

Soy and Cancer Survivors: Dietary Supplementation with Fermented Soy Nutraceutical, Haelan 951 In Patients Who Survived Terminal Cancers.

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Abstract

Research has now isolated a number of nutrients and micro nutrients in soybeans that have anti-cancer properties. The latest research has focused on the micronutrient isoflavones, protease inhibitors, saponins, phytosterols and phytic acid compounds in soybeans.

The objective of this paper is to present case reports of cancer survivors who have used dietary supplementation with Haelan 951, a fermented soy nutraceutical, within the context of chemoprevention and in therapeutics either as sole mainstay treatment or as adjuvant nutrition to successfully treat patients presenting with diagnosis of cancers.

These case reports were submitted as part of the National Cancer Institute's Best Case Series Program. The Best Case Series focuses on documented case reports of patients diagnosed with cancers who have shown significant improvements in their clinical conditions after using complementary and alternative supplements as mainstay

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Introduction

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 Herbal Medicine. 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.

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. 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 . It has been suggested that the fermentation process increases availability of isoflavones in soy. For example, a study 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. The fermentation process is thought to convert the isoflavone precursors genistin and daidzin to their active anti-cancer isoflavone forms, genistein and daidzein. 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 . 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. Japanese researchers found that the cultured broth of *Saccharomyces cerevisiae* or Brewer's Yeast, produced both *in vivo* 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 produced its own unique anti-carcinogenic activity by strongly inhibiting formation of cellular mutations .

Anti-Carcinogenic Properties of Soy

Some studies have suggested that the isoflavone genistein may have some role as a chemopreventive agent against cancer in humans. Levels of genistein and its beta-glycoside 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, 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.

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. 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 . The literature suggests several situations in which viability is not required for some activities. 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. 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.

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 a \$2.9 million on research to focus just on the role of soy.

Research has now isolated a number of nutrients and micro nutrients in soybeans that have anti-cancer properties. The latest research has focused on the micronutrient isoflavones, protease inhibitors, saponins, phytosterols and phytic acid compounds in soybeans. The NCI published a copy of its report in the April, 1991 issue of the National Journal of Cancer, titled: Commentary: The Role of Soy Products in Reducing Cancer Risks. Some of the issues raised in the NCI report will be discussed in this paper in later sections.

Haelan951, a novel fermented soy supplement that has been sold as a food beverage in the US for past 12 years. The patented 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 phyloquinone (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 . 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. The fermented soy and its metabolites have also been shown to have different biological properties, such as anti-viral, anti-bacterial, anti-inflammatory, anti-mutagenic and anti-carcinogenic activities.

The objective of this paper is to present case reports of cancer survivors who have used dietary supplementation with Haelan 951, a fermented soy nutraceutical, within the context of chemoprevention and in therapeutics either as sole mainstay treatment or as adjuvant nutrition to successfully treat patients presenting with diagnosis of cancers. The case reports presented below were submitted as part of the National Cancer Institute's Best Case Series Program. The Best Case Series focuses on documented case reports of patients diagnosed with cancers who have shown significant improvements in their clinical conditions after using complementary and alternative supplements as mainstay

CASE REPORT #1: Tumor Type: Infiltrating Ductal Carcinoma of the Breast.

PS, a 67 year old married great grandmother, retired nurse and wife of a physician, first noticed a lump in her right breast in August 1997. Ultra-sound breast report in August '97 revealed "..... a solid lesion, mildly lobular, well circumscribed" Mammogram report in October 1997 stated "..... irregular lobular very dense lesion containing several tiny calcifications and coarse calcifications in the right breast , barely upper outer quadrant, roughly measuring 15x 15 x 20 mm, and very suspicious for carcinoma ... no nodes seen." There was no metastasis noted at that time but a breast biopsy in October 1997 revealed a moderately differentiated infiltrating ductal carcinoma of the right breast. A total mastectomy or lumpectomy with removal of the auxiliary lymph nodes and followed by aggressive radiation was recommended but she refused all standard therapy. She was offered mastectomy or lumpectomy with removal of axillary lymph nodes followed by aggressive radiation therapy and hormonal treatment regime . She was given a prognosis of 6months to live without treatment.

PS began taking the fermented soy beverage, Haelan951 as of November 1997 and was followed radiologically via mammograms until the present time. Per her report and confirmed by serial mammograms, she has residual disease that has gradually decreased in size since diagnosis. In January 2001, the area of density measures 7x5x6mm as

compared to the 15x15x20mm at the time of her diagnosis. Her most recent mammogram in February 2004 showed a low density oval mass with circumscribed margins measuring 4mm in the upper outer quadrant. This was thought to be most likely benign in nature. An ultra sound reading done in the same period revealed a 1mm calcification in the same area of the right breast. No mass was detected.

When PS started Haelan951 she initially took one bottle or 8ozs daily in two divided doses for 7 months. This dose was cut down to 4 ozs a day for a further 7 months and then to 2 ozs a day for several months. She is currently on 1 oz a day. PS is clinically well and continues to lead an active life.

CASE REPORT #2: Tumor Type: Infiltrating ductal carcinoma with history of lymphangitic spread, metastases to skin, lungs, bronchi, pericardium and bones.

JH, a 50 year old woman, was first diagnosed to have infiltrating ductal carcinoma of left breast in 1986 when she underwent mastectomy and reconstruction of breast tissue with no adjuvant therapy at that time. She was noted to be estrogen receptor positive. Her tumor was staged at T1N0M0.

She remained clinically well and was followed up as an out patient for the period between 1986 till September 2000. During that visit she presented with a history of gradual weight loss, persistent cough, shortness of breath or dyspnea on exertion and developed a skin nodule in her peri-xiphoid area. She was treated with steroids without significant relief. Her CT scan showed lymphangitic infiltrate and a very large pericardial effusion. There was also a 4 cm mass posterior to the left hilum; additional mass versus consolidation right lung base posteriorly . Infiltrates in the right middle lobe and lingular segment of the left upper lobe. A large pericardial effusion and a smaller right pleural effusion were also noted. JH underwent a 2-D echocardiogram of her heart which showed no evidence of a pericardial tamponade. She underwent bronchoscopy, which

showed the presence of a small tumor nodule that was subsequently diagnosed as an adenocarcinoma. She also had a skin biopsy which also showed metastatic adenocarcinoma. The tumor architecture was described as “non specific but could suggest primary breast ductal carcinoma”. She also had small lymph nodes and a lymph node on her anterior abdomen.

An x-ray of her right humerus in September 2000 revealed on the antero-posterior and lateral views, destructive change in the glenoid process of the right scapula. The humeral head, neck, and shaft appeared normal. Her bone scan in October 2000 showed diffuse bony metastases, unchanged since September 2000, with focal metastatic disease in right parietal bone, right scapula, bilateral ribs. There were also multiple foci of activity in the thoracic and lumbar spine, left iliac bone, sacrum, and left femoral neck.

In September 2000 she was started on a 3 month cycle of Cytosan and Adriamycin with a continuous infusion of 5-FU. She tolerated chemo well without significant side effects. At time of discharge her Hb was 12.6, WBC 8.1, platelets 245. She developed a deep vein thrombosis that resolved with treatment regime of Lovenox and Coumadin.

On follow up visit in April 2002, her estradiol level was at 43 and FSH and LH levels were quite low at premenopausal levels. She was started on Lupron to render her menopausal together with Aredia. Her CT scan showed decreased in size of her hilar mass as well as disappearance of her right pleural effusions but most noticeably she had a very large pericardial effusion. Bone scan showed stable to improved metastatic disease. Pericardiocentesis was done in May 2002 and she underwent pericardial window with pericardial biopsy in June 2002. She refused another round of chemotherapy.

JH started taking Haelan951 in May 2002 just before her surgical procedure to drain the large malignant pericardial effusion. Her physicians at that time warned her of a rapid recurrence of her condition within a few months. Post-operatively, she did well with no difficulties in breathing or recurrence of her malignant pericardial effusion in subsequent follow up visits till last follow up visit in June of 2003. Her clinician noted that despite

her malignant disease state she had done excellently. At present time, JH has no other significant problems. She does a lot of activities on her own and denies any complaints of shortness of breath, nausea, vomiting, diarrhea or constipation, lymphadenopathy or skin changes. Whole body PET Scan in June 2003 showed a marked decrease in number of metastasis with no overt major activity.

JH attributes her improvement in her clinical condition, especially with regards to her breathing and general well being over the past one year as a result of her faith and consuming the fermented soy beverage, Haelan951. She currently plays blue-grass music with her children and does music tours around the country with them.

CASE REPORT #3: Tumor Type: Poorly Differentiated Adenocarcinoma of the Gallbladder.

SS, a 69 year old gentleman was diagnosed with poorly differentiated adenocarcinoma arising from the distal portion of the gallbladder following a laparotomy in September 1995. Prior to diagnosis, he experienced right upper quadrant discomfort, nausea, dark urine, jaundice, and pale stool. A CT scan of the abdomen in September 1995 revealed "... a 2.0cm mass near the porta hepatitis, thought to represent a cholangiocarcinoma with a probable 1.5 cm small lymph node in the porta hepatitis..."

The biopsy report then stated that the tumor "... encompassed the hepatoduodenal ligament and was densely adherent to the duodenum in addition to showing multiple small nodules on the surface of the liver. Biopsies from the gallbladder wall and liver capsule showed poorly differentiated mucin secreting adenocarcinoma involving these regions. Curative resection was not attempted. An ERCP (09/15/95) revealed biliary obstruction and a percutaneous biliary catheter was placed in addition to internal stents. that improved following these interventions.

SS past medical history was significant. He had coronary heart disease with a coronary heart bypass grafting done in 1984; hypertension and chronic obstructive pulmonary disease.

Treatment for the adenocarcinoma included 1 cycle of FAM chemotherapy that was completed in 2 weeks. An oncologist in SS's care documented that SS was considered to be in clinical remission based on CT scan findings in January 1996, where "... no definite tumor was identified in the biliary ductal system...." A normal CXR (01/31/96) and normal CT scan (03/01/96) was noted .

SS underwent a cholecystectomy with liver wedge resection in early 1998 after experiencing post-prandial bloating. A discharge summary (04/02/98) stated that there was no evidence of tumor in the gallbladder and the liver biopsy revealed mild triaditis and interface hepatitis.

SS began taking 8 ozs of Haelan951 from October 1995 till February 1998. The dosage was then decreased to 4 ozs till 2003. He resumed working for past few years and remained active till March 2003 when he passed away in his sleep due to myocardial infarction.

CASE REPORT #4: MYELOPROLIFERATIVE DISORDER

MS, a 84 year old female who was diagnosed with myeloproliferative disorder in July 2002. She also has a significant past medical history for chronic pulmonary obstructive lung disease, chronic atrial fibrillation , hypertension, hyperlipidemia, diabetes. She presented at that time with a marked degree of leukocytosis, with a WBC count of 29,500 and an increased number of giant platelets identified on peripheral blood smear. At her one month follow up, her repeat blood tests have been normal since.

She started taking Haelan951 since middle July at 4ozs a day for a month and since then is presently on 1-2 ozs a day.

CASE REPORT #5: Tumor type: Follicular Lymphoma, grade 2.

BL is a 65 year old white female who has had a long history of “lumps.”

In August of 2002 she had a lump in her left groin that increased in size and was seen by a surgeon for a left inguinal biopsy. This revealed the presence of a follicular lymphoma, grade 2. The microscopic description described both small cleaved cells and medium to large non-cleaved cells.

CT scan in August 2002 of her chest which showed no significant abnormality. A CT Scan of her abdomen however, showed a liver cyst measuring 2.6cm. The liver, spleen, gall bladder, pancreas and adrenal glands were otherwise normal. There was increased soft tissue density in the retroperitoneum along the left side and just beyond the aortic bifurcation, surrounding left common iliac artery and there was a vague increased stranding density in the mesenteric of the lower abdomen continuity with soft tissue massing in the upper posterior aspect of the pelvis. This measured 4 cm in maximum diameter and abutted the loops of bowel. There was also increased soft tissue density in the posterior upper right side of the pelvis along the more distal aspect of the right common iliac arteries. A soft tissue nodular mass was also present in the right groin measuring 4.2 cm x 2.27 cm and soft tissue massing was noted along the course of the right external iliac nodes, All these were assessed to be consistent with a diagnosis of lymphoma.

Bilateral bone marrow biopsy revealed paratrabeular lymphoid infiltrate consistent with involvement of marrow with follicular lymphoma.

Bon Scan done also in Aug of 2002 did not reveal any malignant changes.

NCI-BL denied history of fevers, chills, sweats, weight loss, bleeding, bruising or pain. She was subsequently diagnosed to have Stage IV-A center cell, grade 2 lymphoma (follicular mixed small cleaved and large cell lymphoma) and initiated on R-CHOP on 09/24/02. About 10 days after the initiation she developed an episode of syncope and was hospitalized and subsequently diagnosed to have paroxysmal atrial fibrillation with rapid ventricular response. During the follow up visit in December 2002, despite

recommendation by her physician NCI-BL refused chemotherapy even at a 25% reduction dose.

In Nov 2002, on the advice of friends, NCI-BL started taking Healan951 at a dosage of 8 ozs a day for twenty-one days. She also stated that she took

Follow up review in May 2003, NCI-BL was observed to be well. No history of fevers, chills, weight loss, or lumps. CT of the abdomen in June 2003 revealed that there had been interval improvement with marked reduction in the mesenteric and retroperitoneal adenopathy. There was only mild haziness along the root of the mesentery and left common iliac. The previous mass had now resolved. CT of the pelvis and chest were normal.

Past medical history:

1. Hypertension
2. Tonsillectomy in 1953
3. 2 dilatation and curettages
4. Breast implants
5. Hysterectomy with oophorectomy for non malignant reasons
6. Intestinal obstruction, secondary to adhesions in 1978
7. Removal of small benign urethral tumor
8. Gum surgery in 1955.

CASE REPORT # 6: PROSTATE CANCER

GJ, a 73-year-old gentleman presented 8 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.

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 follow up staging with colonoscopy. CT scan confirmed a lower rectal tumor and adenopathy within his pelvis on CT Scans.

Initially, 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 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.

GJ took Haelan951 in the peri-operative period together with the chemo-radiation therapy. He took the recommended dose of the beverage at 8 ozes 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 ozs a day for a month and then 3 ozs and is now maintained at 2 ozs 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 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: # 7: Infiltrating Adenocarcinoma of the Prostate

SL, a 58 year old African American presented 3 years ago with a gradual rise in his serum 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.

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 8ozs of Haelan in 2 divided doses per day for a period of 3 to 4 months and then tapered to 4 ozs a day in 2 divided doses for a duration of a year. He is presently on a maintenance dose of 2 ozs a day. He also switched to a vegetarian, fruits and fish based diet after his diagnosis of prostate cancer.

Over the last 3 years, SL's serum 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 sonograms or doppler prostate and pelvic vascular ultrasound done in 2000 and in 2001 were normal. SL is currently doing well.

Discussion

This paper supports the contention that there are significant benefits associated with the dietary supplementation of fermented soy nutraceutical such as Haelan 951 for patients diagnosed with cancers, either alone or in conjunction with conventional chemotherapeutic agents.

Role of Adjuvant Nutritional Supplementation in Cancer Therapies

The often neglected area that we want to address in our paper concerns the nutritional support in chemotherapy and radiation therapy patients. This group of patients with advanced stages of cancers frequently begin treatment malnourished, and as treatment progresses malnourishment becomes worse due to treatment-related nausea and vomiting, mucositis, fever, and other side-effects. Abnormalities in carbohydrate metabolism with secondary effects on fat and protein metabolism have been identified in several populations of patients with common cancers. Heber et al (1986) in their review paper observed that pretreatment weight loss representing an alteration in nutritional status is an important, independent factor prognostic of survival in patients with common forms of cancer. For example, they cited that in the case of non-small cell lung cancer, the median survival of patients with weight loss (defined as a 6% loss or more from their usual body weight) was 50% that of patients who were within 5% of their usual body weight. Weight loss has long been known to have a profound effect on survival, and for certain cancers such as non-small cell lung cancer can have a greater influence than available chemotherapy. Nixon (1986) in his review paper critiqued that effective nutritional support would enhance wound healing and visceral function, improve cellular immunity and allow for delivery of adequate drug and irradiation doses, thereby increasing

response rates and prolonging survival. Unfortunately, most standard techniques of parenteral nutritional support have only been met with limited success in patients with advanced cancers. Improvements in parameters such as weight gain and immune function have been proven but definite benefit in response rates and survival with chemotherapy and radiation remains to be seen. Most researchers agree that the indications for parenteral nutritional support in chemotherapy and radiation patients include (1) patients who cannot eat or digest properly because of tumor obstruction, surgical resection of gut, or other complications who have a reasonable life expectancy; (2) cachectic patients with responsive neoplasms who could not tolerate aggressive treatment without short-term nutritional support; (3) patients suitable for trials of nutritionally modified solutions or alterations in standard techniques.

As a group, cancer patients have been observed to have the highest prevalence of malnutrition of any group of hospitalized patients. These patients present with significant changes in energy, carbohydrate, fat and protein metabolism and require different forms of nutrition than healthy individuals. Grant et al (1990) estimated that up to 40% of all cancer patients die from malnutrition, and not from the cancer. They concluded that patients who are about to be involved in intensive and extended treatment regimes involving a combination of surgery, chemotherapy and irradiation, especially elderly patients and those who are expected to be severely stressed during the treatment, have a greater need for adequate scientifically-based adjuvant nutritional support. Examples include patients with abdominal cancers such as ovarian malignancies whose disease progression is often characterized by intermittent small bowel obstruction, radiation therapy with enteritis and frequently, malignant ascites with anorexia. Failure to provide the much needed nutritional support is associated with progressive malnutrition and accelerated weight loss attributed to hyper metabolism. Recovery from this weight loss is difficult if not impossible until the treatment is completed. Studies have shown that providing early adjuvant nutritional support in these patients can help to enhance the effectiveness while reducing the toxic side-effects of chemotherapy and radiation therapies, thus optimizing the chances of a favorable outcome.

Block et al (1992), in their study on the effect of diet on the quality of life in cancer patients, showed that 25-50% of hospitalized cancer patients suffer from protein calorie malnutrition. They reported that those patients receiving adjuvant nutritional therapy with optimal levels of nutrients via food, supplements and /or selected nutrition while receiving standard conventional treatment for their cancers, had a 30% reduction in the length of their hospital stay. There was also a small study of leukemia patients in Mexico that showed that patients with cancer required 6 times the chemotherapy than those patients in the well nourished group. However, the malnourished patients could tolerate only 50% of the chemotherapy of those in the well nourished group. The researchers also found that the 5 year survival rate for the malnourished group was one-third of the well nourished group. In addition, there was a 50% reduction in mortality when adjuvant therapy was instituted when cancer was first diagnosed, irregardless whether the patient was malnourished or not at the time of diagnosis.

Some of the documented benefits of adequate nutrition include better tolerance of surgery, improved wound healing, and fewer post-operative complications. A study by Muller et al in 1982 on 125 malnourished group of patients with gastrointestinal cancer who received adjuvant therapy 10 days prior to surgery found that there was a significant decrease in mortality from 19% to 5% and a similar decrease in morbidity from 32% to 17%. Malnourishment has also been cited as a risk factor for developing post-surgical complications. Blackburn (1992) reported that surgical complications increased from 26% to 47% when surgery was performed on malnourished patients.

Adverse Effects of Cancer Therapies

Cancer patients frequently experience a number of adverse side-effects and reactions associated with the administration of chemotherapy. Cancer related fatigue is reported as being a major distressing symptom during treatment, in the advanced stages of the disease and after curative treatment (Servaes et al 2002) and gives rise to adverse physical, psychosocial, and economic consequences for both patients and caregivers

(Curt et al 2000). A recent multi-site study done by Vogelzang et al (1997) found that, while oncologist believed that pain adversely affected their patients to a greater degree than fatigue (61% versus 37%), patients with cancer felt that fatigue adversely affected their daily lives to a greater degree than pain (61% versus 19%). In a similar study done by Stone et al (2000) in UK, fatigue was also identified as affecting more patients with cancer more of the time than any other symptom and was regarded by the patients as being more important than either pain, nausea or vomiting. The degree of fatigue experienced by patients varied from mild to severe depending on the type of chemotherapeutic regime chosen (Zamagni et al 1998). Other concurrent conditions such as the severity of anemia a result of chronic disease or secondary to bleeding due to cancer and /or chemotherapy or secondary to radiation injury to the bone marrow.

Chemotherapy induced nausea and vomiting are also common symptoms and patients with cancer typically view control of nausea as more important than control of emesis (Bonnetterre et al (1991), while physicians and nurses judge emesis control to be more important to antiemetic efficacy than nausea control. (Lecomte et al 1995). In a number of reports (Lindley et al 1994; Love et al 1989), nausea and vomiting symptoms have each been associated with lowered quality of life, patient distress, disruption of social life, and absence from work. Further studies (Andrykowski et al 1985; Bilgrami et al 1993; Carey et al 1985; Osoba et al 1997) have documented that the fatigue, muscle strain, esophageal tears, and metabolic imbalance are frequently associated with chemotherapy-related nausea and vomiting along with lowered cognitive function, increased anxiety, and increased depression. Patients with cancer also commonly present with inadequate caloric and fluid intake and in these nutritionally compromised patients, poorly controlled nausea and vomiting can further aggravate the cachexia, lethargy, and weakness commonly caused by the disease. Morrow et al (1995) in a review of randomized, controlled, clinical trials, concluded that a number of anti-emetic drugs developed recently, such as the 5-HT₃ receptor antagonists, were effective in controlling nausea and emesis than previous emetic agents. However, Roscoe et al (2000) reported in their study of 5-HT₃ receptor antagonists in a community-based sample of 1413 outpatients that their usage led to a significant reduction in the frequency of post-

treatment vomiting but with an accompanying increase in the duration of post-treatment nausea.

Epidemiological and Animal Studies of Effects of Soy Based Diet on Risk of Developing Cancer.

A review of epidemiological studies by Messina et al (1994) showed that the consumption of soy was associated with a lowered risk of breast cancer, lung cancer, prostate cancer and leukemia in Asian countries such as China and Japan. Western diets on the other hand usually do not include soy products. Soy contains large amounts (1-3mg/g) of the isoflavones, genistein (4', 5,7-trihydroxyisoflavone) and daidzein (4',7-dihydroxyisoflavone). A number of studies on soyfoods and its effect on human consumption (Setchell et al (1984), Murphy (1982), Jones et al (1989) concluded that adding soy to a typical Western based diet increased urinary isoflavones by as much as 1000-fold.

A panel of nutritional and research experts in the field at a workshop sponsored by the National Cancer Institute (Messina M and Barnes S, 1991) made the following recommendations on the role of soy products in cancer prevention: Firstly, that future dietary studies should be carried out on soy products rather than isolated compounds, since soybeans appear to contain several potential anticarcinogens that interact with each other. Secondly, standardized and improved analytical methods are needed so that the contents of all soy-based materials used in soy related research can be accurately described and hence, valid comparisons can be done across all these studies. Thirdly, there was a need to conduct more basic research on the absorption, metabolism and physiology of potential anticarcinogens in human subjects. While a definitive statement that soy reduces cancer risk could not be made at that time, there was sufficient evidence of a protective effect to warrant continued investigation.

We have reviewed some of the relevant in vitro, animal and epidemiological data since the NCI report as well as examined the case reports presented in this paper to consider

seriously whether dietary supplementation with fermented soy nutraceutical such as Haelan 951 could significantly enhance the therapeutic potential of patients diagnosed with terminal cancers undergoing palliative conventional therapy.

Researchers have found that the chemotherapy agents significantly increased nuclear factor-kappaB (NF-kappaB) activity which affects cell survival and determines the sensitivity of cancer cells to cytotoxic agents such as cisplatin, docetaxel, and adriamycin as well to ionizing radiation. Data is now emerging to show that soy isoflavone supplementation may protect cells from oxidative stress-inducing chemotherapeutic agents by inhibiting NF-KB activation and decreasing DNA adduct levels. The phytochemical ingredients in the dietary fermented soy nutraceutical, Haelan951 act as biological response modifiers by promoting immunostimulation, redifferentiation of malignant cells, and inhibiting tumor neovascularization.

Soy foods made from whole soybeans or isolated and purified soy proteins all contain relatively high concentrations of isoflavones, primarily in the form of various β -glycoside conjugates (Coward et al. 1993 , Murphy 1982). A wide range of soy isoflavone extracts and supplements are now commercially available; however, little is known concerning their metabolism and effects. Much is known about the general metabolism of soy isoflavones in animals and humans, but only limited information exists on pharmacokinetics (King and Bursill 1998). When ingested, these conjugated isoflavones undergo hydrolysis by β -glycosidase in the jejunum, releasing the principal bioactive aglycones, daidzein and genistein. Further metabolism takes place in the distal intestine with the formation of specific metabolites (Joanneau et al. 1995). Intestinal metabolism is essential for their subsequent absorption and bioavailability (Setchell et al. 1984) because there is no evidence to support absorption of the conjugated forms of isoflavones.

Soybeans are a unique dietary source of the isoflavone genistein, which possesses weak estrogenic activity and has been shown to act in animal models as an antiestrogen. It has been postulated that genistein, the predominant isoflavone in soy foods may be

principally responsible for the decreased risk of both hormone-dependent and non-hormone-dependant cancers. Genistein is also a specific inhibitor of protein tyrosine kinases; it also inhibits DNA topoisomerases and other critical enzymes involved in signal transduction. In vitro, genistein suppresses the growth of a wide range of cancer cells, with IC50 values ranging from 5 to 40 micron (1-10 micrograms/ml). According to Of the 26 animal studies of experimental carcinogenesis in which diets containing soy or soybean isoflavones were employed, 17 (65%) reported protective effects. No studies reported soy intake increased tumor development. The epidemiological data are also inconsistent, although consumption of nonfermented soy products, such as soymilk and tofu, tended to be either protective or not associated with cancer risk; however, no consistent pattern was evident with the fermented soy products, such as miso. Protective effects were observed for both hormone- and nonhormone-related cancers.

A study by Kanamoto et al showed that soybean resistant proteins could potentially interrupt enterohepatic circulation of bile acids and suppress liver tumor genesis induced by azoxymethane and dietary deoxycholate in rats. The researchers found that that azoxymethane and dietary deoxycholate induced liver tumors in rats. The incidence and the development of the tumor were closely related to the enterohepatic circulation of bile acids. The feeding of a high-molecular-weight fraction of soy protein digest (HMF) suppressed the tumor genesis, probably due to the inhibitory effect of soybean resistant protein on reabsorption of bile acids in the intestine.

A number of animal model studies by Barnes et all (1990), also showed that there was more than one mechanism of action to explain isoflavones' anticarcinogenic activity in decreasing chemically induced rodent mammary cancer through inhibition of mammary tumor genesis. With the consumption of isoflavones in tumors containing a functional steroid receptor system, there was evidence of a decrease in mammary tumor estrogen receptors that paralleled mammary tumor genesis. But alternative mechanisms of action may include inhibition of the activity of tyrosine protein kinase, (e.g. epidermal growth factor receptor tyrosine kinase) (Akiyama et al 1987), DNA topoisomerase II (Okura et al, 1988), ribosomal S6 kinase (Linassier C et al, 1990), induction of specific cytochrome

P450s (Sariaslani FS et al, 1986). Recently there have been some interesting findings in the induction of in vitro and in vivo apoptotic cell death by saturated branched chain fatty acid, 13-Methyltetradecanoic Acid, which was purified from fermented soy products (Zhenhua Y et al, 2000).

Role of Haelan 951, A Dietary Fermented Soy Nutraceutical in Cancer Therapies

There are three fermented soy beverages in the US market namely, EcoNugenics, Soy Unique and Haelan. Of the three a market report analysis by Iowa State University the last of which was done on May 2000 showed that the soy isoflavones, daidzin and genistin as well as the fermented soy isoflavone metabolites were significantly higher in the Haelan samples as compared to the other two products. For this reason we decided to use Haelan951 in the present hepatocellular carcinoma study.

The dietary nutraceutical, Haelan951, which is the subject of this application is a fermented soy supplement made by Haelan951 Products Inc. based in Seattle, USA. Haelan 851 was approved by FDA as a beverage in the complete food category since 1985. Manufacturing, which includes plant cultivation and processing of the soybeans are done in the People's Republic of China. The patented 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. 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.

Clinical and Pre Clinical Trials Done With Haelan, A Novel Fermented Soy Nutraceutical

- (1) At the Third National Traditional Chinese Gerontological Research Co-Operative Conference held in 1986 the results of a study comprising 303 elderly individuals randomized into five treatment groups taking varying doses of Haelan851 (an earlier version of the Haelan951 formula), the fermented soy supplement were reported. Subjects receiving 1 oz of the fermented soy supplementation showed significant improvements in several areas of measures, including cardio-pulmonary function, cognitive performance, enhancement of immune markers and balancing of the sex hormones.
- (2) Another study conducted in 1993 assessed the role of the fermented soy supplement, Haelan851 when used as an adjuvant in 318 patients receiving chemotherapy and or radiotherapy. All of the 117 subjects on Haelan completed the treatment regime without requiring blood transfusions and experienced significantly less chemotherapy-induced side effects such as decrease appetite, nausea, vomiting, diarrhea, constipation, hair loss, stomatitis and hemorrhage when compared with controls. The improvement was also marked in terms of the intervention group having the least decrease in white cell counts and serum hemoglobin levels
- (3) In another study, the fermented soy beverage was also shown to significantly improve the health of malnourished infants and children whose ages ranged from

6 months to 11 years. The intervention group was observed to have a 9.5% increase in body weight, a 6% increase in subcutaneous fat deposition, and increases in levels of trace elements such as iron and zinc by 34% and 15% respectively while serum hemoglobin rose by 6%.

- (4) In one pre-clinical trial, 51 Kunming bread mice were divided into 5 groups and inoculated with H₂₂ liver cancer cells before and after some of the groups were given the nutritional intervention with Haelan, the fermented soy supplement. leucopenia had been induced by cylophosphamide inoculation. In the intervention group, it was noted that the white cell count increased by 86.8%.
- (5) An efficacy study was done in 1998 to evaluate one of the anti-carcinogenic agents in the Haelan 851 Formula , called compound SBA was conducted in MetaMouse Orthotopic model of Human Hepatocellular Carcinoma LC1-D35. The results showed a significantly high tumor inhibitory rate of 64.9% as well as a marked reduction in the final tumor weight for the test compound when compared to controls. There was also no evidence of toxicity.

Conclusion

Recent national research in the United States shows that eight out of 10 cancer patients are using some form of complementary and alternative medicine (CAM) therapy, such as herbs, vitamins, or meditation, and they do so mostly in combination with their conventional medical treatments. This growing trend in the use of CAM therapies exemplifies the increasing popularity of CAM worldwide, despite the lack of scientific research conducted on the procedures and products.

Studies are needed to demonstrate the mechanisms of action and to verify the efficacy of fermented soy supplements. We need to take a deeper look at understanding the benefits and mechanism of action of fermented soy supplementation both in chemoprevention and as a therapeutic dietary supplementation to support the nutritional requirements of patients diagnosed with cancers.

There have been a few clinical trials but no prospective clinical trials have been reported, and no systematic clinical investigations of the effectiveness of the dietary fermented soy nutraceutical Haelan 951, as adjuvant supplementation for advanced cancer have been conducted. Haelan 951 has been in the market for the past 10 years and there have been many thousands of patients in the US, Europe and Asia who have been taking Haelan 951 as an adjunct or stand alone treatment for their cancers. Most of the clinical trials done so far have been conducted in medical and research institutions in China. More research is needed in the US especially in the context of using it as an adjuvant nutraceutical in cancer therapies.

Future research in advocating dietary supplementation with fermented soy nutraceutical such as Healan951, in patients diagnosed with cancers need to address pertinent issues such as: (1) the role of the fermented soy supplement in the prevention and reversal of cancer related asthenia, anorexia and cachexia. (2) The role of the phytochemicals in the fermented soy supplement that may help reduce toxicity and improve the efficacy of conventional cancer therapy and (3) the identification of the nutritional factors in the fermented soy nutraceutical that selectively help to arrest tumor cell growth and metastasis.

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