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# Traditional Indian Medicine Improves Clinical Outcome in Non-alcoholic fatty Liver diseases - A Systematic Review and Meta-analysis

**Review Article**

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## Abstract

Background: Non- Alcoholic Fatty Liver Disease (NAFLD) is a rapidly emerging liver disease linked strongly to metabolic syndrome. In the absence of specific pharmacological agents for the effective treatment of NAFLD, current treatment mainly focuses on lifestyle and dietary modifications. Several agents referenced in Ayurvedic texts have shown promising effects in patients over centuries of use. But the outcomes reported by various randomized clinical trials (RCTs) for the efficacy of herbs in non-alcoholic fatty liver disease (NAFLD) are conflicting. Objective: This study aims to systematically review and conduct meta-analysis of the available evidence to evaluate the efficacy and safety of Ayurveda-referenced drugs. Methodology: The electronic databases PubMed, Web of Science, Embase, Cochrane library, and ARP were searched up to May 2022 to identify relevant studies. Quality of studies was evaluated using modified Jadad Scale. Risk of bias was assessed using Cochrane risk of bias tool. Result: The search retrieved 1352 studies, but only 18 studies were finally evaluated. Statistical analysis showed significant reduction in grades of fatty liver (RR: 2.42, 95% CI; 1.52, 3.86), AST (SMD: -0.91, 95% CI; -1.04, 0.08;) and ALT (SMD = − 0.91; 95% CI; − 1.53, − 0.28; P < 0.00001). Conclusion: Ayurveda drugs have shown positive results in managing NAFLD, as evidenced by the limited available data. More quality-based RCT's using standardized Ayurveda drugs with large sample sizes and taking histological outcomes into consideration must be conducted to generate stronger evidence.

**Key Words:** Ayurveda, Herbal Medicine, Non- Alcoholic Fatty Liver Disease, Meta-analysis, Systematic Review, Yakrit Roga.

## Introduction

The most common liver disorder that has emerged globally recently is non-alcoholic fatty liver disease (NAFLD), affecting almost one-fourth of the world's population.(1,2) NAFLD, a condition strongly linked to metabolic syndrome, occurs when excess fat accumulates in liver cells without the consumption of alcohol. The worldwide occurrence of NAFLD falls in the range of 6-35 percent. In the absence of a substantive history of alcohol consumption, NAFLD spans from mere steatosis without cirrhosis to non-alcoholic steatohepatitis (NASH), which may accompany or without cirrhosis. NASH is a progressive entity affecting almost 5-7 percent of the population and 30-40 percent of patients with raised liver enzymes. NAFLD is fast emerging as a leading non-viral etiological cause of Hepatocellular carcinoma (HCC) (3). The prevalence of NAFLD has been estimated at one-third of the adult American population, whereas it is around 20% to 30% among European and the Middle East people.(4) Recent studies across different parts of India have illustrated that the prevalence of NAFLD varies from 9 to 35%.(1) NAFLD's high prevalence can also be related to the fact that it is the hepatic expression of the metabolic syndrome that is commonly linked to obesity.(5) As a consequence of urbanization and accompanying changes, like a high-fat & carbohydrate-rich diet, sedentary lifestyle, and a higher hereditary predilection for diabetes mellitus, Indians are more susceptible to insulin resistance or metabolic syndrome and its manifestations, such as NAFLD.(6)

Ayurvedic medicine (AyM) has an ancient history of treating liver diseases safely and effectively in the Indian subcontinent. The material-medica of AyM includes plant-based medicines used individually or in combination with certain metals and minerals, which are converted into therapeutically active nanoparticles after rigorous pharmaceutical processes.(7) According to the Ayurveda classical theory, NAFLD may be understood as a disease complex of *Yakṛt Roga* (liver disease) and *Medoroga* (obesity). A vast gamut of diseases comes under *Yakṛt Roga* (liver disease), ranging from simple hepatic steatosis to hepatomegaly to liver cirrhosis. The main etiological factor is *vidāhī* (spicy food) and *abhiṣyandī āhāra* (food that blocks the

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channels or fatty diet), causing *Rakta-kapha duṣṭi* eventually leading to NAFLD.(8) Many clinical studies have been conducted using various interventions of herbal, metal/mineral, or poly ingredient composition as stated in classical texts of Ayurveda. Similarly, different proprietary or patented products are also in practice.(9) Several studies have been published showing concerns about Ayurvedic formulations (especially herbomineral and mineral origin) being unsafe and toxic.(10)

**Need of Study**

Currently, there is no specific pharmacological agent of choice to treat NAFLD effectively. Lifestyle and dietary modifications are advised, and therapy is focused on addressing the risk factors for NASH (i.e., insulin resistance and decreasing delivery of fatty acids to the liver). Plant-based agents having potential hepatoprotective action have also been used with mixed outcomes.(11,12) Ayurvedic therapy can be an effective treatment option for NAFLD, both as a stand-alone and adjunctive therapy, taking into account the disease's national and worldwide burden, clinical profile, prognosis, and the search for hepato-protective intervention. An attempt has been made to systematically review the quantity and quality of evidence of the safety and effectiveness of interventions related to Ayurveda medicine in NAFLD. Assessment of the evidence for efficacy and safety of Ayurveda medicine (AyM) can lead to much better treatment options for NAFLD. The study is presented as per the PRISMA report checklist.(13)

## Materials & Method

**Search Strategy**

The electronic databases were searched systematically using PubMed, Web of Science, Embase, Cochrane library, and ARP (AYUSH Research Portal, Govt. of India) up to May 2022. The data was confined to finding relevant RCTs that investigated the effect of herbal or Ayurveda intervention on patients with NAFLD. The strategy employed for literature retrieval is explained in Table 1.

**Table 1: Strategy employed for literature retrieval**

| | |
|---|---|
| NAFLD | “Nonalcoholic fatty”, “Non-alcoholic fatty”, “Non-alcoholic fatty liver disease" [mesh], “Nonalcoholic” AND "fatty liver" [mesh], “Non-alcoholic” AND "fatty liver" [mesh], NAFLD, "Nonalcoholic steatohepatitis" |
| Ayurveda | “Phytotherapy”, “Herbal medicine”, “Plant preparation”, “Ayurveda medicine”, “Complementary medicine”, “Drugs, Ayurveda herbal” [Mesh], “Medicine, traditional” [Mesh], “Plant preparations” [Mesh], “Medicinal plant”, “Plant medicinal product”, “Herb”. |

**Eligibility criteria and screening**

The title, abstract and full text of each study was reviewed to ensure that they aligned with the inclusion criteria. The screening for inclusion process included two stages of assessment. The preliminary stage comprised the verification of the title and abstract, and the following studies were excluded during the initial phase of screening: (1) non-randomized trial; (2) protocol, review, meta-analysis; (3) studies about diet, nutraceuticals, fortified food, probiotic; (4) other disease studies in patients of NAFLD. In the second stage, the full-text review was conducted to exclude all the non-AYM related RCTs, studies involving metabolites extracted from herbal sources, or herbs not found in Ayurvedic texts. In addition, the studies in the English language evaluating the effect of AyM on at least one of the liver enzymes (ALT, AST), blood lipid profiles (TG, TC, HDL, LDL), glycemic indices (FBS, HOMA-IR, serum insulin, HbA1c) and anthropometric parameters (WC, body weight, BMI) in subjects with diagnosed NAFLD were included in the review.

**Data extraction & analysis**

Two reviewers (PC & NL) independently assessed the titles and abstracts based on the inclusion as mentioned earlier criteria. In addition, the studies with potential relevance were retrieved for detailed assessment. A standard data extraction table was developed to include the following information; (i) name of the authors; (ii) year of publication; (iii) intervention; (iv) sample size; (v) average age of the patients; (vi) intervention duration; (vii) outcome indicators. Zotero 6.0 software was used for cataloging and managing references, and Microsoft Excel 2016 was used to extract and record data. The Risk of Bias was assessed using the RoB 2 tool.(14) The studies included in the review were assessed for quality of reporting using the modified Jadad scale.(15,16) RCTs with a higher score (> 4) were considered high-quality studies, and those with a score < 4 were categorized as low quality.

**Outcome indicators**

The primary outcome was the effect of the intervention on the state of fatty liver assessed by ultrasonography, fibroscan, or NAFLD Activity score (NAS) and changes in levels of alanine transaminase (ALT) and aspartate transaminase (AST). The secondary outcomes include changes in gamma-glutamyl transferase (GGT), total cholesterol (TC), triglyceride (TG), high-density lipoproteins (HDL), low-density lipoproteins (LDL), Fasting blood glucose (FBS), HOMA-IR and BMI.

**Statistical analysis**

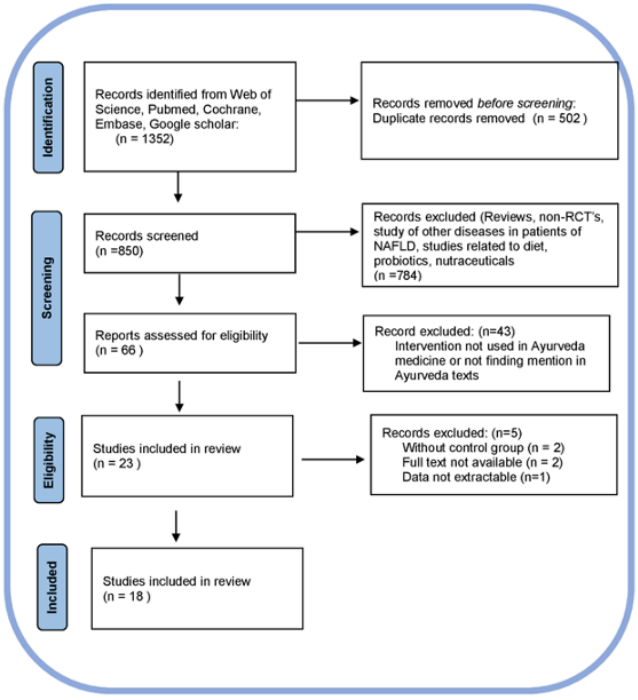
Standard Mean difference (SMD) was reported for all the secondary outcomes. The dichotomous data were assessed by risk ratio (RR) and 95% CI. The Cochrane review manager software RevMan 5.4.1 was used to assess the overall combined effect of interventions. The combined analysis used a 95% confidence interval (CI) as an effect size. Heterogeneity was assessed using the $I^2$ test. If there was no heterogeneity ($I^2 < 50\%$ and $P > 0.1$), a fixed-effect model was used to synthesize the data; Otherwise, for heterogeneity ($50\% < I^2 < 75\%$), a random-effect model was applied. The results were shown using forest plots.

# Results

## Study identification and selection

The initial screening process was conducted per the PRISMA guidelines summarized in the flow diagram as shown in Fig. 1. A total of 1352 studies were identified in the initial searches from the selected electronic databases and related sources. Out of these, 850 potentially relevant articles were retained for further evaluation during the screening process. Next, the titles and abstracts were screened. Another 784 studies were further excluded for multiple reasons (reviews, non-RCTs, studies on comorbidities, diet, and nutraceuticals). Sixty-six articles were then selected for further assessment. The assessment included examining full texts, and subsequently, 43 studies conducted on herbal drugs/interventions not found in Ayurveda texts were further excluded. Twenty-three studies were finally found eligible for final selection. Out of these, five studies were excluded for being a single-arm study or data not extractable. Eventually, 18 studies, all in the English language, were found to satisfy the inclusion criteria and were included in the systematic review. (8,17–33).

**Fig 1 PRISMA flow diagram showing selection methodology of included studies. Out of 1352 studies identified, only 18 studies were finally included in the review**




## Study characteristics & quality assessment

The eighteen randomized clinical trial studies were included for systematic review involving 1097 patients, of which 553 were allocated to the intervention group. The risk of bias assessment is shown in figure 2. Two authors independently assessed each study (PC & NL) separately. All the studies had clearly defined primary outcomes. However, five studies did not report prior methodology for sample size calculation. Thirteen had well-defined randomization and allocation concealment processes. A total of 46 patients were considered dropouts across thirteen studies, while five RCTs did not report the number of dropouts. The mean age of the participants was 45.75. Fourteen studies were 12 weeks long; two studies were 24 weeks and eight weeks each. The quality assessment of the published studies was done using a modified Jadad score. Three studies had a score equal to or less than four and were considered low-quality studies. Liver biopsy to assess histological response as a primary outcome for evaluating the effectiveness of the intervention was reported only in one research.

**Fig 2 (A) Risk of Bias of included studies; (B) Graph showing Risk of Bias**


## Intervention and control comparison

A total of fifteen different interventions were assessed in the clinical trials. Fifteen RCTs were compared against a placebo, while three (8,28,30) studies were compared against dietary changes and lifestyle modifications. Apart from these, participants were advised dietary and lifestyle modifications in five studies(20,21,29,31,32). The interventions assessed in the included studies are listed in Table - 2.

**Table 2: Characteristics of the studies included in the review**

| Sr.No. | Authors | Intervention | Control | Additional confounders | Total No. of Patients | No. of Patients in Intervention group | No. in Control group | Mean age of Participants | Duration | No of dropouts |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Askari F 2013 | *Cinnamomum zeylanicum Blume* | Placebo | Dietary advice + Exercise | 50 | 23 | 22 | 42.2 | 12 weeks | 5 |
| 2 | Babaei A 2020 | *Trigonella foenum-graecum L.* (Hydro Alcoholic extract) | Placebo | Lifestyle changes | 30 | 13 | 11 | 39.3 | 3 months | 6 |
| 3 | Chang HC 2014 | *Hibiscus sabdariffa* | Placebo | None | 36 | 19 | 17 | 37.94 | 12 weeks | 4 |
| 4 | Cossiga V 2019 | *Berberis aristata, Elaeis guineensis* and *Coffea canephora* | Placebo | None | 49 | 26 | 23 | 54.2 | 24 weeks (6 months) | 0 |
| 5 | Daneshi M 2019 | *Elettaria cardamomum L.* | Placebo | None | 87 | 43 | 44 | 50 | 3 months | 6 |
| 6 | Darand M 2019 | *Nigella sativa L* | Placebo | Exercise and balanced diet | 50 | 22 | 21 | 47.4 | 12 weeks | 7 |
| 7 | Hussain M 2017 | *Nigella sativa L* | Placebo | None | 70 | 35 | 35 | 37 | 12 weeks | 0 |
| 8 | Kazemi S 2020 | Sumac (Unani Med) | Placebo | Calorie deficit diet | 84 | 40 | 40 | 41.6 | 12 weeks | 4 |
| 9 | Khonche A 2019 | *Nigella sativa L* | placebo | None | 120 | 60 | 60 | 46.64 | 12 weeks | 0 |
| 10 | M Dinu 2018 | *Triticum turgidum subsp. turanicum* (Khorasan | Control Wheat | None | 40 | 20 | 20 | 55.2 | 3 months | Not shown |
| 11 | Navekar R 2017 | *Curcuma longa L.* | Placebo | None | 46 | 21 | 21 | 41.23 | 12 weeks | 4 |
| 12 | Pour FK 2020 | *Crocus sativus L.* | Placebo | None | 76 | 38 | 38 | 42.7 | 12 weeks | 3 |
| 13 | Rashidmayvan 2019 | *Nigella sativa L.* oil | Placebo | None | 44 | 22 | 22 | 40.61 | 8 weeks | Not Shown |
| 14 | Remya E 2021 | Sharpunkhadi powder | Placebo | Dietary advice + Lifestyle changes | 83 | 43 | 40 | Not specified | 8 weeks | Not shown |
| 15 | Sangouni A 2020 | *Allium sativum, L.* (Garlic) | Placebo | None | 90 | 42 | 42 | 45.75 | 12 weeks | 6 |
| 16 | Singhal P 2015 | Arogyavardhini vati & triphla guggul | Pathya & Diet Lifestyle | None | 32 | 21 | 11 | Not specified | 3 months | Not Shown |
| 17 | Wong VW 2012 | *Phyllanthus urinaria* | Placebo | None | 60 | 40 | 20 | 50 | 24 weeks | 1 |
| 18 | Yari Z 2016 | *Linum usitatissimum (Linn.)* Flax seeds & Lifestyle modification | Lifestyle modification | None | 50 | 25 | 25 | 45 | 12 weeks | NO |

**Outcome**

The reported outcomes of the studies include changes in liver function (AST, ALT, GGT), lipid profile (TG, TC, HDL, LDL), glycemic, (FBS, HOMA-IR, QUICKI) inflammatory markers (hs-CRP, TNF-α) and BMI. These outcomes are summarised in Table-3. Only the outcomes at the end of the trial duration were reported, and no study testified to the follow-up data after the completion of the intervention duration. However, all RCTs reported illustrated statistically positive results in the outcomes in the intervention group compared to the control group. In addition, any RCT reported no adverse effects of the intervention. The impact of interventions on outcomes is shown in Figure 3-6.

**Table 3: Major findings of the studies included in the review**

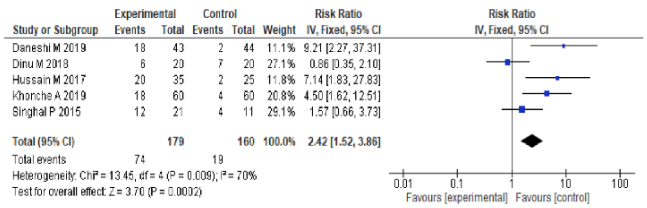
| S.No | Authors | Intervention | Radiological/ Histological Assessment | Liver Function Profile | Body weight | Blood Sugar | Lipids | Others | Jadad Score |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Askari F 2013 | Cinnamon | - | AST, ALT, GGT | BMI | FBS, HOMA-IR, QUICKI | TC, TG, LDL, HDL | hsCRP, TNF- α | 4 |
| 2 | Babaei A 2020 | Fenugreek (HydroAlcoholic extract) | Fibroscan | AST, ALT, GGT | BMI | FBS | TC, TG, LDL, HDL | - | 7 |
| 3 | Chang HC 2014 | Hibiscus sabdariffa | Fibroscan | AST, ALT | BMI | FBS | TC, TG, LDL, HDL | - | 5.5 |
| 4 | Cossiga V 2019 | B. aristata, Elaeis guineensis and Coffea canephora | Fibroscan | AST, ALT, GGT | BMI | FBS, HOMA-IR | TC, TG, LDL, HDL | - | 7 |
| 5 | Daneshi M 2019 | cardamom | USG | - | - | FBS, QUICKI, HOMA-IR | TC, TG, LDL, HDL | - | 7 |
| 6 | Darand M 2019 | Nigella Sativa | Fibroscan | AST, ALT, | BMI | FBS | TC, TG, LDL, HDL | hsCRP, TNF- α | 7 |
| 7 | Hussain M 2017 | Nigella Sativa | USG | AST, ALT | BMI | - | - | - | 5 |
| 8 | Kazemi S 2020 | Sumac (Unani Med) | Fibroscan | AST, ALT | BMI | HbA1C, Quicki, HOMA-IR | - | hsCRP, TNF- α | 7 |
| 9 | Khonche A 2019 | Nigella Sativa | USG | AST, ALT | - | - | TC, TG, LDL, HDL | - | 7 |
| 10 | M Dinu 2018 | Khorasan wheat | USG | AST, ALT, ALP | - | FBS | TC, TG, LDL, HDL | TNF- α | 4 |
| 11 | Navekar R 2017 | Turmeric | - | AST, ALT | BMI | FBS, HOMA-IR | - | - | 7 |
| 12 | Pour FK 2020 | saffron | - | AST, ALT | BMI | - | - | hsCRP, TNF- α | 7 |
| 13 | Rashidmayvan 2019 | Nigella Sativa oil | - | AST, ALT, GGT | BMI | FBS | TC, TG, LDL, HDL | hsCRP, TNF- α | 5 |
| 14 | Remya E 2021 | Sharpunkhadi powder | - | - | - | FBS | TC, | - | 4 |
| 15 | Sangouni A 2020 | Garlic | - | GGT | BMI | FBS, HOMA-IR | TG, HDL | - | 7 |
| 16 | Singhal P 2015 | Arogyavardhini vati & triphla guggul | USG | AST, ALT | BMI | FBS | TC, TG, HDL | - | 3 |
| 17 | Wong VW 2012 | Phyllanthus urinaria | NAS | AST, ALT | BMI | FBS | TC, TG, LDL, HDL | - | 6 |
| 18 | Yari Z 2016 | Flax seeds & Lifestyle modification | Fibroscan | AST, ALT, GGT | BMI | HOMA-IR | TC, TG, LDL, HDL | hsCRP, TNF- α | 6 |

ALT - Alanine transaminase; AST- Aspartate transaminase; GGT- Gamma-glutamyl transferase; TC - Total cholesterol; TG – Triglycerides; HDL - High-density lipoproteins; LDL - Low-density lipoproteins; FBS - Fasting blood glucose; HOMA-IR - Homeostatic Model Assessment for Insulin Resistance; BMI – Body mass index; TNF- α – Tumor necrosis factor-alpha; hsCRP – high sensitivity C-reactive protein.

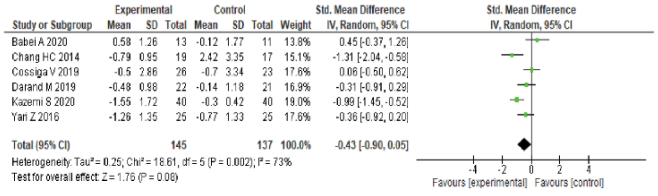
**Effect of intervention on grades of fatty liver and liver stiffness**

Five studies reported changes in grades of fatty liver evidenced by ultrasonography. These studies involved 339 patients, with 179 in the intervention group and 160 in the control group. The combined data of these studies using fixed effects analysis presented a significant reduction in grades of fatty liver (RR: 2.42, 95% CI; 1.52, 3.86; Figure 3A). Six studies reported changes in liver stiffness with herbal intervention involving 282 patients, with 145 in the intervention group and 137 in the control group. The combined data of these studies using random effects analysis exhibited a statistically insignificant reduction in levels of liver stiffness (SMD: -0.43, 95% CI; -0.90, 0.05; Figure 3B).

**Fig 3: Forest Plot showing effect of intervention on (A) Grades of Fatty Liver; (B) Liver Stiffness**




A) Forest Plot of effect of herbal intervention on grades of Fatty Liver - USG




B) Forest Plot showing effect of herbal intervention on Liver Stiffness

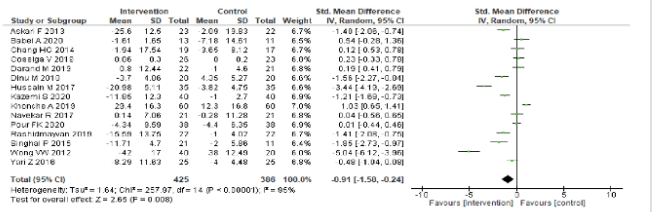
**Effect of intervention on liver enzymes**

The effect on AST & ALT was assessed in 15 studies. These studies involved 811 patients, with 425 in the intervention group and 386 in the control group. The combined data of these studies using random effects analysis depicted significant reduction in levels of AST (SMD: -0.91, 95% CI; -1.04, 0.08; Figure 4A) and ALT (SMD = − 0.91; 95% CI; − 1.53, − 0.28; P < 0.00001) (Figure 4B). Only four studies recorded alteration in GGT levels. These studies involved 227 patients, with 115 in the intervention group and 112 in the control group. The pooled effect of four studies exhibited significant improvement in levels of GGT (SMD = -0.36, 95% CI: -0.69, -0.04; p<0.05; Figure 4C).

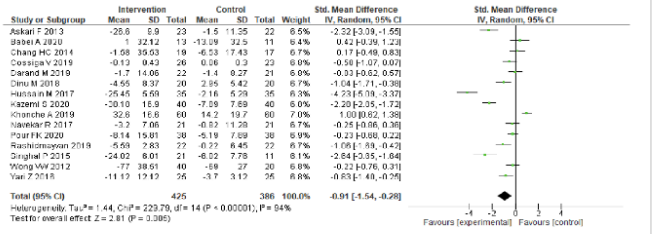
**Effect of intervention on lipid profile**

The effect on Total Cholesterol (TC) was assessed in 12 studies. These studies involved 566 patients, with 301 in the intervention group and 265 in the control group. The combined data of these studies using random effects analysis showed an insignificant reduction in levels of TC (SMD: -0.38, 95% CI; -0.77, 0.01' Figure 5A). The impact on HDL and TG was assessed in 13 studies involving 714 patients, with 376 in the intervention group and 338 in the control group. There was a highly significant improvement in levels of HDL (SMD: 0.43, 95% CI; -0.11, 0.75; Figure 5B). The

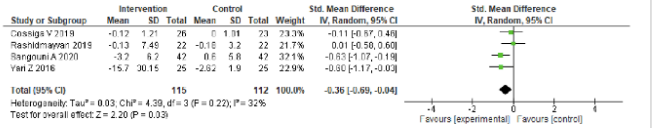
**Fig 4: Forest Plot Showing effect of intervention on changes in (A) AST (Aspartate Transaminase; (B) ALT (Alanine transaminase); (C) GGT (Gamma Glutamyl Transferase)**




A) Forest Plot showing effect of intervention on AST




B) Forest Plot showing effect of intervention on ALT




C) Forest Plot showing changes in GGT

pooled data of these studies also pointed out a highly significant improvement in levels of TG (SMD: -0.46, 95% CI; -0.79, -0.13; Figure 5C). Eleven studies assessed the intervention outcome on LDL involving 598 patients, with 313 in the intervention group and 285 in the control group. There was a significant improvement in levels of LDL (SMD: -0.54, 95% CI; -0.95, -0.12; Figure 5D).

**Effect of intervention on glycemic profile**

The effect on FBS was assessed in 13 studies. These studies included 641 patients, with 339 in the intervention group and 302 in the control group. The combined data of these studies using random effects analysis showed a highly significant improvement in levels of FBS (SMD: -0.34, 95% CI; -0.61, -0.07; Figure 6A). Seven studies assessed the intervention outcome of HOMA-IR involving a total of 437 patients, with 220 in the intervention group and 217 in the control group. Again, there was a significant improvement in levels of HOMA-IR (SMD: -0.66, 95% CI; -1.57, 0.24; Figure 6B).

**Effect of intervention on BMI**

The effect on BMI was assessed in 14 studies. These studies included 735 patients, with 387 in the intervention group and 348 in the control group. The combined data of these studies using random effects analysis highlights the significant improvement in levels of BMI (SMD: -0.28, 95% CI; -0.51, -0.04; Figure 6C).

**Fig 5: Forest Plot Showing effect of intervention on changes in (A) Total Cholesterol; (B) HDL (High Density Lipoproteins); (C) Triglycerides; (D) LDL (Low Density Lipoproteins)**

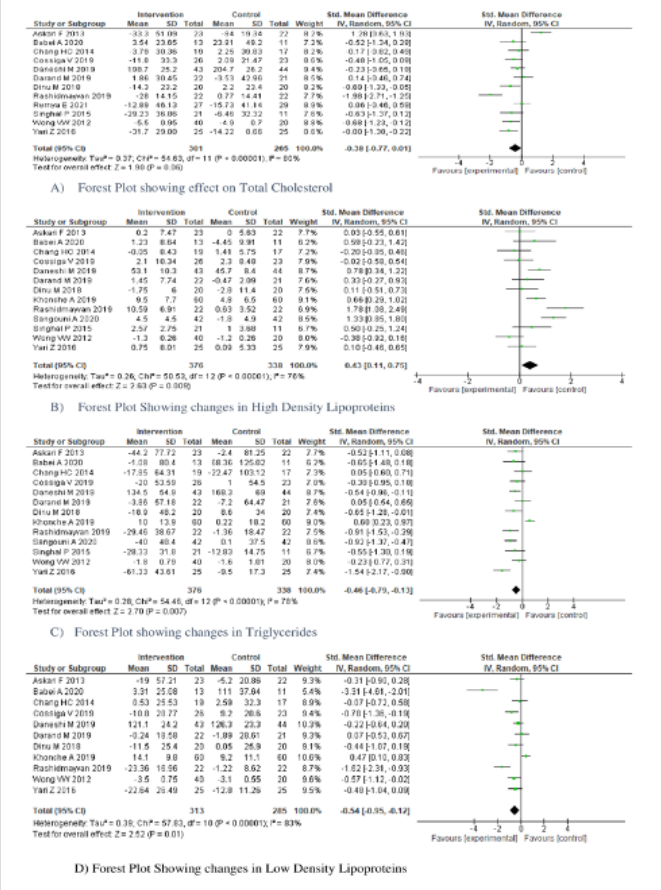
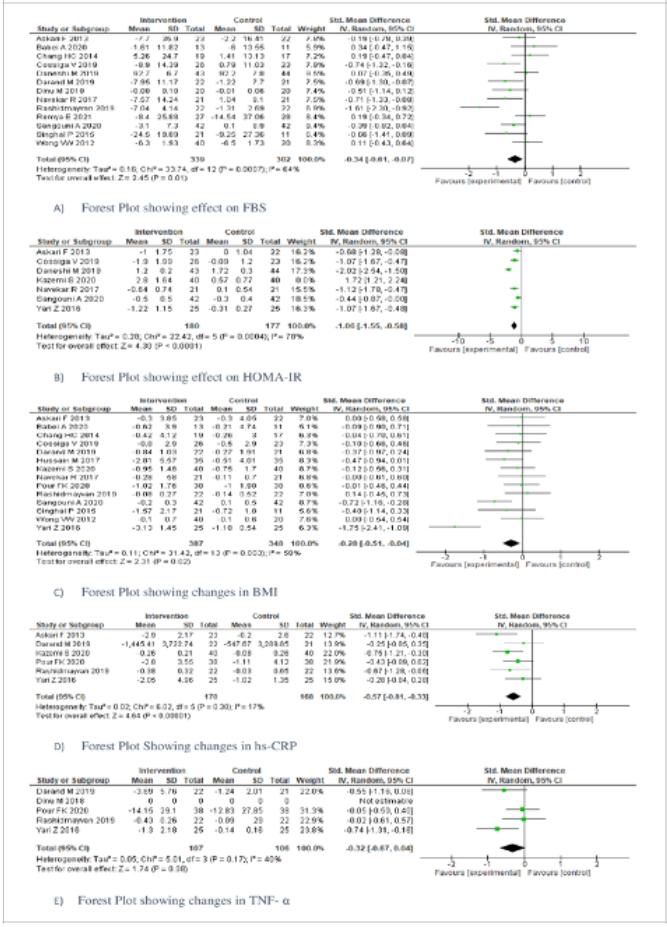


**Fig 6: Forest Plot Showing effect of intervention on changes in (A) FBS (Fasting Blood Glucose); (B) HOMA-IR; (C) BMI; (D) hs-CRP; (E) TNF- α**



### Effect on inflammatory markers

The effect on hs-CRP was assessed in six studies. These studies included 338 patients, with 170 in the intervention group. The combined data of these studies using random effects analysis remarks a significant reduction in levels of hs-CRP (SMD: -0.57; 95% CI; -0.81, -0.33; Figure 6D). The effect on TNF- α was assessed in five studies. These studies included 213 patients, with 107 in the intervention group. The combined data of these studies using random effects analysis shows a significant reduction in levels of TNF-α (SMD: -0.32; 95% CI; -0.67, -0.04; Figure 6E)

## Discussion

Ayurvedic medicines have been used in the Indian subcontinent for centuries. The Ayurvedic texts lay down the principles for healthy living, a good dietary regimen, and optimum seasonal practices. The interventions that have been a part of this systematic review are found in ancient Ayurveda texts having a long history of safe and effective usage. Several form a part of the diet, while others, like *Phyllanthus* and Arogyavardhini vati, are explicitly used as medicines. Numerous Ayurvedic multi-ingredient formulations and also single herbs are known to improve liver functions; however, it is observed that there is a dearth of research focusing on their effectiveness in treating NAFLD. This systematic review discerned RCTs conducted in different parts of the world involving interventions that find reference in Ayurvedic texts and evaluated their use in managing NAFLD. Eighteen such RCTs covering 1097 participants were included. The quality of the studies was good, and the reporting of methodological components of the RCT was sufficient in all except four studies. The description of the randomization process was available for fourteen studies; however, the blinding methods, inclusion and exclusion criteria, and the number of dropouts was clearly stated in most trials. Two studies each were conducted over 24 weeks and eight weeks, while the other fourteen involved assessments over 12 weeks. None of the studies reported any adverse drug reactions. Though the evidence generated based on research is not sufficient to establish the role of AyM in the management of NAFLD, the results have been encouraging. This systematic review and meta-analysis demonstrated the effectiveness of interventions that are also referenced in Ayurveda texts. These AyM had a better effect in lowering the levels of AST & ALT and reversing the fatty changes in the liver compared to placebo. Specific interventions like cinnamon, fenugreek, cardamom, and garlic which form a part of this study, are also a standard component of the Indian diet. Still, the epidemiology of NAFLD in the Indian subcontinent has a wide variation, ranging from 9-35% (1). This paradox may be attributed to the fact that though these interventions are included as a dietary component, their mode of usage is a non-standardized dose added to the cooking process involving deep frying,

which probably negates their beneficiary action on NAFLD.

The current analysis had several limitations. First, the sample size of the studies was too small to establish the outcome. Sample size calculation was described in eight of the studies. A sample size calculation involves determining the minimum number of participants required to estimate a clinically relevant treatment effect. A small sample size may affect the quality of the trial leading to statistical deviations in assessing the effect of an intervention.

Histological studies for the assessment of the efficacy of interventions in NAFLD were not conducted in all the studies. Most of the studies assessed the primary outcome, i.e., changes in the grading of the fatty liver based on ultrasonography and fibro scan. AST and ALT levels were improved significantly; however, changes in liver enzymes cannot be considered the sole criteria for evaluating the treatment efficacy in NAFLD (32). Several instances in clinical practice occur when, despite average values of AST & ALT, fatty changes in the liver were accidentally discovered in ultrasonography.

Fifteen studies were conducted compared to placebo, while lifestyle modifications and diet management were part of the other three studies. The interventions should be assessed against the recommended drugs of choice to analyze their effectiveness better.

Since options for the treatment of NAFLD are limited, the role of AyM as an additional resource for managing NAFLD should be evaluated by conducting quality RCTs'. The outcome of such RCTs' should focus on the hepato-protective actions of Ayurveda drugs along with an effort to establish quality evidence about efficacy and safety.

There was significant heterogeneity ($I^2$ =66.30%) in the pooled analysis of studies. However, it can be attributed to the fact that the number of studies included in the analysis was small.(34) NAFLD is a hepatic manifestation of metabolic syndrome, and subjective assessment should be included for symptomatic patients so that patient care can be provided holistically.

## Conclusion

Traditional products have been used since time immemorial, and several of them have also been studied for effectiveness in NAFLD. The outcomes of these have been propitious. Ayurveda drugs have shown positive results in managing NAFLD, as evidenced by the limited available data. More substantial and long-term evidence must be generated for Ayurvedic medicines to be used as a treatment choice for NAFLD. Therefore, the RCTs involving traditional Ayurveda drugs should be conducted following CONSORT guidelines strictly with a larger sample size and a focused approach. Additionally, histological outcomes should also be assessed.

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**Ethical Statement**

This study does not involve any human or animal experiments, hence statement of ethics is not applicable.

**Conflict of Interest**

The authors declare no conflict of interest.

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