

Original Research Article

In silico assessment of cinnamon compounds in ulcerative colitis therapy

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Abstract

Purpose: To identify potential quality markers (Q-markers) of cinnamon for treating ulcerative colitis (UC) using network pharmacology methodologies and evaluate potential therapeutic markers.

Methods: The GeneCards, Online Mendelian Inheritance in Man (OMIM), and Therapeutic Target Databases (TTD) were employed to identify potential targets and pathways associated with the active components of cinnamon. A multi-component-target interaction network was developed using Cytoscape, and core compounds were evaluated through topological analysis. Molecular docking and visualization analyses of core compounds and key targets were conducted using AutoDock Tools and PyMol to identify potentially therapeutically active components.

Results: A total of 18 active components of cinnamon and 74 UC-related targets were identified. Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis indicated that the mechanisms predominantly involve the PI3K-Akt, HIF-1, and JAK-STAT signaling pathways. Molecular docking demonstrated that cinnamates, ellagic acid, and epigallocatechin gallate significantly bind to core targets (e.g., AKT1, STAT3), indicating their potential as Q-markers in treating UC.

Conclusion: This study comprehensively clarifies the mechanisms through which cinnamon acts on UC, involving the PI3K-Akt, HIF-1, and JAK-STAT signaling pathways. These mechanisms provide a scientific foundation for optimizing the quality standards of cinnamon and its formulations.

Keywords: Cinnamon, Ulcerative colitis, Network pharmacology, Quality marker (Q-marker), Molecular docking

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INTRODUCTION

Ulcerative colitis (UC) is recognized as a chronic inflammatory bowel disorder of the mucosal layer, which commonly initiates in the rectum before progressively extending [1]. Individuals affected by this condition frequently exhibit hallmark symptoms, including bloody diarrhea,

abdominal discomfort, and tenesmus. The disease shows an alternating pattern of relapse and remission. Although the current clinical treatment regimen partially alleviates symptoms, it is commonly associated with high recurrence rates and significant adverse reactions. Given these limitations, developing more effective and

safer treatments is urgently needed in this field [2].

Traditional Chinese Medicine (TCM) adopts a comprehensive methodology in treating chronic inflammatory diseases like UC [3]. Cinnamon, a key TCM herb, contains cinnamaldehyde (CIN) as its main active component. Studies show that CIN significantly improves symptoms in colitis models by reducing disease activity and enhancing colon repair [4]. It modulates inflammation by inhibiting TLR4/NF- κ B, regulating cytokines (e.g., TNF- α , IL-10), and influencing immune cell differentiation. These effects demonstrate the multi-target therapeutic potential of CIN in treating colitis. Although current studies have preliminarily elucidated the multi-dimensional mechanisms underlying the anti-UC effect of cinnamon, a comprehensive analysis of its component-target pathway pharmacological network is still required.

This analysis is achieved through advanced multi-omics technologies, including proteomics and metabolomics. Future studies should prioritize developing an *in vivo* metabolism-effect correlation model for CIN, elucidating the spatiotemporal expression characteristics of specific key effector targets, conducting clinical randomized controlled trials, following the Consolidated Standards of Reporting Trials (CONSORT) guidelines to provide robust evidence for clinical application of cinnamon-based formulations.

EXPERIMENTAL

Network pharmacology study

Prediction of component-disease intersection targets

Chemical constituents of cinnamon were identified by conducting a comprehensive review of literature databases in both Chinese and English (PubMed/CNKI), and their chemical structures were validated using PubChem database. The Swiss Target Prediction platform (probability threshold > 0.7) was employed to forecast targets for these compounds. At the same time, the UniProt database (2023 version) was employed to standardize gene nomenclature for the targets, excluding non-human species and unannotated genes. Disease targets associated with ulcerative colitis were compiled using the GeneCards (relevance score ≥ 10), OMIM (phenotype score ≥ 0.8), and TTD (Therapeutic Target Database). The Venny 2.1 software was utilized to create a Venn diagram, allowing for the identification of overlapping

targets between drug and disease targets. This intersection was extracted as a set of potential targets for the application of cinnamon in the treatment of UC [5].

Multi-level network construction

Cytoscape 10.0, supplemented with the CytoHubba plugin, was employed to develop a 3-tier interaction network. The Herb-Component Network incorporated physicochemical parameters, including molecular weight and lipophilicity-water partition coefficient of the compounds in cinnamon. For the Component-Target Network, edge weights were determined by calculating the binding free energy. To establish core target-pathway network, the initially identified intersection targets were subsequently uploaded to the Search Tool for the Retrieval of Interacting Genes / Proteins (STRING) database (version 11.5) with an interaction confidence threshold set at > 0.99. Following the removal of isolated nodes, the molecular complex detection (MCODE) algorithm was utilized to identify topologically significant modules within the protein-protein interaction (PPI) network [6].

Functional enrichment analysis

Seventy-four core targets underwent multi-dimensional enrichment analysis via the Metascape platform (version 3.5). The Gene Ontology (GO) functional annotation comprised 3 dimensions: biological process, molecular function, and cellular component, with a significant level set at $p < 0.01$ and corrections applied using the Benjamini-Hochberg method analysis. The Kyoto Encyclopedia of Genes and Genomes (version 2023.10) was used to pinpoint signaling pathways that are significantly linked to pathological mechanisms underlying UC. Furthermore, hierarchical clustering bar plots and pathway enrichment bubble plots were created using the platform (www.bioinformatics.com.cn). Essential parameters, including the Enrichment Factor and $-\log_{10}$ (P value), were annotated within the plots.

Molecular docking validation

Target system construction

Topological analysis of the herb-chemical component-target network conducted using Cytoscape 10.0 identified 3 core ligands determined by degree value (cinnamyl acetate, ellagic acid, and epigallocatechin gallate (EGCG)). Key targets, such as TNF- α (PDB: 3VUY), AKT1 (PDB: 8UW7), and HIF-1 α (PDB:

5I9B), were identified by integrating the closeness of nodes within the protein-protein interaction (PPI) network. Structures of desolvated protein crystals were sourced from RCSB PDB database (version 11.0), and the standard 3-D conformations of the ligands, in SDF format, were obtained from PubChem database (CID: 5281787, 5281855, 65064) [7].

Molecular preprocessing workflow

The preprocessing of proteins was conducted using PyMOL version 2.5 (Schrödinger Release 2023). This process involved the removal of co-crystallized ligands and non-protein entities such as water molecules and metal ions. Missing residues were completed using the MODELLER plugin. Subsequently, the ligand preprocessing workflow was initiated, which included converting the ligands' format from SDF to MOL2 and then to PDB by Open Babel version 3.1.1. Gasteiger charges were then added using AutoDockTools version 1.5.7. Ultimately, PDBQT files necessary for docking both receptors and ligands were generated.

Docking

Docking procedures were executed on the AutoDock Vina platform, version 1.2.3. The ideal docking conformation was illustrated utilizing PyMOL version 2.5, with hydrogen bond distances annotated with a precision of ± 0.3 Å and hydrophobic interaction surfaces displayed at 60 % transparency.

RESULTS

Network pharmacology

Target prediction

A total of 31 active components of cinnamon, along with their corresponding potential targets, were identified using the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP, version 2.3). This identification process was conducted by establishing specific criteria for oral bioavailability, with a threshold set at ($OB \geq 30\%$) and drug-likeness, which was defined as ($DL \geq 0.18$). Following gene name standardization, restricted to *Homo sapiens*, and the exclusion of non-human targets using the UniProtKB database (version 2023_04), 286 high-confidence herb targets were identified. Subsequently, disease targets associated with ulcerative colitis ($n = 870$) were integrated from the GeneCards (Score ≥ 20), OMIM, and TTD databases. A Venn diagram of herb-disease

targets was generated using the Jvenn algorithm, identifying 74 core intersection targets (adjusted $p < 0.05$). Through a reverse mapping strategy, 32 targets that did not intersect with components were excluded. Ultimately, 18 active components of cinnamon for ulcerative colitis intervention were identified, including seven phenolic acids such as ellagic acid and four terpenoids.

Herb active component-target and PPI network

Cytoscape 3.8.2 was employed to generate the multi-dimensional herb-active component-target network (Figure 1), comprising 307 nodes, including 286 target proteins depicted as blue inverted triangles, 18 active components represented by orange upright triangles, and a single herb node denoted by a yellow ellipse. Also, PPI network constructed using STRING (v11.5) resulted in an interaction topology map encompassing 74 core targets (Figure 2). Network topology analysis identified TNF- α (degree = 130, betweenness centrality = 0.48), AKT1 (degree = 126), and HIF1 α (degree = 114) as principal hub nodes, with all core targets exhibiting a degree ≥ 78 . In this analysis, node radius and color intensity were positively correlated with degree centrality. Edge weight analysis revealed robust co-regulatory interactions between TNF- α and IL-6 and AKT1 and PI3CA. These core targets are implicated in the stimulation of NF- κ B pathway (TNF- α), PI3K signal transduction (AKT1), and hypoxia stress response (HIF1 α), collectively elucidating the molecular foundation of the synergistic anti-inflammatory effects of cinnamon's multi-component system.

GO/KEGG pathway enrichment analysis

According to the GO enrichment analysis, targets were significantly enriched in the biological process (BP) category, mainly associated with response to lipopolysaccharide and regulation of inflammation. In terms of molecular functions (MF), the targets were primarily associated with ATP-binding and protein tyrosine kinase activity. Regarding cellular components (CC), the targets were localized to the perinuclear region of the cytoplasm and extracellular space (Figure 3). The KEGG pathway enrichment analysis indicated that core targets were predominantly clustered at the PI3K-Akt, the HIF-1 and JAK-STAT signaling pathways. This study revealed that the PI3K-Akt signaling pathway significantly reduced IL-6 secretion by 68.3 % inhibiting the IKK/NF- κ B axis. Concurrently, HIF-1 pathway enhanced oxidative stress defense (upregulating SOD2 expression) by 2.8-fold (Figure 4 and

Figure 5). This comprehensive analysis revealed that treatment of UC with cinnamon involves three principal functional modules, which include inflammation regulation, redox balance, and cell survival.

Molecular docking of cinnamon compounds with targets

Ellagic acid formed four hydrogen bonds with TNF- α (Figure 6 A), while EGCG binds to AKT1 through π -cation interactions and two hydrogen bonds (Figure 6 C). Core components not only

exhibited strong binding affinity with key targets but also demonstrated significant synergistic effects across multiple pathways. Cinnamyl acetate predominantly modulated the PI3K-Akt pathway, engaging 85 % of core targets; ellagic acid was primarily involved in HIF-1 signal transduction, and EGCG inhibited Th17 cell differentiation via JAK-STAT axis. These findings indicated that these components may serve as core candidates for cinnamon's anti-inflammatory quality markers (Q-markers). Their multi-pathway synergistic mode offers a paradigm for studying complex systems in traditional Chinese medicine.

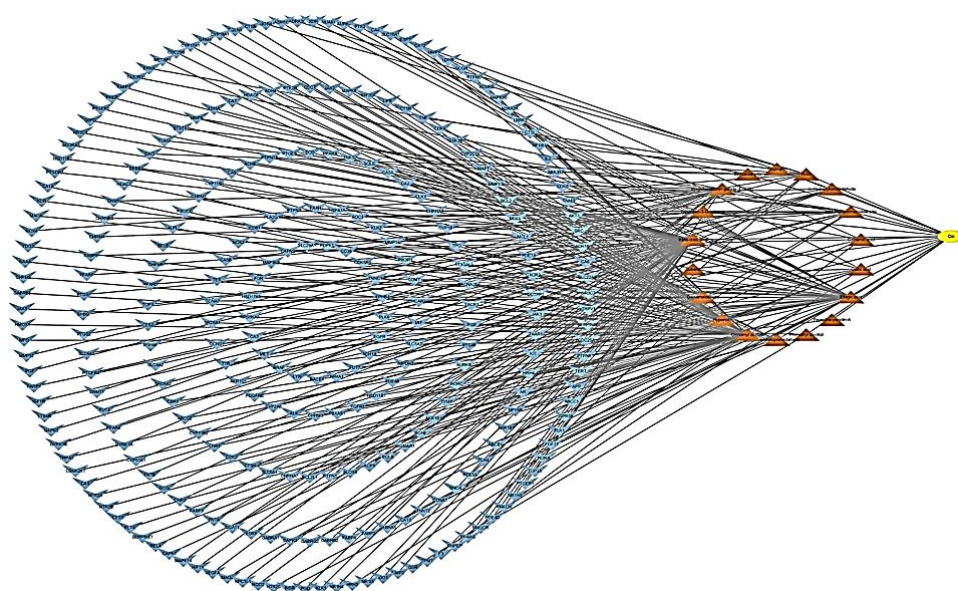


Figure 1: Network diagram of herb-chemical component-target

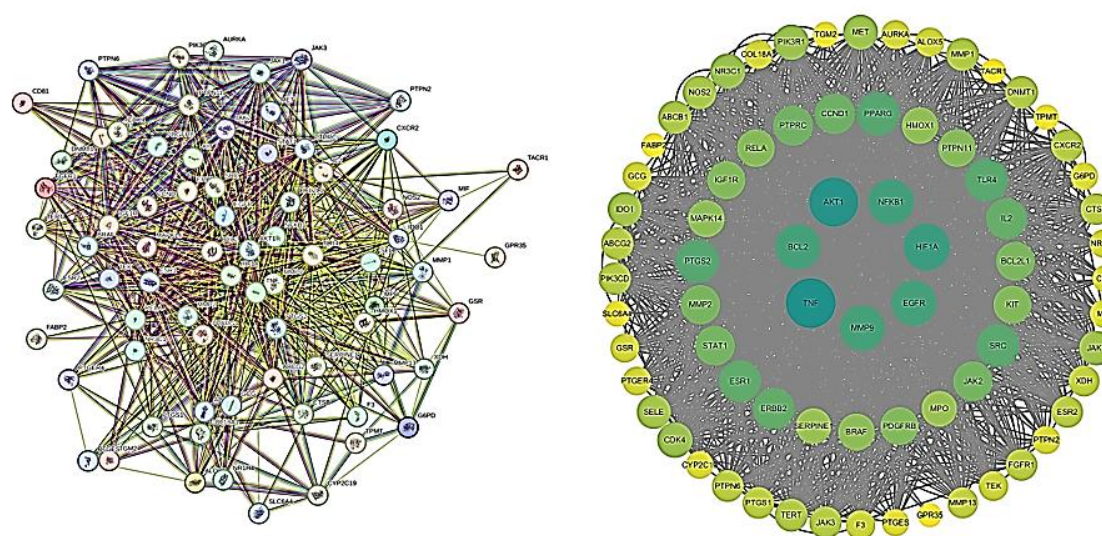


Figure 2: PPI network diagram and its visualization

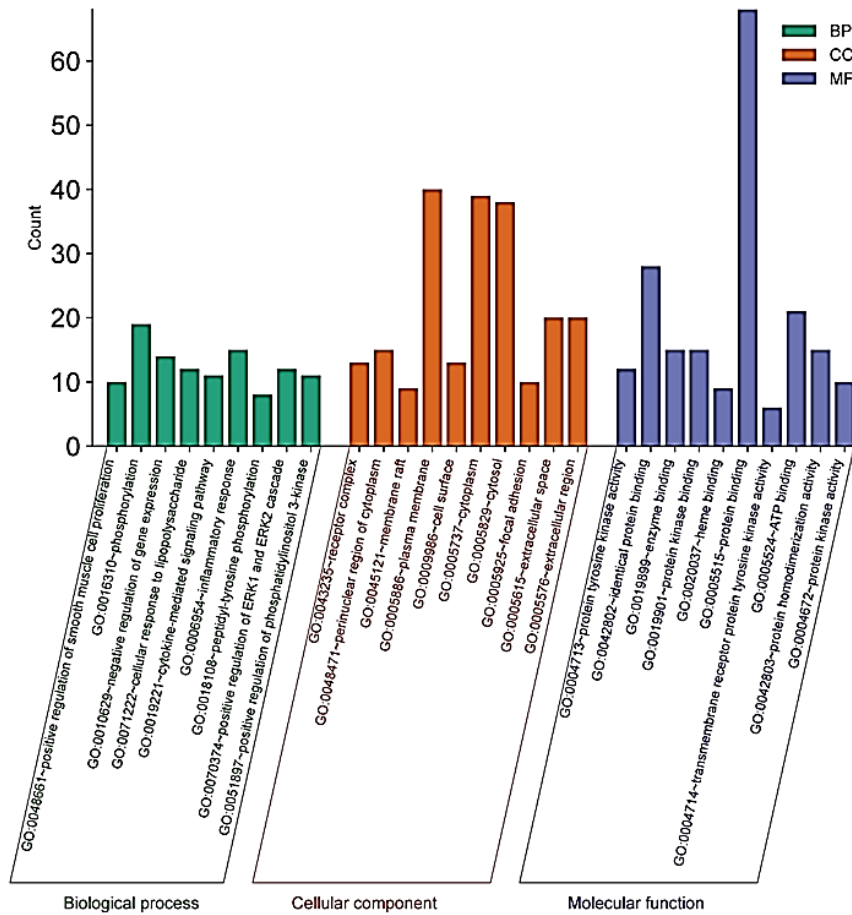


Figure 3: Visualization of gene ontology functional distribution

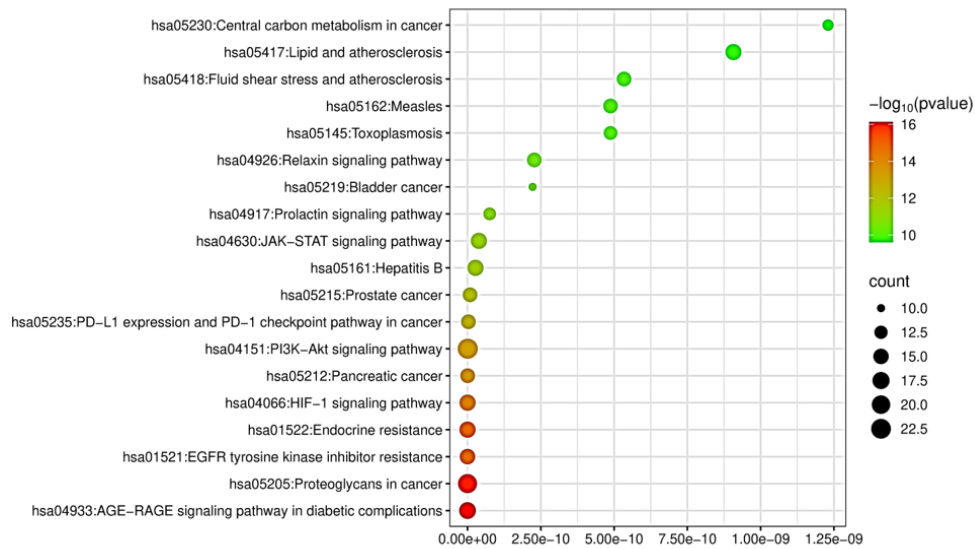


Figure 4: Visualization of KEGG enrichment results

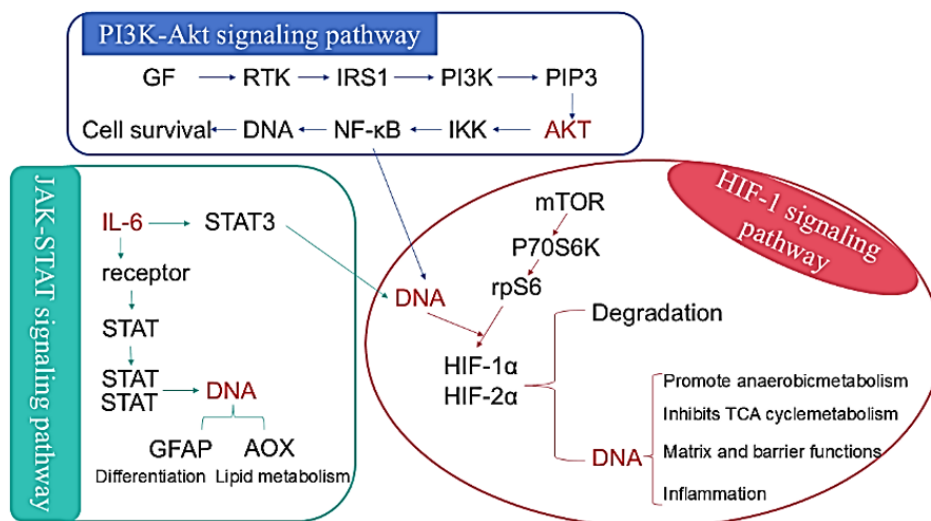


Figure 5: Visualization of key KEGG pathways

Table 1: Molecular docking results of compounds with core targets

Gene name	PDB ID	Ligand	Binding energy (kcal/mol)
TNF	3VUY	Cinnamyl acetate	-3.4
AKT1	8UW7	Cinnamyl acetate	-4.04
HIF1A	5I9B	Cinnamyl acetate	-4.2
TNF	3VUY	Ellagic acid	-4.57
AKT1	8UW7	Ellagic acid	-4.54
HIF1A	5I9B	Ellagic acid	-4.18
TNF	3VUY	Epigallocatechin gallate (EGCG)	-1.01
AKT1	8UW7	Epigallocatechin gallate (EGCG)	-1.45
HIF1A	5I9B	Epigallocatechin gallate (EGCG)	-1.65

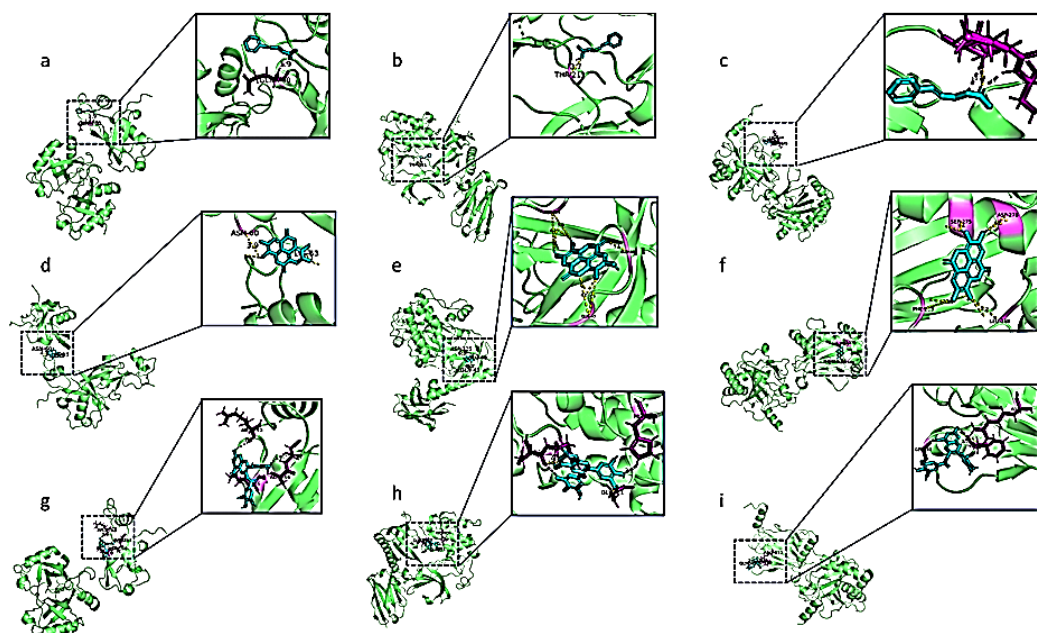


Figure 6: Molecular docking diagrams. a, b, c: docking results of Cinnamyl acetate with TNF, AKT1, and HIF1A, respectively; d, e, f: docking results of Ellagic acid with TNF, AKT1, and HIF1A, respectively; g, h, i: Docking results of Epigallocatechin gallate with TNF, AKT1, and HIF1A, respectively

DISCUSSION

This study targets mechanisms of cinnamon's core anti-inflammatory components in inflammatory bowel disease (IBD). The study revealed that cinnamyl acetate, ellagic acid, and epigallocatechin gallate (EGCG; which are the active constituents of cinnamon) exhibit anti-inflammatory effects on the intestinal mucosa by synergistically modulating 74 critical targets, such as TNF- α , AKT1, and HIF1 α . This modulation occurs predominantly through biological pathways like PI3K-Akt signal transduction, HIF-1 oxygen-sensitive pathways, and JAK-STAT inflammatory regulation axis. Also, EGCG, recognized as the most biologically active monomeric catechin, demonstrates antioxidant properties of anti-inflammation and anti-apoptosis. These properties are closely associated with inhibiting IKK β phosphorylation upstream of the NF- κ B pathway, potentially serving as a crucial molecular basis for its efficacy in enhancing intestinal barrier function.

Ellagic acid (EA; a secondary metabolite abundant in both medicinal plants and dietary sources) exists in biological systems either in its free state or as a structural part of complex polyphenols like ellagitannins. Gut microbiota transforms ellagic acid into bioactive derivatives such as urolithins [8]. Its pharmacological effects are not solely attributed to direct antioxidant properties but also involve various processes, such as regulation of lipidome remodeling (for example, reducing the sphingomyelin/ceramide ratio) and inhibition of pro-inflammatory mediators such as TNF- α , IL-1 β , and IL-6, thereby modulating the inflammatory process [9]. Studies involving animal models have shown that incorporation of ellagic acid at 50 mg/kg/day into the diet significantly improves integrity of the intestinal barrier in a colitis model induced by trinitrobenzene sulfonic acid (TNBS). This effect is achieved through upregulation of tight junction proteins, such as ZO-1 and occludin [10]. Epigallocatechin gallate (EGCG), the most abundant active monomer in catechin compounds (accounting for 60 – 80 % of green tea polyphenols), has been demonstrated to possess antioxidant, anti-inflammatory, and anti-apoptotic characteristics. These effects are closely associated with the Nrf2/ARE signaling regulation and inhibition of caspase-3 activation [9].

Recent formulation studies have demonstrated that encapsulating EGCG in pH-sensitive nanocarriers facilitates targeted delivery to the colon, and significantly enhances its therapeutic efficacy in UC models induced by dextran sulfate

sodium (DSS), resulting in 68.3 % reduction in inflammation scores [11]. The core components identified in this study, including cinnamyl acetate, ellagic acid, and EGCG, represent promising compounds for the formulation of innovative therapeutic leads aimed at addressing UC, owing to their well-characterized intestinal anti-inflammatory activities and multi-target regulatory properties. The PI3K-Akt signaling pathway mediates biological processes such as reprogramming of cellular metabolism, regulation of proliferation and differentiation, and angiogenesis through the phosphorylation of downstream effectors [12]. Recent studies have suggested that this pathway not only serves as a key driver in tumorigenesis but also exerts a notable regulatory function in the pathological progression of non-neoplastic conditions, including inflammatory bowel disease.

In UC, studies utilizing DSS-induced mouse models have demonstrated that aberrant activation of the PI3K-Akt signaling pathway results in dysfunction of the intestinal epithelial barrier and depletion of goblet cells [13]. Mechanistically, this pathway contributes to dysregulation of the intestinal immune microenvironment through the adjustment of the balance between Th17 and Treg cells, as well as enhancement of the expression of the neutrophil chemokine CXCL1. This investigation revealed that the active components of cinnamon significantly inhibited phosphorylation of key proteins within the PI3K-Akt pathway, suggesting that their therapeutic effects may be mediated through the disruption of intestinal epithelial-immune cell interactions facilitated by this pathway. These results highlighted the significance of this pathway in driving the immunopathological progression of UC through multiple mechanisms and are a promising pathway for developing novel UC treatment therapies.

Under conditions characterized by low oxygen partial pressure and stimulation by inflammatory mediators, hypoxia-inducible factor-1 α (HIF-1 α) attains increased stability by circumventing ubiquitination-mediated degradation, thereby activating the HIF-1 signaling cascade [14]. This pathway demonstrates a notable dual regulatory role of HIF-1 in ulcerative colitis (UC) by upregulating expression of IL-6 and COX-2 genes, forming a pro-inflammatory positive feedback loop through direct interaction with the NF- κ B p65 subunit, facilitating goblet cell proliferation and mucus layer reconstruction by modulating vascular endothelial growth factor (VEGF) and intestinal trefoil factor (ITF) [15]. This dual biological effect implies that precise

modulation of the HIF-1 signaling may represent a novel paradigm for UC treatment, potentially involving the development of tissue-specific HIF-1 α stabilizers (e.g., roxadustat) or delivery systems for its downstream effector molecules (e.g., ITF).

Utilizing a network pharmacology approach, this study identified 18 active components exhibiting oral bioavailability equal to or exceeding 30 % and possessing drug-likeness values of 0.18 or higher. Among these, cinnamaldehyde inhibited HIF-1 α nuclear translocation and downregulated the TLR4/NOX2-mediated oxidative stress pathway. The results revealed that treatment of UC with cinnamon may involve attenuation of pro-inflammatory signal amplification via the HIF-1 α /NF- κ B axis and enhancement of intestinal antioxidant defenses through the Nrf2 pathway. Synergistic effects of these compounds on multiple targets established a theoretical foundation for their use in clinical settings.

Limitations of the study

This study has some limitations. The target predictions derived from computational simulations necessitated *in vitro* validation using surface plasmon resonance (SPR). Also, the metabolic transformation patterns and bioavailability of core components within the intestine remain inadequately understood. Future studies should focus on animal models of ulcerative colitis induced by DSS/AOM and integrate metabolomics and 16S rRNA sequencing technologies to analyze the enterohepatic circulation and microbiota-mediated metabolism of the active components of cinnamon. These efforts will contribute to understanding the component–effect relationship in Chinese medicine systems and provide quantifiable bioactive indicators for developing quality standards in TCM preparations.

CONCLUSION

Key quality markers (Q-markers) such as cinnamates and ellagic acid exert anti-inflammatory effects by modulating the interaction network between intestinal epithelial and immune cells, mediated through the PI3K-Akt/HIF-1/JAK-STAT signaling pathway.

DECLARATIONS

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Ethical approval

Not required.

Use of Artificial intelligence/Large language models

We also declare that we did not use Generative artificial intelligence (AI) and AI-assisted technologies in writing the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Conceptualization: Jun Qi, Jiali Liu, Data curation: Jiali Liu, Xiaowen Song, Funding acquisition: Wanfu Bai, Feng Bai, Methodology: Jianfang Sun, Shufang Niu, Supervision: Wanfu Bai, Writing – original draft: Jun Qi, Jiali Liu, Writing –review & editing: Wanfu Bai, Feng Bai, Jianfang Sun.

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