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## EDITORIAL

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## REVIEW

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## ORIGINAL ARTICLE

### Retrospective Cohort Study

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### Observational Study

Alsakarneh S, Khalifa A, Almasaid S, Aburumman R, Kilani Y, Khalid Z, Numan L, Dahiya DS, Karagozian R, Helzberg JH. Sex, racial, and ethnic disparities in United States liver transplantation clinical trials. *World J Hepatol* 2025; 17(9): 110384 [DOI: [10.4254/wjh.v17.i9.110384](https://doi.org/10.4254/wjh.v17.i9.110384)]

### Prospective Study

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## META-ANALYSIS

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## CASE REPORT

Wang L, Liang H, Wang C, Liang MY, Zeng QL, Zhu PF, Lv J. Functional cure in an occult hepatitis B virus infection patient on sequential therapy: A case report. *World J Hepatol* 2025; 17(9): 109340 [DOI: [10.4254/wjh.v17.i9.109340](https://doi.org/10.4254/wjh.v17.i9.109340)]

## LETTER TO THE EDITOR

El-Kassas M, AlNaamani K. Rifaximin and sarcopenia in cirrhosis: Commentary on a promising but complex relationship. *World J Hepatol* 2025; 17(9): 108951 [DOI: [10.4254/wjh.v17.i9.108951](https://doi.org/10.4254/wjh.v17.i9.108951)]

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**Martínez-Sánchez FD, Martínez-Vázquez SE, Gutiérrez-Monterrubio R, Muñoz-Martínez S, Garcia-Juarez I.** Silymarin-alpha lipoic acid and metabolic dysfunction-associated steatotic liver disease: Insights and methodological considerations. *World J Hepatol* 2025; 17(9): 110162 [DOI: [10.4254/wjh.v17.i9.110162](https://doi.org/10.4254/wjh.v17.i9.110162)]

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## Silymarin-alpha lipoic acid and metabolic dysfunction-associated steatotic liver disease: Insights and methodological considerations

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### Abstract

The trial by Cano Contreras *et al* examined a proprietary formulation containing *Silybum marianum* and alpha-lipoic acid (SM-ALA), combined with a Mediterranean diet, in patients with metabolic dysfunction-associated steatotic liver disease. While some metabolic benefits were observed, limitations such as the absence of an SM-ALA-only group, the lack of histological data, and a small sample size reduce the validity of the findings. Future research should follow clinical trial standards for pharmacological studies, including phase 1/2 testing, validated outcomes, and transparency.

**Key Words:** Metabolic dysfunction-associated steatotic liver disease; Silymarin; Alpha lipoic acid; Dietary supplements; Clinical trial design; Nutraceuticals

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**Core Tip:** This commentary reviews a clinical trial that investigated the combination of silymarin and alpha-lipoic acid, along with a Mediterranean diet, in patients with metabolic dysfunction-associated steatotic liver disease. Although some health improvements were noted, issues like small sample size, lack of a supplement-only group, and poor tracking of adherence make the results less reliable. The letter suggests future studies should use stronger designs, clear outcomes, balanced sex representation, and transparent reporting to improve the usefulness and accuracy of research findings.

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## TO THE EDITOR

We read the recent article by Cano Contreras *et al*[1], published in the *World Journal of Hepatology*, with great interest. The article examines the effects of a combined supplement containing *Silybum marianum* (*S. marianum*) and alpha-lipoic acid (SM-ALA) along with a Mediterranean diet on patients with metabolic dysfunction-associated steatotic liver disease (MASLD). While the authors present potentially encouraging results, a closer evaluation of the study's methodology reveals several critical weaknesses that limit the validity, reliability, and clinical applicability of its conclusions.

### Current situation

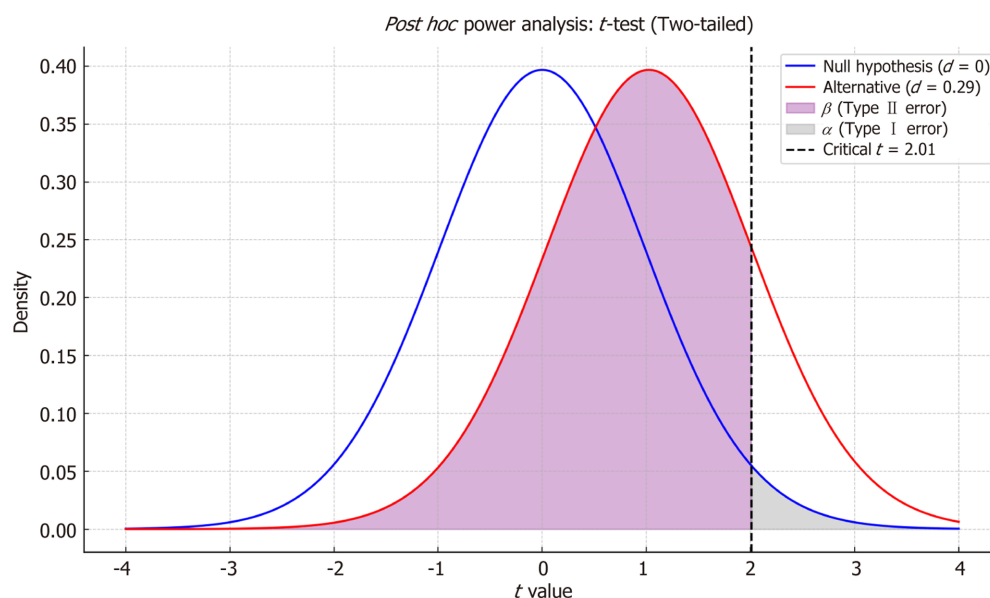
This first study (a mixture of phase 1 and 2 clinical research) employed a randomized, double-blind design comparing SM-ALA, a formulation never studied before, plus a Mediterranean diet (intervention group) with placebo plus Mediterranean diet (control group) over 24 weeks. According to the authors, patients receiving SM-ALA experienced significant reductions in visceral fat, umbilical circumference (not a MeSH-recognized term), and liver fat content as measured by controlled attenuation parameter (CAP) *via* transient elastography[1]. Mild adverse events were reported similarly in both groups, suggesting good tolerability; however, adherence to either the diet or supplement was not reported.

The trial's design makes it impossible to isolate the effects of SM-ALA from those of calorie restriction or the Mediterranean diet, both of which are independently known to improve insulin sensitivity, reduce intrahepatic lipid content, and decrease liver stiffness and body weight[2-5]. Previous clinical trials using alpha-lipoic acid or *S. marianum* alone have shown modest improvements in alanine aminotransferase (ALT) levels, insulin sensitivity, and hepatic fat content[6,7]. Due to the overlapping effects of dietary changes and supplementation, a third arm receiving SM-ALA without dietary intervention would have been necessary to identify the supplement's specific impact. This design flaw introduces a major confounding factor that undermines internal validity.

Additionally, the study lacks histological confirmation of hepatic changes[8]. The authors relied solely on transient elastography to assess steatosis and stiffness. Although widely used, this method cannot capture the full histopathological spectrum of MASLD, including ballooning, inflammation, and fibrosis regression[9]. The current trend in MASLD studies is to implement non-invasive tools to replace the need for liver biopsy; however, these are still not widely accepted for evaluating changes in liver fat, and data are needed to validate this as an accepted primary outcome for predicting clinical events. Furthermore, baseline transaminase levels were within the normal range in both groups, which limited the potential to detect biochemical improvement and suggested that participants had predominantly mild disease. According to the policies of international regulatory agencies, the study cannot claim meaningful liver injury or disease modification resolution without biopsy data[9].

Another significant limitation is the small sample size and its calculation, which was based on a study that evaluated improvement only by ultrasound-graded steatosis. Although the trial was registered on ClinicalTrials.gov (NCT05304538), specific design features, such as the absence of a third comparator arm and phase-appropriate testing, raise concerns regarding its alignment with regulatory and ethical standards. Previous randomized clinical trials evaluating *S. marianum* or alpha-lipoic acid in MASLD included over 100 at-risk participants, who demonstrated mild but statistically significant improvements in liver markers[10]. In contrast, with only 25 participants per group, this study was underpowered to detect differences in many secondary outcomes. Importantly, the primary outcome is not fully described in the methods, leaving the results as only informative. For example, changes in low-density lipoprotein cholesterol (LDL-C) and C-reactive protein failed to reach statistical significance. The borderline reduction in LDL-C in the intervention group ( $P = 0.056$ ) should be interpreted cautiously. A post hoc power analysis using G\*Power, based on an estimated effect size of  $d = 0.29$  and a sample size of 25 participants per group, yielded a statistical power of only 17.1%, which is well below the conventional 80% threshold (Figure 1). This limited power substantially increases the risk of both type I and type II errors. It highlights the need for adequately powered trials to confirm these findings[10]. Future studies should include prospective sample size estimations based on clinically meaningful outcomes and expected effect sizes. Adaptive trial designs may also be considered to allow for interim analyses and sample size re-estimation in response to observed variability, thus improving the robustness and efficiency of MASLD nutraceutical trials.

Additionally, the study population was predominantly female (74%), which may limit generalizability. Given sex-specific variations in visceral adiposity, hormonal influences, and differential responses to dietary and nutraceutical



**Figure 1** Post-hoc power analysis based on comparing low-density lipoprotein cholesterol levels between groups (effect size  $d = 0.29$ ,  $n = 25$  per group). It displays the null distribution ( $d = 0$ , blue) and the alternative distribution ( $d = 0.29$ , red), with a two-tailed alpha level of 0.05 and a critical  $t$ -value of 2.01. The shaded purple area represents the type II error ( $\beta$ ), and the gray area represents the type I error ( $\alpha$ ). The achieved power for this test was 17.1%.

interventions, future trials should ensure balanced recruitment and consider sex-stratified analyses.

Moreover, the reliance on surrogate endpoints, such as visceral fat percentage and waist circumference (referred to as umbilical circumference), is problematic. These markers reflect body composition but do not directly translate into improved clinical outcomes. While CAP is commonly used to estimate liver steatosis, it lacks prognostic value and is susceptible to the “burn-out phenomenon” in advanced disease stages. In contrast, liver stiffness measurement correlates more closely with long-term clinical outcomes and fibrosis progression. CAP value reductions, while informative, lack correlation with patient-centered outcomes such as liver-related morbidity, health-related quality of life, or cirrhosis progression[9]. Furthermore, given the chronic and progressive nature of MASLD, future studies should incorporate long-term follow-up to evaluate sustained effects on fibrosis progression, liver-related events, and overall clinical outcomes, rather than relying solely on short-term metabolic improvements.

Dietary adherence assessment was also limited. All participants were instructed to follow a Mediterranean diet, central to the intervention’s potential effects. However, adherence was evaluated only through a self-reported tool, without objective verification such as dietary records, nutritional biomarkers, or third-party monitoring. This weakens comparability across groups and leaves room for significant interindividual variation in compliance[11].

Furthermore, the supplement tested is a proprietary product not widely available outside the country of origin. The authors disclose that the manufacturer provided the product, and at least one author declared a conflict of interest. Although transparency is acknowledged, the compound's proprietary nature limits the findings' external generalizability, particularly in regions where similar products may vary in composition or dosage[12]. Additionally, financial ties with the manufacturer may have influenced key aspects of the study design (including endpoint selection, emphasis on surrogate markers, and interpretation of results), which should be considered when evaluating the objectivity and applicability of the findings.

Given the absence of prior pharmacokinetic and pharmacodynamic data for SM-ALA, phase I trials are essential to establish safety, optimal dosing, and bioavailability. Without early-phase evidence, the interpretation of efficacy signals in phase II or III studies remains limited. Regulatory standards for drug development support this sequential approach, especially when nutraceuticals are proposed for disease modification.

### Key aspects of dietary clinical trials

Designing a clinical trial in nutrition requires specific considerations due to numerous lifestyle-related confounding factors. Unlike pharmacologic agents, diets cannot be blinded, and adherence is heavily influenced by culture, access, and personal preferences. Therefore, meticulous supervision and measurement of dietary adherence are essential to avoid false positives or misinterpretation of outcomes[13]. Although designing adequate placebos for nutraceuticals, such as ALA, can be challenging due to their organoleptic and physicochemical properties, it is possible to conduct transparent and reproducible interventions[14].

Moreover, promoting adherence to a diet that is not culturally or geographically typical for the population may result in lower compliance. When a supplement with only mild expected benefits is added to such a dietary pattern, the risk of overestimating its clinical impact increases. A rigorous trial design must account for these limitations to ensure reliable conclusions. It is also important to acknowledge that dietary intervention trials face unique challenges distinct from those of pharmacologic studies, including variable adherence, cultural acceptability, and difficulties in designing placebos. Future research should consider incorporating culturally adapted dietary patterns, employing validated patient-reported

**Table 1** Key methodological considerations for future nutraceutical trials in metabolic dysfunction-associated steatotic liver disease

Domain	Recommendation
Trial arms	Include three arms: SM-ALA + diet, SM-ALA only, and diet only
Primary outcomes	Use validated non-invasive endpoints ( <i>e.g.</i> , MRI-PDFF, ELF score)
Sample size	Perform power analysis; consider adaptive designs with interim analyses
Adherence monitoring	Combine self-report with biomarkers ( <i>e.g.</i> , plasma carotenoids), apps, third-party
Regulatory considerations	Include early-phase PK/PD and safety data (phase I) before efficacy claims
Mechanistic support	Provide preclinical or translational evidence on SM-ALA's pathways
Reporting transparency	Follow CONSORT and report manufacturer involvement and conflicts of interest

SM-ALA: *Silybum marianum* and alpha-lipoic acid; PK: Pharmacokinetics; PD: Pharmacodynamics; MRI-PDFF: Magnetic resonance imaging-proton density fat fraction; ELF: Enhanced liver fibrosis; CONSORT: Consolidated Standards of Reporting Trials.

outcomes, and using composite clinical endpoints to capture subjective and objective benefits better.

Another important thing missing was an explanation of why the specific dosage of SM-ALA was chosen. Although the product is commercially available, there are no pharmacokinetic, dose-response, or phase I trial data to support the chosen dose. This raises questions about whether the intervention was effective or not. In addition, although the authors provide results for each group separately, they don't present a structured between-group comparison (SM-ALA + mediterranean diet *vs* placebo + mediterranean diet). There are some between-group *P*-values cited, but the paper doesn't provide enough information about whether the changes in critical parameters, such as visceral fat, CAP, or inflammatory markers, were significantly greater in the intervention group than in the control group. Because of this, it's difficult to determine how much more SM-ALA helps than just a diet. A full head-to-head comparison, including effect sizes and confidence intervals, would have made the results easier to understand and more useful in a clinical setting.

From a design standpoint, we recommend that future trials include three parallel arms: SM-ALA plus Mediterranean diet, SM-ALA alone, and Mediterranean diet alone. This design would enable more accurate attribution of effects to each component. Additionally, validated non-invasive tools such as magnetic resonance imaging-proton density fat fraction or the enhanced liver fibrosis score should be considered primary endpoints when liver biopsy is not feasible[15,16]. Recent evidence further emphasizes the need for rigorous trial design in nutraceutical research. A recent meta-analysis confirmed that silymarin monotherapy significantly reduces transaminase levels (aspartate aminotransferase and ALT) among MASLD patients, underscoring the importance of isolating the added effect of the combined interventions[17].

To strengthen adherence measurement in future trials, we suggest combining self-reported data with objective methods such as plasma carotenoid levels, digital food photography applications, or third-party assessments, as these strategies have demonstrated improved reliability in dietary studies. Furthermore, the use of wearable devices or mobile applications for real-time tracking may help reduce recall bias and enhance data accuracy. In parallel, supplement adherence was monitored only *via* phone follow-up; future studies should incorporate structured verification tools, such as pill counts, serum drug levels, or validated compliance biomarkers, to ensure accurate interpretation of intervention effects. To assist researchers in designing robust future trials, we summarize key methodological considerations for nutraceutical-based MASLD interventions in Table 1.

## Conclusion

The authors made a commendable effort in presenting a clinical trial evaluating a nutraceutical-based intervention for MASLD[1], a condition of increasing global prevalence and a leading cause of cirrhosis worldwide[18]. As the burden of MASLD continues to rise, such research initiatives are valuable and much needed. Nevertheless, significant methodological constraints, including the lack of a supplement-only control group, the absence of histological validation, a limited sample size, and insufficient evaluation of dietary adherence, necessitate careful interpretation of the results. Future clinical trials must employ rigorous designs that differentiate the impacts of each intervention component, utilize proven clinical outcomes, and ensure cultural and nutritional relevance. Transparent reporting and accessible treatments are essential for enhancing repeatability, external validity, and informing therapeutic practice. Public registries of proprietary supplement compositions could also be encouraged to enhance transparency and reproducibility. Future clinical trials should incorporate three-arm designs, objective adherence metrics, validated non-invasive endpoints, and include pharmacokinetic/pharmacodynamic exploration to define optimal dosing strategies. In addition, positioning SM-ALA within current MASLD treatment paradigms requires evidence of safety and biochemical efficacy and long-term benefits on fibrosis progression, which remains to be demonstrated.

## FOOTNOTES

**Author contributions:** Martínez-Sánchez FD and Garcia-Juarez I conceptualized and designed the commentary; Martínez-Sánchez FD drafted the manuscript; Martínez-Sánchez FD, Martínez-Vázquez SE, Gutiérrez-Monterrubio R and Muñoz-Martínez S conducted the

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