# Host-driven hepatic conversion of gut microbiota-derived putrescine to spermidine mediates mannose's protective effects against hepatic steatosis in zebrafish

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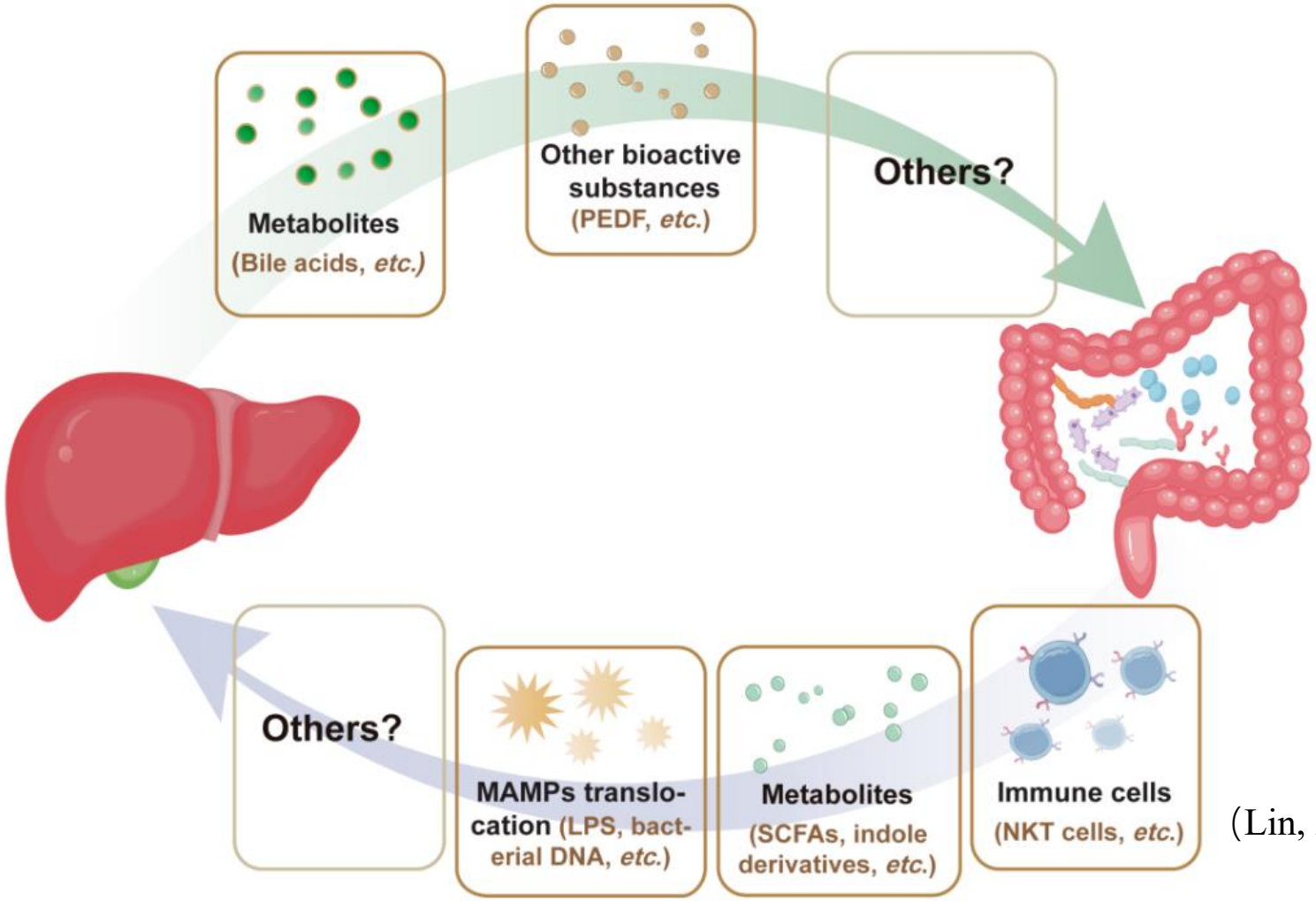
Delong Meng, Zhen Zhang, Tsegay Teame, Benjamin Earl Niemann, Rui Xia, Shichang Xu, Yajie Zhao, et al. 2025. Host-driven hepatic conversion of gut microbiota-derived putrescine to spermidine mediates mannose's protective effects against hepatic steatosis in zebrafish. ***iMeta*** 4: e70101. https://doi.org/10.1002/imt2.70101

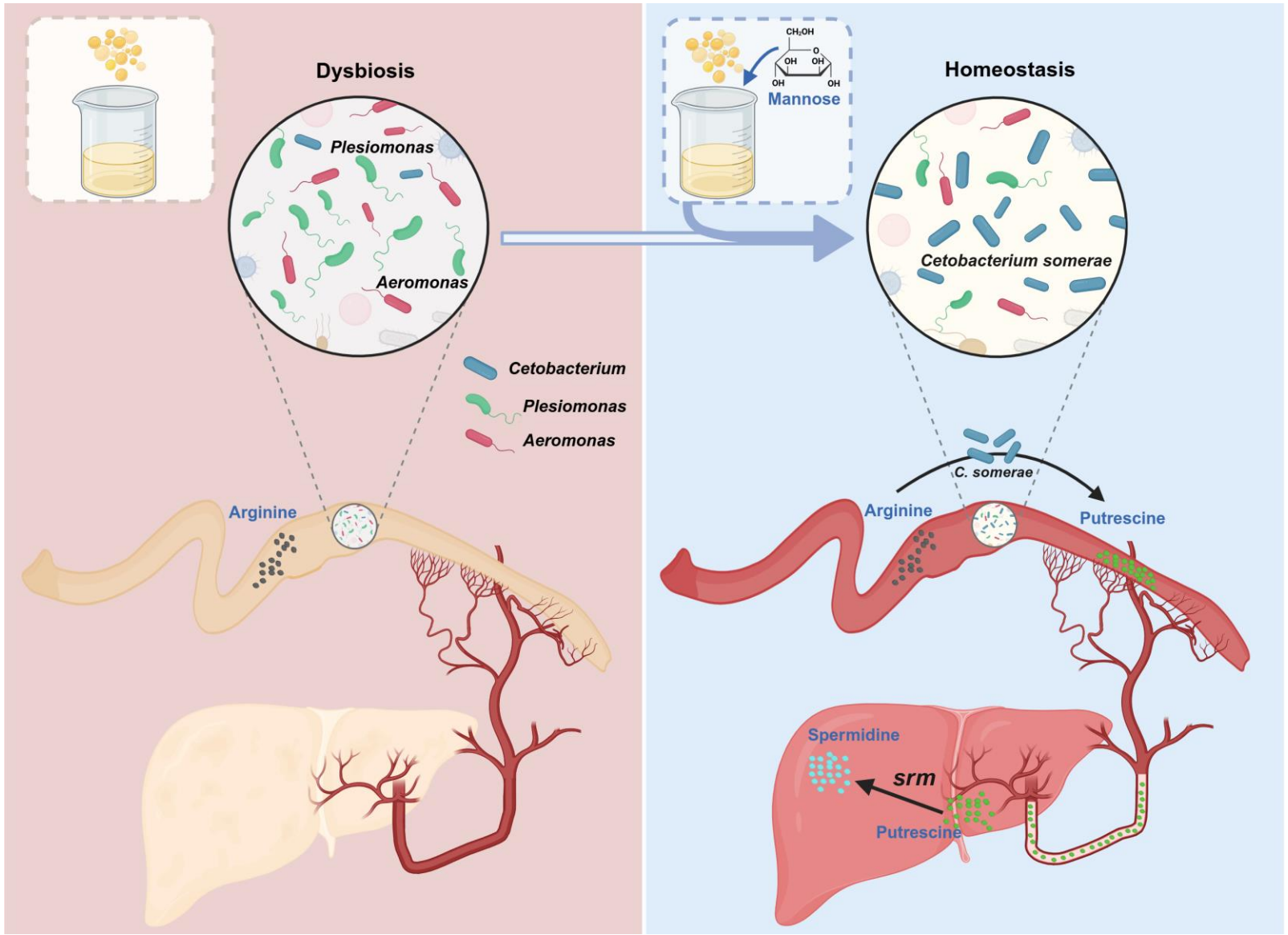
# Introduction




(Lin, 2025 *iMeta*)

- The gut microbiota and the host can be mediated through local and systemic interactions, among which the gut-liver axis has been most studied.
- Host-bacterial interaction: Through the cellular components or secreted active substances of microbes.

# Highlights




- **Clarifying the Dietary Intervention Pathway:** Mannose specifically promotes the growth of *C. somerae* to initiate beneficial metabolic processes, rather than acting directly.
- **Elucidating the Complete Metabolic Pathway:** The complete metabolic chain spanning gut microbes and the host, from "arginine → putrescine → spermidine.“
- **Revealing a Novel Gut-Liver Collaborative Mechanism:** For the first time, it was discovered that gut microbes (*C. somerae*) collaborate with the liver to convert arginine into putrescine, which is then transformed by the liver into spermidine to improve fatty liver.
- **Proposing a New Co-Metabolism Paradigm:** Direct evidence was provided for the concept of "microbe-host co-metabolism producing active substances," expanding new perspectives for disease treatment.

# Supplementation of mannose alleviated high-fat diet-induced fatty liver in zebrafish

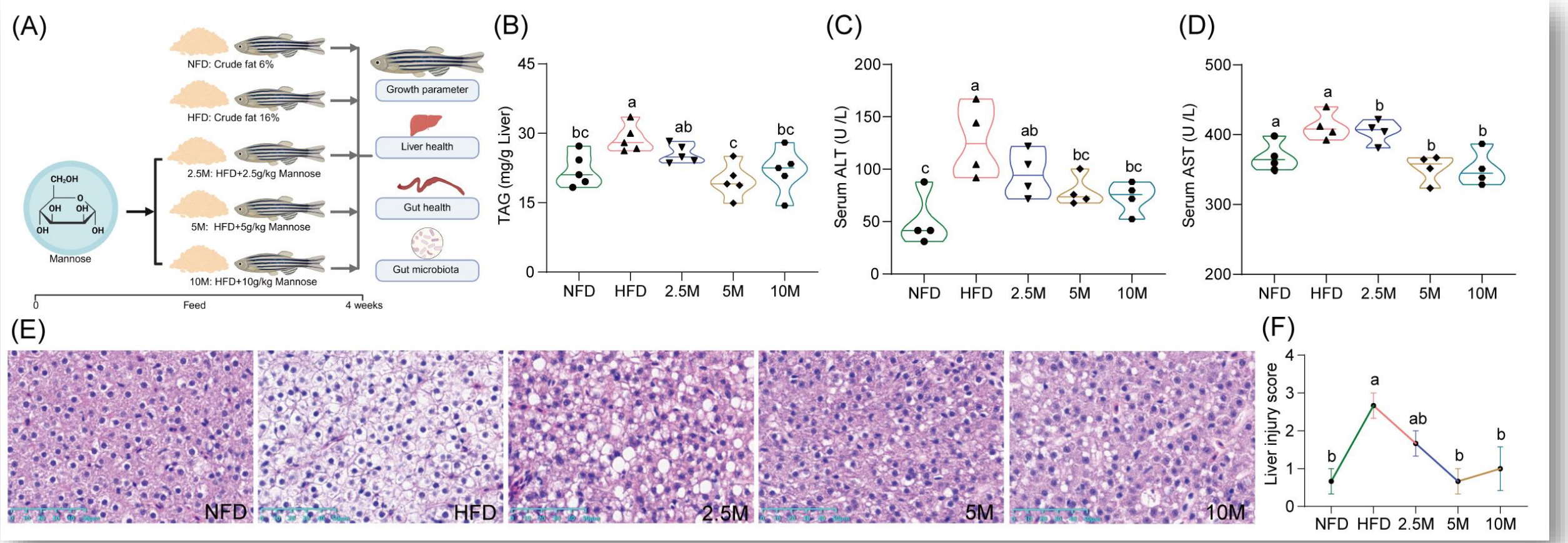



**Figure 1. (A)** One-month old zebrafish were fed normal-fat diet (NFD), high-fat diet (HFD) and three treatment diets supplemented with 2.5 g/kg (2.5M), 5 g/kg (5M) and 10 g/kg (10M) mannose for four weeks, respectively. This feeding experiment was set up in 5 groups, where every group had 5 replicate tanks containing 24 zebrafish. **(B)** Triacylglycerol (TAG) content in zebrafish liver. **(C)** Alanine aminotransferase (ALT) and **(D)** aspartate aminotransferase (AST) contents in zebrafish serum. **(E)** Liver hematoxylin and eosin (H&E) sections. **(F)** Liver injury scores.

# Mannose supplementation altered gut microbiota and selectively enriched *Cetobacterium*

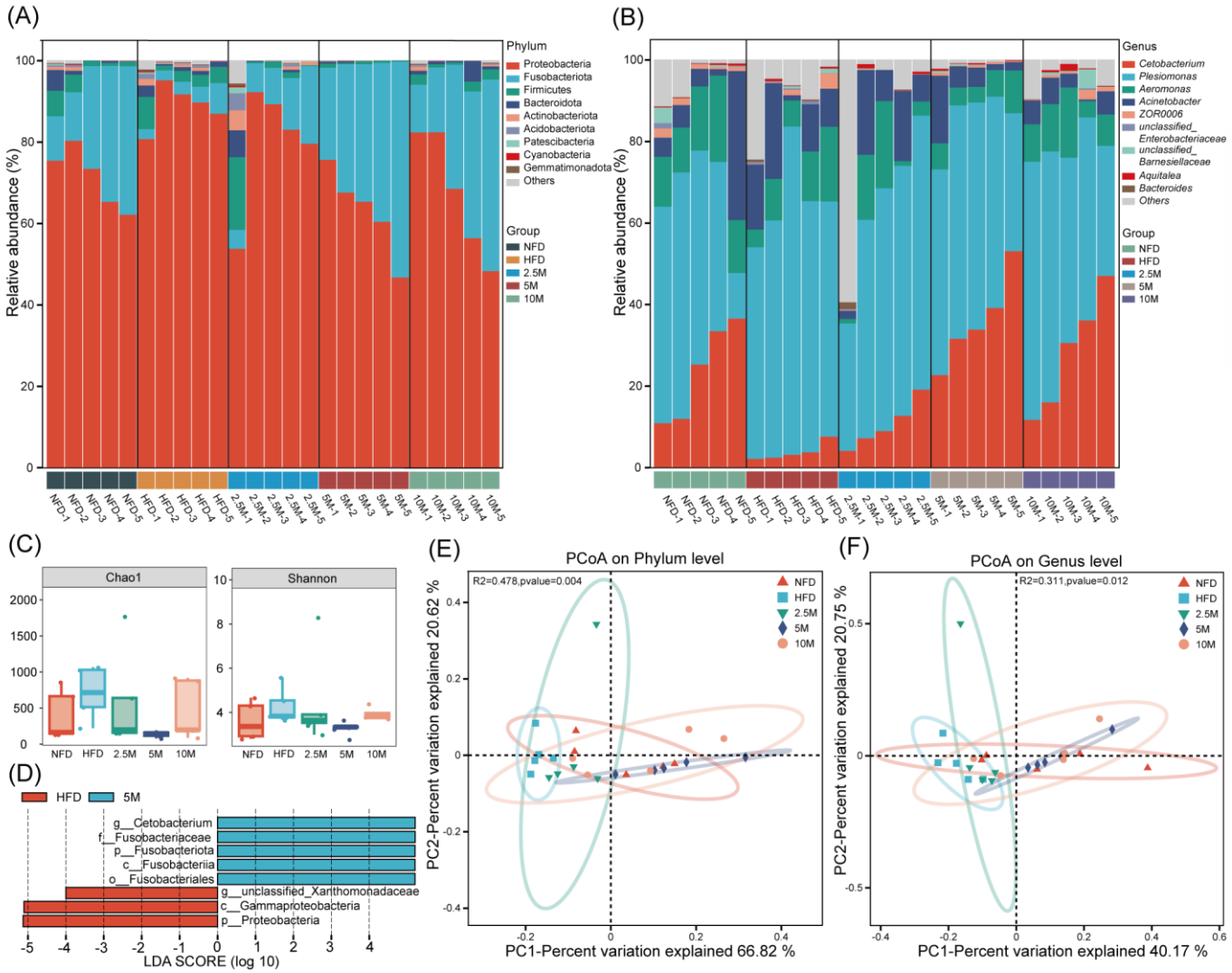



**Figure S4. (A)** The relative abundance of gut microbiota at the phylum level. **(B)** The relative abundance of gut microbiota at the genus level. **(C)** Alpha diversity analysis of gut microbiota. **(D)** LEfse analysis of gut microbiota at the species level. **(E)** PCoA analysis of gut microbiota at the phylum level. **(F)** PCoA analysis of gut microbiota at the genus level.

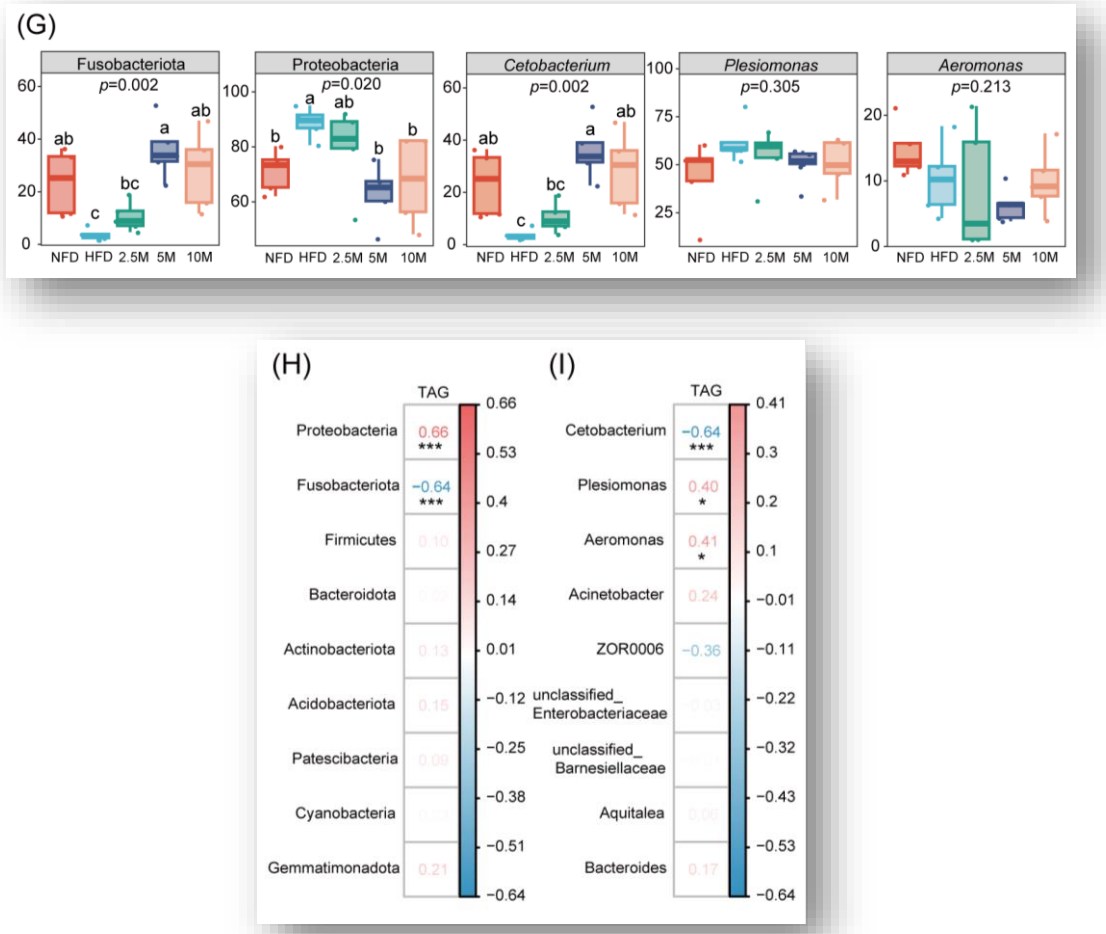
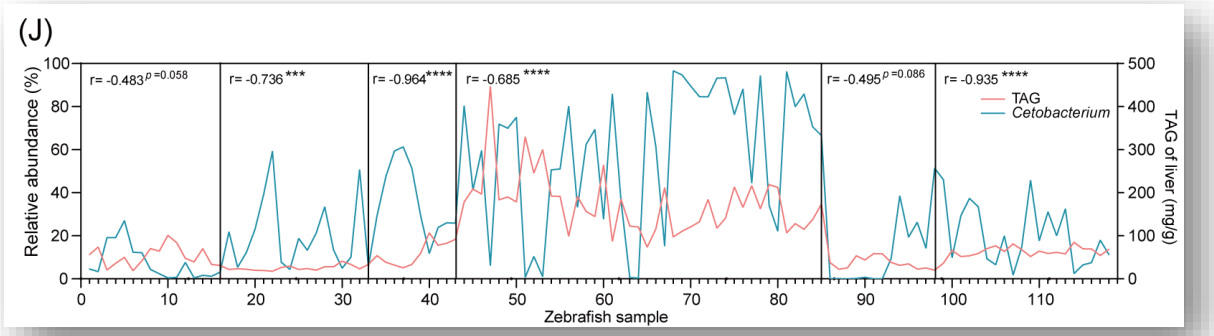
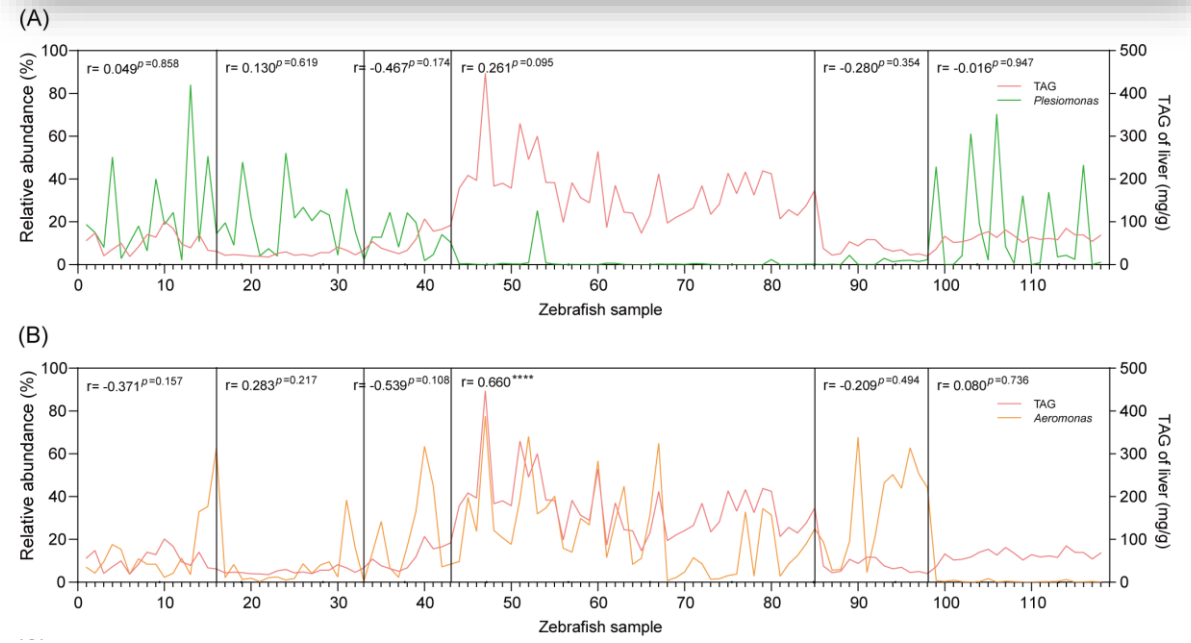



**Figure 1. (G)** The relative abundance difference analysis of gut microbiota at the phylum and genus. **(H)** Spearman correlation analysis between TAG content and the main phyla of gut microbiota. **(I)** Spearman correlation analysis between TAG content and the main genera of the gut microbiota.

# Meta-analysis of the gut microbiota of fish



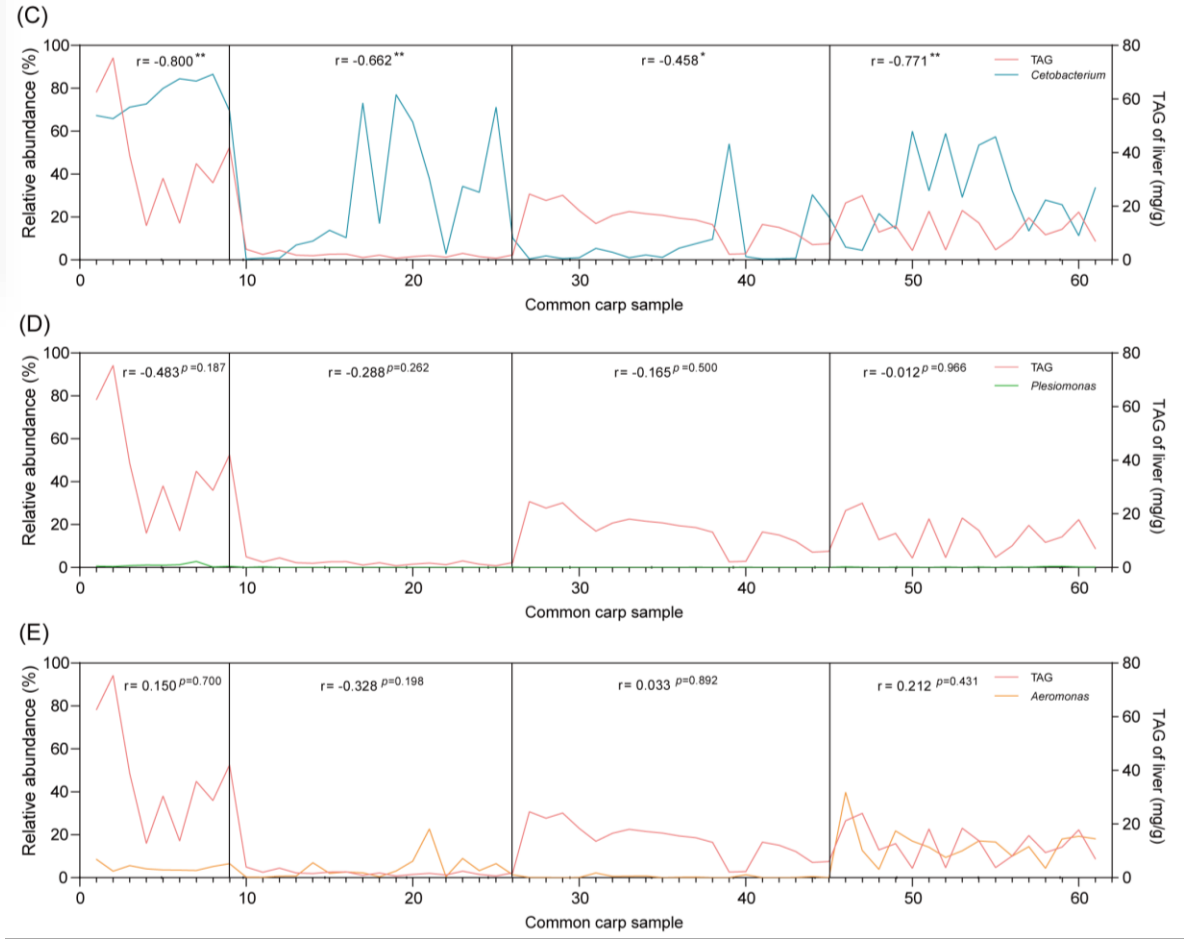




**Figure 1. (J)** The relationship between *Cetobacterium* and the liver TAG content in zebrafish by Spearman correlation analysis.

**Figure S5. (A)** The relationship between *Plesiomonas* and the liver TAG content in zebrafish. **(B)** The relationship between *Aeromonas* and the liver TAG content in zebrafish. **(C)** The relationship between *Cetobacterium* and the liver TAG content in *Cyprinus carpio*. **(D)** The relationship between *Plesiomonas* and the liver TAG content in *Cyprinus carpio*. **(E)** The relationship between *Aeromonas* and the liver TAG content in *Cyprinus carpio*.

# Genomic analysis of *C. somerae* revealed its ability to metabolize mannose

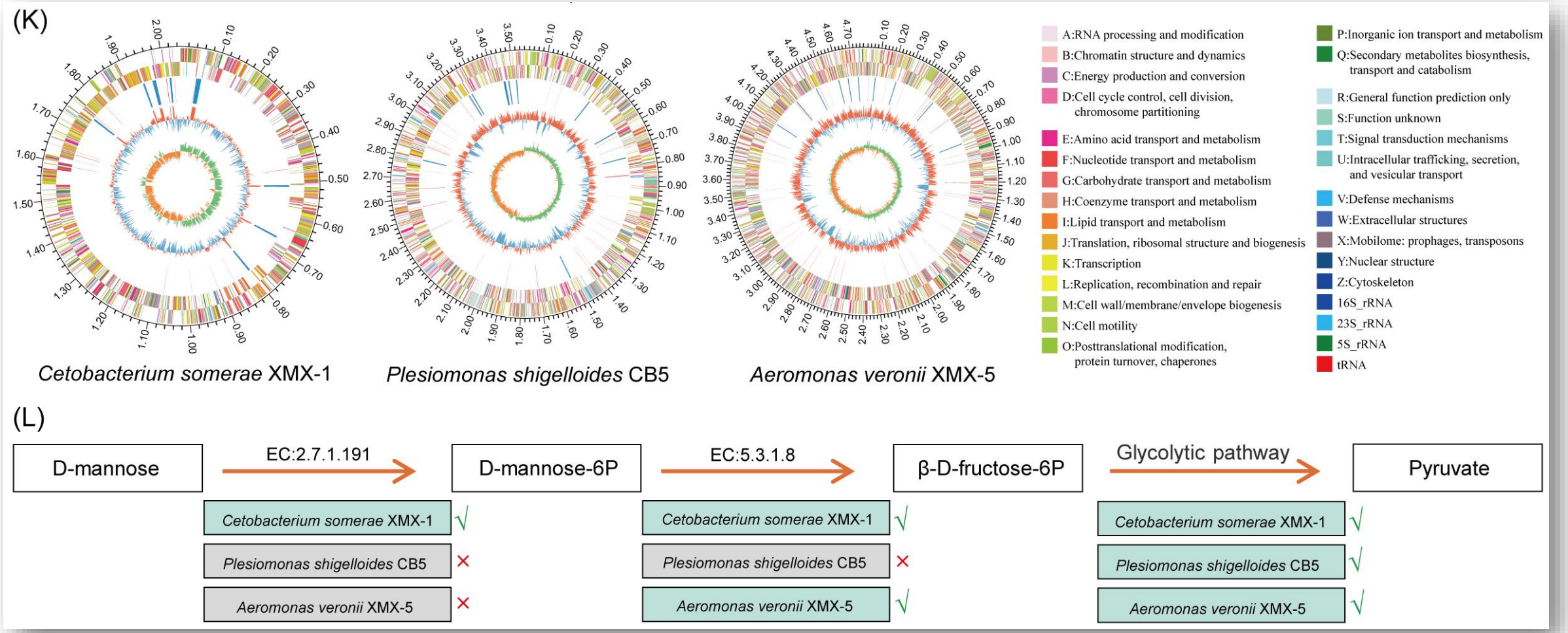



**Figure 1. (K)** Chromosome circos diagram of *C. somerae* XMX-1, *P. Shigeloides* CB5 and *A. veronii* XMX-5. **(L)** Annotation results of the key genes in Mannose metabolism of the three representative strains.

# Gut *C. somerae*, not mannose, reduced liver fat accumulation in zebrafish

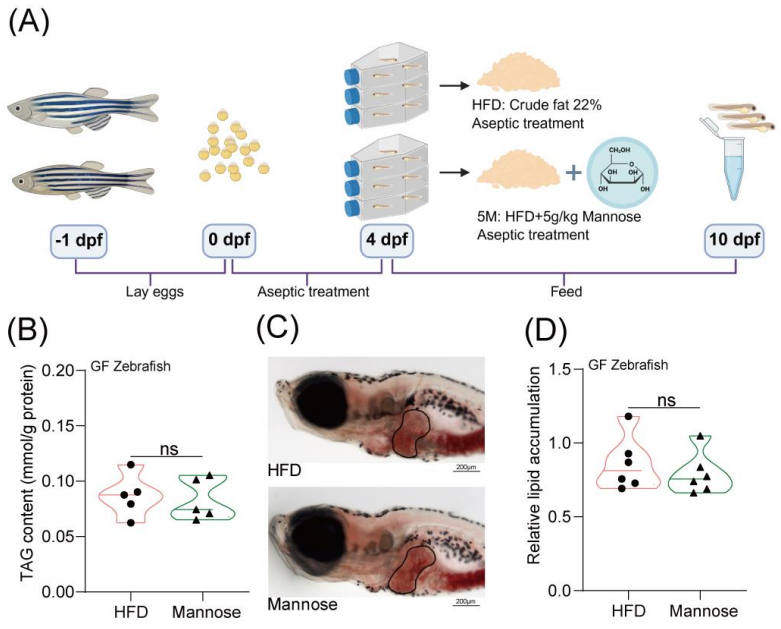



**Figure S7. (A)** Germ-free zebrafish larvae were fed sterile HFD supplemented with mannose. **(B)** TAG content of GF zebrafish larvae. **(C)** Oil red staining of GF zebrafish larvae. **(D)** Quantification of oil red staining of GF zebrafish larvae.

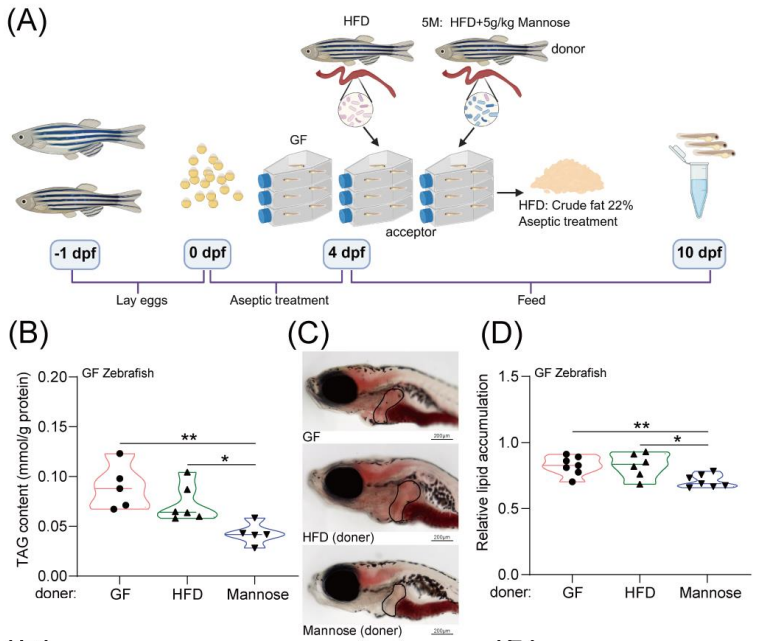



**Figure S8. (A)** Germ-free zebrafish larvae that were transferred the gut microbiota from the HFD and Mannose groups were fed a HFD. Three groups were divided into GF, HFD-GM and HFD-MO-GM groups. **(B)** TAG content of GF zebrafish larvae. **(C)** Oil red staining of GF zebrafish larvae . **(D)** Quantification of oil red staining of GF zebrafish larvae.

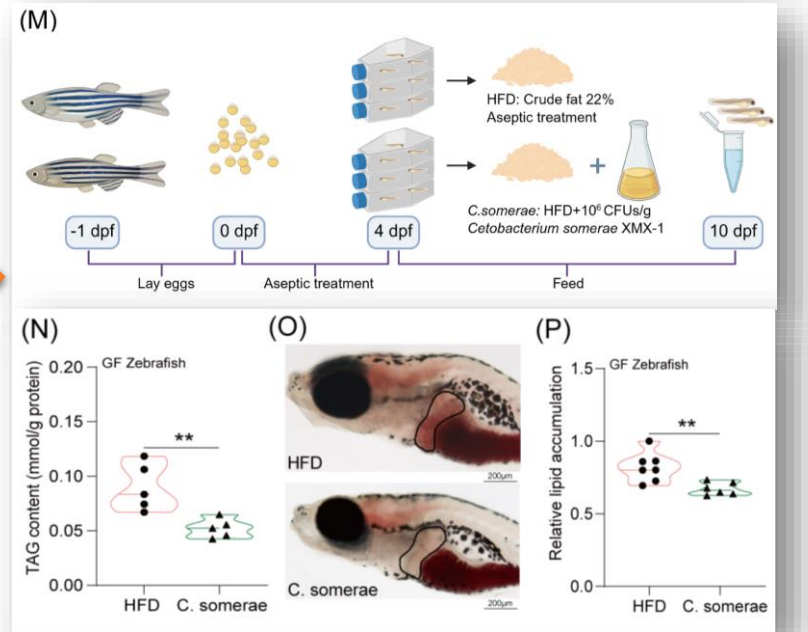



**Figure 1. (M)** Germ-free zebrafish larvae were directly fed a HFD supplemented with *C. somerae*. **(N)** TAG content of GF zebrafish larvae. **(O)** Oil red staining of GF zebrafish larvae. **(P)** Quantification of oil red staining of GF zebrafish larvae.

# Combined metabolomics and genomics analysis revealed key metabolites of *C. somerae*

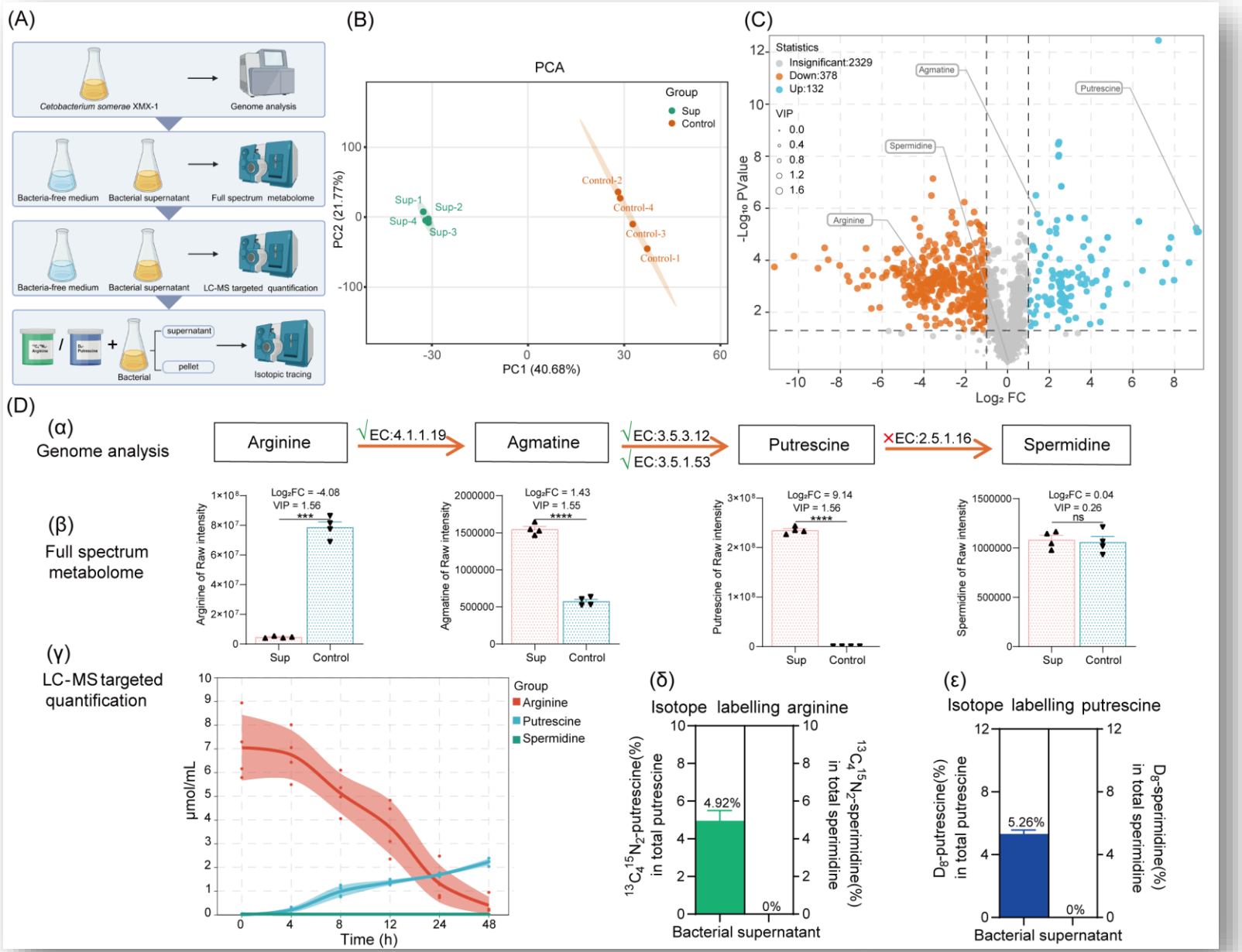



**Figure 2. (A)** Diagram of methods employed to explore *C. somerae* metabolites; genomic analysis of *C. somerae* XMX-1, full spectrum metabolome mining of metabolites and LC-MS targeted quantitative analysis of key metabolites, in addition to isotope tracing. **(B)** PCA diagram of each sample of the full spectrum metabolome. **(C)** Volcano diagram of differential metabolites. **(D)** Analysis of putrescine metabolism in *C. somerae* XMX-1 by genome analysis on KEGG pathway (α), the abundance of four metabolites by full spectrum metabolome (β), LC-MS targeted quantitative analysis (γ), the $^{13}C_6{}^{15}N_4$- arginine isotope tracer (δ), and the $D_8$-putrescine isotope tracer.

# Putrescine had no direct effect on liver function, but its downstream metabolite spermidine alleviated fatty liver

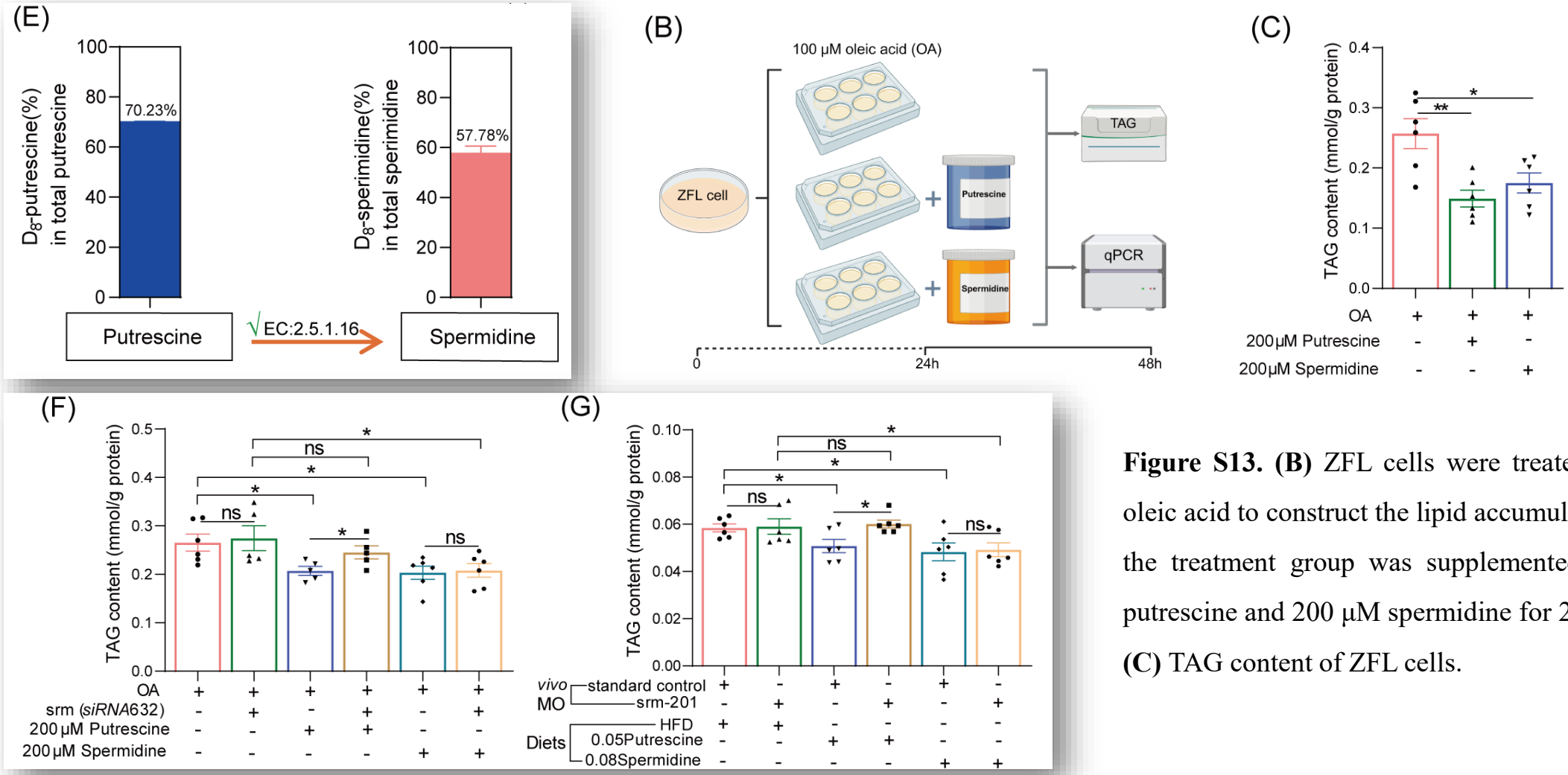



**Figure S13. (B)** ZFL cells were treated with 100 μM oleic acid to construct the lipid accumulation model, and the treatment group was supplemented with 200 μM putrescine and 200 μM spermidine for 24h, respectively. **(C)** TAG content of ZFL cells.

**Figure 2. (E)** Genomic analysis and isotope tracing of the ability of ZFL cells to metabolize putrescine to spermidine. **(F)** TAG content of ZFL cells after knocking down spermidine synthase by *si*RNA 632. **(G)** TAG content of zebrafish larvae after knocking down spermidine synthase by *vivo* MO srm-201.

# Isotope tracing of putrescine metabolic pathways in zebrafish

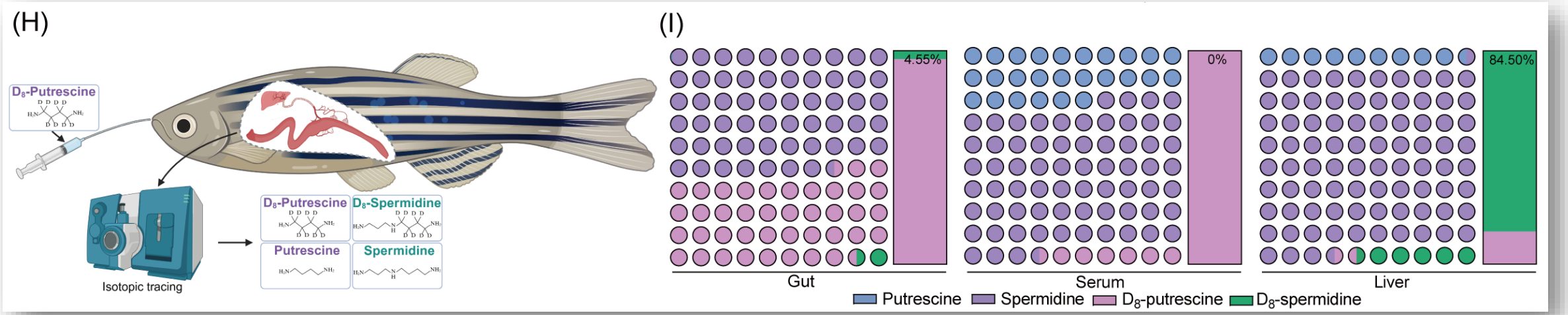
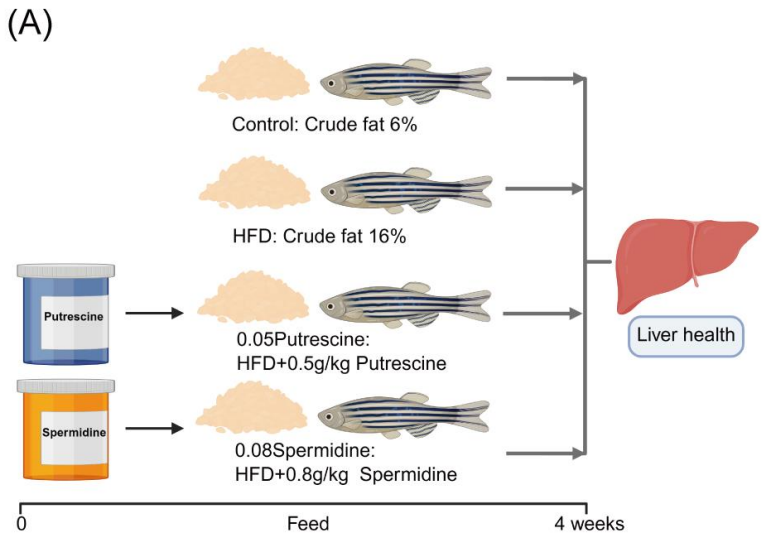
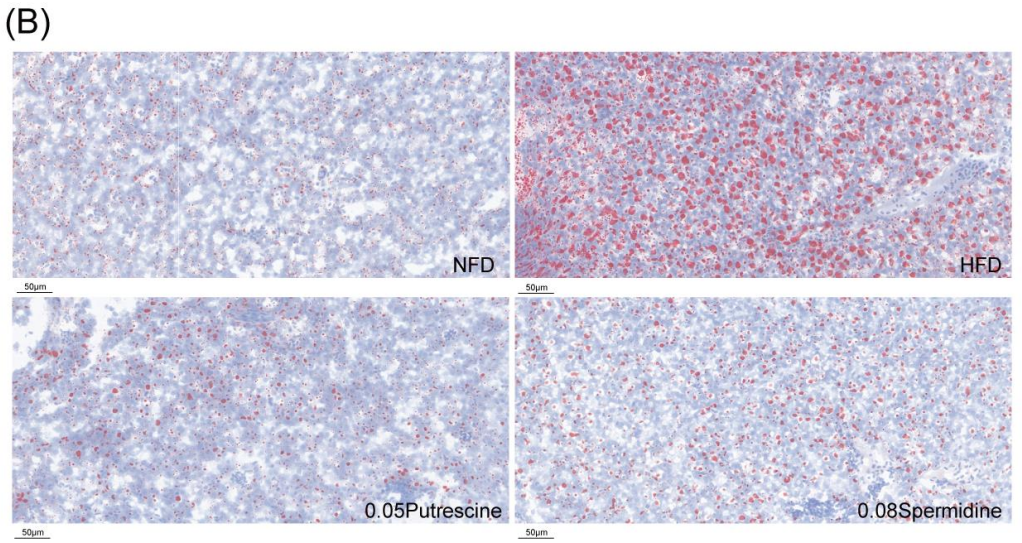



**Figure 2. (H)** Zebrafish were fed with $D_8$-putrescine for 2 consecutive days, and the content of the metabolites $D_8$-putrescine, $D_8$-spermidine, putrescine and spermidine were detected in the gut, serum and liver of zebrafish after the last feeding for 2h. **(I)** The contents of $D_8$-putrescine, $D_8$-spermidine, putrescine and spermidine in the gut, serum and liver.

# The effects of putrescine and spermidine in HFD zebrafish model



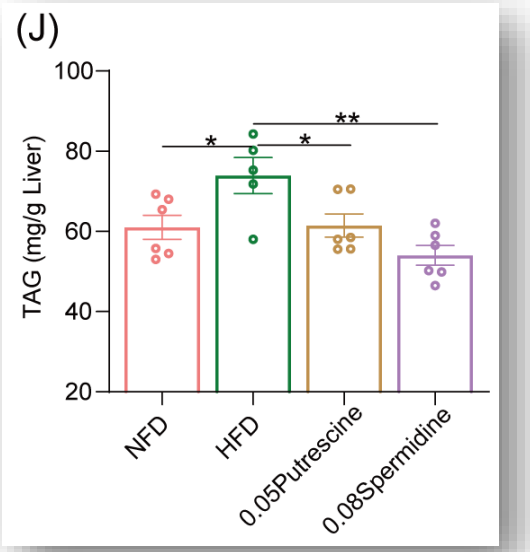
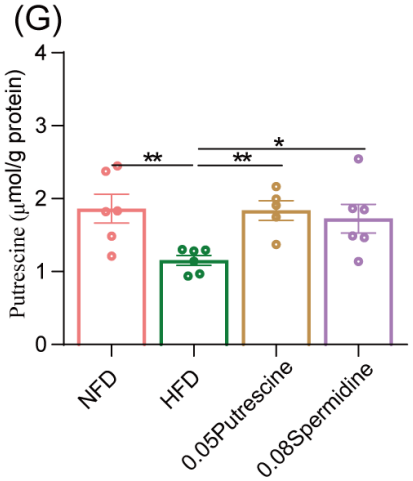
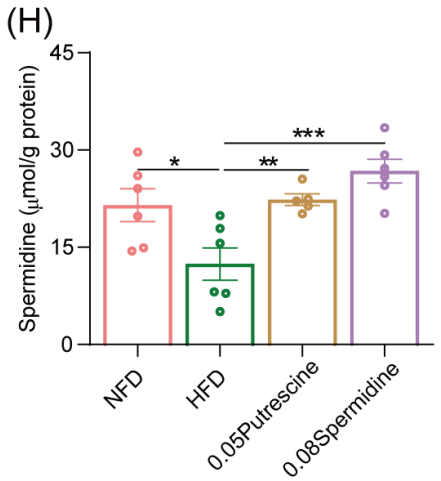




**Figure 2. (J)** TAG content in zebrafish liver.



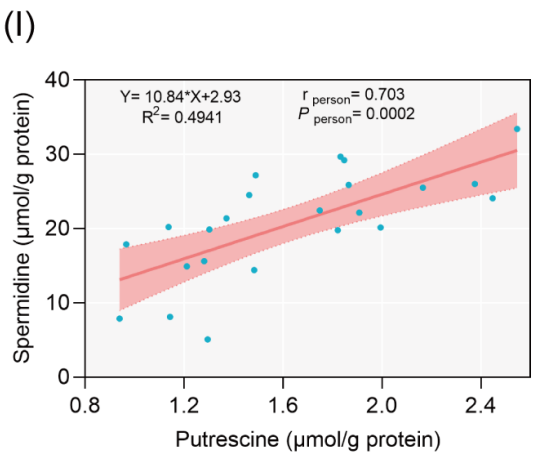




**Figure S15. (A)** One-month old zebrafish were fed with diets supplemented with 0.5 g/kg putrescine and 0.8 g/kg spermidine (with equimolar amounts of putrescine and spermidine) for four weeks. Four groups were divided into normal-fat diet (NFD), high-fat diet (HFD), 0.05putrescine and 0.08spermidine groups. **(B)** Oil red staining of zebrafish liver. **(G)** The content of putrescine in liver. **(H)** The content of spermidine in liver. **(I)** Linear regression analysis of the content of putrescine and spermidine in liver.

# Discovery of putrescine-spermidine cross talk in the HFD zebrafish model

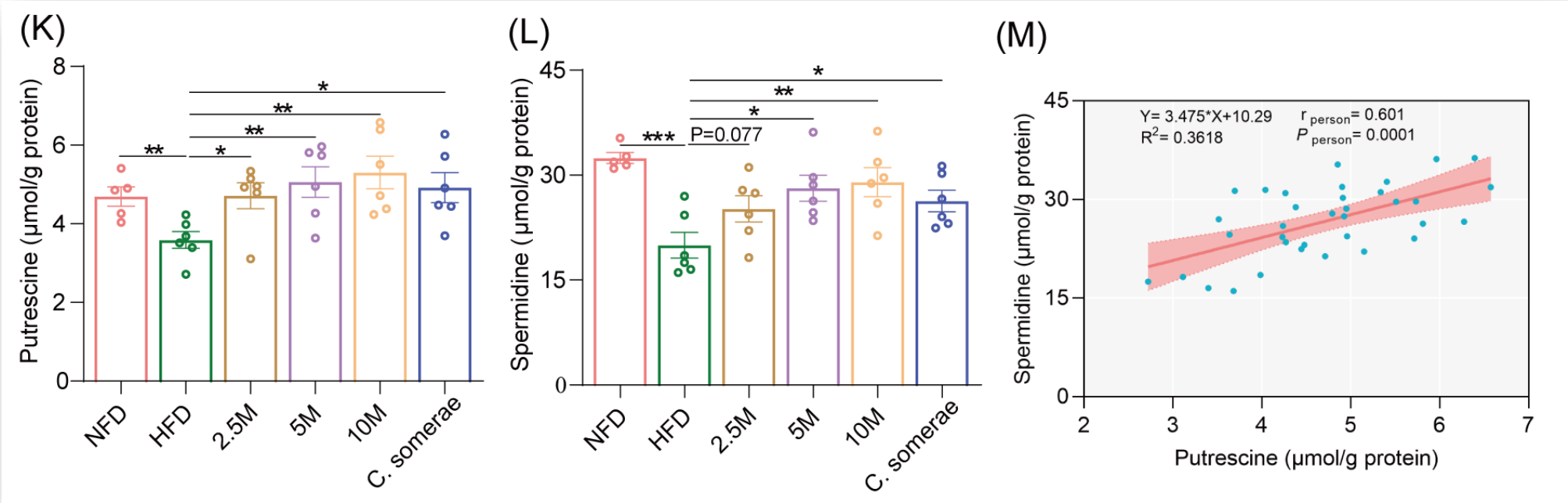



**Figure 2. (K)** The content of putrescine in liver of Zebrafish fed with mannose and *C. somerae*. **(L)** The content of spermidine in liver of Zebrafish fed with mannose and *C. somerae*. **(M)** Linear regression analysis of the liver content of putrescine and spermidine in Zebrafish fed with mannose and *C. somerae*.

# Summary

- Mannose supplementation did not directly mitigate HFD-induced liver steatosis, but promote the growth of *C. somerae.*
- Large amount of putrescine was produced in the gut by *C. somerae* from arginine.
- Putrescine was transported to the liver and converted by the host cell to spermidine.
- A novel host-microbiota collaborative mechanism in which the arginine-putrescine-spermidine metabolic pathway is completed through inter-kingdom cooperation to ameliorate hepatic steatosis.

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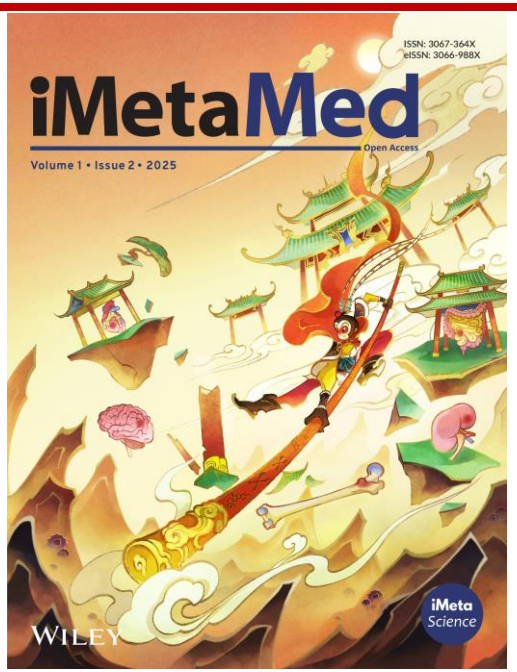



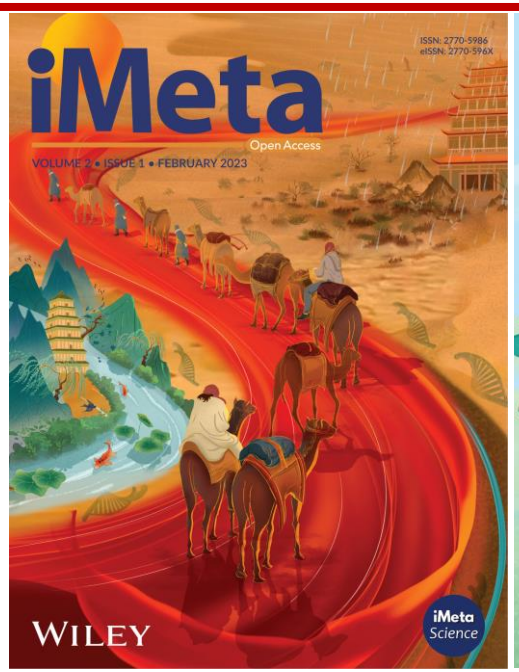




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