



Opinion

Food and medicine homology components ameliorate metabolic diseases *via* dual pathways: blood absorption and nonabsorptive pathways

Shu-Yue Zhai^{1,†}, Ling-Ru Li^{2,†}, Jing-Han Jia¹, Ya-Xin Cao², Meng-Yao Li³ (✉), Yan-Fei Zheng² (✉), Wen-Long Sun¹ (✉)

¹ School of Life Sciences and Medicine, Shandong University of Technology, Zibo 255000, China

² National Institute of Traditional Chinese Medicine Constitution and Preventive Medicine, Beijing University of Chinese Medicine, Beijing 100000, China

³ State Key Laboratory of Systems Medicine for Cancer, Shanghai Cancer Institute, Renji Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai 200127, China

[†] Shu-Yue Zhai and Ling-Ru Li contributed equally to this work.

Received: 2 August 2025 / **Revised:** 23 August 2025 / **Accepted:** 24 August 2025

1 Introduction

With the fast pace of modern lifestyles and changes in dietary patterns, the incidence of metabolic diseases, including diabetes mellitus, obesity, and nonalcoholic fatty liver disease, continues to rise. Metabolic diseases are becoming important factors threatening human health. Therefore, the prevention and treatment of such diseases should receive increased attention. Current Western medical interventions rely primarily on lipid-lowering agents (e.g., statins), insulin sensitizers (e.g., biguanides), and insulin biologics. These drugs usually target a specific pathological mechanism for treatment, yet their single target may not be able to comprehensively improve the complex causes of metabolic diseases. In addition, the application of probiotics, such as butyrate-producing bacteria and the mucin-degrading bacterium *Akkermansia muciniphila*, provide ideas for the treatment of metabolic diseases^[1]. However, the therapeutic effects of probiotics are often influenced by individual differences and the selection of strains, making it difficult to ensure consistent therapeutic outcomes. In contrast, food and medicine homology (FMH) components contain abundant bioactive components that typically exert therapeutic effects through multiple pathways and multitarget mechanisms. This characteristic enables them to show broader potential in the prevention and treatment of metabolic diseases. However, the complexity of the components and mechanisms of FMH components poses significant challenges in elucidating their underlying processes, thus constraining their application in clinical practice. Consequently, investigating the mechanisms and research methods of FMH components in metabolic diseases can provide important scientific basis for the development of new therapeutic strategies. FMH components usually play a role in improving metabolic diseases *via* two pathways: 1) the blood absorption pathway, in which the bioactive FMH components directly enter systemic circulation to mediate broad therapeutic effects, and 2) the nonabsorptive pathway, in

which the bioactive FMH components alter the gut microbiota metabolites, which regulate host metabolic homeostasis through an axis, thus indirectly participating in the occurrence and development of metabolic disorders.

2 Blood absorption pathway

The treatment of metabolic diseases is a long-term process, with oral administration being the most common route for therapeutic drugs. After oral intake, the initial site of drug absorption is the stomach. Because the pH of gastric juice is less than 3, weakly acidic components are mostly in a free state in this environment, so they are readily absorbed^[2]. The primary site for the absorption of other components in the gastrointestinal tract is the intestine. The small intestine contains abundant villi and rich capillary networks, so it has large endothelial pores and extensive blood flow. The large intestine features various glands, digestive juices, and mucosal folds that increase the surface area and prolong drug retention. Some active FMH components (such as polyphenols, alkaloids, and terpenes), either in their original form or after being decomposed by digestive fluids/the gut microbiota, are absorbed into the bloodstream through the intestine. Water-soluble small molecules are absorbed through filtration *via* aqueous channels in cell membranes driven by hydrostatic or osmotic pressure. Lipophilic components dissolve in the lipid bilayer of cell membranes and undergo simple diffusion along concentration gradients. Specialized transmembrane proteins in the intestinal epithelium, including uptake transporters (organic anion transporting polypeptides (OATPs), organic cation transporters (OCTs), and a proton-coupled oligopeptide transporter (PepT1))^[3] and efflux transporters (P-glycoprotein (P-gp), multidrug resistance proteins (MDRs), and multidrug resistance-associated proteins (MRPs))^[4], transport specific components. This process may require energy consumption. Although rare, some components enter systemic circulation *via*

endocytosis/exocytosis.

After being absorbed by the intestines, these active FMH components first pass through the liver, and some of the metabolic products may be excreted back into the intestines. The components that enter the bloodstream are distributed to target tissues and organs. They can specifically bind to molecular targets (such as receptors, enzymes or signal molecules) in specific target organs and then regulate cell signaling pathways. For instance, after being absorbed, polyphenols can inhibit the formation of advanced glycation end products (AGEs) through multiple mechanisms, thereby regulating glycolipid metabolism^[5]. In addition, natural alkaloids can enhance energy metabolism and inhibit the proliferation and differentiation of fat cells, thereby alleviating obesity and related diseases^[6]. Through the above mechanism of action, FMH components can promote glucose and lipid metabolism and have anti-inflammatory effects. For example, *Panax notoginseng*, a medicinal and edible herb, contains *P. notoginseng* saponins as its active components, predominantly ginsenosides Rb1 (GRb1) and Rg1 (GRg1). Owing to their lipophilic nature, both GRb1 and GRg1 are absorbed in the intestine via unregulated passive diffusion, independent of transporter-mediated processes^[7]. After being absorbed, GRb1 can upregulate the SIRT1/Nrf2 signaling pathway to inhibit the generation of malondialdehyde (MDA), which is a lipid peroxidation product, and promote lipid metabolism^[8]. GRg1 can inhibit the activation of the TLR4/NF- κ B pathway, thereby suppressing the production of inflammatory cytokines^[9].

3 Nonabsorptive pathway

Metabolic diseases are closely related to the imbalance of the gut microbiota. FMH components are rich in a variety of bioactive components with potential health benefits. Although some components, such as polysaccharides, have low oral bioavailability, they may regulate the intestinal microbial community structure and metabolites through a prebiotic-like mechanism. Upon oral administration, some low-oral-bioavailability FMH components interact with the gut microbiota. Consequently, the bioactive components may undergo metabolism, and the production of beneficial metabolic products by the gut microbiota could be enhanced, contingent upon the diversity and abundance of microorganisms present. This process is often accompanied by significant changes in the abundance of characteristic microbiota. For example, components such as polysaccharides, flavonoids, and saponins act as prebiotics, resisting gastric acid degradation to reach the intestinal tract undigested. These components modulate the intestinal pH, selectively promoting beneficial bacterial proliferation while suppressing pathogenic colonization, thereby ameliorating metabolic dysbiosis. Moreover, these bioactive components promote the production of many gut beneficial metabolites, such as short-chain fatty acids (SCFAs) and indole derivatives, which not only perform their function within the intestinal tract but also exert their effects through a complex network of interactions known as the "gut-X axis". These beneficial metabolites are involved in regulating immune responses and metabolic homeostasis, and influencing inflammatory responses and oxidative stress. The mechanisms of FMH components in treating metabolic diseases include the following: relieving mitochondrial dysfunction and endoplasmic reticulum stress^[10], activating metabolic pathways that promote glycolipid metabolism (such as the AMPK/SIRT1 pathway)^[11], and regulating the insulin signaling pathways^[12]. Furthermore, they can regulate

neuroendocrine signals and participate in the control of feeding behavior. Myricetin, a natural bioactive flavonol found in onion, berries, and other dietary sources, has low oral bioavailability (10%) and exhibits preferential intestinal distribution post-administration. Our team has demonstrated that myricetin significantly decreases the Firmicutes/Bacteroidetes (F/B) ratio in high-fat diet (HFD)-fed rats while simultaneously increasing microbial diversity and promoting species evenness. It exerts prebiotic activity by increasing the abundance of butyrate-producing bacteria^[13].

4 Synergistic effects of multiple pathways

The pathogenesis of metabolic diseases manifests as dysregulated carbohydrate and lipid metabolism, characterized by a multifactorial etiology and complex mechanisms involving multiple organs and tissues. Conventional Western medicines, which are characterized by targeted mechanisms and well-defined pharmacological actions, face limitations due to their singular therapeutic targets. FMH components are rich in a variety of natural bioactive components (such as polysaccharides, flavonoids, polyphenols, and saponins). These components regulate bodily metabolism in a 'multicomponent, multitarget, multipathway' manner through synergistic effects and have unique advantages in the treatment of metabolic diseases. Specifically, on the one hand, these components can directly enter blood circulation after absorption; on the other hand, the active components can indirectly play a role by regulating the composition of the gut microbiota and its metabolites. Through this multipathway regulatory mechanism, FMH components can simultaneously act on key metabolic pathway targets, such as peroxisome proliferator-activated receptor γ (PPAR γ), adenosine 5'-monophosphate-activated protein kinase (AMPK) and nuclear factor kappa-B (NF- κ B), thus playing a multidimensional role in improving metabolic diseases^[14] (Fig. 1). For example, Chinese yam is a traditional FMH with the potential to regulate metabolic diseases via multi-pathway synergistic mechanisms. One of its phytosterol components, dioscin, can be absorbed in the entire intestine of rats through passive diffusion^[15]. Post-absorption, dioscin directly scavenges free radicals and peroxides and inhibits the activation of oxidative stress signaling pathways, thereby exerting antioxidant effects. In addition, Yam polysaccharides ameliorate type 2 diabetes-induced gut microbiota dysbiosis in mice, increase total microbial species abundance and diversity, and reduce the F/B ratio^[16]. Concurrently, these polysaccharides are metabolized by the gut microbiota to produce SCFAs to promote fatty acid oxidation and glycogen storage.

5 Research methodology design for elucidating the mechanisms by which FMH components ameliorate metabolic disorders

FMH components often share pharmacokinetic characteristics during absorption and metabolism. Therefore, a universal research method can be designed to investigate the therapeutic effects and pharmacological mechanisms of FMH components in metabolic diseases. This systematic investigation provides a methodological foundation for elucidating multitarget and multipathway interactions (Fig. 2). First, animal experiments need to be conducted to verify the therapeutic effects and pharmacological effects of FMH components on metabolic diseases. Step one involves verifying the therapeutic effect. The experimental groups

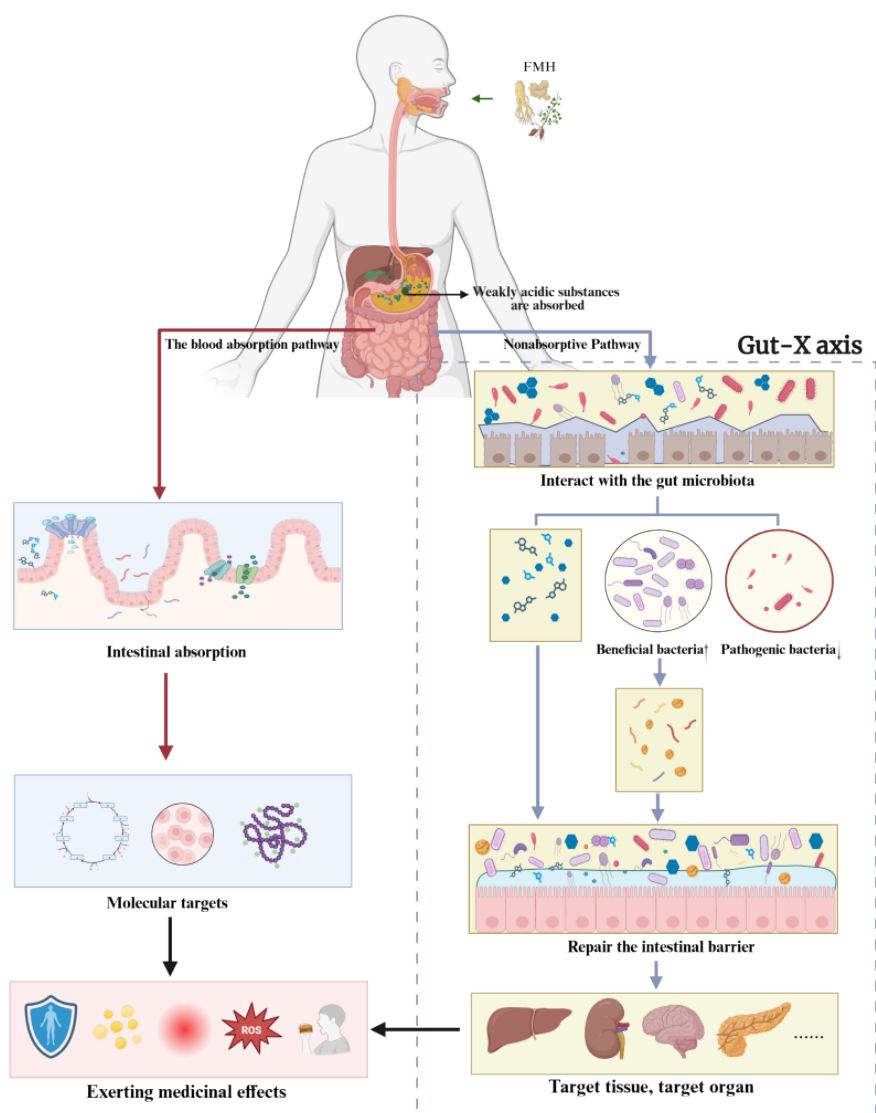


Figure 1 Dual pathways of FMH. The active components of FMH can be absorbed into the bloodstream through the digestive tract and exert therapeutic effects by interacting with the gut microbiota.

can be divided into four cohorts: a control group (healthy baseline), a disease model group (pathological baseline), a treatment group and a positive control group. Disease induction protocols are applied to the model, treatment and positive control groups. The treatment group receives specified doses of the test substance, and the positive control group receives the corresponding positive control drugs. All animals should be raised in the same environment, and physiological parameters should be longitudinally monitored to quantify therapeutic efficacy. The second step involves research on the pharmacological mechanism. The mechanism can be further explored through two pathways. On the one hand, one can explore whether FMH components exert therapeutic effects by regulating the gut microbiota. Fecal bacteria transplantation (FMT) is the key method for this research. Through FMT, the gut microbiota of the control group is transplanted into healthy model animals, and the gut microbiota of the disease model group and the treatment group are transplanted into disease model animals. On the other hand, one could explore whether FMH components are absorbed into the body to exert therapeutic effects. This experiment requires a germ-free (GF) animal to repeat step one, with the aim of eliminating

interference by the gut microbiota. Second, we can further use multiomics technology to explore how these substances can improve the understanding of the molecular mechanism of metabolic diseases. 16S rRNA sequencing technology is used to characterize microbial community structure^[17]. By analyzing the changes in the abundance and composition of the gut microbiota, pathogenic and beneficial bacteria are screened out. LC-MS/MS analysis can be used to screen the key bioactive components and possible metabolic pathways of FMH components in the body. RNA sequencing (RNA-Seq) technology can be used to determine the mRNA transcripts of specific tissues or cells. The targets and metabolic pathways of FMH components are further analyzed at the genetic level. Spatial metabolomics analysis can be used to conduct imaging analysis on the spatial distribution of endogenous components and exogenous chemical components^[18], systematically obtaining spatial distribution information of biological tissues, cells and gut microbiota. Network pharmacology research integrates data from various network pharmacology databases to construct a target network for treating metabolic diseases, which is cross-verified with the results of transcriptomic and metabolomic studies. With the development

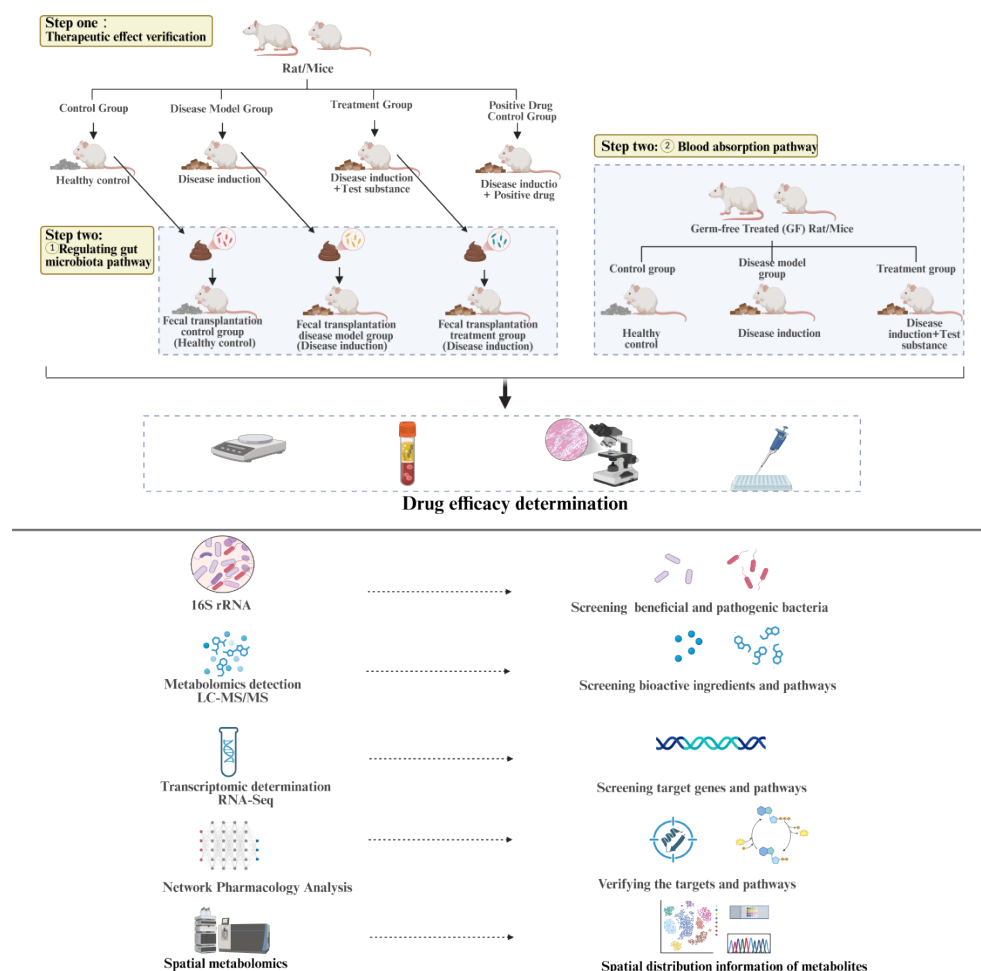


Figure 2 Research methodology design for elucidating the mechanisms of action of FMH components. Animal experiments verified that FMH can be used to treat metabolic diseases through multiple pathways. Multiomics techniques are used to explore the pharmacological mechanisms by which FMH components treat metabolic diseases.

of artificial intelligence technology, the intelligent analysis models can be constructed to accurately identify low-intensity and complex related metabolites, thus breaking through the bottleneck of complex and difficult data processing in traditional analysis^[19]. In the future, the method that combines machine learning algorithms with multi-omics analysis to systematically analyze the mechanism of FMH components in treating metabolic diseases may become a new trend in this field. On the basis of these findings, an evidence-based framework is established for the multitarget and multipathway therapeutic application of FMH components to treat metabolic disorders.

In conclusion, FMH components exhibit multicomponent synergistic characteristics in exerting therapeutic effects. Elucidating the key bioactive components in FMH components and their multipathway mechanism of action to improve metabolic diseases is crucial for in-depth analysis of the scientific basis of disease prevention and treatment. This opinion article not only reveals the potential therapeutic value of FMH but also provides a theoretical basis for the development of new metabolic disease intervention strategies based on multitarget regulation.

Conflicts of interest

The authors declare that there are no conflicts of interest in this work.

Acknowledgements

This work was supported by the Taishan School Foundation of Shandong Province (No. tsqn202312184, China)

References

- [1] Le Barz, M., Anhê, F. F., Varin, T. V., et al. Probiotics as complementary treatment for metabolic disorder. *Diabetes & Metabolism Journal*, **2015**, 39: 291–303. <https://doi.org/10.4093/dmj.2015.39.4.291>
- [2] Abuhelwa, A. Y., Williams, D. B., Upton, R. N., et al. Food, gastrointestinal pH, and models of oral drug absorption. *European Journal of Pharmaceutics and Biopharmaceutics*, **2017**, 112: 234–248. <https://doi.org/10.1016/j.ejpb.2016.11.034>
- [3] Zou, L. H., Zhang, Z. B., Chen, J. Q., et al. β -Cyclodextrin-Grafted chitosan enhances intestinal drug absorption and its preliminary mechanism exploration. *AAPS PharmSciTech*, **2022**, 23: 221. <https://doi.org/10.1208/S12249-022-02380-Z>
- [4] Verma, N., Ahuja, V., Paul, J. Profiling of ABC transporters during active ulcerative colitis and in vitro effect of inflammatory modulators. *Digestive Diseases and Sciences*, **2013**, 58: 2282–2292. <https://doi.org/10.1007/s10620-013-2636-7>
- [5] Wang, S., Zhang, Y. Q., Li, W., et al. Effects and mechanisms of dietary polyphenols in ameliorating glycolipid metabolic disorders: Inhibition of advanced glycation end products. *Fitoterapia*, **2025**, 184: 106668. <https://doi.org/10.1016/J.FITOTE.2025.106668>
- [6] Ma, Z. Q., Wang, S. G., Miao, W. W., et al. The roles of natural

- alkaloids and polyphenols in lipid metabolism: Therapeutic implications and potential targets in metabolic diseases. *Current medicinal Chemistry*, **2023**, 30: 3649–3667. <https://doi.org/10.2174/0929867330666221107095646>
- [7] Zheng, Y., Feng, G. F., Sun, Y. F., et al. Study on the compatibility interactions of formula Ding-Zhi-Xiao-Wan based on their main components transport characteristics across Caco-2 monolayers model. *Journal of Pharmaceutical and Biomedical Analysis*, **2018**, 159: 179–185. <https://doi.org/10.1016/j.jpba.2018.06.067>
- [8] Jiang, N., Zhang, Y. W., Yao, C. H., et al. Ginsenosides Rb1 attenuates chronic social defeat stress-induced depressive behavior via regulation of SIRT1-NLRP3/Nrf2 pathways. *Frontiers in Nutrition*, **2022**, 9: 868833. <https://doi.org/10.3389/FNUT.2022.868833>
- [9] Xue, L. P., Hu, M., Zhu, Q., et al. GRG1 inhibits the TLR4/NF- κ B signaling pathway by upregulating miR-216a-5p to reduce growth factors and inflammatory cytokines in DR. *Molecular Biology Reports*, **2023**, 50: 9379–9394. <https://doi.org/10.1007/S11033-023-08895-3>
- [10] Tang, C. W., Yuxin, Chen, D., et al. Natural polysaccharides protect against diet-induced obesity by improving lipid metabolism and regulating the immune system. *Food Research International*, **2023**, 172: 113192. <https://doi.org/10.1016/J.FOODRES.2023.113192>
- [11] Putri, A., Hadi, K., Sri Adi, S., et al. Role of the AMPK/SIRT1 pathway in non-alcoholic fatty liver disease (Review). *Molecular Medicine Reports*, **2023**, 27: 35. <https://doi.org/10.3892/MMR.2022.12922>
- [12] Metz, M., Ohare, J., Cheng, B., et al. Brain insulin signaling suppresses lipolysis in the absence of peripheral insulin receptors and requires the MAPK pathway. *Molecular Metabolism*, **2023**, 73: 101723–101723. <https://doi.org/10.1016/J.MOLMET.2023.101723>
- [13] Sun, W. L., Li, X. Y., Dou, H. Y., et al. Myricetin supplementation decreases hepatic lipid synthesis and inflammation by modulating gut microbiota. *Cell reports*, **2021**, 36: 109641. <https://doi.org/10.1016/J.CELREP.2021.109641>
- [14] Zhang, L. J., Li, S. Y., Fan, S. L., et al. Hepatoprotective activity of mulberry extract in NAFLD mice for regulating lipid metabolism and inflammation identified via AMPK/PPAR- γ /NF- κ B axis. *Journal of ethnopharmacology*, **2025**, 24: 120108. <https://doi.org/10.1016/j.jep.2025.120108>
- [15] Yin, L. H., Zheng, L. L., Xu, L. N., et al. In-silico prediction of drug targets, biological activities, signal pathways and regulating networks of dioscin based on bioinformatics. *BMC Complementary and Alternative Medicine*, **2015**, 15: 41. <https://doi.org/10.1186/s12906-015-0579-6>
- [16] Liu, W., Jin, R. M., Ma, F. Y., et al. Effects of Dioscorea opposita polysaccharides on insulin resistance and gut microbiota in high-fat-diet induced type 2 diabetic rats. *International Journal of Biological Macromolecules*, **2025**, 304: 141004. <https://doi.org/10.1016/J.IJBIOMAC.2025.141004>
- [17] Wang, B. W., Cao, X. Y., Ren, W. H., et al. A comparative study on gut microbiota and metabolomics in atlantic salmon salmo salar at different growth stages. *Journal of Ocean University of China*, **2025**, 24: 404–416. <https://doi.org/10.1007/S11802-025-5925-9>
- [18] Chen, Y., Liu, Y., Li, X. M., et al. Recent advances in mass spectrometry-based spatially resolved molecular imaging of drug disposition and metabolomics. *Drug Metabolism and Disposition*, **2023**, 51: 1273–1283. <https://doi.org/10.1124/DMD.122.001069>
- [19] Wadie, B., Stuart, L., Rath, C. M., et al. METASPACE-ML: Context-specific metabolite annotation for imaging mass spectrometry using machine learning. *Nature Communications*, **2024**, 15: 9110. <https://doi.org/10.1038/S41467-024-52213-9>