

Recent studies have shown that polysaccharides and polysaccharide-protein complexes from this mushroom have significant anti-cancer activity (Hishida *et al.*, 1988, Kurashige *et al.*, 1997). A limited number of clinical studies in Japan and the USA have shown that a purified fraction of polysaccharide is highly effective against cancers of the breast, lung, liver, prostate and brain. Details of clinical trials will be discussed later. Other fractions from *G. frondosa* exhibit immunological enhancement together with properties of anti-HIV, antihypertension, antidiabetic, and antiobesity (Zhuang and Mizuno, 1999). It is interesting to note that the  $\beta$ -glucan fractions from this mushroom are now being used by over 3,000 health professionals in the US for the prevention and treatment of :

Flu and common infection (bacteria and viruses)

AIDS (HIV)

Diabetes mellitus

Hypertension

Hypercholesterolemia

Urinary tract infections (particularly for women) (Professor Konno – personal communication).

Capsules with dried Maitake form widely accepted dietary supplements and apart from the Far East are now being extensively marketed in US and in Europe. Other examples are Maitake tea, whole Maitake powder and a Maitake drink.

*Key active constituents:*

1,3 and 1,6 Beta glucans (antitumour and immunomodulating)  
Commercial product “Grifolan”

## ***Flammulina velutipes***

This is one of the most popular edible mushrooms in China and Japan where it is known as *Enokitake*. In nature it grows on stumps or decayed wood of hardwood trees as a typical mushroom. It is now mostly produced by artificial cultivation from jars of sawdust mix. After growth through the sawdust medium and as the primordia form on the surface, a plastic collar is placed around the neck of the jar and with special environmental conditions, results in the formation of elongated stipes and tiny mushroom heads. While they may be cooked in various ways they can also be used directly in salads. This is a major edible mushroom. It can be slightly salty and bitter in taste and is used in traditional Chinese medicine to treat liver diseases and gastric ulcers. Polysaccharides from this mushroom have been shown to inhibit the growth of cancers in a number of xenograph models. Flammulin, a basic simple protein from *F. velutipes* is able to markedly inhibit tumour cells (Komatsu *et al.*, 1963). Flammulin has been purified to a crystalline state and clinical trials are now in progress (Zhang *et al.*, 1999). The first scientific paper stating that edible mushrooms were effective against a solid tumour was with *Flammulina*.

A new antitumour glycoprotein has been isolated from cultured mycelium of this fungus - Proflamin. It is useful in combination therapy with other chemotherapy agents (Ikekawa, 1995).

Furthermore, an epidemiological study in Nagano Prefecture, Japan showed that the cancer death rate among farmers producing *F. velutipes* was remarkably lower than that of other people in the Prefecture and in Japan overall (Ikekawa, 2001).

*Key active ingredients:*

Beta-glucan-protein (antitumour and immunomodulating)  
Beta-glycoprotein-Proflamin (antitumour)

**Fig. 8a** *F. velutipes* growing naturally on tree stump



**Fig. 8b** *F. velutipes* growing artificially on sawdust mix



***Pleurotus ostreatus***

The fruit-body of this mushroom is oyster-shaped and hence the common name Oyster Mushroom. It grows in layered clusters on deciduous trees in many parts of the world. It is one of the easiest to grow, most often on straw or sawdust

Fig. 9a *P. ostreatus* growing on decayed timber



logs, and has become one of the most popular edible mushrooms with a pleasant odour and taste. In the Sung dynasty (A.D. 420-479) it was referred to as “the mushroom of flower heaven” (Stamets, 1993, Hobbs, 1995).

**Fig. 9b** *P. ostreatus* growing on sawdust mixture



The medicinally beneficial effects of *Pleurotus* spp. were discovered independently on different continents. The awareness of their medicinal properties comes not only from Asia but from the folklore of central Europe, South America and African (Gunde-Cimerman, 1999). While first artificially cultivated in USA, production is now worldwide. There have been a number of studies suggesting a

role in numerous diseases with its anti-cancer activity, immunomodulating effects, and antiviral, antibiotic and anti-inflammatory activities. The major cause of death in the Western hemisphere is coronary artery disease with hypercholesterolemia as a primary risk factor. Drug therapy for lowering cholesterol has made considerable use of the pharmacologic agent lovastatin (mevinolin) and its analogues. Species of the genus *Pleurotus* are excellent producers of lovastatin and as such, *Pleurotus* could be considered as a functional food with natural cholesterol-lowering ability (Gunde-Cimerman, 1999). However, large scale production of lovastatin from fruit-bodies is not deemed commercially viable because of variability in fruit-body composition. Lovastatin is normally found only in the lamella and basidiospores and not in the stipe and cap. Mycelial cultivation could be the way ahead.

*Key active constituents:*

Beta-glucans (antitumour, immunomodulation)

Lovastatin (cholesterol-lowering)

### ***Trametes (Coriolus) versicolor***

This is a fungus with many synonyms but *Trametes* is now the accepted genus name. The multicoloured cap resembles a 'turkey tail' and occurs as overlapping clusters on dead logs in most parts of the world. This is not an edible fungus but hot water extracts have been used in traditional Chinese medicine from historical times for a wide range of ailments (Ying *et al.*, 1987). Modern studies have produced two extremely important compounds, PSK or "Krestin", a water-soluble protein-bound polysaccharide and PSP, a polysaccharide-peptide both derived from mycelial cultures of the fungus. PSK has been shown to act directly on tumour cells (cytostatic and cytotoxic) as well as indirectly in the host to boost cellular

**Fig. 10** *Trametes versicolor* growing naturally on fallen timber



immunity (Tsukagoshi, 1984). PSK also shows antiviral activity through stimulation of interferon production. PSP is a powerful immunostimulant and anti-cancer agent (Yang, 1993, Ng, 1998). There have been a wide range of clinical trials for a range of human cancers. In most cases when taken with traditional chemotherapy or radiotherapy there have been significant increases in patient longevity. In 1987 “Krestin” accounted for 25% of the total expenditure of anti-cancer agents in Japan (Fukushima, 1989). A polysaccharopeptide isolated from this mushroom has been shown to inhibit the HIV-1 (Collins and Ng, 1997) while a polysaccharide showed chemopreventive activity in an *in vitro* model (Kun *et al.*, 1999). PSP and PSK are

just beginning to be available in the US and Europe. These compounds will be extensively discussed in later Chapters.

*Key active constituents:*

Beta-glucan-proteins (antitumour, antiviral, immunomodulating)  
Ergosterol (provitamin D2)

### ***Tremella mesenterica and T. fuciformis***

This fungus is commonly known as the “white auricularia” or “white jelly fungus”, and in Japan, *Shirokikurage*, with a jelly-like, translucent fruiting-body which usually grows on deciduous trees in warm climates worldwide. It can now be grown artificially and is being increasingly consumed in Asia.

It has a long historical use in traditional Chinese medicine as an immune tonic and for treating debility and exhaustion together with many other ailments including skin-care. It contains acidic polysaccharides especially glucuronoxylomannan, readily extracted with hot water giving a smooth and stable solution used in Oriental cuisine. The polysaccharides of this fungus show anti-cancer activity and can enhance immune functions (Hobbs, 1995). Clinical trials have shown it to be effective in treating radio- and chemo-therapy-induced leukopenia, boosting immunological functions and stimulating leukocyte activity (Hu and But, 1987). Med Myco Ltd. (Israel) have developed a submerged fermentation method to produce Tremellastin from *T. mesenterica* mycelium which contains 50% glucuronoxylomannan, together with proteins rich in amino acids, dietary fibre and vitamins of the B group. Dietary supplements from *Tremella* are only now beginning to expand into the Asian market, and they will certainly be of special significance in the cosmetic industry.

**Fig. 11a** *T. mesenterica* growing naturally on deciduous tree



**Fig. 11b** *T. fuciformis* growing naturally on deciduous tree



*Key active constituents:*

Acidic polysaccharides (glucuronoxylomannan) (antitumour, immunostimulatory, antidiabetic, skin enhancing)

***Cordyceps sinensis and C. sobolifera***

The fungi grow as *parasites* in larvae of Lepidoptera, gradually taking over the entire larval body. The diseased larvae bury themselves in the soil and die. Later the fungal mass or *stroma* grows out of the pupa and can be identified and collected.

The caterpillar fungus or *Tochukaso* has been highly regarded in Chinese medicine for many centuries. It is not a mushroom type fungus and the fruiting structure cannot be cultivated or cultured. The complete structure can be used in many forms, whole, powdered or extracted and has many applications in Chinese medicine (Hobbs, 1995; Halpern, 1999). Anti-cancer polysaccharides have been isolated from several species of *Cordyceps* and some have been shown to have hypoglycaemic activity as well (Jones, 1997; Itami and Yahagi, 1990; Kun 1998). A major concern with herbal medicine using *Cordyceps* collected from nature is quality and safety.

However, the pure mycelium of these parasitic fungi can now be easily cultivated in fermentors and is attracting considerable interest as an agent to treat fatigue and improve motor function (Mizuno, 1999). The major chemical, pharmacological and toxicological studies on *Cordyceps sinensis* have been reviewed for English and Chinese literature by Zhu *et al.* (1988a,b). These studies show that the main activities of the fungus are in oxygen-free-radical scavenging.

Fig. 12 *Cordyceps* spp. stroma growing out of colonised insects



With this particular fungus it is clear that there will be increased usage of fermenter-produced mycelium. Such methods use selected media under aseptic conditions, providing better quality and homogeneity through process control.

*Key active constituents:*

Galactomannans (antitumour, immunostimulating)  
Cordycepin  
Sterols

### ***Schizophyllum commune***

This is a small, whitish fungus with no stalk which grows on dead trees throughout the year. It is a very common fungus and has worldwide distribution (Hobbs, 1995). Pharmacologically it is extremely important because it produces the polysaccharide Schizophyllan which shows considerable anti-cancer activity in xenograph and clinical practice. There have been numerous clinical trials with Schizophyllan which will be discussed later (Ooi and Liu, 2000).

*Key active constituents:*

Beta-glucans (antitumour and immunomodulation).

**Fig. 13a** *S. commune* growing naturally on dead deciduous tree



**Fig. 13b** *S. commune* view of underside of fruitbody



## ***Agaricus blazei***

This mushroom was first discovered in the USA in the 1940s but its main commercial cultivation now occurs in Japan and Brazil. In Japan it is called *Himematsutake* and is one of the most expensive medicinal mushrooms. A novel polysaccharide-protein complex has been shown to be highly active against a variety of xenographs (Ito *et al.*, 1997).

### *Key active constituents:*

Beta (1,3)-D-glucan, Beta (1-4)-D-glucan, Beta (1-6)-D-glucan (antitumour and immune enhancing)  
Proteoglucans (antitumour).

**Fig. 14 *Agaricus blazei*, Himematsutake or the Almond Portobella, grown in cased leachate cow manure (Stamets, 2000)**



## References

- Aziawa, K. 1998. Antitumour-effective mushroom, meshimakobu, *Phellinus linteus*. *Gendai-shorin*, Tokyo.
- Bensky, D. and Gamble, A. 1993. *Chinese Materia Medica* 2<sup>nd</sup> ed. Eastland Press, Seattle.
- Chang, R.Y. 1995. Effective dose of *Ganoderma* in humans. In *Ganoderma: Systematics, Phytopathology and Pharmacology*. 5<sup>th</sup> International Congress, Vancouver.
- Chang, R.Y. 1999. Role of *Ganoderma* supplementation in cancer management. In *Advanced Research in PSP*, 1999. Ed. Yang Qing-yao. The Hong Kong Association for Health Care Ltd., Hong Kong, pp. 346-350.
- Chang, S-T. 1999. *Ganoderma lucidum* (Curt.: Fr.). P. Karst. (Aphylo-phoromycetideae) – a mushrooming medicinal mushroom. *International Journal of Medicinal Mushrooms* 1, 139-146.
- Chen, A.W. 1999. A practical guide for synthetic log cultivation of the medicinal mushroom *Grifola frondosa* (Dick.:Fr.) S. Fr. Gray (Maitake). *International Journal of Medicinal Mushrooms* 1, 153-168.
- Chen, A.W. and Miles, P.G. 1996. Biomedical research and the application of mushroom nutraceuticals from *Ganoderma lucidum*. Proceedings of 2<sup>nd</sup> International Conference on Mushroom Biology and Mushroom Products (ed. Roycse, D.J.), Penn State University, PA.
- Chihara, G. 1992. Immunopharmacology of lentinan, a polysaccharide isolated from *Lentinus edodes*: its application as a host defense potentiator. *International Journal of Oriental Medicine*, 17, 57-77.
- Collins, R.A. and Ng, T.B. 1987. Polysaccharopeptide from *Coriolus versicolor* has potential for use against human immunodeficiency virus type 1 infections. *Life Science* 60, 383-387.
- Fujimiya, Y., Susuki, Y., Oshiman, K.I., Kobori, H., Moriguchi, K., Nakashima, H., Matumoto, Y., Takahara, S., Ebina, T. and Katakura, R. 1998. Selective tumoricidal effect of soluble proteoglycan extracted from the basidiomycete *Agaricus blazei* Murrill, mediated via natural killer cell activation and apoptosis. *Cancer Immunology and Immunotherapy* 46, 147-159.
- Fukushima, M. 1989. The overdose of drugs in Japan. *Nature* 342, 850-851.
- Gunde-Cimerman, N. 1999. Medicinal value of the genus *Pleurotus* (Fr.) P. Karst. (Agaricales S.I., Basidiomycetes). *International Journal of medicinal Mushrooms* 1, 69-80.

- Halpern, G.M. 1999. *Cordyceps*: China's healing mushroom. *Avery Publishing Group*, New York, USA, pp. 116.
- Hishida, I., Nanba, H. and Kuroda, H. 1988. Antitumour activity exhibited by orally administered extracts from fruit-body of *Grifola frondosa* (maitake). *Chemical and Pharmaceutical Bulletin* 36(5), 1819-1827.
- Ho, B. and Chen, Q. 1991. Antifertility action of *Auricularia auricula* polysaccharide. *Zhongguo Yacke Daxus Xuebao* 22, 48-49.
- Hobbs, C. 1995. *Medicinal Mushrooms: An Exploration of Tradition, Healing and Culture*. Botanica Press, Santa Cruz, CA.
- Hu, B. and But, P. 1987. Chinese material medicines for radiation protection. *Abstracts of Chinese Medicines* 1, 475-490.
- Ikekawa, T. *et al.* eds. "Twenty years of studies on antitumour activities of mushrooms". Nagamo Prefectural Research Institute of Rival Industry, 1989.
- Ikekawa, T., 1995. Enokitake, *Flammulina velutipes*: antitumour activity of extracts and polysaccharides. *Food Review International* 11, 203-206.
- Ikekawa, T. 2001. Beneficial effects of mushrooms, edible and medicinal, on health care. *International Journal of Medicinal Mushrooms* abstracts, p. 79. (A full paper to be published in this Journal 2002).
- Itami, H. and Yahagi, N. 1996. Japanese Tochukaso, Challenges for Terminal Cancer. *Metamoru shyupan*, Tokyo, 140 pp.
- Ito, H., Shimura, H., Itoh, M. and Kurode, M. 1997. Antitumour effects of a new polysaccharide-protein complex (ATOM) prepared from *Agaricus blazei* (Iwade Strain 101) Himematsuke and its mechanisms in tumour-bearing mice. *Anticancer Research* Jan-Feb. 17, (IA), 277-284.
- Jong, S.C. and Birmingham, J.M. 1992. Medicinal benefits of the mushroom *Ganoderma*. *Advances in Applied Microbiology*. 37, 101-134.
- Jong, S.C. and Donovick, R. 1989. Antitumour and antiviral substances from fungi. *Advances in Applied Microbiology* 34, 183-262.
- Kanatsu, N., Terakawa, H., Nakanishi, K. and Watanabe, Y. 1963. Flammulin, a basic protein of *Flammulina velutipes* with antitumour activities. *Journal of Antibiotics*. Ser. A., 16, 139-143.

- Kim, H.S., Kacew, S. and Lee, B.M. 1999. *In vitro* chemopreventative effects of plant polysaccharides (*Aloe barbadensis* Millar, *Lentinus edodes*, *Ganoderma lucidum*, and *Coriolus versicolor*). *Carcinogenesis* 20, 1637-1640.
- Kim, Y. (ed.) 1991. Impact experiences for 50 people come back from the depths of death with vegetable wasps and Tochukaso. From the last stages of cancer. Nishinhodo, Tokyo, 207 pp.
- Kurashiga, S., Akuzawa, Y. and Eudo, F. 1997. Effects of *Lentinus edodes*, *Grifola frondosa* and *Pleurotus ostreatus* administration on cancer outbreaks and activities of macrophages and lymphocytes in mice treated with a carcinogen *N*-butyl-*N*<sup>1</sup>-butamolinitreso-amine. *Immunopharmacology and Immunotoxicology* 19, 175-183.
- Liu, B. and Bau, Y.S. 1980. *Fungi Pharmacopoeia (Sinicas)* Kinoko Co., Oakland, California.
- Liu, G-T. 1999. Recent advances in research of pharmacology and clinical applications of *Ganoderma* (P. Korst.) species (Aphyllphoromycetideae) in china. *International Journal of Medicinal Mushrooms* 1, 63-67.
- Mizuno, T. (ed.) 1995. *Mushrooms: the versatile fungus – food and medicinal properties. Food Reviews International* (Special issue), Vol. II., 1-235.
- Mizuno, T. 1995. Yamabushitake, *Hericium erinaceus*: bioactive substances and medicinal utilisation. *Food Review International* 11, 173-178.
- Mizuno, T. 1996. Medicinal effects and utilisation of *Cordyceps* (Fr. Link (Ascomycetes) and *Isaria* Fd. (Mitosporic Fungi) Chinese caterpillar fungi “Tochukaso” (Review). *International Journal of Medicinal Mushrooms* 1, 251-261.
- Mizuno, T. 1999. Bioactive substances in *Hericium erinaceus* (Bull.: Fr.) Pers. (Yamabushitake), and its medicinal utilisation. *International Journal of Medicinal Mushrooms* 1, 105-119. (contains list of numerous Japanese Patents).
- Mizuno, T. 2000. Development of an antitumour biological response modifier from *Phellinus linteus* (Berk. Et Curt.) Teng (Aphyllphoromycetideae) (Review). *International Journal of Medicinal Mushrooms* 2, 21-33.
- Mizuno, T., Wasa, T., Ito, H., Suzuki, T. and Ukai, N. 1992. Antitumour-active polysaccharides isolated from the fruiting body of *Hericium erinaceus*: an edible and medicinal mushroom called Yamabushitake or Houton. *Bioscience Biotechnology and Biochemistry* 56, 347-348.

- Ng, T.B. 1998. A review of research on the protein-bound polysaccharide (polysaccharopeptide PSP) from the mushroom *Coriolus versicolor* (Basidiomycetes: Polyporaceae). *General Pharmacology* 30, 1-4.
- Ooi, V.E.C. and Liu, F. 2000. Immunomodulation and anticancer activity of polysaccharide-protein complexes. *Current Medicinal Chemistry* 7, 715-728.
- Stamets, P. 1993 and 2000 (3<sup>rd</sup> edition). *Growing Gourmet and Medicinal Mushrooms*. Ten Speed Press, PO Box 7634, Olympia, WA.
- Stamets, P. 1999 and 2000 (3<sup>rd</sup> edition). *MycoMedicinals*, an informative booklet on medicinal mushrooms. Mycomedica, Olympia, Washington.
- Teng, S.C. 1996. In *Fungi of China*, Korf, R.P. ed. Mycotaxon Ltd., Ithaca, NY.
- Tsakagoshi, S. 1984. Krestin (PSK). *Cancer Treatment Reviews* 11, 131-155.
- Wang, S.Y., Hsu, M.L., Hsu, H.C., Tzeng, S.S., Lee, S.S., Shiao, M.S. and HO, C.R. 1997. The antitumour effect of *Ganoderma lucidum* is mediated by cytokines released from activated macrophages and T-lymphocytes. *International Journal of Cancer* 70(6), 669-705.
- Wasser, S.P. and Weis, A.L. 1999a. Medicinal properties of substances occurring in higher Basidiomycetes mushrooms: current perspectives (Review). *International Journal of Medicinal Mushrooms* 1, 31-62.
- Wasser, S.P. and Weis, A.L. 1999b. General description of the most important medicinal higher Basidiomycetes mushrooms. 1. *International Journal of Medicinal Mushrooms* 1., 351-370.
- Yang, G.Y. 1993. A new biological response modifier. PSP. In *Mushroom Biology and Mushroom Products*. Chinese University Press, 247-259.
- Ying, J.Z., Mao, X.L., Ma, Q.M., Zong, Y.C. and Wen, H.A. 1987. *Icons of Medicinal Fungi from China* (Transl. Xu, Y.H.), Science Press, Beijing.
- Zhang, H., Gong, F., Feng, Y. and Zhang, C. 1999. Flammulin purified from the fruit bodies of *Flammulina velutipes* (Curt.: Fr.) P. Karst. *International Journal of Medicinal Mushrooms* 1, 89-92.
- Zhao, J.-D. and Zhang, X-Q. 1994. Resources and taxonomy of Lingzhi (*Ganoderma*) in China. From program and extracts of the 1994 International Symposium in *Ganoderma* Research, Beijing, Beijing Medical University.

- Zhou, S., Gao, Y., Chen, G., Dai, X. and Ye, J. 2001. A phase I/II study of a *Ganoderma lucidum* extract (Ganopoly) in patients with advanced cancer. *International Journal of Medicinal Mushrooms* (submitted).
- Zhu, J.S., Halpern, G.M. and Jons, K. 1998a. I. The scientific rediscovery of an ancient Chinese herbal medicine: *Cordyceps sinensis*. *Journal of Alternative Complementary Medicine* 4, 189-303.
- Zhu, J.S., Halpern, G.M. and Jones, K. 1998b. II. The scientific rediscovery of an ancient Chinese herbal medicine: *Cordyceps sinensis*. *Journal of Alternative Complementary Medicine* 4, 429-457.
- Zhuang, C. and Mizuno, T. 1999. Biological responses from *Grifola frondosa* (Dick.: Fr. (S.F. Gray-Maitake (Aphylophoromycetideae). *International Journal of Medicinal Mushrooms* 1, 317-324.

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