Botanicals and Medicinal Mushrooms that Modulate Healthy Immune Response

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DISCUSSION

MEDICINAL MUSHROOMS

Known to the Greeks, Romans, Egyptians, and Asians, they were used medicinally throughout Asia since at least 3000 BC.[1-3] Hot-water decoctions of medicinal mushrooms such as Reishi and Chaga were widely used throughout ancient Asia and eastern Russia.[4] In traditional Chinese herbal medicine, mushrooms like Reishi (Ganoderma lucidum) and Turkey Tail (Trametes versicolor) were used to strengthen the body, tonify organ function, and calm the nervous system. Modern research reveals how these medicinal mushrooms achieve their traditionally-defined actions at the cellular and molecular levels.

Decades of research support traditional knowledge that regular consumption of medicinal mushrooms enhances human health. These health benefits are attributed to their abundant bioactive constituents.[3,5] Mushrooms are rich in polysaccharides (particularly beta-glucans), polysaccharide peptides, terpenes, phenols, lectins, alkaloids, fatty acids, and sterols. Edible and medicinal mushrooms are highly nourishing, offering an abundance of proteins, fiber, vitamins, and minerals.[1;5-7]

Medicinal mushrooms and their bioactive components are primarily recognized as potent immunomodulators that can potentiate, stimulate, or down-regulate immune response to enhance healthy function. Because of their wide range of activity, immunomodulators are also known as biological response modifiers. The immunomodulatory influence of medicinal mushrooms encourages anti-inflammatory and antioxidant activity.[6,10] These activities are intrinsic to their profound capacity to protect and support healthy function of the cellular, hepatic, cardiovascular, neurological, and kidney systems.[1,6,8-10]

BETA-D-GLUCAN IS THE KEY MARKER OF QUALITY MEDICINAL MUSHROOMS

Beta-d-glucans polysaccharides are a major structural component of mushroom cell walls, comprising about half of the cell wall's mass.[11] Beta-d-glucan is the key marker used to assess the quality and therapeutic activity of medicinal mushrooms.[1,7]

Basidiomycete (fungal) beta-glucans are found to be more structurally complex and more immunologically active than cereal beta-glucans.[11] Fungal beta-glucans are especially known as potent immunomodulators, having the ability to activate immune cells and potentiate innate immunity.[10,12,13] Mushroom polysaccharides stimulate the production of cytokines that mediate the intercellular immune response and modulate the inflammatory response.[1,7]

OTHER MAJOR COMPONENTS OF MEDICINAL MUSHROOMS

Terpenes and their subgroups are major bioactive compounds in medicinal mushrooms.[14] Triterpenoids – lipid compounds found in mushrooms – exert hepatoprotective, antioxidant, and anti-inflammatory activity. They are found to lower lipid levels, inhibit histamine release, and to work in conjunction with beta-glucans to activate immunity. Reishi and Chaga mushrooms are notably high in triterpenoids, which contribute to their bitter taste.[11]

Triterpenes are notable for their cytotoxic activity against various cancer cell lines. They are found to inhibit tumor invasion through reducing matrix metalloproteinase expression. They can help prevent tumor binding to endothelial tissue, which inhibits tumor metastasis.[15]

Ergosterol and its analogues are triterpenoids but are classified as a separate category since they are structurally similar to cholesterol in humans. Ergosterol is a key marker for fungal presence. Ergosterol, a precursor to vitamin D2, is found to exert antioxidant and antitumor activity.[11]

IMMUNOMODULATORY MUSHROOMS SUPPORT INNATE AND ADAPTIVE IMMUNE RESPONSE

Mushrooms have evolved complex defense systems

and possess an abundance of immunostimulating phytochemicals[16] that modulate immune function, are antioxidant and anti-inflammatory, and are cytoprotective through a wide spectrum of activity.[3,6]

Immunostimulation is valued as an important strategy to support immune response in elderly people and in those with certain chronic diseases.[7] Mushrooms exert a wide influence on the immune system, including hematopoietic stem cells, lymphocytes, macrophages, T-cells, dendritic cells, cytokine production, and NK (natural killer) cells.[1,3,4,6,7;11-13] Their anti-inflammatory influence downregulates iNOS, COX-2, and TNF, and suppresses NFKB activation.[4] They exert significant antioxidant, antimicrobial, anti-inflammatory, and antitumor activity.[1,4,5,6,10,17]

Because fungal beta-glucans are noted for their ability to modulate both innate and adaptive immune response.[,6,7,12,13,18,19] they are often called biological response modifiers.[8,11,19] They pass intact through the stomach, are not broken down by digestive enzymes, and interact with beta-glucan receptor sites in the small intestine.[11-13]

ENHANCE CELLULAR DEFENSES AND PROMOTE HEALTHY CELLULAR RESPONSE

Decades of research confirms the antitumor properties of fungal beta-glucans from Shiitake, Reishi, Chaga, and other medicinal mushrooms.[20] They are found to regulate tumor genes and demonstrate the ability to decrease angiogenesis and increase phagocytosis of unwanted cells.[1] Three compounds found in medicinal mushrooms – beta-d-glucans, triterpenoids, and ergosterol and its analogues – are of great interest to researchers because of their influence on the immune system and their anticarcinogenic properties.[4,20]

Medicinal mushrooms stimulate macrophages to release IL1, IL6, IL8, TNF (tumor necrosis factor), and NO (nitrous oxide), factors that induce tumoricidal activity in macrophages.[4] Terpenes are noted for their anti-inflammatory activity and are found to exert a wide spectrum of antitumor influence.[3,8,14] Some triterpenes are found to exert strong cytotoxic activity.[14]

Mushroom polysaccharides with antitumor activity are found to prevent oncogenesis and to prevent tumor metastasis.[17] They are also found to offer additional benefits when used during chemotherapy or radiotherapy.[1,17] Some are found to exert a protective influence on bone marrow, protecting against bone marrow suppression.[1]

Image Reference for Immunomodulatory Mushrooms Support Innate and Adaptive Immune Response

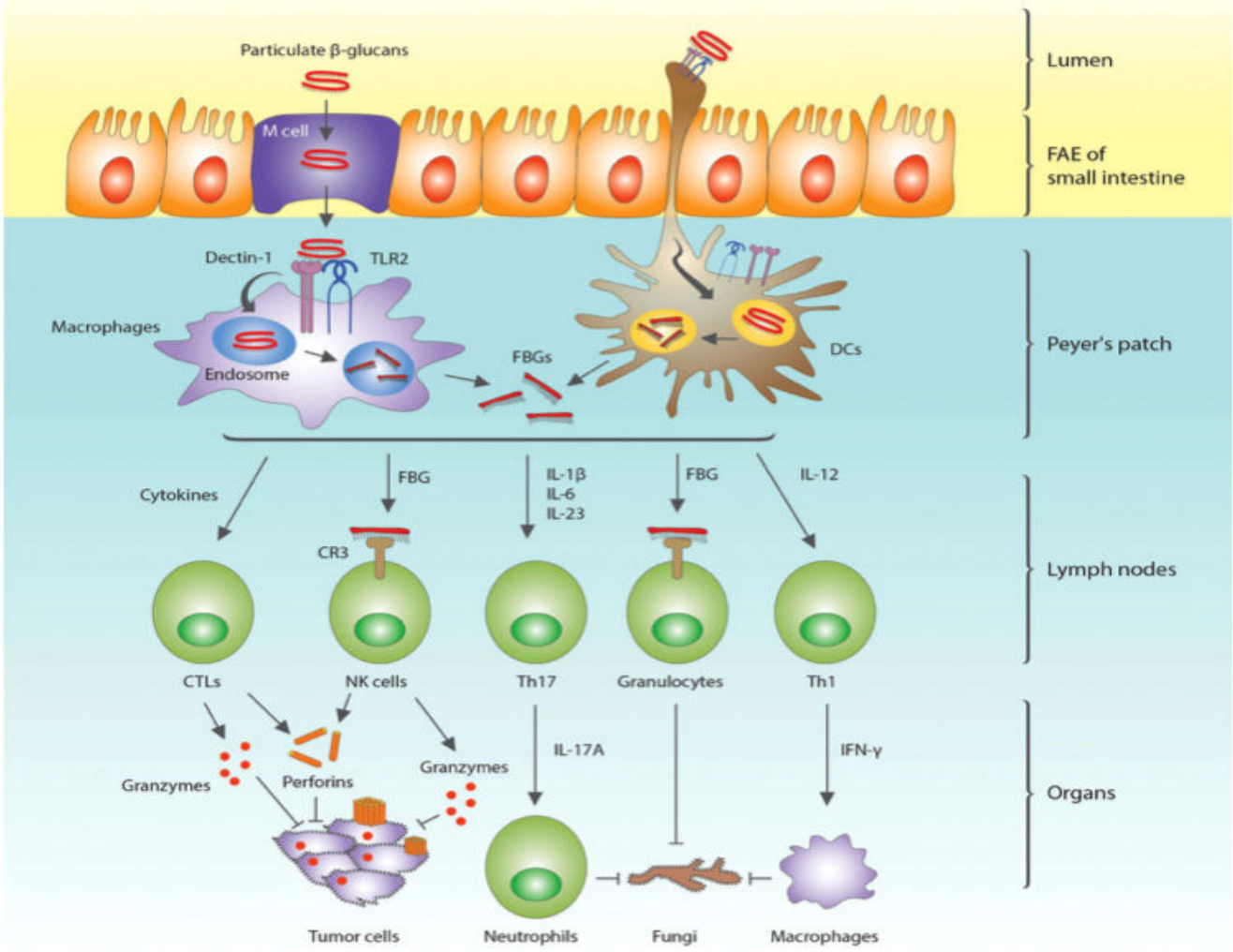
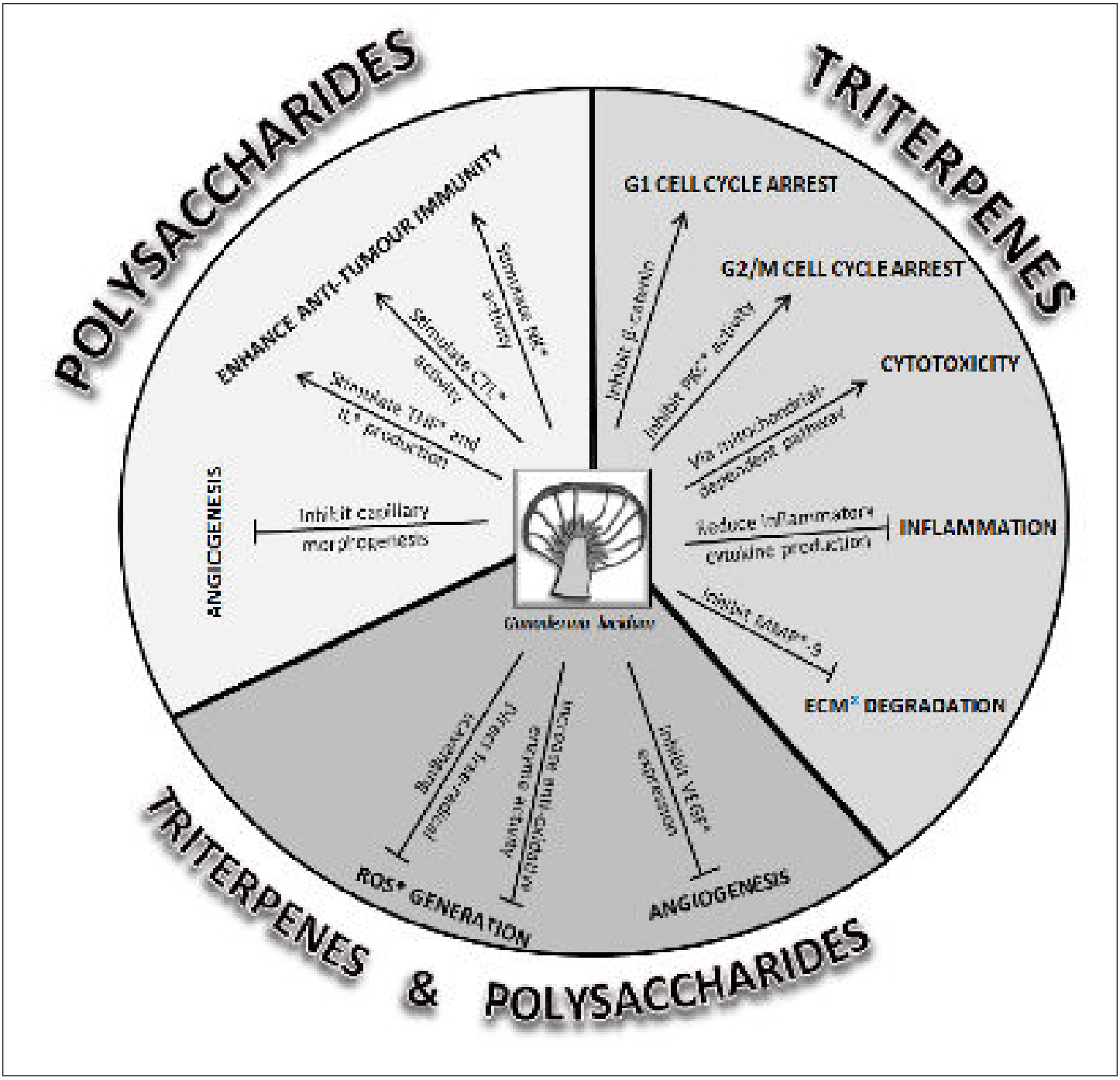


Fig. 1. Uptake of β-glucan in the small intestine and activation of innate and adaptive immune cells of Peyer's patches, lymph nodes, and systemic organs. Orally administered β-glucans can be either absorbed through M cells or through binding to the projected tips of dendritic cells (DCs) in the follicle-associated epithelium (FAE) of Peyer's patches, and subsequently bind to dectin-1 and TLR2. The macrophages or DCs engulf β-glucans and fragmented β-glucans (FBGs) are secreted in the lymph nodes. FBGs, like soluble β-glucans, bind to dectin-1, but are unable to activate macrophages and DCs. However, FGBs can activate NK cells and granulocytes by binding to complement receptor 3 (CR3) on these cells. The NK cells and cytokine-stimulated cytotoxic T lymphocytes (CTLs) secrete perforins and granzymes, which make pores and fragmenting the DNA in tumor cells, respectively. The FBG-bound granulocytes together with activated neutrophils and macrophages then remove the infecting fungi.

Batbayar S, Lee DH, Kim HW. Immunomodulation of Fungal B-Glucan in Host Defense Signaling by Dectin-1. Bimol Ther (Seoul). 2012 sep. 20(5):433-445.

Source: *See reference #12*

Image Reference for Enhance Cellular Defenses and Promote Healthy Cellular Response



An overview of anti-cancer pathways affected by the triterpenes and polysaccharides from *G. lucidum* [*CTL Cytotoxic T-lymphocytes; ECM Extracellular matrix; IL Interleukin; MMP matrix metalloproteinase; NK Natural killer cells; PKC Protein Kinase C; ROS Reactive oxygen species; TNF Tumour necrosis factor; VEGF Vascular endothelial growth factor]

Source: *See reference #8*

PROTECTIVE AND RESTORATIVE ACTIONS

Adaptogen botanicals are those that modulate a wide array of biological responses to restore allostasis through influencing multiple systems including the immune, nervous, endocrine, metabolic, and cellular systems. Many adaptogens excel in their capacity to protect cells, tissues, organs, and systems of the body. Because of their broad modulatory and nourishing influence, medicinal mushrooms and adaptogenic botanicals are also extremely useful in a restorative capacity to help restore function, health, and well-being after illness, health challenges, and medical regimens. Modern research attributes this success to the wide spectrum of influence on modulating physiological homeostasis.

PREMIER QUALITY ORGANIC MEDICINAL MUSHROOMS

Nammex® is the company considered as having set the gold standard in the medicinal mushroom industry. Nammex ®sustainably grows certified organic, whole fruiting body mushrooms under natural conditions to promote the same index of compounds found in mushrooms. Nammex® mushrooms are tested for the ideal fungal beta-d-glucans profile, the primary marker for medicinal quality mushrooms.

Mushrooms grown on natural substrates are high in beta-d-glucans, very low in starch, and have the precursors to produce important secondary metabolites, such as triterpenoids. Mushrooms or mycelium produced on cereal grains lack these precursors.[20] While testing may show a high polysaccharide content, this reflects high alpha-glucan and low to no beta-d-glucans. [11,21,22] Many products on the market today are produced from mycelium and/or whole mushroom products grown on grain because it is economical. However, these products do not contain the therapeutic constituents naturally found in medicinal mushrooms.[11,22]

Nammex® was founded by mushroom pioneer Jeff Chilton in 1989 after many years of experience in the field. Namm®ex carefully selects mushroom cultivars that have been developed in China over centuries of using mushrooms as food and medicine. Currently, 85% of the world mushroom supply is produced in China. Jeff has been working closely with organic mushroom producers there for over 20 years in areas deep in the mountains, far from industrial pollution.

Nammex® mushrooms are grown on natural substrates, such as protein-enriched sawdust or hardwood logs, that offer the necessary precursors for growing truly full-spectrum medicinal mushrooms. They thrive in natural sunlight and fresh air and are watered with fresh water from deep wells.

After being hand-harvested, the mushrooms are carefully sun- or air-dried and tested for purity and for medicinal markers, including beta-glucans and terpenoids. Through all stages, the mushrooms are carefully tended and go through a rigorous testing process to ensure the highest quality.

SYNERGISTIC BOTANICAL EXTRACTS

Medicinal mushrooms should be combined with standardized and full-spectrum botanical extracts to enhance the therapeutic effectiveness of the formulation. When botanicals are carefully chosen to target specific conditions, address pathological factors, and direct their effect toward specific areas of the body, they provide synergistic immunomodulatory, cytoprotective, antioxidant, anti-inflammatory, and adaptogenic influence. The herbs frequently combined with medicinal mushrooms are known for their capacity to protect and support healthy function of the hepatic, cardiovascular, neurological, and kidney systems.

Reishi Mushroom (*Ganoderma lucindum*)

Reishi has been revered in Chinese medicine for over 2,000 years as a longevity herb and elixir of immortality. This glossy, deep reddish-brown, woody mushroom is a popular motif in Taoist and Chinese art, often portrayed in the hands of Chinese sages. Ling Zhi can be translated as Plant of Immortality, Herb of Spiritual Potency, or Spirit Plant of Longevity.

In Chinese medicine, Reishi is particularly valued for enhancing the deep reserve energy of the kidney energetic system and for its ability to strengthen the body according to the ancient Fu Zheng (nourish the upright) tradition.[15,23,24]

Reishi, like most mushrooms, is suitable and beneficial to use over a long period of time.[25] With its nourishing and restorative influence, Reishi modulates homeostasis and supports the body's ability to respond well to stress. [26,27]

Its active constituents include polysaccharides, triterpenoids, and plant sterols. [26,27] The bitter taste of Reishi, due to its triterpenoid content, can be used as a quick test of the quality of a Reishi product.[11] Over 140 types of triterpenes and triterpenoids have been identified in Reishi.[28] Triterpenes in Reishi are shown to exert antioxidative activity in vitro. They are found to reduce oxidative damage through their free radical scavenging activity and through their ability to increase the activity of antioxidant enzymes.[28]

Reishi is currently used in China to prevent and treat disease, such as bronchitis, hepatitis, hypertension, tumors, and immunological diseases.[24] Reishi is well-known for its wide-reaching biological activity as a potent immunomodulator that exerts a wide range of anti-inflammatory and antioxidant activity, and helps protect cells from oxidative damage.[24,26,27,29] It modulates antigen-presenting cells, NK (natural killer) cells, and T- and B-lymphocytes.[24,29]

Reishi is found to exert antitumor and cytotoxic activity on multiple types of cancer cells in vitro and in vivo.[15,24,25,30] It is noted for its antiproliferative, antimetastatic, anti-angiogenic actions, and for its ability to promote apoptosis.[30]

Reishi is found to exert chemoprotective capacity, enhance effects of radiotherapy, and reduce chemotherapy-induced nausea.[15,22] Extensive research shows Reishi to be powerfully hepatoprotective,[3,15] nephroprotective[31,32] and neuroprotective.[9,29,31,33]

Turkey Tail Mushroom (*Trametes versicolor*)

Turkey Tail is the common name for Trametes versicolor (also called *Coriolus versicolor*). It naturally grows as a bracket, or shelf, mushroom on fir, pine, and some deciduous trees. Valued worldwide as a powerful medicinal, [1,2,34-36] the ancient Chinese revered Turkey Tail to promote health, strength, and longevity.[36]

Its bioactive compounds include proteins, polysaccharides, and flavonoids.[35] Turkey Tail's wide range of biological activity influencing immune response is largely attributed to its abundance of beta-glucan polysaccharides.[2,34,36,37]

Turkey Tail is noted for its wide-reaching influence on the immune system through potent modulation, stimulation, and potentiation. [2,34] It effects both adaptive and innate immune responses, and downregulates oxidative stress.[8,36,37] The polysaccharopeptides (protein-bound polysaccharides) in Turkey Tail are notable as potent immunopotentiators and for their antitumor influence.[2,36]

Numerous studies in vitro and in vivo show its antitumor, cytotoxic, antimicrobial, and antiviral activity.[8,10,35,36,38] Many in vitro and in vivo studies and some clinical studies show that Turkey Tail's antitumor action is due to its immunomodulatory influence.[36] As a potent antioxidant, it induces production of SOD (superoxide dismutase) and glutathione peroxidase, and supports healthy liver function.[2,39] It also exerts a calming influence on the central nervous system.[2]

Coriolus is one of many mushroom compounds studied for its ability to support healthy immune function during radiotherapy and chemotherapy, and to counter the immunosuppressive effects of some medical procedures. [2,10] Because of this, Coriolus versicolor extracts are currently used in China and Japan as adjunct therapy along with chemotherapy and radiotherapy. The extracts are found to ameliorate the adverse effects of those procedures and to improve quality of life in patient groups.[36,37,39]

Coriolus is neuroprotective and anti-neurodegenerative. [10,36,39] This is largely attributed to its anti-inflammatory and antioxidant capacity. It is noted for its ability to help regulate the brain's cellular stress response pathway and to calm the central nervous system.[10,39]

Shiitake Mushroom (*Lenintula edodes*)

Shiitake is an edible mushroom used widely in East Asian cooking. It is readily found wild growing

on decaying wood throughout the forest and is the second most-produced edible mushroom worldwide.[40] .

Shiitake is high in protein, lipids, fats, minerals, and vitamins.[40] The primary polysaccharide, lentinan (beta-1,3-glucan) is notable for its antitumor, antioxidative, and immunomodulatory actions.[8;40-43]

It exerts antidiabetic, lipid-lowering, antimicrobial, cardioprotective, and hepatoprotective influence.[30;40-43] Shiitake is found to lower cholesterol through its ability to facilitate lipid processing in the liver[40] and is protective against development of liver fibrosis.[45]

Shiitake is used worldwide for immune-related diseases and contains antibiotic, antitumor, and antiviral components including lentinan, lectins, and ertiadenine.[44] Known for being an immunopotentiator,[45] one study noted an immunomodulatory response from a water-soluble extract from the mycelia that helped restore radiation-damaged bone marrow in mice.[4,45]

Poria Sclerotium (*Poria cocos*)

Poria sclerotium, also known as China root or Tuckahoe root, is called *Fu Ling* in Chinese and *Hoelen* in Japanese. This highly revered medicinal fungus grows on the moist underground roots of pine trees. The Chinese differentiate four different layers of the fungus, each used for specific medicinal indications.[46] The middle layer of the sclerotium (outer covering) is widely used in traditional Chinese medicine as a powerful adjunct herb in formulas. Fu Ling is valued for its ability to regulate fluid balance and for its tonic properties.[46]

Poria contains a natural abundance of polysaccharides and triterpenes.[47] It also contains steroids, amino acids, choline, and potassium salts.[46] Poria exerts immunomodulatory activity and demonstrates the ability to stimulate secretion of factors that potentiate the immune response.[46] Studies find that Poria exerts antioxidant and strong anti-inflammatory activity.[46,48,49] Poria is found to be a potent COX-2 inhibitor and to downregulate NF-kB.[46,50]

Chaga Sclerotium (*Inonotus obliquus*)

Since the 16th century, Chaga has been used in Russia and Western Siberia to treat the digestive system, liver and heart conditions, tuberculosis, and certain kinds of cancer.[51,52] Traditional herbalists used it to purify the blood and for pain relief.[16] In Russian traditional medicine, Chaga is valued as a diuretic and antitumor herb.[8,53]

Chaga is a parasitic fungus that appears as a large, gall-like formation on tree bark.[52] It is a sterile conk consisting of a solid mycelial mass termed a sclerotium. Chaga is plentiful in secondary metabolites, the most notable being the triterpenoids inotodiol, trametolenic acid, and betulinic acid. These are derived from the precursors in the Birch trees on which Chaga naturally grows. While it is most commonly found growing on Betula species (Birch), it also naturally grows on Alder, Beech, and other hardwood trees throughout Russia, North American, Eastern Europe, and Japan.[16,51]

Over 20 bioactive compounds in Chaga have been identified, including polysaccharides, oxygenated triterpenes, polyphenols, lignans, alkaloids, steroids, betulinic acid, folic acid derivatives, and tannins. It contains inotoidiol (a precursor of vitamin D2)[51,52] and is high in oxalic acid.[53]

Chaga is well-known to exert anti-inflammatory, antioxidant, antiviral, antimicrobial, and antitumor activity.[16,51,53,54] It is also found to be a potent hepatoprotective and immunomodulatory agent.[52,53] Studies find it helps the bone marrow system recover from damage.[16]

Chaga is found to be anti-aging because of its ability to strengthen the immune system.[51] Polysaccharides extracted from Chaga mycelia are found to activate B-cells and macrophages.[52] The hot water extract of Chaga is found to exert powerful immunomodulatory influence. It helps potentiate the host immune system through regulating the network of cytokines and their expression.[16] Because of this, studies report it has potential to be used with immunocompromised or immunosuppressed individuals.[16]

SYNERGISTIC BOTANICALS

Chinese Baikal Skullcap (*Scutellaria baicalensis*) and Baicalin

Scutellaria baicalensis has been used for over 2,000 years in Chinese medicine to treat and clear heat conditions present in many diseases. This yellow root, known as Huang Qin (Yellow Gold) in Chinese medicine, is one of the renowned Three Yellows of Chinese medicine that are used to powerfully alleviate inflammatory and infectious conditions.[55]

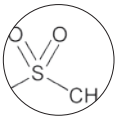
Baikal Skullcap offers a rich source of over 50 flavonoids along with terpenoids, alkaloids, phytosterols, essential oils, and polysaccharides.[55-57] Baikal Skullcap extract and its bioactive compounds exert antitumor, anti-inflammatory, antipyretic, antiviral, antimicrobial, and antibacterial activity.[55,56,58,59]

Baikal Skullcap extract is found to inhibit multiple inflammatory pathways, including cytokine, NF-kB, and VEGF

production.[60,61] It inhibits LOX and IL expression and prevents COX-2 gene expression and prostaglandin synthesis.[60-64]

Baikal Skullcap is noted to promote normal cell-cycle function.[65] Modern studies find that Baikal Skullcap is neuroprotective, cardiovascular-protective, and hepatoprotective.[55,56,58,59,66,67]

Baicalin



Baicalin, considered the plant's primary bioactive compound, is often regarded as a marker for the quality of Baikal Skullcap, according to the Chinese Pharmacopoeia (2010).[55] It is highly studied due to its impressive anti-inflammatory and antioxidant qualities.[55,59]

Baicalin is found to influence innate immune response and to act as an immune modulator.[56,57] Baicalin downregulates TNF (tumor necrosis factor), NF-kB (nuclear factor kappa-beta), and other pathways.[55]

Baicalin demonstrates anti-inflammatory and antiviral activity in vitro and in vivo against influenza and other viruses with many mechanisms of action. It is shown to block virus attachment and inhibit viral replication.[56]

An extract of Baikal Skullcap enriched with baicalin was found to stimulate nonspecific antiviral immunity and reduced TNF and IL-10 production in bone marrow cells of ALL (acute lymphoblastic leukemia) patients.[57]

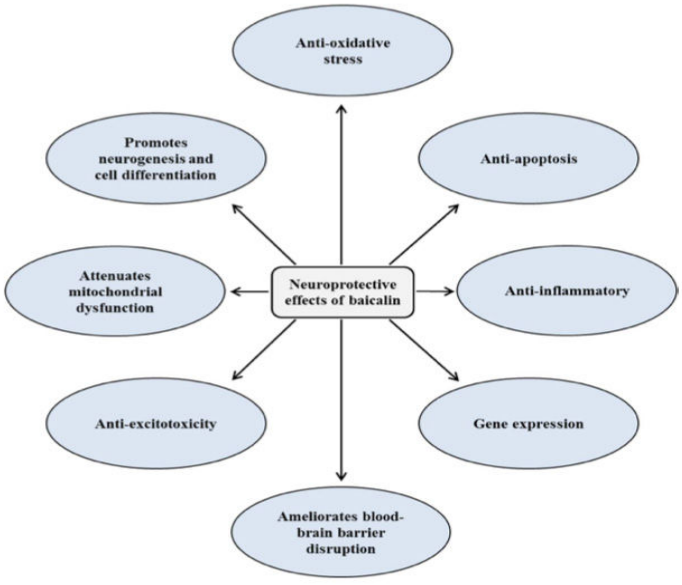


Figure 2. Mechanisms of neuroprotective and cognitive enhancement effects of baicalin.

Sowndhararajan K, Deepa P, et al. Neuroprotective and Cognitive Enhancemenet Potentials of Baicalin: A Review. Brain Sci. 2018 Jun. 8(6):104. doi: 10.3390/brainsci8060104

Source: *See reference #59*

Baikal Skullcap exerts a broad influence on cell-signaling networks and is able to inhibit cell proliferation.[68-70] Baicalin is found to promote normal cell-cycle function.[69,70] It is able to cross the blood-brain barrier and is found to be neuroprotective largely through its ability to inhibit oxidative stress.[55,59,67,71]

Milk Thistle (*Silybum marianum*) & Silymarin

Milk Thistle is a renowned weed that has been used in herbal medicine for centuries to treat liver and gall bladder disorders. It was utilized by Pliny the Elder, a Roman naturalist, and by the skilled English herbalist Nicolas Culpepper.[72,73]

Silymarin, considered the active component of Milk Thistle, consists of a complex of compounds, including numerous silybins and flavonolignans.[72,74] Milk Thistle is widely known for its hepatoprotective and nephroprotective benefits which are attributed to its potent antioxidant properties.[72-77]

Milk Thistle is protective of glutathione and can help prevent its depletion.[76] Milk Thistle extract and silymarin are found to scavenge free radicals and help prevent formation of free radicals through their ability to inhibit specific enzymes that produce ROS (reactive oxygen species).[75] This also benefits mitochondrial integrity and enhances cellular regeneration.[72,75]

Milk Thistle is considered immunomodulatory.[76] Silymarin is found to decrease the inflammatory response through inhibition of NF-kB and other pathways.[72,75,77]

Ashwaganda (*Withania somnifera*)

Ashwaganda, or Winter Cherry, is a powerful herb that has been revered in Ayurvedic medicine for over 5,000 years. It is a woody shrub in the Solanaceae family that grows in diverse regions, such as Africa, India, and the Mediterranean. Often called Indian Ginseng, it belongs to an elite class of Ayurvedic restorative tonic herbs known as Rasayana.

Historically used to enhance longevity and protect from disease, this ancient herb possesses significant adaptogenic activity, enhancing a restorative response to stress in all systems of the body. Ashwaganda supports healthy anabolic activity and nourishes those in a weakened physical or mental condition.[78-80] Ashwaganda helps normalize biological markers induced by stress, including blood sugar, cortisol levels, and adrenal function.[81] Ashwaganda is known for its neurocognitive benefits and known to benefit neurological conditions and support nervous system restoration.[81-84]

Ashwaganda is found to exert antioxidant and anti-

inflammatory activity. One study reports that an extract of Ashwaganda significantly suppresses production of proinflammatory cytokines in both healthy individuals and in rheumatoid arthritis patients.[85]

Schisandra (*Schisandra chinensis*)

The beautiful orange-red Schisandra berry has a long history of medicinal and food use in China, Japan, Korea, Tibet, and Russia. Throughout time, hunters in the wilds of Siberia have used the dried berries, chewed or prepared as a tea, to provide energy, stave off exhaustion, and improve night vision during long trips. Known as the Five Flavor Fruit in Chinese medicine, it is considered a tonic that benefits all five energetic/organ systems according to Chinese medical principles. Schisandra was used particularly to support the lung and liver systems.[23] Schisandra fruit contains powerful adaptogenic compounds, including high amounts of lignin compounds called schisandrins.[86]

Multiple studies report that Schisandra increases mitochondrial glutathione redox status and plays a role in preventing oxidative stress.[87,88] It is known to protect the liver and DNA from damage due to chemicals. [87,88] Schisandra is neuroprotective and is found to protect neuronal cells and enhance cognition.[89,90]

Rabdosia (*Rabdosia rubescens*)

Rabdosia leaves are used in Chinese medicine as a medicinal decoction for multiple kinds of pain, especially that induced by inflammation. Bioactive components include phenolic acids, diterpenoids, and flavonoids.[91,92]

Rabdosia offers neuroprotective influence.[93,94] Its diterpene component, oridonin, demonstrates anti-inflammatory effects, including inhibition of neuroinflammation. It is found to inhibit glial activation and to decrease release of inflammatory cytokines in the hippocampus.[93,94] The whole plant extract is found more effective than an extract of an isolate.[91]

Chinese Salvia (*Salvia miltiorrhizae)*

Known as Dan Shen in Chinese medicine, Salvia is noted as a shen, or spirit herb, that can be used long-term offering multiple benefits. Traditionally used to nourish the blood and invigorate blood circulation, it is traditionally and currently valued as a restorative tonic for the blood, heart, and cardiovascular system, and used for cardiovascular and cerebrovascular conditions.[23,95-97] Chinese Salvia is noted to be antioxidative, endothelial protective, and myocardial protective.[96]

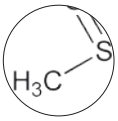
Additionally, the whole plant and many of its constituents are neuroprotective.[95,98]

The three main groups of bioactive compounds include the lipophilic terpenoids (such as the tanishones), the hydrophilic phenolic acids (especially salvianolic acid), and polysaccharides.[96,99] The terpenoids in Chinese salvia are found to exert a wide range of activity including antitumor, antioxidant, anti-inflammatory, neuroprotective.[99]

Both the tanishones and salvianic acid are noted for their neuroprotective and antioxidant activity[95,100] and are found to contribute to the cardiovascular protective actions of the whole plant.[97,98]

Salvianolic acid exerts a protective effect on brain injury, and is found to improve brain mitochondria[101] and to enhance cognitive performance.[102] In one study, the antioxidant activity of salvianolic acid was found to exceed that of Ginkgo extract and, like Ginkgo, shows promise in treating oxidative damage-derived neurodegenerative disorders.[103]

MSM (methylsulfonylmethane)



MSM is a naturally rich source of sulfur, a key nutrient that influences cellular health. MSM is most abundant in cow's milk and is also found in fruits, vegetables, and tea. It is comprised of sulfur oxygen and methyl groups and is about one-third sulfur. MSM is found to exert anti-inflammatory and antioxidative activity. Studies show it plays a role in glutathione (GSH) synthesis and can directly decrease production of ROS (reactive oxidative species).[104-106] MSM supplementation is found to lower oxidative stress biomarkers.[107]

Sulfur compounds, which play a role in many organs and tissues, are found in the hair, skin, and nails. Many amino acids, the building blocks of protein, have sulfur as a component. Found throughout the human brain, sulfur will also cross the blood brain barrier.[104] MSM is found to transport compounds across biological membranes and can enhance cellular permeability.[108]

MSM has been shown to enhance the biological activity of beta glucans and other polysaccharide derivatives. Sulfated polysaccharide derivatives have been shown to possess a variety of biological activities and could significantly improve structure characteristics, promote bioactivities, and add new bioactivities to polysaccharides. [109]

Hibiscus *(Hibiscus sabdariffa*)

Hibiscus is a culinary and medicinal herb traditionally used in Egypt, Mexico, Africa, Asia, and China. While all parts of the plants are used, the flower is

especially known for its high nutritional content and is used to make jams, jellies, and herbal teas.[110,111]

Nutrients include carbohydrates, malic acid, ascorbic acid, beta-carotene, and minerals (especially calcium and iron).[111] The flowers are naturally abundant in phenolic acids, flavonoids, and polysaccharides, and get their deep red color from an abundance of anthocyanins.[112,113]

Hibiscus extracts are noted for their wide range of antibacterial, antimicrobial, and potent antixodiant activity.[110,112] Hibiscus is found to be both hepatoprotective and nephroprotective.[110,113]

Ginger (*Zingiber officinale*)

This world-renowned and well-loved herb has been used as cooking spice, herbal remedy, and revered medicine for centuries. It is a daily household remedy for digestive upset, sore throat, colds, and flu. Known as a valuable anti-nausea remedy, Ginger is also a wonderful digestive carminative.[114]

Ginger is traditionally known to exert a thermogenic and diaphoretic effect. Ginger aids circulation and is used to warm the system during cold weather. Herbalists also use Ginger to enhance the effectiveness of other herbs in a formula by supporting digestion and circulating the herbs.[115]

Ginger demonstrates impressive antioxidant[85] and anti-inflammatory activity.[116,117] It is found to inhibit expression of COX-2 and activation of NF-kB inflammatory pathways. [116,117]

BioPerine® Black Pepper *(Piper nigrum)* 95% Piperine

Black Pepper is widely known for its ability to enhance the bioavailability of herbs and nutrients. In Chinese and Ayurvedic medicine, it is added to formulas for its ability to move other compounds and carry them throughout the body.

Bioperine® is a patented black pepper fruit that is standardized to 95% piperine content that has demonstrated the ability to increase the bioavailability of co-administered nutrients. Piperine is thought to enhance bioavailability through influencing the cellular biomembrane and intestinal enzymes.[118-120] Piperine is found to reduce levels of pro-inflammatory mediators, including COX-2, IL factors and TNF-alpha. It also supports healthy glutathione and SOD (super oxide dismutase) levels.[121,122] It is found to inhibit VEGF and to modulate cytokine and growth factor responses.[123] Piperine is known to be antioxidative, antimutagenic, antibacterial, and hepatoprotective.[119,124]

For more information on any of the ingredients listed here, including extensive research or individual monographs compiled by Donnie Yance, please contact Natura at 888.628.8720.

Therapeutic Effects of Medicinal Mushrooms and Botanicals

Therapeutic Effects	Mushrooms	Herbs and Botanicals
Immunomodulatory	Reishi, Turkey Tail, Shiitake, Poria, Chaga	Baikal Skullcap, Milk Thistle, Chinese Salvia, Hibiscus, Black Pepper
Anti-Inflammatory/ Antioxidant	Reishi, Turkey Tail, Shiitake, Poria, Chaga	Baikal Skullcap, Milk Thistle, Ashwagandha, Schisandra, Rehmannia, Chinese Salvia, NSM, Hibiscus, Ginger, Black Pepper
Cytoprotective	Reishi, Turkey Tail, Shiitake, Poria, Chaga	Baikal Skullcap, Milk Thistle, Schisandra, Rehmannia, Chinese Salvia, Hibiscus, Ginger, Black Pepper
Antitumor/ Cytotoxic	Reishi, Turkey Tail, Shiitake, Poria, Chaga	Baikal Skullcap
Hepatoprotective	Reishi, Shiitake, Chaga	Baikal Skullcap, Milk Thistle, Schisandra, Hibiscus, Black Pepper
Nephroprotective	Reishi	Milk Thistle, Hibiscus
Neuroprotective	Reishi, Poria	Baikal Skullcap, Ashwagandha, Schisandra, Rehmannia, Chinese Salvia
Cardioprotective	Reishi, Shiitake	Salvia, Hibiscus, Ginger
Adaptogenic	Reishi	Ashwagandha, Schisandra

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This specific product has not been tested for any of the potential benefits listed herein. The following references apply to studies and/or research conducted with certain ingredients, or combinations of ingredients used in formulating this product. Such ingredients may not be from the same source or processed in the same way as the ingredients used in this product.

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