

Original Article**Effects of silybum marianum on patients with chronic hepatitis C**

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Abstract

BACKGROUND: Silymarin derived from silybum marianum (milk thistle), a flowering member of the daisy family, may benefit liver function in people infected with the hepatitis C virus. The aims of this pilot study were to assess the efficacy and safety of silymarin on serum hepatitis C virus (HCV) RNA, serum aminotransferases (ALT, AST) levels, liver fibrosis and well-being in patients with chronic hepatitis C (CHC).

METHODS: This prospective self-controlled trial study was conducted from March to September 2006 at Department of Gastroenterology, Isfahan University of Medical Sciences, Isfahan, Iran. 55 patients with HCV (10 female and 45 male) with a mean age of 31.8 ± 6.4 years (10-67 years) were participated in the study. Patients received 24 weeks of silymarin (630 mg/day). Baseline virological biochemical, liver fibrosis (by a serum fibrosis markers, including YKL-40 and Hyaluronic acid), and SF-36 questionnaire were performed with biochemical tests repeated at the end of the treatment period.

RESULTS: There was statistically difference in mean of ALT (108.7 ± 86.6 vs 70.3 ± 57.7) before and after the treatment ($p < 0.001$). The means of AST were 99.4 ± 139.7 and 59.7 ± 64.32 before and after the treatment with statistically differences ($p = 0.004$). After the treatment, nine patients were found with negative HCV-RNA ($p = 0.004$) and statistically significant improvement in results of liver fibrosis markers were found only in fibrosis group ($p = 0.015$). Quality of life was improved significantly ($p < 0.001$).

CONCLUSIONS: This study indicated that in patients with CHC performing silymarin (650 mg/day) for 6 months, improved serum HCV-RNA titer, serum aminotransferases (ALT, AST), hepatic fibrosis and patient's quality of life. More future studies are warranted.

KEYWORDS: Hepatitis C Virus (HCV), Quality of life, Serum Aminotransferases.

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Hepatitis C is a major cause of liver - related morbidity and mortality.^{1,2} Ribavirin plus interferon combination therapy, is presently considered the optimal treatment for patients with chronic hepatitis C, but the recommended treatment regimen is associated with considerable expense, adverse effects and poor efficacy in some patients with hepatitis C. Therefore, many hepatitis C patients use the herb silymarin (milk thistle), an alternative therapy for hepatitis C, in addition

to or instead of standard treatment for chronic hepatitis C virus infection.³

Although the popularity of silymarin has been increased in people with liver disease^{4,5} but a little evidences with controversial results exist in effect of silaymarin on chronic hepatitis C. In one study in Egypt,⁶ a dose of 420 mg/day of silymarin has been used for one year. The quality of life of the patients improved very well, but the level of liver enzyme did not change. An exhaustive search strategy

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identified 148 papers that studied silymarin compounds in liver disease. Of these, four trials included patients with hepatitis C which only two trials reported a decrease in serum transaminases.^{7,8}

According to existence of little evidences with controversial results and increasing popularity of using silymarin in chronic hepatitis C, this study was conducted to evaluate the effect of higher doses of silymarin (630 mg/day) for 6 months, on patients with hepatitis C along with liver biopsy.

Methods

This prospective self-controlled trial study was conducted from March 2006 to September 2006 at Department of Gastroenterology, Isfahan University of Medical Sciences, Isfahan, Iran.

Inclusion criteria contained confirmed chronic hepatitis C (HCV Ab (+), HCV-RNA [with PCR] (+)), normal or increased liver enzymes (ALT and AST) and not using interferon or ribavirin due to patient sensitivity or not consenting. The pregnant patients and patients with side effect which confirmed with rechallenge test were excluded. The ethics committee of Isfahan University of Medical Sciences approved the study and all of participants signed an inform consent after explaining the aims and protocol of the study to them. The study was registered at ClinicalTrials.gov (Identifier: NCT01292161).

After measuring the baseline outcomes, we performed 630 mg/day silymarin a product of Goldaru pharmaceutical Co. Isfahan, Iran for six months. Following serum components were measured before and after the treatment: liver enzymes (ALT and AST), HCV-RNA (with PCR) and markers for liver fibrosis such as YKL 40 and Hyaluronic Acid (HA). YKL 40 was measured with YKL 40-EIA Kit, Quaidel comp. San Diego. CA. with cut off value of 284.8 ng/ml (sensitivity 80% and specificity 71%)⁹ and HA was assessed by enzyme linked binding protein assay (corgenix inc Denver) with the cut-off value of 110 mg/l (sensitivity 79.2% and specificity 89.4%).¹⁰

According to liver fibrosis markers (YKL 40

and HA) results before treatment, patients were divided into three stages:

Fibrosis group: YKL 40 > 150 ng/ml and HA > 60 ng/ml or YKL 40 > 150 ng/ml or HA > 100 ng/ml; Non-fibrosis group: YKL 40 < 100 ng/ml and HA < 20 ng/ml; Intermediate group: the results with no agree with above levels.

After the treatment patients were divided to three groups according to their liver fibrosis markers results. Fibrosis activity progress group: YKL 40 > 100 ng/ml or HA > 50 ng/ml more than the level before treatment. Fibrosis activity regression group: YKL 40 decreased more than 75 mg/ml or HA decreased \geq 30 ng/ml compared with before treatment levels. Fibrosis stable group: the level of liver fibrosis markers were not agreed with above level after treatment. For the determination of quality of life, we used the Iranian version of short form healthy survey (SF-36) questionnaire¹¹ before and after treatment which it's validity and reliability was established. The SF-36 questionnaire is a generic measure of health that is used to measure quality of life. It consists of 36 questions (items) which altogether score from 0 to 100.

Data were analyzed with the paired t-test, McNemar, and chi-square statistical methods. All analysis were done with SPSS v.16.

Results

Seventy seven patients were enrolled in the study. One patient died and 21 patients did not participate in follow-up process. Finally, 55 patients (10 female and 45 male) with the means age of 31.8 ± 6.4 years (10-67 years) completed the study.

The mean of ALT before and after the treatment were 108.7 ± 86.6 and 70.3 ± 57.7 . According to paired t-test analysis there was a statistical difference before and after the treatment with silymarin ($p < 0.001$). The mean of AST were 99.4 ± 139.7 and 59.7 ± 64.32 before and after the treatment. According to paired t-test analysis there was statistically different from before the treatment with silymarin ($p = 0.004$).

After the treatment, nine patients were found

Table 1. Liver fibrosis markers (YKL 40 and HA) results before and after the treatment

| Groups | Before treatment | Progression after treatment | Stable after treatment | Regression after treatment |
|--------------------|------------------|-----------------------------|------------------------|----------------------------|
| Fibrosis n (%) | 42 (76%) | 11 (26%) | 14 (33%) | 17 (40%) |
| Non-fibrosis n (%) | 4 (7%) | 0 (0%) | 4 (100%) | 0 (0%) |
| Intermediate n (%) | 9 (16%) | 2 (22%) | 7 (77%) | 0 (0%) |

with negative HCV-RNA which in regard to McNemar test, it was significantly difference before and after the treatment ($p = 0.004$).

The results of liver fibrosis markers are showed in table 1. According to hi-square method, there was a statistical improvement only in fibrosis group ($p = 0.015$).

The means of SF-36 score were 51.06 ± 21.8 and 61.49 ± 22.8 before and after the treatment respectively. According to paired t-test analysis, there was a statistical improvement in quality of life of patients ($p < 0.001$).

Discussion

Silymarin has been claimed to have a beneficial effect on various types of liver injury, including alcoholic liver disease, drug and toxin induced hepatotoxicity, and acute and chronic viral hepatitis.⁸ Our results showed that performing silymarin was significantly improved the serum liver enzymes, HCV-RNA titer, hepatic fibrosis and patient's quality of life.

The mechanism of silymarin might be by protecting liver cell injury with free radical scavenging, stabilization of liver cell membranes, stimulation of hepatocyte protein synthesis, and modulation of the immune response.¹² Also recently determined silymarin had antiviral effects against hepatitis C virus cell culture infection that included inhibition of virus entry, RNA and protein expression, and infectious virus production.¹³

There is a little evidence for using this drug for hepatitis C. Previous studies^{8,14} have reported an improvement in a number of liver chemistries, including ALT, following treatment with *S. marianum* and our results supported their findings. Tanamly et al in a double-blinded trial evaluated silymarin in preventing complications of chronic hepatitis C. Although they showed an improvement in patient's symptoms and quality of life, but no

significantly improvement in their liver enzymes, liver fibrosis markers and HCV-RNA was achieved. Our results were not agreed with their findings respectively. The difference might be because of the performed dose of silymarin, the study design and the genotypes of patients.⁶

Gordon et al in a randomized, double-blind, placebo-controlled, crossover study examined the effects of silybum marianum on patients with chronic hepatitis C and showed no significant effect on serum HCV-RNA, alanine aminotransferase levels, quality of life or psychological well-being.⁷ Our findings did not support their findings respectively. It may be due to their low sample size or study design which may influence the results.

Adverse drug effects related to silymarin have been published in studies and case reports involving a total of over 7000 patients and those confirmed that it is safe, with only three reports of significant adverse reactions.^{5-12,14-18} Thus, it seems from the current data that patients with chronic hepatitis C are to benefit from taking silymarin.

Conclusions

This study indicated that in patients with chronic hepatitis C performing silymarin (650 mg/day) for 6 months, improved serum HCV-RNA titer, serum aminotransferases (ALT, AST), hepatic fibrosis and patient's quality of life. More future studies are warranted.

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Conflict of Interests

Authors have no conflict of interests.

Authors' Contributions

HK carried out the design and coordinated the study, participated in most of the experiments and prepared the manuscript. ZSH and TGH provide assistance in the design of the study, coordinated and carried out all the experiments and participated in manuscript preparation. MH and VS provided assistance for all experiments. All authors have read and approved the content of the manuscript.

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