse range of activities. *Myo*-inositol is one of nine distinct isomers of inositol. It is essential for the growth of rodents, but not for most animals, including humans. Humans can make *myo*-inositol endogenously, which they do from glucose, and, even though *myo*-inositol is sometimes referred to as a vitamin, it is not a vitamin for humans or most animals. However, the dietary intake of *myo*-inositol can influence the levels of circulating and bound *myo*-inositol in the body and may influence certain biological activities. Nutritional supplementation of this cyclitol may affect behavior and may have anti-depressant and anti-anxiety activities. For more information on Inositol supplementation, see Inositol Hexanicotinate.

Myo-inositol intake from the average diet is approximately one gram daily. The major dietary forms of *myo*-inositol are inositol hexaphosphate or phytic acid, which is widely found in cereals and legumes and associated with dietary fiber, and *myo*-inositol-containing phospholipids from animal and plant sources.

Myo-inositol is also known as inositol, hexahydroxycyclohexane, cyclohexanehexol, mouse antialopecia factor and, chemically, as cis-1,2,3,5-trans-4,6-cyclohexanehexol. *Myo*-inositol is abbreviated as Ins and sometimes as just I. It is represented by the following chemical structure:



myo-Inositol

Another naturally occurring isomer of inositol, D-*chiro*-inositol, has been found to have activity against insulin resistance. However, at present, D-*chiro*-inositol is neither available as a nutritional supplement nor as a drug. A hexanicotinate conjugate of *myo*-inositol, inositol niacinate or inositol nicotinate, is available in Europe as a drug for the treatment of circulatory problems.

ACTIONS AND PHARMACOLOGY

ACTIONS

Myo-inositol may have antidepressant and antianxiety activity.