Journal of Pain Research

Dovepress
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RESPONSE TO LETTER

# Metabolomics Analysis Reveals Gut Microbiota-Associated Sakuranin Modulates Endometrial Stem Cell Differentiation and Inflammation to Alleviate Pain in Endometriosis [Response to Letter]

Wen Shi[1–3,*], Minyi Wang[1–3,*], Zhuang Jin[1–3], Xiaochuan Chen[1–3], Jinbo Li[1–3], Huiling Lai[1–3], Xiao Li[1–3], Qiyu Zhong[1–3], Ye Chen[1–3], Shuqin Chen[1–3]

[1]Department of Gynecology, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, People's Republic of China; [2]Key Laboratory of Human Microbiome and Chronic Diseases (Sun Yat-sen University), Ministry of Education, Guangzhou, Guangdong, People's Republic of China; [3]Biomedical Innovation Center, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, People's Republic of China

*These authors contributed equally to this work

Correspondence: Shuqin Chen, Department of Gynecology, Block B, 12th Floor, Building 1, The Sixth Affiliated Hospital of Sun Yat-sen University, No. 26, Yuancun Erheng Road, Tianhe District, Guangzhou, Guangdong, 510655, People's Republic of China, Tel +86-13825039699, Email chshqin@mail.sysu.edu.cn



## Dear editor

We thank Liu Y. for the thoughtful comments and for their interest in our work. We appreciate the opportunity to further discuss key aspects of our study and clarify mechanistic and translational considerations raised in the Letter to the Editor.

First, concerning the systemic circulation of sakuranin and its physiological significance, we recognize that our present study focused on fecal metabolomics to identify microbiota-associated metabolites linked to dysmenorrhea in endometriosis. Although plasma levels of sakuranin were not assessed in this cohort, the observed fecal deficiency may serve as an indicator of gut–host metabolic interactions. The lack of plasma metabolite measurements represents a limitation of the current study. Future studies will incorporate targeted plasma metabolomics to evaluate correlations between circulating sakuranin levels and clinical pain scores, and to determine whether systemic concentrations reach levels comparable to those used in our in vitro endometrial stem cells assays. These analyses will help bridge gut-derived discoveries with peripheral pharmacological effects, which may further support its translational relevance.

Second, we concur that intraperitoneal (IP) injection bypasses the gastrointestinal interface and may not fully recapitulate microbiota-dependent metabolism in vivo. IP administration at 80 mg/kg was selected to ensure consistent systemic exposure and to directly assess the pharmacological activity of the parent compound. This approach is commonly used to evaluate the intrinsic pharmacological activity of candidate compounds under controlled systemic exposure. Importantly, efficacy was observed even in microbiota-depleted mice, suggesting that sakuranin may possess intrinsic biological activity independent of microbial deglycosylation. We agree that future studies using oral administration in animals with intact microbiota are warranted to better simulate physiological conditions and to assess the contribution of gut-mediated metabolism to therapeutic effects.

Third, regarding the analgesic effects observed in the murine model, we acknowledge the distinction between disease-modifying and direct nociceptive pathways. Sakuranin treatment reduced ectopic lesion size as well as the expression of sympathetic (TH) and sensory (SP) nerve markers. While these findings suggest that reduced inflammatory burden contributes to pain relief, we cannot exclude the possibility that sakuranin directly modulates nociceptive signaling. At present, our data do

https://doi.org/10.2147/JPR.S608988
Received: 13 March 2026
Accepted: 24 March 2026
Published: 16 April 2026

not allow definitive discrimination between these mechanisms. Further mechanistic studies using nerve-specific assays or conditional models will be necessary to disentangle these effects and refine its potential role as a dual-acting agent.

In conclusion, we thank Liu Y. for their valuable suggestions, which help contextualize our findings. Our study supports sakuranin's potential as a targeted treatment for endometriosis and encourages further research on its direct pain-relief effects, microbiota-related metabolism, and systemic pharmacokinetics.

## Disclosure

The authors report no conflicts of interest in this communication.



https://doi.org/10.2147/JPR.S608988