Drugs in Context

drugsincontext.com

CASE REPORT

# Role of silymarin in the management of deranged liver function in non-alcoholic steatohepatitis: a case report

Yeong Yeh Lee[1], Vincent Tee[1]

[1]Department of Medicine, Hospital Universiti Sains Malaysia, Kota Bharu, Malaysia

## Abstract

Non-alcoholic fatty liver disease is one of the main causes of elevated liver enzymes and chronic liver disease worldwide. It ranges from steatosis to steatohepatitis, leading to cirrhosis and related liver dysfunction. Silymarin is a herbal medicine, mostly used for liver disorders owing to its supposed hepatoprotective action. This report recommends silymarin in a patient with diabetes and grade II non-alcoholic steatohepatitis, confirming significant hepatoprotective effects as shown by the reduction of liver enzyme activities.

This article is part of the *Current clinical use of silymarin in the treatment of toxic liver diseases: a case series* Special Issue: https://www.drugsincontext.com/special_issues/current-clinical-use-of-silymarin-in-the-treatment-of-toxic-liver-diseases-a-case-series

**Keywords:** deranged liver enzymes, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, silymarin.

## Citation

Lee YY, Tee V. Role of silymarin in the management of deranged liver function in non-alcoholic steatohepatitis: a case report. *Drugs Context*. 2023;12:2023-2-10. https://doi.org/10.7573/dic.2023-2-10

# Introduction

Non-alcoholic fatty liver disease (NAFLD) is the leading cause of incidental elevation of liver enzymes in North America and Europe.[1] The spectrum of disease is variable, with simple steatosis, with a benign prognosis, able to progress to non-alcoholic steatohepatitis (NASH) and cirrhosis, increasing the disease morbidity and mortality.[1] Type 2 diabetes, insulin resistance, hyperlipidaemia and obesity are all risk factors for developing primary NAFLD.[1–3] In particular, 50% of patients with diabetes are affected by NAFLD, reaching 76% in the case of patients with obesity.[1]

Silymarin, a milk thistle extract, is a herbal treatment mainly used for the management of liver disorders. Its antioxidant properties may reduce lipid peroxidation and free-radical species production, all suspected mechanisms of NASH liver injury.[3]

In this case report, silymarin treatment was recommended to a patient with diabetes and grade II NASH, with an attempt to manage and decrease his abnormal liver enzyme activities.

# Ethics statement

No information is reported that could enable the patient to be identified; therefore, no patient consent was required. This manuscript was prepared according to CARE guidelines.

# Case report

A healthy-weight, 40-year-old male, chronic smoker, and former heavy alcohol drinker (stopped in 2017) with an AUDIT-C of seven points (scores ≥5 are consistent with alcohol misuse and possible liver damage[4]) presented in January 2018 for a physical examination due to deranged liver enzymes.

The patient had a medical history of type 2 diabetes, diagnosed 10 years prior and currently maintained with

Metformin XR 500 mg once daily (OD). Furthermore, he was diagnosed with JAK2-positive polycythaemia vera in 2017, for which he was initially treated with an alternate day basis of hydroxyurea 500 mg OD. In addition, he was on treatment with fenofibrate 150 mg OD and ezetimibe 10 mg OD due to hyperlipidaemia, previously treated with statins. The patient was compliant with the follow-up appointments and polytherapy treatment.

On 8 January 2018, at the physician's examination, the liver was one finger-breadth palpable and the spleen was three finger-breadth palpable. As expected, the liver function tests revealed abnormal enzymatic increases, especially for alanine transaminase (ALT), aspartate transaminase (AST) and alkaline phosphatase (ALP) levels (Table 1). Although not investigated, the authors believed that polytherapy may have contributed to elevated liver enzymes. In addition, an abnormal lipidic profile with high total cholesterol (265 mg/dL or 6.86 mmol/L) and high triglycerides (215 mg/dL or 2.43 mmol/L) was also observed.

On 28 September 2019, the patient was recruited to a separate study due to his elevated liver enzymes. During the study, an ultrasound-guided liver biopsy was performed, and the patient was diagnosed with grade II NASH, the advanced form of NAFLD.

To manage the liver enzyme activity, treatment with silymarin 140 mg three times daily (TDS) for 2 years was prescribed (from 8 January 2018 to 10 March 2020), as no other suitable treatment options were available and the patient was not eligible for clinical trials due to his medical conditions; moreover, considering that the patient had already been treated multiple times, a drug with well-known safety profile and minimal adverse events, such as silymarin, was preferred.

At routine blood and liver function tests, altered liver enzyme levels were progressively decreasing; during the two follow-up visits (on 7 July 2020 and 19 August 2020), 2 years following silymarin treatment, ALT, AST and ALP levels were significantly reduced and comparable to physiological levels (Table 1). Furthermore, the lipidic profile also improved over the treatment, with a reduction in both total cholesterol (192 mg/dL or 4.95 mmol/L) and triglyceride (111 mg/dL or 1.25 mmol/L) levels. The treatment adherence was good, and the patient did not develop any adverse events.

The patient's clinical events are summarized in Table 2.

# Discussion

NAFLD is a complicated metabolic disorder frequently observed in clinical practice by several healthcare specialists, including primary care physicians, gastroenterologists, cardiologists, radiologists and gynaecologists.[5]

In 2020, given the close correlation between NAFLD and metabolic disorder components, and to reflect more precisely on the disease pathogenesis, a global panel of experts proposed changing the NAFLD terminology to metabolic-associated fatty liver disease (MAFLD).[6] Thus, MAFLD is identified by hepatic steatosis together with overweight or obesity, diabetes, or other metabolic dysfunctions.[6,7]

**Table 1. Liver function outcomes at baseline and at different follow-up examinations.**

| | 8 January 2018 – Baseline | 7 July 2020 | 19 August 2020 |
|---|---|---|---|
| ALT (U/L) | 299 | 71 | 72 |
| AST (U/L) | 73 | 47 | 42 |
| ALP (U/L) | 169 | 73 | 68 |
| TB (μmol/L) | 14 | 12 | 19 |
| TP (g/L) | 75 | 80 | 78 |
| Alb (g/L) | 43 | 51 | 54 |
| Globulin (g/L) | 32 | 29 | 24 |
| Total cholesterol (mg/dL) | 265 | – | 192 |
| Triglyceride (mg/dL) | 215 | – | 111 |

Alb, albumin; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; TB, total bilirubin; TP, total protein.

**Table 2. Relevant data from this episode of care organized as a timeline.**

| Date | Events |
|---|---|
| 8 January 2018 | Physician's examination:<br>Liver one finger-breadth palpable<br>Spleen three finger-breadth palpable<br>Abnormal liver enzymatic increases |
| 8 January 2018 to 10 March 2020 | Silymarin 140 mg three times daily treatment |
| 28 September 2019 | Ultrasound-guided liver biopsy:<br>Diagnosis of grade II non-alcoholic steatohepatitis |
| 7 July 2020 | Follow-up with significant reduction of liver activity |
| 19 August 2020 | Follow-up with significant reduction of liver activity |

NAFLD and MAFLD can progress from simple steatosis to steatohepatitis (NASH). Histologically, NASH generally presents with macrovesicular steatosis, lobular inflammation, hepatocyte balloon degeneration, and pericellular fibrosis and could lead to cirrhosis and related liver disorder.[5] Liver biopsy is usually recommended as the 'gold standard' for diagnosis and quantification of hepatic steatosis damage. However, liver biopsy is an invasive and expensive technique with a significant margin of sampling error.[2]

Metformin, peroxisome proliferator-activated receptor-γ agonists and ezetimibe have been proposed as NAFLD therapy strategies but, to date, no effective NAFLD treatments are available.[2]

Silymarin is a complex extract of plant-derived elements, mostly flavonolignans, flavonoids and polyphenolic molecules, with silibinin as the most prevalent and biologically active flavonolignan isomer.[8] Silymarin highlighted antioxidant properties by protecting the cell membrane from radical-induced damage and increasing the superoxide dismutase activity of lymphocytes and erythrocytes.[2,9] Silymarin also highlighted potent anti-inflammatory and antifibrogenic properties in the liver. These effects were mostly associated with hepatic stellate cell activation through the expression of transforming growth factor-β1 and stabilization of mast cells in the fibrotic liver. Moreover, silymarin significantly decreased serum ALT and AST levels[2,10] and reduced hepatic fat accumulation as demonstrated by changes in hepatorenal brightness index at ultrasonography imaging.[2]

Herein, the use of silymarin 140 mg TDS (Legalon®) demonstrated significant hepatoprotective effects on NASH, as shown by the lowered serum ALT, AST and ALP levels, and ensured good treatment adherence during long-term liver function tests and follow-up (Table 1). In addition, the lipid profile improved over the treatment course, with a reduction of both total cholesterol and triglyceride levels. Noteworthy, several uncontrolled factors might impact the lipid profile change, such as the effect of polytherapy treatments, diet modification and alcohol abstinence. In this context, a synergistic effect of silymarin with other treatments (statins, fibrates and ezetimibe) on the patient's health status is highly likely to occur. With regard to other liver function indicators, such as total bilirubin, total protein, albumin and globulin levels, no important changes were observed after silymarin treatment in the direction of the initial values (Table 1).

These results confirmed that silymarin treatment appears to be beneficial in biochemical improvements and in decreasing transaminase levels in patients with NASH.[10] Additionally, silymarin should be considered a safe herbal product as no adverse events occurred in conjunction with the properly designed therapeutic dosages.[11]

It must be stressed that there is currently no effective recommended treatment for NASH with or without fibrosis. Some drugs, such as pioglitazone, are effective but have significant weight gain as a side effect. Many other drug options are in the stage of clinical trials at the time of this publication. Hence, without any robust recommendation and in a resource-restrained situation, the use of silymarin may be considered, as highlighted by its efficacy and good safety profile in the management of grade II NASH.

# Conclusion

NAFLD is the most common silent liver disease worldwide, distinguished by steatosis in the liver and liver biochemical abnormalities. To date, no effective pharmacologic agents have been approved for NAFLD or NASH treatment but silymarin, the active ingredient in milk thistle, has well-documented antioxidant, anti-inflammatory and antifibrogenic properties and has been used for a long time to manage several liver diseases.

In this case report, silymarin 140 mg TDS highlighted moderate efficacy and a good safety profile in the management of grade II NASH, as it decreased serum ALT, AST and ALP levels over treatment with no side-effect development, supporting silymarin as a promising supportive intervention aimed at normalizing liver activity in NAFLD.

**Contributions:** All authors contributed equally to the preparation of this manuscript. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole and have given their approval for this version to be published.

**Disclosure and potential conflicts of interest:** The authors declare that they have no conflicts of interest relevant to this manuscript. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at: https://www.drugsincontext.com/wp-content/uploads/2023/05/dic.2023-2-10-COI.pdf

**Acknowledgements:** Editorial assistance was provided by Francesca Cappellini, PhD, Mattia Zamboni, Valentina Attanasio and Aashni Shah (Polistudium SRL Milan, Italy). This assistance was supported by Viatris Inc.

**Funding declaration:** This project was conducted with the non-conditioning assistance of Viatris Inc.



**Article URL:** https://www.drugsincontext.com/role-of-silymarin-in-the-management-of-deranged-liver-function-in-non-alcoholic-steatohepatitis-a-case-report

**Correspondence:** Yeong Yeh Lee, Department of Medicine, Hospital Universiti Sains Malaysia, Kota Bharu, Malaysia. Email: yylee@usm.my

**Provenance:** Submitted; externally peer reviewed.

**Submitted:** 20 February 2023; **Accepted:** 29 March 2023; **Published:** 13 June 2023.

*Drugs in Context* is published by BioExcel Publishing Ltd. Registered office: 6 Green Lane Business Park, 238 Green Lane, New Eltham, London, SE9 3TL, UK.

BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252 7720 07.

For all manuscript and submissions enquiries, contact the Editorial office editorial@drugsincontext.com

For all permissions, rights and reprints, contact David Hughes david.hughes@bioexcelpublishing.com

# References

1. Raman M, Allard J. Non alcoholic fatty liver disease: a clinical approach and review. *Can J Gastroenterol*. 2006;20(5):345–349. https://doi.org/10.1155/2006/918262
2. Cacciapuoti F, Scognamiglio A, Palumbo R, et al. Silymarin in non alcoholic fatty liver disease. *World J Hepatol*. 2013;5:109–113. https://doi.org/10.4254/wjh.v5.i3.109
3. Navarro VJ, Belle SH, D'Amato M, et al. Silymarin in non-cirrhotics with non-alcoholic steatohepatitis: a randomized, double-blind, placebo controlled trial. *PLoS One*. 2019;14:e0221683. https://doi.org/10.1371/journal.pone.0221683
4. Bush K, Kivlahan DR, McDonell MB, et al. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. *Arch Intern Med*. 1998;158:1789–1795. https://doi.org/10.1001/archinte.158.16.1789
5. Vuppalanchi R, Chalasani N. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: selected practical issues in their evaluation and management. *Hepatology*. 2009;49:306–317. https://doi.org/10.1002/hep.22603

6. Eslam M, Newsome PN, Sarin SK, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. *J Hepatol*. 2020;73:202–209. https://doi.org/10.1016/j.jhep.2020.03.039
7. Kaya E, Yilmaz Y. Metabolic-associated fatty liver disease (MAFLD): a multi-systemic disease beyond the liver. *J Clin Transl Hepatol*. 2022;10:329–338. https://doi.org/10.14218/JCTH.2021.00178
8. Gillessen A, Schmidt HH. Silymarin as supportive treatment in liver diseases: a narrative review. *Adv Ther*. 2020;37(4):1279–1301. https://doi.org/10.1007/s12325-020-01251-y
9. Surai PF. Silymarin as a natural antioxidant: an overview of the current evidence and perspectives. *Antioxidants*. 2015;4:204–247. https://doi.org/10.3390/antiox4010204
10. Hajaghamohammadi AA, Ziaee A, Rafiei R. The efficacy of silymarin in decreasing transaminase activities in non-alcoholic fatty liver disease: a randomized controlled clinical trial. *Hepat Mon*. 2008;8:191–195.
11. Solhi H, Ghahremani R, Kazemifar AM, et al. Silymarin in treatment of non-alcoholic steatohepatitis: a randomized clinical trial. *Caspian J Intern Med*. 2014;5:9–12.