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A COMPARATIVE CLINICAL STUDY ON THE EFFECT OF ANUPANA BHEDA TRIVRUTTA CHURNA NITYA VIRECHANA IN YAKRUTA VIKARA (LIVER DISORDERS) WITH ABNORMAL LIVER FUNCTION TEST

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Abstract

Background: liver is a key organ, which performs many functions related to metabolism, energy storage, and detoxification of waste from the body. It helps to digest food, convert it to energy and store the energy until its need. Along with this, it helps to filter toxic substances out of bloodstream. Liver disease is a wide-ranging term that refers to any condition affecting liver. These conditions may develop for different reasons, but can all damage to liver and impacts its functions. In the *Ayurvedic* classics, *Yakut* (Liver) is a *Moola Sthana* of *Ratktavaha Strotas.* So, the liver diseases come under the disorders of *Raktavaha Strotas.* In the relation of treatment part of *Raktavaha Strotas Vikara, Virechana Karma* has got prime importance. **Aim and Objective:** To study the effect of *Trivrutta Churna Nitya Virechana* (Purgation) in *Yakrut Vikara* (Liver Diseases) with abnormal liver function test. **Methodology:** In present comparative clinical trial, 74 patients of liver disease will be divided into 2 groups (37 in each). In group A (Interventional Group) - *Trivrutta Churna* (in the form of Nitya *Virechana*) 7 gms along with *Anupana Sharkhara* 14 gms will be administered once in the morning for a period of 3 weeks; and in Group B (Comparative Group) - *Trivrutta Churna* (in the form of *Nitya Virechana*) 7 gms along with *Anupana Goghruta* 14 gms will be administered once in the morning for a period of 3 weeks. These subjects will be followed further for another 3 weeks after treatment period. Assessments will be recorded on 0, 11th 21st and 42nd day. **Results**: The outcomes will be evaluated on the objective and subjective parameters. **Conclusion:** *Nittya Virechana* with *Trivrutta Churna* will be effective and safe in normalising abnormal LFT in liver disorders.

Keywords: *Goghruta*; Liver disease; *Raktavaha Strotas Vikara*; *Sharkhara*; *Trivrutta*; *Virechana Karma*

Background and rationale:

Liver is a vital organ of the body, which plays a major role in metabolism, detoxification of metabolic end products, blood purification, protein synthesis, glycogen storage, and production of bio-chemicals necessary for

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digestion. It is a susceptible target of injury from various factors like drugs, alcohol, bacteria and viruses. Most of these factors cause liver cell injury by variety of mechanisms viz. by impairing metabolism, increasing oxidative stress and mitochondrial dysfunction, impairing proteasome functions and causing hypoxia to liver tissues [5].

Liver diseases can be categorized based on characteristic features as acute or chronic hepatitis (inflammatory disease), alcoholic liver disease, non-alcoholic fatty liver disease, hepatosis (non-inflammatory diseases), cirrhosis (degeneration disorders resulting in fibrosis of the liver) and hepatocellular carcinoma. In the present era, Liver disorders are found to be one of the major causes of morbidity and mortality. According to the office of National Statistics in the UK, liver disease is the 5th most common cause of death after heart disease, stroke, chest disease and cancer. In India, research study exhibited that the prevalence of non-ALDs was 75% and ALD was 25% of total liver diseases [1-4].

Once liver cells start getting injured due to etiological factors, deposition of fibrilar collagen and other extracellular matrix proteins takes place which leads to progressive fibrosis. The progression of liver fibrosis can further leads to cirrhosis; characterized by distortion of the normal architecture, septae and nodule formation, altered blood flow, portal hypertension, hepatocellular carcinoma, and ultimately liver failure [6]. Patients with liver disease often present with signs and symptoms including but not limited to digestive complaints, jaundice, nausea, vomiting, abdominal pain and distension, oedema, dark urine and loose motion. Clinical symptoms, few investigational techniques such as blood biochemistry, radiological imagining tests and USG are useful in diagnosing the problems [4-7].

Management of liver diseases mainly involves use of preventive measures such as, healthy diet, abstinence from alcohol, nutritional support and vaccination. However, pharmacological and surgical techniques are used along with preventive measures in majority of cases. As many of these treatment options have various serious side effects, physicians tend to move toward the alternative treatment approaches for the management of liver disorders [5-7].

Rationale of the study-

In the *Ayurvedic* classics; *Yakruta* (Liver) is a *Moola Sthana* of *Ratktavaha Strotas*[8]. So, the liver diseases come under the disorders of *Raktavaha Strotas.* Clinical symptomatology of *Yakrut Vikaras* resembles with *Kamala Lakshana Samucchyaya*[9] and *Yakrutdalyudara Lakshana* Samucchyay[10]. Hence *Yakrut Vikara* treatment principles, comes under the treatment principles of *Raktavaha Srotas Vyadhi*, *Kamala* and *Yakrutdalyudara*.

Virechana Karma is a *Panchakarma Shodhana* principle in *Raktavaha Strotas Vyadhi*[11], *Kamala* and *Yakrutdalyudara*[12]. In *Kamala[13]* and *Udara[12]*, *Nitya Virechana* is indicated by *Acharyas*. Charaka has advised *Mruudu Virechana* in *Kamala*, which will also be a treatment principle in *Yakrutdalyudara* and *Raktavaha Strotas Mula Vyadhi*. For *Virechana* in *Kamala, Charkacharya* has recommended *Sasharkara Trivrutta Churna Virechana Karma.* So considering these all things, the *Trivrutta Churna Nitya Virechana* with *Anupana* of *Sashakara* and *Goghruta* in liver diseases will be studied in the present study

AIM AND OBJECTIVE:
Aim: to study the effect of *Trivrutta Churna Nitya Virechana* in *Yakrut Vikara* (Liver Diseases) with abnormal liver function test.
Objectives:
To access the effect of *Sasharkara Nitya Virechana* in the liver disorder.
To access the effect of *Sagoghruta Nitya Virechana* in the liver disorder.
To compare the effect of *Nitya Virechana* with S*harkara* and *Goghruta*.
To measure the incidence of adverse events, adverse drug reactions, safety lab parameters and vital during the study.
Case definition-
Diagnosed cases Liver diseases with abnormal LFT.

Research Question:

Is *Trivrutt Churna Nitya Virechana Karma* with Sharkhara, effective in normalising abnormal liver function tests in liver disorder patients as compared with *Anupana* difference of Gog*hruta*?

Hypothesis:

Trivrutt Churna Nitya Virechana Karma will positively affect Abnormal Liver Function parameters in the liver disorders.

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Null Hypothesis:

Trivrutt Churna Nitya Virechana Karma has no effect over Abnormal Liver Function parameters in liver disorders.

Trial design: A Randomized, open label, parallel-group, prospective, interventional, comparative clinical study on two parallel group having ratio 1:1.

METHODOLOGY:

Study setting: the study will be conducted at the academic hospital MGACH&RC, Salod(H), Wardha.

Registration Number: CTRI/2019/09/021072 [Registered on: 05/09/2019]

Eligibility criteria

Subjects of Age between 18 to 65 years of either sex, willing to give written informed consent will be assisted for study. Diagnosed cases having Infectious hepatitis (excluding known case of Hepatitis-B and Hepatitis-C), alcoholic liver disease drug-induced hepatitis and pre-cirrhotic conditions with abnormal LFT, having Serum total bilirubin level ≥ 2 mg/dl, and/or clinically significant increase in AST or ALT levels (at least more than 2.5 times of its normal limits) and represented with clinical icterus as exhibited by one or blend of the symptoms like dark-coloured urine, light colour stools, fever, nausea, vomiting, anorexia, pruritus, pruritic red hives and right upper abdominal discomfort, pain or feeling of pressure. Where as, subjects reported as a pregnant or lactating woman, suffering from active hepatitis B or C, obstructive Jaundice (Diagnosed clinically and biochemically), progressive liver diseases (e.g. ascites, bleeding oesophageal varices, hepatic encephalopathy and hepatic cancer), subjects having serious ailments (e.g. uncontrolled diabetes, multisystem diseases, HIV, sever renal insufficiency, serious cardiovascular disease, patient history of Gastritis, peptic ulcers, bleeding ulcer); are excluded.

Interventions:

Table 1: Intervention group details

Interventional Drug	Dose	Anupana with quantity	Kala	Freqency	Duration
Group A – Trivrutta Churna	7 gms	Sharkhara- 14 gms	Morning	Once in a day	21 days
Group B – Trivrutta Churna	7 gms	Goghruta- 14 gms	Morning	Once in a day	21 days

Criteria for discontinuation or modification of allocated intervention: Subject can be withdrawn from the study at their own request at any time; if any unfortunate incidence like features of drug sensitivity or any other problem arises.

Expected Outcome

A] Primary Outcomes

Assessment of the changes in the serum total bilirubin, ALT and AST levels from baseline to the end of the therapy in the both groups

B] Secondary Outcomes

Assessment of the changes in the serum total bilirubin, AST and ALT levels from baseline to each study visit i.e. on day 11^{th}, on day 21^{st} and on day 42^{nd} in both groups.

Percentage assessment of changes in the subjective clinical improvement assessment scale from baseline to day 11^{th} and 21^{st} in both groups.

Safety assessment

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Incidences of adverse events, adverse drug reactions, safety lab parameters and vitals during the study period will be assessed.

Sample size: Considering 20% dropout, 74 subjects will be enrol to get 66 total evaluable cases (33 in each group).

Sample size Estimation: Sample size was calculated by comparing two mean of previously done research study.
Allocation and Recruitment of the subjects: Each subject shall be identified by a unique sequential allocation number which will be in ascending order, starting with the smallest number. Subjects who discontinue or withdraw the numbers will not be reassigned. Allocated Subjects will be randomised to one of the two groups as per computer generated randomization list after fulfilment of inclusion/exclusion criteria. Subject will be given unique randomization number which will be in the ascending order starting with smallest number. The randomised subjects who discontinue or withdraw, the numbers will not be assigned. A single subject cannot be assigned more than one randomization number.

Methods: Subjects of Liver disorders, attending outpatient clinic will be screened for eligibility criteria. On screening visit, a written informed consent will be taken, history of past illness and medications will be recorded and his/her physical and systemic examinations will be done. Subject will be assessed and enrolled in the study if he/she meets all the inclusion & exclusion criteria and will be randomized for the study. After recruitment in the study, interventional drug will be given to the subject and will be advised to consume it with all proper instructions for 21 days. Subjects will be advised to follow up on regular intervals i.e. first follow up visit will be at 11^{th} days and second follow up at 21^{st} Days. After stopping of treatment, additional follow up after 21 days will be done. On every visit, subjects will undergo general and systemic examinations. Subject's clinical examination will be done based on Subjective clinical assessment scale. On every follow up visit Liver Function Test will be done.

Statistical Methods and data analysis:

A confidence interval of 95% will be kept for evaluation for all study parameters starting from baseline to follow up visits. T test will be applied to evaluate the same. Analysis between the two groups will be done by one way ANOVA, followed by the turkey's multiple comparison tests for evaluation efficacy and safety variables.

Data Collection Methods:

Assessment subjective Parameters- cardinal symptoms of the jaundice like- Jaundice, Fatigue, Loss of Appetite, Nausea, Vomiting, Itching will be assessed before and after treatment..

Assessment Objective Parameters - Liver functional parameters e.g. Serum bilirubin (Total, Direct and Indirect), AST/SGOT (aspartate aminotransferase or serum glutamic-oxaloacetic transaminase), ALT /SGPT (alanine aminotransferase or serum glutamic pyruvic transaminase), CBC, ESR, Serume Creatinine, Blood Urea and Blood sugar level- Fasting, Serum Cholesterol, Serum Electrolytes will be assessed before and after treatment.

Data management: The data management will be done by Principal investigator.

Follow up period – 0, 11^{th}, 21st and 42^{nd} day

Time duration till follow up : the patients will be followed up for 42 days during treatment..

Time Schedule of Enrolment, intervention: Drug will be given from 1^{st} to 21^{st} days.

Ethics and Dissemination: research ethics approval: Institutional ethical approval has be taken for the research trial. No- Rrf.No.DMIMS(DU)IEC/Jun-2019/8113 of dated 15-07-019.

Written inform Consent process: On screening visit, voluntary written informed consent form, printed in the language best understood by them will be obtained from the subjects.. During Informed consent process, subjects will be explained the objectives, design and possible risks and benefits of the study. They will be given enough time to fully understand the study and other related documentation will be provided to them. If the subject is illiterate, an impartial witness will read the ICF, printed in the language best understood by the subject. After hearing to the ICF, if the subject agrees to participate in the study, his/her thumb impression will be taken on the ICF and also the signature (with date) of impartial witness will be obtained on the same ICF. Confidentiality of each subject will be maintained during the research trial.

Dissemination policy: The data will be disseminated by paper publications.

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Authorship eligibility guidance and any intended use of professional writers.

Discussion:

In the present scenario, liver diseases come to be a world health issue, lacking helpful therapeutic approach. There are so many plants proven as hepatoprotective agents in alternative systems of medicine[14, 15]. Among them, *Trivrutta i.e. Operculina turpethum* (L.) Silva Manso, is reported to posses hepatoprotective in the animal study [16]. In *Ayurvedic* literature, *Trivrutta* is considered to be the best among all the *Virechana* (purgation) drugs [17], but its purgative effect is not on records. In the *Ayurvedic* management of *Yakrut Vikaras*, *Virechana* (Purgation) is clinically found to be useful but not documented yet. It is therefore, essential to evaluate the scientific basis of *Virechana* (purgative) effect of *Trivrutta* in the liver disorders. Gedam et al studied about liver enzymes dysfunction among alcohol dependent individuals[18]. Jain et al reported on magnitude of peripheral neuropathy in cirrhosis of liver patients from central rural India [19]. Mittal et al did normal measurements of liver by USG [20]. Zawar et al reported on management of Hepatitis B (Carrier Stage) through Ayurved[21]. Other related studies were reported bu Kirnake et al [22] and Kurhade et al [23].

Uncertainty *Nittya Virechana* in the form of *Trivrutta Churna* works and able to improve the hepatic deranged functions will cure the liver disorders ranging from infective, drug induced, and alcoholic origin. The *Anupana* (vehicle) used in this study, *Sharkhara* and *Goghruta* having bile salt reducing and bile expulsing property respectively, will be have some supportive action on the expulsion of the accumulated bile from the liver.

Strengths:

Unfortunately, if the present research study found positive outcomes then it will give the parallel modality for management of liver disorders.

Limitations: In the context of *Pandu Chikitsa*, *Acharyas* have mention *Trivrutta Churna Virechana* with *Anupana* of *Sharkhara* for the management of *Kamala*, so this group is consider as the interventional group in the present study. But the another group, in which *Goghruta* is given along with *Trivrutta Churna* for *Virechana* will have some contradictions from modern medicine, as fats are supposed to be restricted in jaundice. Considering bile expulsing quality of the fat, in the second study group, *Goghruta* (Fat) is taken as a *Anupana* for the pharmaceutically acting drug (i.e. *Trivrutta*) for the *Virechana* effect.

Figure 1 Gantt chart (in quarterly based)

	Q1	Q2	Q3	Q4	Q5	Q6
Enrolment of the Subjects						
Research Drug Preparation						
Data Collection						
Writing thesis parts up to Methodology						
Data Analysis						
Writing remaining part of the Thesis						
Submission						

CONCLUSION: Conclusion will be drown after analysing the complete data.

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