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Active Hexose Correlated Compound (AHCC) and Immune Outcomes in Humans: A Review

By Barry W. Ritz, PhD

Abstract

Active hexose correlated compound (AHCC) is a fermented mushroom extract that is commercially available and promoted for immune support. This review focuses on safety and efficacy results from human clinical trials that have included subjects with a variety of cancers, as well as healthy populations. Animal data are also briefly discussed in the context of recent human data, with an emphasis on the possible applications of AHCC in promoting resistance to influenza virus infection. Available data suggest that AHCC supplementation clearly affects immune outcomes and immune cell populations—especially natural killer cell activity. Additional human studies are needed, as well as studies to explore the mechanistic rationale for these reported effects.

Introduction

The use of mushroom preparations for immune support has a long history, and sales of mushroom products are estimated at $9 billion worldwide. Active hexose correlated compound (AHCC) is an enzyme-fermented extract of the *Basidiomycetes* mushroom that is available as a dietary supplement. The complex compound contains a mixture of polysaccharides, amino acids, lipids, and minerals. The predominant components are oligosaccharides, totaling approximately 74% of the total dry weight. Of these, nearly 20% are partially acetylated α-1,4-glucans, which are believed to constitute the active compounds in AHCC.

Supplementation studies with AHCC have demonstrated positive effects on immune function in humans and animal models, including decreased tumor formation[1–3]; increased resistance to viral and bacterial infection[4–9]; enhanced natural killer (NK) cell activity[6,10,11]; increased dendritic cell function[12]; increased T-cell proliferation, including altered T-cell activity[3,13]; altered cytokine production[3,5,13,14]; suppressed dexamethasone-induced thymic apoptosis in rats[15]; increased nitric oxide release by peritoneal cells[13]; and antioxidant[16–18] and anti-inflammatory effects.[19] Clinical effects and safety have been demonstrated in humans with malignancy,[11,20–26] as well as in healthy subjects,[12,27,28] most recently in a report investigating the potential application of AHCC as an immune adjuvant in influenza vaccination.[29] The effects of AHCC on resistance to infection have been well studied in animals, especially in response to influenza virus,[30] although human data are not available.

The aim of the current review is to provide a comprehensive yet concise summary of the clinical effects of AHCC in human cancers and healthy populations, with an emphasis on the effects of AHCC on innate and cellular components of the immune response. The most recent efforts to establish the role of AHCC in promoting the immune response to influenza vaccination will be discussed in the context of the body of animal literature supporting the role of AHCC in promoting resistance to influenza virus infection. Finally, limitations in the available literature and recommendations for further research will be proposed.

AHCC and Human Cancers

The human clinical effects of AHCC supplementation were first explored in malignancy, although the quality of studies varies greatly from prospective, placebo-controlled to open-label studies and case reports (see Table). Overall, AHCC has been suggested to enhance prognosis and quality of life in a variety of cancers, as well as to elicit potentially positive changes in cytokine production and lymphocyte populations—most notably increased NK cell activity. From a clinical standpoint, the application of AHCC supplementation, or any integrative therapy, must be considered in the context of standard medical treatment. Accordingly, AHCC has generally been administered as an adjunct in combination with surgery and chemotherapy or radiation.[21,24–26,31] The exception here is the report by Cowawintaweewat and colleagues, in which AHCC alone was administered in addition to basic supportive care in advanced liver cancer patients who were not candidates for surgery or chemotherapy.[20] In this prospective cohort study, AHCC at a dose of 6 g/day was associated with improved prognosis and quality of life.

The compatibility of AHCC with chemotherapy has been explored. In a study by Mach and colleagues, AHCC hepatic metabolism was analyzed according to high-throughput cyto-

chrome p450 metabolism inhibition (*in vitro*) and induction potential (*ex vivo*).[32] Specifically, CYP450 3A4, 2CB, 2C9, and 2D6 were analyzed to determine the possibility of drug interactions. According to the results, there was no inhibition of CYP450; however, assays indicated that AHCC induced CYP450 2D6, suggesting a potential drug-nutrient interaction in this pathway (e.g., doxorubicin, ondansetron, selective serotonin reuptake inhibitors, tamoxifen). Therefore, the authors concluded that current data suggest that AHCC is likely safe to administer with most chemotherapy agents that are not metabolized by the CYP450 2D6 pathway. Further, the positive influence of AHCC on the reduction of cisplatin-evoked side effects in tumor-bearing mice was reported by Hirose and colleagues.[33] Unpublished results recently presented have further suggested non-immune modulated cytotoxic activity when AHCC was given in combination with Doxil.[34] In the report, AHCC supplementation demonstrated a 64.1% reduction in tumor growth compared to the untreated group. There was a 31.2% improvement in tumor response with a combination regimen compared to Doxil alone, which achieved a 48.9% tumor reduction compared to untreated mice. No difference in toxicity was observed in the control or treatment groups. Thus, in animals AHCC as a chemotherapy adjunct has demonstrated a decrease in the side effects associated with anticancer chemotherapy and a potential improvement in activity. Finally, although data are limited, those reports in which human subjects with mixed cancers were administered AHCC in combination with chemotherapy, including phenethyl isothiocyanate,[21] Lupron,[24] Camptosar, 5-fluorouracil, and Cisplatin,[26] have supported the safety of AHCC as a chemotherapy adjunct, and results have further included improved prognosis and liver function. Additional confirmatory clinical study is warranted.

AHCC and Immune Outcomes in Healthy Populations

The safety and efficacy of AHCC supplementation have also been assessed in healthy adult populations (see Table). Terakawa and colleagues assessed immune outcomes in healthy volunteers, noting an increase in dendritic cell (DC) number and function. The same study reported no changes in T cell proliferation in response to mitogen stimulation, cytokine production, or NK cell activity.[12] Notably, such immune outcomes might not be expected, or desired, in healthy subjects in response to supplementation, since supplementation alone is not expected to induce an immune response. In animal studies, for example, supplementation with AHCC does not affect basal NK cell activity but enhances NK cell induction when superimposed with an infection.[6] The reported effect of AHCC on DCs in healthy individuals is intriguing, though, and may have more to do with the potential mechanism of action by which AHCC may be recognized by these sentinel cells of the innate immune system and may thus prime the immune system for a subsequent response. This final point is purely theoretical but underscores the importance of additional studies to investigate the mechanism by which AHCC supplementation interfaces with the immune system.

Most recently, Gardner and colleagues presented data suggesting that AHCC may promote the immune response to influenza vaccination in healthy, older adults.[29] In a randomized, double-blind, placebo-controlled study, 29 subjects were administered AHCC (3 g/day) or placebo concomitant with the seasonal influenza vaccine and for 2 weeks post-vaccination. Blood analyses at 2 weeks post-vaccination demonstrated increases in the total T cell, CD8+ T cell, and NK cell populations. The effects of AHCC on immune cell phenotypes were most pronounced following vaccination in those subjects over 60 years of age. These preliminary data suggest that short-term AHCC supplementation may promote a protective response to influenza vaccination, although additional data are needed and studies are ongoing. Notably, the elderly represent an important target for such vaccine adjuvants, as an age-associated decrease in the immune response to influenza vaccination is well established and is believed to contribute to the increased morbidity and mortality of the elderly in response to seasonal influenza.

AHCC and Resistance to Influenza Infection in Animals

Although no human data are available at this time, the effects of AHCC in response to acute influenza infection in animals have been thoroughly investigated. It is important to note that studying the immune response to influenza infection requires the use of animal models, as it is unethical to infect humans in a clinical research setting. The alternative is to assess the occurrence of "flu-like symptoms" in a large population of healthy subjects, which introduces certain limitations. Such studies employing the use of AHCC to prevent infection in otherwise healthy subjects are not available at this time.

In a series of studies in mice, however, supplementation with AHCC at human equivalent doses ranging from 500 mg/day to 5 g/day resulted in a less severe illness in response to common influenza virus infection, increased survival, enhanced NK cell activity, more rapid virus clearance from lungs, and expedited recovery.[6,35] Similar results were demonstrated in a mouse model of H5N1 avian influenza virus infection, in which mice exhibited increased survival when supplemented with either AHCC alone[8] or AHCC in combination with H5N1 vaccination.[36]

Conclusions and Future Directions

In summary, the available literature clearly suggests that AHCC is an immune-modulating compound, with consistent effects on NK cell activity when induced by either the presence of an active tumor or a viral infection. Originally described as null lymphocytes, because their activity was unknown, NK cells were later discovered as a distinct lymphocyte population with spontaneous cytolytic activity against tumor cells that could be further induced upon activation. NK cells are now known to comprise anywhere from 5% to 20% of total lymphocytes in secondary lymphoid organs and act as potent innate effector cells with not only antitumor, but also antimicrobial and antiviral, activities. Although

the importance of NK cells in the response to infections, such as influenza, have remained controversial, data in animals now confirm that NK cells are essential for controlling virus titers in the lung early during the course of infection.[37] Further, NK cell activity appears to be highly susceptible to nutritional manipulations.[38,39] Thus, as early, nonspecific innate effectors with broad-ranging generally positive effects on the immune response, NK cells are an attractive therapeutic target for a natural medicine approach. However, there remains a huge gap between the assessment of NK cell activity and clinical outcomes, such that data are desperately needed to establish NK cell activity as a pertinent immune biomarker as a surrogate measure for the prevention or progression of human disease. Further, regarding the specific role of AHCC as an agent to prime NK cell responses, studies are needed to establish the mechanism of action by which this compound interacts with cells of the immune system (possibly at the site of the intestinal epithelium) and how such interactions may result in systemic effects affecting immune competency. The activities of ß-glucans derived from mushrooms and yeast cell walls have been investigated and appear to activate innate immunity by binding to innate pattern recognition receptors, such as toll-like receptors (TLRs). It remains unknown whether α-1,4-glucans may mediate immunity through a similar mechanism, although such studies have been proposed.

Table. Summary of immune outcomes reported in AHCC human clinical studies in subjects with cancers and in healthy populations.

Study Design	Subjects	N	AHCC Dose and Duration	Outcomes	Reference
Human Cancers					
Prospective cohort study, AHCC vs. placebo	Liver cancer; Ages 34-72 yrs	44	6 g/d 12 months	– Improved prognosis – Slight increase in Quality of Life (self-perceived questionnaire) – Increase in albumin level (at 1 month) – Increased % lymphocytes (at 2 months) – Reduced increase in AST and ALT levels (ns)	20
Prospective cohort study, AHCC vs normal control group	Confirmed hepatocellular carcinoma, undergoing surgical resection; Ages 57–70 yrs	269	3 g/d 9 yrs follow up (1992–2001)	– Improved prognosis – Longer period without recurrence – Improved liver function (serum AST, GGT, cholinesterase)	21
Case report	Mixed cancers (rhabdomyosarcoma, multiple myeloma, breast)	3	3–6 g/d 2 wks	– Increased NK cell activity	22
Open label	Mixed cancers (ovarian, 3; multiple myeloma, 2; stomach, 2; breast, 5; lung,2; rhabdomyosarcoma, 1; prostate, 2)	17	3 g/d 2–6 wks	– Increased NK cell activity – No change in the % of NK cells in blood	23
Open label	Solid tumors	38	Dose not specified 6 months	– Increased NK cell activity compared to baseline – Increased IL-12 and IFN-γ production by PHA-stimulated PBMCs compared to baseline – Similar to normal controls	11
Open label	Mixed cancers (prostate, 3; ovarian, 3; multiple myeloma, 2; breast, 3); Ages 36–65 years	11	3 g/d	– Increased NK cell activity compared to baseline (at 2 wks) – *In vitro* suppression of tumor cell growth	24
Open label	Mixed cancers, undergoing chemotherapy	12	3–6 g/d 9 months	– Maintained WBC count, hematocrit during chemotherapy – Increased NK cell activity (at 3 and 6 months)	25
Prospective study, non-controlled	Gastric cancer, post-operative; Ages 28–82 yrs	132	3–6 g/d 7 yrs follow up (1995-2002)	– Improved 5-yr prognosis compared to other institutions (Stage IA and IIIA)	26
Prospective study, non-controlled	Colon cancer, post-operative; Ages 26–85 yrs	113	3–6 g/d 7 yrs follow up (1995–2002)	– Improved 5-yr prognosis compared to other institutions (Stage II and IIIA)	26
Retrospective, non-controlled	Breast cancer, post-operative	47	Dose not specified 6 yrs follow up (1996-2002)	– Improved prognosis in Stage IV compared to national average	21
Prospective study, non-controlled	Breast cancer I (5), II (13), III (10), IV (19)	47	6 years (1996–2002) Dose not specified	– Improved prognosis of stage IV patients as compared to national average	39

Healthy Populations					
Double-blind, placebo-controlled	Healthy volunteers; Mean age 60 yrs	21	3 g/d 4 wks	– Increase in DC number and function (mixed lymphocyte reaction) compared to baseline and placebo – No effect on PHA-stimulated T cell proliferation, NK cell activity, or cytokine production	12
Open-label safety study	Health volunteers; Ages 18–61 years	26	9 g/d 14 days	– Safety assessed by comprehensive laboratory parameters (e.g., blood pressure, blood chemistry, liver enzymes) and symptoms questionnaire at 7 and 14 days – No change in laboratory values from baseline – 4 subjects reported minor, transient adverse effects (headache, toe cramp, mild diarrhea, fatigue)	27
Open label	Healthy elderly volunteers	30	Dose not specified 60 days	– Altered CD4+ and CD8+ T cell percentages and cytokine production following PHA-stimulation of PBMCs	28
Randomized, double-blind, placebo-controlled	Healthy volunteers	29	3 g/d administered with influenza vaccine and for 2 wks post-vaccination	– Increased % of T cells, CD8+ T cells, and NK cells over baseline – Increased effect in AHCC-supplemented subjects over yrs of age	29*

* Unpublished data, presented orally, manuscript in preparation.

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; DC, dendritic cell; IFN, interferon; IL, interleukin; GGT, gamma-glutamyl transferase; NK, natural killer; PBMC, peripheral blood mononuclear cell; PHA, phytohemagglutinin A (T cell mitogen).

About the Author

Barry W. Ritz, PhD, is the Vice President of Scientific Affairs at Atrium Innovations, Inc., and is an active researcher in the emerging field of nutritional immunology. Dr. Ritz completed his master's and doctorate degrees at Drexel University. He is involved in a number of professional organizations, including the American Society for Nutritional Sciences. Dr. Ritz has presented his research at national and international meetings, has numerous publications in scientific journals, and recently completed a chapter on the use of nutraceuticals for immune restoration in the elderly in the Handbook on Immunosenescence: Basic Understanding and Clinical Applications.

Editor's Note: The author has no current conflict of interest regarding any direct relationship with the manufacturer. However, in the past (2005–2008) as a research professor at Drexel University, he received a non-restrictive research grant from the manufacturer of AHCC, Amino Up Chemical Company, Sapporo, Japan. He currently does not receive any research funding from Amino Up Chemical Company, and he received no payment from Amino Up or any of its affiliates related to the publication of this review. Finally, as the vice president of scientific and regulatory affairs for Atrium Innovations, Dr. Ritz is involved in the commercialization of many natural products, including AHCC. Currently, two Atrium companies, Douglas Laboratories and Pure Encapsulations, commercialize products that contain AHCC as an ingredient.

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