

REVIEWER'S REPORT

Manuscript No.: JNHM- 155

Title: From Bugs to Drugs: Harnessing the Cardioprotective Metabolome for Next-Generation Cardiovascular Therapeutics: A Narrative Review.

Recommendation:

Accept after minor revision

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

Reviewer's ID: JPR-Bilqees Hamza

Detailed Reviewer's Report

Overview

- This manuscript is a narrative review titled "*From Bugs to Drugs: Harnessing the Cardioprotective Metabolome for Next-Generation Cardiovascular Therapeutics*," prepared in accordance with the Scale for the Assessment of Narrative Review Articles (SANRA) guidelines. The authors present a synthesis of literature published between January 2020 and May 2026, evaluating how commensal gut microbiota-derived metabolites—specifically short-chain fatty acids (SCFAs), urolithin A, secondary bile acids, and indole derivatives—modulate host physiology to protect against cardiovascular diseases (CVD).
- The narrative effectively traces the conceptual shift from deleterious microbial outputs (such as trimethylamine N-oxide/TMAO) to the therapeutic potential of the cardioprotective metabolome. The authors discuss key signaling pathways (e.g., GPR41/43, Pink1/Parkin, TGR5/FXR, and AhR) and detail emerging translational platforms, such as small-molecule gut-restricted enzyme inhibitors and engineered live biotherapeutic products (LBPs) entering early-phase clinical evaluation.
- **Detailed Suggestions for Improvement**
- **1. Formatting, Line-by-Line Edits, and Typographical Refinements**

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- **Heading and Line-Number Integration Errors:** In the introductory sections, several line numbers are directly adjacent to body text without appropriate spacing or separation (e.g., lines 1–39 in the abstract and lines 40–80 in the introduction). Ensure all line numbers are maintained strictly in the margins during final layout proofing.
- **Typographical and Citation Encoding Errors:**
 - Line 97 & Line 101: Clean up formatting artifacts around the section headers ("—Inclusion Criteria:|" and "—Exclusion Criteria:|").
 - Line 170: The formula for changes in mitochondrial membrane potential is rendered as ($\Delta\Psi_m$). Render this cleanly as $\Delta\Psi_m$.
 - Line 186: Correct the subscript formatting in IL-1 β . Ensure $\text{IL-1}\beta$ is formatted consistently.
 - Line 188: Correct the bracket enclosure in ApoE^{-/-} to proper superscript syntax ($\text{ApoE}^{\{-/-\}}$).
 - Line 548: Remove the stray text fragment "UNDER PEER REgy Society (IC-OS). Eur Heart" appearing at the very end of the manuscript footer.
- **2. Methodological Clarifications and Literature Scope**
 - **Explicit Reporting of Database Results:** Section "Methodology" outlines the search string and inclusion/exclusion criteria, noting that 64 references were selected. However, adding a brief flow description or SANRA-compliant summary diagram illustrating the total number of records retrieved versus screened would enhance transparency.
 - **Clarification of Clinical Trial References:** In the "Discussion" section, several preclinical models and clinical trials from 2024–2026 are cited (e.g., references 13, 20, 31, 39, 45, 54, 63). Ensure that trial registration numbers (e.g., ClinicalTrials.gov NCT identifiers) are included in the narrative for all referenced Phase I–III human trials (such as the LBP safety trials and HFpEF Urolithin A trials).
- **3. Structural and Discussion Enhancements**
 - **Visual Synthesis / Summary Table:** The narrative covers four distinct metabolic pathways (SCFAs, Urolithin A, Bile Acids, Indoles). The draft would benefit significantly from a structured summary table comparing:
 - Metabolite Class & Primary Gut Precursor/Bacterial Producers
 - Primary Molecular Targets/Receptors
 - Key Cardiovascular Mechanisms
 - Current Translational/Clinical Status

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- **Integration with Standard Guidelines:** The discussion in Section "Guideline Alignment and the Therapeutic Horizon" rightly notes synergy with SGLT2 inhibitors and PCSK9 inhibitors. Expanding slightly on potential pharmacological interactions or metabolic competition between oral therapeutics and the gut microbiota would strengthen the translational depth.
- **4. Reference List Standardization**
- Review the bibliography (lines 310–547) for consistency in formatting:
- Standardize all journal title abbreviations according to Index Medicus/MEDLINE formatting.
- Reference 22 (line 387): "JCO. 2022;40(6_suppl):112-123" should have the journal title fully spelled out or standardly abbreviated (*J Clin Oncol*).
- Reference 34 (line 427): Fix missing punctuation in publication year and volume: "2015 21(11):702-314" $\rightarrow$ "2015;21(11):702-714".
- Reference 45 (line 461): Remove duplicate author initials ("Sordillo JE, JE, Manson JE").
- **Recommendation for the Editor**
- **Decision:** Accept with Minor Revision
- **Justification:** The manuscript provides a well-structured, timely, and comprehensive narrative review of the cardioprotective metabolome, adhering strictly to the SANRA framework. The biological mechanisms described are clear and backed by contemporary literature from 2020 to 2026. The requested revisions are minor and primarily involve fixing LaTeX/typographical artifacts, standardizing bibliographic citations, adding trial registration identifiers, and incorporating a summary comparison table to maximize readability.