

## Role of Silymarin in the Management of Non-alcoholic Fatty Liver Disease: Time to Clear the Mist

Kuhu Roy<sup>1</sup> and Uma Iyer<sup>2</sup>

<sup>1</sup>Independent Nutrition Consultant, Content writer-author, Vadodara-390007, Gujarat, India,

<sup>2</sup>Professor, Department of Foods and Nutrition, The M.S. University of Baroda, Vadodara-390007, Gujarat, India.

**Corresponding author:** Kuhu Roy, PhD, Independent nutrition consultant, content writer-author, Vadodara-390007, Gujarat, India.

**Submission Date:** July 31, 2018, **Acceptance Date:** May 28<sup>th</sup>, 2019 **Publication Date:** May 30<sup>th</sup>, 2019

**Citation:** Roy K., Iyer U. The role of silymarin in the management of non-alcoholic fatty liver disease: Time to clear the mist. *Functional Foods in Health and Disease* 2019; 9(5):126-133. DOI: <https://doi.org/10.31989/bchd.v2i5.622>

### ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) has become a common, chronic liver disease, across the globe. It occurs in individuals without a history of significant ethanol consumption, and it encompasses a wide spectrum of hepatic disorders. It ranges from simple steatosis, to the advanced form, non-alcoholic steatohepatitis (NASH), as well as fibrosis, cirrhosis to even hepatocellular carcinoma. In fact, hepatocellular carcinoma (HCC) can also develop even in the absence of cirrhosis. The prevalence of NAFLD is on the rise primarily because of the common metabolic conditions such as, insulin resistance, type 2 diabetes, central obesity and dyslipidemia. Therefore, NAFLD is associated with adverse metabolic consequences. Other than the detrimental hepatic outcomes mentioned above, the cases of NAFLD have a very high predisposition to cardiovascular disease. Therefore, management of NAFLD is of paramount importance. However, the challenge lies in the fact that there are no approved therapeutic drug regimens for the treatment of NAFLD. Currently, the standard care comprises of treating the underlying co-existing metabolic abnormalities along with a strong focus on lifestyle modification.

Under the purview of the dietary management of NAFLD, antioxidants have been used as a therapy, because oxidative stress is also a risk factor for NAFLD and its advancement. One of the less explored antioxidants with respect to NAFLD is silymarin, the bioactive component of milk thistle. Milk thistle (*Silybum marianum*) is a Mediterranean herb belonging to the Asteraceae/Compositae family. It is postulated that silymarin, inhibits the production of pro-inflammatory cytokines and acts against lipid peroxidation by free radical scavenging, thereby functioning as an antioxidant. In addition, it is also anti-inflammatory and anti-fibrotic in nature and has membrane stabilizing properties. The bioactive component in milk thistle is a lipophilic extract from its seeds and fruits which is collectively known as silymarin. The collective term 'silymarin' refers to a complex set of flavonolignans; silibin A, silibin B, isosilibin A, isosilibin B, silichristin, isosilichristin, silidianin and a single flavonoid, taxifolin. Among the flavonolignans, silibin is the most biologically relevant component of silymarin, although the

biological mechanism is not understood. Treatment with silymarin in cases of fatty liver, has shown to improve the hepatic biochemical profile, especially alanine amino transferase, but the data is very limited in nature and often conflicting. The existing evidence, with its own set of methodological drawbacks, presents a mix of findings that support or refute using silymarin alone or in combination with other compounds in the management of NAFLD. This review is therefore, aimed at clearing the mist surrounding silymarin and its potential in managing NAFLD. Long term studies of multicentric nature are further required to better elucidate the dosage, duration, underlying molecular mechanisms, safety and the overall impact in terms of changes in liver histology of silymarin therapy in the management of NAFLD.

**Keywords:** Non-alcoholic fatty liver disease, antioxidants, milk thistle, silymarin, flavonolignans, silibin

## BACKGROUND

Non-alcoholic fatty liver disease (NAFLD) refers to a spectrum of hepatic disorders ranging from simple steatosis, to steatohepatitis (non-alcoholic steatohepatitis), fibrosis and cirrhosis, in individuals in the absence of significant ethanol consumption [1,2]. Due to about one quarter of the global population and one third of the population afflicted with NAFLD in industrialised countries, NAFLD has become the most common liver disease diagnosed globally [3-6]. The prevalence of NAFLD is on the rise, from a mere <10% in the 1980s to about 15-30% today [4] primarily due to the diabesity epidemic [7,8], although the mechanism is not understood [9]. Insulin resistance sets the course for the pathogenesis of NAFLD, which leads to altered lipid metabolism (increased lipolysis) that accrues the free fatty acids deposition in the hepatocytes [10]. Other factors leading to the development of NASH may include reactive oxygen species (ROS) production (superoxide radical, hydroxyl radical, hydrogen peroxide, and lipid peroxide radicals) [11], oxidative stress causing mitochondrial dysfunction, cytokines/adipokines, dyslipidemia and obesity [12, 13]. NASH, if untreated, may progress onto fibrosis, cirrhosis and even hepatocellular carcinoma (HCC) [5, 6, 10]. HCC may, however, still develop in the absence of cirrhosis [14, 15]. Moreover, patients with NASH have a higher predisposition to cardiovascular disease (CVD) [5], which is the predominant factor for high mortality in NAFLD patients [16]. Thus, the management of NAFLD is warranted.

However, the challenge remains in the fact that there is no evidence based pharmacological guidelines for the treatment of NAFLD [2, 17]. The current guidelines emphasize on managing the co-existing morbidities in NAFLD and incorporating lifestyle changes. Oxidative stress, as mentioned above earlier, is implicated in the pathogenesis of NAFLD/NASH that activates the pro-inflammatory cytokines [1, 4, 9]. Therefore, vitamin E, ursodeoxycholic acid, gemfibrozil, metformin pioglitazone, and orlistat have been tried as drug treatments for NAFLD, yet antioxidant therapy has been under investigated [1,9], silymarin, in particular, has limited literature on monotherapy and combination therapy.

## Silymarin

Milk thistle is extracted from the fruits and seeds of *silybum marinum*, a Mediterranean herb [18] which belongs to the *Asteraceae/Compositae* family [11, 19]. It is a flavonoid complex comprising of family of flavonolignans (silybin, isosilybin, silychristin, isosilychristin, and silydianin) and a flavonoid (taxifolin), of which 50-70% is silybin, the biologically active component [11, 18]. This active component is a lipophilic extract composed of four isomer flavonolignans (silibinin, isosilibin, silidianin and silichristine), which is collectively known as silymarin [11, 19].

### **Mechanism of action**

While the data of impact of silymarin on NAFLD patients is limited, silymarin imparts antioxidant, anti-inflammatory and anti-fibrotic properties [18, 19]. Although the biological mechanism of action is not entirely understood [9], it modulates the cytokine production [9]. It works as an antioxidant, possibly, by increasing the superoxide dismutase activity in erythrocytes and lymphocytes. Silymarin, has also shown to increase serum glutathione and glutathione peroxidase levels [21] and also influence the enzyme systems associated with glutathione and superoxide dismutase [6, 22]. Therefore, it improves the oxidative profile by the means of inhibiting the pro-inflammatory cytokines production [23]. Silybin has also shown to act as a mild chelator of iron that aids in inhibiting leukotriene formation by Kupffer cells and prevents depletion of glutathione from hepatocytes [24].

Silymarin has membrane stabilising properties that stabilise the hepatocyte membrane structure, thereby, preventing toxins from entering the hepatocyte via the entero-hepatic recirculation. It also promotes liver regeneration by stimulating nucleolar polymerase A and increasing ribosomal protein synthesis [6, 25].

Silymarin retards lipid peroxidation by scavenging of free radical and acts as an anti-fibrotic agent that induces hepatic stellate cells apoptosis or induces degradation of collagen deposits [21, 26]. Recently, anti-cancer properties have been reported too, primarily by modulating different molecular patterns [23].

### **Safety of Silymarin**

Silymarin has been demonstrated to be a safe and well tolerated medication in hepatic diseases with chronic toxicity studies in rodents demonstrating very low toxicity [6], with no health hazards or known side effects when administered in therapeutic dosage [27]. In fact, at very high doses in rodents, it reduced the incidence of spontaneous neoplasias [6]. Taking into consideration all the RCTs, uncontrolled studies and case reports, adverse side effect was reported in relation to silymarin [28]. Side effects, although rare, may include laxative effect, nausea, epigastric discomfort, arthralgia, pruritis, and urticaria.

### **Bioavailability of Silymarin**

Oral administration of silymarin, has a low bioavailability due to inefficient absorption in the intestine and high first-pass metabolism. However, when complexing it with phosphatidylcholine [29] or  $\beta$ -cyclodextrin [11], the absorption and the solubility can be improved. The available pharmacokinetic data shows a strong correlation between the state of liver damage and the bioavailability of silymarin [6]. Data shows, a minimum of three daily intakes are required for silymarin in order to attain sustained blood level because silymarin has a short half-life. Moreover, there are no clinically relevant interactions that have been reported between silymarin and other drugs [6].

## **CLINICAL STUDIES ON SILYMARIN WITH RESPECT TO NAFLD**

There is very limited clinical data available on the impact of silymarin alone or in combination with other therapy on patients with NAFLD/NASH. We further discuss the available medical literature to delve into the findings, conclusions, and the recommendations of these studies.

### **Silymarin as a mono-therapy**

Silymarin as an antioxidant was used in a randomized controlled trial for a period of 18 months on NASH patients with elevated liver enzymes. The NASH patients were randomised into two groups, 50 in each arm; treatment group receiving 280mg silymarin for 24 weeks and the

placebo group. The serum alanine aminotransferase (ALT) level reduced significantly from 113.03 and 73.14 IU/mL ( $P = 0.001$ ) in the silymarin group along with ALT normalisation (ALT <40) in 52%, and aspartate aminotransferase (AST) normalisation (AST <40) in 62% of the cases, therefore having a greater impact on AST improvement as it reduced significantly in comparison to placebo group. There was no significant difference in ALT after treatment between the silymarin and placebo group. No side effects were reported in each of the cases. The study concluded that silymarin may aid in improving the biochemical profile by decreasing the transaminase levels in NAFLD patients, although there was no histological data available after the treatment [9]. Importantly, silymarin was safe and well tolerated by the study subjects.

When patients with cirrhosis and diabetes were treated with silymarin for a period of 12 months at a dose of 600mg/day, it reduced insulin resistance and significantly decreased the fasting insulin levels, indicating an improvement in endogenous and exogenous insulin activity [30].

In another clinical trial to evaluate the efficacy of silymarin as a monotherapy [2], NASH patients were randomly allocated into two groups; the treatment group that received 210mg/day oral silymarin for 8 weeks and the placebo group, in addition to being advised a low-fat, low-carbohydrate diet, to engage in physical activity and to lose a minimum of four kilograms of weight. After the completion of the treatment period, the NASH patients were evaluated for liver enzymes that showed a marked improvement for both, in particular, ALT. However, the patients were not evaluated for insulin resistance, ultrasonographic or histopathological changes after the treatment.

With the aim of assessing whether silymarin improves aminotransferases in NASH patients, a double blind, randomised, placebo-controlled trial was performed. 100 NASH subjects were randomly allocated to receive 140mg twice daily for three months and placebo. ALT declined significantly from 84.06 to 68.54 IU/ml and AST from 71.94 to 54.7 IU/ml in the treatment group, although there was an insignificant change in the placebo group. The authors concluded that silymarin aided in reducing the liver enzymes in NASH patients [31].

In a randomised trial to assess the impact of silymarin on cases of biopsy proven NASH [32], 99 subjects (most of them diabetic, centrally obese) were randomised to receive either 700mg oral silymarin for 48 weeks or placebo. About 30% of the NASH subjects had an improvement in NAFLD activity score in the repeat liver biopsy, but there was no significant difference in inflammation, ballooning and NAFLD activity score between both the groups. However, the silymarin group, had significant improvement in fibrosis as compared to placebo, highlighting the anti-fibrotic properties of silymarin. The study concluded that silymarin was safe and well tolerated by NASH patients and maybe used as a combination therapy along with other drugs for treatment of NASH.

### **Silymarin in combination therapy**

In a randomised controlled trial comprised of 50 NAFLD patients, patients were treated with 140 mg of silymarin for 8 weeks, followed by another two months of follow up, compared to metformin and pioglitazone. Liver enzymes improved with a marked decrease in ALT levels from 103.1 to 41.4 IU/ml and AST levels from 53.07 to 29.1 IU/ml [33], in the silymarin group. The reduction was more evident in the silymarin group as compared to the metformin group. Another interesting observation was that, silymarin had a weak impact on triglycerides, fasting blood sugar and insulin levels.

A study was carried out to assess the impact of metformin, pioglitazone, and silymarin in NAFLD (N=66). The NAFLD patients, all with similar baseline characteristics, were randomly allocated into three groups; the first group receiving 15mg/day pioglitazone, the second group

receiving 500mg/day metformin and the third group receiving 140mg/day silymarin for 8 weeks. In all the three groups, there was a significant reduction in fasting blood sugar, ALT, AST, serum insulin level. However, the most evident reduction in ALT and AST occurred in the silymarin group [34].

NAFLD cases who were treated with silymarin vitamin E phospholipids complex for a period of 6 months (four pieces per day), along with another six month of follow up, showed improvement in insulin resistance, liver enzymes and the degree of steatosis [35].

A pilot study was conducted to evaluate the impact of oral silymarin and S-Adenosyl-L-Methionine (SAME) supplementation for 12 months in NAFLD patients [3]. The supplementation significantly improved total cholesterol, insulin, ALT and alkaline phosphatase. To further support the impact of supplementation, there was a regression in the degree of hepatic steatosis. The authors of the study concluded that, silymarin and SAME could be used as an adjunctive therapy to improve the metabolic profile and hepatic steatosis in NAFLD patients, especially those who fail to change their lifestyle. However, a delimitation of the study was the limited number of subjects. Moreover, there is no evidence or consensus on the stipulated dosage and duration of supplementation of silymarin with SAME for NAFLD.

In a pilot study on NAFLD patients [17], a new silybin-vitamin E complex (silybin (94mg) + vitamin E (90mg) + phospholipids (194mg) at a dose of four pills/day for 6 months) was tried. It was found to significantly improved the liver enzymes, insulin resistance and the echographic score of liver steatosis.

The findings of this study were further confirmed in a placebo-controlled, double-blind, randomized clinical trial [27], that assessed the efficacy of the silybin-vitamin E complex in the same dosage in NAFLD patients (two pills/day for 1 year). The liver enzymes, insulin resistance, and liver histology were improved with the silymarin complex and there were few side effects.

In a randomized study comparing the effects of a hypocaloric Mediterranean diet versus a diet with silybin, phosphatidylcholine, and vitamin E complex for six months in overweight NAFLD subjects, it showed a positive impact of the diet, as well as of the complex that brought about significant changes in the anthropometric indices, total cholesterol and triglycerides, and improvement in insulin resistance in the silymarin vitamin E complex group [36].

In a meta-analysis to assess the therapeutic effect of silymarin in the treatment of NAFLD, eight RCTs were included [18]. It was observed that silymarin reduced the ALT and AST more significantly than the control group. In fact, silymarin as a monotherapy, compared to other interventions, had a more significant difference in decreasing the ALT and AST. The meta-analysis concluded that silymarin can be considered as phytotherapy for NAFLD subjects and that it was not dose dependent.

A study was carried out to assess the therapeutic effect of silymarin in combination with simvastatin in NASH patients (N=70). They were randomly allocated into treatment group comprising of silymarin (70mg twice daily) plus simvastatin and control group that received liver protecting tablet plus vitamin E for 12 weeks. ALT reduced significantly in the silymarin group and so did the lipid parameters that were aberrated prior to the treatment. There were no severe side effects reported during the treatment. The study concluded that silymarin in combination with simvastatin was an effective treatment for NASH patients [37].

## CONCLUSIONS

While the studies have demonstrated the antioxidant, anti-fibrotic properties of silymarin and its role as a possible insulin sensitizer, the studies on the impact of silymarin in the management of NAFLD are in a very nascent stage. More robust studies with large sample size, double

blinded, randomised prospective trials and multicentric studies are required before arriving at any conclusion. The studies to date, have been marred with some or the other methodological issues; smaller sample size, uncontrolled studies, short duration trials, no or short follow up period, no hepatic end points, mono-combo therapy, heterogenous groups, that refrain from drawing any externally valid recommendations about the efficacy of silymarin. It is equally important to clearly demarcate the hepatic end points to validate the effectiveness of the treatment with silymarin, as biochemical tests alone do not suffice and ultrasonographic or histological data is required to validate the same. There is no consensus on the appropriate dosage and duration of supplementation with silymarin, standardization with other formulations, while keeping in mind the pharmacokinetics, also needs to be investigated to achieve the desired therapeutic effect.

**Abbreviations:** NAFLD, Non-alcoholic fatty liver disease; NASH, Non-alcoholic steatohepatitis, HCC, Hepatocellular carcinoma, ROS, Reactive oxygen species; CVD, Cardiovascular disease; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; SAME, S-Adenosyl-L-Methionine; RCT, Randomized controlled trial

**Competing Interest:** None declared

**Authors' Contributions:** Both the authors had an equal contribution towards the manuscript.

**Acknowledgements and Funding:** No funding was received for this manuscript

## REFERENCES

1. Angulo P: Nonalcoholic fatty liver disease. *N Engl J Med.* 2002;346(16):1221-31.
2. Solhi H, Ghahremani R, Kazemifar AM, Hoseini Yazdani Z. Silymarin in treatment of non-alcoholic steatohepatitis: a randomized clinical trial. *Caspian J Intern Med* 2014; 5(1): 9-12.
3. Giangrandi I, Dinu M, Pagliai G, Sofi F, Casini A: Efficacy of Oral Supplementation with Silymarin and S-Adenosyl-L-Methionine in Patients with Non-Alcoholic Fatty Liver Disease –A Pilot Study. *Altern Integr Med* 2016; 5: 224.
4. Rinella ME: Nonalcoholic fatty liver disease: a systematic review. *JAMA* 2015; 313: 2263-2273.
5. Bellentani S, Scaglioni F, Marino M et al: Epidemiology of non-alcoholic fatty liver disease. *Dig. Dis.* 2010; 28(1), 155–161.
6. Claus Hellerbrand, Jorn M. Schattenberg, Philipp Peterburs, Anja Lechner and Reto Brignoli: The potential of silymarin for the treatment of hepatic disorders *Clinical Phytoscience* 2016; 2:7.
7. Nascimbeni F, Pais R, Bellentani S et al: From NAFLD in clinical practice to answers from guidelines. *J. Hepatol.* 2013; 59(4), 859-871.
8. Carr RM, Oranu A, Khungar V: Nonalcoholic fatty liver disease: pathophysiology and management. *Gastroenterol Clin North Am* 2016, 45:639–52.
9. Hashemi SJ, Hajiani E, Sardabi EH: A Placebo-Controlled Trial of Silymarin in Patients with Nonalcoholic Fatty Liver Disease. *Hepatitis Monthly* 2009; 9(4): 265-270.
10. Sanyal AJ: AGA technical review on nonalcoholic fatty liver disease. *Gastroenterology.* 2002;123(5):1705-25.

11. Abenavoli L, Capasso R, Milic N et al: Milk thistle in liver diseases: past, present, future. *Phytother. Res.* 2010; 24(10):1423–1432.
12. Loria P, Adinolfi LE, Bellentani S et al: Practice guidelines for the diagnosis and management of nonalcoholic fatty liver disease. A decalogue from the Italian association for the study of the liver (AISF) expert committee. *Dig. Liver Dis.* 2010; 42(4):272–282.
13. Abenavoli L, Milic N, Di Renzo L, Preveden T, Medic-Stojanoska M, De Lorenzo A: Metabolic aspects of adult patients with nonalcoholic fatty liver disease. *World J Gastroenterol* 2016; 22:7006-7016.
14. Benedict M, Zhang X: Non-alcoholic fatty liver disease: an expanded review. *World J Hepatol* 2017; 9:715–732.
15. Bellentani S: The epidemiology of non-alcoholic fatty liver disease. *Liver Int* 2017;37(Suppl 1):81–84.
16. Athyros VG, Alexandrides TK, Bilianou H, et al: The use of statins alone, or in combination with pioglitazone and other drugs, for the treatment of non-alcoholic fatty liver disease/non-alcoholic steatohepatitis and related cardiovascular risk. An Expert Panel Statement. *Metabolism* 2017; 71:17–32.
17. Loguercio C, Federico A, Trappoliere M, et al: The effect of a silybin-vitamin e-phospholipid complex on nonalcoholic fatty liver disease: a pilot study. *Dig Dis Sci* 2007; 52: 2387-95.
18. Zhong S, Fan Y, Yan Q, Fan X, Wu B, Han Y, Zhang Y, et al.: The therapeutic effect of silymarin in the treatment of nonalcoholic fatty disease. A meta-analysis (PRISMA) of randomized control trials. *Systematic Review and Meta-Analysis. Medicine* (2017) 96:49(e9061).
19. Colica C, Boccuto L, Abenavoli L: Silymarin: An option to treat non-alcoholic fatty liver disease. *World J Gastroenterol* 2017 December 21; 23(47): 8437-8438.
20. Cacciapuoti F, Scognamiglio A, Palumbo R, Forte R, Cacciapuoti F: Silymarin in non-alcoholic fatty liver disease. *World J Hepatol* 2013; 5: 109-113.
21. Saller R, Meier R, Brignoli R: The use of silymarin in the treatment of liver diseases. *Drugs* 2001; 61(14):2035–2063.
22. Vladimir-Knezevic S, Cvijanovic O, Blazekovic B, Kindl M, Stefan MB, Domitrovic R: Hepatoprotective effects of *Micromeria croatica* ethanolic extract against CCl<sub>4</sub>-induced liver injury in mice. *BMC complementary and alternative medicine.* 2015; 15:233.
23. Federico A, Dallio M, Loguercio C: Silymarin/silybin and chronic liver disease: a marriage of many years. *Molecules* 2017; 22:2.
24. Masini A, Ceccarelli D, Giovannini F, Montosi G, Garuti C, Pietrangelo A: Iron-induced oxidant stress leads to irreversible mitochondrial dysfunctions and fibrosis in the liver of chronic iron-dosed gerbils. The effect of silybin. *J Bioenerg Biomembr.* 2000;32(2):175-82.
25. Loguercio C, Festi D: Silybin and the liver: from basic research to clinical practice. *World J. Gastroenterol.* 2011; 17(18), 2288–2301.
26. Gazak R, Walterova D, Kren V: Silybin and silymarin—new and emerging applications in medicine. *Curr. Med. Chem.* 2007; 14(3), 315–338.
27. Loguercio C, Andreone P, Brisc C, et al: Silybin combined with phosphatidyl choline and vitamin E in patients with nonalcoholic fatty liver disease: A randomized controlled trial. *Free Radic Biol Med* 2012; 52: 1658-65.

28. Polyak SJ, Ferenci P, Pawlotsky JM: Hepatoprotective and antiviral functions of silymarin components in hepatitis C virus infection. *Hepatology* (Baltimore, Md). 2013;57(3):1262–71.
29. Kim NC, Graf TN, Sparacino CM, et al: Complete isolation and characterization of silybins and isosilybins from milk thistle (*Silybum marianum*). *Org Biomol Chem* 2003; 1:1684–1689.
30. Velussi M, Cernigoi AM, De Monte A, Dapas F, Caffau C, Zilli M: Long-term (12 months) treatment with an antioxidant drug (silymarin) is effective on hyperinsulinemia, exogenous insulin need and malondialdehyde levels in cirrhotic diabetic patients. *J Hepatol*. 1997;26(4):871-9.
31. Masoodi MRA, Panahian M, Vojdani M: Effects of silymarin on reducing liver aminotransferases in patients with nonalcoholic fatty liver diseases. *GOVARESH*. 2013;18(3):181–5.
32. Chan W-K, Nik Mustapha NR, Mahadeva S: A randomized trial of silymarin for the treatment of nonalcoholic steatohepatitis. *Clin Gastroenterol Hepatol* 2017;15:1940–1949.
33. Hajjaghamohammadi 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(3):191-5.
34. Hajjaghamohammadi AA, Ziaee A, Oveisi S, Masroor H: Effects of metformin, pioglitazone, and silymarin treatment on non-alcoholic fatty liver disease: a randomized controlled pilot study. *Hepat Mon* 2012; 12: 1-6.
35. Federico A, Trappoliere M, Tuccillo C, et al.: A new silybinvitamin E-phospholipid complex improves insulin resistance and liver damage in patients with non-alcoholic fatty liver disease: preliminary observations. *Gut*. 2006;55(6):901-2.
36. Abenavoli L, Greco M, Nazionale I, Peta V, Milic N, et al: Effects of Mediterranean diet supplemented with silybin-vitamin E-phospholipid complex in overweight patients with non-alcoholic fatty liver disease. *Expert Rev Gastroenterol Hepatol* 2015; 9: 519–527.
37. Han M, Wen P, Wen J, et al: Clinical effect of silymarin combined with simvastatin on patients with nonalcoholic steatohepatitis. *Chin J Liver Dis* 2011; 3:15–8.