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CLINICAL TRIAL REPORT

The Effect of Liv.52 DS in Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD): A Pilot, Randomized, Double-Blind, Placebo-Controlled, Clinical Study

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Purpose: Metabolic dysfunction-associated fatty liver disease (MAFLD) is considered a major global health concern. Considering the preliminary trend of hepatoprotective function of Liv.52 DS, the present study was conducted to explore its role in MAFLD.

Patients and Methods: This randomized, double-blind, placebo-controlled, prospective, multicenter study was performed at four tertiary care hospitals in India. A total of 52 randomized subjects were administered either Liv.52 DS or placebo tablets twice daily for six months. Liver Stiffness Measurement (LSM) and Controlled Attenuated Parameter (CAP) values were compared at baseline and 6 months. After completion of the study, data from 47 subjects were available for analysis (31 in the Liv.52 DS group and 16 in the placebo group).

Results: The mean LSM score, was reduced from 7.3 to 6.0 (Change From Baseline = 17.5%) in the active group with statistically significance (p = 0.007) compared to placebo group with LSM score reduction from 7.5 to 6.9 (CFB = 7.29%). A shift in the mean value from fibrosis (>6.0 kPa) to almost no significant fibrosis (<6.0 kPa), as per the Indian National Association for the Study of the Liver (INASL) cutoff, was achieved in the Liv.52 DS Group. Improvement was also observed in CAP values with Liv.52 DS, where 71% of the subjects showed an overall improvement in steatosis grade. The other liver markers like alanine transaminase (ALT) and aspartate aminotransferase (AST) were within the normal range. There were no cases of nephrotoxicity (common concern for herbal formulation), and no drug-related adverse events were reported.

Conclusion: A significant improvement in LSM and improvement in CAP was observed after 6 months of treatment with Liv.52 DS using fibroscan. This suggests that Liv.52 DS should be further explored for its potential role in the treatment of unmet medical needs in MAFLD patients.

Keywords: metabolic dysfunction-associated fatty liver disease, MAFLD, Liv.52 DS, hepatoprotective polyherbal formulation, hepatic fibrosis, liver stiffness measurement

Introduction

The liver, a vital organ responsible for numerous metabolic and detoxification processes, is susceptible to a spectrum of disorders that can significantly impair its function and overall health representing a growing global health concern due to its increasing prevalence.[1–3]

Among these, non-alcoholic fatty liver disease (NAFLD) has emerged as the most prevalent liver disorder worldwide, characterized by hepatic steatosis in the absence of significant alcohol consumption or other secondary causes.[4] Alcohol-related liver disease (ALD) similarly involves fat accumulation in the liver but is directly attributable to excessive alcohol

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intake.[5] Drug-induced liver injury (DILI) represents another major category, where various medications or supplements can precipitate hepatic damage, sometimes exacerbated by underlying metabolic dysfunction or fatty liver.[6] Fatty liver (FL), whether due to metabolic, alcoholic, or drug-related causes, often serves as a common pathological substrate for these disorders. Key liver function test (LFT) parameters like liver enzymes, bilirubin levels, albumin, and total protein and hormones help to assess the liver's ability to perform its functions and can indicate potential liver damage or disease.[7,8]

In recent years, the concept of metabolic dysfunction associated fatty liver disease (MAFLD) has gained prominence, reflecting a paradigm shift in the understanding of fatty liver disorders. Unlike NAFLD, MAFLD recognizes the central role of metabolic dysfunction and allows for coexistence with other liver diseases, offering a more inclusive and clinically relevant framework for diagnosis and management.[4,9]

MAFLD is considered a major public health challenge predominantly related to obesity, sedentary lifestyle, and comorbidities such as diabetes and dyslipidemia. The global prevalence of NAFLD is estimated to be 30.2% (95% CI: 28.7–31.7%).[10] In India, the prevalence is estimated to be as high as 38% in adults, with the highest prevalence reported in high-risk individuals with obesity or diabetes.[11] Since a group of international experts recommended renaming NAFLD as MAFLD in 2020, it is considered a multifactorial disease in which its pathogenesis is suggestive of metabolic disorders affecting the liver involving multiple pathways involving hepatic inflammation, steatosis, and fibrosis.[12–14] Therapeutic options for MAFLD are limited to diet and lifestyle modifications targeting weight loss, management of co-morbidities (controlling blood sugar levels), and antioxidants (Vitamin E). According to recent global guidelines from the American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL), and Indian National Association for the Study of the Liver (INASL), the primary endpoint for assessing the effect of pharmacological intervention for MAFLD is reduction in fibrosis, as it is associated with considerable morbidity and mortality associated with the disease.[15]

Liv.52 DS Tablet is a polyherbal formulation consisting of extracts of *Capparis spinosa, Cichorium intybus*, Mandura Bhasma, *Solanum nigrum, Terminalia arjuna, Cassia occidentalis, Achillea millefolium*, and *Tamarix gallica*. The active ingredients of Liv.52 DS are considered to possess potent hepatoprotective properties. Liv.52, launched in 1955, has been extensively studied preclinically and clinically for its safety and efficacy in various hepatic disorders and published elsewhere.[16–18] The mechanism of action of Liv.52 is through hepatoprotective, anti-inflammatory, antioxidant, and immunomodulatory effects (Figure 1). Considering the preliminary evidence of the hepatoprotective functions of Liv.52, the present study was conducted to explore its possible role in MAFLD.

Materials and Methods

Study Population

This randomized, double-blind, placebo-controlled, prospective, multicenter study was conducted at four tertiary care hospitals in India (SRM Medical College Hospital & Research Centre, Chennai; Karnataka Gastro Centre, Bengaluru; Jeevandan Multicare Hospital, Bhopal; and Kovai Diabetes Speciality Centre & Hospital, Coimbatore) between August 2022 and September 2023.

Patients, aged 18 to 65 years, diagnosed with MAFLD according to the criteria outlined in the consensus guidelines were included in this study.[12] MAFLD was diagnosed as hepatic steatosis (through non-invasive FIBROSCAN) along with anyone of the three categories (Overweight or obesity, Type 2 Diabetes Mellitus, Lean or normal weight). Patients with fibrosis (Liver Stiffness Measurement or LSM 6.2–9.8 kPa) and steatosis (Controlled Attenuated Parameter or CAP >238 db/m) were enrolled in the study. Subjects with underlying medical conditions such as obesity, type 2 diabetes, and other comorbidities [Anemia, Gastroesophageal reflux disease (GERD), Hypertension (HTN) (Blood pressure ≥130/85 mmHg), Dyslipidemia (Plasma triglycerides ≥150 mg/dl (≥1.70 mmol/L) or Plasma HDL-cholesterol <40 mg/dl (<1.0 mmol/L) for men and <50 mg/dl (<1.3 mmol/L) for Women), etc.] included in the study. Existing modalities to control MAFLD like Life-style modifications (healthy diet, exercise targeting weight loss), antioxidants (like Vitamin E) and management of other co-morbidities (like diabetes, hypertension) were continued as per investigator's discretion; Exclusion criteria were MAFLD with advanced fibrosis (LSM > 9.8 kPa or histological evidence of advanced fibrosis), liver diseases with other etiologies like

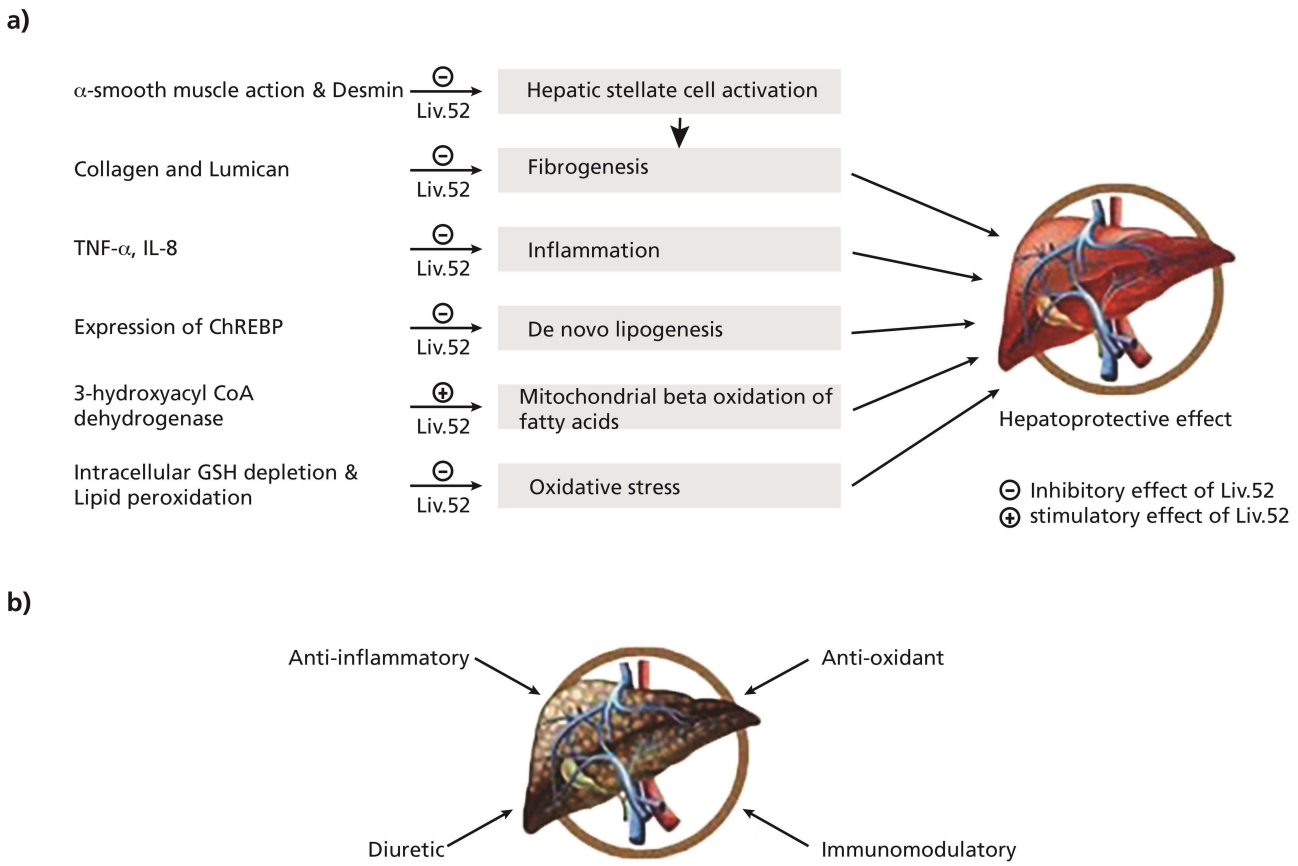

Figure 1 Mechanism of action of Liv.52. (**a**) Hepatoprotective Effect. (**b**) Benefits in Liver Fibrosis.

hepatocellular carcinoma, cirrhosis, or its complications (signs of de-compensation like portal hypertension, ascites, etc.), individuals with significant alcohol intake (Alcohol Use Disorder Identification Test or AUDIT score >8/4 for men/women) or known alcoholic liver disease, hepatitis (infective – acute or chronic, auto-immune, drug-induced, etc.), deranged metabolic parameters like type I diabetic or poorly controlled type 2 diabetic (Glycated hemoglobin, HbA1C >9%) or any other known clinically significant disease conditions like cardiovascular, respiratory, kidney diseases etc.

In this study, the treatment intervention was performed for 6 months, and subjects were followed up every 4–6 weeks telephonically or physically as per the study schedule. The subjects were advised to take Liv.52 DS or placebo at a dose of two tablets twice a day for 6 months, as per the allotted randomized group. Randomization was performed by a statistician using a computer-generated software algorithm with non-stratified blocks of equal size (three). As this is a proof-of-concept and exploratory study, the allocation of subjects in the Liv.52 DS and placebo groups was performed in a ratio of 2:1. This was performed to maximize exposure in the active group (Liv.52 DS) and minimize exposure to placebo, which also assisted in collecting additional safety information. The placebo was identical to the active study drug in terms of shape, size, color, and texture and was designed to be pharmacologically inert. Data related to protocol deviations and scheduled visits were collected, and compliance with the study drug was analyzed by counting the test products as per standard clinical research practice; both subjects and investigators were blinded to the test product (active or placebo). The objective of this exploratory study was to determine the effect of Liv.52 DS on regression and non-worsening of hepatosteatosis and fibrosis in MAFLD, as determined by FibroScan.

Measurement and Investigations

During screening, laboratory investigations, including liver function tests and liver fibroscans, were performed for all subjects. At the end of the study (6 months after the administration of the test product), these investigations were repeated

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to record any changes in LSM, CAP, and parameters, such as alanine transaminase (ALT), aspartate aminotransferase (AST), and HbA1c. Fibroscans were performed by experienced technicians at the respective institutions. The procedure was performed after overnight fasting of the right lobe of the liver, while keeping the patients in the supine position. Ten successful acquisitions were performed on the same patient, IQR/M ratios were calculated for LSM and CAP values (interquartile range [IQR] and median [M]), and the IQR/M level was validated to be <0.3 as a reliable indicator of intrinsic variability. No failure of the Fibro Scan procedure was reported.

Statistical Analysis

Continuous data were analyzed using parametric and non-parametric tests depending on the normality of the data. Intergroup comparisons were performed by unpaired *t*-test with p value less than 0.05, considered to be statistically significant. Categorical variables were summarized as numbers and percentages. All statistical tests and confidence intervals were two-sided. Statistical analysis was performed using GraphPad Prism Soft-ware Version 6.07 for Windows (GraphPad Software, San Diego, California, USA). Randomization was performed by a statistician using a computer-generated software algorithm with non-stratified blocks of equal size (three). As this was a pilot exploratory study, no formal sample size calculations were performed.

Ethics Standard

The study protocol was approved by the respective institutional ethics committee and was prospectively registered with the Clinical Trials Registry, India (CTRI/2022/03/041481). This study was conducted in accordance with the ethical standards of the World Medical Association Declaration of Helsinki (1975, revised in 2013) for medical research involving human subjects, and the Guidelines of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) – Good Clinical Practices (GCP). All patients provided written informed consent prior to screening.

Results

A total of 79 subjects were screened, of which 52 were randomized according to the eligibility criteria of the study protocol. The details of the subjects considered for screening, randomization, discontinuation, and completion are shown in the CONSORT diagram (Figure 2).

Three major protocol deviations necessitated exclusion of these subjects from the analysis. One subject was unable to follow the dietary restrictions (as advised by the investigator), and the other two had a steatosis score of CAP < 200 (incorrect inclusion), indicating no significant steatosis.

A total of 22 patients with diabetes with their preexisting medications at a stabilized dosage (Table 1) were included in the study (18 in the Liv.52 DS group and 4 in the placebo group). The baseline demographic characteristics of the participants are presented in Table 1.

Fibroscan Assessment

Detailed assessments related to FibroScan at baseline and 6 months are presented in Tables 2, 3, Figures 3 and 4.

The mean LSM value indicating fibrosis at baseline was 7.33 kPa in the Liv.52 DS and 7.45 kPa in the placebo group. At baseline, the difference in the mean LSM values between the two groups was not statistically significant. Most of the subjects at baseline fibrosis levels between 6.1 and 8.1 kPa (F1) with 27 (87%) subjects in Liv.52 DS group and 12 (75%) subjects in placebo group belonging to this category and remaining 4 (13%) subjects in Liv.52 DS group and 4 (25%) subjects in placebo group belonging to 8.2 to 9.6 kPa (F2).

Fibroscan parameter related to fibrosis, LSM value showed reduction after 6 months with mean value reducing from 7.33 kPa to 6.05 kPa (Change From Baseline or CFB = 17.54%) in Liv.52 DS group indicating a shift of the mean value from fibrosis (>6.0 kPa) to almost no significant fibrosis (<6.0 kPa) as per INASL cutoff.[11] The mean LSM value in placebo group reduced from 7.45 kPa to 6.94 kPa (CFB = 7.3%). At the end of the study, the Liv.52 DS group showed a statistically significant reduction in the mean LSM value compared to the placebo group (p = 0.007).

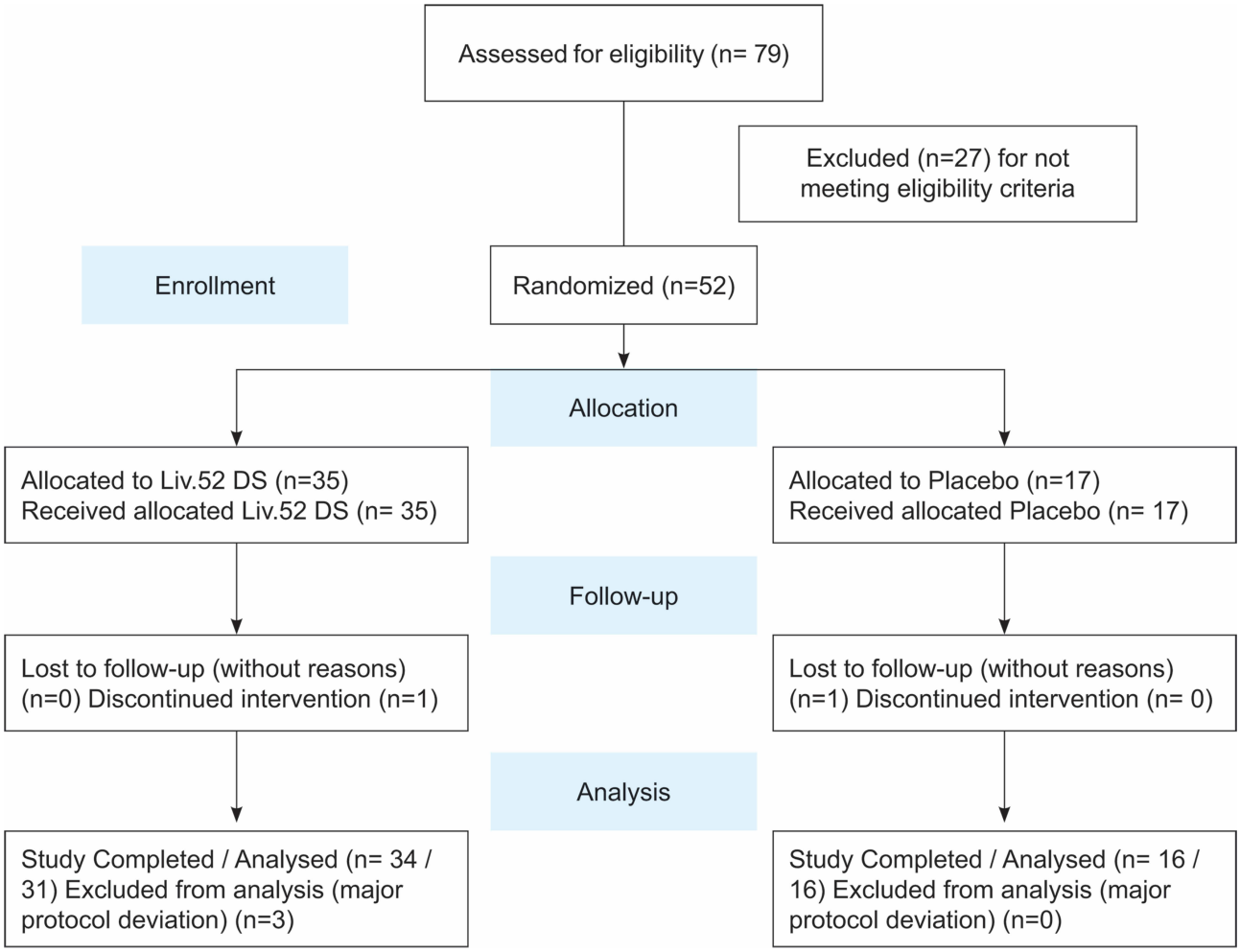

Figure 2 CONSORT DIAGRAM: Overview of the patient enrollment and treatment assignment.

For shift in grade of fibrosis and steatosis, in the Liv.52 DS group, 13 of the 31 subjects (42%) with fibrosis at baseline (>6.1 kPa) shifted to no significant fibrosis (<6.0 kPa) at EOS. All patients with F2 (significant fibrosis) at baseline in the Liv.52 DS group shifted to not significant fibrosis at the EOS. In contrast, in the placebo group, only four of the 16 subjects (25% of subjects) with fibrosis at baseline (>6.1 kPa) shifted to significant fibrosis unlikely (<6.0 kPa) at EOS.

Table 1 Demographic Characteristics of Study Population

Characteristics	Liv.52 DS N=35	Placebo N=17
Male: Female	20:15	10:7
Age (years); Mean±SD	45.89±10.38	48.59±10.87
Waist circumference (cms); Mean±SD	96.17±8.38	95.03±9.86
Height (cms); Mean±SD	167.6±8.71	167.1±10.24
Weight (kgs); Mean±SD	79.54±11.81	80.5±15.92
BMI (kg/m^2); Mean±SD	28.17±3.36	28.64±4.59

(*Continued*)

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Table 1 (Continued).

Characteristics	Liv.52 DS N=35	Placebo N=17
Comorbidities; n (%)		
Diabetes (Type 2)	18 (51.4%)	4 (23.5%)
Hypertension	4 (11.4%)	7 (41.17%)
Dyslipidemia	8 (22.85%)	3 (17.6%)
Details of concomitant medications for Diabetes (Type 2); n (%)		
Metformin	18 (51.4%)	4 (23.5%)
Sulfonylurea (Glimepiride)	2 (5.7%)	–
Gliflozin (Remogliflozin)	2 (5.7%)	–
DPP4 (Vildagliptin)	3 (8.5%)	–
α-glucosidase inhibitor (Voglibose)	1 (2.8%)	–

Abbreviations: BMI, body mass index; DPP4, Dipeptidyl peptidase 4.

Table 2 Fibro Scan (LSM and CAP Values)

Fibro Scan	Liv.52 DS (N=31)	Placebo (N=16)	*p* value
LSM (kPa)			
Baseline	7.33 (0.68)	7.45 (0.92)	0.6201 (ns)
EOS	6.05 (0.93)	6.94 (1.47)	0.0144
CFB	−1.29 (0.78)	−0.51 (0.94)	0.0054
%CFB	−17.54 (10.46)	−7.29 (13.3)	0.007 (<0.05)
CAP (db/m)			
Baseline	270.3 (37.02)	272.6 (24.62)	ns
EOS	240.9 (42.9)	256.5 (31.74)	ns
CFB	−29.42 (32.63)	−16.13 (36.92)	ns
%CFB	−10.67 (11.6)	−5.33 (13.8)	ns

Abbreviations: LSM, liver stiffness measurement; CAP, controlled attenuated parameter; ns, not significant; EOS, end of study; CFB, change from baseline.

Table 3 Shift in Grade of Fibrosis and Steatosis

Shift in Liver Fibrosis Grade (LSM)								
LSM Score: (kPa)	**Liv.52 DS, N=31**				**Placebo, N=16**			
	Baseline		**EOS**		**Baseline**		**EOS**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
<6.0 kPa (F0): Significant Fibrosis Unlikely	0	0	13	41.9	0	0	4	25
6.1 to 8.1 kPa (F1)	27	87.1	18	58.1	12	75	9	56.3
8.2 to 9.6 kPa (F2): Significant Fibrosis	4	12.9	0	0	4	25	3	18.8

(*Continued*)

Table 3 (Continued).

Overall improvement in steatosis grade (CAP)		
	Liv.52 DS (N=31)	**Placebo (N=16)**
	EOS n (%)	**EOS n (%)**
No Steatosis (S0) [a]	15 (48%)	2 (12.5%)
Improvement in steatosis grade [b]	7 (23%)	6 (37.5%)
No change in grade	8 (26%)	6 (37.5%)
Deteriorate	1 (3%)	2 (12.5%)
Overall improvement in steatosis grade [a+b]	22 (71%)	8 (50%)

Abbreviations: LSM, liver stiffness measurement; CAP, controlled attenuated parameter; ns, not significant; EOS, end of study; N, total number of subjects; n, number of subjects.

Similar to LSM, an improvement in CAP values was also observed. The mean CAP value, indicating steatosis at baseline, was 270 db/m in the Liv.52 DS group and 272 db/m in the placebo group (statistically non-significant). Reduction in mean CAP value was observed from 270 db/m to 240.9 db/m (CFB = 10.6%) in Liv.52 DS group and from 272.6 db/m to 256.5 db/m (CFB = 5.3%) in placebo group. However, the difference in the reduction in the mean CAP value of Liv.52 DS was not statistically significant compared with placebo.

The steatosis grades considered in this study were S0:<238 db/m, S1:238–259 db/m, S2:260–292 db/m, and S3:293 dB/m]. Overall grade improvement in steatosis was observed in the Liv.52 DS group in 22 subjects (71%), with 15 subjects (48%) coming down from S1, S2, S3 to S0; 7 subjects (23%) showed grade reduction but not to S0; 8 subjects (26%) showed no change in grade and only 1 subject (3%) showed grade deterioration at the end of treatment for 6 months. In the placebo group, an overall improvement in steatosis grade was observed in 8 subjects (50%), with only 2 subjects (12.5%) coming down from S1, S2, and S3 to S0. Six subjects (37.5%) showed grade reduction but not S0, six subjects (37.5%) showed no change in grade, and two subjects (12.5%) showed grade deterioration at the end of 6 months (Table 3).

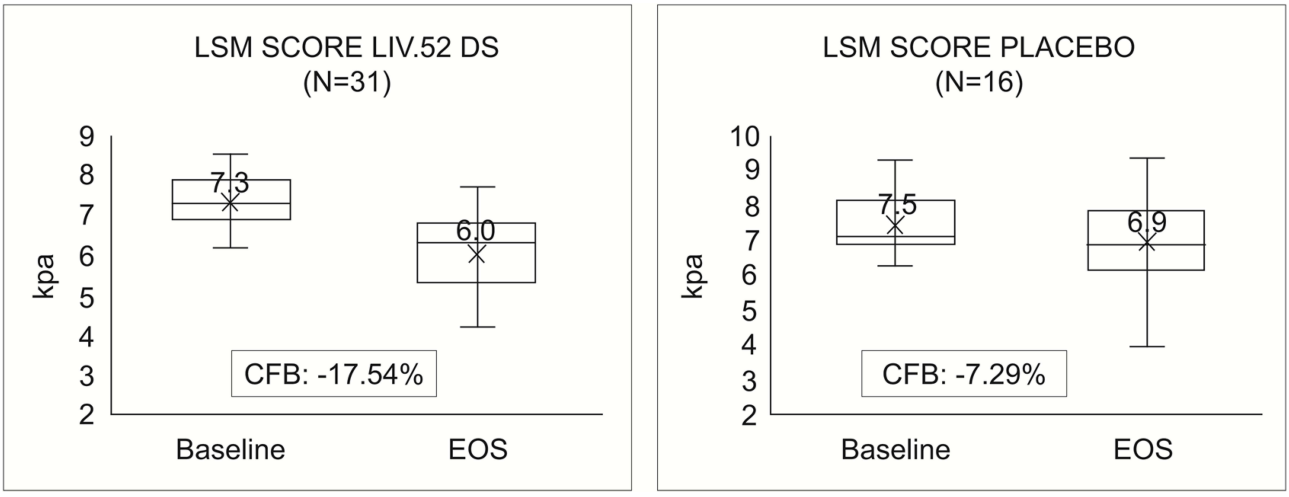

Figure 3 Mean Change in LSM values (kPa). Comparisons between the groups were performed using unpaired t-tests. Data were collected after six months of randomization.
Abbreviations: LSM, liver stiffness measurement; CFB, change from baseline; EOS, end of the study.

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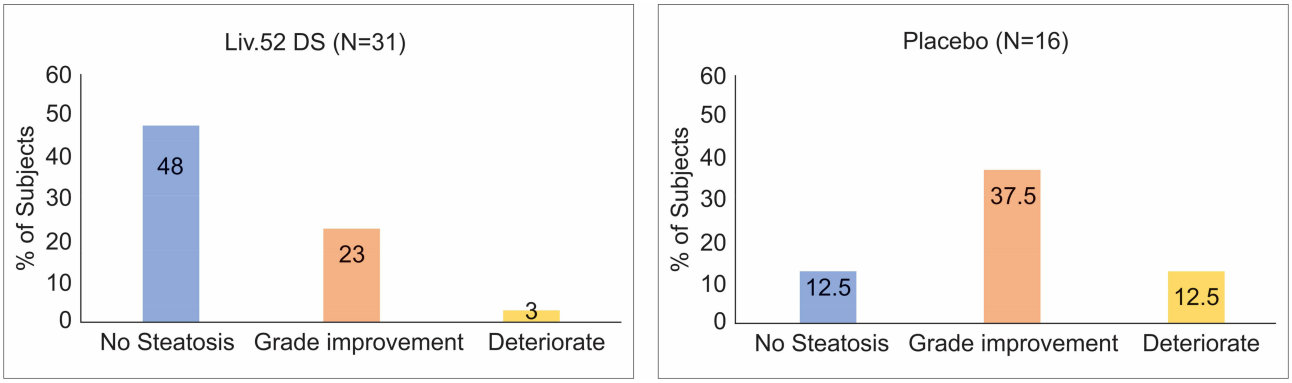

Figure 4 Comparison of Overall Improvement in Steatosis at the end of study.

Assessment of Laboratory Parameters

The majority of subjects in both the Liv.52 DS and placebo groups had normal baseline ALT and AST levels. Liver enzyme levels showed no worsening from baseline in either the Liv.52 DS or placebo groups after treatment of 6 months. No worsening of HbA1C was observed in either group (Table 4).

Assessment of Safety

Liv.52 DS was well tolerated for 6 months, as none of the subjects had any issues related to tolerability and were able to complete the treatment dose of two tablets twice daily for 6 months. Adverse events were analyzed for all enrolled subjects (safety population), and a total of 44 adverse events were reported in the study, including fever, cold, and headache, of which 31 adverse events were reported in the Liv.52 DS group in 20 (57%) subjects and a total of 13 adverse events were reported in the placebo group in 11 (65%) subjects. Common adverse events were fever (9 in active

Table 4 Laboratory Parameters

Subjects with Normal Liver Enzymes at Baseline, N (%)		
Parameters	**Liv.52 DS (N=31)**	**Placebo (N=16)**
AST	29 (94%)	14 (88%)
ALT	30 (97%)	15 (94%)
Laboratory parameters at baseline and EOS, Mean (SD)		
ALT/SGPT (U/L)		
Visits	**Liv.52 DS (N=31)**	**Placebo (N=16)**
Baseline	21.35 (16.33)	28.13 (35.33)
EOS	22.54 (11.49)	25.19 (16.9)
CFB	1.19 (14.74)	−2.94 (37.69)
AST/ SGOT (U/L)		
Baseline	21.96 (6.85)	24.63 (13.72)
EOS	25.2 (8.19)	30.56 (31.6)
CFB	3.24 (8.74)	5.94 (35.27)

(*Continued*)

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Table 4 (Continued).

HbA1C (%)		
Baseline	7.06 (1.11)	6.29 (0.51)
EOS	6.97 (1.48)	6.21 (0.76)
CFB	−0.09 (1.41)	−0.08 (0.88)

Abbreviations: AST, aspartate aminotransferase; ALT, alanine transaminase; SGPT, serum glutamic pyruvic transaminase; SGOT, serum glutamic oxaloacetic transaminase; HbA1c, glycated haemoglobin; SD, standard deviation; U/L, upper limit; EOS, end of study; CFB, change from baseline.

and 5 in placebo), cold (3 in active), and headache (3 each in active and placebo). All adverse events were mild to moderate in nature, and none were found to be related to the study drug as per the World Health Organization – Uppsala Monitoring Centre (WHO-UMC) causality assessment, and there were no serious adverse events in the study.[19]

Discussion

Liv.52 DS Tablet is a hepatospecific formulation designed to manage liver disorders. The synergistic polyherbal activity of Liv.52 DS in MAFLD is attributed to various ingredients that possess potent hepatoprotective and hepatocurative properties. *Capparis spinosa* (Himsara) and *Cichorium intybus* (Kasani) containing esculetin and p-methoxybenzoic acid has antioxidative and hepatoprotective effects.[20–23] While *Solanum nigrum* (Kakamachi) significantly shields hepatocytes from the DNA damage brought on by free radicals, Arjunolic acid and flavonoids, separated from Arjuna, raised glutathione levels.[24–27] Antioxidative and hepatoprotective effects were also found in *Cassia occidentalis* (Kasamarda) and *Achillea millefolium* (Biranjasipha).[28,29] Ingredients Mandura bhasma, *Terminalia arjuna* (Arjuna), and *Tamarix gallica* (Jhavaka) have hepato-protective activities mainly mediated through their antioxidant properties.[27,30,31] Additionally, anti-viral property has been reported for *Capparis spinosa, Solanum nigrum,* and *Terminalia arjuna*.[32–34] The balanced blend of herbs and mineral in the intended combination is expected to deliver hepatoprotective effects through the synergistic effects derived from its active constituents such as alkaloids, glycosides, polysaccharides, tannins, flavonoids, saponins, and minerals such as Calcium, Magnesium, Zinc, Copper, and others.

The effect of Liv.52 as a hepatoprotective agent was tested in different studies with experimental models like, Hepatoxin and Drug-induced liver injury (DILI), Alcohol-induced liver damage (ALD), High fat diet-induced fatty liver, Chologogue, and Choleretic activity, etc.[17] The mechanism of action of Liv.52 in fatty liver diseases is due to the improvement in fat metabolism, attenuating hepatic stellate cell activation, and reducing fibrogenesis.[35]

The effects of Liv.52 DS on liver function based on multiple clinical studies have shown hepatoprotective outcomes with improvement in clinical symptoms and liver enzyme levels.[18,36] The present study results show a preliminary trend in the effect of the herbal formulation Liv.52 DS in reducing liver fibrosis (indicated by a significant reduction in LSM values in Fibroscan, and most of the patients converted from fibrosis to almost no significant fibrosis) in patients with MAFLD after 6 months of treatment. Although some medicines have documented the effect of a drug on NAFLD,[37] this randomized, double-blind, placebo-controlled study showed the effect of herbal formulations in MAFLD through specific endpoints such as LSM and CAP by FibroScan, as recommended by the leading hepatology guidelines (AASLD, EASL, INASL).

The LSM score indicating liver fibrosis is an ideal endpoint for MAFLD, and the study results show preliminary encouraging results with a statistically significant reduction in LSM in the Liv.52 DS group compared to placebo at 6 months. In the Liv.52 DS group, there was a 17.54% [95% CI (−21.38, −13.71)] reduction in mean LSM values as compared to placebo group with a reduction of 7% [95% CI (−14.38, −0.2)] from the baseline after 6 months in the study, which was found to be statistically significant ($p < 0.007$). A shift in the mean value from fibrosis (>6.0 kPa) to almost no significant fibrosis (<6.0 kPa), as per the INASL cutoff, was achieved in the Liv.52 DS Group.

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CAP score, which indicates hepatic steatosis, is an important pathological component of MAFLD. In this study, we observed an improvement in liver steatosis in the Liv.52 DS group after treatment of 6 months. Furthermore, 71% of the subjects in the Liv.52 DS group showed improvement in CAP grade. A possible mechanism for the beneficial effect of Liv.52 DS can be drawn from the outcome observed in the in vitro study, where the effect of Liv.52 DS on the upregulation of cellular antioxidants and glucose uptake in oleic acid-induced hepatic steatosis in HepG2 cells, an in vitro model for NAFLD, was studied. Findings in this study indicated that Liv.52 DS effectively attenuated molecular perturbations associated with NAFLD in HepG2 cells.[38] The beneficial effect of Liv.52 DS seen in this study is a further extension of another clinical study conducted in Indonesia, where beneficial effects were observed in patients with NAFLD after treatment with Liv.52 DS in certain laboratory parameters.[39]

One of the challenges of using LSM and CAP cutoff values to infer the severity of liver fibrosis and steatosis is the non-uniformity in their cutoff values, according to various guidelines. According to the AASLD guidelines, a Vibration Controlled Transient Elastography (VCTE)-LSM <8 kPa can rule out advanced fibrosis, LSM between 8 and 12 kPa may be associated with fibrotic non-alcoholic steatohepatitis (NASH), and LSM >12 kPa can be associated with advanced fibrosis. The EASL guidelines were recently updated in 2023 on the use of non-invasive tests for the evaluation of liver disease severity and prognosis,[40] and a cut-off LSM of <8 kPa is indicated to rule out advanced fibrosis in clinical practice. In the Indian context, the INASL guidelines,[41] suggest a cut-off for significant fibrosis unlikely (F0, F1) of less than 6.0 kPa. As this study was conducted in India in an Asian population, the mean LSM reaching the cutoff for significant fibrosis unlikely (<6.0 kPa) as per INASL guidelines may be considered suitable for interpreting the outcomes of Liv.52 DS in this study.

Although liver biopsy is considered the gold standard for assessing the liver condition in MAFLD, several studies have indicated the accuracy of non-invasive measurements, such as LSM and CAP by fibroscan, for measuring hepatic fibrosis and steatosis. In the AASLD guidelines, the importance of non-invasive assessments, such as FibroScan, for the detection and quantification of fibrosis and steatosis is enumerated in detail. Furthermore, these assessments are essential to overcome the limitations of risk, cost, and resource utilization of liver biopsies.[42] Similarly, in the EASL guidelines, non-invasive assessment is recommended as a first-line assessment for the identification of individuals with increased metabolic risk for NAFLD, reducing the need for liver biopsies.[43] Also, this study has shown a better LSM outcome of Liv.52 DS as compared to 10% reduction ($p = 0.0261$) from baseline as seen in a single-arm clinical study with a dual peroxisome proliferator activated receptor agonist in patients with NAFLD with diabetic dyslipidemia (NAFLD and metabolic dysfunction) for a duration of 6 months.[44]

Liver enzymes (ALT and AST) are markers of hepatic inflammation and important components of MAFLD. The liver enzyme levels in this study are in line with several studies that have indicated that liver enzyme levels may be completely normal in subjects with this condition.[41,45] In this study, we also found that the majority of subjects had normal liver enzyme levels at baseline; however, a significant finding was that there was no worsening of liver enzymes after treatment of 6 months, indicating control of inflammation.

A possible mechanism underlying the ameliorative effect of Liv.52 DS can be considered, based on the outcomes observed in experimental NASH model. The results obtained in experimental animals indicate that the Liv.52 DS extract effectively reverses metabolic and histological changes associated with high-fat diet (HFD) induced NASH.[46] The hepato-protective effect of Liv.52 has also been reported in other independent clinical studies involving patients with chronic liver disease.[47] Also, some studies have indicated that weight reduction in overweight or obese patients with non-alcoholic fatty liver disease can lead to a reduction in hepatic fibrosis (LSM).[47] However, in our study, weight reduction was not observed between baseline and EOS. Therefore, the efficacy of Liv.52 DS in reducing fibrosis was further indicated by a significant reduction in the mean LSM value, despite no reduction in the mean weight between the baseline and EOS.

The study drug was well tolerated, as no drug-related adverse events were reported (evaluated according to the causality assessment defined by the WHO). No case of nephrotoxicity was observed, as serum creatinine and creatinine kinase levels were well within the normal limits/NCS for all subjects at the EOS (which is a concern for any herbal formulation). This further validates the safety of the Liv. 52 DS, which has been described in various publications available for this formulation.

Along with the robust methodology adopted in this research, certain limitations should be considered before interpreting the outcomes of this study. First, the number of subjects in this study was small (N = 51). However, considering the pilot and exploratory nature of the study, this small number of subjects was considered optimal to explore the preliminary efficacy of the herbal formulation and to confirm the possibility of proceeding with a larger sample size. "Liver biopsy" which is considered as gold standard for such condition was not opted due to its limitation in the real world as expressed by various guidelines also, additionally, due to preliminary exploratory nature of the study a non-invasive measurement like Fibroscan was more suitable. Additionally, in real-world settings, liver biopsies for routine MAFLD are rarely considered. This study adhered to the current therapeutic guidelines for this condition. Non-homogeneous subjects with different comorbidities may also pose different challenges in data interpretation. Co-morbidities such as diabetes and dyslipidemia are thought to significantly affect liver condition and disease progression in MAFLD, necessitating the contemplation of a robust, powered, longer-duration study with a more granular representation of patients with MAFLD and specific comorbidities and further follow-up after the 6-month intervention to assess relapse, which further confirms and validates the efficacy of the study drug.

Owing to the lack of an established pharmacological agent for the management of MAFLD, further studies with statistically derived large numbers of subjects and a longer duration of intervention are encouraged to assess and validate the beneficial effects of Liv.52 DS in this condition.

Conclusion

As the current management options for MAFLD are limited to lifestyle modifications, antioxidants, and management of comorbidities, Liv.52 DS may be well-suited to meet the unmet need for a safe and well-tolerated formulation for this condition. Based on the preliminary favorable trend observed for 6 months in the treatment of MAFLD with robust assessment using Fibroscan, Liv.52 DS seems to have the potential to be an effective treatment option for MAFLD, fulfilling the unmet need for safe medication along with lifestyle modification.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

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Disclosure

Dr. Rajesh Kumawat is an employee of Himalaya Wellness Company. The authors declare that they have no other conflicts of interest for this work.

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