



OPEN ACCESS

EDITED AND REVIEWED BY

Pietro Ghezzi,
Brighton and Sussex Medical School,
United Kingdom

*CORRESPONDENCE

Jin-Yi Wan

✉ wanjinyi1128@163.com

RECEIVED 10 August 2025

ACCEPTED 18 September 2025

PUBLISHED 29 September 2025

CITATION

Yao H, Mo S, Sui P, Wan C and Wan J-Y
(2025) Editorial: Natural products and
intestinal mucosal immunity.
Front. Immunol. 16:1682978.
doi: 10.3389/fimmu.2025.1682978

COPYRIGHT

© 2025 Yao, Mo, Sui, Wan and Wan. This is an
open-access article distributed under the terms
of the [Creative Commons Attribution License](#)
(CC BY). The use, distribution or reproduction
in other forums is permitted, provided the
original author(s) and the copyright owner(s)
are credited and that the original publication
in this journal is cited, in accordance with
accepted academic practice. No use,
distribution or reproduction is permitted
which does not comply with these terms.

Editorial: Natural products and intestinal mucosal immunity

Haiqiang Yao^{1,2}, Shanlan Mo³, Pinpin Sui⁴, Chunping Wan⁵
and Jin-Yi Wan^{1,2*}

¹School of Traditional Chinese Medicine, Beijing University of Chinese Medicine, Beijing, China,

²National Institute of Traditional Chinese Medicine Constitution and Preventive Medicine, Beijing

University of Chinese Medicine, Beijing, China, ³State Key Laboratory of Quantitative Synthetic

Biology, Shenzhen Institute of Synthetic Biology, Shenzhen Institutes of Advanced Technology,

Chinese Academy of Sciences, Shenzhen, China, ⁴The University of Texas Health Science Center at

San Antonio, San Antonio, TX, United States, ⁵First Affiliated Hospital of Yunnan University of

Traditional Chinese Medicine, Kunming, China

KEYWORDS

natural products, intestinal mucosal immunity, intestinal diseases, gut microbiome,
intestinal inflammation, gut barrier

Editorial on the Research Topic

Natural products and intestinal mucosal immunity

The gastrointestinal tract is the largest immunological interface of the body. Mucosal immunity maintains a delicate equilibrium in this surveilled environment by balancing tolerance to commensal bacteria with defense against pathogens (1). Disruption of this equilibrium can trigger the pathogenesis of inflammatory bowel disease (IBD), metabolic disease, and extra-intestinal inflammatory disorders (2). Natural agents, including phytochemicals, herbal extracts, and dietary constituents, are emerging as potent modifiers of intestinal immunity (3). Their pleiotropic mechanisms, favorable safety profiles, and ability to synergize with the host physiology confer specific advantages compared to conventional immunomodulatory approaches. This Research Topic compiles pioneering research that elucidates how natural molecules modulate intestinal immunity at the molecular, cellular, and multi-omic levels. The ten articles included here explore diverse mechanisms from mitochondrial homeostasis and cell death mechanisms to microbiome crosstalk and clinical translation, collectively advancing natural products from empirical remedies to rationally based therapeutics.

At the forefront of intestinal defense, disruption of the epithelial barrier initiates inflammatory cascades. Cai et al. demonstrated that hyperglycemia exacerbates barrier damage by activating neutrophil extracellular traps (NETs). These are extracellular chromatin structures that disrupt tight junctions. The flavonoid baicalin can prevent NET formation by inhibiting histone citrullination, a key modulator of NETosis; this preserves intestinal integrity in diabetes models. Zhou et al. revealed that aberrant mitochondrial dynamics play a critical role in ulcerative colitis (UC) pathogenesis. The accumulation of dysfunctional mitochondria was found to generate reactive oxygen species (ROS), which trigger the NLRP3 inflammasome and perpetuate inflammation. Phytochemicals such as curcumin and resveratrol enhance mitophagy via the PINK1/Parkin and AMPK pathways. This selective mitochondrial elimination reduces epithelial apoptosis and restores redox balance; thus, mitochondrial quality control was established as a target for treating IBD with natural compounds.

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway is a key target of natural compounds that modulate mucosal immunity. According to Long et al., berberine suppresses STAT1/STAT3 phosphorylation, and *Tetragium hemsleyanum* polysaccharide induces SOCS1 expression, serving as a natural JAK inhibitor. These agents promote Th17/Treg cell balance and improve colitis without the hematologic toxicity associated with synthetic JAK inhibitors. Pan et al. observed that the flavonoid kurarinone inhibits Th17 differentiation and increases IL-10-producing regulatory T cells by upregulating Blimp-1. Cell death pathways also revealed their multi-mechanistic roles, and Zhao and Lin found PANoptosis, an integrated cell death program involving pyroptosis, apoptosis, and necroptosis, to be a primary force in IBD. The authors demonstrated how berberine blocks caspase-8-mediated epithelial apoptosis, suggesting that natural products may intercept PANoptosis at multiple levels to ensure mucosal viability.

The microbiome, serving as both a target and a mediator of natural products, is essential in regulating intestinal immunity. According to Zhu et al., commensal fungi utilize pattern recognition receptors such as Dectin-1 and TLRs to modulate host gut immunity. Pan et al. demonstrated that kurarinone augments beneficial gut genera such as *Lactobacillus* and *Ruminiclostridium*, contributing to the modulation of intestinal mucosal inflammation. Guan et al. investigated the microbial-metabolite-immune axis of gastroesophageal reflux disease (GERD). Lower GI microbiome dysbiosis may indirectly induce GERD by changing gut dynamics, and this could be mitigated by ingredients in Chinese herbal medicine. These compounds restore microbial richness and enhance mucin secretion and thus illustrate how prebiotic-like natural compounds enhance mucosal protection by modulating the gut microbiome.

Natural compounds demonstrate clinical relevance beyond IBD to iatrogenic diseases such as immune checkpoint inhibitor-induced colitis (irColitis). Dong et al. described how traditional Chinese medicine formulas such as Gegen Qinlian decoction alleviate irColitis by inhibiting JAK/STAT and NF- κ B signaling pathways. Similarly, Wang et al. demonstrated that cimifugin acts on the gut-organ axis to modulate UC-associated lung injury by inhibiting JAK1/STAT1-dependent macrophage M1 polarization, underscoring the systemic impacts of gut-targeted immunomodulation with botanical compounds.

Future research priorities for this field encompass several key areas. First is the development of precision-targeted nanoparticle formulations to achieve maximum bioavailability and tissue-selective targeting. Second is engineering protective microbiomes through the synergistic combination of phytochemical prebiotics, probiotics, and other applicable approaches. Third is identifying additional natural products with the ability to modulate intestinal mucosal immunity and establishing a multidimensional methodological approach to elucidate the mechanisms of action, thereby laying a foundation for further clinical applications. Fourth is conducting rigorous clinical benchmarking via randomized

controlled trials comparing natural products with biologics in UC, irColitis, and related conditions, to further validate the clinical effectiveness of natural products.

This Research Topic illuminates the cutting-edge advances in this field. Natural products are evolving from complementary therapies to emerge as potent immunomodulatory agents with selective molecular targets. With applications ranging from the inhibition of NETosis and the regulation of PANoptosis to the activation of mitochondria and the alteration of the microbiome, natural products modulate the intestinal immune system with remarkable breadth. The included studies integrate ethnopharmacology with molecular medicine, offering promising approaches to addressing conditions that are associated with gut mucosal immunity.

Author contributions

HY: Writing – review & editing, Writing – original draft. SM: Writing – original draft, Writing – review & editing. PS: Writing – original draft, Writing – review & editing. CW: Writing – review & editing. J-YW: Writing – original draft, Writing – review & editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The authors declare that they were editorial board members of Frontiers at the time of submission. This had no impact on the peer review process and the final decision.

Generative AI statement

The authors declare that no Generative AI was used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Takeuchi T, Nakanishi Y, Ohno H. Microbial metabolites and gut immunology. *Annu Rev Immunol.* (2024) 42:153–78. doi: 10.1146/annurev-immunol-090222-102035
2. Yang S, Li Y, Zhang Y, Wang Y. Impact of chronic stress on intestinal mucosal immunity in colorectal cancer progression. *Cytokine Growth Factor Rev.* (2024) 80:24–36. doi: 10.1016/j.cytogfr.2024.10.007
3. Cao Z, Wang Z, Yang L, Li T, Tao X, Niu X. Reshaping the immune microenvironment and reversing immunosenescence by natural products: Prospects for immunotherapy in gastric cancer. *Semin Cancer Biol.* (2025) 110:1–16. doi: 10.1016/j.semcancer.2025.02.002