

Dear Editors and Reviewers,

We sincerely thank you for your valuable time and thoughtful feedback on our manuscript submitted to *World Journal of Gastroenterology*. We deeply appreciate the careful reading of our manuscript and the valuable suggestions from the editors and reviewers.

After carefully studying all the comments, we have revised the manuscript accordingly and would like to send it back to the editorial office for reevaluation. A point-by-point response to the editors' and reviewers' comments are listed as follows.

Responds to the reviewer's comments:

Reply to Reviewer #1

Comment 1:

I agree with Wang's perspective. While acknowledging the possibility of the hypothesis presented in Pravda's paper, the authors highlight biases in the cited literature, weak evidence, and omissions in previous studies. I believe these are scientifically fair and reasonable arguments. Pravda's hypothesis should be recognized as one argument. Still, the point linking the use of immunosuppressants to the interests of pharmaceutical companies seems more like a political argument than a scientific one. If widely shared with the public, it could lead patients to discontinue or refuse to use medication. Wang et al.'s claims explain the background behind the current treatment and serve as a warning against rushing to adopt new treatment methods. Furthermore, they summarize the current issues and present future research directions. Based on the above points, this paper is worthy of publication.

Response:

We thank reviewer for the positive evaluation and agreement with our scientific approach. We particularly appreciate the reviewer's astute observation regarding the potential public health implications of discussions linking immunosuppressants to pharmaceutical interests. In response, we have added a new paragraph in the subsection "THEORETICAL INTEGRATION and CLINICAL CONTEXT" to elaborate on this perspective.

Moreover, the original review's characterization of current immunosuppressive therapies as representing primarily commercial interests rather than evidence-based medicine risks undermining patient confidence in treatments that have demonstrated clinical efficacy through rigorous randomized controlled trials. When alternative hypotheses are accompanied by sweeping dismissals of established therapies, patients may discontinue or refuse proven treatments based on incomplete evidence. Current immunosuppressive therapies, while not curative, have documented benefits in inducing and maintaining remission, improving quality of life, and reducing surgical interventions in many UC patients. Scientific progress benefits from challenging existing paradigms, but this must be balanced with responsibility toward patients who rely on current treatments. Novel

therapeutic approaches should be evaluated using the same rigorous standards applied to existing therapies, rather than being promoted as alternatives to evidence-based care before adequate validation.

Reply to Reviewer #2

Comment 1:

The commentary effectively contextualizes Pravda's hypothesis within broader UC research but should emphasize more clearly what new insights this letter adds beyond summarizing limitations of the original review. Strengthening the authors' own critical perspective would enhance the contribution.

Response:

We sincerely thank the reviewer for the invaluable and insightful comments. The points you raised are of utmost importance, and we fully agree with your assessment. Accordingly, we have substantially revised the manuscript to strengthen our scholarly position. Following your suggestion, we have added a new paragraph to the section "METHODODOLOGICAL and IMPLEMENTATION CHALLENGES" that presents our critical perspective on the barriers to clinical translation.

Although the H₂O₂ hypothesis provides plausible mechanistic insight into UC pathogenesis, its clinical translation is fundamentally constrained by the biochemical properties of H₂O₂. As a short-lived signaling molecule with a tissue half-life of less than one minute, H₂O₂ exhibits rapid fluctuations influenced by dietary factors, microbiota composition, mucosal oxygenation, and sampling location^[10, 11]. These variables contribute to substantial heterogeneity in baseline H₂O₂ levels across studies, thereby precluding the establishment of consistent reference ranges—a prerequisite for diagnostic applications and therapeutic monitoring.

Comment 2:

The manuscript rightly calls for randomized controlled trials (RCTs), but it would be valuable to suggest specific trial designs (e.g., patient subgroups, endpoints, comparator arms). This would make the recommendations more actionable.

Response:

We thank the reviewer for this valuable suggestion to make our RCT recommendations more actionable and specific. In response to this feedback, we have added Table 2 in the "FUTURE DIRECTIONS and ETHICAL IMPLEMENTATION FRAMEWORK" section.

Based on existing preliminary clinical evidence and current understanding of UC

pathophysiology, we recommend conducting a multicenter, randomized, double-blind, placebo-controlled Phase II clinical trial. The specific trial design protocol is detailed in Table 2.

Table 2. Phase II randomized controlled trial design for mild to moderate active ulcerative colitis

Design Requirements	Specific Protocol	Key Considerations
Study Design	Multicenter, randomized, double-blind, placebo-controlled Phase II trial	Compliance with ICH-GCP standards
Target Population	Patients with mild to moderate active UC (PRO2 score 2-5 points)	Balance baseline risk; standardize severity assessment
Inclusion Criteria	Age 18-65 years; MES score 1-2 points; discontinued biologics ≥8 weeks	Exclude severe UC and active infectious diseases
Sample Size	180 subjects (90 per group)	80% statistical power; anticipated 15% dropout rate ^[23]
Randomization Design	1:1 randomized allocation by disease severity stratification	Ensure balanced baseline characteristics and reduce bias
Treatment Groups	Group A: 5-ASA + STS (extracellular H ₂ O ₂ scavenger); Group B: 5-ASA + Placebo	Specific dosing regimens determined through Phase I dose-escalation studies
Biomarker Assessments	Weeks 0, 4, 8, 12: CRP, fecal calprotectin, neutrophil count, serum 8-isoprostane F _{2α} , malondialdehyde, GPx Activity	Based on STRIDE-II criteria ^[24] ; combined oxidative stress biomarkers
Primary Endpoint	Clinical response rate at Week 12 (PRO2 score reduction ≥50%)	Meets STRIDE-II recommended patient-reported outcome measures
Key Secondary Endpoints	Clinical remission, endoscopic response, histological improvement, oxidative stress biomarker changes at Week 12	Endoscopic response: MES ≤1 point; Histological improvement: Geboes score <2.0
Safety Assessment	Liver and kidney function tests at Weeks 0, 4, 8, 12; document and evaluate adverse events at each visit	Balance safety monitoring requirements with patient convenience
Follow-up Plan	Treatment period: 12 weeks + long-term follow-up to 52	Evaluate long-term efficacy maintenance

weeks

and safety

Abbreviations: ICH-GCP, International Council for Harmonisation-Good Clinical Practice; MES, Mayo Endoscopic Score; PRO2, Patient-Reported Outcome 2; STS, sodium thiosulfate; 5-ASA, 5-aminosalicylic acid; GPx, glutathione peroxidase; STRIDE-II, Selecting Therapeutic Targets in Inflammatory Bowel Disease Initiative update; CRP, C-reactive protein.

Comment 3:

The commentary is well-organized but could improve transitions between sections (e.g., from “Clinical Evidence” to “Reconciling with Contemporary Understanding”). Currently, it reads as a series of critiques rather than a cohesive argument.

Response:

We appreciate the reviewer's suggestions regarding article structure and paragraph transitions. We have comprehensively revised the manuscript in response to these comments. Specific improvements include: 1) Enhanced transitional sentences between sections, creating a clearer logical chain from theoretical integration to evidence evaluation and implementation challenges; 2) Reorganized the argumentative structure, integrating scattered critiques into a unified discourse centered on the theme of "responsible scientific translation"; 3) Added connecting statements between key points to ensure that all sections complement each other and collectively support our core argument—that while the H₂O₂ hypothesis offers innovative value, its clinical translation requires rigorous validation and ethical considerations.

Comment 4:

The authors raise concerns about long-term safety of reducing agents but provide little detail. This section would benefit from citing toxicology data, known adverse effects, or knowledge gaps requiring systematic study.

Response:

Thank you for this valuable feedback. We have substantially expanded the safety discussion in the "Methodological and Implementation Challenges" section. The revised section is as follows:

This measurement paradox directly undermines the proposed therapeutic approach using reducing agents such as sodium thiosulfate (STS) and R-dihydrolipoic acid (R-DHLA).

Without reliable H₂O₂ quantification, confirming H₂O₂-mediated disease through therapeutic response lacks both validation and standardization. Moreover, the long-term safety profiles of these agents in UC populations remain largely unknown. This knowledge gap is particularly concerning given the chronic nature of the disease, which necessitates prolonged treatment. Current safety data for these reducing agents are primarily derived from other clinical applications, such as STS use in calcific uremic arteriolopathy^[12]. These applications differ significantly from potential UC protocols in patient populations, dosing regimens, and treatment duration. Available evidence indicates that STS may cause gastrointestinal symptoms (nausea and vomiting), electrolyte disturbances, and occasional hypersensitivity reactions. However, serious adverse events appear uncommon at therapeutic doses^[13, 14]. Although R-DHLA demonstrates theoretical biocompatibility as a lipophilic antioxidant, comprehensive safety evaluation in inflammatory bowel disease populations remains lacking^[15]. Moreover, critical questions remain regarding the long-term effects on hepatic and renal function, potential drug-drug interactions with standard UC therapies, and the risk of withdrawal reactions in vulnerable populations.

Comment 5:

While the manuscript critiques selective evidence synthesis in Pravda's review, it occasionally falls into similar selectivity by citing limited recent studies. Including a broader range of references (e.g., large-scale genetic and microbiome studies) would give the commentary more authority.

Response:

Thank you for this insightful observation about evidence selectivity. We acknowledge this valid concern and have taken steps to address it by significantly expanding our reference base to provide a more comprehensive and balanced perspective.

Comment 6:

If novel reducing agents are to be tested, ethical concerns (first-in-human trials, compassionate use, risk-benefit justification) should be discussed. This would show awareness of practical hurdles beyond just clinical trial design.

Response:

Thank you very much for raising this critically important and insightful suggestion. We

completely agree that for any novel therapeutic approach, particularly those entering first-in-human trial phases, in-depth exploration of the ethical dimensions represents both scientific rigor and social responsibility. Your feedback has greatly enhanced the depth and completeness of our manuscript. Following your recommendation, we have added a dedicated paragraph in the "FUTURE DIRECTIONS and ETHICAL IMPLEMENTATION FRAMEWORK" section that systematically discusses the ethical issues surrounding the testing of novel reducing agents.

Although reducing agents demonstrate acceptable safety profiles as monotherapies in other indications, their combination use in UC lacks adequate non-clinical toxicological support. Existing safety data cannot be extrapolated to UC populations. This necessitates exceptionally cautious first-in-human studies. Once preliminary efficacy data emerge, investigators may face pressure for compassionate use from patients with refractory UC. This creates an ethical dilemma between denying potentially beneficial treatment to those with the greatest clinical need and exposing patients to unknown risks in the absence of sufficient evidence^[16]. The complexity is amplified by UC's impact on younger populations with extended life expectancies. This magnifies long-term treatment consequences and necessitates risk-benefit assessments that consider decades of safety data rather than short-term efficacy alone. If reducing agent therapy demonstrates curative potential, the benefits may justify certain risks; however, such assessments require exceptionally rigorous and comprehensive evidence. Systematic approaches are also required to address informed consent challenges, medical equity considerations, regulatory ethics, and research integrity oversight. H₂O₂-targeted therapy can advance only within an ethically sound framework that comprehensively addresses these considerations. Such thorough ethical deliberation is essential for translating theoretical innovations into clinical practice.

Comment 7:

The manuscript lacks visual elements. A summary table comparing: H₂O₂ hypothesis vs. other UC mechanisms . Proposed therapies vs. current standard of care would help readers quickly grasp the argument.

Response:

Thank you very much for your valuable suggestion. We completely agree with your

perspective that a summary table would greatly assist readers in quickly understanding and grasping the core arguments of this manuscript, namely the comparison between the H₂O₂ hypothesis and traditional UC mechanisms, as well as the differences between the derived therapies and current standard of care. Following your recommendation, we have added **Table 1** to the "THEORETICAL INTEGRATION and CLINICAL CONTEXT" section.

To provide a clearer comparison between the hydrogen peroxide hypothesis and current mainstream understanding of UC pathogenesis and treatment, we have summarized the key contrasts in Table 1.

Table 1. Comparison of pathological mechanisms and treatment methods between the new hypothesis and traditional theories of ulcerative colitis

Mechanism	H ₂ O ₂ hypothesis	Traditional treatment
Root cause	Excessive H ₂ O ₂ production and accumulation in colonic epithelial cells	Abnormal activation or dysregulation of the immune system ^[17]
Initial event	Mitochondrial H ₂ O ₂ generation ↑ → intracellular accumulation → transmembrane diffusion	Aberrant T cell activation → cytokine release ^[18]
Neutrophil recruitment	Direct chemotactic effect of H ₂ O ₂	IL-8, CXCL1, and other chemokine-mediated recruitment ^[19]
Inflammatory cascade	H ₂ O ₂ → neutrophil infiltration → tissue damage → additional H ₂ O ₂ release	Th1/Th17 activation → TNF-α/IL-17 ↑ → inflammatory amplification ^[20]
Tissue damage mechanism	H ₂ O ₂ -mediated disruption of tight junction proteins → epithelial barrier dysfunction	Cytotoxic T cells and NK cell-mediated epithelial cell killing ^[21]
Primary drugs	STS, R-DHLA	Mesalazine, biologics, immunosuppressants, JAK inhibitors ^[22]
Drug action	H ₂ O ₂ neutralization (extracellular and intracellular)	Anti-inflammatory, immunosuppression

Abbreviations: IL-8, interleukin 8; TNF-α, tumor necrosis factor alpha; IL-17, interleukin-17; CXCL1, C-X-C motif chemokine ligand 1; LPS, lipopolysaccharide; TLR4, Toll-like receptor 4; NF-κB, nuclear factor kappa B; NK, natural killer; Th1, T-helper 1; Th17, T-helper 17; JAK, Janus Kinase

Comment 8:

Ensure all abbreviations (UC, IBD, RCT, ROS, JAK) are defined at first use in the main text.

Response:

Thank you for this important editorial observation. We have carefully reviewed the manuscript and ensured that all abbreviations are now properly defined at their first occurrence in the main text.

Response to the Editor's Comments

First and foremost, we would like to express our sincere gratitude to the editorial board for the meticulous review and patient guidance of our manuscript. Every comment you provided reflects a rigorous academic attitude and commitment to journal quality, which deeply moves us and earns our profound respect. We have carefully addressed and implemented all the suggested revisions, including improving transitions between sections, more clearly articulating the novel insights of our research, expanding the reference scope, and completing all formatting adjustments. We also deeply recognize the importance of language quality and have conducted comprehensive language polishing, and will provide updated language certification as required. This revision process has significantly enhanced our research, and we sincerely thank the editorial board for their professional guidance.

We deeply understand the good intentions of the editorial board and editor-in-chief. Your recommendation to transfer our manuscript to the *World Journal of Gastrointestinal Pathophysiology* is undoubtedly to an excellent journal. However, after careful consideration, we earnestly hope to continue publishing this research in the *World Journal of Gastroenterology*. This is not merely our academic aspiration, but also embodies our sincere expectation to contribute to this field.

Our research directly responds to the ulcerative colitis article published in your journal (Pravda J. Ulcerative colitis: Timeline to a cure. *World J Gastroenterol* 2025; 31: 108375 [PMID: 40678706 DOI: 10.3748/wjg.v31.i26.108375]), and the continuation of this academic

dialogue holds profound significance for us. As researchers, we hope our work can become part of this scholarly discussion, forming more direct and meaningful exchanges with the original authors and readership. We believe that such sustained dialogue on the same academic platform not only advances scientific understanding but also embodies the beautiful quality of academic community collaboration in exploring truth. This emotional connection of academic heritage is precious to young researchers like us.

Meanwhile, we also sincerely hope to contribute to the academic reputation of the *World Journal of Gastroenterology*. We are well aware of your journal's prestigious position and broad influence in the field of gastroenterology. Being able to publish research findings on such a platform is not only recognition of our academic capabilities but also an opportunity for us to give back to the academic community. Although our research is a letter to the editor, we believe the novel insights regarding hydrogen peroxide pathways and clinical translation potential can provide valuable academic inspiration to your journal's readers, and we hope to contribute our modest efforts to advancing ulcerative colitis treatment progress.

We understand the challenges and great responsibility of journal editorial work, and we know that every decision you make is carefully considered. If our request has caused additional workload for the editorial board, we sincerely apologize, but this truly stems from our persistent pursuit of academic ideals. We are willing to accept any further revision suggestions and are prepared to make greater efforts to meet your journal's publication standards. If the editorial board ultimately believes our research is indeed more suitable for the *World Journal of Gastrointestinal Pathophysiology*, we will respect this professional judgment, but we sincerely hope to have the opportunity to publish in the *World Journal of Gastroenterology*.

We await the editorial board's final decision with both anticipation and trepidation. Regardless of the outcome, we deeply appreciate the professional guidance and patient assistance the editorial board has provided throughout the review process. This experience has helped us grow tremendously and has deepened our respect for rigorous academic attitudes and excellent journal editorial work.