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RESEARCH ARTICLE

Effect of curcumin supplementation on disease severity in patients with liver cirrhosis: A randomized controlled trial

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Recent reports indicated that curcumin had beneficial effects in animal models of liver injury and cirrhosis. Current study aimed to investigate the effects of curcumin supplementation in patients with liver cirrhosis. In this randomized double-blind placebo-controlled trial, 70 patients with liver cirrhosis aged 20–70 years were randomly divided into two groups to receive 1,000 mg/day curcumin (n = 35) or placebo (n = 35) for 3 months. Model for end-stage liver disease (MELD) (i), MELD, MELD-Na, and Child–Pugh scores were used to assess the severity of cirrhosis. Sixty patients (29 in the curcumin group and 31 in the placebo group) completed the study. MELD(i) (15.55 ± 3.78 to 12.41 ± 3.07), MELD (15.31 ± 3.07 to 12.03 ± 2.79), MELD-Na (15.97 ± 4.02 to 13.55 ± 3.51), and Child–Pugh (7.17 ± 1.54 to 6.72 ± 1.31) scores decreased significantly in the curcumin group after 3-month intervention (p < .001, p < .001, p = .001, and p = .051, respectively), whereas they increased significantly in the placebo group (p < .001, p < .001, p < .001, p = .001, respectively). Significant differences were only observed between the two groups in MELD(i), MELD, MELD-Na, and Child–Pugh scores after 3-month intervention (p < .001 for all of them). In this pilot study, beneficial effects of curcumin supplementation were observed in decreasing disease activity scores and severity of cirrhosis in patients with cirrhosis.

KEYWORDS
controlled clinical trial, curcuma, curcumin, end-stage liver disease, liver cirrhosis

1 | INTRODUCTION

Liver cirrhosis is an end-stage condition and a complicated situation identified by progressive fibrosis and disruption of the liver tissue. It has been considered as a significant risk factor for hepatocellular carcinoma and the prominent cause of liver disease-associated morbidity and mortality (Schuppan & Afdhal, 2008; Zhao et al., 2014). The prevalence of cirrhosis has increased 1.5-fold to twofold during the past two decades (Moon, Singal, & Tapper, 2019), and it is indicated that chronic liver disease and cirrhosis account for two million deaths worldwide every year (Moon et al., 2019). The incidence of cirrhosis in Europe, East Asia, and Southeast Asia is estimated to be 26.0, 16.5, and 23.6 per 100,000, respectively (Wong et al., 2019). Chronic liver injury leads to an inordinate accumulation of molecules such as collagen, proteoglycans, and so forth in the extracellular matrix causing organ fibrosis, portal hypertension, increased loss of liver function, and even death (Friedman, 2008). It seems that histological changes resulting from cirrhosis are irreversible; however, liver fibrosis, even the more advanced phases, can be ameliorated with proper treatment (Ismail & Pinzani, 2009). Furthermore, amelioration of liver fibrosis not only prevents the development of liver cirrhosis but also decreases the liver cancer development and improve survival (Ismail & Pinzani, 2009).

Currently, there are no approved agents available for prevention and treatment of liver fibrosis; however, possible antifibrotic treatments are used for inhibiting fibrogenic cells activation, inducing

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activated hepatic stellate cells (HSCs) apoptosis, and/or preventing extracellular matrix proteins deposition (Wu, Huang, Xiong, & Wu, 2016). Recently, more attention has been paid to natural herbal remedies as a potential therapy for liver cirrhosis, particularly due to their plentiful source of antifibrogenic agents as well as their lesser adverse effects, lower costs, and higher acceptability.

Curcumin is a natural polyphenol and the major active ingredient in the *Curcuma longa* (generally known as turmeric) that is widely used as a medicinal plant in different countries (Qiu et al., 2017). Curcumin has various biologic and pharmacologic effects including anti-inflammatory, antioxidant, anticancer, antimicrobial, antiangiogenic, antithrombotic, wound-healing properties, and so forth (Qiu et al., 2017) and has been the main subject of research in recent years. Its action is mediated by either direct interaction with molecular targets or modifying gene expression and signaling pathways (Cai et al., 2017). Recent reports indicated that curcumin had beneficial effects in animal models of liver injury and cirrhosis (Bisht et al., 2011; Bruck et al., 2007; Rivera-Espinoza & Muriel, 2009; Wu et al., 2016). It has been suggested that curcumin inhibits liver cirrhosis through its action on multiple pathways such as inhibiting the NF-κB pathway and suppressing inflammation, reducing oxidative stress, and inhibiting angiogenesis. Therefore, curcumin has gained attention as a promising agent for prevention and treatment of different hepatic disorders including liver fibrosis (Cai et al., 2017; Zhang et al., 2014).

To the best of our knowledge, there is no study investigating the effects of curcumin in patients with liver cirrhosis, and majority of studies regarding the effects of curcumin on liver cirrhosis were limited to animal and in vitro models; therefore, we designed this study as the first clinical trial to determine the effects of curcumin supplementation in liver cirrhotic patients.

2 | METHODS

2.1 | Study design

This parallel randomized double-blind placebo-controlled trial was a Phase III clinical trial and was performed between October 2018 and July 2019 in a tertiary center. The study protocol was approved by the Medical Ethics Committee of Tabriz University of Medical Sciences and registered on the Iranian Registry of Clinical Trials (registration code: IRCT20180802040678N1). All patients were informed about the content of the study, and a written informed consent was gained from all participants.

2.2 | Study participants

Eligibility criteria included patients with liver cirrhosis aged 20–70 years with model for end-stage liver disease (MELD) score > 11 and arterial oxygen pressure > 60 mmHg who were selected from the gastroenterology outpatient clinic of Tabriz University of Medical Sciences. Exclusion criteria were any history of malignancy, hepatopulmonary syndrome, pulmonary hypertension (mean pulmonary artery pressure > 25 mmHg), hyperoxaluria, cystic fibrosis with FEV1 < 40%, gallstones and/or bladder stones, use of antiplatelet and/or anticoagulant medications, and taking polyphenol supplements within 3 months prior to the study.

2.3 | Sample size

The sample size was calculated based on data obtained from the study by Rahmani et al. (2016) on serum aspartate aminotransferase (AST) concentration. Considering a confidence level of 95% and power of 80%, the sample was determined at least 28 cases in each group. The sample size was increased to 35 cases in each group for a possible dropout rate of 25%.

2.4 | Randomization

Patients who had the eligibility criteria were randomly divided into intervention and placebo groups using a block randomization procedure (Random Allocation Software; block size = 2), which matched subjects to each block based on age, sex, and MELD score. A computer-generated random number was maintained in a remote secure place. To maintain blinding, the allocation was conducted by an investigator with no involvement in the study. Furthermore, participants and those involved in enrolling participants, administering interventions, and assessing outcomes remained blind throughout randomization and allocation until all data were obtained and analyzed.

2.5 | Interventions

Patients in the intervention group (n = 35) received an oral dose of 1,000 mg curcumin per day divided into two equal doses of one 500 mg capsule for 3 months (curcumin, Karen Pharmaceutical & Nutrilife Co., Yazd, Iran). The control group (n = 35) received placebo according to the same regimen and for the same duration (placebo, Karen Pharmaceutical & Nutrilife Co.). Placebo capsules contained inactive ingredients with no therapeutic activity and were identical to supplements in shape and color. Subjects were advised to take the supplements with breakfast and dinner meals. The participants were asked to maintain their usual dietary intakes and physical activity during the study period. Patients were monitored weekly for any side effects of curcumin supplementation. A diagram of the study design is shown in Figure 1.

2.6 | Outcomes

At the beginning of the study, all patients underwent routine physical examinations. Body weight was measured to the nearest 0.1 kg using a Seca scale (Hamburg, Germany), and height was also measured using a mounted tape to the nearest 0.5 cm. Body mass index was

calculated by dividing weight (in kilograms) by the square of height (in meters; Hammond & Litchford, 2012).

At the beginning and at the end of the study, 5 ml of venous blood samples were collected after a 12-hr overnight fasting. As a primary outcome, Child–Pugh score, MELD(i) (pre-2016), MELD, and MELD-Na scores were used to determine the severity of cirrhosis (Kamath et al., 2001; W. R. Kim et al., 2008; Pugh, Murray-Lyon, Dawson, Pietroni, & Williams, 1973; Wiesner et al., 2003). The following formulas were used for MELD(i), MELD, and MELD-Na calculation, respectively:

$$\mathrm{MELD(i)} = 0.957 \times \ln(\mathrm{Cr}) + 0.378 \times \ln(\mathrm{bilirubin}) + 1.120 \times \ln(\mathrm{INR}) + 0.643,$$

$$\mathrm{MELD} = \mathrm{MELD(i)} + 1.32 \times (137 - \mathrm{Na}) - [0.033 \times \mathrm{MELD(i)} \times (137 - \mathrm{Na})],$$

$$\mathrm{MELD - Na} = \mathrm{MELD\ Score} - \mathrm{Na} - 0.025 \times \mathrm{MELD} \times (140 - \mathrm{Na}) + 140.$$

All score calculations were performed using MDCalc medical calculator application (MD Aware, LLC, New York, NY).

As a secondary outcome, prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR) tests were performed. Serum AST, alanine aminotransferase (ALT), and alkaline phosphatase (ALP) as well as serum albumin, creatinine, bilirubin, and sodium were measured using routine enzymatic assays with commercial kits (Pars-Azmoon, Tehran, Iran).

2.7 | Statistical analysis

Statistical analysis was performed using SPSS version 16.0 software (SPSS Inc., Chicago, IL). Normality of variables distribution was evaluated using the Kolmogorov–Smirnov test. Qualitative and normally distributed quantitative variables were displayed as numbers (percentages) and means ± standard deviation, respectively. The differences between variables before and after the intervention were compared by paired *t* test. Between-group comparisons were made by chi square or independent sample *t* test, as appropriate. Analysis of covariance (ANCOVA) was used to identify any differences between the two groups at the end of the study. The Sign and Mann–Whitney *U* tests were used for intragroup and intergroup comparisons of the qualitative data, respectively; $p < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Characteristics of study subjects

From 70 individuals who met the inclusion criteria and enrolled to the study, six subjects in the curcumin group and four subjects in the placebo group were withdrawn due to lost to follow-up and mortality (Figure 1). It should be mentioned that the cause of mortality was due to the severity of liver cirrhosis. Therefore, data were reported for 60 patients (29 in the curcumin group and 31 in the placebo group). The means ± standard deviation age, body mass index, and duration of disease in study participants were 45.95 ± 11.61 years, 24.82 ± 3.05 kg/m^2, and 4.41 ± 3.06 years, respectively. Thirty-one participants (52%) were males and 29 subjects (48%) were females. As illustrated in Table 1, there were no significant differences in demographic characteristics or in the duration of disease between the study groups at baseline ($p > .05$).

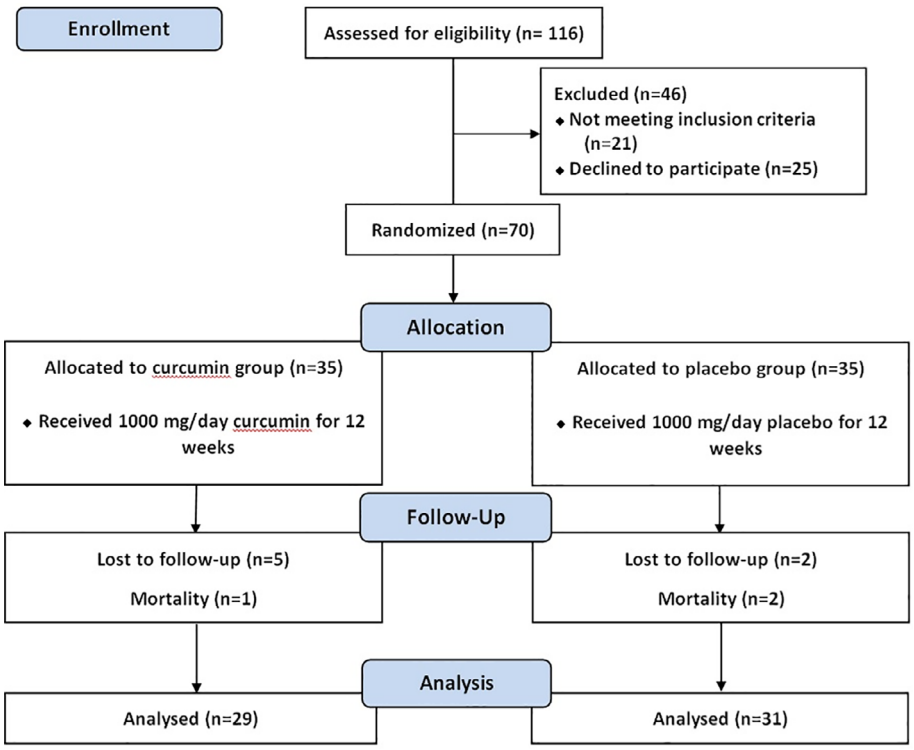

FIGURE 1 Study flow diagram

3.2 | Effects of curcumin supplementation on biochemical variables

Table 2 demonstrates biochemical parameters before and after intervention in the curcumin and placebo groups. No significant differences were observed between the two groups in terms of AST, ALT, ALP, bilirubin, INR, albumin, creatinine, sodium, PT, and PTT levels at baseline ($p > .05$). Serum ALP level decreased significantly in the curcumin group ($p = .019$), whereas it did not change significantly in the placebo group ($p > .05$) after the experimental period. Furthermore, serum bilirubin and INR levels decreased significantly in the curcumin group ($p = .041$ and $p < .001$, respectively), whereas they increased significantly in the placebo group ($p < .001$ and $p = .001$, respectively) after the experimental period. In addition, PT level did not change significantly in the curcumin group ($p > .05$), whereas it increased significantly in the placebo group ($p = .007$) after the study. No significant changes were observed in AST, ALT, albumin, creatinine, sodium, and PTT levels neither in the curcumin group nor in the placebo group after the trial ($p > .05$). At the end of the study, results of ANCOVA test showed statistically significant differences between the two groups only in ALP ($p = .002$), bilirubin ($p < .001$), INR ($p < .001$), and PT ($p = .002$) levels (Table 2).

TABLE 1 Baseline characteristics of study subjects

Variable	Curcumin group ($n = 29$)	Placebo group ($n = 31$)	p[a]
Age (years)	45.82 ± 12.78	46.06 ± 10.61	.938
Sex, n (%)			.611
Male	14 (48)	17 (55)	
Female	15 (52)	14 (45)	
Causes of liver cirrhosis, n (%)			.850
Cryptogenic	10 (34.5)	8 (25.8)	
Autoimmune	9 (31)	8 (25.8)	
HBV	3 (10.3)	4 (12.9)	
HCV	2 (6.9)	2 (6.5)	
PSC	2 (6.9)	2 (6.5)	
PVT	2 (6.9)	2 (6.5)	
Alcoholic	1 (3.4)	3 (9.7)	
Fatty liver	0 (0.0)	2 (6.5)	
Duration of liver cirrhosis (years)	4.52 ± 2.88	4.31 ± 3.25	.792
Weight (kg)	70.24 ± 8.74	70.74 ± 9.66	.834
BMI (kg/m^2)	24.85 ± 2.97	24.80 ± 3.17	.948

Note: Continuous variables were reported as mean ± standard deviation, whereas categorical variables were expressed as frequency (percentage); $p < .05$ was considered significant.

Abbreviations: BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; PSC, primary sclerosing cholangitis; PVT, portal vein thrombosis.

[a]p values indicate comparison between groups (independent sample t test or chi square, as appropriate).

3.3 | Effects of curcumin supplementation on disease activity scores

Table 3 depicts disease activity scores before and after intervention in the curcumin and placebo groups. No significant differences were observed between the two groups in terms of MELD(i), MELD, MELD-Na, and Child–Pugh scores at baseline ($p > .05$). MELD(i), MELD, MELD-Na, and Child–Pugh scores decreased significantly in the curcumin group after 12-week intervention ($p < .001$, $p < .001$, $p = .001$, and $p = .051$, respectively), whereas these scores increased significantly in the placebo group ($p < .001$, $p < .001$, $p < .001$, and $p = .001$, respectively). At the end of the study, results of ANCOVA test showed statistically significant differences between the two groups in MELD(i), MELD, MELD-Na, and Child–Pugh scores ($p < .001$ for all of them; Table 3).

As demonstrated in Figure 2, at baseline and after 12 weeks of treatment, there were no significant differences in MELD-Na score classification between the two groups ($p > .05$). Results of the sign test did not show significant intragroup changes in MELD-Na score classification in the curcumin group ($p > .05$), whereas changes were significant in the placebo group ($p = .002$).

3.4 | Safety of curcumin supplementation

Participants did not report any adverse effects or symptoms with the curcumin or placebo consumption during the study, which confirmed the safety of curcumin in the present study as well as previous investigations.

4 | DISCUSSION

Curcumin has gained increasing attention as a therapeutic agent in recent years and shows potential utility in prevention and treatment of various health problems such as diabetes, cancers, respiratory conditions, cardiovascular, metabolic, neurologic, and infectious disorders (Khan, Ullah, & Nabavi, 2019). It has also been indicated that curcumin possesses hepatoprotective effects and exhibits therapeutic functions in different liver diseases including hepatitis, alcoholic liver disease, nonalcoholic fatty liver disease (NAFLD), drug-induced hepatotoxicity, liver cancer, biliary cirrhosis, and primary sclerosing cholangitis (Nabavi, Daglia, Moghaddam, Habtemariam, & Nabavi, 2014). To the best of our knowledge, this is the first randomized double-blind placebo-controlled trial to assess the effects of curcumin supplementation in patients with liver cirrhosis. Our results indicated that curcumin supplementation led to a significant reduction in serum levels of ALP, bilirubin, and INR compared with the baseline and those in the placebo group. Moreover, curcumin caused significant reduction in PT compared with the placebo group. Our research also showed that curcumin supplementation contributed to a significant reduction in disease activity scores and severity of cirrhosis compared with the baseline and those in the placebo group. These findings were in

TABLE 2 Comparison of biochemical variables in treatment groups before and after intervention

Variable	Measurement period	Curcumin group (n = 29)	Placebo group (n = 31)	p^a
AST (IU/L)	Baseline	61.79 ± 60.19	55.61 ± 30.29	.622
	After 12 weeks	54.58 ± 45.45	65.00 ± 43.29	.367
	p^b	.160	.254	
ALT (IU/L)	Baseline	46.31 ± 44.57	48.80 ± 35.09	.810
	After 12 weeks	41.13 ± 28.15	45.41 ± 31.06	.579
	p^b	.294	.597	
Alkaline phosphatase (IU/L)	Baseline	334.62 ± 195.85	349.71 ± 216.27	.778
	After 12 weeks	278.65 ± 118.67	341.87 ± 147.65	.002
	p^b	.019	.683	
Bilirubin (mg/dl)	Baseline	2.54 ± 1.16	2.12 ± 1.22	.176
	After 12 weeks	2.15 ± 1.10	2.87 ± 1.43	<.001
	p^b	.041	<.001	
Albumin (g/dl)	Baseline	3.67 ± 0.59	3.51 ± 0.65	.336
	After 12 weeks	3.63 ± 0.66	3.39 ± 0.66	.146
	p^b	.873	.391	
Creatinine (mg/dl)	Baseline	0.95 ± 0.19	1.00 ± 0.36	.488
	After 12 weeks	0.95 ± 0.16	1.01 ± 0.36	.518
	p^b	.890	.415	
Sodium (mmol/L)	Baseline	139.55 ± 3.69	139.93 ± 2.71	.647
	After 12 weeks	138.52 ± 3.11	138.74 ± 2.35	.787
	p^b	.262	.042	
PT (s)	Baseline	16.67 ± 2.13	16.02 ± 4.51	.477
	After 12 weeks	15.81 ± 2.82	17.61 ± 4.56	.002
	p^b	.066	.007	
INR	Baseline	1.57 ± 0.46	1.38 ± 0.47	.107
	After 12 weeks	1.39 ± 0.44	1.68 ± 0.67	<.001
	p^b	<.001	.001	
PTT (s)	Baseline	37.62 ± 7.28	40.60 ± 14.48	.913
	After 12 weeks	35.62 ± 3.07	41.95 ± 18.65	.361
	p^b	.370	.469	

Note: Values are means ± standard deviation; $p < .05$ was considered significant.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time.

[a]p values indicate comparison between groups (independent sample t test at baseline and analysis of covariance test after 3 months).

[b]p values indicate comparison within groups (paired t test).

agreement with the results of previous studies indicating that curcumin attenuated liver fibrosis and had beneficial effects in experimental and animal models of liver injury and cirrhosis (Bisht et al., 2011; Bruck et al., 2007; Kyung et al., 2018; Reyes-Gordillo et al., 2008; Rivera-Espinoza & Muriel, 2009; Shu, He, Lv, Ye, & Wang, 2009; Wu et al., 2016). Furthermore, our study was in line with Selmanovic et al. (2017), who noted that curcumin significantly improved morphological characteristics of the liver in individuals with metabolic syndrome. In addition, two recent studies in patients with NAFLD demonstrated that curcumin decreased the portal vein diameter and increased vein flow as well as improved liver ultrasonographic parameters and ameliorated disease severity (Panahi et al., 2017; Rahmani et al., 2016). It seems that therapeutic potential of curcumin and its hepatoprotective effects mainly attributed to its antioxidant characteristics (Farombi, Shrotriya, Na, Kim, & Surh, 2008; Menon & Sudheer, 2007). Curcumin is found to be more active antioxidant than vitamin E (Shishodia, Sethi, & Aggarwal, 2005). It has been reported that curcumin improves oxidative stress and raises glutathione level as well as activity of various antioxidant enzymes including glutathione peroxidase, glutathione transferase, superoxide dismutase, catalase, and heme-oxygenase-1 through modulating Nrf2 signaling pathway; therefore, it protects against free radical damage (Ak & Gulcin, 2008; Jagetia & Rajanikant, 2015; Motterlini, Foresti, Bassi, & Green, 2000). In addition to Nrf2, curcumin also stimulates the expression and

TABLE 3 Comparison of disease activity scores in treatment groups before and after intervention

Variable	Measurement period	Curcumin group (n = 29)	Placebo group (n = 31)	p^a
MELD(i) score	Baseline	15.55 ± 3.78	13.74 ± 4.08	.080
	After 12 weeks	12.41 ± 3.07	17.03 ± 4.11	<.001
	p^b	<.001	<.001	
MELD score	Baseline	15.31 ± 3.07	13.61 ± 3.76	.062
	After 12 weeks	12.03 ± 2.79	16.97 ± 3.97	<.001
	p^b	<.001	<.001	
MELD-Na score	Baseline	15.97 ± 4.02	13.87 ± 4.26	.056
	After 12 weeks	13.55 ± 3.51	17.74 ± 4.19	<.001
	p^b	.001	<.001	
Child–Pugh score	Baseline	7.17 ± 1.54	6.61 ± 1.72	.191
	After 12 weeks	6.72 ± 1.31	7.39 ± 1.91	<.001
	p^b	.051	.001	

Note: Values are means ± standard deviation; $p < .05$ was considered significant.
Abbreviation: MELD, model for end-stage liver disease.
[a]p values indicate comparison between groups (independent sample t test at baseline and analysis of covariance test after 3 months).
[b]p values indicate comparison within groups (paired t test).

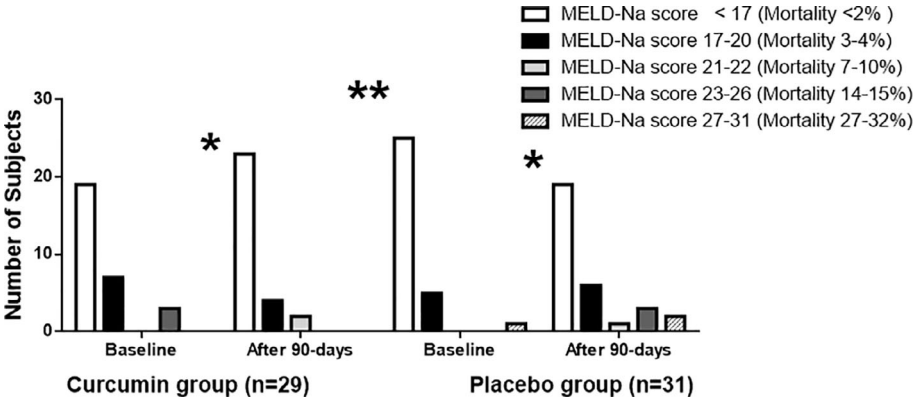

FIGURE 2 Number of subjects according to MELD-Na score classification in treatment groups before and after intervention. *Sign test for intragroup changes (p = .065 for the curcumin group and p = .002 for the placebo group). **Mann–Whitney U test for intergroup changes (at baseline: p = .177 and after 3 months: p = .092)

activity of farnesoid X receptor in the liver, thereby inhibiting hepatic steatosis and preventing liver injury (Lu et al., 2015). In addition to the role of oxidative stress in liver damage, inflammation is also known as an important factor in the initiation and development of liver fibrosis and cirrhosis. Chronic hepatic inflammation is accompanied by the upregulation of proinflammatory cytokines and chemotactic mediators that activate HSCs (Friedman, 2008; U. E. Lee & Friedman, 2011). Downregulating transcription factors such as activator protein-1, CREB binding protein, STAT proteins, and NF-κB is responsible for anti-inflammatory effects of curcumin (Gupta, Patchva, Koh, & Aggarwal, 2012). Of note, suppressing NF-κB activation has been demonstrated as one of the main central inflammatory mediators of curcumin (Aggarwal, Gupta, & Sung, 2013). Moreover, curcumin inhibited the nuclear binding of NF-κB and inducible nitric oxide synthase protein expression, thereby improving survival in rats with thioacetamide-induced hepatotoxicity (Shapiro et al., 2006). Furthermore, curcumin modulated farnesoid X receptor that could suppress the inflammatory genes, such as TNF-α, IL-1β, IL-6, and inducible nitric oxide synthase, thereby controlling the inflammation pathway (Vavassori, Mencarelli, Renga, Distrutti, & Fiorucci, 2009; Woolbright et al., 2015). It has been noted that in response to chronic liver injuries, HSCs are changed to active contractile myofibroblasts and cause microcirculation disturbances (Garbuzenko, Arefyev, & Belov, 2016). It also directly targets and alleviates inflammatory cytokines and mediators (Gupta et al., 2012; Selmanovic et al., 2017). Curcumin mitigates proliferation and activation but elevates apoptosis in HSCs. It also inhibits extracellular matrix formation by increasing HSCs matrix metalloproteinase expression through peroxisome proliferator-activated receptor gamma and by suppressing connective tissue growth factor expression (O'Connell & Rushworth, 2008). Furthermore, curcumin can induce the senescence of activated HSCs. When senescence of activated HSCs occurs, the senescent HSCs express all the components essential for natural killer cell recognition, thereby become vulnerable to natural killer cells killing (Jin et al., 2016); thus, curcumin may be a therapeutic antifibrous agent and can play a key role in improving liver fibrosis. Recent investigations also indicated that hepatic angiogenesis was related to fibrogenesis (Iwakiri, Shah, & Rockey, 2014), which could be improved by curcumin. According to

Yao et al.'s (2013) study, curcumin ameliorated intrahepatic angiogenesis and sinusoid capillarization in cirrhotic rats. In addition, Zhang et al. (2014) observed that curcumin reduced angiogenesis in liver fibrosis and inhibited HSCs angiogenic activities. Previous studies in the rat and hamster models of cirrhosis also revealed that curcumin decreased liver damage, thereby indicating that curcumin probably had its antihepatofibrotic effects (Chenari, Safari, & Moradi, 2017; Macias-Perez et al., 2019). Similarly, Huang et al. (2016) demonstrated that curcumin ameliorated fibrosis in vivo possibly via targeting Gr1hi and Ly6Chi monocytes infiltration by lowering monocyte chemoattractant protein-1. Moreover, in biliary cirrhosis, curcumin showed antifibrogenic activities associated with the downregulation of transforming growth factor-β (Reyes-Gordillo et al., 2008). Furthermore, this antifibrotic feature of curcumin has been noticed in a transforming growth factor-β-driven model of fibrotic lung and kidney disorders (Gaedeke, Noble, & Border, 2004; Rivera-Espinoza & Muriel, 2009). Further studies are needed to address the mechanism of antifibrotic effect of curcumin in order to search its clinical usefulness as a hepatoprotective treatment.

Based on our study, curcumin supplementation did not cause significant changes in serum AST, ALT, albumin, creatinine, sodium, and PTT levels compared with the baseline and those in the placebo group, which was not consistent with animal studies that showed curcumin decreased serum ALT and AST levels (Y.-J. Kim, You, & Jun, 2012; H. Y. Lee et al., 2016; Naik, Thakare, & Patil, 2011). Moreover, previous studies in subjects with NAFLD (Rahmani et al., 2016) and with elevated ALT levels (S. W. Kim et al., 2013) reported that curcumin significantly reduced serum ALT and AST concentrations, but it did not change serum ALP and total bilirubin levels significantly. This discrepancy between our findings with mentioned studies may originate from differences in studied population, baseline serum AST and ALT status, curcumin doses, duration of the intervention, and research methodology. Notably, AST and ALT are not prognostic factors in liver cirrhosis and more attention should be paid to coagulation pathways, bilirubin, and metabolic function of the liver. Furthermore, Child–Pugh and MELD scores have been widely used to predict the outcomes of cirrhotic patients. According to Peng, Qi, and Guo (2016) study, Child–Pugh and MELD scores had similar prognostic values in majority of cases, and therefore, they may be a reliable prognostic scoring for disease severity in cirrhotic patients, which is used in the current study. Moreover, the study outcomes may be influenced by the supplement formulation. It is proposed that native curcumin has low bioavailability due to its hydrophobic nature, whereas nanoparticles formulation improves curcumin bioavailability and therapeutic efficacy (Garcia-Nino & Pedraza-Chaverri, 2014).

There were some limitations in the present study. First, we assessed liver state only by measuring liver enzymes and did not perform computed tomography scans, magnetic resonance scans, or liver biopsies. Second, we did not evaluate antioxidant enzyme activity and/or inflammatory mediators for better interpretation of the results. The strengths of current study were a relatively large sample size and long intervention period as well as monitoring patients' status by a telephone call and high acceptance of curcumin in patients.

In conclusion, despite observed beneficial effects of curcumin supplementation in decreasing serum levels of ALP, bilirubin, INR, and PT as well as disease activity scores and severity of cirrhosis in patients with cirrhosis, further studies are required to advise curcumin as a safe complementary treatment in these patients.

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CONFLICT OF INTEREST

The authors declared that there was no conflict of interest.

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