RESEARCH ARTICLE

Study on the active components and mechanism of *Cinnamon* in the treatment of dysmenorrhea based on network pharmacology

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Traditionally, cinnamon has been employed for its potential therapeutic effects for the treatment of dysmenorrhea. However, its active components and mechanisms are yet to be fully understood. Using network pharmacology and molecular docking techniques, this research pinpointed 37 active substances extracted from cinnamon including encompassing esters, terpenoids, aldehydes, and hydrocarbons, among which six principal compounds demonstrated strong affinities to bind to dysmenorrhea-related targets. Potential targets were screened using SwissADME and SwissTargetPrediction and overlapping genes with dysmenorrhea-associated pathways identified from Genecards. Protein-protein interaction (PPI) networks developed using STRING and Cytoscape focused on NF-κB1, AKT1, STAT3, PTGS2, and ESR1 as primary targets. Functional enrichment analysis (GO/KEGG) showed significant correlations with inflammatory and pain-related pathways including IL-17 and TNF signaling. Molecular docking simulations (Maestro, PyMOL, AutoDock Vina) revealed stable interactions among cinnamaldehyde and key targets, which were primarily mediated by hydrophobic effects, hydrogen bonds, and π-π stacking. These findings suggested that the anti-dysmenorrhea effects of cinnamon might involve multi-component, multi-target regulation of inflammatory and pain-related pathways, supporting further exploration on cinnamon as a candidate for phytotherapy-based drug development.

Keywords: *Cinnamon*; Dysmenorrhea; network pharmacology; molecular docking; cinnamaldehyde; anti-inflammatory mechanisms; traditional Chinese medicine; pain-related pathways.

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Introduction

Dysmenorrhea, characterized with cyclic cramping pain during menstruation, is one of the most prevalent gynecological disorders influencing women around the world. Epidemiological studies indicate that 45% to 95% of women suffer from this disease, while data from China shows that 60% to 70% of women of childbearing age are affected with more than 200 million cases nationwide [1]. Pain is frequently accompanied by systemic symptoms including fatigue and nausea, and in severe cases, significantly impairing quality of life and productivity and syncope [2]. Current management approaches mainly rely on hormonal contraceptives and non-steroidal anti-inflammatory drugs (NSAIDs). While effective for several patients, these conventional therapeutic approaches suffer from limitations including cardiovascular risks, gastrointestinal complications, and hormonal side effects, which restrict their long-term application [2]. In addition, a significant proportion of patients

present inadequate responses to existing treatments, highlighting the requirement for safer and more effective therapeutic alternatives.

Cinnamon (*Cinnamomum* spp.), a traditional medicinal herb, has presented great potential in pain management. Modern pharmacological research has revealed diverse bioactivities of cinnamon including significant analgesic and anti-inflammatory effects [3-5]. Cinnamaldehyde, the main active component of cinnamon, has been found to modulate pain perception through the regulation of TRPV1 channel and inhibition of COX-2 pathway [6-8]. Clinical evidence further supported its efficacy in alleviating pain, while its favorable safety profile suggested potential for long-term management [9, 10]. However, the systematic understanding of the multi-target mechanisms of cinnamon against dysmenorrhea remains largely unexplored.

Network pharmacology provided a powerful framework to decipher complex compound-target-pathway relationships in herbal medicine [11], while molecular docking enabled precise prediction of ligand-receptor interactions at molecular level [12]. This research applied an integrated approach by combining molecular docking and network pharmacology to systematically identify the active components of cinnamon against dysmenorrhea, explore the integrated mechanisms underlying its efficacy, and predict their therapeutic targets. The findings of this study would provide a comprehensive theoretical foundation to understand the anti-dysmenorrhea effects of cinnamon, supporting its potential for development as an evidence-based phytotherapeutic agent. In addition, this study demonstrated the value of systems biology approaches in bridging modern scientific validation with traditional medicine knowledge.

Materials and methods

Establishment of chemical databases

A comprehensive chemical database for cinnamon was developed by the integration of several data sources including primary mass spectrometry data for primary compound annotation from ChemSpider database (http://www.chemspider.com/), high-resolution tandem mass spectrometry (MS/MS) data against mzVault and mzCloud (https://www.mzcloud.org/) spectral libraries for precise fragment ion validation and structural confirmation, PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and relevant scientific literature for cross-verification. The curated database included essential chemical information such as common and International Union of Pure and Applied Chemistry (IUPAC) names, molecular formulas, relative molecular weights, molecular ion patterns $[M+H]^+$/$[M-H]^-$, 2D/3D structures, characteristic MS/MS fragmentation pathways, and Chemical Abstracts Service (CAS) registry numbers. To ensure analytical rigor, mass tolerances of precursor and fragment ions were set at ± 5 ppm and ± 10 ppm for ions, respectively. This integrated approach laid a reliable foundation for the subsequent identification of bioactive components.

Analysis of chemical components by gas chromatography-mass spectrometry (GC-MS)

The chemical analysis of cinnamon was performed using gas chromatography-mass spectrometry (GC-MS) to identify semi-volatile and volatile compounds. Briefly, 10 mg of cinnamon essential oil was dissolved in ethyl acetate and diluted with distilled water to a final concentration of 1 mg/mL in a 10 mL volumetric flask. Prior to injection, the solution was filtered through a 0.22 µm membrane. Chromatographic separation was conducted on an HP-5MS capillary column with dimensions of 30 m × 0.25 mm × 0.25 µm. High-purity helium was used as the carrier gas at 1.0 mL/min constant flow rate. The temperature of the injection port was set at 250°C with a split ratio of 20:1 and injection volume of 1 µL. Oven temperature was programmed as 70°C for 2 minutes, ramped to 230°C at 20°C/min for 1 minute, then increased

to 250°C at 10°C/min. Mass spectrometric detection was performed with an electron ionization (EI) source operated at 70 eV. The temperatures of the ion source and quadrupole were set at 230°C and 150°C, respectively. Solvent delay was 3 minutes and data was collected in full scan mode over the mass range of 30 - 650 m/z. Compounds were identified by comparing the mass spectra of eluted peaks with the reference spectra in NIST14.L library. Area normalization method was applied to obtain the relative content of each component.

Screening of bioactive components in cinnamon

The bioactive components of cinnamon were screened using SwissADME database (https://www.swissadme.ch/) with GI absorption being set as "High" and at least two "Yes" results among Lipinski's, Ghose's, Veber's, Egan's, and Muegge's drug likeness rules, supplemented by relevant literature review to finalize the validated constituents [14, 15].

Screening of key anti-dysmenorrhea targets in cinnamon

SwissTargetPrediction (http://www.swisstargetprediction.ch/) and SuperPred (https://prediction.charite.de/) databases were employed to predict the potential protein targets of the bioactive components of cinnamon with the species limited to *Homo sapiens*. Redundant entries were removed to obtain a unique set of compound-related targets. Meanwhile, targets associated with dysmenorrhea were retrieved from GeneCards (https://www.genecards.org/) and DrugBank (https://go.drugbank.com/) databases using the search keyword of "dysmenorrhea". The retrieved disease targets were consolidated and deduplicated to generate a comprehensive dysmenorrhea target dataset. Venny online platform (https://bioinfogp.cnb.csic.es/tools/venny/) was applied to identify and visualize the intersection between compound-predicted and disease-associated targets. These overlapping targets were considered as the key targets mediating the therapeutic effects of cinnamon against dysmenorrhea and were applied for subsequent analysis.

Network construction of cinnamon bioactive components-disease targets

Active cinnamon elements and common targets were integrated into Cytoscape (version 3.7.2) (https://cytoscape.org/) to develop a network linking cinnamon active components and dysmenorrhea disease targets. The topological parameters of the developed network were evaluated using CytoNCA plugin (https://apps.cytoscape.org/apps/cytonca), where the degree value was crucial in pinpointing key active elements and important targets. This method evaluated the interactions between dysmenorrhea-associated targets and potential active component-related targets of cinnamon.

Construction of cinnamon bioactive components - core targets and core targets network

To construct a protein-protein interaction (PPI) network, the potential anti-dysmenorrhea targets of *Cinnamon* were uploaded to STRING web platform (https://string-db.org/). The organisms were limited to *Homo sapiens*, and a minimum interaction confidence score of > 0.4 was set. The developed PPI network was imported into Cytoscape (version 3.7.2) to perform topological analyses. Key core targets were identified based on their median values of degree, betweenness, and closeness centrality using CytoNCA plugin. The corresponding bioactive components of these core targets were then identified. Cytoscape was applied to visualize and construct both comprehensive "*Cinnamon* bioactive components - disease targets" and core targets network.

GO and KEGG pathway enrichment analyses

Prospective targets of cinnamon against dysmenorrhea were examined *via* network pharmacology techniques on Metascape platform, focusing on Gene Ontology (GO) functional annotation and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis at the significance level of $P < 0.05$). Bar charts were drawn to present the top 20 enriched terms in each GO category including cellular component (CC), biological process (BP),

and molecular function (MF), while bubble plots illustrated the top 20 KEGG pathways with color intensity denoting enrichment significance and bubble size indicating gene count *via* Microbioinformatics online platform. This analysis provided a theoretical foundation to elucidate the molecular mechanisms underlying the anti-dysmenorrhea effects of cinnamon.

Molecular docking between bioactive components and core targets

3D configurations of ESR1 and PTGS2 proteins were retrieved from protein data bank (PDB) (https://www.wwpdb.org/) and were processed using Maestro 12.8 software (https://www.schrodinger.com/platform/products/maestro/), encompassing processes of hydrogenation, dehydration (exceeding 5.00 Å), and reduction of energy consumption. The SDF format files of bioactive components were obtained from PubChem database, while those not available in PubChem were converted to SDF format using ChemDraw software (https://revvitysignals.com/products/research/chemdraw). Small bioactive component molecules were then imported into Maestro 12.8 for energy minimization and other preprocessing steps. The preprocessed proteins and small molecules were docked using Maestro 12.8, where higher absolute docking scores indicated more stable receptor-ligand interactions.

Results

Drug-disease common targets

Ultra-performance liquid chromatography (UPLC) with a quadrupole time-of-flight (Q-TOF) mass spectrometry (UPLC-Q-TOF-MS) analysis results were applied to screen 18 bioactive components using SwissADME database. A search in GeneCards database revealed 460 dysmenorrhea-related targets. The intersection between component and disease targets was identified with 137 shared targets. Specifically, 536 targets (53.8%) were unique to cinnamon components, 382 (38.4%) were disease-specific, and the 78 shared targets accounted for 7.8% of the total target pool. These 78 overlapping targets including key players of TNF, AKT1, and SRC were identified as the core group mediating the potential anti-dysmenorrhea effects of cinnamon and were selected for subsequent network analysis.

Construction of the drug active ingredients - core targets network

To generate a PPI network diagram, 78 crucial target genes were uploaded onto STRING platform. The developed network comprised 78 designated protein nodes, each containing 584 interaction edges, showing an average node degree of 15 and mean betweenness centrality of 0.557 (Figure 1). The topological examination of the developed PPI network resulted in 18 primary targets. The target networks were then constructed based on screening criteria (Figure 2). The most highly connected nodes of the PPI network included AKT1, STAT3, PPARG, PTGS2, ESR1, NFKB1, MMP9, BCL2， CASP3, and STAT3 (Table 1).

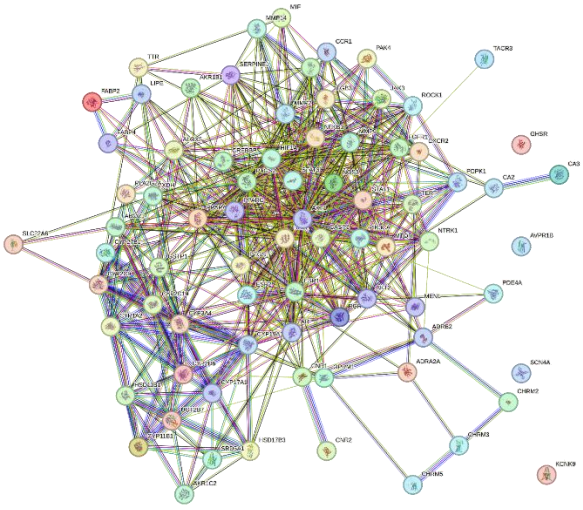

Figure 1. Protein-protein interaction (PPD) network diagram.

GO functional and KEGG pathway enrichment analyses

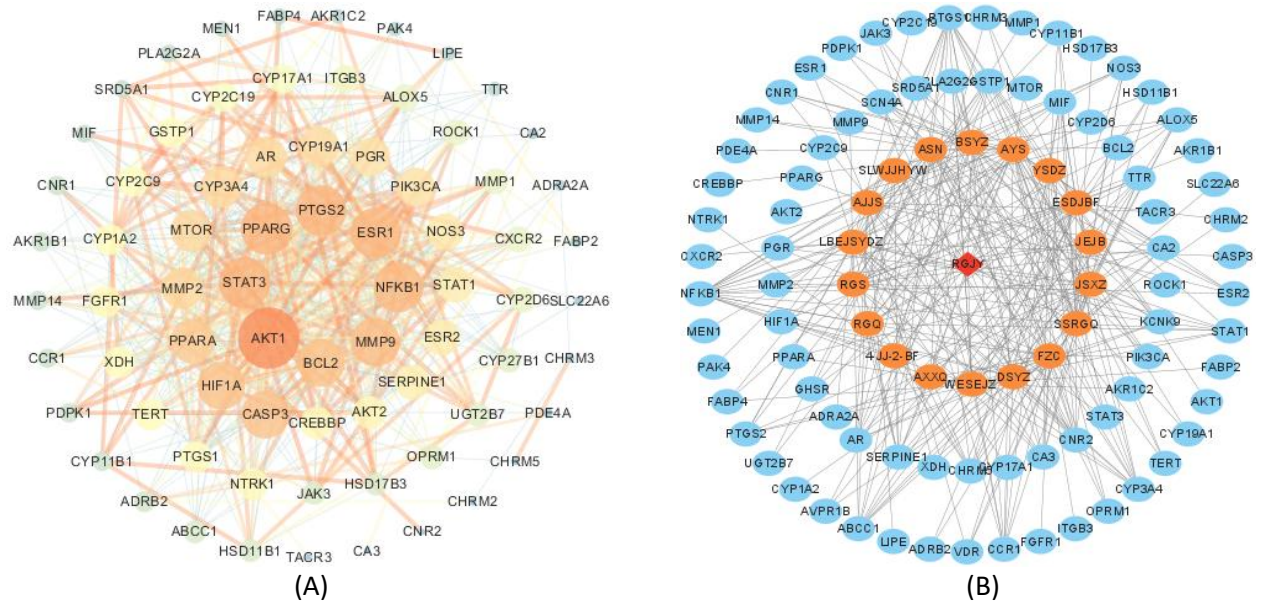

Figure 2. Network pharmacological analysis of cinnamon bioactive compounds and core targets. **A.** "Cinnamon-active ingredients-disease targets" network diagram. **B.** "Cinnamon-bioactive components-core targets" network.

Table 1. Core target information.

Target	Betweenness	Closeness	Degree
AKT1	658.1625859	0.009900990	47
STAT3	192.7606220	0.008849558	37
PPARG	377.1557646	0.008849558	37
PTGS2	262.2352787	0.008771930	36
ESR1	219.2217161	0.008771930	36
NFKB1	135.2737528	0.008474576	35
MMP9	256.9799661	0.008547009	34
BCL2	112.0631041	0.008547009	33
CASP3	123.6784184	0.008547009	33
HIF1A	112.5763147	0.008474576	33
PPARA	186.7966148	0.008000000	30
CYP3A4	257.6469886	0.008064516	27
PTGS1	131.6779452	0.007299270	17
AR	175.4118185	0.007812500	26
CYP19A1	272.3548341	0.007874016	26
FGFR1	153.0778001	0.007092199	17

The functional analysis of GO and enrichment of KEGG pathways in crucial target genes were categorized based on increasing *P* values. The results showed that the top 10 GO enrichment terms in the BP identified "response to xenobiotic stimulus" as significantly enriched, while CC presented significant enrichment for "perinuclear region of cytoplasm", and MF for "protein homodimerization activity". For KEGG pathway enrichment, the top 10 pathways were displayed, while bubble size represented the count value (number of enriched genes), where larger bubbles indicated higher gene counts (Figure 3).

Molecular docking of bioactive compounds with dysmenorrhea-related target proteins

The molecular docking results of primary constituents with core targets were shown in Figure 4A, while the docking of cinnamaldehyde with ESR1 (binding energy -5.8 kcal/mol) and its docking with PTGS2 (binding energy -6.0 kcal/mol) were demonstrated in Figures 4B and 4C, respectively.

Discussion

This research systematically explored the anti-dysmenorrhea mechanisms of cinnamon by developing an integrated network pharmacology and molecular docking approach. Six key bioactive components were identified with cinnamaldehyde and 2,4-di-tert-butylphenol as the main constituents. Network pharmacology

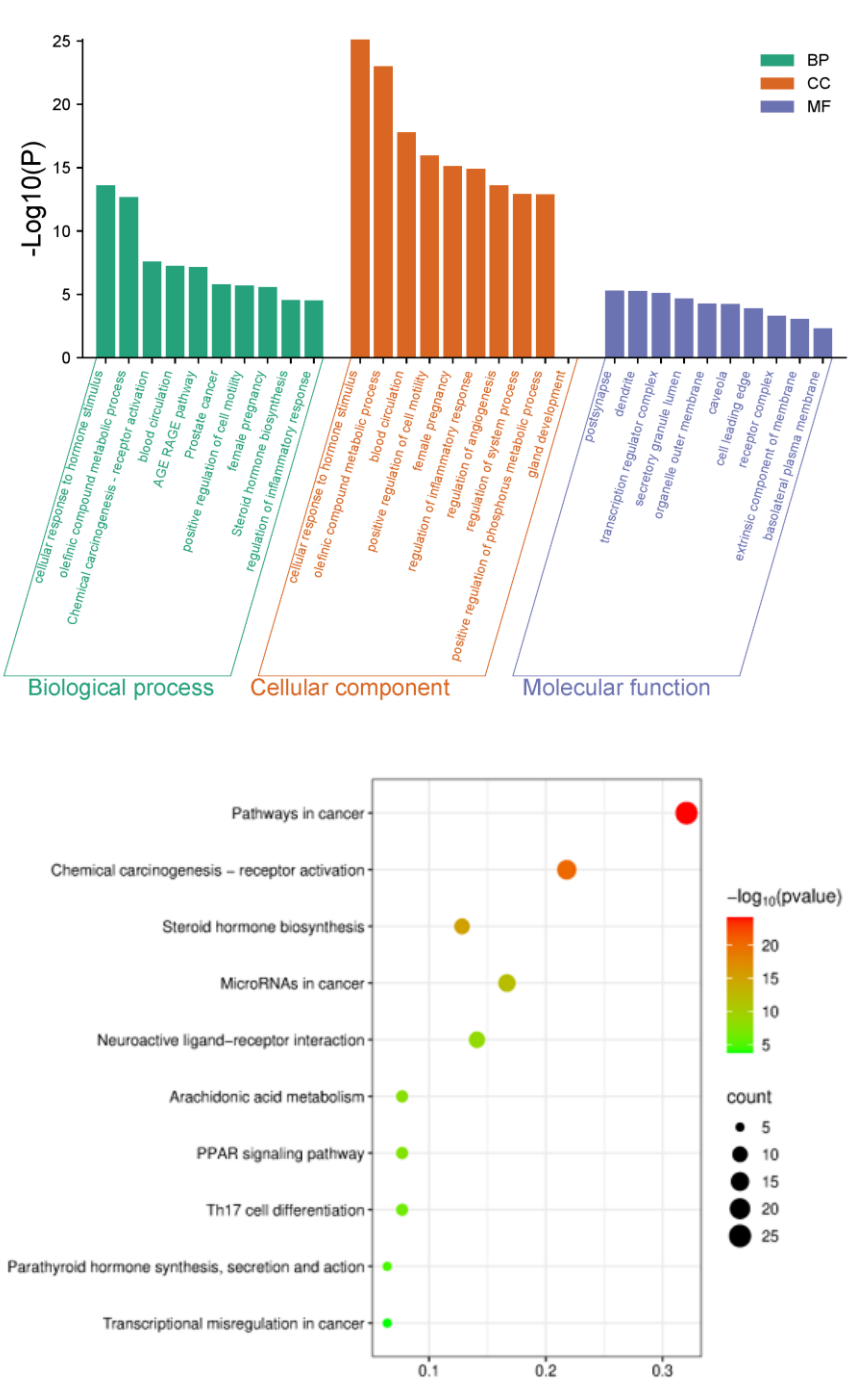

Figure 3. Enrichment analysis of key targets. **A.** GO. **B.** KEGG pathway.

predictions showed that these components potentially targeted several core proteins including NFKB1, AKT1, STAT3, PTGS2, and ESR1 to exert synergistic therapeutic effects. The results of this study aligned with existing pharmacological evidence. Cinnamaldehyde and its derivatives were shown to suppress cyclooxygenase such as PTGS2 function, inhibit NF-κB transcriptional activity, and decrease the production of pro-inflammatory mediators including IL-1β and PGE2 [16–18]. In addition, cinnamaldehyde was found to downregulate

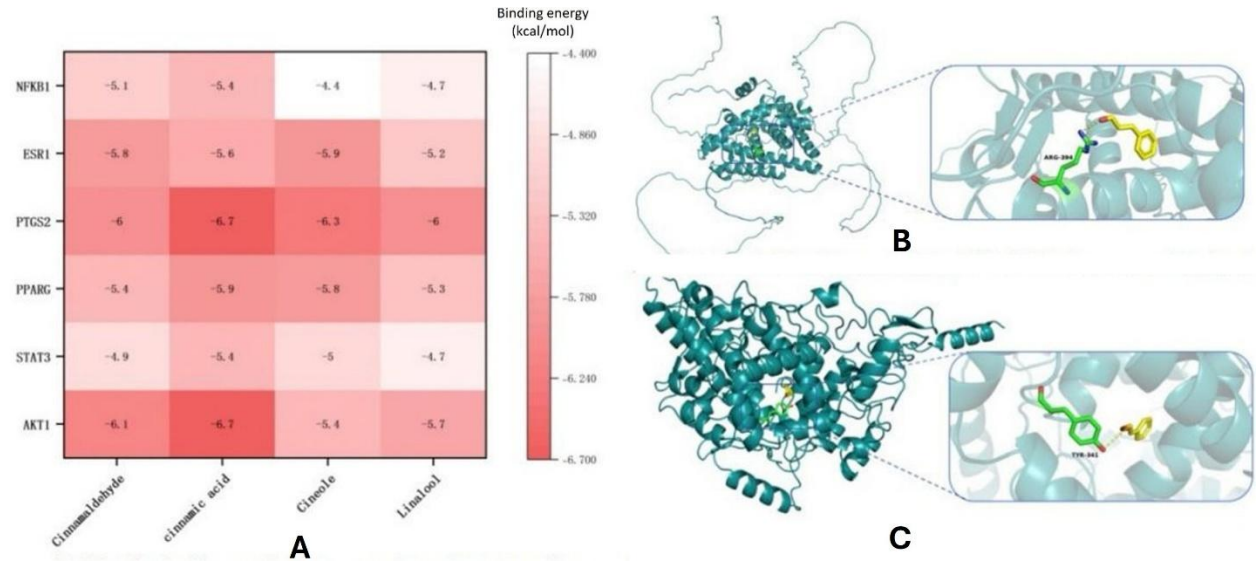

Figure 4. Molecular docking validation of the interaction between core components and key targets. **A.** Molecular docking results between major components and core targets. **B.** Molecular docking of cinnamaldehyde with ESR1 (binding energy -5.8 kcal/mol). **C.** Molecular docking of cinnamaldehyde with PTGS2 (binding energy -6.0 kcal/mol).

nitric oxide synthase expression, enhance antioxidant capacity, and modulate key signaling pathways including JNK and AP-1 [19, 20]. The anti-inflammatory potential of cinnamaldehyde derivatives such as α-bromo-4-chlorocinnamaldehyde further supported the relevance of these compounds in the management of inflammatory conditions [21]. Further analyses revealed that the bioactive components of cinnamon likely regulated dysmenorrhea-related biological processes by affecting inflammatory and pain-signaling pathways such as IL-17 and TNF signaling pathways. Molecular docking simulations showed that core components, particularly cinnamaldehyde, formed stable interactions with key targets of PTGS2 and ESR1, primarily through hydrogen bonding, hydrophobic effects, and π–π stacking.

This research demonstrated that cinnamon exerted anti-dysmenorrhea effects through a multi-component, multi-target, and multi-pathway mechanism, mainly involving the regulation of pain and inflammation pathways. These results not only provided a theoretical basis for the clinical application of cinnamon in dysmenorrhea management but also offered critical insights for further development of plant-based therapeutics. Future research should prioritize experimental validation of the predicted targets and pathways and clinical trials to verify the efficacy and safety of cinnamon preparations.

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