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REVIEWER'S REPORT

Manuscript No.: IJAR- 59620

Title: Self-Tolerance, Autoimmunity and Individualized Therapeutics: Exploring the Role of Homoeopathic Individualization in Immune Regulation.

Recommendation:
Accept as it is .....
Accept after Minor revision.....
Accept after Major revision
Do not accept (*Reasons below*)

Rating	Excel.	Good	Fair	Poor
Originality		✓		
Techn. Quality		✓		
Clarity			✓	
Significance			✓	

Reviewer Name: Dr. ANAPANA GOPAL

Reviewer's Comment for Publication.

General Comments

The manuscript presents a narrative review and conceptual analysis exploring the potential relationship between individualized homoeopathic treatment and immunological self-tolerance in autoimmune diseases. It discusses central and peripheral immune tolerance, regulatory T cells, the breakdown of immune regulation, and the available clinical evidence concerning individualized homoeopathy.

The manuscript addresses an interesting interdisciplinary topic linking immunology, autoimmune disease, and individualized therapeutic approaches. Its major strength is the explicit distinction between preliminary clinical observations and the proposed biological mechanism. The conceptual figures and tables provide a useful framework for understanding self-tolerance and for designing future studies.

However, the manuscript requires further improvement in the critical appraisal of clinical evidence, the transparency of the literature-review methodology, and the scientific justification of the proposed hypothesis. Although the authors acknowledge that direct evidence linking individualized homoeopathy to restoration of self-tolerance is lacking, the discussion should more clearly distinguish a testable hypothesis from an established or biologically plausible therapeutic effect.

The manuscript would benefit from a more systematic presentation of the evidence, stronger discussion of methodological limitations in the cited studies, and a more explicit account of how future research could distinguish treatment-specific effects from placebo effects, natural disease fluctuations, and concurrent conventional treatment.

Content and Originality

The manuscript offers a conceptual framework connecting the principle of homoeopathic individualization with contemporary understanding of immune regulation. The discussion of central tolerance, peripheral tolerance, regulatory T

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cells, and autoimmune pathogenesis provides an appropriate scientific foundation for the proposed research question.

The originality of the manuscript lies primarily in proposing self-tolerance as a hypothesis for future investigation rather than claiming that homoeopathic treatment has already been shown to restore immune tolerance.

However, several aspects require further development:

- The authors should explain more clearly how the proposed framework advances existing research on individualized treatment and autoimmune disease.
- The manuscript should distinguish conventional precision medicine, which may use clinical, molecular, and genetic characteristics to guide treatment, from homoeopathic individualization, which is based on characteristic symptoms.
- The clinical evidence should be evaluated critically, particularly regarding study design, risk of bias, statistical significance, clinical relevance, and reproducibility.
- The proposed relationship between individualized homoeopathic treatment and immune regulation should remain explicitly hypothetical unless supported by direct experimental evidence.
- The authors should discuss alternative explanations for reported clinical improvements, including placebo effects, regression to the mean, natural disease variation, and concurrent medical treatment.
- The potential scientific contribution would be strengthened by explaining how the proposed hypothesis could be falsified through well-designed experimental studies.

Overall, the manuscript has conceptual value, but its novelty and scientific contribution need to be articulated more precisely.

Technical Quality

The manuscript requires improvement in review methodology, evidence assessment, and the proposed experimental framework.

1. Literature-review methodology: The manuscript identifies itself as a narrative review and conceptual analysis but does not provide a sufficiently detailed account of how the literature was identified and selected. The authors should specify the databases or information sources searched, search terms, relevant search dates, and criteria used to select the studies discussed.

2. Assessment of clinical evidence: The manuscript cites a 2014 systematic review and meta-analysis, a 2024 systematic review of rheumatological conditions, and a randomized trial in rheumatoid arthritis. These studies should be evaluated individually in terms of sample size, methodological quality, risk of bias, attrition, and limitations. Findings from heterogeneous medical conditions should not be assumed to apply directly to autoimmune diseases.

3. Interpretation of the rheumatoid arthritis trial: The manuscript appropriately acknowledges that only 58 of the 112 enrolled participants completed the cited trial and that improvements were not clearly attributable to active homoeopathic treatment over placebo. This limitation should receive greater emphasis when discussing the clinical evidence.

4. Evidence for immunological mechanisms: The manuscript does not present direct experimental evidence that individualized homoeopathic medicines increase regulatory T-cell function, eliminate autoreactive lymphocytes, or restore central or peripheral

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tolerance. These mechanisms should continue to be described as unverified hypotheses rather than demonstrated effects.
5. Research design: The proposed framework in Figure VI provides a useful starting point, but it requires greater methodological detail. Future studies should specify the control group, randomization procedures, blinding, sample-size calculation, follow-up duration, and statistical analysis plan.
6. Selection of biomarkers: Table V lists regulatory T cells, B-cell subsets, autoantibodies, cytokines, complement components, and inflammatory markers. The authors should identify which biomarkers are most relevant to the particular autoimmune disease under investigation and define primary and secondary outcomes in advance.
7. Clinical outcomes and confounding: The proposed framework should account for disease-specific treatment, changes in conventional medication, adherence, baseline disease severity, and other factors that could influence clinical or immunological outcomes.
8. Statistical analysis: Future studies should specify how differences between treatment and control groups will be assessed, how missing data will be handled, and how multiple biomarker comparisons will be controlled. Associations between clinical improvement and biomarker changes should not automatically be interpreted as evidence of a causal mechanism.
9. Safety and ethical considerations: Proposed clinical investigations should include adverse-event monitoring and ensure that participants continue to receive appropriate evidence-based treatment. Experimental interventions should not replace established treatment for autoimmune diseases.
10. Reproducibility: The authors should explain how individualized prescribing decisions will be documented and standardized sufficiently to permit replication while retaining the stated individualization approach.

Language and Presentation

The manuscript is generally well organized and readable. The terminology is mostly appropriate, and the figures and tables support the conceptual discussion. Nevertheless, several improvements are recommended.

- Standardize the spelling of "homoeopathy" and "homeopathy" according to the journal's preferred style.
- Correct minor grammatical errors, punctuation inconsistencies, and irregular spacing throughout the manuscript.
- Standardize abbreviations such as Treg, ESR, CRP, ANA, and anti-CCP, defining each at first use.
- Ensure consistent formatting of scientific terminology, particularly references to FOXP3-expressing regulatory T cells and immunological self-tolerance.
- Improve the readability of tables, especially Tables II and III, by ensuring consistent column widths, spacing, and alignment.
- Review all figure captions and ensure that abbreviations, arrows, and dashed lines are explained clearly.
- Avoid wording that could imply an established therapeutic mechanism when the evidence supports only a proposed hypothesis.
- Reduce repetition in the abstract, discussion, and conclusion, particularly concerning the absence of direct evidence for restoration of self-tolerance.

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The manuscript would benefit from careful proofreading and a final consistency check between the abstract, tables, figures, and main text.

Structure and Organization

The manuscript follows a logical sequence from immunological background to clinical evidence, hypothesis development, and future research. The overall structure is appropriate for a narrative review and hypothesis paper.

However, the following improvements are recommended:

- Abstract: Clearly distinguish the review's objectives, evidence sources, principal findings, limitations, and proposed research hypothesis.
- Introduction: Strengthen the research gap and explain why the relationship between individualized homoeopathy and immune tolerance warrants investigation despite the absence of direct mechanistic evidence.
- Immunological background: Retain the discussion of central and peripheral tolerance but ensure that the background directly supports the subsequent research question.
- Clinical evidence: Organize the evidence by study design and methodological quality, distinguishing systematic reviews from individual randomized trials.
- Self-tolerance hypothesis: Clearly separate the conceptual model from established immunological knowledge.
- Testing the hypothesis: Expand the proposed research framework to include appropriate controls, blinding, prespecified outcomes, statistical methods, and safety monitoring.
- Discussion: Provide a more critical assessment of evidence limitations, alternative explanations, and the implications of the current uncertainty.
- Conclusion: Emphasize that the proposed relationship requires rigorous testing and avoid suggesting that clinical improvement necessarily indicates restoration of self-tolerance.

The conceptual figures are useful, but their placement and accompanying explanations should reinforce the distinction between established biological mechanisms and the hypothesized effects of individualized homoeopathic treatment.

References and Citations

The manuscript includes references on immunological tolerance, regulatory T cells, autoimmune pathogenesis, and clinical studies of individualized homoeopathy. The references are generally relevant to the subject, but several improvements are needed.

- Verify the accuracy and completeness of all bibliographic details, including author names, article titles, journal names, publication years, volume numbers, page ranges, and DOI information.
- Ensure that all in-text citations correspond to the correct entries in the reference list.
- Standardize the reference formatting according to the journal's guidelines.
- Ensure that claims regarding clinical efficacy are supported by the actual findings and limitations of the cited studies.
- Include relevant recent literature on immune tolerance, regulatory T-cell dysfunction, and autoimmune disease mechanisms.
- Consider additional high-quality evidence syntheses and relevant studies that critically evaluate the efficacy and limitations of homoeopathic interventions.

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- Ensure that references concerning conventional precision medicine are used appropriately and are not presented as direct evidence supporting homoeopathic treatment.
- Verify that the cited systematic reviews and randomized trial are accurately summarized, particularly regarding the quality of evidence and the distinction between within-group improvement and treatment effects relative to placebo.

The reference list should be checked carefully to ensure scientific accuracy, balance, and appropriate support for the manuscript's claims.

Overall Recommendation

Minor Revision

The manuscript addresses an interesting conceptual question at the intersection of immunological self-tolerance, autoimmune disease, and individualized therapeutic approaches. Its principal strength is the explicit recognition that restoration of self-tolerance through individualized homoeopathic treatment remains an unverified hypothesis. The conceptual figures, biomarker tables, and proposed research framework provide a useful basis for further discussion.

However, the manuscript requires a more transparent literature-review methodology, stronger critical appraisal of the available clinical evidence, and greater methodological detail in its proposed research design. The authors should also strengthen the distinction between established immunological mechanisms, reported clinical outcomes, and speculative therapeutic mechanisms.

Addressing these concerns would improve the manuscript's scientific rigor, balance, and usefulness as a hypothesis-generating review.

Final Decision

Minor Revision.

The manuscript may be reconsidered after the authors improve the transparency of the literature-review process, critically evaluate the cited clinical studies, strengthen the discussion of evidence limitations, and provide a more rigorous framework for testing the proposed hypothesis.

The revised manuscript should maintain a clear distinction between clinical observations and demonstrated biological mechanisms. In particular, any claim that individualized homoeopathic treatment restores immunological self-tolerance must remain provisional unless supported by appropriately controlled clinical and experimental evidence. A further review is recommended after resubmission.