

# Medicinal Mushroom Substances as Cancer Molecular Therapy

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Medicinal mushrooms possess a variety of health promoting qualities as well as being a potential source of a variety of pharmaceuticals for some diseases, including cancer. Although most of the attention for their anticancer activity revolved around the activity of high-molecular-weight polysaccharides with no clear mechanism of action, our focus is on low-molecular-weight mushroom substances with a well-defined mechanism of action.

A neoplasm is an abnormal mass or colony of cells produced by a relatively autonomous new growth of tissue arising from the clonal expansion of a single cell that has undergone neoplastic transformation, which is usually accompanied by the loss of some specialized functions and the acquisition of new biological properties mediated by alteration in the expression or function of specific molecular targets. Our research interest is on mushroom substances that specifically modulate molecular targets implicated in carcinogenesis, especially in chronic myelogenous leukemia (CML) and prostate cancer (PCa).

CML is a malignancy of pluripotent hematopoietic cells characterized by distinctive cytogenetic abnormality resulting in the creation of a p210 Bcr-Abl fusion protein with increased tyrosine kinase activity.

Imatinib is a potent inhibitor of Bcr-Abl and is used as standard therapy for CML. Unfortunately, clinical efficacy continuously decreases with the advancement of the disease. Secondary resistance is mostly due to the acquisition of point mutations in Bcr-Abl, which argues for the need of develop-

ing alternative inhibitors of Bcr-Abl.

Medicinal mushrooms exhibiting selective anti-CML activity were selected. Active mushroom substances induced apoptosis and erythroid differentiation in CML cells and caused a reduction in Bcr-Abl levels. Focusing on mushroom #540 and #514, we show that medicinal mushroom substances were effective in inhibiting auto-phosphorylation from wild types as well as from imatinib-resistance mutants of Bcr-Abl.

PCa is the second leading cause of death in Western men. Primary PCa is hormone dependent and is manageable by hormonal therapy. However, it rapidly develops into hormone-refractory tumors due to the accumulation of mutations in the androgen receptor (AR) or to the acquisition of alternative cellular pathways that support proliferation and inhibit apoptosis of PCa in androgen-independent mechanisms.

Whereas PCa is very common in Western countries, its levels are very low in several countries in Asia. Several reports linked Eastern diets and cancer occurrence, especially for PCa. Of special interest is the implication of several mushrooms in the prevention of PCa in Asia.

We evaluate the ability of mushroom substances extracted from our collection of mushroom strains to interfere selectively with the activity of AR, the leading molecular target implicated in the development and maintenance of hormone-refractory PCa. Data showing anti-prostate cancer activity and the ability to modulate AR and other molecular targets will be presented.