Reprinted from

WELL BEING JOURNAL

VOL. 11, NO. 6 NOVEMBER / DECEMBER 2002

HERALDING THE INTEGRATION OF NATURAL MEDICINE WITH THE ART AND SCIENCE OF MODERN MEDICINE

Fermented Soy

An Aid to Cancer Prevention & Therapy

By Vijaya Nair, M.D., M.S. and Vic Hernandez, M.P.H.

Fermentation is the oldest known form of food biotechnology; records of barley conversion to beer date back more than 5000 years. The traditional fermentation process serves several functions, including the enrichment of food substrates biologically with protein, essential amino acids, essential fatty acids, vitamins, polyamines, carbohydrates, and numerous anti-oxidants and phytosterols [1]. The fermentation process, for example, with lactobacilli, increases the quantity, availability, digestibility, and assimilation of nutrients in the body [2].

It is being increasingly recognized, for example, that soy and soy protein isolates have potentially anti-nutritive value due to their high phyate and oxalic acid levels, cultured soy products such as miso, natto, and tempeh have enhanced nutritive bioavailability without the possible ill effects of the uncultured soy supplements [1,3]. Uncultured soy with its high phytate levels has been shown in a number of studies to block absorption of vital nutrients such as calcium [4]. The use of soy as a culturing medium is also advantageous because iron is naturally available in soy [3]. Iron in an elemental form is potentially toxic and pro-oxidative, but a lack of iron in the body potentiates development of anaemia and can thus be lethal [4]. Culturing soy has been shown to enhance the bioavailability of iron and copper and hence rendering the deliver of these nutrients in their most advantageous forms [5,6].

The Western diet has undue emphasis on the consumption of "smart" products that are processed or genetically altered

The World Health Organization reported in 2000 [7] that the Japanese, with their extensive consumption of cultured soy products, such as miso, natto together with accompanying foods like ginger, ocean herbs and green tea, have the longest "healthiest life expectancy" of any other people on Earth. Americans, on the other hand, do not even appear on the top 20 of the list for healthy life expectancy. The Western diet has undue emphasis on the consumption of "smart" products that are processed or genetically altered. Unfortunately, the abandonment by consumers in developing countries of their more traditional fermented foods in exchange for the "sophisticated" Western dietary products could have serious con-

sequences. For example, the replacement of indigenous fermented cereal drinks with cola beverages that have empty calories, could have a serious negative impact on the daily nutrition of many of these consumers in developing countries when the extensive medical benefits of consuming the traditional sources of probiotic whole-food nutrition is lost [1,3].

Soy has been a staple of the Southeast Asian diet for nearly five millennia and both its medicinal and nutritional values are deeply rooted in Traditional Chinese Medicine and herbalism [8,9]. On the other hand, consumption of soy in the United States and Western Europe has been limited to the 20th century. Asians on the average eat twenty to fifty times more soy than Americans [10,11].

Typically soy foods are divided into two categories: non-fermented and fermented soy products. Traditional nonfermented soy foods include fresh green soybeans, whole dry soybeans, soy nuts, soy sprouts, whole-fat soy flour, soymilk and soymilk products, tofu, okara and yuba. Traditional fermented soy foods include tempeh, miso, soy sauces, natto and fermented tofu and soymilk products [12]. In Asia, the traditional fermented soy foods are considered to have more health promoting benefits when consumed in moderate amounts than the super-processed soy products that are consumed in the West [9,10]. It has been suggested that the fermentation process increases the availability of isoflavones in soy [12,13]. For example, a study [14] of the culturing method involved in the production of the Japanese traditional food miso, came to the conclusion that the culturing process itself led to a "lower number of cancers per animal" and a "lower growth rate of cancer compared to controls." The researchers also indicated that it was not the presence of any specific nutrient that was cultured along with the soyabean paste but rather the cultured soy medium itself that was responsible for the health benefits associated with miso consumption. Miso, a fermented or probiotic form of soyabean, is particularly rich in the isoflavone aglycones, genistein and daizein, which are believed to be cancer chemopreventatives [15]. Their fermentation process is thought to convert the isoflavone precursors genistin and daidzin to their active anti-cancer isoflavone forms, genistein and daidzein [16].

The cultured soy medium had produced its own unique anti-carcinogenic activity by strongly inhibiting formation of cellular mutations

It is unfortunate that in the United States, health-conscious consumers, especially women concerned about developing breast cancer are urged by media and is traditionally consumed in Japan [3]. The overwhelming majority of soy consumed in Asian countries such as Japan, China, Korea and Indonesia is in its cultured or probiotic form enhanced with genistein and daidzein [3]. Japanese researchers found that the cultured broth of *Saccharomyces cerevisiae* or Brewer's Yeast, produces both invivo and in vitro experiments, bio-antimutagenic and anticlastogenic activity with mutagen formation reduced by 47% just by the administration of the cultured broth. The cultured soy medium had thus produces its own unique anti-carcinogenic activity by strongly inhibiting formation of cellular mutations [15].

A recent Korean study concluded that tofu was one of the foods that decreased the rates of certain cancers such as stomach cancer while heavy salt consumption and cooking methods increased the rates [17]. The limited epidemiological evidence so far from these cultures with diets high in fermented soy products indicates that such diets may reduce the risk of breast, colon, lung and stomach cancers, as well as offer some protection from cardiovascular diseases, osteoporosis and menopausal symptoms [17,18,19,20,21,22,23].

But the clinical data to date is often flawed with poor design and other methodological issues and the role of isoflavone in chemoprevention especially in the hormonally dependent cancers such as breast and prostate cancers while promising is still lacking unequivocal evidence [24].

The controversy over the role of soy in preventing and treating chronic illnesses such as cancer was recently addressed at the 4th International Symposium held in San Diego in November 2001 [25]. To date, there has been a paucity of literature regarding soy, particularly the use of fermented soy products in clinical trials. Part of the reason may be the costly technology required in the processing and manufacturing of these fermented soy products and supplements for large-scale use. Studies have been done to determine if the phytoestrogen content of these products are affected by processing or whether there are chemical modifications of the isoflavonoids due to the conditions present during the processing [26,27,28]. Traditional sources of fermented soy foods that are not prepared under the astringent standards lack the full benefits. Tempeh production, for example, requires a fermentation process utilizing whole soybeans but there have been few clinical reports on the effects of its chemically modified isoflavonoids [27,28,29].

Some studies [11,28,29,30] have suggested that the isoflavone genistein may have some role as a chemopreventive agent against cancer in humans. Levels of genistein and its beta-glucoside conjugate, genistin, ingested in soybeans and related bean products by the Japanese were quantified by HPLC, to estimate daily intake of these compounds. A Japanese study [28] found that the level of genistein in the fermented soybean products was higher than in soybeans and soybean products such as soymilk and tofu. This and other studies have postulated that the beta-glycosyl bond of genistin is cleaved to produce genistein by microbes during fermentation to yield miso and natto. Soy sauce was also found to contain both isoflavones, but at levels lower than in miso and natto. On the basis of these data for average annual consumption of soybeans and related products, 6.3-8.3 mg/person, respectively. These levels are much higher than those for Americans or Western Europeans, whose mortality rates for breast, colon and prostate cancers are greater than the Japanese [28,31,32,33].

One underlying theoretical paradigm is that primary active ingredients in complex fermented soy "foods" act synergistically with secondary compounds. A second paradigm is that secondary compounds mitigate the undesirable side effects caused by the predominant active ingredients. Another possibility is that the multiple ingredients act through multiple discrete pathways to therapeutically affect the host, and that lower concentrations of each of the botanicals or soy phytochemicals can therefore be more efficacious when used together then when used individually [34,35]. Studies can also compare complexes versus single agents. The benefits of using these complex fermented soy "foods" have historically been based on empirical observation. These concepts help determine which combinations are truly likely to be efficacious.

It seems likely that the culturing in and of itself creates nutrients that are of extraordinary value in promoting health

We may never really understand precisely how probiotics help enhance our health and well being but the four main probiotic factors that play an important role include: bacteriocins, phospholipids, beta-glucans and glutathione [14,16,36,37,38,39,40,41]. The literature suggests several situations in which viability is not required for some activities [40,41,42]. Improved digestion of lactose, for example, in yogurt, fermented soy and other fermented drinks, for example, that deliver live active

culture, some immune system modulation and anti-hypertensive effects have been linked to nonviable cells such as cell components, enzyme activities or fermentation products [3,35,38,41,44,45,46,47]. It seems likely that the culturing in and of itself, apart from any vitamin or mineral enhancement, apart even from the presence of like active culture in the food, creates nutrients that are of extraordinary value in promoting health.

CHEMICAL COMPOSITION AND POSSIBLE MECHANISM OF ACTION OF HAELAN951: A NOVEL FERMENTED SOY BEVERAGE

There have been a few clinical trials [36,48,49,50,51,52], but no long term prospective clinical studies done on the effectiveness of the fermented soy phytochemical nutrient, Haelan951 as an adjuvant treatment for advanced cancer.

Haelan951, is a fermented soy supplement made by Haelan951 Products Inc. based in Seattle, USA. Manufacturing, which includes plant cultivation and processing of the soybeans are done in the People's Republic of China. The patented [53] fermentation process involved in the manufacture of Haelan951 hydrolyzes many of the soybean proteins into amino acids and compounds that are rich in nitrogen, polysaccharides, and saponins, phytosterols and inositol hexphosphate compounds in soybeans. The unique process uses the autogenic antiammonia azotobacter mutant strain, induced from *Azotobacter vinelandii* as inoculum in an industrial fermentation. They are specific bacterial strains belonging to the species *Stenotrophomonas maltophilia* Q-can. The soy beverage is a concentrated nutritional supplement that is rich in soybean proteins, selenium, zinc, beta-carotene (vitamin A), riboflavin (vitamin B1), thiamine (vitamin B2), cyanocobalamin (vitamin B12), ascorbate (vitamin C), cholecalciferol (vitamin D3), alpha tocopherol (vitamin E), and phylloquinone (vitamin K1). It also contains additional micronutrients such as daidzein, genistein, protease inhibitors, saponins, phytosterols, and inositol hexphosphate, and essential fatty acids such as linolenic and linolic acids, polysaccharide peptide, and twenty of the twenty-two amino acids including ornithine [54]. It takes over 25 pounds of soybeans to make one concentrated eight ounce bottle of the Haelan951 beverage. Of these naturally occurring nutritional items in the Haelan951 formula, more than 20 of them are known individually for their ability to enhance the nutritional profiles of individuals with cancers [3,35,53,54].

Over the last 16 years there has been a number of investigations done to examine the active components in the fermented soy solution that play a major role in killing the carcinogenic cells. There have been a few pilot studies that have reported on the anti-oxidant properties of soy isoflavones, especially genistein. It is postulated that the soy supplementation decreases levels of oxidative DNA damage in humans and that this may be one of the mechanisms behind the anti-carcinogenic effects of soy isoflavones [55,56,57].

It is postulated that the soy supplementation decreases levels of oxidative DNA damage in humans

Some of the clinical trials done so far have indicated that although some of the soy isoflavones such as daidzein, genestein and saponins may have contributed to the anti-carcinogenic activities of the fermented soy beverage, there are also studies that have isolated branched chain fatty acids called small biosynthetic anticancer agents (SBAs) from Haelan, that have significant tumor-inhibition effects [36]. The structural and biochemical analysis has shown that SBAs represent a group of terminally branched-chain saturated fatty acids (C 15-21) and have isolated the active anti-carcinogenic ingredient as largely

being contributed by 13-methyltetradecanoic acid and 12-methyltetradecanoic acid. Further research on these compounds have indicated that the mechanism of action of these specific branched-chain fatty acids are associated with the induction of 13-methyltetradecanoic acid daily up to 800 mg/kg to mice did not reach the LD50 level (50% lethal dose).

EPIDEMIOLOGICAL STUDIES ON PROSTATE CANCER AND SOY NUTRIENT STUDIES

Prostate cancer is the most common type of non-skin cancer found in American men [61]. Although men of any age can get prostate cancer, it is found most often in men over 50. In fact, more than 8 out of ten of the men with prostate cancer are over the age of 65 [62,63]. The American Cancer Society estimated that in the year 2002 there will be about 180,400 new cases of prostate cancer in the United States and about 31,900 men will die of this disease [61]. The evidence does suggest that prostate cancer develops as a result of both inherited and environmental factors [62,63]. Race-ethnicity is one of the more will studied risk factors [64,65] African-American men, for example, have one of the highest rates of prostate cancer in the world as compared to native Japanese and Chinese men who have the lowest rates [64]. Chinese and Japanese immigrants to the United States have an increased risk and mortality from prostate cancer when compared with men who remain in the native country [66,67,68,69]. The incidence of prostate cancer among Japanese men in Japan has also been noted to be on the rise as the traditional Japanese diets and life-styles have been replaced by Western diets and life-styles [31,32,63]. By and large a number of epidemiological studies have shown that Western type of diets may be a strong environmental risk factor in the development of prostate cancer [33,70,71,72,73,74,75,76,77,78].

Soy isoflavones have also been shown to increase prostate cancer latency and decrease the development of clinically significant prostate cancer

Latent or clinically insignificant prostate cancer occurs in large but equal rates in autopsy studies among men in Asian countries and the United States but the rate of clinically significant prostate cancer is 80 fold higher in the United States [63,79,80]. Prostate cancer mortality is very low in Asian countries where soy foods are consumed [8,9,10,11,81]. Soy isoflavones have also been shown to increase prostate cancer latency and decrease the development of clinically significant prostate cancer [19].

One of the problems facing prostate cancer patients is the uncertainty of many issues surrounding the detection, diagnosis and management of the disease [82,83,84,85,86]. About 80 percent of men diagnosed with prostate cancer have early stage disease [63]. Decisions about treatments are not easy to make. One problem is that it is difficult for a physician to predict whether a tumor will grow slowly with no health consequences to the patient, or will grow quickly and become life threatening. Also, there are no definitive clinical studies that compare the relative benefits of treating early stage patients with radiation therapy, radical prostatectomy (surgical removal of the entire prostate gland along with nearby tissues), or watchful waiting (following the patient closely and postponing aggressive therapy unless the symptoms of the disease progress) [86,87,88,89,90,91,92].

The prognosis for prostate cancer is good only if the disease is localized with a 5-year survival rate of 78% in the US. Once the disease has spread, survival rates are much lower ranging from 68% to 23% depending on the clinical stage at diagnosis [61].

PREVIOUS IN VITRO AND IN VIVO PROSTATE STUDIES DONE WITH HAELAN

Animal studies [36,93] using athymic BALB/c nude mice between 4 and 5 weeks old were conducted at the University of Southern California. The researchers isolated one of the active anti-carcinogenic agents (SBA or small biologically active agent, found in the fermented Haelan851 formula (an earlier version of Haelan951 formula). The compound SBA was shown to reduce prostate cancer cell size, cell growth and reduce the formation of blood vessels in prostate cancer tissue was seen in all the Haelan treated groups at varying dosages of the titrated beverage. The results were statistically significant when compared to the control groups for the treated groups at doses of 35 mg/kg ($p=0.042$), 70 mg/kg ($p=0.007$) and 105 mg/kg ($p=0.022$). All treated groups had a tumor inhibitory rate of more than 50%, indicating that SBAs had strong antitumor effects. There was no evidence of toxicity.

A pilot study [94] was done in 1998 on an earlier version of the fermented formula, Haelan 851 (Soy Extract Q-can) with patients diagnosed to have varying stages of prostate cancer by a group of oncologists at the Prostate Cancer Research and Education Foundation (California). The sample size for the initial pilot study was small with only 12 evaluable patients who were diagnosed to have history of recurrent prostate cancer, clinically staged at being T1c-T2c and rising PSA levels. The mean age of the subjects was 68 years. This yet unpublished report found that half of the 12 patients in the study were reported to have responded to the fermented soy beverage as reflected by a decline in the PSA velocity when compared to the measured values prior to the soy nutritional treatment.

The compound SBA was shown to reduce prostate cancer cell size and cell growth and reduce the formation of blood vessels in prostate tumors

CASE REPORTS

Case report #1

This is a 73-year-old gentleman Mr. GJ, who presented 7 years ago with a history of an elevated PSA of 5.0. He was referred to M.D. Anderson for evaluation. There was a family history of prostate cancer. The patient's brother had died of the disease in 1982. A transrectal ultrasound revealed a hypoechoic lesion and he had a directed biopsy of that area. Additionally he also had sextant biopsies of the prostate. The pathology report confirmed adenocarcinoma, M.D. Anderson Grade II and a Gleason score of 7 in the left apex, a M.D. Anderson Grade III/Gleason score 8 in the left mid and a focus of adenocarcinoma of the left base. There was also a high grade PIN in the right apex. On digital examination he was found to be a Stage T2b.

Mr. GJ was originally then scheduled to have a radical prostatectomy but at the time of surgery he was found to have lymph node infiltration as well as cancer of the lower rectal region. Instead bilateral orchiectomies and bilateral lymph node resection were performed and the prostate gland left intact. Biopsies 3 weeks later confirmed the presence of moderately differentiated invasive adenocarcinoma of the rectum and metastatic adenocarcinoma of the left and right pelvic lymph nodes that was consistent with the primary prostate tumor. Subsequent follow up staging with colonoscopy. CT scan confirmed a lower rectal tumor and adenopathy within his pelvis on CT scans.

Initially, Mr. GJ's oncology team recommended a regime of preoperative adjuvant therapy with chemotherapy and radiation therapy for his rectal tumor followed by surgical resection of his prostate and rectal tumor with follow up of adjuvant systemic chemotherapy. He was started on a 8-week course of chemo-radiation 45Gy and 5

FU and folinic acid and a transanal excision of the tumor site. The biopsy of the anal site came back as showing no evidence of neoplasia. He had protoscopic and colonoscopic examination done after 2 weeks with no evidence of any malignant lesions and a normal anal wall. He was also started on Casodex for his prostate.

Mr. GJ took Haelan951 in the peri-operative period together with the chemo-radiation therapy. He took the recommended dose of the beverage at 8 ounces a day for 2 weeks initially before the transanal excision surgery. When the biopsies, CT scans and colonoscopy examinations came back as being negative he cut down the Haelan951 dosage to 4 ounces a day for a month and then 3 ounces and is now maintained on 2 ounces a day for the past 5 years. He was not on any other herbal supplements during this period.

During the follow up period he denied any urinary or bowel symptoms or pelvic or sciatic pain. He subsequently went back to the clinic for every few month for monitoring of his PSA levels, repeat CEA and CT scan to assess for change in adenopathy. His blood tests for the past 5 years following his diagnosis of prostate and rectal tumor with secondary lymph node infiltration have been normal with a CEA of less than 1 and PSA levels less than 0.1. Subsequent repeat colonoscopic examination and CT scans of the abdomen and pelvis for the past year has not revealed any evidence of metastatic disease.

Case report #2

Mr. SL is a 58 year old African American who presented 3 years ago with a gradual rise in his PSA levels. When he saw his primary care physician in September 1999, his PSA was 2.9 ng/ml (normal < 4.0). Clinically he had complaints of frequency of micturition at night for the preceding one week. Pre rectal examination revealed a suspicious nodule in the prostate gland. A biopsy was taken and came back as being positive for infiltrating adenocarcinoma with a Gleason score 6. The report also indicated the presence of benign prostatic hyperplasia and focal chronic prostatitis.

Mr. SL started on Haelan951 2 weeks after his diagnosis of prostate cancer. His urologist strongly recommended a radical perineal prostatectomy. He was also given an option for brachytherapy. The patient refused both options and instead opted to continue with Haelan951 and herbal supplements. Mr. SL initially started with 8 ounces of Haelan in 2 divided doses per day for a period of 3 to 4 months and then tapered to 4 ounces a day in 2 divided doses per day for a duration of a year. He is presently on a maintenance dose of 2 ounces a day. He also switched to a more vegetarian, fruits and fish based diet after his diagnosis of prostate cancer.

Over the last 3 years, Mr. SL's PSA levels have remained stable at values around 3.5 or less than 4.0 ng/ml, which is within normal for his condition. His last clinical and per rectal examination in November 2001 did not reveal anything abnormal with his prostate gland. The last two pelvic sonagrams or doppler prostate and pelvic vascular ultrasound done in 2000 and in 2001 were normal. Mr. SL is currently doing well.

PRIMARY CHEMOPREVENTION OF PROSTATE CANCER USING HAELAN951

We need to conduct systematic clinical trials to examine the potential chemopreventative role of using fermented soy supplements such as Haelan951 to see if the laboratory and epidemiological data, which mostly show benefits in the medical literature, can be translated into definite clinical benefits. Anecdotal case reports such as the above case summaries on Mr. GJ who has remained free of prostate (and rectal) cancer for the past 5 years and Mr. SL who has not shown any clinical evidence of worsening or spread of his prostate disease for the past 2 years are compelling. They demonstrate the need to investigate the role of fermented soy products such

as Haelan951 as potential chemo preventive to prevent recurrence of prostate cancer. The role for soy in cases of patients diagnosed to have prostatic intraepithelial neoplasia, also called PIN, is an exciting area for nutritional based research. Because of the atypical shape of PIN cells, it is thought to be pre-cancerous condition of the prostate. Therefore, patients who are found to have PIN are at high risk for developing prostate cancer. Studies have shown that patients with PIN have a 66% chance of developing prostate cancer [62,79,81].

The use of a fermented soy beverage such as Haelan951 as a chemopreventative agent has both laboratory and clinical relevance

There are no standard forms of therapy for patients with PIN. Current recommendations include having a PSA test every 3 to 6 months and repeat biopsies if a significant change in the PSA is noted [82,83,85,86,87,88,89]. The use of a fermented soy beverage such as Haelan 951 as a chemopreventive agent has both laboratory and clinical relevance. It has been shown that genistein, a product found in soy products, has anti-tumor activity in prostate cancer [73]. Molecular studies have shown that genistein has an effect on a tumor bearing protein known as epidermal growth factor [58,95]. The addition of genistein to mammalian cells has down regulated the expression of this receptor [58,95,59]. A recent study has revealed that genistein can induce cell death or apoptosis in prostate cancer cells. This study [60] revealed that genistein and one of its precursors, biochanin A have an inhibitory effect on the LnCaP cell line in vitro with a dramatic reduction in PSA secretion as well inhibit the growth of hormone sensitive and hormone-insensitive cancer cell lines [59,96,97,98,99,105]. Genistein and its metabolites have also been postulated to inhibit prostate cancer growth by interfering with tyrosine kinase growth factor [79], other related growth factors and receptors [101], inhibiting angiogenesis [102], impacting topoisomerase II [103] or through other mechanisms such as inducing apoptosis through cell adhesion [104]. The clinical case report of Mr. GJ who began daily consumption of a bottle of Haelan951 for 2 weeks prior to his scheduled surgery for radical prostatectomy supports the notion that the fermented soy phytochemicals, notable genistein, in Haelan951 may have influence over the control of apoptosis. The patient's subsequent tests confirmed the absence of malignancy for the past 5 years following his diagnosis. In the case of Mr. SL, the apparent lack of clinical or ultrasound or biochemical evidence of the spread of an invasive prostate tumor in the absence of history of undergoing any form of conventional cancer therapies for a period of 2 years warrants further investigation and long-term follow-up and monitoring. The possible chemopreventative role of fermented soy products such as the Haelan951 will need to be investigated further using well controlled randomized clinical trials.

Acknowledgment

The authors wish to thank Aaron Katz, M.D., for his comments and Lee Classen for secretarial help rendered. We also want to thank our two patients Mr. GJ and Mr. SL for their valuable input.

References

1. Haard N, Odunfa SA, Lee C et al. Fermented cereals: A global perspective. Food and Agricultural Organization of the united Nations Rome 1999. ISBN 92-5-104296-9.

2. Gorbach SL. Lactic acid bacteria and human health. Annals of Internal Medicine 1990; 22 (1): 37-41.

3. Sarnat R, Schulick P, Newmark TM. The life bridge: The way to longevity with probiotic nutrients. Herbal Free Press, Brattleboro, VT 05301. 2002. ISBN 0-9716548-0-8

4. Ghanem KZ, Hussein L. Calcium bioavailability of selected Egyptian foods with emphasis on the impact of fermentation and germination. Inter J of Food Sciences and Nutrition 1999; 50: 351-6.

5. Howard D. Acquisition, transport and storage of iron by pathogenic. Clin Microbiological Reviews 1999; (12): 0893-8512.

6. Qin HS. A study on the effect of fermented soybean in preventing iron deficiency anaemia in children. Chinese J Prev 1989; 23 (6): 352-4.

7. WHO issues New Healthy Life Expectancy Rankings. World Health Organization 2000 June 2000. Press Release, Washington D.C. and Geneva, Switzerland.

8. Rose DP, Boyar AP, Wynder EL. International comparison of mortality rates for cancer of the breast, ovary, prostate and colon, and per capita food consumption. Cancer 1986; 58: 2363-2371.

9. Messina, M., Barnes, S. The Role of Soy Products in Reducing Risk of Cancer. J. Nat. Cancer Institute 1991; 83(8): 541-546.

10. Messina MJ, Persky V, Setchell KD, et al. Soy intake and cancer risk: A review of the in vitro and in vivo data. Nutr Cancer, 1994; 21: 113-131.

11. Messina M, Messina V. Increasing use of soy foods and their potential role in cancer prevention 1991; J Am Diet Assoc. 1991; 91: 836-840.

12. Golbitz P. Traditional soy foods: processing and products. J Nutr 1995 Mar;125 (Supply. 3):570S-572S

13. Hutchins AM, Slavin JL, Lampe JW. Urinary isoflavonoid phytoestrogen and lignan excretion after consumption of fermented and unfermented soy products. J Am Diet Assoc 1995 May;95(5):545-51

14. Baggott JE, Ha T, Vaughn WH et al. Effect of miso and NaCl on DMBA-induced rat mammary tumors. Nutr Cancer 1990; 14(2): 103-9.

15. Gotoh T, Yamada K, Ito A et al. Chemoprevention of N-nitroso-N-Methylurea-induced rat mammary cancer by miso and tamoxifen, alone and in combination. Jpn J Cancer Res 1998; 89(5): 487-95.

16. Takahashi C, Kikuchi N, Katou N et al. Possible anti-tumor promoting activity of componenets in soybean fermented food, Natto: effect on gap junctional intercellular communication. Caarcinogenesis 1995; 16(3): 471-6.

17. Lee JK, dietary factors and stomach cancer: A case-control study in Korea. Int. J Epi. 1995; 24: 33-41.

18. Barnes S, Peterson TG, Coward L. Rationale for the use of genistein-containing soy matrices in chemoprevention trials for breast and prostate cancer. J Cell Biochem, 1995; 22: 181-187.

19. Severson RK, Nomura AMY, Grove JS, Stemmermann GN. A prospective study of demographics, diet, and prostate cancer among men of Japanese ancestery in Hawaii. Cancer Res 1989; 49: 1857-1860.

20. Stephens FO. Phytoestrogens and prostate cancer: possible preventive role. Med J Aust 1997; 167: 138-140.

21. Lissin LW, Cooke JP. Phytoestrogens and cardiovascular health. J Am Coll Cardiol. 2000; 35(6): 1403-1410.

22. Ingram D, Sanders Kolybaba M et al .Case-control study of phytoestrogens and breast cancer. Lancet, 1997; 350(9083): 990-994.

23. Gardiner T, Ramberg J. Plant estrogens: Importance in health and disease. Glycoscience and Nutrition 2001; 2(8): 1-12.

24. Sirtori, CR. Risks and benefits of soy phytoestrogens in cardiovascular diseases, cancer, climacteric symptoms and osteoporosis. Drug Saf 2001; 24(9): 665-682.

25. Fourth International Symposium on the role of soy in preventing and treating chronic diseases, held in San Diego Nov 9-11, 2001.

26. Murphy PA. Phytoestrogen content of processed soybean products. Food Technology 1982: 60-64

27. Gyorgy, P, Murata K, Ikehata H. Antioxidants isolated from fermented soybeans (tempeh). Nature 1964; 203: 870.

28. Grun IU, Adhikari K, Li C, et al. Changes in the profile of genistein, daidzein, and their conjugates during thermal processing of tofu. J Agric Food Chem 2001 Jun;49(6):2839-43

29. Fukutake M, Takahashi M, Ishida K, et al. Quantification of genistein and genistin in soybeans and soybean products. Food Chem Toxicol 1996 May;34(5):457-61

30. Messina M. Modern applications for an ancient bean: soybeans and the prevention and treatment of chronic disease. J Nutr 1995 Mar;125(3 Suppl):567S-569S.

31. Wynder EL, Fujita Y, Harris RE et al. Comparative epidemiology and cancer between the United States and Japan, 1991; A second look. Cancer 67: 746-763.

32. Boyle P, Kevi R, Lucchuni F et al. Trends in diet related cancers in Japan: A conundrum? Lancet, 1993; 342: 752.

33. Cassidy, A. Physiological Effects of Phyto-oestrogens In Relation to Cancer and Other Human Health Risks. Proceedings of the Nutri. Soc.,1996; (55): 399-417.

34. Walker, M. Soybean isoflavones lower risk of degenerative diseases. Townsend Letter for Doctors and Patients.. Aug/Sept. 1994: 374-378

35. Stephen Holt. Soya for health. Mary Ann Liebert, Inc., Larchmont, NY, 1996.

36. Yang Z, Liu S, Chen X, et al. Induction of Apoptotic Cell Death and in Vivo Growth Inhibition of Human Cancer Cells by a Saturated Branched-Chain Fatty Acid, 13-Methyltetradecanoic Acid; Cancer Research, 2000; 60: 505-509.

37. Matsuo M, Nakamura N, Shidoji Y et al. Antioxidative mechanism andapoptosis induction by 3-hydroxyanthranilic acid, an antioxidant in Indonesian food, Tempeh, in the human hepatoma-derived cell-line. J Nutr Sci Vitaminol 1997; 43(2): 249-59.

38. Perdigon G, Valdez JC, Rachid M et al. Antitumour activity of yogurt: study of possible immune mechanisms. Dairy Res 1998; 65 (1): 129-38.

39. Santiago LA, Hiramatsu M, Mori A et al. J Nutr Sci Vitaminol 1992; (3): 297-304. Japanese soybean paste miso scavenges free radicals and inhibits lipid peroxidation.

40. Pichler H, Gaigg B, Hrastnik C et al. A subfraction of the yeast endoplasmic reticulum associates with the plasma membrane and has a high capacity to synthesize lipids. Eur J Biochemistry 2001; (8): 2351-61.

41. Manjunath N, Ramganathan B. Cytotoxic activity of lactobacilli isolated from plant and dairy sources. Indian J EXP boil 1989; (1): 72-5.

42. Zhang X, Ohta Y. Anticlastongenic and bio-anti-mutagenic activity of cultures broth of Saccharomyces cerevisiae 28 on mutagens. Mutation research 1993; 300(3-4): 201-6.

43. Bodana AR, Rao DR. Antimutagenic activity of milk fermented by Streptococus Thermophilus and Lactobacillus bulgarius. J Dairy Sci 1990; 73(12): 3379-84.

44. Perdigon G, Rachid M, Aguero G et al. Immune system stimulation by probiotics. J Dairy Sci 1995; 78(7): 1597-606.

45. Izawa S, Inou Y, Kimura A. Oxidative stress response in yeast: effect of glutathione on adaptation to hydrogen peroxide stress in Saccharomyces cerevisiae. FEBS Lett 1995; 368(1): 73-6.

46. Okamoto A, Hanagata H, Kawamura Y et al. Anti-hypertensive substances in fermented soybean, natto.Plant Foods for Human Nutr 1995; 47(1): 39-47.

47. Barfoot SF, Nettles CG. Antibiosis revisited: bacteriocins produced by dairy starter cultures. J Dairy Sci 1993; 76(8): 2366-79.

48. Yang G, Ji N, Wang J, Chen C. Chinese Journal of Prevention of Parasitic Diseases 3(3): 240-241.

49. Huang Z. Research and Teaching Department of Pharmacology,Fujian Medical College. (unpublished report, 1992) Lowering toxic effects of chemotherapy and radiation with Haelan 851.

50. Huang Z. Research and Teaching Department of Pharmacology,Fujian Medical College. The role of Haelan851 in protecting the liver. Paper presented at the Academy of Traditional Chinese Medicine and Pharmacy, 1991.

51. Lin Jui Cheng. Traditional Chinese Medical Research Institute. Anti-aging study using Haelan 851 nutritional products (unpublished data, 1993)

52. Huang Ziqiang. Fujian Medical College Pediatrics Department of Union Hospital Nutritional clinical study on youth using Haelan851 ages 6months to 11 years.

53. United States Patent Number 4,877,739 filed Sept. 30th 1996.

54. Central Analytical Laboratories, Inc., 101 Woodland HWY., Belle Chasse, Louisiana 70037. Quality analysis report on Haelan951 (2001)

55. Djuric Z, Chen G, Doerge DR, Heilbrun LK, Kucuk O. Effect of soy isoflavone supplementation on markers of oxidative stress in men and women. Cancer Lett 2001 Oct 22;172(1):1-6

56. Marnett L. Oxyradicals and DNA damage. Carcinogenisis, 2000; 21:361-370.

57. Davis JN, Kucuk O, Djuric Z, Sarkar FH. Soy isoflavone supplementation in healthy men prevents NF-kappaB activation by TNF-alpha in blood lymphocytes. Free Radic Biol Med 2001 Jun 1;30(11):1293-302.

58. Kim H, Peterson TG, Barnes S. Mechanisms of action of the soy isoflavone genistein: emerging role for its effects via transforming growth factor beta signaling pathways. American Journal of Clinical Nutrition. 1998 Dec; 68 (6):1418S-1425S.

59. Kyle, E., Neckers, L., Takimoto, C., Curt, G., Gergan, R. Genistein-Induced apoptosis of prostate cancer cells is preceded by a specific decrease in focal adhesion kinase. Molecular Pharm. 1997, 51:193-200.

60. Onozawa M, Fukuda K, Ohtani M, Akaza H, Sugimura T, Wakabayashi K. Effects of soybean isoflavones on cell growth and apoptosis of the human prostatic cancer cell line LNCaP. Japan Journal of Clinical Oncology. 1998 Jun; 28(6):360-3

61. The American Cancer Society, 2002.

62. Donn AS, Muir CS. Prostate cancer: some epidemiological features. Bulletin de Cancer, 1985; 72(5): 381-390.

63. Yip, I., Herber, D., Aronson, W. Nutrition and prostate cancer. Urological clinics of North America. 1999; 26(2): 403-409.

64. Waterhouse J, Muir C, Shanmugaratnam K et al. Cancer incidence in five continents. Caner Incidence, 1982; 6 (42). IARC Publication. Lyon, France.

65. Ross RK, Henderson BE. Do diet and androgens alter prostate cancer risk via a common etiologic pathway? J Natl. Cancer Inst., 1994; 86: 252-254.

66. Muir CS, Nectoux J, Staszewski J. The epidemiology of prostate cancer: Geographical distribution and time-trends. Acta Oncol, 1991; 30: 133-140.

67. Shimizu H, Ross RK, Bernstein L. Cancers of the prostate and breast among Japanese and white immigrants in Los Angeles County. Br. J Cancer, 1991; 63: 963-966.

68. Shellman SD, Wang QS. Cancer mortality in Chinese immigrants to New York City: comparison with Chinese in Tianjin and with United States-born Whites. Cancer, 1994; 73: 1270-1275.

69. Whittemore AS, Kolonel LN, Wu AH et al. Prostate cancer in relation to diet, physical activity, and body size in blacks, whites, Asians in the United States and Canada. J Natl. Cancer Inst., 1995; 87: 652-661.

70. Stephens FO. Phytoestrogens and prostate cancer: possible preventive role. Medical J Aust., 1997; 167:138-140.

71. Moyad, M.A. Soy, disease prevention, and prostate cancer. Seminars in urologic oncology. 1999, 17,2, 97-102.

72. Adlercreutz, H.. Western Diet and Western Diseases: Some Hormonal and Biochemical Mechanisms and Associations. Scand.J.Clin.Lab.Invest., 1990; 50 (201):3-23.

73. Adlercreutz H, Mazur W. Phyto-oestrogens and Western diseases. Annals of Medicine 1997 Apr;29(2):95-120

74. Adlercreutz H, Mazur W, Bartels P, et al. Phytoestrogens and prostate disease. Amer. Soc. For Nutr. Sciences. J Nutr. , 2000; 130: 658S-659S.

75. Adlercreutz, H., Mousavi, Y., Clark, J. et al. Dietary Phytoestrogens and Cancer: In Vitro and In Vivo Studies. J. Steroid Biochem. Molec. Biol., 1992; 41(3-8): 331-337.

76. Jefferson, N., Retha, R., Newbold, R. Potential endocrine-modulating effects of various phytoestrogens in the diet. J. Nutrition. 2000; 16(7): 658-662.

77. Bingham, S.A., Atkinson, C., Liggins, J., et al. Phyto-oestrogens: where are we now? Brit. J. Nutrition. 1998; 79: 393-406.

78. Knight, D.C., Eden, J.A. A review of the clinical effects of phytoestrogens. Obstetrics & Gynecology, 1996; 87 (5): 897-904.

79. Yatani R, Chigusa I, Akazaki K et al. Geographic pathology of latent prostatic carcinoma. Int. J. Cancer, 1982; 9: 611-616.

80. Parker SL, Tong T, Bolden S et al. Cancer Statistics, 1997. CA Cancer J Clin, 1997; 47: 5-27.

81. Herbert JR, Hurley TG, Olendzki BC, et al. Nutritional and socioeconomic factors in relation to prostate cancer mortality; A cross-national study. J Natl Cancer Inst., 1998. 90: 1637-1647.
81. Herbert JR, Hurley TG, Olendzki BC, et al. Nutritional and socioeconomic factors in relation to prostate cancer mortality; A cross-national study. J Natl Cancer Inst., 1998. 90: 1637-1647.
82. Zlotta AR, Schulman CC. Etiology and diagnosis of prostate cancer: what's new?. Eur. Urol., 1998; 33:351-358.

83. P Scardino, Problem of prostate cancer. J Urol., 1994; 152: 1677-1678.

84. Bunting PS.Screening for prostate cancer with prostate-specific antigen: beware the biases. Clin Chim Acta. 2002; 315(1-2):71-97.

85. Bostwick DG, Grignon DJ, Hammond MEH et al. Prognostic factors in prostate cancer. College of American Pathologists consensus statement 1999. Arch. Pathol. Lab. Med., 2000; 124: 995-1000.

86. Leak B, Wei JT, Gabel M et al. Relevant patient and tumor considerations for early prostate cancer treatment. Semin Urol Oncol 2002 Feb;20(1):39-44

87. Austenfeld MS, Thompson IM, Middleston RG, Meta-analysis of the literature: guideline development for prostate cancer treatment. J Urol.,1994; 152: 1866-1869.

88. Wasson, J H; Cushman, C C; Bruskewitz, R C et al. A structured literature review of treatment for localized prostate cancer. Archives of Family Medicine, 1993; 2 (5): 487-493

89. Fowler FJ, Collins MM, Albertsen PC et al. Comparison of recommendations of urologists and radiation oncologists for treatment of clinically localized prostate cancer. JAMA, 2000; 283: 3217-3222.

90. Fleming, C, Wasson, JH, Albertsen, PC et al. A decision analysis of alternative treatment strategies for clinically localized prostate cancer. JAMA, 1993; 269(20): 2650-2658

91. Gardner BG, Zietman AL, Shipley WU et al. Late normal tissue sequelae in the second decade after high dose radiation therapy with combined photons and conformal protons for locally advanced prostate cancer. J Urol. 2002;167 (1):123-126.

92. Wei JT, Dunn RL, Sandler HM et al. Comprehensive comparison of health-related quality of life after contemporary therapies for localized prostate cancer. J Clin Oncol. 2002 ;20(2):557-66.

93. Sun F, Magna R, Hoffman R. Efficacy Evaluation of compound SBA in prostate cancer DU145 MetaMouse Model. (unpublished report) 1998. Anticancer Incorp. CA 92111.

94. Barken I, Geller J. The effects of Soy Extract Q-can in patients with relapsed prostate cancer (PSA Relapse) following radiation or radical prostatectomy (unpublished paper, 1999).

95. Barnes, S., Peterson, T. Biochemical Targets of the Isoflavone Genistein in Tumor Cell Lines . Soc. Expl. Bio. & Med., 1995; 208: 103-108.

96. Peterson G, Barnes S. Genistein and biochanin-A inhibit the growth of human prostate cancer cell lines but not epidermal growth factor receptor tyrosine autophosphorylation. Prostate, 1993; 22:335-345.

97. Hempstock J, Kavanagh JP, George NJR. Growth inhibition of primary human prostatic cells by phytoestrogens. J Urology, 1998; 159 :11(abstr.4)

98. Rokhlin OW, Cohen MB. Differential sensitivity of human prostatic cancer cell lines to the effects of protein kinase and phosphatase inhibitors. Caancer Lett., 1995; 98: 103-110.

99. Aldercreutz H, Makela S, Pylkkanen L et al. Dietary phytoestrogens and prostate cancer. Proc Am ASSOC cancer Res., 1995; 36: 687 (abstr.)

100. Akiyama, T., Ishida, J., Nakagawa, S., et al. Genistein, A Specific Inhibitor of Tyrosine-Specific Protein Kinases. J. Bio. Chem., 1987; 262(12): 5592-5595.

101.Linnassier C, Pierre M, Le Pecq JB, et al. Mechanisms of action in NIH-3T3 cells of genistein, an inhibitor of EGF receptor tyrosine kinase activity. Biiochem Pharmacol, 1990; 39: 187-193.

102.Fotsis T, Pepper M, Aldercreutz H, et al. Genistein, a dietary ingested isoflavonoid, inhibits cell proliferation and in vitro angiogenesis. J Nutr 1995; 125: S790-S797.

103.Markovits J, Linassier C, Fosse P, et al. Inhibitory effects of the tyrosine kinase inhibitor genistein on mammalian DNA topoisomerase II. Cancer Res., 1989; 49: 5111-5117.

104.Kyle E, Neckers L, Takimoto C, Curt G, Bergan R. Genistein-induced apoptosis of prostate cancer cells is preceded by a specific decrease in focal adhesion kinase activity. Molecular Pharmacology. 1997 February;51(2):193-200

105.Papazisis, K., Zambouli, D., Kimoundri, O., et.al.. Protien tyrosine kinase inhibitor, genistein, enhances apoptosis and cell cycle arrest in K562 cells treated with γ-irradiation. Cancer Letters. 2000, v.160: 107-113.