Medicinal Mushrooms: A New Source for Breast Cancer Therapeutics

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It is known that advanced breast cancers do not respond well to chemotherapy, and their gene expression arouses uncontrolled growth. Although ER-positive breast cancers respond to hormonal therapy, the treatment of ER-negative cancers is more complicated. Despite the positive results of most of the chemotherapeutic regimes, cellular adaptations have enabled tumor cells to evade many of the chemotherapeutic drugs. One of these cellular chemoresistance factors is the transcription factor nuclear factor-kappa B (NF-κB). NF-κB can be such a target in breast cancer treatment, and its removal by an inhibitor can reverse the specific antiapoptosis of cancer cells. Therefore, NF-κB was selected as the main target in the present study.

Recently, the application of low-molecular-weight compounds with fungal origin as natural therapeutics in cancer treatment has been gaining more attention. There are studies demonstrating that these biologically active fungal substances could be used as a novel pharmaceutical source in breast cancer therapy (Petrova et al., 2005). For

instance, the caffeic acid phenethyl ester (CAPE), which specifically inhibits DNA binding of NF-κB and showed some promising results in human breast cancer MCF-7 cells, is found to be produced by *Agaricus bisporus* (J.E. Lange) Imbach, *Lentinus edodes* (Berk.) Singer, and *Phellinus linteus* (Berk. et M.A. Curtis) Teng (Mattila et al., 2001; Nakamura et al., 2003). Low-molecular-weight compounds isolated from fruit bodies and spore extracts of *Ganoderma lucidum* (W.Curt.: Fr.) P. Karst. also exhibited breast cancer and, more specifically, NF-κB inhibitory activity (Sliva et al., 2002; Sliva, 2003; Jiang et al., 2004).

Following these perspectives, we started a screening program of 75 strains of 67 species, kept in the Culture Collection of the Institute of Evolution, University of Haifa (HAI), belonging to different taxonomical and ecological groups. Mycelia were grown in submerged conditions for biomass production. Three organic solvents with different polarities (ethyl alcohol, ethyl acetate, and diethyl ether) were used for dry biomass extraction in order to isolate fungal secondary metabolites. Moreover, the culture broth, left after the mycelia filtration, was also extracted with ethyl acetate in order to receive bioactive compounds produced in the media during fungal growth.

Our aim was to isolate some bioactive low-molecular-weight compounds from mycelia and culture broth in order to investigate their potential NF-κB inhibitory effect in human breast cancer. For this purpose in the present study, different types of breast cancer cell lines that express a reporter gene (luciferase) under the control of NF-κB responsive element, were examined. Using these cell lines we tested the ability of our fungal extracts to affect the reporter activity. Positive extracts were further evaluated for their effect on the expression and function of NF-κB using Western blotting.

In order to determine the chemical structure of the active substances, all extracts that show desired activity were subjected to chemical fractionation.

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