



Short Communication

Elastographic liver evaluation of *Katukyadi churna* in the management of Non-Alcoholic Steatohepatitis (NASH) – A single arm clinical trial.Shruti Tarapore ^a, Basavaraj R. Tubaki ^{b, *}, Siddhi Khot ^b^a Department of Kayachikitsa, Seth Govindji Raoji Ayurved Medical College, Solapur, Maharashtra, 413001, India^b Department of Kayachikitsa, Shri BMK Ayurveda Mahavidyalaya, A Constituent Unit of KLE Academy of Higher Education & Research, Belagavi, Karnataka, India

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ABSTRACT

Non Alcoholic Steatohepatitis (NASH) is the most severe histological form of non-alcoholic fatty liver disease (NAFLD). It progress to cirrhosis in 20% population and 40% will have death due to liver pathology. Still consensus on pharmacotherapy is yet to be evolved and till date there is no US FDA approved drug for NASH. Ayurveda formulation *Katukyadi churna* is explored in the possible management of NASH. Study is a single arm with pre and post test design. Sonologically diagnosed patients of fatty liver (n = 30) were screened. 11 patients meeting elastographic criteria (6.4–11.7 kPa) were enrolled in the study. *K. churna* was administered in the dose of 6 g twice a day with water at the middle of the meal for a period of 6 months. Subjective parameters were *Aruchi* (Anorexia), *Agnimandhya* (loss of appetite), *Ajeerna* (indigestion), *Gouravata*. Follow up assessments were done on every 30th day. Study showed that *K. churna* produced significant improvement in various parameters. Significant decrease in weight, (p < 0.001), BMI (p < 0.001), Elastography (p = 0.001), total bilirubin (p = 0.02), Alanine Aminotransferase (ALT) (p < 0.001), Aspartate Aminotransferase (AST) (p = 0.001), Albumin (p = 0.04), Triglycerides (p = 0.005) were observed. Subjective symptoms like *Ajeerna* (p = 0.002), *Agnimandhya* (p = 0.004), *Arochaka* (p = 0.001), *Gouvravata* (p = 0.002) showed significant improvement. *K. churna* showed clinical significance in terms of improvement from pathological ranges to normative ranges in elastography, total bilirubin, AST, Albumin. *K. churna* reduced weight, BMI, hardness and stiffness of the liver, liver function derangements, triglycerides and improved other subjective clinical parameters. Drug has promising results in NASH and warrants further studies.

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1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is wide spectrum of disease comprising from adipose infiltration in liver to steatosis, steatohepatitis, and cirrhosis. NAFLD is defined as the presence of more than 5% hepatic steatosis without evidence of hepatocyte ballooning. Non-alcoholic steatohepatitis (NASH) is a commonly occurring silent liver and forms a component of non-alcoholic fatty liver disease (NAFLD). NASH is a metabolic liver disease characterized by the presence of more than 5% hepatic steatosis along with hepatocyte inflammation with or without hepatic

fibrosis [1]. NAFLD comprises of a simple steatosis, NASH, fibrosis and cirrhosis.

Prevalence of NAFLD in Indian population based on Ultra sound was 17% [2]. MRI based study in US reported prevalence of 31% [3]. About 90% patients of NAFLD have simple steatosis [4], 10–30% will progress to NASH and 25–40% progress to liver fibrosis and to cirrhosis in 20–30% [5,6]. NASH is frequently seen in the age group of 35–55 years and in females. 6% of all chronic hepatitis patients do suffer from NASH [7], 20–25% of patients with NASH will progress to cirrhosis [8]. NASH cirrhosis have increased risk of development of hepato cellular carcinoma [9], liver mortality and cardiovascular death [10]. Indian population study showed that the prevalence of NAFLD and steatohepatitis ranges from 15 to 39% and 1.2–4.8% respectively in the patients undergoing liver biopsy. Imaging studies have shown the ranges of steatosis and steatohepatitis as 9.7–23% and 1.2–4.8% respectively [11].

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Aetiology for NASH is not clearly known. Predisposing factors are insulin resistance, release of toxic inflammatory cytokines by fat cells and oxidative stress. Post orthotopic liver transplantation, recurrence of NASH suggests the role of extra hepatic metabolic factors like genetic and acquired abnormalities of fatty acid turnover and oxidative stress. The alcohol consumption should not exceed 30 g/day for men and 20 g/day for women according to the second NIH Consensus Conference statement [12]. Steatohepatitis is the inflammation in the hepatocytes caused due to various factors like alcohol, drug induced and dietary factors. Various drugs like antiarrhythmic drugs, methotrexate, tamoxifen, valproic acid, nucleoside reverse transcriptase inhibitors, and chemotherapy have a possible role in induction of NASH [13]. In NASH histologically changes are macrovesicular steatosis, balloon degeneration of hepatocytes, lobular inflammation with neutrophilic cells infiltrate, and zone-3 pericellular fibrosis [14].

NASH has associations with Type 2 Diabetes mellitus, family history of Type 2 diabetes mellitus, insulin resistance with or without glucose intolerance, central obesity, hypertriglyceridaemia, rapid and massive weight loss in overweight subjects. Hence prevalence of NASH may rise with the global rise in obesity and T2DM. NASH manifestations include asymptomatic phase to fatigue, weight loss, weakness in the advanced stages and to cirrhosis.

Liver biopsy is the gold standard for diagnosis of NASH and for disease progression risk prediction. NASH and fatty liver can be only differentiated through biopsy. However biopsy has various limitations like being an invasive technique has potential mortality, morbidity [15] and sampling error. Hence NASH remains to be under diagnosed in clinical practise [16]. Non invasive laboratory tests like serum hyaluronic acid levels, aspartate aminotransferase (ASAT) to platelet ratio index, Fibrotest, assess the extent of liver fibrosis. Fibrometer have their own advantages and limitations. Ultra sonography and computerized tomography are sensitive to hepatic steatosis but cannot differentiate NASH from other variants of NAFLD.

Ultrasound based Transient Elastography [Fibroscan] (TE) has promising results in assessing liver fibrosis by evaluating liver stiffness [17]. EASL-ALEH Clinical Practice Guidelines [18] recommends, Transient elastography assessment as the first line procedure for identification of patient with low risk to severe fibrosis or cirrhosis. It evaluates the stiffness, hardness and is the diagnostic and prognostic marker for NAFLD [19]. Liver stiffness occurs before the onset of fibrosis and this could be due to changes in cellular matrix characters, micro environment leading to transformation of hepatic stellate cells into a fibrogenic phenotype [20] Liver stiffness assessments can be affected by space occupying liver tissue abnormalities like edema, inflammation, extra hepatic cholestasis. Transient elastography results range from 1.5 to 75 kPa. Indian population based study [20] showed cut off ranges for liver stiffness measures in healthy individuals was 5.4 kPa and in NAFLD was 5.9 kPa. In NAFLD with no fibrosis/minimal fibrosis 7.79, moderate fibrosis 11.73, advanced fibrosis 24.88 ± 13.0 kPa. In NASH score was 6.4 kPa [21]. NASH with no fibrosis or minimal fibrosis with TE values of 6.4–11.7 kPa were included in the study.

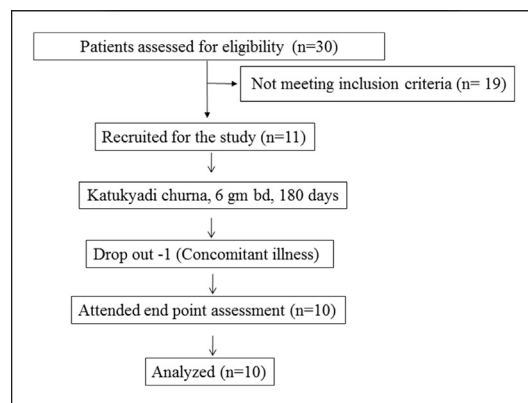


Fig. 1. Study flow chart.

NASH can be compared with *Kaphaja yakrut roga* in Ayurveda as there is similarity in their manifestations. Manifestations of *kaphaja yakrut roga* [22] are *Mandha vyatha* (mild aches), *Kathinyata* (increase in hardness), *Gouvrvavata* (increase in heaviness), *Arochaka* (Deranged taste), *Agnimandhya* (decrease in digestion). NASH has similar presentations like pain in right upper quadrant, enlarged, hard liver, feeling of heaviness and loss of appetite.

Effective management of NASH can prevent the possible risks of cirrhosis, terminal liver failure and hepatocellular carcinoma. Current treatment of NASH is only through dietary changes and life style modifications. No pharmacological agent has received FDA or EMEA approval [23]. However studies have shown weight reduction [24], poly-unsaturated fatty acid (PUFA) therapy [25] and exercise [26] have beneficial role. Ayurveda herbal drugs have shown beneficial effect on liver. Many of the Ayurveda drugs have hepatotrophic activity. Drugs like *Katuki* (*Picrorhiza kurroa* Royle Benth.), *Nimba* (*Azadirachta indica* A. Juss.), *Amritha* (*Tinospora cordifolia* Miers.), *Bhringraj* (*Eclipta alba* Hassk.), *Bhumyamalaki* (*Phyllanthus niruri* Linn.) having Tikta predominant rasa have action on *Yakrit* (Hepatotrophic action). *Katukyadi churna* has shown beneficial effect in liver disorders in our clinical settings. Hence *Katukyadi churna* formulation is explored for its possible role in management of NASH.

2. Materials and methods

The objective of the study was to evaluate the effect of *Katukyadi churna* in patients of Non-alcoholic steatohepatitis.

Patients attending OPD and IPD of the KAHER's Shri B.M.K. Ayurveda Mahavidyalaya & Hospital were selected for the study.

2.1. Patients

Thirty patients sonologically diagnosed as fatty liver were subjected to Elastographic assessments. 11 patients meeting the diagnostic criteria of steatohepatitis (sonological and elastographic)

Table 1

Katukyadi churna- Ingredients, part used, chemical constituents and proportion.

| S.no | Name of the drug | Botanical name and Family | Part Used | Important chemical constituents | Proportion |
|------|--------------------|---------------------------------------|-------------|--|------------|
| 1 | <i>Katuki</i> | <i>Picrorhiza kurroa</i> Royle Benth. | Roots | Phenolic glycoside, Iridoid glycoside, Cucurbitacins glycoside, Aliphatic homomonocyclic glycosides. Sesquiterpene | 1 part |
| 2 | <i>Nimba</i> | <i>Azadirachta indica</i> A.Juss. | Stem bark | Tannins, Saponins, Phlobatanins, Flavanoids, Cardiac glycosides, alkaloids | 1 part |
| 3 | <i>Amrita</i> | <i>Tinospora cordifolia</i> Miers. | Stem | Phenols, Flavanoids, Alkaloids, Saponins, cardiac glycosides, steroids | 1 part |
| 4 | <i>Bhringaraj</i> | <i>Eclipta alba</i> Hassk. | Whole plant | Alkaloids, Flavanoids, glycosides, triterpenoids, polyacetylenes | 1 part |
| 5 | <i>Bhumyamalki</i> | <i>Phyllanthus niruri</i> Linn. | Whole plant | Alkaloids, Tannins, Saponin, Phlobatannins, Sterols, glycosides, Resins. | 1 part |

Table 2
Patient profile: Expressed in Mean, standard deviations (S.D.) and percentage.

| S.No | Clinical Profile | Number | Percentage (%) |
|------|--------------------------------|---------------|----------------|
| 1 | Age (yrs) | 43.09 ± 10.70 | |
| 2 | Sex | | |
| | Male | 5 | 45.45 |
| | Female | 6 | 54.5 |
| 3 | Socio Economic Status | | |
| | Poor | 2 | 18.18 |
| | Middle class | 9 | 81.1 |
| 4 | Food | | |
| | Vegetarian | 7 | 63.63 |
| | Mixed | 4 | 36.36 |
| 5 | Educational Status | | |
| | Primary | 1 | 9 |
| | Secondary | 7 | 63.63 |
| | Graduate | 3 | 27.27 |
| 6 | Lifestyle | | |
| | Sedentary activity | 9 | 81.1 |
| | Moderate activity | 1 | 9 |
| | Heavy activity | 1 | 9 |
| 7 | Prakurti (Body constitution) | | |
| | Vatapradhana Pitta | 5 | 45.45 |
| | Pitta pradhanaKapha | 1 | 9 |
| | VatapradhanaKapha | 1 | 9 |
| | Pitta pradhanaVata | 2 | 18.18 |
| | kaphapradhanaVata | 2 | 18.18 |
| 8 | Agni | | |
| | Abhyavaharan Shakti – Avara | 7 | 63.63 |
| | Madhyama | 4 | 36.36 |
| | Jarana shakti – Avara | 10 | 90.9 |
| | Madhyama | 1 | 9 |
| 9 | Duration of illness (In Years) | 1.92 ± 1.33 | |
| 10 | Weight (Kgs) | 74.30 ± 12.51 | |
| 11 | BMI | 29.59 ± 7.20 | |
| 12 | Drop outs | 1 | 9 |
| 13 | Study completed | 10 | 90.9 |
| 14 | Total | 11 | |

were recruited from patients visiting outpatient department of KAHER's Shri. BMK Ayurveda Hospital Belagavi, Karnataka, India.

2.1.1. Inclusion criteria

Patient of either sex, between the age group of 20–60 yrs, Sonologically diagnosed cases of fatty liver, elastographic reading between 6.4 and 11.7 kPa.

2.1.2. Exclusion criteria

Alcoholic stetohepatitis, cirrhosis of liver, pregnant and lactating women.

2.1.3. Screening methods

All patients included in this study were examined thoroughly and data was recorded systematically. Various laboratory and Ayurveda variables were assessed. Laboratory investigations were carried out at clinical laboratory, KAHER's Shri BMK Ayurveda Mahavidyalaya, Belagavi in all patients at baseline and on 180th day of intervention. Elastography evaluation were done at Dr Varadaraj Gokak's Liver & Gastroenterology clinic, Belagavi. Clinical trial was conducted from October 2016 to December 2017.

2.2. Study design

The study was an open label clinical study. Study has single arm with pre and post test design. The scholars involved in distribution and administration of study articles were different from the investigators. The flow chart of the study is depicted in Fig. 1.

2.2.1. Intervention

Raw drugs of the Katukyadi churna were procured from authentic source. Identification, raw material assessment, quality assessment of final product (analytical and microbial) was done at AYUSH Approved drug testing laboratory for ASU Drugs, Govt. of India, KLE Shri B M Kankanawadi Ayurveda Mahavidyalaya & Research Centre, Belagavi. (Table 1). Katukyadi churna was

prepared in GMP certified KLEU's pharmacy Belagavi as per the standard procedures for Churna (Powder) preparations.

K. churna was administered in the dose of 6 gm (Sachets) twice a day with water. For 180 days. Administration was in the middle of the food intake. Observations were made on 30th, 60th, 90th, 120th, 150th & 180th day of intervention.

Study obtained permission from the Institutional Ethics Committee of KAHER's Shri B.M.K. Ayurveda Mahavidyalaya & Hospital (BMK/15/PG/KC/02. Dated 19/02/2016). CTRI Number (CTRI/2018/01/011490). Patients were asked to adhere to the treatment protocol and report any adverse event to the investigators at the earliest. All such manifestations were screened for the possible adverse events.

Table 3
Clinical Manifestations in the patients.

| S.No | Manifestation | Number | Percentage % |
|------|--|--------|--------------|
| 1 | Ajeerna (Indigestion) | 11 | 100 |
| 2 | Agnimandya (loss of appetite) | 11 | 100 |
| 3 | Gouravata (heaviness of body) | 10 | 90.9 |
| 4 | Arochaka (Anorexia) | 11 | 100 |
| 5 | Mild abdominal Pain (Right hypochondriac Region) | 7 | 63.63 |
| 6 | Amlapitta (Sour eractions) | 7 | 63.63 |
| 7 | BMI Normal (18.5–22.9) | 2 | 18.18 |
| 8 | Over weight (23–24.9) | 1 | 9 |
| 9 | Pre Obese (25–29.9) | 4 | 36.36 |
| 10 | Obese- Type 1 (30–40) | 3 | 27.27 |
| 11 | Obese- Type 2 (40–50) | 1 | 9 |
| 12 | Increased Total Bilirubin (>1.2 mg/dL) | 5 | 45.45 |
| 13 | Increased Direct Bilirubin (>0.3 mg/dL) | 6 | 54.54 |
| 14 | Increased AST (>40 IU/mL) | 7 | 63.63 |
| 15 | Increased ALT (>45 IU/mL) | 3 | 27.27 |
| 16 | Hypoalbuminemia (<3 mg/dL) | 1 | 9 |
| 17 | Increased Total Cholesterol (<200 mg/dL) | 3 | 27.27 |
| 18 | Decreased HDL (40–59 mg/dL) | 2 | 18.18 |
| 19 | Deranged LDL (100–129 mg/dL) | 8 | 72.72 |

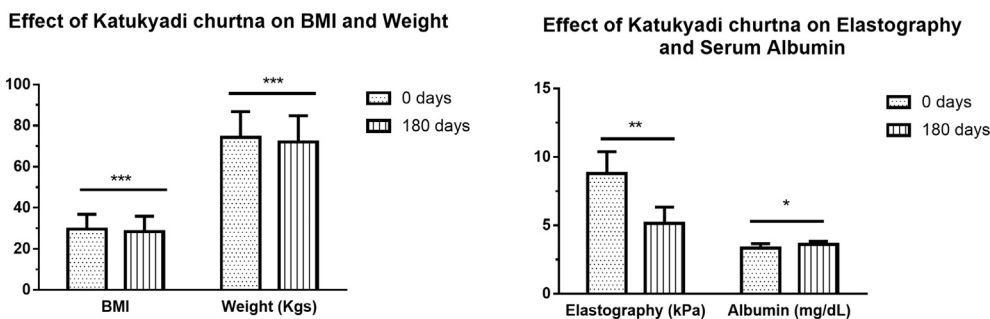


Fig. 2. Effect of Katukyadi churtna on BMI Weight, Elastography and serum Albumin.

2.3. Criteria for assessment criteria-

Patients screening was done for viral markers for Hepatitis B & C.

2.3.1. Primary outcome

Elastography (Model 402, Echosens Company, medium probe). Elastography is a novel, non invasive technique which measures elastic properties of soft tissue like liver through quantitative or qualitative methods. Mechanism includes transmission of vibration to the tissue by a vibrator. Elastic shear wave induced by vibrator propagates through the tissue. Concurrently pulse-echo ultrasonic acquisitions are done to follow shear wave propagation and its velocity. Harder the tissue faster is the propagation. It is expressed in kilopascal (kPa) [27].

2.3.2. Secondary outcome

Subjective symptoms like *aruchi* (Anorexia), *agnimandhya* (decrease in digestion), *ajeerna* (indigestion), *gouravata* (Subjective feeling of heaviness in whole body). Random blood sugar, liver function test (serum bilirubin total, serum bilirubin direct, alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum total protein, serum albumin, albumin/globulin (A/G) ratio, serum alkaline phosphatase). Normal reference ranges of liver function tests used for this study are: Total bilirubin: 0.0–1.5 mg/dL, AST: 5–34 U/L, ALT: 0–55 U/L, Alkaline phosphatase: 50–125 U/L, albumin is 3.5–5.0 g/dL [28]. Lipid profile (Cholesterol total, HDL, LDL, Triglyceride) and were assessed. Normal reference ranges of lipid profile used for this study are LDL<100, TC < 200, HDL<40, Triglyceride<150 [29].

2.4. Statistical methods

Statistical analysis was carried out using SPSS Version 20. Comparison at different time points was carried out by Student’s ‘t’ test for parametric test and for non-parametric McNemar’s test was

applied. Values are reported as mean ± standard deviation. All tests were considered statistically significant at p < 0.05.

3. Results

A total of 11 patients participated in the study. Two patients suffered from loose stools 2–3 times/day for the first 8 days. However patients did not suffer from dehydration and had no disturbance to their daily functioning. And no remedial measures were done. One patient dropped out of our study due to concomitant illness of Nephrolithiasis (Fig. 1).

3.1. Patient characteristics

Mean age of patients was 43.19 yrs, mean duration of the illness was 1.9 yrs, maximum number of patients were female (54.5%), vegetarians (63.63%), secondary level education (63.63%), sedentary activity (81.1%), Vata pradhana pitta prakurti (45.45%) (see Table 1). Mean weight of the participants was 74.3 Kgs and mean BMI was 29.5. Manifestations profile in the patient showed decrease in *abhyavara* (63.63%) and *jarana shakti* (90.9%). They had *Ajeerna* (100%), *Agnimandya* (100%), *Arochaka* (100%), *Gouravata* (90.9%), *sour eructation* (63.63%), mild pain in right hypochondriac abdominal region (63.63%). Other manifestations were increase in BMI (63.63%), Total bilirubin (45.45%), direct bilirubin (54.54%), AST (63.63%), ALT (27.27%), Total Cholesterol (27.27%) and Triglycerides (63.63%). Derangement in LDL (72.72%) and decrease in HDL (18.18%) were observed (Tables 2 and 3).

3.2. Primary outcome

Study showed significant improvement in Elastography readings (p = 0.001). Intervention of *K. churtna* produced significant reduction in elastographic reading to normalcy at 180th day of intervention (Fig. 2) (Table 5).

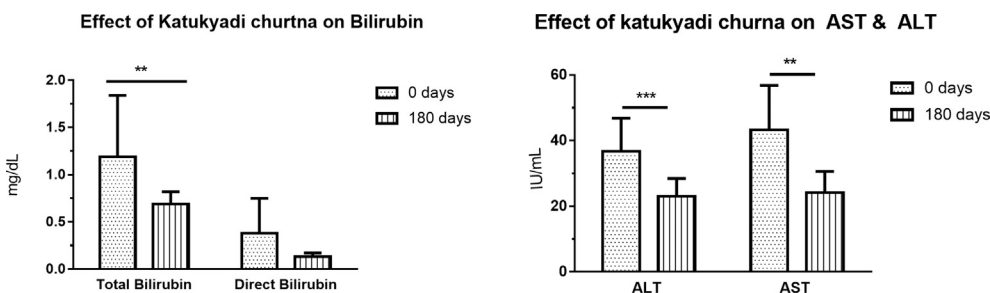


Fig. 3. Effect of Katukyadi churtna on bilirubin, AST and ALT

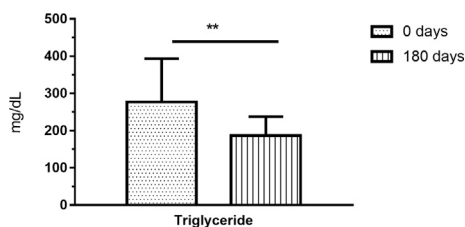


Fig. 4. Effect of Katukyadi churna on triglycerides.

3.3. Secondary outcomes

K. churna intervention showed improvement in LFT parameter like total bilirubin ($p = 0.02$), ALT ($p < 0.001$), AST ($p = 0.001$), albumin ($p = 0.04$). Significant improvement in triglyceride ($p = 0.005$) was observed among the lipid profile assessments. Reduction in *Ajeerna* ($p = 0.002$), *Agnimandhya* ($p = 0.004$), *Arochaka* ($p = 0.001$), *Gouvrvata* ($p = 0.002$), Weight ($p < 0.001$) and BMI ($p < 0.001$) were observed (Figs. 2–4) (Table 4 and 5).

4. Discussion

The study showed that *K. churna* is effective in the management of NASH. *K. churna* showed not only significant reduction in the elastographic values but also in reducing to the normative liver values. *K. churna* also showed significant reduction in *Ajeerna*, *Agnimandhya*, *Arochaka*, *Gouravata*, weight, BMI, total bilirubin, ALT, AST, albumin values, triglycerides. Increased AST and hypo albuminemia changed to normative levels post intervention. Intervention did not produce any major adverse effects and had good compliance. Loose motions in two patients could be due to the *bhedana* (piercing quality producing purgative action) [30] effect of the drug *Katuki*.

Majority of the patients were suffering from grade II fatty liver (72.7%) and few were with grade I fatty liver (27.3%) in sonography findings. Patients noticed symptoms which could be related to NASH since 2–3 years. All the patients were diagnosed with NASH for the first time. Majority of the patients were in middle age (43 yrs) similar to the findings (35–55yrs) in other study [31]. Our study showed predominant female gender involvement (55%) which was similar to the observation of other study [32], where biopsy proven NASH among female and male was in the 2:1 ratio. This could be due to gender specific biology. *Prakurtti* assessment showed predominant *vata pittaja prakurtti* (46%). Patients had irregularity in diet and dietary patterns. Diet was more of *Abhishyandhi ahara* [*picchila* (thick), *guru* (heavy), *dravam* (liquid), *sroto avarodhaka* (obstructing the channels) which causes more of *Kapha* properties], *vidahi* (causes burning sensation and increase in *pitta dosha*), *madhura* (sweet), *guru* (heavy) properties. Dietary patterns were *vishamashana* (deranged eating practises), and *adhyashana* (excess food consumption). Digestion was impaired with decreased (64%) *abhyavarana shakti* (quantity of food intake) and *jarana shakti* (time required for food digestion) in 91% patients. Sedentary

activity (91%) was prevalent in patients. Hence probable pathogenesis in NASH or *Kaphaja Yakruta Roga* based on our observation is predominant intake of *vidahi*, *abhishyandi*, *guru*, *madhur* foods. Derangement in dietary patterns are *vishamashana* and *adhyashana* along with sedentary activity. These etiological factors can cause *agnimandhya* (decrease in *abhyavaharana shakti*, and *jarana shakti*) and increase in *ama* (product of deranged metabolism) production. *Kapha* and *Pitta* dosha gets increase in *annava srotas* (Gastro intestinal tract) and *Yakruta*. Increase of *kapha* dosha and *ama* in location of *pitta* like liver and *pachamanashaya* (digital part of stomach) causes excess fat accumulation in hepatic cells (*kapha vrudhhi*) and *Soroavrodha* (obstruction to channels). Manifestations includes metabolic derangements like *ajeerna* (indigestion), *yakruta guruta* and *kathinata* leading to *Kaphaja Yakruta roga*. However in the current patients *kathinata* of liver or abdomen was not observed and it might manifest in the advanced stages of NASH. However subclinical presentations of hardness and stiffness was demonstrated through elastographic evaluations.

Katukyadi churna contains 5 drugs like {*Katuki* (*P. kurroa* Royle Benth.), *Nimba* (*A. indica* A. Juss.), *Amritha* (*T. cordifolia* Miers.), *Bhringraj* (*E. alba* Hassk.), *Bhumyamalaki* (*P. niruri* Linn.)}. (Table 1) This formulation was conceptualised considering the *tikta pradhana rasa*, hepatotropic action and *rasayana* (regenerative) effect of these drugs. *Katukyadi choorna* interventions in patients of liver disorders with predominant *pitta* and *kapha dosha* showed beneficial effect in our hospital settings (unpublished). Hence the current study was planned. Administration of the drug was in the middle of food as it is the time administered for *samana vayu* and *agni* derangements. The study showed that intervention produced significant improvement in gastro intestinal parameters like *agnimandhya*, *ajeerna*, *aruchi*, *gouravata*. Hardness and stiffness of the liver are the indicators of NASH. These could be due to *kapha* increase in the locations of *pitta* like liver. Intervention for 180 days showed reverting of deranged elastographic values ($p = 0.001$) to the normative levels. This effect could be due to properties of the *Katukyadi churna* ingredients like *ushna virya* (hot potency), *tikta rasa*, *ruksha*, *laghu guna*, *srotoshodhaka* and *kapha pitta shamana*.

Liver function evaluation showed significant improvement and restoration to normative ranges post intervention. Significant reduction was noted in total bilirubin ($p = 0.02$), AST ($p = 0.001$) and ALT ($p < 0.001$) and improvement in Albumin ($p = 0.04$). Derangement in synthesis and elimination of triglycerides cause lipid accumulation in hepatocytes. This can cause progressive inflammation and derangements in AST and ALT leading to steatohepatitis. ALT specifically indicates hepatic necrosis and AST reflects cholestatic damage. Normalization of AST and ALT values were noted with the intervention. These effects could be due to pharmacological activities of ingredients of *Katukyadi churna*. They have properties like *tikta* (bitter) *rasa*, *deepana*, *pachana*, *grahi*, *yakrit uttejaka*, *kleda shoshana*, *srotoshodhana*, *Kapha pittahara*, *medahara* effects. Studies have shown that all ingredients have properties like hepatoprotective, Anti-inflammatory, Anti oxidant, immunomodulatory effects and anti NAFLD effects. *Katuki* (*P. kurroa* Royle Benth.) [33] through contents of picroside I showed

Table 4
Effect of interventions on parameters- *Ajeerna*, *Agnimandhya*, *Arochaka*, *Gouvrvata*.

| S.No | Parameters | 0 TH DAY | 30 TH DAY | 60 TH DAY | 90 TH DAY | 120 TH DAY | 150 TH DAY | 180 TH DAY | 0–30 | 0–60 | 0–90 | 0–120 | 0–150 | 0–180 |
|------|--------------------|---------------------|----------------------|----------------------|----------------------|-----------------------|-----------------------|-----------------------|-------|-------|-------|-------|--------|--------|
| 1 | <i>Ajeerna</i> | 1.00 ± 0.00 | 1.00 ± 0.00 | 0.82 ± 0.40 | 0.80 ± 0.42 | 0.60 ± 0.51 | 0.10 ± 0.31 | 0.00 ± 0.00 | 0.50 | 0.50 | 0.50 | 0.125 | 0.004 | 0.002 |
| 2 | <i>Agnimandhya</i> | 1.00 ± 0.00 | 1.00 ± 0.00 | 0.82 ± 0.40 | 0.90 ± 0.31 | 0.70 ± 0.48 | 0.60 ± 0.51 | 0.10 ± 0.31 | 0.50 | 0.50 | 1.00 | 0.250 | 0.125 | 0.004 |
| 3 | <i>Arochaka</i> | 1.00 ± 0.00 | 1.00 ± 0.00 | 0.73 ± 0.46 | 0.64 ± 0.50 | 0.36 ± 0.50 | 0.09 ± 0.30 | 0.00 ± 0.00 | 0.25 | 0.25 | 0.125 | 0.016 | 0.002 | 0.001 |
| 4 | <i>Gouvrvata</i> | 0.91 ± 0.30 | 0.91 ± 0.30 | 0.82 ± 0.40 | 0.45 ± 0.52 | 0.45 ± 0.52 | 0.27 ± 0.46 | 0.00 ± 0.00 | 1.00 | 1.00 | 0.063 | 0.063 | 0.016 | 0.002 |
| 5 | Weight (Kgs) | 74.30 ± 12.51 | 74.13 ± 12.63 | 73.90 ± 12.58 | 73.29 ± 13.07 | 73.03 ± 12.93 | 72.64 ± 13.15 | 72.02 ± 12.79 | 0.083 | 0.019 | 0.002 | 0.003 | <0.001 | <0.001 |
| 6 | BMI | 29.59 ± 7.20 | 29.39 ± 7.30 | 29.23 ± 7.44 | 29.06 ± 7.79 | 28.91 ± 7.66 | 28.69 ± 7.69 | 28.42 ± 7.48 | 0.171 | 0.036 | 0.012 | 0.003 | <0.001 | <0.001 |

Table 5
Effect of interventions on parameters of liver and lipid.

| S.No | Parameters | 0 TH DAY | 180 TH DAY | P value |
|------|------------------------------|---------------------|-----------------------|---------|
| 1 | Elastography (kPa) | 8.78 ± 1.60 | 5.14 ± 1.19 | 0.001 |
| 2 | Total Bilirubin (mg/dL) | 1.19 ± 0.65 | 0.69 ± 0.13 | 0.020 |
| 3 | Direct Bilirubin (mg/dL) | 0.38 ± 0.37 | 0.13 ± 0.04 | 0.068 |
| 4 | ALT (IU/mL) | 36.7 ± 10.13 | 23.00 ± 5.49 | <0.001 |
| 5 | AST (IU/mL) | 43.3 ± 13.53 | 24.20 ± 6.44 | 0.001 |
| 6 | Total Protein (mg/dL) | 6.69 ± 0.16 | 6.53 ± 0.37 | 0.27 |
| 7 | Albumin (mg/dL) | 3.33 ± 0.34 | 3.62 ± 0.22 | 0.04 |
| 8 | A/G ratio | 0.96 ± 0.18 | 1.06 ± 0.22 | 0.322 |
| 9 | Alkaline Phosphatase (IU/mL) | 73.5 ± 13.08 | 77.10 ± 7.51 | 0.309 |
| 10 | Total Cholesterol (mg/dL) | 191.1 ± 46.41 | 169.7 ± 27.93 | 0.12 |
| 11 | HDL (mg/dL) | 45.8 ± 5.67 | 43.30 ± 5.53 | 0.069 |
| 12 | LDL (mg/dL) | 85.1 ± 30.14 | 88.4 ± 24.15 | 0.645 |
| 13 | Triglyceride (mg/dL) | 276.9 ± 116.44 | 186.8 ± 51.08 | 0.005 |
| 14 | Random Blood Sugar (mg/dL) | 102.7 ± 48.07 | 106.9 ± 49.14 | 0.490 |

hepatoprotective effect and decrease in triglycerides, ALT, AST, fatty infiltration of liver, anti NAFLD effect in NAFLD animal model. Nimba (*A. indica* A.Juss.) leaf extract [34] has hepatoprotective effect may be through phytochemicals like Azadirachtin, Nimbidin, Nimbin, Nimbinin. Guduchi (*T. cordifolia* Miers.) [35] has anti-inflammatory, immunomodulatory, hepatoprotective, antioxidant and antidiabetic effects. *E. alba* Hassk. [36] has also hepatoprotective effect. *P. niruri* Linn. (*Bhumyamalaki*) [37] in animal model showed decrease in hepatomegaly, visceral fat weight, serum total cholesterol, low-density lipoprotein, free fatty acids (FFAs), ALT, ALP, insulin concentration, homeostatic model assessment of insulin resistance (HOMA-IR), hepatic content of cholesterol, triglyceride, malondialdehyde, prevented fibrosis, and has anti NAFLD effect. *Katukyadi churna* produced significant reduction in BMI ($p < 0.001$), weight ($p < 0.001$) and Triglyceride ($p = 0.005$) values. These could be due to decrease in *kapha* and *meda*, *apatarpana*, *lekhaneya* and *langhana* effects. Drugs reducing insulin resistance like metformin and thiazolidinediones [38,39] have shown beneficial effect. Cochrane analysis of probiotic treatment in NAFLD and NASH did not show beneficial outcome.

Alternative and complimentary medication have shown beneficial effect in NAFLD and NASH. Clinical studies have shown that Polyherbal formulation [40], Yiqi Sanju Formula (YQSJF) (traditional Chinese herbal medicine) [41], extracts of grape seed [42] and *Gynostemma pentaphyllum* [43] have demonstrated beneficial outcome in patients with NAFLD/NASH.

Significance of the study is that a 6 months intervention of a polyherbal Ayurveda formulation showed significant improvement in subjective and objective parameters. Parameters of gastrointestinal manifestations, liver functions and elastographic values reverted to normal values. Assessment was through non invasive method of elastography. Attempt was made to understand the pathophysiology as per Ayurveda through the observations made during the study.

Study has limitations like small sample size, open clinical trial, single arm with no comparator. Small sample was selected as available patient pool was less and also due to difficulty in access to elastography instrument. Comparator arm would have been helpful in giving clarity of clinical improvement. Clinical improvement may not be due to placebo, spontaneous or natural history improvement. As NASH is a silent and progressive disorder. Non Liver biopsy based NASH diagnosis is a limitation of this study.

5. Conclusion

K. churna showed promising results in the management of NASH. Improvement were observed in both subjective and

objective parameters. Change from deranged levels to normative levels were observed in liver function and elastography parameters. Hence further studies through randomized controlled trial design are needed. Assessment of biological effect of *Katukyadi churna* on liver histopathological changes of NASH will be beneficial.

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Conflict of interest

None.

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