

Subject: National Cancer Institute Study;  
\$2.9 Million Focus on Soybeans

In 1989 the National Cancer Institute funded a \$20 million, five year program aimed at examining the potential role of common foods, including soybeans, in preventing cancer. In 1990 the NCI added \$2.9 million to focus harder on soybeans.

Clinical studies have shown that a diet using soy protein lowers cholesterol below levels reached by a traditional low-fat, low cholesterol diet. In addition, soy proteins have been shown to reduce the levels of calcium excreted in the urine for those who eat soybean products. The National Cancer Institute, however, is not concerned with the cholesterol lowering levels of soybean proteins or their ability to lower the calcium loss in urine, which increases the risk in humans of osteoporosis and calcium stone formation in the urinary tract<sup>1,2,3,4</sup>. The National Cancer Institute is investigating the possibility that soybeans may contain the "magic bullet" or "bullets" that may prevent cancer as well as contribute to the effective treatment of cancers.

Research has isolated dozens of nutrients and micronutrients in soybeans that have anticancer properties. Included in these are the anticancer vitamins, minerals, fatty acids, amino acids, and more than a half dozen other micronutrients that are now recognized for their anticancer physiological effects. It is easy to understand why the NCI is interested in researching soybeans further. The latest studies have been focused on the micronutrient isoflavones, protease inhibitors, saponins, phytosterols and phytic acid compounds in soybeans.

There have been more than 200 scientific papers written in recent years on the soybean isoflavone genistine, a crystalline protein, which according to published research reverses malignant cells to normal cells<sup>5,6</sup>. A German study published in the April, 1993 *Proceedings of the National Academy of Sciences* found that genistein blocks angiogenesis, the process by which new blood vessels grow - and which is required to nourish tumors. It is believed that tumor necrosis or regression is achieved by inhibiting not only new blood vessel development that is needed to support tumor growth, but also by inhibiting the development of replacement blood vessels needed for the fragile blood vessels associated with tumors, which are constantly being broken down. By inhibiting the development of the replacement blood network the new blood vessel growth is shut down in tumors and they necrose, which means they die from lack of blood supply.

In addition to genistine, soybeans contain a number of compounds, as mentioned previously, that are thought to protect against cancer. These include phytoestrogens, of which some are structurally related to tamoxifen, a drug extracted from the Pacific yew tree, and used in the United States to treat breast cancer<sup>7,8</sup>. The United Kingdom withdrew from further studies on the use of tamoxifen when it was discovered that tamoxifen's manufacturer withheld unpublished data indicating that the drug may induce liver tumors in rats. It has also been reported that tamoxifen produces potentially carcinogenic DNA alterations, called adducts, in the livers of at least 2 types of rodents. A few studies have indicated an increased risk of thrombophlebitis,

endometrial cancer and new cancers of all kinds among women on tamoxifen<sup>9</sup>. Other data shows tamoxifen is carcinogenic, with a 60% increase in cancer in the tamoxifen treated humans<sup>10</sup>. Meanwhile, in the United States the NCI is continuing to move forward in clinical trials to use tamoxifen for the prevention of breast cancer with high risk women.

Vegetarians, who may have a lower risk of certain cancers, excrete higher levels of phytoestrogens and therefore some researchers conclude that the phytoestrogens may have a role in the reduction of a vegetarian's breast cancer risks<sup>11</sup>. These diphenolic compounds seem to affect hormone metabolism and production and cancer cell growth by many different mechanisms making them candidates for a role as cancer protective substances<sup>12</sup>.

Other research has shown that soybean phytic acid compounds may also be responsible for a reduction in breast cancer risks<sup>13</sup>. In addition, phytic acid compounds have been shown to reduce the number of pulmonary metastases in tumor bearing mice that received murine transplanted and metastatic fibrosarcoma tumors<sup>14</sup>. Since breast cancer in the United States affects one in every nine women the phytoestrogen connection is exciting to cancer researchers.

The National Institute of Cancer published the results of it's study on the anticancer properties of the soybean micronutrient isoflavones, protease inhibitors, saponins, phytosterols and phytic acid in the April, 1991 issue of the National Journal of Cancer, titled *Commentary: The Role of Soy Products in Reducing Cancer Risks*.

The NCI report concluded that genistein, one of the isoflavone micronutrient proteins found in soybeans, is a natural anticancer agent similar to tamoxifen. It was postulated by the NCI researchers that the anticancer effects of genestein was the primary factor involved in oriental women, who have soybeans in their diets on a regular basis, having breast cancer rates that are one fifth of U.S. women. They noted that when these oriental women migrated to the U.S. and ate a western diet which excludes the soybeans, these women developed breast cancer at the same elevated rates as American women.

Animal studies conducted by Drs. Stephen Barnes and Kenneth D.R. Setchell showed that rats with induced mammary tumors, who were given diets rich in soybean protein isoflavones, developed 70% fewer tumors than the group not receiving the soybean isoflavones in their diet. It was noted that the more soybean proteins that were given to the rats, the fewer the number of tumors that developed<sup>15</sup>. Other published work by Drs. G. Peterson and Barnes concluded that genistein also inhibited the growth of human prostate cancer cells<sup>16</sup>.

Dr. Barnes concluded in the NCI study that the anticarcinogenic activity of isoflavones may not be limited to tumors containing a functional steroid receptor system. Alternative mechanisms of actions may include inhibition of the activity of tyrosine protein kinases (eg, epidermal growth factor receptor tyrosine kinase) DNA topoisomerase II, and ribosomal S6 kinase, as well as induction of specific cytochrome P450s.

An additional report was published by Dr. Kenneth D.R. Setchell in February, 1993 referring to his studies on soybean proteins and breast cancer. . Dr. Setchell, noting trials of tamoxifen

therapy for women at high risk of breast cancer but with no evidence of the disease, said he believes "that a diet of soy protein may be equally effective in preventing breast cancer in this group of women."<sup>17</sup>

Drs. Ann Kennedy, David Brandon and Irvin Liener focused their NCI research on soybean protease inhibitors. They noted that protease inhibitors are unique in that they cause an irreversible suppressive effect on the carcinogenic process. They noted that the Bowman-Birk protease inhibitor (BBI) either inhibits or prevents development and metastasis of experimentally induced colon<sup>18</sup>, oral<sup>19</sup>, lung<sup>20</sup>, liver<sup>18</sup>, and esophageal cancers<sup>21</sup>. The NCI research work performed by Drs. Kennedy, Brandon and Liener used a soybean extract containing approximately 50% protease inhibitor with the remaining contents unknown. The researchers reported in the NCI report that the extract they worked with may have included isoflavones as well as other potential anticarcinogens contained in soybeans. The NCI report stated that commercial food processing destroyed 99.9% of the protease inhibitor content levels in raw soybeans in the production of infant formulas, which indicates a high degree of heat sensitivity in processing.

Dr. A. Venket Rao conducted the NCI work on saponins and phytosterols, two groups of compounds in soybeans that are believed to be anticarcinogens by many researchers. Dr. Rao presented evidence for reduction of colon cancer risk by phytosterols and saponins. Both substances are common constituents of plants, but the concentration in soybeans is particularly high<sup>22</sup>. Phytosterols are structurally similar to the animal sterol cholesterol and inhibits cholesterol absorption, which results in very little intestinal absorption of cholesterol in humans<sup>23</sup>

Dietary saponins from soybeans have been shown to enhance immunity<sup>24,25</sup>, are cytotoxic to Sarcoma 37 cells<sup>26</sup>, inhibit DNA synthesis in tumor cells<sup>27</sup>, decrease the growth of human epidermoid carcinoma cells<sup>28</sup>, and inhibit Epstein-Barr virus genome expression<sup>29</sup>

Dr. Ernst Graf researched inositol hexaphosphate (phytic acid), the last nutrient in soybeans being studied for its anticarcinogenic effects. Dr. Graf postulated that there was no apparent correlation between the consumption of high fiber foods and a reduction in colon cancer and noted that the correlation was more likely to be in the consumption of phytic acid, the anticancer agent that is found in high fiber foods<sup>30</sup>, fruits and vegetables.

Phytic acid is a natural plant antioxidant that is found in cereals, nuts, legumes, oil seeds, pollen and spores. Its antioxidant properties may function in the preservation of seeds. Its addition to foods inhibits lipid peroxidation and concomitant oxidative spoilage, such as discoloration, putrefaction, and syneresis<sup>31</sup>.

Phytic acid forms chelates with various metals and suppresses damaging iron-catalyzed redox reactions. Since colonic bacteria have been shown to produce oxygen radicals in appreciable amounts, dietary phytic acid may suppress oxidant damage to intestinal epithelium and neighboring cells. Data from animal models indicate that phytic acid may provide substantial protection against experimentally induced colonic cancer.

Outside of the NCI report, Dr. Alison M. Stephen, head of the Division of Nutrition and dietetics in the University of Saskatchewan's College of Pharmacy, has reported that dietary starch may help prevent colon cancer and may also help lower serum cholesterol. Dr. Stephen noted that much of the starch we eat is "resistant starch" and is not digested. Fermentation of this "resistant starch" and dietary fiber in the colon by resident microflora can increase fecal bulk and produce a number of byproducts, including the short chain fatty acids acetate, propionate and butyrate. Research has shown that it is through the production of propionate that soluble fiber may lower serum cholesterol. Dr. Stephen noted that recent studies show starch produces a much larger proportion of butyrate than any type of fiber ingested. She added that this may be important because butyrate is preferentially used as an energy source by the colonic mucosal cells and has been shown to have anticancer properties in a number of cell lines from different tissues<sup>31</sup>.

Starch digestion can be influenced by the physical form of the food consumed, the type of granule present, and the cooking and processing of the starch prior to consumption.

These NCI findings, and other research from around the world, linking nutrition with cancer has become so overwhelming that the National Cancer Institute has instigated a "Designer Foods Division" which is charged with researching the various known anticancer substances in food. In addition, The Office of Technology Assessment, an advisory branch of Congress, listed nutrition as one of the few credible alternative cancer approaches.

While the U.S. is moving forward in the research of "designer nutritional products", the NCI and other research is shedding light on the mechanisms by which some "folk remedies" and natural foods "heal" people. Oriental countries, particularly Japan and China have worked on soybean nutritional products for years and have performed extensive research on the anticancer properties of soybeans and other health benefits associated with various soybean products. A search of the literature indicates that many of the conclusions of the NCI study are extensions or confirmations of other research performed prior to 1989 in major soybean consuming countries, particularly Japan and China, which has caused the anticancer and other health benefits of soybean dietary nutrients to surface<sup>32</sup>.

It is significant to note that all of the NCI and other published studies on genistein, protease inhibitors, saponins, phytosterols, and phytic acid compounds have been in laboratory and/or on animal test studies. However, there is one group that has extensive experience with human consumption of concentrated soybean nutritional beverages that have patented anticancer claims. This group filed for a U.S. Patent on September 30, 1986, which predates the NCI work on soybeans by nearly five years. Although these fermented soybean products are sold as oral nutritional products, the issued United States patent does include cancer and other health claims listed in the patent application<sup>33</sup>.

Clinical studies published in earlier U.S. Research Reports, Nos. 101 and 103, evaluated several of the fermented soybean beverages manufactured by this group with the patented fermentation technology including the cancer claims. These products were researched as nutritional products for both effectiveness and physiological results. Clinical studies using these products proved to be exceptional in immune system stimulation and provided extensive health benefits without adverse

side effects. The fermented soybean beverages contain a variety of vitamins ( including vitamin B<sub>12</sub> ), minerals, 20 amino acids, essential fatty acids, and cultured soybean protein compounds.

Vegetarians should note that the manufacturers of these fermented soybean products, Haelan Products, Inc., states their factories are extremely careful in processing these fermented soybean nutritional products in order not to destroy the bacteria that produce vitamin B<sub>12</sub> in these products. Other commercial fermenting processes used to manufacture foods, such as soy-based tempeh and miso, have been shown to destroy the bacteria that would otherwise produce the vitamin B<sub>12</sub>. Two recent studies published in the American Journal of Clinical Nutrition indicate that some edible algae and sea vegetables, foods that macrobiotics and vegetarians have long considered good sources of vitamin B<sub>12</sub>, may also fail to provide this nutrient. In addition, this issue is complicated by the existence of vitamin B<sub>12</sub> analogues, the inactive forms of the vitamin that do not satisfy human nutritional needs. When these analogues are analyzed in the laboratory, even though certain algae and sea vegetables appear to be rich in vitamin B<sub>12</sub>, and the blood tests of those who eat them also appear to contain adequate quantities of the vitamin B<sub>12</sub>, the laboratory analyses cannot distinguish vitamin B<sub>12</sub> from the analogues. In order to determine if a person is suffering from a vitamin B<sub>12</sub> deficiency, researchers must assess the condition of the person's red blood cells or bone marrow. One method is to measure a person's corpuscular volume (MCV), which indicates the volume of the average red blood cells in a sample. A high MCV indicates a vitamin B<sub>12</sub> deficiency. In one of the two Journal studies a group of researchers from the Netherlands found that when children suffering from vitamin B<sub>12</sub> ate the sea vegetable nori or edible algae, their blood plasma B<sub>12</sub> levels increased but their MCV continued to increase. Previous studies had shown that when children with a vitamin B<sub>12</sub> deficiency were given a daily supplement of as little as 0.1 microgram of vitamin B<sub>12</sub> supplement their bone marrow returned to normal after one month. However those children in this study were given 27 times this amount of vitamin B<sub>12</sub> daily from sea vegetables for four to six consecutive months and they showed no improvement. The second Journal study assessed the diet of a macrobiotic community. Researchers found that those who ate tempeh, miso or sea vegetables (including wakame and kombu which have been considered to be highest in vitamin B<sub>12</sub>) showed evidence of vitamin B<sub>12</sub> deficiency. The conclusion of the study was that sea vegetables should not be recommended as a source of vitamin B<sub>12</sub><sup>35</sup>. In conclusion of the vitamin B<sub>12</sub> subject, the manufacturers of Haelan products are aware of vitamin B<sub>12</sub> analogues and control conditions to produce vitamin B<sub>12</sub> in their products that is usable for human nutrition needs.

A comprehensive study of the issued U.S. Patent and the nutritional clinical studies published in U.S. Research Reports Nos. 101 and 103, clearly indicate that the health benefits associated with the use of these biologically produced soybean products are far greater than would be expected from a diet of soybeans, tofu, soy milk, tempeh, etc., or any combination of them cooked by a world class chef. These are internationally award winning nutritional products that have been improved for more than 10 years with the help of hospitals, physicians, medical schools, nutritionists, and medical researchers. Low temperature cooking, special processing, and a patented fermentation process combined with the use of selected species of soybeans, organically grown with ideal growth and soil mineral content, are all reported to be key manufacturing elements required to enhance and protect the micronutrients in the end products. The manufacturer also reports that the nutritional content of soybeans varies as much as 50%

depending on the age of the plants and in addition changes with the age of the beans, therefore all of their beans are hand picked at the right time to insure maximum nutritional content in their products.

In addition, assimilation and physiological effects resulting from the use any dietary nutrients must be considered to evaluate the body's efficiency and ability to use those nutrients. The patent and clinical studies indicate a high degree of perfection in processing, with specialized equipment, that could not be duplicated in the best of restaurants or home kitchens. The manufacturer reports that it requires more than 25 pounds of cultured soybeans to produce one eight fluid ounce bottle of the most concentrated fermented soybean beverage they produce. which is their Platinum Formula product.

An examination of the nutrients contained in these fermented soybean products reveals that more than 25 individual nutrients have anticancer properties in and of their own merit<sup>36</sup>. Adequate literature has been published regarding nutrition and cancer, including U.S. Research Report No. 100, which deals with Adjuvant (helpful) nutrition for cancer patients.

There is little public awareness in the United States of the health benefits associated with the fermented soybean products that are reported on herein. This is apparently because the manufacturer, Haelan Products, Inc., sells their products in the United States as a nutritional product and therefore does not make any claims concerning the product. However, in Mexico and other foreign countries, where medical claims are allowed for nutritional products, various health claims are made for these products. It is obvious from a study of the research and published data that many of the benefits attributable to these fermented soybean products are directly related to the soybean nutrients genistein, daidzein, protease inhibitors, saponins, phytosterols, phytic acid and other soybean compounds that are the subject of the NCI soybean anticancer nutrient research program.

The patent claims and clinical studies using Haelan 851 oral nutritional products clearly demonstrate not only superiority<sup>32, 33, 36</sup> to other oral nutritional products in immune system stimulation and antiaging physiological effects but, in addition demonstrate a synergistic effect from combining biological principles, organic production, sophisticated handling, genetically selected, and prepared raw materials. The results are highly anticancer super nutritious oral beverages that produce extensive beneficial physiological improvements in humans without adverse side effects.

Clinical studies detailing these physiological benefits were reported, in whole, by Research Reports, Inc. previously but references to them are included herein because they give insight into human use of products that contain high concentrations of the micronutrients currently being studied by the NCI for their anticancer activity.

A clinical study of cancer patients receiving Haelan 851 nutritional supplementation, while receiving chemotherapy and/or radiation therapy has demonstrated the product's ability to improve immune system functions in spite of the chemotherapy and/or radiation treatments administered to the patients. Reports indicate that higher dosage levels, including record levels,

of chemotherapy may be administered to patients who are nutritionally supplemented with the Haelan 851 , Platinum Formula oral nutritional beverage when it is consumed at the rate of one eight fluid ounce bottle per day.

Medical reports from China, and other areas, indicate higher patient recovery and cure rates for cancer patients when surgery, radiation and chemotherapy are combined with nutritional support using the Haelan 851 soybean based Platinum Formula product. Clinical studies indicate the product is well suited for hospital use as an oral dietary supplement for cancer and other malnourished hospital patients, including children<sup>37</sup>. Reports also indicate significant results, with inoperable cancers as well as cases where tumors were resistant to chemotherapy drugs.

Although more than 25 anticancer nutrients have been identified in the Haelan 851 Platinum formula oral liquid, literature indicates that the soybean protein genistein produced some, if not all of the anticancer properties and results listed in the patent application claims for the products produced with the fermentation process. This is based on the fact that one of the claims in the U.S. Patent stated that the product killed human stomach cancer. In March, 1993, Japanese researchers published the results of their study on the soybean derived protein genistein in the journal *Cancer Research*. This research report stated that "Genistein inhibited in a dose-dependent manner the growth of HGC-27 cells derived from human gastric cancer"<sup>38</sup>, which ties in directly with the 1986 patent claim made for the Haelan 851 first generation products<sup>32</sup>.

Efficient assimilation by the body of the nutrients in the Haelan 851 oral nutritional products is demonstrated by the fact that patented claims for the product demonstrate protein blood serum levels were increased significantly (approximately 8.5%) with this Enteral (oral) product. This ability to promote serum (blood) protein synthesis and improve protein nutrition in protein deficient conditions in the body is extremely beneficial to cancer patients, since most of them suffer from protein malnutrition. These results are exceptional for an oral product and fares extremely well in terms of cost effectiveness and nutritional profiles results when compared to Total Parenteral Nutrition (TPN), which is the intravenous nutrition a hospital Metabolic Support Team of physician, nurse, dietitian and pharmacist provide to a patients when they cannot eat foods orally. TPN nutrition for hospital patients normally increases blood serum protein levels between 8.5% and 11% and cost approximately \$600 per day in U.S. hospitals.

After an examination of the Mexican literature for the Haelan 851 fermented soybean beverages, U.S. Patent #4,877,739, clinical studies using these products, and several other medical reports published concerning the physiological responses to the soybean protein micronutrients genestein, and the other nutrients that are contained in the Haelan 851 nutritional products, we have confirmed that the various health benefits associated with this product are remarkable, extensive and without adverse side effects. For those interested in the nutritional benefits of these products with young children, U.S. Research Report No. 102 deals with malnourished youth. Research Report No. 102 reported the results of a clinical study using the Haelan 851 fermented soybean nutritional oral beverage with malnourished children ranging in age from 6 months to 11 years old. This study involved 101 cases of child malnutrition.

### SUMMARY

The biological response modifications brought about by the micronutrient isoflavones, protease inhibitors, saponins, phytosterols, phytic acid compounds and other non-nutritive dietary compounds studied in this literature have demonstrated the ability to play a major role in the recovery, cure and treatment of patients with cancer and other immune and auto-immune system diseases. Most textbook literature has placed emphasis on nutritional items with little regard to the role of micronutrients and non-nutritional components of food and their physiological roles. Existing epidemiological studies focusing on fruits and vegetables cannot yield information on starch and the fermentation products produced in the digestive system that produce beneficial health results, particularly in the area of colon cancer treatment and its prevention. We should expect new evidence to unfold that would indicate starch is something we should be eating. Further, it should be obvious from the literature presented herein that vegetable proteins, as compared to animal proteins, may play a major role in the health advantages vegetarians have enjoyed for years.

Nutritional products containing the micronutrients genistein, daidzein, protease inhibitors, saponins, phytosterols, phytic acid and other compounds studied in this literature have already played a major role in the treatment, recovery and cure of patients with widespread diseases of the body, of which many are a direct result of malnutrition, or indirectly through immune system impairment as a result of malnutrition. Malnutrition in many of these cases include the lack of micronutrients that are lacking in the diet but have not been recognized as being important but in reality may be necessary for the maintenance of optimum immune system and organ functioning, particularly over a long term.

While the NCI study focused on the anticancer properties of several micronutrients in soybeans, the "designer cocktail" produced Haelan 851 concentrated nutritional products have focused on a wholesome nutritional product with the anticancer micronutrients being part of a nutritional product that provides the following protective mechanisms as a food source:

1. Increase the body's production of toxin scavengers, like GSH
2. Improve the immune system
3. Stimulating certain detoxifying enzyme systems
4. Shutting down the oncogene in one's cells that promote cancer growth
5. Directly killing tumor cells (e.g. anticancer agents)
6. Directly killing viruses that may cause cancer and other health problems
7. By binding up substances like bile acids that can decay into a carcinogenic substance
8. By chelating heavy metals and carrying them out of the body
9. By attaching to fats to stop the carcinogenic fat oxidation process
10. By providing the known essential and unknown important nutrients that the body needs to better defend itself against pollutants

While the NCI study was on specific identified soybean anticancer agents, none of them were isolated and given to humans as a single dietary nutrient in high concentrations to establish safe limits for human consumption. Some of the NCI researchers used soybean proteins that were

thought to contain more than one anticancer agent contained within soybeans, and therefore some of the results credited to one nutrient may have been a result of several anticancer nutrients.

Haelan 851 concentrated nutritional soybean products are the closest in concept to being a "designer cocktail" having concentrations of the anticancer agents that are found within soybeans, as well as other important dietary nutrients. These products are hospital proven, in China, with extensive clinical studies and proven results. The fermentation process, low temperature preparation and selection of the hand picked soybeans used to manufacture these biological products indicate extensive research into the effective use of soybean micronutrients and other dietary nutrients as biological response modifiers for both the prevention and treatment of chronic disease.

In summary, the inclusion of the dietary foods or nutritional supplements that contain the micronutrients genistein, daidzein, protease inhibitors, saponins, phytosterols, phytic acid and other compounds studied in this report may be important, if not necessary, to maintain long term optimum health. Several nutritional beverages containing high concentrations of these micronutrients have been clinically tested and shown to produce superior nutritional profiles for those who use these dietary foods. Other soybean products have not produced the biological responses which are attributed to selection of soybean species, soil and growth conditions, the age of the soybeans used in the products, processing and other conditions that influence the quality of the end products. All soybean products do not provide the same quantity, quality, or combination of dietary nutrients and micronutrients studied in the NCI report. Therefore, the health benefits, biological responses, nutritional profiles, and selling price of soybean products should be expected to vary greatly. This appears to be a situation where the selling price is an indication of quality and greater benefits should be expected from the more expensive soybean based products.

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