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Screening for Potential Pathways of Drug-Supplement Interactions Between Ahcc® and Common Medications

Rachel E. Carlson[1], Anjali Gaikwad[2], Lata Mathew[2], Judith A.Smith*[2]

[1]*University of Texas Health Science Center Medical School at Houston, TX USA*

[2]*Department of Obstetrics, Gynecology and Reproductive Sciences, University of Texas Health Science Center Medical School, Houston, TX, 77030, USA*

Abstract

AHCC® is a standardized extract of cultured Lentinula edodes mycelia. It is utilized for its proposed immunomodulatory and anti-tumor effects in conjunction with chemotherapy agents, as general immune support and even in supporting clearance of chronic viral infections such as the human papillomavirus (HPV). With the integration of natural supplements becoming more common in the healthcare arena across all disciplines, it is important to review the safety of use of supplements like AHCC® in combination with common medications, including possible drug-supplement interactions. Overall, ex vivo metabolism studies and confirmatory animals suggest AHCC does not interact with majority of the drug metabolism pathways. However, these studies did also suggest that AHCC® has induction effects in the cytochrome P450 (CYP450) 2D6 metabolism pathway and of aromatase inhibitor activity. In addition, AHCC® did exhibit potential inhibitor effects in the quinone oxidoreductase (QOR) phase II hepatic metabolism pathway, and potential induction effects of uridine diphosphate (UDP) – glucuronosyltransferase (UGT) 1A3 and 1A6 pathways. The primary objective of this manuscript is to synthesize and review data on proposed phase I and phase II hepatic metabolism pathways of AHCC in discuss the safe use of AHCC® in combination with most common medications, including chemotherapy

Keywords: AHCC®, Metabolism, Drug interactions, Nutritional supplements

Corresponding author: Judith A. Smith

Department of Obstetrics, Gynecology and Reproductive Sciences, University of Texas Health Science Center Medical School, Houston, TX, 77030, USA. Tel: 713-500-6408,

E-mail: Judith.Ann.Smith@uth.tmc.edu

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Introduction

AHCC® ((trademark of Amino Up Chemical Co, Ltd., Sapporo, Japan) is a standardized extract of cultured Basidiomycete mushroom (Lentinula edodes) mycelia that is obtained through cell culture, incubation, sterilization, concentration, and freeze-drying. In recent years there have been attempts to generate similar compounds to AHCC® that are not structurally nor compositionally the same compounds often also described AHCC hence the importance here of use of the trademark to focus on the original AHCC® product evaluated in our research. (Figure 1) The main active component of AHCC® is alpha-glucans, which allows for its proficient absorption because of their small molecular weight of 5,000 Da Beta-glucans, with a larger molecular weight of 10,000 to 500,000 Da, make up less than 0.2% of AHCC®. AHCC® has both immunomodulatory, anti-viral, and anti-tumor effects, and has been shown to decrease the side effects seen with anticancer chemotherapy [1-6]. Data supports AHCC® use in oncology patients as well as other conditions that benefit from immune support that is mediated via its proposed effects on natural killer cells, macrophages, and cytokines. While AHCC® is used in the patient care setting, there has been little information presented on its effects on the toxicity or efficacy of common medications. Several studies have been conducted to characterize AHCC® hepatic metabolism to identify possible pathways of AHCC®-drug interactions, particularly with chemotherapy agents.

Understanding Hepatic Metabolism of drugs and supplements

Hepatic metabolism plays a role in the activation and elimination of many pharmaceutical and supplemental agents and is the focus of many studies examining the mechanism of drug-drug or drug-supplement interactions. Hepatic metabolism can be further divided into phase I, phase II, and phase III pathways. Phases I and III consist of cytochrome P450 (CYP450) enzyme metabolism pathways, and function primarily through hydrolysis, oxidation, and reduction reactions. There are several CYP450 isoenzymes involved in drug metabolism, including 1A2, 2C8, 2C9, 2D6, and 3A4. Substrates of CYP450 pathways are metabolized through these various CYP450 pathways and could be impacted by either inhibitors or inducers of these pathways. Clinically monitoring for interactions is necessary because the inhibition or induction of CYP450 pathways could lead to enhanced toxicity or decreased efficacy of common medications that are substrates of these pathways. For example, in the oncology arena

many chemotherapy agents are CYP450 substrates such as but not limited to cyclophosphamide, docetaxel, doxorubicin, ifosfamide, imatinib, irinotecan, olaparib, paclitaxel, rucaparib, tamoxifen, and topotecan. Since AHCC® is often used with anticancer chemotherapy, these agents have been the focus of many studies evaluating the potential for supplement/drug interactions with use of AHCC®.[7-10]

Phase II hepatic metabolism has more recently been included as a subject of pharmacologic studies in the scope of drug/compound interactions including evaluation for potential drug/supplement interactions. It is associated with glutathione S-transferase (GST), quinone oxidoreductase (QOR), catechol-O-methyltransferases (COMT), and uridine diphosphate (UDP) glucuronosyltransferase (UGT) reactions. GST pathways catalyze conjugation of electrophilic substrates to glutathione. QOR is a detoxification enzyme that contributes to both the detoxification of quinone and the antioxidant function maintenance of cells. COMT plays a role in detoxification of reactive catechol estrogen intermediates. [7] Estradiol metabolism by CYP450 produces four estrogen metabolites, some of which are associated with estrogen-mediated cancers. COMT assists in detoxifying two of the estradiol metabolites (2-OHE2 and 4-OHE2) [7]. UGT also plays a role in detoxification in phase II metabolism by catalyzing glucuronidation of substrates.

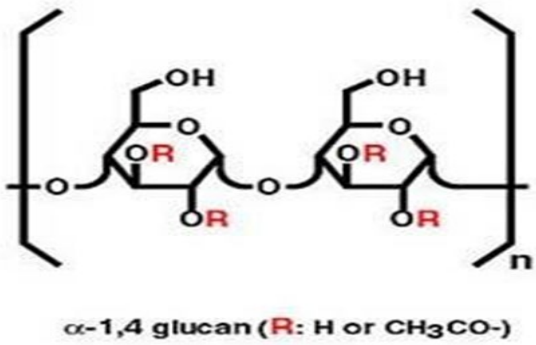

Figure 1: AHCC® Structure

Several studies have examined the ability of AHCC® to act as a substrate, inducer, or inhibitor of phase I or phase II hepatic metabolism. Again, by definition a substrate is any compound that undergoes hepatic metabolism, either via CYP450 (Phase I or III) or GST, QOR, COMT, or UGT (phase II). An inducer causes increased metabolism of a substrate by increasing the function of hepatic enzymes. This leads to faster elimination of the parent compound and an increase in concentration of metabolites. Decreasing the concentration of the parent compound may contribute to decreased efficacy of the drug. However, in the case of pro-drugs, which are drugs that require metabolism to form their active component, induction of hepatic metabolism may lead to increased active metabolite concentration and in turn increased toxicity. One such example of a pro-drug is doxorubicin or cyclophosphamide. Inhibitors may decrease or cease hepatic metabolism, leading to accumulation of the parent compound in the systemic circulation. This may lead to toxicity, especially in drugs that have a narrow therapeutic index.

AHCC® and Phase I Hepatic Metabolism Interactions

To screen for the potential of AHCC® interactions with drugs metabolized by CYP450, in vitro isoenzyme inhibition assays and ex vivo human hepatocyte models have been performed.[8] Mach and colleagues evaluated AHCC inhibitory effects on CYP450 isoenzymes 3A4, 2C8, 2C9, and 2D6 by comparing AHCC® activity against inhibitor positive controls and assessed the extent of CYP450 inhibition via IC50 values and the amount of metabolized products. AHCC showed no inhibitory effects against CYP450 pathways.[8] This study data also supported that AHCC® is a substrate of the CYP450 2D6 pathway. [8] The ex vivo human hepatocyte model was used to gauge CYP450 metabolism induction potential of AHCC on CYP450 3A4, 2C8, 2C9, and 2D6. AHCC® was compared against a well-known inducer, rifampicin as the positive control. The induction metabolism assay exhibited that AHCC is a potential inducer of the CYP450 2D6 pathway.[8] With action in the CYP450 2D6 pathway, both as a substrate and an inducer, AHCC use should be carefully considered when patients are taking drugs known to be metabolized through this pathway as there is potential for drug-supplement interactions. [Table 1] This data suggests that AHCC® is otherwise safe for use in conjunction with medications, including chemotherapy agents, that are metabolized via the CP450 1A2, 3A4, 2C8 or 2C9 pathways. Due to the potential for AHCC to interact with the 2D6 pathway, a common clinical question has been if AHCC® would affect tamoxifen since its a substrate for CYP450 2D6 pathway. This interaction was examined in two orthotopic human estrogen receptor positive breast cancer mouse models of both COMT variant type (MCF-7) and COMT wild-type (ZR-75).[9] Results showed that the combination of AHCC and tamoxifen was similar to the use of tamoxifen alone based on primary efficacy endpoint that measured of reduction in tumor size. AHCC did not affect the activity of tamoxifen in these models.[9]

The potential for induction of the CYP450 2D6 pathway can also be advantageous when being given in combination with a substrate that is a "pro-drug" such as doxorubicin that requires metabolic activation to its active substrate, doxorubicinol to exert its cytotoxic activity. Hunter and colleagues conduct animal study in a platinum resistant orthotopic SKOV3-IP1 human ovarian cancer mouse model that demonstrated the synergistic activity when AHCC® was given in combination with liposomal doxorubicin.[10] Additional molecular studies revealed down-regulation of the bcl-2 the lead to induction of the apoptosis pathway that likely contributed to synergistic activity observed.[10] Preclinical data here suggested that the combination of AHCC® with doxorubicin can be beneficial and warrants further evaluation to confirm these findings in the clinical setting.

AHCC® and Phase II Hepatic Metabolism Interactions

Coffer and colleagues examined the interactions of AHCC® with the four main components of phase II hepatic metabolism, GST, QOR, COMT, and UGT. In vitro inhibition assays were used to demonstrate inhibition of GST, UGT, or QOR by AHCC® . AHCC® showed no inhibitory effects on GST or UGT2B17, UGT1A3 or UGT1A6A pathways, but did demonstrate inhibition of the QOR pathway, similar to the extent of the control inhibitor.[7] Induction of COMT and UGT pathways was

evaluated with the ex vivo human hepatocyte model. AHCC® did not show induction of the COMT pathway but did exhibit potential induction of UGT1A3 and UGT1A6 pathways.[7]

Mathew and colleagues also assessed the interaction of AHCC® with letrozole, which is a substrate of the CYP450 3A4 pathway. This metabolism pathway was not shown to be affected by AHCC® .[7] However, letrozole also plays a role in estrogen metabolism in COMT pathways, a phase II hepatic metabolism pathway, and aromatase pathways as an aromatase inhibitor. In vitro estrone and 17β-estradiol immunoassays were utilized to evaluate the effect of AHCC® on the aromatase activity of letrozole.[9] Immunoassay data conveyed that AHCC® is a potential inducer of aromatase activity.[9] When administered in COMT wild-type models, AHCC did not show interaction with the aromatase inhibitor activity of letrozole and there was a significant reduction in tumor growth.[9] In COMT variant models, however, AHCC® caused a significant reduction in letrozole activity, possibly due to the aromatase induction activity of AHCC® .[9] The difference in results seen between COMT wild-type and COMT variant models may be due to the decreased COMT metabolic activity already associated with COMT variant genes.

Discussion

Integration of natural supplements is becoming more common in the healthcare arena across all disciplines, especially in the oncology setting. It is important to review the safety of use of supplements like AHCC® in combination with common medications, including possible drug-supplement interactions. AHCC®, for example, has been used for many years and is reported to be well-tolerated with minimal side effects in clinical studies [11]. To successfully integrate AHCC® use in clinical arena settings, it is vital to understand the safety data for the AHCC® supplement, particularly the potential for drug-supplement interactions. Multiple studies have been conducted to elucidate the effects of AHCC® on phase I and phase II metabolic pathways.[7-10] With a better appreciation of the hepatic metabolism mechanisms, one can extrapolate this data to minimize potential drug-supplement interactions with drugs that are involved in the same pathways across all areas of clinical practice.

AHCC® did not show to be an inhibitor of the major CYP450 isoenzymes, and thus is unlikely to cause toxicity when administered with drugs involved in these metabolic pathways [Table 2]. The observed induction effect of AHCC® on CYP450 2D6 pathways is important to consider when used in combination with drugs that are also metabolized through this pathway. [Table 1] Increased induction of metabolism with co-administration of AHCC® may lead to decreased efficacy and patients should be closely monitored when taking these drugs or agents together. In cases of CYP450 2D6 substrates that are pro-drugs, such as doxorubicin, patients should just be closely monitored, as induction may lead to beneficial increase efficacy as well as potential increase risk for toxicity too. In the study by Mathew and colleagues, AHCC® did not exhibit an impact on the metabolism and efficacy of tamoxifen, a known substrate to the CYP450 2D6 pathway [9]. Tamoxifen acts selectively on estrogen receptors to inhibit cell growth, while AHCC® is not known to interact with estrogen receptors. This could illustrate why tamoxifen plus the presence of AHCC®, although a modifier of the CYP450 2D6 pathway, did not significantly alter tumor growth compared to tamoxifen alone. This illuminates the need for more research to accurately predict potential drug-supplement interactions.

The data regarding phase II metabolism pathways adds to the safety information about AHCC®. AHCC® does not appear to affect drugs or agents that act as substrates to GST, COMT, or UGT2B17 pathways.[8] When patients are co-administered drugs or agents that are substrates to the QOR, UGT1A3 and UGT1A6 pathways [Table 1] while taking AHCC®, they should be closely monitored for increased toxicity from inhibitory effects of AHCC® on QOR pathways, or decreased efficacy from induction effects of AHCC® on UGT1A3 and 1A6.[8]

These studies show that the potential for drug-supplement interactions while limited still exists and highlight the need for healthcare providers to monitor patients for potential drug-supplement interactions. It is advisable to document all nutritional supplements, over-the-counter (OTC) medications, and prescription medications patients are taking when considering initiating new medications, including nutritional supplements like AHCC®. When co-administering AHCC® with a drug/agent with which there is any potential for drug-supplement interaction, patients should be monitored for adverse side effects, increased toxicity, or decreased efficacy. It is important that patients know the expected side effects of their medications, so they can accurately report any changes with symptoms resulting from possible interactions.

Drugs Metabolized by CYP 2D6 Enzyme			
ANALGESICS	**CARDIOVASCULAR**	**CHOLINESTERASE INHIBITORS**	
codeine	carvedilol	donepezil	
hydrocodone	clonidine		
oxycodone	diltiazem	**COUGH SUPPRESSANT**	
phenacetin	disopyramide	dextromethorphan	
tramadol	flecainide		
	S-metoprolol	**PSYCHOTROPICS**	
ANESTHETICS	mexiletine	amitriptyline	nortriptyline
lidocaine	nebivolol	amphetamine	paroxetine
	propafenone	aripiprazole	perphenazine
ANORECTICS	propranolol	atomoxetine	pimozide
dexfenfluramine	sparteine	chlorpromazine	risperidone
	timolol	clomipramine	sertraline
ANTIEMETIC/PROKINETICS		desipramine	thioridazine
metoclopramide		duloxetine	venlafaxine
ondansetron		fluoxetine	zuclopenthixol
		fluvoxamine	
ANTIHISTAMINES		haloperidol	
chlorpheniramine		iloperidone	
promethazine		imipramine	
		methamphetamine	
ANTINEOPLASTICS		methoxyamphetamine	
tamoxifen		minaprine	

Drugs Metabolized by UGT1A3 Enzyme	
ANTIPARASITIC	**NSAID**
dapsone	diclofenac
	flurbiprofen
ANTIPSYCHOTIC	
clozapine	**OPIOID AGONIST/ANTAGONIST**
	buprenorphine
HORMONE	
estrogen/estrone	**PSYCHOTROPIC**
	amitriptyline

Drugs Metabolized by UGT1A6 Enzyme	
ANALGESIC	**OPIOD**
acetaminophen	morphine
ANTIEPILEPTIC	**SELECTIVE ESTROGEN RECEPTOR MODULATOR**
valproate	raloxifene

Drugs Metabolized by QOR Enzyme	
ANALGESIC	**ANTIEPILEPTIC**
acetaminophen	phenobarbital

Table 1: List of Common Compounds of Hepatic Metabolism Potentially Impacted by AHCC®®

Table Abbreviations: Cytochrome P450 (CYP450), uridine glucuronosyltransferase (UGT), quinone oxidoreductase (QOR)

Phase I Metabolism Pathways				
	Substrate	Inhibitor	Inducer	No Interactions
CYP450 3A4				x
CYP450 2C8				x
CYP450 2C9				x
CYP450 2D6	x		x	
Phase II Metabolism Pathways				
GST				x
COMT				x
QOR		x		
UGT 2B17				x
UGT 1A3			x	
UGT 1A6			x	

Table 2: Summary of AHCC supplement Impact on the Phase I and Phase II Metabolism Pathways.

Conclusion

Based on data from in vitro and ex vivo hepatic metabolism studies, overall data supports AHCC® can safely be used in combination with majority of medications. However, patients should be monitored closely when combining AHCC® with substrates of CYP450 2D6 pathway, aromatase pathway, QOR pathways or UGT 1A3 and 1A6 pathways. As AHCC® continues to be used more commonly in the clinical setting, more data will be collected to confirm the clinical application and translation of the preclinical in vitro, in vivo, and ex vivo hepatic metabolism study's findings in the patient care arena.

Conflict of Interest

RC, AG, and LM have no conflicts of interest with respect to research, authorship, and/or publication of this article. JAS has served as principal investigator on unrestricted research grants to her institution.

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