

Effectiveness of Vitamin C Supplementation on Treatment Outcome in Newly Diagnosed Pulmonary Tuberculosis Patients**V. Karthik¹, Raghu N.², Jayanth G.S.³, Jayashree V. Nagaral⁴, Deepak P.⁵, Manjula MJ⁶, Anusha J.⁷**¹Assistant Professor, Department of Pharmacology, Chandramma Dayanand Sagar Institute of Medical Education and Research (CDSIMER), Harohalli, Ramanagara, India²Assistant Professor, Department of Pharmacology, Sri Siddhartha Institute of Medical Science, T. Begur, Nelamangala Tq., Bangalore, India³Associate Professor, Department of Pharmacology, Sri Siddhartha Institute of Medical Science, T. Begur, Nelamangala Tq., Bangalore, India⁴Assistant Professor, Department of Pharmacology, Hassan Institute of Medical Sciences, Hassan, Karnataka, India⁵Associate Professor, Department of Pharmacology, Hassan Institute of Medical Sciences, Hassan, Karnataka, India⁶Assistant Professor, Department of Pharmacology, Rajarajeshwari Medical College and Hospital, Bengaluru, Karnataka, India⁷Assistant Professor, Department of Pharmacology, Sri Venkateshwaraa Medical College, Hospital and Research Centre, Puducherry, India

Received: 01-08-2026 / Revised: 15-09-2026 / Accepted: 03-10-2026

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Conflict of interest: Nil

Abstract**Introduction:** Tuberculosis remains a major public health problem, and adjunctive strategies that improve treatment response and minimize treatment-related toxicity are of clinical interest. Vitamin C possesses antioxidant, immunomodulatory, and potential antimycobacterial properties. This study evaluated the clinical, microbiological, and liver biochemical changes associated with adjunctive vitamin C supplementation during anti-tubercular therapy.**Materials and Methods:** A hospital-based, open-label, randomized interventional study was conducted among 220 newly diagnosed sputum-positive pulmonary tuberculosis patients from February 2021 to February 2022. Participants were randomized into a Vitamin C group (n=110), receiving standard anti-tubercular treatment plus vitamin C 500 mg once daily for 8 weeks, and a control group (n=110), receiving standard anti-tubercular treatment alone. Clinical parameters, sputum microscopy, chest radiography, and liver function tests were assessed at baseline, 4 weeks, and 8 weeks. Data were analyzed using SPSS 22.0 and R 3.2.2.**Results:** Mean age was comparable between groups. Appetite improved in both groups, while body weight increased from 60.74 ± 8.17 kg to 62.84 ± 7.93 kg in the Vitamin C group but declined in controls. By 8 weeks, sputum microscopy was negative in all participants in both groups, with no significant intergroup difference. Bilirubin, total protein, and albumin showed significantly different changes between groups. AST, ALT, and ALP increased at 4 weeks and subsequently declined, with significant overall differences between groups (*P* = 0.006, <0.001, and <0.001, respectively).**Conclusion:** Adjunctive vitamin C supplementation was associated with favorable clinical and liver biochemical changes during intensive-phase anti-tubercular therapy, although sputum conversion was comparable between groups. Larger studies are warranted to confirm its potential clinical and hepatoprotective benefits.**Keywords:** Pulmonary tuberculosis; Vitamin C; Anti-tubercular therapy; Liver function tests; Hepatotoxicity.**DOI:** 10.25258/ijcpr.18.10.66This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided original work is properly credited.**Introduction**Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, remains a major global public health

problem and continues to contribute substantially to morbidity and mortality, particularly in low- and

middle-income countries [1]. India carries one of the highest burdens of TB worldwide. According to the Global Tuberculosis Report 2021, the estimated incidence of all forms of TB in India in 2020 was approximately 188 cases per 100,000 population [2]. The National TB Prevalence Survey of India (2019–2021) reported a prevalence of microbiologically confirmed pulmonary TB of approximately 316 per 100,000 population among individuals aged ≥ 15 years, with considerable geographical variation across the country [3]. Despite the availability of effective anti-tubercular therapy (ATT), prolonged treatment duration, adverse drug reactions, treatment adherence, and the emergence of drug resistance continue to pose important challenges in TB control [4].

Several adjunctive strategies have therefore been investigated to improve treatment response and reduce treatment-related toxicity [5]. Nutritional and antioxidant supplementation, including vitamins C, A, D and E, zinc, and protein supplementation, has received increasing attention as a supportive approach in patients receiving ATT [6]. Vitamin C is an essential water-soluble micronutrient with important antioxidant and immunomodulatory properties. It accumulates in phagocytic cells and supports chemotaxis, phagocytosis, generation of reactive oxygen species, and microbial killing [7,8]. In addition, vitamin C acts as a reducing agent and cofactor for several enzymatic reactions and contributes to the regulation of inflammatory and oxidative processes. These properties provide a biological rationale for its potential role as an adjunct to conventional TB therapy [9].

Experimental evidence has further demonstrated direct antimycobacterial activity of vitamin C. High concentrations of vitamin C have been shown to exert bactericidal activity against drug-susceptible and drug-resistant *M. tuberculosis* strains and may interfere with the development of drug-tolerant persisters [10]. This activity has been associated with iron-dependent Fenton and Haber–Weiss reactions, resulting in increased reactive oxygen species generation, DNA damage, lipid alterations, and disruption of redox homeostasis. Vitamin C has also been investigated for its ability to enhance mycobacterial respiration and thereby reduce persister formation [11]. In addition to its potential antimycobacterial effects, its antioxidant properties may be relevant in limiting oxidative stress and hepatocellular injury associated with anti-tubercular drugs, as demonstrated in experimental models. Although these experimental findings provide a strong rationale for vitamin C supplementation, clinical evidence regarding its effectiveness as an adjunct to ATT remains limited, particularly in the Indian population. There is therefore a need to evaluate whether vitamin C

supplementation can improve clinical and microbiological treatment outcomes while potentially mitigating alterations in liver function during ATT. Hence, the present study aimed to evaluate the effectiveness of vitamin C supplementation on treatment outcomes in newly diagnosed pulmonary tuberculosis patients and to assess its effect on liver function tests during anti-tubercular treatment.

Materials and Methods

A hospital-based, interventional, open-label, randomized comparative study was conducted in the Department of Pharmacology in collaboration with the Department of Respiratory Medicine at a tertiary care hospital. The study was conducted from 1 February 2021 to 28 February 2022 and included newly diagnosed, sputum-positive pulmonary tuberculosis patients attending the Respiratory Medicine outpatient department.

Patients aged 18–50 years who were willing to provide written informed consent were eligible for participation. Patients with comorbidities such as diabetes mellitus and hypertension were also eligible. Patients with a history of alcoholism, known hepatic disease, HIV infection, or those aged below 18 years or above 65 years were excluded. All eligible participants were informed about the purpose and procedures of the study, and written informed consent was obtained before enrolment.

The required sample size was estimated based on the prevalence of pulmonary tuberculosis among the outpatient population of the hospital. The prevalence was approximately 7% in 2020. Using the formula ($n = 4pq/d^2$), where p was the prevalence, q was $(1-p)$, and d was the allowable error of 5%, the calculated sample size was approximately 105 participants. To account for practical considerations and ensure adequate group size, the final sample comprised 220 participants. Eligible participants were allocated using a computer-generated randomization sequence into two equal groups of 110 participants each. Group A (Vitamin C group) received standard anti-tubercular treatment (ATT) along with Vitamin C 500 mg once daily as a chewable tablet, administered in the morning after breakfast for 8 weeks corresponding to the intensive phase of ATT. Group B (control group) received standard ATT alone. The study was open-label, and no masking was performed. Vitamin C tablets were procured through the hospital pharmacy system. Treatment adherence was assessed through direct questioning during follow-up visits and telephone contact, and participants were also monitored for any adverse effects related to ATT or Vitamin C. At baseline, a detailed demographic and clinical assessment was performed by the treating physician

or medical officer in the Department of Respiratory Medicine. Demographic characteristics, presenting symptoms, comorbidities, smoking history, and findings on general physical examination were recorded in a structured data collection proforma. Baseline investigations included sputum microscopy, cartridge-based nucleic acid amplification test (CBNAAT), chest radiography in posteroanterior view, random blood glucose, and liver function tests comprising serum bilirubin, total protein, albumin, globulin, albumin/globulin ratio, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP). Relevant information was also obtained from the standard Revised National Tuberculosis Control Programme (RNTCP) treatment card. Participants were reassessed at the fourth and eighth weeks after initiation of ATT.

At each follow-up visit, clinical improvement in fever, appetite, cough, and weight was assessed, along with general physical examination, sputum microscopy, chest radiography, and liver function testing. Medication adherence and the occurrence of adverse effects were documented. Telephone follow-up was performed periodically to reinforce compliance and identify any interim adverse events. At the end of 8 weeks, Vitamin C supplementation was discontinued in Group A, and participants were subsequently followed according to the standard ATT schedule for assessment of clinical outcome.

Statistical analysis was performed using SPSS version 22.0 and R environment version 3.2.2.

Continuous variables were expressed as mean $\pm$ standard deviation (SD), while categorical variables were presented as frequency and percentage. The independent Student's *t*-test was used to compare continuous variables between the two groups, with Levene's test used to assess homogeneity of variance. The chi-square test or Fisher's exact test was used for comparison of categorical variables, with Fisher's exact test applied when expected cell frequencies were small. All tests were two-tailed, and a *p* value <0.05 was considered statistically significant. A *p* value of $0.05\text{--}<0.10$ was considered suggestive of significance, $0.01\text{--}\leq 0.05$ as moderately significant, and ≤ 0.01 as strongly significant.

Results

The mean age of patients was 43.14 ± 13.98 years in the Vitamin C group and 44.61 ± 13.25 years in the control group, with no significant difference between the groups ($P = 0.424$). The most common age group was 41–50 years in the Vitamin C group (27.3%) and 31–40 years in the control group (30.9%). Males predominated in both groups, accounting for 75.5% and 60.0%, respectively, with a significant difference in gender distribution ($P = 0.014$). Low socioeconomic status was more frequent in the control group than the Vitamin C group (68.2% vs. 45.5%; $P = 0.001$). The mean duration of cough was comparable between groups, whereas fever duration was significantly longer in the Vitamin C group ($P < 0.001$). (Table 1)

Table 1: Baseline demographic and clinical characteristics of the study groups

Variable	Category	Vitamin C group (n=110)	Control group (n=110)	P value
Age (years)	<20	8 (7.3%)	5 (4.5%)	0.424
	20–30	18 (16.4%)	9 (8.2%)	
	31–40	26 (23.6%)	34 (30.9%)	
	41–50	30 (27.3%)	26 (23.6%)	
	51–60	13 (11.8%)	20 (18.2%)	
	>60	15 (13.6%)	16 (14.5%)	
	Mean $\pm$ SD	43.14 ± 13.98	44.61 ± 13.25	
Gender	Male	83 (75.5%)	66 (60.0%)	0.014
	Female	27 (24.5%)	44 (40.0%)	
Socioeconomic status	Low	50 (45.5%)	75 (68.2%)	0.001
	Middle	60 (54.5%)	33 (30.0%)	
	Upper	0 (0%)	2 (1.8%)	
Duration of cough (days)	Mean $\pm$ SD	44.43 ± 10.63	41.55 ± 13.13	0.075
Duration of fever (days)	Mean $\pm$ SD	20.30 ± 0.63	17.64 ± 0.60	<0.001

Comorbid conditions were present in 33.6% of patients in the Vitamin C group and 40.9% of controls, with diabetes mellitus being the most frequent comorbidity. Chronic smoking was significantly more common among patients receiving Vitamin C than controls (47.3% vs.

30.0%; $P < 0.01$). Pallor was present in all patients in both groups, while icterus was observed in 12.7% and 13.6%, respectively, without a significant difference. None of the patients had cyanosis, clubbing, lymphadenopathy, or edema. (Table 2)

Table 2: Comorbidities, smoking history, and general physical examination findings

Parameter	Vitamin C group (n=110)	Control group (n=110)
Comorbid conditions	37 (33.6%)	45 (40.9%)
Diabetes mellitus	34 (30.9%)	24 (21.8%)
Diabetes mellitus + hypertension	3 (2.7%)	10 (9.1%)
Hypertension	0 (0%)	11 (10.0%)
Chronic smoking	52 (47.3%)	33 (30.0%)
Pallor	110 (100%)	110 (100%)
Icterus	14 (12.7%)	15 (13.6%)

Appetite was reduced in all patients at baseline and improved by the fourth week, with normalization by the eighth week in both groups.

Mean body weight increased from 60.74 ± 8.17 kg at baseline to 62.84 ± 7.93 kg at the eighth week in the Vitamin C group, whereas it changed from 60.83 ± 8.27 kg to 57.52 ± 12.67 kg in controls.

Decreased breath sounds, crepitations, and pleural effusion were observed at baseline in both groups, while pulmonary opacities were the predominant radiological abnormality.

Clinical and radiological improvement was observed in both groups during follow-up. (Table 3)

Table 3: Clinical and radiological findings at baseline and during follow-up

Parameter	Category	Vitamin C group (n=110)	Control group (n=110)
Appetite	Baseline	Reduced (100%)	Reduced (100%)
	4th week	Improving (100%)	Improving (100%)
	8th week	Normal (100%)	Normal (100%)
Body weight (kg), mean $\pm$ SD	Baseline	60.74 ± 8.17	60.83 ± 8.27
	4th week	58.08 ± 9.16	56.58 ± 12.55
	8th week	62.84 ± 7.93	57.52 ± 12.67
Chest examination at baseline	Decreased breath sounds	23.6%	26.3%
	Crepitations	11.8%	10.0%
	Pleural effusion	9.1%	5.0%
Radiological findings at baseline	Opacities	90.0%	89.0%
	Infiltration	5.4%	4.3%
	Hilar lymphadenopathy	1.8%	0.5%
Radiological findings	4th week	Clinical and radiological improvement	Clinical and radiological improvement
	8th week	Clinical and radiological resolution	Clinical and radiological resolution

At baseline, sputum smears showed 2+ positivity in 68.2% of the Vitamin C group and 71.8% of controls, while 3+ positivity was observed in 31.8% and 28.2%, respectively. By the fourth week, most patients had 1+ positivity, accounting for 86.4% in the Vitamin C group and 91.8% in

controls. By the eighth week, all patients in both groups had achieved sputum conversion to negative status (100%). No significant intergroup difference was observed at baseline, fourth week, or eighth week ($P = 0.950, 0.641, \text{ and } 1.000$, respectively). (Table 4)

Table 4: Sputum microscopy findings at baseline, 4th week, and 8th week

Sputum microscopy	Category	Vitamin C group (n=110)	Control group (n=110)	P value
Baseline	Negative	0 (0%)	0 (0%)	0.950
	1+	0 (0%)	0 (0%)	
	2+	75 (68.2%)	79 (71.8%)	
	3+	35 (31.8%)	31 (28.2%)	
4th week	Negative	0 (0%)	0 (0%)	0.641
	1+	95 (86.4%)	101 (91.8%)	
	2+	15 (13.6%)	9 (8.2%)	
	3+	0 (0%)	0 (0%)	
8th week	Negative	110 (100%)	110 (100%)	1.000
	1+	0 (0%)	0 (0%)	
	2+	0 (0%)	0 (0%)	
	3+	0 (0%)	0 (0%)	

Serum bilirubin increased at the fourth week and subsequently declined by the eighth week in the Vitamin C group, reaching 0.67 ± 0.70 compared with 1.07 ± 0.69 in controls, with a significant overall difference ($P < 0.001$). Total protein showed a modest reduction at the fourth week followed by improvement at the eighth week, while

albumin increased to 3.55 ± 0.61 in the Vitamin C group compared with 3.38 ± 0.52 in controls. The differences in total protein and albumin were statistically significant ($P = 0.009$ and 0.026 , respectively), whereas globulin and A/G ratio showed no significant differences. (Table 5)

Table 5: Comparison of liver function parameters at different study time points

Parameter	Vitamin C group Baseline	4th week	8th week	Control group Baseline	4th week	8th week	P value
Bilirubin	1.17 ± 1.13	1.34 ± 1.23	0.67 ± 0.70	1.10 ± 1.05	1.15 ± 0.56	1.07 ± 0.69	<0.001
Total protein	5.54 ± 1.47	5.41 ± 1.02	5.71 ± 0.98	5.53 ± 1.41	5.32 ± 1.01	5.37 ± 0.93	0.009
Albumin	3.32 ± 0.46	3.31 ± 0.55	3.55 ± 0.61	3.32 ± 0.46	3.31 ± 0.55	3.38 ± 0.52	0.026
Globulin	3.11 ± 0.68	3.17 ± 0.64	3.07 ± 0.67	3.12 ± 0.69	3.18 ± 0.63	2.99 ± 0.65	0.365
A/G ratio	0.97 ± 0.10	1.01 ± 0.08	0.98 ± 0.08	0.97 ± 0.10	1.01 ± 0.07	0.99 ± 0.08	0.342

All three liver enzymes demonstrated an increase at the fourth week followed by a decline at the eighth week. In the Vitamin C group, AST decreased from 98.07 ± 106.44 IU/L at the fourth week to 42.38 ± 40.30 IU/L at the eighth week, while the corresponding values in controls were $97.75 \pm$

100.16 and 62.34 ± 63.61 IU/L. ALT and ALP showed similar patterns, with lower eighth-week values in the Vitamin C group than controls. The overall differences were statistically significant for AST, ALT, and ALP ($P = 0.006$, <0.001, and <0.001, respectively). (Table 6)

Table 6: Comparison of liver enzymes at different study time points

Liver enzyme	Vitamin C group Baseline	4th week	8th week	Control group Baseline	4th week	8th week	P value
AST (IU/L)	16.58 ± 5.47	98.07 ± 106.44	42.38 ± 40.30	16.15 ± 4.64	97.75 ± 100.16	62.34 ± 63.61	0.006
ALT (IU/L)	27.59 ± 13.39	75.16 ± 46.51	34.77 ± 20.85	26.06 ± 10.30	52.65 ± 43.79	32.85 ± 22.85	<0.001
ALP (IU/L)	54.50 ± 22.22	104.48 ± 57.65	50.78 ± 29.00	54.98 ± 22.44	115.73 ± 42.11	63.65 ± 20.67	<0.001

Among patients with elevated liver enzymes, AST increased markedly at the fourth week and subsequently declined by the eighth week in both groups, with a greater reduction in the Vitamin C group. ALT decreased from 152.11 IU/L at the fourth week to 81.44 IU/L at the eighth week in the

Vitamin C group, compared with a reduction from 125.36 to 89.81 IU/L in controls. Similarly, ALP decreased from 151.67 to 82.66 IU/L in the Vitamin C group and from 177.90 to 116.81 IU/L in controls by the eighth week. (Table 7)

Table 7: Liver enzyme values among patients with elevated liver enzymes

Liver enzyme	Vitamin C group (n=9) Baseline	4th week	8th week	Control group (n=11) Baseline	4th week	8th week
AST (IU/L)	35.20	243.33	120.44	36.40	273.40	236.80
ALT (IU/L)	29.60	152.11	81.44	26.54	125.36	89.81
ALP (IU/L)	42.96	151.67	82.66	45.18	177.90	116.81

Discussion

The present study demonstrated clinical improvement during the intensive phase of anti-tubercular therapy in both groups. Appetite improved by the fourth week and was reported as normal by the eighth week, while body weight

increased from 60.74 ± 8.17 kg at baseline to 62.84 ± 7.93 kg at eight weeks in the vitamin C group, whereas the control group showed a decline in mean weight. This finding is consistent with the recognized association between active pulmonary TB and nutritional impairment. Karyadi et al.

reported poor micronutrient status among patients with active pulmonary TB, supporting the importance of nutritional factors during treatment [12]. However, evidence regarding whether micronutrient supplementation improves treatment-related weight gain remains inconsistent. A Cochrane review by Grobler et al. concluded that nutritional supplementation may produce a modest increase in weight during TB treatment, while evidence for improvement in cure and treatment completion remained limited [13]. Thus, the greater weight gain observed in the present vitamin C group may indicate a potential supportive effect, although it should be interpreted cautiously because vitamin C was administered as an adjunct to standard ATT and the study was not designed to isolate nutritional effects on weight.

Sputum microscopy showed marked microbiological improvement in both groups. At baseline, most participants had sputum grades of 2+ or 3+; by the fourth week, the majority had converted to 1+, and by the eighth week all participants were sputum-negative. There was no significant difference between the groups at baseline, fourth week, or eighth week. Therefore, the present findings do not demonstrate an additional sputum-conversion advantage of vitamin C over standard ATT. This is important because the biological rationale for vitamin C is considerably stronger than the available clinical evidence. Vilchèze et al. demonstrated that vitamin C can kill *M. tuberculosis* through an iron-dependent Fenton reaction and generation of reactive oxygen species in vitro [14]. In a subsequent murine study, Vilchèze et al. demonstrated that vitamin C potentiated the activity of isoniazid and rifampicin against *M. tuberculosis* [15]. Conversely, clinical evidence with micronutrient supplementation has been mixed. Chandra et al. reported improved sputum smear clearance with a multivitamin and trace-element preparation, but this intervention contained several micronutrients and cannot be attributed specifically to vitamin C [16]. Similarly, Volchegorskii et al. reported favorable effects of ascorbic acid as an adjunct in infiltrative pulmonary TB, including enhanced mycobacterial eradication and earlier radiological improvement; however, the study used intravenous ascorbic acid and therefore differs substantially from the oral 500-mg regimen used in the present study [17].

An important finding in the present study was the more favorable evolution of liver biochemical parameters in the vitamin C group. Bilirubin, total protein and albumin showed greater improvement by the eighth week in the vitamin C group, while globulin and albumin/globulin ratio did not differ significantly. AST, ALT and ALP increased during the fourth week in both groups, followed by a decline by the eighth week, with significantly

different overall values between the groups. Among participants with elevated liver enzymes, the reductions in AST, ALT and ALP were numerically greater in the vitamin C group. These findings are biologically plausible because first-line ATT, particularly isoniazid, rifampicin and pyrazinamide, can produce oxidative stress, mitochondrial dysfunction, inflammation and hepatocellular injury. Yew et al. described oxidative stress and disturbance of redox homeostasis as important mechanisms involved in first-line ATT-induced hepatotoxicity [18]. Chowdhury et al. also demonstrated lower glutathione and higher malondialdehyde levels in patients with antitubercular drug-induced hepatotoxicity, providing clinical evidence for an oxidative-stress component [19]. More recently, Baskaran and Sabina summarized the contribution of oxidative stress and reactive metabolites to antitubercular drug-induced liver injury [20]. The antioxidant properties of vitamin C could therefore provide a plausible explanation for the more favorable biochemical recovery observed in the present study, although direct clinical evidence specifically supporting vitamin C for prevention of ATT-induced liver injury remains limited.

The liver-related findings should nevertheless be interpreted cautiously because improvement in liver enzymes does not necessarily establish prevention of clinically defined anti-tubercular drug-induced liver injury. Clinical trials of other antioxidant or hepatoprotective adjuncts have produced conflicting results. For example, Luangchosiri et al. found that silymarin reduced the incidence of anti-TB drug-induced liver injury in a small randomized trial, whereas other randomized studies failed to demonstrate consistent hepatoprotective effects [21]. In a randomized controlled trial in China, Zhang et al. compared silymarin with vitamin C as an adjunct to ATT and found no significant preventive advantage of silymarin over vitamin C for probable liver injury; bacterial clearance outcomes were also similar [22]. These observations emphasize that antioxidant supplementation should not be assumed to prevent ATT-related hepatotoxicity solely on the basis of biochemical improvement. Nevertheless, the present study, together with experimental evidence demonstrating antimycobacterial and redox-modulating effects of vitamin C, provides clinical support for further adequately powered trials specifically evaluating oral vitamin C as an adjunct to standard ATT [14].

Conclusion

Adjunctive vitamin C supplementation during the intensive phase of anti-tubercular therapy was associated with favorable clinical and biochemical changes in newly diagnosed pulmonary tuberculosis patients. Although sputum conversion

occurred effectively in both groups without a significant between-group difference, the vitamin C group demonstrated greater improvement in body weight and more favorable changes in bilirubin, albumin, total protein, AST, ALT, and ALP during follow-up.

These findings suggest that vitamin C may have a supportive role during ATT, particularly with respect to recovery of liver biochemical parameters; however, larger randomized controlled studies with longer follow-up are warranted to confirm its clinical and hepatoprotective benefits.

Acknowledgement: None

Funding: None

Conflict of Interest: None

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