GINSENG AND CANCER

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Ginseng (*Panax ginseng*) is well known as a tonic herb which can improve mental and physical performance and general well-being. However, research from Korea has identified an important new use of ginseng root in relationship to cancer, most notably in the prevention of cancer. How might such a subtle herbal agent help to prevent the biggest killer in the industrialized world? At this stage of our understanding we can only speculate, but it is relevant in this context to review a recent paper which describes the beginnings of a new approach to the treatment (and prevention) of cancer.

A NEW INSIGHT INTO CANCER THERAPY

The conventional approach to cancer is based on surgery, radiation and chemotherapy. Many have questioned the value of this approach in isolation, since it regards the tumor as the “disease” in an otherwise healthy body. In alternative circles, cancer is viewed as a disease of the whole person. However, with the development of new information about the regulation of cancer cells and the discovery of the process of apoptosis (programmed cell death), many scientists and oncologists (cancer specialists) are beginning to doubt the conventional model.

This emerging viewpoint and the implications for the future research have been presented in a discussion paper published in *The Lancet*.[1] The underlying theme is that cancer is a process, not a morphological entity. In other words, the tumor is **not** the disease. The new model stresses that cancer is an aberrance in the control of cellular behaviour in an otherwise normal cell. This leads to approaches to therapy aimed at re-institution of normal regulatory processes, rather than eradication of every last cancer cell. The tumor is not considered autonomous of the host but in

dynamic disequilibrium because regulatory and metabolic control pathways, which normally regulate growth, local cell motility, invasion and metastasis (secondary tumors) are defective. This has led to the concept of differentiation therapies which aim to normalise the behaviour of the cancer cell. In this context, the word “differentiation” means that the cell changes from being malignant to being more normal following cell division (cancer cells divide often).

So radical is this new viewpoint, and so consistent with approaches to cancer embodied in natural therapies, it is worthwhile quoting sections of this paper.

“Growth, invasion and metastasis require host and tumor cells to interact... This interaction allows two therapeutic targets, cell and milieu, and suggests that assessment of tumor cell behaviour in a two-dimensional homogeneous environment is too simplistic to predict clinical outcome. A three-dimensional environment inhabited by both normal and tumor cells and their products is required. We believe that this complex system exists at the edge of chaos, and is exquisitely sensitive to initial conditions as defined by chaos theory. Trivial degrees of perturbation can contribute to either the death or cure of the patient.

The therapeutic consequences of such a system are revolutionary. In theory, the trauma of surgery resulting in a complex cascade of biological phenomena could kick-start metastatic foci by tipping them over the edge of some chaotic boundary. If so, rather than trying to cure cancer by killing off every last cell, it would make more sense to control the disease, and extend latent “disease-free” periods by enhancing or encouraging the factors which maintain that state of dynamic equilibrium where progression is self-limiting. This could be accomplished by predisposing the tumor toward differentiation, or apoptosis, or by reducing the degree of angiogenesis within the tumour, allowing natural attrition to occur among the tumor cells...”

In this radical model, trivial degrees of perturbation can contribute to the cure of the patient. In other words, a very mild therapy which changes the milieu of the cancer cell in a favourable way can lead to a functional cure, whereas more aggressive therapies may fail or be counterproductive. This model therefore provides a useful rationale for gentle natural treatments for cancer. Recent research shows that natural cancer treatments, including herbal therapy, might act by inducing differentiation, inducing apoptosis, inhibiting angiogenesis (the growth of new blood vessels which nourish the tumor) and modifying immunological regulation of the tumor cell. Such therapeutic strategies are endorsed by this new model.

RESULTS FOR GINSENG IN THE LAB

Considerable interest has been shown among researchers in the ways that ginseng might prevent or assist in the treatment of cancer. It has been implied that the tonic and adaptogenic effects of ginseng could lead to improved natural resistance against malignant tumors.[2] However, the research summarized below suggests that more specific mechanisms could also apply, some of which are consistent with the above model.

Ginseng extract, ginsenosides (its main active components) and other components in the root such as the polyacetylenic alcohols have inhibited the growth of various tumor cell lines in several test tube experiments.[3-9] Various molecular mechanisms behind this antiproliferative activity have been studied.[10-13]

One interesting property of the ginsenosides is their marked ability to induce differentiation in cancer cell cultures. This has been demonstrated for cultures of various cancer cell lines such as Morris hepatoma cells,[14] mouse melanoma cells[15] and teratocarcinoma cells.[16] This activity may involve interaction of the ginsenoside with a glucocorticoid receptor in the cell.[16]

Early animal experiments on the antitumor activity of ginseng yielded mainly inconclusive or negative results.[17] One group of scientists focussed on the activity of ginsenoside Rh_2, finding that oral doses prolonged survival of mice bearing human ovarian cancer cells,[18] and acted synergistically with the anticancer drug cisplatin.[4] Another component of ginseng root, panaxytriol (a polyacetylenic alcohol), produced significant tumour growth delays ($p<0.01$) at an injected dose of 40 mg/kg in mice transplanted with B16 melanoma cells.[19] The most positive study on ginseng extract suggests that it acts best in conjunction with other anticancer treatments. Oral administration of ginseng extract, radiation treatment and the combination of both increased the survival of intrahepatic sarcoma-180 tumour-bearing mice to 20.4%, 16.9% and 82.1% respectively. Radiation treatment destroyed both cancer and liver cells, but ginseng extract seemed to help recovery of healthy liver cells from radiation treatment and inhibited the infiltration of cancer cells.[20]

More conclusive results have been reached in anticarcinogenicity experiments where ginseng was co-administered with a known cancer-causing agent. This can be interpreted as an experimental model for prevention of chemical-induced cancer. For example prolonged administration of red ginseng extract (1 mg/mL in drinking water) to mice significantly inhibited the incidence and proliferation of tumors produced by 9,10-dimethyl-1,2-benz(α)anthracene (DMBA), urethane and aflatoxin B1, but not N-2-fluorenylacetamide (FAA) and tobacco smoke condensate.[21] The same authors found that red ginseng had more activity that white ginseng (although both have good cancer-preventing activity) and that activity increased with the age of the root.[21] Ginseng prevented cancer caused by benzo(α)pyrene,[21] and may do so by altering its metabolism.[22]

Some ginsenosides appear to inhibit metastasis. Injection of ginsenoside Rg_3 in rats significantly decreased the incidence of cancer metastases induced by the chemicals azoxymethane and bombesin,[23] and in other *in vivo* (animal) models.[24] Ginsenoside Rg_3 was also found to be a potent inhibitor of invasion by various tumor cell lines when tested in a cell monolayer invasion model.[24] However, other ginsenosides were inactive in this model.[24] Ginsenoside Rb_2 inhibited tumor angiogenesis and metastasis produced by melanoma cells in mice. Intravenous administration of ginsenoside Rb_2 after tumor inoculation achieved a remarkable reduction in the number of blood vessels oriented towards the tumor mass, but did not cause a significant inhibition of tumor growth. In contrast, intra-tumoral or oral administration caused a marked inhibition of both new blood vessel growth and tumor growth.[25]

As alluded to above, ginseng extract or its components can potentiate the activity of cytotoxic drugs. This has additionally been demonstrated for the drug mitomycin C in both *in vitro*[26] and *in vivo* experiments.[27] The *in vivo* results suggest that this effect happens without an increase in toxicity to the host.[28]

Ginseng may also prevent cancer through effects on the immune system. The effects of long-term oral administration of ginseng extract (30 and 150 mg/kg per day) on levels of immunoglobulin types were studied in mice. Serum levels of gamma-globulin fell dose-dependently ($p<0.05$) after ginseng. Among the immunoglobulin isotypes, only serum IgG_1 was decreased ($p<0.05$). The authors suggested that since IgG_1 is rarely involved in killing cancer cells, and can act as a blocking antibody, this effect of ginseng may be beneficial for the prevention and inhibition of cancer.[29] Experiments have also shown that the anticarcinogenic activity of ginseng may be related to the augmentation of natural killer cell activity.[30]

The above studies suggest that ginseng might particularly act to prevent cancer, and this is supported by epidemiological studies (studies of disease in human populations) from Korea.

GINSENG AND CANCER PREVENTION IN HUMAN POPULATIONS

South Korea is in a unique position. As the socioeconomic status of Korea began to improve about 15 to 20 years ago, and Koreans began to prefer their traditional herbal teas, many Koreans started to drink ginseng tea. Nowadays in Korea, ginseng tea is served as often as coffee and the use of other forms of this herb are equally as widespread. This provides an opportunity to observe the effects of the large-scale consumption of what is a powerful medicinal plant.

A group of Korean clinicians and epidemiologists have taken advantage of this opportunity. In their first study, they found an inverse association between ginseng intake and cancer incidence.[31] The scientists have now extended this initial study to a case-controlled study on 1987 pairs.[32]

The cancer sites studied were all primary tumors classified according to WHO guidelines. All cases were confirmed by cytological and/or histopathological examination and were admitted to the Korea Cancer Centre Hospital. Controls were selected from a pool of patients diagnosed as having other diseases. Each cancer case was matched with one control, based on year of birth, sex and admission date. The types of diseases in controls were mainly acute diseases.

Cases and controls were interviewed personally by trained interviewers who were unaware of the category of their interviewees. Standard questionnaires were checked for consistency, completeness and accuracy. To evaluate the accuracy of the answers, 10% of subjects were reinterviewed one year later. Agreement between these and the initial interviews was found to be excellent. Corrections for

confounding factors such as age, sex, education, marital status, smoking and alcohol consumption were performed during the statistical analysis of results.

Overall, the relative risk of cancer for ginseng users was 50% lower than for ginseng non-users. Concerning the type of ginseng, the relative risk of cancer was 37% for fresh ginseng extract users, 57% for white ginseng extract users, 30% for white ginseng powder users and a remarkable 20% for red ginseng users. However, users of fresh ginseng slice, fresh ginseng juice and white ginseng tea showed no reduction in cancer risk. (Red ginseng is the same plant as white ginseng. The root is steamed before drying which gives it a red colour.)

There was a decrease in risk with rising frequency and duration of ginseng intake, showing a clear dose-response relationship. Not all cancers were affected by ginseng. For cancers of the female breast, cervix, bladder and thyroid gland there was no association (positive or negative) with ginseng intake.

Smokers particularly benefitted from ginseng intake, with incidences of cancers of the lung, lip, oral cavity and pharynx substantially lower in smokers who were ginseng users compared to smokers who were not. There was no significant difference in cancer risk between those who began to use ginseng between the ages of 30 to 39 and after age 60. In both groups the preventative effect appeared one year after the first ginseng intake and increased with duration of consumption.

The authors concede that the greatest weakness of their study was the inability to adjust for diet for cancers of the digestive organs and sexual behaviour for reproductive cancers.

The same authors conducted a cohort study in a ginseng-growing area of Korea on 4634 adults over 40 years of age.[33] There were 79 deaths from cancer over 5 years.

Ginseng users had only a 48% chance of contracting cancer when compared to non-users.

CONCLUDING COMMENTS

American ginseng (*Panax quinquefolium*) may show similar benefits for cancer prevention, but studies are needed to confirm this. It is always important to use good quality ginseng root – in other words the main or lateral roots, not the inferior hair roots. A good, safe dose of Asian ginseng root to take on a regular basis is 1 g or its equivalent in tincture form, or 200 mg of a 5:1 standardized extract in tablet or capsule form.

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