Therapeutic effects of Silybum marianum in the treatment of liver fibrosis and cirrhosis

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ABSTRACT

Background: Cirrhosis is the late, symptomatic stage of chronic liver disease which occurs when scar tissue (fibrosis) largely replaces healthy liver tissue, compromising the function of the organ and predisposing to liver failure and hepatocellular carcinoma. It is mainly caused by hepatitis B and C virus infections or prolonged excessive consumption of alcohol.

Aims and Objective: To study the therapeutic effects of Silybum marianum on liver fibrosis and cirrhosis in patients with chronic hepatitis C virus infection with Child Pugh Stage A & B.

Materials and Methods: In this study 119 patients were treated for 6 months with Silybum marianum, their Liver stiffness measurements were carried out through Fibroscan, which is a non-invasive technique to assess liver fibrosis. Liver Fibrosis Scores viz; Aspartate aminotransferase/platelet ratio index (APRI) and fibrosis index based on four factors (FIB-4) were also employed at baseline and end of treatment. Results: Pre-treatment Liver Stiffness Measurement (LSM) score was 22.54 kilopascals (kPa) and post treatment was 17.30 kPa, a statistically significant change of 5.24 kPa (P < 0.01) was observed, the mean percent change was 23.24%, its impact was observed in all METAVIR stages. Of the 72 (60.5%) patients with LSM ≥ 12.5 kPa (cirrhosis) at baseline 23 (32%) proved to have no cirrhosis (≥ 1 decrease in fibrosis stage) at post treatment. Similarly, 19 patients moved to stage F0-F1, 28 patients in F2 and 23 in F3. Overall fibrosis stage was improved (≥ 1 decrease in fibrosis stage) in 46 (38.7%) of 119 patients after 6 months of treatment. Serum fibrosis scores APRI and FIB-4 significantly decreased in comparison to baseline values. APRI values dropped from 1.24 to 0.83. FIB-4 score changed from 3.90 to 2.10. Conclusion: Our result suggests significant improvement with Silybum marianum in the patients status of liver fibrosis and cirrhosis associated with hepatitis C related chronic liver disease. Silybum marianum shows therapeutic effect in real life setting on the entire aspect of disease, as evaluated with the fibroscan and serum fibrosis score.

Key words: Silybum marianum; Cirrhosis; Fibrosis; Herbal treatment

INTRODUCTION

Hepatitis is becoming world health problem, viral hepatitis is more common in developing countries, like Pakistan and Egypt, with the highest prevalence rate in the world, whereas alcoholic hepatitis is still prevalent in the developed countries.¹ ² It is estimated that over 400 million people are infected with viral hepatitis worldwide, whereas 1.5 million people lost their lives each year. Viral hepatitis is a chronic disease which carries serious complications resulting in liver cirrhosis, end stage liver disease and hepatocellular carcinoma.³

According to a research conducted by Pakistan medical research council in 2007, prevalence of hepatitis B & C in Pakistan is around 8%, one in twelve Pakistanis is infected with either HBV or HCV. Considering these alarming facts Lancet in a publication declares that Pakistan is a Cirrhotic State”. Chronic hepatitis B & C which causes most of the cirrhosis are the “HIV/AIDS of Pakistan.”
Once the diagnosis of cirrhosis has been established, available methods of treatment seem to offer poor chances for survival. Treatment and cure of cirrhosis has become a challenge to the medical profession. No approved medicine is available for the treatment of cirrhosis, (to halt or reverse the hepatic fibrosis).

Considering the gap in this therapeutic segment and a dire need of effective therapy for liver fibrosis and cirrhosis, this research has been carried out to find a meaningful solution. Herbs are being used since ages by mankind to treat different ailments, a large number of modern medicines are derived from plants including half of all prescribed anti-cancer medicine are derived from natural origin. There exists a widely held view that Silybum marianum commonly called (Silymarin/milk thistle) promotes liver health through its anti-oxidant, anti-inflammatory, anti-proliferative, anti-fibrotic and immunomodulatory effects. In fact, silymarin is one of the top 10 natural products consumed in western society by patients with hepatitis C. There are compelling in vitro and animal data supporting the hepatoprotective effects of silymarin and inhibition of in vitro HCV infection, clinical data suggesting a protective effect of silymarin against progression of liver disease including liver cirrhosis and fibrosis.

In this research we studied the effect of *Silybum marianum* on patients with Chronic Hepatitis C virus infection with Child-Pugh Class A and B. Liver stiffness measurements were carried out through Fibroscan, which is a non-invasive technique to assess liver fibrosis. Liver Fibrosis Scores viz; Aspartate aminotransferase/platelet ratio index (APRI) and fibrosis index based on four factors (FIB-4) were also employed.

Transient elastography is a new, non-invasive reproducible technique that measure tissue stiffness, liver stiffness measurement (LSM) has been demonstrated to be a reliable tool for assessing hepatic fibrosis and cirrhosis in patients with CHC. LSM were performed on each patient, 10 successful measurement were taken and their success rate were calculated as the number of validated measurements divided by total numbers of measurement. The results were reported in kilopascals (kPa).

**MATERIALS AND METHODS**

Prospective, exploratory study conducted according to the ethical guidelines laid down in the declaration of Helsinki approved by the Institutional ethics committee. Written informed consent was obtained from every participant. Two hundred thirty consecutive patients with HCV were screened at the outpatient facility of the university hospital from January 2011 to June 2017. One hundred forty-three patients were enrolled based on fulfilling the study criteria, 119 patients completed the study. Data collected for analysis at baseline and end of treatment. Our target population was male and female infected with chronic HCV infection, ≥ 18 years of age. Inclusion criteria were, measurable HCV RNA, positive anti-HCV antibodies, compensated liver disease, Child-Pugh class A & B and able to give written informed consent. Exclusion criteria included pregnant and lactating women, co-infection with HIV or HBV, history/other causes of chronic liver diseases, not associated with HCV, alcoholic liver disease, autoimmune hepatitis, exposure to hepatotoxic materials, hemochromatosis, or other conditions associated with decompensated liver disease. Evidence of hepatocellular carcinoma, history of severe psychiatric illness and any significant cardiovascular disease.

**LIVER STIFFNESS MEASUREMENT& SERUM FIBROSIS SCORES**

Fibro scanning was performed on the right lobe of the liver at the liver institute of Dow University Hospital, a total of 10 measurement were taken expressed in kPa at each assessment. LSM score range from 2.50 to 75 kPa, these measurements were used to estimate METAVIR fibrosis stages at baseline and end of treatment.

F0 – F1: 2.5 – 6.9 kPa, F2: 7 – 9.4 kPa, F3: 9.5 – 12.4 kPa, F4: ≥ 12.5 kPa (cirrhosis). For serum fibrosis scores (APRI & FIB-4) were used, cutoff values for determination of fibrosis and cirrhosis were adopted from European Association for the Study of the Liver Diseases (EASL) guidelines which was calculated using baseline and end of treatment lab results. FIB-4 score > 1.45 reflects significant fibrosis, score > 3.25 indicate cirrhosis. Greater than 0.77 APRI regarded as significant fibrosis, and score > 0.84 indicate cirrhosis.

Silybum marianum seeds are considered highly bioactive which contains concentrated amount flavonoids and flavonolignans commonly known as silymarin, 1 gram of Silybum marianum capsules contain dry seed powered was given to the study patients three times a day for 6 months.

**STATISTICAL METHODS**

Continuous variable data was expressed as mean and range. Categorical variable data were expressed as absolute numbers and percentages. Data was entered and analyzed by SPSS version 20 using two tailed paired t-test for continuous data, chi square test was applied on categorical data, correlations were determined by pearson’s coefficient
RESULTS

Baseline characteristics of 119 patients are presented in Table 1. There were 79 men and 40 women participated in this study with the mean age of 53.29 ± 7.61 years.

Pretreatment LSM ranged from 3.7 kPa to 72.4 kPa with a mean of 22.5 ± 17.08 kPa. Based on LSM score at baseline the estimated METAVIR fibrosis stage of distribution was F0 – F1: 7.6%, F2: 16.8%, F3: 15.1%, F4: 60.5% (cirrhosis).

According to Child-Pugh classification 57 (48%) patients were in class A, while 62 (52%) patients were in class B.

IMPACT OF TREATMENT ON LIVER STIFFNESS AND FIBROSIS STAGE

The mean pre-treatment LSM score was 22.54 kPa and post treatment was 17.30 kPa, a statistically significant change of 5.24 kPa (P < 0.01) was observed, mean percent change was 23.24%, its impact was observed in all METAVIR stages. Of the 72 (60.5%) patients with LSM ≥ 12.5 kPa (cirrhosis) at baseline 23 (32%) proved to have no cirrhosis (≥ 1 decrease in fibrosis stage) at post treatment. Similarly, 19 patients moved to stage F0-F1, 28 patients in F2 and 23 in F3. Overall fibrosis stage was improved (≥ 1 decrease in fibrosis stage) in 46 (38.7%) of 119 patients after 6 months of treatment.

The change in the METAVIR stage pre and post treatment is presented in Table 2. The mean change was similar in male and female and did not differ in the two groups (5.13 kPa in men and 5.45 kPa in women).

The mean change in liver stiffness values in patient at stage F4 (Cirrhosis) was almost 6 times higher than in patients at F1, Figure1. Despite the favorable changes occurred in many patients 49 of 72 patients (68%) who were cirrhotic pre-treatment remain in stage F4 at the end of treatment.

Impact of Treatment on Clinical Laboratory Values

Difference in pre-treatment and post treatment were calculated for various laboratory parameters viz; ALT, AST, Total bilirubin, AFP, INR, Albumin, creatinine, hemoglobin, platelets, BMI (Table 3). In post treatment we witnessed statistically significant increase in platelets P <0.01 and albumin P<0.01, and decrease in ALT & AST P <0.01, hemoglobin was decreased but the change was not significant P = 0.615. In 29 of 67 patients with platelets counts below lower limit normal (150 x10^3 cells/µL) at baseline had post treatment platelets count in normal range, significantly decreasing the population with thrombocytopenia P < 0.01.A significant association is found in the decrease in ALT & AST and the percent decrease in the LSM, P <0.01. AFP decreased from 7.2 ng/mL to 5.1 ng/mL, a statistical significant change of – 2.1 ng/mL is noted.

Impact of Treatment on Serum Fibrosis Score

Serum fibrosis scores APRI and FIB-4 significantly decreased in comparison to baseline values. APRI values drooped from 1.24 to 0.83. FIB-4 score changed from 3.90 to 2.10

Reduction is HCV viral load was noted in 86 patients, which was dropped from 3.2x10^6 to 2.1x10^6 IU/ml whereas in 7 patients viral load become undetectable at end of treatment.

DISCUSSION

There are several clinical features related to chronic liver disease in our population, Modern medicines for...
hepatitis C, both interferon containing and interferon free are available, but mostly out of reach of masses because of the high cost and severe side effects particularly related to interferon containing medicine. The primary aim of treating such patient is to prevent disease progression to liver cirrhosis and hepatocellular carcinoma. There are reports that long term therapy with these medicines may leads to reversal of hepatic fibrosis and cirrhosis.

With the objective of finding such activity in the indigenously available herbs this research was initiated, after careful evaluation of the numerous herbs used to treat liver problem in our population, Silybum marianum was finally selected to be studied further, as it is most commonly used herbs to treat liver ailment for centuries.

Our test drug showed promising results to our knowledge this is the first study in Pakistan where we study the safety and efficacy of Silybum marianum on cirrhotic patients. This study showed that mean LSM was decreased from 22.55 kPa to 17.30 kPa during the treatment period of 6 months, consistent with the findings of other studies,18-21 there was no significant difference between men and women.

The mean change in LSM in patients with liver cirrhosis was 6 fold greater than in non-cirrhotic 5.43kPa to 29.88 kPa, p<0.01. In 32% cirrhotic patients LSM decreases to the extent that they do not consider to be cirrhotic, despite improvement 47 out of 72 patients who were in cirrhotic pretreatment group remain cirrhotic, this is consistent finding with early studies,22-26 there was no significant difference between men and women.

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### Table 2: Change in METAVIR fibrosis stage at end of treatment

| METAVIR stage | Baseline | End of treatment | Change | P value |
|---------------|----------|------------------|--------|---------|
| F0-F1         | 9 (7.6%) | 19 (16%)         | 111%   | (P<0.01) |
| F2            | 20 (16.8%) | 28 (23.5%) | 40%   | (P<0.01) |
| F3            | 18 (15.1%) | 23 (19.3%) | 27%   | (P<0.02) |
| F4            | 72 (60.5%) | 49 (41.2%) | 31%   | (P<0.01) |

### Table 3: Clinical labs baseline and end of treatment. Patients (n=119)

| Characteristics | Pre treatment | Post treatment | Change | P value |
|-----------------|--------------|----------------|--------|---------|
| ALT [IU/L; mean (range)] | 56.35 (14-147) | 38.81 (23-52) | 17.54 | P<0.01 |
| AST [IU/L; mean (range)] | 65.87 (28-197) | 44.63 (23-85) | 21.24 | P<0.01 |
| Albumin [g/dL; mean (range)] | 3.36 (1.30-4.80) | 3.75 (2-5) | 0.40 | P<0.01 |
| Total Bilirubin [mg/dL; mean (range)] | 1.30 (0.34-3.00) | 0.95 (0.40-2.00) | 0.35 | P<0.01 |
| Creatinine [mg/dL; mean (range)] | 1.10 (0.40-2.95) | 0.79 (0.35-2.10) | 0.31 | P<0.01 |
| INR [mean (range)] | 1.22 (0.98-1.56) | 1.05 (0.90-1.40) | 0.17 | P<0.01 |
| AFIP [ng/mL mean (range)] | 7.2 (4-16) | 5.1 (3-9) | 2.1 | P<0.01 |
| Hemoglobin [g/dL; mean (range)] | 12.87 (9.30-16.20) | 12.91 (9.10-15.50) | 0.04 | P=0.615 |
| Platelets x10⁹ [µL; mean (range)] | 154 (65-276) | 167 (83-299) | 13 | P<0.01 |
| HCV RNA [IU/mL; mean (range)] | 3.2×10⁶ (5.14×10³-433×10⁶) | 2.1×10⁶ (4.30×10³-3.80×10⁶) | 1.2×10⁹ | P<0.01 |

### Table 4: Fibroscan and serum fibrosis scores. Patients (n=119)

| Cirrhosis assessment | Pre treatment | Post treatment | Change | P value |
|----------------------|--------------|----------------|--------|---------|
| LSM [kPa; mean (range)] | 22.55 (3.70-72.40) | 17.30 (3.50-61.70) | 5.24 | P<0.01 |
| APRI [mean (range)] | 1.24 (0.29-2.93) | 0.83 (0.30-1.71) | 0.41 | P<0.01 |
| FIB-4 score [mean (range)] | 3.90 (1.30-4.60) | 2.10 (1.20-4.00) | 1.80 | P<0.01 |

**Figure 1:** Liver Stiffness Measurement Decrease at End of Treatment In Kpa

**Figure 2:** Serum Fibrosis Scores
Overall fibrosis stage was improved in 46 of 119 patients (38.9%) in 6 months of treatment reflecting effectiveness of SM in this cohort. Fibrosis regression has been shown to decrease the risk of cirrhosis and hepatocellular carcinoma and mortality.27,28 This study shows improvement in major laboratory parameters viz; AST, ALT, INR, AFP, platelets, albumin, bilirubin, creatinine. We found significant improvement in platelets count, forty three percent of patients with platelet count below normal limit at baseline had values in normal range at end of treatment, which is in accordance with previous studies.29-31 In our study AST, ALT, AFP also decreased, which is consistent to other studies.32,33 Compared to baseline we found significant increase in albumin values (p<0.01), which is also proved in the study by Deterding et al, albumin levels became normal in most of his patients.30 We found significant decrease in bilirubin levels at end of treatment (p<0.01), which is desirable in hepatic patients. In this study we found decrease 2.1 ng/mL AFP (p<0.01), levels as compared to baseline, finding is consisting with previous studies.34

Findings of the validated fibrosis scores APRI & FIB-4 were similar like LSM in this study, both of these fibrosis scores declined significantly at the end of treatment period and the findings correlated well with each other.35

Silybum marianum is well tolerated in our patients, no significant side effects were reported during the study.

CONCLUSION

In conclusion our results suggest a significant improvement with Silybum marianum in the patients status of liver fibrosis and cirrhosis associated with hepatitis C related chronic liver disease. Silybum marianum shows therapeutic effect in real life setting on the entire spectrum of disease, as evaluated with the fibroscan and serum fibrosis markers.

In the longer term, follow-up LSM could be applied to evaluate residual liver damage and weather there is a trend towards normalization of fibrosis over time.

Our study results warrants further prospective studies with more robust study design in large cohort.

Conflict of Interest

Authors certify that there is no conflict of interest, we further certify that all work contained in this article is original and we claim full responsibility for the contents of the article. The article has been neither published nor submitted for publication simultaneously. All the authors contributed significantly to this work.

REFERENCES

1. Hajari zalehdeh B, Grebely J and Dore GJ. Epidemiology and natural history of HCV infection. Nature reviews Gastroenterology & Hepatology 2013; 10(9):553.
2. Nelson PK, Mathers BM, Cowie B, Hagan H, Des Jarlais D, Horynaki D, et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. The Lancet 2011;378(9791):571-583.
3. Perz JF, Armstrong GL, Farrington LA, Hutin YJ and Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. Journal of Hepatology 2006; 45(4):529-538.
4. Ahmad K. Pakistan: a cirrhotic state? Lancet (London, England). 2004; 364(9448):1843-1844.
5. Harvey AL. Natural products in drug discovery. Drug discovery today 2008;13(19-20):894-901.
6. Seef LB, Curto TM, Szabo G, Everson GT, Bonkovsky HL, Dienstag JL, et al. Herbal product use by persons enrolled in the hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) Trial. Hepatology 2008;47(2):605-612.
7. Strader DB, Bacon BR, Lindsay KL, La Brecque DR, Morgan T, Wright EC, et al. Use of complementary and alternative medicine in patients with liver disease. The American Journal of Gastroenterology 2002;97(9):2391-2397.
8. Polyak SJ, Morishima C, Shuhart MC, Wang CC, Liu Y and Lee DY. Inhibition of T-cell inflammatory cytokines, hepatocyte NF-κB signaling, and HCV infection by standardized silymarin. Gastroenterology 2007;132(5):1925-1936.
9. Freedman ND, Curto TM, Morishima C, Seef LB, Goodman ZD, Wright EC, et al. Silymarin use and liver disease progression in the Hepatitis C Antiviral Long-Term Treatment against Cirrhosis trial. Alimentary Pharmacology & Therapeutics 2011;33(1):127-137.
10. Sandrin L, Fourquet B, Hasquenoph JM, Yon S, Fournier C, Mal F, et al. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. Ultrasound in Medicine & Biology 2003;29(12):1705-1713.
11. Foucher J, Chanteloup E, Vergniol J, Castéra L, Le Bail B, Adhoute X, et al. Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. Gut 2006;55(3):403-408.
12. Castéra L, Forns X and Alberti A. Non-invasive evaluation of liver fibrosis using transient elastography. Journal of Hepatology 2008;48(5):835-847.
13. Simonetti RG, Cammì C, Fiorello F, Cottone M, Rapicetta M, Marino L, et al. Hepatitis C virus infection as a risk factor for hepatocellular carcinoma in patients with cirrhosis: a case-control study. Annals of Internal Medicine 1992;116(2):97-102.
14. Soresi M, Giannitrapani L, Cervello M, Licata A and Montalto G. Non invasive tools for the diagnosis of liver cirrhosis. World Journal of Gastroenterology 2014;20(48):18131.
15. Castéra L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. Gastroenterology 2005;128(2):343-350.
16. European Association for the Study of the Liver. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. Journal of Hepatology 2015; 63(1):237-264.
17. Polyak SJ, Morishima C, Lohmann V, Pal S, Lee DY, Liu Y, et al. Identification of hepatoprotective flavonolignans from silymarin. Proceedings of the National Academy of Sciences 2010;107(14):6009-6014.
the patients with chronic hepatitis C. Hepatology Research 2010;40(4):383-392.
19. ANRS C. Regression of liver stiffness after sustained hepatitis C virus (HCV) virological responses among HIV/HCV-coinfected patients. AIDS (London, England) 2015;29(14):1821.
20. Hézode C, Castéra L, Roudot-Thoraval F, Bouvier-Alías M, Rosa I, Roulot D, et al. Liver stiffness diminishes with antiviral response in chronic hepatitis C. Alimentary Pharmacology & Therapeutics 2011;34(6):656-663.
21. Wang JH, Changchien CS, Hung CH, Tung WC, Kee KM, Chen CH, et al. Liver stiffness decrease after effective antiviral therapy in patients with chronic hepatitis C: Longitudinal study using FibroScan. Journal of Gastroenterology and Hepatology 2010;25(5):964-969.
22. Poynard T, McHutchison J, Manns M, Trepo C, Lindsay K, Goodman Z, et al. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. Gastroenterology 2002;122(5):1303-1313.
23. Mallet V, Martinot–Peignoux M, Fontaine H, et al. Brief communication: the relationship of regression of cirrhosis to outcome in chronic hepatitis C. Annals of Internal Medicine 2008;149(6):399-403.
24. Maylin S, Papastergiou V, Lisgos P, Prodromidou K, Karatapanis S. Durability of a sustained virological response, 150 patients. Hepatology 2009;49(3):729‑738.
25. Maruoka D, Imazeki F, Arai M, Kanda T, Fujiwara K and Yamasaki S. Longitudinal changes of the laboratory data of chronic hepatitis C patients with sustained virological response on long-term follow-up. Journal of Viral Hepatitis 2012;19(2):e97-e104.
26. Detersing K, Höner-Zu Siederdissen C, Port K, Solbach P, Sollik L, Kirscher J, et al. Improvement of liver function parameters in advanced HCV-associated liver cirrhosis by IFN-free antiviral therapies. Alimentary Pharmacology & Therapeutics 2015; 42(7):889-901.
27. Tachi Y, Hirai T, Ishizu Y, Honda T, Kuzuya T, Hayashi K, et al. α-fetoprotein levels after interferon therapy predict regression of liver fibrosis in patients with sustained virological response. Journal of Gastroenterology and Hepatology 2016;31(5):1001-1008.
28. George SL, Bacon BR, Brunt EM, Mihindukulasuriya K, Hoffmann J and Di Bisceglie AM. Clinical, virologic, histologic, and biochemical outcomes after successful HCV therapy: a 5-year follow-up of 150 patients. Hepatology 2009;49(3):729-738.
29. Papastergiou V, Stampori M, Pselas C, Prodromidou K and Karatapanis S. Durability of a sustained virological response, late clinical sequelae, and long-term changes in aspartate aminotransferase to the platelet ratio index after successful treatment with peginterferon/ribavirin for chronic hepatitis C. A prospective study. European Journal of Gastroenterology & Hepatology 2013;25(7):798-805.
30. Talwalkar JA, Kurtz DM, Schoenleber SJ, West CP and Montori VM. Ultrasound-based transient elastography for the detection of hepatic fibrosis: systematic review and meta-analysis. Clinical Gastroenterology and Hepatology 2007;5(10):1214-1220.

Authors Contribution:
AA and AS – Concept and design of study, literature search; AA and MR – Carried out study, data collection, review of literature; KU and AA – Data feeding and statistically analysis, contributed to the interpretation of results, preparation of draft manuscript. All authors discussed and critically review the results and contributed to the final manuscript.

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