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Letter to the Editor

Forsythoside B Protects Cartilage and Subchondral Bone in Osteoarthritis by Regulating the Nrf2/NF-κB Signaling Pathway: Letter to the Editors

Meihong Zhang[1], Chuanbin Wu[1,2,3] and Zhengwei Huang[1,3*]

[1]*State Key Laboratory of Bioactive Molecules and Druggability Assessment, Guangdong Basic Research Center of Excellence for Natural Bioactive Molecules and Discovery of Innovative Drugs, College of Pharmacy, Jinan University, Guangzhou, Guangdong, China;* [2]*Jiangmen Wuyi Hospital of Traditional Chinese Medicine, Affiliated Jiangmen Traditional Chinese Medicine Hospital of Jinan University, Jiangmen, Guangdong, China;* [3]*National Engineering Research Center of Genetic Medicine, Guangzhou, Guangdong, China*

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Dear Editors,

Forsythoside B (FTS-B) is a natural phenylethanoid glycoside isolated from the dried fruit and leaves of *Forsythia suspensa* (Thunb.) Vahl, a traditional Chinese medicinal herb.[1] We recently came across an interesting study published in *International Immunopharmacology* by Zhang *et al*.[2] The major findings were that FTS-B prevented the degradation of cartilage and subchondral bone in osteoarthritis (OA) through the activation of the nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) axis and the deactivation of nuclear factor kappa-B (NF-κB) and mitogen-activated protein kinases pathways.[2] *In vitro* and *in vivo* models were established to validate the bioactivity of FTS-B, which revealed positive outcomes. Relevant studies have also confirmed the positive role of the Nrf2–HO-1 signaling pathway in OA.[3] We appreciate the authors' work, which offers new insights into phytochemical-based therapy for OA.

It is believed that the experimental framework of the original research was logically sound, and thus the conclusions were largely convincing. From the standpoint of drug research and development (R&D), we herein propose some further recommendations for the clinical translation of FTS-B-based therapy.

According to the Methods section of the original research, the mouse OA models were constructed on the right knee. Subsequently, different dosages of FTS-B were administered via intraperitoneal injection. We note that the expected therapeutic effects were observed, but the selection of the administration route can be reconsidered. OA can be regarded as a local disease, while intraperitoneal injection is commonly intended for systemic administration.[4] During the future R&D process, the FTS-B formulations for intraperitoneal injection in mice may be converted into intravenous injection for human use. It should be noted that systemic exposure of FTS-B, such as through conventional oral and intravenous drug delivery methods, may lead to adverse effects or even toxicities, including potential risks arising from its extensive distribution in non-target organs, as well as possible pseudoallergic reactions.[5]

To mitigate this issue, one may choose intra-articular injection for FTS-B, which is pertinent to local drug delivery.[6] In this way, FTS-B can concentrate at the OA lesion site, and the systemic toxicity can be reduced. Moreover, some low-pain or painless injection techniques are currently available for intra-articular injection, which can improve patient compliance. Most importantly, FTS-B possesses a moderate molecular weight ($C_{34}H_{44}O_{19}$) and favorable water solubility, suggesting a potential physicochemical basis for its formulation as an intra-articular injection solution and initially supporting its compatibility with low-pain injection technologies. For instance, intelligent insulin pens, as mature and portable injection devices, alleviate instantaneous pain during puncture through their ultra-fine needles.[7] Patients can master self-administration at home with simple guidance and perform regular injections independently, significantly lowering the threshold for use. Microneedle technology utilizes arrayed microneedles with diameters ranging from tens to hundreds of micrometers to penetrate the skin and superficial tissues surrounding the joint.[8] By avoiding regions dense with nerve endings, microneedles achieve a near-painless effect. However, it is noteworthy that insulin pens and microneedles are mostly designed for shallow joint injections, not for deep joint delivery. We anticipate that low-pain/painless intra-articular injection is particularly suitable for maintenance treatment of patients with mild-to-moderate OA, as well as for patient populations intolerant to systemic administration or sensitive to injection-related pain. However, it should be specifically noted that the therapeutic effects of intra-articular injections are time-limited, with limited short-term efficacy and insufficient long-term symptom relief.[9] Additionally, there is a potential risk of inducing systemic allergic adverse reactions.[10] Therefore, the compatibility between FTS-B formulations and these techniques must be investigated in depth.

Although this letter aims to provide some suggestions for R&D considerations, the findings of the original research are sufficiently

***Correspondence to:** Zhengwei Huang, National Engineering Research Center of Genetic Medicine, China, Guangzhou 510632, China. ORCID: https://orcid.org/0000-0003-2351-7347. Tel: +86-13580481121, E-mail: huangzhengw@jnu.edu.cn

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significant. We thank the authors for demonstrating the potential value of FTS-B in OA management.

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Conflict of interest

The authors have no conflict of interest related to this publication.

Author contributions

Study concept and design, drafting of the manuscript (MZ), critical revision of the manuscript for important intellectual content, and study supervision (CW, ZH). All authors have made significant contributions to this study and approved the final manuscript.

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