



Gut microbiome and metabolome characteristics of patients with cholesterol gallstones suggest the preventive potential of prebiotics

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Introduction

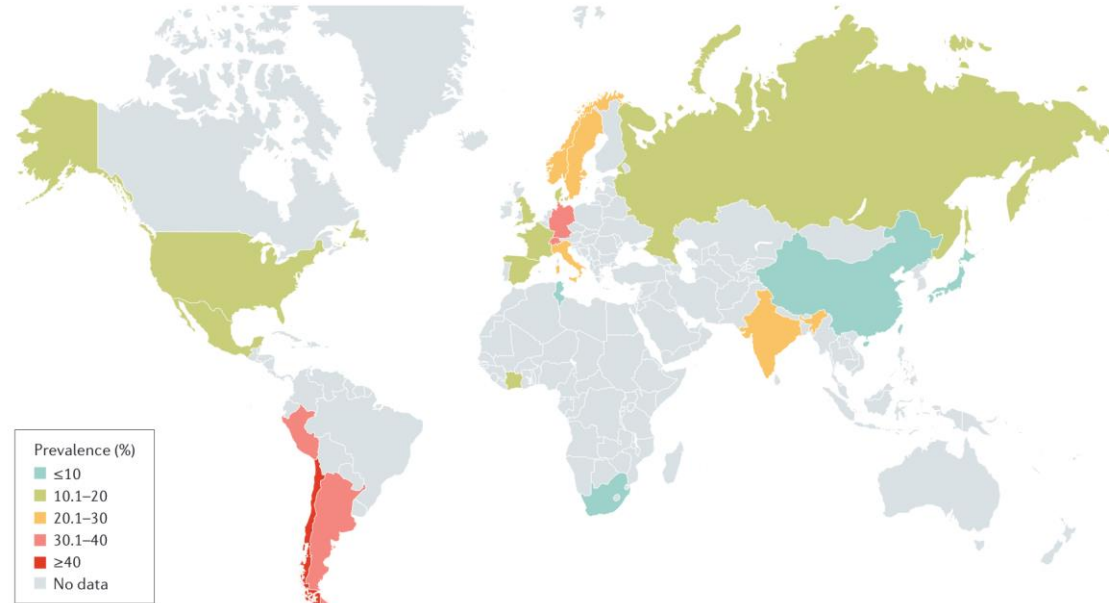
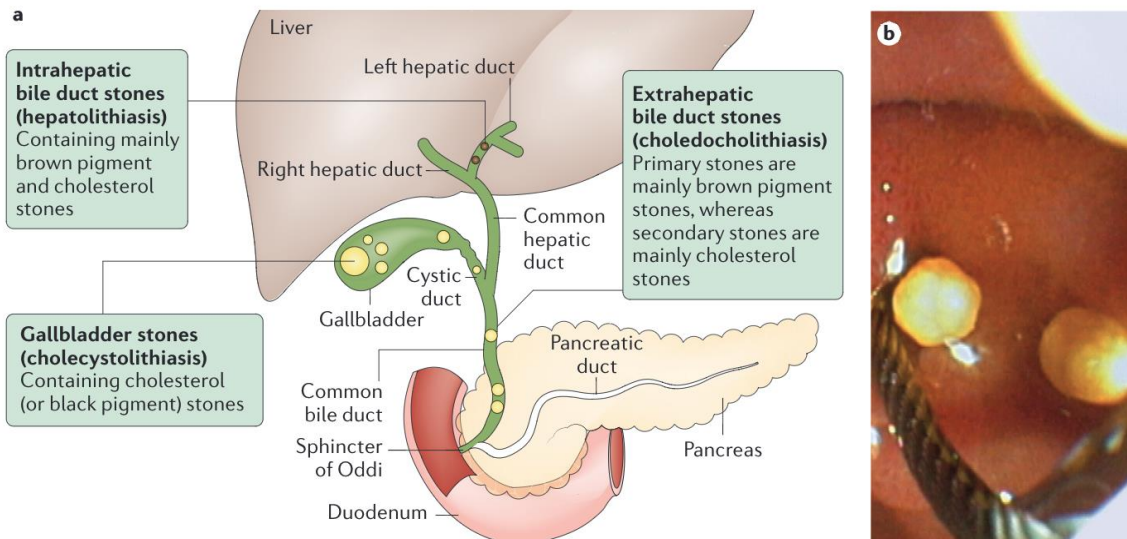


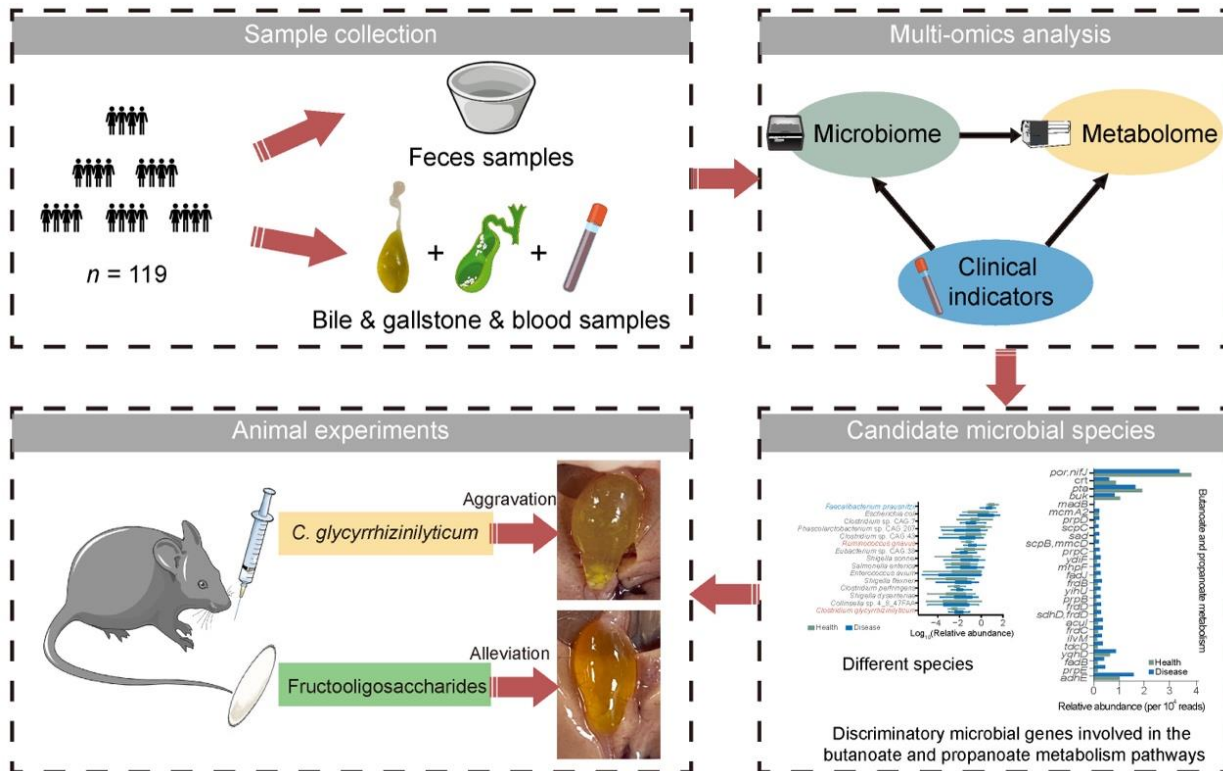
Figure 2 | **Global prevalence of gallstones.** Prevalence rates of gallstones as determined by ultrasonography in women 50–60 years of age (Supplementary information S1 (table)). No corresponding data are available for the grey regions.

- Gallstones are a common disease that occurs frequently. Gallstones affect around 10%–15% of adults, leading to significant discomfort.
- To date, cholecystectomy remains the most effective treatment for chronic carriers with gallbladder lithiasis.
- As a result, gut microbiota and its metabolites, including SCFAs, hold potential as novel therapeutic targets for gallstones.
- This cross-sectional study aims to comprehensively evaluate potential biomarkers in patients with gallstones and assess the effects of microbiome-targeted interventions in mice.





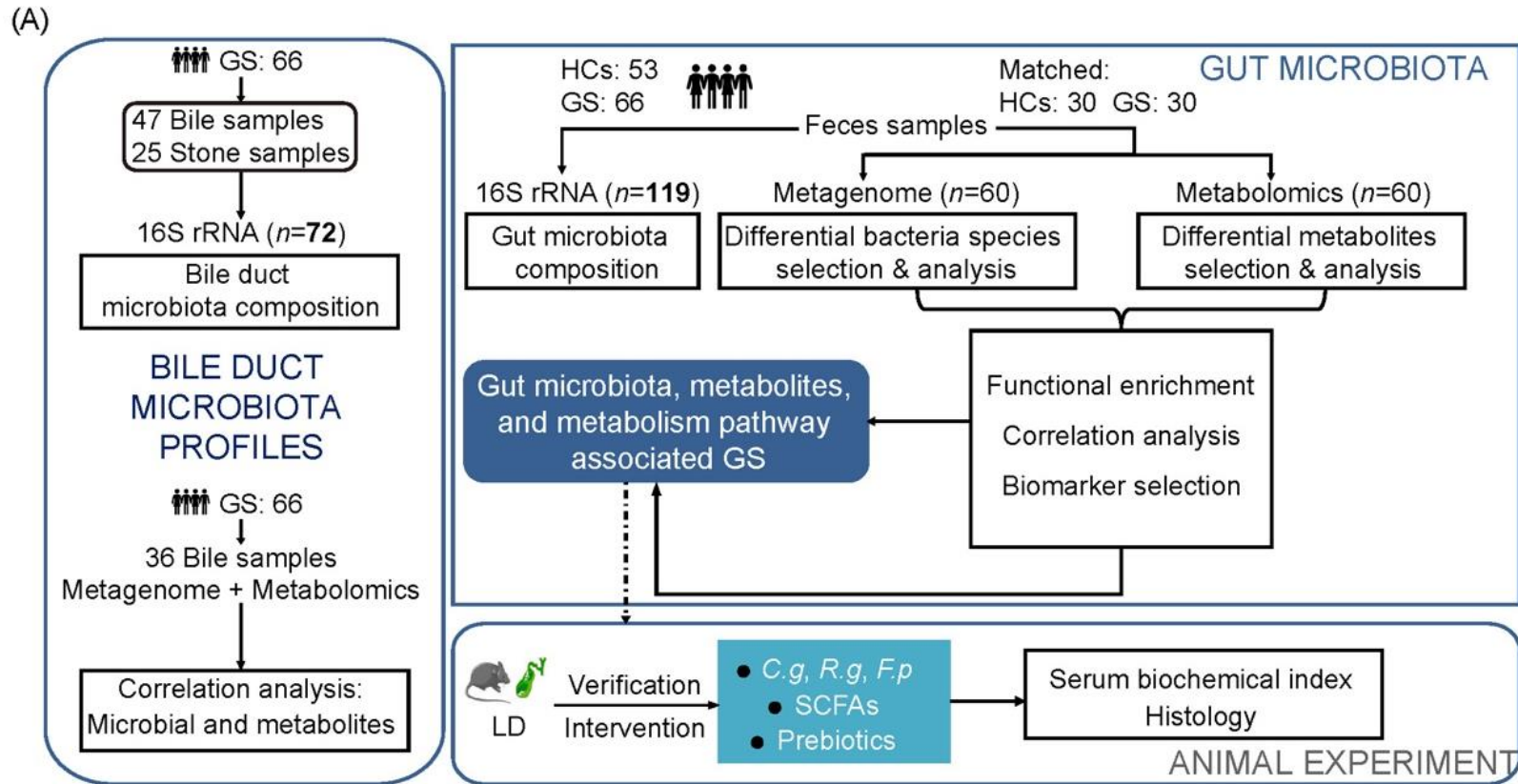
Highlights



- ❑ Metabolites of amino acids, fatty acids, and nicotinic acid may affect the synthesis, transport, or metabolism of cholesterol, thereby impacting gallstone formation.
- ❑ Oral administration of *C. glycyrrhizinilyticum* can contribute to cholesterol gallstone formation.
- ❑ Fructooligosaccharides could serve as an inexpensive microbiota-targeted therapeutic option for cholesterol gallstones.



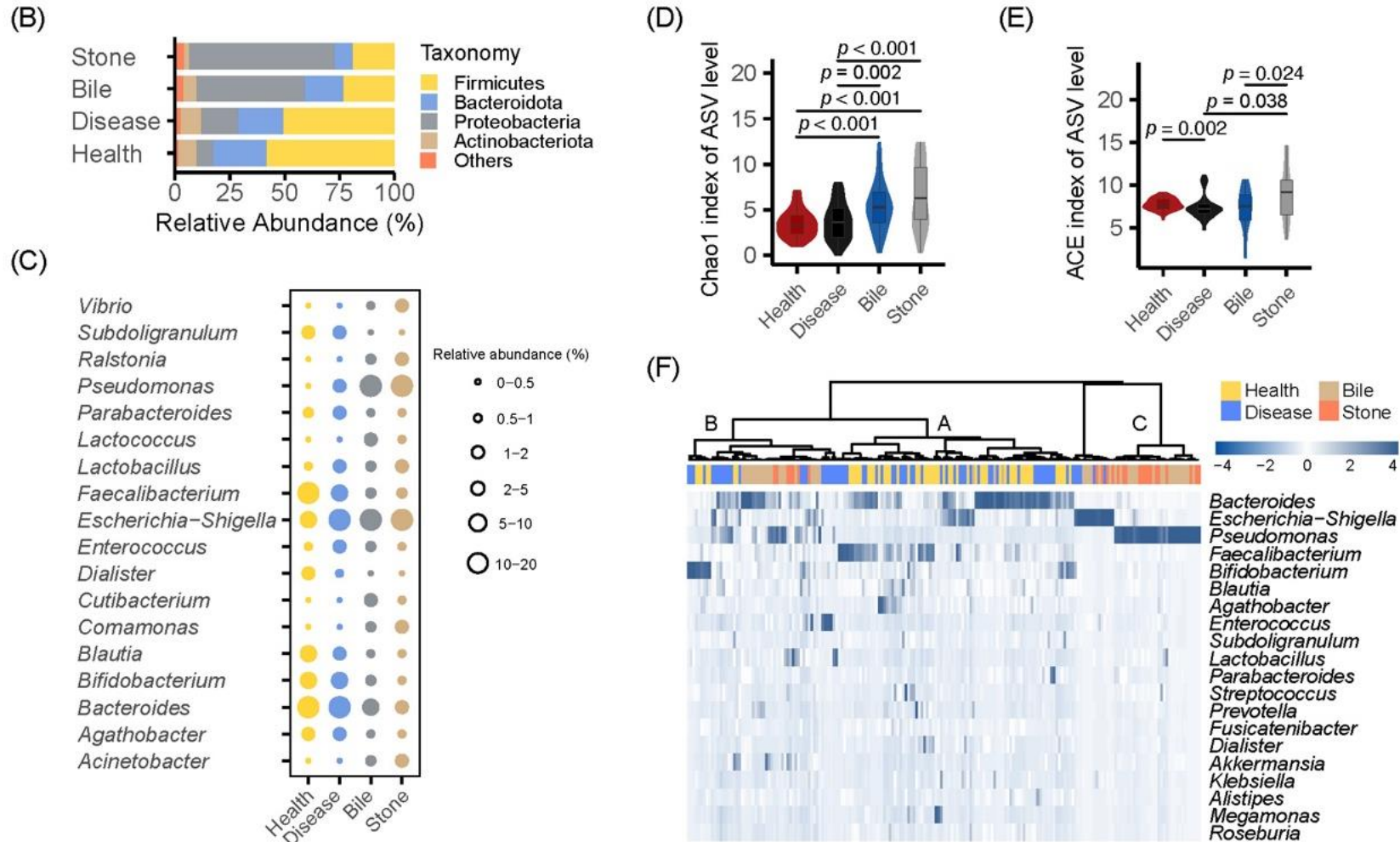
Study design



- ❑ A total of 66 subjects with a clinical diagnosis of cholesterol gallstones and 53 healthy controls were recruited from Beijing Hospital.
- ❑ After matching for age and sex variables, differential analysis was performed. Biomarkers were identified using linear and logistic regression statistical methods.
- ❑ Experimental validation was conducted for candidate species, SCFAs, and prebiotics.



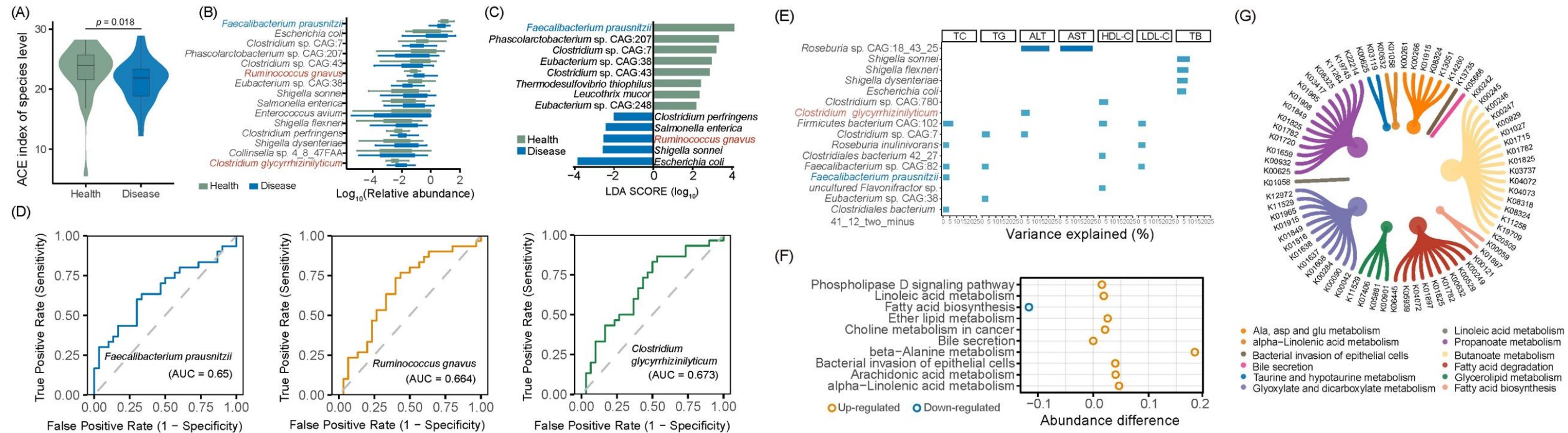
Biliary tract and gut microbial community



- The biliary microbiota is significantly different from the gut microbiota. Our results divided 191 samples into three distinct clusters (A–C) at the genus level, characterized by gut microbiota, the crossover between gut and biliary tract microbiota, and the biliary tract microbiota.



Differential analysis



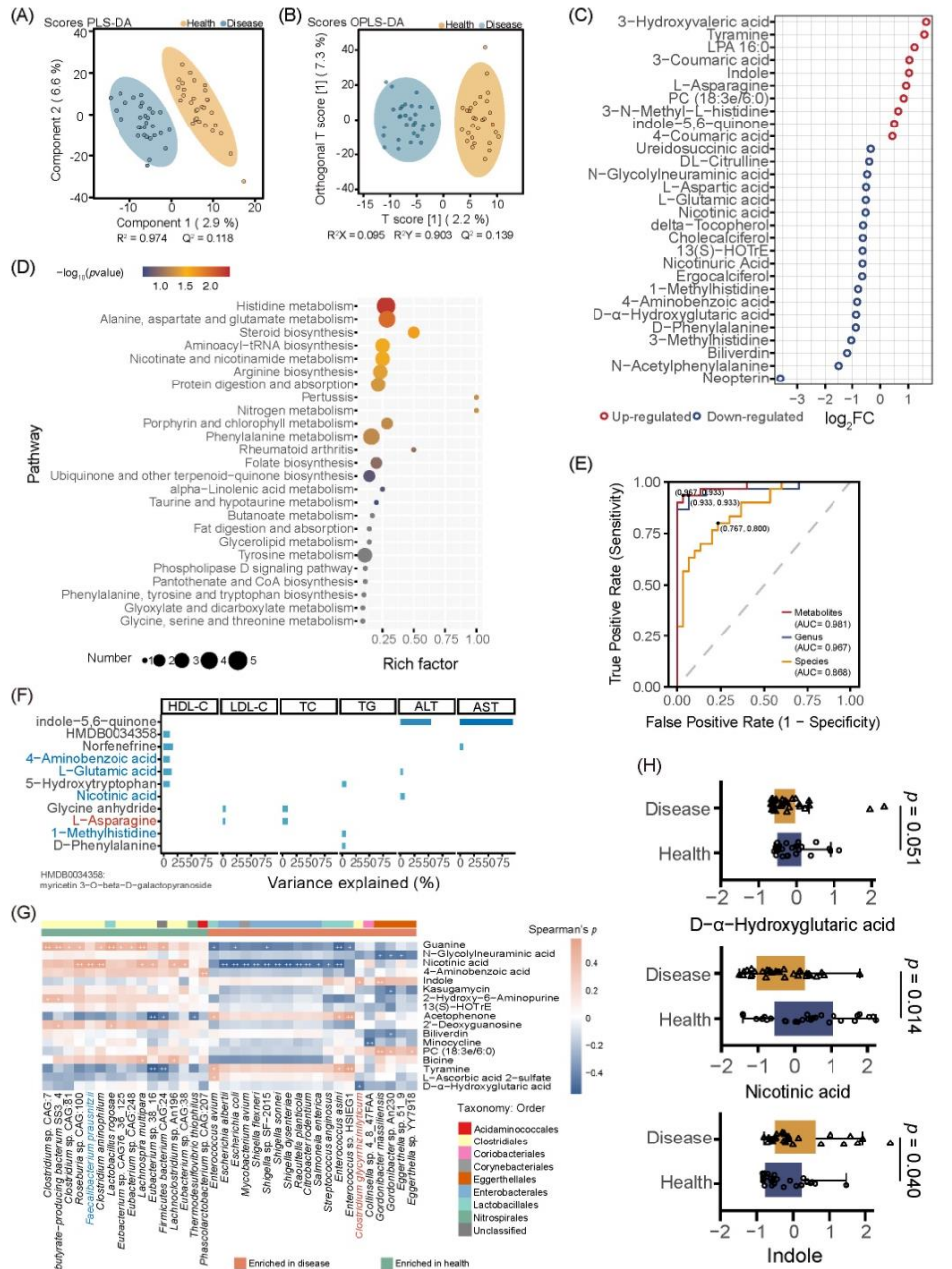
❑ A total of 56 differential species were identified through the analysis, including *Clostridium perfringens*, *R. gnavus*, *C. glycyrrhizinilyticum*, *F. prausnitzii*, *Thermodesulfovibrio thiophilus*, and *L. rogosae*.

❑ LEfSe analysis identified 13 key features at the species level. The AUC values of the candidate species ranged from 0.65 to 0.68.

❑ Functional enrichment analysis revealed a significant increase in the activity of lipid metabolism pathways, including linoleic acid, arachidonic acid, α-linolenic acid, and ether lipid metabolism pathways. Differential genes were concentrated in butanoate and propanoate metabolism, fatty acid degradation, and glyoxylate and dicarboxylate metabolism.



Metabolic profiling



Specifically, 76 metabolites, such as indole, PC (18:3e/6:0), and LPA 16:0, were found to be elevated, while 45 metabolites, including nicotinic acid, 4-Hydroxyisoleucine, and 13(S)-HOTrE, were reduced in CGS.

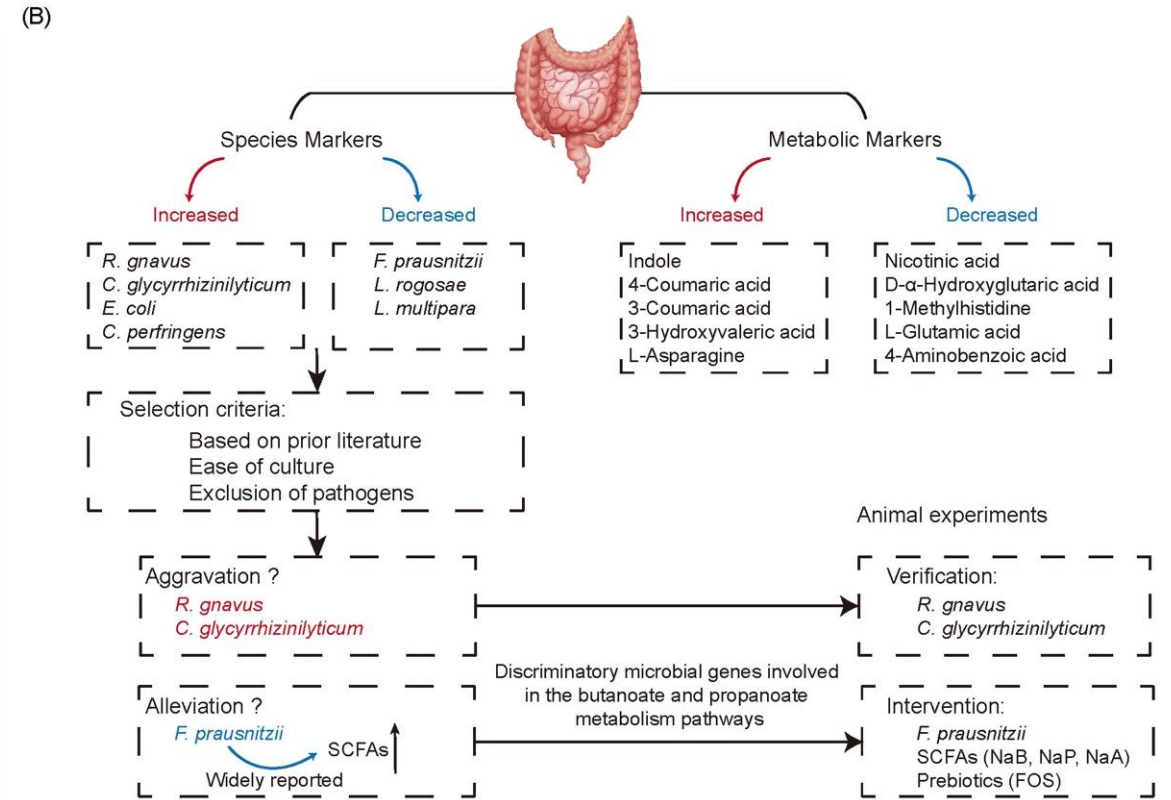
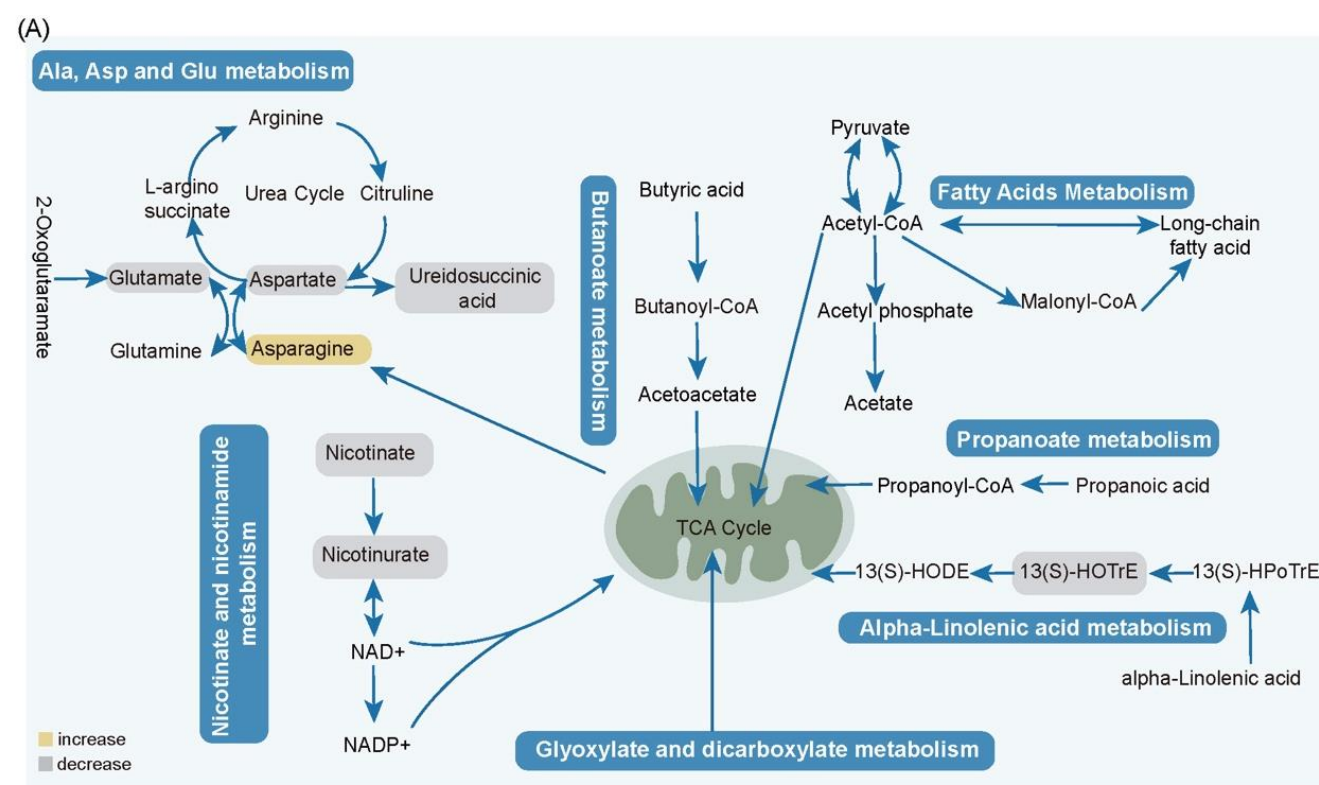
Representative differential metabolites were primarily classified into amino acids, carbohydrates, hydroxycinnamic acids, pyridine carboxylic acids, lipids, pterins and derivatives, and benzenoids.

Functional pathways were predominantly enriched in histidine metabolism, taurine and hypotaurine metabolism, butanoate metabolism, and α -linolenic acid metabolism.

The candidate genera, species, and metabolites were able to distinguish CGS patients from healthy controls, with AUC values of 96.7%, 86.8%, and 98.1%, respectively.



Integrative multi-omics signatures

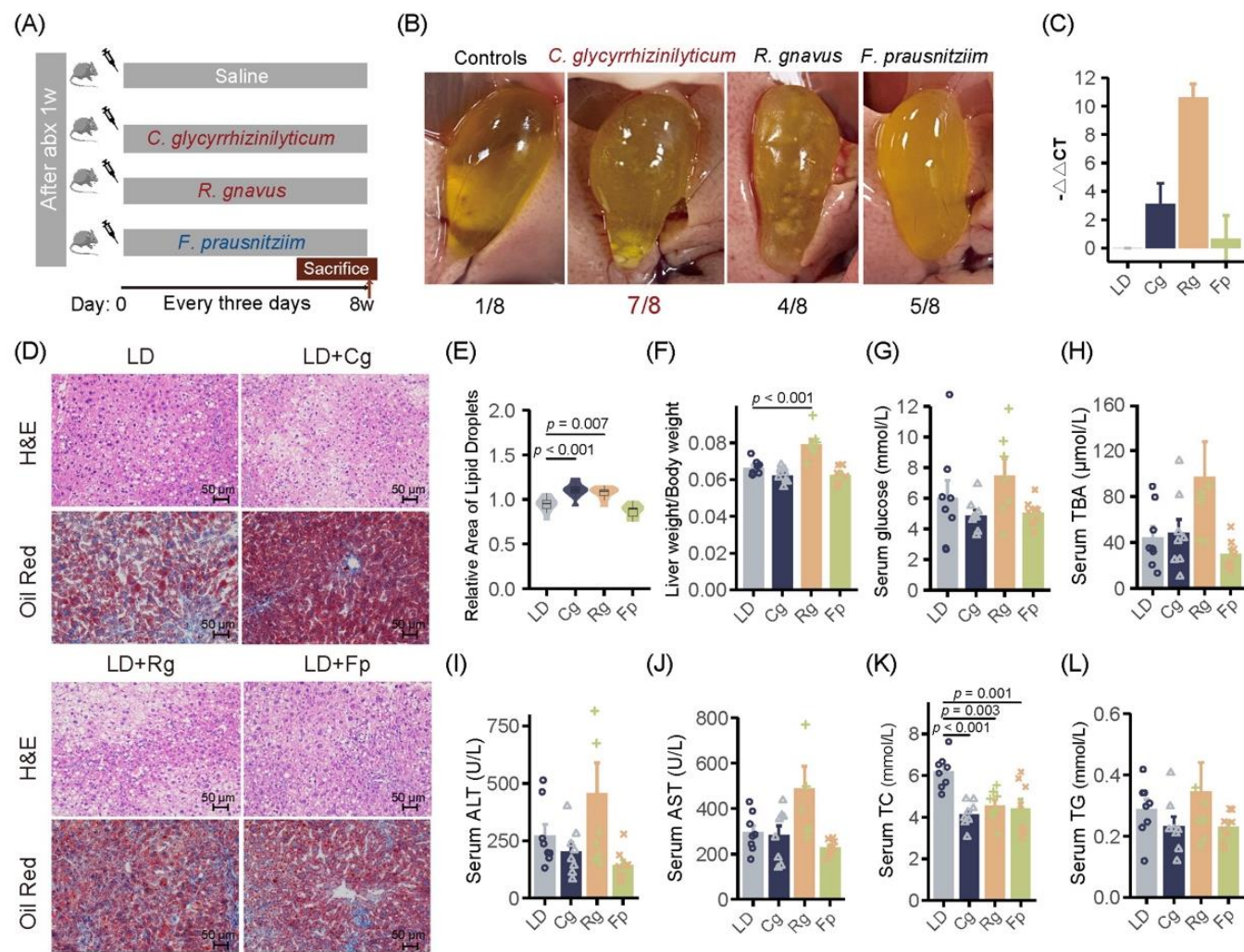


❑ Various differential metabolites, including 13(S)-HOTrE, nicotinic acid, nicotinamide, L-glutamate, N-carbamoyl-L-aspartate, L-aspartate, L-asparagine, and 1-methylhistidine, were involved in alpha-linolenic acid metabolism, alanine, aspartate and glutamate metabolism, nicotinate and nicotinamide metabolism, and histidine metabolism.

❑ Summarize the identification of potential biomarkers at the species and metabolite levels, and perform experimental validation for the candidate species biomarkers.



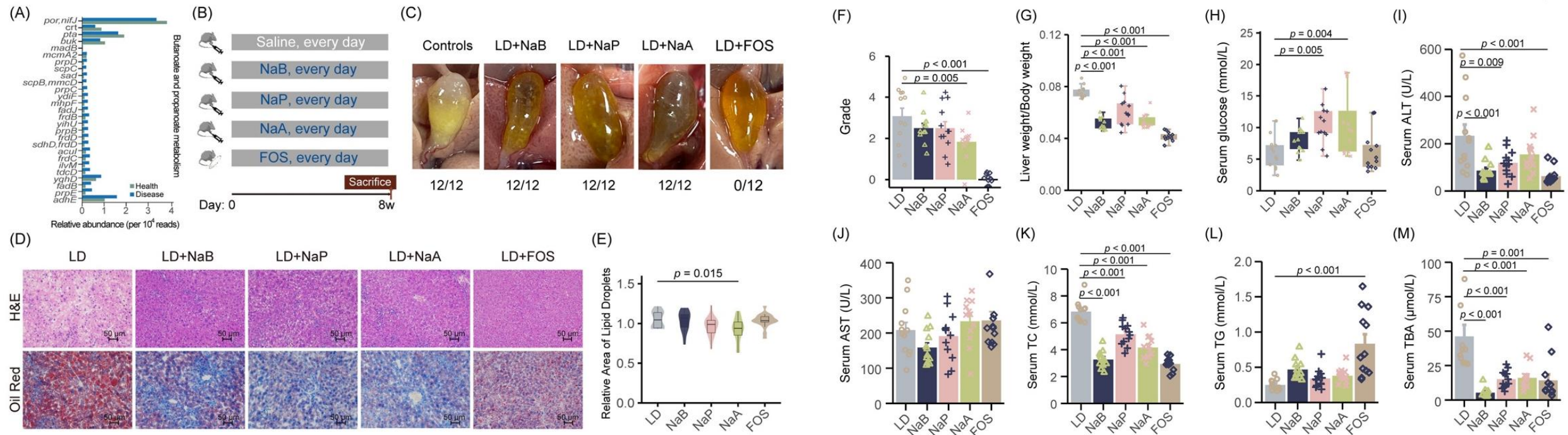
C. Glycyrrhizinilyticum by oral gavaged aggravated gallstone formation



- The presence of *C. glycyrrhizinilyticum* significantly increased gallstone formation with visible leaflet crystals or cholesterol particles observed in gallbladder.
- *R. gnavus* intervention also led to a notable increase in gallstone formation but without statistical significance.
- Mice gavaged with *F. prausnitzii* still developed gallstones.
- Marked liver histological damage in the *C. glycyrrhizinilyticum* and *R. gnavus* groups compared to control.



FOS supplementation reduced LD-induced gallstones



- ❑ Sodium butyrate, sodium propionate, or sodium acetate did not eliminate cholesterol particles from the gallbladders, although they reduced leaflet crystals or stratified crystals compared to the LD group.
- ❑ Mice treated with FOS showed no visible leaflet crystals or cholesterol particles in their gallbladders.
- ❑ Grade of experimental gallstones in control mice was significantly higher than that in mice treated with NaA and FOS.

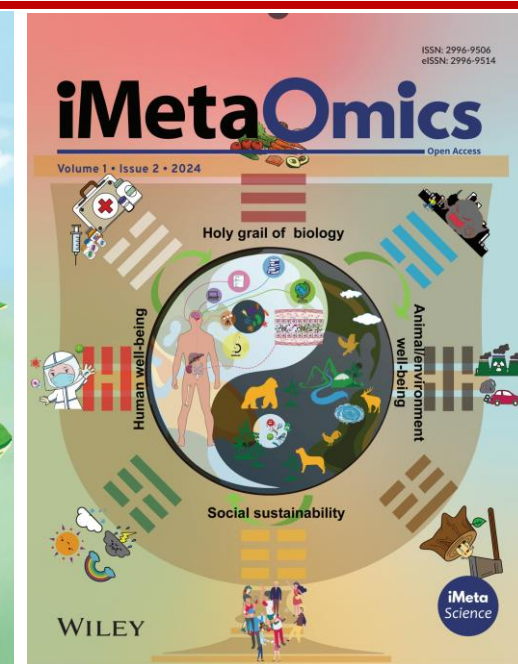
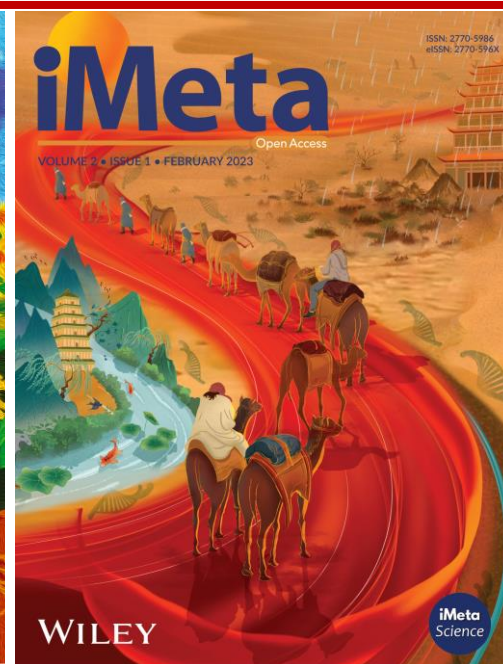


Summary

- ❑ The study outlined the microbiome and metabolome characteristics of patients with cholesterol gallstones, summarized the related metabolic pathways, and identified disease biomarkers.
- ❑ Discovered a stone-promoting bacterium, *C. glycyrrhizinilyticum* which exacerbates gallstone formation in mice.
- ❑ Prebiotics (fructooligosaccharides) may serve as a potential microbiota-targeted preventive or therapeutic strategy for cholesterol gallstones.




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