

CASE REPORT

Changes in Liver Biochemical Parameters Following the Combined Use of Three Medicinal Plants in a Patient with Hepatitis C: A Case Report

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Abstract

Introduction: liver diseases and its incidence in the whole world rendering the use of alternative medicine to be used for treatment protocols. This study evaluates the protective effect of a combination of three medicinal plants namely *Silybum marianum* (SM), *Cichorium intybus* (CI) and *Ziziphus vulgaris* (ZV) on a patient with hepatitis C whom his liver injury index enzymes has been increased.

Case report: Patient was a 46-year-old man who affected by hepatitis C like symptoms and with mounted levels of liver injury index enzymes. Medicinal plants – based treatment was used on the combination of treatment of CI extract SM pulverized seeds and ZV fruit.

Discussion: The results showed that the combination of CI, SM and ZV could significantly reduce the elevated levels of serum enzymes of AST, ALT and ALP in the patient, so that his levels were reached up to 43.0 ± 3.00 ; 44.0 ± 2.64 and 215.7 ± 6.43 U/L, respectively. Furthermore, the total amounts of flavonoids and phenols received by the patient were 422.57 and 332.10 mg/day, respectively, and may have played a key role in this regard. The bioactive components in the extracts of these three plants can play a protective role in eliminating oxidative stress and cellular damage through vital mechanisms.

Conclusion: Based on this study, it is concluded that the combination of CI, SM, and ZV can have protective effects through strengthening antioxidant defense systems; it will overcome inflammations caused by oxidative stress resulting from HCV, followed by normalizing liver enzymes in this patient using these plants.

Keywords: Hepatitis C, Liver Diseases, Chemical and Drug Induced Liver Injury, Medicinal plants, Combined Modality Therapy

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INTRODUCTION

The liver is a vital organ responsible for a wide range of essential metabolic processes in the body. One of the most important functions attributed to liver is to detoxify environmental materials and chemical drugs in addition to its main role, which is metabolism of biomolecules [1]. Severe damage to this organ can impair this potential and lead to chronic liver diseases such as hepatitis and liver cancer. Despite many advances in medical research, treating liver diseases remains challenging [2]. Liver dysfunction

may cause pharmacokinetic changes in patients with hepatitis [3]. Some direct-acting antivirals (DAAs) have the potential to interact with “common” drugs such as antihypertensive, antiplatelet, antiarrhythmic, and cholesterol-lowering drugs. Therefore, knowledge of drug interactions can help healthcare professionals in their clinical practice to influence patient outcomes [4]. Also, the high cost of treatment further limits access to life-saving treatments [5].

Hepatitis C virus (HCV) is an important disease which leads to liver damage. HCV- caused infections are often

seen without therapeutic symptoms and because of this issue the disease chronically becomes liver fibrosis and cirrhosis [6]. The most ordinary ways of this viral infection is through contacting the blood products, dialysis and also blood transfusion [7]. In recent decades, some efforts have been made regarding the protective and therapeutic effects of some medicinal plants worldwide [8-10]. The output of these researches showing the key role of medicinal plants and also their components and natural constituents for prevention, protection and treatment of liver diseases [11]. In this study, Milk thistle or *Silybum marianum* (SM), Chicory or *Cichorium intybus* (CI) and *Ziziphus vulgaris* (ZV) are herbal plants belonging to Asteraceae and Rhamnaceae plant families, respectively [12, 13]. These plants have been used for the treatment of several diseases such as hepatitis and liver disorder since many years before [6]. The aim of this study was to attenuate liver hurt progress and the subordinated toxicity formed during this organ damage in a patient whom has been affected by HCV. Given the limited sample size and the simultaneous use of these three plants for the first time, it may also affect the final conclusions and impose limitations.

CASE PRESENTATION

The patient was a 46-year-old man with a weight of 90 Kg who was affected by hepatitis C like symptoms and with a history of blood transfusion. The patient had an increased average level of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) enzymes (69.2 ± 8.52 and 80.0 ± 14.5 U/L, respectively) and, the other biochemical tests of the patient were in the normal range. In hematology tests, the numbers of platelets were less than normal (table 1). The patient had a history of chronic liver disease; however, detailed virological characterization, including HCV RNA levels and genotype, as well as fibrosis staging and the presence or absence of cirrhosis, was not available. The patient had no history of cigarette smoking or alcohol consumption. However, the assessment of potential confounding factors, including coinfections, metabolic liver disease, and other possible causes of elevated liver enzyme levels, was limited by the availability of clinical information. The treatment protocol was carried out on the patient in accordance with the ethical principles within the framework of the Declaration of Helsinki [14] and with the full consent of the patient using the three aforementioned medicinal plants. Written and informed consent for the treatment protocol and publication of the case report was obtained from the patient.

Treatment Protocol

Treatments were based on the combination of treatment of CI extract SM pulverized seeds and ZV fruit. The plants were selected based on previous reports of antioxidant and anti-inflammatory properties and their potential relevance to experimental investigations of hepatic injury [15-21]. SM seeds were provided from Kelardasht district in Mazandaran province placed in northern Iran. The other two medicinal plants namely ZV and CI were collected from Kashan city

placed in Isfahan province of Iran. Botanical identification was performed by a botanist at the IHEC Herbarium the preparation procedures followed previously published methods [15]. SM seeds are firstly extracted from capitula and dried at temperature of 45 °C under shadow and away from direct sun radiation [15]. Then, the dried seeds were powdered by automatic mixer. The upper part of CI (flowering organ) was dried under shadow, and then it was spliced to unified size by an automatic mixer. These unified parts of CI were used to be extracted by steam distillation method and through Clevenger apparatus for 2 hours. The ratio of 1/2 (w/v) was used for CI distillate. The ripe fruits from ZV were dried under sun radiation and open atmosphere and these dried fruits were used for treatment. All preparation procedures of three above-mentioned medicinal plants were based on standard methods that in before studies have been mentioned [15-21].

The dosage used of these combined treatment for the patient was considered as CI extract (240 mg /kg of body weight /day), SM pulverized seeds (5.5 mg/kg of body weight/day) and ZV (167 mg/kg of body weight/day) which continued for 4 weeks. All preparation procedures of three medicinal plants were based on standard methods in before studies [15]. After this period, all herbal medicines in this patient was discontinued except for CI which followed by another one-month treatment at the same dosage. The treatment regimen reported in the present study differs from previously published versions of the protocol. Therefore, all three dosages were verified against the original treatment records and the relevant references [10, 11]. During the implementation of this protocol, the patient was not taking any specific synthetic drugs; therefore, there were no issues regarding interactions with other medications.

Biochemical Analyses and Analytical Devices

Biochemical parameters were measured using a Selectra E automated chemistry analyzer (Vital Scientific, Netherlands) with quantitative assay kits supplied by Pars Azmun Co. (Tehran, Iran). Complete blood cell counts, including hemoglobin concentration and hematocrit, were determined using a Sysmex KX-21 hematology analyzer (Sysmex Corporation, Kobe, Japan). Prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR) were measured using Thermo Scientific assay kits (Thermo Fisher Scientific, Waltham, MA, USA) according to the manufacturer's instructions.

Statistical Analysis

Biochemical parameters were analyzed descriptively. Serial laboratory values obtained before and after treatment were presented in tabular form, along with the corresponding percentage changes relative to the values measured before treatment. Percentage changes were calculated as follows:

Percentage change (%) = $\frac{[(\text{Post-treatment value} - \text{Before-treatment value}) / \text{Before-treatment value}] \times 100}{}$

Given the single-patient nature of this case report, no inferential statistical tests were performed, and no p-values

were calculated. Reference ranges presented in the original study table were verified against the laboratory's reference intervals. Given the single-patient nature of this case report, no inferential statistical tests were performed, and no p-values were calculated.

DISCUSSION

A continuous decreasing trend in elevated liver enzyme levels was observed throughout the treatment period. After one month of treatment, AST and ALT levels showed a clear decline compared with the pretreatment values, decreasing to 46.0 ± 4.24 and 46.4 ± 2.30 U/L, respectively (Table 1). This reduction represented approximately 33.5% and 42.0%

decreases in AST and ALT levels compared with baseline values. During the same period, ALP also showed a downward trend, decreasing to 218.0 ± 7.07 U/L, corresponding to an approximately 10.1% reduction from the pretreatment value, while remaining within the normal reference range. The decreasing trend continued during the second month of treatment, with further reductions in all measured liver enzymes compared with the one-month values and baseline levels. AST, ALT, and ALP demonstrated overall reductions of approximately 37.9%, 45.0%, and 11.1%, respectively, compared with pretreatment values. Accordingly, the mean serum activities of AST, ALT, and ALP after two months of treatment were

Table 1. Blood parameter levels measurement of the patient, before and after treatment using combination of three medicinal plants

Chemical parameters	Unit	Baseline	Month 1	Change (%)	Month 2	Change (%)	Reference range (Men)
Fasting blood sugar	mg /dL	101.0 ± 2.64	87.3 ± 3.05	-13.6	90.0 ± 2.00	-10.9	70-110
Urea	mg /dL	20.0 ± 2.00	19.0 ± 1.00	-5	21.0 ± 1.00	+ 5	19-44
Creatinine	mg /dL	1.20 ± 0.10	1.30 ± 0.00	+8.3	1.30 ± 0.10	+8.3	0.7-1.4
Uric Acid	mg /dL	5.26 ± 0.23	5.43 ± 0.11	+3.2	5.20 ± 0.10	-1.1	3.6-8.20
Total Cholesterol	mg /dL	146.0 ± 8.54	130.0 ± 5.00	- 11	132.0 ± 3.60	-9.6	up to 200
HDL- Cholesterol	mg /dL	42.0 ± 2.00	39.0 ± 1.00	-7.1	41.0 ± 1.00	-2.4	At least 35
LDL- Cholesterol	mg /dL	72.0 ± 2.00	63.0 ± 2.00	-12.5	66.0 ± 1.00	-8.3	up to 130
Triglycerides	mg /dL	67.0 ± 8.18	72.0 ± 2.64	+7.5	70.0 ± 2.00	+4.5	up to 200
Calcium	mg /dL	9.06 ± 0.11	8.93 ± 0.12	-1.4	9.10 ± 0.10	+0.4	8.3-10.3
Phosphorus	mg /dL	3.33 ± 0.06	3.60 ± 0.10	+8.1	3.40 ± 0.10	+2.1	2.5- 4.5
Na	mEq/L	137.0 ± 1.00	138.0 ± 0.00	+0.7	137.0 ± 1.00	0	135-145
K	mEq/L	4.50 ± 0.10	4.40 ± 0.20	-2.2	4.60 ± 0.10	+2.2	3.5-5
AST	U/ L	69.2 ± 8.52	46.0 ± 4.24	-33.5	43.0 ± 3.00	-37.9	< 37
ALT	U/ L	80.0 ± 14.5	46.4 ± 2.30	-42	44.0 ± 2.64	-45	< 41
ALP	U /L	242.6 ± 15.8	218.0 ± 7.07	-10.1	215.7 ± 6.43	-11.1	64 - 306
Bilirubin total	Mg/dL	1.30 ± 0.10	ND	-	1.20 ± 0.10	-7.7	0.2-1.4
Bilirubin direct	mg /dL	0.33 ± 0.05	ND	-	0.30 ± 0.00	-0.9	≤ 0.3
Creatine phosphokinase	U/ L	80.7 ± 2.08	ND	-	85.0 ± 2.64	+5.3	24-195
Lactate dehydrogenase	U /L	345.0 ± 5.00	ND	-	351.0 ± 1.73	+1.7	< 480
White blood cell	$\times 10^3/ \mu\text{L}$	5.33 ± 0.30	5.70 ± 0.10	+6.9	5.50 ± 0.20	+3.2	4-10
Red blood cell	$\times 10^6/ \mu\text{L}$	4.29 ± 0.02	4.35 ± 0.15	+1.4	4.73 ± 0.14	+10.3	3.9 – 5.8
Hemoglobin	g/dL	13.03 ± 0.25	13.0 ± 0.26	-0.2	13.3 ± 0.10	+2	14 - 18

Table 1. Continued

Chemical parameters	Unit	Baseline	Month 1	Change (%)	Month 2	Change (%)	Reference range (Men)
Hematocrit	%	38.93 ± 0.21	39.33 ± 0.58	+1	40.3 ± 0.17	+3.5	40 - 54
Platelet	×10 ³ /μL	102.0 ± 12.12	99.0 ± 3.60	-2.9	102.0 ± 7.00	0	150 - 450
Prothrombin time	seconds	14.2 ± 0.10	14.1 ± 1.00	-0.7	13.9 ± 0.1	-2.1	12–13.5
Partial thromboplastin time	seconds	35.0 ± 1.00	36.0 ± 1.00	2.9	36.0 ± 1.00	2.9	24–36
International normalized ratio		1.2	1.2	0	1.1	-8.3	up to 1

Values are mean ± SD of different replicates (N=3) from five times of measurements.

43.0 ± 3.00, 44.0 ± 2.64, and 215.7 ± 6.43 U/L, respectively (Table 1). Although AST and ALT remained slightly above their respective reference limits, their progressive decline indicated a reduction in enzyme levels without complete normalization. In contrast, ALP was within the normal reference range at baseline and remained within the normal reference range throughout the study, showing a gradual reduction during treatment. Overall, the sequential decline observed from baseline to one month and subsequently to two months demonstrated a sustained and progressive improvement in biochemical liver parameters following the treatment approach. However, the obtained results pertaining to the specific sample used in this protocol, and the limitation regarding the sample size should be taken into account.

Safety and Tolerability

No adverse events were reported during the observation period, according to the available clinical records. This observation is limited to the reported follow-up and does not establish the absence of potential toxic effects.

The total phenolic and flavonoid contents received by the patient through the medicinal plants during the study are presented in Table 2.

HCV infection may be a significant risk factor for severe hepatotoxicity in some patients. Therefore, close monitoring of liver function is essential during some important and

critical therapies for HCV patients [22]. Also, in some treatments, HCV-related toxicity can prevent appropriate treatment for the patient, and this is one of the most important limitations in modern and effective immune chemotherapy programs for patients [23].

Some hepatitis, such as HBV and HCV, are able either to decrease the antioxidant capacities or to increase the levels of lipid peroxidation in human [24]. This action can lead to impact on the immune cells and accordingly liver damage will be emerged. More importantly, it seems that HCV in inducing oxidative stress will be more potent when compared with HBV [25].

Silymarin is a potent antioxidant with anti-toxic, anti-inflammatory and anti-fibrogenic properties and induces beneficial therapeutic effects on liver diseases. SM is able to exert hepatoprotective effects through different mechanisms including, cell membrane stabilization, and free radicals inhibition due to having its valuable flavonoids including silymarin (Silybin, Silychristin and Silydianin) [16, 17]. Obviously, the presence of total flavonoid measured in SM and the received amount of 227.49 mg/day of this kind of flavonoids by the patient can be one of the reasons forming this protective role against HCV- caused liver toxicity. Therefore, one of the important reasons that caused the SM seeds to come through the study. On the other side, the antioxidant activity attributed to CI is due to their

Table 2. Daily amounts of flavonoids, phenols, and silymarin received by the patient during the study

Plant	Amount of total Flavonoids* (mg/day)	Amount of total Phenols** (mg/day)	Silymarin (mg/day)
SM	227.49	203.90	20.46
ZV	5.56	4.81	
CI	189.52	123.39	
Total	422.57	332.10	

SM (*Silybum marianum*) ZV (*Ziziphus vulgaris*) and CI (*Cichorium intybus*), are respectively used for combination therapy and calculated based on *Quercetin equivalent (QEE);**Gallic acid equivalent (GAE).

flavonoids and phenolic acids which present in the seeds of this plant. This activity causes to support and bolster defense mechanisms against oxidative stress formed by free radicals [18].

The plausible mechanisms of hepatoprotective properties of chicory extracts are mainly attributed to the presence of phenolic compounds, especially chicoric acid, its anti-inflammatory properties and antioxidant activity, which are able to control the production of reactive oxygen species (ROS) [19], and as shown in our result due to presence the noticeable amount of these phenolic compounds (332.10 mg/day) based on Gallic acid equivalent could have had a reducing and adjusting these free radicals. Also, natural products such as chicory extracts may play a protective role against pathological manifestations through the activation of the PI3K/AKT/Nrf-2/HO-1 signaling pathway. Chicoric acid in chicory extract can also synergistically produce cytoprotective effects [20]. Based on the above-mentioned issues it is presumptive that CI, together with SM, due to high amount of total flavonoids measured based on potent antioxidant equivalent, namely, quercetin, caused this patient received the high level of antioxidant compounds (417.01 mg/day) through taking these two medicinal plants.

Jujube is used in traditional medicine to enhance liver function and prevent liver diseases. Jujube improves liver disorders by activating the body's antioxidant system and inhibiting inflammatory responses. The protective effects of jujube in hepatotoxicity may be associated with potential mechanisms involving the activation of antioxidant defenses through the Nrf2 (nuclear factor erythroid 2-related factor 2) pathway and the modulation of inflammatory responses through the NF- κ B (nuclear factor kappa-light-chain-enhancer of activated B cells) pathway. However, these mechanisms remain hypothetical in the present case and were not directly investigated [21].

The concurrent use of three medicinal plants namely SM, CI and ZV in this study showed that; the serum levels of the enzymes of AST, ALT and ALP in patient were noticeably reduced and therefore, the liver function got back the normal status. In this regard, as shown in Table 1, the increased levels of AST and ALT were reduced two months after beginning of the study; the reduction in AST, ALT and ALP levels were 37.9%, 45.0% and 11.1%, respectively, compared with baseline values. From a medical toxicology perspective, the present study provides descriptive clinical information regarding the potential protective effects of the concurrent use of the three aforementioned medicinal plants against HCV-associated liver injury. The results of this protocol indicated that, within the specified timeframe and through the use of the recommended herbs, the patient's serum enzyme levels decreased rather than evidence of therapeutic efficacy or established safety. It can be speculated that the bioactive components present in the extracts of these three plants can play a synergistic role in

cell protective effects. Free radical scavenging activity and antioxidant activities in these plants have shown a protective role against pathological manifestations, along with a vital mechanism for survival and elimination of oxidative stress and cellular damage. The presence of important compounds such as flavonoids, phenolic compounds, chicoric acid, caffeic acid, terpenoids, and vitamins stimulates the immune system and inhibits free radicals, ultimately returning the increased levels of AST, ALT, and ALP enzymes towards normal ones (Figure 1).

The limitations of this study include the single-case design and the limited sample size, which restrict the generalizability of the findings. Furthermore, the precise molecular mechanisms underlying the potential effects of these medicinal plants and the optimal therapeutic doses require further detailed molecular and clinical investigations. Considering the diversity and abundance of medicinal plants in Iran and their potential role in complementary medicine, larger-scale clinical trials with appropriate controls and extended follow-up periods are recommended to evaluate their safety, efficacy, and therapeutic potential in patients with HCV and other liver disorders.

CONCLUSION

It can be concluded that the medicinal plants used in this case may have contributed to the improvement of liver biochemical parameters, possibly through strengthening antioxidant defense mechanisms, promoting liver tissue regeneration through the normalization of liver enzyme activities in the patient, and reducing oxidative stress associated with HCV infection. During the treatment period, a progressive decline in liver enzyme levels was observed. These findings suggest a potential beneficial effect of the herbal preparations on liver function; however, the observed biochemical improvements in this single case should be interpreted cautiously and cannot be generalized to the wider HCV population. The findings provide a clinical observation that may warrant further investigation, but they do not establish definite hepatoprotective efficacy, synergistic activity, complete improvement in HCV infection, or a constant causal relationship between the herbal preparations and the biochemical changes.

Ethical Consent

The patient provided written informed consent for the publication of this report, and the corresponding author was responsible for obtaining this consent.

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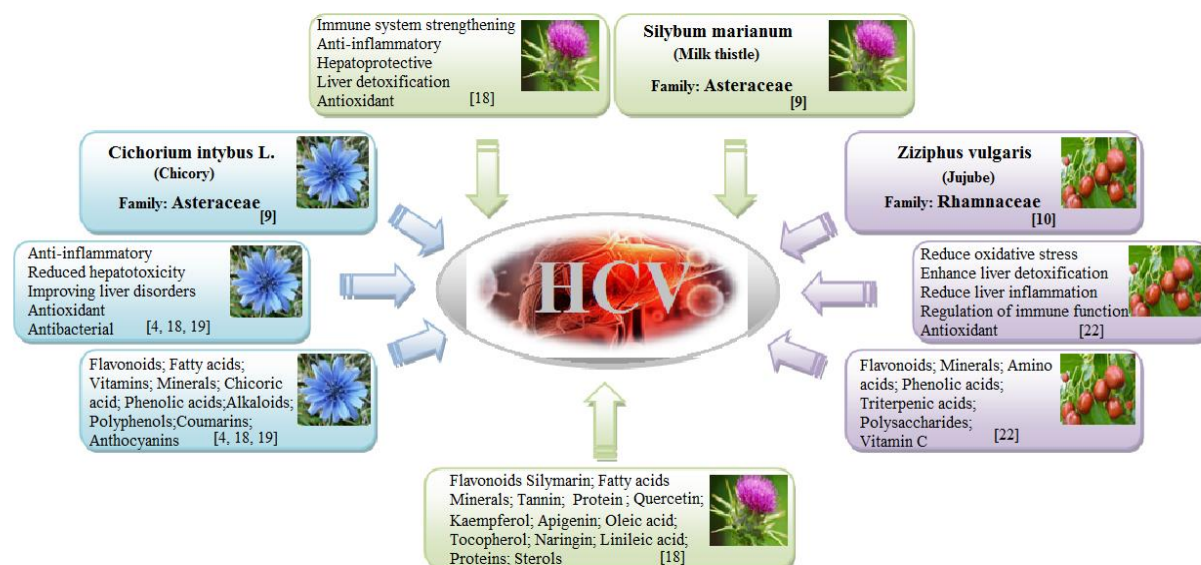


Figure 1. The simultaneous use of three medicinal plants, jujube, chicory, and milk thistle, in this treatment protocol activated vital mechanisms that through different pathways and various phytochemical compounds affecting HCV

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