Krishnendu P R[1], Subin Mary Zachariah[1],
Krishna Das Madhu[2]

[1]Department of Pharmaceutical Chemistry, Amrita School of Pharmacy, Amrita Viswa Vidyapeetham, AIMS Health Sciences Campus, AIMS Ponekkara P.O., Kochi, Kerala-682041, India

[2]Department of Pharmacology, Amrita School of Pharmacy, Amrita Viswa Vidyapeetham, AIMS Health Sciences Campus, AIMS Ponekkara P.O., Kochi, Kerala-682041, India

Molecular mechanism of sesamol in inflammatory bowel disease: Integrative computational, microbiome, and biological evaluation targeting jak1 pathway

ABSTRACT

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder driven by impaired intestinal barrier function, gut dysbiosis, immune dysregulation, and oxidative stress. The JAK-STAT signalling pathway plays a central role in promoting pro-inflammatory cytokine responses in IBD. This study aimed to comprehensively elucidate the therapeutic potential of sesamol, a natural lignan with potent antioxidant and anti-inflammatory properties, through an integrative computational, microbiological, and biological approach. Potential sesamol-associated targets were identified using network pharmacology and protein-protein interaction analysis. Gene Ontology and KEGG pathway enrichment analyses highlighted the significance of JAK-STAT signalling. Molecular docking, molecular dynamics simulations, and MM-GBSA binding free energy calculations (Schrödinger V14.1.38) demonstrated that sesamol exhibits strong binding affinity towards JAK1, forming a highly stable complex compared to JAK2. In vivo validation was performed using the dextran sulfate sodium (DSS)-induced micex colitis model. Sesamol treatment significantly ameliorated clinical symptoms, reduced inflammatory cytokine levels, normalized elevated JAK1 expression in colonic tissue, and restored intestinal barrier integrity. Additionally, 16S rRNA sequencing revealed that sesamol effectively modulated the gut microbiome by increasing beneficial genera such as Lactobacillus and Bifidobacterium, decreasing pathogenic taxa, and improving microbial diversity, thereby reversing dysbiosis. These findings collectively demonstrate that sesamol exerts multi-target protective effects in IBD by inhibiting JAK-STAT signalling, reducing inflammation and oxidative stress, restoring gut barrier function, and positively modulating the intestinal microbiome. Sesamol emerges as a promising natural multi-target candidate for IBD management.

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BIOGRAPHY

Krishnendu P R is a Research Scholar in the Department of Pharmaceutical Chemistry at Amrita School of Pharmacy, Amrita Viswa Vidyapeetham, Kochi. Her research interests include medicinal chemistry, natural compounds, prodrug design, and computational drug discovery. Currently, she is focused on the computational and experimental evaluation of natural compounds for the management of inflammatory bowel disease, with emphasis on JAK-STAT signalling and gut microbiome modulation. She has expertise in network pharmacology, molecular modelling, and in vivo disease models.