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LETTER

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

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Dear editor

We read with interest the study by Shi et al investigating the role of sakuranin in modulating endometrial stem cell (EnSC) differentiation and alleviating pain in endometriosis[1] The authors utilize a multi-level approach integrating clinical metabolomics with primary human cell assays and murine models to provide a compelling foundation for exploring gut-derived metabolites as therapeutic candidates for chronic pain. To further strengthen the translational impact of these findings, we offer a few considerations regarding the physiological integration of the systemic axis and the pharmacological context of the administration route.

The identification of sakuranin deficiency in the feces of endometriosis patients with dysmenorrhea provides an intriguing starting point for exploring gut-host interactions. The proposed mechanism suggests that this metabolite enters the systemic circulation to act distally on ectopic lesions. While fecal abundance is a robust indicator of the intestinal environment, the integration of clinical plasma data would further substantiate this systemic axis. Given that flavonoids often undergo significant biotransformation, it would be of great interest to ascertain whether clinical plasma levels of sakuranin correlate with pain scores in a manner consistent with the fecal findings. Establishing that sakuranin achieves physiologically relevant concentrations in the blood—comparable to those used in the in vitro EnSC assays—would bridge the current gap between intestinal discovery and peripheral action.

The animal validation phase utilized intraperitoneal (IP) administration of sakuranin at $80~mg/kg$ in a microbiota-depleted model. While this effectively demonstrates the pharmacological potency of the molecule itself, it presents an interesting point for discussion regarding the "microbiota-associated" context. Flavonoid glycosides typically require microbial deglycosylation within the gastrointestinal tract to enhance their bioavailability.[2] Since the IP route bypasses the gut interface, the observed efficacy in microbiota-depleted mice suggests that sakuranin possesses direct biological activity independent of microbial processing. Further studies utilizing oral administration (gavage) in models with an intact microbiota could clarify whether the clinical therapeutic effect is primarily driven by the parent compound or if it is augmented by microbial metabolites in a natural physiological setting.

A fascinating aspect of this work is the concurrent reduction in ectopic lesion weight and the modulation of sympathetic (TH) and sensory (SP) nerve markers. It remains an open question whether the alleviation of pain is a secondary outcome of the reduced inflammatory load and lesion size, or if sakuranin exerts a direct regulatory effect on the nociceptive fibers. Distinguishing between these disease-modifying and direct analgesic pathways would significantly refine the clinical positioning of sakuranin.

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These considerations are intended to complement the valuable metabolic landscape delineated by Shi et al[1] We believe that reinforcing the link between gut-derived signals and systemic exposure will further enhance the potential of sakuranin as a precision medicine approach for endometriosis.

Disclosure

The author reports no conflicts of interest in this communication.

References

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