

## **I. Introduction:**

### **What is AHCC - Active Hexose Correlated Compound?**

- ∅ A natural substance made from medicinal mushrooms containing bioactive and low molecular weight hexose molecules
- ∅ Created by reacting specific enzymes with several species of medicinal mushrooms Basidiomycetes
- ∅ Since 1986, AHCC has mostly been used in immune suppressed patients (Cancer, HIV, Hepatitis) .
- ∅ Cancer patients have benefited from AHCC's ability to:
  - Increase immune system strength, stamina, and well-being
  - Improve Quality of Life parameters
  - Increase survival time
  - Reduce the negative side effects of chemotherapy and radiation
  - Enhance the tumor killing effects of chemotherapy and radiation
- ∅ Oral consumption has ranged between 3 – 6 grams daily with no side effects

### **AHCC and the Immune System:**

The immune system is our body's primary means of defense against pathogens and invaders. When functioning optimally, it eliminates bacteria, viruses, parasites, and cancerous cells. But, when compromised, it cannot defend the body against pathogens and uncontrolled growth of tumors or cancerous cells. AHCC has been found to be very effective in strengthening and optimizing the capacity of the immune system. Furthermore, there are no side effects to taking AHCC as an immune enhancing supplement. AHCC also functions in reducing the side effects of radiotherapy and chemotherapy, as well as helps improve patients' quality of life (reduction of nausea, increase of appetite, decrease anxiety).

### **Development of AHCC**

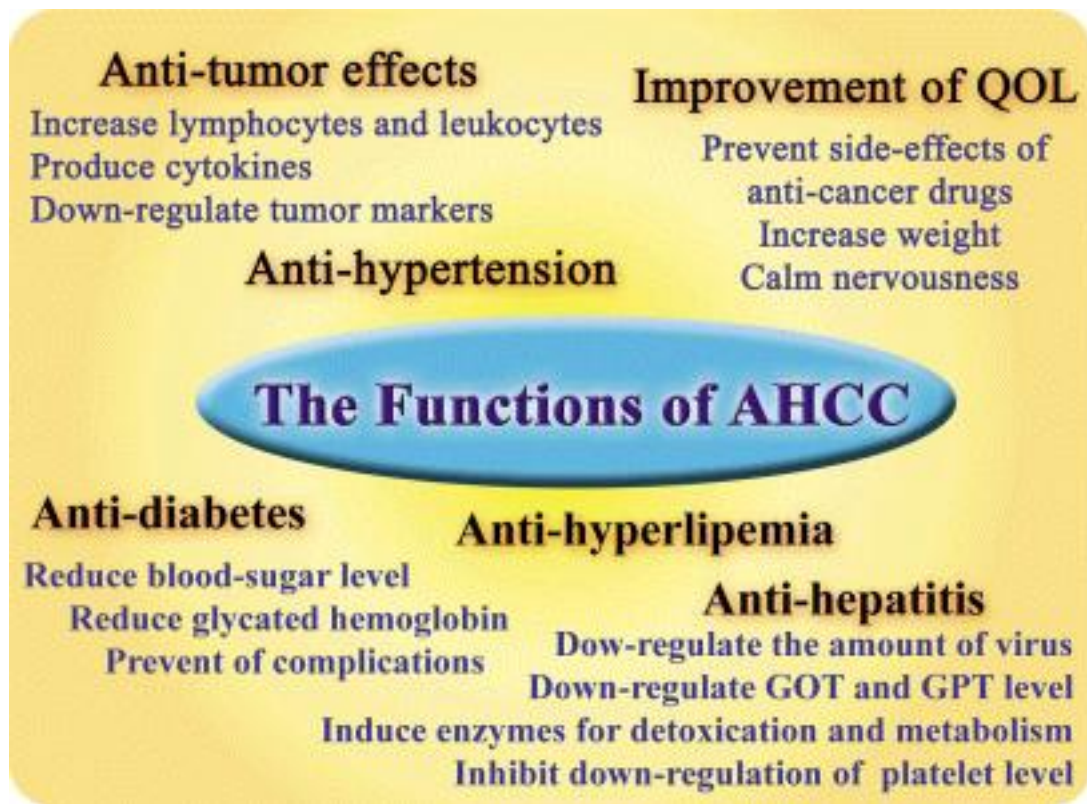


AHCC was jointly researched and developed by Amino Up Chemical Co., Ltd. and Dr. Toshihiko Okamoto at The Pharmaceutical Department of Tokyo University in 1989.

AHCC, rich in nutrients and dietary fiber, has been marketed as a supplement for cancer patients since its launch.

The AHCC Research Association, established in 1994, consists of over 300 clinical doctors, researchers, and other medical professionals involved with AHCC. Each year, the association hosts a symposium during which all the members

gather to discuss their latest findings and scientific research on AHCC.



### Manufacturing Process of AHCC

AHCC is extracted from a myceloid of Basidiomycetes mushrooms, which are cultured in a large tank. The plant's germ-free facilities pass the GMP standards of manufacturing in quality control for medical products. ISO 9002 and HACCP certification was acquired in 2001.

Basidiomycetes form colonies during their pre-cultivation phase, and then are cultured further in the main tank (15 tons at largest) for 45 days. AHCC is obtained after undergoing cultivation, oxygen-decomposition, sterilization, compression, and freeze-drying (a patented process). AHCC's special ingredients are obtained by this unique cultivation method and thus cannot be found in typical mushrooms.

## Active ingredients of AHCC

AHCC's active ingredients include **acetylated a- and b-glucans** which are oligosaccharide obtained during the Basidiomycetes' cultivation process, and most importantly, AHCC contains the patented **GI-saccharides** which do not exist in any other mushroom or immune enhancing product. This GI-saccharide has a molecular weight under 1,000 and is in glycoside form, making it easily digestible and the most potent compound found to boost the immune system. More specifically, GI-saccharide has been found to significantly increase IFN-gama, IL-2, and IL-12.

In addition, AHCC contains a high concentration of 10% oligosaccharides (alpha-1,4 glucan) with a molecular weight under 5,000 Daltons. (Molecular weight of most oligosaccharides is usually over 200,000 Daltons which makes mushroom products very hard to digest. Thus, AHCC's very low molecular weight is a critical feature allowing for optimal bioavailability. (*The 5th Japanese Association of Cancer Prevention, Jul 1998, & The 57th Japanese Association of Cancer Research, Sep 1998*)

## Dosage of AHCC

AHCC is brown powder made of fine granules. It is water-soluble, water-stable, and micro-coated with Candelilla wax (to improve solubility in intestines). Typically, each soft gelatin coated capsules contains 500 mg AHCC.

## Recommended Use

AHCC is authorized by the FDA of China and Thailand to be used alone or in combination with other supplements such as PMP and GCP for its immune modulating effects.

## Indications and Dose

Maintenance of General Health & Prevention of Diseases	1g – 3g /day
Prevention of Reoccurring Cancer	3g /day (apx)
Treatment of Cancer, Prevention of cancer drugs' side effects	3g – 6g /day

## Length of Time for Results

- 2 weeks for QOL improvement
- 3 months for cancer re-evaluation

## 2- Safety of AHCC

AHCC has been demonstrated to be safe enough as a nutritional supplement.

- ⊙ The mushrooms used in AHCC are edible for humans since ancient times.
- ⊙ There are many thousands of people taking AHCC to date and no obvious side effect is reported.
- ⊙ The LD<sub>50</sub> of AHCC is over 12 g/kg in acute toxicological study in rats by oral and over 8.5 g/kg by intraperitoneal.

For thousands of years and all over the world, various Basidiomycetes mushrooms have been used as a food and for traditional folk medicine, especially in Asia and Europe. Among these mushrooms is Shiitake, a well-known edible mushroom. AHCC's primary ingredients consist of these various types of edible Basidiomycetes mushrooms, thus it would be logical that AHCC's consumption is safe when consumed orally. Moreover, during its 15 years of use, AHCC has demonstrated to be safe as a nutrition supplement. There are currently hundreds of thousands of people taking AHCC and no side effects have been reported.

Although there have not been any toxicological problems or side effect with AHCC to date, acute and subacute toxicological studies were conducted in animals at The Safety Research Institute for Chemical Compounds Co., LTD. All the toxicological studies were done in correspondence with GLP standards and guidelines for toxicological experiments. Acute toxicology studies of rats show the LD<sub>50</sub> of AHCC taken orally to be over 12 g/kg, and over 8.5 g/kg while given intraperitoneally.

**High tech hill shin-ei, 363-24, Shin-ei, Sapporo, Japan 004-0839**

Date • Jun. 10.1996 • Sep. 12.1996

### 1) Oral single dose toxicity study of AHCC FD in rats

**Animals:** ••• male SD rats (5 weeks old), and female SD rats (6 weeks old).

**Dose:** The maximum dose was 12,500mg/kg for AHCC FD. Thus the single dose toxicity for orally administered AHCC FD was at a dose of 0 for the control or 12,500mg/kg for the experimental

group. Each male and female group consisted of 10 rats.

**Results:** No death occurred during the observation period of the control group or 12,500mg/kg AHCC group. The LD<sub>50</sub> was more than 12,500mg/kg for oral single dose toxicity of AHCC FD. It was concluded that oral administration of AHCC FD had little acute toxicity potential.

## 2) Intraperitoneal single dose toxicity study of AHCC FD in rats

**Animals:** ••• male SD rats (5 weeks old), and female SD rats (6 weeks old).

**Dose:** In this study, rats were administered AHCC FD intraperitoneally at a dose of 0 for the control, and 6,250, 7,430, 7,870, 8,340, 8,840, 9,370, 10,500, or 12,500 mg/kg body weight. Each male and female group consisted of 5 rats.

**Histopathological findings**•Organs and tissues of male rats died within 24 hr in the 12,500mg/kg group and those of the female rat died within 48 hr in the 8,840mg/kg group. These organs and tissues were examined histopathologically.

**Results:** LD<sub>50</sub> was 8,490 mg/kg in male rats and 9,849 mg/kg in female rats. The minimum lethal dose of AHCC FD was 7,430mg/kg in male rats and 8,340mg/kg in female rats.

**Conclusion:** The minimal lethal dose of intraperitoneally administered AHCC was lower in the male rats than in the female rats, at 7,430mg/kg and 8,340mg/kg respectively.

## 3) Oral subchronic toxicological study of AHCC

This study was conducted at the Biochemistry Department of Amino Up Chemical, Co., Ltd.

**Animals:** 24 male and 24 female SD rats (7 weeks old) were used for this study.

**Administration of AHCC:** AHCC was incorporated into SE-2 standard powder diet in the proportion of 1% and 5%. The experimental groups, which consisted of 8 male and 8 female rats, received this AHCC diet for 16 weeks. The control group was fed the standard powder diet without AHCC.

**Methods:** The rats in the experimental groups were weighed every 2 days and body measurements were taken every week. After 16 weeks, the rats were executed, and their blood cell count was taken. Assays on liver function were performed, as were histopathologies of the liver, kidney, spleen and heart.

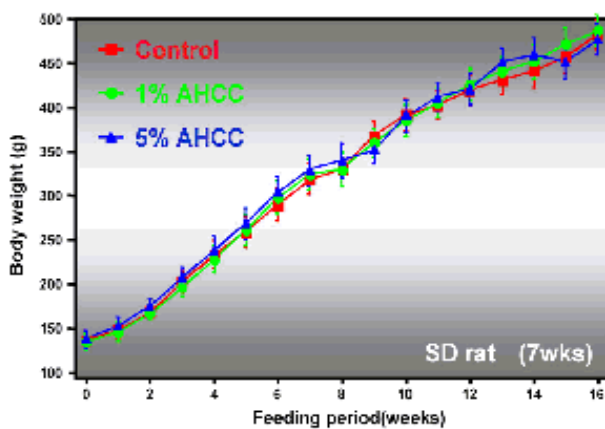
**Results:** There were no overt signs of toxicity in either male and female rats in the two AHCC-treated groups. Food consumption was not affected by the incorporation of AHCC into diet. The daily consumption of AHCC was 0.61g/kg body weight in 1% AHCC-treated group and 2.95 g/kg in 5%

## AHCC-treated group.

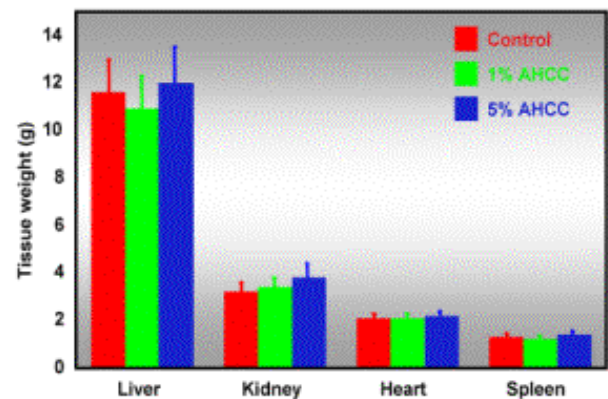
§ *Weight* - No significant changes in weight gain were noticed in the three groups (as shown in Fig. Left). The weights of their livers, hearts, and kidneys are shown in Fig. Right. Although there were no significant differences, the weight of the kidneys in the 5% AHCC-treated rats was higher than those of control group and the 1% AHCC-treated group.

§ *Blood Cells* - The numbers of red blood cells in the AHCC-treated groups were more than that of the control group, but the number of white blood cells was same in three groups. The sGTP, sGOP, albumin, and globulin levels were not significantly different in the three groups.

§



Body weight change of rat fed 1% and 5%AHCC



Tissue weight of rat fed 1% and 5%AHCC

*Organs* - There was no inflammation, cell infiltration, hydropic degeneration, or other pathological changes in livers, kidneys or hearts.

**Conclusion:** The administration of AHCC to rats in the doses of 0.61 and 2.95 g/kg/day for 16 weeks caused no significant changes in body weight, organ weight, blood cell count, or organ pathology between either AHCC-treated groups and the control group. Furthermore, no toxicity was seen as measured by physiological, biochemical and histopathological indexes. Therefore, AHCC should be safe when administered orally under a daily dose of 2.95 g/kg.

## The Functions of AHCC

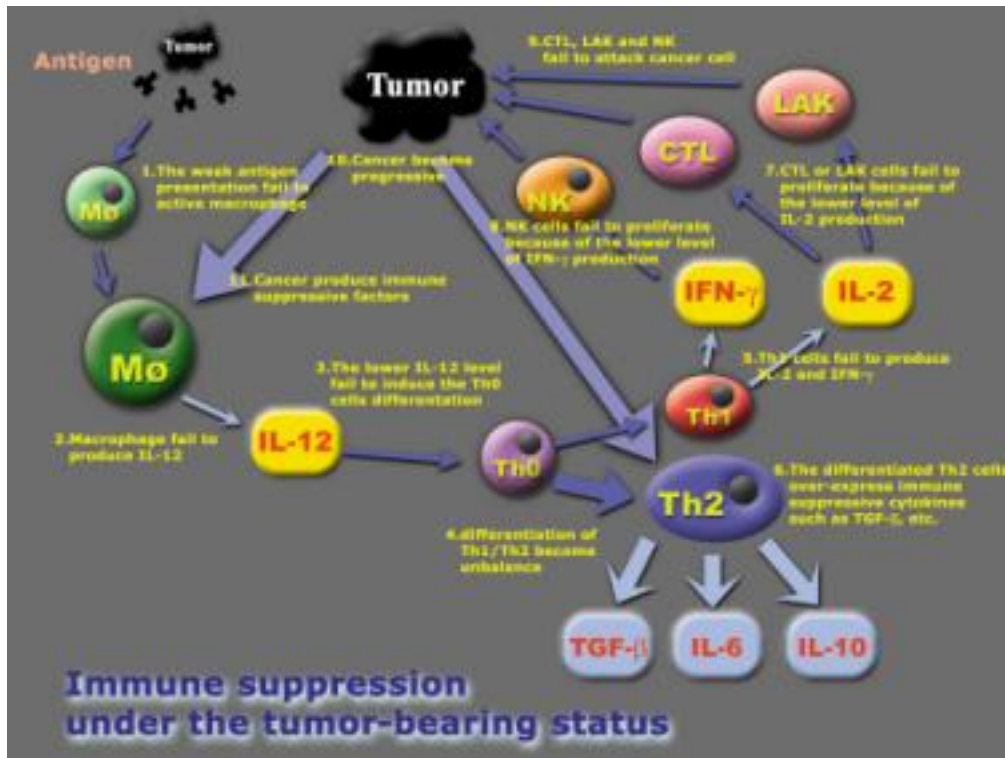
### AHCC's immune system effects

- ⊙ Enhances immune response.
- ⊙ Activates the immune cells including macrophage, NK and LAK cells.
- ⊙ Induces and increases production of cytokines including  $\text{TNF-}\alpha$ ,  $\text{IFN-}\gamma$ , IL-1, IL-2 and IL-12, etc.
- ⊙ Inhibits suppressive cytokines such as  $\text{TGF-}\beta$ .
- ⊙ Improves Th1/ Th2 balance.

### 3-1 Effect of AHCC on the Immune System

#### Carcinogenesis and Immune Response in Cancer

The body is composed of billions of cells, which are all subject to free radical damage and mutations caused by various carcinogens. Free radicals and carcinogens cause cells to become mutated and abnormal. The immune surveillance system plays a critical role in prevention of cancer by recognizing the formation of these abnormal cells. T-cells in particular are valuable for their ability to distinguish the mutated cells from normal cells. Yet, when the immune system is suppressed, the mutated carcinoma cells are not recognized by the immune surveillance system and the cells grow uncontrollably and become cancerous.

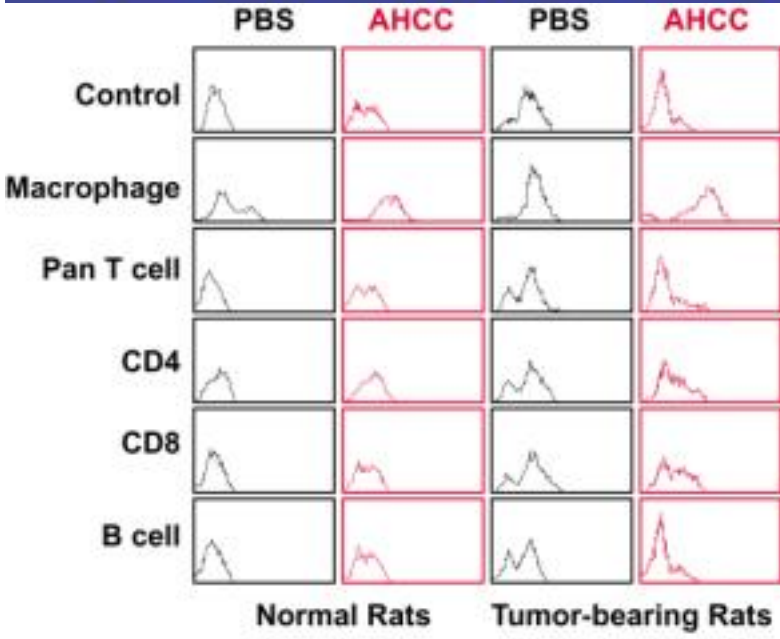
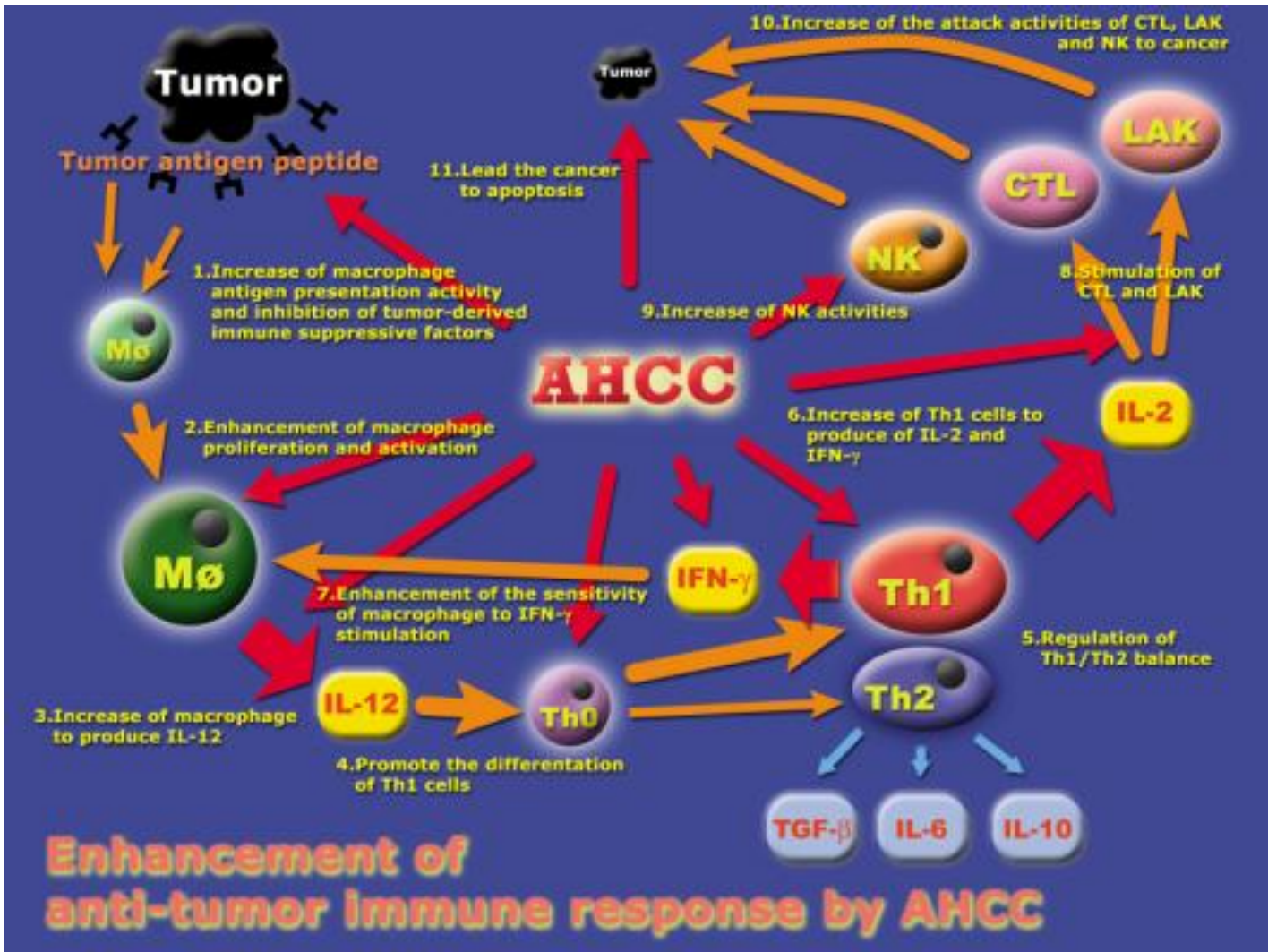


Cancer cells release several kinds of immune suppressive factors, which inhibit antigen and macrophage activity. T-cells in a suppressed immune system do not recognize cancer cells. The suppressed macrophage cells fail to produce IL-12 and thus the Th0 cells cannot proliferate or differentiate into Th1/Th2 cells. The suppressed Th1 cells cannot exert their anti-tumor effects which include production of IL-2 and IFN- $\gamma$ . Finally, the anti-cancer immune response fails when the proliferation of CTL, LAK or NK cells fails.

Cancer is a disease of the immune system whereby immune suppression allows cancerous cells to not be recognized and grow uncontrollably. Thus, reversing and restoring the suppressed immune system should be a very important part of cancer treatment.

### AHCC : The Most Effective Product to Enhance Immune Response in Cancer Treatment

AHCC restores and reverses a suppressed immune status by stimulating and activating the immune system and finally wiping out cancerous cells. The mechanism of AHCC in enhancement of immune system is described in the following figure.



### Sub-population of PEC

### Tumor Bearing Mice Treated with AHCC and its Fraction

### 1) Basic Research

#### Enhanced Macrophage Proliferation and Activity

The Institute for Genetic Medicine at Hokkaido University found that the macrophage population harvested from AHCC peritoneal treated rats increased twice as much as rats in the control group, for both normal rats and in tumor-bearing rats. This result demonstrated that AHCC increased the proliferation and activation of macrophages.

*(The 4th Symposium of AHCC Research Association, Jun. 1997).*

#### Increased Cytokine Expression in the Splnocytes of

AHCC was extracted and separated into low and high molecular fractions. The fractions were evaluated

in tumor bearing mice for their effects on cytokine expression. The result showed that AHCC, used as a whole molecule, increased IL-2 and TNF- $\alpha$  expression, while AHCC's low molecular fraction was the strongest enhancer for the IL-12 expression in the splenocytes of the tumor-bearing mice. Furthermore, AHCC and its fractions were found to inhibit the immune suppressive cytokine TGF- $\beta$  expression derived from tumor tissue.

(The 6th Symposium of AHCC Research Association, Nov. 1998)

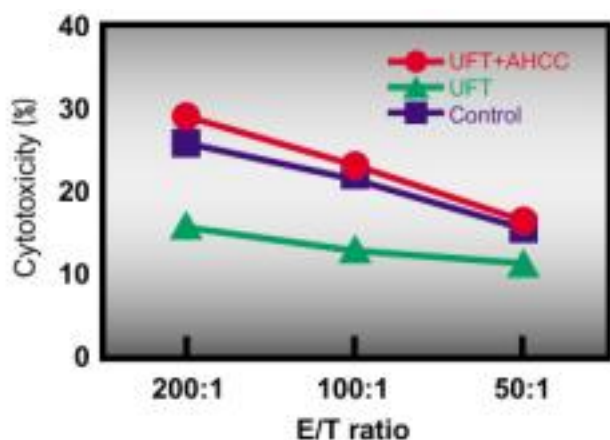
**Expression of cytokines in tumor-bearing mouse treated with AHCC and its fractions**

Cytokines	Control	AHCC	Low molecular fraction	High molecular fraction
<b>Splenocyte</b>				
IL-2	—	+++	++	++
IL-12	—	++	+++	—
TNF- $\alpha$	—	+++	++	++
<b>Tumor tissue</b>				
TGF- $\beta$	+++	—	—	—

(—) No expression, (+) Slight expression, (++) Moderate expression, (+++) Strong expression

**Improvement of  
Chemotherapy-  
Induced Immune  
Suppression by  
AHCC**

Chemotherapy is a main therapy for cancer but it often induces some serious side effect such as immune suppression. When the immune system is suppressed, infections result, and then cancerous cells proliferate further. Therefore, it is very important to improve the immune suppression induced by chemotherapy during cancer treatment.



**NK cell activity of spleen cells in ST-2-bearing rats administered AHCC**

macrophages (PEC) were harvested from breast cancer bearing rats treated with UFT or UFT+AHCC. The nitrogen oxide (NO) production was measured from the culture supernatants of the macrophages. Result showed that the NO production in the UFT+AHCC treated group was higher than that in UFT

The Institute for Genetic Medicine in Hokkaido University evaluated the effects of AHCC on its ability to lessen immune suppression induced by UFT chemotherapy. Results showed that the UFT treated group had weakened NK activity; yet, the UFT+AHCC group had less suppression of NK activity. This result suggested that AHCC reversed chemotherapy-induced immune suppression.

In addition, testing was done to determine AHCC's effects on chemotherapy-induced inhibition of macrophage activity. The

only treated group. This suggested that AHCC restored the chemotherapy-induced inhibition of macrophage activity.

(*Anti-cancer Drugs*, 1998, 9, 343-350)

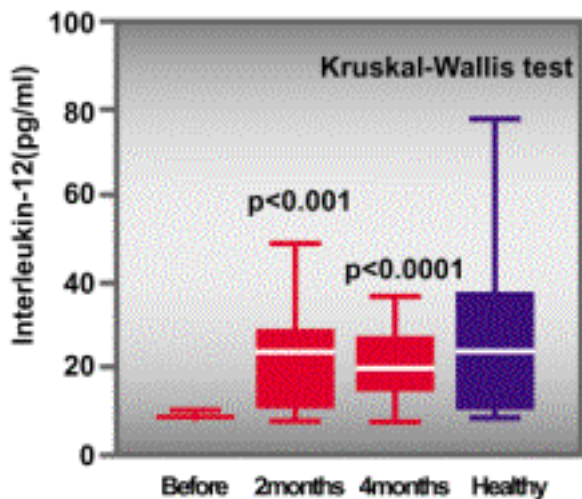
### **NO production and cytotoxicity of peritoneal macrophage obtained from rats administered AHCC**

Treatment	E:T ratio			
	NO production( $\mu$ M)			Cytotoxicity against SST-2(%)
	100:1	50:1	25:1	100:1
<b>UFT+AHCC</b>	<b>5.44</b>	<b>2.74</b>	<b>1.53</b>	<b>15.32</b>
<b>UFT</b>	<b>3.08</b>	<b>2.00</b>	<b>0.78</b>	<b>13.27</b>
<b>Control</b>	<b>1.62</b>	<b>0.49</b>	<b>0.00</b>	<b>10.82</b>

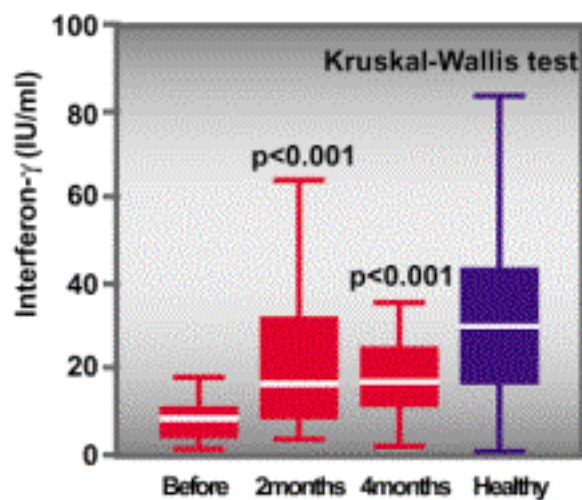
2)  
Clinical  
Research

*AHCC as*

*an Immunotherapy for Cancer Patients*



**Gradual increase of IL-12 level in cancer patients after AHCC treatment**



**Gradual increase of IFN- $\gamma$  level in cancer patients after AHCC treatment**

Dr. Uno (Comfort Medical Foundation, Japan) reported that AHCC exerted its anti-tumor effect by improving the relationship between the cancer and its host. As shown in Figure, the serum of 47 cancer patients administered with AHCC showed gradual increases in IL-12 levels.

AHCC + PSK was also administered to 520 cancer patients not treated with chemotherapy or BRM agents. The dose of AHCC was 6g/day, and that of PSK was 3g/day. Before the AHCC treatment began, IL-12 levels were 7.8 pg/ml (an undetectable level). Yet, they reached normal level after 2 to 4 months of AHCC treatment. In result, AHCC treatment increased IFN- $\gamma$  level as seen by IL-12 pattern.

The therapeutic effects of AHCC were shown in Table. Several parameters were evaluated including CR (complete response), PR (partial response), NC (No change) and PD (progressive disease). The patients were selected to be subjects only if they could undergo 6 months of treatment. The results showed that AHCC treatment lead to improvements in PR (49.7%), CR (8%), and Quality of Life (60 %).

*(Biotherapy, 2000, 14 (3), 303 - 307).*

**Therapeutic effectiveness of AHCC treatment**

	CR	PR	NC	PD
<b>Patients</b>	17	97	27	54
<b>Rate</b>	8.8%	49.7%	13.8%	27.7%

**The Clinical Effectiveness of AHCC Treatment in Cancer Patients with Progressive or Metastasized Cancers: An Observation of Immune Parameters.**

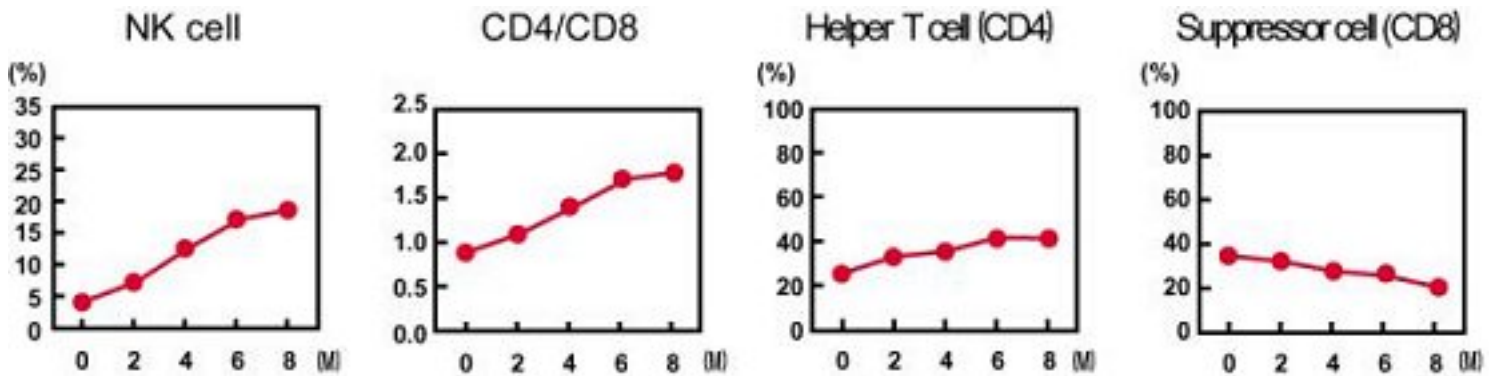
Dr. Gye Hoon Ahn *et al* (OK-Chem Hospital, Korea) evaluated the immune parameters from patients with progressive cancers. All the patients were diagnosed as either Stage III (3 patients) or stage IV (9 patients) by roentgenological image and pathological

examination. The types of cancers ranged from breast, gastric, lung, liver, uterine, and ovarian. Of the 12 cases, 9 cases were treated with AHCC and the other three cases were treated with AHCC plus shark cartilage. The immune parameters were examined every two months. There were no side effects found

in any of the patients.

Results showed that a one-month administration of AHCC caused an increase in NK activity, which lasted up to six months. CD4 count increased smoothly while CD8 count was found to decrease gradually. The CD4/CD8 ratio significantly increased after 8 months of AHCC treatment. As for clinical efficacy, there were 3 cases of tumor regression. The result also suggested that AHCC restored the immune suppression in the patients who underwent chemotherapy.

*(The 8th International Symposium of AHCC Research Association, Aug. 2000)*



In summary, the results of the basic and clinical research indicated AHCC is a powerful anti-tumor substance, which works by activating and enhancing the cells of the immune system. The powerful immune regulating effects of AHCC could be used in a variety of immune related diseases.

## AHCC is very effective on several types of cancers

- ⊙ Data from thousands of cancer patients who use AHCC indicates that 60% of users find the product has been either very effective, moderately effective, or a bit effective.
- ⊙ AHCC acts as an anti-cancer agent in the human body by reducing tumor growth and often shrinking tumors completely.
- ⊙ AHCC can inhibit the metastasis and recurrence of cancers, thus prolonging a patient's survival period.
- ⊙ Furthermore, AHCC has been particularly effective on hepatic carcinomas, gastrointestinal cancers, breast cancer, thyroid carcinomas, ovarian cancer, testicular cancer, tongue cancer, renal cancer, and pancreatic carcinomas.

### 3-2 Anti-Tumor Effects of AHCC

Cancer has become one of our leading causes of death, with over 600,000 dying each year from it, and 1.5 million new cases each year. Since the 1980s, one of every four people in developing countries died of some sort of cancer.

Conventional therapies for cancer treatment include surgery, radiation and chemotherapy.

Immunotherapy has been introduced as yet another modality of treatment acting as a biological response modifier (BRM). AHCC has been found to be the most effective immunotherapy, helping patients raise their resistance to cancers by optimizing all their organ systems including their immune system.

Over the past 10 years, there have been over 100,000 patients with various kinds of cancers taking AHCC successfully as an immunotherapy. Currently, there are approximately 700 hospitals, clinics, and universities conducting ongoing studies on AHCC's efficacy.

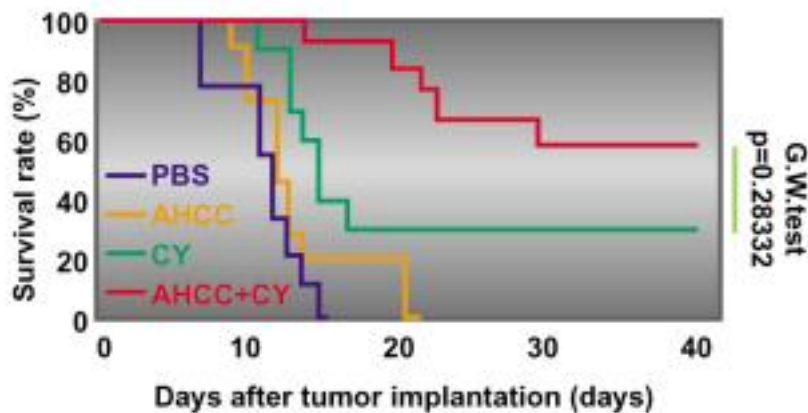
#### 1) What do studies indicate about AHCC's function?

- Reduces or eliminates tumors by enhancing immune system strength.
- Improves quality of life (QOL) levels of cancer patients by promoting mood and appetite, and preventing hair loss, nausea, and vomiting.
- Inhibits the side effects of chemotherapeutics or radiation as well as to increase chemo's therapeutic effects.
- Prolong the survival period of cancer patients by inhibiting metastasis and recurrence of tumors.

AHCC has remarkable benefits on the immune system. It stimulates Natural Killer (NK) and Lymphokine Activated Killer (LAK) cells, thus acts to inhibit tumor cells. In fact, experimental trials with rats show that administration of AHCC during chemotherapy (UFT) significantly reduces tumor activity as compared to groups undergoing UFT alone.

Furthermore, combination treatments of AHCC and chemotherapy showed successful in inhibiting metastases to the lungs and lymph nodes. In particular, metastasis to the lymph nodes was completely inhibited by this combination. All rats in the UFT only group died after the original tumors were surgically removed, yet the rats receiving UFT plus AHCC had a significantly prolonged survival rate.

(The 4th Symposium of AHCC Research Association, Aug 1996)



### Survival curves of KMT-17-bearing rats treated with AHCC and/or CY

### 2) Improved Prognosis of Postoperative Hepatocellular Carcinoma Patients Treated with AHCC

Dr. Kamiyama *et al* from the First Department of Surgery, Kansai Medical University, in Osaka, Japan, treated postoperative hepatocellular carcinoma patients with AHCC to study its effects on disease-free survival rates. Data was collected retrospectively from February 1992 to March 2000. All the patients were confirmed to have hepatocellular carcinoma and all of them underwent macroscopically curative resection of liver tumors. Of the 167 patients, 83

received AHCC (3g/day) orally after undergoing surgery. Survival and disease-free survival rates of the 83 patients in the AHCC group were compared with a control group of 84 patients who did not receive AHCC after surgery. There were no significant differences in the clinical backgrounds of the two groups. Recurrence was determined by CT, MRI or angiogram. Furthermore, disease-free survival was defined as the period from surgery to date of recurrence.

Results showed that overall survival in the AHCC group was significantly higher than that of the control group. Disease-free survival rates after five years were 34% for the AHCC group, and 20% for the control group, showing that the survival rate was significantly prolonged by AHCC administration.

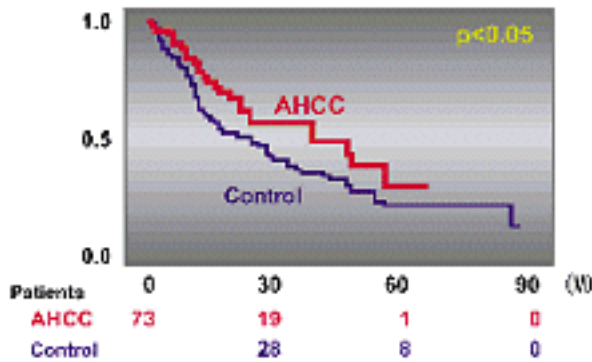
Furthermore, AST,  $\gamma$ -GTP, and bilirubin values for liver function parameters were significantly lower in the AHCC group 4 years after surgery.

In conclusion, AHCC supplementation was proven to be beneficial for hepatitis, disease-free survival, and general survival of postoperative hepatocellular carcinoma patients without adverse effects.

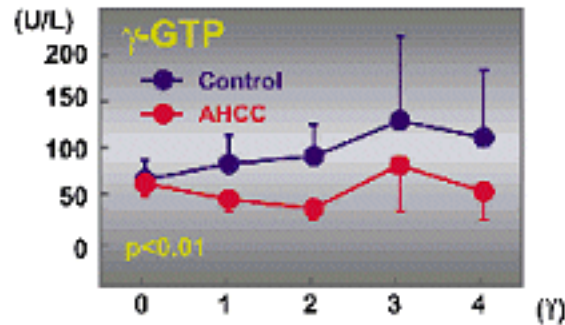
Therefore, AHCC treatment is a valuable adjuvant therapy as an alternative medicine or biological response modifier for these patients. (*The 32-34th Congress of the European Society for Surgical Research (ESSR), May 1997; May 1998; Apr 1999*)

### Effect of AHCC on cancers of digestive organs

Cancer	Stage	Patients	Died	Survival (month)	Survival rate(%)	Average in Japan
Stomach cancer	0-I	6	0/6		100.0	
	II	1	0/1		100.0	
	III	6	2/6	27.0	66.7	35.0
	IV	15	12/15	14.4	20.0	8.0
Colon cancer	0-I	2	0/2		100.0	
	II	8	0/8		100.0	
	III	18	2/18	10.2	89.9	55.9
	IV	14	10/14	13.1	28.6	21.0



Disease-free survival in the patients with hepatocellular carcinoma after hepatic resection with AHCC



Biochemical parameters in the patients with hepatocellular carcinoma after hepatic resection with AHCC

### Effects of AHCC on Gastrointestinal Cancers

Dr. Kawaguchi *et al* of the Department of Surgery, Fujimoto Hospital, analyzed 229 cases of cancer patients. Among them, 127 cases were treated with AHCC and 102 were not. Treatment took place between July 1995 and Sept. 1998. For almost of the cancer patients, AHCC was treated by combination with low doses of 5FU, CDDP or other anti-cancer agents.

The mean survival term (MST), mean survival rates (MSR) in the AHCC-treated group, especially of the gastric, colon and breast cancer were compared with control group (without AHCC treatment) by referring to the statistical data of Japan. The results were shown in the table, AHCC treatment prolonged the survival terms of all the cancers.

(*The 6th Symposium of AHCC Research Association, Nov 1996*)

### 4) The Effect Of AHCC On Breast Cancer

Data was also obtained from Kawaguchi *et al* of Fujimoto Hospital. In breast cancer patients, groups treated with AHCC had higher than average MSR.

### Effects of AHCC on breast cancer

Cancer	Stage	Patients	Died	Survival		Average in Japan
				(Month)	(%)	
Breast cancer	O-I	6	0/6		100.0	
	II	8	0/6		100.0	
	III	2	0/2	27.0	100.0	70.0
	IV	4	2/4	30.0	50.0	35.0

(The Sixth Symposium of AHCC Research Association, Nov 1996)

### 5) The Effect Of AHCC On Lung Cancer

In the last three years, Uno *et al* of the Comfort Hospital Foundation, have treated over 500 cancer patients with AHCC. Almost all of them were lung cancer patients. The results were quite significant, as AHCC combination treatment resulted in a 35% Complete Response (CR) or Partial Response (PR).

### Results of treatment for tumor patients administered AHCC alone

Results	Number	%
Complete Response (CR)	2	5.2
Partial Response (PR)	11	29.0
No Change (NC)	14	36.8
Progression Disease (PD)	11	29.0

### 6) AHCC and Other Cancers

Besides the cancers mentioned above, AHCC was also studied in thyroid carcinoma, esophagus cancer, ovarian cancer, prostate cancer, testicular cancer, renal cancer, tongue cancer, and pancreatic cancer patients. In general, except for the cancers of the blood, AHCC is has been found to be suitable and effective for all cancers.

(The 8th International Symposium of AHCC Research Association, Aug. 2000)

As seen in the data, many thousands of cancer patients treated with AHCC have benefited from its effects, and suffered no side effects. Approximately 20% of patients found AHCC to be either “very effective” or “reasonably effective”. And on the whole, over 40% of those using AHCC find it to be effective. In conclusion, AHCC has shown to be a promising safe and effective type of immunotherapy for cancer patients.

## AHCC can prevent side effects caused by cancer chemotherapy

- ⊙ AHCC protect patients from alopecia induced by chemotherapy and remove their distress.
- ⊙ AHCC relieve myelosuppression induced by chemotherapy and make patients recover from anemia and white cell reduction
- ⊙ AHCC protect patients from liver injury induced by chemotherapy.
- ⊙ AHCC improve symptom such as loss of appetite, vomiting, nausea and so on.

### 3-3 AHCC's Ability to Reduce Side Effects Induced by Anti-Cancer Agents

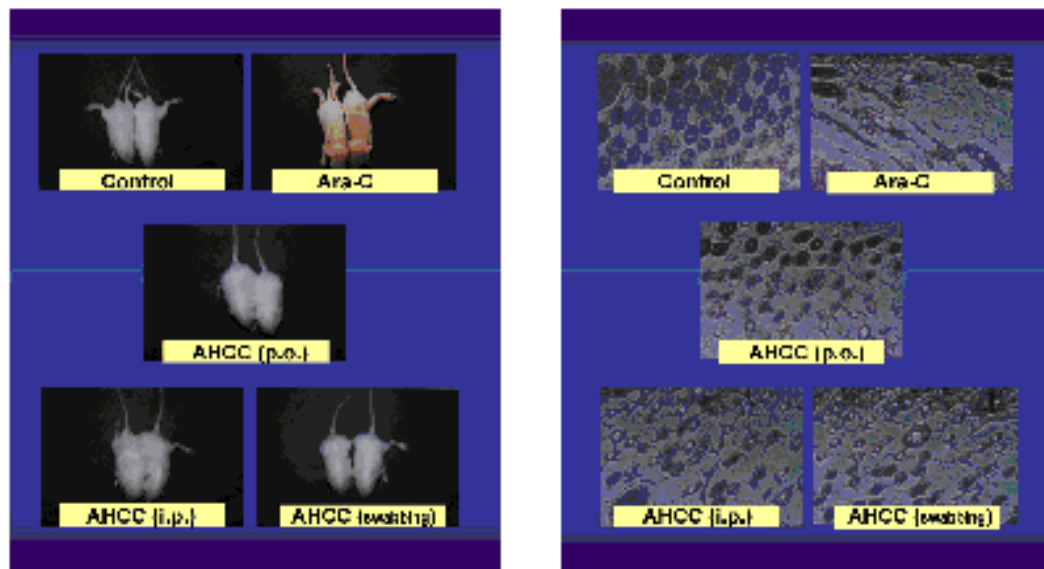
Cancer patients are well aware of the numerous side effects, which result from undergoing chemotherapy. These side effects include nausea, vomiting, hair loss, fatigue, loss of appetite, liver damage, and decreased red and white blood cell platelet count. Above all, alopecia is often singled out as the most psychologically distressing side effect of chemotherapy treatment. Additionally, the liver is the primary target following acute high-level exposure to chemotherapeutic agents, and it frequently causes serious liver damage. Medical doctors and researchers have reported that AHCC actually prevents and relieves these side effects.

#### 1) Alopecia

Chemotherapy-induced alopecia is a common and distressing side effect of many widely used chemotherapeutic agents. Several medical doctors have reported that patients given AHCC were protected against chemotherapy-induced alopecia.

#### Alopecia grade of the new-born rat model treated with Ara-C or Ara-C plus AHCC

	n	Alopecia grade			
		1	2	3	4
Control	3	3	0	0	0
Ara-C	7	0	1	1	5
Ara-C+AHCC(p.o.)	9	4	2	2	1
Ara-C+AHCC(i.p.)	10	1	5	2	2
Ara-C+AHCC(swabbling)	10	3	3	2	2



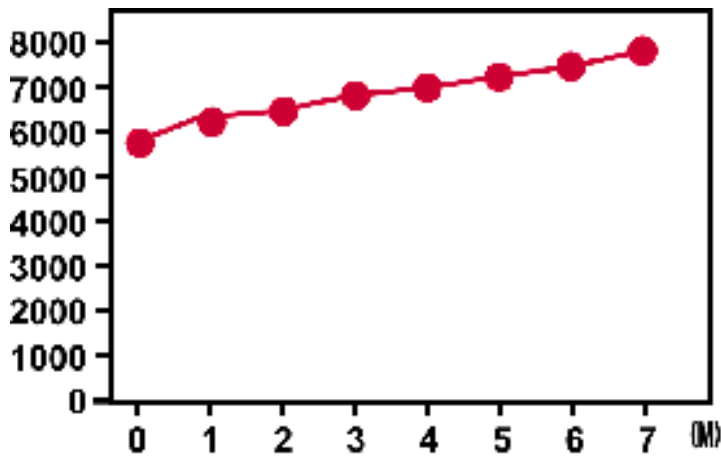
**Effects of AHCC on Ara-C-induced alopecia rat model**  
**Left: Alopecia suppression, Right: Skin biopsies (× 100)**

To confirm that AHCC really improves this side effect, researchers at Amino Up Chemical Co. Ltd. carried out an animal experiment using newborn rats. First, a chemotherapeutic agent, Cytosine arabinoside (Ara-C), was administered to the rats for seven days to induce the alopecia. At the same time, AHCC was given to these rats orally, intra-peritoneally, and by applying to the skin. Table shows that out of the seven rats treated with Ara-C, five animals showed severe alopecia and two animals showed moderate alopecia. In contrast, rats treated with Ara-C plus AHCC were protected from alopecia. More specifically, the animals treated with Ara-C combined with oral AHCC showed the most beneficial protection. Moreover, microscopic skin analyses showed severe loss of hair follicles in the Ara-C treatment group but few losses of hair follicles in the Ara-C plus AHCC treatment groups. From these results, it was clear that AHCC offers excellent protection against alopecia induced by chemotherapeutic agent. •*The 57th Japanese Cancer Association, Sep 1998*••*The 1st Japanese Society for Alternative medicine & Treatment, Nov 1998*•

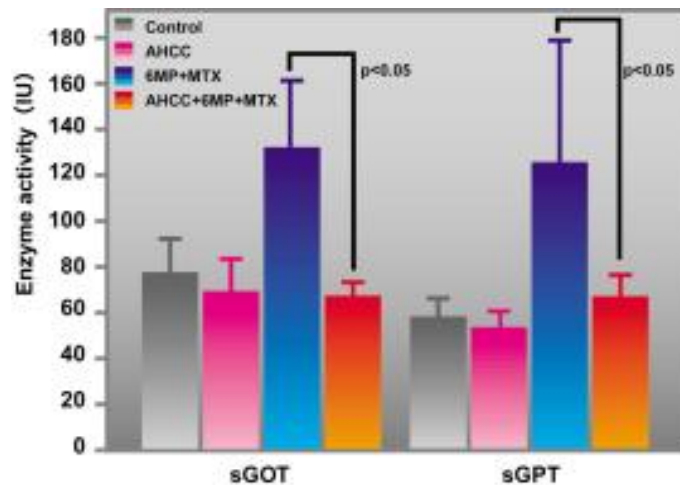
## 2) Myelosuppression

The intensive use of chemotherapeutic agents is a standard treatment for malignant tumors. However, myelosuppression often results causing leucopenia, infections, anemia, and thus is a common and serious complication. Therefore, the prevention of myelosuppression or restoration of impaired hemopoiesis is required to get a gratifying result for the cancer chemotherapy.

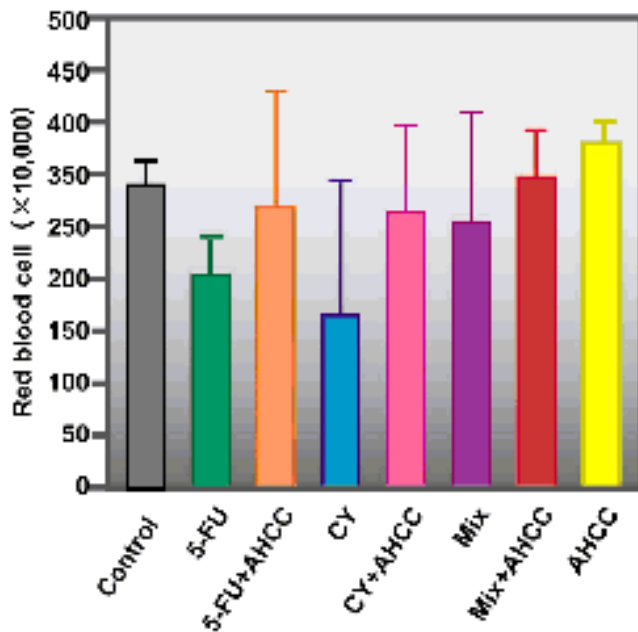
Gye Hoon Ahn in Ok-Cherm Hospital reported that oral treatment of AHCC raised total leukocyte count remarkably in cancer patients. Furthermore, researchers at Amino Up Chemical Co. Ltd. found that AHCC protects mice from hemopoietic damage caused by sub-lethal doses of chemotherapeutic agents. In this experiment, the chemotherapeutic agents fluorouracil (5-FU) and cyclophosphamide monohydrate (CY) were used to cause the myelosuppression. Although 5-FU and CY decreased the number of erythrocyte, AHCC co-administration normalized it. This data suggests that AHCC is a useful nutritional supplement used to avoid myelosuppression on patients receiving chemotherapy. •*The 8th International Symposium of AHCC Research Association, Aug 2000*••*The 4th Research Association of Cancer Prevention, May 1997*•



**Changes of leukocyte in cancer patients treated with AHCC**



**Effects of AHCC on activity of sGOT and sGPT in mice treated with anti-cancer drugs**



**Suppressive effect of AHCC on decreasing number of red blood cells induced by anti-cancer drugs**

### 3) Liver damage

Scientific trials at Amino Up Chemical Co. Ltd. have shown that AHCC has potential protective effect against the liver damage, which occurs during use of chemotherapeutic agents. A liver injury model was created by treating mice with 6-mercaptopurine (6-MP) and Methotrexate (MTX). One group received AHCC orally, while the other group did not. At the end of the experimental trial, GOT and GPT enzyme levels were measured. These enzymes are typically released by damaged liver cells. As shown in Figure 4, the group receiving only chemotherapeutic agents had large increases in GOT and GPT levels; however, the group receiving both the chemotherapy and AHCC had enzyme levels as low as the control group. This data indicates that AHCC has excellent preventive effect against liver damage induced by

chemotherapeutic agents.

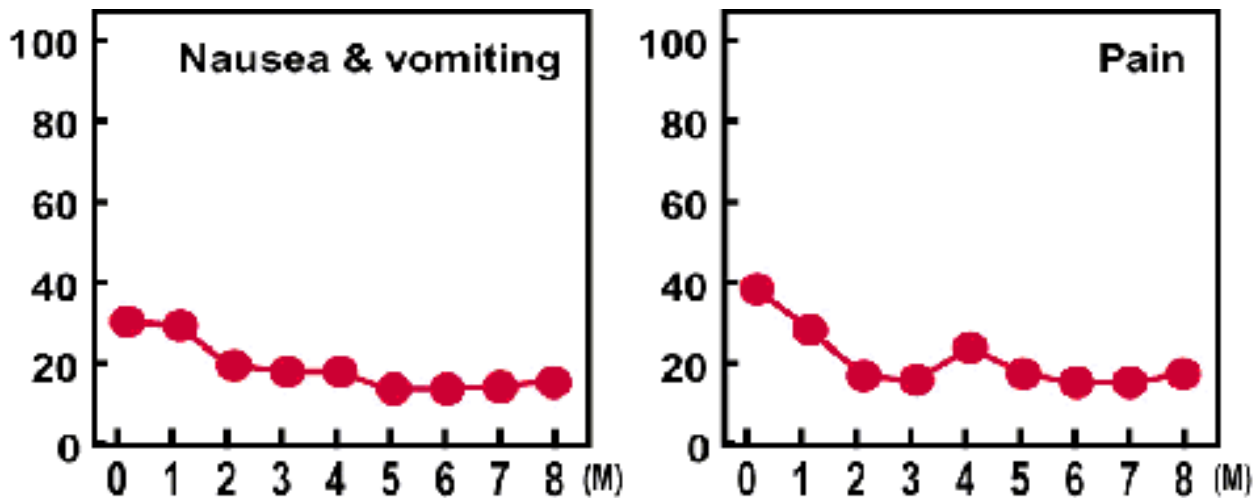
•The 4th International Symposium on Predictive Oncology and Therapy, Oct 1998•

•The 119th Pharmaceutical Society of Japan, Mar 1999•

#### 4) Nausea & Vomiting

Another seriously disturbing side effect of chemotherapy is nausea and vomiting. The side effects can be so devastating that patients often abandon therapy in hope for a better quality of life (QOL). Dr. Gye Hoon Ahn examined stage • & • cancer patients to determine if AHCC could improve their QOL. His research revealed that AHCC remarkably improved the patients QOL score for nausea and vomiting

•The 8th International Symposium of AHCC Research Association, Aug 2000•



## QOL improvement in cancer patients treated with AHCC

#### 5) Loss of Appetite

Many cancer patients undergoing chemotherapy also suffer from loss of appetite. AHCC has been found to help improve appetite, and is currently being used by over 700 hospitals and clinics for this effect.

Studies indicate that use of AHCC helps gradually increase patients' body weight and appetite.

Furthermore, overall feelings of well-being and QOL were improved.

#### Conclusion

AHCC shows many benefits against the side effects caused by chemotherapy. These include improvement of alopecia, myelosuppression, liver damage, nausea, vomiting, mood, and loss of appetite. Most importantly, AHCC shows to be most valuable for cancer patients because it not only enhances cancer

treatment, but also diminishes patients' physical and mental suffering.

•*The 90th American Association for Cancer Research, Apr. 1999*•

### 3-4 Improvement in Quality of Life (QOL)

#### Quality of Life Parameters Improved with AHCC

- ⊗ Physical function and performance
- ⊗ Psychological state
- ⊗ Social interaction

Progress in treatment methods have improved for chronic and incurable diseases such as cancer, diabetes, hypertension, and heart disease. Although this has allowed patients more longevity, it has not spared them suffering from physical illness, dementia, and emotional pain. Some conditions may not improve physically, but it is important for patients to feel mentally stable and be able to interact socially. Ideally, the disease treatment itself (chemo, radiation) should not significantly impair Quality of Life (QOL).

There are three parameters used to measure QOL.

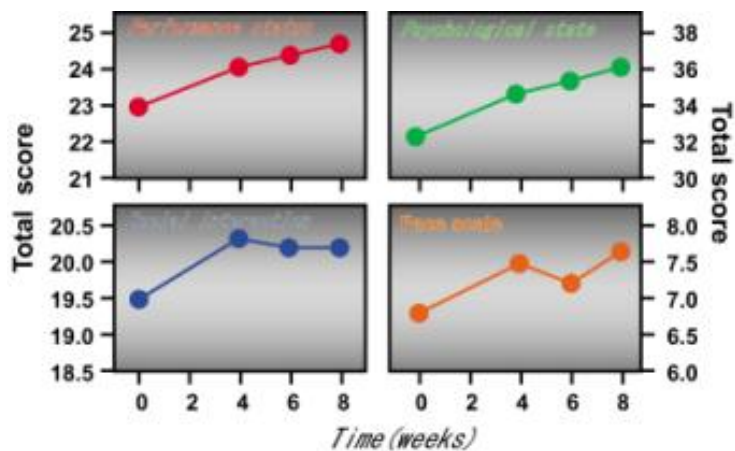
- *Physical Function and Performance* • Physical ability in daily life, and Performance status (PS) as an indicator of this function.
- *Psychological State* • Uneasiness, emotional state, fear, and depression
- *Social Interaction* • Ability to keep relationships running smoothly

Immunotherapy achieves its effects on improved QOL by activating immunocyte. There are numerous benefits to using Immunotherapies such as AHCC. These include anti-tumor and longevity effects, as well as reduction of side effects from chemotherapy. Chemotherapy side effects ameliorated by AHCC include appetite, liver damage, alopecia, nausea, vomiting, pain, and myelosuppression.

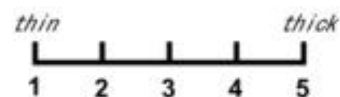
#### •• AHCC Investigation on Quality of Life (QOL)

Dr. Iwamoto of The Enzankai Medical Corporation examined Dr. Ishihara's notes (*Tokyo Women's Medical University*) in order to research AHCC effects on QOL. He analyzed the QOL data of 28 patients having taken AHCC for 2 months and found significant improvement in three of the parameters for QOL (Physical Function and Performance, Psychological State, and Social Interaction). In addition, face scales that were used as an indicator of emotional state were also improved.

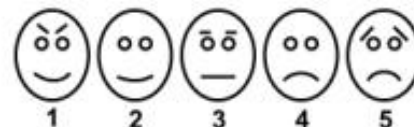
(*The 7th Symposium of AHCC Research Association, Aug. 1999*)



30. Did your hair change?



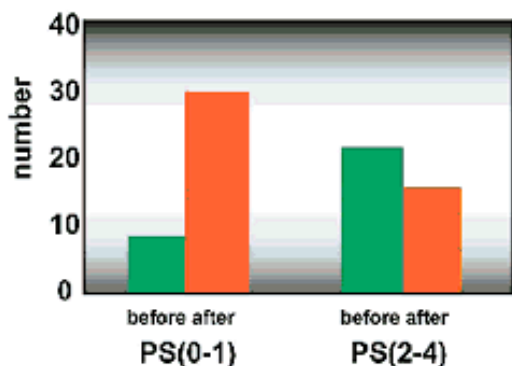
31. Check the number showing your recent condition.



**2) Effects of AHCC on Performance Status (PS)**

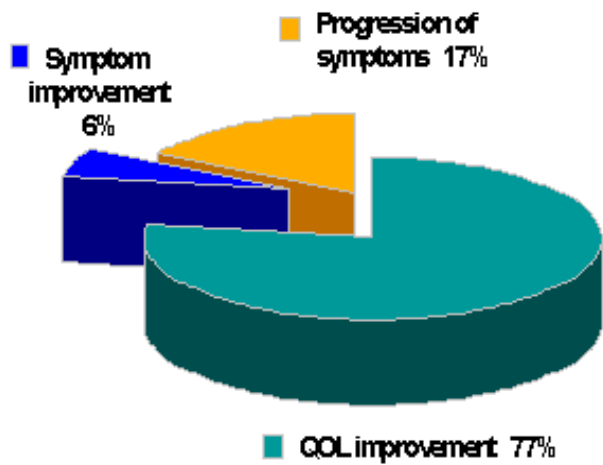
Dr. Uno (*Comfort Medical Foundation, Japan*) studied effects of AHCC on PS (an indicator of QOL). He analyzed QOL data of 38 patients who had used AHCC for 6 months. Results showed that PS was improved significantly.

•*Biotherapy*, 2000: 14 (3)•303-307•



- PS 0 : No problem on one's daily life
- PS 1 : Can walk and take care of oneself
- PS 2 : Sometimes need support
- PS 3 : Sleeping more than 50%
- PS 4 : Sleeping all day long

**3) AHCC Plus Chemotherapy**



### Subjective response to AHCC + chemotherapy

Dr. Contreras (*Oasis of Hope Hospital, Tijuana, Mexico*) studied QOL effects of combining AHCC with chemotherapy. He gathered the QOL data of 18 patients who started using AHCC for 6 months. Results showed that 77% of patients undergoing chemotherapy improved their QOL. Another 6% had improvement in at least three symptoms. Overall, 83% of the patients were affected positively by the addition of AHCC. AHCC can prevent the deterioration of QOL by ameliorating both the symptoms of cancer itself, and the side effect of chemotherapy. In conclusion, AHCC can dramatically enhance the effect of conventional cancer treatment such as chemotherapy and radiation.

*(The 6th Symposium of AHCC Research Association, Nov. 1998)*

In conclusion, it isn't clear exactly how AHCC works to improve QOL, but the positive effects on alopecia, nausea, appetite, and liver function all work to improve mood and overall well-being. When patients feel good, their immune system improves and the body's various organ systems begins to work against cancer. As a result, patients taking AHCC for a variety of ailments can expect to live longer and more enjoyable lives.

### 3-5 Hepatoprotective Effect of AHCC on Injured Liver Cells

#### AHCC improves symptoms of liver disorders

- ⊙ Improves viral hepatitis, especially hepatitis C.
- ⊙ Prevents chronic hepatitis from changing to cirrhosis and hepatocellular carcinoma.
- ⊙ Improves symptoms of acute liver injury and fulminant hepatitis caused by chemicals.
- ⊙ Prevents hangovers by improving hepatic detoxification.

It is estimated that there are between one and two million chronic hepatitis patients in Japan. Viral hepatitis makes up 90% of all cases. 20% are type B and 70% are type C. Chronic viral hepatitis can progress into liver cirrhosis and hepatocellular carcinoma. Interferon is a hepatitis treatment option, yet it cannot completely remove the virus, and the patients suffer from extreme side effects including abdominal pain, severe anemia, depression, and anxiety.

In contrast, AHCC, which is made of fiber, protein, minerals and polysaccharide, has no side effects and has been found to be effective for hepatitis and other liver disorders. Below are some investigations in which AHCC showed protective effects on liver injury.

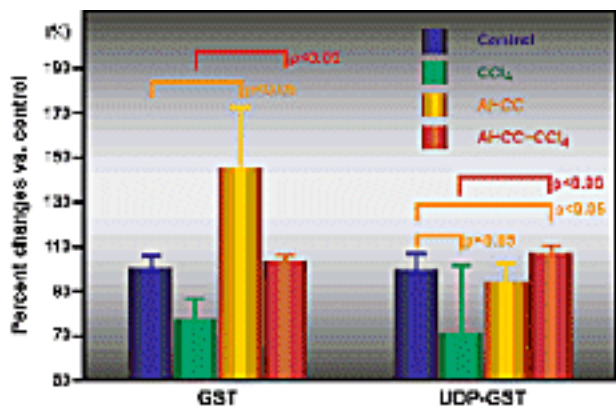
#### 1) Basic study

##### Effect of AHCC on Liver Injury in Mice

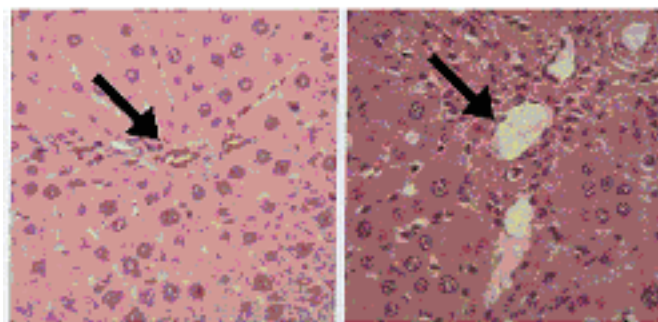
The free radicals produced from carbon tetrachloride (CCl<sub>4</sub>) cause damage to organs, especially the liver. Amino Up Chemical Co. examined AHCC for its protective effects against carbon tetrachloride (CCl<sub>4</sub>)-induced liver injury in mice. This study examined the changes in drug-metabolizing enzymes and damage to liver tissue.

Results showed that the enzymes, which are normally down-regulated by CCl<sub>4</sub> during phase II drug-metabolism (GST, UDP-GT), were enhanced when pre-treated with AHCC. Also, the liver tissue destruction was minimized and actually improved. The drug-metabolizing enzyme effects of CCl<sub>4</sub> induced injury are most likely related to the AHCC's hepatoprotective effects.

•*Natural Medicines, 1997, 51 (4), 310-315*•



Changes of contents of GST and UDP-GST from CCl<sub>4</sub> or AHCC treated hepatic microsomes in mice



AHCC protects liver cells from necrosis induced by CCl<sub>4</sub>

### Effect Of AHCC on Acute Liver Injury in Mice

Galactosamine (GalN) can induce acute liver injury in mice and its administration in large doses can result in fatality. Dr. Yamazaki *et al.* investigated the preventive effect of AHCC on the hepatitis induced by GalN. In a 24 hours period, the group of mice receiving both GalN and AHCC all survived while three of ten mice died in the group receiving no AHCC. The AHCC co-administration inhibited the sGPT, and sGOT increase significantly. These results suggest that AHCC protects the liver from the toxicity of drugs and might improve hepatic dysfunction.

•The 4th Symposium of AHCC Research Association, June 1997•

### Other Effects

AHCC has many other protective effects on the liver including the ability to protect against injury induced by alcohol or anti-cancer drugs. Clinical trials show that AHCC treatment improves liver hypertrophy caused by alcohol intake, prevents serum albumin abnormality, improves triglyceride levels, and enhances the activities of liver drug-metabolism enzymes from anticancer drug treatment.

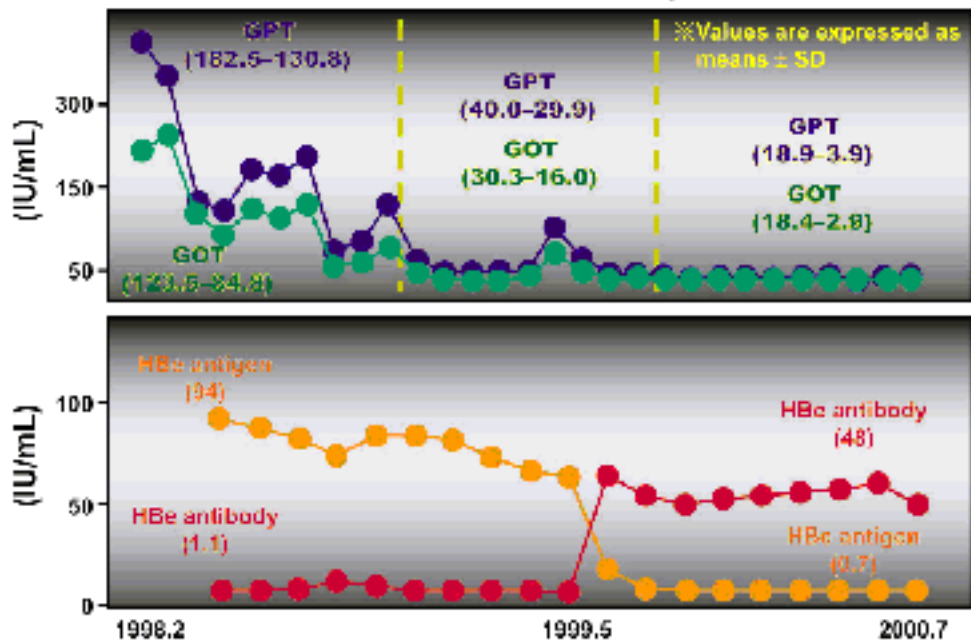
•The 4th Symposium of AHCC Research Association, June 1997•

## 2) Clinical Study

### Effect of AHCC on Chronic Viral Hepatitis Patients

Chronic viral hepatitis and low platelet count can progress into liver cirrhosis and hepatocellular carcinoma. AHCC administration can prevent this deterioration and progression. Dr. Iwamoto *et al* observed many hepatitis patients who were given AHCC.

### Case1 K.M. (32, Male) Type B Hepatitis



•Case• Hepatitis Type B patient given 3 g/day. After AHCC treatment, HBe antigen levels (cello-conversion) became markedly low while antibody levels became markedly high. Furthermore, GOT and GPT were maintained at normal levels from May 1999 to July 2000. AHCC destroyed the hepatitis virus by enhancing immune activity.

•Case •Hepatitis type C patient. Before the start of the AHCC treatment, platelet value was in the range of 170,000 /L, and its mean value from March to May 2000 was

154,000 /L showing a continuous progression into chronic liver cirrhosis. Three months after AHCC treatment, the average value of GOT was  $62.7 \pm 11.8$  IU/mL. It then decreased to a normal value of 43 IU/mL after 4 – 6 months. At the same time, GPT also adjusted to normal range.

At the start of treatment, AFP - a tumor marker, showed 1,380 ng/mL, which exceeded standard value of 20 ng/mL. After 2 months, it decreased to 800 ng/mL and kept constant. In this case, AHCC prevented the development of liver cirrhosis by stabilizing the platelet count and decreasing and stabilizing AFP values.

(The 8th International Symposium of AHCC Research Association, Aug. 2000)

### Effects of AHCC on Hepatocellular Carcinoma Patients

Dr. Kamiyama *et al.* reported that AHCC had the ability to decrease the viral load of hepatocellular carcinoma patients (HCV-RNA) over time.

•34th Annual Meeting of Liver Cancer Study Group, Oct. 1998•.

In conclusion, the administration of AHCC was critical in stopping the progression of hepatitis and cirrhosis, and in increase survival rates of hepatocellular carcinoma patients.

## **AHCC used for medical treatment of diabetes**

- **Decrease in blood glucose levels**
- **Normalization of glycated hemoglobin level**
- **Helps treat and prevent diabetes**

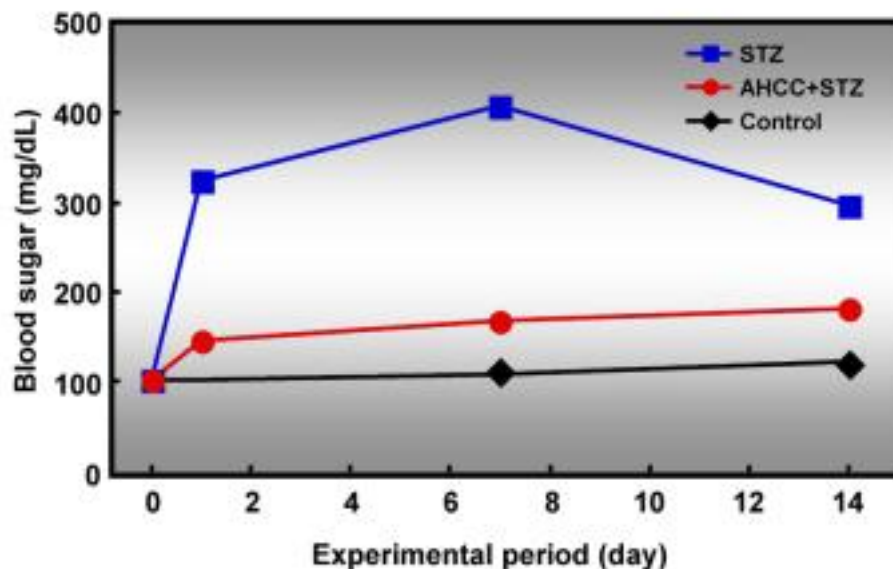
**3-6  
Effects of  
AHCC  
on  
Diabetes**

Diabetes is one of the most common adult diseases in which the patient experiences steep rises in blood glucose levels. These rises are due to either lack or insensitivity of insulin, or failed blood glucose metabolism. Common diabetes treatments include hypoglycemic drugs, low-glycemic diets, exercise, and nutritional supplements. There are several complications, which can result from diabetes including diabetic nephropathy, diabetic coma, diabetic gangrene, and diabetic neuropathy. Thus, diabetes can have serious consequences on overall health. Many clinical doctors and researchers have reported that AHCC intake can reduce blood glucose level in diabetic patients.

### **1) AHCC's Effect on Induced Diabetes**

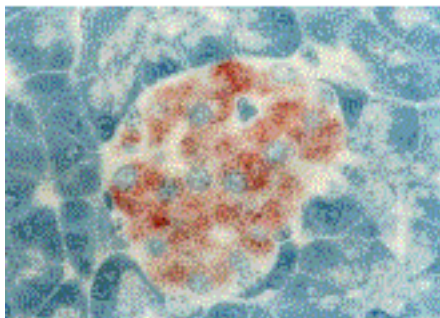
The biochemical laboratory of Amino Up Chemical Company studied the effects of AHCC on diabetes in animals by injecting Streptozotocin (STZ). STZ is a reagent known to destroy the  $\beta$  cells of the Islet of Langerhans in the pancreas. In order to observe the preventive effect of AHCC on STZ-inducing diabetes, 4% AHCC was orally administered to rats for 7 days before the STZ injection. After 2 weeks of STZ injections, the body weight, blood glucose level, insulin level and pathological changes of the rat pancreases were measured.

The body weight of the control group continued to increase throughout the experimental period; however, the body weight of the induced-diabetic STZ group dramatically decreased and clearly appeared to be in poor general condition (low weight and a deterioration in quality of the fur). These results were visible starting on the second day of STZ injections. In contrast, the 4% AHCC plus STZ group did not show these effects of decreased body weight or deteriorated fur. The blood glucose levels of the diabetic-induced STZ group increased while those in the 4% AHCC group decreased significantly. The pancreatic tissue of both groups was analyzed by microscope. Results showed that the STZ group had extensive destruction of  $\beta$  cells of the pancreas, whereas the 4 AHCC + STZ group had numerous undamaged  $\beta$  cells. Moreover, the insulin levels of the STZ group had clearly decreased, while that of the 4 AHCC group increased

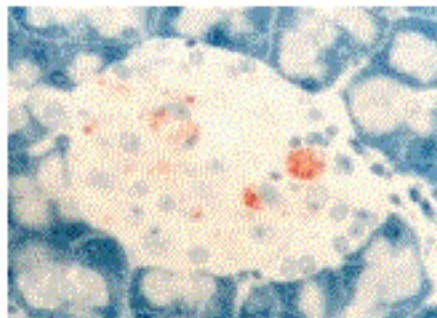


**Effects of AHCC on STZ-induced diabetic rat model**

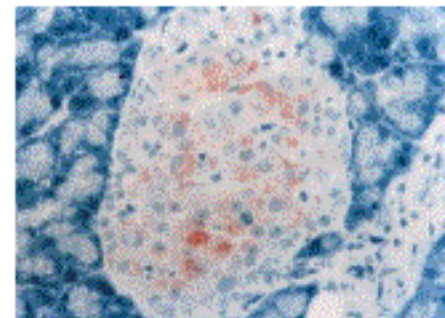
*Control*



**STZ**



**STZ + AHCC**



**$\beta$  cells in the Islet of Langerhans of the pancreas**

*The 119th Pharmaceutical Society of Japan, Mar 1999 & Biomedical Research, 20(3), 145-152, 1999•*

These results suggest that AHCC treatment inhibits an increase in blood glucose level commonly seen in diabetic animals. AHCC prevented the destruction of the  $\beta$  cells in the Islet of Langerhans by helping to decrease insulin. The study conducted at Teikyo University confirmed the results obtained by Amino Up Chemical Co., which showed that AHCC prevented diabetes in STZ treated animals.

*(The 6th Symposium of Faculty of Pharmaceutical Sciences, Nov 1998)*

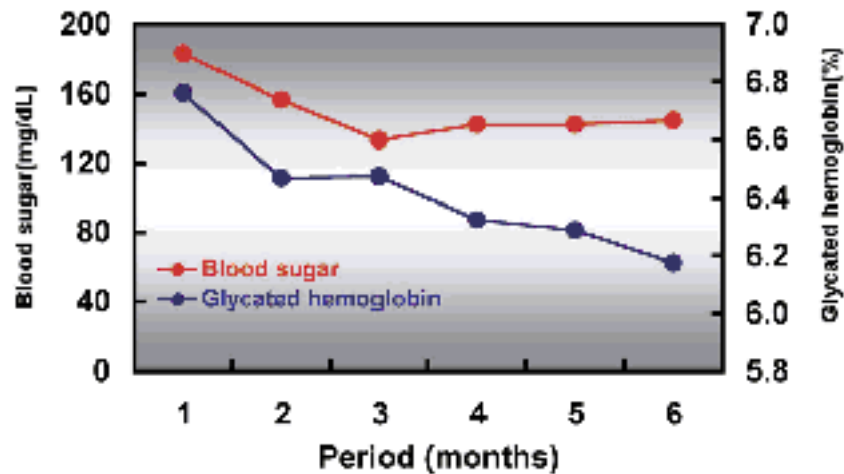
## **2) Clinical trials on Glycated hemoglobin Levels of Diabetic Patients**

It is sometime difficult to show the effects of AHCC in diabetic patient since blood glucose levels are so easily affected through various other factors. Yet glycated hemoglobin levels, which represent the combination of glucose and hemoglobin, is a very stable parameter of blood glucose. Furthermore, glycated hemoglobin expresses the average of blood glucose level from the last 1 or 2 months. In many cases, glycated hemoglobin levels are high because glucose combines with hemoglobin. If the glycated hemoglobin level rises above 7%, there is possibility of heavy complications in the diabetic patients.

Thus the glycated hemoglobin level is a critical indicator during clinical examinations and to guide clinical treatment.

Dr. Iwamoto (Enzankai Medical Corporation) examined 13 patients who were administered 3 g/day of AHCC over a 6 months period. Figure shows the average blood glucose level and the glycated hemoglobin level of these 13 patients. Both these parameters tended to go down in the AHCC treated diabetic patients.

•The 2nd Meeting of Japanese Society for Alternative Medicine & Treatment, Oct 1999•.



**Changes of blood sugar and glycated hemoglobin levels in diabetic patients treated with AHCC**

The following cases are results obtained by treatment of diabetics with AHCC:

### Case 1

Before AHCC treatment, blood glucose level was over 250 mg/dL. The glycated hemoglobin level was 9.1%. After 6 month of AHCC administration, blood glucose level became normal and glycated hemoglobin level decreased to 6.8%.

### Case 2

A patient with a combination of diabetic neurosis and paralysis of the left leg underwent 2 months of AHCC treatment. After 1 month, his high blood glucose level normalized, and, glycated hemoglobin

levels went down to a normal level of 6%. Also, the AHCC treatment caused his paralysis to disappear.

In conclusion, AHCC is a promising and effective agent against diabetes. Not only does it improve glycated hemoglobin level by inhibiting the combination of glucose and hemoglobin, but it also helps to lower blood glucose levels.

## AHCC has anti-inflammatory effect

- ⊙ AHCC is effective on rheumatoid arthritis.
- ⊙ AHCC suppresses the level of TNF, inflammatory cytokines.
- ⊙ AHCC suppresses the proliferation of *Candida*, the primary cause of nosocomial infection.

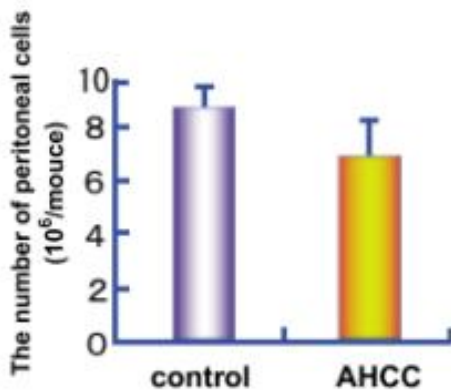
### 3-7 Anti-inflammatory effect of AHCC

Inflammation is a biological defense system in tissue level against noxious stimulus. But if there is an excessive inflammation that is outside the range of defense system, it has a bad influence on body such as organ injury. So an excessive inflammation must be suppressed. In general, steroidal drugs and non-steroidal drugs are used as anti-inflammatory drugs. But some of these drugs have strong side effects.

It is known that AHCC enhances biological immune system. On the other hand, AHCC suppress an excessive inflammation to maintain biological level. On the animal experimentation, for example, it has been reported that AHCC has suppressive effect on liver diseases and diabetes generated by pancreas inflammation.

#### ••The suppressive effect of AHCC on acute inflammation

Dr. Yui *et al* (Teikyo University) reported as follows. The dead cell of *Enterococcus faecalis*, intestinal bacteria, was administered to peritoneal cavity in mice to make mouse peritonitis model, then afterward the number of peritoneal exudate cells was counted.

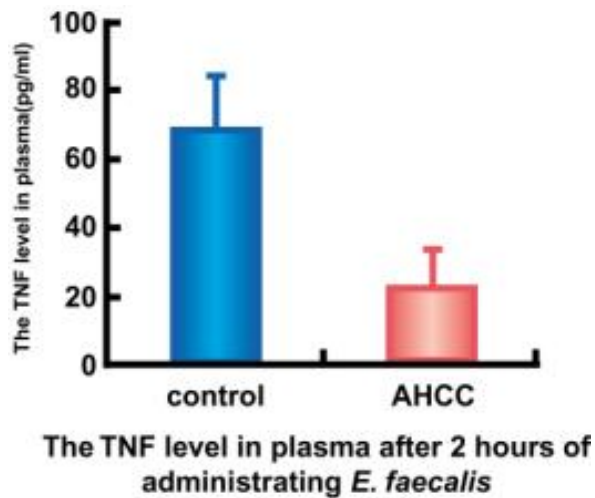


The number of peritoneal cells after 24 hours of administering *E. faecalis*

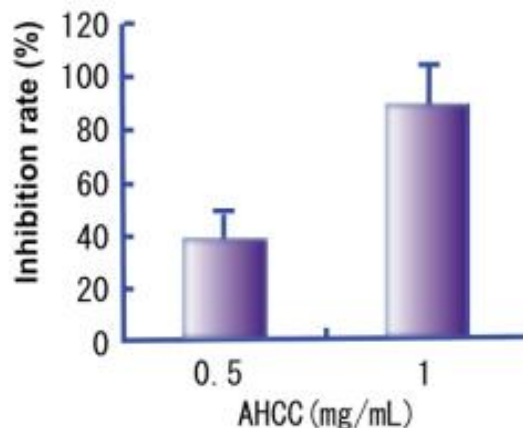
If there is an exceeding inflammation, there will be a lot of peritoneal cell accumulation. AHCC fed group accumulated less peritoneal cell number compared with control group, to suppress inflammation.

Moreover the TNF (tumor necrosis factor) level in plasma was reduced in AHCC fed group. TNF represents inflammatory cytokines. This showed to be suppressed inflammation in AHCC fed group. Furthermore, the fat weight of peritoneal cavity was decreased and the leptin level in serum was increased in AHCC fed group. Leptin is a hormone both to control fat and to effects on immunobiological defense system. So it is suggested that AHCC improve

biological fat metabolism and modulate immune system by enhancing production of leptin. (*The 7th Symposium of AHCC Research Association, Aug. 1999*) (*The 8th International Symposium of AHCC Research Association, Aug. 2000*)



••The effect of AHCC on cytotoxicity induced by calprotectin



Calprotectin is a protein in neutrophile. It is known that calprotectin markedly increase in serum of the patients who have an inflammation or in the body for it in the area where there is inflammation. When the cells are incubated with calprotectin, cell death is induced by cytotoxicity of calprotectin. However Dr. Yui *et al* (Teikyo University) reported that cell death was

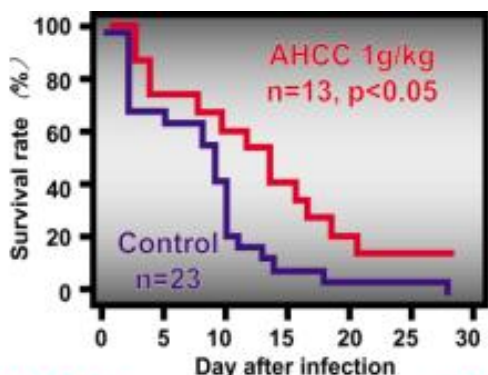
inhibited dose-dependently by co-culture of AHCC.

•The 7th Symposium of AHCC Research Association, Aug. 1999•

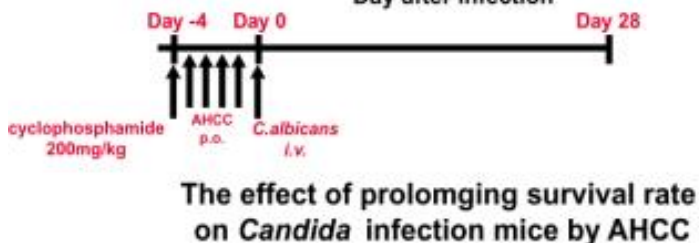
••Clinical study

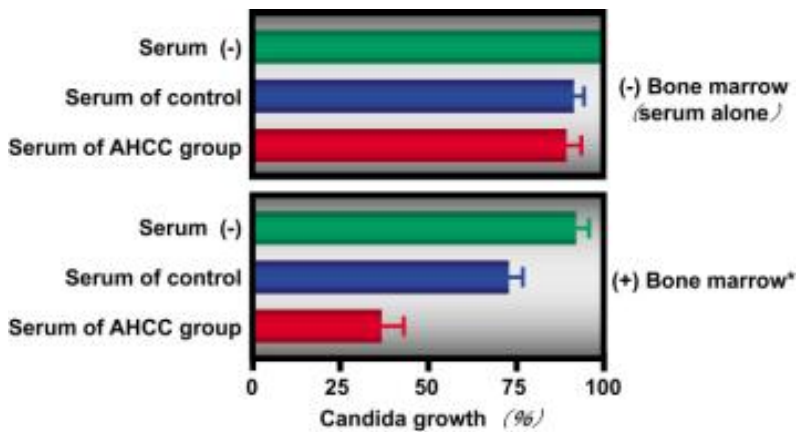
Rheumatoid arthritis is a chronic inflammatory disease. At first, symptom is only arthritis, but born and joint are destructing in progress. Dr. Iwamoto *et al* (Medical Corporation Enzankai) reported that rheumatoid arthritis became quite better when the patient took AHCC to prevent the recurrence of cancer. Calprotectin is found in a large amount in the synovia of rheumatoid patients, and it causes the symptom worse. AHCC can improve the symptom of rheumatoid arthritis by suppressing of TNF production and inhibiting of cytotoxicity of calprotectin.

••The protective effect of AHCC on the infectious disease



Opportunistic infection is usually result by the suppression of immune system, so it is a serious problem for cancer, diabetes and HIV patients. There are not so many therapeutic drugs to treat these infections at present. For example, fungi such as *Candida* and *Aspergius*, *Pseudomonas aeruginosa* and MRSA (Methicillin Resistance Staphylococcus Aureus) cause opportunistic infection. It has been reported that AHCC has protective effect on the infectious disease.





### The effect of bone marrow cells to suppress the proliferation of Candida

\*Bone marrow was co-cultured for 24 hours with 2.5% each serum.

marrow cells, however, the serum obtained from the mice treated with AHCC activated bone marrow cells to suppress the bacteria proliferation by reason that AHCC-treated mouse serum increased the number of neutrophile leukocyte in bone marrow cells. That is to say AHCC-treated mouse serum enhances to suppress the proliferation of *C. albicans* by effecting on bone marrow cells. •*The 7th Symposium of AHCC Research Association, Aug. 1999*•

Dr. Abe *et al* (Teikyou University) reported as follows. Mice were treated with cyclophosphamide as the anti-cancer drug to raise the sensibility to infection. Thereafter bacteria were inoculated intravenously to make the experimental lethal infection model. As a result of that, AHCC prolonged the survival time of *C. albicans* lethal infection mice by intraperitoneal and oral administration. The same effect was observed in *P. aeruginosa* and MRSA lethal infection model.

It has been reported that AHCC protect neutrophile decrease induced by cyclophosphamide. Because neutrophile was produced in bone marrow, Dr. Abe *et al* cultured bone marrow cells with AHCC or AHCC-treated mice serum, then added viable *C. albicans* into the culture medium and examined the capacity of bone marrow cells to suppress the proliferation of *C. albicans*.

As a result of that, AHCC did not show direct influence to bone

## AHCC's synergistic effect

### AHCC

- ⊙ Suppresses side effects and enhance tumor shrinking effect of chemotherapy.
- ⊙ Amplifies immune activating effects of other immunotherapies.
- ⊙ Enhances tumor shrinking effects of GCP.
- ⊙ Enhances cancer preventive effects of PMP and other antioxidants.

### 3-8 Combination of AHCC and other treatments

As seen from the immune system research, AHCC is a powerful activator of the immune cells and also protects against the side effects induced by chemotherapeutic agents. Since AHCC has no side effects, it has been used in combination with various kinds of treatments such as chemotherapy, radiation, immunotherapies, and anti-inflammatory agent, etc.

#### 1) Fundamental Studies

##### Combination of AHCC with Chemotherapy

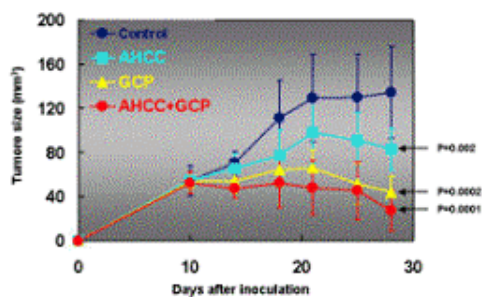
Dr. Hosokawa *et al* (Institute for Genetic Medicine, Hokkaido University) conducted a basic study about the use of AHCC in combination with chemotherapy (UFT). When AHCC is administered alongside with UFT treatment, tumor growth and metastasis is suppressed more so than in the UFT only treatment group. (*The 4th Symposium of AHCC Research Association, Jun. 1997*) •*Anti-Cancer Drugs, 1998, 9, 343-350*•

### The effects of AHCC with UFT on the growth of primary tumor and on the metastasis of breast cancer

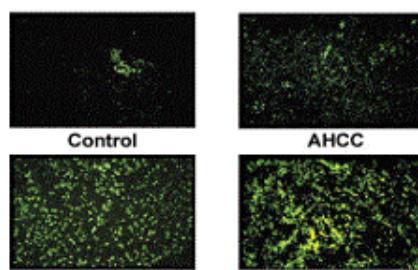
Treatment	Primary tumor		Metastatic tumor			
	Weight(g)	Suppressive rate(%)	Lung	Weight(g)	Lymph node	Weight(g)
control	57.5-4.5	-	5/5	1.86-0.15	5/5	9.00-11.48
UFT	42.8-3.3	25.7	5/5	2.83-0.83	5/5	3.77-1.89
AHCC+UFT	35.1-9.0	39.1	4/5	2.05-0.47	0/5	-

(n=5)

##### Combination of AHCC with GCP, an Anti-Tumor Substance



Tumor size changes in lung cancer cell bearing mice



Apoptosis in lung cancer tissues

GCP•Genistein Concentrated Polysaccharide• is a product of soybean isoflavones shown to have anti-angiogenesis activity and apoptosis induction effects. The synergistic effects of GCP and AHCC have been investigated by Amino Up

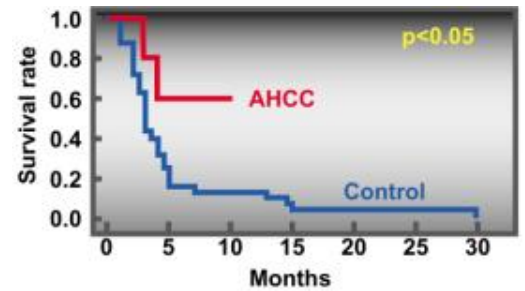
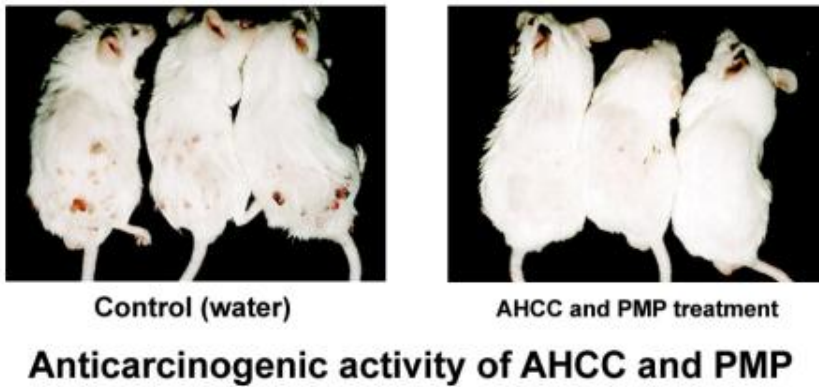
Chemical Co. Ltd. They implanted pulmonary carcinoma cells in mice and gave them either AHCC, GCP, or a combination of AHCC+GCP. Results showed a large synergistic effect from AHCC+GCP treatment after two weeks, as well as induced apoptosis.

(*The 92nd American Association for Cancer Research, Mar. 2001*).

##### Combination of AHCC with PMP Antioxidant

PMP•Polyphenolic Mixture of Plant•is a polyphenol mixture produced from buckwheat, which is known for its strong antioxidant activity. Antioxidants can

block every step of carcinogenesis such as initiation, promotion, and progression induced by chemical substances. The preventive effects of PMP +AHCC against cancer by inducing skin cancer in test rats via use of a chemical compound have been investigated by Amino Up Chemical Co. Ltd. Results showed there were far more tumors in the control group than in the AHCC + PMP group. •*The 2nd Annual Meeting of the Japanese Society for Alternative Medicine & Treatment, Oct. 1999*•*The 37th Annual Meeting of the Japanese Society of Cancer Treatment, Oct. 1999*•



**The prognosis of the patients with non-excision pancreatic carcinoma**

#### Clinical Studies

##### Studies on Non-Excision Pancreatic Carcinoma

Dr. Kamiyama *et al* (First Department of Surgery, Kansai Medical University) has studied the prognosis of patients with non-excision pancreatic carcinoma. The control group consisted of patients receiving only chemotherapy and radiation, while the AHCC group received both treatments plus AHCC. Results showed that the AHCC group's tumor size gradually shrunk, and tumor markers decreased significantly showing an excellent prognosis.

(*The 6th Symposium of AHCC Research Association, Nov. 1998*)

##### Studies on AHCC and Carcinomatous Peritonitis

Dr. Kawaguchi *et al* (Fujimoto Hospital) used a combination of AHCC and chemotherapy on patients whose tumor could not be removed due to carcinomatous peritonitis, or whose tumor could be removed but were incurable due to liver metastasis. Results showed that chemotherapy alone was not effective on such cases, but combination with AHCC was more effective.

(*The 4th Symposium of AHCC Research Association, Jun. 1997*)

##### Combination of AHCC with Low Dose Chemotherapy

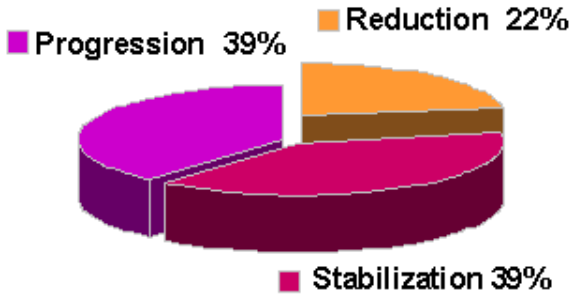
Dr. Hosokawa *et al* (Institute for Genetic Medicine, Hokkaido University) has proposed combination therapy of AHCC and low dose chemotherapy. While low dose anticancer agents cause the release of immunosuppressive substances, which effect cancer cells, AHCC activates and strengthens the immune system. Thus, AHCC works will in combination with low dose anticancer agents to suppress cancer growth, reduce side effects of the drug, and improve QOL. Dr. Hayasaka (Gekakinen Hospital, Sapporo) has investigated this combination in clinical studies. Clinical trials using AHCC and 5-FU, which is one-fifth of usual in stage II breast cancer patient, resulted that the prognosis of these patients improved dramatically after surgery.

##### Combination of AHCC with Alimentary Therapy

Dr. F. Contreras (Oasis of Hope Hospital, Mexico) investigated the combination of AHCC and alimentary therapy on 18 patients who had already failed conventional therapy such as chemotherapy and radiation. Results showed the combination of AHCC and alimentary therapy lead to a 22% tumor reduction, and 39% tumor stabilization.

(*The 6th Symposium of AHCC Research Association, Nov. 1998*)

As shown in the fundamental and clinical studies, AHCC has been applied alongside various treatments such as chemotherapy, radiation, alimentary therapy, and other immunotherapy with great success. AHCC has shown to work synergistically with other therapies, enhancing their positive effects, and helping minimize the negative side effects.



**Combination with alimentary therapy**

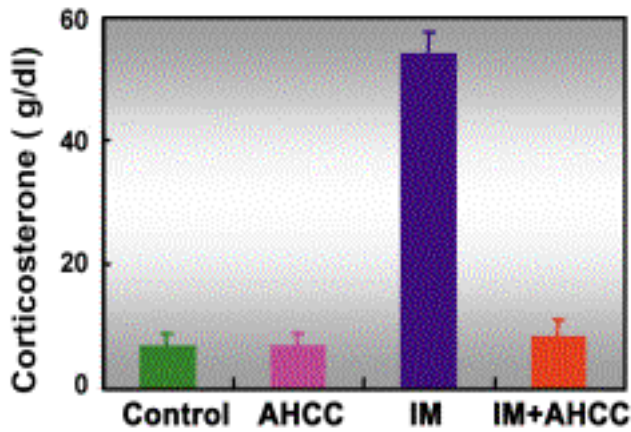
## AHCC has various functions

- ⊙ **Helps modulate endocrine system**
- ⊙ **Improve QOL of AIDS patients by stimulating immune response against HIV**
- ⊙ **Lowers and normalizes blood pressure and intraocular pressures**
- ⊙ **Markedly decreases neutral fats**
- ⊙ **Potentially beneficial effects on ventricular arrhythmias**

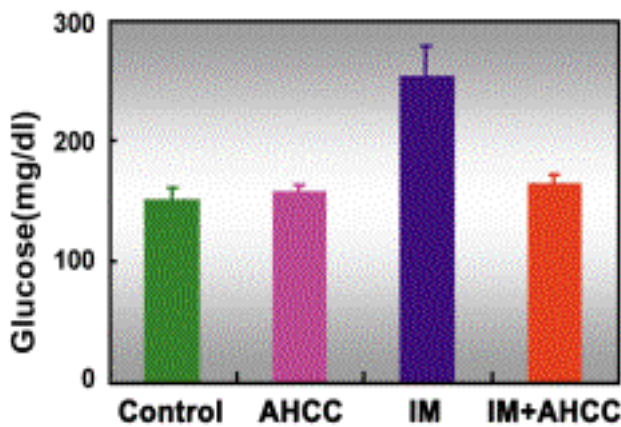
### 3-9 The Other Functions of AHCC

Research shows that AHCC improves a variety of conditions in addition to cancer and the side effects of chemotherapeutic agents. Other conditions that have shown benefit include HIV, hypertension, hypoglycemia, and endocrine system modulation.

## 1) Endocrine System Modulation



**Effects of immobilization (IM) and AHCC on serum corticosterone level**



**Effects of immobilization (IM) and AHCC on serum glucose level**

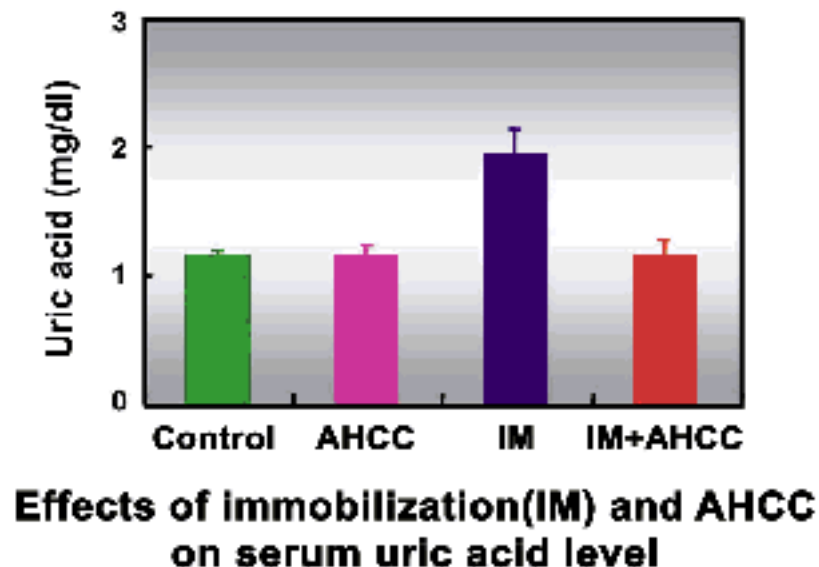
those of the AHCC non-treated rats increased immediately. These results indicate that AHCC suppressed adrenalin and corticosterone secretion.

The endocrine system interacts with the immune system and nervous system to help regulate the body's vital functions for survival. When the body is burdened with stress, glucocorticoid (GC) production increases causing the immune response to diminish. The vital forces of the immune system are diminished due to thymocyte apoptosis, a decrease in cytokine production, and an increase of immune inhibition proteins.

Dr. S. Matsuzaki *et al* (Dokkyo University School of Medicine) reported that AHCC helps suppress the decreased immune response by modulating hormone function, and increasing various other blood test parameters. When AHCC pre-treated rats were subjected to immobilization stress, their corticosterone production did not increase. Furthermore, acute stress normally causes adrenalin secretion, which in turn increases blood glucose levels. Yet, the AHCC pre-treated rats did not experience an increase in blood glucose levels.

In addition, after being subjected to stress, the uric acid level of the AHCC pre-treated rats stayed at normal levels, while

*(The 7th Symposium of AHCC Research Association, Aug 1999)*



## 2) AHCC's Function in HIV

Dr. D. Rubin (Naturopathic Family Care, Inc., Arizona) reported that AHCC improved immune activity of cells, which had been weakened by HIV infection. Treatment of 20 HIV positive men with AHCC for 12 months resulted in significant induction of NK cytotoxicity after only one month (220%). A maximum increase of 440% attained and maintained at 3 months. Further, a marked increase was observed in the absolute CD4<sup>+</sup> cell counts in 14 of 20 patients (120%) at one month, and CD8<sup>+</sup> cell counts in 12 of 20 patients (137%).

*(The 7th Symposium of AHCC Research Association, Aug 1999)*

## 3) Hypertension and Hyperglycemia

Dr. F. Pescatore (The Center for Integrative and Complementary Medicine, New York) reported that AHCC enhances the activity of NK cells significantly, playing an active role in immune reaction and defense against stress induced hypertension and cardiopathy. It was also reported that hypertension patients treated with AHCC noticed normalization in their blood pressure.

*(The 8th International Symposium of AHCC Research Association, Aug 2000)*

Another trial consisting of hypertensive and hyperglycemic male patients in their 50s and 60s tested the effects of AHCC administration. Results indicated that the AHCC acted to normalize their blood pressure and intraocular pressure, as well as markedly decrease neutral fats.

*(The 5th Symposium of AHCC Research Association, Dec 1997)*

## 4) Ventricular Arrhythmias and Cancer Prevention

Dr. Iwamoto (En-Zan-Kai medical cooperation) reported some beneficial effects of AHCC on ventricular arrhythmias. And lastly, cancer preventive effect of AHCC was observed by Amino-Up Chemical Co. Ltd.

*(The 7th Symposium of AHCC Research Association, Aug 1999)*

*(Critical Appraisal of Unconventional/Alternative Interventions for Carcinoma of the Prostate, May 1998)*

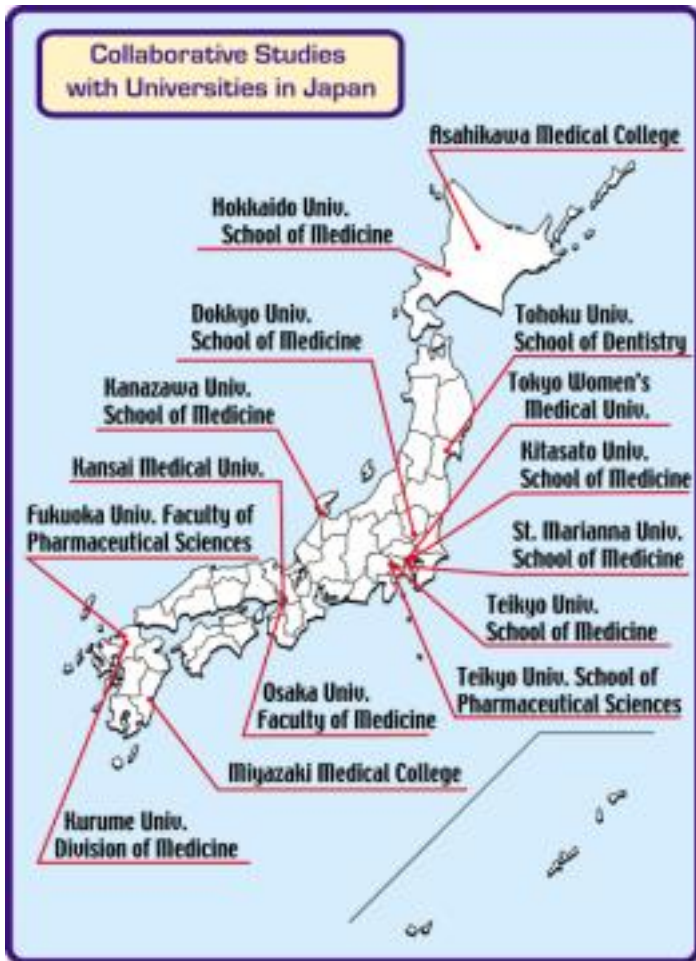
## 4- Worldwide Collaboration of Research on AHCC

Various basic and clinical studies on AHCC have been conducting at about 30 research institutions and universities and 600 hospitals, clinics in Japan and in foreign countries. There have been many results and reports published at academic meetings and journals. There is an organization called AHCC Research Association to hold anniversary meetings every year for exchanging research results among the AHCC researchers in the world.

The main collaboration institutes and research titles are as follows:

### Japan

**Hokkaido Univ.:** *Basic and clinical studies related to immune enhancement of AHCC*



**Sapporo Medical Univ.:** *Clinical trials using AHCC*

**Asahikawa Medical College:** *Clinical trials in cancer patients*

**Hokkaido College of Pharmacy:** *Component assay of AHCC*

**Teikyo Univ.:** *Basic studies on biological activities*

**Dokkyo Medical Univ.:** *Effects of AHCC on stresses and endocrine system*

**Tokyo Woman's Medical Univ.:** *Preparation of QOL protocols*

**Kitasato Univ. Medicine School:** *Clinical trials in blood vessel carcinoma patients*

**St. Marianna Univ. School Of Medicine:** *Clinical trials in breast cancer, gastrointestinal cancer patients*

**Osaka Univ.:** *Basic studies concerning immune regulation*

**Kansai Medical Univ.:** *Clinical studies in liver cancer, hepatitis and cirrhosis patients.*

**Kurume Univ.:** *Clinical trial in hepatitis patients*

**Fukuoka Univ.:** *Basic studies related to biological regulation*

## Outside Japan

**California Univ. Davis School (USA):** *Clinical pilot study in prostate cancer patients*

**Columbia Univ. (USA):** *Clinical trials in prostate cancer patients*

**Faulkner Hospital. (Mass, USA):** *Clinical study in hepatitis C patients*

**AIDS Center of Arizona State (USA):** *Clinical trial in AIDS patients*

**Oasis Hospital (Mexico):** *Clinical trials related to the combination of AHCC and chemotherapy*

**Fujian Univ. of Traditional Chinese Medicine (China):** *Clinical trial in colon cancer patients*

**Beijing Univ. Medicine School (China):** *Clinical trials in cancer patients*



**Kunming Institute of Botany, Chinese Academy of Sciences (China):** *Studies in basidiomycetes*

**King Bhumibol Hospital (Thailand):** *Clinical study in HIV patients*



## 5- References

S. Tasaki, Y. Kamiyama *et al.*, Immunotherapy with AHCC in hepatocellular carcinoma patients,

The 32nd Congress of the European Society for Surgical Research, May 1997.

B. Sun *et al.*, Anti-mutagenic effects of AHCC,

The 4th Research Association of Cancer Prevention, May 1997.

B. Sun *et al.*, Protective effects of AHCC on carbon tetrachloride induced liver injury in mice, *Natural Medicines* 51(4), 310-315, Aug 1997.

B. Sun, K. Kosuna, Effects of AHCC (Active Hexose Correlated Compound) in Both the prevention and treatment of carcinomas, *Critical Appraisal of Unconventional/Alternative Interventions for Carcinoma of the Prostate*, May 1998.

H. Kitade, Y. Matsui, S. Takai, A. Imamura, Y. Kawaguchi, Y. Kamiyama, B. Sun, K. Kosuna, Preventive Effect of Active Hexose Correlated Compound (AHCC) on the Recurrence of Postoperative Hepatocellular Carcinoma Patients,

The 33rd Congress of the European Society for Surgical Research (ESSR), May 1998.

T. Kanazawa *et al.*, The components in AHCC activating macrophage and inhibiting tumor cell proliferation,

The 5th Research Association of Cancer Prevention, Jul 1998.

B. Sun *et al.*, Fractions of AHCC (Active Hexose Correlated Compound) and their effects on macrophages and tumor cell lines,

The 57th Annual Meeting of the Japanese Cancer Association, Sep 1998.

T. Mukoda *et al.*, Active Hexose Correlated Compound (AHCC) protects against cytosine Arabinoside induced alopecia in the newborn rat animal model,

The 57th Annual Meeting of the Japanese Cancer Association, Sep 1998.

K. Matsushita *et al.*, Combination therapy of active hexose correlated compound (AHCC) plus UFT significantly reduces the metastasis of rat mammary carcinoma,

*Anti-Cancer Drugs*, 343-350, Sep 1998

B. Sun, M. Fukuhara, K. Kosuna, Reduction of side effects of anti-cancer drugs by AHCC, mycelian extracts of cultured basidiomycetes,

The 4th International Symposium on Predictive Oncology and Therapy, Oct 1998.

Y, Matsui *et al.*, Effects of the postoperative therapy with AHCC administration on postoperative hepatocellular carcinoma patients,

The 34th Annual Meeting of Liver Cancer Study Group, Oct 1998.

B. Sun *et al.*, Improving effect of Active Hexose Correlated Compound (AHCC) on anemia and alopecia induced by anti-cancer drugs,

The 1st Annual Meeting of the Japanese Society for Alternative Medicine & Treatment, Nov 1998.

B. Sun, M. Fukuhara, K. Kosuna, Reduction of side effects of anti-cancer drugs by AHCC, mycelian extracts of cultured basidiomycetes,

IMPACT OF BIOTECHNOLOGY ON CANCER (NICE, FRANCE), Nov 1998.

K. Wakame, Effect of Active Hexose Correlated Compound (AHCC) on diabetes induced by streptozotocin in the rat,

The 119th Annual Meeting of the Japanese Society for Pharmacology, Mar 1999.

B. Sun, Improving Effect of Active Hexose Correlated Compound (AHCC) on liver injury induced by anticancer drugs,

The 119th Annual Meeting of the Japanese Society for Pharmacology, Mar 1999.

B. Sun *et al.*, Reduction of the side effects of anticancer drugs by active hexose correlated compound,

The 90th Proceedings of the American Association for Cancer Research, Apr 1999.

Y. Kamiyama *et al.*, Improving Effect of Active Hexose Correlated Compound (AHCC) on the prognosis of postoperative hepatocellular carcinoma patients,

The 34th Congress of the European Society for Surgical Research (ESSR), Apr 1999.

M. Iwamoto *et al.*, Effects of AHCC on Diabetes by Clinical and Basic Researches,

The 2nd Annual Meeting of the Japanese Society for Alternative Medicine & Treatment, Oct 1999.

M. Iwamoto *et al.*, A Study on dose-dependence of AHCC for Cancer Patients,

The 2nd Annual Meeting of the Japanese Society for Alternative Medicine & Treatment, Oct 1999. •

K Uno *et al.*, The introduction of immunological parameters to the screening of cancer, The 2nd Annual Meeting of the Japanese Society for Alternative Medicine & Treatment, Oct 1999.

A. Ishiguro *et al.*, Anticarcinogenic activity of AHCC and PMP,

The 2nd Annual Meeting of the Japanese Society for Alternative Medicine & Treatment, Oct 1999.

B. Sun *et al.*, Anti-carcinogenic effect of AHCC and buckwheat polyphenol,

The 37th Annual Meeting of Japanese Society of Cancer Treatment, Oct 1999.

K. Wakame, Protective effect of Active Hexose Correlated Compound (AHCC) on the onset of diabetes induced by streptozotocin in the rat,

Biomedical Research, 20(3) 145-152, Oct 1999.

K. Uno *et al.*, Active Hexose Correlated Compound (AHCC) improves immunological parameters and Performance Status of Patients with Solid Tumors,

Biotherapy, 14(3) 303-307, May 2000.