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Review Article

# Diosmetin Modulates Macrophage Polarization in Osteoarthritis via PI3K/Akt Inhibition: A Mechanistic Insight and Therapeutic Perspective

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Osteoarthritis (OA), the most prevalent degenerative joint disease, affects over 500 million individuals worldwide and constitutes a leading cause of chronic pain and disability [1,2]. Historically conceptualized as a cartilage-centric "wear-and-tear" condition, OA is now recognized as a multifactorial whole-joint disorder in which synovial inflammation (synovitis) plays a pivotal role in disease pathogenesis and progression [3]. Within the inflamed synovium, macrophages serve as central regulators of immune responses, and their phenotypic plasticity enables them to adopt either a pro-inflammatory (M1) or an anti-inflammatory, tissue-reparative (M2) state [4]. In the OA milieu, damage-associated molecular patterns (DAMPs) released from degrading cartilage promote macrophage polarization toward the M1 phenotype, thereby perpetuating inflammation and accelerating tissue destruction [5]. strategies aimed at reprogramming synovial macrophages from a pro-inflammatory M1 to a pro-resolving M2 phenotype have emerged as a promising disease-modifying approach for OA.

In our recent study published in the Journal of Natural Medicines [6], we investigated diosmetin, a naturally occurring flavonoid abundant in citrus fruits and olive leaves, as a potential modulator of macrophage polarization in OA. While diosmetin has previously demonstrated anti-inflammatory and anti-remodeling effects in subchondral bone, its direct influence on synovial inflammation and the underlying mechanisms had remained unexplored.

To address this gap, we employed a surgically induced OA mouse model. Our findings revealed that oral administration of diosmetin (5 mg/kg, twice weekly for 8 weeks) effectively mitigated cartilage degeneration and alleviated pain, with a therapeutic efficacy comparable to that of celecoxib and no overt signs of toxicity. Mechanistically, diosmetin did not directly protect chondrocytes or modulate fibroblast-like synoviocytes (FLSs) *in vitro*. Instead, it facilitated a phenotypic shift from M1 to M2 macrophages, as evidenced by flow cytometry and immunofluorescence analyses. This effect was mediated through inhibition of the PI3K/Akt signaling pathway, a mechanism confirmed by the reversal of diosmetin's effects following treatment with the pathway activator SC79. Furthermore, in a transwell coculture system, chondrocytes cultured with diosmetin-treated M2 macrophages exhibited preserved extracellular matrix (ECM) integrity, suggesting a paracrine protective mechanism.

The findings indicated that oral administration of diosmetin (at a dosage of 5 mg/kg, twice a week for 8 weeks) was effective in mitigating cartilage degeneration and relieving pain. Its therapeutic effect was comparable to that of celecoxib. Notably, no evident signs of toxicity were detected. Mechanistically diosmetin did not directly safeguard chondrocytes or regulate fibroblast - like synoviocytes (FLSs) *in vitro*. Instead, it facilitated a phenotypic shift from M1 to M2 macrophages, as demonstrated by flow cytometry and immunofluorescence. This effect was mediated through the inhibition of the PI3K/Akt signaling pathway, which was verified by using the pathway activator SC79. The use of SC79 reversed the effects of diosmetin.

Our observations are consistent with a growing body of literature highlighting the therapeutic potential of macrophage-targeted strategies in OA. For instance, mesenchymal stem cell-derived extracellular vesicles [4], natural compounds such as kongensin A [5] and songorine [7], platelet-rich plasma [8], and even surgical interventions like high tibial osteotomy [9] have been shown to restore M1/M2 balance and ameliorate OA progression. Notably, kongensin A also targets the PI3K/Akt pathway to modulate macrophage polarization [5], suggesting that this signaling node may represent a common mechanistic target for diverse therapeutic agents.

Diosmetin offers several distinct advantages, including oral bioavailability, a dietary origin, and a favorable safety profile. Its capacity to modulate the upstream inflammatory environment could potentially complement existing cytokine-targeted biologics. However, several critical questions remain to be addressed. First, the precise molecular interaction between diosmetin and components of the PI3K/Akt pathway has yet to be elucidated. Second, given its previously reported role in subchondral bone remodeling [10]. further investigation using lineage-specific knockout models is warranted to determine whether

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diosmetin exerts dual effects on macrophages and osteoclasts. Third, the translational relevance of our findings depends on validating cytokine modulation in human synovial fluid and exploring patient-specific factors—such as metabolic status or obesity—that may influence macrophage behavior and therapeutic response [11].

In conclusion, our study identifies PI3K/Akt-mediated macrophage reprogramming as a novel mechanism underlying the chondroprotective effects of diosmetin in OA. This work not only contributes to the expanding field of immunomodulation in degenerative joint diseases but also provides a strong rationale for the further development of diosmetin as a disease-modifying agent for osteoarthritis.

## Conflicts of Interest

The authors declare no conflict of interest.

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