A Systematic Review of the Safety and Efficacy of Ayurveda Interventions for Hepatitis: A Protocol for Systematic Review

Amrish P Dedge1, Tushar K Mandal2, Manohar S Gundeti3, Laxman W Bhurake4, Shyam G Kale5, Parth P Dave6

INTRODUCTION

Description of the Condition

Hepatitis (inflammation of the liver due to viruses, alcohol, drugs) of any type (acute/chronic, viral hepatitis, alcoholic hepatitis, nonalcoholic steatohepatitis (NASH)) is a challenge for medical sciences. Conventional medicine focuses on prevention and hepatoprotection. The World Health Organization Global Hepatitis Report 20171 focuses on hepatitides B and C, which are responsible for 96% of hepatitis mortality. In 2015, viral hepatitis was responsible for 1.34 million deaths, and life-threatening complications such as cirrhosis (720,000 deaths) and hepatocellular carcinoma (470,000 deaths) have accounted for 96% of the deaths due to viral hepatitis, with an increase in mortality of 22% since the year 2000.

Alcoholic hepatitis is a liver injury in patients with alcohol abuse and can present as acute/chronic liver failure associated with a decline in liver function and consequent mortality.

For liver diseases including hepatitis, Ayurveda proposes a line of treatment including Panchakarma procedures (five internal biocleansing therapies) along with medicinal treatment. This is based on treatment of diseases such as Kamala (NAMSTP code ABB-13, ED-3)2 (condition similar to jaundice due to various causes), Udara (NAMSTP code EK-3) (ascites due to various causes), and Shotha (NAMSTP code EK-4) (edema due to metabolic, infectious causes) mentioned in classical texts,3 as these conditions can be correlated with liver diseases to large extent. The treatment of various liver diseases (like steatohepatitis, viral hepatitis, alcoholic hepatitis, cirrhosis) based on classical treatment protocols has been safely and effectively done for many centuries.

An attempt will be made to systematically review the evidence generated through clinical research regarding Ayurveda for hepatitis published in scientific journals.

This protocol is written by considering PRISMA-P (Protocols) 2015 checklist. The recommended items to address in a systematic review protocol are covered.

1Ministry of AYUSH, Government of India, INA, New Delhi, India
2Regional Ayurveda Research Centre, Agartala, Tripura, India
3–6Raja Ramdeo Anandilal Podar (RRAP), Central Ayurveda Research Institute for Cancer, Mumbai, Maharashtra, India

Corresponding Author: Amrish P Dedge, Ministry of AYUSH, Government of India, INA, New Delhi, India, e-mail: vdamrish@gmail.com


Source of support: Central Council for Research in Ayurvedic Sciences, Ministry of AYUSH, Govt. of India, New Delhi, India

Conflict of interest: None

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Description of the Intervention

Ayurveda intervention for hepatitis is based on a classically mentioned treatment protocol of “Kamala” disease (NAMSTP code ABB-13, ED-3) (a condition similar to jaundice due to various causes). To some extent, protocols for Udara (NAMSTP code EK-3) disease (ascites due to various causes) and Shotha disease (NAMSTP code EK-4) (edema due to metabolic, infectious causes) are also applicable for the same.

Various medicinal interventions of herbal, polyherbal, herbomineral, and mineral origin are used in Ayurveda clinical practice. Along with classically mentioned formulations, various proprietary and patented products are also in practice for many decades. These formulations are used in various forms such as tablet, capsule, fine powder, decoction, etc., through oral administration.

How the Intervention Might Work

Many classical, herbal products, patented, and proprietary formulations are used for various liver disorders for many decades and centuries. Also, shreds of evidence from in vitro and animal studies are available for their hepatoprotective, antibacterial, anti-inflammatory, and immunomodulatory activities on hepatocytes.

However, precise mechanisms underlying the said properties are currently unclear.

Need—Why it is Important to Perform this Review

For the treatment of viral hepatitis, the conventional medicinal system focuses on prevention with vaccination and behavioral modifications (hygiene, safe use of needles, etc.) and management with antiviral medications and steroidal treatment.

However, considering the national as well as the global burden of disease, clinical picture, and prognosis of the condition and quest for hepatoprotective and hepatocorrective measures, Ayurveda can provide a good option of treatment, both as a stand-alone and as an add-on therapy for hepatitis.

Furthermore, there are several publications showing concerns about Ayurvedic formulations (especially of herbomineral and mineral origin) being unsafe and toxic. An attempt will be made to look for data regarding adverse drug reactions (ADRs)/adverse events (AEs)/safety evidence of Ayurveda formulations which are in practice since not only decades but centuries.

This review will try to analyze the quantity and quality of evidence of the safety and efficacy of various Ayurveda interventions in hepatitis.

Understanding the efficacy and safety of Ayurveda interventions will allow to provide a good option to treat the condition with Ayurveda.

This is a new work and not any update of previously done review work.

Objectives

Thus, we propose to undertake a systematic review to assess the safety and efficacy of Ayurveda interventions for the treatment of hepatitis.

Materials and Methods

Eligibility Criteria

Criteria for considering studies for this review.

Types of Studies

The randomized controlled trials (RCTs), controlled clinical trials, parallel-group trials, and single-group clinical studies will be included in the review.

Case studies, case series, and studies done for acquiring educational qualifications such as doctor of medicine, doctor of philosophy, and master of science (dissertations and abstracts) will not be considered.

Studies conducted at any settings, i.e., outpatient as well as inpatient departments will be considered. Similarly published studies without any restriction of publication year will be considered. Search will be limited to English language. However, if any significant clinical work with good methodology in said domain is found, it will be analyzed by using online translation tools or with discussion with an expert in concerned language.

The review question will be addressed in PICO format—i.e., participants, interventions, comparators, and outcomes.

Types of participants

The studies having diagnosed hepatitis cases will be included. Hepatitis of any type (viral A/B/C/D/E, alcoholic, NASH) and any duration (acute/chronic) will be considered. Studies who have diagnosed hepatitis on the basis of the clinical picture, biochemical evaluation, and viral marker assessments will be considered. However, per the facilities available at the time of publication year, viral marker assessment will be considered accordingly. We shall include studies involving adults (age of 18 years and above), i.e., both male and female population.

Types of Interventions

We shall include those trials using Ayurveda intervention alone or as combined therapy with conventional therapy. Ayurveda intervention is defined as any formulation with herbal (single herb/polyherbal), herbomineral, mineral origin, which is classical, proprietary, or patented and is mentioned to be “Ayurvedic”. Thus, any classical, proprietary, or patented Ayurvedic formulation can be included. There will be no limitation on the number of herbs used, the dosage, the forms of medication, or the duration of the treatment.

Any necessary Panchakarma, or any other classically mentioned therapeutic procedure in Ayurveda, if mentioned will be considered.

Types of Comparators

Any comparator, i.e., placebo, conventional treatment, other Ayurveda intervention, can be considered during the review.

Types of Outcomes

The following outcome measures will be assessed based on the analyses of the data obtained in the included studies.

Primary Outcome

- Changes in clinical signs and symptoms.
- Changes in liver function test values (i.e., serum bilirubin, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, alkaline phosphatase, total proteins).
- Changes in status and values of viral biomarkers (if available).
- Changes, as determined through imaging techniques (if available).

Secondary Outcomes

- Withdrawals due to ADRs, AEs, lack of efficacy, or the inconvenience of the therapy/treatment.
The number of patients with specific AEs.

Any reported or suspected hepatotoxicity will also be assessed, for both herbal and mineral medicines.

Information Sources and Search Strategy

Search Methods for Identifying the Studies

Electronic search: We shall search the following electronic bibliographic databases: PubMed, AYUSH Research Portal, Digital Helpline for Ayurveda Research Articles (DHARA), Google Scholar, and The Cochrane Library (the Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL), and the Cochrane Methodology Register).

The search strategy will include only terms relating to or describing the intervention.

There will be no restrictions with regard to the year of publication.

The search will be rerun just before the final analyses and further studies will be retrieved for inclusion.

Searching other resources: References will be searched from studies collected from the above electronic searches. Snowballing of the studies will be performed to fetch all possible available data. If needed, we shall also contact the authors of the studies and experts in the field for any clarification and missing data.

Study Records

Data Management, Selection, Collection, and Analysis Process

Selection of studies: Two of the review teams (AD, TM, MG, LB, SK, and PD) will independently screen the titles and abstracts of the searched studies, perform the study selection, and record their decisions. Senior team members TM, MG, and LW will decide on the study selection when a consensus cannot be reached. The details of the selection process will be shown in the PRISMA flow diagram (Flowchart 1).

Study selection will follow the PRISMA guidelines\(^{11}\) and study quality will be assessed by the CONSORT\(^{12}\) checklist for RCTs, TREND\(^{13}\) checklist for nonrandomized controlled trials (NRCTs) and CONSORT extension\(^{14}\) for Pilot, and feasibility studies for pilot studies. Risk of bias assessment will be performed with the help of Cochrane RoB2\(^{15}\) tool for RCTs and ROBINS-I tool\(^{16}\) for NRCTs (Flowchart 2).

Data extraction and management

Three of the authors (AD, SK, and PD) will independently extract the data and resolve disagreements through discussion before analysis. When the reported data are insufficient or ambiguous, two of the authors (AD and LB) will contact the corresponding authors of the clinical trials by e-mail or telephone to request additional information or clarification.

Risk of Bias in Individual Studies

Assessment of Risk of Bias in the Included Studies

We shall independently assess the risk of bias in the eligible studies according to the criteria described in the Cochrane RoB2 tool, which includes components such as randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of the reported result, and overall bias. The quality of the study will be classified as low, unclear, or high risk of bias. If necessary, we shall contact the authors of eligible trials for clarification. Any differences in opinion will be resolved by discussion and consensus.

Measures of the Treatment Effect

For continuous data, mean difference (MD) will be used to measure the treatment effect at a 95% CI. We will convert other forms of data into MDs. In case of outcome variables with different scales, we will use the standard MD with a 95% CI. For dichotomous data, treatment effects will be presented as a relative risk or risk difference with 95% CIs. Based on these results, we will calculate the associated numbers needed to treat.

Unit of Analysis Issues

Data from parallel-group studies (RCTs and controlled clinical trials (CCTs)) will be considered for meta-analysis.

Managing Missing Data

We will request missing data from the original authors, whenever possible. If it is not possible to do this, we will only analyze the available data.

Assessment of Heterogeneity

If a meta-analysis is possible, we will use the \( I^2 \) statistic to assess heterogeneity among the included studies. An \( I^2 \) value of >50% will be considered indicative of substantial heterogeneity. If heterogeneity is observed, we will conduct a subgroup analysis and sensitivity analysis to explore its possible causes.\(^{17}\)

Flowchart 1: Study selection flow diagram

Flowchart 2: Quality assessment and risk of bias assessment of studies
Assessment of Reporting Biases
Funnel plots will be prepared to assess the reporting biases if sufficient studies are available.\(^1\) However, funnel plot asymmetry is not the same as publication bias; therefore, we will attempt to distinguish the different possible reasons for the asymmetry, such as small-study effects, poor methodological quality, and the true heterogeneity of the included studies.\(^12,19\)

Data Synthesis
Data synthesis for comparable trials with comparable outcomes will be performed using Review Manager (RevMan), V.5.2.6.

Subgroup Analysis and Investigation of Heterogeneity
If the data are available, a subgroup analysis will be conducted to assess the heterogeneity of different studies, including the following:
- Acute vs chronic hepatitis
- Viral hepatitis/alcoholic hepatitis/NASH.

Sensitivity Analysis
It will principally be performed as follows:
- Company-sponsored trials,
- Sample size (e.g., more or less than 40 participants in each group), and
- Low risk of bias (e.g., allocation concealment or the blinding of participants/assessors).

Confidence in Cumulative Evidence
The strength of the body of evidence will be assessed with Grading of Recommendations Assessment, Development and Evaluation (GRADE) analysis system.

Study Duration
Duration of the study will be of 9 months.

DISCUSSION
Ethical clearance is obtained from the Institutional Ethical Committee of RRAP-CARIC on May 27, 2019.

The systematic review will be published in a peer-reviewed journal. It will also be disseminated electronically and in print. The review will be updated, and a GRADE evaluation\(^20\) of the quality of evidence will be conducted to provide summaries of the future state of the evidence for the efficacy of interventions utilizing Ayurveda interventions in hepatitis. The review may guide healthcare practices and policies regarding Ayurveda interventions in hepatitis.

CONTRIBUTORS
The protocol was drafted by all authors. It was revised and the final version approved by all authors.

Provenance and Peer Review
Not commissioned; externally peer reviewed.

FUNDING
This research received a grant from Central Council for Research in Ayurvedic Sciences (CCRAS), New Delhi, as Intra-Mural Research Project. Central Council for Research in Ayurvedic Sciences is an autonomous body—a research council—under the Ministry of AYUSH, Government of India.
हिंदी सारांश

हिपेटाइटिस के लिए आयुर्वेद के चिकित्सा की सुरक्षा और प्रभावकारिता: सिस्टेमेटिक रिव्यू के लिए प्रोटोकॉल

अमरिष पी. देंगे, तुषार के. मण्डल, मनोहर एस. गुंडेटी, लक्ष्मण डब्बू, भुरके, शाम जी. काले, पार्ष्व पी. दवे

परिचय: प्रकाशित चिकित्सकीय संशोधन कार्य के विश्लेषण के माध्यम से हिपेटाइटिस के लिए आयुर्वेद के चिकित्सा की सुरक्षा और प्रभावकारिता की परीक्षणार्थ एक सिस्टेमेटिक रिव्यू की योजना है।

पद्धति और विश्लेषण: हम हिपेटाइटिस के लिए आयुर्वेद चिकित्सा के प्रकाशित चिकित्सा व अनुसंधान कार्य की व्यवस्थित समीक्षा (सिस्टेमेटिक रिव्यू) करेंगे। इस कार्य में निम्नलिखित डेटाबेस की प्रकाशन वर्ष के निर्णयस्वरूप इलेक्ट्रॉनिक खोज की जाएगी: पबमेड, आयुर्वेद अनुसंधान पोर्टल, डिजिटल हेल्पलाइन पार्टी आयुर्वेद रिसर्च अर्थकल्प (डीएचएएए- थारा), कोक्रेन लाइब्रेरी (सिस्टेमेटिक रिव्यू की कोक्रेन डेटाबेस, कोक्रेन कंट्रोल रजिस्टर ऑफ ट्रायल्स (सेटल) और कोक्रेन मेथोडोलोजी रजिस्टर), गूगल स्कॉर्लर। पूर्ण उपलब्ध साहित्य प्राप्त करने के लिए प्रत्येक किताब खोज, अध्ययनों की सनो-बोलिंग तथा परस्पर प्रभावित स्रोत भी की जाएगी। अध्ययनों का चयन, उपलब्ध माहिती का चयन और सथापन शोधकर्ता की दो सांख्य द्वारा स्वतंत्र रूप से किया जाएगा। संपूर्ण समीक्षा संख्य की सर्वसम्मति से एक निष्कर्ष निकाला जाएगा। प्रकाशित रिपोर्टिंग आयटम्स ऑफ सिस्टेमेटिक रिव्यूज़ और मेडिया-पानालिसिस (PRISMA) में निर्देशित सूची का पालन किया जाएगा।

अध्ययन गुणवत्ता का मूल्यांकन RCTs के लिए CONSORT सूची, NRCTs के लिए TREND सूची और पायलट अध्ययन के लिए CONSORT की विशिष्ट सूची अर्थात CONSORT extension for Pilot and feasibility studies for pilot studies के आधार पर किया जाएगा। रिस्क ऑफ बायस परीक्षणार्थ, आरसीटी के लिए कोक्रेन "आरोडॊ 2 उपकरण" और एनआरसीटीईस के लिए "रंबिनस-आय उपकरण" की योजना होगी। यदि पर्याप्त और उचित डेटा उपलब्ध हैं, तो एक मेडिया-पानालिसिस किया जाएगा। आवश्यक और व्यवहार पार्श्व के चिन्ह उपसमूह विश्लेषण और संवेदनशीलता विश्लेषण (अर्थात सब-स्रोत पानालिसिस तथा संस्टीटिविटी पानालिसिस) किया जाएगा।

विकीर्तन: भारी सिस्टेमेटिक रिव्यू प्रभित्यांश अनुसंधान पत्रिका में प्रकाशित किया जाएगा। समीक्षा को इलेक्ट्रॉनिक और प्रिंट में भी प्रसारित किया जाएगा। स्वस्थ्य सेवा, अत्याचार और नीति को सुधार करने और मार्गदर्शन करने के लिए सिस्टेमेटिक रिव्यू के अद्वितीय योगदान किया जाएगा।

परीक्षण पंजीकरण संख्या: PROSPERO 2019: CRD420191031155