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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

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Abstract

Background Multiple trauma has serious complications, which increases the risk of morbidity and mortality in the patients. This study aimed to evaluate the impact of supplementation with phytosomal curcumin on clinical and laboratory factors in critically ill patients with multiple trauma.

Methods In this double-blind trial, 53 patients with multiple trauma, who were admitted to the intensive care unit (ICU) were randomized to receive either 2 capsules, each capsule containing 250 mg phytosomal (a total of 500 mg daily) as an intervention group or 2 identical capsules (placebo capsules), each containing 250 mg maltodextrin for 7 days. Clinical and laboratory were parameters assessed before and after the intervention.

Results After seven days of intervention, the mean increase from baseline in the Glasgow coma scale (GCS) score was significantly higher in the curcumin compared with the placebo group (*P*-value: 0.028), while the reduction in the APACHE-II score in the curcumin group was greater than that the placebo group in a marginally non-significant fashion (*P*-value: 0.055). Serum total bilirubin (*P*-value: 0.036) and quantitative C-reactive protein (CRP) (*P*-value: 0.044) levels significantly decreased while potassium (*P*-value: 0.01) significantly increased in the curcumin compared with the placebo group. Moreover, supplementation with phytosomal curcumin significantly increased platelet count (*P*-value: 0.024) as compared with placebo. The 28-day mortality rate was 7.7% (*n*: 2 patients) and 3.7% (*n*: 1 patients) in the placebo and curcumin groups, respectively (*P*-value > 0.05).

Conclusion Phytosomal curcumin had beneficial effects on several clinical and laboratory factors including GCS, APACHEII, serum total bilirubin, CRP, and platelet count in ICU-admitted patients with multiple trauma.

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Trial registration IRCT20090306001747N1, Available on: https://www.irct.ir/trial/52692. The first registration date was 12/01/2021.

Highlights

- Phytosomal curcumin had a considerable favorable effect on serum total bilirubin and quantitative C-reactive protein (CRP) levels in critically ill patients with multiple trauma.
- Phytosomal curcumin significantly increased potassium and platelet count in critically ill patients with multiple trauma.
- Phytosomal curcumin non-significantly reduced the 28-day mortality rate in critically ill patients with multiple trauma.

Keywords Curcumin, Inflammation, Critically ill patients, ICU, Phytomedicine, Trauma

Introduction

Polytrauma or multiple trauma involves traumatic injuries to multiple anatomical areas of the body at the same time. Traumatic brain injury (TBI) is typically present in polytrauma, which can result in disability or other life-threatening complications [1]. Primary brain injury or uncontrolled hemorrhage is the main reason for early death in polytraumatized patients. However, secondary brain damage or failure in the host's defense system causes late traumatic death [2]. As a result of traumatic stress, in addition to local changes in the area of injury, systemic changes also occur with acute or prolonged responses [2]. Stimulation of the immune system following traumatic injury triggers the release of hormonal mediators, proinflammatory cytokines, and acute phase reactants, which leads to a systemic inflammatory response. This response exacerbates the primary organ damage and increases the risk of infection, sepsis, and failure of remote organs [2, 3]. Multiple organ failure (MOF) and acute lung failure/acute respiratory distress syndrome (ALI/ARDS) are recognized as the main causes of late traumatic death [4]. Despite these serious complications which increase the risk of morbidity and mortality in patients with multiple trauma, management of the disease is associated with many complexities and there is an urgent need for new therapeutic modalities.

Curcumin is a lipophilic polyphenol derived from turmeric [5]. It has been proven that this natural compound possesses various salutary effects including anti-inflammatory, antioxidant, anti-tumor, and neuroprotective properties [6–15]. Owing to these pharmacological effects, curcumin has been the subject of increasing attention from researchers as a therapeutic agent to improve the clinical status of individuals with different diseases [15–17]. Some studies conducted on critically ill patients have shown that curcumin supplementation exerts favorable changes in patients' clinical and paraclinical indices [18–21].

An important point to consider for clinical utilization of curcumin is the relatively low stability, low aqueous solubility, and rapid metabolism and elimination of this phytochemical that lower its oral bioavailability, and arguably limit the putative therapeutic effects [9, 22, 23]. To enhance curcumin's bioavailability, various pharmaceutical methods like using adjuvants, solid dispersion, copolymeric micelles, complexes of curcumin with cyclodextrins, polymeric or lipid-based nanoparticles, and microemulsions have been evaluated [9, 22, 24]. In this regard, the phytosomal delivery system has been recommended as an efficient strategy to boost the bioavailability and pharmacological actions of curcumin [25]. Phytosomes have amphiphilic properties, which contribute to the dispersion of their cargo in hydrophilic and lipophilic environments due to the existence of phospholipids. Phytosomal curcumin is a solid dispersion preparation composed of curcumin and phospholipids such as phosphatidylcholine and phosphatidylserine [25]. Phosphatidylserine not only has efficient absorption in the body but also can cross the blood-brain barrier (BBB) [26].

The application of phytosomal curcumin in animal studies has been shown to increase systemic absorption and plasma concentration of curcumin [27, 28]. Many clinical studies have shown that phytosomal curcumin can be effective and safe in treating a wide range of diseases [25].

Based on the evidence presented earlier, patients with multiple trauma seem to benefit from phytosomal curcumin's positive effects. Hence, the current randomized controlled trial aimed to investigate the effectiveness of phytosomal curcumin supplementation in ICU-admitted patients with multiple trauma.

Methods

Study design and participants

This parallel randomized, double-blind, placebo-controlled clinical trial was conducted between November 2021 to September 2022 in Al-Zahra Hospital, an academic hospital, affiliated with Isfahan University of Medical Sciences, Isfahan Iran. This trial was approved by the ethics committee of Isfahan University of Medical Sciences (code: IR.MUI.MED.REC.1399.758). This

study was also registered in the Iranian Registry of Clinical Trials dependent on WHO (registration ID: IRCT20090306001747N1). The first registration date was 12/01/2021 and the last registration update was 17/01/2023. This trial was conducted by the principles of the Declaration of Helsinki. All patients or their legal guardians were asked to fill out the written informed consent before the study.

Critically ill patients with multiple trauma, who were admitted to the trauma ICU of Al-Zahra hospital, were included in this study. Inclusion and exclusion criteria are presented in Table 1.

Trial randomization and blinding

Patients who were eligible to take part in this study were randomized in a ratio of 1:1 to the intervention or the control group. Stratified randomization was used based on age, applying of a permuted block size of 4. An independent statistician using a random number table performed the assignment sequences and then kept them in envelopes, which were opaque, sealed, and numbered until the end of the evaluation of the eligibility criteria. Until the completion of data analyses, researchers and all patients were not aware of treatment assignments. In this double-blind study, before the studies began, the company (Indena SpA, Milan, Italy) put curcumin and placebo capsules in the same packages and labeled them as A and B. Curcumin was provided by Indena SpA, Milan, Italy. Curcumin and placebo capsules were prepared by the School of Pharmacy at the Isfahan University of Medical Sciences (Isfahan, Iran). The appearance of the capsules was identical, and their color, size, shape, and odor were similar. Researchers, nurses, physicians, patients, laboratory staff, outcome assessors, and data analyzers were unaware of the treatment assignment until the completion of data analyses.

Each curcumin capsule contained 250 mg of phytosomal curcumin (250 mg containing 20% curcuminoids and 20% phosphatidylserine) and each placebo capsule contained 250 mg maltodextrin. The intervention group received 2 daily capsules of curcumin containing a total of 500 mg of phytosomal curcumin and the control group received 2 daily placebo capsules of a total of 500 mg of maltodextrin per day.

Intervention

Trauma patients who had the inclusion criteria, after 24–48 h of admission to the ICU with hemodynamically stable status were included in this study. Patients received supplemental nutrition through enteral tube feeding with the goal of 25 kcal/kg/day energy and 1.3 g/kg/day protein with the same formula for all patients (hospital gavage). Bolus feeding method (7 times a day, every 3 h from 6:00 to 24:00) was used for nutritional support. Patients in the intervention group received 2 capsules, each capsule containing 250 mg phytosomal curcumin (250 mg containing 20% curcuminoid and 20% phosphatidylserine), at 9:00 and 21:00 along with enteral nutrition (a total of 500 mg daily). Patients in the control group received 2 identical capsules (placebo capsules), each containing 250 mg maltodextrin (a total of 500 mg daily) at the same time. The intervention duration was 7 days in both groups. Capsules were provided by Indena SpA, Milan, Italy. All patients in both groups received their standard treatment and common medications under the prescription of their physicians without any changes and our intervention was considered as an adjunct therapy. Patients were visited by a physician every day as a routine of their care and unfavorable effects were assessed and reported by the physician. The physician was asked to exclude patients if undesirable side effects, which seem to be related to the intervention, were observed.

Outcomes

A five-milliliter blood sample was collected before and after the study. After centrifugation of the samples for 10 min at room temperature, the serum was stored at -80 °C. Using enzymatic methods on auto-analyzer, complete blood count (CBC), potassium (K), calcium (Ca), sodium (Na), magnesium (Mg), alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood glucose (BG), albumin (ALB),

Table 1 Inclusion and exclusion criteria

Inclusion Criteria	Exclusion criteria
18 < Age < 70 Years	Impossibility of intestinal feeding in the first 24–48 h of admission
Gastrointestinal tract with normal function and intestinal nutrition criteria	The unwillingness of the patient or his legal guardian to participate in the project
Diagnosis of moderate or severe trauma based on GCS index (4–15)	Patients who are hospitalized in the intensive care unit for less than 24 h
Trauma diagnosis based on Injury Severity Score (ISS) between minor to severe	Pregnancy and lactation
	Severe septic shock or sepsis
	Any history of heart disease
	Intestinal inaccessibility
	Prognoses of death or moves from ICU to other hospital wards before 7 days
	Incomplete resuscitation and hemodynamic instability
	Patients who receive nutritional support through complete intravenous feeding
	Taking anticoagulants such as heparin, warfarin, aspirin, etc.

blood urea nitrogen (BUN), serum creatinine (Cr), international normalized ratio (INR), bilirubin total (BIL-T), bilirubin direct (BIL-D), lactate dehydrogenase (LDH), and creatine phosphokinase (CPK) were assessed.

All measurements were conducted in the laboratory of Al-Zahra Hospital as a routine assessment using standard kits. The severity of the disease was assessed by Acute Physiology and Chronic Health Evaluation II (APACHE II), Glasgow Coma Scale/Score (GCS), the sequential organ failure assessment (SOFA) score, and nutritional status was evaluated by Nutrition Risk in the Critically Ill (NUTRIC) Score. All outcomes were assessed at baseline and the 7th day after the intervention.

Statistical analysis

The SPSS software version 16 (SPSS Inc., Chicago, IL, USA) was applied to analyze data. The normality of the data was assessed by the Q-Q plot and Kolmogorov-Smirnov test. Independent samples *t*-test (for continuous variables), and chi-square or Fisher's exact test (for categorical variables) were applied to assess the baseline values. Paired samples t-test was used to assess the intergroup comparisons of pre-intervention and postintervention. Intragroup comparisons with considered baseline adjustment were carried out using analysis of covariance (ANCOVA). Data were reported as frequency (percentage) or mean ± standard deviation (SD). A *P*-value of less than 0.05 was considered to indicate statistical significance.

Results

Among the 161 patients, a total of 53 eligible patients with multiple trauma were randomly assigned to receive phytosomal curcumin (*n*: 27) or the matching placebo (*n*: 26). The CONSORT flowchart is illustrated in Fig. 1. Because the study was conducted in hospitalized patients, no dropout was observed in the study and all participants completed the study. The majority of patients were male (*n*: 43) and had no established diabetes mellitus (*n*:47), hypertension (*n*: 44), and ischemic heart disease (*n*: 48). Demographic characteristics of the participants are shown in Table 2. There was no significant difference between the two groups in the demographic data.

Table 3 shows the adjusted mean changes from baseline in patients' disease severity according to several ICU scoring systems. As shown, the baseline scores of APACHE II, NUTRIC, SOFA, and GCS did not differ significantly between the two groups (*P*-value > 0.05). After the intervention period, the mean APACHE II, NUTRIC, and SOFA scores were significantly decreased, while the mean GCS scores were significantly increased in the curcumin group (*P*-value < 0.05). On the other hand, the mean APACHE II and SOFA scores were significantly decreased, and the mean GCS scores were significantly increased in the placebo group (*P*-values > 0.05). After adjustment for baseline values, using the ANCOVA test, the mean change from baseline in the GCS score was significantly higher in the curcumin group than in the placebo group (2.47 ± 1.85 vs. 1.32 ± 1.85; *P*-value: 0.028). Furthermore, the reduction of APACHE II score in the curcumin group was marginally more than the placebo group (-5.24 ± 1.45 vs. -4.45 ± 1.45; *P*-value: 0.055). Table 4 shows the adjusted mean changes from baseline in biochemical parameters and arterial blood gas. Except for albumin concentrations which were significantly higher in the placebo group compared to the curcumin group (*P*-value:0.007), no significant difference was observed between the two groups in the baseline values of other biochemical parameters and arterial blood gas (*P*-value > 0.05). After the intervention period, a significant reduction in serum levels of blood glucose, AST, bilirubin, total (BIL-T), bilirubin, direct (BIL-D), LDH, CKP, and CRP and a significant increase in K, ALB, arterial pH, arterial pressure of CO_2 and HCO_3 were observed in the curcumin group (*P*-value < 0.05). In the placebo group, based on the pair T-test, there was a significant reduction from baseline in blood glucose, CKP, CRP, and arterial pressure of CO2 while a significant increase in ALP, BIL-T, BIL-D, LDH, pH, and arterial pressure of HCO3 was observed (*P*-value < 0.05). The adjusted mean changes of K, BIL-T, and CRP significantly differed between the two groups (*P*-value < 0.05). A significant reduction in serum BIL-T and CRP levels and a significant increase in serum K levels were observed in the curcumin group compared to the placebo group. Table 5 shows the adjusted mean changes from baseline in hematological parameters in both groups. As shown, subjects in the placebo group had higher red blood cell (RBC) count and hematocrit (Hct) levels at baseline compared to the curcumin group (*P*-value < 0.05). A significant reduction in white blood cell (WBC), red blood cell (RBC), hematocrit (HCT), and hemoglobin (Hb) values in the placebo group, and a significant reduction in neutrophils count in the curcumin group were observed at the end of the intervention period (*P*-value < 0.05). After the adjustment of baseline values, supplementation with phytosomal curcumin significantly increased platelet (PLT) (*P*-value: 0.024) count as compared with placebo. In addition, in the placebo group, the reduction in WBC count was higher than in the curcumin group (*P*-value: 0.048).

The 28-day mortality rate was 7.7% (*N*: 2 patients) and 3.7% (*N*: 1 patient) in the placebo and curcumin groups, respectively. The adjusted odds of survival with curcumin supplementation were 1.37 (0.35–53.74; *P*-value: 0.86) as compared with placebo. The mean hospital stay duration was 10.23 ± 3.83 days in the placebo group and 10.11 ± 4.17 days in the curcumin group (*P*-value: 0.914).

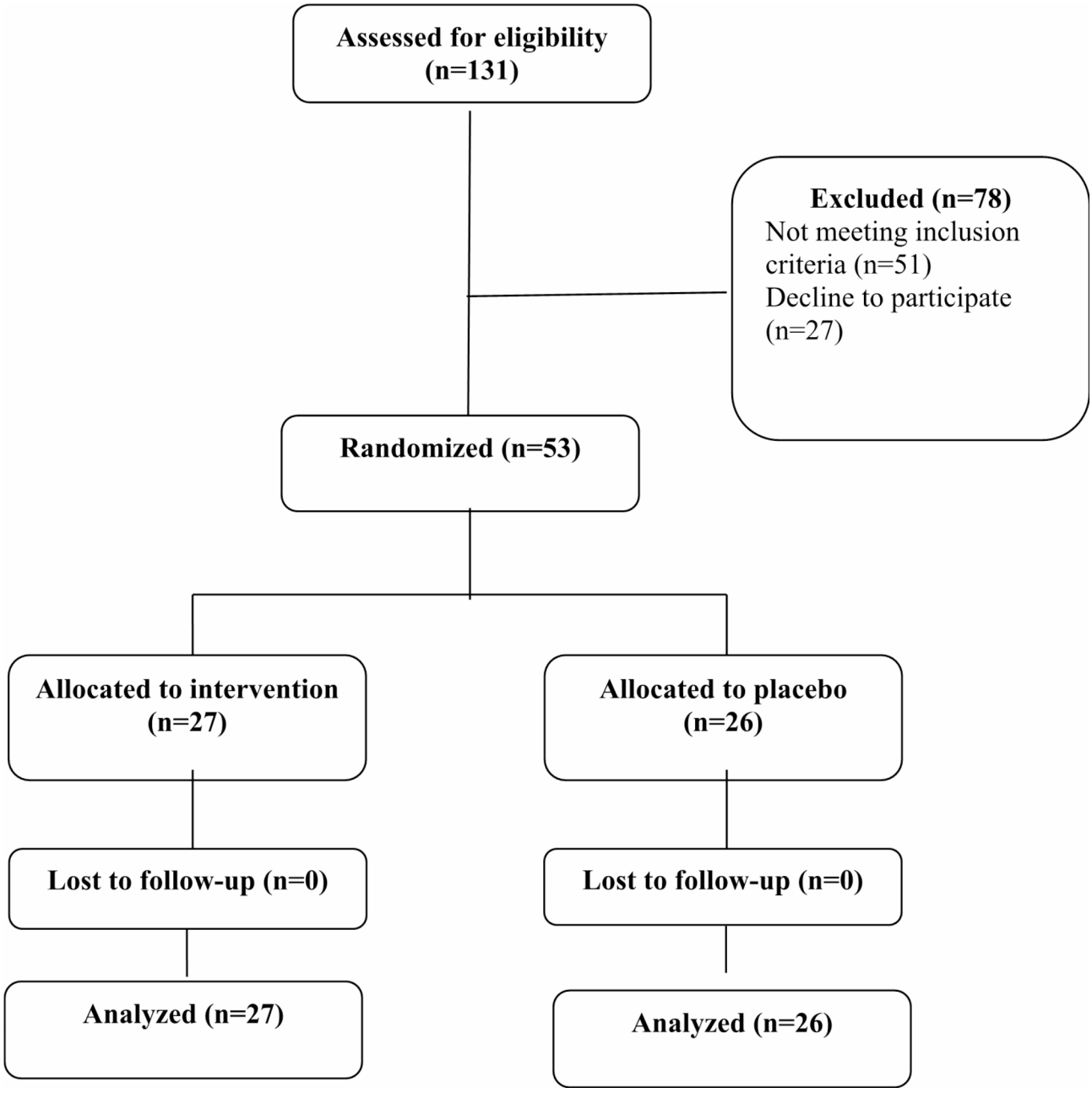

Fig. 1 Patient's flow diagram

Table 2 Demographic characteristics of participants in the curcumin and placebo groups

Variables	Total	Curcumin group (*N*:27)	Placebo group (*N*:26)	*P*-value*
Age, years	41.83 ± 16.41	43.92 ± 16.01	39.62 ± 16.86	0.34
Female, *n* (%)	10	3 (11.1%)	7 (26.9%)	0.17
Diabetes mellitus, *n* (%)	6	4 (14.8%)	2 (7.7%)	0.67
Hypertension, *n* (%)	9	4 (14.8%)	5 (19.2%)	0.73
Ischemic heart disease, *n* (%)	5	2 (7.4%)	3 (11.5%)	0.67
Cancer, *n* (%)	1	0	1 (3.8%)	0.49

Data are shown as means ± standard deviation or frequencies (percentage)

P-values were obtained from Fisher's exact test or independent sample T-test*

Table 3 Changes from baseline in the severity of disease in the curcumin and placebo groups

Variables	Group	Before intervention	After intervention	*P*-value**	Mean changes#
APACHE II	Curcumin (n:27)	7.11 ± 5.6	2.71 ± 1.43	0.001	-5.24 ± 1.45
	Placebo (n:26)	9.31 ± 7.63	4.00 ± 2.62	0.001	-4.45 ± 1.45
	P-value	0.237*	0.029*	-	0.055
NUTRIC	Curcumin (n:27)	2.29 ± 1.38	1.70 ± 0.61	0.018	-0.65 ± 1.178
	Placebo (n:26)	2.5 ± 1.86	2.00 ± 1.83	0.157	-0.44 ± 1.178
	P-value	0.65*	0.43*	-	0.52
SOFA	Curcumin (n:27)	3.44 ± 2.04	2.22 ± 1.45	0.003	-1.179 ± 1.305
	Placebo (n:26)	3.31 ± 2.62	2.26 ± 1.64	0.015	-1.083 ± 1.305
	P-value	0.83*	0.91*	-	0.78
GCS	Curcumin (n:27)	10.33 ± 4.12	12.88 ± 2.83	0.001	2.47 ± 1.85
	Placebo (n:26)	10.77 ± 4.86	12.00 ± 3.74	0.002	1.32 ± 1.85
	P-value	0.72*	0.34*	-	0.028

Abbreviations: APACHE II; Acute Physiology and Chronic Health Evaluation II, NUTRIC; Nutrition Risk in Critically ill, SOFA; Sequential Organ Failure Assessment, GCS; Glasgow Coma Scale

Data are shown as means ± standard deviation

*P-values were obtained from independent sample T-test, **paired-sample T-test, and #analysis of covariance (ANCOVA) with the adjustment for baseline values

Discussion

This study was the first randomized controlled trial examining a phytosomal formulation of curcumin in ICU-admitted patients with multiple trauma. Supplementation with 500 mg phytosomal curcumin for seven days significantly improved several biochemical and hematological parameters in the patients. In some parameters, both groups experienced improvements, which can be explained by the fact that both groups were affected by the beneficial effects of medical therapy and enteral nutrition. However, a statistically significant difference was observed in the GCS scores, potassium, BIL-T, CRP, WBC, and PLT levels between the intervention and control groups. We also observed that the intervention group had a marginally meaningful improvement in APACHE II compared with the placebo group at the end of the study. Considering that multiple trauma is associated with increased inflammatory factors, our finding has important implications for patients admitted to the ICU who have increased inflammatory markers. Based on the current findings, curcumin reduced APACHE II, NUTRIC, and SOFA, and increased GCS levels. This result is almost in line with the results of a previous randomized controlled trial in which 500 mg curcuminoids in combination with 5 mg piperine was administered for seven days to ICU-admitted patients with TBI. Several factors including NUTRIC and APACHE-II scores were reduced, while SOFA scores did not change significantly. In this study, proinflammatory cytokines such as TNF-α, MCP-1, CRP, and IL-6 were also reduced [29]. Karimi et al. discovered that administration of 160 mg nanocurcumin for 10 days reduced SOFA but not APACHE-II score [18]. Previous studies used different preparations of curcumin, which may explain why APACHE II and SOFA scores did not decrease simultaneously.

In this study, a solid dispersion preparation of curcumin in phosphatidylserine was used. Phosphatidylserine is highly absorbed in the gastrointestinal system and can cross the blood-brain barrier [30]. Therefore, this preparation of curcumin may exert its beneficial effects by enhancing neurological functions and the antioxidant status of the brain, such as increasing malondialdehyde levels [31]. The reduction in APACHE II and SOFA scores found in the present study could be interpreted as an indication of improved organ function through the reduction of organ dysfunction [32]. Another investigation demonstrated that the administration of curcumin alleviated the cognitive impairment of rats who had sustained a TBI [33]. The precise mechanisms behind the potential impact of curcumin supplementation on APACHE II, NUTRIC, SOFA, and GCS scores remain unclear due to limited research in this area. The underlying mechanisms may involve antioxidant and anti-inflammatory actions [34–39]. In this regard, Sabir et al. demonstrated that IL-10, which is an anti-inflammatory cytokine, correlates with GCS [40]. On the other hand, phytosomal curcumin has been shown to increase the production of interleukin-10 [41]. Furthermore, curcuminoids may positively influence APACHE II components [42].

Several studies have supported the positive effects of phytosomal curcumin on blood glucose. In a double-blind placebo-controlled clinical trial, 800 mg of phytosomal curcumin reduced fasting plasma glucose in overweight subjects [43]. The beneficial effects of phytosomal curcumin in diabetics have also been discussed in a review [25]. It has been demonstrated that curcumin can affect several pathways that are involved in insulin resistance and diabetes [25]. There is evidence suggesting that curcumin can protect against the decline of β-cell functions [44]. The antioxidant properties of curcumin

Table 4 Changes from baseline in biochemical parameters and arterial blood gas in the curcumin and placebo groups

Variables	Group	Before intervention	After intervention	*P*-value**	Mean changes#
BUN	Curcumin (n:27)	17.00 ± 10.63	16.37 ± 10.94	0.541	-0.472 ± 7.75
	Placebo (n:26)	14.92 ± 5.70	16.88 ± 10.10	0.312	1.79 ± 7.75
	P-value	0.38*	0.86*	-	0.29
Cr	Curcumin (n:27)	0.92 ± 0.51	0.92 ± 0.98	0.99	-0.026 ± 0.43
	Placebo (n:26)	1.01 ± 0.29	0.99 ± 0.51	0.791	-0.50 ± 0.43
	P-value	0.44*	0.76*	-	0.52
BG	Curcumin (n:27)	147.9 ± 55.3	122.6 ± 33.9	0.003	-28.92 ± 34.27
	Placebo (n:26)	160.0 ± 55.7	134.2 ± 44.7	0.007	-22.03 ± 34.27
	P-value	0.43*	0.31*	-	0.49
Na	Curcumin (n:27)	138.1 ± 2.6	138.5 ± 3.5	0.67	0.087 ± 4.05
	Placebo (n:26)	138.8 ± 2.77	138.8 ± 4.6	0.99	0.22 ± 4.05
	P-value	0.41*	0.77*	-	0.91
K	Curcumin (n:27)	3.95 ± 0.42	4.27 ± 0.31	0.007	0.33 ± 0.39
	Placebo (n:26)	3.92 ± 0.37	3.90 ± 0.45	0.81	-0.04 ± 0.39
	P-value	0.99*	0.65*	-	0.01
AST	Curcumin (n:27)	103.07 ± 189.0	70.50 ± 83.23	0.002	-30.17 ± 228
	Placebo (n:26)	93.03 ± 110.87	133.50 ± 320.87	0.15	37.14 ± 228
	P-value	0.81*	0.34*	-	0.29
ALT	Curcumin (n:27)	59.14 ± 54.54	59.76 ± 55.82	0.24	-8.82 ± 199.6
	Placebo (n:26)	94.42 ± 122.20	125.88 ± 277.57	0.29	41.41 ± 199.6
	P-value	0.18*	0.24*	-	0.37
ALP	Curcumin (n:27)	158.37 ± 51.06	140.07 ± 201.71	0.93	73.71 ± 175.40
	Placebo (n:26)	192.00 ± 95.26	223.66 ± 140.78	0.016	38.87 ± 175.40
	P-value	0.11*	0.74*	-	0.49
BIL-T	Curcumin (n:27)	1.18 ± 0.56	1.12 ± 0.59	0.001	-0.052 ± 0.29
	Placebo (n:26)	1.04 ± 0.37	1.17 ± 0.48	0.001	0.129 ± 0.29
	P-value	0.34*	0.73*	-	0.036
BIL-D	Curcumin (n:27)	0.36 ± 0.23	0.34 ± 0.20	0.001	-0.020 ± 0.11
	Placebo (n:26)	0.34 ± 0.19	0.35 ± 0.17	0.002	0.002 ± 0.11
	P-value	0.75*	0.86*	-	0.49
LDH	Curcumin (n:27)	1107.9 ± 1049.7	911.37 ± 504.4	0.001	-276.06 ± 1148
	Placebo (n:26)	998.00 ± 469.62	1040.3 ± 1714.9	0.011	20.15 ± 1148
	P-value	0.63*	0.71*	-	0.54
CKP	Curcumin (n:27)	4499 ± 14,246	1233 ± 3048	0.001	-2546 ± 876
	Placebo (n:26)	2650 ± 2845	1085 ± 1084	0.44	-2313 ± 876
	P-value	0.53*	0.82*	-	0.35
ALB	Curcumin (n:27)	3.25 ± 0.55	3.30 ± 0.96	0.05	-0.084 ± 0.605
	Placebo (n:26)	3.68 ± 0.54	3.33 ± 0.49	0.21	-0.213 ± 0.605
	P-value	0.007*	0.87*	-	0.46
pH	Curcumin	7.31 ± 0.06	7.38 ± 0.05	0.001	0.080 ± 0.076
	Placebo	7.30 ± 0.10	7.38 ± 0.09	0.002	0.079 ± 0.076
	P-value	0.93*	0.66*	-	0.97
CO_2	Curcumin	40.22 ± 6.19	42.40 ± 7.84	0.001	0.914 ± 7.65
	Placebo	43.4 ± 13.28	38.92 ± 7.61	0.001	-3.103 ± 7.65
	P-value	0.27*	0.11*	-	0.063
HCO_3	Curcumin	22.14 ± 4.79	25.25 ± 6.45	0.001	2.99 ± 6.36
	Placebo	22.57 ± 5.18	25.03 ± 6.94	0.001	2.58 ± 6.36
	P-value	0.75*	0.90*	-	0.812

Table 4 (continued)

Variables	Group	Before intervention	After intervention	*P*-value**	Mean changes#
CRP	Curcumin	127.93 ± 81.97	71.68 ± 52.08	0.001	-56.40 ± 46.55
	Placebo	135.62 ± 96.89	99.87 ± 65.59	0.06	-28.78 ± 46.55
	P-value	0.75*	0.09*	-	0.044

Abbreviations: CBC; complete blood count, K; potassium, Ca; calcium, Na; sodium, Mg; magnesium, ALP; alkaline phosphatase, ALT; alanine aminotransferase, AST; aspartate aminotransferase, BG, blood glucose, ALB; albumin, BUN; blood urea nitrogen, Cr; serum creatinine, BIL-T; bilirubin total, BIL-D; bilirubin direct, LDH; lactate dehydrogenase, CPK; creatine phosphokinase, CRP, C-reactive protein

Data are shown as means ± standard deviation

P-values were obtained from independent sample T-test*, paired-sample T-test**, and analysis of covariance (ANCOVA) with the adjustment for baseline values

Table 5 Changes from baseline in hematological parameters in the curcumin and placebo groups

Variables	Group	Before intervention	After intervention	*P*-value**	Mean changes#
WBC	Curcumin	10.73 ± 3.59	10.73 ± 3.67	0.99	-0.288 ± 3.33
	Placebo	11.57 ± 3.71	9.11 ± 3.32	0.014	-2.21 ± 3.33
	P-value	0.43	0.11	-	0.048
NUT	Curcumin	84.00 ± 8.01	78.82 ± 5.98	0.007	-1.02 ± 7.13
	Placebo	75.31 ± 19.97	78.46 ± 7.94	0.428	-0.52 ± 7.13
	P-value	0.057	0.85	-	0.81
EOS	Curcumin	9.33 ± 5.39	12.26 ± 4.65	0.034	-0.580 ± 5.82
	Placebo	16.23 ± 16.00	13.41 ± 6.43	0.401	0.275 ± 5.82
	P-value	0.055	0.48	-	0.62
RBC	Curcumin	3.46 ± 0.63	3.50 ± 0.53	0.847	-0.289 ± 0.617
	Placebo	4.07 ± 0.65	3.50 ± 0.61	0.006	-0.291 ± 0.617
	P-value	0.002	0.99	-	0.99
Hb	Curcumin	10.54 ± 1.78	10.43 ± 1.29	0.797	-0.957 ± 1.48
	Placebo	11.42 ± 2.05	10.04 ± 1.47	0.019	-0.629 ± 1.48
	P-value	0.12	0.33	-	0.43
Hct	Curcumin	31.69 ± 5.44	31.61 ± 4.21	0.940	-1.530 ± 4.72
	Placebo	34.81 ± 5.25	30.84 ± 4.96	0.013	-2.673 ± 4.72
	P-value	0.048	0.57	-	0.42
PLT	Curcumin	248.0 ± 181.7	333.8 ± 214.52	0.091	98.34 ± 155.4
	Placebo	208.9 ± 64.67	213.92 ± 92.97	0.782	-6.07 ± 155.4
	P-value	0.31	0.013	-	0.024
PT	Curcumin	12.85 ± 1.37	13.04 ± 1.87	0.606	0.169 ± 2.86
	Placebo	12.88 ± 2.02	13.42 ± 3.57	0.534	0.555 ± 2.86
	P-value	0.94	0.62	-	0.626
PTT	Curcumin	27.81 ± 2.80	29.07 ± 3.08	0.084	0.923 ± 7.70
	Placebo	28.57 ± 3.77	31.53 ± 10.36	0.183	3.311 ± 7.07
	P-value	0.41	0.24	-	0.265
INR	Curcumin	1.13 ± 0.12	1.09 ± 0.11	0.096	-0.039 ± 0.280
	Placebo	1.13 ± 0.19	1.16 ± 0.39	0.754	0.029 ± 0.280
	P-value	0.91	0.38	-	0.389

Abbreviations: WBC; white blood cell count, RBC; red blood cell, PLT; Platelet, Hb, hemoglobin; Hct, Hematocrit, EOS; eosinophils, PT; prothrombin time, PTT; partial thromboplastin time, INR; international normalized ratio

Data are shown as means ± standard deviation

**P*-values were obtained from independent sample T-test, **paired-sample T-test, and #analysis of covariance (ANCOVA) with the adjustment for baseline values

increase islet viability and delay the production of ROS in the islets [45]. In addition, curcumin depolarizes the membrane potential and activates anion channels, which leads to insulin release [46]. Curcumin increases transcription of the TCF7L2 gene [47], which is linked to type 2 diabetes [48].

The current investigation demonstrated a significant increase in potassium levels following the administration of curcumin. Curcumin inhibits the activation of NLRP3 inflammasomes and restores potassium levels in cells. Furthermore, curcumin's inhibitory effect on NLRC4 and AIM2 inflammasomes may be attributed to its suppression of K+efflux [49].

In the intervention group, biochemical parameters such as AST, BIL-T, BIL-D, LDH, CKP, and CRP were improved by the end of the follow-up. Additionally,

phytosomal curcumin supplementation decreased ALP levels. Despite its non-statistically significant decrease, this decrease might be valuable from a clinical perspective (The mean ALP level decreased in the intervention group from 158 to 140, while it increased in the control group from 192 to 223). Compliant with our findings, a previous study demonstrated that daily consumption of curcumin (1000 mg) was associated with a significant reduction in BIL-T and BIL-D levels in individuals with β-thalassemia [30]. Furthermore, 8 weeks of daily intake of phytosomal curcumin (250 mg) was shown to lower AST levels in patients with non-alcoholic fatty liver disease [50]. The hepatoprotective effect of phytosomal curcumin might be mediated by enhancing Bcl-2, SOD, GSH, and GPx levels while reducing lipid peroxidation and H_2O_2 levels, which reduce cytochrome c and caspase-3 [51]. The effect of curcumin on myocardial protection in rats has been demonstrated by reducing the levels of LDH, CPK, AST, ALT, and ALP. Antioxidant properties of curcumin may also contribute to its cardioprotective effects; some of these properties include the ability to neutralize free radicals, inhibit oxidative enzymes like cytochrome P450, and disarm the oxidative properties of metal ions like iron [52].

The effectiveness of curcuminoids as CRP-lowering agents is supported by a meta-analysis [53]. There is evidence suggesting curcuminoids significantly inhibit the NF-kB signaling pathway and reduce the synthesis of inflammatory cytokines including IL-6, TNF-α, and IL-1β. CRP expression in human hepatocytes is regulated by these cytokines [54].

In line with prior research [55, 56], the current study also revealed that while phytosomal curcumin supplementation had a favorable impact on some clinical and laboratory parameters, its effect on reducing mortality did not reach statistical significance. Nevertheless, it is important to note that the mortality rate in the intervention group was approximately half of that in the control group (3.7% vs. 7.7%), suggesting that phytosomal curcumin was clinically effective. The lack of statistical significance is likely attributed to the limited sample size. Therefore, further trials with a larger sample size are needed to assess the efficacy of this supplementation on mortality as a primary endpoint.

It is noteworthy that this study was the first double-blind randomized placebo-controlled trial to examine the effects of phytosomal curcumin in patients with trauma admitted to the ICU. However, some limitations need to be considered such as the relatively short duration of follow-up and small sample size. This study's short follow-up was mostly due to imminent death, transfer of patients to the ward, or total parenteral nutrition use. It was also not possible to evaluate the effectiveness of phytosomal curcumin as monotherapy because of ethical issues.

Conclusion

In conclusion, phytosomal curcumin supplementation containing phosphatidylserine might benefit ICU-admitted patients suffering from multiple trauma. However, due to the limited research in this field, further studies are still needed. It is recommended that future studies be conducted with large sample sizes and longer follow-up durations to confirm the present results.

Abbreviations

ALB	Albumin
ALI	Acute lung failure
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
APACHE II	Acute Physiology and Chronic Health Evaluation II
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
BG	Blood glucose
BIL-D	Bilirubin direct
BIL-T	Bilirubin total
BUN	Blood urea nitrogen
Ca	Calcium
CBC	Complete blood count
CPK	Creatine phosphokinase
Cr	Creatinine
CRP	C-reactive protein
GCS	Glasgow Coma Scale/Score
INR	International normalized ratio
K	Potassium
LDH	Lactate dehydrogenase
Mg	Magnesium
MOF	Multiple organ failure
Na	Sodium
NUTRIC	Nutritional status was evaluated by Nutrition Risk in the Critically Ill
SD	Standard deviation
SOFA	Sequential organ failure assessment
TBI	Traumatic brain injury

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Author contributions

Author contributionsConception and design of study: (A) Sahebkar, (B) Alikiaii, Sh. Hassanizadeh, M. Bagherniya; acquisition of data: M. Mirjalili, Z. Kiani, S. Amini, S. Abbasi; analysis and/or interpretation of data: D. Soleimani, Gh. Askari, SA. Moallem, M. Bagherniya.Drafting the manuscript: M. Mirjalili, Z. Kiani, Sh. Hassanizadeh, D. Soleimani, S. Amini, M. Bagherniya; Revising the manuscript critically for important intellectual content: (A) Sahebkar, (B) Alikiaii, Gh. Askari, SA. Moallem, S. Abbasi.Approval of the version of the manuscript to be published: M. Mirjalili, (A) Sahebkar, Sh. Hassanizadeh, Z. Kiani, D. Soleimani, S. Amini, (B) Alikiaii, SA. Moallem, Gh Askari, S. Abbasi, M. Bagherniya.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The current study was approved by the Research Ethics Committee of Isfahan University of Medical Sciences (code: IR.MUI.MED.REC.1399.758). This trial is registered in the Iranian Registry of Clinical Trials dependent on WHO (registration ID: IRCT20090306001747N1). The first registration date was 12/01/2021 and the last registration update was 17/01/2023. Written informed consent was obtained from all of the participants or their families before beginning the study.

Consent for publication
All authors approved the final version of the manuscript and agreed for all aspects of the work to be published.

Competing interests
The authors declare no competing interests.

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References

1. Scott SG, Scholten JD, Latlief GA, Humayun F, Belanger HG, Vanderploeg RD. Chap. 136 - Polytrauma Rehabilitation. In: *Essentials of Physical Medicine and Rehabilitation (Second Edition).* edn. Edited by Frontera WR, Silver JK, Rizzo TD. Philadelphia: W.B. Saunders; 2008: 787–791.
2. Soucacos PN, Johnson EO. Multiple Trauma. In: *Encyclopedia of Stress (Second Edition).* edn. Edited by Fink G. New York: Academic Press; 2007: 795–800.
3. Lord JM, Midwinter MJ, Chen Y-F, Belli A, Brohi K, Kovacs EJ, Koenderman L, Kubes P, Lilford RJ. The systemic immune response to trauma: an overview of pathophysiology and treatment. Lancet. 2014;384(9952):1455–65.
4. Pape HC, Moore EE, McKinley T, Sauaia A. Pathophysiology in patients with polytrauma. Injury. 2022;53(7):2400–12.
5. Kotha RR, Luthria DL. Curcumin: Biological, Pharmaceutical, Nutraceutical, and Analytical aspects. Molecules 2019, 24(16).
6. Bagheri H, Ghasemi F, Barreto GE, Rafiee R, Sathyapalan T, Sahebkar A. Effects of curcumin on mitochondria in neurodegenerative diseases. BioFactors. 2020;46(1):5–20.
7. Marjaneh RM, Rahmani F, Hassanian SM, Rezaei N, Hashemzehi M, Bahrami A, Ariakia F, Fiuji H, Sahebkar A, Avan A, et al. Phytosomal curcumin inhibits tumor growth in colitis-associated colorectal cancer. J Cell Physiol. 2018;233(10):6785–98.
8. Panahi Y, Fazlolahzadeh O, Atkin SL, Majeed M, Butler AE, Johnston TP, Sahebkar A. Evidence of curcumin and curcumin analogue effects in skin diseases: a narrative review. J Cell Physiol. 2019;234(2):1165–78.
9. El-Saadony MT, Yang T, Korma SA, Sitohy M, Abd El-Mageed TA, Selim S, Al Jaouni SK, Salem HM, Mahmmod Y, Soliman SM, et al. Impacts of turmeric and its principal bioactive curcumin on human health: Pharmaceutical, medicinal, and food applications: a comprehensive review. Front Nutr. 2022;9:1040259.
10. Gupta SC, Patchva S, Aggarwal BB. Therapeutic roles of curcumin: lessons learned from clinical trials. AAPS J. 2013;15(1):195–218.
11. Mohseni M, Sahebkar A, Askari G, Johnston TP, Alikiaii B, Bagherniya M. The clinical use of curcumin on neurological disorders: an updated systematic review of clinical trials. Phytother Res. 2021;35(12):6862–82.
12. Mahdavi A, Moradi S, Askari G, Iraj B, Sathyapalan T, Guest PC, Bagherniya M, Sahebkar A. Effect of Curcumin on Glycemic Control in patients with type 2 diabetes: a systematic review of Randomized clinical trials. Adv Exp Med Biol. 2021;1291:139–49.
13. Alikiaii B, Bagherniya M, Askari G, Sathyapalan T, Sahebkar A. Evaluation of the effect of curcumin on pneumonia: a systematic review of preclinical studies. Phytother Res. 2021;35(4):1939–52.
14. Alikiaii B, Bagherniya M, Askari G, Johnston TP, Sahebkar A. The role of phytochemicals in sepsis: a mechanistic and therapeutic perspective. BioFactors. 2021;47(1):19–40.
15. 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. Phytother Res 2023.
16. Hassanizadeh S, Shojaei M, Bagherniya M, Orekhov AN, Sahebkar A. Effect of nano-curcumin on various diseases: a comprehensive review of clinical trials. BioFactors 2023.
17. Heidari Z, Daei M, Boozari M, Jamialahmadi T, Sahebkar A. Curcumin supplementation in pediatric patients: a systematic review of current clinical evidence. Phytother Res. 2022;36(4):1442–58.
18. Karimi A, Naeini F, Niazkar HR, Tutunchi H, Musazadeh V, Mahmoodpoor A, Asghariazar V, Mobasseri M, Tarighat-Esfanjani A. Nano-Curcumin supplementation in critically ill patients with sepsis: a randomized clinical trial investigating the inflammatory biomarkers, oxidative stress indices, endothelial function, clinical outcomes and nutritional status. Food Funct. 2022;13(12):6596–612.
19. Karimi A, Pourreza S, Vajdi M, Mahmoodpoor A, Sanaie S, Karimi M, Tarighat-Esfanjani A. Evaluating the effects of curcumin nanomicelles on clinical outcome and cellular immune responses in critically ill sepsis patients: a randomized, double-blind, and placebo-controlled trial. Front Nutr. 2022;9:1037861.
20. Zahedi H, Hosseinzadeh-Attar MJ, Shadnoush M, Sahebkar A, Barkhidarian B, Sadeghi O, Najafi A, Hosseini S, Qorbani M, Ahmadi A, 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. Phytother Res. 2021;35(8):4605–15.
21. Khayatan D, Razavi SM, Arab ZN, Niknejad AH, Nouri K, Momtaz S, Gumpricht E, Jamialahmadi T, Abdolghaffari AH, Barreto GE et al. Protective effects of curcumin against traumatic brain injury. Biomed Pharmacotherapy 2022, 154.
22. Allam AN, Komeil IA, Abdallah OY. Curcumin phytosomal softgel formulation: development, optimization and physicochemical characterization. Acta Pharm. 2015;65(3):285–97.
23. Lopresti AL. The problem of curcumin and its bioavailability: could its gastrointestinal influence contribute to its overall health-enhancing effects? Adv Nutr. 2018;9(1):41–50.
24. Ma Z, Wang N, He H, Tang X. Pharmaceutical strategies of improving oral systemic bioavailability of curcumin for clinical application. J Controlled Release: Official J Controlled Release Soc. 2019;316:359–80.
25. Mirzaei H, Shakeri A, Rashidi B, Jalili A, Banikazemi Z, Sahebkar A. Phytosomal curcumin: a review of pharmacokinetic, experimental and clinical studies. Biomed Pharmacother. 2017;85:102–12.
26. Glade MJ, Smith K. Phosphatidylserine and the human brain. Nutrition. 2015;31(6):781–6.
27. Marczylo TH, Steward WP, Gescher AJ. Rapid analysis of curcumin and curcumin metabolites in rat biomatrices using a novel ultraperformance liquid chromatography (UPLC) method. J Agric Food Chem. 2009;57(3):797–803.
28. Marczylo TH, Verschoyle RD, Cooke DN, Morazzoni P, Steward WP, Gescher AJ. Comparison of systemic availability of curcumin with that of curcumin formulated with phosphatidylcholine. Cancer Chemother Pharmacol. 2007;60:171–7.
29. Zahedi H, Hosseinzadeh-Attar MJ, Shadnoush M, Sahebkar A, Barkhidarian B, Sadeghi O, Najafi A, Hosseini S, Qorbani M, Ahmadi A. Effects of curcuminoids on inflammatory and oxidative stress biomarkers and clinical outcomes in critically ill patients: a randomized double-blind placebo-controlled trial. Phytother Res. 2021;35(8):4605–15.
30. Shojaei M, Sahebkar A, Khorvash F, Fallahpour S, Askari G, Bagherniya M. The effects of phytosomal curcumin supplementation on clinical symptoms, and inflammatory and oxidative stress biomarkers in patients with migraine: a

protocol for a randomized double-blind placebo-controlled trial. Avicenna J Phytomedicine. 2023;13(1):45–57.
31. Wu A, Ying Z, Schubert D, Gomez-Pinilla F. Brain and spinal cord interaction: a dietary curcumin derivative counteracts locomotor and cognitive deficits after brain trauma. Neurorehabilit Neural Repair. 2011;25(4):332–42.
32. Vahdat M, Hosseini SA, Soltani F, Cheraghian B, Namjoonia M. The effects of taurine supplementation on inflammatory markers and clinical outcomes in patients with traumatic brain injury: a double-blind randomized controlled trial. Nutr J. 2021;20(1):53.
33. Wu A, Ying Z, Gomez-Pinilla F. Dietary curcumin counteracts the outcome of traumatic brain injury on oxidative stress, synaptic plasticity, and cognition. Exp Neurol. 2006;197(2):309–17.
34. Kahkhaie KR, Mirhosseini A, Aliabadi A, Mohammadi A, Mousavi MJ, Haftcheshmeh SM, Sathyapalan T, Sahebkar A. Curcumin: a modulator of inflammatory signaling pathways in the immune system. Inflammopharmacology. 2019;27(5):885–900.
35. Mohammadi A, Blesso CN, Barreto GE, Banach M, Majeed M, Sahebkar A. Macrophage plasticity, polarization and function in response to curcumin, a diet-derived polyphenol, as an immunomodulatory agent. J Nutr Biochem. 2019;66:1–16.
36. Shafabakhsh R, Pourhanifeh MH, Mirzaei HR, Sahebkar A, Asemi Z, Mirzaei H. Targeting regulatory T cells by curcumin: a potential for cancer immunotherapy. Pharmacol Res 2019, 147.
37. Panahi Y, Ghanei M, Hajhashemi A, Sahebkar A. Effects of curcuminoids-Piperine combination on systemic oxidative stress, clinical symptoms and quality of life in subjects with chronic pulmonary complications due to Sulfur Mustard: a Randomized Controlled Trial. J Diet Supplements. 2016;13(1):93–105.
38. Ahmadi A, Jamialahmadi T, Sahebkar A. Polyphenols and atherosclerosis: a critical review of clinical effects on LDL oxidation. Pharmacol Res. 2022;184:106414.
39. Dehzad MJ, Ghalandari H, Nouri M, Askarpour M. Antioxidant and anti-inflammatory effects of curcumin/turmeric supplementation in adults: a GRADE-assessed systematic review and dose-response meta-analysis of randomized controlled trials. Cytokine. 2023;164:156144.
40. Sabir S, Umer N, Shoaib M, Zulfiqar S. Correlation of interleukin-10 with Glasgow coma scale in patients of stroke. Pakistan J Med Health Sci. 2016;10(1):63–5.
41. Ali Hosseinian S, Mehrzad J, Reza Mirhafez S, Saeidi J, Zhiani R, Sahebkar A. Evaluation of the effect of phytosomal curcuminoids on oxidative stress and inflammatory markers in NAFLD: a randomized double-blind placebo-controlled trial. J Funct Foods. 2022;96:105202.
42. Wongcharoen W, Phrommintikul A. The protective role of curcumin in cardiovascular diseases. Int J Cardiol. 2009;133(2):145–51.
43. Cicero AFG, Sahebkar A, Fogacci F, Bove M, Giovannini M, Borghi C. Effects of phytosomal curcumin on anthropometric parameters, insulin resistance, cortisolemia and non-alcoholic fatty liver disease indices: a double-blind, placebo-controlled clinical trial. Eur J Nutr. 2020;59(2):477–83.
44. Zhang D-w, Fu M, Gao S-H, Liu J-L. Curcumin and diabetes: a systematic review. Evidence-Based Complement Altern Med. 2013;2013:636053.
45. Meghana K, Sanjeev G, Ramesh B. Curcumin prevents streptozotocin-induced islet damage by scavenging free radicals: a prophylactic and protective role. Eur J Pharmacol. 2007;577(1–3):183–91.
46. Best L, Elliott AC, Brown PD. Curcumin induces electrical activity in rat pancreatic β-cells by activating the volume-regulated anion channel. Biochem Pharmacol. 2007;73(11):1768–75.
47. Khalooghi K, Hashemi S, Mehraban N, Amiri P, Bazzaz JT, Larijani B, Amoli MM. In vitro modulation of TCF7L2 gene expression in human pancreatic cells. Mol Biol Rep. 2009;36:2329–32.
48. Yan Y, Klein R, Heiss G, Girman CJ, Lange EM, Klein BE, Rose KM, Boerwinkle E, Pankow JS, Brancati FL. The transcription factor 7-like 2 (TCF7L2) polymorphism may be associated with focal arteriolar narrowing in caucasians with hypertension or without diabetes: the ARIC Study. BMC Endocr Disorders. 2010;10:1–10.
49. Gong Z, Zhou J, Li H, Gao Y, Xu C, Zhao S, Chen Y, Cai W, Wu J. Curcumin suppresses NLRP3 inflammasome activation and protects against LPS-induced septic shock. Mol Nutr Food Res. 2015;59(11):2132–42.
50. Mirhafez SR, Azimi-Nezhad M, Dehabeh M, Hariri M, Naderan RD, Movahedi A, Abdalla M, Sathyapalan T, Sahebkar A. The effect of curcumin phytosome on the treatment of patients with non-alcoholic fatty liver disease: a double-blind, randomized, placebo-controlled trial. Pharmacol Prop Plant-Derived Nat Prod Implications Hum Health 2021:25–35.
51. Al-Kahtani M, Abdel-Daim MM, Sayed AA, El-Kott A, Morsy K. Curcumin phytosome modulates aluminum-induced hepatotoxicity via regulation of antioxidant, Bcl-2, and caspase-3 in rats. Environ Sci Pollut Res. 2020;27(17):21977–85.
52. Swamy AV, Gulliaya S, Thippeswamy A, Koti BC, Manjula DV. Cardioprotective effect of curcumin against doxorubicin-induced myocardial toxicity in albino rats. Indian J Pharmacol. 2012;44(1):73.
53. Gorabi AM, Abbasifard M, Imani D, Aslani S, Razi B, Alizadeh S, Bagheri-Hosseinabadi Z, Sathyapalan T, Sahebkar A. Effect of curcumin on C-reactive protein as a biomarker of systemic inflammation: an updated meta-analysis of randomized controlled trials. Phytother Res. 2022;36(1):85–97.
54. Panahi Y, Hosseini MS, Khalili N, Naimi E, Majeed M, Sahebkar A. Antioxidant and anti-inflammatory effects of curcuminoid-piperine combination in subjects with metabolic syndrome: a randomized controlled trial and an updated meta-analysis. Clin Nutr. 2015;34(6):1101–8.
55. Askari G, Bagherniya M, Kiani Z, Alikiaii B, Mirjalili M, Shojaei M, Hassanizadeh S, Vajdi M, Feizi A, Majeed M, et al. Evaluation of Curcumin-Piperine supplementation in COVID-19 patients admitted to the Intensive Care: a Double-Blind, randomized controlled trial. Adv Exp Med Biol. 2023;1412:413–26.
56. Karimi A, Mahmoodpoor A, Kooshki F, Niazkar HR, Shoorei H, Tarighat-Esfanjani A. Effects of nanocurcumin on inflammatory factors and clinical outcomes in critically ill patients with sepsis: a pilot randomized clinical trial. Eur J Integr Med. 2020;36:101122.

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