Curr Top Med Chem. 2025;25(21):2513-2532. doi: 10.2174/0115680266387622250519052501.

7-Hydroxyflavone Mitigates Osteoporosis *Via* Key Signaling Pathways in a Dexamethasone-induced Rat Model

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PMID: 40415321 DOI: 10.2174/0115680266387622250519052501

Abstract

Background: Osteoporosis is a deteriorating skeletal bone disorder that affects in a silent, asymptomatic way. On-demand for new therapeutic strategies, natural products have gained attention as a significant alternative for treating osteoporosis. 7-Hydroxyflavone (7HF) is one of the well-known natural flavones for its anti-inflammatory, anti-oxidant, anti-diabetic, and neuroprotective, which was investigated at the molecular level for restoring bone homeostasis against dexamethasone-induced osteoporosis *in vivo* with a focus on modulation of oxidative stress (caspase-3), GATA-3, and NF-kB signaling along with in silico ADMET analysis.

Methods: Adult male rats were divided into four groups, containing six in each group. I- Control, II- Dexamethasone (Dexa)-treated disease control, III & IV - 7HF treated group (50, 100mg/kg). Animals in all groups, except the control, were injected with dexamethasone sodium phosphate at the dose level of 7mg/kg, intramuscularly, once a week for five weeks. The third and fourth group animals received 7HF-1 and 7HF-2 as a fine suspension with 2% carboxy methyl cellulose at a dose of 50 and 100mg/kg, respectively, by oral route once daily, starting from the second week of dexamethasone treatment. At the end of the 5th week, blood was collected from the femoral vein after anaesthesia, and the femur bones were dissected. Histopathology, immunohistochemistry of bone, biochemical serum analysis for ALP, TRAP 5b, RANKL, OPG, antioxidants and cytokines, as well as protein expression for RunX2, Bcl2 and Bax were performed. In addition, an analysis of absorption, distribution, metabolism, excretion, and toxicity (ADMET) was conducted for 7HF.

Results: Immunohistochemistry of GATA-3, NF-kB, and caspase-3 on femur bone sections evidenced the suppression of dexamethasone-induced osteoporosis by 7HF. It was found that 7HF lowered the serum levels of cytokines, ALP, TRAP 5b, and RANKL. 7HF elevated the serum level of antioxidants and OPG. In addition, the protein expression of RunX2, and anti-apoptotic Bcl2 was elevated, and the level of pro-apoptotic Bax in rat femur bone tissues was reduced through the use of 7HF. The aforementioned effects of 7HF were more prominent at the dose of 100mg/kg ($p<0.001$). 7HF exhibited good solubility and efficient absorption in the human intestine, though it showed limited permeability in MDCK cells. It demonstrated positive BBB permeability and Caco- 2 permeability values. 7HF interacted with P-glycoprotein, had an optimal VD, high PPB, and was a substrate and inhibitor of CYP450 enzymes. It functioned effectively as a hERG blocker without inducing human hepatotoxicity. Comprehensive toxicity assessments highlight 7HF as a more suitable option for drug development.

Conclusion: The study data confirmed that concurrent treatment of 7HF showed evident effects in the protection against dexamethasone-induced osteoporosis through the modulation of the GATA-3/Caspase-3/NF-KB pathway. Collectively, the ADMET analysis suggests that 7HF possesses promising pharmacokinetic and toxicological attributes, making it a viable candidate for drug development.

Keywords: 7-Hydroxyflavone; ADMET analysis.; Caspase-3; GATA-3; NF-kB; dexamethasone; osteoporosis.

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