Original Article

# Effects of Active Hexose Correlated Compound (AHCC®) on Clinical and Laboratory Response of Pulmonary Tuberculosis Patients

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## Abstract

**Backgrounds:** Active Hexose Correlated Compound (AHCC), an α-glucan extracted from *Lentinula edodes*, is known for its immunomodulatory properties. It is suspected that the strong nutrients contained in AHCC are very safe and without side effects, including in tuberculosis patients. This study evaluated the effect of AHCC on clinical and hematologic responses in pulmonary tuberculosis (TB) patients

**Methods:** A double-blind randomized controlled trial was conducted involving 60 pulmonary TB patients receiving standard anti-TB therapy. Participants were randomly assigned to receive either AHCC (3 g/day) or a placebo for six months. Clinical and laboratory parameters were assessed before and after treatment.

**Results:** Patients in the AHCC group showed greater improvement in clinical symptoms (reduced cough, improved appetite, and weight gain) and significant enhancement of hematological and immunological markers compared with placebo ($P$<0.05). AHCC supplementation significantly increased $CD4^+$ and $CD8^+$ lymphocyte counts, suggesting improved immune recovery and modulation of host defense against *Mycobacterium tuberculosis* infection.

**Conclusion:** AHCC supplementation alongside standard anti-TB therapy improves clinical outcomes and immune responses in patients with pulmonary tuberculosis.

**Keywords:** AHCC, clinical symptoms, hematology, immunology, tuberculosis

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## INTRODUCTION

Tuberculosis (TB) remains a leading infectious cause of death worldwide. According to the WHO Global Tuberculosis Report 2023, an estimated 10.6 million people developed TB and 1.3 million died from the disease in 2022. Despite effective anti-tuberculosis therapy, TB remains a major global health problem, especially in countries with high rates of malnutrition, HIV co-infection, and socioeconomic inequality.[1,2]

The host immune response to *Mycobacterium tuberculosis (M. tuberculosis)* involves coordinated interactions between innate and adaptive immune mechanisms. Following infection, antigen-presenting cells such as macrophages and dendritic cells initiate the immune cascade by recognizing mycobacterial components and producing pro-inflammatory cytokines. $CD4^+$ T helper type 1 (Th1) lymphocytes are pivotal in orchestrating protective immunity through the secretion of interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α), which synergistically activate macrophages to eliminate intracellular bacilli. In parallel, $CD8^+$ cytotoxic T lymphocytes contribute to bacterial clearance by inducing apoptosis of infected host cells and releasing perforin- and granzyme-mediated cytotoxic molecules. Deficiencies in cell-mediated immunity—commonly observed in individuals with malnutrition, HIV co-infection, or advanced age substantially increase susceptibility to active tuberculosis due to impaired containment of *M. tuberculosis* within granulomatous lesions.[3]

It was reported that active hexose correlated compound (AHCC) can enhance the immune response of CD4+ and CD8+ T cells in healthy individuals by increasing the production of IFN-γ and TNF-α from T cells. AHCC can modulate Natural

Killer (NK) cells against infection or tumor cells. Additionally, AHCC modulates whole blood lymphocyte, polymorphonuclear, and monocyte cell counts. It is suspected that the strong nutrients contained in AHCC are very safe and without side effects.[4]

Active hexose correlated compound itself is a nutritional supplement produced from Shiitake mushroom micelles, which contain a mixture of polysaccharides, amino acids, and minerals.[5–7] The active ingredients of AHCC are -glucan, -glucan acetate, and -glucan of polysaccharides. Among the main components of AHCC, β-glucan acetate is known to have beneficial effects on the immune system. AHCC appears to trigger early immune activation, promoting faster bacterial clearance and recovery.[6–9]

Thus, the study aims to determine the effect of AHCC on clinical symptoms and laboratory responses (hematological/blood chemistry and immune status) in pulmonary TB patients. Investigators hope that the beneficial effects of AHCC as a supplement with strong nutrition will be quite helpful as an additional supplement in the future for all symptoms of pulmonary TB and side effects of its drugs.

## METHODS

This was a randomized, double-blind clinical trial in which AHCC and placebo supplementation were administered for 6 months. At the time of the study, investigators did not know which AHCC and placebo were (double-blind). This study was conducted at the Lung Polyclinic-DOTS RSUD Labuang Baji, Makassar. The study was conducted following the Indonesian Ministry of Health and all procedures involving humans were approved by the Ethics Committee of the Faculty of Medicine, Universitas Hasanuddin, Indonesia (270/UN4.6.4.5.31/PP36/2020).

The study included 60 newly diagnosed pulmonary TB patients treated at Labuang Baji Hospital, divided equally into AHCC (n=30) and placebo (n=30) groups. During the 6-month follow-up, participants were monitored monthly. Any withdrawals, adverse events, or loss to follow-up were recorded. Inclusion criteria were adults aged ≥18 years with newly diagnosed pulmonary TB who had not received prior anti-TB therapy and agreed to avoid pregnancy during the study. Exclusion criteria were pulmonary TB patients with impaired liver function before treatment, patients with ATT or TB-RO resistance, patients refusing to participate in the study, and severe malnutrition.

Subjects were divided into two groups: the AHCC group received standard anti-tuberculosis therapy (ATT) plus AHCC 3 g/day (500 mg per capsule, three capsules twice daily) for six months, and the placebo group received ATT plus matched placebo capsules containing dextrin and malt extract. Both patients and researchers were blinded to treatment allocation (coded as AHCC1 or AHCC2) until study completion. The AHCC used in this study was supplied by Amino Up Chemical Co., Ltd., Sapporo, Japan.

Baseline characteristics included sex, age, employment status, smoking history, and clinical symptoms before treatment. Patient visits to assess clinical symptoms were carried out 3 times by doing anamnesis before and after treatment (after the 3rd month and after the 6th month) and the patient could come at any time if there were side effects during supplementation. Blood sampling was carried out 3 times in the study, namely before treatment, after the 3rd month, and the end of the treatment or after the 6th month.

The levels of CD4+ and CD8+ T lymphocytes from peripheral blood were examined by the flow cytometry method. CD4+ and CD8+ were examined before treatment and after the 3rd month and after the 6th month. Hematology and blood chemistry examinations needed in the treatment of pulmonary TB patients were only performed 2 times before and after treatment. The examinations were RBC, HB, Ht, Plt, WBC, Albumin, SGOT/SGPT, Gamma GT, Alkaline Phosphate, and LDH. This blood test was carried out at the PRODIA Makassar laboratory.

Clinical symptoms were cough, coughing up blood, fever, shortness of breath, decreased

appetite, weight loss, nausea, and vomiting. The normal values used in the CD4+ and CD8+ tests were absolute CD4 (404–1,612 cells/µl), CD4% (33–58%), absolute CD8 (220–1,129 cells/µl), CD8% (13–39%) and CD4:CD8 ratio (0.69–2.83). Likewise, the normal values used for hematological and blood chemistry examinations are adjusted to the examination laboratory values. All assessments in this study of clinical symptoms, hematological, and immunological status (CD4+, CD8+) were compared between TB patients receiving AHCC and placebo.

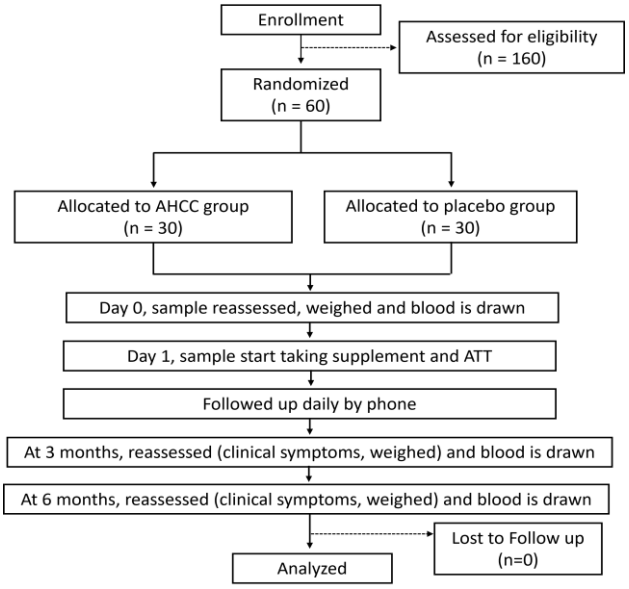


Figure 1. Study Flowchart

The total number of samples analyzed in this study was 30 AHCC groups and 30 placebo groups. From the beginning to the end of the study, no one was excluded. From the study, it was obtained a description of the demographic characteristics before treatment and a comparison of clinical symptoms of patients before and after treatment (after the 3rd month and after the 6th month) were obtained. To detect a significant difference between these two treatments with a power of 90% and a type I error of 5%, the calculated number of patients was 30 per group.

Data were analyzed using the statistical package SPSS Version 21. Normal data distribution was tested with the Kolmogorov-Smirnov test. Parametric descriptive data describes the mean±SE or percentage and comparison with the chi-square test or Fisher exact test or non-parametric data compared with the Mann-Whitney test. Wilcoxon's test was performed on hematological images. Statistical significance was considered if $P<0.05$.

## RESULTS

The study included 60 patients, divided equally into AHCC (n=30) and placebo (n=30) groups. The basic characteristics of the study included gender, age, employment status, smoking, and clinical symptoms of patients before treatment (Table 1).

Table 1. Patient's Baseline Characteristics (n=30)

| Variable | Placebo | AHCC | *P* |
|---|---|---|---|
| Sex | | | |
| Males | 15 (50.0%) | 20 (66.7%) | 0.295 |
| Females | 15 (50.0%) | 10 (33.3%) | |
| Age (years) | | | |
| Mean±SE | 43±2.74 | 39.4±2.37 | 0.119 |
| Range | 18–69 | 21–60 | |
| Median | 42.5 | 37.5 | |
| Job Status | | | |
| Work | 15 (50.0%) | 22 (73.3%) | 0.110 |
| No | 15 (50.0%) | 8 (26.7%) | |
| Smoking | | | |
| Yes | 16 (53.3%) | 17 (56.7%) | 0.795 |
| No | 14 (46.7%) | 13 (43.3%) | |
| Symptoms | | | |
| Cough | 27 (90.0%) | 25 (83.3%) | 0.448 |
| Hemoptysis | 9 (30.0%) | 4 (13.3%) | 0.105 |
| Fever | 19 (63.3%) | 22 (73.3%) | 0.404 |
| Dyspnoea | 21 (70%) | 12 (40.0%) | 0.201 |
| Decreased Appetite | 30 (100.0%) | 30 (100.0%) | N/A |
| Weight Loss | 30 (100.0%) | 0 (0.0%) | 0.001 |
| Nausea | 9 (30.0%) | 10 (33.3%) | 0.500 |
| Vomiting | 2 (6.7%) | 2 (6.7%) | 0.694 |

Note: SE=Standard Error

In the AHCC group, 66.7% were male, with a median age of 37.5 years (mean±SE = 39.4±2.37). The minimum age of patients in this group is 21 years, with a maximum age of 60 years. As many as 73.3% who workers and have a history of smoking 56.7%. The most frequent pre-treatment symptoms were decreased appetite (100%), cough (83.3%), and fever (73.3%). Meanwhile, the dominant clinical symptoms in the placebo group before treatment were a decrease in appetite, followed by weight loss of 100%, cough of 90%, and fever of 63.3%.

Clinical symptoms of pulmonary TB patients consist of cough, coughing up blood, fever, shortness of breath, decreased appetite, weight loss, nausea, and vomiting, as shown in Table 2.

Table 2. Clinical Symptoms of Pulmonary TB Patients Before and After Administration of AHCC compared to Placebo

| Symptoms of Pulmonary TB | Placebo | | | AHCC | | |
|---|---|---|---|---|---|---|
| | 0 month | 3 months | 6 months | 0 month | 3 months | 6 months |
| Cough | | | | | | |
| Persistent | 27 (90.0%) | 22 (73.3%) | 3 (10.0%) | 25 (83.3%) | 13 (43.3%) | 0 (0.0%) |
| Decrease | 3 (10.0%) | 8 (26.7%) | 27 (90.0%) | 5 (16.7%) | 17 (56.7%) | 30 (100.0%) |
| Hemoptysis | | | | | | |
| Persistent | 9 (30.0%) | 0 (0.0%) | 0 (0.0%) | 4 (13.3%) | 0 (0.0%) | 0 (0.0%) |
| Decrease | 21 (70.0%) | 30 (100.0%) | 30 (100.0%) | 26 (86.7%) | 30 (100.0%) | 30 (100.0%) |
| Fever | | | | | | |
| Persistent | 19 (63.3%) | 0 (0.0%) | 0 (0.0%) | 22 (73.3%) | 0 (0.0%) | 0 (0.0%) |
| Decrease | 11 (36.7%) | 30 (100.0%) | 30 (100.0%) | 8 (26.7%) | 30 (100.0%) | 30 (100.0%) |
| Dyspnea | | | | | | |
| Persistent | 21 (70.0%) | 1 (3.3%) | 0 (0.0%) | 12 (40.0%) | 2 (6.7%) | 0 (0.0%) |
| Decrease | 9 (30.0%) | 29 (96.7%) | 30 (100.0%) | 18 (60.0%) | 28 (93.3%) | 30 (100.0%) |
| Decreased Appetite | | | | | | |
| Persistent | 30 (100.0%) | 0 (0.0%) | 1 (3.3%) | 30 (100.0%) | 5 (16.7%) | 0 (0.0%) |
| Decrease | 0 (0.0%) | 30 (100.0%) | 29 (96.7%) | 0 (0.0%) | 25 (83.3%) | 30 (100.0%) |
| Weight Loss | | | | | | |
| Persistent | 0 (0.0%) | 3 (10.0%) | 5 (16.7%) | 7 (23.3%) | 5 (16.7%) | 0 (0.0%) |
| Decrease | 30 (100.0%) | 0 (0.0%) | 5 (16.7%) | 0 (0.0%) | 25 (83.3%) | 0 (0.0%) |
| Nausea | | | | | | |
| Persistent | 9 (30.0%) | 5 (16.7%) | 0 (0.0%) | 10 (33.3%) | 0 (0.0%) | 0 (0.0%) |
| Decrease | 21 (70.0%) | 25 (83.3%) | 30 (100.0%) | 20 (66.7%) | 30 (100.0%) | 30 (100.0%) |
| Vomiting | | | | | | |
| Persistent | 2 (6.7%) | 0 (0.0%) | 0 (0.0%) | 2 (6.7%) | 0 (0.0%) | 0 (0.0%) |
| Decrease | 28 (93.3%) | 30 (100.0%) | 30 (100.0%) | 28 (93.3%) | 30 (100.0%) | 30 (100.0%) |

Note: Persistent=symptom unchanged from baseline; Decreased=partial improvement; TB=tuberculosis; AHCC=active hexose correlated compound

Table 3. Immunological Parameters of Pulmonary TB Patients

| Variabel | Baseline | | *P* | After 3 months | | *P* | After 6 months | | *P* |
|---|---|---|---|---|---|---|---|---|---|
| | AHCC | Placebo | | AHCC | Placebo | | AHCC | Placebo | |
| CD4 absolute | 519.3±39.4 | 473.7±47.5 | 0.506 | 695±52.1 | 637.5±50.4 | 0.574 | 728.6±60.5 | 653.5±52.5 | 0.344 |
| CD8 absolute | 488.8±46.9 | 367.5±39.8 | 0.071 | 628.7±101.9 | 480.2±42.2 | 0.501 | 531.8±41.1 | 482.9±54.3 | 0.375 |
| CD4% | 35±1.8 | 32.5±1.6 | 0.391 | 36.1±1.8 | 34.7±1.8 | 0.701 | 36.4±1.9 | 37.2±1.8 | 0.929 |
| CD8% | 30.3±1.7 | 25.2±1.4 | 0.044* | 28.8±1.8 | 25.3±1.3 | 0.114 | 27.7±1.4 | 24.4±1.3 | 0.107 |
| CD4:CD8 | 1.3±0.11 | 1.4±0.10 | 0.367 | 1.4±0.14 | 1.4±0.1 | 0.594 | 1.4±0.1 | 1.7±0.1 | 0.274 |

Note: *statically significant if P<0.05; Anlysis used Mann-Whitney test; SE=standar error; AHCC=active hexose correlated compound

Following AHCC supplementation, progressive clinical improvement was observed in both the AHCC and placebo groups. However, patients receiving AHCC demonstrated a faster and more complete resolution of key systemic symptoms. After three months, improvement in cough and weight loss was observed in 43.3% and 83.3% of AHCC patients, compared with 26.7% and none in the placebo group, respectively. By six months, all patients in the AHCC group achieved complete resolution of cough, appetite loss, and weight loss, whereas recovery was incomplete in the placebo group.

The immunological parameters assessed in this study were CD4+, CD8+, CD4 and CD8 percentages, and CD4:CD8 ratio (Table 3). Comparison of immune status before treatment between the AHCC vs placebo group (mean±SE) was absolute CD4+ (519.3±39.4 cells/µl vs 473.7±47.5), absolute CD8 (488.8±46.9 vs 367.5±39.8 cells/µl), CD4% (35±1.8 vs 32.5±1.6), CD8% (30.3±1.7 vs 25.2±1.4), and CD4:CD8 ratio (1.3±0.11 vs 1.4±0.10). There was a significant difference in CD8% levels before administration of AHCC and placebo (*P*=0.044).

After 6 months, the immune status of the AHCC group was superior to that placebo, namely absolute CD4 (728.6±60.5 vs 653.5±52.2 cells/µl), absolute CD8 (531.8±41.1 vs 482.9±54.3 cells/µl), CD4% (36.4±1.9 vs 37.2±1.8), CD8% (27.7±1.4 vs 24.4±1.3), and CD4:CD8 ratio (1.4±0.1 vs 1.7±0.1).

Table 4. Comparison of hematology features (before and after-treatment) between AHCC and placebo in pulmonary TB patients

| Variables | Placebo | | *P* | AHCC | | *P* |
|---|---|---|---|---|---|---|
| | Before | After | | Before | After | |
| Red blood cell ($10^6$/µL) | 4.0±0.2 | 3.7±0.1 | 0.005* | 4.5±0.09 | 4.7±0.05 | 0.002* |
| Hemoglobin (g/dl) | 12.3±0.3 | 12.5±0.2 | 0.027* | 11.3±0.1 | 12.4±0.1 | 0.0001* |
| Haematocrit (%) | 35.3±0.5 | 36.8±0.2 | 0.205 | 37.0±0.8 | 41.9±0.6 | 0.0001* |
| Platelet ($10^3$/µL) | 292±22 | 243.5±12.5 | 0.093 | 266.1±20.0 | 325.3±16 | 0.0001* |
| White blood cell ($10^3$/µL) | 6.3±0.3 | 6.2±0.3 | 0.367 | 8.5±0.4 | 6.9±0.2 | 0.001* |
| Neutrophil (%) | 47.9±3.0 | 53.2±2.6 | 0.005 | 53.2±2.1 | 57±1.5 | 0.002* |
| Lymphocyte (%) | 16.7±1.2 | 22.2±1.3 | 0.0001* | 25.2±0.7 | 29.6±0.8 | 0.0001* |
| Monocyte (%) | 2.6±0.3 | 2.1±0.06 | 0.142 | 2.9±0.2 | 3.2±0.07 | 0.0001* |
| Eosinophil (%) | 1.4±0.1 | 1.9±0.1 | 0.0001* | 2.3±0.08 | 3.2±0.09 | 0.0001* |
| Basophil (%) | 0.07±0.03 | 0.1±0.03 | 0.001* | 0.2±0.06 | 0.04±0.01 | 0.008* |

Note: *statically significant if P<0.05; Before=baseline; After=6th month; SE=standard error; AHCC=active hexose correlated compound

A comparison of hematology, including blood chemistry before and after administration of AHCC and placebo in pulmonary TB patients, is shown in Table 4. Basically, there is not much difference between the mean hematological features of patients who received a placebo before and after compared to patients who received before and after treatment AHCC. Red blood cell (RBC) levels (4.0-5.106/µl) in pulmonary TB patients who received AHCC were better (normal). Patients who received a placebo tended to decrease or below normal (RBC 4.0±0.2 vs 3.7±0.1), compared to patients who received AHCC (RBC 4.5±0.09 vs 4.7±0.05).

Based on the Wilcoxon test, there were significant differences that were only found in the placebo group before and after treatment, while the placebo group had no significant differences in haematocrit (*P*=0.0001), Platelet (*P*=0.0001) and WBC (*P*=0.001) levels. Other hematological parameters showed significant within-group changes in both the AHCC and placebo groups (*P*<0.05).

## DISCUSSION

Active hexose correlated compound is an extract derived from the shiitake mushroom (*Lentinula edodes*) containing polysaccharides, amino acids, and minerals.[7] Approximately 74% of AHCC consists of oligosaccharides and 20% of them contain α-1,4-glucan, which can increase the biological activity of AHCC.[8] Alpha-glucan can stimulate the phagocytic system, increase the defense mechanism of the immune system in general and stimulate defense reactions against infections, including possibly pulmonary TB infection.[10,11] In several studies on chemotherapy patients, AHCC can improve side effects or reduce patient symptoms and is even safe for consumption.

Active hexose correlated compound supplementation demonstrated a positive trend in clinical and immunological outcomes, though differences did not reach statistical significance. Previous studies, such as Kulkarni et al, reported that AHCC reduced symptom severity and improved survival in animal models of viral, bacterial, and fungal infections.[12] In addition, numerous studies have demonstrated a common mechanism by which AHCC® maintains immune homeostasis in the body. Symptoms of nausea also disappeared after the 3rd month of AHCC, while the placebo was still 16.7%.[7]

These results are partly consistent with Suknikhom et al, who reported significant elevation of $CD8^+$ and $CD4^+$ T-cell counts after AHCC administration in animal models, implying that AHCC may stimulate early immune activation and accelerate microbial clearance. However, unlike Suknikhom's preclinical study, the present clinical trial did not demonstrate statistical significance, likely due to differences in sample size, duration of supplementation, and host immune status in active tuberculosis patients.[7] This finding suggests a possible immunomodulatory effect rather than a definitive enhancement of adaptive immunity.[13–15]

Several other studies have also described AHCC's immunostimulatory activity through cytokine-mediated pathways. For instance, supplementation has been shown to enhance IL-12, IL-6, and interferon-γ secretion, promoting Th1 polarization

and NK-cell activation in both healthy and immunocompromised populations. These cytokines play a key role in controlling intracellular pathogens such as *Mycobacterium tuberculosis*, yet the absence of cytokine measurement in our study limits the mechanistic interpretation of the observed immune trends.[16–18]

In contrast, clinical trials in oncology and geriatric populations have reported more pronounced $CD4^+$ and $CD8^+$ elevation following 30 days of AHCC intake. Such discrepancies may be explained by disease-specific immune suppression, drug interactions from anti-TB therapy, or nutritional differences that influence immune recovery. These variations highlight that AHCC's immune effects are context-dependent and may require longer exposure or higher doses to achieve measurable outcomes in tuberculosis patients.[16,18]

Hematologic features after AHCC administration were better than placebo. Hematocrit, platelets, and WBC were found to be significantly improved after AHCC administration ($P$=0.0001, $P$=0.0001, and $P$=0.001). Similar to the research by Yanagimoto et al, cancer patients receiving chemotherapy and the AHCC group ingested 6 g of AHCC for 2 months had a better hematological effect than the control group.[19]

The literature also mentions that AHCC has a molecular weight of only 5000 daltons, which is partly mushroom extract. The reduction in molecular weight increases the effectiveness of nutrients being absorbed and used without elimination. All this ensures that the powerful nutrients contained in AHCC are rapidly assimilated by white blood cells to strengthen the immune system.[20]

Sun et al in their study showed that mice induced by 6-mercaptopurine (6-MP) and Methotrexate (MTX) and treated with AHCC significantly increased body weight, erythrocytes, leukocytes, and serum albumin, improved liver hypertrophy and degeneration, normalized the activity of serum glutamate oxaloacetate transaminase (SGOT) and serum glutamate pyruvate transaminase (SGPT), and increased hepatic metabolic enzymes.[8]

## LIMITATION

This study has several important limitations that should be acknowledged. The sample size was small and drawn from a single center, which may limit the generalizability of the findings to broader tuberculosis populations. Moreover, the six-month follow-up period may have been insufficient to fully assess the long-term clinical and immunological effects of AHCC supplementation.

Another limitation lies in the concurrent administration of standard anti-tuberculosis therapy to all participants, making it difficult to clearly distinguish the independent effects of AHCC from those of conventional treatment or their possible synergistic interaction. Additionally, the absence of cytokine profiling and other mechanistic biomarker assessments restricts a more detailed understanding of the immunomodulatory pathways involved.

Future research with larger, multicenter cohorts, longer follow-up durations, and integrated cytokine and molecular analyses is warranted to clarify the independent and combined roles of AHCC as a potential host-directed adjunct in pulmonary tuberculosis management.

## CONCLUSION

This clinical study indicates that AHCC supplementation alongside standard anti-tuberculosis therapy is safe and well-tolerated. AHCC use was associated with clinical improvements such as appetite recovery and weight gain, along with modest increases in $CD4^+$ and $CD8^+$ T-cell counts after six months. Although these immunological changes were not statistically significant, they suggest early immune recovery and improved host responsiveness during treatment.

Future research with larger, multicenter cohorts, longer follow-up durations, and integrated cytokine and molecular analyses is warranted to clarify the independent and combined roles of AHCC as a potential host-directed adjunct in pulmonary tuberculosis management.

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## CONFLICT OF INTEREST

There are no conflicts of interest.

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