

Professor Tetsuro Ikekawa on His 80th Birthday

On the 8th of July 2011, Professor Tetsuro Ikekawa will celebrate his 80th birthday. Professor T. Ikekawa is a prominent scientist in the area of medicinal mushrooms and one of the founders of this whole area of science. I would like to use his jubilee as an opportunity to tell about his life and studies. Because our scientific community of medicinal mushrooms researchers is not very large and it is extremely diverse, knowing each other better will help us in mutual understanding and solidarity. T. Ikekawa is for many years editor of the *International Journal of Medicinal Mushrooms*.

T. Ikekawa graduated from the Faculty of Pharmaceutical Sciences of the University of Tokyo in 1957. He started his scientific career in the area of chemistry of natural products. Yet, he dealt with mushrooms from the very beginning, when at the graduate school he studied the metabolic products of fungi (in the laboratory of Dr. Shoji Shibata at the University of Tokyo). In 1962, T. Ikekawa received a Ph.D. degree (he defended his work at the University of Tokyo). He was then appointed as a Chief Scientist at the laboratory of Prof. Hamao Umezawa in the Institute of Microbial Chemistry. Three years later he came to the National Cancer Center Research Institute of Japan. First as a member of the research staff and then as a senior scientist, he worked there for most of his career. He was absent from the Cancer Center for only half a year, when in 1968 he was a post-doctoral fellow at Purdue University in the United States.

In 1991, he became a Professor in the Laboratory of Life Sciences at Kanazawa University. He worked in that department until his retirement in 1997 (owing to the age restrictions of the University). He now works as Professor Emeritus in Hebei Medical University (China). He fills yet two other important positions: He is a manager of the Japanese Society for Complementary-Alternative Medicine and Treatment; and recently he is a manager-in-general of the Japanese Association for Integrative Medicine.

T. Ikekawa first reported on the efficacy of soluble extracts from several different Basidiomycetes in inhibiting transplanted Sarcoma180 in mice (Ikekawa et al., 1968).^{*} That was one of the first pioneering steps of what later became a science of medicinal mushrooms. Of the species tested, several proved their effectiveness against Sarcoma 180 cancer. The extracts from *Phellinus linteus* (Berk. et Curt.) Teng, *Trametes versicolor* (L.: Fr.) Lloyd, *Ganoderma applanatum* (Pers.) Pat., and *Daedaleopsis tricolor* (Bull.) Bond. were the most active.

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The discovery of antitumor activity of *Lentinus edodes* (Berk.) Singer turned out to be of special importance for future science. This initial research was performed by T. Ikekawa before 1969 with his colleagues at the National Cancer Center Research Institute in Tokyo (Ikekawa et al., 1969). They found that water extracts of *L. edodes* produced high rates of tumor inhibition in mice (72–92%). Following this research, a glucan was isolated from *L. edodes* by T. Ikekawa, Dr. G. Chihara, and their collaborators at that time. It was named and became famous as lentinan. It came into clinical use in Japan.

^{*}In 2006 we published a special edition of the International Journal of Medicinal Mushrooms (Issue no. 2, Vol. 8, 2006:97–195) dedicated to Professor T. Ikekawa's 75th birthday. In that issue we listed all of his main publications. The whole the list of publications can be found in IJMM, pp. 99–101. Therefore, we will not list the publications of Professor T. Ikekawa again here.



Of course, the discovery of the antitumor activity of *Phellinus linteus* was also very important (Ikekawa et al., 1968; Sasaki et al., 1971). A new polysaccharide, song gen or meshimakobu, obtained from cultured mycelium of *Ph. linteus*, the fourth major anticancer substance from medicinal mushrooms, is an heir to those early studies.

Later, the major focus of T. Ikekawa's activity moved to another Japanese edible and medicinal mushroom, *Flammulina velutipes* (W. Curt.: Fr.) Singer (enokitake). Its antitumor activity was proved in a series of experiments, and soon active polysaccharides were isolated and characterized (Yoshioka et al., 1973). T. Ikekawa worked with those polysaccharides from *F. velutipes* for a number of years.

Four major polysaccharides were obtained from this mushroom. The first one turned out to be β -D-glucan of the same type as lentinan and other anticancer polysaccharides (Ikekawa et al., 1982). The low-molecular-weight protein-bound polysaccharide EA6 was found to be the active antitumor substance in *F. velutipes* extract (Okhuma et al., 1982; Otagiri et al., 1983). Interestingly, it is not active against sarcoma after injection, but is active after oral consumption (Ikekawa, 1995a).

In addition to the studies of the fruiting bodies of *F. velutipes*, the laboratory of T. Ikekawa looked for new antitumor agents in the mycelia and broth filtrates of the mushrooms. The antitumor screening tests of the mycelia substances indicated that active ingredients were not simple polysaccharides, but rather lower molecular weight substances. They modified the methods of purification, and finally isolated a novel glycoprotein of molecular weight of about 13,000. It was a different compound from the glycoprotein isolated from the fruiting bodies of *F. velutipes*. This novel substance acquired the name "proflamin" (Ikekawa et al., 1985). It proved its effectiveness against both allogeneic and syngeneic tumors through oral administration. It is especially useful in combination therapy with other antitumor agents (Ohkuma et al., 1983). T. Ikekawa studied in depth the synergistic effect of combining proflamin and cryosurgery (Ohkuma et al., 1982; Ikekawa et al., 1985).

The next medicinal mushroom T. Ikekawa worked with a great deal was *Hypsizygos marmoreus* (Peck) Bigel., one of the most popular Japanese edible mushrooms (bunashimeji). Its antitumor activity was investigated (Ikekawa et al., 1992). The aqueous extract was found to be highly active in inhibiting growth of solid sarcoma 180.

The polysaccharide β -(1-3)-D-glucan was isolated from *H. marmoreus* and showed very high antitumor activity (Ikekawa, 1995b). T. Ikekawa's laboratory showed its preventive effect against lung metastasis of Lewis lung carcinoma using the Winn test (Saitoh et al., 1997). The water solubility of this polysaccharide was much higher than that of polysaccharides isolated from other mushrooms. Its activity was connected to antioxidative effects, that is, fighting free radicals (Matsuzawa et al., 1997, 1998). Dried mushroom powder from *H. marmoreus* is believed to stimulate the radical-trapping activity of blood (Ikekawa, 1995b). Excessive free radicals in the bloodstream are believed to hasten cancer and the aging process. The fact that *H. marmoreus* increases antioxidative activity in the plasma of tumor-bearing mice can be one of the mechanisms of its cancer preventive effects.

T. Ikekawa with collaborators also studied whether eating *H. marmoreus* mushrooms showed any cancer-preventive effects in mice. Those experiments also had positive results. They correlated well with epidemiological studies of people who eat this mushroom as part of their normal diets and have lower incidences of cancer (Ikekawa, 1995b).

Throughout his scientific career, T. Ikekawa worked with several other mushrooms as well. In the 1970s, he showed that injection of *Pleurotus ostreatus* (Jacq.: Fr.) P. Kumm. extract into tumor-bearing mice produced 75.3% inhibition of tumors (Yoshioka et al., 1972). At the same time, acidic polysaccharides with antitumor properties were isolated from *P. ostreatus* and characterized in his laboratory (Yoshioka et al., 1975).

T. Ikekawa is now participating in an epidemiological case-control study on the relationship between cancer incidence and intake of mushrooms in collaboration with the National Cancer Center Research Institute of Japan. Based on his long and thorough investigations, the extracts of edible mushrooms (registered name "EEM") were developed. They make promising supplements or functional foods, and studies of their activities and modes of action are ongoing.

T. Ikekawa is a joint author of two books on chemistry and chromatography, two books on natural products, and one monograph on chemistry and biochemistry of mushrooms. He also published a book titled “Edible mushrooms and cancer (Lowering cancer incidence by intake of mushrooms)” in 1997. All of these books, unfortunately for most of us, are published in Japanese. We are more fortunate to be able to read his more than 70 original articles and reviews in English.

T. Ikekawa was on the editorial board of the *International Journal of Medicinal Mushrooms* from its start in 1999. From 2001 until now he has been the Editor. He is a very diligent and clever reviewer. A clear appreciation of his achievements was the fact that T. Ikekawa was unanimously elected as President of the first international conference Perspectives of Medicinal Mushrooms in Health Care and Nutrition in the 21st Century, which was held in Kiev (Ukraine) in September of 2001. He did much for the preparation of the conference, and presented a keynote lecture there entitled “Beneficial effects of mushrooms, edible and medicinal, on health care.” In 2003 he was one of the organizers and an invited speaker at the second International Conference on Medicinal Mushrooms “From Traditional Knowledge to Modern Biotechnology,” which was held in July 2003 in Pattaya (Thailand). In 2005 he was an invited speaker and a member of the Scientific Committee of the Third International Medicinal Mushroom Conference, Port Townsend, Washington (October 2005, USA).

In May 2003 Professor T. Ikekawa, because of his great reputation and scientific contributions to his field, was elected Foreign Professor of General Biology Department of the National Academy of Science of Ukraine.

Professor T. Ikekawa is not only a creative and gifted scientist, but also an intellectual with a broad education. He celebrates his 80th birthday at the peak of his creative activity. On behalf of the IJMM Editorial Board and all scientists studying medicinal mushrooms, I want to heartily congratulate Professor Ikekawa and to wish him good health, happiness in all his activities, new creative achievements, good fortune, and many more fruitful and joyful years to come.

Solomon P. Wasser