Published online 2026 July . **Original Article**

The effect of Curcumin Supplementation on Mortality Rate and Clinical Status of Traumatic ICU-Admitted Patients: A Study Protocol for a Randomized, Triple-Blind, Placebo-Controlled Clinical Trial

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Received 2026 April 28**; Accepted** 2026 July 09.

Abstract

Background: Traumatic injuries significantly contribute to worldwide death and disability rates, often necessitating patient admission to the intensive care unit (ICU), and there is an increased risk of disabilities, poor clinical outcomes, and mortality. Suppressing inflammatory processes in these cases is associated with reduced mortality.

Objectives: This research aims to evaluate the effectiveness of curcumin, a polyphenolic phytochemical known for its anti-inflammatory and various health benefits, in improving clinical outcomes and reducing mortality among ICU patients.

Methods: The current study is a randomized, triple-blind, placebo-controlled trial in patients with traumatic injuries. This study will enroll 327 patients admitted to the ICU for traumatic injury at Bahonar Hospital in Kerman, Iran. Participants will be randomly assigned in a 1:1:1 ratio to one of three groups: (1) high-dose curcumin, (2) low-dose curcumin, and (3) placebo. The first intervention group will receive two tablets, each containing 500 mg of Curcumin and 5 mg of Piperine. The second intervention group will receive one tablet with 500 mg of Curcumin and 5 mg of Piperine, along with one placebo tablet. The control group will receive two placebo tablets. All patients will receive their tablets once a day for 7 days. The primary outcomes will be the 8-day ICU mortality, 30 days and 60 days mortality rates, while secondary outcomes will include the Acute Physiology and Chronic Health Evaluation (APACHE II), Sequential Organ Failure Assessment (SOFA), Modified Nutrition Risk in Critically Ill (mNUTRIC) score, Glasgow Coma Scale (GCS), mortality rates at 120- and 180-days, duration of hospital/ICU stay, and laboratory results. All factors will be evaluated before and after interventions.

Result: This article presents the protocol for an ongoing randomized controlled trial; therefore, no results are available yet.

Discussion: If this study's results indicate that curcumin supplementation effectively improves the outcomes of ICU patients with traumatic injuries, it could offer a cost-effective and readily available treatment to improve patient outcomes and reduce the burden of traumatic injuries on healthcare systems.

Trial Registration: IRCT20130829014521N21 (https://www.irct.ir/); Registration date: 23.04. 2023

Keywords: curcumin; trauma; ICU; mortality; inflammation; phytomedicine

1. Introduction

Trauma is defined as any mechanical injury to the body resulting from an external force. Trauma is the leading cause of death in the working population and the eighth leading cause of death across all age groups worldwide. It is also a major contributor to disability-adjusted life years (DALYs) (1). Traumatic injuries frequently necessitate patient admission to the Intensive Care Unit (ICU), and individuals are at an elevated risk for adverse clinical outcomes and increased mortality rates (2-6). The in-hospital mortality rate among trauma patients admitted to the ICU is linked to severe Traumatic Brain Injury (TBI) and the occurrence of Multiple Organ Failure (MOF) (7). Prior studies have indicated that multi-organ failure arises from an uncontrolled and progressive response to critical injury or stress, leading to a general inflammatory state. This inflammatory response triggers the synthesis or release of various mediators, including complement proteins, coagulation factors, fibrinolytic agents, and kinins. The inflammatory cascades are characterized by four principal events: vasodilation, increased microvascular permeability, cellular adhesion, and activation of the coagulation cascade (8). Vasodilatation and increased microvascular permeability contribute to tissue swelling, edema, and increased local oxygen and nutrient supply. The process of cellular adhesion and coagulation activation involves a range of molecules and cells, including Interleukins (IL), Tumor Necrosis Factor (TNF-α), monocytes/macrophages, Polymorphonuclear Leukocytes (PMNs), and endothelial cells (9). Recent research has demonstrated that curcumin is a highly versatile compound that targets various molecular pathways. Curcumin is a compound found in the rhizomes of Curcuma longa L. (turmeric), a member of the Zingiberaceae family. It has been recognized as safe by the U.S. Food and Drug Administration as "Generally Recognized as Safe" (GRAS) (10) and possesses various pharmacological actions (11). Numerous clinical trials and meta-analyses have clearly shown the significant potential of curcumin in modulating inflammatory factors such as C-Reactive Protein (CRP), Total Anti-Oxidant Capacity (TAC), Malondialdehyde (MDA), and interleukin 6 (IL-6) (12, 13). Studies have demonstrated that curcumin can reduce inflammation, oxidative stress, and tissue damage in traumatic injury models (14, 15). This effect is attributed to curcumin's ability to regulate specific molecular targets, such as pro-inflammatory cytokines and transcription factors. Additionally, previous research has shown that curcumin inhibits the activation of Nuclear Factor Kappa B (NF- κB) induced by Lipopolysaccharides (LPS) (9).

Despite advances in critical care management, elevated levels of inflammation and oxidative stress in ICU patients are associated with poor treatment outcomes, increased disability, and a high rate of mortality. Numerous studies have confirmed the beneficial anti-inflammatory and antioxidative effects of curcumin in various diseases; however, there is a lack of clinical evidence on the effectiveness of curcumin supplementation in improving outcomes for ICU patients with traumatic injuries. Therefore, this study protocol outlines a randomized, triple-blind placebo-controlled clinical trial designed to investigate the impact of curcumin supplementation on the mortality rate and clinical status of traumatic ICU patients.

2. Materials and Methods

2.1. Study design

This is a parallel, three-group, placebo-controlled randomized trial. The study will involve a total of 327 trauma patients admitted to the Intensive Care Units (ICUs) of Bahonar Hospital (the main trauma

center hospital) affiliated with Kerman University of Medical Sciences in Kerman, Iran. This study is a Phase II Randomized Controlled Trial (RCT), and the protocol was indexed in the Iranian Registry of Clinical Trials (IRCT) on 23rd April, 2023 (IRCT20130829014521N21). The flow diagram of the study design is presented in Figure 1.

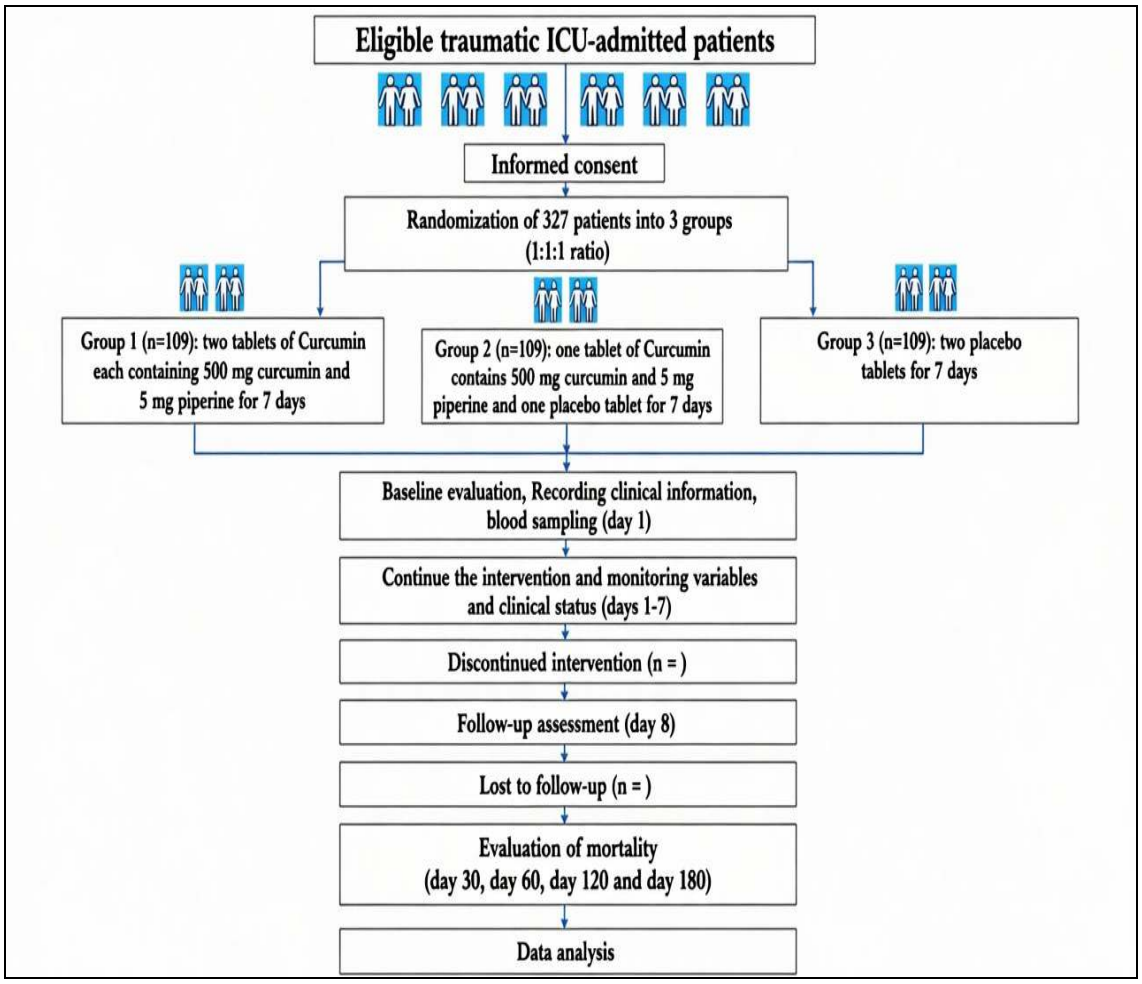

Figure 1: Flow diagram of the study design

2.2. Inclusion and Exclusion Criteria

Participants will be included if they are at least 12 years old and have been admitted to the ICU due to trauma. Trauma, as an inclusion criterion, refers to any injury to the body resulting from blunt or penetrating forces. Both single and multi-organ traumas will be included. Additionally, patients must have oral or enteral feeding (nasogastric or orogastric tube). All eligible patients will be recruited if they or their legal guardians provide informed consent, and pediatric participants (12–17 years) provide assent, after a comprehensive explanation of the study's objectives and procedures.

Pregnant or lactating individuals, as well as patients experiencing severe and active bleeding, as judged by the attending physician, those with a history of obstructive liver or biliary disorders, and individuals with an allergy to turmeric, will not be eligible to participate in the trial. Additionally, we will exclude patients who

have been re-hospitalized or those referred from other hospitals or intensive care units (ICUs). If patients or their legal guardians are unwilling to cooperate, they will also be excluded from the study.

2.3. Randomization and blinding

After verifying the inclusion and exclusion criteria, patients will be randomly assigned to three groups in a 1:1:1 allocation ratio. We will use randomly varying block sizes to randomize the participants. The block randomization method will be implemented using the tool available at www.sealedenvelope.com to generate the A/B/C codes. The randomized list will be prepared by a researcher who is not directly involved in the sampling process. There will be 327 small ziplock bags, each similar in shape and numbered from 1 to 327. Neither the patients nor the physicians or nurses will be able to distinguish among the tablets, other than by the numbers on the ziplock bags. As each new eligible patient is enrolled, the researcher will take the corresponding ziplock bag number, and the participants will follow the specified intervention. After all data collection is complete and the data are entered into SPSS, the numbers 1 to 327 will be converted to codes A/B/C, and a blinded analyst will analyze the data. Patients, physicians, researchers, nurses, laboratory staff, outcome assessors, and the analyst will all remain blinded to the allocated codes. The allocation key linking the treatment groups to the A/B/C codes will only be unblinded after completion of the final data analysis.

2.4. Intervention and assessment

The patients will be randomly assigned to two intervention groups and one control group as follows: group 1 (n=109) will receive two tablets of Curcumin, each containing 500 mg of curcumin and 5 mg of piperine; group 2 (n=109) will receive one Curcumin tablet containing 500 mg of curcumin and 5 mg of piperine, along with one placebo tablet; group 3 (n=109) will receive two placebo tablets containing microcrystalline cellulose. Sami-Sabinsa Group Limited, India, will manufacture curcumin and placebo tablets. All patients will take their tablets once a day for 7 days. The placebo tablets are identical in every respect to the tablets in the intervention groups, including shape, size, taste, odor, and color, to ensure the blind condition, and are produced by the same factory.

The patient will be assessed for demographic, clinical, and laboratory parameters at the beginning of the study (day 1) and at the conclusion of the intervention (day 8). If a patient is discharged from the ICU before the eighth day, the follow-up assessment will be conducted prior to discharge. Additionally, patient survival will be monitored on the 30th, 60th, 120th, and 180th days following enrollment. A summary of the intervention schedule and assessments is presented in Figure 2 according to the SPIRIT (Standard Protocol Items: Recommendations for Clinical Interventional Trials) guideline. All patients will receive their standard treatment as prescribed by their physicians, without any modifications. The patients will be examined daily for changes in the severity of their underlying conditions and for the presence of any adverse effects.

Safety will be assessed daily by the attending research team. All adverse events will be recorded and reported in accordance with the International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) guidelines.

	TRIAL PERIOD													
	Enrollment		Post-randomization							Follow-up				
TIMEPOINT	$-t_1$ to 0	0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 30	Day 60	Day 120	Day 180
	ENROLLMENT													
Eligibility screen (inclusion/exclusion criteria)	X													
Informed consent	X													
Randomization		X												
Demographic data and baseline assessment		X												
	INTERVENTION/ COMPARATOR:													
Curcumin			X	X	X	X	X	X	X					
Placebo			X	X	X	X	X	X	X					
	ASSESSMENTS													
Monitoring patients and recording clinical information			X	X	X	X	X	X	X	X				
APACHE II /SOFA/ mNUTRIC scores			X							X				
GCS			X	X	X	X	X	X	X	X				
Inflammatory factor (Quantitative CRP)			X							X				
ALT, AST, Bilirubin			X							X				
CBC, Na, K, BUN, Cr, BS, CPK			X							X				
30-day mortality											X			
60-day mortality												X		
120-day mortality													X	
180-day mortality														X

Figure 2: Schedule of enrollment, interventions, and outcome assessments timepoints along the study period

2.5. Outcomes

The primary outcomes of the current trial are ICU (8-day) mortality during the intervention and 30- and 60-day mortality.

The analysis will be per-protocol, and adjustments will be made for variables that show significant differences between study groups at baseline ($p < 0.25$).

For the secondary outcomes, we will assess the following items before and after

the intervention (on Day 8): Acute Physiology and Chronic Health Evaluation (APACHE II), Sequential Organ Failure Assessment (SOFA), Modified Nutrition Risk in Critically Ill (mNUTRIC), Glasgow Coma Scale (GCS) score. Additionally, 120-day and 180-day mortality, mechanical ventilation duration, and lengths of hospital and ICU stay were recorded. Readmission to hospital and secondary complications related to trauma, hospitalization, and ICU stay were documented at 180-day mortality follow-up.

Additionally, laboratory findings will be assessed, including quantitative C-Reactive Protein (CRP), complete blood count (CBC), aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, electrolyte assessments (Na and K), blood sugar (BS), Blood urea nitrogen (BUN), Creatinine, and creatine phosphokinase (CPK) using routine commercial kits.

Vital signs (blood pressure, pulse rate, respiratory rate, and temperature) and GCS were recorded daily in the first week.

The Glasgow Coma Scale (GCS) is used to assess level of consciousness based on three components: eye opening, motor responses, and verbal responses. The GCS score ranges from 3 to 15 (16, 17).

Acute Physiology and Chronic Health Evaluation II (APACHE II) is a tool used to assess disease severity in critically ill patients (18). APACHE II is based on three main factors: acute physiological status, age, and chronic health conditions. The final score ranges from 0 to 71, with higher scores indicating a more severe condition (19, 20).

Sequential Organ Failure Assessment (SOFA) is a scoring system that evaluates the number and severity of dysfunction in six organ systems, with each system scored on a scale from 0 to 4. A score of 0 indicates normal function, while a score of 4 represents the most severe dysfunction (21, 22).

The modified nutrition risk in critically ill (mNUTRIC) score is an effective tool for assessing mortality risk and evaluating nutritional status in critically ill patients. In this modified version of the NUTRIC score, interleukin-6 (IL-6) is excluded. Only the following four criteria are utilized: APACHE II score, SOFA score, number of comorbidities, age, and the number of days from hospitalization to ICU admission. The mNUTRIC score ranges from 0 to 9 (23, 24).

2.6. Sample size calculation

According to a primary review of the medical records from Bahonar Hospital, the main trauma center in Kerman, Iran, the in-hospital mortality rate for trauma patients admitted to the ICU during six months in 2022 was approximately 20%. Given the researcher's estimated 15% decrease in mortality, the sample size calculation was conducted using PASS11 software with $\alpha = 0.05$ and $\beta = 0.2$. Given the dropout rate, the final sample size was calculated to be 109 patients per group, yielding a total of 327.

2.7. Statistical Analysis

The normality of the quantitative variables will be assessed using the Kolmogorov-Smirnov test. All variables will be reported as mean ± standard deviation or as frequency (percentage). Depending on the data distribution, either ANOVA or the Kruskal-Wallis test will be used to compare the variables across the three study groups. For within-group analysis, a paired t-test or a Wilcoxon signed-rank test will be used. Moreover, survival analysis will be conducted using the Log-Rank test or a Cox regression model, and adjustment will be made for variables that show significant differences between study groups at baseline ($p < 0.25$). Statistical analysis will be conducted using SPSS software.

2.8. Ethics Approval

This trial has been approved by the Research Ethics Committees of Mashhad University of Medical Sciences (IR.MUMS.REC.1401.403). Additionally, it is registered in the Iranian Registry of Clinical Trials (IRCT) under the code IRCT20130829014521N21 as of 23rd April 2023. The recruitment process began in Spring 2023, and we anticipate completing it by Spring 2025.

3. Discussion

Multiple trauma and stress can lead to a systemic inflammatory response that is most pronounced during the first week after trauma, characterized by marked elevations in pro-inflammatory mediators and an increased risk of systemic inflammatory response syndrome and multiple organ dysfunction, making this period a critical therapeutic window (25). This inflammatory response involves the activation of inflammatory cascades, cytokine release, and endothelial cell dysfunction (26). As a result, several organ functions deteriorate, including lung, liver, intestine, and kidney failure. Currently, multi-organ failure is the leading cause of morbidity and mortality among ICU patients. Hypermetabolism and negative nitrogen balance are the primary factors contributing to disease progression during multi-organ failure (9). (figure3)

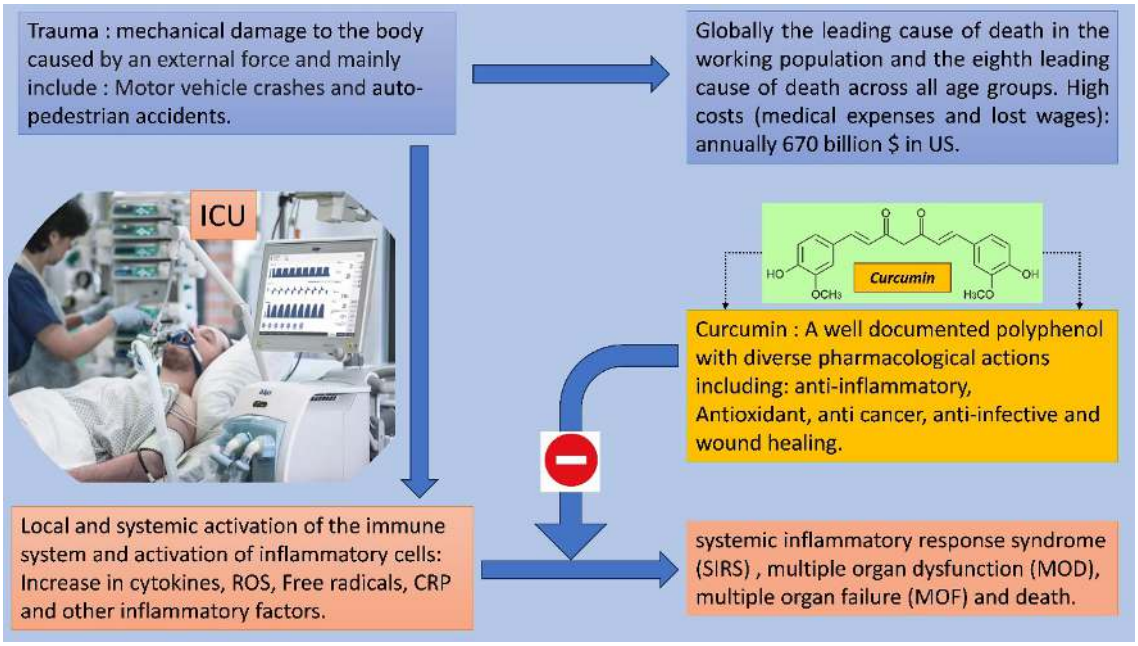

Figure 3. Proposed pathophysiological rationale for curcumin supplementation in traumatic ICU patients. Traumatic injury induces inflammatory cascades and oxidative stress, contributing to multi-organ dysfunction and poor clinical outcomes. In contrast, curcumin may mitigate these processes through its anti-inflammatory and antioxidant effects (1, 3-6, 27-29).

Curcumin, a natural polyphenol responsible for turmeric's yellow color, has been shown in previous studies to possess anti-inflammatory properties across various disease models. Research indicates that curcumin can inhibit IL-1 and TNF-α production in human monocytic macrophages and LPS-induced NF-κB activation (30), consistent with its putative anti-inflammatory actions (31, 32). Furthermore, curcumin may alleviate sepsis and septic shock by reducing oxidative

stress, cytokine production, and PMN infiltration, while also attenuating multiple organ dysfunction syndrome (MODS) caused by endotoxemia (33, 34). Other studies suggest that curcumin can suppress the Toll-like receptor 4 (TLR4)-mediated NF-κB signaling pathway and inhibit NF-κB activation via IκB kinase and AKT, thereby suppressing NF-κB-dependent gene expression (35). One potential limitation for the clinical efficacy of curcumin is its low oral bioavailability, even when co-administered with piperine, leading to the development of various pharmaceutical preparations to tackle this issue (36, 37). This issue may be particularly relevant in critically ill patients with traumatic injuries, who frequently experience gut dysmotility, reduced splanchnic perfusion, or malabsorption. Although piperine has been shown to enhance curcumin bioavailability by inhibiting intestinal and hepatic metabolism, its effectiveness in ICU settings remains uncertain. In this study, curcumin is co-administered with piperine, which is a pepper-derived alkaloid (inhibitor of UDP-glucuronosyltransferase and CYP3A4, and a P-glycoprotein blocker) shown to limit intestinal and hepatic metabolism of curcumin, thereby enhancing its bioavailability (38-40). Previous clinical trials have demonstrated the efficacy and safety of a formulation containing curcuminoids plus piperine in a variety of conditions (41).

Mirjalili et al. administered 500 mg/day of phytosomal curcumin for 7 days in 53 ICU patients with multiple traumas. They reported improvements in several clinical and inflammatory parameters (42). Similarly, Zahedi et al. evaluated 500 mg/day of curcuminoids administered enterally for 7 consecutive days in 62 critically ill patients with traumatic brain injury and observed beneficial effects on inflammatory biomarkers, clinical outcomes, and nutritional status (43)

In addition to curcumin, several nutraceuticals have been evaluated as adjunctive therapies for critically ill patients. Omega-3 fatty acids have demonstrated immunomodulatory and anti-inflammatory properties by reducing pro-inflammatory cytokine production and promoting the resolution of inflammation (44). Vitamin C has also been investigated because of its antioxidant effects and its role in maintaining endothelial integrity and attenuating oxidative stress (45). Likewise, selenium, an essential trace element involved in antioxidant defense, has been associated with reduced oxidative injury and improved clinical outcomes in selected critically ill and trauma populations (46, 47). Nevertheless, despite encouraging biological effects, current evidence suggests that the clinical benefits of these nutraceuticals remain inconsistent across studies, emphasizing the need for adequately powered randomized clinical trials to identify the patients most likely to benefit from these interventions. Curcumin appears to share several of these anti-inflammatory and antioxidant mechanisms. However, its efficacy in critically ill trauma patients requires further confirmation in large studies.

This study has limitations deserving acknowledgment. While the pragmatic design reflects the real-world population of ICU-admitted patients with trauma and increased external validity, the heterogeneous trauma population may influence treatment responses. In addition, the concurrent use of multiple standard ICU therapies makes it difficult to isolate the specific effects of curcumin supplementation. Furthermore, the limited oral bioavailability of curcumin, despite co-administration with piperine, may have affected its therapeutic efficacy. Despite these limitations, this study has several strengths. It is randomized, triple-blind, placebo-controlled, and has a large sample

size, which enhances the validity of the findings. In addition, assessing both clinical outcomes and inflammatory biomarkers provides a comprehensive evaluation of curcumin supplementation. Furthermore, this study focuses on critically ill trauma patients, a population for which evidence regarding the efficacy of curcumin supplementation remains limited.

If the results of this study demonstrate the effectiveness of curcumin plus piperine supplementation in improving outcomes for patients with traumatic injuries admitted to the ICU, it could represent a promising adjunctive therapeutic strategy to enhance patient outcomes and reduce the burden of traumatic injuries on healthcare systems.

Acknowledgment: The authors would like to thank Sami-Sabinsa Group Limited for manufacturing curcuminoid and placebo tablets.

Competing interests: None

Funding: This study was financially supported by The Mashhad Universdity of Medical Sciences Research Council.

Consent for publication: NA

Availability of data and material: NA

Ethics approval and consent to participate: This trial has been approved by the Research Ethics Committees of Mashhad University of Medical Sciences (IR.MUMS.REC.1401.403). Additionally, it is registered in the Iranian Registry of Clinical Trials (IRCT) under the code IRCT20130829014521N21 as of 23rd April 2023. This research adhered to the ethical principles outlined in the Declaration of Helsinki for studies involving human subjects

Authors' contributions: Conceptualization: NAG, AS; Investigation: NAG, ME, TJ, MS, AS; Writing-original draft: NAG, ME, TJ; Writing-review & editing: MS, AS

References

1. Halvachizadeh S, Mariani D, Pfeifer R. Impact of trauma on society: S. Halvachizadeh et al. European Journal of Trauma and Emergency Surgery. 2025;51(1):155. https://doi.org/10.1007/s00068-025-02824-8
2. Ulvik A, Wentzel-Larsen T, Flaatten H. Trauma patients in the intensive care unit: short-and long-term survival and predictors of 30-day mortality. Acta anaesthesiologica scandinavica. 2007;51(2):171-7. https://doi.org/10.1111/j.1399-6576.2006.01207.x
3. Van Breugel JM, Niemeyer MJ, Houwert RM, Groenwold RH, Leenen LP, Van Wessem KJ. Global changes in mortality rates in polytrauma patients admitted to the ICU-a systematic review. World Journal of Emergency Surgery. 2020;15:1-13. https://doi.org/10.1186/s13017-020-00330-3
4. Alberdi F, García I, Atutxa L, Zabarte M. Epidemiology of severe trauma. Medicina Intensiva (English Edition). 2014;38(9):580-8. https://doi.org/10.1016/j.medine.2014.06.002
5. Khorgami Z, Fleischer WJ, Chen Y-JA, Mushtaq N, Charles MS, Howard CA. Ten-year trends in traumatic injury mechanisms and outcomes: a trauma registry analysis. The American Journal of Surgery. 2018;215(4):727-34. https://doi.org/10.1016/j.amjsurg.2018.01.008
6. Peitzman AB, Fabian TC, Rhodes M, Yealy DM, Schwab CW. The trauma manual: trauma and acute care surgery: Lippincott Williams & Wilkins; 2012.
7. Papadimitriou-Olivgeris M, Panteli E, Koutsileou K, Boulovana M, Zotou A, Marangos M, et al. Predictors of mortality of trauma patients admitted to the ICU: a retrospective observational study. Brazilian Journal of Anesthesiology. 2021;71:23-30. https://doi.org/10.1016/j.bjane.2020.12.006
8. Marshall JC. SIRS and MODS: what is their relevance to the science and practice of intensive care? Shock. 2000;14(6):586-9. https://doi.org/10.1097/00024382-200014060-00002

9. Liu S, Zhang J, Pang Q, Song S, Miao R, Chen W, et al. The protective role of curcumin in zymosan-induced multiple organ dysfunction syndrome in mice. Shock (Augusta, Ga). 2016;45(2):209. https://doi.org/10.1097/SHK.0000000000000502
10. Hewlings SJ, Kalman DS. Curcumin: A review of its effects on human health. Foods. 2017;6(10):92. https://doi.org/10.3390/foods6100092
11. Fu YS, Chen TH, Weng L, Huang L, Lai D, Weng CF. Pharmacological properties and underlying mechanisms of curcumin and prospects in medicinal potential. Biomed Pharmacother. 2021;141:111888. https://doi.org/10.1016/j.biopha.2021.111888
12. Jakubczyk K, Drużga A, Katarzyna J, Skonieczna-Żydecka K. Antioxidant potential of curcumin-A meta-analysis of randomized clinical trials. Antioxidants. 2020;9(11):1092. https://doi.org/10.3390/antiox9111092
13. Tabrizi R, Vakili S, Akbari M, Mirhosseini N, Lankarani KB, Rahimi M, et al. The effects of curcumin-containing supplements on biomarkers of inflammation and oxidative stress: A systematic review and meta-analysis of randomized controlled trials. Phytotherapy Research. 2019;33(2):253-62. https://doi.org/10.1002/ptr.6226
14. Wang P, Liu Q. Effects of Curcumin Nanoparticles Combined with Dexmedetomidine on Cartilage Damage in Traumatic Arthritis Rats. Journal of Biomedical Nanotechnology. 2023;19(6):990-6. https://doi.org/10.1166/jbn.2023.3611
15. Peng Y, Ao M, Dong B, Jiang Y, Yu L, Chen Z, et al. Anti-inflammatory effects of curcumin in the inflammatory diseases: Status, limitations and countermeasures. Drug design, development and therapy. 2021:4503-25. https://doi.org/10.2147/DDDT.S327378
16. Jain S, Iverson LM. Glasgow Coma Scale: StatPearls; 2023.
17. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet (London, England). 1974;2(7872):81-4. https://doi.org/10.1016/S0140-6736(74)91639-0
18. Bahtouee M, Eghbali SS, Maleki N, Rastgou V, Motamed N. Use of the APACHE II Score for the Assessment of Outcome and Mortality Prediction in an Iranian Medical-Surgical Intensive Care Unit. Archives of Anesthesiology and Critical Care. 2018;4(4):521-6.
19. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Critical care medicine. 1985;13(10):818-29. https://doi.org/10.1097/00003246-198510000-00009
20. Mumtaz H, Ejaz MK, Tayyab M, Vohra LI, Sapkota S, Hasan M, et al. APACHE scoring as an indicator of mortality rate in ICU patients: a cohort study. Annals of medicine and surgery (2012). 2023;85(3):416-21. https://doi.org/10.1097/MS9.0000000000000264
21. Jones AE, Trzeciak S, Kline JA. The Sequential Organ Failure Assessment score for predicting outcome in patients with severe sepsis and evidence of hypoperfusion at the time of emergency department presentation. Critical care medicine. 2009;37(5):1649-54. https://doi.org/10.1097/CCM.0b013e31819def97
22. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive care medicine. 1996;22(7):707-10. https://doi.org/10.1007/BF01709751
23. Rahman A, Hasan RM, Agarwala R, Martin C, Day AG, Heyland DK. Identifying critically-ill patients who will benefit most from nutritional therapy: Further validation of the "modified NUTRIC" nutritional risk assessment tool. Clinical nutrition (Edinburgh, Scotland). 2016;35(1):158-62. https://doi.org/10.1016/j.clnu.2015.01.015
24. Wang N, Wang MP, Jiang L, Du B, Zhu B, Xi XM. Association between the modified Nutrition Risk in Critically Ill (mNUTRIC) score and clinical outcomes in the intensive care unit: a secondary analysis of a large prospective observational study. BMC Anesthesiology. 2021;21(1):220. https://doi.org/10.1186/s12871-021-01439-x
25. Guisasola MC, Alonso B, Bravo B, Vaquero J, Chana F. An overview of cytokines and heat shock response in polytraumatized patients. Cell stress and chaperones. 2018;23(4):483-9. https://doi.org/10.1007/s12192-017-0859-9
26. Remick DG. Pathophysiology of sepsis. The American journal of pathology. 2007;170(5):1435-44. https://doi.org/10.2353/ajpath.2007.060872
27. Valparaiso AP, Vicente DA, Bograd BA, Elster EA, Davis TA. Modeling acute traumatic injury. Journal of surgical research. 2015;194(1):220-32. https://doi.org/10.1016/j.jss.2014.10.025
28. Gülcher SS, Bruins NA, Kingma WP, Boerma EC. Elevated C-reactive protein levels at ICU discharge

as a predictor of ICU outcome: a retrospective cohort study. Annals of intensive care. 2016;6:1-8. https://doi.org/10.1186/s13613-016-0105-0

29. Lobo SM, Lobo FR, Bota DP, Lopes-Ferreira F, Soliman HM, Meélot C, et al. C-reactive protein levels correlate with mortality and organ failure in critically ill patients. Chest. 2003;123(6):2043-9. https://doi.org/10.1378/chest.123.6.2043
30. Sun S-C. The non-canonical NF-κB pathway in immunity and inflammation. Nature Reviews Immunology. 2017;17(9):545-58. https://doi.org/10.1038/nri.2017.52
31. Peng Y, Ao M, Dong B, Jiang Y, Yu L, Chen Z, et al. Anti-Inflammatory Effects of Curcumin in the Inflammatory Diseases: Status, Limitations and Countermeasures. Drug Des Devel Ther. 2021;15:4503-25. https://doi.org/10.2147/DDDT.S327378
32. Sadeghi M, Dehnavi S, Asadirad A, Xu S, Majeed M, Jamialahmadi T, et al. Curcumin and chemokines: mechanism of action and therapeutic potential in inflammatory diseases. Inflammopharmacology. 2023;31(3):1069-93. https://doi.org/10.1007/s10787-023-01136-w
33. Li R, Fang H, Shen J, Jin Y, Zhao Y, Wang R, et al. Curcumin alleviates LPS-induced oxidative stress, inflammation and apoptosis in bovine mammary epithelial cells via the NFE2L2 signaling pathway. Toxins. 2021;13(3):208. https://doi.org/10.3390/toxins13030208
34. Memis D, Hekimoglu S, Sezer A, Altaner S, Sut N, Usta U. Curcumin attenuates the organ dysfunction caused by endotoxemia in the rat. Nutrition. 2008;24(11-12):1133-8. https://doi.org/10.1016/j.nut.2008.06.008
35. Olivera A, Moore TW, Hu F, Brown AP, Sun A, Liotta DC, et al. Inhibition of the NF-κB signaling pathway by the curcumin analog, 3, 5-Bis (2-pyridinylmethylidene)-4-piperidone (EF31): Anti-inflammatory and anti-cancer properties. International Immunopharmacology. 2012;12(2):368-77. https://doi.org/10.1016/j.intimp.2011.12.009
36. Hegde M, Girisa S, BharathwajChetty B, Vishwa R, Kunnumakkara AB. Curcumin Formulations for Better Bioavailability: What We Learned from Clinical Trials Thus Far? ACS Omega. 2023;8(12):10713-46. https://doi.org/10.1021/acsomega.2c07326
37. Ma Z, Wang N, He H, Tang X. Pharmaceutical strategies of improving oral systemic bioavailability of curcumin for clinical application. J Control Release. 2019;316:359-80. https://doi.org/10.1016/j.jconrel.2019.10.053
38. Suresh D, Srinivasan K. Tissue distribution & elimination of capsaicin, piperine & curcumin following oral intake in rats. Indian J Med Res. 2010;131:682-91.
39. Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PS. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. Planta Med. 1998;64(4):353-6. https://doi.org/10.1055/s-2006-957450
40. Tabanelli R, Brogi S, Calderone V. Improving curcumin bioavailability: current strategies and future perspectives. Pharmaceutics. 2021;13(10):1715. https://doi.org/10.3390/pharmaceutics13101715
41. Heidari H, Bagherniya M, Majeed M, Sathyapalan T, Jamialahmadi T, Sahebkar A. Curcumin-piperine co-supplementation and human health: A comprehensive review of preclinical and clinical studies. Phytotherapy Research. 2023;37(4):1462-87. https://doi.org/10.1002/ptr.7737
42. Mirjalili M, Sahebkar A, Hassanizadeh S, Kiani Z, Soleimani D, Amini S, et al. The effectiveness of phytosomal curcumin on clinical and laboratory parameters of patients with multiple trauma admitted to the intensive care unit: a double-blind randomized placebo-controlled trial. BMC Complementary Medicine and Therapies. 2024;24(1):335. https://doi.org/10.1186/s12906-024-04639-3
43. Zahedi H, Hosseinzadeh-Attar MJ, Shadnoush M, Sahebkar A, Barkhidarian B, Sadeghi O, et al. Effects of curcuminoids on inflammatory and oxidative stress biomarkers and clinical outcomes in critically ill patients: A randomized double-blind placebo-controlled trial. Phytotherapy Research. 2021;35(8):4605-15. https://doi.org/10.1002/ptr.7179
44. Calder PC. Omega-3 fatty acids and inflammatory processes: from molecules to man. Biochemical Society Transactions. 2017;45(5):1105-15. https://doi.org/10.1042/BST20160474
45. Yong S, Suping L, Peng Z, Dong L, Qing W. The effects of vitamin C supplementation in the critically ill patients outcomes: A systematic review and meta-analysis of randomized controlled trials. Medicine. 2024;103(12):e37420. https://doi.org/10.1097/MD.0000000000037420

46. Huang J, Hsu C, Ouyang C, Cheng C, Wang C, Liao C, et al. The Impact of Selenium Supplementation on Trauma Patients-Systematic Review and Meta-Analysis. Nutrients 2022, 14, 342. s Note: MDPI stays neutral with regard to jurisdictional claims in published …; 2022. https://doi.org/10.3390/nu14020342

47. Lu X, Wang Z, Chen L, Wei X, Ma Y, Tu Y. Efficacy and safety of selenium or vitamin E administration alone or in combination in ICU patients: A systematic review and meta-analysis. Clinical nutrition ESPEN. 2023;57:550-60. https://doi.org/10.1016/j.clnesp.2023.07.092