ORIGINAL ARTICLE

Evaluation of the safety and efficacy of CurcuVail® in patients with non-alcoholic fatty liver disease - A prospective randomized, double blind, placebo controlled, parallel group study

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Abstract

Introduction: The prevalence of non-alcoholic fatty liver disease (NAFLD) has increased to 38.2%. Curcuminoids hold promise, but curcumin's clinical use is limited. CurcuVail® improves absorption and effectiveness. This study assesses CurcuVail®'s efficacy, safety, and tolerability in NAFLD patients. **Materials and Methods:** We conducted a prospective, double-blind, placebo-controlled, and parallel-group study in 30 NAFLD patients. Subjects were assigned at random to receive either CurcuVail® or Placebo. The primary efficacy endpoint was the improvement in fatty liver grading based on liver ultrasound from baseline to day 60. Secondary efficacy endpoints included changes in aspartate aminotransferase (AST) to platelet ratio index (APRI) score, Fibrosis score, controlled attenuation parameter (CAP) score, total cholesterol (TC), and liver enzymes. **Results:** The demographic data of both groups were identical. The overall mean change in NAFLD grading based on liver USG from baseline to the end of treatment was observed to be −0.27 ± 0.458 in the test group and −0.07 ± 0.258 in the placebo group. Remarkable and statistically significant differences were observed between the test and placebo treatment groups from baseline to the end of treatment in various parameters, including mean changes in APRI score (−0.38 ± 0.190 vs. −0.18 ± 0.286), Fibrosis Score (−0.91 ± 0.364 vs. −0.17 ± 0.135), and CAP score (−20.67 ± 6.651 vs. −5.27 ± 3.105). Significant reductions were also observed in mean changes of TC, serum alanine aminotransferase, and serum AST from baseline to the end of treatment. No safety or tolerability issues were reported. **Discussion:** CurcuVail® was found to improve NAFLD grading, FibroScan® parameters, and biochemical markers associated with NAFLD with a good safety profile. However, long-term investigations are necessary to fully evaluate the clinical efficacy and safety profile of the test product. **Conclusion:** CurcuVail®, a dietary supplement, was found to be clinically safe and effective in NAFLD subjects after 60 days of administration.

Key words: Curcumin, hepatic steatosis, lipid levels, liver enzymes, non-alcoholic fatty liver disease

INTRODUCTION

Accounting more than 2 million deaths, liver diseases are responsible for 4% of the mortality worldwide, about 2/3rd of which occurs in the male subset of population. Deaths are largely identified as complications of cirrhosis and hepatocellular carcinoma, along with acute hepatitis which accounts for a smaller ratio of deaths. Cirrhosis ranks as the 11th most prevalent cause of mortality. The most predominant causes of cirrhosis are linked to viral hepatitis, alcohol and non-alcoholic fatty liver disease (NAFLD).[1]

Over the last few decades, the prevalence of NAFLD has increased to 38.2% (2016–2019). In the recent years, these rates of prevalence have driven parallel to pandemic of obesity and type 2 diabetes mellitus.[2] NAFLD is characterized by excessive hepatic fat accumulation, linked to insulin

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resistance and identified by the presence of steatosis in more than 5% of hepatocytes in connection with metabolic risk factors (obesity and type 2 diabetes mellitus) and in the absence of excessive alcohol consumption (≥30 g/day in men and ≥20 g/day in women) or other chronic liver diseases. NAFLD comprises two distinct pathological conditions with varied prognosis: NAFL that includes steatosis with or without mild inflammation and non-alcoholic steatohepatitis (NASH) which is additionally characterized by the presence of hepatocellular injury (hepatocyte ballooning) and includes various degrees of fibrosis, cirrhosis, and hepatocellular carcinoma. Disease progression and response to treatment is heterogenous and may vary to a large extent among patients.[3,4] Extensive scientific research has linked NAFLD to metabolic syndrome, type 2 diabetes, dyslipidemia, insulin resistance, oxidative stress, and lipid peroxidation injury in inclusion to liver pathogenesis. Genetic predisposition, epigenetic factors, and role of environment factors have been associated with risk factors that lead to NAFLD.[5]

Lifestyle modifications include physical activity, exercise, caloric restriction, and time restricted feeding. These approaches focus on controlling bodyweight and metabolic disorders. Dietary and lifestyle changes remain the cornerstone of management because there is no FDA-approved treatment for NAFLD. Use of insulin-sensitizing agents, lipid-lowering agents, hepatoprotective drugs, and several medications are in the course of development, while pioglitazone and Vitamin E persists as a strategy for disease management and prevents progression of NAFLD to NASH.[6] The efficacy of these therapies, however, is inadequate; some drugs may even cause liver toxicity. Therefore, it is crucial to explore and develop novel therapies that demonstrate both effectiveness and safety in treating NAFLD.

Curcuminoids have emerged as potential options for the treatment of various pathological conditions due to their pleiotropic effects. Curcumin, the primary bioactive unit of curcuminoids, is non-toxic and non-mutagenic. It is derived from the herbal plant Turmeric (*Curcuma longa*) of the *Zingiberaceae* family. Curcumin is a renowned yellow pigment with medicinal properties, widely used as a culinary spice. The unique structure of curcumin, characterized by phenolic hydroxyl groups, a heptadiene chain, and a diketone moiety, is responsible for its therapeutic activities. Turmeric reduces histamine production, improves circulation to eliminate toxins from joints, boosts cortisol's anti-inflammatory effects, and aids digestion as a cholagogue by promoting bile secretion and liver detoxification.[7]

Despite the significance of hepatic disorders, the number of research studies examining the effects of curcumin on the liver diseases remains limited. In a study conducted by Adhvaryu *et al*., *C. longa*, in a herbal formulation with *Tinospora cordifolia*, demonstrated significant improvement in the prevention of hepatotoxicity caused by anti-tuberculosis treatment.[8] Various pre-clinical studies have confirmed that curcumin prevents the progression of hepatic disorders including NAFLD and improves associated lab parameters.[9-11]

However, curcumin's clinical utility is constrained by its diminished water solubility, restricted absorption, and subsequent low bioavailability. CurcuVail developed by K Patel Phyto Extractions Pvt. Ltd-Mumbai, India, is a unique curcumin formulation utilizing dispersion technology to enhance bioavailability and absorption in the body, resulting in quicker effectiveness. It is available as a dietary supplement in the form of 250 mg capsules containing *C. longa* Extract with 35% Curcuminoids. The objectives of this study are to evaluate the efficacy of CurcuVail® in patients with NAFLD and to assess its safety and tolerability.

METHODS

Study Settings and Design

The present study was carried out at a single investigational site (Sanjivani Super Speciality Hospitals Pvt. Ltd.) in Ahmedabad, Gujarat, India. A prospective, double-blind, placebo-controlled, and parallel-group study was conducted on adult male and female patients with NAFLD.

Screening

To include/exclude subjects into the study, an initial screening was carried out using demographic criteria and a fatty liver grade scale (Grade 1–3) based on patients diagnosed with liver ultrasonography. The subjects underwent thorough screening based on their prior medical history (including hepatic, coronary, renal, pulmonary, and thyroid diseases), medication history, physical examination, body weight, vital signs, height, BMI, urine pregnancy test (for females of childbearing potential), Fibroscan®, liver ultrasound, and laboratory tests (Complete Blood Count, aspartate aminotransferase (AST) to platelet ratio index [APRI] Score, Lipid Profile, Serum AST and Serum alanine aminotransferase [ALT]). The study excluded participants with secondary causes of NAFLD, history of immoderate alcohol consumption or hypersensitivity, other liver infections, and those who were pregnant or lactating. On written informed consent process, a total of 30 patients were enrolled into the study after screening.

Randomization and Masking

A block randomization code (sheet) was generated using statistical analytical system (SAS) software, version 9.4, with a 1:1 allocation ratio for CurcuVail® and Placebo treatment. Patients were assigned a unique screening number (starting from S0101), indicating screening, site ID, and sequential patient number. The screening numbers of screen failure

patients were not reused. Patients were randomized using unique IDs (starting from R00X) in chronological order. Investigators and subjects were masked to the treatment group allocation, and appropriate masking was ensured through identical appearance, packaging, and labeling of the product bottles.

Allocation

Subjects were then randomly allocated into two groups to receive either CurcuVail® (n = 15) or Placebo (n = 15). Subjects underwent four visits during the 60-day treatment period: a screening visit at Day −14–−1 (Visit 1), a baseline/randomization visit at day 0 (Visit 2), an interim visit at Day 30 ± 2 (Visit 3), and an end of treatment visit at day 61 ± 2 (Visit 4). In addition, a telephonic safety follow-up was conducted on day 67 ± 2.

Study Procedure

Participants were instructed to take either CurcuVail® capsule (250 mg/capsule) or placebo (250 mg/capsule) twice daily with meals starting on day 1 and continuing throughout the study. Treatment compliance was assessed at subsequent visits (Visits 3 and 4) based on recorded details in patient diaries. Compliance was established as consuming 75–125% of the planned doses. Non-compliance was defined as taking <75% or >125% of the planned doses or missing scheduled administrations for one continuous week until the end of treatment visit, resulting in exclusion from the per-protocol (PP) population. Unused or empty product kits were accounted for in the accountability logs.

Study Outcomes

The primary efficacy endpoint was the percentage of patients with improved fatty liver grading and changes in fatty liver grading based on liver ultrasound (USG) from baseline to day 60. Secondary efficacy endpoints included changes in APRI score, controlled attenuation parameter (CAP) score and Fibrosis score based on FibroScan® assessment, and lipid profile total cholesterol (TC), and liver enzymes (ALT and AST) from baseline to day 60. Adverse events (AE) and serious AE (SAE) were recorded as safety endpoints.

Data Collection

Data collection occurred in two phases. First, face-to-face examinations were conducted by examiners at the study site during the initial visit, subsequent visits, and end-of-treatment visit to collect demographic details, clinical history, medication history, and liver ultrasound (USG) data, which were recorded in the designed Case Report Forms. Following the completion of treatment, safety assessments were conducted through telephonic interviews. The data were managed by the contract research organization (CRO) in accordance with their data management policy.

Data Analysis

Statistical analyses were performed using SAS® version 9.4. Continuous data were presented as mean (±SD), while categorical variables were expressed as frequency and percentage. The primary efficacy endpoint, measured as the proportion of patients showing improvement in fatty liver grading based on liver ultrasound (USG) from baseline to day 60, was assessed using a two-sample proportion test. Changes in fatty liver grading, APRI score, CAP score, and Fibrosis score from baseline to day 60 were compared between the two groups using a two-sample t-test. Statistical tests were conducted at a significance level of 5% ($P < 0.05$). Both efficacy and safety analyses were conducted on the PP populations, as no patients discontinued early from the study. All reported AEs and SAEs were coded and classified according to the Medical Dictionary for Regulatory Activities (MedDRA) version 24.1, and grouped by preferred term and system organ class.

Human Participant Protection

The study was approved by the Institutional Ethics Committee of Sanjivani Super Speciality Hospitals Pvt. Ltd. in Ahmedabad, Gujarat, India. The study adhered to the protocol and complied with ethical principles outlined in the Declaration of Helsinki, the international council for harmonization guidelines, the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants by the Indian Council of Medical Research, and the Good Clinical Practice Guidelines for Clinical Trials in Ayurveda, Siddha, and Unani Medicine by the Department of Ayush, Ministry of Health and Family Welfare, Government of India. The clinical site and CRO implemented policies and mechanisms to ensure data quality. No deviations from the protocol were observed.

RESULTS

A total of 35 patients were screened for inclusion in the study. Of these, five patients were excluded based on the exclusion criteria outlined in the study protocol. The flow of participants through the various stages of the study is depicted in Figure 1. All 30 patients who were enrolled in the study completed it successfully.

The baseline characteristics of the two study populations are outlined in Table 1. On randomization, each arm of the study consisted of 15 patients. The gender distribution between the two arms was identical, with both groups being predominantly male. In fact, 80% of the patients in each group were male [Table 1].

Table 1: Baseline demographics characteristics of study groups

Characteristics	CurcuVail® 250 mg (*n*=15)	Placebo (*n*=15)
Age, years	31.4±6.08	36.9±10.50
Gender		
Male	12 (80.0)	12 (80.0)
Female	3 (20.0)	3 (20.0)
Race and ethnicity		
Asian race	15 (100)	15 (100)
Not Hispanic or Latino ethnicity	15 (100)	15 (100)

Values are expressed as mean±standard deviation (range) or *n* (%)

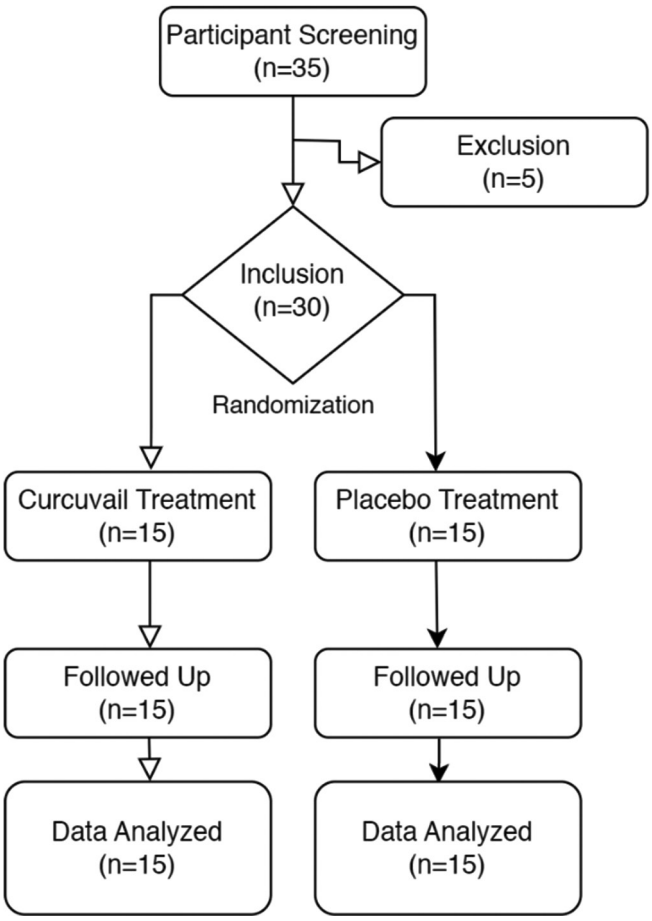

Figure 1: Flow of participants in study

The mean age of the population was 31.4 ± 6.08 years in the CurcuVail® group and 36.9 ± 10.50 years in the placebo group. All subjects included in the study were of Asian ethnicity, with no representation from Latino or Hispanic populations. In short, the demographic data of both groups were observed to be identical, indicating that any observed differences between the two groups can be attributed to the intervention rather than to baseline differences between the groups.

The improvement in NAFLD (fatty liver) grading and between the two treatment groups was compared as a change from baseline to Visit 4 (Day 60 ± 2), based on liver USG. The mean change and *P*-value for the primary and secondary endpoints, including the change in APRI, CAP score and Fibrosis score based on FibroScan®, and changes in lipid profile and liver enzymes (TC, serum ALT and AST), are presented in Table 2 and Figure 2.

A proportionate improvement was observed in all primary and secondary endpoint parameters of the study in the test treatment group compared to the placebo treatment group. A distinct improvement was observed in the primary endpoint, the fatty liver grading scale, after 60 days from baseline. In the test treatment group, 4 patients (26.7%) showed improvement on the scale, compared to 1 patient (6.7%) in the placebo group. However, using a two-sample proportion test, the findings did not show a statistically significant difference between the test and placebo groups.

The overall mean change in NAFLD grading based on liver USG from baseline to the end of treatment was observed to be −0.27 ± 0.458 in the test group and −0.07 ± 0.258 in the placebo group. The difference between the two groups was statistically significant ($P < 0.05$) in favor of the test treatment group [Table 2 and Figure 2].

Remarkable and statistically significant differences were observed between the test and placebo treatment groups from baseline to the end of treatment in various parameters, including mean changes in APRI score (−0.38 ± 0.190 vs. −0.18 ± 0.286), Fibrosis Score (−0.91 ± 0.364 vs. −0.17 ± 0.135), and CAP score (−20.67 ± 6.651 vs. −5.27 ± 3.105) [Figure 3]. Significant reductions were also observed in mean changes of TC, serum ALT, and serum AST from baseline to the end of treatment [Table 2 and Figure 4].

No safety or tolerability issues were reported by the end of treatment, and no SAEs or fatalities were recorded.

DISCUSSION

The present study evaluated the safety and efficacy of CurcuVail® in NAFLD patients. The findings suggest that, compared to placebo, CurcuVail® significantly reduced

fatty liver grading, APRI score, Fibrosis Score, and CAP score from baseline to the end of treatment (Day 60 ± 2). In addition, CurcuVail® significantly reduced related biochemical parameters of lipid profile and liver enzymes, such as TC, serum ALT, and serum AST.

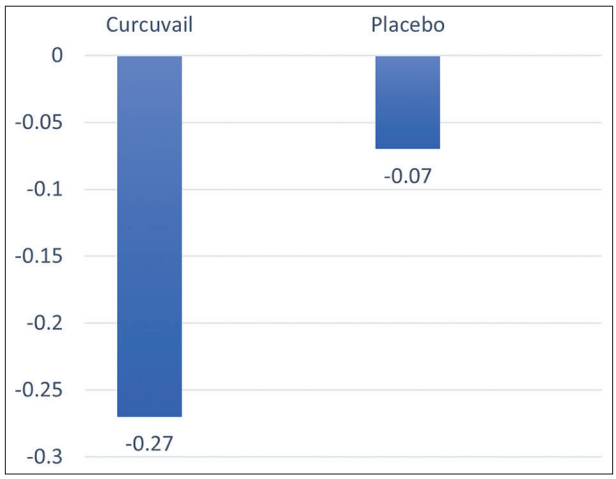

Figure 2: Change in fatty liver grading

The pathophysiology of NAFLD is complex and multifactorial, with various genetic and environmental factors contributing to its development. The "two-hit hypothesis" of NASH proposes that lipid deposition in the liver (first hit) is followed by oxidative and hepatotoxic processes (second hit), driven by mechanisms that remain partially comprehended. Factors such as genetics, epigenetics, and environmental elements can stimulate hepatocyte fat deposition and insulin resistance, leading to secondary pathological events such as oxidative stress, lipid peroxidation, inflammation, hepatic fibrosis, and apoptosis. Further factors such as lipotoxicity, endotoxemia, and adipocytokines could potentially exacerbate oxidative stress within the liver, thereby facilitating the progression of NAFLD to NASH.[12-17]

Evidence suggests that due to its anti-steatotic properties, curcumin supplementation can reduce steatosis levels in the

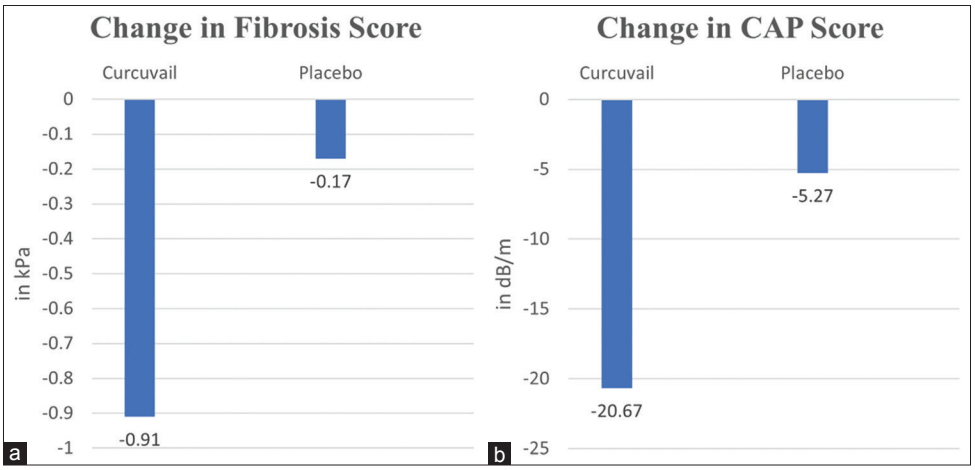

Figure 3: Change in FibroScan® parameters – (a) Fibrosis score (b) controlled attenuation parameter score

Table 2: Efficacy outcomes *(Per protocol analysis)*

Efficacy endpoint	Curcuvail® (*n*=15)	Placebo (*n*=15)	*P*-value*
Primary Endpoint†‡			
% Improvement in fatty liver grading	4 (26.7)	1 (6.7)	0.1416
Change in fatty liver grading	−0.27±0.458	−0.07±0.258	0.152
Secondary endpoints‡			
Change in APRI	−0.38±0.190	−0.18±0.286	0.031
Change in Fibrosis Score•‖	−0.91±0.364	−0.17±0.135	0.000
Change in CAP score?	−20.67±6.651	−5.27±3.105	0.000
Reduction in total cholesterol**	4.87±5.805	0.27±4.350	0.021
Reduction in Serum ALT††	36.09±10.920	6.81±11.834	0.000
Reduction in Serum AST††	22.05±8.589	9.85±15.400	0.012

Values are expressed as mean±standard deviation (range) or n (%). ALT: Alanine transaminase, APRI: AST to platelet ratio index, AST: Aspartate aminotransferase, CAP: Controlled attenuation parameter. *Calculated on basis of two sample t-test, †based on liver ultrasound, ‡from base line to day 60, •based on Fibroscan®, ‖expressed in kPa, ?expressed as dB/m, **expressed in mg/dL, ††expressed in U/L

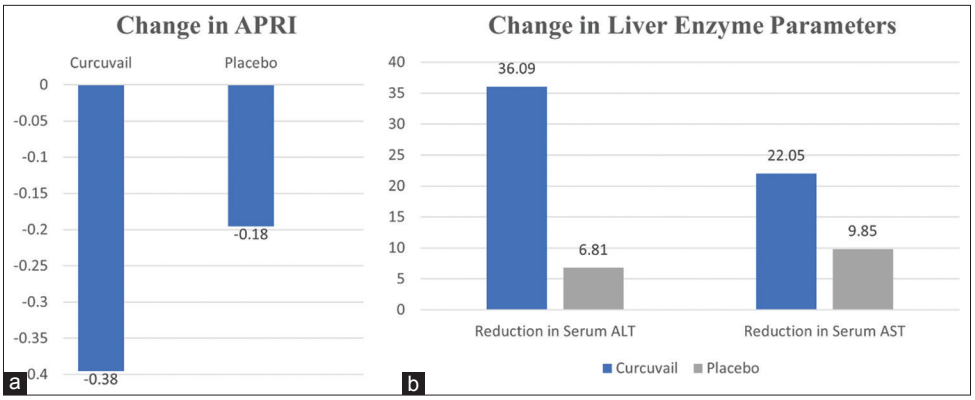

Figure 4: Change in liver enzyme parameters: (a) AST to platelet ratio index, (b) Serum alanine aminotransferase and serum aspartate aminotransferase (in U/L)

liver and decrease fatty liver grading, a primary parameter related to NAFLD. These findings are consistent with previous trials demonstrating the beneficial effects of curcumin on NAFLD.[18-20] Curcumin is known to regulates hepatic lipogenesis through AMP-activated protein kinase activation which leads to inhibition of hepatic lipid accumulation.[21] The present study demonstrated a proportionate improvement in the number of patients with improved fatty liver grading. Furthermore, the change in NAFLD grading was found to be statistically significant in the test group.

NAFLD may progress to hepatic fibrosis, which is commonly detected through invasive methods such as liver biopsy. However, non-invasive methods such as Fibroscan® and the estimation of non-invasive marker panels including FIB-4, NFS, APRI, and BARD have also proven effective in assessing hepatic fibrosis.[22] In this study, we incorporated the use of fibrosis score based on Fibroscan® and APRI, both of which demonstrated significant reductions following the use of CurcuVail® compared to the placebo treatment group. Specifically, a 2-fold greater decrease in APRI score and a 5.4-fold greater decrease in fibrosis score were observed in the CurcuVail® group compared to the placebo treatment group.

The activation and proliferation of hepatic stellate cells play a crucial role in liver fibrosis. Through peregrine mechanisms, hepatic stellate cells produce large amounts of extracellular matrix (ECM) and activate matrix metalloproteinase inhibitors. This restrains the activity of collagen enzymes, leading to reduced ECM degradation and excessive ECM deposition, resulting in the formation of liver fibrosis. Given the critical role of hepatic stellate cells in the pathogenesis of hepatic fibrosis, inducing their apoptosis has become a potentially important strategy for preventing or treating hepatic fibrosis. Studies have evidenced that curcumin is adept at effectively inhibiting the proliferation of hepatic stellate cells and induce their apoptosis in a dose-dependent manner.[23] In addition, curcumin has been shown to improve fibrosis scores in patients with NAFLD, consistent with the results of this study.[22,24]

Abdominal ultrasound is the primary diagnostic modality for detecting hepatic steatosis; however, its sensitivity is limited when liver fat content is below 30%. Alternative imaging techniques, while more accurate, are often prohibitively expensive and not accessible to all patients. The CAP score has demonstrated both high sensitivity and specificity in the detection of fatty liver. Our study demonstrated a statistically significant improvement in the CAP score among subjects treated with CurcuVail®, with a 3.9-fold greater reduction compared to the placebo group. These findings are consistent with the previous studies utilizing formulations containing curcumin, the primary constituent of CurcuVail®.[25] The reduction can be attributed to the inhibition of hepatic lipid accumulation.[21]

Preclinical and clinical studies have demonstrated improvement in lipid parameters using curcumin in NAFLD mice model and patients.[26-28] NAFLD is associated with hepatic metabolic disorders, resulting in over accumulation of fatty acids, triglycerides, and cholesterol. Although of limited clinical significance, our study observed a greater reduction in TC levels among subjects treated with CurcuVail® compared to the placebo group, with an 18-fold greater decrease. These results are in line with previous investigations.[29] The underlying mechanism has been previously discussed.[21]

Aspartate transaminase (AST) and alanine transaminase (ALT) are enzymes involved in amino acid metabolism and protein catabolism within hepatocytes, respectively. Elevated serum levels of AST and ALT are indicative of hepatic tissue damage and inflammation, resulting in the release of these enzymes into the bloodstream. In our study, treatment with CurcuVail® demonstrated a positive effect on hepatic tissue damage and inflammation, with a 3-fold greater reduction in AST levels and a 3.7-fold greater reduction in ALT levels compared to the placebo group. The results were supported on the basis of the previous evidences.[20,30]

Our study was conducted over a 60-day period. Long-term investigations are necessary to fully evaluate the clinical efficacy and safety profile of the test product.

CurcuVail® exhibited significant therapeutic effects at a lower dose (250 mg) which may be linked to its enhanced bioavailability, achieved through specialized formulation by K Phyto Extractions Pvt. Ltd. This may also contribute to the favorable safety and tolerability profile of CurcuVail®, as no AE were observed during the course of treatment.

CONCLUSION

The present study demonstrated the potential of CurcuVail® to improve clinical outcomes in patients with NAFLD. Over the course of 2 months of treatment, significant improvements were observed in the APRI score, fibrosis score, CAP score, TC levels, serum AST levels, and serum ALT levels. A longer treatment duration may have resulted in clinically meaningful and statistically significant improvements in NAFLD grading based on liver ultrasound. No safety or tolerability concerns were observed during the 60-day treatment period; however, further studies are necessary to fully evaluate the long-term safety profile of CurcuVail®.

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ETHICS STATEMENT

The following study was approved by Sanjivani Hospital Ethics Committee, Ahmedabad [Reg No.: ECR/183/Inst/Ahm/2013/RR-19]. The study was also registered on Clinical Trials Registry – India **(**CTRI) [CTRI No.: CTRI/2021/01/030302]

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