Title
Hot Tea or Hot Air? Immunomodulatory Effects of Panax Ginseng in the Prevention of Cancer

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Introduction

Panax Ginseng is a traditional Chinese medicinal herb that has occupied an esteemed position among the tonic medications since antiquity and has become quite popular among the patrons of health food stores. The term ginseng means "essence of man" because it has been touted as a revitalizing agent. Ginseng has been used for several thousands of years in the Orient as a tonic, prophylactic agent, and restorative. Other people have found that it enhances the immune system and possess anti-tumor effects. Recent studies have reported that saponin from Panax ginseng protects against myocardial and cerebral ischemic damage in different animal models (1). Some studies have confirmed its usefulness as an important drug for the adjunctive treatment of various diseases, including diabetes mellitus (2)and hypertension (3). Extensive literature also deals with the effects on the central nervous system in memory, learning, carbohydrate metabolism, and neuroendocrine function (4).

Panax ginseng is used in traditional Chinese medicine to enhance stamina and capacity to cope with fatigue and physical stress. Over the past three decades, many athletes have turned to nutritional supplements such as ginseng in hope of gaining a competitive edge without threatening their health. However, the use of ginseng as an ergogenic aid during exercise remains controversial. Indeed, most of the support finding the use of ginseng to enhance physical performance is of a testimonial nature. In fact, recent articles suggest that there is little if any marked improvement in sports performance or aerobic exercise (5).

Perhaps one of the most fascinating and potentially therapeutic effects of Panax ginseng is its ability to enhance the immune response in the body. Recent studies have investigated the effects of ginseng on the immune system in order to find new possible components that may support the treatment of infectious and immunodeficient diseases. Ginseng has been shown to slow growing tumors and inhibit the incidence of lung adenoma (6). In epidemiological studies, ginseng uptake reduces the incidence of human cancer (6). It has been suggested that ginseng may increase activity in the nonspecific resistance of an organism to combat tumor growth. This paper will evaluate the effects of ginseng on the immune system in animal studies and recent clinical evaluations. Perhaps by understanding the effects of Panax ginseng, we can study its possible effects of preventing cancer.

Immuno-mediating Effects

The landmark paper which first evaluated the effect of ginseng extract on the expression of humoral and cell mediated immune responses showed that the number of antibody forming cells, as well as the titers of circulatory antibodies, are enhanced if test animals are pretreated with ginseng extract. On the fourth day after the injection of the antigen (sheep's red blood cells) in mice, the antibody titer of the ginseng treated group was two-fold higher than that of the control group; on the tenth day, the treated group showed a four-fold higher titer. They also had data that showed elevated natural killer (NK) cell

activity in comparison to control animals. These experiments led the way in determining ginseng's immunostimulatory effects (7).

The use of polysaccharides from plants and herbs as immunostimulants has aroused great interest in recent years. Immunotherapy is currently receiving great attention as support treatment modalities in the management of cancer and AIDS patients whose immune function is compromised. The polysaccharides extracted from Panax ginseng have been investigated to determine their effects on the immune system. These polysaccharide fractions were all tested for their anticomplementary activities using human serum and antibody-sensitized sheep RBC. Complement systems play an important role in fighting against various infections and tumors. Those active polysaccharides were found to be able to stimulate the complement system possibly by enhancing the production of interferon y (INF-y) by activated T-cells. INF-y is important in immune defense against various viral infections and in the regulation of cell-mediated immune response. Interferons are secreted by an infected cell as an early, non-specific defense before specific antibodies appear. Interferons can protect uninfected cells by stimulating the production of proteins that inhibit viral replication. Furthermore, the defense is not virus-specific; interferons produced in response to one viral strain confer resistance to unrelated viruses. Thus, interferons are most effective in controlling short-term infections, such as cold and influenza. This effect of ginseng is confirmed by Scoglione et al. (11) which shows that a standardized extract of ginseng could induce a higher immune response in vaccination against influenza. In a randomized, placebo controlled, double blind investigation of 227 volunteers, the frequency of influenza or the common cold was significantly less ($p<0.001$) in volunteers who received daily oral doses of ginseng as opposed to a placebo group (11). By the eighth week, antibody titers rose to an average of 272 units in the treatment group as opposed to 171 units in the placebo group ($p<0.0001$).

At concentrations from nanomolar to low micromolar range, ginseng polysaccharides can significantly induce the production of TNF-a by mouse peritoneal macrophages (8). TNF-a has profound effects in the immune system, including tumor, cytotoxic, antiviral, and anti-parasitic activities. TNF-a also causes inflammation and endotoxic shock, which may be responsible for some possible side effects of polysaccharides. Thus, one of the hypothesized activities of ginseng extracts is that they stimulate the complement system by enhancing the production of INF-y and TNF-a .

Ginseng has also significantly enhanced natural killer cell function, which is part of the body's nonspecific defense mechanisms. The ability of ginseng to boost NK cell activity hints at its cancer preventive mechanisms. NK cells do not attack microorganisms directly, but rather destroy the body's own infected cells. The NK cells also assault and lyse aberrant cells that could form tumors. Peripheral blood mononuclear cells (PBMC) either from normal individuals or from patients with either AIDS or chronic fatigue syndrome (CFS) were treated with increased concentration of Panax ginseng extract. For each group, increased concentrations of the herb progressively increased both the antibody dependant cellular cytotoxicity and natural killer cell function (9). The presence of ginseng extract significantly enhanced NK-function by PBMC from normal controls at concentrations of greater than 10 ug/ml and cells from patients with either CFS or AIDS

at concentrations of greater than 1 ug/ml. Thus, extracts of Panax ginseng enhance cellular immune function of PBMC both from normal individuals and patients with depressed cellular immunity. NK cells have been demonstrated to lyse HIV infected cells (10). If the clinical efficacy of immune stimulation in CFS and/or HIV-infected patients were eventually demonstrated, the use of immune modulators may be an attractive therapeutic alternative.

Even in healthy individuals, ginseng has been shown to be an immunopotentiating agent. A controlled, double-blind study with standardized Panax ginseng extract against a placebo found that a randomized group of 60 healthy volunteers given ginseng showed significant increases in chemotaxis and NK activity as well as rises in phagocytosis function (12). This group also demonstrated significant ($p < 0.001$) increases in total lymphocytes (T3) and helper T4 percentages after consuming a capsule (100-mg ginseng extract) every 12 hours for eight weeks. These data show that ginseng extracts are able to stimulate an immune response in humans.

Isolated fractions of an immunomodulator from ginseng were used to test its tumor inhibitory activity. Ethanol-insoluble extracts of ginseng were first demonstrated to generate active killer T- cells through endogenously produced IL-2 (13). Peripheral blood lymphocytes derived from humans or animals can be activated by IL-2 and become highly cytotoxic against various malignant cells. IL-2 is a cytokine that signals other lymphocytes to grow and proliferate. Thus, they can increase the supply of T lymphocytes that can differentiate into cytotoxic T-cells. Because cancer cells carry distinctive non-self molecular markers, cytotoxic T-cells can target the cancer cells and lyse them. The injection of IL-2 can therefore mediate regression of selected metastatic tumors in mice and humans. Yun et al. tested whether the endogenously produced IL-2 mediated the in vivo anti-tumor activity through the activation of lymphocytes (14). Isolated IL-2 fractions that activated natural killer cells were tested in a benzo[a]pyrene (BP) induced autochthonous lung tumor model. BP is an environmental carcinogen. The incidence of lung tumor in the BP alone group was 55% at the ninth week after BP treatment and it was significantly deceased by the treatment with ginseng extract. The incidence decreased by 60% ($p<0.05$) in mice concurrently administered drinking water containing 2 mg/ml ginseng extract for 6 weeks(14). The inhibition of lung tumor incidence was dose dependent, indicating that ginseng can have specific effects that can be augmented by increasing concentrations. Furthermore, Yang (15) found that injection of ginseng partially restored the number and colony of activity in bone marrow cells, which significantly enhanced the production of interleukin-1, interleukin-3, and interleukin-6 like substances from immune cells.

Since 1978 Yun et al. have set out to investigate if ginseng can inhibit carcinogenesis. These researchers demonstrated that Panax ginseng extract has anticarcinogenic effects against pulmonary tumors induced by various chemical carcinogens. Mice injected subcutaneously with BP within 24 hours of birth and which continued to receive ginseng extracts in drinking water showed a significant decrease in incidence of lung adenoma. This report is consistent with the anticarcinogenic effects of Panax ginseng described earlier. These researchers then began a human case-control study to further determine the

effect of ginseng consumption in cancer resistance. In a recent study of almost 2,000 patients and matched controls in the Korea Cancer Center, ginseng intake resulted in a decreased risk for cancer (odds ratio= 0.5) (16). In addition, their results showed a decreased risk with rising frequency of ginseng intake. However, this study may have many confounding variables, including selection bias. Cancer requires hospitalization and it seems reasonable to expect that differential rates of hospitalization for exposed and non-exposed cases and controls can distort the odds ratio. Another confounding variable may be that diet and sexual behavior were not controlled for cancer.

Conclusion

Ginseng has been used for nearly 2,000 years for its prophylactic and anti-tumor effects. Also, as Panax ginseng sales and public use continue to grow nationally, it is important to encourage efforts to study the efficacy of ginseng in humans.

The results of the above experiments and epidemiological studies confirm that Panax ginseng has various anticarcinogenic and immunomodulatory effects. While the exact mechanism of ginseng pharmacology remains to be solved, these studies suggest that Panax ginseng contains ingredients that stimulated humoral and cell mediated immune responses. Enhanced production of interferons can help to inhibit viral replication, helping to prevent infection. Increased antibody and lymphocyte titers may be very useful in helping cancer and AIDS patients, whose immune functions are compromised. Stimulating NK can cytotoxic T-cell activity can lyse and help fight or prevent against growing tumor cells. These promising results may perhaps one day offer a powerful adjunct to immuno- and cancer therapy.

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