RESEARCH ARTICLE

Exploring the mechanism of Citri Reticulata Pericarpium Viride essential oil in the treatment of bronchial asthma through network pharmacology

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Bronchial asthma (BA) manifests through airway inflammation involving diverse cellular elements. The essential oil of Citri Reticulata Pericarpium Viride, also referred to Qing Pi (QP), is noted for its anti-inflammatory and antibacterial attributes. However, the detailed mechanisms by which QP essential oil ameliorates BA remain elusive. This study aimed to explore the main material basis and mechanism of action of QP essential oil in the treatment of BA. The constituents of QP essential oil were elucidated *via* gas chromatography-mass spectrometry (GC-MS). Network pharmacology was utilized to pinpoint the essential ingredients, principal BA targets, and the pathways of QP essential oil's effects. Furthermore, molecular docking simulations were conducted to evaluate the interactions between the primary therapeutic targets and pertinent compounds. The results showed that GC-MS identified 14 main volatile components. The "component-target-disease" network revealed that α-Copaene, β-Caryophyllene, β-elemene, d-Limonene, and α-selinene were key components. The protein-protein interaction (PPI) network indicated IL6, IL1B, TNF, PTGS2, NR3C1, and CASP3 as core targets. Enrichment analysis mainly involved signaling pathways such as the Calcium signaling, IL-17 signaling, and TNF signaling pathways. Molecular docking analysis showed that the key components bound to the core targets with favorable binding affinities. The results confirmed that the key components in QP essential oil acted on core targets to regulate the Calcium signaling, IL-17 signaling, and TNF signaling pathways, offering a potential therapeutic approach to BA.

Keywords: gas chromatography-mass spectrometry; Citri Reticulata Pericarpium Viride; essential oil; network pharmacology; bronchial asthma.

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Introduction

Bronchial asthma (BA) is a common chronic respiratory disease that affects various populations regardless of age or ethnicity [1, 2]. The World Health Organization's "Global Asthma Burden Report" estimates that 300 million people worldwide suffer from BA, and this number is expected to increase to 400 million by 2025 [3]. This disease is a heavy burden economically and poses serious health risks including life-threatening conditions. BA manifests clinically with sustained inflammation, airway hyperresponsiveness, and structural changes within the airways leading to dyspnea, chest tightness, and wheezing [4]. The treatment protocols in use primarily involve β2-receptor agonists, leukotriene receptor antagonists, and glucocorticoids [5, 6], all of which come with side effects that range from arrhythmias to gastrointestinal issues, decreased immunity, and even increased possibilities of resistance towards drugs upon continued use for an extended period [7]. Consequently, there is a critical need to discover more effective treatments with fewer adverse effects.

Regarding the growing alternative medicines, essential oils derived from Chinese herbs are widely found to be active in treating BA. Low toxicity, low side-effects, high in solubility, and brief biological half-lives make the compounds valuable for usage in medical applications. Essential oil from Bupleurum chinense modulates ectopic olfactory receptors to treat asthma [8], and the oil derived from Artemisia argyi could alleviate asthma due to interference of the 5-LOX-CysLTs and IDO-1-KYN pathways [9]. Additionally, the essential oil of Abies holophylla leaves is effective against asthmatic airway inflammation [10]. These results emphasize the profound anti-asthmatic potential of essential oils. Qing Pi (QP) stands for a qi-balancing agent from Rutaceae plant, which is so much valued in Chinese traditional medicine practice [11], and has numerous pharmacological potential benefits that interfere with the cardio-cerebrovascular, gastrointestinal, respiration systems, and smooth muscle efficiency [12]. Clinically, QP is usually administered to treat gastrointestinal disorders, remove phlegm, treat asthma, and improve myocardial performance [13]. This medicinal plant contains abundant essential oils, which are its main pharmacodynamic agents [14]. The essential oils promote the regulation and adjustment of qi and possess antibacterial and anti-inflammatory properties and thus have huge potential in BA therapy [15]. Although QP's essential oil has demonstrated some clinical value in treating BA, the key components and mechanisms of action remain largely undefined. Thus, identifying these elements and elucidating their mechanisms represent critical challenges for future research.

Network pharmacology provides a comprehensive method for elucidating and forecasting the complex pharmacodynamic properties of Chinese herbal compounds. This approach involves a systemic examination of molecular interactions between therapeutic agents and their targets, which is crucial for understanding how natural compounds influence disease processes [16]. Complementary to this, molecular docking analyzes the potential interactions between drug molecules and protein targets to forecast binding efficacy and specificity [17]. In addition, gas chromatography-mass spectrometry (GC-MS) makes use of the separation principle of gas chromatography coupled with the detection principle of mass spectrometry in identifying and quantifying volatile agents [18]. The present study conducted qualitative and quantitative analysis of QP using GC-MS, and then, by integrating network pharmacology and molecular docking, unveiled the basic ingredients and action mechanisms of QP essential oil for the treatment of BA, which would establish a sound scientific basis for its clinical application and the development of new drugs.

Materials and methods

Vapor distillation extraction of QP essential oil

QP was sourced from Anhui Huifeng National Medicine Co., Ltd. (Bozhou, Anhui, China). 40 g of QP powder was added to a 1,000 mL round-bottom flask along with 400 mL of water, soaked for 2 hours, and then refluxed for 5 hours to distill the mixture of essential oils. Subsequently, an appropriate amount of n-hexane (AR, purity ≥ 97.0%) (Sinopharm Chemical Reagent Co., Ltd., Shanghai, China) was added, the mixture was stirred thoroughly and allowed to settle for 30 minutes to facilitate phase separation. The top layer enriched with essential oil was purified using a SY-2000/5000 rotary evaporator (Shanghai Yarong Biochemical Instrument Factory, Shanghai, China) to extract the n-hexane. And then, 0.5 g of anhydrous sodium sulfate (AR, purity ≥ 99.0%) (Tianjin Kermel Chemical Reagent Co., Ltd., Tianjin, China) was introduced to the oil to remove any residual moisture. The resultant essential oil was stored in a dark glass bottle under refrigeration and sealed to preserve its integrity until further analysis.

Component analysis

The composition of QP essential oil was determined using an Agilent 7890A/5975C GC-MS instrument (Agilent Technologies, Santa

Clara, California, USA). The chromatographic peaks detected were matched with entries in the NIST08 spectral library (National Institute of Standards and Technology, Gaithersburg, MD, USA). Quantitative evaluation involved the correlation of peak areas with the concentrations of chemical constituents, given their direct proportionality. These peak areas were measured automatically by the instrument and processed using MSD ChemStation software (Agilent Technologies, Santa Clara, California, USA) to perform integral calculations. The quantitative analysis of each chemical component is then achieved using the peak area method.

Network pharmacology

(1) Target protein retrieval

Target proteins correlating with the chemical composition were identified using the Swiss Target Prediction (http://swisstargetprediction.ch/) and Herb database (http://herb.ac.cn/) with a selection criterion of "Probability > 0." BA targets were sourced from the GeneCards database (https://www.genecards.org/). The Venny 2.1.0 tool (https://bioinfogp.cnb.csic.es/tools/venny/) was employed to intersect the chemical composition targets with BA targets, identifying potential therapeutic targets of QP essential oil for BA treatment.

(2) Construction of the network model

The STRING database (https://string-db.org/) was used by choosing the "Homo sapiens" configuration to look for protein-protein interactions (PPI) involving the identified targets. The PPI network diagram was created by importing the output results into Cytoscape 3.7.1 (https://cytoscape.org/) from TSV format. By utilizing Cytoscape 3.7.1's “Network Analyzer” function, the network metrics were examined, and the core targets were chosen according to their degree of connectedness. Key components were also found by analyzing their connectivity within a built component-target-disease network diagram.

(3) Investigation of Gene Ontology (GO) function and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment

Potential targets were uploaded to the DAVID database (https://david.ncifcrf.gov/) utilizing “official gene symbol” as the identifier and configuring the list type as “gene list” for the species “Homo sapiens”. A *P* value threshold of less than 0.05 was employed for the purpose of filtering. Data pertaining to KEGG pathways, biological processes (BP), molecular functions (MF), and cellular components (CC) were acquired and subjected to visual analysis.

(4) Molecular docking

Three-dimensional models of key components were constructed using Chemdraw (https://www.chemdraw.com.cn/) after downloading their SDF files from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). The structures of target proteins were obtained in PDB format from the PDB database (https://www.rcsb.org/). Molecular docking was performed with AutoDock 1.5.7 (https://autodocksuite.scripps.edu/adt/) to explore the potential interactions between the active ingredients of QP essential oil and BA targets. Visualization of these interactions was accomplished by using PyMOL 2.3 (https://pymol.org/).

Results and discussion

Identification of QP essential oil composition

The composition of QP essential oil was analyzed using GC-MS. This analysis detected 37 chemical substances with those having a matching degree ≥ 90% being classified as the primary components (Table 1). These 14 principal substances accounted for 73.54% of the overall essential oil composition.

QP essential oil main component targets and disease target screening

Target screening of the main components was performed using Swiss Target Prediction database and Herb database. After integrating

Table 1. Main components of QP essential oil.

No.	Retention time (min)	CAS	Compound	Molecular formula	relative content (%)	Matching degree
1	8.98	5989-27-5	d-Limonene	$C_{10}H_{16}$	5.34	94
2	9.88	99-85-4	p-Mentha-1,4-diene	$C_{10}H_{16}$	0.75	95
3	19.20	20307-84-0	δ-elemene	$C_{15}H_{24}$	0.94	97
4	20.44	3856-25-5	α-Copaene	$C_{15}H_{24}$	8.09	95
5	21.02	515-13-9	β-elemene	$C_{15}H_{24}$	11.17	99
6	21.84	87-44-5	β-Caryophyllene	$C_{15}H_{24}$	2.76	99
7	22.90	6753-98-6	α-Caryophyllene	$C_{15}H_{24}$	3.05	98
8	23.85	23986-74-5	GermacreneD	$C_{15}H_{24}$	3.68	96
9	24.04	17066-67-0	β-selinene	$C_{15}H_{24}$	3.11	99
10	24.36	473-13-2	α-selinene	$C_{15}H_{24}$	3.54	98
11	24.53	31983-22-9	α-muurolene	$C_{15}H_{24}$	0.83	99
12	24.90	502-61-4	farnesene	$C_{15}H_{24}$	8.70	93
13	25.50	483-76-1	d-Cadinene	$C_{15}H_{24}$	5.67	95
14	32.83	515-17-3	γ-selinen	$C_{15}H_{24}$	15.91	98

and removing duplicates from both databases, 75 component targets were established. Additionally, 1,008 BA targets were sourced from the GeneCards database. Analysis with the Venny 2.1.0 program identified 28 potential targets, illustrated in Venn diagrams (Figure 1).

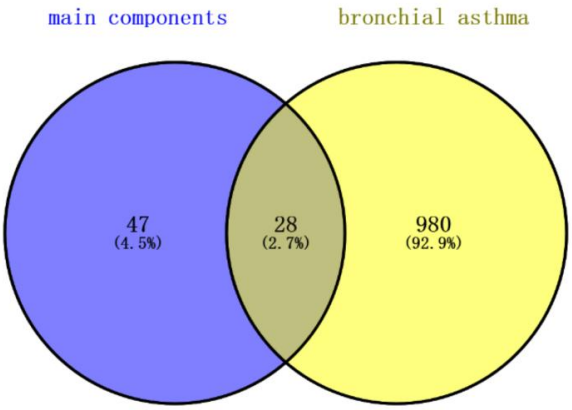


Figure 1. Venn diagram of components and disease targets.

Construction of a component-target-disease network diagram and analysis

By utilizing Cytoscape 3.7.1 software, a network diagram incorporating 14 main components and 28 targets was constructed (Figure 2). The network consisted of 43 nodes and 132 edges with interactions quantified by degree values. The "CytoNCA" plug-in was utilized for analysis. Components with a degree value of ≥ 10 were identified as key components of QP essential oil including α-Copaene, β-Caryophyllene, β-elemene, d-Limonene, and α-selinene. Recent studies have shown that α-Copaene can reduce airway inflammation in rats by inhibiting the TLR4 signaling pathway [19]. β-Caryophyllene has been found to suppress the expression of mucin genes in respiratory epithelial cells, thereby controlling mucin overproduction in asthma [20]. β-elemene impacts the ILK/Akt signaling pathway, easing airway constriction and reducing asthma symptoms [21]. d-Limonene is effective in alleviating allergic asthma [22]. α-selinene demonstrates significant anti-inflammatory, antibacterial, antioxidant, and anticancer activities [23]. Through the analysis of these key components, the therapeutic potential of QP essential oil in treating BA is further substantiated.

PPI network construction and analysis

The 28 potential targets were imported into the STRING database, setting the species to "Homo sapiens" to derive protein-protein interaction relationships. These results were then visualized in Cytoscape 3.7.1, producing PPI network

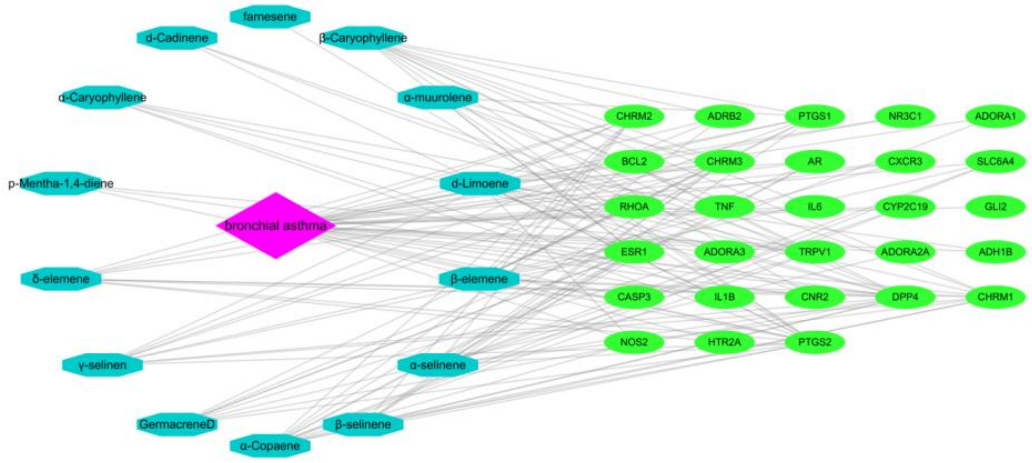


Figure 2. Compound-target-disease network diagram.

Table 2. Core targets in the PPI network.

No.	Gene abbreviation	Description	Degree
1	IL6	Interleukin 6	18
2	IL1B	Interleukin 1 Beta	18
3	TNF	Tumor Necrosis Factor	17
4	PTGS2	Prostaglandin-Endoperoxide Synthase 2	14
5	NR3C1	Nuclear Receptor Subfamily 3 Group C Member 1	14
6	CASP3	Caspase 3	14

diagram (Figure 3). The network contained 28 nodes and 117 edges. The "CytoNCA" plug-in was used to analyze the targets, identifying those with a degree of ≥ 14 as core targets, including IL6, IL1B, TNF, PTGS2, NR3C1, CASP3 (Table 2).

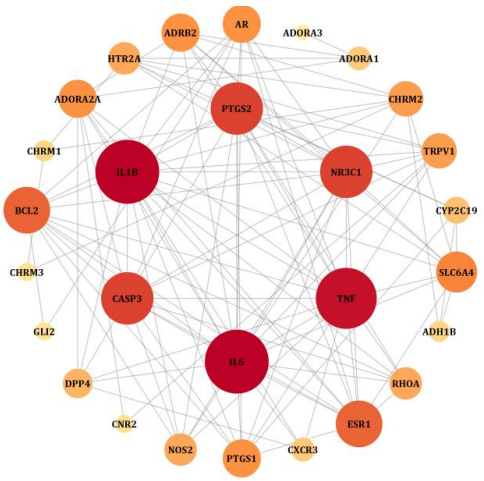


Figure 3. PPI network diagram.

Further analysis supported by relevant literature explored the potential impacts of these core targets on the progression of BA. IL6, a pro-inflammatory factor, significantly increases after infection, promoting the secretion and expression of mucin, thereby enhancing airway resistance and exacerbating BA [24]. IL1B produced by lung macrophages post-infection promotes neutrophilic inflammation and aggravates airway inflammation. Inhibiting IL1B production may alleviate the discomfort experienced by BA patients [25]. TNF activates ILC2 cells, which in turn secrete various pro-inflammatory factors increasing mucin secretion. Inhibiting TNF or its pathway can help reduce BA inflammation [26]. PTGS2 is involved in the arachidonic acid metabolism pathway, leading to increased PGD2 synthesis and inducing a hyperresponsive state in bronchial smooth muscle [27]. Variants of the NR3C1 gene may regulate BA inflammation by influencing IL-5 and

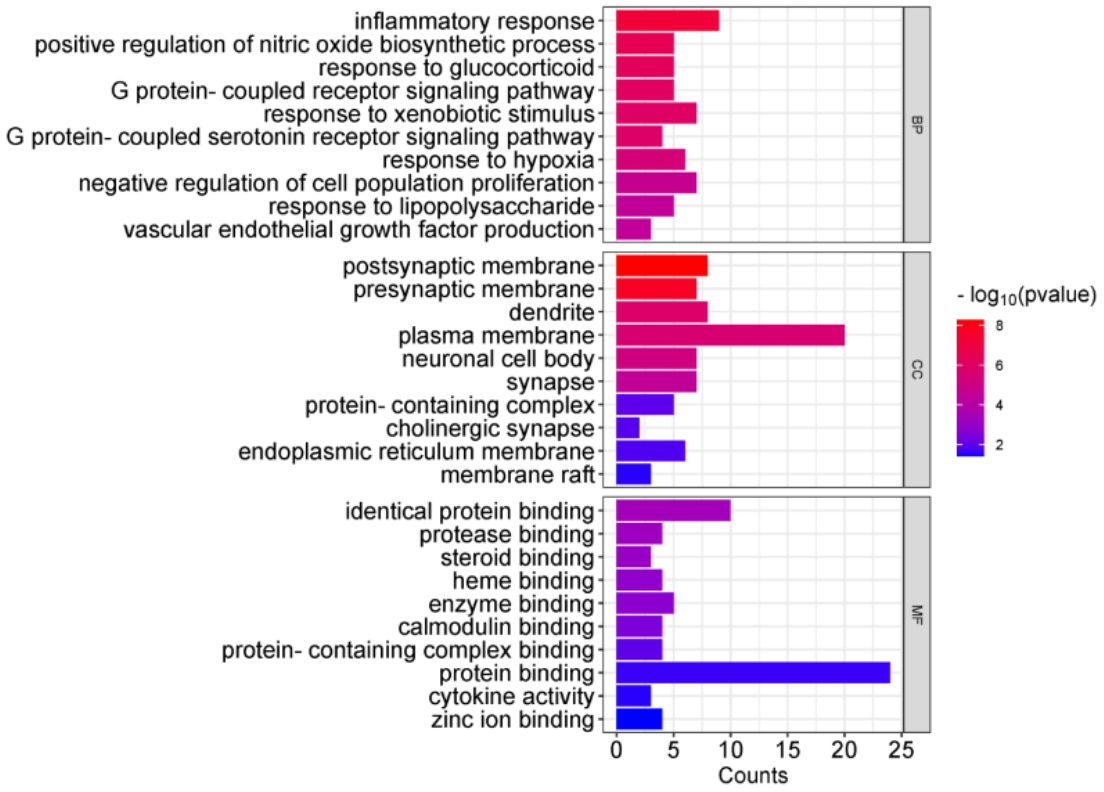


Figure 4. GO functional enrichment analysis.

IL-15 mRNA expression [28]. CASP3, a crucial apoptosis regulator, is implicated in acute respiratory distress syndrome (ARDS)-induced lung cell apoptosis, which compromises lung function and exacerbates BA symptoms [29]. This analysis affirmed the critical role these core targets play in BA treatment.

GO functional enrichment analysis

A total of 100 entries were obtained from the GO enrichment analysis carried out on the 28 possible targets using the DAVID database. These entries were organized in descending order of *P* value, and they included 62 BP, 14 CC, and 24 MF. A graphic representation of the top ten outcomes for BP, CC, and MF was presented in Figure 4. Inflammatory reactions, glucocorticoid responses, G protein-coupled receptor signaling, and negative regulation of cell population proliferation were all uncovered by BP analysis. CC analysis suggested that QP essential oil impacted the plasma membrane, neuronal cell bodies, protein-containing complexes, and membrane rafts, while MF analysis linked treatment of BA to identical protein binding, protease binding, heme binding, and enzyme binding.

KEGG pathway enrichment analysis

KEGG pathway enrichment analysis was performed on 28 potential targets using the DAVID database, yielding 55 significant signaling pathways. These pathways were ranked in ascending order of *P* value, and the top 20 were illustrated in a bubble chart (Figure 5). This analysis indicated that the primary pathways through which QP essential oil acted on BA included the calcium signaling pathway, IL-17 signaling pathway, and TNF signaling pathway, affecting genes such as IL6, IL1B, TNF, PTGS2, NR3C1, and CASP3. The literature indicates that dysregulated activation of the calcium signaling pathway increases intracellular calcium ion levels in airway smooth muscle cells, facilitating their

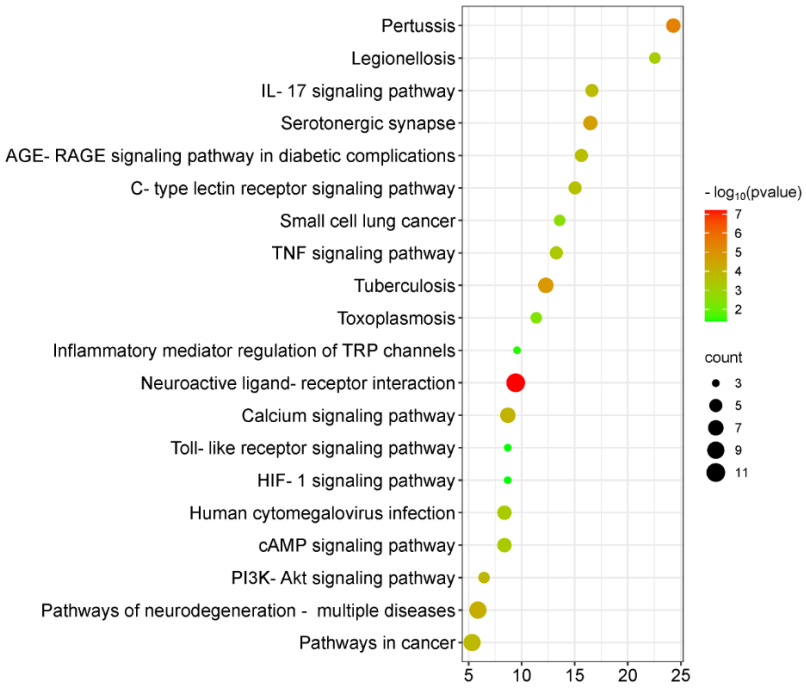


Figure 5. KEGG pathway enrichment analysis.

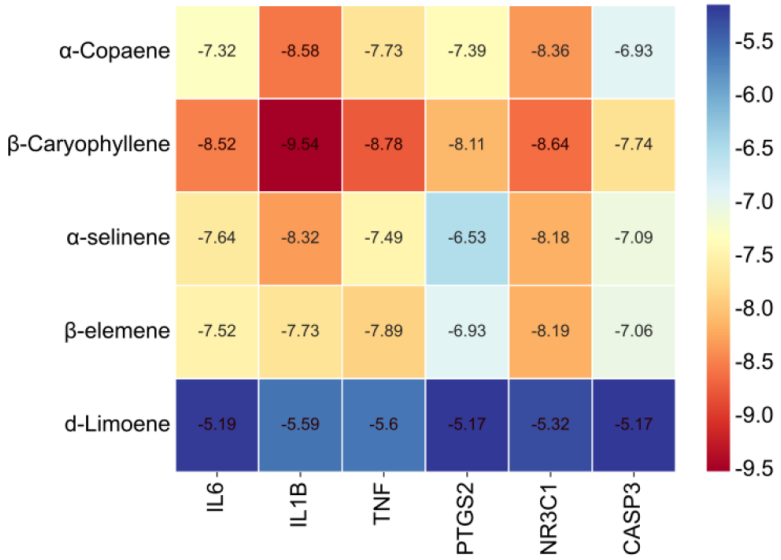
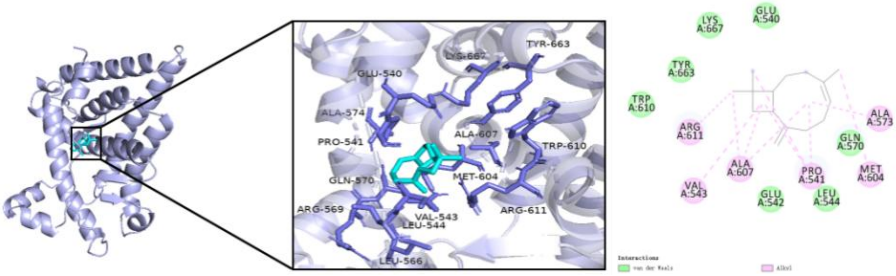


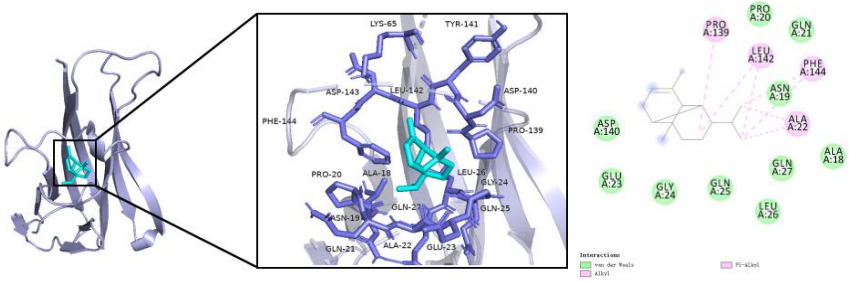
Figure 6. Molecular docking results (heat map).

contraction, which in turn narrows the airways and enhances resistance [30]. The IL-17 signaling pathway stimulates the activation of neutrophils and T cells, and in conjunction with other pro-inflammatory factors, suppresses anti-inflammatory agents, resulting in collagen production by airway epithelial cells. This process leads to the thickening and fibrosis of the airway walls, intensifying airway remodeling [31]. Activation of the TNF signaling pathway occurs when TNF-α binds to its receptor, causing airway epithelial and smooth muscle cells to release

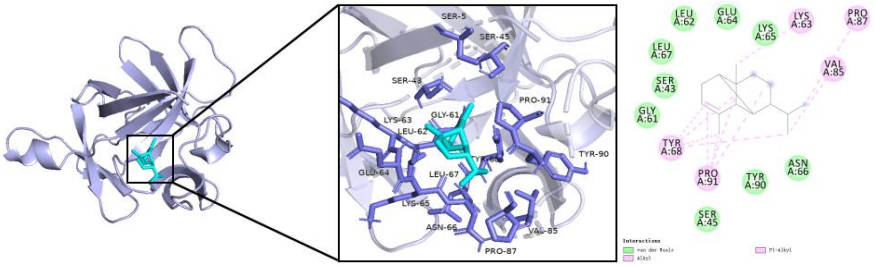
A. α-Copaene and NR3C1



B. β-Caryophyllene and TNF



C. β-Caryophyllene and IL1B



D. α-Copaene and IL1B

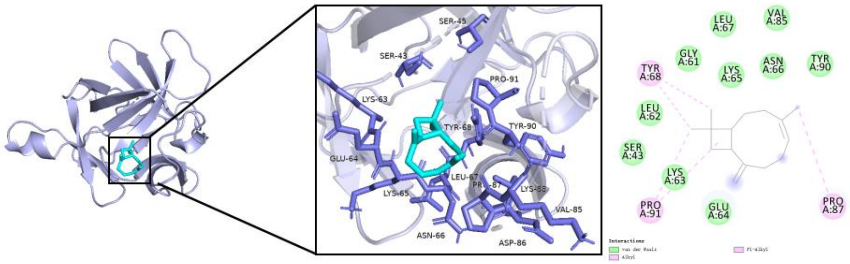


Figure 7. Molecular docking visual analysis.

various inflammatory mediators that enhance airway hyperresponsiveness and mucus production, thereby aggravating BA symptoms [32]. The pathways identified in this research corresponded closely with those recognized as critical in BA pathophysiology, confirming that the components of QP essential oil mitigated BA by modulating multiple pathways and synchronizing their actions.

Molecular docking verification

Molecular docking of 6 core targets and 5 key components was performed using binding energy as a metric. The results demonstrated that all docking binding energies were below -5kJ/mol, signifying robust interactions between core targets and key components (Figure 6). Significant interactions included α-Copaene with IL1B (-8.58 kJ/mol) and NR3C1 (-8.36 kJ/mol), as well as β-Caryophyllene with IL1B (-9.54 kJ/mol)

and TNF (-8.78kJ/mol), supplemented by visual analysis (Figure 7).

Conclusion

This study initially demonstrated that key components of QP essential oil such as α-Copaene, β-Caryophyllene, and β-elemene specifically targeted core proteins like IL-6, TNF, and PTGS2. These interactions modulated key signal transduction pathways, particularly the calcium signaling, IL-17 signaling, and TNF signaling pathways, effectuating a therapeutic impact on BA. This evidence provided a robust basis for further clinical application and pharmaceutical development. While network pharmacology clarified the principal material basis and action mechanisms by which QP volatile oil potentially treated BA, these findings carried certain limitations. Consequently, additional validation through cellular and animal experiments is imperative to enhance the comprehension of the mechanisms by which QP essential oil influences BA treatment.

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