ORIGINAL ARTICLE

# Vitamin C Intake and Anti-Tuberculosis Drugs-Induced Hepatitis in Pulmonary Tuberculosis Patients

**Hadiati Rabbani[1*], Fariz Nurwidya[2], Diyah Eka Andayani[1], Heidy Agustin[2], Shaogi Syam[3]**
[1]Department of Nutrition, Faculty of Medicine, Universitas Indonesia/Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia.
[2]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Indonesia/Persahabatan National Respiratory Referral Hospital, Jakarta, Indonesia.
[3]Respiratory Medicine, Division of Medicine, University College London, London, United Kingdom.

**ARTICLE INFO**

*Article history:*
Received 10 June 2024
Received in revised form
22 August 2024
Accepted 9 September 2024
Available online 30 September 2024

*Keywords:*
Drug-induced hepatitis,
Pulmonary tuberculosis,
Tuberculosis,
Vitamin C intake.

*Cite this as:*
Rabbani H, Nurwidya F, Andayani DE, *et al*. Vitamin C Intake and Anti-Tuberculosis Drugs-Induced Hepatitis in Pulmonary Tuberculosis Patients. *J Respi* 2024; 10: 214-221.

**ABSTRACT**

**Introduction:** Drug-induced hepatitis (DIH) is one of the serious side effects of anti-tuberculosis drugs (ATD) that can reduce patient compliance with tuberculosis (TB) treatment, increase the risk of treatment failure, or develop drug resistance. Vitamin C is a potential antioxidant known to have a protective effect against DIH. This study examined the relationship between vitamin C intake and the incidence of ATD-induced hepatitis (ATDIH) in pulmonary TB patients at Persahabatan National Respiratory Referral Hospital, Jakarta.

**Methods:** This was a cross-sectional study of 108 patients with drug-sensitive pulmonary TB. Data was collected using a sociodemographic questionnaire, anthropometric measurements, semi-quantitative food frequency questionnaire (SQ FFQ), and data on the subject's liver function laboratory results in the last 1 month. Fisher exact test was utilized to analyze the association between adequacy of vitamin C intake and DIH.

**Results:** The proportion of DIH in pulmonary TB patients in this study was 6.5%. Most subjects were males (54.6%) with a median age of 41. The median vitamin C intake was 66.65 mg/day, with 63.0% of patients having an intake below the recommendation. Fisher's exact test showed that vitamin C intake was not statistically significantly associated with the incidence of ATDIH (OR 3.77 95% CI 0.44-32.55, p-value 0.256). No factors also influenced the incidence of ATDIH in this study.

**Conclusion:** No association was found between vitamin C intake and other factors related to the incidence of ATDIH. This is the first study in Indonesia to link vitamin C and E intake with the incidence of DIH in drug-sensitive pulmonary TB patients, providing information for future studies.

## INTRODUCTION

Tuberculosis (TB) is an infectious disease that is still a major problem in Indonesia. According to data from the Global Tuberculosis Report 2023, Indonesia is the second-highest country in terms of the burden of TB cases in the world after India, with a total of 1,060,000 incidents, an increase from the previous year.[1] The first-line treatment regimen for pulmonary TB in Indonesia is isoniazid, rifampicin, pyrazinamide, and ethambutol for 6 months.[2] These four antibiotics have proven effective for TB treatment, but they have various side effects.[2–4] The most common major adverse effect is drug-induced hepatitis (DIH) associated with the three first-line anti-TB drugs (ATD), rifampicin, isoniazid, and pyrazinamide.[2,5] ATD-induced hepatitis (ATDIH) is a concern in TB treatment because it requires the discontinuation of ATD and can cause morbidity and mortality if not detected early.[4,6] The prevalence of DIH in several studies conducted worldwide varies and ranges from 2-39%, with a higher incidence in developing countries.[7]

In patients with pulmonary TB and those with DIH, oxidative stress is observed due to an imbalance

*Corresponding author: hadiati.rabbani@ui.ac.id

Jurnal Respirasi (Journal of Respirology), p-ISSN: 2407-0831; e-ISSN: 2621-8372.
Accredited No. 79/E/KPT/2023; Available at https://e-journal.unair.ac.id/JR. DOI: 10.20473/jr.v10-I.3.2024.214-221

between free radicals and antioxidant levels.[8] Consumption of ATD can induce oxidative stress by forming reactive metabolites, disrupting the mitochondrial respiration chain, reducing antioxidant enzyme pools, and causing a redox cycle.[5] TB patients also experience decreased antioxidant status due to increased free radicals produced in response to TB infection and low vitamin intake.[9] A previous study reported that vitamin C intake in patients with pulmonary TB was less than the recommended dietary adequacy due to the patients' low economic status and decreased appetite due to ATD.[10]

Vitamins C and E are exogenous antioxidants with anti-inflammatory and antiapoptotic effects that may protect against oxidative stress and liver damage.[11,12] It is also known that vitamin C has a protective effect against liver damage in both animals and humans,[13] but it is still inconclusive in humans for vitamin E.[14] Animal studies have shown that vitamin C and omega 3 can be hepatoprotectors in rats with methotrexate-induced hepatitis and can normalize aminotransferase, gamma glutamine, alkaline phosphatase, lactate dehydrogenase, malondialdehyde, and serum albumin levels in intoxicated animals.[12] Vitamin C can also strengthen the activity of enzymatic antioxidants in the body, and its protective effect is beneficial in patients with nonalcoholic steatohepatitis and fatty liver.[13] In addition, in vitro studies have shown that vitamin C has a protective effect on liver damage due to isoniazid[15] and rifampicin toxicity without affecting its bactericidal activity.[11]

Some clinical trials related to the protective effect of antioxidants against drug-induced liver damage are still inconclusive, limited to animal experimental studies, and are otherwise difficult to conduct.[16] There is still a lack of data regarding the intake of antioxidants, substances that can scavenge reactive species, and the incidence of ATDIH, which is limited to animal experiments and in vitro studies. Therefore, this study aimed to observe the relationship between vitamin C intake, one of the antioxidants with potential hepatoprotective effects, and the incidence of ATDIH in pulmonary TB patients.

## METHODS

### Study Design and Participants

This cross-sectional study using a consecutive sampling method was conducted from February to March 2024 at Persahabatan National Respiratory Referral Hospital, Jakarta. The Ethics Committee of Health Research Persahabatan National Respiratory Referral Hospital approved the study procedure (No 168/KEPK-RSUPP/12/2023). The study participants were TB patients undergoing first-line ATD treatment, aged ≥ 18 years old, and agreed to participate by signing the written consent form. Subjects with a history of chronic liver disease (hepatitis B, hepatitis C, cirrhosis), who had been taking herbal supplements over the past 3 months, who were pregnant or breastfeeding, or who had incomplete laboratory medical results were excluded.

### Data Collection

Data on the patient's socio-demographic details and medical history was collected through a questionnaire. Bacteriological status and liver function test results within 1 month were obtained from the subject's medical record. The criteria for ATDIH used were based on the Medical Services for TB Management National Guidelines and Indonesian Society of Respirology (ISR) as follows: an elevated level of serum glutamic oxaloacetic transaminase (SGOT) or serum glutamic pyruvic transaminase (SGPT) to 3x the upper limit of normal (ULN) in symptomatic patients, or up to 5x ULN without the presence of symptoms, or their bilirubin level reaching 2x ULN in the absence of symptoms.[2] The referred symptoms were jaundice, anorexia, abdominal pain, nausea, and vomiting in the ATD treatment obtained from anamnesis.

### Dietary Intake

Vitamin C intake from food sources and supplementation was collected using a semi-quantitative food frequency questionnaire (SQ FFQ) for the past month. Vitamin intake was calculated based on data on local and Asian countries' food composition. The adequacy of vitamin intake categorized as sufficient or insufficient was based on 2019 Indonesia's Recommended Dietary Allowance (RDA), which is 90 mg/day for men and 75 mg/day for women.[17]

### Anthropometric Measurements

The height and weight measurements were performed twice using ShorrBoard, with an accuracy of 0.1 cm for height and SECA 876 with a precision of 0.1 kg for weight. The average value used to calculate body mass index (BMI) was calculated by dividing body weight (kg) by the square of height (m). The results were categorized based on the World Health Organization (WHO) Asia Pacific classification as underweight (<18.5 kg/m$^2$), normal (18.5-22.9 kg/m$^2$), overweight (23.0-24.9 kg/m$^2$), and obese (≥25 kg/m$^2$).

### Data Analysis

The International Business Machines Corporation (IBM) Statistical Package for the Social Sciences (SPSS) version 25 was used for data analysis, and NutriSurvey 2007 (Germany) was used for the dietary

intake analysis. Categorical data was presented as frequency and percentage. Meanwhile, continuous data was presented as mean and standard deviation (SD) or median and interquartile range (IQR) depending on the distribution based on the Kolmogorov-Smirnov test result. The Chi-square test or Fisher exact test was utilized to analyze the association between the adequacy of vitamin C intake and other categorical variables with the incidence of DIH. All variables with a p-value ≤ 0.25 in the bivariate analysis were entered into the multivariable logistic regression analysis. An odds ratio (OR) with a 95% confidence interval (CI) was used to determine the strength of association, and p-values of less than 0.05 were considered statistically significant.

## RESULTS

### Participant Characteristics

A total of 108 patients met the inclusion criteria. The proportion of DIH in pulmonary TB patients in this study was 6.5%. Most subjects were males (54.6%), with a median age of 41 years old. The subjects were predominantly underweight (40.7%) based on the WHO-Asia Pacific classification, had completed secondary school education (73.1%), and had a low income (72.2%). A total of 40.7% had comorbidities, 4.6% were human immunodeficiency virus (HIV) positive, 43.5% took other drugs along with ATD, 52.8% did not smoke, and 7.4% of subjects consumed alcohol. More than half of the subjects were in the intensive phase (56.5%) and had positive bacteriological status (50.9%). Many subjects did not take vitamin C supplements (85.2%) (Table 1).

### Characteristics of the Participants based on Patient Vitamin Intake

The study subjects' median vitamin E intake was 1.20 mg/day, with the majority (97.2%) having an insufficient intake. The median vitamin C intake was 66.65 mg/day, with 68 subjects (63.0%) having an intake that was less than the requirements based on the 2019 RDA (Table 2).

### Association between Vitamin C Intake and ATDIH

The relationship between vitamin C intake and ATDIH was assessed using the Fisher exact test. There was no significant relationship between vitamin C adequacy and the incidence of ATDIH in pulmonary TB patients (OR 3.77 95% CI 0.44-32.55, p-value 0.256) (Table 3). Additionally, no other factors (patient characteristics) related to ATDIH were found in this study. Multivariate analysis was not performed because only a single variable had a p-value <0.25 (Table 1).

**Table 1.** Subject characteristics and the association between variables with anti-tuberculosis drugs-induced hepatitis

| Characteristic | ATDIH | | Total (N = 108) | p-value | OR (CI 95%) |
|---|---|---|---|---|---|
| | Yes (n = 7) | No (n = 101) | | | |
| Age (years old) | 23 (39) | 42 (32) | 41 (32) | 0.253[mw] | |
| Gender, n(%) | | | | 1.00[f] | 1.12 (0.24-5.24) |
| Male | 4 (6.8) | 55 (93.2) | 59 (54.6) | | |
| Female | 3 (6.1) | 46 (93.9) | 49 (45.4) | | |
| Body Mass Index, n (%) | | | | 0.427[f#] | 2.21 (0.47-10.42) |
| Underweight | 3 (6.8) | 41 (93.2) | 44 (40.7) | | |
| Normal | 4 (9.5) | 38 (90.5) | 42 (38.9) | | |
| Overweight | 0 (0) | 8 (100) | 8 (7.4) | | |
| Obese | 0 (0) | 14 (100) | 14 (13.0) | | |
| Education Level, n (%) | | | | 1.00[f#] | 0.97 (0.11-8.64) |
| No education | 0 (0) | 3 (100) | 3 (2.8) | | |
| Elementary school | 0 (0) | 11 (100) | 11 (10.2) | | |
| Junior/senior high school | 6 (7.6) | 73 (92.4) | 79 (73.1) | | |
| University | 1 (6.7) | 14 (93.3) | 15 (13.9) | | |
| Income Level, n (%) | | | | 0.671[f] | 2.42 (0.28-20.97) |
| Low | 6 (7.7) | 72 (92.3) | 78 (72.2) | | |
| Enough | 1 (3.3) | 29 (96.7) | 30 (27.8) | | |
| Comorbidities | | | | 1.00[f] | 1.1 (0.23-5.17) |
| Yes | 3 (6.8) | 41 (93.2) | 44 (40.7) | | |
| No | 4 (6.3) | 60 (93.8) | 64 (59.3) | | |
| HIV Status, n (%) | | | | 0.289[f#] | 4.04(0.39-42.01) |
| Positive | 1 (20.0) | 4 (80.0) | 5 (4.6) | | |
| Negative | 4 (5.1) | 75 (94.9) | 79 (73.1) | | |
| Unknown | 2 (8.3) | 22 (91.7) | 24 (22.2) | | |
| Co-Medication, n (%) | | | | 1.00[f] | 0.97 (0.21-4.57) |
| Yes | 3 (6.4) | 44 (93.6) | 47 (43.5) | | |
| No | 4 (6.6) | 57 (93.4) | 61 (56.5) | | |
| Smoking History, n (%) | | | | 0.429[f#] | 0.34(0.04-2.97) |
| Smoker | 1 (2.9) | 33 (97.1) | 34 (31.5) | | |
| Former smoker | 2 (11.8) | 15 (88.2) | 17 (15.7) | | |
| Not smoker | 4 (7.0) | 53 (93.0) | 57 (52.8) | | |

| | | | | | |
|---|---|---|---|---|---|
| Alcohol Consumption, n (%) | | | | 1.00[f] | n/a |
| Yes | 0 (0) | 8 (100) | 8 (7.4) | | |
| No | 7 (7) | 93 (93) | 100 (92.6) | | |
| Treatment Phase, n (%) | | | | 0.135[f*] | 5.02 (0.58-43.21) |
| Intensive phase | 6 (9.8) | 55 (90.2) | 61 (56.5) | | |
| Continuation phase | 1 (2.1) | 46 (97.9) | 47 (43.5) | | |
| Bacteriological Status, n (%) | | | | 1.00[f] | 1.31 (0.28-6.14) |
| Positive | 4 (7.3) | 51 (92.7) | 55 (50.9) | | |
| Negative | 3 (5.7) | 50 (94.3) | 53 (49.1) | | |
| Vitamin C Supplementation, n (%) | | | | 1.00[f] | 0.96 (0.11-8.51) |
| Yes | 1 (6.3) | 15 (93.8) | 16 (14.8) | | |
| No | 6 (6.5) | 86 (93.5) | 92 (85.2) | | |
| Vitamin E Intake, n (%) | | | | 1.00[f] | n/a |
| Insufficient | 7 (6.8) | 98 (93.3) | 105 (97.2) | | |
| Sufficient | 0 (0) | 3 (100.0) | 3 (2.8) | | |

f: Fisher exact test, mw: Mann Whitney test, ATDIH: anti-tuberculosis drugs-induced hepatitis, OR: odds ratio, CI: confidence interval, HIV: human immunodeficiency virus
[#] p value obtained after recategorization
[*] p value <0.25

**Table 2.** Subject characteristics based on vitamin intake

| Variable | Results (N = 108) |
|---|---|
| Vitamin E intake | 1.20 (2.25) (mg/day) |
| Insufficient | 105 (97.2) |
| Sufficient | 3 (2.8) |
| Vitamin C intake | 66.65 (101.05) (mg/day) |
| Insufficient | 68 (63.0) |
| Sufficient | 40 (37.0) |

**Table 3.** Association between vitamin C intake and anti-tuberculosis drugs-induced hepatitis

| Vitamin C Intake | ATDIH | | Total, n (%) | p-value | OR (CI 95%) |
|---|---|---|---|---|---|
| | Yes, n (%) | No, n (%) | | | |
| Insufficient | 6 (8.8) | 62 (91.2) | 68 (63.0) | 0.256[f] | 3.77(0.44-32.55) |
| Sufficient | 1 (2.5) | 39 (97.5) | 40 (37.0) | | |
| Total, n (%) | 7 (6.5) | 101 (93.5) | 108 (100) | | |

f = Fisher exact test

## DISCUSSION

In this study, the median intake of vitamin C and E was found to be low, with most subjects in the insufficient category. Previous studies obtained similar results, indicating that most pulmonary TB patients had low vitamin E and C intake.[3,10,18–20] The low vitamin E intake was due to the main food source of sunflower seeds, sunflower seed oil, safflower oil, and wheat oil, not being commonly consumed among the study subjects. The low vitamin C intake in pulmonary TB patients was due to their low purchasing power, where most subjects had less income and a decreased appetite, either due to the disease or ATD side effects.[10] Unbalanced eating habits can prevent people with high economic status from fulfilling their vitamin C needs.[21] Lower middle-income countries that consume rice as their staple food tend to have lower vitamin C intake.[22] It has been proven by the Indonesia Health Survey 2023 that the proportion of eating less fruit and vegetables (<5 servings per day in a week) as a source of vitamin C in Indonesia reached 96.7%.[23] Adequate intake of vitamin C and E is necessary in patients with TB, which can be met from food sources by eating a varied diet in sufficient quantities. Supplementation may be needed to maintain optimal vitamin levels in those deficient and have suboptimal intake, such as pulmonary TB patients, due to low appetite.[22]

This study found that 7 subjects (6.5%) had hepatitis due to ATD. Previous hospital-based studies in Indonesia reported various prevalences ranging from 5.4% to 23.75%.[24–27] In other countries, it varies from 3.8% to 10%.[28–31] This variation in proportion is because of differences in the study population, subject criteria, patient characteristics, case criteria, and drug regimens administered.

In this study, 6 out of 7 subjects who experienced DIH had insufficient vitamin C intake, which was not statistically significant. Furthermore, there was no association between vitamin C supplementation and hepatotoxic events due to ATD. Vitamin C is reported to have hepatoprotective effects,[13] but animal studies have shown that high doses of vitamin C do not have a more potent antioxidant effect than low doses,[15] and that vitamin C supplementation is generally given in high doses that exceed the RDA. Excess vitamin C in the body will be excreted because vitamin C is not widely stored.[32] Several things could confound this relationship

because of vitamin C's work as an antioxidant, which is the main core of its role as a hepatoprotector. It is also influenced by other antioxidants such as vitamin E, omega 3, beta carotene, and endogenous antioxidants. Vitamin C intake cannot describe the total antioxidant levels. Vitamin C levels are also influenced by other factors such as age, gender, smoking status, socioeconomic status, BMI, physical activity, and disease status. Infectious diseases such as TB can reduce vitamin C levels, meaning there must be more intake than healthy patients.[22] As there is no vitamin C recommendation intake for TB patients, this study used RDA as a criterion for adequacy, which may require greater adequacy in TB patients.

Wang, *et al*. (2021) obtained similar results in that vitamin C intake had no significant association with the risk of liver dysfunction or damage during ATD treatment.[3] However, the study showed that a low intake of vegetables was associated with an increased risk of liver damage and that a low intake of cooking oil reduced the risk of liver damage and liver dysfunction in patients undergoing TB treatment.[3] In addition to their high vitamin and mineral content, vegetables are rich in phytochemicals such as phenols, flavonoids, and carotenoids that help reduce drug-induced liver damage.[3] Animal studies have reported the protective effects of these substances on the liver by increasing glutathione (GSH) levels, counteracting free radicals, modulating the phase II hepatic metabolism, inhibiting NF-κB transcription and translocation, and decreasing pro-inflammatory cytokines.[33–35]

Clinicians in Indonesia often use curcumin for patients with hepatotoxicity. Several case reports have shown significant reductions in SGOT and SGPT values from curcumin administration and ATD discontinuation in TB patients with ATDIH.[36] Curcumin is known to counteract reactive oxygen/nitrogen species. It has antioxidant effects by inhibiting the initiation of styrene oxidation and controlling deoxyribonucleic acid (DNA) damage and lipid peroxidation caused by free radicals.[37] Some cellular mechanisms of curcumin as a hepatoprotector include inducing GSH synthesis by increasing the gene expression of the enzyme and glutamate cysteine ligase, reducing the number of lipid peroxidation products such as lipid hydroperoxides and malondialdehyde. In addition, curcumin increases the expression of SIRT3, which can reduce reactive oxygen species (ROS) levels by increasing the expression of manganese superoxide dismutase (MnSOD) and mitochondrial IDH2.[38] In this study, subjects who consumed curcumin were excluded.

Other mechanisms of ATDIH aside from oxidative stress are dose-dependent and immune-mediated mechanisms.[4] These mechanisms may explain the absence of an association between vitamin C and DIH. This needs to be proven by assessing whether oxidative stress mediates the occurrence of ATDIH in humans, which was not performed in this study. In addition, other stronger DIH risk factors, such as genetic polymorphisms, may confound the association.

This study found no variables that might be statistically significant confounders with the incidence of DIH in pulmonary TB patients. Based on previous studies, the role of the variables studied regarding the incidence of ATDIH still has different results. Nutritional status assessed by BMI in this study was not found to be associated with the incidence of ATDIH. Several previous studies have reported similar results.[3,28,39] Other studies have shown the contrary that low nutritional status and BMI in TB increase the risk of ATD-induced hepatotoxicity.[27,31,40] Malnutrition is associated with decreased GSH reserves, which makes people with malnutrition susceptible to oxidative damage.[39] In addition, nutritional status affects metabolic integrity in the liver and cytochrome P450 enzymes that play a role in detoxifying TB drugs.[6] Assessment of nutritional status based on BMI is not a sufficient predictor for ATDIH. Albumin levels and weight loss may be necessary to assess a subject's nutritional status as a risk factor for ATDIH.[6,41]

HIV infection is known to increase the risk of ATD hepatoxicity by 4 times.[6] In this study, 1 in 5 HIV-positive subjects experienced ATDIH, and the same OR value was obtained. Even so, no significant association was found, similar to a study in India.[31] HIV patients with acute disease experience changes in oxidative pathway activity that increase the risk of ATDIH. However, why TB-HIV patients have such a high risk of developing DIH remains contradictory. Although hepatic damage from rifampicin and pyrazinamide may be immunologically mediated, and there is reduced immune function in people with HIV, there is no evidence to support this hypothesis.[41] In addition, the subjects in this study were not severely immunocompromised.

N-acetylcysteine (NAC), one of the most prescribed cough medicines in pulmonary TB patients, is known to have hepatoprotective effects against rifampin and isoniazid. Experimental studies in rats showed that NAC at 0.2 mg/dL effectively protected HepG2 cells against rifampin toxicity ($p < 0.01$).[11] A clinical trial reported improved liver function, decreased malondialdehyde, and increased GSH in pulmonary TB patients in relation to first-line ATD who took NAC for 4 weeks.[42] These effects persisted until week 8.[42] The hepatoprotective effect of NAC is known to be due to its activity as a substrate of GSH synthesis, able to inhibit lipid peroxidation and reduce superoxide dismutase

levels.[43] In this study, subjects who took NAC were categorized into groups taking drugs along with ATD, which may confound the results of the association of co-medication with the incidence of DIH. In addition, differences in the dose and duration of other drugs need to be considered when assessing the association of the occurrence of hepatotoxic reactions.[44]

This study is similar to the study by Wang, *et al*. (2021) and Jiang, *et al*. (2021), who found no association between alcohol consumption and liver damage.[3,28] However, a cohort study by Abera, *et al*. (2016) gave different results and found that high alcohol intake (>35 units for men and 28 units for women per week for 10 years) was associated with the incidence of ATDIH with a crude OR (cOR) 9.35 (95% CI 1.8-47, p <0.007).[39] Molla, *et al*. (2021) found significant results in the bivariate analysis but not the multivariate analysis.[29] Alcohol is known to induce the production of enzymes in the liver that can potentially increase toxic metabolites that damage the liver in turn.[6,40,41] Alcohol is metabolized in the liver. The metabolic process increases the production of ROS and causes mitochondrial dysfunction.[45] This difference in results is due to differences in the level of alcohol consumption between populations, which in this study did not measure the quantity and frequency of drinking alcohol.

Anti-tuberculosis drugs-induced hepatitis (ATDIH) usually occurs 2 months after ATD treatment, with the peak incidence occurring in the first 2 weeks.[4] Several studies have reported the median and mean onset of ATD hepatotoxicity on day 10, 20, and 26.[30,31,39] These studies have it in common that the onset of ATDIH occurs in the intensive phase.[7] This is possible because more drugs are administered in the intensive phase and larger doses than in the continuation phase. This study also found that most patients experienced DIH in the intensive phase (first 2 months), although the treatment phase was not associated with the incidence of ATDIH.

An animal experiment by Nehra, *et al*. (2016) showed that vitamin E has a hepatoprotection effect against isoniazid, rifampicin, and pyrazinamide at doses of 5 mg, 20 mg, and 25 mg, respectively, per kg BW for 90 days.[46] The effect was seen from the decrease in alanine transaminase (ALT) levels after administering alpha-tocopherol 200mg/kg BW orally, given together with ATD.[46] Adikwu (2013) found that the hepatoprotective effect of vitamin E in humans is still contradictory, although it has been proven in animals. In humans, the protective effect of vitamin E is seen to be beneficial in non-alcoholic steatohepatitis, hemochromatosis, obese children with non-alcoholic fatty liver disease (NAFLD), hepatitis B, and hepatitis C.[14] This study showed that vitamin E intake was not associated with the incidence of ATDIH in drug-sensitive pulmonary TB patients.

This is the first study in Indonesia that links vitamin C and E intake with the incidence of ATDIH in drug-sensitive pulmonary TB patients, providing information for future studies. However, recall bias and measurement bias were present due to the SQ FFQ usage, which was minimized when using food photo books. In addition, due to limited resources, vitamin C levels were not measured, which has a more objective value than vitamin C intake. However, the assessment of serum levels is influenced by the last intake. Therefore, serum vitamin C levels cannot be used to measure status in individuals with a regular high intake or irregular fruit and vegetable consumption.[47]

## CONCLUSION

Despite the lack of statistical significance, there was a higher proportion of ATDIH in the group with insufficient vitamin C intake than in the group with adequate intake. Clinicians can still educate pulmonary TB patients on vitamin C adequacy as it has benefits in terms of the effectiveness of TB therapy. Factors influencing the incidence of ATDIH were not found in this study. Further research is needed with more objective measurements of vitamin C levels rather than intake while considering other nutrients with hepatoprotective effects and other DIH risk factors such as genetic polymorphisms.

### Acknowledgments
The authors would like to thank Persahabatan National Respiratory Referral Hospital, Jakarta, and all of the study participants.

### Conflict of Interest
The authors declared there is no conflict of interest.

### Funding
This study was self-funded by the authors.

### Authors' Contributions
Designed the study, collecting, analyzing, and interpreting the data, and writing the manuscript: HR. Providing guidance, contributing significant intellectual content during drafting and revising the manuscript: FN, DEA, HA, SS. All authors contributed and approved the final version of the manuscript.

## REFERENCES

1. World Health Organization (WHO). *Global Tuberculosis Report 2023*. Geneva, https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-

2023 (2023).
2. Kementerian Kesehatan Republik Indonesia. *Pedoman Nasional Pelayanan Kedokteran Tata Laksana Tuberkulosis*. Jakarta: Kementerian Kesehatan Republik Indonesia, 2020. [Website]
3. Wang J, Xiong K, Xu L, *et al.* Dietary Intake of Vegetables and Cooking Oil was Associated with Drug-Induced Liver Injury During Tuberculosis Treatment: A Preliminary Cohort Study. *Front Nutr* 2021; 8: 652311. [PubMed]
4. Soedarsono S, Riadi ARW. Tuberculosis Drug-Induced Liver Injury . *J Respirasi* 2020; 6: 49–54. [Journal]
5. Villanueva-Paz M, Morán L, López-Alcántara N, *et al*. Oxidative Stress in Drug-Induced Liver Injury (DILI): From Mechanisms to Biomarkers for Use in Clinical Practice. *Antioxidants (Basel, Switzerland)*; 10. Epub ahead of print March 2021. [PubMed]
6. Ramappa V, Aithal GP. Hepatotoxicity Related to Anti-Tuberculosis Drugs: Mechanisms and Management. *J Clin Exp Hepatol* 2013; 3: 37–49. [PubMed]
7. Singh A, Prasad R, Balasubramanian V, *et al*. Prevalence of Adverse Drug Reaction with First-Line Drugs among Patients Treated for Pulmonary Tuberculosis. *Clin Epidemiol Glob Heal* 2015; 3: S80–S90. [ScienceDirect]
8. Patel S, Chaturvedi A, Dubey N, *et al.* Ascorbic Acid Ameliorates Isoniazid-Rifampicin-Induced Hepatocellular Damage in Rats. *iLIVER* 2022; 1: 72–77. [ScienceDirect]
9. Alli J, Kehinde A, Kosoko A, *et al.* Oxidative Stress and Reduced Vitamins C and E Levels are Associated with Multi-Drug Resistant Tuberculosis. *J Tuberc Res* 2014; 2: 52–58. [Journal]
10. Alaina D. The Relationship of Energy Intake, Protein, Vitamin B6, Vitamin C with the Nutritional Status of Lung Tuberculosis Patients in the Kemuning Room, Dr. M. Yunus Bengkulu in 2020. *SANITAS J Teknol dan Seni Kesehat* 2021; 12: 149–158. [Journal]
11. Vahdati-Mashhadian N, Jafari MR, Sharghi N, *et al*. Protective Effects of Vitamin C and NAC on the Toxicity of Rifampin on Hepg2 Cells. *Iran J Pharm Res IJPR* 2013; 12: 141–146. [PubMed]
12. Alorabi M, Mohammed DS, Mostafa-Hedeab G, *et al*. Combination Treatment of Omega-3 Fatty Acids and Vitamin C Exhibited Promising Therapeutic Effect against Oxidative Impairment of the Liver in Methotrexate-Intoxicated Mice. *Biomed Res Int* 2022; 2022: 4122166. [PubMed]
13. Adikwu E, Deo O. Hepatoprotective Effect of Vitamin C (Ascorbic Acid). *Pharmacol Pharm* 2013; 2013: 84–92. [Journal]
14. Adikwu E, Nelson B. Hepatoprotective Effect of Vitamin E. *Am J Pharmacol Toxicol* 2013; 7: 154–163. [Journal]
15. Ergul Y, Erkan T, Uzun H, *et al*. Effect of Vitamin C on Oxidative Liver Injury due to Isoniazid in Rats. *Pediatr Int* 2010; 52: 69–74. [PubMed]
16. Niu H, Sanabria-Cabrera J, Alvarez-Alvarez I, *et al*. Prevention and Management of Idiosyncratic Drug-Induced Liver Injury: Systematic Review and Meta-Analysis of Randomised Clinical Trials. *Pharmacol Res* 2021; 164: 105404. [PubMed]
17. Kementerian Kesehatan Republik Indonesia. Peraturan Menteri Kesehatan Republik Indonesia Nomor 28 Tahun 2019 tentang Angka Kecukupan Gizi yang Dianjurkan untuk Masyarakat Indonesia. 28, Indonesia, http://hukor.kemkes.go.id/uploads/produk_hukum/PMK_No__28_Th_2019_ttg_Angka_Kecukupan_Gizi_Yang_Dianjurkan_Untuk_Masyarakat_Indonesia.pdf (2019).
18. Xiong K, Wang J, Zhang J, *et al*. Association of Dietary Micronutrient Intake with Pulmonary Tuberculosis Treatment Failure Rate: ACohort Study. *Nutrients*; 12. Epub ahead of print August 2020. [PubMed]
19. Fitri ML, Nurwidya F, Manikam NRM, *et al*. Fat and Vitamin E Intake Affect Multidrug-Resistant Tuberculosis Patients' Quality of Life: A Cross-Sectional Study. *J Pak Med Assoc* 2021; 71(Suppl 2): S53–S57. [PubMed]
20. Ren Z, Zhao F, Chen H, *et al*. Nutritional Intakes and Associated Factors among Tuberculosis Patients: A Cross-Sectional Study in China. *BMC Infect Dis* 2019; 19: 907. [PubMed]
21. Carr AC, Maggini S. Vitamin C and Immune Function. *Nutrients*; 9. Epub ahead of print November 2017. [PubMed]
22. Carr A, Rowe S. Factors Affecting Vitamin C Status and Prevalence of Deficiency: A Global Health Perspective. *Nutrients* 2020; 12: 1963. [PubMed]
23. Badan Kebijakan Pembangunan Kesehatan. SKI 2023 dalam Angka. *BKPK*, https://www.badankebijakan.kemkes.go.id/ski-2023-dalam-angka/ (2023, accessed 6 May 2024).
24. Rifai A, Herlianto B, Mustika S, *et al.* Insiden dan Gambaran Klinis Hepatitis Akibat Obat Anti Tuberkulosis di Rumah Sakit Umum Daerah Dr. Saiful Anwar Malang. *J Kedokt Brawijaya* 2015; 28: 238–241. [Journal]
25. Pranata JR, Mariadi IK, Somayana G. Prevalensi dan Gambaran Umum Drug-Induced Liver Injury Akibat Obat Anti Tuberkulosis pada Pasien Tuberkulosis RSUP Sanglah Denpasar Periode Agustus 2016 – Juli 2017. *E-Jurnal Med Udayana*; 8, https://ojs.unud.ac.id/index.php/eum/article/view/53031 (2019).
26. Nur M, Iskandar H, Daud N, *et al.* Factors that Influence the Incidence of Drug Induced Liver Injury in Pulmonary Tuberculosis Patient. *Int J Med Rev Case Reports* 2019; 3: 1. [Journal]
27. Dasuki AA, Muti AF, Yusmaini H. Faktor Resiko Kejadian Peningkatan Kadar Transminase pada Penggunaan Obat Antituberkulosis Pasien Tuberkulosis Paru di RST Wijayakusuma Purwokerto. *JFIOnline* 2020; 12: 134–144. [Journal]
28. Jiang F, Yan H, Liang L, *et al*. Incidence and Risk Factors of Anti-Tuberculosis Drug Induced Liver

Injury (DILI): Large Cohort Study Involving 4652 Chinese Adult Tuberculosis Patients. *Liver Int* 2021; 41: 1565–1575. [PubMed]
29. Molla Y, Wubetu M, Dessie B. Anti-Tuberculosis Drug Induced Hepatotoxicity and Associated Factors among Tuberculosis Patients at Selected Hospitals, Ethiopia. *Hepat Med* 2021; 13: 1–8. [PubMed]
30. Gaude GS, Chaudhury A, Hattiholi J. Drug-Induced Hepatitis and the Risk Factors for Liver Injury in Pulmonary Tuberculosis Patients. *J Fam Med Prim Care* 2015; 4: 238–243. [PubMed]
31. Ali N, Gupta N, Saravu K. Malnutrition as an Important Risk Factor for Drug-Induced Liver Injury in Patients on Anti-Tubercular Therapy: An Experience from a Tertiary Care Center in South India. *Drug Discov Ther* 2020; 14: 135–138. [PubMed]
32. Gropper SS, Smith JL, Carr TP. *Advanced Nutrition and Human Metabolism*. Cengage Learning, https://books.google.co.id/books?id=vggVEAAAQBAJ (2021).
33. Pingili RB, Challa SR, Pawar AK, *et al*. A Systematic Review on Hepatoprotective Activity of Quercetin against Various Drugs and Toxic Agents: Evidence from Preclinical Studies. *Phytother Res* 2020; 34: 5–32. [PubMed]
34. Madrigal-Santillán E, Madrigal-Bujaidar E, Álvarez-González I, *et al*. Review of Natural Products with Hepatoprotective Effects. *World J Gastroenterol* 2014; 20: 14787–14804. [PubMed]
35. Bishayee A, Darvesh AS, Politis T, *et al*. Resveratrol and Liver Disease: From Bench to Bedside and Community. *Liver Int* 2010; 30: 1103–1114. [PubMed]
36. Mahayanti NKS, Sudarsana IPA. Laporan Kasus: Drug-Induced Liver Injury pada Pasien Tuberkulosis Relaps. *Intisari Sains Medis* 2022; 13: 792–795. [Journal]
37. Rahmani AH, Alsahli MA, Aly SM, *et al*. Role of Curcumin in Disease Prevention and Treatment. *Adv Biomed Res* 2018; 7: 38. [PubMed]
38. Farzaei MH, Zobeiri M, Parvizi F, *et al*. Curcumin in Liver Diseases: A Systematic Review of the Cellular Mechanisms of Oxidative Stress and Clinical Perspective. *Nutrients*; 10. Epub ahead of print July 2018. [PubMed]
39. Abera W, Cheneke W, Abebe G. Incidence of Antituberculosis-Drug-Induced Hepatotoxicity and Associated Risk Factors among Tuberculosis Patients in Dawro Zone, South Ethiopia: A Cohort Study. *Int J Mycobacteriology* 2016; 5: 14–20. [PubMed]
40. Soedarsono S, Mandayani S, Prayuni K, *et al*. The Risk Factors for Drug Induced Hepatitis in Pulmonary Tuberculosis Patients in Dr. Soetomo Hospital. *Indones J Trop Infect Dis* 2018; 7: 73–79. [Journal]
41. Tostmann A, Boeree MJ, Aarnoutse RE, *et al*. Antituberculosis Drug-Induced Hepatotoxicity: Concise Up-to-Date Review. *J Gastroenterol Hepatol* 2008; 23: 192–202. [PubMed]
42. Sukumaran D, Usharani P, Paramjyothi GK, *et al*. A Study to Evaluate the Hepatoprotective Effect of N-Acetylcysteine on Anti Tuberculosis Drug Induced Hepatotoxicity and Quality of Life. *Indian J Tuberc* 2023; 70: 303–310. [PubMed]
43. Yani MS, Singh G. Efek Hepatoprotektif N-Asetilsistein dalam Mencegah Drug-Induced Liver Injury Akibat Obat Antituberkulosis: Laporan Kasus Berbasis Bukti. *Indones J CHEST Crit Emerg Med* 2015; 2: 86–90. [Journal]
44. Aithal GP, Watkins PB, Andrade RJ, *et al*. Case Definition and Phenotype Standardization in Drug-Induced Liver Injury. *Clin Pharmacol Ther* 2011; 89: 806–815. [PubMed]
45. Yew WW, Chang KC, Chan DP. Oxidative Stress and First-Line Antituberculosis Drug-Induced Hepatotoxicity. *Antimicrob Agents Chemother*; 62. Epub ahead of print August 2018. [PubMed]
46. Nehra R, Vishwakarma P, Nehra M, *et al*. Effect of α-Tocopherol on Antitubercular Drugs Induced Hepatotoxicity. *Int J Res Med Sci* 2016; 4: 1158–1162. [Journal]
47. Fahmida U, Dillon DHS, *Handbook Nutritional Assessment*. 2nd ed. SEAMEO-TROPMED RCCN, University of Indonesia, 2011.