

## Haelan 951

# A Novel Fermented Soya Beverage and Safe Nutritive Adjunct in Prostate Cancer Therapies: is There a Possible Chemopreventive Role?

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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 antioxidants and phytochemicals.<sup>1</sup> The fermentation process, for example, with lactobacilli, increases the quantity, availability, digestibility, and assimilation of nutrients in the body.<sup>2</sup>

It is being increasingly recognized that while, for example, soy and soy protein isolates have potentially anti-nutritive value due to their high phytate 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.<sup>1,3</sup> Uncultured soy with its high phytate levels has been shown in a number of studies to block absorption of vital nutrients such as calcium.<sup>4</sup> The use of soy as a culturing medium is also advantageous because iron is naturally available in soy.<sup>3</sup> 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.<sup>4</sup> Culturing soy has been shown to enhance the bioavailability of iron and copper and hence rendering the delivery of these nutrients in their most advantageous forms.<sup>5,6</sup>

The World Health Organization reported in 2000<sup>7</sup> 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 consequences. 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.<sup>1,3</sup>

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.<sup>8,9</sup> 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 20 to fifty times more soy than Americans.<sup>10,11</sup>

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.<sup>12</sup> 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.<sup>9,10</sup> It has been suggested that the fermentation process increases availability of isoflavones in soy.<sup>12,13</sup> For example, a study<sup>14</sup> 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 daidzein, which are believed to be cancer chemopreventatives.<sup>15</sup> The fermentation process is thought to convert the isoflavone precursors genistin and daidzin to their active anti-cancer isoflavone forms, genistein and daidzein.<sup>16</sup> It is unfortunate that in the United States, health-conscious consumers, especially women concerned about developing breast cancer are urged by media and consumer reports to consume soy or soy protein isolates which are not the forms that soy is traditionally consumed in Japan.<sup>23</sup> 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.<sup>3</sup> Japanese researchers found that the cultured broth of *Saccharomyces cerevisiae* or Brewer's Yeast, produced both *in vivo* and *in vitro* experiments, bioantimutagenic and anticlastogenic activity with mutagen formation reduced by 47% just by the administration of the cultured broth. The cultured soy medium had thus produced

its own unique anti-carcinogenic activity by strongly inhibiting formation of cellular mutations.<sup>15</sup>

There is also a recent Korean study which 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.<sup>17</sup> The limited epidemiological evidence so far from these cultures with diets that are 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.<sup>17-23</sup> But the clinical data to date is often flawed with poor design and other methodological issues and the role of isoflavones in chemoprevention especially in the hormonally dependent cancers such as breast and prostate cancers while promising, is still lacking unequivocal evidence.<sup>24</sup>

The controversy over the role of soy in preventing and treating chronic illnesses such as cancer was addressed at the 4th International Symposium held in San Diego in November 2001.<sup>25</sup> To date, there has been a paucity of literature on especially, 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.<sup>26-28</sup> Traditional sources of fermented soy foods that are not prepared under the stringent 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.<sup>27-29</sup> Some studies<sup>11,28-30</sup> 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<sup>28</sup> 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, daily intake of genistein and genistin by the Japanese was calculated to be 1.5-4.1 and 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.<sup>28,31-33</sup>

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 than when used individually.<sup>34,35</sup> Studies are needed to demonstrate the mechanisms of action and to verify the efficacy. 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.

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.<sup>14,16,36-41</sup> The literature suggests several situations in which viability is not required for some activities.<sup>40-42</sup> 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.<sup>3,35,38,41,44-47</sup> It seems likely that the culturing in and of itself, apart from any vitamin or mineral enhancement, apart even from the presence of live 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,<sup>36,48-52</sup> 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 is done in the People's Republic of China. The patented<sup>53</sup> 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 fermentation metabolites of the naturally occurring isoflavones, protease inhibitors, saponins, phytosterols and inositol hexaphosphate 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 hexaphosphate, and essential fatty acids such as linolenic and linolic acids, polysaccharide peptide, and twenty of the twenty-two amino acids including ornithine.<sup>54</sup> 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.<sup>3,35,53,54</sup>

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 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.<sup>55-57</sup>

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 anticarcinogenic 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.<sup>36</sup> 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 programmed cell death (apoptosis).<sup>58-60</sup> But just as importantly it was observed that the specific branched fatty acids do not kill normal cells but inhibit the growth of cancer cells without any toxic effects. In animal studies, intraperitoneal injection of 13-methyltetradecanoic acid daily up to 800 mg/kg to mice did not reach the LD50 level (50% lethal dose).

#### **Soy and Prostate Cancer: Evidence to Date**

Prostate cancer is the most common type of non-skin cancer found in American men.<sup>61</sup> 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.<sup>62,63</sup> 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.<sup>61</sup> The evidence does suggest that prostate cancer develops as a result of both inherited and environmental factors.<sup>62,63</sup> Race -- ethnicity is one of the more well studied risk factors.<sup>64,65</sup> 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.<sup>64</sup> Chinese and Japanese immigrants to the United States have an increased risk and mortality from prostate cancer when compared with men who remain in their native country.<sup>66-69</sup> 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 lifestyles have been replaced by Western diets and life-styles.<sup>31,32,63</sup> By and large, a number of epidemiological studies have shown that Western diets may be a strong environmental risk factor in the development of prostate cancer.<sup>33,70-78</sup> 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.<sup>63,79,80</sup> Prostate cancer mortality is very low in Asian countries where soy foods are consumed.<sup>8,9-11,81</sup> Soy isoflavones have also been shown to increase prostate cancer latency and decrease the development of clinically significant prostate cancer.<sup>19</sup>

One of the problems facing prostate cancer patients is the uncertainty of many issues surrounding the detection, diagnosis and management of the disease.<sup>82-86</sup> About 80% of men diagnosed with prostate cancer have early stage disease.<sup>63</sup> 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 symptoms of the disease progress).<sup>86-92</sup>

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.<sup>61</sup>

#### **Previous *in vitro* and *in vivo* Prostate Studies Done with Haelan**

Animal studies<sup>36,93</sup> 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 Haelan 951 formula). The compound SBA was shown to reduce prostate cancer cell size, cell growth and reduce the formation of blood vessels in prostate tumors. The efficacy of compound SBA against DU145 human 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 all the treated groups at doses of 35mg/kg ( $p=0.042$ ), 70mg/kg ( $p=0.007$ ) and 105mg/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<sup>94</sup> 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 with a 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

their PSA velocity when compared to the measured values prior to the soy nutritional treatment.

## 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 resections 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 followup 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 followup of adjuvant systemic chemotherapy. He was started on a 8-week course of chemoradiation 45Gy and 5 FU and folic 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 perioperative period together with the chemoradiation. He took the recommended dose of the beverage at 8 oz/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 oz a day for a month and then 3 oz and is now maintained at 2 oz a day for the past 5 years. He was not on any other herbal supplements during this period.

During the followup period he denied any urinary or bowel symptoms or pelvic or sciatic pain. He subsequently went back to the clinic every few months 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 2.9ng/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 oz of Haelan in 2 divided doses

per day for a period of 3 to 4 months and then tapered to 4 oz a day in 2 divided doses for the duration of a year. He is presently on a maintenance dose of 2 oz 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 rectal examination in November 2001 did not reveal anything abnormal with his prostate gland. The last two pelvic sonograms 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 Haelan 951 as potential chemopreventative to prevent recurrence of prostate cancer. The potential for a chemopreventative role for soy in cases of patients diagnosed with 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 a 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.<sup>62,79,81</sup>

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.<sup>82,83,85-89</sup> The use of a fermented soy beverage such as Haelan951 as a chemopreventative 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.<sup>73</sup> Molecular studies have shown that genistein has an effect on a tumor bearing protein known as epidermal growth factor.<sup>58,95</sup> The addition of genistein to mammalian cells has down regulated the expression of this receptor.<sup>58,95,59</sup> A recent study has revealed that genistein can induce cell death or apoptosis in prostate cancer cells. This study<sup>60</sup> 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 as inhibit the growth of hormone sensitive and hormone-insensitive cancer cell lines.<sup>59,96-99,105</sup> Genistein and its metabolites have also been postulated to inhibit prostate cancer growth by interfering with tyrosine kinase growth factor,<sup>79</sup> other related growth factors and receptors,<sup>101</sup> inhibiting angiogenesis,<sup>102</sup> impacting topoisomerase II<sup>103</sup> or through other mechanisms such as inducing apoptosis through cell adhesion.<sup>104</sup> The clinical case report of Mr. GJ who began daily consumption of a bottle of Healan951 for 2 weeks prior to his scheduled surgery for radical prostatectomy supports the notion that the fermented soy phytochemicals, notably genistein, in Healan951 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 diagnoses. 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 Healan951 will need to be investigated further using well controlled randomized clinical trials.

#### Acknowledgement

The authors wish to thank Aaron Katz, MD 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 invaluable input.

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