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Silymarin-choline combination versus ursodeoxycholic acid in non-alcoholic fatty liver disease: A randomized double-blind clinical trial

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ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) is an influential cause of liver disease burden. However, there is no evidence-based standard of care. Considering that oxidative stress and diet deficiency of choline plays a role in the pathophysiology of hepatic damage, natural compounds such as silymarin, choline, and ursodeoxycholic acid (UDCA) represent popular therapeutic options. **Aims and Objectives:** The present study aimed to compare the efficacy, safety, and adherence of the silymarin-choline combination and UDCA in patients with NAFLD. **Materials and Methods:** A double-blind parallel arm study where 88 NAFLD-diagnosed patients were randomized to receive either silymarin-choline bitartrate or UDCA for 6 months, along with lifestyle modification recommendations. Weight, body mass index, liver enzyme levels, lipid profile parameters, homeostatic model assessment of insulin resistance, liver stiffness measurement, and liver biopsy were monitored at baseline and 6 months. Adverse events and adherence were monitored. **Results:** A total of 39 patients received a tablet of silymarin-choline bitartrate, while 40 received UDCA. A significant improvement was observed in aspartate aminotransferase (U/L) levels from 54.18 (17.02) to 37.23 (9.94) (P = 0.000), NAFLD activity score from 6.5 (0.37) to 2.7 (1.26) (P = 0.000), and transient elastography (kilopascal) scores, more in patients receiving the silymarin-choline combination, whereas for those receiving UDCA, a significant improvement was observed in total cholesterol (mg/dL) from 187.88 (27.49) to 171.45 (28.47) (P = 0.000) and low-density lipoprotein levels. No major safety issues were observed in both groups. **Conclusion**: NAFLD is currently treated by treating associated comorbidities, which cannot always stop its progression. Silymarin-choline bitartrate can be used as a better alternative to UDCA for the treatment of NAFLD.

Key words: Non-alcoholic steatohepatitis; Liver function test; Transient elastography; NAFLD activity score; Liver biopsy

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) has become one of the most important liver illnesses globally.[1] There are 27% Asians, 32% Middle Easterners, and up to 30% Westerners who suffer from NAFLD.[2] The progression of NAFLD can lead to non-alcoholic steatohepatitis (NASH), cirrhosis of the liver, and hepatocellular carcinomas (HCC). Despite the absence of liver cirrhosis, NASH patients can develop HCC. NAFLD patients have a 1.7-fold increase in standardized age and gender-matched mortality.[3]

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The treatment of NAFLD is of prime concern to health-care professionals and patients due to the significant morbidity and mortality. The standard medications for NAFLD remain experimental and without evidence based. At present, treatment is focused on lifestyle modification and management of associated comorbidities, with a possible role for some hepatic protective agents. Medicines such as metformin, atorvastatin, vitamin E, silymarin, choline, and ursodeoxycholic acid (UDCA) remain experimental without any consistent evidence-based responses, and some of them come with significant side effects. The need for an effective medicinal agent is high, particularly when NAFLD is isolated without other comorbidities.[4-7]

Since oxidative stress is associated with the pathophysiology of hepatic insult, the use of natural compounds with antioxidant properties such as UDCA, silymarin, and choline holds a hopeful treatment option for NAFLD.[8-10]

The liver is sensitive to the availability of choline. A choline-deprived diet can lead to hepatic steatosis, fibrosis, and carcinomatosis. Choline can influence the epigenetic regulation of gene expression responsible for the development of fatty liver, hepatic fibrosis, and hepatocellular carcinoma.[10] UDCA, a tertiary bile acid, can decrease serum tumor necrosis factor alpha concentrations and endoplasmic reticulum stress and improve hepatic insulin sensitivity, whereas silymarin, a flavonolignan from the "milk thistle" (*Silybum marianum*) plant, acts by anti-oxidative, anti-fibrotic, anti-inflammatory, and immunomodulatory mechanisms.[2,11,12]

This study has been conducted to compare and assess the efficacy and safety profile of silymarin-choline combination and UDCA when prescribed to patients with NAFLD and NASH in improving the liver function test (LFT) (decrease or normalization of the elevated liver enzyme levels), liver stiffness measurement (using the non-invasive method of transient elastography), and liver inflammation score by NAFLD activity score (NAS).[13,14]

Aims and objectives

To compare the change of different biochemical and histological profiles of liver in Nonalcoholic fatty liver disease after six months of therapy with Sylimarin-choline and UDCA.

MATERIALS AND METHODS

The study protocol was approved by the Institutional Ethics Committee, Medical College and Hospital, Kolkata, India (EC Approval No. MC/KOL/IEC/NON-SPON/134/08-2018) and the Clinical Trials Registry, India (CTRI/2019/04/018550).

Trial design

This is a randomized double-blind clinical trial to compare and assess the efficacy and safety profile of the silymarin-choline combination versus UDCA while prescribed for patients with NAFLD and NASH in improving the LFT (decrease or normalization of the elevated liver enzyme levels), liver stiffness measurement (by non-invasive method, transient elastography), and liver inflammation score by NAS. The medication adherence of the participants was assessed by the pill count method.

Participants, randomization, and blinding

The sample size was calculated by leveraging previous studies from PubMed literature searches[15,16] based on post-treatment values of alanine transaminase (ALT). Considering the power of the study at 0.80, alpha of 0.05, and attrition rate of 10%, the total calculated sample size was 78. One hundred and three (103) NAFLD (ultrasound finding of fatty liver) patients aged between 18 and 65 years who visited the outpatient Department of Gastroenterology, Medicine, and Clinical Pharmacology of Medical College and Hospital, Kolkata, India, within the period from August 2019 to February 2020, were screened for the study. Eighty-eight patients with NAFLD who met the eligibility criteria were recruited and randomized by the balanced blocked randomization method with the help of etcetera (WinPepi Software) for MAC into two groups to receive either tablet Silymarin-Choline (Mariliv) or tablet UDCA (Ursocol) (Flow Diagram 1).

Interventions

All drugs bearing the same batch number were procured at once using investigators' funds.

All the drugs are marketed in formulations that are mandatory good manufacturing practice-compliant and ensure compliance with quality control guidelines.

Tablet Mariliv (manufacturer: EMCEE Pharmaceuticals (P) Ltd.): A combination of tablet silymarin (140 mg) and choline bitartrate (450 mg) 1 tablet thrice daily for 1 month (continued till 6 months).

Or, Tablet ursocol (UDCA) 300 mg (manufacturer: Sun Pharmaceutical Industries Ltd.): UDCA 300 mg, 1 tablet twice daily for 1 month (continued till 6 months).

Participants were given medicines once a month for 6 months and encouraged to lifestyle modification and brisk walking (30 min every day for 5 days or 150 min a week).

Both participants and investigators were masked regarding treatment allocation.

Inclusion criteria

Participants in this study were chosen from either gender, aged 18–65 years, who had been diagnosed with NAFLD by ultrasound findings of fatty liver at the beginning of the study, and who understood and consented to participate.

Exclusion criteria

Individuals with a history of ethanol consumption exceeding 20 g/day, ingestion of drugs known to induce fatty liver disease (such as steroids, estrogens, amiodarone, tamoxifen, or other chemotherapeutic agents), diabetes, viral hepatitis (hepatitis B virus, hepatitis C virus), HIV infection, severely ill patients requiring hospital inpatient or critical care services, and pregnancy were excluded from the study.

All the participants were provided with a patient information sheet and informed written consent form in three vernaculars (Bengali, Hindi, and English).

Allocation concealment

Sequentially numbered, opaque, sealed envelopes were used for allocation concealment. The silymarin-choline combination (used as one tablet) and UDCA were received following a randomization code. The silymarin-choline combination was given thrice daily and UDCA twice daily, to maintain the blinding, identical-looking dummy, was given along with the UDCA daily dosage. Medicines were distributed in identical packages each month.

Baseline parameters

Baseline characteristics of the participants include age, sex, height, weight, body mass index (BMI), biochemical parameters (homeostatic model assessment of insulin resistance [HOMA–IR], aspartate aminotransferase [AST], ALT, triglycerides [TG], cholesterol, low-density lipoprotein [LDL], and high-density lipoprotein [HDL]), radiological parameters (transient elastography score), and liver biopsy findings (n=34) were noted in the case record form (CRF).

Study visits

In total, two study visits were conducted (to compare the efficacy of the silymarin-choline combination with UDCA) to assess the improvement in elevated liver enzyme levels and liver stiffness (measured by non-invasive transient elastography). A liver biopsy was done with random selection on 34 participants, 17 from each group, at baseline and after 6 months of therapy. NAS measurement was done in each participant at baseline and after 6 months of therapy. Test results were recorded in the patients' CRF. The 1st visit was conducted before commencing medication (silymarin-choline combination/UDCA), and the 2nd visit was conducted after 6 months of therapy to monitor the above-mentioned factors. During monthly medicine collection visits, side effects and adherence (monitored by the pill count method) were monitored and noted in patients' CRFs.

Outcomes

The primary outcome parameters included changes in the liver enzyme and lipid profile levels, liver stiffness measurement, and liver inflammation score. Liver enzymes such as ALT and AST were measured using the International Federation of Clinical Chemistry Methods.[17] For lipid profile measures, serum total cholesterol (TC) was measured by the enzymatic (CHOD-POD) method,[18] while serum TG was measured by the glycerol-3-phosphate (GPO)-peroxidase (POD) chromogenic method.[19] Other lipid measures, such as HDL and LDL, were measured using the homogeneous enzymatic method.[20] Liver stiffness was measured using a non-invasive, ultrasound-based technology – transient elastrography[21]– during which a low-frequency elastic shear wave is used to propagate through tissues, the propagation speed being proportional to the stiffness of the tissues crossed. Specific software is used to obtain tissue stiffness measurements, expressed in kilopascals (kPa) and ranging from 2.5 to 75 kPa. Liver inflammation was estimated using NAS. The NAS is a measure of grade and is the sum of numerical scores applied to steatosis (0–3), hepatocellular ballooning (0–2), and lobular inflammation (0–3). Accordingly, the NAS[22] ranges from 0 to 8. Monitoring and reporting of associated adverse events and medication adherence by patients were considered secondary outcomes. Adherence to treatment was assessed using the pill count method. Adherence, measured by pill count, was calculated as the percentage of the number of prescribed pills corrected for the number of returned pills divided by the period (in days) multiplied by 100%.[23]

Statistical methods

The collected data were checked for completeness and statistically analyzed. Means and percentages were used to represent descriptive data. Different levels were expressed at a 95% confidence interval. A $P<0.05$ was considered statistically significant. Where applicable, mean and median values were compared with hypothesis testing and correlation analysis was conducted for various grades and scores. The normality test was done using the Shapiro–Wilk test. Quantitative data were analyzed using a paired or unpaired student's t-test as per the requirement. All statistical analyses for various measures were performed using various statistical software packages, such as the Statistical Packages for the Social Sciences (SPSS version 28) and Microsoft Excel.

RESULTS

Study participants

A total of 103 patients were screened. 88 patients meeting the eligibility criteria were randomly assigned to receive

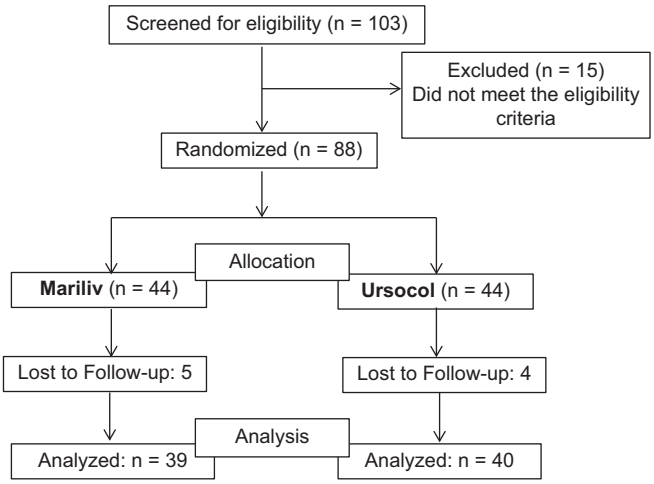
either tablet mariliv or tablet ursocol. Participants were given medicines once a month for 6 months. A total of 9 participants were lost to follow-ups 5 and 4 from group mariliv and group ursocol, respectively (Flow Diagram 1).

The mean age of the participants was 39.44 (9.31) years, with 41 (51.89%) females and 38 (48.11%) males. The baseline distributions of age, sex, weight, BMI, transient elastography score (kpa), HOMA-IR, liver, lipid profile parameters, and NAS score were not significantly different (clinically or statistically) between the two groups (Table 1).

Outcome parameters

Efficacy measures

The primary and secondary outcome parameters were compared within each study group and between them.



Flow Diagram 1: Study design

Both groups showed significant improvements in transient elastography, NAS score, ALT, AST, TC, and LDL levels. AST, ALT levels, transient elastography scores, and NAS scores significantly improved more in patients receiving mariliv (silymarin-choline); however, TC and LDL levels significantly improved more in patients receiving ursocol (UDCA). After therapy, anthropometric parameters (bodyweight and BMI) and HOMA-IR scores did not change significantly in either group (Tables 2 and 3).

Liver stiffness measurement

Transient elastography

(kp) scoring improved significantly more in the mariliv arm than the ursocol arm (1.36 U/L [95% CI: 1.01–1.69, P=0.000] vs. 0.76 U/L [95% CI: 0.35–1.17, P=0.001]).

Liver inflammation scoring

There was a significant improvement in the NAS score in the mariliv arm as compared to the ursocol arm (3.86 [95% CI: 3.15–4.57, P=0.000] vs. 1.72 U/L [95% CI: 1.06–2.37, P=0.000]).

Liver profile

The mean improvement in ALT (U/L) levels was significantly higher in the mariliv arm compared to the ursocol arm (39.18 [95% CI: 34.09–44.26, P=0.000] vs. 37.65 U/L [95% CI: 32.09–43.21, P=0.000]).

The mean improvement in AST (U/L) levels was significantly higher in the mariliv arm compared to the ursocol arm (16.95 [95% CI: 9.39–24.51, P=0.000] vs. 16.38 U/L [95% CI: 9.25–23.49, P=0.000]).

Table 1: Baseline characteristics of patients

Baseline parameters (1st visit)	Mariliv® (SILYMARIN-CHOLINE)	Ursocol® (ursodeoxycholic acid)	P-value (inter-group)
Age	39.33 (9.39)	40.63 (10.63)	0.124
Gender			
Male n (%)	21 (56.8)	16 (43.2)	0.218
Female n (%)	18 (42.9)	24 (57.1)	
Weight (kg)	72.87 (4.21)	72.95 (4.22)	0.929
Body mass index (kg/Mt^2)	29.35 (1.22)	29.32 (2.07)	0.000
Homeostatic model assessment of insulin resistance	1.302 (0.49)	1.303 (0.68)	0.002
Liver panel			
ALT (U/L)	78.72 (13.65)	78.23 (13.56)	0.938
AST (U/L)	54.18 (17.02)	54.40 (16.48)	0.659
Lipid panel			
Total cholesterol (mg/dL)	187.08 (31.11)	187.88 (27.49)	0.154
Triglycerides (mg/dL)	163.36 (31.69)	163.83 (33.79)	0.812
High-density lipoprotein (mg/dL)	41.41 (7.69)	40.50 (6.99)	0.884
Low-density lipoprotein (mg/dL)	135.74 (31.20)	136.18 (31.04)	0.992
Liver stiffness measure			
Transient elastography score (kpa)	7.68 (0.97)	7.61 (0.66)	0.006
Liver Inflammation			
NAFLD activity score	6.5 (0.37)	6.7 (0.24)	0.214

*Values expressed as mean (SD), ALT: Alanine aminotransferase, AST: Aspartate transaminase, NAFLD: Non-alcoholic fatty liver disease

Table 2: Comparison of change of variable values

Parameters	Mariliv (silymarin-choline)			Ursocol (ursodeoxycholic acid)			Mariliv versus ursocol	
	1st visit	2nd visit	P-value (intra group)	1st visit	2nd visit	P-value (intra group)	Mean difference at 2nd visit (95% confidence interval)	P-value (inter group)
Weight (kg)	72.87 (4.21)	72.41 (4.39)	0.071	72.95 (4.22)	72.23 (4.58)	0.070	−0.19 (−2.19–1.82)	0.74
Body mass index (kg/Mt^2)	29.35 (1.22)	29.16 (1.43)	0.072	29.32 (2.07)	29.04 (2.31)	0.077	−0.13 (−0.99–0.74)	0.004
Homeostatic model assessment of insulin resistance	1.302 (0.49)	1.306 (0.49)	0.968	1.303 (0.68)	1.306 (0.71)	0.984	0.0001 (−0.273–0.272)	0.063
Liver panel								
ALT (U/L)	78.72 (13.65)	39.54 (9.54)	0.000	78.23 (13.56)	40.58 (9.67)	0.000	1.04 (−3.27 to 5.34)	0.97
AST (U/L)	54.18 (17.02)	37.23 (9.94)	0.000	54.40 (16.48)	38.03 (7.94)	0.000	0.79 (−3.23–4.82)	0.02
Lipid panel								
Total cholesterol (mg/dL)	187.08 (31.11)	178.77 (29.69)	0.000	187.88 (27.49)	171.45 (28.47)	0.000	−7.32 (−20.35–5.71)	0.223
Triglycerides (mg/dL)	163.36 (31.69)	162.28 (31.45)	0.001	163.83 (33.79)	162.65 (33.15)	0.003	0.37 (−14.12–14.85)	0.917
High-density lipoprotein (mg/dL)	41.41 (7.69)	41.51 (7.59)	0.544	40.50 (6.99)	40.80 (7.02)	0.054	−0.713 (−3.99–2.56)	0.884
Low-density lipoprotein (mg/dL)	135.74 (31.20)	128.82 (27.96)	0.000	136.18 (31.04)	125.48 (27.35)	0.000	−3.35 (−15.74–9.05)	0.602
Liver stiffness measure								
Transient elastography score (kpa)	7.68 (0.97)	6.32 (1.26)	0.000	7.61 (0.66)	6.85 (0.98)	0.001	0.52 (0.02–−1.03)	0.752
Liver inflammation								
NAFLD activity score	6.5 (0.37)	2.65 (1.26)	0.000	6.7 (0.24)	4.95 (1.37)	0.000	2.29 (1.37–3.21)	0.074

NAFLD: Non-alcoholic fatty liver disease, ALT: Alanine aminotransferase, AST: Aspartate transaminase

Lipid profile

In the ursocol arm, TC (mg/dL) levels improved significantly more than in the mariliv arm (16.43 [95% CI: 10.61–22.24, P=0.000] vs. 8.31 [95% CI: 4.65–11.97, P=0.000]). The mean improvement in LDL (mg/dL) levels in the ursocol arm was also significantly higher than that in the mariliv arm (10.70 [95% CI: 6.96–14.43, P=0.000] vs. 6.92 [95% CI: 3.73–10.11, P=0.000]).

Safety measures

There were no major side effects in either group; however, 8 (20.51%) out of 39 mariliv participants (silymarin-choline) and 9 (22.5%) out of 40 ursocol (UDCA) participants complained of constipation and loose stools, respectively. There were a few participants from both groups who complained of nausea, bloating, and loss of appetite. The side effects were managed in the outpatient department of -the study set-up (Table 4).

Adherence

Therapy adherence of trial participants to therapy was satisfactory. Adherence to treatment was comparable in both arms. Adherence, as measured using the pill count method, was assessed to be 96.67% in the mariliv arm and 97.09% in the ursocol arm.

DISCUSSION

Transient elastography score, HOMA-IR score, anthropometric parameters, LFT, lipid profile, and liver biopsy were considered in this randomized, double-blinded clinical trial.

There was a significant improvement in transient elastography score, liver inflammation, ALT, AST, TC, and LDL levels in each group (mariliv and ursocol) after 6 months of treatment.

There was a significant improvement in transient elastography score, AST, ALT, and biopsy parameters in patients receiving mariliv (silymarin-choline); however, significant improvements in TC and LDL levels were observed more in patients receiving ursocol.

In both groups, the changes in anthropometric parameters (body weight and BMI) and HOMA-IR score after the therapy were insignificant.

There were no major side effects in either group; however, 8 (20.51%) out of 39 mariliv participants (silymarin-choline) and 9 (22.5%) out of 40 ursocol (UDCA) participants complained of constipation and loose stools, respectively. The side effects were managed in the outpatient department of the Medical College and Hospital, Kolkata.

Table 3: Comparison of mean difference change in two groups

Mean difference (CI) (within groups/intragroup)	Mariliv (silymarin-choline) (1st visit vs. 2nd visit)		Ursocol (ursodeoxycholic acid) (1st visit vs. 2nd visit)	
	Mean difference (95% CI)	P-value	Mean difference (95% CI)	P-value
Weight (kg)	0.46 (−0.04–0.97)	0.071	0.73 (−0.06–1.51)	0.070
Body mass index (kg/Mt^2)	0.21 (−0.005–0.418)	0.06	0.28 (−0.039–0.605)	0.084
Homeostatic model assessment of insulin resistance	−0.004 (−0.224–0.215)	0.968	−0.003 (−0.308–−0.302)	0.984
Liver panel				
ALT (U/L)	39.18 (34.09–44.26)	0.000	37.65 (32.09–43.21)	0.000
AST (U/L)	16.95 (9.39–24.51)	0.000	16.38 (9.25–23.49)	0.000
Lipid panel				
Total cholesterol (mg/dL)	8.31 (4.65–11.97)	0.000	16.43 (10.61–22.24)	0.000
Triglycerides (mg/dL)	1.08 (0.45–1.70)	0.001	1.18 (0.43–1.92)	0.003
High-density lipoprotein (mg/dL)	−0.08 (−3.74–3.59)	0.966	−0.28 (−0.58–0.02)	0.062
Low-density lipoprotein (mg/dL)	6.92 (3.73–10.11)	0.003	10.70 (6.96–14.43)	0.000
Liver stiffness measure				
Transient elastography score (kpa)	1.36 (1.01–1.69)	0.000	−0.76 (0.35–1.17)	0.001
Liver inflammation				
NAFLD activity score	3.86 (3.15–4.57)	0.000	1.72 (1.06–2.37)	0.000

CI: Confidence interval, NAFLD: Non-alcoholic fatty liver disease, ALT: Alanine aminotransferase, AST: Aspartate transaminase

Table 4: Comparison of adverse effects

Safety	Mariliv (silymarin-choline) (%)	Ursocol (ursodeoxycholic acid) (%)
Constipation	8 (20.51)	-
Loose stools	-	9 (22.5)
Nausea	3 (7.69)	5 (12.50)
Bloating	4 (10.26)	6 (15.00)
Loss of appetite	4 (10.26)	4 (10.00)

Silymarin,[24] a flavonolignan obtained from the Silybum marianum plant, is used for its hepatoprotective action. It acts through its antioxidative, antifibrotic, anti-inflammatory, and immunomodulatory effects.

A randomized placebo-controlled clinical trial was conducted by Solhi et al., on 64 patients with NASH, where the case group received 210 mg/day of silymarin orally for 8 weeks. After 8 weeks of treatment, the silymarin group showed more improvement in hepatic enzyme levels.[12] In our study, significant improvements in hepatic enzyme levels were also noticed in the mariliv group.

A randomized, double-blind, placebo-controlled clinical trial was conducted by Wah Kheong et al., on 99 participants with NAFLD and NASH, where the case group received 700 mg of silymarin thrice daily for 48 weeks. After 48 weeks of therapy, silymarin was noticed to reduce liver fibrosis; however, the NAS score was not reduced by 30% or more.[24] A significant reduction of NAS in the silymarin group was noticed in our study. Although a reduction of NAS was also noted in the UDCA group, the reduction was not below three (<3).

A randomized double-blind placebo-controlled trial was conducted by Anushiravani et al., on 150 participants with NAFLD, where the participants of the silymarin group received silymarin 140 mg/day for 3 months. After 3 months, significant improvement in hepatic enzyme level was noticed in the silymarin group, but improvement in lipid profile was not noticed. Silymarin was well tolerated.[7]

In our study, improvement in TC and LDL levels, along with AST and ALT, was noticed in the mariliv group after 6 months of therapy. Mariliv was well tolerated by our study participants, but few complained of constipation.

The liver is sensitive to the availability of choline in the diet. The role of choline availability in the progression of liver injury and serious hepatic illnesses needs further attention.[9]

A randomized double-blind placebo-controlled multicenter trial was conducted by Ratziu et al., on 126 participants with NASH, where the case group received UDCA (28–35 mg/kg/day) for 12 months. A significant improvement in ALT level and liver fibrosis was noticed in the UDCA group after 12 months of therapy. UDCA was well tolerated.[10]

UDCA therapy was found to be effective in NAFLD patients in a meta-analysis conducted by Zhang et al. A significant improvement in ALT level was noticed.[25]

TC, LDL, AST, and ALT levels in the ursocol group improved after 6 months of therapy in our study. The study participants tolerated ursocol well, but few complained of loose stools.

Limitations of the study

This study was a single-center study with a limited follow-up period; hence, the study result cannot be generalized. This study lacks a placebo arm. Future research should try to overcome these limitations.

CONCLUSION

NAFLD is an increasing cause of liver disease burden across the world. The accepted treatment protocol is to treat the associated comorbidities, which cannot stop the progression of the disease at times. In this study, clinical, non-invasive, and invasive biochemical parameters related to NAFLD were assessed. The result of this study infers that tablet silymarin-choline bitartrate is effective and tolerable and reduces liver inflammation significantly compared to UDCA when combined with lifestyle modification. Tablet silymarin-choline bitartrate can be utilized as a better alternative to UDCA in the treatment of NAFLD. There is a need for more studies in the future to develop evidence-based treatment approaches for NAFLD.

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REFERENCES

1. Beaton MD. Current treatment options for nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Can J Gastroenterol. 2012;26(6):353-357.
https://doi.org/10.1155/2012/725468
2. Zhong S, Fan Y, Yan Q, Fan X, Wu B, Han Y, et al. The therapeutic effect of silymarin in the treatment of nonalcoholic fatty disease: A meta-analysis (PRISMA) of randomized control trials. Medicine (Baltimore). 2017;96(49):e9061.
https://doi.org/10.1097/MD.0000000000009061
3. Dajani AI, Abu Hammour AM, Zakaria MA, Al Jaberi MR, Nounou MA and Semrin AI. Essential phospholipids as a supportive adjunct in the management of patients with NAFLD. Arab J Gastroenterol. 2015;16(3-4):99-104.
https://doi.org/10.1016/j.ajg.2015.09.001
4. Uygun A, Kadayifci A, Isik AT, Ozgurtas T, Deveci S, Tuzun A, et al. Metformin in the treatment of patients with non-alcoholic steatohepatitis. Aliment Pharmacol Ther. 2004;19(5):537-544.
https://doi.org/10.1111/j.1365-2036.2004.01888.x
5. Bugianesi E, Gentilcore E, Manini R, Natale S, Vanni E, Villanova N, et al. A randomized controlled trial of metformin versus vitamin E or prescriptive diet in nonalcoholic fatty liver disease. Am J Gastroenterol. 2005;100(5):1082-1090.
https://doi.org/10.1111/j.1572-0241.2005.41583.x
6. Belfort R, Harrison SA, Brown K, Darland C, Finch J, Hardies J, et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. N Engl J Med. 2006;355(22):2297-2307.
https://doi.org/10.1056/NEJMoa060326
7. Anushiravani A, Haddadi N, Pourfarmanbar M and Mohammadkarimi V. Treatment options for nonalcoholic fatty liver disease: A double-blinded randomized placebo-controlled trial. Eur J Gastroenterol Hepatol. 2019;31(5):613-617.
https://doi.org/10.1097/MEG.0000000000001369
8. Parikh P, Ingle M, Patel J, Bhate P, Pandey V and Sawant P. An open-label randomized control study to compare the efficacy of vitamin E versus ursodeoxycholic acid in nondiabetic and noncirrhotic Indian NAFLD patients. Saudi J Gastroenterol. 2016;22(3):192-197.
https://doi.org/10.4103/1319-3767.182451
9. Sherriff JL, O'Sullivan TA, Properzi C, Oddo JL and Adams LA. Choline, its potential role in nonalcoholic fatty liver disease, and the case for human and bacterial genes12. Adv Nutr. 2016;7(1):5-13.
https://doi.org/10.3945/an.114.007955
10. Ratziu V, de Ledinghen V, Oberti F, Mathurin P, Wartelle-Bladou C, Renou C, et al. A randomized controlled trial of high-dose ursodesoxycholic acid for nonalcoholic steatohepatitis. J Hepatol. 2011;54(5):1011-1019.
https://doi.org/10.1016/j.jhep.2010.08.030
11. Mehedint MG and Zeisel SH. Choline's role in maintaining liver function: New evidence for epigenetic mechanisms. Curr Opin Clin Nutr Metab Care. 2013;16(3):33945.
https://doi.org/10.1097/MCO.0b013e3283600d46
12. Solhi H, Ghahremani R, Kazemifar AM and Hoseini Yazdi Z. Silymarin in treatment of non-alcoholic steatohepatitis: A randomized clinical trial. Caspian J Intern Med. 2014;5(1):9-12.
13. Hellerbrand C, Schattenberg JM, Peterburs P, Lechner A and Brignoli R. The potential of silymarin for the treatment of hepatic disorders. Clin Phytoscience. 2017;2(1):7.
https://doi.org/10.1186/s40816-016-0019-2
14. Practitioners TRAC of G. RACGP - FibroScan and Transient Elastography. Available from: https://www.racgp.org.au/afp/2013/july/fibroscan [Last accessed on 2018 Aug 16].
15. Cacciapuoti F, Scognamiglio A, Palumbo R, Forte R and Cacciapuoti F. Silymarin in non alcoholic fatty liver disease. World J Hepatol. 2013;5(3):109-113.
https://doi.org/10.4254/wjh.v5.i3.109
16. Lindor KD, Kowdley KV, Heathcote EJ, Harrison ME, Jorgensen R, Angulo P, et al. Ursodeoxycholic acid for treatment of nonalcoholic steatohepatitis: Results of a randomized trial. Hepatology. 2004;39(3):770-778.
https://doi.org/10.1002/hep.20092
17. Wong E. Clinical laboratory diagnostics: Use and assessment of clinical laboratory results. Lothar Thomas. Frankfurt/Main, Germany: TH-Books Verlagsgeselschaft, 1998, 1727 pp., $149.00. ISBN 3-9805215-4-0. Clin Chem. 1999;45(4):586-587.
https://doi.org/10.1093/clinchem/45.4.586a
18. Richmond W. Preparation and properties of a cholesterol oxidase from *Nocardia* sp. and its application to the enzymatic assay of total cholesterol in serum. Clin Chem. 1973;19(12):1350-2356.
19. Kawano M, Hokazono E, Osawa S, Sato S, Tateishi T,

Manabe M, et al. A novel assay for triglycerides using glycerol dehydrogenase and a water-soluble formazan dye, WST-8. Ann Clin Biochem. 2019;56(4):442-449.

https://doi.org10.1177/0004563219830715

20. Miida T, Nishimura K, Hirayama S, Miyamoto Y, Nakamura M, Masuda D, et al. Homogeneous assays for LDL-C and HDL-C are reliable in both the postprandial and fasting state. J Atheroscler Thromb. 2017;24(6):583-599.

    https://doi.org/10.5551/jat.40006

21. Tsochatzis EA, Gurusamy KS, Ntaoula S, Cholongitas E, Davidson BR and Burroughs AK. Elastography for the diagnosis of severity of fibrosis in chronic liver disease: A meta-analysis of diagnostic accuracy. J Hepatol. 2011;54(4):650-659.

    https://doi.org/10.1016/j.jhep.2010.07.033

22. Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology. 2005;41(6):1313-1321.

    https://doi.org/10.1002/hep.20701

23. van Onzenoort HA, Verberk WJ, Kessels AG, Kroon AA, Neef C, van der Kuy PH, et al. Assessing medication adherence simultaneously by electronic monitoring and pill count in patients with mild-to-moderate hypertension. Am J Hypertens. 2010;23(2):149-154.

    https://doi.org/10.1038/ajh.2009.207

24. Wah Kheong C, Nik Mustapha NR and Mahadeva S. A randomized trial of silymarin for the treatment of nonalcoholic steatohepatitis. Clin Gastroenterol Hepatol. 2017;15(12):1940-1949.e8.

    https://doi.org/10.1016/j.cgh.2017.04.016

25. Zhang W, Tang Y, Huang J and Hu H. Efficacy of ursodeoxycholic acid in nonalcoholic fatty liver disease: An updated meta-analysis of randomized controlled trials. Asia Pac J Clin Nutr. 2020;29(4):696-705.

    https://doi.org/10.6133/apjcn.202012_29(4).0004

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