Efficacy and safety of Ayurveda interventions for Primary Open-Angle Glaucoma and Ocular Hypertension in India over the last 40 years: A Systematic Review and Meta-Analysis Protocol

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Table of Contents

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Abstract

Background: Primary Open-Angle Glaucoma (POAG) and Ocular Hypertension (OHT) are major causes of irreversible blindness globally, with a significant disease burden in India. Conventional treatments primarily aim at reducing intraocular pressure (IOP) through pharmacological agents, laser therapy, and surgery, but these approaches are often limited by side effects, poor adherence, and disease progression despite optimal IOP control. Ayurveda, the traditional medical system of India, offers therapeutic interventions such as Kriyakalpa (specialized ocular procedures), Panchakarma (purificatory therapies), and herbal or herbo-mineral formulations that may provide a neuroprotective and IOP-lowering effect in POAG and OHT. However, the clinical evidence supporting the efficacy and safety of these interventions remains fragmented and inconsistent.

Objective: This systematic review and meta-analysis aim to evaluate and synthesize evidence on the efficacy and safety of Ayurveda interventions for the management of POAG and OHT in various institutes of India over the last 40 years (1984–2024).

Methods: A comprehensive search will be conducted in electronic databases, including Cochrane Complementary Medicine Trial Register, Annotated Bibliography of Indian Medicine, Web of Science, MEDLINE via PubMed, PubMed Central, Cochrane Central Register of Controlled Trials, National Institute of Science Communication and Information Resources, Scopus, EMBASE, Directory of Open Access Journals, Google Scholar, and Digital Helpline for Ayurveda Research Abstracts. The search will cover clinical trials, including randomized controlled trials (RCTs), controlled clinical trials (CCTs), observational studies, and single-arm trials. The primary outcome measures will include reduction in IOP, visual field progression, and optic nerve head health. Secondary outcomes will include adverse events associated with Ayurveda interventions. Risk of bias will be assessed using the Cochrane Risk of Bias (RoB 2) tool for RCTs and the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool for non-randomized studies. A random-effects model will be used for quantitative synthesis, and a narrative synthesis will be conducted for heterogeneous data.

Results: Protocol is developed. Since this is a systematic review protocol, no definitive results are available at this stage.

Conclusions: This systematic review will provide comprehensive insights into the role of Ayurveda in managing POAG and OHT, including its therapeutic efficacy and safety. The findings will contribute to the development of clinical guidelines and inform future research on integrative approaches in glaucoma management. Clinical Trial: PROSPERO 2024 CRD42024592392 https://www.crd.york.ac.uk/PROSPERO/view/CRD42024592392

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Systematic review registration number:
PROSPERO 2024 CRD42024592392

Keywords: Ayurveda, Glaucoma, POAG, OHT, Systematic Review, Meta-Analysis

Introduction

Primary Open-Angle Glaucoma (POAG) and Ocular Hypertension (OHT) are leading causes of irreversible blindness worldwide, with a significant disease burden in India.[1] POAG is characterized by progressive optic neuropathy and visual field loss, often associated with elevated intraocular pressure (IOP), while OHT involves increased IOP without detectable glaucomatous damage.[2] Conventional management primarily focuses on lowering IOP through pharmacological agents, laser therapy, and surgical interventions.[3] However, the long-term efficacy and safety of these treatments are limited by side effects, poor adherence, and progression despite optimal IOP control.[4]

Ayurveda, the traditional medical system of India, offers a range of therapeutic interventions for managing ocular diseases, including POAG and OHT.[5,6] Ayurvedic treatments encompass Kriyakalpa (specialized ocular procedures), Panchakarma (detoxification therapies), and herbal or herbo-mineral formulations aimed at improving ocular health and maintaining neuroprotection. Existing clinical evidence on the efficacy and safety of these interventions remains fragmented and inconsistent. Systematic evaluation of this evidence is essential to establish the therapeutic potential of Ayurveda in managing POAG and OHT.

This systematic review and meta-analysis aim to synthesize available evidence on the efficacy and safety of Ayurveda interventions for POAG and OHT in India over the past 40 years (1984–2024). The review will include randomized controlled trials (RCTs), controlled clinical trials (CCTs), observational studies, and single-arm trials to assess the impact of Ayurveda-based therapies on IOP reduction, visual field progression, and optic nerve health. The findings will provide a comprehensive understanding of the role of Ayurveda in glaucoma management, informing future clinical practice and research.

Review questions

What is the efficacy and safety of Ayurveda interventions for the management of Primary Open-Angle Glaucoma (POAG) and Ocular Hypertension (OHT) in studies conducted in India from 1984 to 2024?

Inclusion criteria

Types of study to be included:

1. Randomized Controlled Trials (RCTs) evaluating the efficacy of Ayurveda interventions for Primary Open Angle Glaucoma (POAG) and Ocular Hypertension (OHT).
2. Controlled Clinical Trials (CCTs): Non-randomized studies that include a comparison group (such as standard modern medicine treatments or placebo) to assess the effectiveness of Ayurveda interventions.
3. Observational Studies: These include cohort and case-control studies, providing insights into the long term effects and safety of Ayurveda interventions in real-world settings.
4. Single-Arm Trials: Studies without a comparator group will also be included, particularly to capture data on outcomes such as intraocular pressure (IOP) following Ayurveda interventions.

Exclusion:

1. Qualitative studies: Studies that solely provide qualitative data (e.g., interviews or case reports) without quantitative outcomes will be excluded.
2. Non-clinical studies: Laboratory studies, animal experiments, and in-vitro research will not be included.

Condition or domain being studied

This review focuses on the management of Primary Open-Angle Glaucoma and/ or Ocular Hypertension with Ayurveda interventions.

Participants

Inclusion:

Adults aged 18 years -70 years diagnosed with POAG or OHT in clinical studies.

Exclusion:

Studies involving other forms of glaucoma or non-clinical (animal/in-vitro) studies.

Interventions

Inclusion:

1. Kriyakalpa: Involving specialised ocular therapeutics, such as Ashchyotana (eye drops), Netra Seka (ocular irrigation), Pindi (therapeutic eye bandage), Bidalaka (transdermal application of medicated paste over closed lids), Tarpana (retention of medicated ghee over the eyes), Putapaka (retention of medicated processed juices over the eyes), Anjana (collyrium).
2. Panchakarma: Purificatory therapies, including Virechana (therapeutic purgation), Nasya (nasal administration of medicines), and Vasti (therapeutic enema), Raktamokshana (bloodletting).
3. Formulations: Use of single or poly herbal, herbo-mineral or mineral Ayurveda formulation in managing POAG and OHT.

Exclusion:

1. Ayurveda interventions focusing solely on conditions unrelated to glaucoma or ocular hypertension
2. Interventions that do not include any specific Ayurveda-based therapy but focus on modern allopathic treatments or other alternative medicine systems.
3. Non-clinical therapies or wellness approaches like general dietary supplements or lifestyle recommendations not specifically targeting POAG or OHT.
4. Surgical interventions and other invasive procedures, even if combined with Ayurveda post-operative care.

Comparators

Inclusion:

1. Standard Modern Medicine Treatments: This includes allopathic interventions for POAG and OHT, such as topical medications (e.g., prostaglandin analogues, beta-blockers, carbonic anhydrase inhibitors) aimed at lowering intraocular pressure (IOP), or systemic medications routinely prescribed for these conditions.
2. Placebo or No Comparator: Studies using placebo interventions, where participants receive an inactive substance, or single-arm trials without any comparator will be included to assess the effectiveness of the Ayurveda interventions.
3. Other Ayurveda Interventions: Studies comparing different Ayurveda-based interventions, either between various Ayurveda treatments or using one Ayurveda intervention as an adjunct to another, will also be included.

Exclusion:

1. Comparisons with Other Alternative Medicine Systems: Studies involving interventions from other traditional medicine systems, such as Traditional Chinese Medicine (TCM) or homeopathy, will be excluded unless combined with Ayurveda treatments.
2. Surgical Interventions: Studies where surgical treatments, such as trabeculectomy or laser therapy, are the primary intervention without any Ayurveda-based treatment as a comparator will be excluded.

Context

This review will include studies conducted in hospitals, Ayurveda research institutions, and clinical setups across India.

Main outcomes

- Reduction in intraocular pressure (IOP).
- Change in visual field progression and optic nerve head health.

Measures of effect

Intraocular Pressure (IOP): The mean difference in IOP reduction from baseline to follow-up will be reported for each study. Where applicable, a weighted mean difference (WMD) will be calculated for meta-analysis.
Visual Field Progression: Changes in visual field progression or optic nerve damage will be reported, depending on the study design and outcome data. For continuous outcomes, the mean difference (MD) will be calculated.

Additional outcome

Adverse events associated with Ayurveda interventions.

Methods

Search strategy

The search strategy for this systematic review will include several sources to ensure comprehensive coverage of relevant studies. Electronic databases such as Cochrane Complementary Medicine Trial Register, Annotated Bibliography of Indian Medicine (ABIM), Web of Science, MEDLINE via PubMed, PubMed Central, Cochrane Central Register of Controlled Trials (CENTRAL}, National Institute of Science Communication and Information Resources (NISCAIR), Scopus, EMBASE, Directory of Open Access Journals (DOAJ), Google Scholar, and Digital Helpline for Ayurveda Research Abstracts (DHARA) will be searched. Additionally, the AYUSH Research Portal and the Clinical Trials Registry of India (CTRI) will be utilised. Dissertations available in the public domain will be sourced from Shodhganga. Hand searching will be conducted using the Ayurvedic Research Database (ARD) and relevant journals, grey literature, and library resources from universities or institutions, where necessary and with permission.
Studies published between 1984 and 2024 will be included, with a language restriction to English-language studies only. Unpublished studies will also be sought through clinical trial registries and expert contacts. Rayyan software will be used for the screening process, ensuring blinding during title and abstract screening and assisting in resolving conflicts between reviewers. To ensure up-to-date results, the search will be re-run prior to the final analysis, capturing any newly published studies.

Study Selection

Review Process: Two independent reviewers (Reviewer 3 and Reviewer 4) will apply the eligibility criteria to screen studies for inclusion. All titles and abstracts will be reviewed independently using Rayyan software, ensuring reviewers are blinded to each other's decisions.[7]
Disagreement Resolution: Any disagreements between the two reviewers will be resolved through discussion. If a consensus cannot be reached, Reviewer 1 and Reviewer 2 will be consulted to make the final decision.
Software for Screening: Rayyan software will be used to manage and document the screening process, tagging studies for inclusion, exclusion, or further review.

Data Extraction

Data to be Extracted: Information extracted from each study will include following: Study design and methodology, Participant demographics and baseline characteristics, Intervention details (type, dose, duration), Comparator details (placebo, standard care, or other Ayurveda interventions), Main outcome measures (IOP reduction, visual field progression, optic nerve health), Adverse events or complications associated with the interventions.
Reviewers: Three independent reviewers (Reviewer 1, Reviewer 2, and Reviewer 3) will extract data using a predesigned extraction form. Any discrepancies will be resolved through discussion, involving Reviewer 5 and Reviewer 6 as needed.
Handling Missing Data: If important data are missing, study investigators will be contacted to obtain additional details or unreported data.
Tools for Data Management: Data extraction and management will be conducted using Cochrane RevMan and Systematic Review Data Repository-Plus (SRDR+) software.[8] All data will be recorded and stored systematically to ensure consistency and accuracy.

Risk of bias (quality) assessment

For randomized controlled trials (RCTs}, the Cochrane Risk of Bias (RoB 2) tool will be used to assess the risk of bias. [9] For non-randomized studies, the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool will be employed.[10]

Characteristics Assessed

Randomization: Methods of random sequence generation and allocation concealment.
Blinding: Whether participants, personnel, and outcome assessors were blinded.
Outcome Data: Completeness of outcome data, handling of missing data, and reporting of all prespecified outcomes.
Treatment Allocation: Appropriateness and description of intervention allocation, including any deviations from the intended intervention.
Other Biases: Consideration of other potential sources of bias, such as funding sources or conflicts of interest.
Assessment Level: Bias will be assessed at the study level for general methodological quality and at the outcome level for specific key outcomes such as intraocular pressure (IOP) reduction and visual field progression.
Reviewers: Two independent reviewers (Reviewer 1 and Reviewer 2) will assess the risk of bias in each study. If discrepancies arise between the reviewers, they will be resolved through discussion. If an agreement cannot be reached, Reviewer 5 and Reviewer 6 will be consulted.

Strategy for data synthesis

Criteria for Data Synthesis:

Studies will be synthesized if there are at least two or more studies with comparable interventions, populations, and outcomes. Heterogeneity will be assessed using the I^2 statistic.[11] A threshold of $I^2 \leq 50\%$ will be considered acceptable for combining data in a meta-analysis. For higher heterogeneity ($I^2 > 50\%$), a narrative synthesis will be used, or sensitivity analyses will be conducted to explore the sources of heterogeneity.

Quantitative Synthesis:

For outcomes such as intraocular pressure (IOP) reduction and visual field progression, a meta-analysis will be performed using a random-effects model to account for variability across studies. The summary effect measures will include Mean differences (MD) or standardized mean differences (SMD) for continuous outcomes (e.g., IOP reduction in mmHg). Odds ratios (OR) or relative risks (RR) for binary outcomes (e.g., visual field progression or adverse events). The random-effects model will be used to estimate pooled effects, accounting for variation between studies due to differences in population, interventions, or outcome measurements.

Narrative Synthesis:

If significant heterogeneity exists (I^2 > 50%) and meta-analysis is not appropriate, a narrative synthesis will be conducted. This will involve a structured description of the study characteristics, interventions, and outcomes, focusing on patterns or trends in the findings. Studies that do not meet the criteria for quantitative synthesis will be included in the narrative summary, with an emphasis on comparing interventions, study design, and patient populations.

Tools for Synthesis:

RevMan will be used for conducting standard meta-analyses. JASP or Stata will be used for advanced statistical analyses such as network meta-analysis, meta regression, or to explore potential sources of heterogeneity.

Sensitivity Analysis:

Sensitivity analyses will be performed by excluding studies with a high risk of bias or those contributing to substantial heterogeneity. The robustness of the overall findings will be evaluated by comparing results with and without these studies.

Analysis of subgroups or subsets:

Rationale: Subgroup analysis is necessary to investigate whether specific factors, such as the type of Ayurveda intervention, baseline intraocular pressure (IOP) levels, treatment duration, or severity of Primary Open-Angle Glaucoma (POAG) and Ocular Hypertension (OHT), influence the effectiveness of interventions.

Subgroups:

Type of Ayurveda Intervention: Different interventions (e.g., Kriyakalpa, Panchakarma, herbal or herbo mineral formulations) may have varying effects on IOP reduction or optic nerve health.
Baseline IOP Levels: Studies will be categorized based on participants' initial IOP measurements (e.g., low, moderate, high) to determine whether the effectiveness of Ayurveda interventions differs based on baseline severity.
Duration of Treatment: Studies with different treatment durations (e.g., short-term vs. long-term) will be grouped to assess the impact of the duration of Ayurveda interventions on outcomes.
Severity of Glaucoma: Participants will be grouped by glaucoma severity (e.g., early-stage vs. advanced stage POAG) to evaluate whether the effectiveness of interventions differs based on the stage of disease progression.
Analytic Approach: Subgroup analyses will be conducted using RevMan for standard analyses.
For more complex analyses, such as investigating potential effect modifiers or interactions between subgroups, Stata will be used.
The results of subgroup analyses will be presented as pooled effect estimates within each subgroup (e.g., mean differences in IOP reduction or odds ratios for visual field progression), and the interaction between subgroups will be tested for statistical significance.
Meta-regression will be used if multiple covariates need to be analysed simultaneously, allowing for a more nuanced understanding of how these factors influence treatment outcomes.

Results

Since this is a systematic review protocol, no definitive results are available at this stage. However, the review is expected to identify and analyse clinical studies conducted over the last 40 years (1984–2024) that evaluate Ayurveda interventions for POAG and OHT in India. The findings will include data on intraocular pressure (IOP) reduction, visual field progression, and optic nerve health in patients undergoing Ayurveda-based treatments, including Kriyakalpa, Panchakarma, and herbal or herbo-mineral formulations. Safety outcomes, including reported adverse events, will also be assessed to determine the risk-benefit profile of these interventions. The anticipated results will

contribute to understanding the effectiveness and potential limitations of Ayurveda therapies in glaucoma management, helping to establish evidence-based recommendations for future clinical practice and research.

Discussion

This systematic review and meta-analysis aim to synthesize evidence on the efficacy and safety of Ayurveda interventions for Primary Open-Angle Glaucoma (POAG) and Ocular Hypertension (OHT) in India over the past 40 years. The review will evaluate clinical trials, including randomized controlled trials (RCTs), controlled clinical trials (CCTs), observational studies, and single-arm trials to assess the impact of Ayurveda-based therapies on intraocular pressure (IOP) reduction, visual field progression, and optic nerve health. The findings will contribute to understanding the role of Kriyakalpa (specialized ocular procedures), Panchakarma (purificatory therapies), and Ayurveda formulations in glaucoma management, particularly in the context of neuroprotection and IOP regulation. Additionally, safety profiles and adverse effects of Ayurveda interventions will be systematically assessed to inform future clinical applications and integrative treatment strategies.

Conclusion

This systematic review and meta-analysis will provide comprehensive insights into the efficacy and safety of Ayurveda interventions in managing Primary Open-Angle Glaucoma (POAG) and Ocular Hypertension (OHT). By systematically evaluating clinical evidence from the past 40 years, the findings will highlight the role of Kriyakalpa, Panchakarma, and herbal/herbo-mineral formulations in reducing intraocular pressure (IOP), preserving optic nerve health, and slowing disease progression.

Limitations

The study may face several limitations, including the heterogeneity of Ayurveda interventions, variations in study design, and differences in outcome assessment methods. The inclusion of single-arm trials and observational studies may introduce bias due to the lack of control groups. The long timeframe (1984–2024) may also present challenges in standardizing methodologies across studies, particularly given the evolving nature of clinical trial designs in Ayurveda research. Additionally, variations in diagnostic criteria and IOP measurement techniques over time may impact data consistency.

Acknowledgment

None.

Conflict of interest

None.

Abbreviations

POAG: Primary Open-Angle Glaucoma
OHT: Ocular Hypertension
IOP: Intraocular Pressure
RCT: Randomized Controlled Trial
CCT: Controlled Clinical Trial
ROB: Risk of Bias
ROBINS-I: Risk of Bias in Non-Randomized Studies of Interventions
AYUSH: Ayurveda, Yoga & Naturopathy, Unani, Siddha, and Homeopathy
CTRI: Clinical Trials Registry of India

CENTRAL: Cochrane Central Register of Controlled Trials
NISCAIR: National Institute of Science Communication and Information Resources
ABIM: Annotated Bibliography of Indian Medicine
DHARA: Digital Helpline for Ayurveda Research Abstracts
WMD: Weighted Mean Difference
MD: Mean Difference
SMD: Standardized Mean Difference
OR: Odds Ratio
RR: Relative Risk
SRDR+: Systematic Review Data Repository-Plus

Data availability

No datasets were generated or analysed during the preparation of this protocol.

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