

# Treatment of Cancer with Mushroom Products

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**ABSTRACT.** Cancer has been attributed to 3 causes: pollution, infection, and poor nutrition. Conventional treatments include surgery, chemotherapy, and radiotherapy. The author proposes that immunotherapy also be considered. Among other environmental influences, dietary deficiencies and carcinogenic viral infections must be investigated and treated wherever possible. It has been suggested that mushrooms, in particular, have a structure that is immunomodulatory because it resembles the proteoglycan structure in the human extracellular matrix, and both are metabolically active. Inasmuch as mitochondria have a bacterial origin, proteoglycans may have a mushroom origin. The author describes a study which shows that natural killer cells can double in number with 8 wk of treatment with *Coriolus versicolor*. Also described is an epidemiological survey of cancer deaths among *Flammulina velutipes* farmers in Japan, which found that the mushroom farmers had lower rates of cancer deaths than controls who were not involved in mushroom farming.

<Key words: cancer, *Coriolus versicolor*, immunotherapy, matrix, mushrooms>

THE GLOBAL INCIDENCE OF CANCER has been attributed to 3 principal causes. Of 10 million cancer cases diagnosed each year worldwide, 3 million are attributed to tobacco smoking, 3 million to poor diet (inadequate or incorrect nutrition), and 1.5 million to infection, in particular by viruses. The remaining 2.5 million cases of cancer have no identifiable cause.<sup>1</sup>

Pollutant-caused cancers are predominantly attributable to the use of tobacco products, and involve the lung, oropharynx, larynx, bladder, and kidney. Causes related to diet involve the stomach, colon, esophagus, breast, liver, oropharynx, and prostate. Infectious causes affect the stomach; cervix; liver; nasopharynx; neural, hematological, and lymphatic systems; and bladder.

Current treatments for cancer consist principally of surgery for eradication or bypass of a diagnosed mass, and chemotherapy and radiotherapy directed at ablation of the abnormal growth of cells by direct effects on the development of cancerous tissue. In the future, cancer treatment may include these modalities in combination with immunotherapy alone, or with targeted immunotherapy, in which chemotherapeutic agents are linked both chemically and structurally to an antibody

that targets cancerous tissue, which allows direct transport of the agent to the site of primary or secondary tumors.

Treatment of cancer has focused on fighting the *established* cancer; however, treatment of the 3 principal causes is not managed well. Inasmuch as biological systems are integrated to ensure long-term survival, the clinician should address both treatment of a cancer *and* its causes, to protect against conditions favorable for initiation or recurrence of the disease. For example, cancer of the lung is more likely to recur in a persistent smoker—without strong encouragement and effort to stop smoking, the provocation remains. Similarly, because asbestos and other pollutants act synergistically with tobacco smoke, appropriate avoidance strategies must be considered.

Among other environmental influences, poor diet or incorrect nutrition must also be addressed, and carcinogenic viral infections<sup>2-4</sup> must be investigated and treated wherever possible. Ironically, chemotherapy causes immune suppression, which allows infectious causes to flourish and possibly increase the likelihood of recurrence or secondary spread.<sup>5</sup> The relationship be-

tween diet and cancer is complex. We have to eat, but our food, its preparation, and interactions between dietary components during digestion and assimilation can cause significant changes in levels of hormones and other cellular messengers. Pollutant contaminants (e.g., polychlorinated biphenyls [PCBs], dioxins, and pesticides) can be estrogen mimics.<sup>6,7</sup>

Certain diets—such as high-fiber, low-fat diets with a high content of fresh fruit and vegetables—protect against cancers because many phytonutrients enhance immunity and are free-radical scavengers. Conversely, the low-fiber, high-fat (or its contaminants) diets common in Northern Europe and the United States are associated with increased cancer risk.<sup>8</sup>

Infection is also important as a cause of cancer. Papillomavirus infection induces cervical cancer—the 5th most common cancer in humans and the 2nd most common cause of cancer death in women. At least 90% of all cervical carcinomas are thought to be related to human papillomavirus infection (HPV),<sup>2</sup> with the HPV-16 strain accounting for more than 50% of cases worldwide, and the HPV-18 strain for about 14%.<sup>3</sup> Hepatitis viruses are associated with increased risk of liver cancer and hepatoma,<sup>9</sup> and Epstein-Barr virus (EBV)<sup>4,10</sup> is associated with increased risk of lymphoma. It may be possible to immunize against such infections; for example, researchers in Taiwan have shown that immunization against hepatitis reduced the incidence of childhood hepatoma by 50%.<sup>9</sup>

Pollution causes cancer by promoting the production of abnormal fragments of deoxyribonucleic acid (DNA). Chemical irritants such as tobacco smoke, physical agents such as ionizing radiation, and infectious agents such as viruses can cause cancer many years after initial exposure. The time delay may be associated with a cytokine shift from a Th1 to Th2 pattern, which weakens the Th1 immune response (i.e., the antiviral, antibacterial cell-mediated immune response). If a Th1-to-Th2 shift occurs over a period of time, proinflammatory cytokines may be induced and may maintain a heightened state of humoral response, during which triggers (individually or in combination) continue to weaken the immune system. As stated previously, nutrition can exert a major influence on hormonal systems. For example, it has been shown that folic acid deficiency causes patchy loss in colonic mucosa, which is a precursor to colon cancer; estrogen and its mimics (e.g., pesticide pollutants, phthalates from plastics, or PCBs) can deplete folic acid.<sup>11</sup>

Cancer prevention and treatment should, therefore, include reversal of the cytokine Th1-to-Th2 shift, allowing for the periodic restoration of Th1 activity through the use of biological agents that restore or support Th1 immune response activity. Personal pollution (e.g., tobacco smoking, exposure to estrogen mimics in the diet or wider environment) should be reduced or eliminat-

ed. Knowledge of disease causation frequently results in effective prevention and treatment, and avoidance of cause may prevent recurrence.

### ***Coriolus versicolor* and Chronic Fatigue**

Very few agents are effective for both treatment and prevention of disease, but our research has shown that certain mushrooms can be used in this way. The fungus *Coriolus versicolor* is found almost worldwide; however, its bioactivity varies depending on the habitat in which it grows. To eliminate these variations, Gourmet Mushrooms, Inc. (Sebastopol, California) established the CV-OH1 strain approximately 15 yr ago. This strain demonstrates rapid and aggressive colonization and far outmatches other isolates in bioactivity and vigor. A mother culture of strain CV-OH1 has been developed and maintained to produce spawn. In-house checks confirm that the mother culture does not alter from the original isolate. The production process involves the inoculation of sterile organic edible grain with spawn from the mother culture. The fungus is allowed to completely colonize the growth medium aseptically. At the correct stage of development—at maximum bioavailability—the living biomass is aseptically air-dried, granulated, and tested microbiologically.

This reproducible technique produces a raw material that is sterile, contains no pesticides or heavy metals, and is free from foreign matter. The material is shipped to a U.K. GMP (Good Manufacturing Practice) pharmaceutical facility (Mycology Research Laboratories Ltd (MRL) [East Yorkshire, U.K.]), where it is manufactured into 500-mg tablets (*Coriolus-MRL*<sup>®</sup>) with the addition of cellulose, silica, a granulating agent, and a tablet press lubricant. The finished tablet complies with the British Pharmacopoeia requirements for tablets. The long-term stability of this product is being established with total viable count and polymerase chain reaction (PCR) tests. A PCR/electrophoresis method is being developed to determine the DNA of this product, as an additional means of quality control.

We studied 30 patients who fulfilled international criteria for the diagnosis of chronic fatigue.<sup>12,13</sup> The patients ranged in age from 17 to 83 yr, with a female-to-male ratio of 2:1. We measured the following 8 immunological parameters in each patient: (1) T lymphocyte subsets, (2) natural killer cells CD3-CD16+ CD56+,<sup>14</sup> (3) EBV viral capsid antibody immunoglobulins IgG and IgM, (4) EBV early antigen antibody diffuse IgG, (5) EBV nuclear antigen antibody, (6) EBV nuclear antigen IgM, (7) human herpes virus 6 (HHV6) IgG, and (8) cytomegalovirus (CMV) IgG and IgM. Patients were then given 6 *Coriolus-MRL*<sup>®</sup> tablets daily for 15 days, followed by 3 tablets daily for 45 days.

Before treatment, all patients were found to have combinations of high antibody levels to EBV and/or

HHV6 or CMV. The results of our study revealed that T cells (percent CD3+CD26) showed increased activation in two-thirds of the patients initially and, following review of the patients after 8 wk, T cell depression in 22% of patients. The T cell level was unchanged in 11% of the patients.

The normal range of natural killer cells in humans is 5%–20% of the lymphocyte population; the normal cell count is 75–1,800/mm<sup>3</sup>. Natural killer cells were low in our patients prior to treatment (average = 129.64/mm<sup>3</sup>). Following treatment with *Coriolus*, the average cell count was 175/mm<sup>3</sup>—an increase of 35%.<sup>15</sup> Thus, we have demonstrated that natural killer cell production can be induced by use of a mushroom product. These findings indicate an increased probability of immunological improvement in patients suffering from chronic fatigue.

### *Flammulina velutipes* and Cancer

It has been well documented that tumor growth can be inhibited through functional modulation of the following components and processes: cytotoxic macrophage activity, monocytes, neutrophils, natural killer cells, dendritic cells, cytokines (e.g., interleukins, interferons, and colony-stimulating factors), induction of gene expression, cytokine receptors, T cells (i.e., cell-mediated cytotoxicity), and B cells (i.e., antibody production). Each of these functions can be affected by mushroom products.<sup>16</sup>

In Japan, Korea, and China, Phase I, II, and III clinical trials are under way on the use of mushrooms as adjuncts to chemotherapy. Various immune-modulating mushroom polysaccharides have been identified (e.g., lentinan from *Lentinula edodes*; schizophyllum from *Schizophyllum commune*; PSK Krestin [polysaccharide-Krestin] and PSP [polysaccharide-peptide], components of *Coriolus*; and grifon D from *Grifola frondosa*). Lentinan and schizophyllum increase numbers of T helper cells and macrophages, which are involved in altering acute-phase proteins and colony-stimulating factors; they also alter activation of macrophages, neutrophils, and complement. PSK Krestin and PSP are immunostimulators that increase total white blood cell counts, gamma interferon, and interleukin 2.<sup>16</sup>

The National Cancer Center Research Institute of Japan, founded in 1966, has established that basidiomycetes (the fungal group with freestanding fruiting bodies, often used as an edible mushroom) can have anticancer activity. Protective properties of mushrooms were demonstrated in a 15-yr epidemiological study (1972–1986) in the Nagano area of Japan, where farmers grow the edible mushroom *Flammulina velutipes*. In that study of 174,505 individuals, investigators compared the cancer death rates of farmers who produced this edible mushroom with death rates of controls, with the assumption that the farmers would eat some of the

mushroom species they farmed. Results showed a cancer death rate in controls of 160.1 per 100,000, compared with 97.1 per 100,000 among the mushroom farmers (Fig. 1).<sup>17</sup>

### Discussion

It is thought that eukaryotic organisms evolved through incorporation of bacteria into cells as mitochondria.<sup>18</sup> Thus, it could be further postulated that the proteoglycans in mushrooms formed the evolutionary background for the matrix in human connective tissue.<sup>19</sup> Polysaccharides are important mushroom components. Monosaccharides with glycosidic links can produce branched molecules with a huge variation in linkages. There are as many as 35,560 permutations for 4 monosaccharides, providing enormous diversity and flexibility of linkages. In the matrix of the connective tissue between human cells, the principal linked polysaccharides are attached to a protein core in much the same way as seen in mushroom polysaccharides (Fig 2).<sup>18</sup> Mushroom proteoglycans may represent an information transmission system, inasmuch as the diversity and flexibility of glycosidic linkages of the carbohydrate saccharides permit rapid transmission of information. It

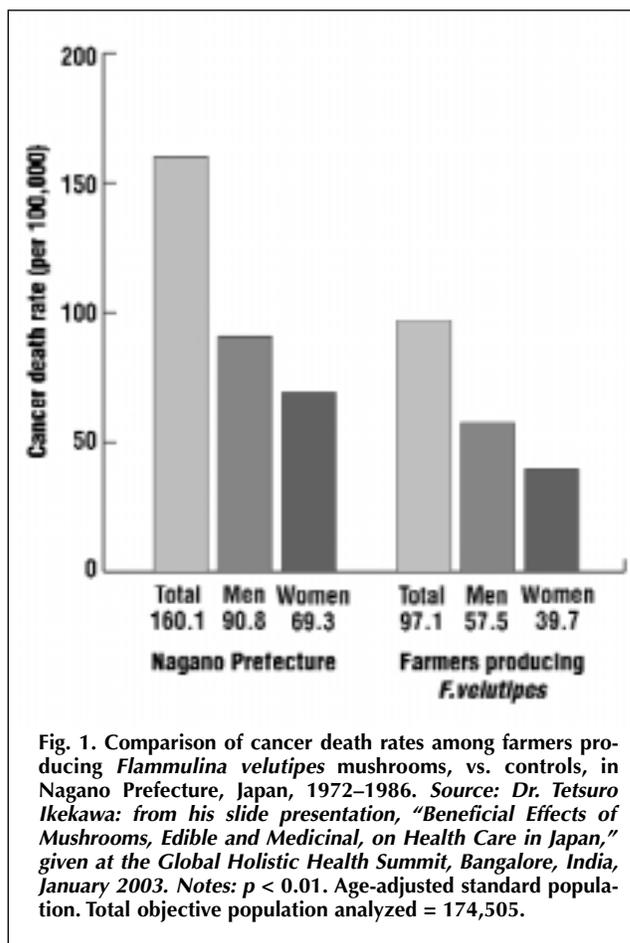


Fig. 1. Comparison of cancer death rates among farmers producing *Flammulina velutipes* mushrooms, vs. controls, in Nagano Prefecture, Japan, 1972–1986. Source: Dr. Tetsuro Ikekawa: from his slide presentation, “Beneficial Effects of Mushrooms, Edible and Medicinal, on Health Care in Japan,” given at the Global Holistic Health Summit, Bangalore, India, January 2003. Notes:  $p < 0.01$ . Age-adjusted standard population. Total objective population analyzed = 174,505.

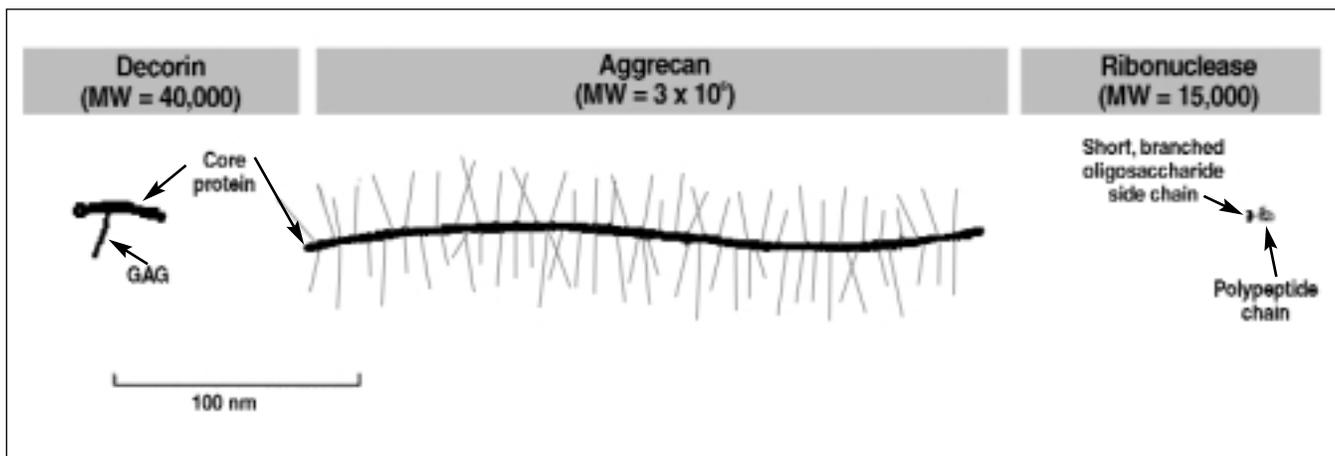


Fig. 2. Similar polysaccharide linkages are found in the extracellular matrices of human cell connective tissue and in mushroom cells. Source: Reproduced from Reference 18, p 976, by permission of the publisher. Notes: Aggrecan is a high-molecular-weight proteoglycan, and decorin is a low-molecular-weight proteoglycan. GAG = glycoaminoglycan, and MW = molecular weight.

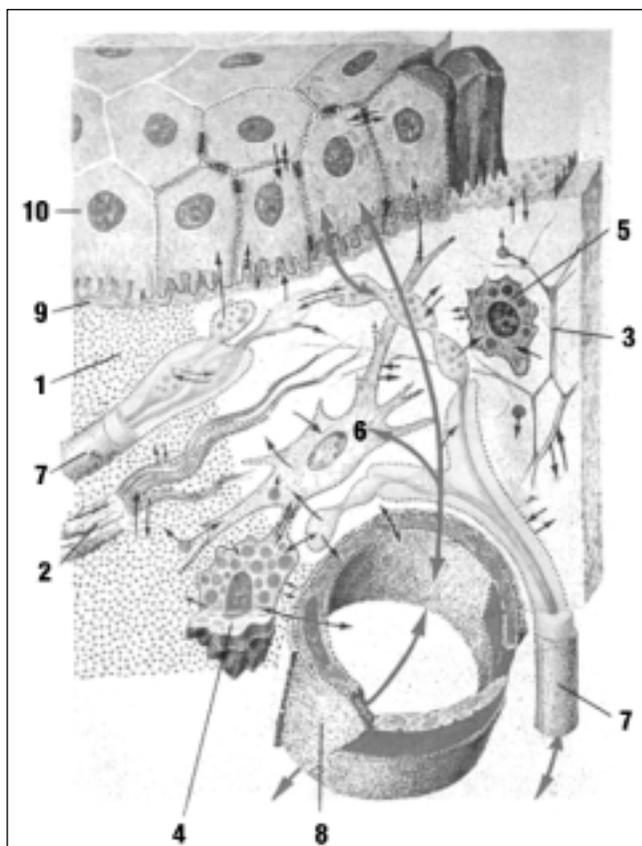


Fig. 3. Reciprocal relationships (arrows) between capillaries (8), ground substance (matrix; proteoglycans and structural glycoproteins [1], collagen [2], and elastin [3]), connective tissue cells (mast cell [4], defense cell [5], and fibrocyte [6]), terminal autonomic axons (7), and organic parenchymal cells (10); basement membrane (9). The fibrocyte (6) is the regulatory center of the ground substance. Only this type of cell is able to synthesize extracellular and nervous components. The main mediators and filters of information are the proteoglycans, structural glycoproteins, and the cell surface sugar film (glycocalyx [dotted line on all cells], collagen, and elastin). Source: Reproduced from Reference 19, p 21, by permission of the publisher.

could be that evolutionary development from unicellular to multicellular organisms requires information transmission; this transmission through the extracellular matrix of higher organisms can occur, it is said, at the speed of sound (Fig 3).<sup>16,19</sup> Perhaps, in mushrooms, similar information transmission is part of the structural function of proteoglycans (Fig 2).<sup>18</sup>

Natural killer cells recognize high-molecular-weight glycoproteins on virally infected cells. Perforin, apoptosis, tumor necrosis factor, proteases, natural killer cytotoxic factors, and ionized adenosine triphosphate apoptosis are all involved in natural killer cell effects. Both virally infected cells and cancer cells are killed by cytotoxic T cells and antibody-dependent, cell-mediated cytotoxicity.<sup>20</sup>

Our research has demonstrated that mushrooms may be useful in protecting against virally induced cancers through enhancement of natural killer cells, and may also play a role in the prevention of cancers induced by diet and poor lifestyle choices. Thus mushrooms may have a significant role in cancer treatment.

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