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Review

Active hexose correlated compound in ovarian cancer: A systematic review of clinical and preclinical evidence

[Compuesto correlacionado de hexosa activa en el cáncer de ovario: revisión sistemática de la evidencia clínica y preclínica]

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Abstract

Context: Ovarian cancer is commonly diagnosed at an advanced stage and remains associated with high recurrence, limited survival, and treatment-related toxicity. Active hexose correlated compound (AHCC), a standardized extract of cultured *Lentinula edodes* mycelia, has been investigated as a possible adjunct to chemotherapy because of its immunomodulatory and antitumor properties.

Aims: To systematically synthesize the available clinical and preclinical evidence on the effects of AHCC in ovarian cancer.

Methods: PRISMA-guided searches were performed in PubMed, ScienceDirect, the Cochrane Library, and Google Scholar up to 20 August 2025. Eligible studies evaluated AHCC in ovarian cancer or related experimental models. Clinical and preclinical evidence were synthesized narratively because of substantial heterogeneity.

Results: Four studies were included: two clinical studies and two preclinical studies. One randomized trial in ovarian/peritoneal cancer suggested preservation of CD8+ T-cell levels and reduced nausea and vomiting during chemotherapy. One before–after study in mixed advanced cancers, including a small ovarian subgroup, suggested reduced hematologic and hepatic toxicity and improved quality of life. Preclinical studies showed inhibition of ovarian cancer cell proliferation, induction of apoptosis, suppression of STAT3 signaling, and enhanced response to pegylated liposomal doxorubicin. No study reported progression-free survival or overall survival.

Conclusions: AHCC showed preliminary biological activity and possible supportive effects during chemotherapy, but the clinical evidence remained very limited. Larger, well-designed ovarian cancer trials are required.

Keywords: complementary therapies; dietary supplements; immunomodulation; ovarian neoplasms; shiitake mushrooms; signal transducer and activator of transcription 3.

Resumen

Contexto: El cáncer de ovario suele diagnosticarse en estadios avanzados y se asocia con alta recurrencia, supervivencia limitada y toxicidad por el tratamiento. El compuesto correlacionado con hexosa activa (AHCC), un extracto estandarizado del micelio cultivado de *Lentinula edodes*, se ha investigado como posible complemento de la quimioterapia por sus propiedades inmunomoduladoras y antitumorales.

Objetivos: Sintetizar sistemáticamente la evidencia clínica y preclínica disponible sobre los efectos del AHCC en el cáncer de ovario.

Métodos: Se realizaron búsquedas guiadas por PRISMA en PubMed, ScienceDirect, la Biblioteca Cochrane y Google Scholar hasta el 20 de agosto de 2025. Se incluyeron estudios sobre el AHCC en cáncer de ovario o en modelos experimentales relacionados con el cáncer de ovario. La evidencia clínica y preclínica se sintetizó de forma narrativa debido a la heterogeneidad.

Resultados: Se incluyeron cuatro estudios: dos clínicos y dos preclínicos. Un ensayo aleatorizado en cáncer de ovario/peritoneal sugirió la preservación de linfocitos T CD8+ y una menor incidencia de náuseas y vómitos durante la quimioterapia. Un estudio antes-después en cánceres mixtos avanzados (subgrupo pequeño de ovario) sugirió menor toxicidad hematológica y hepática y una mejor calidad de vida. Los estudios preclínicos mostraron inhibición de la proliferación celular, inducción de apoptosis, supresión de STAT3 y una mayor respuesta a la doxorrubicina liposomal pegilada. Ningún estudio informó sobre supervivencia libre de progresión ni sobre supervivencia global.

Conclusiones: El AHCC mostró actividad biológica preliminar y posibles efectos de apoyo durante la quimioterapia, pero la evidencia clínica fue muy limitada. Se requieren ensayos más amplios en el cáncer de ovario.

Palabras Clave: cáncer de ovario; hongos shiitake; inmunomodulación; suplementos dietéticos; terapias complementarias; transductor de señales y activador de la transcripción 3.

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AHCC: Active Hexose Correlated Compound; **GRADE:** Grading of Recommendations Assessment, Development and Evaluation; **HHV-6:** Human Herpesvirus 6; **OS:** Overall survival; **PFS:** Progression-free survival; **PLD:** Pegylated liposomal doxorubicin; **PRISMA:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **QoL:** Quality of life; **RCT:** Randomized controlled trial; **RoB 2:** Cochrane Risk of Bias 2 tool; **ROBINS-I:** Risk Of Bias In Non-randomized Studies of Interventions; **SHP-1:** Src homology region 2 domain-containing phosphatase-1; **STAT3:** Signal Transducer and Activator of Transcription 3; **SYRCLE:** Systematic Review Centre for Laboratory Animal Experimentation; **Th:** T helper cell; **VEGF:** Vascular endothelial growth factor.

INTRODUCTION

Ovarian cancer is one of the most lethal gynecologic malignancies worldwide and remains a major clinical challenge despite advances in diagnosis and treatment. According to GLOBOCAN 2020 estimates, approximately 313,000 new cases and 207,000 deaths from ovarian cancer were reported globally, making it one of the leading causes of gynecologic cancer mortality (Sung et al., 2021). The disease is frequently asymptomatic in its early stages, and many patients are diagnosed only after the disease has progressed to an advanced stage. More than 70% of patients present with stage III–IV disease, when treatment is more complex and prognosis is substantially poorer (Salas Bolívar et al., 2025). Even after optimal cytoreductive surgery followed by platinum- and taxane-based chemotherapy, long-term outcomes remain unsatisfactory. Advanced ovarian cancer is associated with a five-year survival rate below 30–40%, and recurrence occurs in a large proportion of patients within the first few years after completion of primary therapy (Cortez et al., 2018; Greening et al., 2022). These data highlight the need for additional strategies that may improve treatment tolerance, preserve immune function, and support quality of life (QoL) in patients undergoing conventional therapy.

Recent ovarian cancer treatment strategies remain centered on cytoreductive surgery, platinum- and taxane-based chemotherapy, and targeted therapies, including poly(adenosine diphosphate-ribose) polymerase inhibitors, angiogenesis inhibitors, and immune-based therapies (Banerjee et al., 2021; Nero et al., 2021). Despite these advances, recurrence, drug resistance, treatment-related toxicity, and unequal access to care remain major clinical challenges. Chemotherapy-related adverse effects, including myelosuppression, gastrointestinal symptoms, fatigue, and hepatic or hematologic toxicity, may impair QoL and contribute to dose reduction or treatment delay. These limitations have encouraged interest in complementary and integrative approaches that may support patients during treatment. In this context, natural products with potential immunomodulatory or supportive effects have attracted attention, although their clinical use requires careful evaluation through evidence-based methods.

Active hexose correlated compound (AHCC) is a standardized extract derived from the cultured mycelia of *Lentinula edodes*, commonly known as shiitake mushroom. It has been investigated as a dietary supplement with possible immunomodulatory and antitumor effects. In oncology-related research, AHCC has been studied for its effects on immune parameters, treatment tolerance, and tumor-related biological pathways. However, the extent to which these properties are applicable to ovarian cancer remains uncertain because the available evidence is limited and heterogeneous. Therefore, any interpretation of AHCC in ovarian cancer must distinguish between direct ovarian cancer evidence and broader mechanistic or supportive evidence from other disease contexts.

Preclinical ovarian cancer evidence suggests that AHCC may exert direct antitumor effects through modulation of intracellular signaling pathways. Choi et al. (2018) reported that AHCC inhibited the proliferation of ovarian cancer cells by suppressing constitutive signal transducer and activator of transcription 3 (STAT3) phosphorylation. This effect was associated with upregulation of Src homology region 2 domain-containing phosphatase-1 (SHP-1) and downregulation of STAT3-regulated proteins, including cyclin D1, Bcl-2, Mcl-1, survivin, and vascular endothelial growth factor (VEGF), ultimately leading to reduced cell viability and induction of apoptosis. In another preclinical study, Hunter et al. (2011) evaluated AHCC in combination with pegylated liposomal doxorubicin (PLD) in ovarian cancer models. The combination produced additive growth inhibition *in vitro* and reduced tumor growth in a xenograft model without evidence of additional toxicity. These findings provide a mechanistic basis for further investigation of AHCC as a potential adjunctive agent, but they remain preclinical and cannot be directly translated into clinical benefit without confirmatory human trials.

Clinical evidence is also limited. Suknikhom et al. (2017) conducted a randomized controlled trial (RCT) evaluating AHCC supplementation in patients with epithelial ovarian cancer or primary peritoneal cancer receiving platinum-based chemotherapy. The study found no significant overall differences in CD4+ or CD8+ T-cell counts between groups during treatment; however, CD8+ T-cell levels were higher in the AHCC group at the sixth cycle of chemotherapy. The AHCC group also experienced less severe chemotherapy-induced nausea and vomiting, although myalgia was more frequently reported. Ito et al. (2014) evaluated

AHCC in a before–after study involving patients with mixed advanced cancers, including a small subgroup of patients with ovarian cancer. In that study, AHCC supplementation during chemotherapy was associated with reduced hematologic and hepatic toxicity, lower salivary human herpesvirus 6 (HHV-6) DNA levels, and improved QoL scores compared with the preceding chemotherapy cycle without AHCC. Because this study was not restricted to ovarian cancer and did not include a parallel control group, its findings should be interpreted cautiously.

Taken together, available evidence suggests that AHCC may have supportive and mechanistic relevance in ovarian cancer, particularly in relation to immune modulation, chemotherapy-related toxicity, and STAT3-associated tumor pathways. Nevertheless, the evidence base remains small and preliminary. Only one clinical trial was restricted to ovarian or primary peritoneal cancer, while another clinical study included only a small ovarian cancer subgroup within a mixed advanced-cancer population. Furthermore, available clinical studies did not evaluate progression-free survival (PFS), overall survival (OS), or robust tumor-response outcomes. Therefore, the current evidence is insufficient to establish AHCC as an effective adjunctive therapy in ovarian cancer.

This review was undertaken to systematically identify, appraise, and synthesize the available clinical and preclinical evidence on AHCC in ovarian cancer. The review focuses on immune modulation, chemotherapy-related toxicity, QoL, tumor-related mechanisms, and the absence or presence of clinically meaningful outcomes such as PFS, OS, and tumor response. By separating clinical and preclinical evidence, this review seeks to clarify the current state of knowledge, identify limitations in the evidence base, and inform the design of future studies evaluating AHCC in ovarian cancer.

MATERIAL AND METHODS

Review methodology

This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (Page et al., 2021) and was registered in the PROSPERO under registration number CRD420261537805. The review included literature identification, title and abstract screening, full-text eligibility assessment, data extraction, risk-of-bias assessment, and narrative synthesis. Clinical and preclinical evidence were analyzed separately because they represented different levels of evidence.

Eligibility criteria

Eligibility criteria were defined separately for clinical and preclinical studies. Clinical studies were eligible if they included adult patients with ovarian cancer or primary peritoneal cancer who received AHCC, either alone or as an adjunct to standard oncological treatment. Eligible comparators included placebo, no AHCC, or standard therapy without AHCC. Outcomes of interest included immune parameters, chemotherapy-related adverse events, QoL, tumor response, PFS, OS, and safety outcomes.

Preclinical studies were eligible if they evaluated AHCC in ovarian cancer-related *in vitro* or *in vivo* models. Eligible outcomes included cell viability, apoptosis, tumor growth inhibition, chemotherapy interaction, and molecular signaling pathways. RCTs, quasi-experimental studies, observational studies, and original preclinical studies were considered. Reviews, systematic reviews, meta-analyses, editorials, letters, conference abstracts without full text, case reports, and case series were excluded. Studies were also excluded if AHCC was not clearly evaluated, if its independent effect could not be assessed, or if no relevant outcome was reported. Only English-language full-text articles were included.

Information sources

The literature search was conducted in PubMed via MEDLINE, ScienceDirect, the Cochrane Library, and Google Scholar. The final search was performed on 20 August 2025. Reference lists of included studies were also screened manually to identify additional eligible articles. No manufacturers, organizations, or study authors were contacted.

Search strategy

The search strategy combined terms related to AHCC and ovarian cancer. The core search string was: ("Active Hexose Correlated Compound" OR AHCC OR "Lentinula edodes mycelia" OR "shiitake mycelia") AND ("ovarian cancer" OR "ovarian carcinoma" OR "ovarian neoplasm" OR "peritoneal cancer"). The search syntax was adapted for each database. Complete database-specific search strategies are provided in Supplementary Tables S1-S3. No date restriction was applied. English-language and accessible full-text criteria were applied during screening.

Selection process

Two reviewers independently screened titles and abstracts. Full-text articles were then assessed independently using the predefined eligibility criteria. Disagreements were resolved by discussion or consultation with a third reviewer. Reference management

software, Mendeley, was used to identify duplicates and mark clearly ineligible records before manual verification. No machine-learning classifier, artificial intelligence tool, crowdsourcing method, or previously screened dataset was used to replace reviewer judgment. The selection process was summarized using a PRISMA 2020 flow diagram.

Data collection process

Two reviewers independently extracted data using a standardized form. Extracted data included author, year, country, study design, population or model, sample size, AHCC dose and duration, comparator, outcomes, follow-up duration, main findings, funding source, and conflicts of interest. For preclinical studies, experimental models, treatment combinations, molecular assays, tumor outcomes, apoptosis-related outcomes, and toxicity observations were also extracted. Disagreements were resolved by consensus.

Data items

For clinical studies, extracted outcomes included immune modulation, chemotherapy-related toxicity, QoL, tumor response, PFS, OS, and safety. For preclinical studies, extracted outcomes included cell viability, tumor growth inhibition, apoptosis, chemotherapy interaction, and molecular signaling, including STAT3, SHP-1, cyclin D1, Bcl-2, Mcl-1, survivin, and VEGF. If an outcome was not reported, it was recorded as not reported rather than estimated.

Risk of bias assessment

The randomized clinical trial was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool (Sterne et al., 2019). The non-randomized clinical study was assessed using the Risk of Bias in Non-randomized Studies of Interventions tool (ROBINS-I) (Sterne et al., 2016). The *in vivo* preclinical study was assessed using an appraisal informed by the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) risk-of-bias tool (Hooijmans et al., 2014), while the *in vitro* study was evaluated qualitatively based on methodological clarity, experimental controls, reproducibility, and relevance to ovarian cancer. Two reviewers independently performed the assessment, and disagreements were resolved through discussion.

Effect measures

Effect measures were extracted as reported in the original studies. Continuous outcomes were extracted as means, medians, standard deviations, ranges, or p-values when available. Dichotomous outcomes were extracted as event numbers and total participants when reported. Preclinical outcomes were extracted as reported, including percentage tumor reduction, cell viability changes, apoptosis-related findings, and molecular expression changes. No effect estimates were recalculated or transformed.

Synthesis methods

Clinical and preclinical studies were synthesized separately. Meta-analysis was not performed because the included studies differed substantially in design, population or model, comparator, and outcome reporting. Clinical evidence was summarized according to immune outcomes, chemotherapy-related toxicity, QoL, and survival or tumor-response reporting. Preclinical evidence was summarized according to cell viability, apoptosis, tumor growth inhibition, chemotherapy interaction, and molecular signaling. Results were presented using narrative synthesis, evidence tables, and the PRISMA flow diagram.

Subgroup analysis, meta-regression, and sensitivity analysis were not performed because of the small number of included studies. Reporting bias could not be assessed using funnel plots or statistical tests. Certainty of clinical evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Guyatt et al., 2008). Preclinical evidence was not graded using this approach and was interpreted qualitatively as mechanistic evidence.

RESULTS

Study selection

A total of 547 records were identified through database searches, including 6 records from PubMed, 501 from Google Scholar, 3 from the Cochrane Library, and 37 from ScienceDirect. No duplicate records were removed. Before screening, 20 records were marked as ineligible by automation tools according to the predefined rule described in the Methods. A total of 527 records were screened by title and abstract, of which 220 were excluded because they did not meet the review criteria.

The remaining 307 reports were sought for full-text retrieval, and all were successfully retrieved. Therefore, no report was classified as not retrievable. After full-text eligibility assessment, 303 reports were excluded. The main reasons for exclusion were ineligible study design or publication type (n = 161), intervention unrelated to AHCC (n = 101), non-ovarian cancer population or model (n = 39), and absence of relevant outcome reporting (n = 2). Four studies fulfilled the eligibility criteria and were included in the final review. These consisted of two clinical studies and two preclinical studies. The PRISMA 2020 flow diagram is shown in Fig. 1.

Characteristics of included studies

The four included studies consisted of two clinical studies and two preclinical studies. The clinical evidence included one RCT in patients with epithelial ovarian cancer or primary peritoneal cancer and one quasi-experimental before–after study in patients with mixed advanced cancers, including a small ovarian cancer subgroup. The preclinical evidence included one *in vitro* study using human ovarian cancer cell lines and one combined *in vitro* and *in vivo* xenograft study. The clinical and preclinical evidence was synthesized separately because the study designs, populations, models, comparators, and outcome domains were substantially different.

Clinical evidence synthesis

The RCT by Suknikhom et al. (2017) included 28 patients with epithelial ovarian cancer or primary peritoneal cancer receiving platinum-based chemotherapy. AHCC was given orally at 3 g/day during six cycles of chemotherapy and was compared with placebo. Outcomes included CD4+ and CD8+ T-cell counts, bone marrow suppression, adverse events, and QoL. The study reported no significant differences in CD4+ or CD8+ T-cell counts between groups during most of the treatment period. However, at the sixth cycle of chemotherapy, the AHCC group had a significantly higher CD8+ T-cell level than the placebo group. The reported median CD8+ T-cell count was 392.5 cells/μL in the AHCC group and 259.5 cells/μL in the placebo group ($p = 0.03$). The study also reported lower severity of chemotherapy-induced nausea and vomiting in the AHCC group, while myalgia was more frequent. No significant difference was reported for bone marrow suppression or overall QoL score.

The quasi-experimental before–after study by Ito et al. (2014) included 24 patients with mixed advanced cancers, of whom seven had ovarian cancer. AHCC was administered orally at 3 g/day during the second chemotherapy cycle, and outcomes during this cycle were compared with the first chemotherapy cycle without AHCC in the same patients. Reported outcomes included chemotherapy-related toxicity, salivary HHV-6 DNA level, and QoL. The study reported reduced hematologic and hepatic toxicity, lower salivary HHV-6 DNA level, and improved QoL scores during the AHCC-supplemented cycle. However, the outcomes were reported for the overall mixed-cancer population and were not presented separately for the ovarian cancer subgroup.

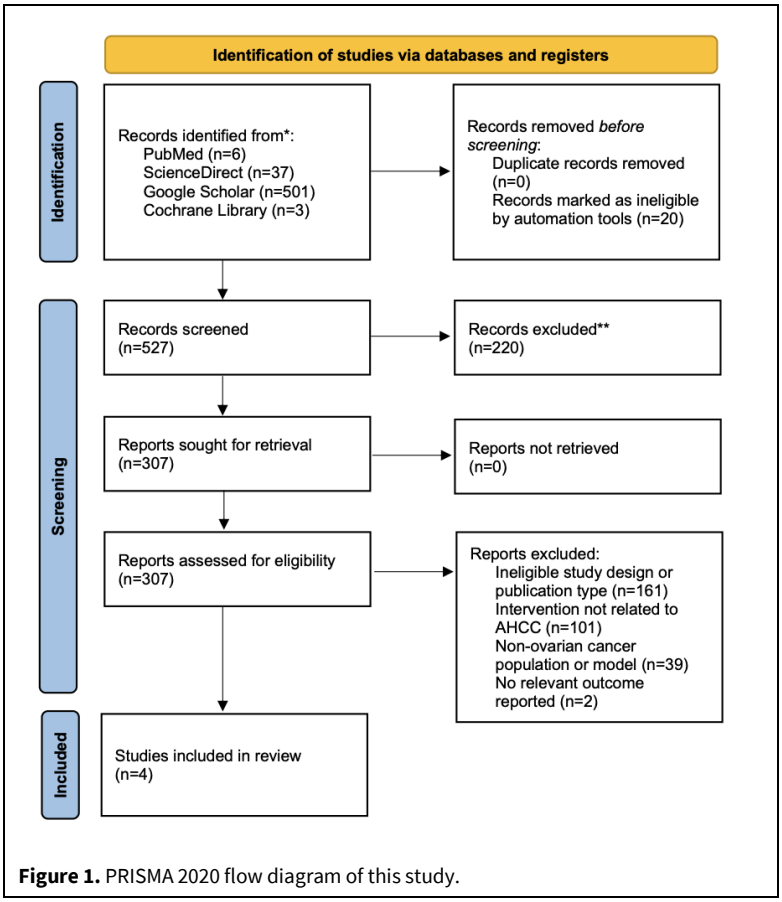

Figure 1. PRISMA 2020 flow diagram of this study.

Table 1. Clinical evidence summary.

Author, year	Study design	Population	Intervention	Comparator	Outcomes	Key findings
Suknikhom et al., 2017	Randomized, double-blind, placebo-controlled trial	Patients with epithelial ovarian cancer or primary peritoneal cancer receiving platinum-based chemotherapy (n = 28)	AHCC 3 g/day orally during six chemotherapy cycles	Placebo	CD4+ and CD8+ T-cell counts, bone marrow suppression, adverse events, QoL	CD8+ T-cell level was higher at chemotherapy cycle 6 in the AHCC group than in the placebo group (392.5 vs. 259.5 cells/μL, p = 0.03). Nausea and vomiting were less severe in the AHCC group, while myalgia was more frequent. No significant difference was reported for bone marrow suppression or QoL
Ito et al., 2014	Quasi-experimental before–after study	Patients with mixed advanced cancers, including seven patients with ovarian cancer (total n = 24)	AHCC 3 g/day orally during the second chemotherapy cycle	Same patients during the first chemotherapy cycle without AHCC	Chemotherapy-related toxicity, salivary HHV-6 DNA level, QoL	Hematologic and hepatic toxicity were reduced during the AHCC-supplemented cycle. Salivary HHV-6 DNA level was lower, and QoL scores improved. Ovarian cancer subgroup-specific results were not reported

Across the two clinical studies, reported findings included preservation of CD8+ T-cell level at the end of chemotherapy in one randomized trial, reduced chemotherapy-related toxicity in both studies, and improvement in QoL outcomes in one before–after study. No included clinical study reported tumor response, PFS, or OS. The clinical evidence is summarized in Table 1.

Preclinical evidence synthesis

Two preclinical studies were included. Choi et al. (2018) conducted an *in vitro* study using human ovarian cancer cell lines. The study evaluated the effect of AHCC on ovarian cancer cell proliferation and molecular signaling. AHCC suppressed constitutive STAT3 phosphorylation and upregulated SHP-1 phosphatase. It also downregulated downstream proteins related to proliferation, survival, angiogenesis, and apoptosis regulation, including cyclin D1, Bcl-2, Mcl-1, survivin, and vascular endothelial growth factor. These changes were accompanied by reduced ovarian cancer cell viability and induction of apoptosis.

Hunter et al. (2011) evaluated AHCC in combination with PLD using ovarian cancer cell lines and a mouse xenograft model. *In vitro* experiments reported additive growth inhibition when AHCC was combined with PLD. In the xenograft model, the combination reduced tumor growth by 64.1% compared with untreated controls and by 31.2% compared with PLD alone (p = 0.03). No additional toxicity was reported in the combination group.

Across the two preclinical studies, AHCC was reported to reduce ovarian cancer cell proliferation, induce apoptosis, suppress STAT3-related signaling, and enhance the tumor growth inhibitory effect of PLD in a xenograft model. The preclinical evidence is summarized in Table 2.

Funding source and conflicts of interest of included studies

Suknikhom et al. (2017) was funded by the Ratchadapiseksompotch Research Fund, Faculty of Medicine, Chulalongkorn University. AHCC Thailand Co., Ltd. supplied AHCC and placebo but had no other role in study design, data collection, or analysis. Ito et al. (2014) reported no funding or conflict of interest statement, although AHCC was donated by Amino Up Chemical Co., Ltd. in Sapporo, Japan. Choi et al. (2018) were supported by Seoul National University Bundang Hospital and declared no relevant conflicts of interest. AHCC was purchased from KCFKOREA Co., Ltd. in Seoul, South Korea. Hunter et al. (2011) received an unrestricted research grant from Amino Up Chemical Co., Ltd., the AHCC manufacturer, and two of the six authors were affiliated with the company.

Risk of bias in included studies

Risk-of-bias assessment was performed according to study design. The RCT was judged to have some concerns, mainly because of the small sample size and limited reporting of allocation concealment and blinding details for subjective outcomes. The quasi-experimental before–after study was judged to have serious risk of bias because it had no parallel control group, included a mixed advanced-cancer population, and did not report ovarian subgroup-specific outcomes.

Table 2. Preclinical evidence summary.

Author, year	Study design	Model	Intervention	Comparator	Outcomes	Key findings
Choi et al., 2018	*In vitro* study	Human ovarian cancer cell lines	AHCC added to cell cultures	Untreated cells	STAT3 signaling, oncogenic protein expression, cell viability, apoptosis	Suppressed STAT3 phosphorylation; upregulated SHP-1; downregulated cyclin D1, Bcl-2, Mcl-1, survivin, and VEGF; reduced cell viability; induced apoptosis
Hunter et al., 2011	*In vitro* and *in vivo* xenograft study	Ovarian cancer cell lines and tumor-bearing mice	AHCC combined with pegylated liposomal doxorubicin	PLD alone or untreated control	Tumor growth inhibition, apoptosis-related outcomes, toxicity	Additive inhibition *in vitro*; 64.1% tumor growth reduction compared with untreated controls and 31.2% greater reduction compared with PLD alone ($p = 0.03$); no additional toxicity reported

Table 3. Risk-of-bias assessment of included studies.

Study	Design	Assessment tool	Main concerns	Overall judgment
Suknikhom et al., 2017	RCT	RoB 2	Small sample size; limited reporting of allocation concealment; possible concern in subjective outcome assessment	Some concerns
Ito et al., 2014	Quasi-experimental before–after study	ROBINS-I	No parallel control group; potential confounding; mixed advanced-cancer population; ovarian subgroup-specific outcomes not reported	Serious risk of bias
Choi et al., 2018	*In vitro* study	Qualitative methodological appraisal	Experimental model only; indirect applicability to clinical outcomes	Methodologically acceptable for mechanistic evidence
Hunter et al., 2011	*In vitro* and *in vivo* xenograft study	SYRCLE-informed appraisal	Limited reporting of randomization, allocation concealment, and blinding in the animal experiment	Unclear risk of bias

The *in vivo* xenograft study had unclear risk of bias because randomization, allocation concealment, and blinding procedures were incompletely reported. The *in vitro* study was considered methodologically acceptable for mechanistic interpretation, but its clinical applicability was indirect. The risk-of-bias assessment is summarized in Table 3.

Certainty of clinical evidence

The certainty of clinical evidence was assessed using the GRADE approach. Certainty was rated as low or very low across all clinical outcomes because of small sample sizes, imprecision, risk of bias, indirectness, and limited outcome reporting. PFS, OS, and tumor response were not assessed because no included clinical study reported these outcomes. The certainty of clinical evidence is summarized in Table 4.

Results of synthesis

Statistical meta-analysis was not performed because only four studies were included and because the clinical and preclinical studies differed substantially in design, population or model, comparator, and outcome reporting. Clinical and preclinical evidence were therefore synthesized narratively and presented separately. Subgroup analysis, meta-regression, sensitivity analysis, and formal assessment of reporting bias using funnel plots were not performed because of the small number of included studies and the absence of pooled effect estimates.

DISCUSSION

This systematic review identified four studies evaluating AHCC in ovarian cancer or ovarian cancer experimental models. The evidence consisted of one randomized clinical trial in epithelial ovarian or primary peritoneal cancer, one before–after study in mixed advanced cancers with a small ovarian cancer subgroup, one *in vitro* study, and one combined *in vitro* and *in vivo* xenograft study (Choi et al., 2018; Hunter et al., 2011; Ito et al., 2014; Suknikhom et al., 2017). The limited number of studies, small clinical samples, and heterogeneity across designs support a cautious interpretation of the findings.

The clinical evidence was limited to immune-related, toxicity-related, and QoL outcomes. Suknikhom et al. (2017) evaluated AHCC at 3 g/day during platinum-based chemotherapy in patients with epithelial ovarian cancer or primary peritoneal cancer.

Table 4. Summary of findings and certainty of evidence (GRADE).

Outcome	Studies	Participants	Main finding	Certainty of evidence	Main reasons for certainty rating
CD8+ T-cell level	1	28	Higher CD8+ T-cell level at chemotherapy cycle 6 in the AHCC group	Low	Small sample size and imprecision
CD4+ T-cell level	1	28	No significant difference between groups	Low	Small sample size and imprecision
Chemotherapy-induced nausea and vomiting	1	28	Lower severity reported in the AHCC group	Low	Small sample size and subjective outcome assessment
Hematologic and hepatic toxicity	1	24 mixed-cancer patients; 7 with ovarian cancer	Reduced toxicity during the AHCC-supplemented cycle	Very low	Non-randomized before–after design, indirectness, and lack of ovarian subgroup-specific results
QoL	2	52 total; 35 with ovarian or primary peritoneal cancer	Findings were limited and inconsistent across studies	Very low	Small sample size, design limitations, and heterogeneity
Tumor response	0	0	Not reported	Not assessable	No clinical study reported this outcome
PFS	0	0	Not reported	Not assessable	No clinical study reported this outcome
OS	0	0	Not reported	Not assessable	No clinical study reported this outcome

The AHCC group showed a higher CD8+ T-cell level at the sixth chemotherapy cycle and lower severity of nausea and vomiting. No significant difference was observed in CD4+ T-cell levels, bone marrow suppression, or global QoL scores. Myalgia was reported more frequently in the AHCC group. The trial did not evaluate tumor response, PFS, or OS. These findings suggest a possible supportive effect during chemotherapy, without evidence of direct clinical antitumor benefit (Suknikhom et al., 2017).

The immune-related finding from Suknikhom et al. (2017) is biologically plausible when considered alongside previous AHCC immunology studies outside ovarian cancer. Terakawa et al. (2008) reported immunological effects of AHCC in healthy volunteers, including assessment of circulating dendritic-cell number and function after AHCC intake. Yin et al. (2010) reported increased frequencies of CD4+ and CD8+ T cells producing interferon-gamma and tumor necrosis factor-alpha in healthy adults receiving AHCC. Lee et al. (2012) showed that AHCC-treated human monocytes promoted T helper 1 (Th1) and Th17 responses through interleukin-1 beta-dependent mechanisms. Smith et al. (2022) reported that AHCC 3 g/day supported immune-mediated clearance of persistent high-risk human papillomavirus infection and was well tolerated in a phase II randomized trial. These studies do not provide ovarian cancer efficacy data, but they support the immunological rationale for further evaluation of AHCC in cancer-related supportive care.

The study by Ito et al. (2014) provides indirect clinical evidence. The study included patients with mixed advanced cancers, with only seven patients diagnosed with ovarian cancer. AHCC supplementation during the second chemotherapy cycle was associated with reduced hematologic and hepatic toxicity, lower salivary HHV-6 DNA levels, and improved QoL scores compared with the preceding chemotherapy cycle. The outcomes were not reported separately for the ovarian cancer subgroup. The before–after design also lacked a parallel control group. These factors limit the interpretation of its relevance to ovarian cancer.

The toxicity-related findings are consistent with previous AHCC studies in other chemotherapy settings. Yanagimoto et al. (2016) reported that AHCC intake was associated with reduced chemotherapy-related adverse events in patients with unresectable pancreatic ductal adenocarcinoma. Shigama et al. (2009) reported an alleviating effect of AHCC on anticancer drug-induced side effects in non-tumor-bearing mice, including effects related to myelosuppression and organ toxicity. These studies provide supportive-care context for AHCC during chemotherapy, but their populations and models differ from ovarian cancer.

The preclinical evidence supports biological plausibility. Choi et al. (2018) showed that AHCC suppressed constitutive STAT3 phosphorylation in ovarian cancer cells. This effect was accompanied by upregulation of SHP-1 and downregulation of cyclin D1, Bcl-2, Mcl-1, survivin, and VEGF. These molecular changes were associated with reduced cell viability and apoptosis induction. The results suggest that AHCC may affect pathways related to proliferation, survival, angiogenesis, and apoptosis in ovarian cancer cell lines.

The relevance of STAT3 in ovarian cancer is supported by previous ovarian cancer research. Liang et al. (2020) described STAT3 signaling as a pathway involved in ovarian cancer proliferation, survival, invasion, angiogenesis, stemness, immune modulation, and chemoresistance. Sato et al. (2025) reported that YHO-1701, a specific STAT3 inhibitor, suppressed ovarian cancer cell growth, reduced survivin expression, induced apoptosis, and inhibited tumor growth in ovarian cancer experimental models. These studies do not provide direct evidence for AHCC efficacy. They support the biological relevance of the STAT3 pathway observed in the AHCC-treated ovarian cancer cell-line study.

Hunter et al. (2011) evaluated AHCC with PLD in ovarian cancer experimental models. The combination produced additive growth inhibition *in vitro* and reduced tumor growth in a xenograft model compared with PLD alone. No additional toxicity was reported in the experimental model. This finding supports further evaluation of AHCC as a chemotherapy adjunct. Xenograft evidence remains indirect for clinical decision-making because it cannot fully represent human tumor heterogeneity, immune microenvironment, pharmacokinetics, or treatment complexity. This study received an unrestricted research grant from the AHCC manufacturer, and two authors were affiliated with the company. It was also published in a journal not indexed in PubMed. Potential industry influence cannot be excluded, and the findings should therefore be interpreted with caution.

Other AHCC studies outside ovarian cancer provide contextual support for treatment-combination research. Park et al. (2022) reported that AHCC enhanced the antitumor effect of dual immune checkpoint blockade in a murine colon cancer model, with immune-related effects involving tumor-infiltrating CD8+ T cells. Merchand-Reyes et al. (2023) reported direct and indirect effects of AHCC against chronic lymphocytic leukemia, including effects on leukemia-cell survival and potential enhancement of existing treatment approaches. These studies suggest that AHCC may interact with immune-related and treatment-response pathways across different disease contexts. They remain indirect for ovarian cancer and should not be interpreted as clinical evidence of AHCC efficacy in ovarian cancer.

Clinical evidence from non-ovarian conditions shows that AHCC-related effects may vary by disease context and endpoint. Atlihan et al. (2025) evaluated AHCC as an adjuvant after condyloma cauterization and found no significant difference in recurrence presence between AHCC users and non-users, while recurrent lesions among AHCC users had a lower number and smaller diameter. This mixed finding supports a cautious interpretation of AHCC-related clinical benefit and highlights the need for disease-specific endpoints.

Safety evidence remains insufficient. No included clinical study was designed or powered to evaluate AHCC safety comprehensively in ovarian cancer patients. Suknikhom et al. (2017) reported no increased bone marrow suppression in the AHCC group, with a higher frequency of myalgia. Ito et al. (2014) reported reduced toxicity during the AHCC-supplemented chemotherapy cycle, with interpretation limited by its mixed-cancer population and uncontrolled design. Smith et al. (2022) reported good tolerability of AHCC 3 g/day in women with persistent high-risk human papillomavirus infection. The current evidence does not show a major safety signal in small preliminary studies. A reliable safety profile in ovarian cancer still requires larger clinical trials with standardized adverse-event monitoring.

The certainty of clinical evidence remains low to very low. The main limitations include small sample sizes, one mixed-cancer clinical study with a small ovarian subgroup, absence of ovarian subgroup-specific outcomes in Ito et al. (2014), limited safety assessment, lack of clinically decisive endpoints, and industry involvement in three of the four included studies through grant support or product supply from AHCC producers. No clinical study reported tumor response, PFS, or OS. Preclinical studies provide mechanistic support, with indirect applicability to patient-level outcomes. AHCC remains an investigational complementary agent in ovarian cancer, and future studies should use ovarian cancer-specific randomized designs, standardized dosing, systematic safety monitoring, immune profiling, and clinically meaningful endpoints (Choi et al., 2018; Hunter et al., 2011; Ito et al., 2014; Suknikhom et al., 2017). Future clinical research should prioritize an adequately powered randomized trial of AHCC added to platinum and taxane chemotherapy in epithelial ovarian or primary peritoneal cancer, guided by biomarkers, with toxicity specified in advance, immune profiling, and QoL, PFS, and OS as endpoints. Mechanistic studies should validate the STAT3 and SHP-1 dependency, test AHCC with carboplatin, paclitaxel, and PLD in platinum-sensitive and resistant models, use immune-competent mouse models, and define pharmacokinetic and drug interaction profiles.

CONCLUSION

The available evidence on AHCC in ovarian cancer remains limited and preliminary. Clinical evidence is restricted to two small studies, with findings mainly related to CD8+ T-cell preservation, chemotherapy-related toxicity, and QoL. No clinical study reported

tumor response, PFS, or OS. Preclinical evidence suggests that AHCC may affect ovarian cancer cell proliferation, apoptosis, STAT3-associated signaling, and chemotherapy response in experimental models. The certainty of clinical evidence remains low to very low because of small sample sizes, indirectness, risk of bias, and limited outcome reporting. AHCC should be regarded as an investigational complementary agent in ovarian cancer. Adequately powered ovarian cancer-specific randomized trials with standardized dosing, systematic safety assessment, immune profiling, and clinically meaningful oncological endpoints are required before clinical recommendations can be made.

CONFLICT OF INTEREST

The research was conducted entirely free from any involvement in commercial, financial, or personal matters that might be perceived as a possible conflict of interest or that could have influenced the outcomes or interpretation of the study.

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GENERATIVE ARTIFICIAL INTELLIGENCE (AI)

The authors declare that no generative artificial intelligence (AI) or AI-assisted technologies were used in the preparation, writing, or editing of this manuscript. All content was developed solely by the authors, who take full responsibility for its accuracy and integrity.

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Design	x	x	x		x
Definition of intellectual content	x	x		x	x
Literature search	x	x		x	x
Data acquisition	x			x	
Data analysis	x			x	x
Manuscript preparation	x	x			x
Manuscript editing	x		x	x	
Manuscript review	x	x	x	x	x

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Supplementary data

Table S1. Full database-specific search strategies.

Database	Platform/ interface	Date searched	Search field(s)	Exact search strategy	Limits/ filters	Records retrieved	Record handling	Syntax reference
PubMed	PubMed (MEDLINE), National Library of Medicine	20 August 2025	MeSH terms and Title/Abstract	((("Active Hexose Correlated Compound"[Title/Abstract]) OR (AHCC[Title/Abstract]) OR ("Lentinula edodes mycelia"[Title/Abstract]) OR ("shiitake mycelia"[Title/Abstract])) AND (("Ovarian Neoplasms"[MeSH Terms]) OR ("Peritoneal Neoplasms"[MeSH Terms]) OR ("ovarian cancer"[Title/Abstract]) OR ("ovarian carcinoma"[Title/Abstract]) OR ("ovarian neoplasm*"[Title/Abstract]) OR ("peritoneal cancer"[Title/Abstract])))	No date restriction. English-language and accessible full-text eligibility were applied during screening.	6	Records transferred to reference-management software for screening and deduplication.	https://pubmed.ncbi.nlm.nih.gov/help/
ScienceDirect	ScienceDirect Advanced Search (Elsevier)	20 August 2025	Title, abstract, or author-specified keywords	("Active Hexose Correlated Compound" OR AHCC OR "Lentinula edodes mycelia" OR "shiitake mycelia") AND ("ovarian cancer" OR "ovarian carcinoma" OR "ovarian neoplasm" OR "ovarian neoplasms" OR "peritoneal cancer")	No date restriction. English-language and accessible full-text eligibility were applied during screening.	37	Records transferred to reference-management software for screening and deduplication.	https://service.elsevier.com/app/answers/detail/a_id/25974/supporthub/sciencedirect/
Cochrane Library	Cochrane Library Search Manager (Wiley); CENTRAL and Cochrane Reviews	20 August 2025	MeSH descriptors; title, abstract, and keyword fields	#1 MeSH descriptor: [Ovarian Neoplasms] explode all trees #2 MeSH descriptor: [Peritoneal Neoplasms] explode all trees #3 "ovarian cancer":ti,ab,kw #4 "ovarian carcinoma":ti,ab,kw #5 "ovarian neoplasm*":ti,ab,kw #6 "peritoneal cancer":ti,ab,kw #7 #1 OR #2 OR #3 OR #4 OR #5 OR #6 #8 "Active Hexose Correlated Compound":ti,ab,kw #9 AHCC:ti,ab,kw #10 "Lentinula edodes mycelia":ti,ab,kw #11 "shiitake mycelia":ti,ab,kw #12 #8 OR #9 OR #10 OR #11 #13 #7 AND #12	No date restriction. English-language and accessible full-text eligibility were applied during screening.	3	Records transferred to reference-management software for screening and deduplication.	https://training.cochrane.org/handbook/current/chapter-04-technical-supplement
Google Scholar	Google Scholar	20 August 2025	All searchable fields; exact phrases in quotation marks	("Active Hexose Correlated Compound" OR AHCC OR "Lentinula edodes mycelia" OR "shiitake mycelia") ("ovarian cancer" OR "ovarian carcinoma" OR "ovarian neoplasm" OR "peritoneal cancer")	All years. Interface language set to English. Patents and citation-only records excluded. All 501 displayed results were screened; no arbitrary result limit was applied.	501	Records were documented and screened; eligible citations were transferred to the review database.	https://scholar.google.com/intl/us/scholar/help.html
Total records identified through database searching						**547**	**Total as reported in the manuscript: 547**	

Table S2. Line-by-line search strategy details.

Database	Line	Concept	Exact line / command	Purpose
PubMed	P1	AHCC concept	("Active Hexose Correlated Compound"[Title/Abstract] OR AHCC[Title/Abstract] OR "Lentinula edodes mycelia"[Title/Abstract] OR "shiitake mycelia"[Title/Abstract])	Captures the standardized product name, abbreviation, and mycelial-source terminology.
PubMed	P2	Ovarian/peritoneal cancer concept	("Ovarian Neoplasms"[MeSH Terms] OR "Peritoneal Neoplasms"[MeSH Terms] OR "ovarian cancer"[Title/Abstract] OR "ovarian carcinoma"[Title/Abstract] OR "ovarian neoplasm*"[Title/Abstract] OR "peritoneal cancer"[Title/Abstract])	Combines controlled vocabulary with free-text disease terms for clinical and experimental evidence.
PubMed	P3	Final combination	P1 AND P2	Final PubMed retrieval set.
ScienceDirect	SD1	AHCC concept	("Active Hexose Correlated Compound" OR AHCC OR "Lentinula edodes mycelia" OR "shiitake mycelia")	Entered in the Title, abstract, or author-specified keywords field.
ScienceDirect	SD2	Ovarian/peritoneal cancer concept	("ovarian cancer" OR "ovarian carcinoma" OR "ovarian neoplasm" OR "ovarian neoplasms" OR "peritoneal cancer")	Entered in the same advanced-search field.
ScienceDirect	SD3	Final combination	SD1 AND SD2	Final ScienceDirect retrieval set.
Cochrane Library	#1	Ovarian cancer MeSH	MeSH descriptor: [Ovarian Neoplasms] explode all trees	Controlled vocabulary.
Cochrane Library	#2	Peritoneal cancer MeSH	MeSH descriptor: [Peritoneal Neoplasms] explode all trees	Controlled vocabulary.
Cochrane Library	#3	Ovarian cancer free text	"ovarian cancer":ti,ab,kw	Title, abstract, keyword.
Cochrane Library	#4	Ovarian carcinoma free text	"ovarian carcinoma":ti,ab,kw	Title, abstract, keyword.
Cochrane Library	#5	Ovarian neoplasm free text	"ovarian neoplasm*":ti,ab,kw	Truncation captures neoplasm/neoplasms.
Cochrane Library	#6	Peritoneal cancer free text	"peritoneal cancer":ti,ab,kw	Title, abstract, keyword.
Cochrane Library	#7	Disease set	#1 OR #2 OR #3 OR #4 OR #5 OR #6	Combined disease concept.
Cochrane Library	#8	AHCC full name	"Active Hexose Correlated Compound":ti,ab,kw	Exact phrase.
Cochrane Library	#9	AHCC abbreviation	AHCC:ti,ab,kw	Abbreviation.
Cochrane Library	#10	Mycelial source	"Lentinula edodes mycelia":ti,ab,kw	Exact phrase.
Cochrane Library	#11	Common-source term	"shiitake mycelia":ti,ab,kw	Exact phrase.
Cochrane Library	#12	Intervention set	#8 OR #9 OR #10 OR #11	Combined AHCC concept.
Cochrane Library	#13	Final combination	#7 AND #12	Final Cochrane retrieval set.
Google Scholar	GS1	Exact query	("Active Hexose Correlated Compound" OR AHCC OR "Lentinula edodes mycelia" OR "shiitake mycelia") ("ovarian cancer" OR "ovarian carcinoma" OR "ovarian neoplasm" OR "peritoneal cancer")	Quotation marks preserve phrases; spaces represent AND between the two concept groups; OR entered in uppercase.

Table S3. Search log and retrieval counts.

Source	Date searched	Search completed by	Records identified	Date restriction	Language handling	Full-text handling	Notes
PubMed	20 August 2025	Two-reviewer review team	6	None	English eligibility applied during screening	Accessible full text required at eligibility stage	Known eligible studies checked against retrieval.
ScienceDirect	20 August 2025	Two-reviewer review team	37	None	English eligibility applied during screening	Accessible full text required at eligibility stage	Advanced-search field: title, abstract, or author keywords.
Cochrane Library	20 August 2025	Two-reviewer review team	3	None	English eligibility applied during screening	Accessible full text required at eligibility stage	Search Manager with MeSH and ti,ab,kw terms.
Google Scholar	20 August 2025	Two-reviewer review team	501	All years	English interface; eligibility applied during screening	Accessible full text required at eligibility stage	All displayed results screened; no arbitrary cap reported.
Total database records			**547**	**Reported total: 547 records**			