SUMMARY OF THE BENEFICIAL CHEMISTRY IN MEDICINAL MUSHROOMS

Here is a summary of the beneficial chemistry of the strains of the various species used in our blend of medicinal mushrooms. All of our mushrooms have been grown in sterile, clean room laboratories.

Issues Relevant to Commercial Production

Cultivating medicinal mushroom strains at large scales requires methods to provide consistent, safe, effective and reliable products. The current production methods and standards in the market need upgrading before they can achieve these results. Product quality can also be impacted by the fact that many manufacturers and resellers rely on several sources of mushrooms, and some are of dubious origins. These different sources often show considerable variation with respect to substrates used and manufacturing practices. Unfortunately, the perceived future growth of this market has also resulted in an ever-increasing number of less-reputable companies, and their questionable practices will inevitably lead to more intensive scrutiny of the medicinal mushroom market as a whole. There is urgency for the medicinal mushroom manufacturing industries to develop and adopt acceptable and reproducible protocols for growing the raw product and for the processing of the final products. Enforcing these standards will ensure high-quality, standardized, and safe products. Such practices are essential for earning and maintaining the public trust, which is vital for securing expanding markets in the future.

In evaluating the attached descriptions of studies done on Medicinal Mushrooms used in our formulas, please consider the following factors:

- Each study on medicinal mushrooms only describes the generic species used and not the strain or the substrate used to cultivate the mushroom used in each study.
- Many research group's focus is to determine what molecules from the mushrooms cause various beneficial activities in mammalian chemistry and then to make a drug or biologic from it.
- The following studies are from those research teams we have collaborated with and/or from which we used a specific strain of the species they cultivated and used or developed.

Agaricus

This mushroom contains traces of many valuable vitamins such as A, B1 C, K and bioflavonoids, and taken regularly helps prevents debility (weakness), loss of appetite, indigestion, and insufficient breast milk secretion. It also helps alleviate the rupturing of capillaries, gum and abdominal bleeding, and pellagra [Pellagra is a disease that occurs when a person does not get enough niacin (one of the B complex vitamins) or tryptophan (an amino acid)].

Natural killer (NK) cells circulate and become active in the body in response to cytokines. Upon activation, they seek out tumor cells, attach themselves, inject a substance, and dissolve them. They then move on and can destroy up to twenty-seven cancer cells before they die themselves. Often forgotten is that the number of NK-cells is not a measure of the body's immune system efficacy. It is their activity, how well they recognize and find tumor cells, that is most important. The low

molecular weight of some of the molecules that make up the medicinal mushroom chemistry makes them more easily absorbed.

Iodine is present in trace amounts in this strain of mushrooms (130 to 230 micrograms per kilogram), which is somewhat rare for a land-based food.

The mushroom strain contains campestrin, a natural antibiotic effective against Gram negative and some Gram-positive bacteria and has been used traditionally to treat tuberculosis and sinusitis.

It contains Coenzyme Q10 (ubiquinone), which is associated with energy production on a cellular level. The fruiting body and cultured mycelia contain hetero-auxin that act as a growth inhibitor on higher plants and stimulating the los ones.

The fruit bodies contain ergosterol, fungisterol, and proteolytic enzymes, which may have anti-coagulative properties.

Retine, or alpha-ketoaldehyde, inhibits the growth of certain types of cancer, including sarcoma 180 and Ehrlich carcinoma.

It contains lectins that bind with erythrocytes and leukocytes; as well as basid-iolipids that are novel immune adjuvants (jennemann et al. 1999).

Have been shown to possess significant antiviral potential, particularly against poliomyelitis (Poliomyelitis (polio) is a highly infectious viral disease, which mainly affects young children), perhaps due to the presence of (S)-agaridoxin and indigo (Cochran 1978).

Work by Jordinson et al. (1999) found agglutinin cytotoxic or inhibit tumor cells in LS174T, SW1222 and HT human colon cancer cells.

The lectins inhibits Caco-2 human colorectal cells, Tennon's firoblasts, retinal pigment endothelial and RPE mediated collagen matrix contraction in vitro (Wenkel et al. 1999). ABL lectins do not exhibit cytotoxicity compared to wheat germ and other lectins.

ABL lectin is immune modulating, inducing up-regulation of IL-1beta and TNF-alpha in splenocytes for up to twenty-four hours (Ooi et al. 2002).

This mushroom contains ergosterol peroxide, this compound is both anti-inflammatory and anticancer (Kobori et al. 2007)

Ergosterol and ergosterol peroxide suppress LPS induced inflammation via NFkappaB and other pathways. The latter compound also suppresses STAT q mediated inflammation by altering redux state in HT29 cells (Kobori et al. 2007).

Fortes, RC; Novaes, MRCG; Recova, VL; Melo, AL (2009). "Immunological, hematological, and glycemia effects of dietary supplementation with Agaricus sylvaticus on patients' colorectal cancer". *Experimental Biology and Medicine* **234** (1): 53–62. doi:10.3181/0806-RM-193. PMID 18997106.

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Hetland, G.; Johnson, E.; Lyberg, T.; Bernardshaw, S.; Tryggestad, A. M. A.; Grinde, B. (2008). "Effects of the Medicinal Mushroom *Agaricus blazei* Murill on Immunity, Infection and Cancer".

Scandinavian Journal of Immunology **68** (4): 363–70. doi:10.1111/j.1365-3083.2008.02156.x. PMID 18782264.

Takaku, Takeshi; Kimura, Yoshiyuki; Okuda, Hiromichi (May 2001). "Isolation of an antitumor compound from Agaricus blazei Murill and its mechanism of action". *The Journal of Nutrition* **131** (5): 1409–13. PMID 11340091. http://jn.nutrition.org/cgi/pmidlookup?view=long&pmid=11340091.

A study of guinea pigs at the National Cancer Center, Tokyo University, and Tokyo Pharmacology Institute found sarcoma 180 cancers showed a 99.4 percent prevention rate and a 90 percent recovery rate with a daily dose of ten milligrams.

Immune modulators increase the level of function, not the numbers, of NK-cells.

Activates granulocytes that help control acute inflammatory reactions.

Toshiro et al. (2003) found GABA **(**gamma-aminobutyric acid) decrease both systolic and diastolic blood pressure.

Cordyceps

The chemicals in the mushroom strains of Cordyceps:

Various sterols, polysaccharides, galactomannans, cordyceptic acid, protein, adenine, adenosine, uridine, uracil, cordycepin, mannitol, amino acids, ergosterol, vitamin B 12, trace elements, and fatty acids, beta sitosterol, D-mannitol.

It contains CO-N, SN-C, and CO-1, three compounds that possess antitumor activity (Ohmori et al. 1988a, 1988b, 1989). (Yamada et al. 1984)

Cordycepin shows reverse transcriptase inhibition (Pennman et al. 1970). Cordycepin suppresses TNF-alpha gene expression, 1kBalpha phosphorylation and nuclear translocation of p65. It also decrease the expression of COX-2 and iNOS due to the down regulation of NFkappaB activation, Ak1 and p38 phosphorylation (Kim, H.G. et al. 2006). At lose doses, cordycepin inhibits the growth and division of cancer cells, while at high doses it stops cells from sticking together. Its effects on translation and mTOR are similar to Metformin (without side effects), and as an inhibitor of Akt and activation of AMPK (**5' AMP-activated protein kinase** or **AMPK** or **5' adenosine monophosphate-activated protein kinase** is an enzyme (EC 2.7.11.31) that plays a role in cellular energy homeostasis, largely to activate glucose and fatty acid uptake and oxidation when cellular energy is low. It belongs to a highly conserved eukaryotic protein family and its orthologues are SNF1 and SnRK1 in yeast and plants, respectively. It consists of three proteins (subunits) that together make a functional enzyme, conserved from yeast to humans. It is expressed in a number of tissues, including the liver, brain, and skeletal muscle. In response to binding AMP and ADP, the net effect of AMPK activation is stimulation of heptic fatty acid oxidation, ketogenesis, stimulation of skeletal muscle fatty acid oxidation and glucose uptake, inhibition of cholesterol synthesis, lipogenesis, and triglyceride synthesis, inhibition of adipocyte lipogenesis and activation of lipolysis , and modulation of insulin secretion by pancreatic beta-cells. *Winder WW, Hardie DG (July*

1999). "AMP-activated protein kinase, a metabolic master switch: possible roles in type 2 diabetes". Am. J. Physiol. ***277*** *(1 Pt 1): E1–10.)*

Induces apoptosis and growth inhibition of U937 Leukemia cells. The regulation of several major growth gene products such as Bcl-2 family expression and caspase protease activity suggests therapeutic potential for human leukemia (Park, C. et al. 2005).

Cordlan, a polysaccharide isolated from this specie, increases dendritic cell maturation through TLR4-signaling pathways (Kim, H.S. et al. 2010)

Inhibits liver cirrhosis induced in rats, (Xia Zhang el al 2004).

Cordyceps is considered to be a medicinal mushroom in classical Asian pharmacology, as well as traditional Chinese and Tibetan medicines. The Pharmaceutical Society of Japan's *Biological and Pharmaceutical Bulletin* recently reported the mushroom to be valuable for protection against Alzheimer's as it prevents neuronal cell death and memory loss through its antioxidant and anti-inflammatory effects.

Other studies proved that Cordyceps is non-toxic and promotes cognitive health.

Lupus nephritis, resulting from an auto immune condition, responds favorably taking daily after meals. The showed to prevent recurrence if Lupus nephritis and protect kidney function in a five-year study (Lu, L. 2002)

Metastasis to lungs and liver was significantly inhibited, and level or Bcl-2 decreased. Exoploy-saccharides significantly elevate immunocyte activity in tumor-bearing mice (Zhang, W. et al. 2008).

Modulate immune parameters through immunoglobulin production; this results from decreased T lymphocyte helper 2 cytokine secretion and reduced cytokine secretion in mesenteric lymph node lymphocytes (Park, D. K. et al. 2008).

Immune-potentiating effect from an increase in interleukin 11 production, as well stimulation of myocardial ATP generation and enhancement in mitochondrial electron transport (Siu et al. 2004).

Shows both in vitro and in vivo stimulation of testosterone levels in lab studies (Hsu, C. C. et al. 2003).

In a large two-month trial of 273 patients received one gram three times a day, cholesterol levels dropped an average of 17 percent.

This mushroom may be useful in the regulation of blood sugar levels. In a clinical trial of forty-two diabetic patients, half received an herbal formula including cordyceps, and half just the herbs. Fifty-five percent of the patients in the latter group showed improvement of blood sugar levels after thirty days, while 95 percent of those taking the formula including the mushroom showed improvement. This may be due to CS-F30 polysaccharide composed of galactose, glucose, and mannose.

Chen, Steve; Li, Zhaoping; Krochmal, Robert; Abrazado, Marlon; Kim, Woosong; Cooper, Christopher B. (2010). "Effect of Cs-4® (*Cordyceps sinensis*) on Exercise Performance in Healthy Older Subjects:

A Double-Blind, Placebo-Controlled Trial". *The Journal of Alternative and Complementary Medicine* **16** (5): 585–90. doi:10.1089/acm.2009.0226. PMC 3110835. PMID 20804368. http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=3110835.

Gao, HL; Lei, LS; Yu, CL; Zhu, ZG; Chen, NN; Wu, SG (2009). "Immunomodulatory effects of Fomes fomentarius polysaccharides: An experimental study in mice". *Nan fang yi ke da xue xue bao = Journal of Southern Medical University* **29** (3): 458–61. PMID 19304524.

Chen, Wei; Zhao, Zhao; Chen, Shi-Fei; Li, Yong-Quan (2008). "Optimization for the production of exopolysaccharide from Fomes fomentarius in submerged culture and its antitumor effect in vitro". *Bioresource Technology* **99** (8): 3187–94. doi:10.1016/j.biortech.2007.05.049. PMID 17624770.

Ganoderma

It contains gallielalactone, a compound that may have application in the treatment of prostate cancer. Work in Sweden by (Hellsten et al. 2008) have found the compound to be a potent and selective inhibitor of interleukin-6 signaling in HePG2 cells. It has been found to inhibit Stat3 that directly inhibits prostate tumor cells from growing.

The chemical constituents are:

Carbohydrates; amino acids including adenosine, steroids, including ergosterols, sterols, alkaloids, lactones, erogone, protease, lysozymes, lips, triterpenes, alkaloids, vitamins B2 and C, and various minerals including zinc, manganese, iron, copper, and germanium. May contain up to 40 percent beta-glucans. High levels of germanium have been found when cultivated using a substrate rich in the mineral. The spore part includes choline, betaine, palmitic and stearic acid, ergosta-7, 22-dien-3b-ol, tetracosanoic acid, behenic acid, nonadecanoic acid, ergosterol, beta sitosterol, pyrophosphatidic acid, hentriacontane, and tetracosane.

A 1993 study at Shanghai University found this mushroom enhanced bone marrow nucleated cell proliferation, increased production of int

erleukin-1 in vitro, and increased show blood cells and hemoglobin in mice studies. Enhanced natural killer cell activity, improved adrenocortical function, and anti-HIV activity were found both in vivo and in vitro.

Yuen, John; Gohel, Mayur Danny (2005). "Anticancer Effects of Ganoderma lucidum: A Review of Scientific Evidence". *Nutrition and Cancer* **53** (1): 11–7. doi:10.1207/s15327914nc5301_2. PMID 16351502.

Sliva, Daniel (2003). "Ganoderma Lucidum (Reishi) in Cancer Treatment". *Integrative Cancer Therapies* **2** (4): 358–64. doi:10.1177/1534735403259066. PMID 14713328.

Lin, Zhi-bin; Zhang, Hui-na (2004). "Anti-tumor and immunoregulatory activities of *Ganoderma lucidum* and its possible mechanisms". *Acta Pharmacologica Sinica* **25** (11): 1387–95. PMID 15525457. http://www.chinaphar.com/1671-4083/25/1387.pdf.

Kuo, Mei-Chun; Weng, Ching-Yi; Ha, Choi-Lan; Wu, Ming-Jiuan (2006). "Ganoderma lucidum mycelia enhance innate immunity by activating NF-κB". *Journal of Ethnopharmacology* **103** (2): 217–22. doi:10.1016/j.jep.2005.08.010. PMID 16169168.

Wang, Xin; Zhao, Xuan; Li, Dan; Lou, Ya-Qing; Lin, Zhi-Bin; Zhang, Guo-Liang (2007). "Effects of Ganoderma lucidum Polysaccharide on CYP2E1, CYP1A2 and CYP3A Activities in BCG-Immune Hepatic Injury in Rats". *Biological & Pharmaceutical Bulletin* **30** (9): 1702–6. doi:10.1248/bpb.30.1702. PMID 17827724.

Shi, Yanling; Sun, Jie; He, Hui; Guo, Hui; Zhang, Sheng (2008). "Hepatoprotective effects of Ganoderma lucidum peptides against d-galactosamine-induced liver injury in mice". *Journal of Ethnopharmacology* **117** (3): 415–9. doi:10.1016/j.jep.2008.02.023. PMID 18406549.

Morigiwa, A; Kitabatake, K; Fujimoto, Y; Ikekawa, N (1986). "Angiotensin converting enzyme-inhibitory triterpenes from Ganoderma lucidum". *Chemical & pharmaceutical bulletin* **34** (7): 3025–8. PMID 3021351.

Su, Chen-Yi; Shiao, Ming-Shi; Wang, Cheng-Teh (1999). "Predominant inhibition of ganodermic acid S on the thromboxane A_2-dependent pathway in human platelets response to collagen". *Biochimica et Biophysica Acta* **1437** (2): 223–34. doi:10.1016/S1388-1981(98)00012-2. PMID 10064905.

Park, EJ; Ko, G; Kim, J; Sohn, DH (1997). "Antifibrotic effects of a polysaccharide extracted from Ganoderma lucidum, glycyrrhizin, and pentoxifylline in rats with cirrhosis induced by biliary Obstruction". *Biological & pharmaceutical bulletin* **20** (4): 417–20. doi:10.1248/bpb.20.417. PMID 9145221. http://ci.nii.ac.jp/naid/110003639068/.

"Reishi Mushroom". *About Herbs, Botanicals & Other Products*. Memorial Sloan-Kettering Cancer Center. http://www.mskcc.org/mskcc/html/69353.cfm.

Kevei, F. and Peberdy, J.F. Interspecies hybridization after protoplast fusion in *Fungal Protoplast*, Peberdy, J.F. and Ferenczy, L. Eds., Marcel Dekker, New York, 241-257, 1985.

Yamada, O., Magae, Y., Kashiwage, Y., Kakimoto, Y., and Sasaki, T., Preparation and regeneration of mycelial protoplasts of Collybia velutipes and PLeurotus ostreatus, Eur, J. Appl. Microbiol. Biotechnol., 17, 298-300, 1983.

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Trametes, Coriolus Versicolor

The chemicals in the mushroom strains:

PSK (Polysaccharide krestin), PSP (Polysaccharide peptide), lipids (1.7 percent) containing ergosta-7, 22, dien-3 (ol), a major sterol of many polypores, as well as ergost-7-en-3 (ol) and ergopsterol (provitamin D2), polyhydroxysteroids, cerevisterol, tetraol, sitosterols, coriolan; 3 beta, 5 alpha, 9 gamma-trihydroxyergosta-7, 33-dien-6-one, 11 percent protein, 76 percent complex carbohydratesm and various B vitamins and minerals.

Polysaccharide extracts were found to increase macrophages 7.2-fold over controls (Jeong, S.-C. et al. 2006). Krestin was the first mushroom-derived anti-cancer drug approved byt eh Japanese government, and all healthcare plans in that country cover its cost.

PSP consisting of six kinds of monosaccharides, glucose, mannose, galactose, xylose, arabinose, and rhamnose connected with a small molecular protein polypeptide.

PSK is a water-soluble protein-bound poly saccharide with 1,4 glucan as a main component, 1,3 glucan linkages, and 38 percent protein. PSP is 10 percent peptide and 90 percent polysaccharides. It lacks fucose, but contains arabinose and rhamnose, which PSK does not have.

PSK improves the function of blood vessels, normalization of spleen index, immune enhancement, and possible prevention of liver cancer. It prolongs the activity of antibiotics and increases sensitivity in antibiotic-resistant bacteria, working in a synergistic manner in case of MRSA and other resistant strains.

Methanol extracts of this mushroom also exhibit activity against B16 melanoma cells. Extracts have been found to be directly cytotoxic and anti-proliferative to tumor cells and indirectly via macrophage activation.

Possess anti-tumor and anti-neoplastic activity (Jong and Gantt 1987).

It inhibits sarcoma 180 in white mice by 65 percent (Ikekawa et al. 1968).

It is considered an antidote for toxins and is used for arthritis, including gout, as well as for antibacterial and antifungal activity.

PSP has been found to alleviate symptoms and prevent decline in immune status. More than forty studies have looked at PSP from this mushroom inhibit metastasis, angiogenesis, and/or tumor growth in animal studies.

Studies by Ikuzawa (1985) showed that it reverses conditions associated with nephron (kidney) disorders, including proteinuria and proteinemia, and regulates prostaglandin formation and degradation

Grifola frondosa

The chemicals in the mushroom strains:

Ergosterol; Ergostra-4,6,8(14), 22-tetraen-3-one; 1-oleoyl-2-linoleoyl-3-palmitoylglycerol, as well as fatty acids such as palmitic, oleic, and linoleic acid; phospholipids, including phosphatidyl choline, phosphatidyl serine, both lamarian type and curdlan trpe Beta-D-glucans and other

polysaccharides including grifolin, grifolin-LE, MT, MT-2, LELFD, and grifolan NMF-5N; beta 1,3 glucans with beta 1,6 branches and vice versa. If exposed to six to eight hours or sun light (at times of the day when the rays will provide this), the vitamin D2 content increases from 460 IU to 31,900 IU per hundred grams.

Studies show the mushroom contains antidiabetic constituents, as well as hepatoprotective properties. One randomized controlled clinical trial of thirty-two chronic hepatitis B patients showed 72 percent recovery rate.

Polysaccharide fractions who anticancer and immune-enhancing factors. It appears to enhance the activity of macrophages, N-killer cells, and cytotoxic T-cells, with 86 percent inhibition of tumor growth (Mori et al. 1987).

Interleukin-1 that activates T-cells and superoxide anions that destroy tumor cells, and both increases by D-fraction.

D-fraction (a three-branched beta-1,6, glucan with 10 percent protein) is garnering the most attention for its interleukin-1-stimulating effect.

Noriko Kodama et al. (2002) found the D-fraction suppresses tumor growth via NK cell activity and induced IL-12 release from macrophages.

A sulphated proteo-glucan prevents HIV from killing T-cells in vitro. Research in both Japan and the United States has found this strain compares favorably with AZT for treating HIV, without the negative side effects. (Nanba et al. 2000).

The D-fraction was found highly cytotoxic to prostate cancer PC-3 cells, with over 95 percent cell death in twenty-four hours.

It promotes absorption of micronutrients by the intestine, making it a potentially useful transport mechanism for herbal combinations.

One chemical, 5alpha, 8alpha-epidioxyer-gosta-6,22-dien-3-ol, is a potentiator of ADP-induced platelet aggregation (LU, W. et al. 1985).

Hericium

The chemicals in the mushroom strains:

Beta-glucoxylan, glucoxylan, 31 percent protein, hericonene A and B (phenols), 240 international units of calciferol per hundred grams, polyhydroxysteroids include cerevisterol; six ergostane derivatives including 3 beta, 5 alpha, 9 gamma-trihydoxy-ergosta-7, 22-dien-6-one; 3 beta-glucopyranosul-5 alpha, 6 beta-di-hydroxyergosta-7,22-dien, xylan, and glycoxylan. Cyathane derivatives are believed the nerve growth stimulators. Also contains the aromatic compounds erinacines A and B.

One study found in vitro evidence of myelin-generating effect on nerve and cerebellar glia cells.

Hericenones C-H have been found to induce synthesis of nerve growth factor (NGF), which is required by the brain for developing and maintaining important sensory neurons. This may be useful in the amelioration of Alzheimer's and other similar chronic nerve/brain related disease (Kawagishi et al. 1991). The low molecular weight compounds pass through the blood-brain barrier intact.