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## Technical Report

### The Use of Mushroom-Derived Dietary Supplements as Immuno-modulating agents:

An Overview of Evidence-Based Clinical Trials and the Mechanisms and Actions of Mushroom Constituents.

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# **The Use of Mushroom-Derived Dietary Supplements as Immuno-modulating agents: An Overview of Evidence-Based Clinical Trials and the Mechanisms and Actions of Mushroom Constituents.**

**Summary:** The use of natural agents to ward-off or shorten infectious diseases is as ancient and global as the art of medicine itself. Among these natural agents are numerous species of mushrooms, many of which are still used in traditional medicines or as “alternative medicines” today. This overview will describe some of the most frequently used mushroom preparations, outlining the available scientific data based on their mechanisms of action and clinical use as immune modulating-agents.

## **Introduction**

Mushrooms are fungi with spore-producing, umbrella-shaped fruiting bodies, and white thread-like structures called mycelia. About 700 out of 14,000 known mushroom species are reported to possess significant immuno-pharmacological properties.<sup>1,2</sup> Historical and archeological records reveal that humans have been eating mushrooms for thousands of years; in fact, the fruiting bodies of the mushroom birch polypores (*Piptoporous betulinus* (Bull.:Fr.)Karst) were found attached to the clothing of the oldest natural human mummy ever found (aka “The Iceman”). Some mushroom species were even considered a sacred food by the Egyptians as far back as 3000 B.C.E., while the Greeks and Romans appear to have been the early cultivators of mushrooms.<sup>3,4</sup> The more recent history of medicinal mushroom use has come from the past few hundred years, primarily within the medicinal traditions of Japan, Korea, China and Eastern Russia.<sup>1,2</sup> Today, edible cultivated mushrooms such as white or button mushrooms, chanterelles, crimini, enoki, morel, oyster, portobello and many others are used in a wide range of recipes throughout the world.

Mushroom products sold as “dietary supplements” in the U.S. and elsewhere are used in the form of whole mushroom powders (fruiting bodies and mycelia), powdered mycelia, extracts from fruiting bodies or mycelia; or as isolated compounds from shiitake, maitake, reishi, oyster, Brazilian and other edible mushroom species. The raw materials used in powders, capsules and tablets might be sourced from the wild, from cultivated mushrooms in farms, or from cultivation of mycelia in fermenters with liquid or solid substrates.

## **Mushroom bioactive constituents**

Mushrooms have a number of biologically active compounds, although the most studied are the various polysaccharides found in the fruiting bodies, cultured mycelia, and culture broth. These polysaccharides are mostly glucans, where D-glucose monomers are linked with glycosidic bonds oriented either in the axial position ( $\alpha$ -glucans) or in the equatorial position ( $\beta$ -glucans). This subtle difference in structure completely alters the physical characteristics of each

polymer, requiring different enzyme activities to metabolize each (Figure 1). In addition to pure  $\beta$ -glucans, such as lentinan and schizophyllan from shiitake and Schizophyllan mushrooms, some of the mushroom bioactive compounds also include  $\beta$ -glucans bound to peptides. These are also called polysaccharopeptides (PSP) and polysaccharide K (PSK) from turkey tail mushroom.<sup>5</sup>

Active hexose correlated compound (AHCC) represents the major mushroom-derived  $\alpha$ -glucan molecule and is present at relatively high concentration in shiitake mushroom mycelia cultures. Compared to the high molecular weight  $\beta$ -glucans (10,000-500,000 daltons) like lentinan from shiitake mushroom,  $\alpha$ -glucans are of low molecular weight (approximately 5,000 daltons), making them more bio-available upon oral administration.<sup>6</sup> Because of their structural diversity, polysaccharide glucans from different mushroom species display a wide variety of biochemical functions. Although  $\beta$ -glucans are present in fruiting bodies and mycelia, higher concentrations of  $\beta$ -glucans are present in fruiting bodies. The main chain of  $\beta$ -glucans have  $\beta$ -linkages (1 to >3) with additional  $\beta$ -branch points (1 to  $\leq 6$ ), for increased biological action.

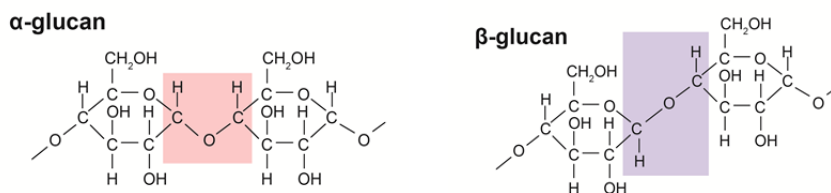


Figure 1.  $\alpha$ -glucan and  $\beta$ -glucan structures

In addition to polysaccharides, medicinal mushrooms also have other bioactive compounds such as triterpenes. For example, some of the bioactive compounds found in reishi mushrooms are a group of triterpenes known as ganoderic acids. Ganoderic acid A and B are the most characterized triterpenes, and their biological actions include the induction of increased macrophage activity, resulting in increased response to harmful bacteria, viruses or tumor cells. Ganoderic acids also promote liver protection, have antitumor effects and inhibit 5- $\alpha$  reductase.<sup>7</sup>

A mushroom called Chaga produces a diverse range of secondary metabolites including lignins, phenolic compounds, melanins, and lanostane-type triterpenoids; and because chaga is parasitic on birch trees, it contains a large amounts of betulin or betulinic acid, a natural substance that is being studied for its anti-cancer properties.<sup>8</sup> Caterpillar mushroom is another medicinal mushroom (*Cordyceps sinensis* (Berk.) Sacc) which contains cordycepin, an adenosine-derivative from the fungus which is an important immuno-regulatory ingredient.<sup>9</sup>

## **Mushrooms as immunomodulators**

A wide variety of medicinal properties have been attributed to mushrooms and mushroom extracts over the millennia. Until recently, these purported medicinal activities have been communicated as traditional or anecdotal observations, albeit very ancient and consistent in many cases. Recent scientific research has indeed discovered mechanisms which could account for the wide variety of medicinal properties of mushroom-based preparations. One primary feature of their medicinal properties is the broad immune-modulatory effects of mushroom species and their metabolites.<sup>2</sup>

The human immune system can be modulated in a number of different ways with the use of foods, supplements or by endogenous bioactive agents by means of cell-to-cell signaling. Of course, immunomodulators can act as immunosuppressants or immunostimulants; or as is often the case with natural substances, in a manner which balances immune function (stimulating some functions while suppressing other). This activity is often referred to as an adaptogenic or tonic effect. Our focus below is to outline and review those which describe mechanisms affecting the modulation or activities of the immune system.

### ***Effect of mushrooms on the Innate Immune System***

The effects of mushroom extracts and their metabolites on various cells of the innate immune system, both *in vitro* and *in vivo* are described in the following paragraphs.

Mushroom bioactives can trigger the secretion of pro-inflammatory cytokines such as TNF- $\alpha$  (tumor necrosis factor-alpha), IFN- $\gamma$  (interferon -gamma) IL-1 $\beta$  (interleukin -1 beta) from immune cells like macrophages, natural killer cells (NK Cells) and even T-lymphocytes. For example, in maitake-D-fraction supplemented mice infected with *Listeria*, activated macrophages produced 2.7 times as much IL-1 $\beta$  as that of control mice. The bactericidal activity of splenic T-cells was also enhanced by 2.6 times of that of control mice; suggesting a clinical benefit of D-fraction similar to the outcome of antibiotic treatment. MD-fraction of maitake is also an inducer of iNOS (inducible nitric oxide synthase), thought by some to contribute partially to the antitumor activity of maitake mushroom.

Another example of interaction of mushroom extract with the innate immune system is the non-toxic, water soluble extract from shiitake mushroom mycelia (PG 101) interacting with macrophages, resulting in the activation of NF- $\kappa$ B (nuclear factor kappa B). This in turn sets off a series of reactions producing mostly pro-inflammatory cytokines (IL-1 $\beta$ , TNF- $\alpha$ , IL-10, IL-12 and others).<sup>2</sup> The impact of these reactions becomes evident in the restoration of normal chemotactic activity of macrophages in carcinogen-treated mice upon supplementation with a shiitake, maitake and oyster mushroom containing diet.<sup>2</sup> Likewise, cancer patients continuously supplemented with D-fraction from maitake mushroom had increased cytotoxic activity of NK cells for 1 year.<sup>10</sup> In another pre-clinical study, tumor growth was suppressed in mice supplemented with D-fraction from maitake, with corresponding increase in the release of TNF- $\alpha$  and IFN- $\gamma$  from spleen cells along with a significant increase in TNF- $\alpha$  secretion in NK cells. D-fraction also increased macrophage-derived cytokine IL-12, which activates NK cell. The

significance of increased NK cell activity in Brazilian mushroom (*Agaricus blazei* Murill) supplemented group of patients, with the corresponding improvement of symptoms, offers the possibility of its use as an adjuvant in chemotherapy.<sup>11</sup>

Dendritic cells (DC) represent yet another group of the innate immune system, and they are important antigen presenting cells (APCs) within the innate immune system. These cells are often slow to mature in many cancer patients, because some tumors secrete factors that inhibit differentiation and function of DC and, in addition, some anticancer chemotherapeutic agents at conventional doses can also suppress DC function. Transformed cells and tumors may escape detection by the immune system in a timely fashion due to DC interference.<sup>12,13</sup> *In vitro* studies using peripheral blood monocytes of healthy patients showed that incubation with PSK, which is extracted from the cultured mycelium of *Coriolus versicolor* (L.er.Fr), a mushroom used as an anti-cancer agent in Japan, increased both maturation and function of DCs.<sup>14</sup> When gastric or colorectal cancer patients were supplemented with PSK one month after surgical resection, PSK was reported to shift the T-helper cells balance (Th1/Th2) toward Th1 dominance and the DC1/DC2 balance toward DC 1 dominance (similar to normal adults studied), allowing for increased immune effectiveness toward cancer cells.<sup>14</sup>

### ***Effect of mushrooms on Adaptive immune system***

Immunosuppressive factors including some carcinogens tend to alter the balance between T helper cell 1 (Th1) and Th2 cells as mentioned above. Data suggests that a variety of mushroom polysaccharides either induce a type 1 immune response, while others favor a type 2 T-helper cell response.<sup>15</sup> For example, lentinan, a  $\beta$ -glucan from shiitake mushroom induces a Th1 response and has been referred to as a “T-cell-oriented adjuvant.”<sup>16</sup> D-fraction of maitake mushroom also stimulates a Th1 response resulting in enhanced cellular immunity and induces a Th1 response in tumor-bearing mice, regardless of the type of default cytokine pattern to which this strain of mouse is predisposed.<sup>17</sup> Maitake-D fraction appears to restore the balance between Th1 & Th2, decreasing the activation of B-cells and activation of T helper cells, resulting in enhanced cellular immunity.<sup>17</sup> Recent pre-clinical studies also showed that oral administration of MD-fraction, significantly inhibited tumor growth in murine models and induced the systemic T cell response and decreased the immunosuppressive elements.<sup>18</sup>

### ***Pattern Recognition receptors and mushroom polysaccharides***

The wide range of immune-related influences attributed to mushroom preparations appears to be mediated, at least in part, by the activation of pattern recognition receptors (PRRs) on a variety of immune cells. These receptors (Toll-like receptors etc.) recognize molecular patterns in a non-specific way. Two general patterns which are readily recognized by PRRs are those associated with pathogens (so called PAMPs- pathogen associated molecular patterns) and those associated with damaged tissues, called damage-associated molecular patterns (DAMPs). Among the patterns recognized on pathogens, the repeating polysaccharide (LPS) on bacteria or their flagella are the best characterized. It appears that a wide variety of mushroom  $\beta$ -glucan

(polysaccharide) structures are molecules which cross-react with the PRRs on or within cells of the immune system- triggering a variety of immune responses.<sup>19</sup> Some examples of immune cell receptors to which  $\beta$ -glucans bind, include complement receptor 3 (CR3), dectin-1, and toll-like receptors (TLR-2) and TLR-4 (Figure 2).<sup>20</sup> TLR-4 is also involved in reishi mushroom polysaccharide-mediated macrophage activation.<sup>21</sup> Immunostimulating activities of  $\beta$ -glucan of reishi mushroom or the genus *Ganoderma* (BGG), are also due to the binding of BGG to dectin-1 receptor and induction of TLRs in mouse macrophages, resulting in the activation of NF- $\kappa$ B and secretion of inflammatory cytokines.<sup>22</sup> While it is still too early to connect how many of the immune-modulatory effects of mushrooms and their extracts are mediated through PRRs, it appears that those which are triggered by the polysaccharide moieties of mushrooms are more than likely mediated through this receptor family. As research into these receptors expands, we will likely be able to learn more about the specific mechanisms allowing the variety of mushroom polysaccharides to stimulate a wide array of immune functions.

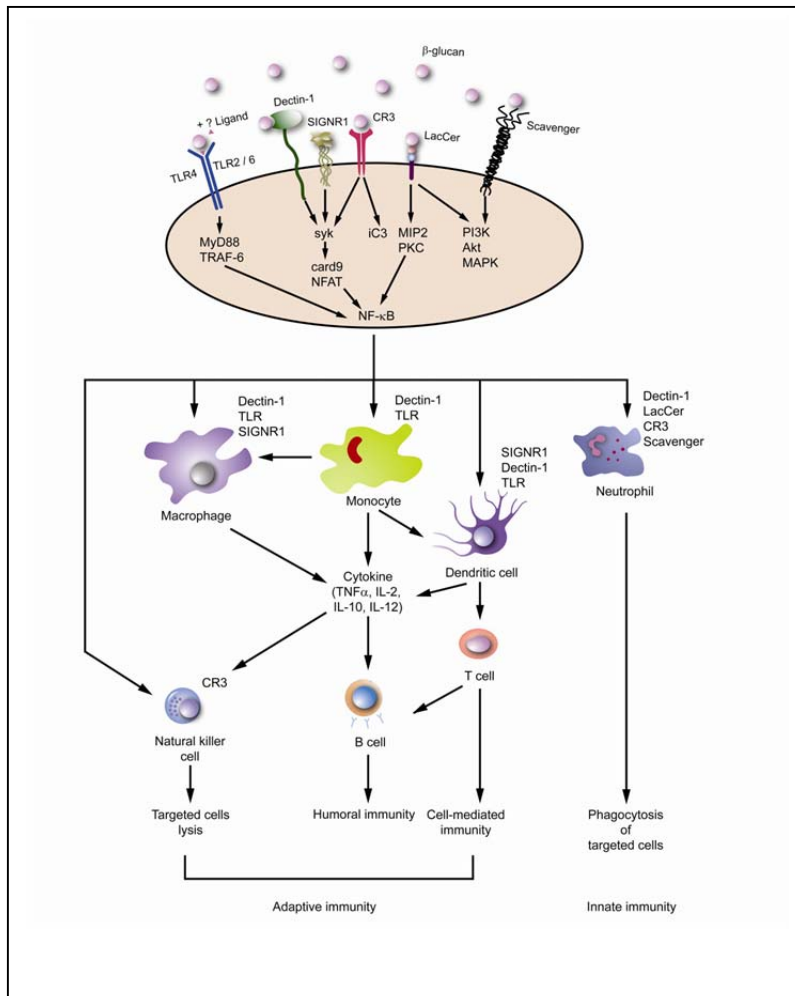


Figure 2: Immune activation by  $\beta$ -glucan through pattern recognition receptors. Diagrammatic representation of  $\beta$ -1, 3-D glucan recognition by cell surface TLR-2 & Dectin-1 receptors and activation of NF- $\kappa$ B and genes for immune responses (After Chan et al; 2009)<sup>20</sup>

### ***Direct Anti-microbial actions of mushrooms***

While mushrooms and their extracts have the ability to modulate immune cells, they also have activities that can act directly on harmful microorganisms. Ganomycins from reishi mushroom (*Ganoderma.pfeifferi* Bres) has been shown to inhibit the growth of methicillin-resistant bacteria called *Staphylococcus aureus* and others.<sup>3,23</sup> Triterpenes from reishi mushroom act as antiviral agents against human immunodeficiency virus type 1 (HIV-1) and influenza virus type A.<sup>24</sup> Mycelial extracts of wood tuft mushroom (*Kuehneromyces mutabilis* (Schaeff.) Singer & A.H.Sm and phenolic compounds from *Inonotus hispidus* (Bull.,Fr),Karst mushroom, demonstrated *in vitro* antiviral activity against influenza viruses type A and B.<sup>3,25</sup> Likewise, both water soluble lignins from chaga and shiitake mushroom mycelial culture medium, were shown to inhibit HIV proteases.<sup>26</sup> and prevent HIV-induced degenerative changes in cells.<sup>27</sup> Protein-bound polysaccharides from turkey tail mushroom also had antiviral effect on HIV and cytomegalovirus *in vitro*.<sup>28</sup> Normalized liver function, as evidenced by liver enzyme levels, was observed in four patients with chronic hepatitis B who were supplemented for one year with *A.blazei* Murill mushroom extract.<sup>29</sup>

### ***Direct Anti-tumor action of mushrooms***

In addition to the immune cell mediated anti-tumor effects induced by the mushroom extracts and mushroom isolates, mushroom extracts also appear to have some direct anti-tumor activities.<sup>30</sup> Anti-tumor action of ethyl acetate extract of the fruiting bodies of the mushroom called cracked-cap polypore (*Phellinus rimosus* (Berk.)Pilat) at 50 mg kg<sup>-1</sup> per day (oral), was comparable to the activity of cisplatin (4 mg kg<sup>-1</sup> per day, intraperitoneal) in ascites and solid tumor models in mice.<sup>31</sup> Ganoderic acids A and C from *G. lucidum* are inhibitors of farnesyl protein transferase, an enzyme that participates in Ras-dependent cell transformation. Inhibitors of this enzyme represent a potential therapeutic strategy for the treatment of cancer.<sup>32</sup> Polysaccharides from Brazilian mushroom *A.blazei* Murill, also exhibited anti-angiogenic activity.<sup>33</sup> Clinical studies documenting some of these anti-tumor benefits are described below.

### **Human Clinical trials with mushrooms**

The long history of mushroom-based medicinal therapies, coupled with the immune-related mechanisms reviewed above has generated hope for specific clinical outcomes using mushroom based preparations. Outlined below are clinical trials attempting to discover the potential of mushrooms as therapeutic agents. Most of these trials are small, but give a window into their therapeutic potential.

### **Maitake mushroom (*Grifola frondosa* (Dicks) Gray)**

Maitake (Japanese for “dancing mushroom”) is an edible mushroom that grows in clusters at the foot of oak trees. For medicinal purposes, maitake is used as a dried powder, hot water extracts, or isolated fractions and compounds.  $\beta$ -glucan is the active polysaccharide extracted or isolated from fruiting bodies and is commercially available as D-fraction, MD fraction and maitake gold -404<sup>®</sup> (MTG) extracts.

In a year-long clinical trial with HIV infected patients, supplementation with 6 grams of dried powder of maitake mushroom (D-fraction) resulted in an increase in CD4 cell count (1.4-1.8 times) in 20 out of 35 patients. Supplementation also resulted in decreased viral load in 10 patients and increased sense of well-being in 85% of the responders.<sup>34</sup> MTG, another maitake extract, was tested at various doses both for its efficacy as immunomodulating agent and for its toxicity in a phase I/II dose escalation trial. 34 post-menopausal breast cancer patients, free of breast cancer after initial treatment, were enrolled at the Memorial Sloan-Kettering Cancer Center. Statistically significant dose- responses were observed, with the greatest effect at an intermediate dose of MTG, for 20 immunologically relevant parameters. Functional changes higher than 50% from baseline were seen in the production of interleukin-10. Similar increases in the production of TNF- $\alpha$  and IL-2 were also observed. IFN- $\gamma$  production, however, decreased by 20% at the highest dose of maitake extract tested (10 mg/kg). No toxicity or serious adverse events were observed even at the highest dosage.<sup>35</sup>

In another non-randomized clinical trial involving 36 cancer patients (stage II-IV); patients either were given maitake D-fraction with crude powder tablets only, or maitake D-fraction crude tablets, in addition to chemotherapy. Supplementation with a combination of MD-fraction and maitake dried powder only, with no chemotherapy, resulted in significant symptom improvement in 11 of 16 breast cancer patients, 7 of 12 liver cancer and 5 of 8 lung cancer patients. Corresponding increases in the number of natural killer cells, macrophages and T lymphocytes to normal levels was also observed.<sup>36</sup> When maitake extracts were taken in addition to chemotherapy, these response rates improved by 12-28 percent.<sup>37</sup> Maitake D-Fraction also prevented the metastatic progress, lessened the expression of tumor markers, and increased NK cell activity in 10 of the patients examined. Cancer progression was repressed in these individuals, mainly by the stimulation of NK cell activity.<sup>10</sup>

### **Shiitake mushroom (*Lentinus edodes* (Berk) Sing)**

Shiitake is an edible fungus native to Asia, and cultivated for food in many countries. Both  $\alpha$  and  $\beta$ -glucans derived from shiitake are considered “bioactives” and both are used as adjuvants in various clinical studies. In Japan, AHCC (active hexose correlated compound), an  $\alpha$ -glucan polysaccharide, isolated from shiitake mushroom mycelial culture, is the second most popular complementary and alternative medicine used by cancer patients.<sup>38</sup>

In an open label trial with healthy individuals older than 50 years, AHCC (3 g/day) supplementation for 60days, modulated immune function by enhancing the immune responses of both CD4 and CD8 T-cells. From a clinical standpoint, AHCC has generally been administered



as an adjuvant in combination with surgery and chemotherapy or radiation. Improved prognosis and liver function were reported in the supplemented group.<sup>39</sup> AHCC supplementation (3 g / day) resulted in increased NK cell activity at 2 weeks (2.5 fold) and was maintained at high level in nine out of eleven patients who were treated with conventional therapies such as surgery, chemotherapy and radiation for advanced malignancy. The observed increase in NK cell activity was due to an increase in NK cell granularity, as well as binding capacity of NK cells to their tumor cell targets. Increase in NK cell activity was also associated with a decrease in the level of tumor associated antigen (TAA) in 8 out of 11 patients with different types of malignancies.<sup>40</sup> AHCC supplementation in one hundred and thirteen post-operative liver cancer patients, resulted in increased survival rate with no recurrence period, when compared to the control group (n=113).<sup>41</sup> Improvements were observed in the quality of life and NK cell activity in seven patients, supplemented with shiitake mushroom mycelial extract along with chemotherapy. These patients were undergoing postoperative adjuvant chemotherapy for breast cancer (n = 3) and to prevent recurrence of gastrointestinal cancer (n = 2).<sup>42</sup>

Lentinan is a  $\beta$ -glucan with a glycosidic 1, 3; 1-6 linkage, isolated from shiitake mushroom with a molecular weight of approximately 500,000 Da. Because of its high molecular weight, it is administered intravenously as an anti-cancer agent in Japan. Superfine dispersed powder of lentinan is used for oral administration, and is used as Lentinex in Europe and Lentinan XP in USA. Supplementation with 1 mg of lentinan along with 1 g of chemotherapeutic agent (tegafur) improved the general condition and quality of life in 25 patients with esophageal cancer compared to 25 patients treated with a chemotherapeutic agent alone.<sup>43</sup> In another clinical trial with 27 patients with advanced gastric cancer, oral supplementation of superfine dispersed lentinan extended the median survival time by 17 months and six out of 26 patients (23%), lived longer than 3 years.<sup>44</sup> Oral administration of superfine dispersed lentinan in pancreatic cancer patients, improved both the quality of life and mean survival time.<sup>45</sup> Intravenous administration of lentinan at 2 mg, three times a week, also improved the balance between TH1 and TH2 cells, with the subsequent increase in CD4, IFN- $\gamma$  and T-cell percentages, in gastric cancer patients.<sup>46</sup>

### **Reishi (*Ganoderma lucidum* (W.Curt:Fr.) P.Karst)**

Reishi mushroom also has a long history of traditional use in the treatment of cancer and case studies of spontaneous remission are reported with the use of this mushroom.<sup>47,48</sup> Reishi mushroom polysaccharide extract supplementation enhanced immune status in advanced lung cancer patients with increases in NK cell activity and Th1 cytokine levels and decrease in Th2 cytokine levels.<sup>49,50</sup> The results of the meta-analysis of 5 random controlled trials (RCTs) showed that patients who had been given *G. lucidum* alongside with chemo/radiotherapy were more likely to respond positively compared to chemo/radiotherapy alone. The results also showed that reishi mushroom supplementation also increased the percentage of CD4 and CD8 cells by 3.91% and 2.02%, respectively. In addition, leukocyte, NK-cell activity and CD4/CD8 ratio were marginally elevated. Four studies showed that patients in the reishi group had relatively

improved quality of life in comparison to controls. No toxicity was reported, although one study recorded minimal side effects, including nausea and insomnia.<sup>51</sup>

Reishi mycelial extract supplementation at 1.5 g / day, for one year, resulted in a decrease in tumor size and number compared to the control group.<sup>52</sup> Improved quality of life relating to decreases in plasma concentrations of cytokines TNF- $\alpha$  and IL-1, was observed in 73.2 % of advanced colorectal cancer patients (N =41) supplemented with reishi mushroom polysachharides (Ganopoly) for 12 weeks. Increase in the counts of CD3, CD4, CD8 and CD56 lymphocytes and NK cell activity was also observed, suggesting a broad immune-modulatory effect of reishi-derived polysachharides.<sup>53</sup>

### **Chaga (*Inonotus obliquus* (Pers., Fr.) Pilat)**

Chaga has been used as a folk medicine in Russia and Western Siberia, since the 16<sup>th</sup> century.<sup>54</sup> Chaga mushroom supplementation resulted in the reduction of DNA damage (54.9%) as observed in lymphocytes collected from 20 patients with inflammatory bowel disease (IBD). Chaga extract reduces oxidative stress in lymphocytes from IBD patients and also healthy individuals when challenged in vitro.<sup>55</sup> In a clinical trial involving 48 patients, reduction in tumor size, decrease in pain with better quality of life was observed in ten breast cancer patients injected with chaga mushroom preparation.<sup>56</sup> Chaga mushroom contains certain amount of betulin and betulinic acid, which it metabolizes from the birch bark on which it grows. These compounds act as efficient scavengers of free radicals that can destroy cancer cells and also induce programmed cell death of cancer cells.<sup>57</sup> Antiviral activity of chaga mushroom grown on birch tree, was evident when tested against human influenza viruses A and B, and horse influenza viruses A(strains A/ H1N1). There was a complete inhibition (100%) against all influenza viruses and this antiviral activity is thought to be mainly due to betulin, lupeol and mycosterols.<sup>58</sup>

### **Turkey tail mushroom (*Coriolus versicolor* (L.er.Fr))**

PSK and PSP, the two protein bound polysachharides isolated from turkey tail mushroom mycelia, have been used in clinical trials in Japan since 1970. In several studies, PSK was effective in extending the survival rate to five years or beyond in patients with stomach, colorectal, esophageal and non-small cell type of lung cancers. PSP was also effective in extending the survival rate to 5 years and beyond in patients with esophageal cancer in phase II and phase III trials in China. Immune cell production was also enhanced along with the improvement in chemotherapy induced symptoms, in both PSK and PSP supplemented groups.<sup>59</sup> In a Meta-analysis of 13 clinical trials, where turkey tail mushroom was used as a supplement, showed a 9% absolute reduction in mortality rate, during a 5-year period. The effect of turkey tail mushroom along with chemotherapy on overall 5-year survival rate, was evident in breast, gastric and colorectal cancer patients.<sup>60</sup> Results of phase 1, two-center clinical trials in 9 breast cancer patients, suggested that the supplementation of freeze-dried turkey tail mushroom mycelial powder, at 6 and 9 grams/day, increased lymphocyte count, and NK cell activity. The

number of CD 8<sup>+</sup> T cells (cytotoxic T cells ) and CD19,<sup>+</sup> B (B-lymphocyte antigen found on the surface of B cells) cells, increased with the increase in the supplement dose.<sup>61</sup>

### **Oyster Mushroom (*Pleurotus ostreatus* (Fr.) Kumm)**

Oyster mushroom is an edible mushroom cultivated throughout the world. Pleuran, is an insoluble  $\beta$ -glucan isolated from this mushroom. Supplementation with pleuran in athletes significantly reduced the incidence of upper respiratory tract infections, and increased the number of circulating NK cells.<sup>62</sup>

### **Brazilian mushroom (*Agaricus blazei* Murill)**

Brazilian mushroom is an edible mushroom native to Brazil and is cultivated widely. A cold-water extract of this mushroom is consumed traditionally in Brazil. KA<sub>21</sub> is the polysachharide fraction of this mushroom with immune-modulating activity containing a  $\beta$ -glucan content of about 12%. Supplementation with 3 grams per day (10 tablets) of this mushroom fraction in healthy volunteers resulted in an increase in NK cell activity, in the supplemented group (n=8), compared to the placebo group. In addition, other health benefits including normalized liver function and decreased blood cholesterol levels, were also observed.<sup>63,64</sup>

Supplementation with mushroom extract of *Agaricus blazei*, along with chemotherapy, in gynecological cancer patients, resulted in increased NK cell cytotoxicity in the mushroom supplemented group (n =39), compared to the group who were on chemotherapeutic regimen only. Mushroom extract also was beneficial in reducing the chemotherapeutic side effects such as nausea, hair loss, loss of appetite, insomnia and other symptoms.<sup>11</sup>

### **Caterpillar mushroom (*Cordyceps sinensis* (Berk.) Sacc)**

In the wild, this mushroom is parasitic on caterpillar with an elongated, cylindrical fruiting body with the mycelium invading and completely covering the caterpillar. This caterpillar fungus or “mushroom” has been used in Chinese medicine for centuries. Because of the scarcity of this mushroom in the wild, the mycelia of this mushroom is now cultivated on solid substrate such as brown rice or in liquid medium for use as a dietary supplements.<sup>65</sup>

In renal transplant patients, Cordyceps mushroom powder supplementation resulted in an increase in the serum level of anti-inflammatory cytokine IL-10 in the mushroom treated group, which was significant compared to the control group.<sup>66</sup> Cordyceps mushroom mycelial powder could effectively protect the liver and kidney, stimulate the formation of cellular components of blood, improve low protein levels, as well as reduce the incidence of infection, in renal transplant patients.<sup>67</sup> The use of mushroom powder also appears to allow for the use of lower doses of cyclosporine A (an immunosuppressive drug) causing fewer side effects, in renal transplant patients.<sup>68</sup>

## **Conclusions**

Mushroom bio-actives and their metabolites display a wide range of pharmacological properties, due to their wide structural diversity. Polysachharides such as lentinan, schizophyllan from shiitake and Schizophyllan mushrooms, PSK and PSP, the protein bound polysachharides from turkey tail mushroom, have been developed as anti-cancer agents in Japan and are now available worldwide.<sup>2</sup> The immunomodulatory effects of many other bioactives, such as protein bound polysachharides, triterpenes, betulins and other bioactives have also been successfully studied in humans. The efficacy of these bioactives is dependent on the method of their preparation, dosage, route of administration, treatment duration, and the subject's immune system function prior to the intervention. Matching a particular type of mushroom bioactive with a specific or non-specific type of immune condition requires a proper evaluation and understanding of the type of immune cells involved and the type of immunomodulation required for the immune cells in question. Still, many questions remain to be answered about the appropriate role of mushroom-derived immunomodulators as many of the published clinical trials have been small and unrepeated in different patient groups. Nonetheless, the safe and non-toxic nature of mushroom-derived compounds offers numerous possibilities within a wide variety of clinical settings where patients can benefit from improved immune system function.

(NR/TGG)

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