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The effects of saffron supplementation on inflammation and hematological parameters in patients with sepsis: a randomized controlled trial

Shirin Hassanizadeh[1,2], Babak Alikiaii[3], Mohammad Hossein Rouhani[2], Shokoofeh Talebi[1,2], Zeinab Mokhtari[2], Manoj Sharma[4] and Mohammad Bagherniya[2,3*]

Abstract

Background Critically ill patients suffering from sepsis are at an increased risk of morbidity and mortality due to its serious complications. Saffron as an herbal medicine has been proven to have anti-inflammatory and anti-oxidative stress effects previously. Hence, this study aimed to determine how saffron supplementation affected inflammatory and hematological factors in patients admitted to the intensive care unit (ICU) with sepsis.

Methods In this double-blind clinical trial, 90 ICU sepsis patients with GCS lower than 13 were randomized to receive either an intervention tablet containing 100 mg of saffron or a placebo tablet containing 100 mg of corn starch for seven days. Before and after the intervention, clinical, inflammatory, hematological, and mortality parameters were assessed.

Results After seven days, the saffron group showed a significantly decline from baseline compared to the placebo group in inflammatory markers, including CRP (-24.58 ± 22.16 vs. -2.42 ± 30.86; $P < 0.001$), ESR (-5.36 ± 28.75 vs. 24.29 ± 28.24; $P < 0.001$), IL-6 (-22.09 ± 25.22 vs. -4.02 ± 20.04; $P < 0.001$), IL-18 (-9.56 ± 9.31 vs. -0.89 ± 3.38; $P < 0.001$), and TNF-α (-2.52 ± 3.79 vs. -0.035 ± 2.35; $P < 0.001$). Regarding clinical outcomes, significant improvements were observed in APACHE II (-2.55 ± 5.47 vs. 0.78 ± 3.37; $P = 0.003$), SOFA (-1 ± 1.07 vs. -0.05 ± 1.53; $P < 0.001$), NUTRIC score (-1.2 ± 1.01 vs. 0.2 ± 0.87; $P < 0.001$), and WBC count (-4176.34 ± 4063.01 vs. 61.57 ± 4118.97; $P < 0.001$). Moreover, the effect sizes (Cohen's d) for these factors ranged from moderate to large, except for IL-6, which had a small effect size (d = -0.38). However, no significant differences were found between the groups in the Glasgow Coma Scale, FOUR Score, 28-day and 90-day mortality rates, or other hematological parameters ($P > 0.05$).

Conclusions Saffron administration in sepsis patients admitted to the ICU led to significant improvements in inflammatory markers and some clinical parameters. However, the clinical significance of these findings remains to be fully established.

Trial registration Iranian Registry of Clinical Trials: IRCT20201129049534N8. It was registered on 17 March 2024.

*Correspondence:
Mohammad Bagherniya
bagherniya@yahoo.com

Full list of author information is available at the end of the article

Keywords Critical illness, Intensive care units, Sepsis, Inflammation, Saffron

Introduction

Sepsis is a syndrome of life-threatening organ failure caused by an abnormal host response to an infection [1]. There is a high incidence of sepsis in intensive care units (ICUs), where it accounts for more than 50% of ICU mortality [2]. Furthermore, sepsis is a global health burden that has a significant economic impact [3]. In patients suffering from sepsis, several systemic cytokines such as tumor necrosis factor (TNF), interleukin-6 (IL-6), and interleukin-18 (IL-18) are released [4]. A high level of these cytokines could be associated with changes in the hematological parameters, especially platelet and white blood cell (WBC) count [5]. It has also been reported that IL-18 plays a role in the development and severity of sepsis [6]. Moreover, free radicals may be involved in the pathogenesis of sepsis through their ability to cause a series of cellular processes leading to the release of nuclear transcription kappa factor-B (NFKB) from its inhibitory protein I kappa B [7]. This allows it to translocate into the nucleus, where it binds to DNA, triggering inflammation-related genes to be transcribed. Acute phase mediators, such as IL-2, TNF-α, and IL-2 receptors, are controlled by NFKB, triggering an inflammatory cascade in turn [7]. Although antibiotics are one of the main treatments for sepsis, it remains one of the primary causes of death in the ICU [8]. In addition, antibiotic resistance may arise because of the overuse of antibiotics [9]. Hence, to optimize clinical outcomes in this population, dietary supplements with minimal or no side effects may be considered adjunctive therapies to combat the symptoms of sepsis. Researchers have discovered that fruits, vegetables, herbs, and spices may contain chemicals that reduce the risk of sepsis [10, 11]. One of these herbal medicines is saffron (Crocus sativus Linn), a member of the Iridaceae family, contains many volatile, non-volatile and aroma-yielding compounds, including lipophilic and hydrophilic carbohydrates, protein, minerals, amino acids, vitamins (particularly B2 and B1), and a wide variety of pigments including crocin, crocetin, anthocyanin, carotene, lycopene, and zigzantin that may contribute in wide range of biological effects [12]. Crocetin and crocin in particular are powerful antioxidants and radical scavengers [13]. So, saffron is a suitable candidate for sepsis management compared to other herbal supplements due to these unique compounds, low potential side effects, and its safety and efficacy in improving inflammatory markers [13].

Several studies have revealed the antioxidant and anti-inflammatory properties of saffron [14, 15]. When administered 100 mg daily, saffron was found to improve erythrocyte sedimentation rate (ESR), CRP, and TNF-α levels in rheumatoid arthritis (RA) patients [16]. The results of a meta-analysis demonstrated that supplementing with saffron is more effective in reducing CRP levels in individuals with baseline CRP levels above 3 mg/L [14].

As far as we know, no clinical trials have examined saffron's effects on sepsis patients. Hence, the purpose of this study was to determine if saffron supplementation affects inflammation, mortality rate, hematological parameters, and clinical outcomes in patients with sepsis in the ICU. This research will hopefully reduce some of the major problems of patients with sepsis.

Materials and methods

Study design and patients

Ninety critically ill patients with sepsis and a GCS lower than 13 were enrolled in this randomized, parallel, double-blinded, placebo-controlled clinical trial. Study patients were recruited from the ICU at Al-Zahra Hospital, an academic hospital affiliated with Isfahan University of Medical Sciences. The ethics committee of Isfahan University of Medical Sciences approved this trial (code: IR.MUI.MED.REC.1402.466). The data presented in this article are part of a larger study and the protocol of this study has been published elsewhere. A written informed consent was obtained from the patients or their legal guardians prior to any investigation. A registration number for this study can be found on the Iranian Registry of Clinical Trials (IRCT) website (http://www.irct.iridentifier: IRCT20201129049534N8). The Declaration of Helsinki was followed in the conduct of this trial. A list of inclusion and exclusion criteria can be found in Table 1.

Sepsis diagnosis

Based on Sepsis-3 definitions published by the Surviving Sepsis Campaign International Guidelines for Management of Sepsis and Septic Shock [17] and a confirmation specialist in anesthesiology or infectious diseases, sepsis and septic shock were diagnosed.

Trial randomization and blinding

Those who met the inclusion criteria for the study were enrolled. Treatment assignments were concealed from researchers, laboratory analysts, and all patients until the completion of data analyses. The assignment sequences were provided by an independent statistician with the use of a random-number table and then were kept in opaque, sealed, numbered envelopes until the end of the eligibility criteria evaluation. To ensure a balanced allocation of participants based on disease severity and age, a stratified randomization was performed. Patients were stratified

Table 1 Inclusion and exclusion criteria

	Inclusion criteria
1	Patients with sepsis who are admitted to the ICU
2	Aged 18 to 80 years old.
3	Filling the written informed consent before the intervention
4	Being able to tolerate enteral nutrition and having a normal digestive function
5	Patients with GCS levels lower than 13
	Exclusion criteria
1	Dissatisfaction of the patient or his legal guardian
2	Patients who stay in the ICU for < 48 h
3	Patients receiving parenteral nutrition or transferring to parenteral nutrition due to contraindications
4	Cancer patients undergoing chemotherapy
5	Patients suffering from pancreatitis, kidney failure, and congenital or immune disorders
6	Patients taking phenobarbital, levetiracetam, and phenytoin
7	Dialysis patients, patients with severe septic shock or sepsis, and DIC (diffuse intravascular coagulation)
8	Pregnancy and breastfeeding
9	Patients with BMI < 18.5 kg/m^2
10	Patients who need blood transfusions frequently
11	Unwanted side effects associated with taking supplements or placebos
12	ICU patients who are expected to die within 2 days of admission.
13	Patients who take other herbal supplements
14	Patients with a spice or herbal supplement allergy
15	Patients with GCS levels greater than 13
16	Patients who passed away during the trial

into two groups based on GCS (3–8 and 9–13) and age (18–50 and 51–80) before the randomization to minimize potential confounding effects. In this double-blind study, tablets (saffron and placebo) were labeled A and B by the company in the packages with the same format. Tablets were similar in terms of size, shape, color, and odor. Investigators, participants, laboratory staff, outcome assessors, and data analyzers were blinded to treatment assignment until the completion of data analyses.

Intervention

Standard treatments were provided to both intervention and control groups. So, saffron and placebo (corn starch) were both used as adjunctive therapies. In the intervention group, patients received saffron tablets daily containing 100 mg. Patients in the control group received 100 mg of corn starch daily. A dose of 100 mg was selected for saffron supplementation because this is the first study evaluating its effects in critically ill patients in the ICU, and the aim was to minimize potential adverse effects. Furthermore, a meta-analysis indicated that 100 mg is the optimal dose for reducing CRP levels with saffron supplementation [14].

The placebo or saffron was administered with enteral nutrition (enteral tube feeding) every day at 9:00 during the 7-day trial. Saffron and placebo tablets were prepared in packages identical to one another in terms of shape, smell, color, and size, and tagged A and B. The saffron powder was sourced from Mojtahedi Company in Mashhad. Then, experts from the Faculty of Pharmacy made the supplement and placebo tablets and performed an HPLC test. The HPLC test was performed in two stages, one on saffron powder and one after turning saffron into tablets. The saffron powder contained 24.4% crocin and the tablet had 20.4 mg, which indicates a high-quality saffron. Both groups received enteral nutritional support via a nasogastric (NG) tube within 24–48 h of hemodynamic stabilization. The nutrition was administered using the bolus method, seven times within 24 h, providing 25 kcal/kg of energy [18]. In addition to all commonly prescribed medicines and routine treatment, the patients were monitored by a physician daily for gastrointestinal issues.

Sample size

Using the formula for randomized clinical trials, the sample size was calculated considering type I error at 5% and type II error at 20% ($\beta = 0.2$; power = 80%). CRP level was considered a main outcome, and based on a previous study, the sample size was calculated to be 35 persons for each group ($\Delta = 3$) [19]. Considering attrition, 90 patients were considered in total, 45 in each group. The choice of CRP for sample size calculation was based on its requirement for a larger sample size to detect significant changes compared to other primary outcomes. By adequately powering our study for CRP, we ensured sufficient power to detect changes in other markers. Additionally, previous studies provided more consistent data on effect sizes and standard deviations for CRP, facilitating a precise sample size calculation. Using other markers would have resulted in smaller sample sizes, potentially undermining our ability to detect meaningful changes.

Outcomes

The primary outcomes were CRP, TNF-α, IL-6, IL-18, and ESR, while hematological parameters and clinical outcomes were categorized as secondary outcomes.

A blood sample was drawn at the start and end of the trial. At 6:00 am before the first gavage, blood was collected to determine serum levels of CBC, CRP, TNF-α, IL-6, IL-18, and ESR. Immediately following the blood collection, the samples were centrifuged at 3600 rpm, the serum separated from the sediment, and it was preserved at -80 °C. Laboratory parameters were measured using commercial diagnostic kits. To measure the cytokines serum levels, a commercial (Karmania Pars Gene Company, Iran) ELISA kit was used, and the procedure was completed according to the manufacturers' instructions. In addition, the 28- and 90-day mortality rates,

GCS, FOUR score, APACHE II score, SOFA score, and NUTRIC score [20, 21], which were secondary outcomes, were calculated using a web-based system to eliminate possible human errors. At baseline, anthropometric variables such as weight, calf circumference, and mid-arm circumference (MAC) were also measured.

Statistical methods

Analysis was performed using SPSS version 22 (SPSS Inc, Chicago, IL, USA). The mean and standard deviation (SD) of quantitative data were reported, while frequency and percent were reported for qualitative data. To determine whether variables had a normal distribution, the QQ-plot or skewness were used [22]. A paired t-test was used to compare the differences in each group before and after the intervention. To compare baseline and endpoint differences between groups, an independent t-test was used [23]. Cohen's d was also calculated by taking the difference between two means (M1 and M2) and dividing it by the pooled standard deviation (spooled). The formula is: d = (M1 - M2) / spooled [24]. Cohen's d is interpreted as follows: a small effect is represented by d = 0.2, a medium effect by d = 0.5, and a large effect by d ≥ 0.8 [24]. We applied analysis of covariance (ANCOVA) to show differences between two treatment groups after adjusting for baseline variables. The intention-to-treat (ITT) analysis using the expectation-maximization (EM) algorithm was carried out for missing data [25]. P-values less than 0.05 were considered statistically significant.

Results

Study population characteristics

In this clinical trial, 90 patients with sepsis were randomly assigned to receive either saffron (n: 45) or a matching placebo (n: 45). In the Saffron and control groups, four and five individuals were excluded, respectively, due to death, intolerance to enteral nutrition, or NPO status. Hence, an intention-to-treat analysis was conducted on 90 patients. In Fig. 1, the CONSORT flowchart of the study is shown. In Table 2, the demographic characteristics of the participants are presented. There was no significant difference in the demographic characteristics of the two groups ($p > 0.05$).

Saffron supplementation and clinical outcome

The baseline levels for APACHE II, NUTRIC, SOFA, GCS, and four scores did not significantly differ between the two groups (P-value > 0.05). However, based on a within-group analysis, a meaningful reduction in the APACHE II (-2.55 ± 5.47 P-value = 0.003),

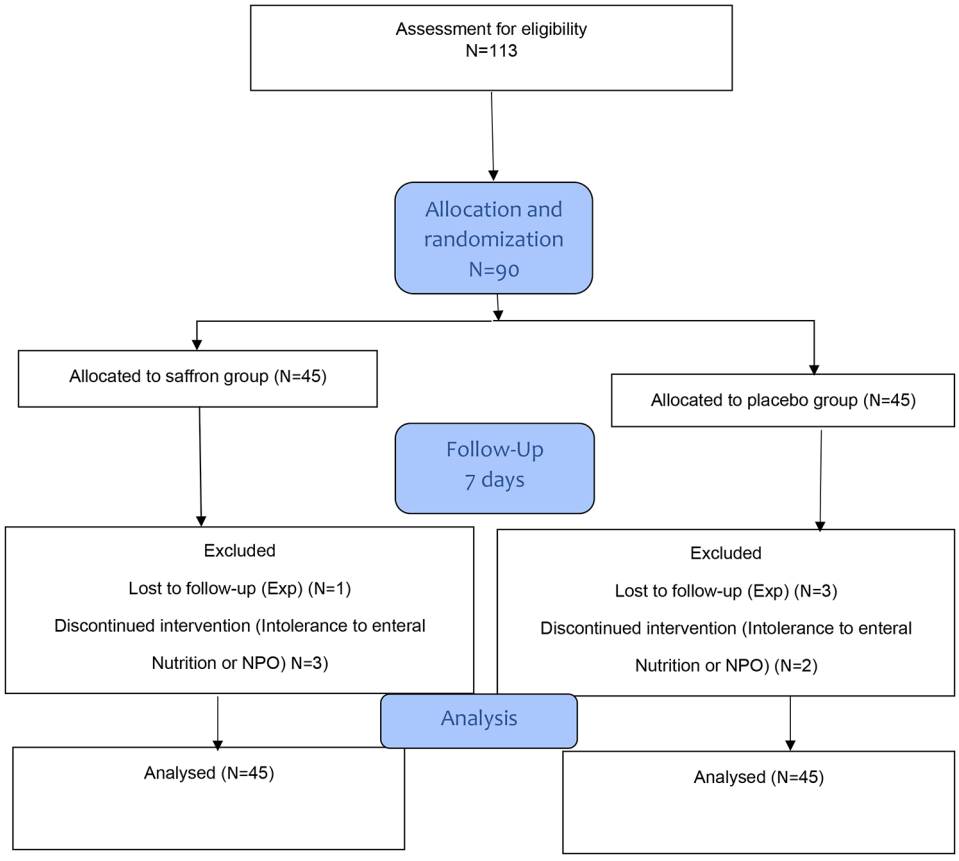

Fig. 1 Study flow diagram

Table 2 General characteristics of study patients

Variables	Saffron group (*N*:45)	Placebo group (*N*:45)	*P*-value*
Age, years	54.33 ± 2.2	54.17 ± 2.48	0.96
Female, n (%)	17 (37.8%)	18 (40%)	0.82
Weight (Kg)	76.80 ± 1.33	73.56 ± 1.35	0.09
Calf circumference (cm)	33.37 ± 0.49	32.12 ± 0.0.47	0.07
MAC (cm)	29.29 ± 0.90	27.31 ± 0.44	0.05
Reason for ICU admission			0.23
Medical	8 (17.8%)	8 (17.8%)	
Trauma	32 (71.7%)	26 (57.8%)	
Surgical	5 (11.1%)	11 (24.4%)	
Energy requirement (Cal)	18,028 ± 20.55	1800.3526 ± 27.18	0.40
Energy intake (Cal)	1807.84 ± 17.48	1785.98 ± 165.78	0.47
Source of sepsis			0.41
Pulmonary infection	35 (77.8%)	28 (62.2%)	
Abdominal infection	3 (6.7%)	5 (11.1)	
CSF infection	1 (2.2%)	3 (6.7%)	
Bacteremia	6 (13.3%)	9 (20%)	
MAP (mmHg)	92.86 ± 1.87	89.68 ± 1.72	0.21
Current medication			
NSAID	40 (88.9%)	37 (82.2%)	0.36
Insulin	4 (8.9%)	6 (13.3%)	0.50
PPI	40 (88.9%)	42 (93.3%)	0.45
Anticoagulant	42 (93.3%)	38 (84.4%)	0.18
Current supplement			
Zinc	34 (75.6%)	37 (82.2%)	0.43
Vitamin C	6 (13.3%)	3 (6.7%)	0.48
Vitamin B1	27 (60%)	25 (55.6%)	0.67
Vitamin D	32 (71.1%)	35 (77.8%)	0.46
Magnesium	6 (13.3%)	12 (26.7%)	0.11
Vitamin B-complex	2 (4.4%)	4 (8.9%)	0.67

Abbreviations: EXP; Expire, MAC; Mid-arm circumference, MAP; Mean arterial pressure, NSAID; Nonsteroidal anti-inflammatory drugs, PPI; Proton pump inhibitors

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

P-values were obtained from the Chi-Square test or independent sample t-test*

NUTRIC (-1.2 ± 1.01; P-value < 0.001), and SOFA (-1.0 ± 1.07; P-value < 0.001) scores were seen in the saffron group after 7 days compared to the baseline. In comparison to the placebo, saffron supplementation significantly reduced APACHE II (-2.55 ± 5.47 vs. 0.78 ± 3.37; P-value < 0.001), NUTRIC (-1.02 ± 1.01 vs. 0.2 ± 0.87; P-value < 0.001), and SOFA score (-1 ± 1.07 vs. -0.05 ± 1.53; P-value = 0.001) after adjustment for baseline values. The effect sizes (Cohen's d) at the end of the intervention were as follows: APACHE II = -0.8, NUTRIC = -0.78, and SOFA = -0.49, indicating that saffron supplementation had a substantial impact on disease severity. Furthermore, there was no significant difference between the two groups in terms of four scores and GCS levels after adjustment for baseline values (P-value > 0.05) (Table 3).

Saffron supplementation and inflammatory biomarkers

At the baseline of the study, there was no significant difference between the groups in terms of inflammatory factors including CRP, ESR, IL-6, IL-18, and TNF-α (P-value > 0.05). Based on within-group analysis, after the intervention period, a significant reduction in serum levels of CRP, ESR, IL-6, IL-18, and TNF-α was found in the saffron group (P-value < 0.05).

Further, after adjusting for baseline values, supplementation with saffron decreased CRP (-24.58 ± 22.16 vs. -2.42 ± 30.86; P-value < 0.001), ESR (-5.36 ± 28.75 vs. 24.29 ± 28.24; P-value < 0.001), IL-6 (-22.09 ± 25.22 vs. -4.02 ± 20.04; P-value < 0.001), IL-18 (-9.56 ± 9.31 vs. -0.89 ± 3.38; P-value < 0.001), and TNF-α (-2.52 ± 3.79 vs. -0.035 ± 2.35; P-value < 0.001) as compared with placebo (Table 4). However, the effect sizes (Cohen's d) at the end of the intervention were large for CRP (d = -1.27) and ESR (d = -0.91), moderate for TNF-α (d = -0.56) and IL-18 (d = -0.47), and small for IL-6 (d = -0.38).

Saffron supplementation and hematological factors

At the baseline of the study, there was no significant difference between the groups in terms of WBC, neutrophils, lymphocytes, Hb, HCT, MCV, MCH, MCHC, and PLT levels (P-value > 0.05). However, the RBC levels in the saffron group were significantly higher than those in the placebo group at the baseline (3.83 ± 0.61 vs. 3.58 ± 0.34; P-value = 0.02). Based on the paired t-test, the levels of WBC significantly decreased in the saffron group (-4176.34 ± 4063.01; P-value < 0.001), and the level of PLT increased in the placebo group (74910.70 ± 108276.04; P-value < 0.001) after 7 days intervention. Moreover, the WBC count significantly decreased in the saffron group in comparison to the placebo group (-4176.34 ± 4063.01 vs. 61.57 ± 4118.97; P-value < 0.001), and the effect size (Cohen's d) at the end of the intervention was large for WBC (d = -1.27). However, intervention group changes in neutrophils, lymphocytes, RBC, Hb, HCT, MCV, MCH, MCHC, and PLT levels were not significantly different from placebo group changes after adjusting for baseline value (P-value > 0.05) (Table 5).

Mortality rate

Although statistical tests showed no significant difference in the rate of mortality, these findings were clinically important. Among the placebo and saffron groups, the 28-day mortality rate was 24.4% (N: 11 patients) and 15.6% (N: 7 patients), respectively, (P-value = 0.21, number needed to treat {NNT} = 11.4), and the 90-day mortality rate was 31.1% (N: 14 patients) and 20% (N: 9 patients), (P-value = 0.16, number needed to treat {NNT}

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

Variables	Group	Before intervention	After intervention	*P*-value**	Mean changes#	*p*-value
APACHE II	Saffron	15.80 ± 5.35	13.25 ± 3.18	0.003	-2.55 ± 5.47	<0.001
	Placebo	15.64 ± 4.93	16.43 ± 4.64	0.12	0.78 ± 3.37	
	P-value	0.88	<0.001			
	Cohen's d effect size (CI)	0.03 (-0.39,0.45)	-0.8 (-1.22, -0.38)			
NUTRIC	Saffron	4.24 ± 1.36	3.22 ± 0.90	<0.001	-1.02 ± 1.01	<0.001
	Placebo	4 ± 1.43	4.18 ± 1.49	0.13	0.2 ± 0.87	
	P-value	0.41	<0.001			
	Cohen's d effect size (CI)	0.17 (-0.25, 0.59)	-0.78 (-1.2, -0.36)			
SOFA	Saffron	5.78 ± 1.48	4.78 ± 0.92	<0.001	-1 ± 1.07	0.001
	Placebo	5.42 ± 1.51	5.36 ± 1.41	0.80	-0.05 ± 1.53	
	P-value	0.25	0.02			
	Cohen's d effect size (CI)I	0.24 (-0.18, 0.66)	-0.49 (-0.91, -0.07)			
GCS	Saffron	7.16 ± 2.14	7.48 ± 1.82	0.30	0.32 ± 2.12	0.33
	Placebo	7.02 ± 2.42	7.09 ± 2.03	0.82	0.06 ± 1.94	
	P-value	0.33	0.52			
	Cohen's d effect size (CI)	0.06 (-0.36, 0.48)	0.2 (-0.22, 0.62)			
Four score	Saffron	9.52 ± 2.54	9.83 ± 2.22	0.26	0.31 ± 1.88	0.50
	Placebo	9.18 ± 2.61	9.88 ± 2.81	0.05	0.70 ± 2.28	
	P-value	0.52	0.93			
	Cohen's d effect size (CI)	0.13 (-0.29, 0.55)	-0.02 (-0.44, 0.4)			

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, CI: confidence interval

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 4 Changes from baseline in inflammatory parameters in the saffron and placebo groups

Variables	Group	Before intervention	After intervention	*P*-value**	Mean changes#	*p*-value
CRP (mg/dl)	Saffron	61.37 ± 19.05	36.78 ± 20.21	<0.001	-24.58 ± 22.16	<0.001
	Placebo	69.42 ± 21.63	66.99 ± 27	0.60	-2.42 ± 30.86	
	P-value	0.06	<0.001			
	Cohen's d effect size (95% CI)	-0.39 (-0.81, 0.02)	-1.27 (-1.69, -0.85)			
ESR (mg/dl)	Saffron	70.29 ± 34.25	64.92 ± 25.4	0.21	-5.36 ± 28.75	<0.001
	Placebo	64.72 ± 34.18	89.02 ± 27.35	<0.001	24.29 ± 28.24	
	P-value	0.44	<0.001			
	Cohen's d effect size (95% CI)	0.16 (-0.26, 0.58)	-0.91 (-1.33, -0.49)			
IL-6 (Pg/ml)	Saffron	108.42 ± 60.12	86.32 ± 53.42	<0.001	-22.09 ± 25.22	<0.001
	Placebo	110.07 ± 54.90	106.04 ± 49.44	0.18	-4.02 ± 20.04	
	P-value	0.89	0.07			
	Cohen's d effect size (95% CI)	-0.03 (-0.45,0.39)	-0.38 (-0.8, 0.04)			
TNF-α (Pg/ml)	Saffron	12.60 ± 4.37	10.07 ± 2.91	<0.001	-2.52 ± 3.79	<0.001
	Placebo	12.44 ± 4.03	12.08 ± 4.19	0.31	-0.35 ± 2.35	
	P-value	0.86	0.01			
	Cohen's d effect size (95% CI)	0.04 (-0.38, 0.46)	-0.56 (-0.98, -0.14)			
IL-18 (Pg/ml)	Saffron	57.59 ± 14.24	48.02 ± 13.58	<0.001	-9.56 ± 9.31	<0.001
	Placebo	55.88 ± 16.16	54.98 ± 15.71	0.08	-0.89 ± 3.38	
	P-value	0.59	0.02			
	Cohen's d effect size (95% CI)	0.11 (-0.31, 0.53)	-0.47 (-0.89, -0.06)			

Abbreviations: CRP; C-reactive protein, ESR; erythrocyte sedimentation rate, IL; interleukin, TNF-α; Tumor necrosis factor alpha; CI: confidence interval

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 saffron and placebo groups

Variables	Group	Before intervention	After intervention	*P*-value**	Mean changes#	*p*-value
WBC (µL)	Saffron	13731.06 ± 3718.4	9554.71 ± 2961.91	<0.001	-4176.34 ± 4063.01	<0.001
	Placebo	13499.43 ± 4790.74	13,561 ± 3316.32	0.92	61.57 ± 4118.97	
	P-value	0.79	<0.001			
	Cohen's d effect size (95% CI)	0.05 (-0.36, 0.47)	-1.27 (-1.69, -0.86)			
Neutrophils (%)	Saffron	74.31 ± 9.59	71.83 ± 15.22	0.34	-2.47 ± 17.37	0.48
	Placebo	77.07 ± 8.43	74.13 ± 7.84	0.05	-2.93 ± 9.95	
	P-value	0.15	0.37			
	Cohen's d effect size (95% CI)	-0.31 (-0.72, 0.11)	-0.19 (-0.61, 0.23)			
Lymphocyte (%)	Saffron	17.19 ± 7.52	17.58.5.37	0.60	0.39 ± 5.09	0.21
	Placebo	14.61 ± 5.82	15.33 ± 5	0.46	0.71 ± 6.46	
	P-value	0.07	0.04			
	Cohen's d effect size (95% CI)	0.38 (-0.04, 0.8)	0.43 (0.01, 0.85)			
RBC (µL)	Saffron	3.83 ± 0.61	3.75 ± 0.45	0.32	-0.080.54	0.18
	Placebo	3.58 ± 0.34	3.54 ± 0.35	0.49	-0.03 ± 0.36	
	P-value	0.02	0.02			
	Cohen's d effect size (95% CI)	0.51 (0.09, 0.93)	0.52 (0.1, 0.94)			
Hb **(g/dL)**	Saffron	10.36 ± 1.49	10.24.1.58	0.62	-0.11 ± 1.55	0.19
	Placebo	10.16 ± 1.42	9.81 ± 1.18	0.10	-0.34 ± 1.38	
	P-value	0.50	0.14			
	Cohen's d effect size (95% CI)	0.14 (-0.28, 0.56)	0.31 (-0.11, 0.73)			
Hct (%)	Saffron	31.44 ± 4.93	32.05 ± 4.87	0.37	0.60 ± 4.54	0.06
	Placebo	30.79 ± 4.57	30.39 ± 2.66	0.56	-0.39 ± 4.55	
	P-value	0.51	0.04			
	Cohen's d effect size (95% CI)	0.14 (-0.28, 0.56)	0.42 (0.00, 0.84)			
MCV (fl.)	Saffron	84.48 ± 6.47	85.15 ± 5.74	0.25	0.66 ± 3.84	0.58
	Placebo	85.06 ± 5.30	85.90 ± 4.39	0.10	0.84 ± 3.44	
	P-value	0.64	0.48			
	Cohen's d effect size (95% CI)	-0.1 (-0.52, 0.32)	-0.15 (-0.57, 0.27)			
MCH **(pg)**	Saffron	27.10 ± 2.65	26.97 ± 1.97	0.54	-0.12 ± 1.43	0.54
	Placebo	27.01 ± 1.77	27.03 ± 1.65	0.86	0.02 ± 0.90	
	P-value	0.86	0.18			
	Cohen's d effect size (95% CI)	0.04 (-0.38, 0.46)	-0.03 (-0.45, 0.39)			
MCHC (g/dl)	Saffron	32.10 ± 1.81	31.66 ± 1.15	0.06	-0.43 ± 1.55	0.28
	Placebo	31.67 ± 1.14	31.80 ± 1.42	0.60	0.12 ± 1.60	
	P-value	0.18	0.61			
	Cohen's d effect size (95% CI)	0.28 (-0.13, 0.70)	-0.11 (-0.53, 0.31)			
PLT (µL)	Saffron	278990.79 ± 130107.67	308031.36 ± 78889.79	0.11	29040.56 ± 120466.12	0.2
	Placebo	243621.4 ± 112479.34	318532.10 ± 108062.43	<0.001	74910.70 ± 108276.04	
	P-value	0.17	0.60			
	Cohen's d effect size (95% CI)	0.29 (-0.13, 0.71)	-0.11 (-0.53, 0.31)			

Abbreviations: WBC; white blood cell count, RBC; red blood cell, PLT; Platelet, Hb, hemoglobin; Hct, Hematocrit, CI: confidence interval

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

= 9) which indicated a lower mortality rate in the saffron group. The small sample size is likely responsible for the lack of statistical significance.

Discussion

This was the first randomized controlled trial to investigate whether saffron supplementation could help ICU patients with sepsis. Results showed that supplementing with 100 mg saffron for seven days improved several clinical, inflammatory, and hematological parameters. There was an improvement in some parameters in both groups, which can be attributed to the positive effects of enteral nutrition and medical therapy, but these improvements were not significant in placebo groups.

APACHE II, NUTRIC, sofa score, CRP, IL-6, IL-18, TNF-A, ESR, and WBC levels were significantly improved in the intervention group in comparison to the placebo group. In contrast, other variables did not

show a significant difference between the two groups. The findings of this study are important for patients with increased inflammatory markers in the ICU due to sepsis being associated with excessive immune responses and systemic inflammation [26]. Since the baseline WBC levels in patients were above normal, the observed decrease in WBC levels may indicate an improvement in their condition, potentially due to the anti-inflammatory effects of saffron supplementation, which helped bring the levels back to normal. However, longer-term studies are recommended to confirm the results. In line with our findings, several studies have indicated saffron's anti-inflammatory properties. Administration of two capsules per day containing 15 mg crocin significantly decreased the serum levels of TNF-α and IL-6 among COPD patients in comparison with the placebo group [27]. Moreover, Crocin reduced IL-8, TNF-α, IL-6, and IL-1β levels in human bronchial epithelial cells [28]. In patients with diabetes, Shahbazian et al. found that 15 mg of saffron two times a day improved serum levels of CRP [29]. 100 mg of saffron decreased serum TNF-α levels in metabolic syndrome patients [30]. In individuals with active rheumatoid arthritis, 100 mg of saffron consumption decreased the ESR [31] Based on a systematic review and meta-analysis of preclinical studies, saffron significantly lowered WBC [32]. Another study assessed 70 ICU patients with sepsis. In this study, patients were divided into a control group, which received continuous blood purification treatment, and a treatment group that received continuous blood purification along with SESYA treatment, an extract of saffron known as saffron yellow A. The results revealed that, compared to the control group, the treatment group experienced a significant reduction in serum functional indicators including lactic acid, procalcitonin, CRP, and coagulation function indicators. Additionally, the treatment group demonstrated improved quality of life scores. Both groups showed a substantial decrease in organ function indicators after treatment, with the treatment group exhibiting significantly greater improvement than the control group [33].

Contrary to our article, a meta-analysis showed that saffron supplementation did not significantly affect serum CRP, TNF-alpha, and IL-6 levels [14]. However, this meta-analysis indicated that in studies with baseline CRP levels of at least 3 mg/L [14], a significant reduction in serum CRP levels was found, which is a condition common to ICU patients. This contradictory effect of saffron may be attributed to the differences in the disease nature, sample size, and concentrations used.

The anti-inflammatory properties of saffron may be mediated by several pathways. Firstly, saffron's active compounds, such as crocin and safranal, may inhibit the nuclear factor kappa B (NF-κB) signaling pathway [34], which plays a crucial role in the expression of pro-inflammatory cytokines [35]. However, this study does not provide direct mechanistic data to confirm this pathway. By modulating this pathway, saffron can decrease the production of IL-6, TNF-α, and WBC [35]. Secondly, saffron might activate antioxidant enzymes, reducing oxidative stress, which activates inflammatory pathways [36]. The third, saffron influences the mitogen-activated protein kinase (MAPK) pathway, which further decreases IL-18 and TNF-α levels [37]. Furthermore, saffron may also inhibit inflammation by modulating macrophage polarization, shifting from pro-inflammatory M1 to anti-inflammatory M2 phenotypes, and decreasing CRP, WBC, and ESR simultaneously [38]. Overall, these mechanisms demonstrate saffron's multifaceted role in inhibiting inflammation and its therapeutic potential in inflammatory disorders.

Beyond its anti-inflammatory effect, previous studies also indicated saffron's immunomodulatory effect [39] that may result in improved clinical outcomes. Studies suggest that saffron modulates both innate and adaptive immune responses through the regulation of immunoglobulin levels, e.g., IgG, IgA, and IgM, which are vital immune defenses [39, 40]. Saffron may also modulate cytokine profiles through the suppression of pro-inflammatory cytokines (e.g., TNF-α, IL-6) and enhancement of anti-inflammatory mediators (e.g., IL-10) [39]. It also participates in Th1/Th2 response balance and T-regulatory cell function maintenance, contributing to immune homeostasis [41].

Furthermore, in the present study, the observed reduction in APACHE II, SOFA, and NUTRIC scores could be attributed not only to reduced organ dysfunction and inflammation but also to saffron's immunomodulatory effects [39], which may enhance immune regulation and promote better clinical outcomes in critically ill patients [42]. These findings indicate that saffron might be an immunonutrition agent in critical care patients. However, the exact mechanisms responsible for the effect of saffron supplementation on APACHE II, NUTRIC, and SOFA scores remain unclear because of a lack of research in this area.

The current study also revealed that although saffron supplementation improved certain clinical and laboratory parameters, it did not reach statistical significance for reducing mortality. However, both 28 and 90-day mortality rates in the intervention group were lower than those in the control group (15.6% vs. 24.4% and 20% vs. 31.1%), suggesting saffron was clinically effective. The small sample size is likely responsible for the lack of statistical significance. Future trials with larger sample sizes are needed to evaluate this supplement's effectiveness on mortality.

Strengths and limitations of the study

Saffron has not previously been studied among septic patients in ICU, as far as we know. Additionally, by randomizing participants, confounding factors could be minimized. However, there are some limitations to this study. Since we did not include refractory septic shock patients in this study, the results cannot be generalized to all sepsis patients. In addition, higher dosages of saffron and a longer supplementation period might increase efficacy. Several factors contributed to the short follow-up of this study, including imminent death, transfers to the ward, or total parenteral nutrition requirements. Lastly, a monotherapy evaluation of saffron was also impossible due to ethical concerns. Future studies should also consider incorporating detailed microbiologic data to better assess the impact of saffron on infection control and immune response in septic patients. Additionally, evaluating immunoglobulin levels, such as IgG, IgA, and IgM, which are vital immune defenses, is recommended in future research to better elucidate the immunomodulatory mechanisms of saffron.

Conclusion

In conclusion, saffron supplements may benefit sepsis patients in the ICU by improving NUTRIC, APACHE-II, and SOFA scores, as well as serum levels of WBC, IL-6, TNF-α, and IL-18. Despite this, further studies in this field are necessary due to a lack of research in this area. It is important to conduct future studies with a longer intervention duration and a larger sample size to get more precise results.

Abbreviations

ICU	Intensive care unit
APACHE II	Acute physiology and chronic health evaluation
SOFA	Sequential Organ Failure Assessment
NUTRIC	Nutrition Risk in the Critically ill
EXP	Expire; MAC: Mid-arm circumference
MAP	Mean arterial pressure
NSAID	Nonsteroidal anti-inflammatory drugs
PPI	Proton pump inhibitors
GCS	Glasgow Coma Scale
CRP	C-reactive protein
ESR	erythrocyte sedimentation rate
IL	interleukin
TNF-α	Tumor necrosis factor alpha
ANCOVA	Analysis of covariance
WBC	White blood cell count
RBC	Red blood cell
PLT	Platelet
Hb	Hemoglobin
Hct	Hematocrit
COPD	Chronic obstructive pulmonary disease
NNT	Number needed to treat
HPLC	High-performance liquid chromatography
IRCT	Iranian Registry of Clinical Trials
NFKB	Nuclear transcription kappa factor-B

Supplementary Information

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Supplementary Material 1

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Author contributions

Design and concept: M.B, MH. R, Sh.H. Data acquisition, analysis, or interpretation: M.B, MH. R, Sh. H, and B.A. Manuscript drafting: Sh. H and Sh.T. Revision of the manuscript: M.B, M.S. Data analysis: Sh.H. M.B. supervises the study and is responsible for the integrity and accuracy of all study data. The final version was read and approved by all authors.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

It was approved by the Medical Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1402.466). Written informed consent was obtained from all of the participants or their families.

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.

Conflict of interest

There are no conflicts of interest among the authors.

Author details

[1]Student Research Committee, Isfahan University of Medical Sciences, Isfahan, Iran
[2]Department of Community Nutrition, School of Nutrition and Food Science, Nutrition and Food Security Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
[3]Anesthesia and Critical Care Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
[4]Department of Social & Behavioral Health, School of Public Health, University of Nevada, Las Vegas, NV, USA

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