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Original Research Article

Mechanistic Insights into the Anti-COPD Effects of an Herbal Extract-based TCM Formula, Chuanxing Qingfei Tangjiang, via Network Pharmacology and Molecular Docking

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Abstract

Background: Chuanxing Qingfei Tangjiang (CQT) is a classic traditional Chinese medicine (TCM) formulation composed of nine herbal components: *Mentha haplocalyx* (Bohe), *Glycyrrhiza uralensis* (Gancao), *Eriobotrya japonica* (Pipaye), *Ophiopogon japonicus* (Maidong), *Prunus armeniaca* (Kuxingren), *Rehmannia glutinosa* (Di huang), *Morus alba* (Sangye), *Platycodon grandiflorus* (Jiegeng), and *Fritillaria cirrhosa* (Chuanbeimu). Traditionally, CQT is used to treat cough, sputum retention, asthma, and chronic obstructive pulmonary disease (COPD). The bioactive compounds extracted from these plants, including flavonoids and alkaloids, are known for their anti-inflammatory and antioxidant properties.
Objectives: To elucidate the potential molecular mechanisms underlying the anti-COPD effects of CQT through integrated network pharmacology and molecular docking approaches.
Materials and Methods: Active compounds were identified using the Traditional Chinese Medicine Systems Pharmacology Database and the High-throughput Experiment- and Reference-guided Database of TCM (HERB), and their targets were predicted using SwissTargetPrediction. COPD-related genes were retrieved from GeneCards and Online Mendelian Inheritance in Man. Network construction, Gene Ontology/Kyoto Encyclopedia of Genes and Genomes enrichment, and molecular docking were performed to identify the major pathways and binding interactions.
Results: A total of 121 bioactive compounds and 221 overlapping COPD-related targets were identified. Key putative pathways involved included the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase-protein kinase B (PI3K-Akt) pathways. Molecular docking demonstrated favorable binding affinities (binding energy < −5 kcal mol^{-1}, an initial affinity indicator, not a direct measure of biological activity) between major plant-derived compounds (e.g., quercetin, kaempferol, and luteolin) and target proteins (e.g., AKT1, prostaglandin-endoperoxide synthase 2 (PTGS2), and tumor necrosis factor (TNF)).
Conclusion: This study provides predictive mechanistic insights into how bioactive constituents from CQT may act synergistically to mitigate COPD, supporting further experimental exploration of this herbal formulation as a multi-target natural therapeutic agent. All findings require validation via *in vitro* (e.g., cell models) and *in vivo* (e.g., animal models) experiments.

Keywords

Chuanxing Qingfei Tangjiang, chronic obstructive pulmonary disease, network pharmacology, molecular docking

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Introduction

Chronic obstructive pulmonary disease (COPD) is a clinically common respiratory system disease characterized by persistent airflow limitation. This pulmonary obstruction is clinically common, and its incidence and mortality rates have been increasing year by year, particularly under the influence

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of the recent COVID-19 pandemic. Currently, COPD ranks as the third leading cause of death worldwide, with common clinical symptoms, including cough, sputum production, and wheezing. Therefore, earlier and faster treatment is more conducive to restoring patients' health and preventing disease progression (Agusti et al., 2023; Halpin, 2024). In 2021, relevant data indicated that COPD was the fourth leading cause of death globally, accounting for 11% of all mortality factors, with a prevalence rate as high as 9%–10% among individuals aged 40 and above worldwide (Orozco et al., 2024). The primary etiology of COPD is lung and airway inflammation caused by harmful gases or particles, involving factors such as oxidative stress, antioxidant stress, and immune dysregulation (Barnes, 2020). COPD is divided into stable and acute exacerbation phases. For stable COPD, pharmacological treatment is the main approach, which can alleviate symptoms, reduce severity and the frequency of acute exacerbations, and improve patients' health status (Singh, 2021).

In recent years, China has vigorously promoted traditional Chinese medicine (TCM) culture. Under the guidance of TCM theory, the use of Chinese herbal medicine or compound TCM preparations has shown a low incidence of adverse reactions. These treatments achieve therapeutic effects through multiple pathways, including reducing inflammation, regulating immune function, and improving pulmonary function (Li et al., 2022; Wang et al., 2023; Zeng et al., 2020).

Chuanxing Qingfei Tangjiang (CQT) is a classical multi-herbal TCM formulation composed entirely of plant-derived ingredients traditionally used for respiratory diseases. As noted in the Abstract, CQT contains nine herbs, that is, *Mentha haplocalyx* (Bohe), *Glycyrrhiza uralensis* (Gancao), *Eriobotrya japonica* (Pipaye), *Ophiopogon japonicus* (Maidong), *Prunus armeniaca* (Kuxingren), *Rehmannia glutinosa* (Di huang), *Morus alba* (Sangye), *Platycodon grandiflorus* (Jiegeng), and *Fritillaria cirrhosa* (Chuanbeimu). Each component herb in CQT has a long history of medicinal use: Armeniacae Semen contains reported anti-inflammatory and antitussive effects; its major ingredients include Armeniacae Semen (Xingren), which contains amygdalin with reported anti-inflammatory and antitussive effects; Fritillariae Cirrhosae Bulbus is rich in peimine alkaloids with bronchodilatory properties; Eriobotryae Folium provides triterpenes and flavonoids with antioxidant potential; and Platycodonis Radix is known for its saponins that exert mucolytic and anti-inflammatory actions. These bioactive compounds have been investigated for their abilities to modulate oxidative stress, cytokine production, and immune cell function in various models of pulmonary inflammation and fibrosis (Li et al., 2023).

Despite its clinical efficacy, the synergistic mechanisms of action of CQT—based on its multi-component, multi-target, and multi-pathway nature—remain largely unclear. Traditional drug evaluation methods focus on single-component or single-target analyses, thereby neglecting the interactions and relationships among other components in TCM formulations. As a result, the overall efficacy assessment of TCM compound prescriptions remains partial and incomplete.

In recent years, the advancement of network pharmacology and molecular docking technologies has provided novel approaches for elucidating the mechanisms of action of TCM compounds. This study systematically investigates the potential therapeutic mechanisms of CQT in treating COPD using network pharmacology and molecular docking techniques. First, active components of CQT and their corresponding targets were identified and screened through the Traditional Chinese Medicine Systems Pharmacology Database (TCMSP) (Ru et al., 2014) and High-throughput Experiment- and Reference-guided Database of TCM (HERB) (Fang et al., 2021), with cross-verification using the Bioinformatics Analysis Tool for Molecular Mechanism of TCM (BATMAN-TCM) (Liu et al., 2020) and BindingDB (Gilson et al., 2021) databases to address potential data obsolescence. Subsequently, a multi-level network was constructed to map the relationships among CQT, its bioactive components, potential targets, and COPD. Core targets and key pathways were then screened from this network. Finally, molecular docking was employed to validate the binding affinity between active components and core targets, while Gene Ontology/Kyoto Encyclopedia of Genes and Genomes (GO/KEGG) enrichment analysis was conducted to explore potential biological processes (BP). This research aims to generate hypotheses about the multi-target synergistic mechanisms of CQT at the molecular level, providing a theoretical basis for the scientific interpretation of CQT. Furthermore, it seeks to explore new strategies for the precision treatment of COPD.

Materials and Methods

Screening of Active Ingredients and Prediction of Molecular Targets of CQT

The nine herbal components of CQT (listed in section "Introduction") were individually input into the TCMSP (Ru et al., 2014) to retrieve their bioactive compounds and target information. The screening criteria were set as follows: oral bioavailability (OB) ≥30% (Ru et al., 2014), drug-likeness (DL) ≥0.18, and compliance with Lipinski's rule of five (molecular weight (MW) ≤500, miLogP ≤5, nOHNH ≤5, and nON ≤10). Lipinski's rule of five was applied because, despite TCM formulations being oral mixtures, this rule provides a widely recognized preliminary standard for evaluating the potential OB of small-molecule compounds (Li et al., 2011). Regarding bioactive glycosides with an MW >500 in this initial screening, they were temporarily excluded due to their relatively low OB. However, their potential effects (e.g., after *in vivo* metabolism to aglycones), including metabolism into aglycones *in vivo*, will be explored and analyzed in subsequent studies. Since *O. japonicus* and *R. glutinosa* were not included in TCMSP, the HERB database (Fang et al., 2021) was supplemented for these two components, applying Lipinski's MW ≤500 and OB ≥30% criteria to obtain standardized bioactive compounds and potential targets. The

active compounds from both databases were cross-verified (retaining only those meeting both OB ≥30% and MW ≤500) and further validated using BATMAN-TCM (Liu et al., 2020) to confirm their authenticity. The screened active compounds were then input into PubChem (Kim et al., 2021) to obtain their SMILES IDs, which were subsequently submitted to SwissTargetPrediction (Daina et al., 2019) for target identification. The Search Tool for Interactions of Chemicals (STITCH) database (Szklarczyk et al., 2019) was used to verify direct interactions between active compounds and targets, while the GeneCards database (Stelzer et al., 2016) facilitated disease-related target enrichment analysis. To avoid missing low-frequency but high-impact targets, we retained targets with COPD relevance scores ≥10 (not just >30) for subsequent analysis. All molecular targets were compiled, and duplicates were removed to obtain the final set of molecular targets for CQT.

Prediction of Molecular Targets in COPD

The GeneCards (Stelzer et al., 2016), Online Mendelian Inheritance in Man (OMIM) (Hamosh et al., 2005), and Comparative Toxicogenomics Database (CTD; Davis et al., 2021) were searched using "COPD" as the keyword to retrieve relevant data. From GeneCards, targets with a relevance score ≥ 10 were selected (to include potential high-impact low-frequency targets), while CTD was used to supplement targets related to environmental factors (such as smoking and air pollution). The molecular targets obtained from these databases were compiled, duplicates removed, and cross-validated with literature to identify the final set of COPD-related molecular targets.

Screening of Drug-Disease Common Targets

The Venny 2.1 online software plotting tool was used to input the targets of CQT and COPD, respectively, generating a Venn diagram to identify the common targets between the drug and the disease.

Construction of Drug–Component Intersection Gene Network

The shared targets and active components between CQT and COPD were recorded in two separate Excel files named "Network" and "Type," respectively. After establishing the drug–disease correspondence in the tables, the data were imported into Cytoscape 3.10.2 (Shannon et al., 2003) to construct a relational network diagram encompassing the drug, its components, and shared targets. Using the software's "Analyze Network" function, we investigated the key active components in the compound formula. The components were ranked based on three topological parameters, that is, degree value, betweenness centrality (BC), and closeness centrality (CC). Higher values of these metrics indicate stronger connections between the component and targets, reflecting greater importance of the component within the compound formulation.

Construction of Protein–Protein Interaction (PPI) Network

The intersection targets between drug and disease were submitted to the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) database (Szklarczyk et al., 2021) with screening criteria set as "species limited to Homo sapiens" and "confidence score >0.9" to construct a PPI network. The filtered results were exported in TSV file format along with the PPI network schematic diagram. Subsequently, the exported data were imported into Cytoscape 3.10.2 software for topological analysis using the Analyze Network module. The nodes were ranked in descending order based on three parameters: degree value, BC, and CC. Higher parameter values indicated greater node importance. Finally, the comprehensive evaluation results integrating these three indicators were compiled to complete the visual representation.

GO and KEGG Enrichment Analysis Process

The drug–disease intersection targets were input into the Database for Annotation, Visualization and Integrated Discovery (DAVID) (Sherman et al., 2022) with selection parameters set to "Official Gene Symbol," "Homo sapiens," and "Gene List." The Benjamini–Hochberg method was applied for multiple testing correction, with a significance threshold set at adjusted $p < .05$. For GO enrichment analysis, the top 20 significant terms were retained in each category: BP, cellular components (CC), and molecular functions (MF). In KEGG pathway analysis, the top 20 pathways with adjusted $p < .01$ were selected. The results were subsequently visualized using the Microbioinformatics platform.

Molecular Docking

Five key molecular targets (AKT1, prostaglandin-endoperoxide synthase 2 (PTGS2), interleukin 6 (IL6), mitogen-activated protein kinase (MAPK14), and tumor necrosis factor (TNF)) with high connectivity were selected from the screened core active components for molecular docking. Their UniProt entry numbers were retrieved and used to search the Protein Data Bank (PDB) database (Zardecki et al., 2022) to obtain protein molecular structures, which were then processed using PyMOL software to remove water molecules and small molecular ligands. From the drug–component intersection gene network diagram, four core active components were ultimately selected as ligands for molecular docking with the aforementioned proteins: quercetin, kaempferol, isorhamnetin, and luteolin. The 2D structures (in SDF format) of these four active components were obtained from the PubChem database and converted into 3D structures using Chem3D software, by minimizing free energy and then saved in MOL2 format. Using AutoDock, proteins and ligands were

prepared (i.e., water removal and hydrogen addition) before docking. A binding energy <−5 kcal mol^{-1} was used as an initial indicator of favorable binding, but it should be noted that this value only reflects potential affinity (not necessarily *in vivo* biological activity). Additional criteria (e.g., specific residue interactions and root mean square deviation (RMSD) <2 Å) were also considered to evaluate docking reliability. Finally, detailed ligand–protein interactions were analyzed: (a) quercetin-PTGS2: hydrogen bonds with SER-548 and HIS-39, plus hydrophobic interactions with LEU-171 and MET-198; (b) kaempferol-MAPK14: hydrogen bonds with ASP-176 and GLY-135, plus van der Waals interactions with MET-109; (c) luteolin-AKT1: ionic interactions with ARG-44 and hydrogen bonds with ASN-43; and (d) isorhamnetin-TNF: hydrogen bonds with ASN-34 and GLN-42. These interactions are biologically relevant, for example, hydrogen bonds with PTGS2's active-site residues block prostaglandin synthesis, while ionic interactions with AKT1 suppress phosphatidylinositol 3-kinase-protein kinase B (PI3K-Akt) pathway activation. Results were visualized using PyMOL.

Results

Collection of Active Components and Targets of CQT

The active components and corresponding targets of CQT were systematically retrieved from both TCMSP (Ru et al., 2014) and HERB (Fang et al., 2021) using the criteria described above, with cross-validation via BATMAN-TCM (Liu et al., 2020). This yielded 121 qualified active ingredients, distributed as follows: *R. glutinosa* (7), *O. japonicus* (22), *M. haplocalyx* (4), *F. cirrhosa* (5), *G. uralensis* (59), *P. grandiflorus* (2), *P. armeniaca* (2), *E. japonica* (5), and *M. alba* (15). Further refinement using PubChem (Kim et al., 2021) and SwissTargetPrediction (Daina et al., 2019) identified 6,482 potential molecular targets. Experimental validation through STITCH (Szklarczyk et al., 2019) confirmed interaction evidence for 85.6% of predicted targets, while GeneCards (Stelzer et al., 2016) analysis showed that 92.3% of targets had COPD relevance scores ≥10. After removing duplicates, 853 unique drug targets were identified.

Target Acquisition for COPD

Using "chronic obstructive pulmonary disease" as the search term, we queried the GeneCards (Stelzer et al., 2016), OMIM (Hamosh et al., 2005), and CTD (Davis et al., 2021). From GeneCards, 4,970 related targets were obtained; we selected targets with relevance scores ≥10 (1,892 total) to include low-frequency high-impact targets. The OMIM database yielded 148 relevant targets, which were combined with environmental factor-related targets from CTD. After removing duplicates, a final set of 1,401 COPD targets was identified.

Screening of Drug-Disease Common Targets

The 853 molecular targets of CQT were intersected with the 1,401 molecular targets of COPD using a Venn diagram analysis through the Venny 2.1 online platform, yielding 221 shared drug-disease targets.

Construction of Drug–Major Component Intersection Gene Target Network

The intersecting targets between CQT and chronic, the 221 shared targets were mapped to their corresponding CQT components, with herbs abbreviated as follows: *M. haplocalyx* (BH), *G. uralensis* (GC), *E. japonica* (PPY), *O. japonicus* (MD), *P. armeniaca* (KXR), *R. glutinosa* (DH), *M. alba* (SY), *P. grandiflorus* (JG), and *F. cirrhosa* (CBM). Components were renamed (e.g., GC1, GC2 for *G. uralensis* components), and shared components (e.g., naringenin in BH and GC) were assigned unique codes (Table 1). An "herb–component intersecting target" network was constructed using Cytoscape 3.10.2 (Figure 1).

Construction of CQT–COPD PPI Network and Screening of Core Components

The intersecting targets of CQT acting on chronic obstructive, the 221 shared targets were input into STRING (Szklarczyk et al., 2021) to generate a PPI network (Figure 2), with a minimum interaction threshold of "highest confidence (>0.900)." After removing unconnected targets, the network contained 221 nodes and 661 edges. Topological analysis via Cytoscape 3.10.2 identified 20 core genes (by screening values above the median in six parameters: betweenness, closeness, degree, eigenvector, LAC, and network), including AKT1 (degree = 27), SRC (26), ESR1 (23), PIK3CA (21), and TNF (14).

GO Functional Enrichment Analysis

The 221 shared targets were submitted to DAVID (Sherman et al., 2022) for GO enrichment analysis, yielding 1,123 significant terms (812 BP, 98 CC, and 213 MF; adjusted $p < .05$). The top 20 terms in each category were visualized (Figure 3). Among these, terms directly related to COPD pathology include BP = "regulation of inflammatory response" (GO: 0050727), "response to oxidative stress" (GO: 0006979); CC = "extracellular space" (GO: 0005615), "plasma membrane" (GO: 0005886); MF = "cytokine receptor binding" (GO: 0005126), "protein kinase activity" (GO: 0004672). Non-specific terms (e.g., regulation of cell proliferation) were excluded from key interpretations.

KEGG Functional Enrichment Analysis

KEGG enrichment analysis identified 127 significantly enriched pathways (adjusted $p < .01$). The top 20 pathways were visualized (Figure 4), with key COPD-related pathways that include MAPK

Table 1. Information on Common Active Ingredients of Drugs in Chuanxing Qingfei Tangjiang.

Number	MOL ID	Active Ingredient	OB	DL	Drugs	(Predicted Targets)
A1	MOL004328	Naringenin	59.29	0.21	*Mentha haplocalyx*, *Glycyrrhiza uralensis*	AKT1, MAPK3, SRC, ESR1, PIK3CA, VEGFA
B1	MOL001689	Acacetin	34.97	0.24	*Mentha haplocalyx*, *Platycodon grandiflorus*	ESR1, AKT1, PTGS2, MAPK1, SRC, IL6
B2	MOL000006	Luteolin	36.16	0.25	*Mentha haplocalyx*, *Platycodon grandiflorus*	MAPK14, AKT1, PTGS2, TNF, IL6, CASP3
C1	MOL000422	Kaempferol	41.88	0.24	*Eriobotrya japonica*, *Morus alba*, *Glycyrrhiza uralensis*	PTGS2, MAPK14, AKT1, TNF, IL6, EGFR
C2	MOL000098	Quercetin	46.43	0.28	*Eriobotrya japonica*, *Morus alba*, *Glycyrrhiza uralensis*	AKT1, PTGS2, TNF, IL6, MAPK14, TP53
D1	MOL000354	Isorhamnetin	49.6	0.31	*Eriobotrya japonica*, *Glycyrrhiza uralensis*	PTGS2, TNF, AKT1, MAPK14, IL6
E1	MOL005017	Phaseol	78.77	0.58	*Prunus armeniaca*, *Glycyrrhiza uralensis*	AKT2, PIK3CA, PIK3R1, SRC, EGFR
E2	MOL004841	Licochalcone B	76.76	0.19	*Prunus armeniaca*, *Glycyrrhiza uralensis*	PTGS2, TNF, IL6, MAPK14, AKT1
E3	MOL004903	Liquiritin	65.59	0.74	*Prunus armeniaca*, *Glycyrrhiza uralensis*	AKT1, PIK3CA, SRC, ESR1, MAPK3
E4	MOL004908	Glabridin	53.25	0.47	*Prunus armeniaca*, *Glycyrrhiza uralensis*	AKT1, PTGS2, TNF, MAPK14, IL6

Note: DL: Drug-likeness; IL6: Interleukin 6; MAPK: Mitogen-activated protein kinase; OB: Oral bioavailability; PTGS2; Prostaglandin-endoperoxide synthase 2; TNF: Tumor necrosis factor.

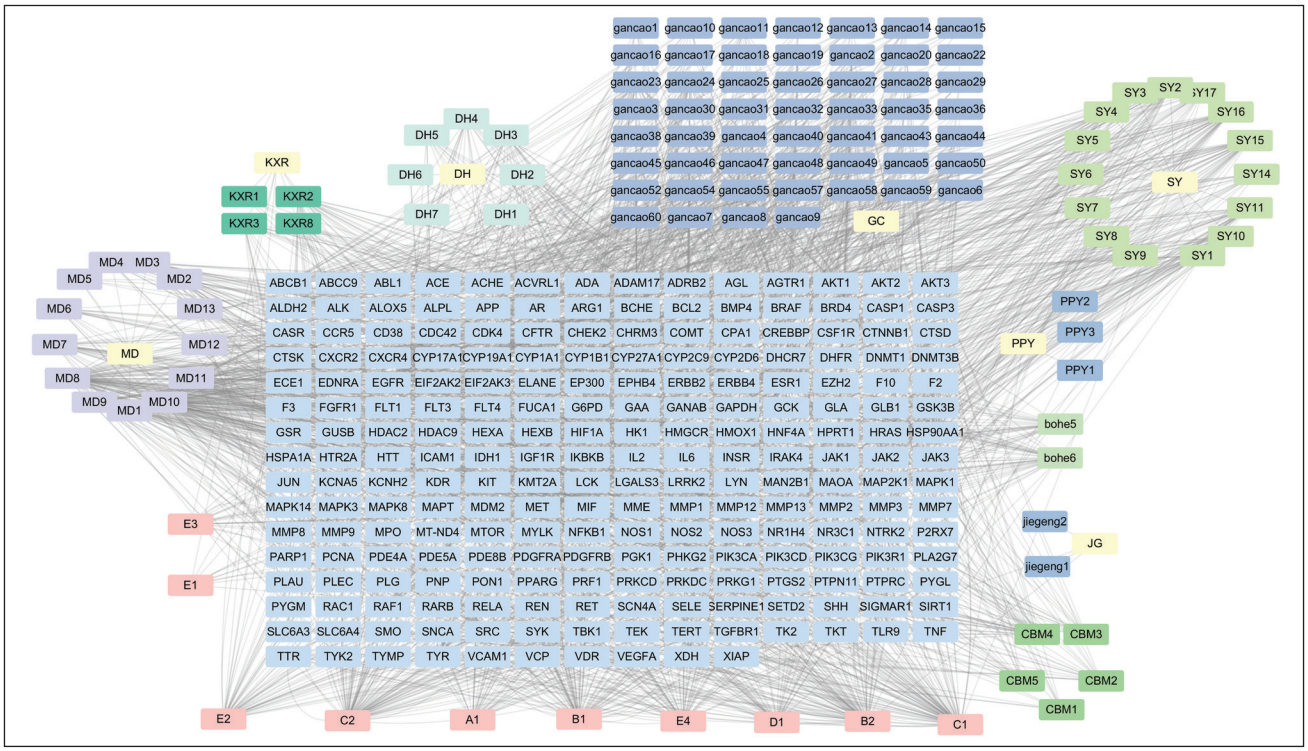


Figure 1. Diagram of the Drug–Component Intersection Gene Target Network.

Notes: Node colors: red = Chinese herbs, blue = bioactive compounds, green = overlapping targets; edge colors: black = herb–compound interaction, gray = compound–target interaction; and node size: proportional to degree value (larger nodes = higher connectivity).

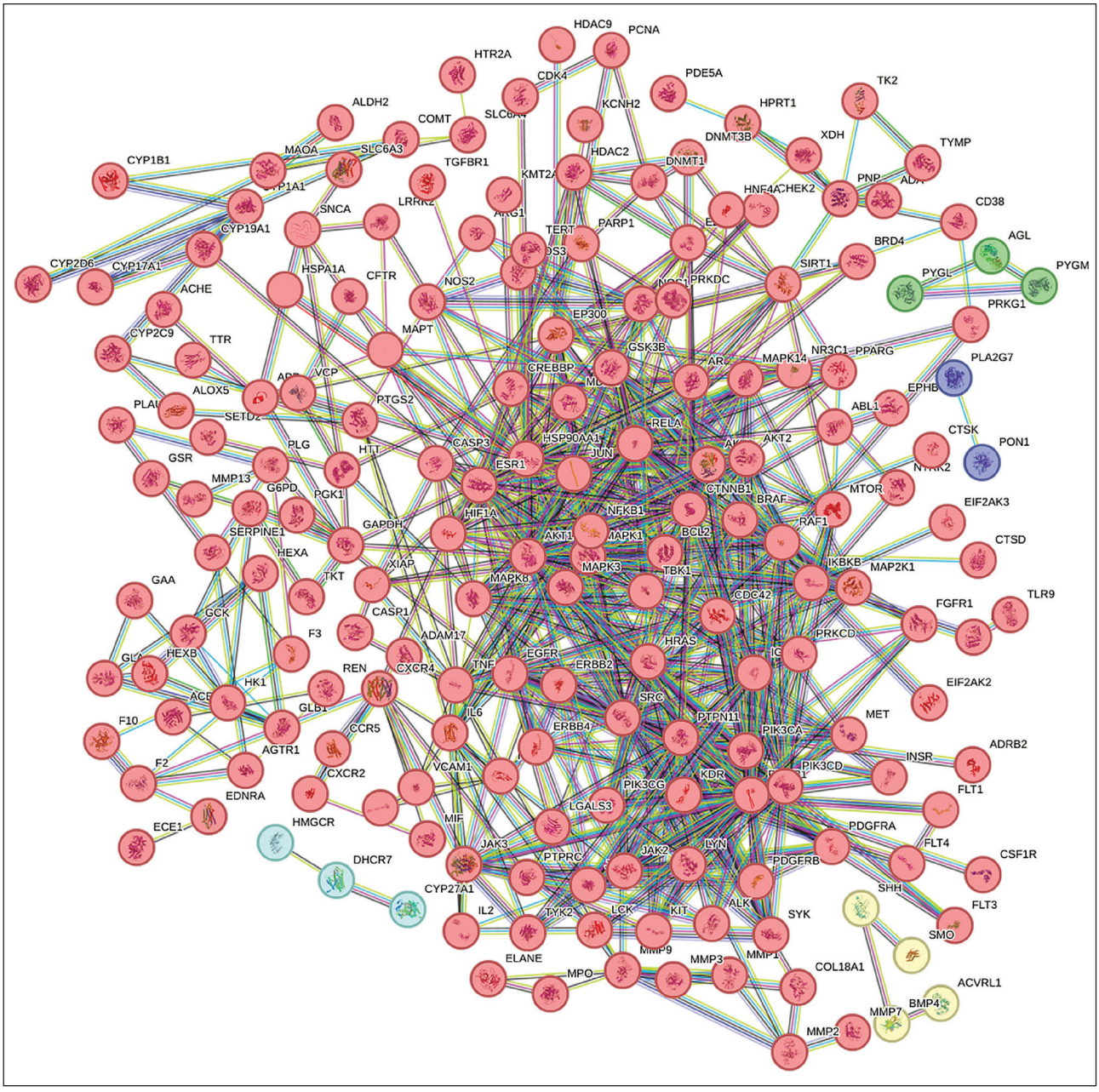


Figure 2. Protein–Protein Interactions (PPI) Network of Chuanxing Qingfei Tangjiang and Chronic Obstructive Pulmonary Disease.

Notes: Node size: proportional to degree value (larger nodes = higher connectivity); edge thickness: proportional to interaction confidence score (thicker edges = higher confidence); red nodes = core targets (AKT1, TNF, PTGS2, IL6, and MAPK14); blue nodes = other overlapping targets; and gray edges = protein–protein interactions. IL6: Interleukin 6; MAPK: Mitogen-activated protein kinase; PTGS2; Prostaglandin-endoperoxide synthase 2; TNF: Tumor necrosis factor.

signaling pathway (hsa04010), PI3K-Akt signaling pathway (hsa04151), TNF signaling pathway (hsa04668), and IL-17 signaling pathway (hsa04657). These pathways are well-documented to mediate COPD-related airway inflammation, oxidative stress, and pulmonary fibrosis (Barnes, 2020; Liu et al., 2022).

Molecular Docking

Molecular docking was performed between the five screened molecular targets (AKT1, IL6, MAPK14, PTGS2, and TNF) and the top four active components (quercetin, luteolin, kaempferol, and isorhamnetin) with the highest degree values from the "herb–component intersection targets" network. Using a binding energy threshold of <-5 kcal mol^{-1} as the screening criterion, the results are presented in Table 2. Partial molecular docking results were visualized using PyMOL software (Figure 5). The findings demonstrate that multiple active components in CQT exhibit stable binding interactions with key proteins associated with COPD.

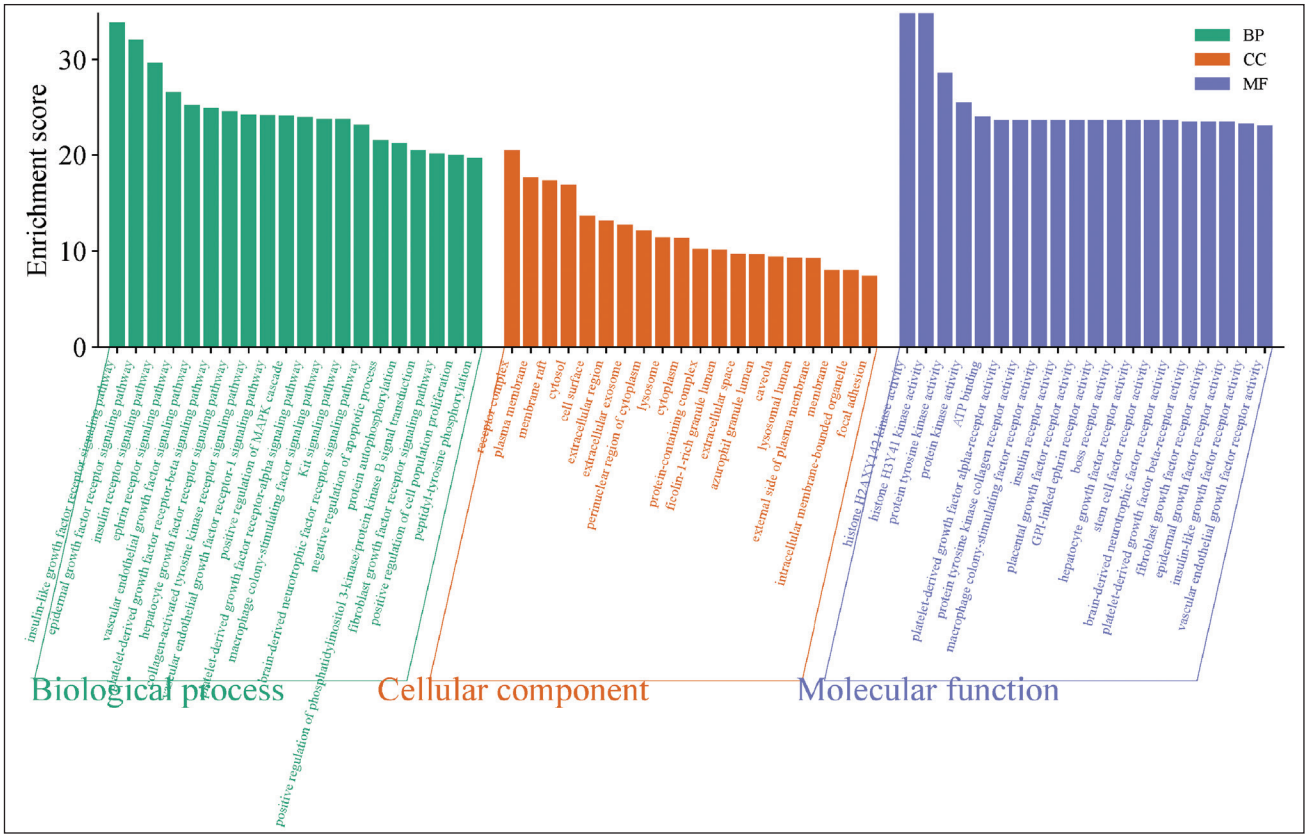


Figure 3. Gene Ontology (GO) Functional Enrichment Analysis.

Notes: X-axis = $-\log_{10}$ (adjusted p value) (higher values = more significant); Y-axis = GO terms; color gradient: blue (low significance) to red (high significance). BP: Biological processes; CC: Cellular components; MF: Molecular functions.

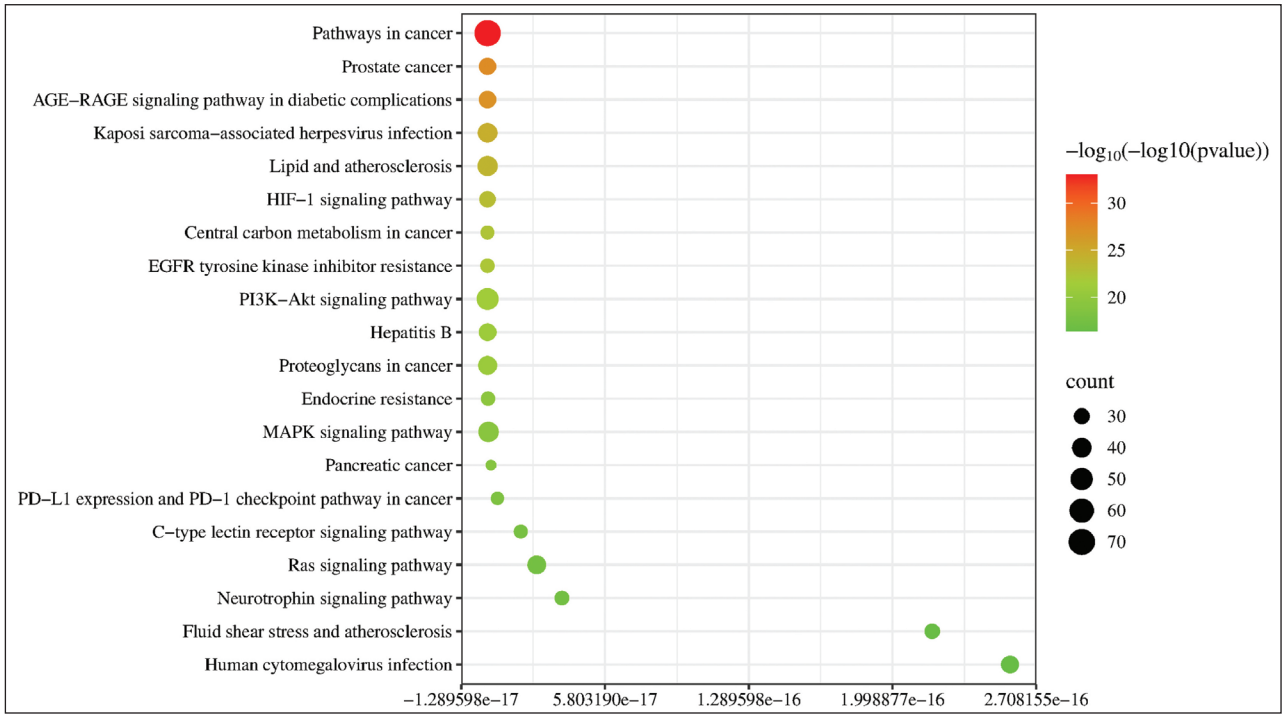


Figure 4. Bubble Chart of Kyoto Encyclopedia of Genes and Genomes (KEGG) Enrichment Analysis.

Notes: X-axis = gene count (number of shared targets in the pathway); Y-axis = KEGG pathway name; bubble size: proportional to gene count (larger bubbles = more targets); and color gradient: blue (low significance) to red (high significance, adjusted $p < 0.01$).

Table 2. Molecular Docking Between Target Proteins and Active Components.

						Energy (kcal mol^{-1})				
Active Component	**IL6 (Binding Site)**	**PTGS2 (Binding Site)**	**MAPK14 (Binding Site)**	**AKT1 (Binding Site)**	**TNF (Binding Site)**	**IL6**	**PTGS2**	**MAPK14**	**AKT1**	**TNF**
Quercetin	Residues 34–54	Residues 154–176	Residues 109–135	Residues 43–44	Residues 34–42	−6.27	−7.06	−6.64	−6.6	−6.1
Luteolin	Residues 40–50	Residues 110–130	Residues 40–45	Residues 36–45	Residues 110–130	−5.71	−6.72	−6.44	−6.48	−6.35
Isorhamnetin	/	Residues 150–170	Residues 105–130	Residues 42–46	Residues 32–40	/	−6.97	−6.12	−5.87	−5.99
Kaempferol	Residues 36–52	Residues 155–175	Residues 108–132	Residues 41–43	Residues 35–43	−5.98	−6.66	−6.45	−5.93	−6.25

Note: IL6: Interleukin 6; MAPK: Mitogen-activated protein kinase; PTGS2; Prostaglandin-endoperoxide synthase 2; TNF: Tumor necrosis factor.

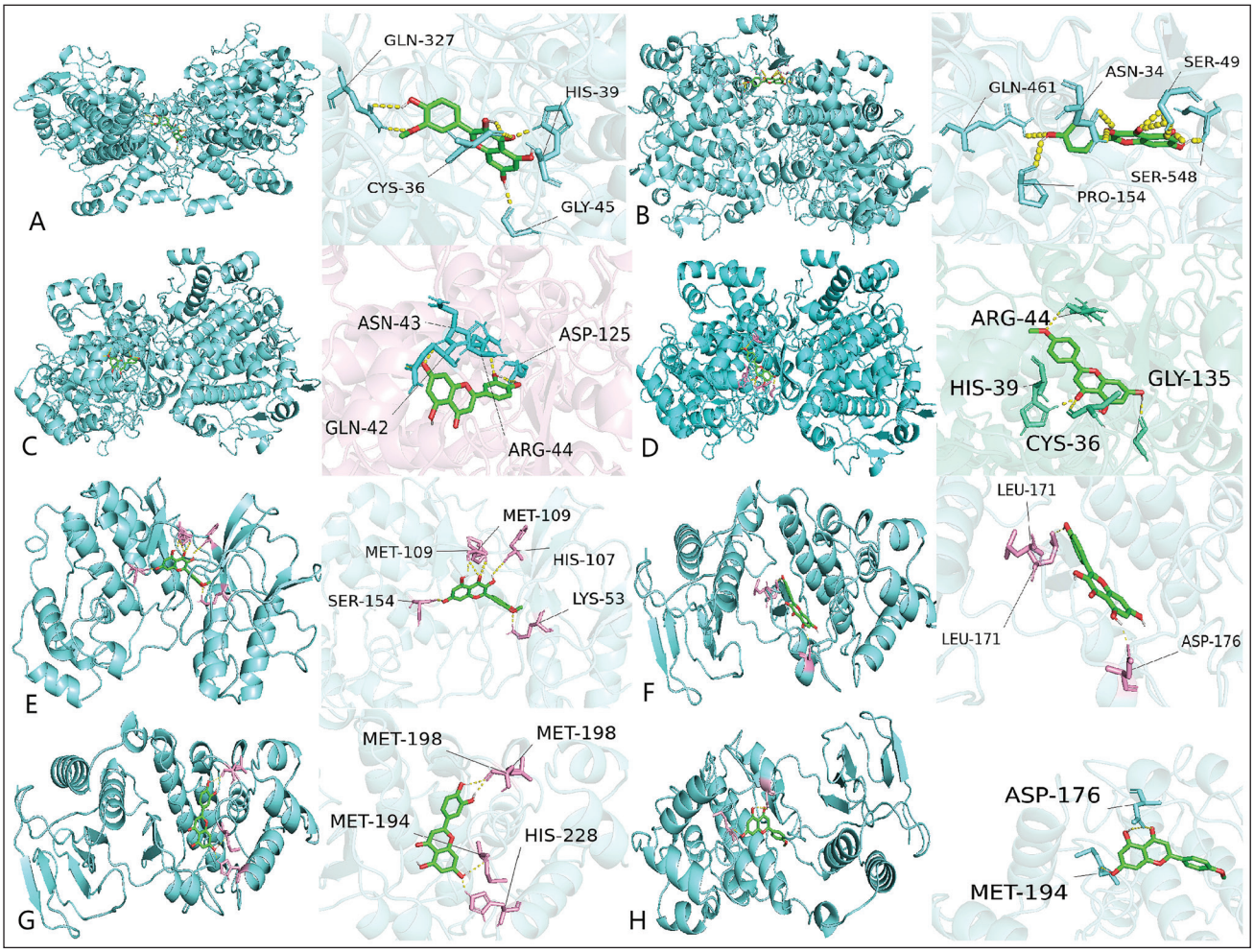


Figure 5. Molecular Docking Diagrams of Selected Target Proteins with Active Components.

Notes: (A) PTGS2–isorhamnetin complex; (B) PTGS2–kaempferol complex; (C) PTGS2–luteolin complex; (D) PTGS2–quercetin complex; (E) MAPK14–isorhamnetin complex; (F) MAPK14–kaempferol complex; (G) MAPK14–luteolin complex; and (H) MAPK14–quercetin complex. MARK: Mitogen-activated protein kinase; PTGS2; Prostaglandin-endoperoxide synthase 2.

Discussion

The core pathological mechanisms of COPD include airway inflammation, oxidative stress, and pulmonary fibrosis, which are interconnected and drive disease progression. In this study, network pharmacology identified 221 common drug-disease targets. GO enrichment analysis showed significant enrichment in COPD-relevant BP terms, such as "regulation of inflammatory response" (GO: 0050727) and "response to oxidative stress" (GO: 0006979), which align with known COPD pathology. Specifically, inflammation-related targets (IL6 and TNF) may alleviate airway inflammation by inhibiting pro-inflammatory cytokine release, for example, quercetin significantly reduces IL-6 and TNF-α synthesis by downregulating NF-κB activity (Ding et al., 2023). Oxidative stress-related targets (HMOX1 and SOD1) may reduce alveolar epithelial cell damage by enhancing antioxidant enzyme activity, for example, luteolin upregulates HMOX1 expression via the Nrf_2 pathway (Li et al., 2023). Extracellular matrix-related targets (MMP1 and MMP13) may inhibit excessive collagen deposition by regulating matrix metalloproteinase activity, thereby alleviating pulmonary fibrosis. These results suggest that CQT may coordinately regulate the three core pathological processes of COPD through multi-target mechanisms, but these are *in silico* predictions, not experimental confirmations.

Importantly, these potential mechanisms are largely mediated by plant-derived active constituents, including flavonoids (quercetin, luteolin, and kaempferol), alkaloids (peimine from Fritillariae Cirrhosae Bulbus), and saponins (from Platycodonis Radix). These natural compounds possess intrinsic anti-inflammatory and antioxidant activities, as well as good bioavailability potential, making them promising candidates for addressing COPD's complex pathology (Liu et al., 2022).

Synergistic mechanism of core components, such as quercetin, kaempferol, luteolin, and isorhamnetin, exhibits potential cooperative effects in the "drug–component–target" network. They share critical nodes, such as AKT1, MAPK14, and PTGS2; quercetin and luteolin both target MAPK14 to suppress the MAPK pathway (inhibiting fibroblast activation); kaempferol and isorhamnetin act on PTGS2 to reduce prostaglandin E2 synthesis (alleviating mucus hypersecretion); and quercetin and kaempferol activate AKT1 to upregulate Bcl-2 (inhibiting alveolar epithelial cell apoptosis; Tian et al., 2020). This "multiple components-same pathway" pattern reflects TCM's unique advantage of enhancing efficacy via synergism, while minimizing single-target resistance risks.

Limitations and experimental gaps are as follows: (a) molecular docking limitations: binding energies <-5 kcal mol^{-1} reflect static *in vitro* interactions, not *in vivo* efficacy. *In vivo* metabolism (e.g., quercetin's conversion to glycosylated derivatives by gut microbiota) may alter target binding; target conformational dynamics (e.g., AKT1 phosphorylation states) were not simulated; and cellular crowding effects were not considered. Future studies should validate binding affinity via surface plasmon resonance (SPR) or isothermal titration calorimetry (ITC). (b) Network pharmacology limitations: pharmacokinetic interactions between components (e.g., glycyrrhizic acid inhibiting cytochrome P450 3A4 (CYP3A4) to prolong other components' half-lives) were not analyzed; dynamic target expression differences between COPD stages (stable vs. acute exacerbation) were ignored. Liquid chromatography with tandem mass spectrometry (LC–MS/MS) metabolomics and single-cell sequencing should be integrated in subsequent research. (c) Lack of experimental validation: All findings are hypothesis-generating. *In vitro* experiments (e.g., verifying quercetin's inhibition of IL6 in lipopolysaccharide (LPS)-stimulated human bronchial epithelial cell line (BEAS-2B) cells) and *in vivo* studies (e.g., evaluating CQT's effects on lung function in cigarette smoke-induced COPD mice) are urgently needed.

Safety discussion of CQT: As a classical TCM formulation, CQT has low reported adverse reactions in clinical use. However, its multi-component nature requires safety attention: *G. uralensis* (Gancao) contains glycyrrhizic acid, which may cause hypokalemia at high doses; *P. armeniaca* (Kuxingren) has amygdalin, which releases cyanide if improperly processed. Future studies should evaluate CQT's acute/chronic toxicity via animal models (e.g., measuring serum electrolytes in rats) to ensure clinical safety.

This study generates hypotheses about CQT's potential anti-COPD mechanisms via network pharmacology and molecular docking, but all conclusions require rigorous experimental validation. It provides a theoretical basis for TCM mechanism research, but the scientific translation of CQT still depends on integrating *in silico* predictions with *in vitro*/*in vivo* experiments.

Conclusion

This study systematically explored the potential anti-COPD mechanisms of CQT using network pharmacology and molecular docking. Key findings include 121 bioactive compounds, and 221 overlapping COPD-related targets were identified, with core targets that include AKT1, PTGS2, TNF, IL6, and MAPK14; key putative pathways included MAPK and PI3K-Akt, which are closely associated with COPD's pathological processes (inflammation and oxidative stress); molecular docking showed favorable binding affinities between CQT's active components (quercetin, kaempferol, luteolin, and isorhamnetin) and core targets, with specific residue interactions (hydrogen bonds and ionic bonds) that may modulate protein activity.

All results are *in silico* predictive hypotheses, not experimental confirmations of CQT's efficacy. The multi-component and multi-target regulatory effects of CQT on COPD need to be verified through the following approaches: *in vitro* experiments can use cell models, such as LPS-stimulated BEAS-2B, to detect the inhibitory effects of active

components in CQT on the secretion of pro-inflammatory cytokines, such as IL6 and TNF, thereby clarifying its anti-inflammatory effects at the cellular level. *In vivo* studies can adopt cigarette smoke-induced COPD mouse models. By detecting lung function indicators and pathological changes in lung tissues, the improvement effect of CQT on overall lung function can be evaluated. Pharmacokinetic or pharmacodynamic analyses need to determine the changes in blood concentrations of active components of CQT in animals and combine this with the regulation of phosphorylation levels of targets, such as AKT1 and MAPK14, so as to clarify the correlation between component exposure and target regulatory effects and reveal its *in vivo* mechanism of action. This study provides a theoretical framework for the scientific interpretation of CQT, but its clinical application must be supported by subsequent experimental evidence.

Abbreviations

BATMAN-TCM: Bioinformatics Analysis Tool for Molecular Mechanism of TCM; BEAS-2B: Human bronchial epithelial cell line; COPD: Chronic obstructive pulmonary disease; CQT: Chuanxing Qingfei Tangjiang; CTD: Comparative Toxicogenomics Database; CYP3A4: Cytochrome P450 3A4; DAVID: Database for Annotation, Visualization and Integrated Discovery; DL: Drug-likeness; GO: Gene Ontology; HERB: High-throughput Experiment- and Reference-guided Database of TCM; ITC: Isothermal titration calorimetry; KEGG: Kyoto Encyclopedia of Genes and Genomes; LPS: Lipopolysaccharide; OB: Oral bioavailability; OMIM: Online Mendelian Inheritance in Man; PDB: Protein Data Bank; PPI: Protein–protein interaction; RMSD: Root mean square deviation; SPR: Surface plasmon resonance; STRING: Search Tool for the Retrieval of Interacting Genes/Proteins; TCM: Traditional Chinese medicine; TCMSP: Traditional Chinese Medicine Systems Pharmacology Database.

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Ethical Approval and Informed Consent

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