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Original Article

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AHCC® Supplementation and Modulation of Serum TGF-β in Advanced Non-small Cell Lung Cancer During Platinum-Based Chemotherapy

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Abstract

Background: Transforming growth factor-beta (TGF-β) is a key immunosuppressive cytokine involved in tumor progression, immune evasion, and therapeutic resistance in non–small cell lung cancer (NSCLC). Active Hexose Correlated Compound (AHCC®), a mushroom-derived immunomodulatory supplement, has been reported to enhance immune responses and potentially modulate cytokine profiles. ***Objective:*** To evaluate the effect of AHCC® supplementation on serum TGF-β levels in patients with advanced NSCLC receiving platinum-based chemotherapy. ***Methods:*** A quasi-experimental study was conducted in 50 patients with histopathologically confirmed NSCLC undergoing chemotherapy. Participants were allocated into two groups: AHCC® (n=25) and control (n=25). The intervention group received AHCC® 3 g/day during chemotherapy cycles. Serum TGF-β levels were measured before the first chemotherapy cycle and after the fourth cycle using ELISA. Statistical analyses were performed using Mann–Whitney and Wilcoxon tests with a significance level of $p<0.05$. ***Results:*** Baseline demographic and clinical characteristics were comparable between groups. Median baseline TGF-β levels were 146.4 pg/mL in the AHCC® group and 67.34 pg/mL in the control group (p=0.961). After four chemotherapy cycles, median TGF-β levels decreased to 54.93 pg/mL and 51.9 pg/mL, respectively (p=0.915). Within-group analyses showed no statistically significant reductions in TGF-β levels in either the AHCC® group (p=0.581) or the control group (p=0.882). Between-group comparison of delta TGF-β also showed no significant difference (p=0.580). ***Conclusion:*** AHCC® supplementation did not significantly reduce serum TGF-β levels in patients with advanced NSCLC undergoing chemotherapy. Further randomized controlled trials with larger sample sizes are needed to clarify its potential immunomodulatory effects and clinical relevance.

Keywords: ***Non–small cell lung cancer; AHCC®; Transforming growth factor-beta (TGF-β); Immunomodulation; Platinum-based chemotherapy.***

Introduction

Lung cancer remains one of the leading causes of cancer-related morbidity and mortality worldwide. Global cancer statistics indicate that lung cancer is among the most frequently diagnosed malignancies and continues to represent the leading cause of cancer-related deaths globally [1]. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases and includes several histological subtypes such as adenocarcinoma, squamous cell carcinoma, and large cell carcinoma [2]. Despite advances in diagnostic and therapeutic approaches, many patients are still diagnosed at advanced stages, resulting in limited treatment options and poor survival outcomes. This condition also represents a significant public health burden in many countries, including Indonesia, where late-stage diagnosis remains common [3,4].

The development and progression of lung cancer involve complex molecular and immunological mechanisms. One of the key regulatory pathways involved is the transforming growth factor beta (TGF-β) signaling pathway. TGF-β exhibits a dual role in cancer biology: acting as a tumor suppressor in early tumorigenesis but

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promoting tumor progression, invasion, metastasis, and immune evasion in advanced stages [5]. In lung cancer, dysregulation of TGF-β signaling has been linked to epithelial–mesenchymal transition (EMT), increased metastatic potential, and resistance to therapy [6]. Furthermore, elevated circulating TGF-β levels have been associated with poor prognosis in lung cancer patients and may reflect tumor-related immunosuppressive activity within the tumor microenvironment [7,8].

Given the critical role of immune regulation in cancer progression, increasing attention has been directed toward complementary immunomodulatory therapies that may enhance host immune responses. One such agent is Active Hexose Correlated Compound (AHCC®), a standardized extract derived from the mycelia of Lentinula edodes. AHCC® has been reported to possess immunomodulatory properties through activation of antigen-presenting cells and enhancement of immune cell activity [9]. Mechanistically, AHCC® and other fungal-derived glycans may stimulate innate and adaptive immune responses through β-glucan–mediated pathways, including activation of dendritic cells, macrophages, and natural killer cells [9-11].

Several studies have suggested that AHCC® supplementation may improve immune function and quality of life in cancer patients undergoing chemotherapy [12]. However, evidence regarding its effects on specific immunological biomarkers, particularly TGF-β in patients with NSCLC, remains limited. Therefore, this study aimed to evaluate the effect of AHCC® supplementation on serum TGF-β levels in patients with non-small cell lung cancer undergoing chemotherapy, in order to better understand its potential role as an adjunct immunomodulatory therapy in lung cancer management.

Methods

Study Design and Setting

This quasi-experimental study evaluated the effect of Active Hexose Correlated Compound (AHCC®) supplementation on serum transforming growth factor-beta (TGF-β) levels in patients with non–small cell lung cancer (NSCLC) undergoing chemotherapy. The primary endpoint was the change in serum TGF-β levels between baseline (cycle 1) and post-intervention (cycle 4), as well as the between-group difference after intervention.

The study was conducted at H. Adam Malik General Hospital and Prof. Dr. Chairuddin P. Lubis Hospital, Medan, Indonesia. Ethical approval was obtained from the Institutional Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara and H. Adam Malik Hospital prior to study initiation. Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

Participants

Eligible participants were adults with histopathologically confirmed NSCLC scheduled to receive platinum-based chemotherapy up to cycle four and with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1. Exclusion criteria included non-NSCLC histology, severe comorbidities affecting immune function, concurrent targeted therapy or immunotherapy, use of other immunomodulatory supplements, and inadequate laboratory specimens. Participants were recruited using consecutive sampling. Baseline demographic and clinical characteristics were recorded to assess comparability between groups.

Intervention and AHCC® Administration

Participants were allocated into two groups:

1. Intervention group: received AHCC® supplementation in addition to standard chemotherapy.
2. Control group: received standard chemotherapy without AHCC®.

AHCC® (Amino Up Co., Ltd., Sapporo, Japan) was administered orally at a total dose of 3 g per day, provided as 500 mg tablets. Participants were instructed to take three tablets twice daily (morning and evening), resulting in six tablets per day. Supplementation was initiated at chemotherapy cycle one and continued daily through cycle four. To reduce measurement bias, supplementation bottles were coded (A and B), and laboratory personnel analyzing TGF-β levels were blinded to group allocation.

Blood Sampling and Laboratory Analysis

Peripheral venous blood samples were collected at chemotherapy cycle one (baseline) and cycle four (post-intervention). Samples were centrifuged, and serum was stored under standardized conditions until analysis. Serum TGF-β levels were quantified using a commercially available human TGF-β enzyme-linked immunosorbent assay (ELISA) kit according to the manufacturer's protocol. All assays were performed in the same laboratory under standardized procedures to minimize analytical variability.

Variables and Bias Control

The independent variable was AHCC® supplementation (3 g/day, twice-daily administration), and the primary dependent variable was serum TGF-β level (pg/mL). Baseline covariates included age, sex, histopathological subtype, clinical stage, and smoking history (Brinkman Index). Potential confounding was addressed through strict eligibility criteria, exclusion of patients receiving targeted or immunotherapy agents, uniform chemotherapy exposure (cycles 1–4), and blinded laboratory assessment. Nevertheless, due to the quasi-experimental design, residual confounding and allocation bias cannot be entirely excluded.

Statistical Analysis

Descriptive statistics summarized baseline characteristics. Normality testing was performed prior to inferential analysis. Within-group comparisons were conducted using paired t-test or Wilcoxon signed-rank test, and between-group differences were analyzed using independent t-test or Mann–Whitney U test as appropriate. A two-tailed p-value <0.05 was considered statistically significant. Effect size estimation was included to complement p-value interpretation and enhance assessment of clinical relevance.

Methodological Limitations

The quasi-experimental design without full randomization may introduce selection bias. The relatively small sample size limits statistical power and generalizability. Additionally, evaluation of a single immunological biomarker (TGF-β) may not fully capture the complexity of immune modulation in NSCLC. However, standardized laboratory procedures, comparable treatment exposure, and blinded outcome assessment were implemented to strengthen internal validity.

Results

Baseline Characteristics

A total of 50 patients with non-small cell lung carcinoma (NSCLC) undergoing chemotherapy were included in the study, consisting of 25 patients in the AHCC® group and 25 in the control group. Baseline demographic and clinical characteristics were comparable between groups (all $p > 0.05$), indicating adequate homogeneity prior to intervention.

Table 1: Baseline Demographic and Clinical Characteristics of NSCLC Patients

Characteristics	AHCC® (n=25)	Control (n=25)	p-value
Sex, n (%)			**1.000**
Male	24 (96)	23 (92)	
Female	1 (4)	2 (8)	
Age, years **Median (Range)**	61 (27–76)	59 (37–71)	0.232
Ethnicity, n (%)			**0.845**
Batak	15 (60)	13 (52)	
Javanese	9 (36)	11 (44)	
Malay	1 (4)	1 (4)	
Family history of lung cancer, n (%)			**1.000**
No	24 (96)	24 (96)	
Yes	1 (4)	1 (4)	
History of tuberculosis, n (%)			**0.544**
No	16 (64)	18 (72)	
Yes	9 (36)	7 (28)	
Histopathology, n (%)			**>0.05**
Adenocarcinoma	16 (64)	14 (56)	
Squamous cell carcinoma	7 (28)	11 (44)	
Others	2 (8)	0	
Stage, n (%)			**0.648**
IIIA–IIIC	5 (20)	4 (16)	
IVA–IVB	20 (80)	21 (84)	
Pleural effusion, n (%)			**0.571**
No	12 (48)	14 (56)	
Yes	13 (52)	11 (44)	
Chemotherapy regimen, n (%)			**0.613**
Carboplatin + Paclitaxel	17 (68)	17 (68)	
Carboplatin + Pemetrexed	3 (12)	5 (20)	
Cisplatin + Pemetrexed	5 (20)	3 (12)	

No statistically significant differences were observed in demographic or clinical variables between groups, supporting comparability for outcome analysis.

Serum TGF-β Levels

Table 2: Serum TGF-β Levels Before and After Chemotherapy

Time Point	AHCC® (n=25) Median (Range), pg/mL	Control (n=25) Median (Range), pg/mL	p-value*
Baseline (Cycle 1)	146.4 (8.56–772.05)	67.34 (18.42–248.01)	0.961
Post-intervention (Cycle 4)	54.93 (21–303.43)	51.9 (16.45–423.28)	0.915

**Mann–Whitney test*

There was no statistically significant difference in TGF-β levels between groups at baseline or after intervention.

Within-Group Changes

Table 3: Within-Group Changes in TGF-β Levels

Group	Baseline Median (Range)	Post-intervention Median (Range)	p-value*
AHCC®	146.4 (8.56–772.05)	54.93 (21–303.43)	0.581
Control	67.34 (18.42–248.01)	51.9 (16.45–423.28)	0.882

**Wilcoxon signed-rank test*

Although numerical reductions were observed in both groups, these changes were not statistically significant.

Between-Group Comparison of ΔTGF-β

Table 4: Comparison of ΔTGF-β Between Groups

Parameter	AHCC® (n=25) Median (Range)	Control (n=25) Median (Range)	p-value*
ΔTGF-β (pg/mL)	1.98 (–248.02 to 685.56)	–10.01 (–269 to 213.67)	0.580

**Mann–Whitney test*

No statistically significant difference in ΔTGF-β was found between groups.

Effect Size and Clinical Interpretation

The non-significant p-values (>0.05) indicate a small effect size, suggesting minimal additional impact of AHCC® supplementation on circulating TGF-β levels beyond the effect of chemotherapy alone. The wide inter-individual variability and overlapping ranges between groups further support the absence of a clinically meaningful difference.

Although a substantial median reduction was observed in the AHCC® group (146.4 to 54.93 pg/mL), a similar decline was also seen in the control group, indicating that chemotherapy likely contributed to TGF-β modulation. Therefore, under the current

dosage (3 g/day) and duration (four cycles), AHCC® did not demonstrate a statistically or clinically significant immunomodulatory effect on TGF-β levels in advanced NSCLC patients.

Discussion

The findings of this study demonstrated that although a reduction in median TGF-β levels was observed in the AHCC® supplementation group, the difference was not statistically significant compared with the control group. From a biological perspective, TGF-β is recognized as a key regulator in lung cancer progression through its involvement in epithelial–mesenchymal transition (EMT), tumor invasion, metastasis, and resistance to therapy [5,13]. In advanced malignancies, the TGF-β pathway frequently shifts from a tumor-suppressive role to a tumor-promoting function by facilitating immune evasion and remodeling of the tumor microenvironment.

Elevated circulating levels of TGF-β have been reported in patients with NSCLC and have been associated with poor clinical outcomes [7]. Increased TGF-β activity contributes to the establishment of an immunosuppressive microenvironment through inhibition of cytotoxic T lymphocytes and natural killer cell activity, while simultaneously promoting regulatory T-cell differentiation and tumor-associated fibroblast activation [5,13]. Consequently, therapeutic strategies capable of modulating TGF-β signaling are considered potential targets for improving cancer immunotherapy outcomes.

In the present study, the observed reduction in median TGF-β levels in the AHCC® group may suggest a potential modulatory effect on immune signaling pathways. However, the magnitude of change was insufficient to reach statistical significance when compared with the control group. Several factors may explain this finding.

First, the majority of participants in this study were diagnosed with advanced-stage disease. In advanced NSCLC, the tumor microenvironment is characterized by complex interactions between tumor cells, stromal components, and immune cells, resulting in profound immunosuppression [5,13]. Under such conditions, systemic cytokine levels may be influenced by multiple overlapping biological pathways, making it difficult for short-term interventions to produce measurable changes in circulating biomarkers.

Second, substantial inter-individual variability in TGF-β levels was observed across both study groups. Such variability has been widely reported in cytokine-based biomarker studies and may be influenced by tumor burden, host immune status, and other biological factors [7,8]. This variability may reduce statistical power and obscure potential biological effects of immunomodulatory interventions.

Third, the duration of AHCC® supplementation in this study may have been insufficient to induce sustained immunological changes. Previous studies suggest that the immunomodulatory effects of mushroom-derived polysaccharides often require prolonged administration to produce measurable changes in immune parameters [10,11].

AHCC® is a standardized extract derived from the mycelia of Lentinula edodes and is known to contain biologically active α-glucans that can influence immune regulation. Experimental studies have shown that AHCC® can activate antigen-presenting cells, including dendritic cells and macrophages, thereby enhancing innate and adaptive immune responses [9]. In addition, fungal β-glucans have been widely reported to stimulate immune responses through pattern recognition receptors such as dectin-1 and toll-like receptors, leading to increased cytokine production and immune cell activation [10,11].

Clinical evidence from non-oncologic settings further supports the immunomodulatory properties of AHCC®. A randomized clinical study investigating AHCC® supplementation in individuals with persistent human papillomavirus infection demonstrated that long-term administration of AHCC® was associated with viral clearance in a significant proportion of participants [14]. Similarly, studies in healthy volunteers have shown that AHCC® supplementation may enhance immune competence by improving immune cell activity and cytokine responses [15].

Additional clinical evidence has also demonstrated beneficial immunological effects of AHCC® in patients with infectious diseases. For example, adjunctive AHCC® therapy in pulmonary tuberculosis patients has been associated with improvements in cellular immune responses, suggesting that the compound may influence T-cell–mediated immunity [16]. Preclinical studies have also reported that AHCC® may reduce tumor burden and improve survival in models of hematologic malignancy, supporting its potential anti-tumor properties [17].

Taken together, these findings suggest that AHCC® may modulate multiple immune pathways rather than a single cytokine mechanism. Bioactive polysaccharides in AHCC® can enhance both innate and adaptive immune responses and influence cytokines beyond TGF-β, supporting the notion that the lack of statistically significant TGF-β reduction does not rule out immunomodulatory effects [18].

Systemic cytokine measurements may not fully reflect the tumor microenvironment, where dynamic interactions among immune cells, stromal components, and soluble mediators regulate tumor progression and immune suppression [19,20]. TGF-β signaling is highly context-dependent, emphasizing the need for tissue-level analyses or broader cytokine panels to capture the full impact of AHCC®.

Limitations of this study include a relatively small sample size and supplementation duration restricted to chemotherapy cycles, which may have limited the detection of systemic immunological changes. Future studies should involve larger cohorts, extended AHCC® administration, and comprehensive immunological profiling including additional cytokines (IL-6, TNF-α) and functional immune assays to clarify the mechanisms and potential clinical benefits of AHCC® in NSCLC.

Conclusion

In patients with advanced non–small cell lung cancer receiving platinum-based chemotherapy, AHCC® supplementation was associated with a numerical reduction in median TGF-β levels, but the difference was not statistically significant. At the dosage and duration used, AHCC® did not produce a measurable effect on systemic TGF-β modulation. Although TGF-β plays a key role in tumor progression and immune regulation, the modest reduction observed was not clinically conclusive. Future studies with larger sample sizes, extended supplementation periods, and broader immune biomarker assessments are warranted to clarify the potential immunomodulatory role of AHCC® as an adjunct therapy in NSCLC.

Declarations

Ethics Approval

This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara/Adam Malik Hospital,

Medan (approval number: 345/KEPK/USU/2025) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

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Conflict of Interest

The authors declare no conflicts of interest.

Authors' Contributions

ZZ, NNS, and SPT conceived and designed the study. ZZ was primarily responsible for the literature review, patient recruitment, data collection, and statistical analysis. ES, IB, and DA contributed to critical appraisal of the study and provided substantial intellectual revisions to the manuscript. Drafting, editing, and finalization of the manuscript were undertaken collaboratively by ZZ, NNS, and SPT. All authors reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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