Exploring the potential of Homoeopathy: A detailed examination of Systematic Review and Meta-analysis procedure - weighing the Pros and Cons

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ABSTRACT
This article delves into the realm of homeopathy, scrutinizing its potential through a comprehensive exploration of systematic review and meta-analysis procedures. The objective is to provide a nuanced understanding of the advantages and disadvantages associated with these research methodologies in the context of homeopathic studies. Through a detailed examination, the article aims to shed light on the reliability and validity of evidence generated through systematic reviews and meta-analyses within the realm of homeopathy. By weighing the pros and cons, this study contributes to the ongoing discourse surrounding the efficacy and credibility of homeopathic treatments, offering valuable insights for researchers, practitioners, and healthcare professionals.

Keywords: Systematic review, Meta-analysis, Narrative synthesis, Homoeopathy.

INTRODUCTION
Evidence-based medicine (EBM) is indeed a practice that emphasizes the integration of the best available evidence from high-quality clinical research with clinical expertise and patients' values in order to make informed decisions about patient care. It aims to improve the quality of healthcare by applying rigorous scientific methods and critical appraisal of evidence. One of the key aspects of EBM is the systematic and efficient search of relevant literature. EBM practitioners need to develop skills in effectively searching and evaluating the available scientific literature to identify the most reliable and relevant evidence for clinical decision-making. This involves staying up-to-date with the latest research findings and being able to critically appraise the validity and relevance of studies [1]. In contrast to traditional medicine, EBM places a stronger emphasis on using research evidence and statistical parameters to guide clinical decisions. Traditional medicine often relies on anecdotal evidence, clinical experience, and expert opinion. While these sources of information can still be valuable, EBM recognizes the need for a more systematic and rigorous approach to evaluating evidence. By promoting the use of high-quality clinical research, EBM aims to enhance patient outcomes, improve the efficiency of healthcare delivery, and reduce unwarranted variations in clinical practice. It encourages healthcare professionals to continually engage in lifelong learning and to adapt their practice based on the best available evidence. Overall, EBM represents a shift towards a more evidence-based and scientifically grounded approach to healthcare, with the ultimate goal of providing the best possible care for individual patients [1]. Evidence-based medicine (EBM) plays a crucial role in family medicine and day-to-day healthcare practices. Here's why EBM is important in these settings (Figure 1) [2].
1. **Informed Decision Making** [2]: EBM provides healthcare practitioners, including family physicians, with the necessary tools and knowledge to make informed decisions about patient care. It integrates the best available evidence from research with clinical expertise and patient values and preferences. By using EBM, family physicians can ensure that their decisions are based on reliable evidence rather than personal biases or anecdotal experiences.

2. **Patient-Centered Care** [2]: Family medicine focuses on building strong patient-doctor relationships and providing personalized care. EBM supports this approach by considering the individual patient’s needs, values, and preferences in the decision-making process. By incorporating the best available evidence, family physicians can offer patient-centered care that aligns with the patient’s goals and values.

3. **Improving Clinical Outcomes** [2]: EBM aims to improve clinical outcomes by using interventions and treatments that have been proven effective through rigorous research. By implementing evidence-based guidelines and recommendations, family physicians can ensure that their patients receive the most appropriate and effective care. This helps to enhance patient outcomes, optimize treatment plans, and reduce the risk of unnecessary interventions or treatments.

4. **Avoiding Harm and Minimizing Costs** [2]: EBM helps family physicians avoid unnecessary or potentially harmful interventions, tests, and treatments. By relying on evidence, healthcare providers can minimize the risk of adverse effects, reduce healthcare costs, and allocate resources efficiently.

5. **Professional Development** [2]: EBM encourages lifelong learning and professional development among family physicians. Staying up-to-date with the latest research and evidence allows healthcare practitioners to provide the best care possible. By integrating EBM into their practice, family physicians can continuously improve their knowledge and skills, ensuring that they deliver the most current and effective care to their patients.

In total, EBM is essential in family medicine and day-to-day healthcare practices because it promotes informed decision-making, patient-centered care, improved clinical outcomes, avoidance of harm, and professional development. By incorporating the best available evidence into their practice, family physicians can provide high-quality, effective, and personalized care to their patients.

In Evidence-Based Medicine (EBM), diverse hierarchies rank study types according to research method strength and precision. While disagreements may arise, a consensus among experts generally places well-designed systematic reviews and meta-analyses at the pinnacle, representing the highest level of evidence, while expert opinions and anecdotal experiences occupy the lower tiers of the hierarchy [3].

Systematic reviews and meta-analyses play a crucial role in addressing complex issues, enhancing estimate precision, and resolving discrepancies. By synthesizing various papers with diverse results, these methods contribute to reaching conclusive decisions and bolstering study precision through increased sample sizes (Figure 2) [3] [4].

A **narrative review** provides a synthesis or description of the literature review without using quantitative methods. **Systematic review** is defined as “a review of the evidence on a clearly formulated question that uses systematic and explicit methods to identify, select and critically appraise relevant primary research, and to extract and analyze data from the studies that are included in the review.”
**Figure 1.** Triad of EBM (source: Google – open domain)

**Figure 2.** Hierarchy of EBM. **Source:** Murad et al., 2016 [3]
The methods used must be reproducible and transparent. Definitely, there are Pros and Cons between systematic and narrative reviews; the major advantage of systematic reviews is that they are based on comprehensive findings and systematic literature searches in all available resources, with minimization of selection bias avoiding subjective selection bias, while narrative reviews if done by experts in certain research area can provide experts intuitive perspectives in focused topics [5].

Intuitive perspective in narrative reviews involves: [5]
1. Subjectivity: Researchers draw on their own understanding, expertise, and insights to interpret the literature.
2. Integration: They integrate various sources of information to construct a cohesive narrative that explains the phenomenon under study.
3. Synthesis: They synthesize findings from diverse sources, often across disciplines, to develop a comprehensive understanding of the topic.
4. Interpretation: Researchers interpret the meaning and significance of the findings within the context of the research question or objective.
5. Exploration: They explore emerging themes, contradictions, and gaps in the literature to guide future research directions.

Meta-analysis, instead, is a quantitative, formal, epidemiological study design used to systematically assess previous research publications to derive conclusions about that body of research. Outcomes from a meta-analysis give a more precise estimate of the effect of treatment or risk factors for disease or other outcomes than any individual study used in pooled analysis [6].

**Steps of doing Systematic Review and Meta-analysis:**

**Step 1: Defining the problem**

In the daily practice of medicine, doctors are frequently tasked with making crucial decisions regarding diagnostic tests, prognoses, and the cost-effectiveness of interventions. Given their demanding schedules, it is essential for physicians to prioritize and refine the questions they address. The ability to search for the latest and best available data allows clinicians to effectively address individual patient problems.

To formulate a good clinical question for systematic reviews and meta-analyses, the **PICO** (Patients/Problem, Intervention, Comparison, Outcome) format is commonly used. This quantitative evidence synthesis approach involves defining the relevant patients, the intervention or management strategy, the comparison or alternative strategy, and the patient-relevant outcomes of interest [6,7].

For qualitative and mixed-method research, the **SPIDER** (Sample, Phenomenon of Interest, Design, Evaluation, Research type) criteria offer a structured framework. While **PICO** is ideal for systematic reviews of clinical trial studies, for observational studies (especially those in tropical and epidemiological contexts), focusing on **P** (patient) and **O** (outcome) may suffice to formulate a research question [6,7].

In essence, clinicians must strategically frame their inquiries using **PICO** or **SPIDER** criteria based on the nature of the study and the type of evidence sought, ensuring clarity, focus, and feasibility in addressing clinical challenges.

**Step 2: Preliminary search and idea validation:** Before embarking on a research study, it is crucial to conduct a preliminary search to identify relevant articles. This step ensures the validity of the proposed idea, helps avoid duplication of previously addressed questions, and ensures a sufficient pool of...
Figure 3. PRISMA flow diagram template used in Systematic Review / Meta-analysis [9].

articles for analysis. The focus should be on healthcare issues that are both relevant and important, taking into consideration global needs and values. Adhering to adopted review methods is essential [8].

Neglecting this preliminary search can lead to the inadvertent duplication of existing studies, potentially resulting in the cancellation of the intended research project. To initiate this process, a simple search using platforms such as PubMed or Google Scholar, employing specific search terms related to the research question, is recommended. This proactive approach lays the foundation for a well-informed and meaningful research endeavor [8].

Step 3: Inclusion and exclusion criteria: The eligibility criteria for the study are determined by employing the PICO approach, considering study design and date restrictions. Exclusion criteria encompass unrelated, duplicated, and unavailable full-text or abstract-only papers, stated beforehand to mitigate bias. Inclusion criteria involve articles containing information pertinent to the research question, focusing on target patients, investigated interventions, or comparisons between study interventions [8]. The PRISMA flow diagram template, as depicted in Figure 3, guides the systematic review/meta-analysis process, ensuring a transparent and comprehensive selection of relevant articles for analysis [9].

Step 4: Search Strategy: To enhance the retrieval of the most relevant results, a standardized search strategy is initially employed in PubMed and later tailored for each specific database. The core of the basic search strategy lies in the formulation of the research question, typically utilizing the PICO framework. This involves constructing a search query with both free-text terms (found in the title and abstract) and relevant subject indexing, such as MeSH (Medical subject heading) terms (controlled vocabulary used by the National Library of Medicine to index
articles in the MEDLINE/PubMed database), to ensure the inclusion of eligible studies. Notably, the strategy avoids incorporating terms for the outcome to prevent hindrance in database searches, as the desired outcome may not always be explicitly mentioned in the articles.

**Step 5: Searching Databases**
The AMSTAR [10] guidelines recommend searching at least two databases in Systematic Reviews/Meta-analysis, emphasizing that increased database searches enhance the likelihood of obtaining accurate and comprehensive results. The order of database selection is contingent upon the nature of the review question. Commonly utilized databases include PubMed, Scopus, Web of Science, EMBASE, GHL, VHL, Cochrane, Google Scholar, ClinicalTrials.gov, mRCTs, POPLINE, and SIGLE. These databases collectively cover a wide range of published articles in tropical medicine and other health-related fields, ensuring a thorough exploration of relevant literature.

**Step 6: Protocol writing, approval from the supervisor, then register it:**
Registration and writing protocol at an early stage guarantees transparency and authenticity in the research process and protects from duplication. It is always recommended for a documented proof of a team blue print of work, research question, eligibility criteria, intervention/exposure, quality assessment, and pre-analysis plan. Many registry sites are available for SR/MA, like those proposed by Cochrane and Campbell collaborations, such as PROSPERO [11] (International Prospective Register of Systematic Review).

**Step 7: Title and abstract screening:**
The decision for further assessment of retrieved articles is based on eligibility criteria in order to reduce the possibility of including irrelevant articles. According to Cochrane guidance, two reviewers are required for this step, but as for junior researchers, it is quite tiresome; thus, it is quite beneficial if three reviewers should work independently to reduce the chance of error. Quality with three reviewers will be better than two because two reviewers can have different opinions, so they cannot decide, while the third opinion is crucial in order to resolve the confusion. When there is doubt about the article, the team should be inclusive rather than exclusive and make a decision after discussion and consensus. All excluded records should be given exclusion reasons.

**Step 8: Full-text downloading and screening:**
Full-text article links are provided by many search engines. In case links are not found, a search can be made on websites such as ResearchGate, which offer the opportunity to place direct full-text requests to authors. Exploring archives of needed journals, or else contacting the Principal Investigator to purchase if it is available. Three (3) reviewers work independently to decide about included full texts according to predefined eligibility criteria, with proper reporting exclusion of each and every excluded article. In case reviewers don’t agree to a single conclusion, the final decision about the inclusion and exclusion of the article will be made after discussion.

**Step 9: Manual Search:**
The author has to make all possible efforts to decrease bias by doing explicit hand-searching for the recovery of reports that are already dropped from the first search. Usually following methods are employed to make manual searching [12]:

- Looking for references from the included studies/reviews.
• Connecting or contacting with author and subject experts.
• Looking at related articles/ cited articles in PubMed and Google Scholar.

Methods to enhance and refine the yield of the manual searching process. Firstly, by searching reference lists of included articles; secondly, through citation tracking in which the reviewers track all the articles that cite each one of the included articles; and thirdly, similar to citation tracking, we follow all "related to" or "similar" articles. Above said methods can be performed by 2-3 independent reviewers, and all the selected articles must undergo scrutiny against the inclusion criteria after following the same record yielded from electronic databases, i.e., Title/Abstract and full-text screening.

Step 10: Data extraction and quality assessment:
Structured extraction Excel sheet is for the process of data collection and extraction from the full-text articles. The purpose of this step is to gather relevant information from the studies to be used in the analysis later on [13]. Following steps can be used for data collection and extraction from the full-text articles.
1. Pilot testing: Before starting the actual data extraction, it is recommended to conduct a pilot test using random studies. This helps ensure consistency and reliability among the reviewers.
2. Adjusted and non-adjusted data extraction: It is advised to extract both adjusted and non-adjusted data. This allows for the inclusion of confounding factors in the analysis by pooling them later.
3. Independent reviewers: The data extraction process should be carried out by 2-3 independent reviewers. This helps minimize bias and increase the reliability of the extracted data. Mostly Tawfik et al. Tropical Medicine and Health (2019) is used for the process.
4. Categories for data extraction: The structured extraction Excel sheet should include categories such as study and patient characteristics, outcomes, and quality assessment (QA) tool. This helps organize the extracted data for further analysis.
5. Extraction of data from graphs: Data presented in graphs should be extracted using software tools like Web plot digitizer [14]. This allows for accurate data collection from graphical representations.
6. Equations for extraction and estimation of standard deviation (SD): equations that can be used for data extraction and estimation of standard deviation from other variables.
7. Quality assessment tools: Different quality assessment tools are recommended depending on the study design. Examples of tools mentioned include ROB-2 Cochrane tool [15] for randomized controlled trials, NIH tool [16] for observational and cross-sectional studies, ROBINS-I tool [17] for non-randomized trials, QUADAS2 tool [18] for diagnostic studies, QUIPS tool [19] for prognostic studies, and CARE tool [20], HOM- CASE [21] (Homoeopathic clinical case report) or WissHom documentation standard guideline [22] or Modified Naranjo criteria [23] for case reports. Independent quality assessment: It is advised that 2-3 reviewers independently assess the quality of the included studies. Their assessments should be added to the data extraction form to reduce the risk of bias.

Step 11: Data checking task:
Process of data checking and verification in a research or literature review context is indeed crucial to ensure the accuracy and reliability of the extracted data. Assigning articles to independent reviewers who were not involved in the initial extraction process helps minimize bias and potential errors. By comparing each included article with its counterpart in an extraction sheet using evidence photos, reviewers can identify any discrepancies or mistakes in the extracted
data. This process adds an extra layer of quality control to the research or review process. When resources are limited, it is practical to assign different articles to each reviewer, particularly those that they did not extract in the previous stage. This approach helps minimize potential bias and allows for a fresh perspective during the data checking phase. Overall, incorporating a data checking step and involving multiple independent reviewers in the process helps enhance the accuracy, reliability, and quality of the research or review findings.

**Step 12: Statistical analysis:**

**Steps of conducting statistical analysis of systematic review and meta-analysis:**

1. Cleaning of data: Before analysis, the data extracted from included studies is organized in a format suitable for analytical software.
2. Types of analysis: The analysis includes qualitative analysis (describing data) and quantitative analysis. Qualitative analysis mostly describes data in SR studies while the quantitative analysis consists of two main types: meta-analysis and network meta-analysis (NMA).
3. Subgroup, sensitivity, cumulative analyses, and meta-regression: These methods can be used to test the consistency of results, investigate the effect of confounders on the outcome, and identify the best predictors.
4. Publication bias assessment: Publication bias refers to the possibility of missing studies that can affect the summary. It should be assessed to investigate its presence.
5. Forest plot: The forest plot is a graphical representation of the meta-analysis results.
6. Heterogeneity and publication bias: Assess the heterogeneity among the included studies using statistical tests [24] (e.g., Cochrane's Q test, \( I^2 \) statistics). High heterogeneity may require subgroup analyses or sensitivity analyses to explore potential sources of variability.
7. Sensitivity analysis: Sensitivity analysis is a procedure where the significance of a dependent variable is assessed by removing one study from the meta-analysis. The sensitivity analysis is not needed in cases where all included study p-values are < 0.05.

**Step 13: Double data checking:**

For more assurance on the quality of results, the analyzed data should be rechecked from full-text data by evidence photos, to allow an obvious check for the PI of the study.

**Step 14: Manuscript writing, revision, and submission:**

The scientific manuscript writing process typically includes four sections: Introduction, Methods, Results, and Discussion. Here's a sample paragraph that incorporates the mentioned sections [25].

- **Introduction:** The introduction section provides background information and rationale for the study. It highlights the importance of the research question and summarizes the current knowledge in the field. It also identifies the gaps or limitations in existing literature that the study aims to address.

- **Methods:** The methods section describes the study design, participants, data collection procedures, and statistical analysis methods. It outlines the inclusion and exclusion criteria, sample size determination, and any ethical considerations. It also specifies the data sources, variables measured, and any tools or instruments utilized. This section provides sufficient detail to allow other researchers to replicate the study.

- **Results:** The results section presents the findings of the study. It includes descriptive statistics, measures of central tendency, and inferential statistical analyses. The results are typically presented in tables, figures, and graphs to facilitate clear and concise reporting. Any statistical significance, effect sizes, or patterns observed are discussed, focusing on the research question and objectives.
Discussion: The discussion section interprets and contextualizes the results. It relates the findings to the existing literature and discusses their implications, strengths, and limitations. It also addresses any unexpected or contradictory results, identifies potential sources of bias or confounding, and suggests avenues for future research. The discussion section provides a comprehensive understanding of the study's contribution to the field.

Conclusion: In conclusion, the scientific manuscript writing process involves carefully crafting each section, including the introduction, methods, results, and discussion. Additionally, creating a characteristic table for study and patient characteristics is essential to summarize important details. After completing the manuscript, it is crucial to seek feedback from the principal investigator (PI) and make necessary revisions. Finally, selecting a suitable journal for submission, considering impact factor and alignment with the manuscript's topic, and adhering to the journal's author guidelines are important steps in the publication process.

PROS AND CONS OF SYSTEMATIC REVIEW AND META-ANALYSIS IN HOMOEOPATHY

Systematic reviews and meta-analyses are valuable research methods in the field of homeopathy, as in any other medical or scientific discipline. Here are the pros and cons specific to their application in the field of homeopathy.

PROS
1. Comprehensive Evaluation: Systematic reviews aim to provide a comprehensive and unbiased summary of the available evidence. This is particularly important in homeopathy, where diverse studies may exist with varying methodologies and outcomes.
2. Evidence Synthesis: Meta-analysis, a statistical technique used in systematic reviews, allows for the quantitative synthesis of data from multiple studies. This can enhance the statistical power of the analysis, potentially leading to more robust conclusions.
3. Identification of Trends and Patterns: Through the systematic review process, researchers can identify trends, patterns, and consistencies across various studies, helping to establish a clearer picture of the effectiveness of homeopathic treatments.
4. Reduced Bias: Systematic reviews follow a predefined protocol, reducing the risk of bias in study selection, data extraction, and analysis. This enhances the reliability of the findings.
5. Informed Decision-Making: Clinicians, researchers, and policymakers can use the results of systematic reviews and meta-analyses to make more informed decisions about the use of homeopathic treatments, potentially improving patient outcomes.

CONS
1. Heterogeneity of Studies: Homeopathic studies often vary in terms of design, patient characteristics, and interventions, leading to high heterogeneity. This can complicate the synthesis of results and reduce the generalizability of findings. The meta-analysis by Shang et al. (2005) scrutinized placebo-controlled trials of homeopathy and allopathy, revealing considerable heterogeneity in study designs, patient characteristics, and interventions. This diversity complicates result synthesis and undermines the generalizability of findings, raising questions about the clinical effects of homeopathy beyond placebo effects [26].
2. Publication Bias: Systematic reviews and meta-analyses are susceptible to publication bias, as studies with positive results are more likely to be published. This can lead to an overestimation of the effectiveness of homeopathic treatments. Linde et al. (1997) indicate that after correcting for publication bias, the odds ratio in favor of homeopathy decreased. Initially, the combined odds ratio for homeopathy was 2.45 (95% CI 2.05, 2.93), but after adjusting for publication bias, the odds ratio in favor of homeopathy decreased. Initially, the combined odds ratio for homeopathy was 2.45 (95% CI 2.05, 2.93), but after adjusting for publication bias, the odds ratio in favor of homeopathy decreased. Initially, the combined odds ratio for homeopathy was 2.45 (95% CI 2.05, 2.93), but after adjusting for publication bias, the odds ratio in favor of homeopathy decreased. Initially, the combined odds ratio for homeopathy was 2.45 (95% CI 2.05, 2.93), but after adjusting for publication bias, the odds ratio in favor of homeopathy decreased. Initially, the combined odds ratio for homeopathy was 2.45 (95% CI 2.05, 2.93), but after adjusting for publication bias, the odds ratio in favor of homeopathy decreased.
bias, the odds ratio reduced to 1.78 (95% CI 1.03, 3.10). This adjustment suggests that publication bias likely inflated the apparent effectiveness of homeopathy in the original analysis, leading to a lower acceptance of homeopathy when bias was accounted for [27]. For more details, see Box 1.

3. Quality of Included Studies: The overall quality of evidence depends on the quality of the included studies. In the field of homeopathy, study quality can be a concern, and low-quality studies may introduce bias into the review [28].

4. Limited Availability of High-Quality Trials: The number of high-quality randomized controlled trials (RCTs) in homeopathy may be limited. This scarcity of robust evidence can impact the ability to draw strong conclusions from systematic reviews and meta-analyses.

5. Challenge of Outcome Measures: Homeopathic treatments often involve individualized remedies, making it challenging to establish standardized outcome measures across studies. This can complicate the comparison and synthesis of results. To address the challenge of establishing standardized outcome measures in homeopathy due to individualized remedies, employing Wisshom [29] and Model validity of homeopathic treatment (MVHT) [30] can aid in selecting the simillimum effectively. Moreover, strict adherence to Transparent Reporting of Evaluation with Nonrandomized design (TREND) (31) and Consolidated Standards of Reporting Trials (CONSORT) [32] guidelines ensures consistency in outcome measures across studies, facilitating comparison and synthesis of results in homeopathic research.
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