Decoding the Anti-IBD Potential of Natural Phenolic Sesamol Through Integrative Network Pharmacology and Docking

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Abstract

Purpose: Inflammatory Bowel Disease (IBD) is a chronic inflammatory disorder characterized by impaired intestinal barrier function, immune dysregulation, dysbiosis, and oxidative stress. The JAK–STAT signaling pathway plays a central role in cytokine-driven inflammation in IBD. Natural antioxidants with anti-inflammatory properties have therefore gained attention as potential therapeutic agents. This study aimed to elucidate the molecular mechanisms underlying the anti-IBD potential of sesamol using an integrated computational and experimental approach.

Methods: Sesamol-associated targets were identified through network pharmacology and protein–protein interaction analyses, followed by Gene Ontology and KEGG pathway enrichment. Molecular docking, molecular dynamics simulations, and MM-GBSA binding free energy calculations (Schrödinger V14.1.38) were employed to evaluate interactions with Janus kinases. Therapeutic relevance was validated in a dextran sulfate sodium (DSS)-induced murine colitis model.

Results: Sixty-three overlapping therapeutic targets were identified, with JAK1 and JAK2 emerging as key signaling nodes. Sesamol demonstrated strong binding affinity toward both kinases, forming a more stable complex with JAK1, as indicated by lower RMSD/RMSF values and favorable MM-GBSA energies. In vivo, elevated colonic JAK1 expression in DSS-induced colitis was significantly normalized by sesamol treatment.

Conclusion: Sesamol mitigates intestinal inflammation by modulating the JAK–STAT pathway, highlighting its promise as a multi-target natural therapeutic candidate for IBD.

Index Terms

Inflammatory Bowel Disease, Sesamol, Network Pharmacology, Janus Kinase 1, Janus Kinase 2, Molecular Docking, Molecular Dynamics, Dextran Sulfate Sodium