# Synergistic Strategies for OA Management: Unveiling Feprazone's Multifaceted Anti-Inflammatory Mechanisms Enhanced by Vitamin D

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## ABSTRACT

**This study illuminates the powerful anti-inflammatory prowess of Feprazone (FEP), an NSAID, in tackling the debilitating effects of osteoarthritis (OA). Leveraging a cutting-edge, in-house 3D chondrocyte model sourced from BMSCs, we reveal FEP's capacity to suppress key inflammatory pathways—specifically SOX-4/ADAMTS-5 and PAR-2 →TNF-a-induced MCP-1 & aggrecan loss. But that's just the tip of the iceberg. Our study takes an unprecedented turn by unveiling FEP's synergistic potency when combined with Vitamin D. This dynamic duo not only downregulates PAR-2—a central player in inflammation—but also significantly inhibits a spectrum of inflammatory markers, from IL-1beta to IL-8. Our findings herald a paradigm shift in OA management, offering a compelling strategy that may revolutionize both pharmacological interventions and clinical practice.**

## BACKGROUND

- OA is a prominent health issue in the Middle East, exacerbated by Western lifestyles, leading to increased obesity and related problems.
- OA hampers work, particularly in physically demanding jobs, due to pain and stiffness.
- Feprazone, an NSAID for OA treatment, inhibits both COX-1 and COX-2.
- Feprazone's impact on other inflammatory pathways remains unclear.

## OBJECTIVES

- Assess Feprazone's efficacy in reducing PAR-2 mediated inflammation in our 3D OA model.
- Evaluate biochemical synergism between Feprazone and Vitamin D in anti-inflammatory action.

## METHODS

- Utilize cell culture techniques to establish a 3D chondrocyte model from BMSCs for evaluating the anti-inflammatory mechanisms of Feprazone and its synergistic effects with Vitamin D.
- Conduct ELISA, Western Blot, and Densitometric analysis to quantitatively assess Feprazone's impact on key inflammatory markers, including PAR-2, TNF-A, IL-1B, IL-6, IL-8, and the SOX-4/ADAMTS-5 pathway.
- Investigate pharmacological synergism between FEP and VD.

## RESULTS

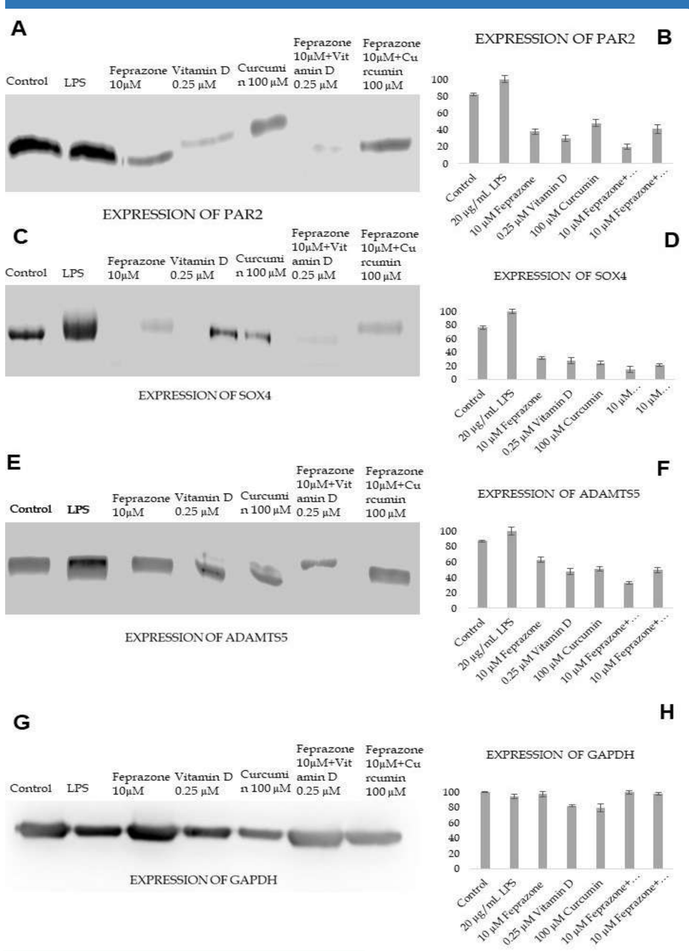
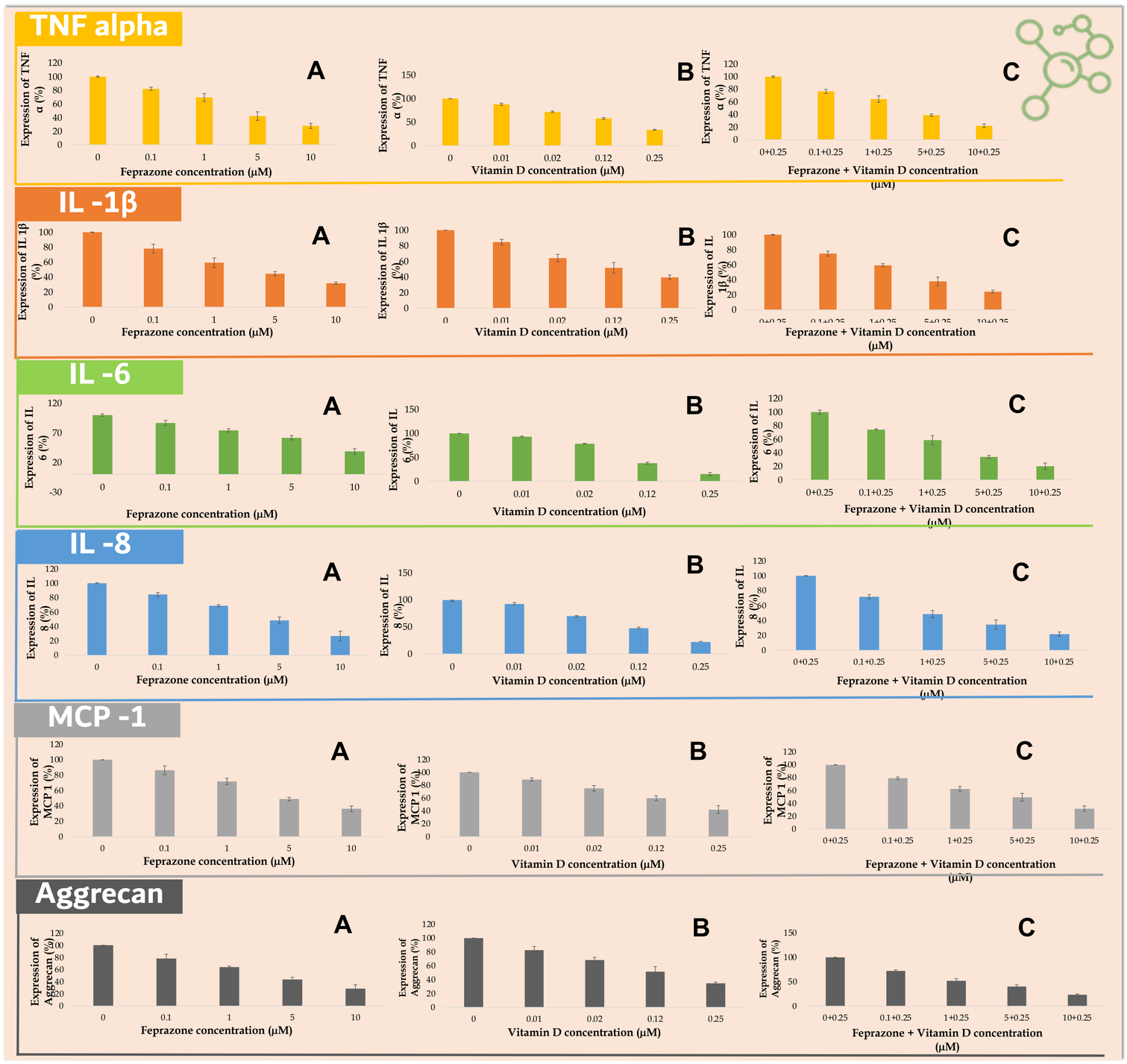


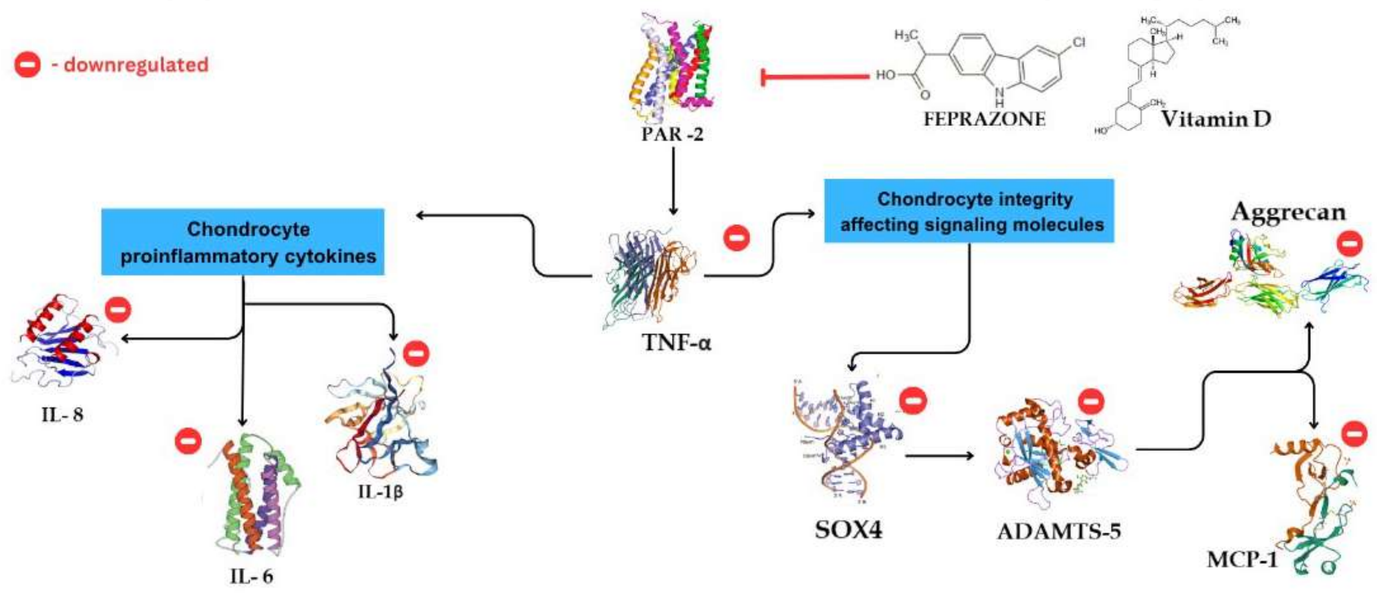

Figure 1. A & B: illustrate the down-regulatory effect of FEP on PAR-2 expression and its synergistic augmentation when combined with VD. In these panels, Curcumin serves as a positive control for PAR-2 downregulation but does not show synergistic behavior with FEP.
C-F: a similar pattern is observed for the downregulation of SOX4 & ADAMTS-5 by FEP in the presence and absence of VD.
G&H: house keeping gene (GAPDH) expression remains unaltered by FEP & VD indicating no effect on cell viability.




Figures A and B demonstrate that both FEP and VD reduce TNF-α expression. This reduction leads to improved levels of other pro-inflammatory cytokines (IL-6, IL-8, and IL-1β) and protective factors for chondrocytes (MCP-1 and aggrecan). Interestingly, panel C the anti-inflammatory activity of 0.25 µM VD serves as the baseline metric, against which the enhanced activity of FEP is measured, thereby illustrating the observed synergism.

## RESULTS SUMMARY

As evidenced through our study, FEP orchestrates a sequential downregulation of PAR-2 expression. This biochemical cascade subsequently attenuates TNF-α levels, culminating in the downregulation of proinflammatory cytokines and other molecular factors deleterious to chondrocyte integrity.




## CONCLUSION

**Our research marks a seismic shift in OA management. Feprazone alone inhibits key inflammatory pathways; combined with Vitamin D, it becomes a game-changing anti-inflammatory powerhouse. This dual approach promises to revolutionize treatment protocols and dramatically improve patient outcomes.**

**Refrences:**

1. Patnaik R, **Jannati S**, Sivani BM, Rizzo M, Naidoo N, Banerjee Y. **Efficient Generation of Chondrocytes From Bone Marrow-Derived Mesenchymal Stem Cells in a 3D Culture System: Protocol for a Practical Model for Assessing Anti-Inflammatory Therapies**. *JMIR Res Protoc*. 2023;12:e42964. Published 2023 Jul 28. doi:10.2196/42964
2. Patnaik, R., Riaz, S., Sivani, B. M., Faisal, S., Naidoo, N., Rizzo, M., & Banerjee, Y. (2023, August). Evaluating the potential of Vitamin D and curcumin to alleviate inflammation and mitigate the progression of osteoarthritis through their effects on human chondrocytes: A proof-of-concept investigation. PLoS One, Accepted.
3. Patnaik, R., **Jannati, S.**, **Chaudhary, E.**, **Nandkishore, S.**, **Amrou, A.**, Naidoo, N., & Banerjee, Y. **Synergistic Anti-Inflammatory Effects of Feprazone and Vitamin D in a 3D Chondrocyte Model: Targeting PAR-2 and Key Inflammatory Pathways for Osteoarthritis Management.** (Under review in Journal of Biological Chemistry) ***( *Results obtained from this study)***

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