Study of Hepatoprotective Effect of Silymarin and Ursodeoxycholic Acid in Chronic Hepatitis C Patients

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Abstract

Hepatitis C virus is a major public health problem causing significant morbidity and mortality. Until recently, the standard treatment with peginterferon and ribavirin was far from being perfect due to its cost, poor tolerability and low sustained virological rates (SVR) rates. Although, the novel direct-acting antiviral agents (DAAs) telaprevir, and boceprevir has dramatically improved SVR rates; issues such as adverse reactions, frequent dosing, and drug interactions still represent a challenge. Even overcoming these challenges with the new revolutionary development of sofosbuvir, its high cost still needs to be addressed. Therefore, the popularity of alternative medicines in chronic hepatitis C (CHC) treatment such as silymarin and ursodeoxycholic acid (UDCA) has increased. The multiple hepatoprotective effects of these drugs have made them attractive for evaluation in patients with different liver diseases. The aim of this study is to compare the hepatoprotective effect of silymarin, UDCA, and a combination therapy of both in chronic hepatitis C patients. Forty CHC patients (32 males and 8 females) were recruited from hepatology clinic at Beni-Suef University. Patients were divided randomly into four equal groups of tens A, B, C and D, who received 420 mg/day silymarin capsules, 500 mg/day UDCA capsules, combined therapy of both, and a placebo treatment, respectively. Serum liver parameters were measured at baseline and repeated 12 weeks after therapy.A statistically significant improvement in mean serum levels of ALT, AST, and bilirubin was obtained with UDCA therapy either when administered alone or combined with silymarin. However, silymarin treatment failed to significantly affect liver function tests.

Key words: Silymarin, ursodeoxycholic acid (UDCA), chronic hepatitis C (CHC), liver function tests

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Introduction

Chronic hepatitis C is a common disease that progresses slowly to cirrhosis and eventually may lead to hepatocellular carcinoma [1-3]. It is a serious global medical problem that affects up to 170 million people worldwide, with over 350,000 patients dying each year from its associated liver diseases [4]. Egypt is even more specifically confronted with hepatitis C virus (HCV) disease burden and has the highest prevalence of (HCV) in the world, estimated nationally at 14.7% [5].

No doubt, that the optimal outcome in chronic hepatitis C treatment is the elimination of the virus. Simply this could not be achieved with the once considered, the mainstay therapy for chronic hepatitis C (CHC) patients of peginterferon and ribavirin. This regimen remained unsatisfactory in many patients as it is not only was associated with considerable expense, adverse effects, but also required up to 48 weeks of treatment with only 40-60% success rates [6-8].

Therefore, the urging need for more efficacious and well-tolerated regimens has led to a rapid change in hepatitis C treatment. In 2011, the addition of the recently approved novel direct-acting antiviral agents (DAAs) telaprevir or boceprevir to pegylated interferon-alfa and ribavirin has dramatically improved sustained virologic response (SVR) rates; however, issues such as adverse reactions, frequent dosing, and drug interactions continued to make treatment challenging [9,10].

Thus, the true revolutionary event in hepatitis C treatment was the development of sofosbuvir in 2014, which is a direct-acting nucleotide polymerase inhibitor. Many of the optimal treatment requirements were satisfied by its high efficacy, short treatment course, well tolerability and the lack of drug-drug interactions [4,11].

Several early studies with sofosbuvir either combined with ribavirin or daclatasvir (an inhibitor of NS5A) have shown an outstanding sustained virological rates (SVR) of 100% [12]. However, even with the fact that sofosbuvir represents a very promising option in chronic hepatitis C treatment, providing the first “interferon free” and ribavirin free treatment, with 80-90% cure rates and with almost no side effects, its use is still limited by issues such as drug resistance and high cost. The twelve-weeks therapy with Sofosbuvir cost about 80.000 US$ [13]. Therefore,

generally antiviral therapy is still unsuitable and unattainable for the majority of HCV-infected persons especially in Egypt and other developing countries where the acccess to such expensive treatment is limited.

As a result, the interest in alternative hepatoprotective drugs such as silymarin and ursodeoxycholic acid (UDCA) have increased and popularized their application in addition to or instead of standard treatment to treat and prevent progression of chronic hepatitis C virus (HCV) infection [14].

Silymarin, the active ingredient in milk thistle (Silybum marianum) has been long known for its multiple hepatoprotective effects. No doubt that the promising antioxidant [15,16], immunomodulatory [17-19], and anti-fibrotic effects [20-22] of silymarin as demonstrated in several clinical studies has made it an attractive drug for evaluation in patients with different liver diseases. Most hepatologists regard sylimarin, as not only the most commonly used herbal supplements but also the most beneficial [23, 24]. However, although, it's wide application in CHC patients, its potential therapeutic benefits are controversial and still needs further investigation.

In addition, UDCA has been used widely in the present clinical environment for several liver diseases and has shown to improve clinical and biochemical indices in a variety of biliary and liver diseases [25]. It is now considered as the first-line treatment for patients with chronic cholestatic liver diseases, such as primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), and intrahepatic cholestasis of pregnancy (ICP) [26]. However, despite the lack of its antiviral effect in CHC patients, it seems beneficial in reducing serum hepatic markers, disease activity or cirrhosis in patients unsuitable to IFN treatment [27].

The aim of this study was to evaluate and compare the hepatoprotective effect of silymarin (420 mg/day), ursodeoxycholic acid (500 mg/day), and a combined therapy of both in patients with chronic hepatitis C.

Material and Method

Initially hundred patients with CHC were collected from hepatology clinic at Beni-Suef university teaching hospital. Only 40 CHC patients (32 males and 8 females) with ages ranged from 23 to 70 years old completed the study. Patients were tested positive for HCV-RNA or

HCV core proteins. After receiving a complete and detailed explanation of the study, they signed an informed consent form. The study was approved by the Ethics Committee of Beni-Suef University teaching Hospital.

General data of patients:-

Inclusion criteria:

Inclusion criteria contained confirmed chronic hepatitis C (HCV Ab (+ve), HCV-RNA [with +ve PCR].

Exclusion criteria:

Patients were excluded from the study if they met one or more of the following criteria; received antiviral treatment (interferon with or without ribavirin) during the preceding six months or were treated with corticosteroids, immunosuppressive drugs, glycyrrhizic acid, cholestyramine or other drugs that may affect liver functions, had decompensated cirrhosis, viral hepatitis other than hepatitis C, alcoholic or had drug-induced liver injury, pregnant or lactating; or using an illicit drug or alcohol more than approximately 30 g/day alcohol.

Study design

On admission, the selected patients were subjected to a complete and detailed medical history, physical and clinical examination. All their baseline demographic and clinical data were recorded. Patients were divided randomly into four equal groups A, B, C and D. Each group consisted of 10 patients. Group A received silymarin capsules three times daily (Legalon® 140 mg capsules, produced by CID company; Cairo, Egypt under license of MADAUS, AG., Freiburg, Germany), Group B received UDCA capsules twice daily (Ursofalk® 250mg, produced by Minapharm), Group C received combined therapy of both, and group D is a placebo group (received capsules with no medication)

Liver biochemistries including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), Albumin, Total bilirubin and prothrombin concentration (PC) were measured at baseline and repeated 12 weeks after therapy.

Modified Child-Pugh classification of severity of liver disease according to the degree of ascites, serum bilirubin and albumin concentrations, the prothrombin time, and the degree of encephalopathy was calculated before and after therapy for all groups.

Compliance with trial medication was assessed with a medication diary and by counting the unused medication, which patients were required to return.

Statistical Analysis: SPSS V17.0 (SPSS Inc, Chicago, USA) was used for statistical calculations. Comparison of effect of silymarin and ursodeoxycholic acid on serum liver parameters between all groups, were accomplished. Student t-test was used for comparison between means of two groups. Paired-samples T test was used for comparison between means before and after therapy of the same group. The calculated P-value is considered significant if ≤ 0.05.

Results

Hundred patients were first recruited in the study. However, sixty patients did not participate in the follow-up process. Some of these patients lacked the time to complete the study, and others traveled abroad. Finally a total of 40 CHC patients completed the study. Treatment details of the remaining 40 subjects are shown in Fig. 1. Patients were randomly assigned into four groups of tens. Group A (7 males and 3 females) with mean age ± SD 53.7 ± 10.5, Group B (8 males and 2 females) with mean age ± SD 49.7 ± 12.6, Group C (10 males and zero females) with mean age ± SD 56.1 ± 8.2, and group D (7 males, 3 females) with mean age ± SD 47.0 ± 11.6.

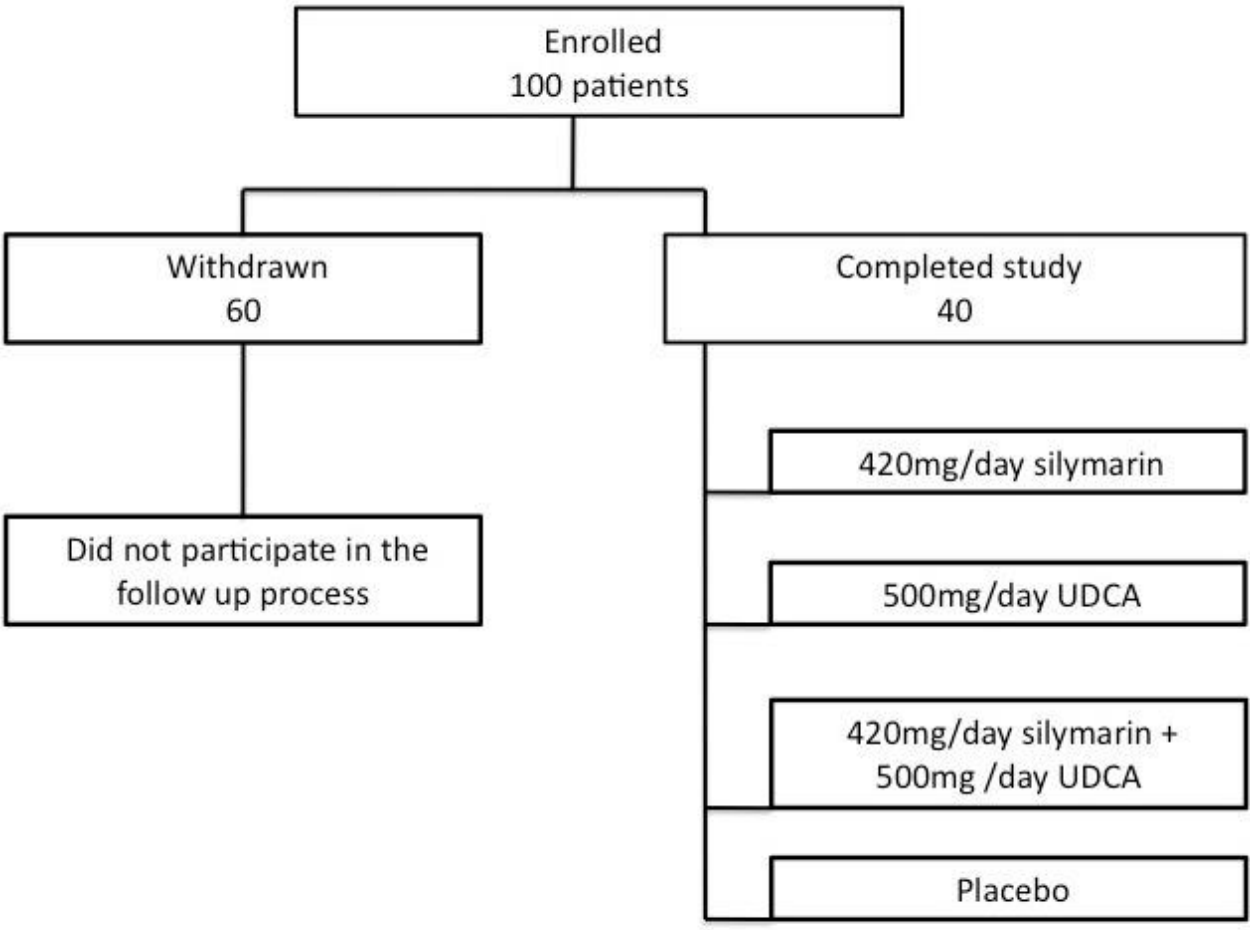

Figure 1: Study treatment details for chronic hepatitis C patients

The demographic and baseline clinical characteristics of each group of patients enrolled in the study are shown in Table 1.

Table 1. The baseline demographic and clinical characteristics of patients enrolled in the study (n =40).

Parameter n or mean±SD	Group A (silymarin 420mg/day)	Group B (UDCA, 500mg/day)	Group C (siymarin 420mg/day + UDCA 500mg/day)	GroupD (placebo)
Age	53.7 ± 10.5	49.7 ± 12.6	56.1 ± 8.2	47 ±11.6
Sex (male/ female)	7/3	8/2	10/0	7/3
Hepatomegally	1	1	1	1
Splenomegaly	2	2	3	3
Ascites	3	3	3	1
Lower limb edema	3	2	2	3
Esophageal varices	2	2	2	2
Appendectomy	0	0	1	0
Cholecystecomy	0	1	0	0
Splenoectomy	2	1	1	1
Pallor	6	4	6	3
Jaundice	3	3	1	3
Dark urine	3	1	3	4
Weight loss	1	1	3	0

As it is evident from Tables 2 and 3, the 12 weeks treatment period of silymarin® (420mg/day) did not show any significant improvement regarding ALT, AST, ALP, GGT, Albumin, T. Bilirubin and PC% compared to baseline and to placebo.

A statistically significant improvement in mean ± SD serum ALT (85.6 ± 21.4 vs. 52.4 ± 15.8, p= 0.025, AST (61.3 ± 14.2 vs. 52.7 ± 15.7, p = 0.016), and T bilirubin levels 1.3 ± 0.5 vs. 1.2 ± 0.5, p = 0.016 was obtained with 500mg/day UDCA therapy.

In addition, the mean ± SD ALT, AST, and T bilirubin levels for the combined therapy group decreased significantly from 54.3 ± 29.5 vs. 44.8 ± 21, p=0.039, 52.4 ± 19.8 vs. 52.1 ± 17.3, p=0.018, and 1.4 ±0.1 vs. 1.2 ± 0.3,p= 0.022, respectively.

Table 2. The mean ±SD serum measurements of the following parameters before and after 12 weeks of oral administration of Legalon® capsule140 mg (420mg/day), Ursofalk® 250 mg (500mg/day), combined therapy of both, and placebo to groups A, B, C, and D respectively.

Serum parameters	Group A (mean ± SD)		Group B (mean ± SD) Ursofalk® (500mg/day)		Group C (mean ± SD) Silymarin®(420mg/day		Group D (mean ± SD) Placebo	
	Before therapy	After therapy	Before therapy	After therapy	Before therapy	After therapy	Before therapy	After therapy
ALT (U/L)	59.8 ± 14.4	57.8 ±13.9	85.6 ±21.4	52.4 ±15.8	54.3 ± 29.5	44.8 ±21.0	59.5 ± 8.6	63.8 ± 6.2
AST (U/L)	62 ± 26.9	60.1 ±24.8	61.3 ±14.2	52.7 ±15.7	58.4 ±19.8	52.1 ±17.3	62.6 ± 17.0	74.4 ±28.3
ALP (U/L)	138.7 ±20.4	141.3 ±17.1	139.5 ±16.1	142.3 ±14.3	140.4 ±12.4	143.1 ±15.5	142.1 ± 12.2	149.6 ±7.8
GGT (U/L)	42.9 ± 8.7	44.2 ±8.8	43.1 ±8.5	46.4 ±8.8	40.3 ±10.5	43.7 ±6.9	42.6 ± 10.0	44.9 ±9.6
Albumin (g/dl)	2.8 ±0.5	2.8 ±0.5	2.9 ±1.0	2.9 ±0.9	2.8 ±0.3	2.9 ±0.2	2.7 ±0.9	2.6 ±0.8
T bilirubin (mg/dl)	1.3 ±0.6	1.4 ±0.6	1.3 ±0.5	1.2 ±0.5	1.4 ±0.1	1.2 ±0.3	1.6 ±1.0	1.8 ±0.7
PC%	67.9 ±16.1	68.7 ±15.5	68.2 ±18.1	69.4 ±15.9	73.4 ±7.8	75.3 ± 12.5	78.8 ±12.6	80.8 ±11.6

ALT, alanine transaminase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, γ-glutamyltransferase; PC%, prothrombin concentration

Table 3. Statistical comparison of the mean difference between serum measurements of the following parameters post oral administration of Legalon® capsule140 mg (420mg/day), Ursofalk® 250 mg (500mg/day), combined therapy of both, and placebo to groups A, B, C, and D respectively for 12 weeks.

Parameter	Comparator	Silymarin	UDCA	Silymarin + UDCA
ALT (U/L)	silymarin	------	------	------
	UDCA	0.428	------	------
	Silymarin + UDCA	0.120	0.372	------
	Placebo	0.230	0.048*	0.013*
AST (U/L)	silymarin		------	------
	UDCA	0.424	------	------
	Silymarin + UDCA	0.413	0.957	------
	Placebo	0.245	0.047*	0.048*
ALP (U/L)	silymarin	------	------	------
	UDCA	0.889	------	------
	Silymarin + UDCA	0.808	0.906	------
	Placebo	0.179	0.174	0.252
GGT (U/L)	silymarin	------	------	------
	UDCA	0.583	------	------
	Silymarin + UDCA	0.889	0.456	------
	Placebo	0.867	0.721	0.753
Albumin (g/dl)	silymarin	------	------	------
	UDCA	0.693	------	------
	Silymarin + UDCA	0.370	0.890	------
	Placebo	0.590	0.436	0.202
T. bilirubin (mg/dl)	silymarin	------	------	------
	UDCA	0.480	------	------
	Silymarin + UDCA	0.458	0.912	------
	Placebo	0.187	0.043*	0.026*
PC%	silymarin	------	------	------
	UDCA	0.922	------	------
	Silymarin + UDCA	0.309	0.369	------
	Placebo	0.063	0.083	0.321

$p < 0.05$, otherwise no significant difference
p value was calculated by student T test.

As illustrated in Table 4, Only the UDCA, and the combined therapy group significantly ($p<0.05$) decreased the mean serum ALT, and AST levels compared to placebo at p values of 0.048, 0.047 and 0.048, 0.013, respectively.

Table 4. Statistical comparison of the mean difference between serum measurements of the following parameters before and after 12 weeks of different study treatments to groups A, B, C, and D.

Serum parameters (mean ± SD)	**Group A (Silymarin® (420mg/day)**	**GroupB (Ursofalk® (500mg/day)**	**GroupC (Silymarin® 420mg/day+Ursofalk® 500mg/day)**	**Group D Placebo**
	P value			
(ALT)	0.395	0.025*	0.039*	0.022*
AST	0.562	0.016*	0.018*	0.038*
ALP	0.213	0.411	0.342	0.055
GGT	0.404	0.076	0.083	0.057
Albumin	0.520	0.876	0.121	0.443
T bilirubin	0.409	0.022*	0.016*	0.166
PC%	0.614	0.660	0.432	0.271

$p < 0.05$, otherwise no significant difference
P-value was calculated by Paired-samples T test

Table 5. The Pugh Modification of the Child score Classification

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirrubin, mg/dL	<= 2	2-3	>3
Albumin, g/dL	>3.5	2.8-3.5	<2.8
Prothrombin time * Seconds over control	>4	4-6	>6
Encephalopathy	None	Grade 1-2	Grade 3-4

Table 6. Mean ± SD number of patients according to each grade of side effect (negative response, mild, and moderate).

Treatment	**Group A (Silymarin®(420mg/day)**			**GroupB (Ursofalk® (500mg/day)**			**Group C (Silymarin®420mg/day+ Ursofalk® 500mg/day)**			**Group D Placebo**		
Clinical Finding	Negative response	Mild	Moderate	Negative response	Mild	Moderate	Negative response	Mild	Moderate	Negative response	Mild	Moderate
Fever	3	3	4	5	2	3	4	4	2	2	3	5
Fatigue	5	2	3	2	3	5	6	3	1	0	3	7
Headache	2	4	4	3	3	4	5	3	2	1	3	6
Nausea	3	4	3	3	2	5	7	2	1	1	3	6
Vomiting	2	4	4	4	3	3	7	3	0	2	2	6
Weight loss	4	3	3	4	3	3	4	3	3	2	3	5
Insomnia	3	3	4	5	3	2	5	4	1	4	1	5
Mean± SD	3.1 ± 1.1	3.3 ± 0.7	3.6 ± 0.5	3.7 ± 1.1	2.7 ± 0.5	3.6 ± 1.1	5.4 ± 1.3	3.1 ± 0.7	1.4 ± 1.0	1.7 ± 1.3	2.6 ± 0.8	5.7 ± 0.8

The severity of liver disease was graded according to the Child-Pugh score using the modification of the score as proposed by Pugh et al presented in Table 5 [28]. Patients were categorized into three Child-Pugh classes A, B, and C before and after therapy according to Pugh's criteria [Score A (5 or 6), B (7-9), or C (10-15)]. Only two patients showed a change in their classes, one in group A (changed from class B to C), and one in group C (changed from class B to A)].

The patients' clinical data including; splenomegally, hepatomegally and ascites showed no significant change during the study period with all treatment groups.

Compliance

During the 12 weeks of treatment, 97.3% of subjects consumed >95% of their medication. There was no significant difference (p>0.64) between the silymarin (97.3%), UDCA (97.4), combined therapy group (97.1) and placebo (97.5%) groups.

Patients' symptoms and examination

The most frequent symptoms during the follow up examination were nausea, vomiting, heartburn, fatigue and weight loss, however, all of these improved during 12 weeks of treatment. In addition, the patients' physical examination showed a decrease in the complaints of jaundice, dark urine and pallor with all study regimens.

Adverse events

A grading scale for reporting adverse events were computed according to the NCI Common Terminology Criteria for adverse events v 4.0 (CTCAE) [29] and were illustrated in Table 6.

The mean ± SD of patients that showed a negative response, mild, and moderate side effects were 3.1 ± 1.1, 3.3 ± 0.7, and 3.6 ± 0.5 for group A, 3.7 ± 1.1, 2.7 ± 0.5, and 3.6 ± 1.1 for group B, 5.4 ± 1.3, 3.1 ± 0.7, and 1.4 ± 1.0 for group C, 1.7 ± 1.2, 2.6 ± 0.8, and 5.7 ± 0.8, respectively.

There were no differences in the types, frequencies of side effects, and patients reported no complications across the treatment period, which indicates that the study drugs were well tolerated.

Discussion

Chronic hepatitis C is a major cause of liver related morbidity and mortality. Its prevalence has increased significantly in several countries [30] and now resulted in a growing incidence of HCV-related hepatocellular carcinomas [31,32].

The high failure rates and the intolerable side effects of the once called the standard CHC therapy of pegylated interferon and ribavirin led patients to explore alternative treatments, such as silymarin or UDCA therapy [6]**.** Even the recent emerging hope for CHC effective treatment by the newly developed direct antiviral agents is still limited by their high cost [9,13]**.**

The mechanisms of action of silymarin are not completely understood, but a variety of mechanisms have been proposed. It has been reported that it may protect liver cell injury with free radical scavenging, stabilization of liver cell membranes, stimulation of hepatocyte protein synthesis, and modulation of the immune response [33]**.** Furthermore, recently, the silymarin antiviral effects through blocking of virus entry, transmission, and infectious virus production have been determined [34]**.** Although the wide use of silymarin in patients with liver disease, the effect of silymarin in chronic hepatitis C patients is controversial and needs further investigations.

In addition, ursodeoxycholic acid (UDCA) has been known to be an effective medical therapy for most patients with primary biliary cirrhosis (PBC) and chronic liver diseases [35,36]**.** However, its exact mechanism of action in delaying fibrosis is yet to be established. Though, it has been suggested that it has cytoprotective, anti-apoptotic, membrane stabilizing, anti-oxidative and immunomodulatory effects [37,38]**.**

Several clinical trials have consistently shown UDCA benefits in improving the biochemical parameters [39,40]**,** slowing down the progression of cirrhosis and even reducing the need for orthotopic liver transplantation (OLT) in primary biliary cirrhosis [41,42]**.** Furthermore, UDCA significantly reduced serum bilirubin levels, as well as serum aminotransferases, gamma-glutamyl transpeptidase and alkaline phosphatase levels in patients with alcoholic liver cirrhosis. However, in CHC patients, despite its therapeutic benefits in biochemical improvement of serum transaminases, it failed to improve either the virological response rate or histological features of the disease **[**43,44]**.** However, UDCA potential therapeutic benefits in different liver diseases still need further investigation

The current study investigated changes in serum hepatic markers, symptomatic improvement and tolerability of CHC patients induced by 12 weeks treatment of 420mg/day silymarin, 500mg/day UDCA, combined therapy of both, and placebo.

The results of this study indicated that despite silymarin significantly improved the symptoms and hence the patients' quality of life during the 12 weeks of treatment, it still failed to show any significant improvement in liver biochemistries. These results are consistent with several previous studies on silymarin that also showed its effect on improving CHC patients' wellbeing but not affecting serum hepatic markers [11,45]**.**

A study by Tanamy et al. 2004 evaluated the effect of a similar dose (420mg/day) of silymarin in preventing complications of CHC for 12 months and still failed to detect any improvement in liver enzymes [11]. Another randomized, double blind, placebo-controlled, crossover study of Gordon et al., 2006, examined the effects of even higher doses (600 or 1200mg/day) of silymarin on CHC patients for 12 weeks and compared the results to a placebo group. The results still showed no significant effects on liver enzymes [45].

In contrast, Kalantari et al., 2011 found that CHC patients receiving 630 mg/day of silymarin for 6 months had improved serum aminotransferases (ALT & AST) [14]. Furthermore, several other studies have contradictingly showed significantly beneficial effects of silymarin on liver enzymes [30,46,47].

The different results in these studies may be attributed to different study doses of silymarin (420 mg/day), different treatment periods, the study design and/or genotypes of the patients, which may influence the results. Furthermore, many of these studies have been criticized for their low methodological quality, low patient number and even not choosing pure CHC patients. Thus, it has been agreed that there is insufficient evidence to indicate silymarin benefits in CHC patients [48].

Regarding ursodeoxycholic acid therapy, the mean serum ALT, AST, and T bilirubin levels before and after therapy for 12 weeks were 58.6 ±21.4 vs. 52.4 ±15.8 (p 0.025), 61.3 ±14.2 vs. 52.5 ±15.7 (p =0.016), and 1.34 ±0.5 vs. 1.19 ±0.5 (p = 0.022) respectively. These results showed significant ($p<0.05$) improvement of ALT, AST and bilirubin after therapy with 500mg/day UDCA for 12 weeks. These results were consistent with Takano et al who also confirmed the efficacy of a 600mg/day dose of UDCA in improving liver functions in CHC patients [49]. Similarly, Omata et al., 2007 studied the effect of different doses of UDCA (150, 600, and 900 mg) in CHC patients and reported that 600 mg/day UDCA was the optimal dose to decrease ALT and AST levels in the those patients [47].

Regarding the combined therapy of 420 mg/day silymarin and 500 mg/day UDCA, the mean of serum levels of ALT, AST, and T bilirubin levels decreased significantly ($p < 0.05$) after 12 weeks treatments from 54.3 ±29.5 vs. 44.8 ±21 (p =0.039), 58.4 ±19.8 vs. 52.1 ±17.3 (p =0.018), and 1.4 ±0.1 vs. 1.2 ±0.3 (p =0.016), respectively.

Although it is still not clear whether a reduction in transaminase levels (with or without normalization) has any clinical significance [50]**.** However, recently the importance of maintaining a low level of ALT for as long as possible in chronic HCV patients for whom IFN therapy is not effective have been stressed [51]. It has been speculated that the key factor for UDCA in delaying cirrhosis may be due to its ability to decrease ALT levels [24,52]. It has been reported by Tarao et al. that lowering ALT levels as low as possible significantly decreased the frequency of hepatocelluar carcinoma recurrence [53]**.**

According to Child-Pugh score classification, none of the treatment groups improved patients' classification, which agrees with our results stating that silymarin did not cause improvement in patients with CHC.

On the other hand, despite the significant improvement in serum bilirubin levels for UDCA treated patients, Child-Pugh score classification still showed no change. This is may be due to the fact that Child-Pugh score is calculated according to five items and bilirubin is one of them.

Therefore, even if UDCA is not a first line treatment for chronic hepatitis C because its effects are not etiologically specific for this disease, practically speaking, it still can be used to supplement other chronic hepatitis therapies. Simply this is because its beneficial effects on lowering elevated serum liver parameters, which has been reported to decrease disease activity, cirrhosis, and hepatocelluar carcinoma recurrence [27,53]**.**

However, regarding silymarin, even with its failure in improving serum liver parameters, its beneficial effects in improvement of symptoms and patients quality of life is still a point that may favour its use in CHC patients. A previous study by Schopen et al found that silymarin significantly improved liver diseases related symptoms [54]**.** Similarly, another recent study bt El-Kamary et al suggested the safety and the potential effects of silymarin in improving symptoms of acute clinical hepatitis despite its failure on affecting biomarkers of the underlying hepatocellular inflammatory process [55]**.**

Nevertheless, all treatment regimens in this study lacked any direct marked detectable effect regarding splenomegally, hepatomegally, and ascites, which did not change before and after therapy. This agrees with previous studies confirming the failure of either silymarin or UDCA in affecting the histological features of the disease [11,46,47]**.**

Conclusions

This study indicated that CHC patients' treatment with silymarin at a dose of 420 mg/day for 12 weeks did not significantly affect liver function tests. However, a 500mg/day dose of UDCA, either when used alone or combined with silymarin (420 mg/day) for the same treatment period has significantly improved ALT, AST and bilirubin results. In addition, all treatment groups had fewer symptoms and reported feeling better than prior to participating in the study. Silymarin, UDCA, and the combined therapy group at the standard recommended doses were well tolerated and caused no side effects.

Author Disclosure Statement

No Conflict of Interest and no competing financial interests

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