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The Effect of Oral Silymarin on Remdesivir-Induced Hepatotoxicity and Clinical Course in Covid-19 Patients; A Double-Blind Randomized Controlled Trial

Saeed Badiei[1], Shima Rahmati[2], Hadi Raeisi Shahraki[3], Zahra Habibi[4*]

1. Resident in Internal Medicine, Clinical Research Development Unit, Hajar Hospital, Shahrekord University of Medical Sciences, Shahrekord, Iran.
2. Ph.D. in Molecular Medicine, Cancer Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran.
3. Assistant Prof., Dept. of Epidemiology and Biostatistics, School of Health, Shahrekord University of Medical Sciences, Shahrekord, Iran.
4. Assistant Prof., Clinical Research Development Unit, Hajar Hospital, Shahrekord University of Medical Sciences, Shahrekord, Iran.

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*** Corresponding author:**
Zahra Habibi,
E-mail:
Dr_z_habibi@yahoo.com

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Abstract

Background: Remdesivir is a nucleoside inhibitor of RNA polymerase with the antiviral activity used in the treatment of COVID-19 pneumonia. One of the remdesivir side effects is hepatotoxicity. Given the growing body of data supporting silymarin's antiviral and hepatoprotective properties, the present research sought to explore the impact of silymarin on laboratory parameters, frequency of symptoms, and liver enzymes in COVID-19 patients.

Materials and Methods: In this double-blind randomized clinical trial 70 patients were divided into two groups of 35. Intervention group received remdesivir + 140 mg Silymarin, 3 times, daily for 1 week, and the control group received remdesivir + placebo. Patients' symptoms and laboratory findings were assessed at baseline and 5,7,10, and 14 days' post enrollment.

Results: Liver enzymes level (aspartate aminotransferase, and alkaline phosphatase), and lactate dehydrogenase were significantly decreased in the intervention group ($p < 0.05$). Among the clinical symptoms, cough (p=0.03), shortness of breath (p= 0.006), headache (p=0.01), and muscle pain (p=0.03) were significantly lower in the treatment group comparing to the control group. Moreover, the severity of disease in the intervention group was substantially lower than that among the control group.

Conclusion: Concomitant use of remdesivir with silymarin might reduce hepatotoxicity and ultimately improve the patients' condition. More clinical trials with different dosages and larger sample sizes are recommended.

Keywords: COVID-19, Liver Enzymes, Silymarin, Remdesivir

Introduction

SARS-CoV-2, a novel coronavirus, was identified as the cause of a cluster of pneumonia cases in Wuhan, China, at the end of 2019. The disease has since spread worldwide which has led to a persistent epidemic [1]. Acute respiratory distress syndrome (ARDS), severe pneumonia, mild upper respiratory infections, and possibly mortality are possible outcomes of the 2019 coronavirus illness, or COVID-19. [2]. Although lung damage is the most common clinical manifestation of COVID-19, clinical-pathological findings can occur in other organs, including liver. COVID-19 can infect liver cells and bile duct cells via the expression of

angiotensin-converting enzyme (ACE2) receptors in liver cholangiocytes and result in abnormal liver function in patients [3]. Liver function indices in the patients with COVID-19 are associated with inflammatory markers such as CRP and the neutrophil-to-lymphocyte ratio (NLR), making NLR an independent risk factor for COVID-19 [4].

Remdesivir, corticosteroids, IL-6R antagonists like tocilizumab (TCZ), IL-1 antagonists like anakinra, TNF-inhibitors, and Janus kinase inhibitors are just a few of the treatment regimens that were developed to control SARS-CoV-2 pandemic [5]. Remdesivir was first created to treat hepatitis C, but it was also used to treat viral illnesses such as Ebola and Marburg before being used to COVID-19. The most frequent adverse effect of Remdesivir in healthy volunteers has been a rise in blood levels of liver enzymes, which is indicative of liver issues [6]. Milk thistle (Silybum marianum), an annual or biennial plant of the Asteraceae family, contains silymarin, an active component that was associated to a variety of health benefits, including liver protection, antioxidant activity, anti-inflammatory activity, and anti-canceractivity [7].Silymarin boosts hepatic glutathione levels by increasing cysteine availability, and inhibits taurine catabolism, potentially boosting antioxidant defenses in the liver [8]. Silymarin can aid in the recovery of liver damage caused by viruses which showed protective effects in acute and chronic viral hepatitis [9].

In light of the COVID-19 pandemic, the dearth of effective treatment approaches, and mounting evidence that certain herbal remedies possess antiviral qualities, the aim of this investigation was to evaluate silymarin's impact on remdesivir-induced hepatotoxicity in Covid-19 patients.

Materials and Methods

This double-blind, Placebo-controlled trial (IRCT20201227049854N1) was conducted from July 2021 to Sept. 2021 in Hajar Hospital of Shahr-e-Kord province, Iran. (Ethical code: IR.SKUMS.REC.1399.198). A total of 70 patients with COVID-19 were enrolled in the study.

The inclusion criteria were RT-PCR positive for SARS-Cov19 receiving remdesivir, a blood oxygen saturation level SpO2of less than 93% or the need for supportive oxygen or mechanical ventilation, pulmonary infiltration in imaging test, the absence of underlying liver disease, such as liver cirrhosis and viral hepatitis, and liver enzymes that were less than five times the normal amount and willingness to participate in the study. All this information was confirmed by a medical specialist. The exclusion criteria included a five-fold increase in liver enzymes, patient dissatisfaction, pregnancy and lactation, and glomerular filtration rate less than 50 mg/min. The patients without underlying heart disease

Patients did not provide demographic information, such as age, gender, or medical history, until they had completed a formal permission form. The permuted block randomization was used to randomly split the patients into two groups. The size of each block was equal to 6 and blocks were generated using Random Allocation software. All patients with estimated glomerular filtration rate (eGFR) >٦0 ml/min and liver enzyme less than five times the upper limit of normal range received remdesivir. The patients were randomly divided into two groups by the blocked randomization.

The intervention group received injection Remdesivir + Livergol(goldaru company), and the control groups received injection Remdesivir + placebo three times daily for one week.On the first day, all participants received 200 mg of Remdesivir by injection, followed by 100 mg daily. Each Livergol capsule contained 140 mg of dried silymarin extract .Furthermore, all patients received proton pump inhibitor or H2-blocker to prevent stress ulcer.

Coagulation, liver, kidney, and inflammatory tests were performed before enrollment, and on days 5, 7, 10, and 14 after enrolment. On days 1, 5, 10, and 14, clinical symptoms also were assessed for the severity of disease using a seven-point scale [10]:

1. mortality 2. hospitalization and need for the mechanical ventilation 3. non-intubated hospitalization with high flow oxygenation 4. hospitalization with no intubation with low flow oxygenation 5. hospitalization without supportive oxygenation, but in need of medical care 6. hospitalization without supportive oxygenation, but in need of medical treatment 7. outpatient.

This study aimed to comparatively investigate the effects of silymarin on COVID-19 inpatients' symptoms, hospital stay length and remdesivir-induced hepatotoxicity.

SPSS software version 26 (SPSS Inc. /IBM Corp., Chicago, IL, USA) was used to analyze the data, which included t-tests, chi-square tests, and analysis of variance with repeated measurements at a significance level of $p = 0.05$.

The findings have been presented as mean ± SD for continuous variables and as a number or percentage for nominal parameters. The McNemar test was used to assess the frequency of muscular soreness, headaches, and disease severity on days 1 and 5, since these factors differed across the groups on day 1.

Results

Totally, 70 eligible COVID-19 patients were enrolled in the study, and completed the trial.

Except for PT, PTT, and LDH, all other variables in the two groups were the same, as shown in Table 1.

Table 1. Comparison of different variables on the first day in the studied groups

Variable	Intervention Mean ± SD	Control Mean ± SD	P-value
PT/sec	91.9±27.2	12.40±5.71	*0.02
PTT/sec	25.34± 6.41	32.34±17.00	*0.030
INR	1.05± .21	1.08± .53	0.720
WBC/µL	7108.57± 2630.29	7137.14± 4471.81	0.970
LYM/µL	14.25 ± 7.32	16.11 ± 8.82	0.330
NEUT/µL	81.45 ± 7.93	79.60 ± 8.98	0.360
Hb (g/dL)	14.28 ± 2.12	14.25 ± 1.60	0.950
PLT/µL	195400.00 ± 85957.39	190428.57 ± 63905.39	0.780
AST(U/L)	64.60 ± 35.29	66.31 ± 50.57	0.870
ALT (U/L)	56.28 ± 29.82	54.77 ± 38.76	0.760
ALKP (U/L)	161.14 ± 82.20	178.94 ± 124.34	0.480
(mg/dL) BILLT	0.64 ± 0.25	0.66 ± 0.30	0.730
(mg/dL) BILLD	0.21 ± 0.08	0.22 ± 0.11	0.640
BUN (mg/dL)	15.22 ± 6.74	15.68 ± 6.07	0.720
Cr (mg/dL)	1.10 ± 1.22	0.80 ± 0.20	0.150
CRP (mg/L)	1.85 ± 1.41	1.57 ± 0.94	0.330
ESR (mm/hr)	47.00 ± 25.98	38.34 ± 19.49	0.120
Fer (mg/dL)	577.02 ± 432.23	508.34 ± 706.92	0.630
LDH (mg/dL)	401.42 ± 187.79	724.82 ± 280.75	*0.001
SPO2 %	84.48 ± 6.56	81.94 ± 4.83	0.07
TEMP ºC	37.67 ± 0.85	37.60 ± 0.60	0.710

PT: Prothrombin Time, PTT: Partial thromboplastin time, INR: International Normalized Ratio, WBC: White Blood Cell, LYM: lymphocytes, NEUT: Neutrophils, Hb: Hemoglobin, PLT: Platelet, AST: Aspartate Aminotransferase, ALT: Alanine Amino transferase, ALKP: Alkaline Phosphatase, BILL T: Bilirubin Total, BILL D: Bilirubin Direct, BUN: Blood Urea Nitrogen, Cr: Creatinine, CRP: C-reactive-protein, ESR: Erythrocyte Sedimentation Rate, Fer: Ferritin, LDH: Lactate Dehydrogenase, SPO2: Oxygen saturation, TEMP: temperature

Analysis of covariance for baseline PT, PTT, and LDH as confounders showed that the LDH levels on days 5, 10, and 14 in the intervention group were significantly lower than in the control group ($p < 0.05$). Furthermore, a comparison of coagulation, hepatic, and renal variables across groups revealed that the PTT values on days 5 and 7 were substantially higher in the control group than in the intervention group ($p < 0.05$), but did not vary on other days. The alkaline phosphatase (ALP) values on days 5, 7, and 10 and aspartate aminotransferase (AST) values on day 14 in the intervention group were significantly lower than in the control group ($p < 0.05$). The other variables were not significantly different over the study period (Table 2).

Chills, fever, runny nose, sore throat, nausea and vomiting, diarrhea, abdominal pain on different days were not statistically different among the groups on different days. The intervention group had reported significantly reduced muscle pain on days 1 and 5, reduced cough on days 10 and 14, reduced headache on day 1, and reduced shortness of breath on day 5 over the control group ($p < 0.05$). (Table 3)

Table 2. Comparison of different variables at different times in the studied groups.

Variable	Group	Day 5	Day 7	Day 10	Day 14
PT	Control	12.08 ± 3.87	12.28 ± 3.87	13.54 ± 6.69	16.12 ± 8.82
	Intervention	10.87 ± 4.99	11.08 ± 5.68	10.66 ± 3.59	20.66 ± 15.05
P-value		0.260	0.380	0.130	0.490
PTT	Control	29.25 ± 7.40	28.51 ± 6.87	30.40 ± 12.29	39.25 ± 32.80
	Intervention	26.00 ± 4.59	25.34 ± 2.05	24.93 ± 3.93	27.16 ± 1.32
P-value		*0.030	* 0.010	0.1	0.390
INR	Control	1.11 ± 0.42	1.10 ± 0.50	1.20 ± 0.60	1.78 ± 1.73
	Intervention	1.19 ± 0.55	1.18 ± 0.66	1.14 ± 0.40	2.23 ± 1.16
P-value		0.500	0.590	0.750	0.630
LYM	Control	16.11 ± 8.82	11.20 ± 5.89	10.18 ± 6.70	6.25 ± 2.76

	Intervention	14.25 ± 7.32	11.00 ± 7.56	10.56 ± 7.69	6.66 ± 2.50
P-value		0.330	0.900	0.870	0.770
Hb	Control	14.25 ± 1.60	13.31 ± 1.30	12.88 ± 2.07	12.00 ± 2.09
	Intervention	14.28 ± 2.12	14.08 ± 2.23	12.80 ± 1.19	13.26 ± 0.98
P-value		0.950	0.900	0.080	0.200
PLT	Control	± 63905.39 190428.57	± 68444.82 260800.00	± 83874.01 271772.72	± 103439.42 225000.00
	Intervention	± 85957.39 195400.00	± 115199.92 255085.71	± 89935.85 241200.00	± 87878.89 195500.00
P-value		780.0	0.800	0.300	0.59
AST	Control	50.11 ± 15.50	45.05 ± 31.51	43.22 ± 41.47	37.00 ± 8.99
	Intervention	41.34 ± 18.78	38.48 ± 16.90	33.26 ± 23.08	23.50 ± 6.41
P-value		0.110	0.270	0.410	*0.01
ALT	Control	61.51 ± 38.81	56.17 ± 31.41	48.95 ± 35.51	44.00 ± 26.93
	Intervention	58.37 ± 35.66	53.40 ± 31.17	39.73 ± 27.74	57.66 ± 31.79
P-value		0.730	0.710	0.400	0.400
ALKP	Control	± 70.92 167.21	± 57.15 160.97	153.31 ± 65.66	142.00 ± 63.07
	Intervention	± 51.60 137.28	± 45.72 128.28	115.26 ± 36.02	128.83 ± 33.10
P-value		*0.04	*0.01	*0.03	0.650
BILLT	Control	0.68 ± 0.34	0.76 ± 0.47	0.84 ±0.71	0.84 ±0.37
	Intervention	0.62 ± 0.27	0.62 ± 0.28	0.71 ±0.46	0.67 ±0.21
P-value		0.380	0.140	0.52	0.34
BILLD	Control	0.24 ± 0.13	0.26 ± 0.13	0.28 ± 0.16	1.66 ± 3.77
	Intervention	0.23 ± 0.12	0.22 ± 0.10	0.25 ± 0.13	0.18 ± 0.07
P-value		0.590	0.150	0.590	0.36
BUN	Control	15.69 ±6.07	18.57 ± 6.74	18.36 ± 6.15	21.37 ± 7.87
	Intervention	16.23 ±6.74	21.37 ± 5.53	20.66 ± 7.79	25.16 ± 11.80
P-value		72.0	*0.05	0.320	0.480
CR	Control	0.80 ± 0.20	0.79 ± 0.17	0.79 ± 0.11	0.72 ± 0.17
	Intervention	1.10 ± 1.22	0.84 ± 0.17	0.84 ± 0.15	0.76 ± 0.10
P-value		0.150	0.200	0.330	0.620
CRP	Control	1.57 ±0.95	0.51 ± 1.17	−0.50 ± 0.96	−0.75 ± 0.70
	Intervention	1.86 ±1.42	0.31 ± 1.51	−0.66 ± 0.89	−0.66 ± 0.81
P-value		0.33	0.540	0.600	0.840
ESR	Control	38.34 ±19.49	26.60 ± 23.26	20.36 ± 25.09	17.37 ± 20.15
	Intervention	47.00 ±25.98	25.82 ± 16.21	20.33 ± 9.96	17.16 ± 10.87
P-value		0.12	0.87	0.990	0.980
Fer	Control	508.3 ±706.9	558.9± 552.0	558.40 ± 654.47	769.62 ± 913.13
	Intervention	577.0 ±432.2	± 574.6 685.77	726.00 ± 705.60	647.50 ± 390.11
P-value		0.63	0.350	0.550	0.750
LDH	Control	727.8 ±280.8	± 346.52 740.2	646.27 ± 272.05	706.50 ± 176.95
	Intervention	401.4 ±187.8	± 180.75 386.7	323.33 ± 155.97	399.16 ± 153.36
P-value		<0.001	#0.02	#0.02	#0.04

PT: Prothrombin Time, PTT: Partial thromboplastin time, INR: International Normalized Ratio, LYM: lymphocytes,Hb: Hemoglobin, PLT: Platelet, AST: Aspartate Aminotransferase, ALT: Alanine Amino transferase, ALKP: Alkaline Phosphatase,BILL T: Bilirubin Total, BILL D: Bilirubin Direct, BUN: Blood Urea Nitrogen, Cr: Creatinine, CRP: C-reactive-protein,ESR: Erythrocyte Sedimentation Rate, Fer: Ferritin, LDH: Lactate Dehydrogenase

Both groups experienced a considerable decrease in muscle pain. Headache decreased from 11.4% to 5.7% in the control group and from 37.1% to 0% in the intervention group. This decrease was significant in the intervention group. On days 1, 5, and 10, the severity of disease in the intervention group was substantially lower than in the control group ($p < 0.05$). (Table 4). The severity of disease (scale 4.) decreased from 68.6% (on day 1) to 50 % (on day 10) in the control group and from 88.6% to 46.7% in the intervention group. This decrease was more in the intervention group.

Table 3. Frequency of symptoms at different times in the study groups

Variable	Day 1			Day 5			Day 10			Day 14		
	Control %	Intervention%	P	Control %	Intervention%	P	Control %	Intervention%	P	Control %	Intervention%	P
Chills	(3.34)12	14(40)	0.08	(4.11)4	(9.2)1	0.18	0(0)	0(0)		0(0)	0(0)	
Shortness of breath	(80)28	(1.77)27	0.177	-	(4.51)18	0.006*	(8.31)7	(7.26)4	0.99	0(0)	(7.16)1	0.429
Fever	(6.48)17	(6.48)17	0.99	(20)7	(9.2)1	0.06	0(0)	(100)15	-	(100)6	0(0)	-
Muscular pain	(3.74)26	(7.45)16	0.03*	(4.29)10	(9.2)1	0.003*	0(0)	0(0)	-	0(0)	0(0)	-
Cough	(100)35	(3.94)33	0.049	(100)35	(3.74)26	0.49	(100)22	(7.46)7	0.001*	(5.87)7	(7.16)1	0.03*
Abdominal pain	(9.2)1	(4.11)4	0.036	(9.2)1	0(0)	0.099	0(0)	0(0)	-	0(0)	0(0)	-
Headache	(4.11)4	(1.37)13	0.01*	(7.5)2	0(0)	0.049	0(0)	0(0)	-	0(0)	0(0)	-
Runny nose and Sore throat	11 (31.4)	4 (11.4)	0.08	0(0)	2 (5.7)	0.25	0 (0)	1 (6.7)	0.41	0(0)	0(0)	-
Gastrointestinal symptoms	10 (28.6)	12 (34.3)	0.80	4 (11.4)	0(0)	0.06	1 (4.5)	0(0)	0.60	0(0)	0(0)	-

Table 4. The severity of disease at different times in the study groups.

Day	Clinical status on seven-point scale	Control %	Intervention%	P
day 1	3	11(31.4)	2(5.7)	*0.01
	4	24(68.6)	31(88.6)	
	5	0(0)	2(5.7)	
day 5	3	8(22.9)	3(9.6)	*0.03
	4	20(57.1)	18(51.4)	
	5	7(20)	8(22.9)	
	6	0(0)	6(17.1)	
day 10	3	3(13.6)	1(6.7)	*0.034
	4	11(50)	7(46.7)	
	5	8(36.4)	2(13.3)	
	6	0(0)	4(26.7)	
	7	0(0)	1(6.7)	
day 14	4	4(50)	6(42.9)	0.12
	5	4(50)	5(16.7)	
	6	0(0)	3(21.4)	

Discussion

This study was conducted to explore the effect of silymarin on Remdesivir-induced hepatotoxicity in COVID-19 patients to introduce the hepatoprotective substance. The total and direct ALT, and bilirubin levels in the intervention and control groups were not statistically different on different days, but the ALP values on days 5, 7, and 10 and the AST values on day 14 in the intervention group were significantly lower than the control group, indicating that silymarin may have played a role in hepatic protection in theCOVID-19 patients.

The present results are supported by the fact that silymarin has been shown in many studies to be beneficial against hepatotoxicity induced by various medicines and hazardous substances, even if its effectiveness against hepatotoxicity produced by antiviral drugs has not been investigated. A meta-analysis of the effect of prophylactic treatment by silymarin (S. marianum) on the liver damage caused by anti-tuberculosis drugs in 1198 patients found that prophylactic

treatment by silymarin significantly reduced serum ALT levels at weeks 2 and 4, AST levels at weeks 4 and 8, and ALP levels at week 8 [11]. In one trial, silymarin (5 mg/kg daily for one month) decreased liver enzyme levels in the patients with antiepileptic drug-induced liver damage[12]. Silymarin was shown to reduce liver enzyme levels in mice with hepatotoxicity caused by paracetamol [13], diclofenac [14], deferasirox[15], carbon tetrachloride [16], and titanium dioxide [17].

In individuals with liver illness, silymarin reduced ALT and AST levels, however the reductions were not clinically meaningful, according to a meta-analysis of 17 trials. Furthermore, studies performed in this area exhibited a high degree of heterogeneity, and low methodological quality; thus, more research is needed [18]. In the current study, in line with the previous studies, participants taking silymarin recorded reduced ALP levels on days 5, 7, and 10 and AST levels on day 14, but not on other days. Thisresult could be due to the short treatment period and low sample size; therefore, it is recommended that more studies with larger sample sizes and longer treatment periods and/or higher doses of drug be performed on COVID-19 patients.

The findings reveal that, on day l, the LDH levels differed significantly between groups, with the control group levels being much higher. The DLH was compared across groups on other days using covariance analysis and baseline LDH value control as confounders. LDH levels in the intervention group were considerably lower than in the control group on days 5, 10, and 14. LDH is a protein that is extensively secreted in bodily tissues as a result of tissue injury as the result of common injuries as well asin diseases such as heart or liver failure [19]. In a model of lipopolysaccharide-induced sepsis, silymarin was found to have a significantly protective effect on the liver and kidney and reduced LDH levels, which confirms the current findings [20].

In the control group, PT values on day 1 and PTT on days 1, 5, and 7 were significanthigher than for the intervention group. The frequency of patients with impaired values among groups was analyzed because of the mismatch between PTT and PT values on day 1, and no significant difference was found. Furthermore, when the mean PT and PTT values of patients with compromised tests were examined across groups at various times, it was shown that there was no significant difference between them. Comparing the changes in coagulation factors during the study period showed no significant differences among the groups, indicating that silymarin had no effect on the coagulation factors. Only a few studies have investigated the preventive role of silymarin against coagulation disorders. In one study, silymarin and its active components were found to reduce the synthesis of thromboxane A2 and malondialdehyde, decreasing COX activity and, thereby, platelet aggregation produced by arachidonic acid metabolism by COX [21].

BUN levels (except on day 5) and creatinine on different days were not statistically different between groups. Silymarin was shown to reduce BUN and creatinine in renal toxicity models [22]. Lack of change in BUN and creatinine among the groups in the present study could relate to them being at normal levels in the patients. Overall, this study has shown that the medication is effective in reducing the symptoms and severity of COVID-19 illness for the first time; this is probably because the medication contains antiviral and anti-inflammatory qualities.

Conclusion

The study's findings show that concomitant use of remdesivir with silymarin might reduce hepatotoxicity and ultimately improve the patients' condition. Silymarin was effective to predict the liver and reducing the severity of the disease and some symptoms in COVID-19 patients. This is likely due to the anti-inflammatory and antiviral properties of drug, which reduced the severity of the disease by counteracting the cytokine storm caused by the virus. To ascertain if silymarin has any effect on the outcomes and clinical trajectory of COVID-19, further studies with bigger sample numbers are required.

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