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HOMEOPATHY FOR GOUT AND/OR HYPERURICEMIA: PROTOCOL FOR A SYSTEMATIC REVIEW

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Abstract:

Background: Gout is a painful type of arthritis that occurs due to an increase in serum uric acid levels i.e. Hyperuricemia. Hyperuricemia is a worldwide health problem that is often dealt with through Homeopathy. The objective of this review will be to assess the role of homeopathic medicines in the management of Hyperuricemia and primary Gout. **Methods/Design:** To conduct a systematic review, authors will search Medline, EMBASE, CENTRAL, AMED, CAM-Quest, CORE-Hom, ChiroACCESS (MANTIS interface), LILACS (Biblioteca virtual em salud interface), Google Scholar studies from January 2001 up to January 2022. The review will include all types of Randomised Controlled Trials (RCTs), Observational studies, well-presented case reports published in all journals, in vitro studies, and animal experimentation. Studies with participants of all ages and both sexes will be included. Cases with either acute gouty attack, those in inter critical period, or chronic gout will also be included. Studies related exclusively to allopathic and other CAMs (Ayurveda, Unani, Siddha, Yoga, and Naturopathy) will be excluded from this review. The methodology will include Jadad scoring for clinical trials, the internal validity of RCTs by the Cochrane collaboration tool, and the internal validity of observational studies and case reports by the Joanna Briggs Institute (JBI) criteria and JBI appraisal checklist, respectively.

Keywords: Gout, Hyperuricemia, Homoeopathy, Observational studies, Randomized control trial

Background:

Description of the condition:

Gout is inflammatory arthritis that results from the deposition of monosodium urate crystals (MSU) in tissues. It is associated with Hyperuricemia. Hyperuricemia is a very common condition, defined as an elevated level of uric acid in the blood, and increased serum uric acid (SUA) above a definite threshold is a condition for the formation of uric acid crystals. It is caused by the disproportion between the production and excretion of uric acid. Concentrations of serum uric acid of more than 6 mg/dL in females and 7 mg/dL in males are considered Hyperuricemia. Approximately two-thirds of Serum uric acid is produced endogenously, and the remaining is a result of dietary purines. It is caused by a harmful, unhealthy lifestyle, including an imbalance in a diet rich in protein, excessive carbohydrates, and excessive alcohol intake[i]. If uric acid levels remain persistently high for a longer period, urate crystals may begin to deposit in joints and tissue such as cartilage, synovial membrane, and bone resulting in pain, activity limitation, disability, and impact on the patient's quality of life which can lead to Gout, nephrolithiasis, and chronic nephropathy. Hyperuricemia is also an indicator of other diseases like diabetes mellitus, cardiovascular disease, metabolic syndrome, and chronic renal disease.

Uric acid levels differ with age and sex. The average serum uric acid is 3.6 mg/dl for both sexes before puberty; post-puberty, it rises to adult levels, with women less than men. The lower level in women is due to estrogen-related augmented renal urate clearance, which disappears at menopause. Many other factors, including exercise, diet, drugs, and state of hydration, may result in transient fluctuations in uric acid levels[ii]. The general prevalence of Gout is 1–4% of the general population. In western countries, it occurs in 3–6% of men and 1–2% of women. In some countries, the prevalence may rise to 10%. Prevalence rises to 6% in women and 10% in men more than 80 years old. The yearly incidence of Gout is 2.68 for every 1000 persons. It occurs in men 2–6 times more than in women[iii]. On the other hand, Hyperuricemia has a

varied prevalence in Asian countries. The prevalence of Hyperuricemia in India was 44.6%, according to a study published in 2012, which was reduced to 25.8% in 2018[iv]. The clinical presentation of Gout may be in the form of asymptomatic Hyperuricemia, acute gouty arthritis, intercritical period, and chronic tophaceous Gout. Diagnosis of Gout and Hyperuricemia is based on laboratory and radiological features. The gold standard of diagnosis is the identification of characteristic MSU crystals in the synovial fluid using polarized light microscopy. Imaging modalities include conventional radiography, ultrasonography, conventional CT, Dual-Energy CT, MRI, nuclear scintigraphy, and positron emission tomography.

Relevance of the review

The treatment of Hyperuricemia includes changes in lifestyle, nutrition, and adjunctive therapies, as well as different classes of drugs that are approved for lowering urate levels: xanthine oxidase inhibitors, uricosuric agents, and uricase agents[v]. There are several drugs used for Hyperuricemia, but the most commonly used hypouricemic medicine is allopurinol. The side effects of allopurinol, although not very common, may be severe or life-threatening and are usually seen in patients with renal insufficiency[vi,vii,viii,ix]. In the conventional system of medicine, non-steroidal anti-inflammatory drugs are usually the drugs of choice for treating acute Gout. The homeopathic literature subsequently suggested several medicines for the conditions mentioned as 'Uric acid diathesis,' 'lithemia,' 'arthritic nodosities,' 'pain joints, gouty,' 'acute gout,' 'nodosities,' 'tophi,' 'Podagra' such as *Colchicum, Urtica urens, Benzoic acid, Ledum pal., Lithium benzoicum, Bryonia alba, Rhustox, Antimonium crudum, Abrotanum, Arnica Montana, Belladonna, Calcarea fluorica, Rhododendron,* etc. Due to adverse drug reactions of various marketed drugs used in modern medicines, there is a need to explore the role of homeopathic medicines in the management of Hyperuricemia and/ or primary Gout. There is, however, no comprehensive review to identify evidence based on Homoeopathy for the treatment

of Gout and Hyperuricemia. This study will identify the research conducted in Homoeopathy for the treatment of Gout and Hyperuricemia. For this review, Homoeopathy will be defined as the use of homeopathic medicines prepared following available official homeopathic pharmacopeias.

Objective:

The objective of the present study is to systematically review all the available literature on homeopathic research from various sources, including clinical, *in vitro*, and *in vivo* experimentations conducted on Gout and/or Hyperuricemia published between January 2001 and January 2022, and to determine the efficacy and effectiveness of homeopathy in the treatment of Gout and/or Hyperuricemia.

Methods/ Design:

Protocol

The methods for this systematic review have been developed according to the recommendations of the preferred reporting items for systematic review and meta-analysis protocols (PRISMA- P) 2015 STATEMENT.

Criteria for including studies for this review:

Population

The population of interest will include patients suffering from Gout and/ or Hyperuricemia of any age and gender. Cases with either acute gouty attack, those in inter critical period, or chronic Gout will be included.

Types of studies

This review will contain studies where the intervention was aimed at treating symptoms related to Gout or preventing its occurrence by treating risk factors associated with it, i.e., Hyperuricemia through Homoeopathy. Any study where symptoms could at least be to some extent attributed to Gout and/ or Hyperuricemia treatment will be included in the review.

Study design

All types of Randomised Controlled Trials (RCTs) and observational studies conducted in any setting

will be included in the review. Well-documented case reports will also be considered. This review will also include in vitro studies and animal experimentation in a laboratory model related to the effect of homeopathic medicines on Hyperuricemia, the most important risk factor in the development of Gout.

Types of intervention

Any homeopathic prescribing strategy will be included.

Exclusion criteria for systematic review:

The clinical studies related exclusively to allopathic and other CAMs (Ayurveda, Unani, Siddha, Yoga, and Naturopathy) will be excluded from this review. Narrative review articles without any contribution to research updates, Book chapters, and pharmacognostic, physiochemical studies of drugs for Gout and/or Hyperuricemia will be excluded.

Search:

Electronic search

A systematic literature search will be conducted in the different international medical search databases, including EMBASE (Elsevier), MEDLINE (via PubMed), Cochrane Central Register of controlled trials (CENTRAL) (Wiley Interface), Allied and complementary Medicine databases (AMED), CAM-Quest, CORE-Hom, Chiro ACCESS (MANTIS interface), LILACS (Biblioteca virtual em salud interface), Google Scholar during the period from January 2001 to Jan 2022. Online Indian Journal of Research in Homoeopathy (An official publication of the Central Council for Research in Homoeopathy [CCRH] [www.ijrh.org]), CCRH e-Library, and clinical series published by the council will also be searched for articles on Gout and Hyperuricemia and its treatment in Homoeopathy. Individual websites of peer-reviewed journals publishing homeopathic articles will also be searched directly.

Manual Search

A manual search will be taken up at CCRH, a research organization that undertakes scientific research in Homoeopathy. The Current Health

Literature Awareness Services (CHLAS), published by CCRH library, indexes the Journals/titles available in the library every quarter. Furthermore, the Bulletin of the National Institute of Homoeopathy will be manually searched on clinical studies related to Gout and Hyperuricemia and its homeopathic treatment. Besides, hand searches will be done in different journals, magazines, meta-analyses, meeting abstracts, bibliographic sections of reviews, and original trial papers.

Search terms

For this search, all keywords related to Gout and Hyperuricemia, such as uric acid, Serum uric acid, Gout, gouty arthritis, tophi, podagra, Hyperuricemia, and Homoeopathy/ Homeopathy will be used. Various search terms will be used for different databases, for example, MEDLINE: homeopath* OR homeopath* AND "gout" OR "hyperuricemia" OR "uric acid" OR "gouty arthritis," EMBASE: homeopath$ OR homoeopath$, CENTRAL: homeopathy (MeSH), CORE-Hom: Specifying the field "musculoskeletal system," Chiro ACCESS: homeopath* OR homeopath*, LILACS: homeopath$ AND random$. The following search strategy will be used to search Medline and other sources (Table 1).

Table 1: Search strategy: homeopathy for Gout and/or Hyperuricemia

Step	Search procedure
1.	Homeopathy
2.	(Homoeopathy or Homoeopathic or Homeopathic).mp [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol, supplementary concept, rare disease supplementary concept, unique identifier]
3.	1 or 2
4.	Gout or Gouty arthritis or Podagra or Tophi
5.	Hyperuricemia
6.	Serum uric acid
7.	Hyperuricemia or Serum Uric acid
8.	Gout and Homoeopathy
9.	Hyperuricemia and Homoeopathy
10.	4 or 7

Selection of studies:

Two authors (PG and MG) will independently review titles and abstracts to select potentially eligible studies. This will be followed by a full-text study of the selected studies to assess compliance with the eligibility criteria. Disagreements will be fixed by discussion first. A third author (ARS) will arbitrate if the disagreement is due to a difference in interpretation. If no clear classification can be made of a selected study, it will be considered as one that is awaiting assessment. Study authors will be communicated for further information if necessary. The third author (ARS) may be asked to categorize the study. The selected studies will then be further assessed for methodological quality (risk of bias).

Data collection process:

A data extraction format will be designed, and the relevant details will be transferred to the standard data extraction sheet after the format is reviewed by all authors. The authors, year of publication, and journal of publication will also be documented. We plan to contact the study authors in case of any difficulty in obtaining the complete research paper or missing information. Two authors (PG and MG) will independently extract data from every included trial to reduce error and lessen potential bias. Disagreements between review authors will be resolved by discussion. A third review author will act as arbiter in case disagreements cannot be resolved.

Data items:

This will cover the following details:

Clinical studies

1. Study design (randomized controlled trials, controlled cohort study, case-control study, case series, case report, etc.);
2. Number of patients that have participated and that have been allocated in each group;
3. Intervention details (Homoeopathy alone or as an add-on to conventional treatment);

4. Type of Homoeopathy; (Individualized homeopathy, mother tincture, or both, individualized homeopathy as adjunct to conventional treatment, anti-miasmatic medicine or partial similimum type, etc.).
5. Assessment/ outcome parameters; (blood parameters like Serum uric acid or questionnaires like Gout Assessment Questionnaire 2 (GAQ 2), Measure Yourself Medical Outcome Profile 2 (MYMOP 2), (Visual Analogue Scale) VAS, etc.)
6. Summary of results;
7. Medicine used and potency;
8. Levels of evidence of the studies and publications are graded as per the criteria mentioned in Tables 2 and 3.

Table 2: Classification of clinical studies

Level of evidence	Study design
1a	Double-blind, randomized clinical trials
1b	Non-blinded randomized clinical trials, including those comparing homeopathy with conventional therapy as control (equivalence studies)
2	Non-randomized controlled clinical trials, including those comparing homeopathy with conventional therapy (equivalence studies)
3	Prospective observational studies without a control Group
4	Retrospective studies of case series

Table 3: Classification of publications according to type

Class	Publication Type
1a	Mainstream medicine indexed, peer-reviewed, Journal
1b	Complementary/ alternative medicine indexed, peer-reviewed, journal
2	Non-indexed journal
3	Book or book chapter, conference proceedings

In-vitro studies

1. Model used;
2. Blinding was done or not;
3. Control group was present or not;
4. Whether randomization was done;
5. Experiment standardization;
6. Intervention/ medicine used with potency;
7. Statistical analysis & presentation done or not;
8. Summary of results and
9. Evidence grade modified Score for assessment of physical experiments on Homoeopathy (SAPEH).

Animal experimentation

1. Model used;
2. Species used;
3. Intervention/ medicine used with potency;
4. Variable measured;
5. Blinding was done or not;
6. Control group was present or not;
7. Whether randomization was done;
8. Summary of results and
9. Comments.

Assessment of risk of bias in studies:

Quality assessment of the included studies will be carried out using two different instruments: (1) Cochrane Collaboration Tool for assessing the risk of bias in RCTs[x] and (2) The Joanna Briggs Institute's critical appraisal checklist developed using the forms included in JBI's reviewers' manual for observational studies and case reports[xi].

Cochrane collaboration tool access six domains of bias: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. Within each domain, assessments are made for one or more items, which cover different aspects of the domain or different outcomes.

The Joanna Briggs Institute (JBI) is an independent, international, not-for-profit research organization that also develops many critical appraisal checklists involving the appropriateness, feasibility, meaningfulness, and effectiveness of healthcare interventions. Methodological quality will be considered as 'low,' 'moderate,' or 'high. 'Criteria used to rank the risk of bias will be a high risk of bias for ≤49%, Moderate risk of bias for 50% to 69%, and low risk of bias for above 70%.

Both instruments will be independently applied by two authors (PG, MG), and any disagreement will be settled by consensus or adjudication with a third author (ARS), if necessary.

Data synthesis:

Relevant data extracted from qualified studies will be filled in evidence tables. A meta-analysis of outcome variables will be conducted if studies are adequately meet the inclusion criterion and uniform in reporting the outcome estimates. A narrative synthesis will provide a summary of the literature on homeopathic research conducted on Gout and/or Hyperuricemia and determine the efficacy and effectiveness of homeopathy in the treatment of Gout and/or Hyperuricemia.

Summary:

This will be the first systematic review of all types of homeopathy for Gout and/ or Hyperuricemia. We

have attempted to propose a robust protocol that should result in an objective and suitable summary of the existing evidence in this area of research. The review will not be limited only to clinical trials, but in vitro and animal experimentation studies published in the English language will also be included. The databases selected for review, index a large number of CAM journals, and the search strategy is likely to find most of the relevant studies that exist.

After the systematic review, eventually, a meta-analysis will be performed to critically examine the world's homeopathic literature on Gout and/or Hyperuricemia. A further outcome will be the outcome of the methodological assessment of the published literature. Finally, conclusions will be drawn from this systematic review regarding the clinical evidence of the effectiveness of Homoeopathy in the treatment of Gout and/ or Hyperuricemia. The classification will be made according to the grade of evidence in six levels, developed by Natural Standard, an international research collaboration that synthesizes and aggregates data on complementary and alternative therapies (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1250333/). The findings will be correlated with the findings of preclinical and animal experiments. The limitations of the studies will be discussed in detail. Gap areas toward generating a strong level of evidence for the effectiveness of homeopathy in this condition will be explored as well as suggestions for future research will also be provided.

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