Efficacy of Ayurvedic Interventions in Rheumatic Arthritis: Protocol for Systematic Review

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ABSTRACT

Introduction: Rheumatoid arthritis (RA) has been treated in Ayurveda, and substantial work has been done in studying the role of Ayurveda interventions in its management. A systematic review is planned to investigate the safety and efficacy of Ayurveda interventions for RA through analyzing published clinical research work.

Materials and methods: This study is intended to systematically review the existing published clinical work including randomized controlled trials (RCTs), controlled clinical trials, parallel-group trials, and single-group clinical studies for Ayurveda interventions for RA. Electronic search of the following databases will be performed: PubMed, AYUSH research portal, digital helpline for Ayurveda research articles (DHARA), Google Scholar, the Cochrane Library (the Cochrane Database of systematic reviews, the Cochrane Central Register of Controlled Trials (CENTRAL), and the Cochrane Methodology Register), Ayurveda college/University websites, databases for dissertation works without any restriction of publication year. Hand search and snowballing of studies will also be performed to fetch complete available literature. The selection of the studies, data abstraction, and validations will be performed independently by two teams of researchers. Conclusion will be derived with consensus of complete review team. Study selection will follow the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines, and study quality will be assessed by CONSORT checklist for RCTs, Transparent Reporting of Evaluations with Non-randomized Designs (TREND) checklist for non randomized controlled trial (NRCTs), and CONSORT extension for Pilot and feasibility studies for pilot studies. Risk of bias assessment will be performed with the help of Cochrane RoB2 tool for RCTs and Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool for NRCTs. If sufficient and appropriate data are available, a meta-analysis will be conducted. Subgroup and sensitivity analyses will be performed if found to be necessary and feasible.

Ethics and dissemination: Formal ethical approval is not required as primary data will not be collected. The results will be disseminated through a peer-reviewed publication. The review will be updated to inform and guide healthcare practice and policy.

Trial Registration Number: International Prospective Register for Systematic Reviews (PROSPERO) number 2019 CRD42019133722.

Keywords: Amavata, Protocol for a systematic review and meta-analysis, Vatarakta.

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INTRODUCTION

Description of the Condition

Rheumatoid arthritis (RA) is a chronic, immune-mediated, painful, and disabling systemic disease. It is an inflammatory rheumatic disease with progressive course affecting articular and extra-articular structures resulting in pain, disability, and mortality.1 Persistent inflammation leads to erosive joint damage and functional impairment in the vast majority of patients.

Classical Ayurvedic texts dating as far back as 1500 BC describe the pathogenesis and treatment of rheumatic diseases which show remarkable similarities to modern arthropathies (Ulrich-Merzenich, Kraft, and Singh, 1999); the disease is being managed per Ayurveda diagnosis of Amavata (NAMC-Code EC-6) and also as Vatarakta (NAMC-Code ED-8).

Rheumatoid arthritis has been treated in Ayurveda and substantial work has been done in studying the role of Ayurveda interventions in its management. Hence, this will be an attempt to systematically review the available evidence in clinical research, regarding the use of Ayurveda for the management of RA, published in scientific journals and/or available in libraries like PG/PhD dissertations of Ayurveda universities and colleges.

Description of the Types of Interventions Commonly Used in the Management of RA

Various medicinal interventions of herbal, polyherbal, herbomineral, and mineral origin are prevalent 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 like tablets, capsules, fine powders, decoctions, etc., for internal administration, while various types of oils and powders are available for external application in inflammatory or degenerative type of arthritis.

Possible Mechanism of Action of Ayurvedic Interventions in RA
Ayurvedic interventions for RA are selected based on the individual’s disease status, the severity of the disease, body constitution, etc., in an attempt to restore the imbalance of the three doshas, thereby striving to reduce symptoms, arrest disease progression, and improve the functioning and quality of life (QOL).

Depending on the basic assessment of the patient (Rogi Pareeksha) and disease (Roga Pareeksha), comprehensive and extensive treatment strategies can be evolved incorporating a wide array of classical herbal formulations, patented, and proprietary formulations and/or various Ayurveda Panchakarma procedures that suite the disease status. These time-tested therapies and interventions still lack tangible evidence in substantiating its efficacy and safety in the management of such recalcitrant illnesses.

Need of the Systematic Review
There are mixed notions about Ayurveda where some readily prefer Ayurveda treatment modalities in RA over the contemporary management, whereas some look at it as just a wellness regimen. In spite of the emerging management modalities in RA such as immunotherapies, biologic agents, etc., along with the conventional pharmacologic approach of nonsteroidal anti-inflammatory drugs, analgesics, glucocorticoids, or the conventional disease-modifying anti-rheumatic drugs (DMARDs), the impact on the outcome and QOL of patients are not promising. The use of traditional systems of medicine such as Ayurveda can offer a better outcome as an adjuvant or as a stand-alone therapy to address the needs of the patient. The available evidence in this arena is lacking a positive thrust, and this systematic review is intended to pool the evidence to bridge the gap in the knowledge of the impact of Ayurveda interventions in RA.

Objectives
To evaluate the efficacy of Ayurveda intervention as stand-alone and as add-on therapy in comparison to the conventional treatment of RA.

Materials and Methods
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 and case series will not be considered.

Studies conducted in any settings, i.e., outpatient and inpatient departments will be considered. Similarly published studies without any restriction of publication year will be considered.

Types of Participants
Diagnosed cases of RA using the standard criteria like American College of Rheumatology (ACR) criteria etc. also studies having data of patients who were selected based on Ayurveda criteria of diagnosis; provided the majority of participants had evidence of joint involvement and other features approximating similar criteria of RA. We shall include studies involving adult (age of 18 years and above) population only.

Types of Interventions
Interventions involved Ayurveda stand-alone or as add-on therapy with conventional therapy. Ayurveda intervention is defined as any formulation with herbal (single herb/polyherbal), herbomineral, and mineral origin, which is classical, patent, or proprietary medicines and is mentioned to be “Ayurvedic,” being used orally or applied locally or any procedure that is mentioned in classical Ayurveda texts or is mentioned under panchakarma. There will be no limitation on the number of herbs used, the dosage, the forms of medication, or the duration of the treatment.

Types of Comparators
Any comparator, i.e., conventional management (DMARDs) or placebo, other Ayurveda intervention will be considered during the review.

Outcomes
Primary Outcome
Improvement in pain, tenderness in joints, swelling in joints, and disability.

Secondary Outcomes
Change in hematological parameters, activity of daily living and QOL, range of motion, and remission.

Search Strategy ELECTronic Searches
Electronic databases such as PubMed, AYUSH research portal, Digital Helpline for Ayurveda Research Articles (DHARA), Google Scholar, the Cochrane Library (the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials (CENTRAL), and the Cochrane Methodology Register), Ayurveda Research Database will be searched. Dissertation work lists will be attempted to be retrieved from different Ayurveda colleges in India. 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 analyzes and further studies will be retrieved for inclusion.

Searching Other Resources
References will be searched from studies collected from the above electronic search. Snowballing of the studies will be performed to fetch all possible available data. If needed, the authors of the studies will be contacted for any clarification and missing data.

Data Collection and Analysis
Selection of Studies
Two of the review teams (SG and AA and AK and RS) will independently screen the titles and abstracts of the searched studies, perform the study selection, and record their decisions. Senior team member SK will decide on the study selection when a consensus cannot be reached. Detailed selection process is shown
through a preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram (Flowchart 1).

Study selection will follow the PRISMA guidelines and study quality will be assessed by CONSORT checklist for RCTs, TRED checklist for NRCTs, CONSORT extension for Pilot, and feasibility studies for pilot studies. Risk of bias assessment will be performed with the help of Cochrane RoB2 tool for RCTs and ROBINS-I tool for NRCTs (Flowchart 1).

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

Data from each included trial will be extracted in a predesigned Word format to capture the following information (when available):

- General study information: title, authors, country, follow-up, year, funding agency, study design, setting, risk of bias, number of patients randomized, number of patients analyzed.
- Characteristics of participants: age, sex, disease duration, concurrent treatments.
- Characteristics of intervention: dosages, methods of administration, frequency, duration of treatment, withdrawals, dropouts.
- Characteristics of control: active or placebo; if active, then drug name, dosages, methods of administration, frequency, duration of treatment, withdrawals, dropouts.
- Outcome variables: all outcomes assessed by the authors.

Assessment of Risk of Bias in the Included Studies
Two authors will independently assess the risk of bias. We will follow the Cochrane Collaboration’s recommendations for assessment (Cochrane RoB2 tool). In a consensus meeting, disagreements among the authors will be discussed and resolved. If disagreement persists, a final decision will be facilitated by a third author. We will summarize the risk of bias assessment for every outcome included in the summary of findings tables within a study.

The quality of the study will be classified as low, unclear, or high risk of bias.

**Measures of the Treatment Effect**
Continuous data will be measured by using mean difference or standardized mean difference to compare the same outcomes measured with different scales and 95% confidence intervals (CIs) will be estimated for all measures of treatment effect. For safety and efficacy outcomes, an intention-to-treat model will also be used to analyze the data. We will report the risk ratio and its 95% CI for the number of patients with adverse events and the number of discontinuations.

**Unit of Analysis Issues**
Treatment allocation will be done at an individual level or at a cluster level based on the studies. Treatment groups will be analyzed separately. Analysis of outcomes will be performed at 12 and 24 weeks. We include the following comparison groups: (i) Ayurveda vs placebo; (ii) conventional treatment + Ayurveda vs conventional intervention (iii) Ayurveda vs conventional treatment.

**Management of Missing Data**
In case of any missing data in the published research work, the author will be contacted, whenever possible. If data retrieval becomes impossible, the analyzes will be done based on the available data.

**Assessment of Heterogeneity**
It will be assessed by using a combination of visual inspection of graphs and consideration of the $I^2$ statistic. Substantial heterogeneity is defined as $I^2$ greater than 50%. If heterogeneity is observed, we will conduct a subgroup analysis and sensitivity analysis to explore its possible cause.
Assessment of Reporting Biases
Funnel plots will be prepared to assess the reporting biases if sufficient studies are available. 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. Even if insufficient trials are identified to interpret a funnel plot appropriately, studies will be appraised individually for reporting bias (i.e., publication, time lag, multiple publication, location, citation, language, and selective reporting).

Data Synthesis
The results of the studies will be analyzed using Review Manager Version 5.3. We summarize the data of clinically homogeneous studies in a meta-analysis. A random-effects model will be used when heterogeneity is present. Data will not be pooled if significant heterogeneity exists. A narrative synthesis of the outcomes of the selected studies will be presented in the final review.

Subgroup Analysis and Investigation of Heterogeneity
If significant heterogeneity is detected, and if data permit, we attempt to explore the reasons for heterogeneity in the following subgroup analyzes:
- Duration of RA (less than 6 months; 6 months to 2 years; more than 2 years)
- Type of Ayurvedic intervention (whole systems approach or medicines only)
- Disease classification per Ayurveda (Amavata or Vatarakta)

Sensitivity Analysis
If sufficient trials are identified, we plan to conduct a sensitivity analysis comparing the results using all trials with high methodological quality: studies classified as having a “low risk of bias” vs those identified as having a “high risk of bias.” Sample size (e.g., more or less than 40 participants in each group); company-sponsored trials, etc.

Conclusion
The systematic review after completion will be published in a peer-reviewed journal. The review may be updated after a definite period of time through Grading of Recommendations Assessment, Development and Evaluation (GRADE) evaluation of the quality of evidence of new studies in this disease condition utilizing Ayurveda management. The study might also help in understanding which disease condition Amavata or Vatarakta is better related to RA or type of RA.

References
हिंदी सारांश

स्मेटोडक आयराइटिस में आयुर्वीदीय चिकित्साओं की प्रभावकारीता - सिस्टेमेटिक रिव्यू के लिए प्रोटोकॉल

सुमित गोयल, श्रृंगि खण्डेकर, अजीज अहमद, अरविंद कुमार, राजेश्वरी सिंह, भोगवली चंद्रेश्वर राव,

नारायणम श्रीकांत

परिचय :आयराइटिस (स्मेटोडक आयराइटिस) कि चिकित्सा आयुर्वीद द्वारा की जाती है, और इसके प्रभाव में आयुर्वीद की भूमिका का अध्ययन करने के लिए पर्याप्त अनुसंधान कार्य किये जा चुके हैं। प्रकाशित मैदानिक कार्यों के विश्लेषण के माध्यम से स्मेटोडक आयराइटिस के लिए आयुर्वीद चिकित्सा की सुरक्षा और प्रभावकारीता की जांच के लिए एक व्यवस्थित समीक्षा (सिस्टेमेटिक रिव्यू) की योजना बनाई गई है।

विधि और विश्लेषण : इस अध्ययन का उद्देश्य संपूर्णता के लिए आयुर्वीद चिकित्सा पर रेंडमाइज्ड कंट्रोल्ड ट्रायल (RCTs), नौन रेंडमाइज्ड कंट्रोल्ड (NRCT), रेंडमाइज्ड/ नौन रेंडमाइज्ड प्लास्टिक कंट्रोल्ड ट्रायल, कंट्रोल्ड कंट्रोल्ड ट्रायल (CCTs), परेल्ड आर्म कंपेटेंट ट्रायल एवं सिग्नल ग्रुप ट्रायल, को सम्मिलित करने हुए मौजूदा प्रकाशित मैदानिक कार्य की व्यवस्थित पुनः समीक्षा करना है। निम्नलिखित डेटाबेस की इलेक्ट्रॉनिक खोज की जाएगी: पबमेड, आयुर्वीद अनुसंधान पोर्टल, आयुर्वीद अनुसंधान लेखों के लिए डिजिटल हेल्थएराइज (डीएचएआरएच), यूरोस्लॉवर, कोक्सन लैंडरी (सिस्टेमेटिक समीक्षाएं की कोणी कंपनी डेटाबेस, निम्नलिखित परीक्षण का केंद्रीय रजिस्टर) (सेंट्रल, और कोक्सन मेंधोडलोजी रजिस्टर), आयराइटिस कोलेज / विश्वविद्यालयों की वेबसाइटें, शेड प्रांत के लिए डेटाबेस को खोजा जाएगा। पूर्ण उपलब्ध साहित्य प्राप्त करने के लिए हेंड सर्चिंग, अध्ययनों की स्थोन मॉर्गिंग तकनीक द्वारा भी खोज जाएगी। अध्ययन का चयन, डेटा अस्पृश्यता और सत्यापन शोधकर्ताओं की दो टीमों द्वारा स्वतंत्र रूप से किया जाएगा। निष्कर्ष पूर्ण समीक्षा टीम की सर्वसम्मति से लिया जाएगा। अध्ययन चयन प्रणालिगत समीक्षा और मेटा-प्लानिफिकेशन के लिए प्रिलिमिनरी अइटम्स (PRISMA) के दिशानिर्देशों का पालन किया जाएगा और RCTs के लिए CONSORT चेकलिस्ट, NRCTs के लिए TREND चेकलिस्ट और पाप्ल सैंस अध्ययन के लिए CONSORT extension पैर पाप्ल और व्यावहारिक अध्ययन द्वारा गुणवत्ता का मूल्यांकन किया जाएगा। Risk of Bias assessment NRCT हेतु Cochrane RoB 2 उपकरण द्वारा एवं RCT हेतु ROBINS-I उपकरण की मदद से किया जाएगा। यदि पर्याप्त और सम्मत डेटा उपलब्ध हों, तो एक मेटा-प्लानिफिकेशन अभावित किया जाएगा। यदि आवश्यक और सम्भव पाया जाता है तो उपस्थित विश्लेषण और संदर्भदर्शनीति विश्लेषण किया जाएगा।

प्रसार : औषधाचारय मैत्री अनुमोदन की आवश्यकता नहीं है क्योंकि प्राथमिक डेटा एकत्र नहीं किया जाएगा। परिणाम को प्रिलिमिनरी रिपोर्ट शोध पत्रिका में प्रकाशित कर प्रायोगिक किया जाएगा। स्वास्थ्य सेवा अभ्यास और नीति को सूचित करने और मार्गदर्शन करने के लिए समीक्षा को अधिकृत किया जाएगा।

सिस्टेमेटिक रिविज़न एक शोध पत्रिका में प्रकाशित किया जाएगा एवं इलेक्ट्रॉनिक और प्रिंट में भी प्रसारित किया जाएगा। स्वास्थ्य सेवा अभ्यास और नीति को सूचित करने और मार्गदर्शन करने के लिए इस रिविज़न को पूँजी संशोधित किया जाएगा।

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