Study Protocol

Evaluation Of Efficacy Of PhalatrikadiGhanVati In Patients Of Non-Alcoholic Fatty Liver Disease Through Reverse Pharmacology Approach – Study Protocol

Abstract

Background: Non-alcoholic fatty liver disease (NAFLD), mostly diagnosed incidentally, is a rapidly emerging liver disorder. In absence of any specific treatment, current management focuses on use of hepatoprotective agents in addition to lifestyle modification and prevention of metabolic syndrome. Several Ayurveda agents have shown promising effects in patients over centuries of use. But this evidence needs to be assessed scientifically through reverse pharmacology approach. A polyingredient Ayurveda drug, *Phalatrikadighanvati* (PGV) has been selected for this study because of its long history of use and that its individual contents have shown positive results in liver disorders.

Objective: Evaluation of efficacy of *Phalatrikadighanvati* in patients of non alcoholic fatty liver disease (NAFLD) along with its pharmaceutical and analytical study.

Material & method: The drug shall be pharmaceutically processed and analyzed as per pharmacopoeial standards.Present study has been designed as a randomized placebo controlled double blind clinical trial in two stages. The first stage shall be a pilot study to decide the best effective and safe dose in patients of NAFLD. The pilot study shall include two groups of 10 patients each in a dose of PGV 500mg and 1gm respectively twice a day for 12 weeks. After selection of best dose, RCT will be conducted on that dose in the second stage.It shall be a Phase 2 trial with 60 patients divided equally in two groups.The patients in group one shall be given a dose as per outcome of pilot study twice a day and other group shall be administered a placebo for a period of 12 weeks.

Observations &Results: Observationsshall be noted and results will be drawn on the basis of observations and applying suitable tests. It will be and noted and presented in form of table, charts and graphs.

Conclusion: PGV is expected to be efficacious in ameliorating the signs and symptoms of NAFLD and act as a potent hepatoprotective agent.

Comment [N1]: Mention name of tests as per your sample size and type of variables required for analysis of data. Vague statement should be avoided in protocol.

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Comment [N3]: As the disease is diagnosed incidently, no specific signs and symptoms are observed in many cases. So it is required to assess the effect of drug on diagnostic parameters i.e lab investigations or radiological or sonological investigations as primary outcome.

Key words: Ayurveda, Non-alcoholic fatty liver disease, phalatrikadighanvati, reverse pharmacology

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a rapidly emerging disease with a prevalence of 6-35 % worldwide [1]. Recent studies across different parts of India have stated the prevalence of NAFLD to vary from 9 to 35% [2]. It is a condition where excess fat gets accumulates in the liver cells in individuals having no significant history of alcohol consumption [3]. The spectrum of NAFLD ranges from mere steatosis without cirrhosis to non-alcoholic steatohepatitis (NASH) which may or may not be accompanied by cirrhosis. NASH is a progressive entity affecting about 5-7 percent of the general population and 30-40 percent of patients with raised liver enzymes. NAFLD is fast emerging as a main non-viral etiological cause of Hepatocellular carcinoma (HCC) [4].

NAFLD is considered as the hepatic expression of the metabolic syndrome that is most typically linked to obesity [5]. Moreover, the Indian diet comprising of high fat & carbohydrates accompanied with a sedentary lifestyle facilitates the pathology leading to metabolic syndrome and its expressions like NAFLD. Currently there is no specific treatment for NAFLD. All the clinical protocol are based on providing hepato protective drugs to improve liver function apart from managing the concurrent symptoms of metabolic syndrome. The liver has a unique capacity to compensate and perform its functions despite stress due to any physical, metabolic or dietary cause. It is only because of this reason that there may be minimal or even absent signs and symptoms of liver disease. As such NAFLD is most of the times detected incidentally during a routine health check-up or while investigating other symptoms.

Recent literature suggests use of herbal or plant based medicines in successfully managing NAFLD and improving the liver function [6-7]. Ayurvedic medicine includes plants and minerals used either single or in polyingredient formulations.A fact that Ayurveda medicines are already in use since centuries demand a different way of approach towards their scientific validation. Despite their use spanning over centuries, scientific evidence regarding their safety and efficacy needs to be documented, which cannot be done via conventional methodology. A novel process, termed as Reverse Pharmacology (RP) can be widely employed in validation of therapeutic actions of Ayurveda drugs, which are already in use traditionally. It follows a bedside to bench side approach. The traditional treatment which is being used since centuries to manage patients, is evaluated in a clinical setting, leading to its phytoanalysis in laboratory. Starting with knowledge/data gained through experience,

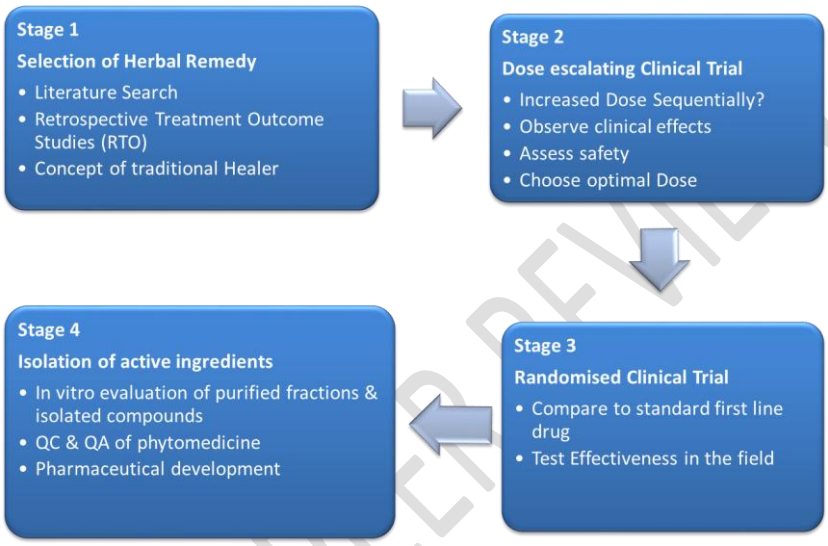
Comment [N4]: You can refere the research work carried out to assess the efficacy and safety of Arogyavardhini Compound (specially indicated for liver disease) in management of metabolic syndrome to establish the link between metabolic syndrome and NAFLD and future expected outcomes. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7685257/

Comment [N5]: Add more references of currunt research work on metabolic syndrome or hepatoprotective drugs and NAFLD.

Comment [N6]: Provide references of some clinical trials carried out on herbal as well as herbomineral formulations for treatment of Metabolic syndrome or NAFLD.

exploratory research, and applicable clinical/experimental studies, RP progresses to the isolation of active components (Figure-1). Taking a cue from this process of RP, the drug, *PhalatrikadiKwath*in the form of its *Phalatrikadi Ghanvati* (PGV, solidified aqueous extract), which is advised for management of liver disorders in the classical medical text of *Chakradatta* [8] has been chosen for the proposed study.

Figure-1, Stages of Reverse Pharmacology



Only first three stages of RP shall be conducted in this study, leaving the stage of isolation of active ingredients out of the scope. Stages of the Reverse Pharmacology approach have been divided in the following manner:

1. Selection of Herbal Remedy
2. Dose- escalating clinical trial –Pilot Study
3. Randomized Clinical Trial

Selection of Herbal Remedy (Stage-1)

The proposed drug under this study is currently being used by Ayurveda physicians for management of *yakrit rog* like acute viral hepatitis. Some studies have also been published for its effective role in acute viral hepatitis. A case study on two patients has also been published for its effectiveness on patients of non alcoholic fatty liver disease [9].

Phalatrikadi Kwath is advised as a choice of drug in liver disorders of varied etiology including NAFLD. It is a combination of eight herbs(Table-1)which have individually been studied for their effect on liver [10].The individual drugs in this combination have shown hepatoprotective effect in NAFLD [11-13]. *Guduchi* has experimentally shown to be therapeutically effective in amelioration of obesity and associated hepatic dysfunction, protection of hepatic function and help to prevent fibrosis and stimulates regeneration of hepatic tissue along with protection from Hepatitis B & E surface antigen, which makes it a potential candidate for use in NAFLD [14-15]. *Kalmegha* has certain bioactive phytonutrients having antioxidant and anti-inflammatory activity which ameliorate rich fat diet-induced steatohepatitis and liver injury [16-17].

Phalatrikadi kwatha is a combination of dried herbs, pulverised to make a coarse powder. This coarse powder is then given to patient for preparation of *Kashaya* (decoction) at home. The preparation of *Kashaya* (decoction) requires following a certain set of principles like fixing ratio of raw herbs to amount of water, duration of heating, quantum of heat to be used for heating and most importantly the dose of drug. Most of the times the patient is unware of these guidelines. Moreover, in the era of globalisation and fast moving life, it does not seem feasible to sacredly prepare decoction every time. Modifying the dosage form on the basis of ancient Ayurveda pharmaceutical principles for increasing patient compliance and to make it easier to administer is the need of the hour.Thus,dried aqueous extract of *Phalatrikadi Kwatha* has been used as a lead drug in the form of pills, that is, *Phalatrikadi Ghanvati* (PGV)for studying its effectiveness in non alcoholic fatty liver disease.

Table -1 Formulation Composition of *PhalatrikadiGhanVati*

S.No.	Contents	Botanical Name	Part used	Ratio
1.	*Amalaki*	*Emblicaofficinalis*Gaertn.	Fruit	1 part
2.	*Haritaki*	*Terminalia chebula*Retz.	Fruit	1 part
3.	*Bibhitaki*	*Terminalia bellerica*Roxb.	Fruit	1 part
4.	*Vasa*	*Adhatodavasica*Nees.	Leaf	1 part
5.	*Guduci*	*Tinosporacordifolia*Miers.	Stem	1 part
6.	*Nimba*	*Azadirachtaindica*A. Juss.	Bark	1 part
7.	*Kutaki*	*Picrorrhizakurroa*Royale ex Benth.	Root	1 part
8.	*Kalmegha*	*Andrographispanniculata*Nees.	Whole plant	1 part
9.	Water			64 parts

Aim and Objectives of Study

Aim: Evaluation of efficacy of *Phalatrikadi ghanvati* in patients of non alcoholic fatty liver disease (NAFLD) along with its pharmaceutical and analytical study.

Objectives:

Primary Objectives:

1. Evaluation of efficacy of *Phalatrikadi ghanvati* in patients of non alcoholic fatty liver disease (NAFLD).

Secondary Objectives:

1. To prepare *Phalatrikadi Ghanvati* described traditionally by preparing its water extract (PGV).
2. To assess the prepared formulation *Phalatrikadi GhanVati* (PGV) for its quality control parameters.

Material and methods:

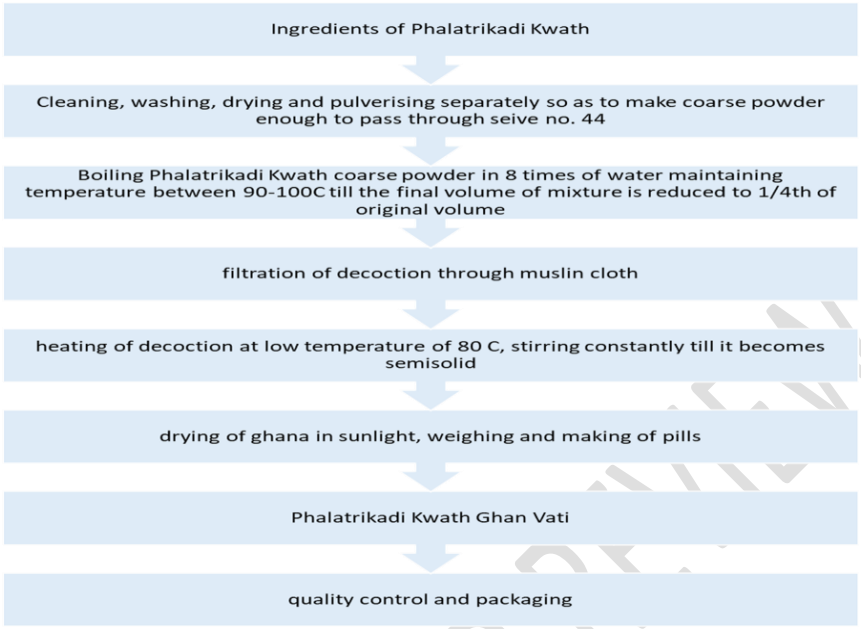
Pharmaceutical study*:*

Three different batches of PGV shall be prepared to establish pharmaceutical standardization. Pharmaceutical study will be done in following steps;

- **Procurement of Raw materials:** All required raw materials will be procured from field and authentic reliable source.
- **Authentication of Raw materials**: Raw drugs will be verified and authenticated by Department of *Dravyaguna* of MGAC & RC, Salod, Wardha. Raw drug will be standardized as per A.P.I. specifications.
- **Preparation of *Phalatrikadi Ghanvati* (PGV):** The contents of PGV shall be pharmaceutically processed to prepare pills of the drug. (Figure-2)

Comment [N7]: Primary objective should be clear and concise as well as measurable. Mention about the key outcome on which the drug is being assessed like any biomarker specific to diaese or any sonological or radiological investigation concerened to disease

Figure-2 Flow diagram of unit procedure of preparation of *PhalatrikadiGhanVati*



Analytical study*:* [18]

Analytical study of finished products, *Phalatrikadi Ghanvati* shall be conducted as per pharmacopoieal parameters.

Organoleptic Characteristics: Appearance, taste & colour

Physico-chemical parameters: Loss on drying at 105°c, Total ash, Water soluble extractive, Alcohol Soluble extractive, Acid insoluble ash, Disintegration Time, Hardness, Identification TLC/HPTLC, Test for heavy/toxic metals – Lead/Mercury/Arsenic, Microbial Contamination.

Methodology

Study design: Randomized Placebo Controlled Double Blind Clinical Trial (Stage 2 & 3 of Reverse Pharmacology). The randomization will be done on the basis of computerized generated table. Allocation of concealment will be done by coding of both the drugs with the help of third person.

Comment [N8]: Provide details about process of blinding. Who will be blind in the study. Who will do blinding? For different doses, how blinding wil be possible to make them identical in size? Clarify it and mention it in detail in methodology.

Comment [N9]: Write the anme of method of allocation concealment.

Study site: Department of Rasa Shastra & Bhaishajya kalpana MGACHRC, Salod,(H) Wardha.

Since the proposed work is based on the principles of Reverse Pharmacology consisting of various stages as depicted in Figure 1, the second & third stage of RP involves administration of drug to human participants for fixation of dose and randomized clinical trials.

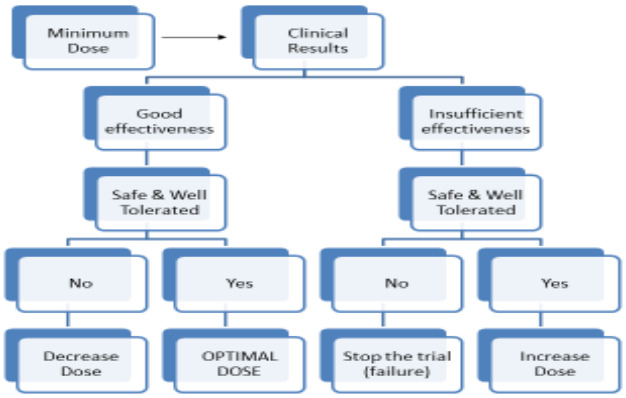
Comment [N10]: These paragraph do not seem relevant under title of study site. Rewrite or delet it.

Dose- escalating clinical trial (Stage 2 Reverse Pharmacology):

A pilot study shall be done to decide the best effective and safe dose in patients of NAFLD (Figure-3). The pilot study shall include two groups of 10 patients of NAFLD each. The patients in group one shall be given a dose of PGV 500mg twice a day and other group shall be administered a dose of 1gm of PGV twice a day. The duration of pilot study shall be 12 weeks.After selection of best dose, randomized placebo control double blind clinical study will be conducted on that dose.

Comment [N11]: What will be the criteria to decide the effectiveness and safety of trial drug. Mention it.

Figure 3: Dose optimisation of a drug through Reverse Pharmacology



Randomized Clinical Trial (Stage 3 - Reverse pharmacology)

A randomised placebo controlled double blind clinical trial with the best effective dose of PGV shall be conducted in this stage. It shall be a Phase-2 trial with 60 patients divided equally in two groups.The patients in group one shall be given a dose as per outcome of Pilot study twice a day and other group shall be administered a placebo for a period of 12 weeks.

Comment [N12]: What will be given as placebo? Mention it.

Informed Consent: The volunteers will be informed about the study protocol. Willing participants shall be randomly selected for different groups. Clinical research format will be prepared and validated. Informed written consent of each participant will be obtained prior to study.

Ethical Approval& Trial Registration: Ethics approval vide no MGACHRC/IEC/july-2021/321 dated 31.07.2021 has been taken from Institutional Ethics Committee of the study centre. Trial shall be registered in CTRI prospectively.

Participant's Inclusion Criteria

- Subjects of either sex, age group 30-60 years, non alcoholics.
- Clinical signs and symptoms suggesting of NAFLD/*YakṛtRoga*, that is, pain in right upper quadrant/epigastric region of the abdomen, feeling of nausea, and vomiting, loss of appetite, burning sensation in the abdomen.
- Incidental finding during investigations for some other disease
- Ultrasonography (USG) abdomen suggestive of NAFLD
- Biochemical: Liver function tests showing raised alanine transaminases (ALT) or aspartate transaminases (AST) levels raised above the normal limits (40 IU/L) up to 300 IU/L and with/without raised lipid profile and fasting/random blood glucose levels within normal limits.

Participant's Exclusion Criteria

- Patients unwilling to participate in study
- Patients with a history of alcohol intake exceeding 20 g/day (Alcohol consumption history shall be separately obtained from the patients and family)
- Patients testing positive for markers of other viral hepatitis

Criteria for discontinuing or modifying allocated interventions: Patients will be **w**ithdrawn from intervention if any harmful incidence, signs of drug allergy or any problem will occur; patient will be offered treatment at free of cost till the disease subsides.

Assessment Criteria

Subjective criteria: After selection, each participant will be evaluated individually for following sign and symptoms [parameters]: *Udaraśūla* (pain in abdomen), *utkleśa* (feeling of nausea and vomiting), *agnimandya* (impaired digestion), *klama* (Fatigue), *aruci* (loss of appetite), *sadana* (malaise). These Ayurvedic parameters will be assessed by gradation scale.

Objective Criteria

Comment [N13]: Before inclusion criteria, describe the scrrening process and standard diagnostic criteria as well.

Comment [N14]: Calrify term non-alcoholics, i.e not taking alcohol currently or never taken alcohol in life etc.

Anthropometric measurement: Weight, height ratio (body mass index [BMI]), Blood Pressure.

Haematological: Hb% , TLC, DLC, ESR

Biochemical Tests: Direct bilirubin, Indirect bilirubin, Total bilirubin, ALT, AST, Alkaline phosphatase, AST/ALT Ratio, Serum Cholesterol, Triglycerides, LDL, HDL, VLDL, FBS/RBS

Radiological: USG abdomen

Follow up: Each participant will receive the respective treatment from day one for 12 weeks (84 days). A dose of 14 days will be given to patients initially. In person follow up will be taken fortnightly to ensure patient compliance for taking medication. After completion of the treatment each participant will be assessed on subjective and objective parameters. Individuals, who will not turn up for follow-up, will be dropped out from the clinical study. All investigations will be done before starting and end of the treatment.

Observation and Results:

Observations will be noted and presented in the form of tables, chart, graphs and the data will be analysed with application of suitable inferential statistics. Post- test assessment will be tabulated as under corresponding to the grades above, noted prior to treatment:

A. Full mitigation: 75 – 100% relief
B. Significant improvement: 50-74% relief
C. Mild improvement: 25 – 49% relief
D. Unsatisfactory: < 25% improvement from the pre-test condition

Methods of statistical analysis

Statistical analysis will be done by applying suitable test. The tool used for the statistical tests will be SPSS. Hypothesis testing will be done using the corresponding tests at significance level of p=.05 so as to validate the statistical significance of the sample population.

Discussion

The treatment components as mentioned in texts of Ayurveda are not fulfilled unless the *Dravya* (substance) is converted into palatable and effective dosage form known as *Bheshaj* (pharmacologically active agent). In *Charaka Samhita*, it is mentioned that the *Matrayukta Aushadha* (optimum dosage) has *Laghupakam* (easily metabolised), *Sukhaswadam* (palatable), *Vyadhinashana* (therapeutic efficacy) properties. In Ayurveda

Comment [N15]: Is this assessment critera or initial screening tools to asses eligibility of participants. ? if it is assessment criteria, write its utility in this disease condition.

Comment [N16]: Describe the each term. What are the criteria to say full mitigation etc. ?

Comment [N17]: Write the sample size calculation method adopted and name of tests being employed for this study.

various drugs and preparations are mentioned to keep the body healthy and disease-free. Formulations described in Ayurveda treatese are of different varieties, innovative and compounded to increase the potentiality of the therapeutics [19]. A modified dosage form of *Phalatrikadi Kwatha* has been proposed for the current study. Processing of *Phalatrikadi Kwath*a as aquoeous extract in to *Ghanavati* (pills), shall be done pharmaceutically with regards to dosage modification. Since *Ghanvati* is processed as a water extract, it contains a high concentration of water soluble extracts in comparison to decoction form of the same drug, hence proposed for this study. This drug dosage modification has been strategically devised to make the drug easy to administer, palatable for the patient and to maintain a uniformity in dose of drug[20-21].

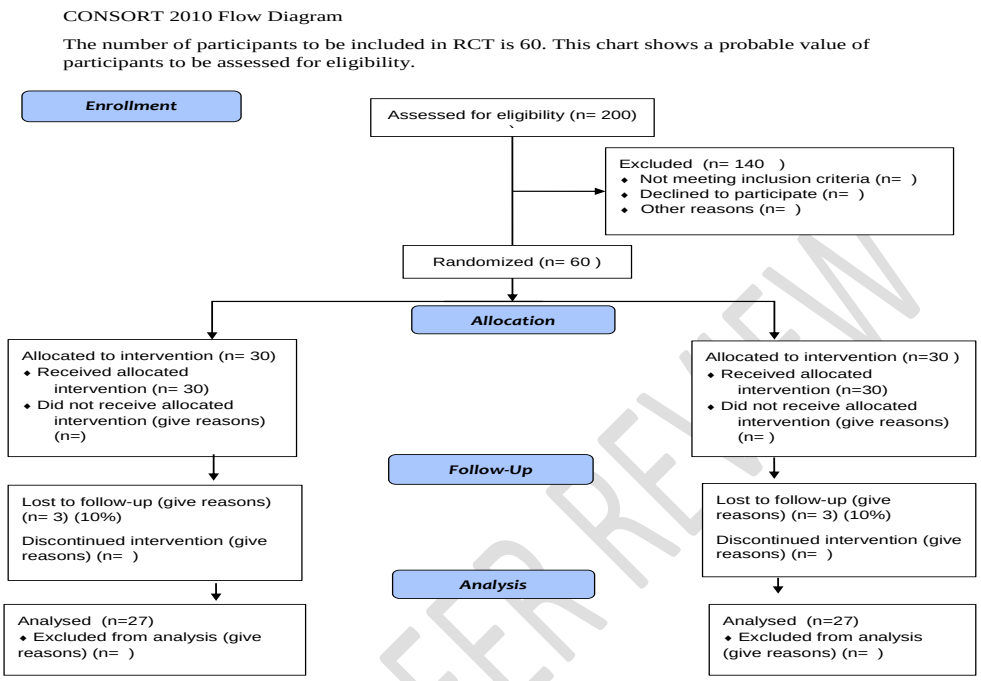
The individual drugs in PGV have shown hepatoprotective effect in NAFLD. Experimental studies have also shown, *Guduchi* to be therapeutically effective in amelioration of obesity and associated hepatic dysfunction. It is also known to stimulate regeneration of hepatic tissue [14-15]. *Kalmegha* has certain bioactive phytonutrients having antioxidant and anti-inflammatory activity which ameliorate rich fat diet-induced steatohepatitis and liver injury [16-17] The combined actions of ingredients of PGV can help improve the hepatobiliary function, protect the loss of functional integrity of the hepatic cell membrane, protecthepatic parenchyma against toxins, promotes hepatocyte regeneration [22]. These actions of the drugs can control the progress ofthe disease and also cause reversal in early stages of NAFLD.

Conclusion

Considering the prevalence and global distribution of NAFLD and its inconspicuous tendency to progress into cirrhosis and further hepatocellular carcinoma, if this study showed potential hepatoprotective action, this drug modification will surely improve patient compliance.PGV is expected to be efficacious in ameliorating the signs and symptoms of NAFLD and act as a potent hepatoprotective agent.

Fig 4. Consort 2010 Flow Diagram

Comment [N18]: It is enough to mention that the consort 2010 guideline will be used to present outcomes in scientific mananer. No need and never possible to predict mentioned details in CONSORT flow chart before completing the trial.



CONSENT AND ETHICAL APPROVAL: Informed written consent of each participant will be obtained prior to study. Prior to clinical study clearance from human ethics committee will be obtained. Prior to the study approval will be taken from IEC, MGACHRC, Salod (H) Wardha and CTRI registration will be done.

Comment [N19]: Has been mentioned already. Remove repetition

NOTE:

The study highlights the efficacy of " Ayurveda " which is an ancient tradition, used in some parts of India. This ancient concept should be carefully evaluated in the light of modern medical science and can be utilized partially if found suitable.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the

advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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