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RESEARCH ARTICLE

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Evaluation of the efficacy of oral nano-silymarin formulation in hospitalized patients with COVID-19: A double-blind placebo-controlled clinical trial

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Abstract

Considering the outbreak pandemic of Coronavirus Disease 2019 (COVID-19), the lack of effective therapeutic strategies for the management of this viral disease, and the increasing evidence on the antiviral potential of silymarin, this study aimed to investigate the effectiveness of silymarin nanomicelles on the symptom's resolution time, laboratory parameters, and liver enzymes in patients with COVID-19. The participants were assigned to the nano-silymarin ($n = 25$) (receiving SinaLive soft gel, containing 70 mg silymarin as nanomicelles) or placebo groups ($n = 25$) three times daily for two weeks. Patients' symptoms and laboratory findings were assessed at baseline and during the follow-up period (one week and one month after the beginning of the treatment). No significant differences were observed between the two groups in terms of symptoms resolution time, laboratory parameters, and hospitalization duration ($p > 0.05$). However, the alanine aminotransferase level decreased significantly in the treatment group, compared to the placebo group ($p < 0.001$). Concomitant use of dexamethasone and remdesivir with silymarin might make the effects of silymarin on the improvement of patients' condition unclear. Further clinical trials are recommended with diverse dosages and larger sample sizes.

KEYWORDS
anti-viral, COVID-19, cytokine release syndrome, SARS-COV-2, silymarin

1 | INTRODUCTION

On January 30, 2020, the World Health Organization declared Coronavirus Disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as a global crisis and public health issue worldwide (Guo et al., 2020). The virus is transmitted through respiratory droplets with a high rate of transmission from human to human. Dyspnea, fever, dry cough, myalgia, and fatigue are common clinical symptoms of the disease. Diarrhea, nausea, and vomiting were also identified in some cases (Li et al., 2020).

In more severe stages, SARS-CoV-2 can cause fatal symptoms, including pneumonia, acute respiratory distress syndrome, lung and other organ failures, and death (Badraoui, Alrashedi, El-May, & Bardakci, 2021). The body may produce large amounts of immune cells in response to this virus resulting in high pro-inflammatory cytokine levels secretion, including interleukin-2 (IL-2) and IL-7, interferon (INF)-γ inducible protein 10, and tumor necrosis factor (TNF)-α. This cytokine storm is one of the leading causes of death in people with COVID-19 disease (Brooks et al., 2020).

Until now, various therapeutic regimens have been developed to control the SARS-CoV-2 pandemic, such as remdesivir, corticosteroids, IL-6R antagonists, including tocilizumab (TCZ), IL-1 antagonists, including anakinra, TNF-α inhibitors, and Janus kinase inhibitors (Sarzi-Puttini et al., 2020; Zhang et al., 2020). New researches recommended the treatment of cytokine storms as a priority in the treatment of COVID-19 patients (Meng et al., 2020; Robinson, Richards, Tanner, & Feldmann, 2020).

Silymarin, an active component of milk thistle (*Silybum marianum*), which contain a mixture of various flavonolignans (silybin, silychristin, silydianin, isosilychristin, and unidentified fractions, such as polymeric and oxidized polyphenolic compounds) is one of phytochemical that acts as an antioxidant, anti-inflammatory, hepatoprotective, anti-cancer, immune response modulator, and antiviral (Hussain, Jassim, Numan, Al-Khalifa, & Abdullah, 2009; Mahi-Birjand et al., 2020; Roozbeh et al., 2011). Silymarin has been used in the treatment of liver disease (alcoholic and non-alcoholic hepatitis), drug-induced liver damage, cirrhosis, mushroom poisoning, and viral hepatitis over the past 40 years (Tian, Li, & Wang, 2017; Zhang et al., 2017).

Silibinin, the major bioactive component of the silymarin extract, has able to target host cellular mechanisms that are stimulated to defend against SARS-CoV-2 infection (e.g., STAT3-driven reactive immune-inflammation) (Bosch-Barrera et al., 2020). Silymarin in doses above 1,500 mg daily has been shown to be safe in clinical trials, and no adverse events have been reported; however, due to the lipophilic nature and very low water solubility of silymarin (0.04 mg/mL), degradation by gastric fluids, rapid hepatic metabolism, and low intestinal absorption, its oral bioavailability is poor at about 20% to 50% (Javed, Kohli, Ali, & m. r., 2011).

Nanomicelles were used in this trial to develop drug delivery and increase solubility and oral absorption (He, Hou, Lu, Zhu, & Feng, 2007; Parveen et al., 2011). Nanomicelles are amphiphilic polymers that in aqueous environment hydrophobic part orients away from the polar solvent and the hydrophilic part orients toward the polar solvent. These spherical nanomicelles have a particle size of about 10 nm, and the percentage of silymarin encapsulation is near to 100% in nanomicelles that increased the solubility of silymarin by 3,000 times in water leading to protect silymarin from the destructive effects of gastric fluids. Moreover, they are stable in the acidic environment of the stomach for at least three hours and reach the small intestine while maintaining their original properties. Nanomicelles facilitate the transport of silymarin from the intact layer on the surface of the intestinal epithelial cells-a barrier to the absorption of fat-soluble compounds-that increase the absorption of silymarin orally (Di Costanzo & Angelico, 2019; Piazzini et al., 2019).

Considering the outbreak pandemic of COVID-19, the lack of effective therapeutic strategies for the management of this viral disease, and the increasing evidence on the antiviral potential of some herbal compounds, this study aimed to use silymarin nanomicelles as an anti-inflammatory agent for controlling the cytokine storm caused by SARS-CoV-2 infection.

2 | MATERIAL AND METHODS

2.1 | Study design

This randomized, double-blinded, placebo-controlled clinical trial was conducted on COVID-19 patients admitted to Imam Reza Hospitals of Mashhad, Iran, from March to September 2021. Delta variant was the common variant of SARS-CoV-2 at the time of our study.

2.2 | Study population

The inclusion criteria were: (1) patients with a diagnosis of COVID-19 based on (a) a positive real-time polymerase chain reaction of the respiratory tract samples and (b) imaging findings highly suspicious for COVID-19 (e.g., ground-glass pattern in chest X-ray), as well as clinical signs/symptoms; (2) age between 18 and 75 years who hospitalized and need low flow supplemental oxygen; (3) arterial oxygen (O_2) saturation < 90% in room temperature; (4) need for respiratory support, including oxygen therapy without the need for full mechanical ventilation, high flow supplemental oxygen or non-invasive ventilation; (5) complete level of consciousness; and (6) willingness to participate in the study.

The exclusion criteria were pregnant and lactating women; those with active liver disease, elevated liver enzymes (aspartate aminotransferase [AST] or alanine transaminase [ALT] more than three times the upper limit of normal), severe renal failure (glomerular filtration rate < 30 mL/min), known history of hypersensitivity to silymarin; as well as patients who were admitted to the intensive care unit or needed intubation with an inability to swallow oral medication.

2.3 | Ethics

The study protocol was approved by the Local Ethics Committee of Artesh University of Medical Sciences, Tehran, Iran (IR.AJAUMS.REC.1399.250), and it was registered at the Iranian Registry of Clinical Trials (IRCT20201024049130N1). All participants were explained and informed of the protocol of the study and signed written consent forms.

2.4 | Study protocol

All included patients were assigned to placebo or treatment (nanomicelles of silymarin) groups. The medicine used in this study was silymarin 70 mg soft gel, which is industrialized in Nanotechnology Research Center of Mashhad University of Medical Sciences, Mashhad, Iran, and marketed by Exir Nano Sina Company, Tehran, Iran.

The treatment group received SinaLive soft gel (containing 70 mg silymarin as nanomicelles) three times a day after meal for two weeks (Hosseini, Rezaei, Moghaddam, Elyasi, & Karimi, 2021). The placebo soft gels were prepared by the same company in exactly the same appearance including all components of medicine soft gel, except for silymarin, with the same dosing (three soft gels, three times per day after meal). In our study patients not being classified as very severe, so subjects in both the treatment and placebo groups received standard treatment (i.e., 6 mg dexamethasone injection daily, 200 mg remdesivir injection on the first day and 100 mg daily the following days, oxygen therapy, and dextromethorphan syrup every 8 hr, 10 cc) according to national diagnosis and treatment guideline (last available version) (Rahmanzade, Rahmanzadeh, Hashemian, & Tabarsi, 2020).

2.5 | Outcome

The patients' information, including demographic characteristics, laboratory profiles, past disease, and medication history, were asked and recorded at the beginning of the study by the researcher. Moreover, the various signs and symptoms of COVID-19 infection (including fever, headache, cough, myalgia, dyspnea, olfactory and taste disturbances, and gastrointestinal symptoms) were evaluated by the infectious diseases physician and researcher considering disorders at the beginning of the study and daily afterwards. The time of each symptom resolution; changes in leukocytes, lymphocytes, white blood cell (WBC) counts; the serum level of C-reactive protein (CRP); and arterial O_2 saturation during the follow-up period were considered the primary outcomes of the study. Any adverse medication reactions were assessed as secondary outcomes.

Routine blood and arterial blood gas tests were performed on all patients at baseline, one week, and one month after the intervention. Fasting blood sugar (FBS), serum creatinine, serum electrolytes (Na, K), and blood urea nitrogen (BUN) were all measured. Blood cell count was performed using an automatic blood cell analyzer, followed by the evaluation of the number of leukocytes, lymphocytes, WBC, and the serum level of CRP, as well as the arterial O_2 saturation. Moreover, liver enzyme levels, including ALT and AST were measured by colorimetric analysis through an automated analyzer.

Mean computerized tomography (CT) scores were assessed at baseline, and a semi-quantitative chest tomography scoring was used to assess the severity of lung parenchymal involvement. The lung lobe CT-scan scorings were subtle (5–25% involvement), mild (26–49% involvement), moderate (50–75% involvement), and severe (more than 75% involvement) (Pan et al., 2020).

In addition, the duration of hospitalization in each group was recorded, and the improvement in oxygen saturation level from 95 to 100% was considered the criteria for patients' discharge.

we considered patients in deterioration situation, when moderate symptoms developed into severe or critical symptoms, based on the patterns of deterioration in moderate patients with COVID-19 (Chen et al., 2020).

Moderate symptoms: fever, mild respiratory symptoms (cough, sore throat, runny nose, etc.), multiple patchy shadowing and ground-glass opacity in lung CT, and normal range of vital signs.

Severe symptoms: Respiratory distress [respiratory rate (RR) ≥ 30 breaths/min and/or $SaO_2 \leq 93\%$ and/or arterial oxygen tension/inspiratory oxygen fraction (PaO_2/FiO_2) ≤ 300 mmHg under resting condition] (1 mmHg = 0.133 kPa) and/or radiology findings showing that the range of pulmonary lesions increased by more than 50% within 24–48 h, but no mechanical ventilation is required, and no organ failure.

Critical symptoms: severe acute respiratory distress syndrome (ARDS) ($PaO_2/FiO_2 \leq 100$ mmHg) and requiring mechanical ventilation and/or shock occurs and/or presence of organ failure.

2.6 | Sample size

Due to the lack of clinical trials on the anti-inflammatory effect of nano-silymarin in patients with COVID-19, this study was proposed as a pilot study. The sample size was estimated at 25 cases considering the NCT formula and according to the rules of thumb using the power of 90%, a standardized effect size of 0.2, and $p < 0.5$ for each intervention arm (Whitehead, Julious, Cooper, Campbell, & m. i. m. r., 2016).

2.7 | Randomization and blinding

Randomization was performed based on a computer-generated list of random allocation sequences. Subsequently, the block randomization of four patients was utilized to ensure a balanced allocation of eligible patients in the control and intervention arms. To blind the study, silymarin and placebo soft gel were filled in the tubes with a similar appearance, which have been labeled by A and B, respectively (Exir Nano Sina Company), and delivered to the pharmacologist. Each tube was filled with 42 soft gel (each containing 70 mg) of silymarin nanomicelles or placebo, and one tube was enough for two weeks. Patients who fulfilled the inclusion criteria were selected by a pharmacologist and were assigned into silymarin or placebo groups. They were then given the gel tubes, labeled with A and B, based on the allocation sequence. The patients' evaluation during treatment was performed by a clinical pharmacist and general medical student, who were unaware of the group allocation of the patients.

2.8 | Statistical method

The data were analyzed in SPSS software (version 26.0) (SPSS Inc. /IBM Corp., Chicago, IL, USA). The results have been reported as

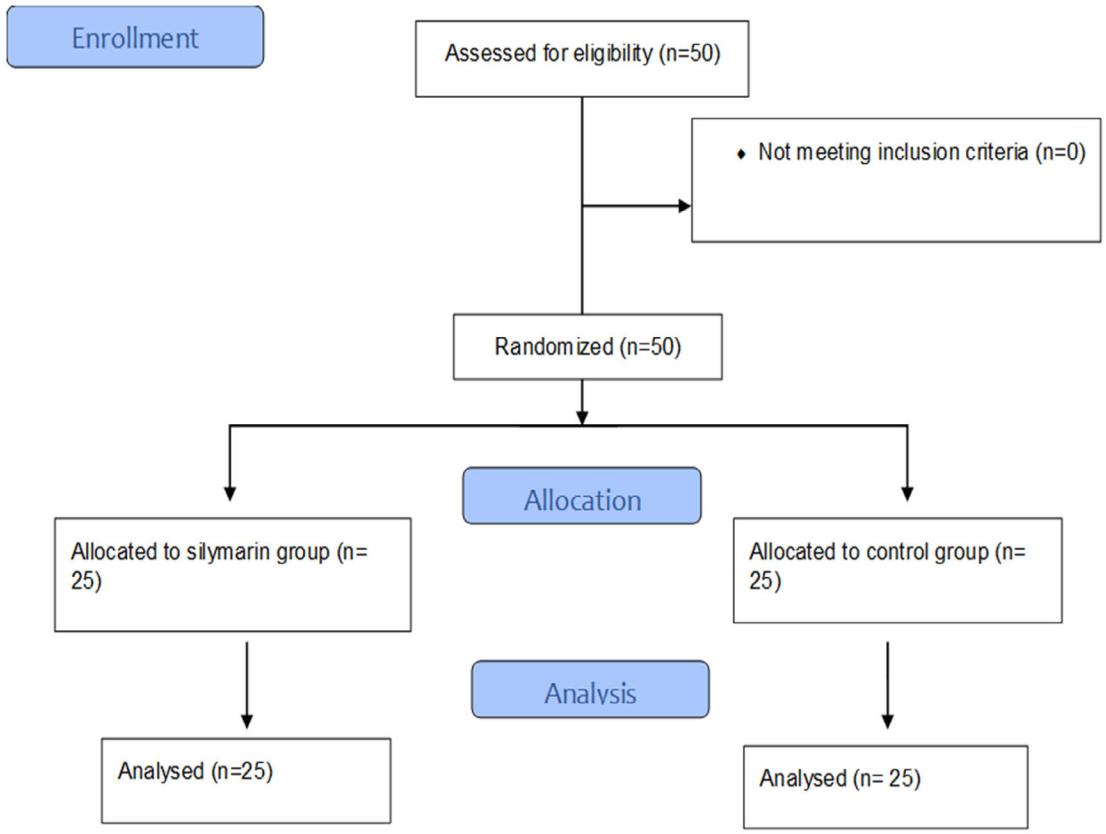

FIGURE 1 Flow diagram of the study

mean ± SD for continuous variables and number or percentage for nominal parameters. Kolmogorov–Smirnov test was employed to assess the normality of the variable distribution. In addition, the categorical variables were presented as numbers (percentages). The independent sample *t*-test or Mann–Whitney *U* test was employed to compare parameters between the silymarin and placebo groups. Moreover, the paired sample t-test was utilized for the mean comparison of variables in order to identify within-group differences. A p-value less than 0.05 was considered statistically significant.

3 | RESULT

Totally, 50 eligible COVID-19 patients were enrolled in the study and completed the trial. It is worth mentioning that none of them were excluded from the study. The consort flow diagram of the study is shown in Figure 1. The mean age of the patients was 49.04 ± 11.14 years, and the majority of the cases were female (52%). The most common symptoms among patients were dyspnea (100%) and cough (90%). There was no significant difference between the nano-silymarin and placebo groups in terms of the baseline characteristics and laboratory findings, including gender, age, baseline symptoms, FBS, serum electrolytes, serum creatinine and BUN level, lymphocyte count, CRP, arterial O_2 saturation, and length of need for O_2 supplement ($p > 0.05$) (Table 1)

Based on results, at the beginning of the study, the AST level was two times higher than normal in 44% of the patients in the treatment group, while it was 28% in the patients in the placebo group ($p = 0.377$). The total lung CT score was obtained at 11.74 ± 0.49. No significant difference was observed between the two groups regarding the CT scan results ($p = 0.930$; Table 2). In addition to the administration of standard medications for COVID-19, patients with underlying diseases including, high blood pressure, diabetes, hypothyroidism, and hyperlipidemia also received their own medications. After comparing the time to symptom resolution related to COVID-19 infection between the treatment and placebo groups, the results showed no significant differences in this regard ($p > 0.05$) (Table 3).

Moreover, based on the follow-up results, no significant difference was observed between the nano-silymarin and placebo groups in terms of laboratory findings, including serum creatinine level, CRP serum level, lymphocyte count, arterial O_2 saturation, and length of need for O_2 supplement ($p > 0.05$) (Table 4). Moreover, the ALT level was significantly lower in the silymarin group one month after treatment, compared to the placebo group ($p < 0.001$), while no significant difference was found between the two groups regarding the AST level at follow-up ($p = 0.073$). The results also indicated that after one month, the ALT and AST levels returned to the normal limit in all patients in the treatment group; however, 10 and 3 cases in the placebo group had the ALT

TABLE 1 Patients' characteristics

Variables	Total patients	Nano-silymarin	Placebo	*p*-value
Gender, *N* (%)				
Female	26 (52)	15 (60)	11 (44)	0.396[a]
Male	24 (48)	10 (40)	14 (56)	
Age (year), mean ± SD	49.04 ± 11.14	48.76 ± 2.27	49.32 ± 2.23	0.861[b]
Baseline sign and symptoms				
Fever, *N* (%), °C				
>37	8 (16)	3 (12)	5 (20)	
37–37.9	35 (70)	18 (72)	17 (68)	0.715[c]
38–39	7 (14)	4 (16)	3 (12)	
Cough, *N* (%)	45 (90)	21 (84)	24 (96)	0.349[a]
Myalgia or fatigue, *N* (%)	43 (86)	20 (80)	23 (93)	0.417[a]
Headache, *N* (%)	18 (36)	6 (24)	12 (48)	0.140[a]
Olfactory and taste disturbances, *N* (%)	15 (30)	7 (28)	8 (32)	1[a]
Dyspnea, *N* (%)	50 (100)	25 (100)	25 (100)	.....
Baseline laboratory findings (mean ± SD)				
Fast blood sugar (mg/dL)	----	143.64 ± 13.55	136.96 ± 16.04	0.580[d]
Serum creatinine level (mg/dl)	----	0.74 ± 0.03	0.74 ± 0.02	0.757[d]
BUN (mg/dL)	----	28.52 ± 2.08	27.92 ± 2.06	0.868[d]
Na (mEq/l)	----	135.64 ± 0.76	136.32 ± 0.62	0.386[d]
k (mEq/l)	----	4.15 ± 0.07	4.06 ± 0.07	0.386[d]
C-reactive protein (mg/L)	----	78.47 ± 10.82	67.06 ± 9.45	0.327[d]
Lymphocyte count × 10^9 /L	----	0.93 ± 0.07	1.27 ± 0.23	0.473[d]
Atrial O_2 saturation (%)	----	84.48 ± 3.72	84.40 ± 2.88	0.694[d]
Length of need for supplement of O_2	----	4.48 ± 0.50	4.56 ± 0.50	0.575[d]
AST (U/l)	----	42.08 ± 3.76	39.64 ± 3.37	0.676[d]
ALT (U/l)	-----	42.36 ± 4.71	42.48 ± 3.85	0.741[d]

[a]Fisher exact test.
[b]Independent sample *t* test.
[c]Chi square test.
[d]Mann–Whitney U test.

TABLE 2 Comparison of lung CT between treatment and placebo group

Variables	Nano-silymarin	Placebo	[a]*p*-value
CT mean score ± SD	11.76 ± 0.72	11.76 ± 0.69	0.930

[a]Mann–Whitney *U* test.

and AST levels upper than the normal limit, respectively. It is worth mentioning that it was less than two times the upper range of normal.

The mean length of hospital stay was shorter in the silymarin group; however, this difference was not significant between the treatment and placebo groups (5.96 ± 2.94 vs.6.48 ± 2.40, $p = 0.306$). It should be noted that no adverse effects related to silymarin were reported, and all patients in this study experienced complete recovery, and no one experienced deterioration.

4 | DISCUSSION

This study was conducted to evaluate the efficacy of silymarin nanomicelles in hospitalized patients with COVID-19 infection as an adjuvant for COVID-19 management and also as a hepatoprotectant. To our knowledge, this clinical trial is the first human study testing the effects of silymarin on clinical parameters and liver enzyme levels of patients with COVID-19.

Many previous studies have shown antiviral activity of silymarin and its derivatives against many viruses, including the influenza, human immunodeficiency virus, flaviviruses (hepatitis C virus and dengue virus), and hepatitis B. They suggested that silymarin or its main component silibinin inhibits viral infection by targeting several stages of the viral life cycle either directly or indirectly (McClure et al., 2012; Song & Choi, 2011; Tanamly et al., 2004; Umetsu et al., 2018; Wagoner et al., 2010).

TABLE 3 Comparison of symptoms resolution time between treatment and placebo group

Symptoms mean ± SD (day)	Nano-silymarin	Placebo	[a]*p*-value
Fever	0.56 ± 0.82	0.56 ± 0.71	1
Cough	3.96 ± 1.27	3.6 ± 1.80	0.419
Myalgia or fatigue,	1.40 ± 1.29	2.12 ± 1.83	0.115
Headache	0.36 ± 0.75	0.68 ± 0.90	0.180
Olfactory and taste disturbances	2.16 ± 4.22	1.52 ± 2.45	0.516
Dyspnea	2.96 ± 1.33	3.60 ± 1.95	0.184

[a]Independent sample *t* test.

TABLE 4 Laboratory findings' changes between treatment and placebo group

Variables		Nano-silymarin	Placebo	[a]*p*-value
Serum creatinine level (mg/dl)	After 1 week	0.86 ± 0.02	0.80 ± 0.02	0.119
C-reactive protein (mg/L)	After 1 week	28.30 ± 4.18	26.00 ± 4.82	0.567
	After 1 month	4.74 ± 0.59	4.67 ± 1.17	0.125
Lymphocyte count × 109 /L	After 1 week	1.17 ± 0.08	1.57 ± 0.19	0.351
	After 1 month	2.66 ± 0.15	2.50 ± 0.17	0.473
Atrial O_2 saturation (%)	After 1 week	90.48 ± 3.61	90.52 ± 2.56	0.639
	After 1 month	94.12 ± 2.00	94.72 ± 1.54	0.301
Length of need for supplement of O_2 (day)	After 1 week	2.48 ± 0.96	2.28 ± 0.54	0.605
	After 1 month	0.24 ± 0.59	0.20 ± 0.40	0.828
AST (U/l)	After 1 week	30.36 ± 3.32	28.48 ± 3.02	0.697
	After 1 month	24.20 ± 1.74	33.56 ± 3.70	0.073
ALT (U/l)	After 1 week	38.04 ± 3.15	48.32 ± 3.39	0.077
	After 1 month	24.52 ± 1.62	48.64 ± 3.76	*<0.001
Hospitalization duration (day)	-----	5.96 ± 2.94	6.48 ± 2.40	0.306

[a]Mann–Whitney U test.
*$p < 0.001$ is considered significant.

An in silico and in vitro study conducted by Sardanelli et al. showed that silybin and silymarin, respectively, are able to bind and inhibit the active site of the SARS-CoV-2 main protease (M^{pro}), which is essential to the lifecycle of the virus (Sardanelli, Isgrò, & Palese, 2021). Molecular docking analysis demonstrated that silymarin interferes with SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD-S) and host angiotensin-converting enzyme-2 protease domain (PD-ACE-2) to inhibit the SARS-CoV-2 infection (Gorla, Rao, Kulandaivelu, Alavala, & Panda, 2021).

It is also reported that silymarin has strong efficacy of about 98% against influenza A/PR/8/34 virus at the concentration of 100 μg/mL by reducing viral mRNA synthesis (Song & Choi, 2011). Silymarin-induced suppression of NF-κB dependent gene expression results in the modulation of 32 mRNAs which are related to many pro-inflammatory functions. In addition, silymarin inhibits a lot of cytokine and chemokine upstream regulators, receptors, and complexes, including transforming growth factor beta, IL-6, and IL-17A. It also caused considerable suppression of many non-cytokine and non-chemokine mRNAs that are associated with the inflammatory response, such as IL-1 receptor associated-kinase 4, which activates NF-κB in both the T-cell receptor and Toll-like receptor signaling pathways, respectively (Lovelace et al., 2015).

According to the findings, in this clinical trial, no significant difference was observed between the treatment and placebo groups in terms of the time to symptom resolution and laboratory parameter changes, except for the ALT level that was significantly lowered in the silymarin group one month after treatment. It should be also mentioned that the rise of ALT/AST serum levels was found in about 28% and 44% of the patients at the beginning of the study in the treatment group, respectively; however, it lowered to zero after one month of treatment.

Some studies revealed that silymarin (140 mg, three times daily) could significantly lower the serum levels of AST, ALT, and alkaline phosphatase in trauma patients with increased levels of liver enzymes (Mirzaei et al., 2021). Another study recommended that the use of silymarin (420 mg per day) in non-alcoholic hepatic steatosis patients could significantly reduce the AST and ALT levels in patients after six months (Abbasirad et al., 2021). The findings of these studies are in line with the results of our study. It was also found that the hospitalization duration was lower in the treatment group, compared to the placebo group; however, it was not significant. No adverse effects of silymarin were reported, and no patients died in the placebo and treatment groups in this study. Due to these findings, it is suggested that receiving 70 mg of silymarin nanomicelles three times daily for two weeks had no efficacy for the management of the symptoms of hospitalized COVID-19 patients. The results of our study contradict those of many studies that have confirmed the role of silymarin in

various immune-pharmacological and regulating cytokine storms (Palit, Mukhopadhyay, & Chattopadhyay, 2021; Sardanelli et al., 2021).

This may be justified by the study population; as we included moderate to severe COVID-19 patients who require oxygen therapy beside medications like remdesivir and dexamethasone. Concomitant use of these drugs with silymarin makes the effects of silymarin on the improvement of patients' condition unclear and invisible. Therefore, the effect of silymarin on improving the condition of patients can be better and more accurately studied in patients with COVID-19 who do not need to be hospitalized and receive oxygen therapy and dexamethasone and remdesivir therapy. However, further well-designed clinical studies should be conducted to assess some vital points, such as exact dosing and time course of therapy based on the severity of the disease to control viral infection. Also, further clinical trials are recommended in patients with mild COVID-19 which does not need dexamethasone and remdesivir treatment.

Regarding the limitations of this study, the first and the most important limitation was the small sample size which made the judgment difficult. The second limitation was the shortness of the intervention period that was limited to two weeks ($\alpha = 5\%$ and $\beta = 10\%$ with a statistical power of 80%). The third limitation was the daily dosage of silymarin (70 mg three times daily), which seemed to require a higher dose to achieve more therapeutic effects. Forth limitation was that we did not assign another group as silymarin in its crude form to compare clinical parameters with silymarin nanomicelles group, and we did not assess the direct cytokines levels due to financial constraints.

5 | CONCLUSION

In conclusion, a significant reduction was observed in the ALT level in the silymarin group at one month follow-up. However, it was reported that supplementation with 70 mg of nanomicelles of silymarin three times daily could not ameliorate the time to symptom resolution and laboratory parameters' correction in the treatment group, compared to the control group in severe hospitalized patients. Further studies with various dosages based on the weight of patients and severity of disease, larger sample sizes, and longer follow-up durations are required to better determine the efficacy of this treatment modality. Also, assessment of the viral load using quantitative PCR techniques recommended to consider in future studies.

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CONFLICT OF INTEREST

Dr. Mahmoud Reza Jaafari, one of the manuscript authors, is the founder of Exir Nano Sina Company which produced the studied medication. Other authors have nothing to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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