**PROTOCOL**

A Systematic Review Protocol to Assess the Effectiveness of Ayurveda Interventions in Gout

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**ABSTRACT**

**Introduction:** Ayurveda offers healthy, harmonious, and long life by its holistic approach. Gout is a form of arthritis caused by excess uric acid in the bloodstream. Gout may be considered as Vatarakta or Vatasonita as per Ayurveda. Even though gout is managed well with conventional medicine, there are a lot of side effects. Ayurvedic treatment is found to be effective in the management of gouty arthritis with very few ill effects. But research works carried out in gout with Ayurvedic medicines are not yet compiled and analyzed. The purpose of this study is to conduct a systematic review of published data and gray literature on Ayurveda management of gout viz-à-viz Vatarakta to establish its safety and clinical effectiveness. Thus, finding more precise estimates of various Ayurveda interventions’ effects in the management of gout either as stand-alone or as an add-on to conventional management.

**Materials and methods:** Source for data analysis involves electronic search done from PubMed, Cochrane Library (Cochrane Central Register of Controlled Trials: Issue 6 of 12, June 2018), AUSHY Research Portal (Govt. of India), DHARA, Google Scholar, Ancient Science of Life, Shodhganga@INFLIBNET, and online clinical trial registers. Manual search in central and departmental libraries of Government Ayurveda College, Trivandrum and IPGT & RA, Gujarat Ayurved University, Jamnagar. There will be no language restrictions. Studies published till date (until March 2019) will be sought. The search will be rerun just before the final analyses, and further studies shall be retrieved for inclusion. Type of studies included randomized controlled trials (RCTs), quasi-experimental trials, single-group clinical trials, comparative clinical trials (CCTs), pragmatic trials, and review papers on Ayurvedic management of Gout, which will all be screened for data analysis. The study selection will follow the preferred reporting items for systematic review and meta-analysis guidelines. Data collection and synthesis: three investigators shall independently screen all citations and abstracts identified by a primary comprehensive search to sort out potentially eligible trials based on inclusion criteria. Data extraction forms for individual study shall be prepared and it may include methods, participant characteristics, intervention, and outcome. When disagreement persists or in case of ambiguity at the time of data extraction, efforts shall be initiated to obtain clarifications directly from authors/coauthors as much as possible. Primary data analysis of both the qualitative and quantitative data will be performed. Heterogeneity among trials will be assessed by inspecting forest plots. If heterogeneity is detected and it is still considered clinically meaningful to combine studies, then a random-effects model (Dersimonian–Laird Model) will be used. In cases where pooled estimates can be obtained, the systematic review will be followed by a meta-analysis (based on the homogeneity of the RCT methodological, appraisal will be done by Cochrane risk-of-bias tool for RCT); others would be presented by narrative synthesis [using Risk of Bias tool in non-randomised clinical trials/non-randomised controlled trials (NRCT)] and shall be represented in tabular and graphical form. The analysis of the systematically collected data shall be analyzed using R software. A sensitivity analysis, to investigate the robustness of the results to the quality components will be done, provided there are sufficient trials. A funnel plot will be utilized to indicate publication bias, heterogeneity of results, or differences in the methodological quality.

**Timelines:** Data collection and analysis: 06 months (from the date of initiation). Journal selection and publication: 03 months (from the date of study completion).

**Dissemination:** The systematic review will be published in a peer-reviewed journal. It will also be disseminated electronically and via print. The review may guide healthcare practices and policy framing in the treatment of gout with Ayurvedic interventions.

**Trial registration number:** PROSPERO 2019: CRD42019131198.

**Keywords:** Ayurveda interventions, Gout, Systematic review, Vatarakta.


**INTRODUCTION**

Ayurveda is an ancient indigenous medical system. Ayurveda offers the way of having a healthy, harmonious, and long life by its holistic approach.¹⁻² Gout is a form of arthritis caused by excess uric acid in the bloodstream. It is a systemic disease that occurs due to the accumulation of monosodium urate crystals in tissues. Hyperuricemia is the main pathogenic cause for gout, but many people with hyperuricemia do not develop gout. Genetic predisposition also plays a major role in the pathogenesis of gout.³⁻⁵ It is a metabolic disorder causing inflammatory arthritis. The accumulation of tiny needle-like uric acid crystals triggers the inflammation.⁶

The globally reported prevalence of gout ranges approximately from 0.1% to 10% and the incidence of gout cases are 0.3–6 cases per 1,000 population.⁷ Although the prevalence of gout is less, most cases of gout are at increased risk for complications such as kidney stones and heart disease.⁸

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**Conflict of interest:** None

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risk of comorbidities and thus are at increased risk of death.\textsuperscript{8} It may also worsen the quality of life (QOL).\textsuperscript{9} A retrospective study across clinics in India shows an increased prevalence of hyperuricemia with increased association of type II diabetes mellitus and hypertension.\textsuperscript{10} Even though gout is managed well with conventional medicine, there are a lot of side effects. Colchicine is the preferred medicine for gout flare management but care should be given while administering in patients with kidney disease, hepatic dysfunction, and other comorbidities.\textsuperscript{11} The incidence of gout in India is not very clear. The prevalence is 0.12% per the International League of Nations Against Rheumatism, Community Oriented Program for Control of Rheumatic Diseases study in Bhigwan village of India.\textsuperscript{12} Gout is the most common form of inflammatory arthritis in a peripheral joint, mostly in the lower limb, exquisite pain, and warm pink shiny swelling usually at the base of a great toe (podagra). Arthritis remits completely within few days with or without therapy and then recurs in the coming days with increasing frequency. After approximately 10 years of recurrent gout arthritis, the patient develops into chronic gout with the appearance of tophi.\textsuperscript{13,14}

Gout may be considered as Vatarakta or Vatasonita per Ayurveda. Vatarakta comes under one of the major diseases that affect the joints. Vatarakta occurs due to the aggravation of Vata and Rakta. The vitiated Rakta obstructs the pathways of Vata, and Vata aggravates by this obstruction and causes Vatarakta. The main feature of Vatarakta is Sandhi Soola (joint pain). The onset is at Hasta or PadoMoolam (small joints of hands and foot) and spreads to other parts like AakhuVisha (rat poison). It produces various symptoms like Ruk (excruciating pain), Swayathu (swelling), Daha (burning sensation), Stabdha Sandhi (joint stiffness), Shyava RaktaVarnata (blackish-red color), and Sarsasahatwa (severe tenderness and hyperesthesia).\textsuperscript{15,16}

Ayurvedic treatment is found to be effective in the management of gouty arthritis with very few ill effects. But research works carried out in gout with Ayurvedic medicines are not yet compiled and analyzed. Hence, it is essential to conduct a systemic review on Ayurveda interventions in this regard. This study will review published data and gray literature on Ayurveda management of gout viz-à-viz Vatarakta to establish its safety and clinical effectiveness. This study shall provide more precise estimates of various Ayurveda intervention’s effects in the management of gout either as stand-alone or as an add-on to conventional management.

**OBJECTIVES**

**Primary Objectives**

- Systematic review of the literature to produce a database of outcome measures used in gout viz-à-viz Vatarakta

**Secondary Objectives**

- A qualitative review of clinical and methodological characteristics of individual studies and patterns across the study in gout viz-à-viz Vatarakta
- Documentation of strength and limitations of individual studies and patterns across the study in gout viz-à-viz Vatarakta

**MATERIALS AND METHODS**

**Study Type**

Systematic review and meta-analysis.

**Purpose**

- Evidence generation for safety and effectiveness of Ayurveda treatment protocols in gout viz-à-viz Vatarakta.
- Documentation of different treatment protocols and their comparisons.
- To document the relevance, strength, and weaknesses of individual studies (Ayurvedic treatment protocols) in gout and also to study the pattern across the study.

**Source for Data Analysis**

- Published data available on search engines, namely, PubMed, Cochrane Library (Cochrane Central Register of Controlled Trials: Issue 6 of 12, June 2018), AYUSH Research Portal (Govt. of India), DHARA, Google Scholar, Ancient Science of Life, and Online clinical trials registers
- Gray literature available from Government Ayurveda College, Trivandrum (Manual Search): IPGT & RA, Gujrat Ayurveda University, Jamnagar; Shodhganga@INFLIBNET.

**TIMELINES**

Data collection and analysis: 60 months
Journal selection and publication: 03 months

**Criteria for Selection of Study**

**Type of Study**

The randomized controlled trials (RCTs), quasi-experimental trials, single-group clinical trials, comparative clinical trials (CCTs), pragmatic trials, and review papers on Ayurvedic management of Gout, which will all be screened for data analysis.

**Types of Interventions**

Ayurvedic treatment protocol (Shamana or Shodhana) with different dosage forms, type, schedule, drug, treatment procedures, with or without Pathayapathy (lifestyle modifications and or specific diet charts) as the intervention group in gout shall be screened for data analysis.

**Comparators/Control**

- Ayurvedic treatment protocol (Shamana or Shodhana) with different dosage forms, type, schedule, drug, treatment procedures, with or without Pathayapathy (lifestyle modifications and or specific diet charts) as the comparative group to intervention(s)/exposure(s) in gout shall be screened
- Placebo and/or sham therapy and/or Shamana therapy and/or non-Ayurveda interventions in gout too shall be screened.

**Types of Participants**

**Inclusion Criteria**

Cases diagnosed with gout by blood tests or symptomatic wise who underwent Ayurvedic treatment protocol (administered from 7 days to 60 days)/cases diagnosed with Vatarakta (symptom wise)
who underwent Ayurvedic treatment protocol (administered from 7 days to 60 days).

Exclusion Criteria
Cases with systemic illnesses other than the musculoskeletal system or any major comorbidities who underwent Ayurvedic treatment protocol for gout/Vatarakta.

Types of Outcome Measures
Effectiveness/efficacy parameters
• Response to treatment (improvement in subjective and/or objective criteria of assessments)
• Improvement in QOL

Timing and effect measures of effectiveness parameters
Administration timings vary from 7 days to 60 days as different categories of medications are included for review.

Safety/Morbidity Parameters
• Serious adverse events resulting in death, disability, or incapacity or complications, which were life-threatening, led to hospitalization or prolonged hospitalization.
• Withdrawals due to adverse events or lack of efficacy or inconvenience of therapy/treatment.
• The number of patients with a specific adverse event.

Timing and Effect Measures of Safety Parameters
During the study period or up to 1 month after completion of the study. No restrictions will be made in the inclusion of study in the review process based on the outcomes mentioned above.

Search Methods for Identification of Studies
The electronic databases are PubMed, Cochrane Library (Cochrane Central Register of Controlled Trials: Issue 6 of 12, June 2018), Google Scholar, AYUSH Research Portal (Govt. of India), DHARA, Ancient Science of Life, Shodhganga@INFLIBNET, online clinical trial registers.

Manual search in central and departmental libraries of Government Ayurveda College, Trivandrum; IPGT & RA, GAU, Jamnagar with due permissions and Ayurveda Research Database from authorities.

There will be no language restrictions. Studies published till date (until March 2019) will be sought. The search will be rerun just before the final analyses and further studies shall be retrieved for inclusion.

Search Strategy (Keywords)
Ayurveda OR Ayurvedic OR Ayurvedic treatment OR Ayurvedic treatment protocol OR Gout OR Goutyarthitis OR Vatarakta OR Vatashonita OR Vatasonita as title, abstract, or keyword.

Data Collection/Synthesis—Data Extraction/management
Three investigators shall independently screen all citations and abstracts identified by a primary comprehensive search to sort out potentially eligible trials. Full articles of potentially eligible trials shall be obtained and independently evaluated for inclusion in the review based on types of participants (inclusion criteria). Data extraction forms for individual study shall be prepared. This shall include (1) methods used in the study (randomization/ allocation concealment/blinding/sampling and sample size calculation/length of follow-up), (2) participant characteristics of individual studies (along with disease characteristics/number of participants randomized/number of participants completing follow-up/reasons for withdrawal from the study), (3) interventions (treatment protocol administered/formulations used/standard operating procedure (SOPs) administered/adverse events while the review protocol), and (4) outcomes (in terms of safety/effectiveness/efficacy/improvement in QOL). For each outcome measured from individual studies, efforts shall be taken to discuss the risk of bias, consistency, precision, and reporting bias. When disagreement persists or in case of ambiguity at the time of data extraction, efforts shall be initiated to obtain clarifications directly from authors/coauthors as much as possible.

Data Analysis
Three investigators shall independently screen all studies identified by a primary comprehensive search to sort out potentially eligible trials. Full articles of potentially eligible trials shall be obtained. Data extraction forms for individual study shall be prepared. When disagreement persists or in case of ambiguity at the time of data extraction, efforts shall be initiated to obtain clarifications directly from authors/coauthors as much as possible. Both qualitative and quantitative data as collected from various sources shall be considered for primary data analysis. In cases where pooled estimates can be obtained, the systematic review will be followed by a meta-analysis (based on the homogeneity of the RCT); others would be presented by narrative synthesis and shall be represented in tabular and graphical form. The analysis of the systematically collected data shall be analyzed using R software. Dichotomous data will be presented and combined using relative risks, and continuous data will be summarized by arithmetic means and standard deviation data will be combined by using weighted mean differences; both will be accompanied by 95% confidence intervals. Medians and ranges will be reported in tables. Heterogeneity among trials will be assessed by inspecting forest plots, to look for overlapping confidence intervals, applying the $\chi^2$ test with a $p$ value of 0.05, indicating statistical significance, and using the $I^2$ test with a value of 50% used to denote moderate levels of heterogeneity. If heterogeneity is detected and it is still considered clinically meaningful to combine studies, then a random-effects model (Dersimonian–Laird Model) will be used. A sensitivity analysis, to investigate the robustness of the results to the quality components will be done provided there are sufficient trials. A funnel plot will be utilized to indicate publication bias, heterogeneity of results, or differences in the methodological quality.

Ethical Considerations
Written approval of Institutional Ethics Committee (IEC) shall be obtained. A voluntary signed, witnessed informed consent shall be obtained from the institutes/practitioners for sharing the unpublished data.

Coordination of Study
Coordinating centers: National Ayurveda Research Institute for Panchakarma, Cheruthuruthy, Thrissur, Kerala (CCRAS), CCRAS Headquarters.

Study Monitoring
As per the approval of the authority of CCRAS, the investigators shall communicate the time for such monitoring activities. The investigator will also ensure that the monitor or other compliance
or quality assurance reviewer is given access to all the above noted study-related documents and has adequate space to conduct the monitoring visit. Particular as an investigator in this study implies acceptance of potential inspection by CCRAS and other external experts.

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**References**

गाउट में आयुर्वेद हस्तक्षेप की प्रभावशीलता का आकलन करने के लिए एक व्यवस्थित समीक्षा प्रोटोकॉल

नलिनुलिकुमार शर्मा, अर्विंद, निरीक्षण एन. सीनी, गृहराज नरेंद्र, अगरवाल श्याम कुमार स्वामी

परिष्कर: आयुर्वेद अपने समय स्थितिकोण से स्वस्थ, सामाजिक-सांस्कृतिक और धीरजीवन प्रदान करता है। गाउट, गठियाद का एक रूप है जो रक्तस्राव में अतिरिक्त मूर्च्छ अणु के कारण होता है। आयुर्वेद के अनुसार गाउट को वातस्राव या वातशोषण माना जा सकता है। हालांकि गाउट को विश्वसनीय चिकित्सा के साथ अच्छी तरह से प्रस्तुत किया जाता है लेकिन इसके बाहर सारे दुष्परिणाम है। आयुर्वेदिक उपचार गठियाद के प्रबंधन में महत्वपूर्ण का भूमिका निभाता है। आयुर्वेदिक दवाएं के साथ गाउट में लगाए खोज कार्य अभी तक संकलित और विश्लेषित नहीं किए गए हैं। इस अध्ययन का उद्देश्य अभी सुरक्षा और नैदानिक प्रभावशीलता को स्थापित करने के लिए वातस्राव के संबंध में गाउट के आयुर्वेदिक प्रबंधन पर प्रभावशील आंकड़ों और पूरे साहित्य की एक व्यवस्थित समीक्षा करना है।

विधि और विश्लेषण: डेटा विश्लेषण के लिए स्रोत: PUBMED, कोलम्बियन पुस्तकालय (नियोजित परिक्षण का कोलम्बियन वेबसाइट, रजिस्टर: 12. 2018 वा वांक), आयुर्वेद अनुसंधान पोर्टल (ब्रह्म सर्कार), DHARA, गूगलस्कॉर्स, Ancient Science of Life, श्रेष्ठगंगा @ INFLIBNET और अन्य देशों के परियोजना रजिस्टर, सामग्री का कैटेगरी और विवरण अभियंता, अन्तर्राष्ट्रीय पुस्तकालयों में दर्शनी जोन, आयुर्वेद कोलेज, विश्वविद्यालय, अपनी और उद्देशीक इंटरनेट जैसे स्रोतों से।

इस अध्ययन का उद्देश्य अभी सुरक्षा और नैदानिक प्रभावशीलता को स्थापित करने के लिए वातस्राव के संबंध में गाउट के आयुर्वेदिक प्रबंधन पर प्रभावशील आंकड़ों और पूरे साहित्य की एक व्यवस्थित समीक्षा करना है।