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Network pharmacology and molecular docking reveal that honeysuckle blood components mitigate smoke inhalation-induced lung injury via NF-κB pathway

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Abstract
The active components of honeysuckle alleviate smoke inhalation-induced lung injury by reducing inflammation and oxidative stress. This study aimed to investigate the intervention mechanism of honeysuckle blood components in smoke inhalation-induced lung injury using network pharmacology and molecular docking technology. The targets of honeysuckle blood-entering components were identified through the Swiss Target Prediction and Similarity Ensemble Approach databases. The target genes associated with smoke inhalation-induced lung injury were retrieved from the GeneCards and CTD databases. Cytoscape 3.7.1 software was employed to construct the blood component-target network of honeysuckle. GO biological process enrichment analysis of target genes related to inhalation-induced lung injury in Flos Lonicerae was performed using the DAVID tool. KEGG pathway enrichment analysis of anti-aspiration lung injury target genes in Flos Lonicera was conducted using the KOBAS 3.0 tool. The top six core targets with the highest PPIs in the network were selected for molecular docking verification. AutoDock was used to perform molecular docking with the blood-entering components of honeysuckle to verify their binding capabilities. A total of 95 targets of the blood components of honeysuckle and 960 targets related to smoke inhalation-induced lung injury were identified through network pharmacological analysis. Fifteen common targets of the blood components of honeysuckle were identified: CTSD, KLF5, TTR, HIF1A, CAPN1, GRIN1, ADAM10, ERAP1, NFE2L2, LGALS3, TLR4, GRB2, NF-κB1, RPS6KA1, and PTPN11. Network PPI analysis indicated that NF-κB1 was among the core targets. GO and

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KEGG enrichment analyses revealed that the components of Lonicerae lonicerae in the blood exerted therapeutic effects by regulating biological processes such as inflammation, apoptosis, oxidative stress, and the NF-κB signaling pathway. Molecular docking results showed that the blood components of honeysuckle exhibited strong binding affinities to IL-1β, NF-κB, and other core targets. This study revealed the potential mechanism of action of honeysuckle blood-entering components against smoke inhalation-induced lung injury through the NF-κB signaling pathway, NF-κB1, and other core targets, using network pharmacology and molecular docking techniques, thereby providing a theoretical foundation for further research on the application of honeysuckle in treating smoke inhalation-induced lung injury.

Introduction

Smoke inhalation-induced lung injury is a common and serious clinical condition resulting from fires, industrial accidents, or other hazardous exposures. This type of injury not only causes direct damage to lung tissue structures—such as airway epithelial cells and alveolar membrane permeability—but also initiates complex inflammatory cascades and oxidative stress. These pathological processes further compromise lung function and pose serious threats to patient survival.[1] Honeysuckle, a traditional Chinese medicine, has a long history of use and is known for its properties in clearing heat, detoxifying, and dispelling wind and heat. Modern research has demonstrated that honeysuckle contains a variety of active compounds that exert significant physiological and pharmacological effects in the body.[2] However, the precise mechanisms through which honeysuckle mitigates smoke inhalation-induced lung injury remain unclear.

In recent years, the development of network pharmacology has offered a novel approach to studying the mechanisms of traditional Chinese medicine. Network pharmacology adopts a systematic perspective to uncover the complex relationships between drugs and diseases by integrating diverse data sources. It enables correlation analysis between the multiple components of traditional Chinese medicine and the various targets associated with diseases, thus breaking away from the traditional single-component, single-target research model. This aligns more closely with the multi-component, multi-target, and synergistic nature of traditional Chinese medicine.[3] Additionally, molecular docking technology can be employed to further verify the interactions between drug components and targets at the molecular level, offering more direct evidence for understanding mechanisms of action. Numerous cytokines and signaling pathways are involved in the pathophysiology of smoke inhalation-induced lung injury. Immune responses are central to its development, as exposure to smoke triggers the release of inflammatory cytokines such as TNF-α and IL-6, which intensify tissue damage and exacerbate the injury. Inflammation and immune dysregulation also contribute to oxidative stress, further impairing lung function. The active components of honeysuckle may help regulate these immune responses by modulating key signaling pathways and exerting anti-inflammatory effects, thereby enhancing the body's defense against the harmful impact of smoke inhalation.[4] Furthermore, regulatory immune mechanisms such as the Nrf2-ARE pathway are essential for maintaining cellular integrity and protecting against oxidative damage.[5] Given that the active components of honeysuckle are known to influence immune responses and inflammatory pathways, they may act as potential modulators of the immune system to alleviate smoke inhalation-induced lung injury. These active components may exert protective effects by interfering with key factors and signaling pathways involved in the injury process. Studies have shown that chlorogenic acid and other constituents in honeysuckle possess antioxidant properties, effectively scavenging free radicals and reducing cellular damage caused by oxidative stress.[6] Additionally, other components may inhibit excessive inflammatory responses by modulating inflammation-related signaling pathways.[7] However, these components exert their effects in vivo primarily in the form of blood components, and comprehensive studies on the mechanisms of honeysuckle's effects through blood components in smoke inhalation-induced lung injury remain limited. With the ongoing advancement of bioinformatics technologies, databases such as Swiss Target Prediction, Similarity Ensemble Approach, GeneCards, and CTD have been continuously refined, providing rich data resources for researchers. These platforms enable the rapid and precise identification of drug targets and disease-associated genes.[8,9] Furthermore, analytical tools such as Cytoscape, DAVID, and KOBAS play significant roles in network construction and enrichment analysis. As a result, extracting meaningful insights from complex data related to the active ingredients of Chinese medicines has become a major research focus and a growing trend.[10]

Previous studies on honeysuckle's therapeutic effects have mainly focused on individual components (e.g., chlorogenic acid) or isolated pathways (e.g., antioxidant activity), lacking a comprehensive perspective on its multi-component, multi-target mechanisms in the context of smoke inhalation-induced lung injury. Traditional pharmacological approaches often fall short in capturing the systemic interactions between bioactive compounds and disease-related pathways. In this study, network pharmacology and molecular docking were integrated to systematically explore the interactions between honeysuckle's blood components and targets associated with lung injury. This approach addresses the limitations of reductionist models and offers novel mechanistic insights into honeysuckle's immunomodulatory and anti-inflammatory functions. The findings of this research are expected to provide new ideas and a theoretical foundation for further exploration in this field.

Methods

Obtaining the targets of the blood-entering components of honeysuckle

Five major blood components—chlorogenic acid, luteolin, inositol, isochlorogenic acid A, and isochlorogenic acid C—were selected from the Swiss Target Prediction database, and their chemical structures were represented using SMILES format (Table 1).

The five major blood components of honeysuckle were entered into the designated input fields of the database. The prediction algorithm was set to the default ligand-based similarity method, with a similarity threshold of 0.5, to obtain the potential target information for these components.

The Similarity Ensemble Approach database was accessed, and the molecular fingerprints (Morgan fingerprint, radius 2) of the five blood components of honeysuckle were uploaded in accordance with the database's operational guidelines. The E-value threshold for the similarity search was set at 1e-5. The corresponding target data were retrieved, and after compiling the results for each component, duplicate targets were removed to obtain a set of unique target information.

Target genes involved in smoke inhalation-induced lung injury

In the GeneCards database, we entered the term "smoke inhalation-induced lung injury" along with related pathophysiological terms ("inflammatory response in smoke injury," "oxidative stress in") into the search box for "lung injury." Using the database's screening and sequencing function, we selected target gene information with a correlation score greater than 5 (out of a maximum score of 10) and extracted the potential target gene data.

The CTD database was accessed, and the retrieval function was used to search based on the disease classification code for smoke inhalation-induced lung injury (the code associated with respiratory tract injury in the ICD-10 system) and known associated genes (genes linked to inflammatory factors). This provided the target gene data stored in the database. Finally, the target genes obtained from both databases were integrated, and duplicates were removed to identify the unique target genes.

Construction of the blood component of the honeysuckle-target network

The honeysuckle composition and target information obtained from the previous steps were organized into a data format compatible with the software requirements of Cytoscape 3.7.1. The components and targets were represented as nodes, with the interactions between them as edges, and node tables were created (including attributes such as node name and type), along with edge tables (including attributes such as start and end nodes). Cytoscape 3.7.1 was used to import the organized data, utilizing the network construction function provided by the software. The force-directed layout algorithm was chosen, with the repulsive force constant between nodes set to 0.7 and the gravitational constant set to 0.3. The honeysuckle blood component-target network was then constructed, and the network was visually adjusted. The honeysuckle component node was represented as a green circle, the target nodes as blue squares, the edges in grey, and the edge thickness was set to 1.5px for clearer analysis and observation.

GO and KEGG enrichment analysis

The honeysuckle anti-inhalation lung injury target genes identified in the Cytoscape network were organized into a file format compatible with DAVID tools and stored in a text file with one gene per line. The DAVID tool interface was accessed, and the sorted gene files were uploaded. Parameters for GO biological process enrichment analysis were selected, with Homo sapiens and the latest version of the gene ontology database chosen for the analysis program. Additionally, the target genes associated with resistance to aspiration lung injury, identified in the previous step, were formatted into the input format required by the KOBAS 3.0 tool and stored in Entrez ID format. The KOBAS 3.0 tool was used to import the gene data, with the KEGG pathway enrichment analysis option selected. Relevant parameters were established based on the prompts, with humans chosen as the species and the hypergeometric distribution test selected as the statistical method. The analysis was then conducted, and the KEGG pathway enrichment results were obtained and analyzed. Both GO and KEGG enrichment analyses were performed with a significance threshold of an adjusted p-value < 0.05 (Benjamini-Hochberg correction). Pathways with a false discovery rate (FDR) < 0.1 were considered statistically significant.

Table 1 SMILES representations of blood components in honeysuckle.

Component name	SMILES format chemical structure
Chlorogenic acid	C1 = CC(= C(C = C1)O)OC(= O)C2 = C(C(= O)C3 = C(C = C(C = C3O2)O)O)O
Luteolin	C1=CC(=CC=C1C2=CC(=O)C3=C(C=C2)OCO3)O
Inositol	OC1C (CO) C (CO) C (CO) O1
Isochlorogenic acid A	C1=CC(=C(C=C1)O)OC(=O)C2=CC(=C(C(=O)O2)OC3=CC(=C(C=C3)O)O)O
Isochlorogenic acid C	C1=CC(=C(C=C1)O)OC(=O)C2=CC(=C(C(=O)O2)OC3=CC(=C(C=C3)O)OC4=CC(=C(C=C4)O)O)O

Molecular docking verification

The information for the top six core targets was extracted from the constructed network, and the molecular structure data for these targets were organized and saved in PDB file format. Similarly, the molecular structure data for the blood components of honeysuckle were prepared and stored in PDB file format, containing atomic coordinate information. The core target and molecular structure data of honeysuckle were imported into AutoDock software, with docking parameters set according to the software's operational guidelines. The grid box size was set to 60x60x60 Å, with a grid point spacing of 0.375 Å. The Lamarckian genetic algorithm was selected for docking, with a population size of 150 and 27,000 evolutionary generations. The molecular docking results were analyzed to assess the binding affinity between the core target and the blood components of honeysuckle. A lower binding energy indicated a stronger binding affinity.

Results

Intersection target of blood components of honeysuckle and lung injury caused by smoke inhalation

First, 95 target points for the components of honeysuckle in blood were obtained, with some of the target information shown in Table 2. A total of 960 disease targets related to smoke inhalation-induced lung injury were retrieved from the GeneCards and DisGeNET databases, and some of this disease target information is presented in Table 3. Using the hiplot online tool, 15 common targets were identified, including CTSD, KLF5, TTR, HIF1A, CAPN1, GRIN1, ADAM10, ERAP1, NFE2L2, LGALS3, TLR4, GRB2, NF-κB1, RPS6KA1, and PTPN11. These common targets are visualized in Figure 1.

Coexpression network of components of honeysuckle in the blood and lung injury caused by smoke inhalation

Cytoscape 3.8.0 software was used to construct a coexpression network illustrating the effects of the blood components of honeysuckle on lung injury induced by smoke inhalation, as shown in the figure below. The blood components of honeysuckle are capable of regulating the progression of smoke inhalation-induced lung injury by modulating targets such as CTSD, KLF5, TTR, HIF1A, CAPN1, GRIN1, ADAM10, ERAP1, NFE2L2, LGALS3, TLR4, GRB2, NF-κB1, RPS6KA1 and PTPN11 genes (Figure 2).

PPI network construction

The coexpressed genes related to blood components and smoke inhalation-induced lung injury were imported into the STRING database (https://cn.string-db.org/) to generate the PPI network. The network was then imported into the software to calculate the DC value. Key targets of pulmonary injury induced by smoke inhalation were identified based on interaction frequency and DC value. The results, shown in the figure below, suggest that CTSD, HIF1A, GRIN1, NFE2L2, LGALS3, TLR4, GRB2, NF-κB1, and PTPN11 may play key regulatory roles in the coexpression network.

Table 2 Predicted target information for the blood-entering components of honeysuckle.

Target	Function
MAPK14 (p38 MAPK)	Inhibits inflammation and reduces cell damage
NF-κB	Inhibit NF-κB signaling pathway and reduce inflammatory response
PI3K/Akt	Inhibit cell proliferation, anticancer effect
TLR4	Regulate inflammation and reduce nerve damage
HIF-1α	It has a protective effect on ischemic injury
Bax/Bcl-2	Induction of apoptosis, anticancer effect
TGF-β/Smad	Inhibition of fibrotic process
IL-6	Inhibit inflammatory response and reduce cytokine release
TNF-α	Inhibits tumor necrosis factor, reduces inflammation and immune response
Keap1/Nrf2	Protects cells through antioxidant action
MMP-9	Inhibit matrix metalloproteinases and prevent tissue degradation
COX-2	Inhibit cyclooxygenase and reduce inflammation
JAK/STAT	Regulates cell proliferation and immune response
CXCL8	Reduce inflammatory response and inhibit chemokine release
NOD-like receptors	Inhibit the formation of inflammatory bodies and reduce inflammatory response
HMGB1	Regulates cell damage and inflammation
TLR2	Regulate immune response and reduce nerve damage
Caspase-3/9	It can induce cell apoptosis and play an anticancer role
EGFR	Inhibits cell proliferation, especially in cancer treatment
FOXO3	Regulates apoptosis and stress response

Table 3 Identified disease-related targets associated with smoke inhalation-induced lung injury.

Target	Function
TP53 (p53)	Regulate apoptosis and play a role in DNA repair
UBC (ubiquitin C)	Protein degradation and cell signal transduction
mTOR	Regulate autophagy and cell metabolism
EGFR	Promote cell proliferation
MAPK3 (ERK1)	Regulate cell proliferation and differentiation
IL-1β	Promote inflammatory response
MMP-13	Participate in matrix degradation
Sox9	Regulate matrix synthesis and maintenance of cells
Nrf2	Key transcription factor in antioxidant stress response
COL2A1 (Collagen II)	Main component of matrix
Aggrecan	Moisture retention and matrix stability
TNF-α	Inflammatory response
PI3K/Akt	Regulate cell survival and proliferation
MMP-1	Matrix metalloproteinase, participate in matrix degradation process
SHP2	Regulate cell signal transduction
ERK1/2	Regulate cell proliferation and survival
IL-6	Participate in inflammatory response
MMP-3	Participate in matrix degradation
NAT	Regulate cartilage generation and osteogenesis process
CRISPR/Cas9	Gene editing

Enrichment analysis

GO enrichment analysis

The results of the GO enrichment analysis revealed that the blood components of honeysuckle were associated with biological processes such as oxidative stress, cellular stress, neutrophil regulation, insulin-like growth factor binding, and phosphorylated binding sites, as shown in Figure 4.

KEGG enrichment analysis

In this study, KEGG enrichment analysis revealed 15 signal transduction pathways significantly associated with smoke inhalation-induced lung injury. These included the NF-κB signaling pathway, neurotrophin signaling pathway, Ras signaling pathway, HIF-1 signaling pathway, apoptosis signaling pathway, MAPK signaling pathway, PI3K-Akt signaling pathway, neurodegeneration pathways involved in diseases such as inflammatory bowel disease, chemical carcinogenesis, and reactive oxygen species, as well as the Toll-like receptor signaling pathway, C-type lectin receptor signaling pathway, T cell receptor signaling pathway, and Th17 cell differentiation. Among these, the NF-κB signaling pathway was the most significantly enriched. Based on the NF-κB signaling pathway, we chose to study the mechanism by which honeysuckle affects blood components in the treatment of smoke inhalation-induced lung injury, providing a novel therapeutic direction for its prevention and treatment, as shown in Figure 5.

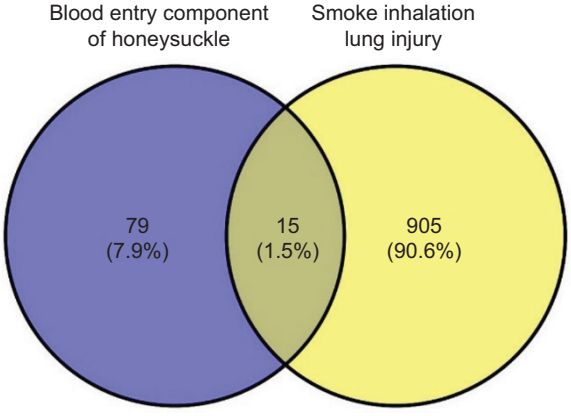

Figure 1 Common targets shared between the blood-entering components of honeysuckle and smoke inhalation-induced lung injury.

Molecular docking

A total of five key targets (GRB2, HIF1A, LGALS3, NF-κB, and TLR4) of genes coexpressed with the blood components of honeysuckle and smoke inhalation-induced lung injury were identified. The combination of the blood components of honeysuckle and the key targets was found to be stable. Since IL-1β is a transcribed protein of NF-κB, molecular docking techniques were employed, revealing that the blood components of honeysuckle bound well to IL-1β, as shown in the figures below (Figures 5-11).

Residues Asp104, Glu71, Arg67, Ser141 and Asn143 on the GRB2 protein receptor form hydrogen bonds with the blood components of Lonicerae, and residues Val105 and Lys109 form hydrocarbon interactions with Lonicerae. The Trp121 residues on the receptor form hydrophobic interactions with the blood components of honeysuckle.

The residues of Gln304, His286, Leu282 and Arg306 on the HIF1A protein receptor form hydrogen bond interactions with the blood component of honeysuckle, and the residues of Asp283, Leu282 and Gln304 form hydrogen interactions with the blood component of honeysuckle.

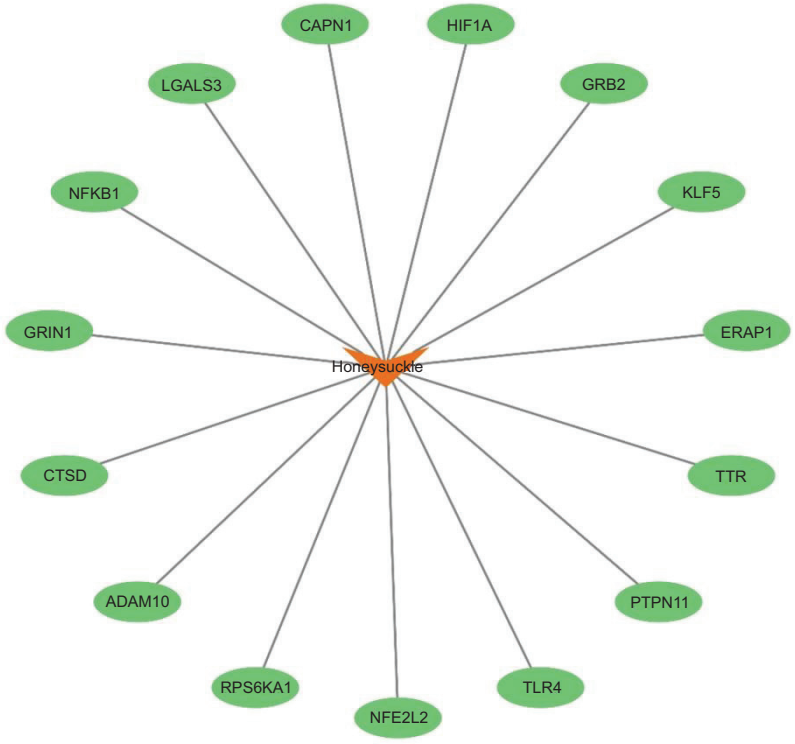

Figure 2 Coexpression network illustrating the interaction between blood components of honeysuckle and targets associated with smoke inhalation-induced lung injury.

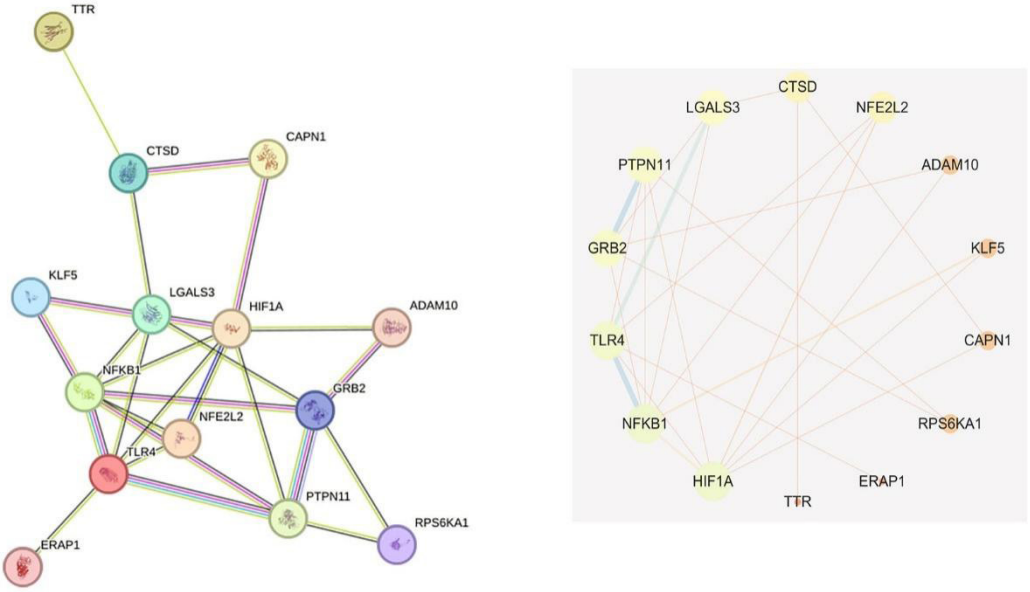

Figure 3 Construction of the PPI network of genes coexpressed with the blood components of honeysuckle flower and smoke inhalation-induced lung injury**.** (A) Construction of the coexpressed gene PPI network between blood components of honeysuckle and smoke inhalation-induced lung injury. (B) Screening of key regulatory targets within the network.

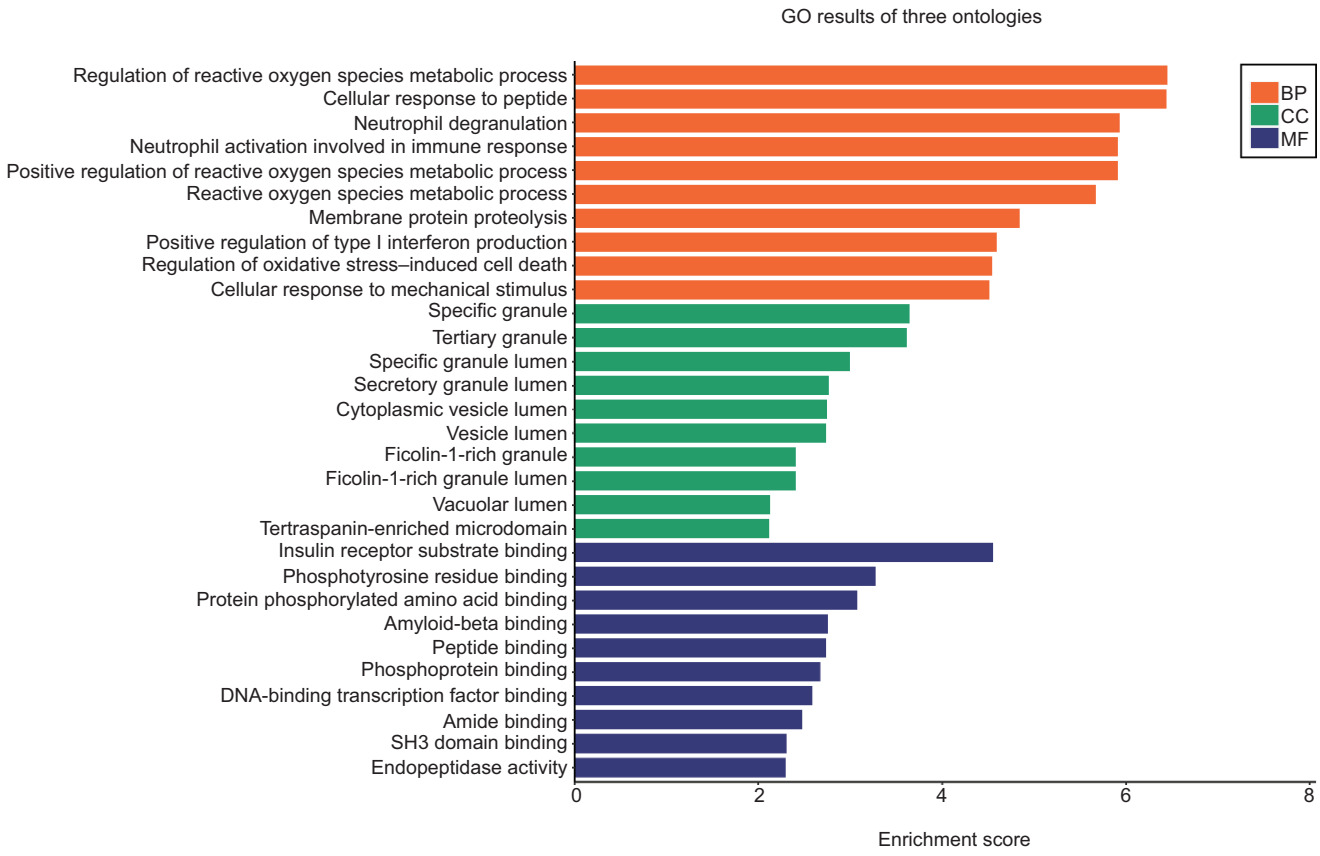

Figure 4 GO enrichment analysis of genes coexpressed between the blood components of honeysuckle and smoke inhalation-induced lung injury.

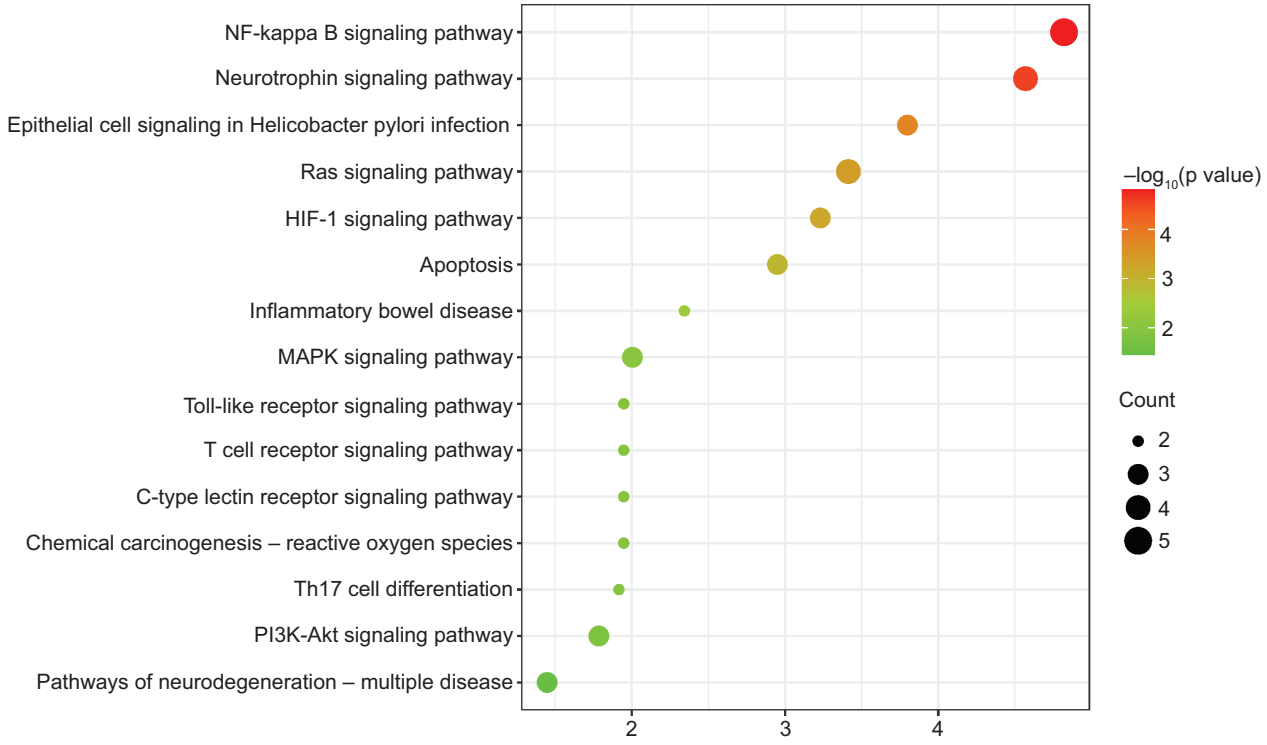

Figure 5 KEGG enrichment analysis of genes coexpressed between blood components of honeysuckle and smoke inhalation-induced lung injury.

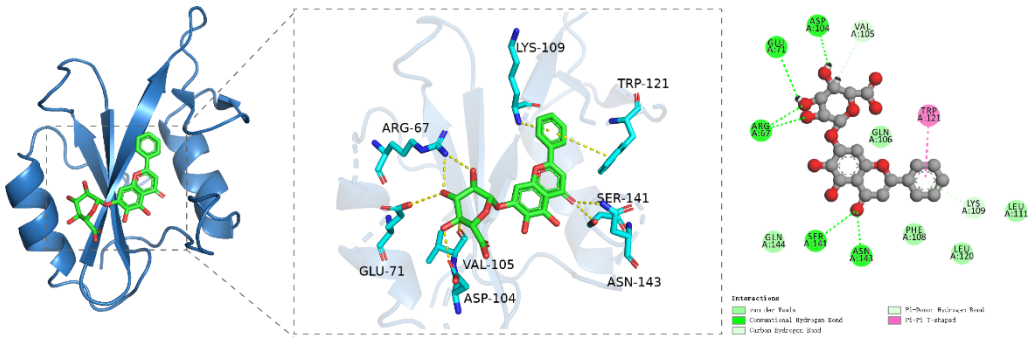

Figure 6 Binding of honeysuckle components to blood via the GRB2 protein receptor.

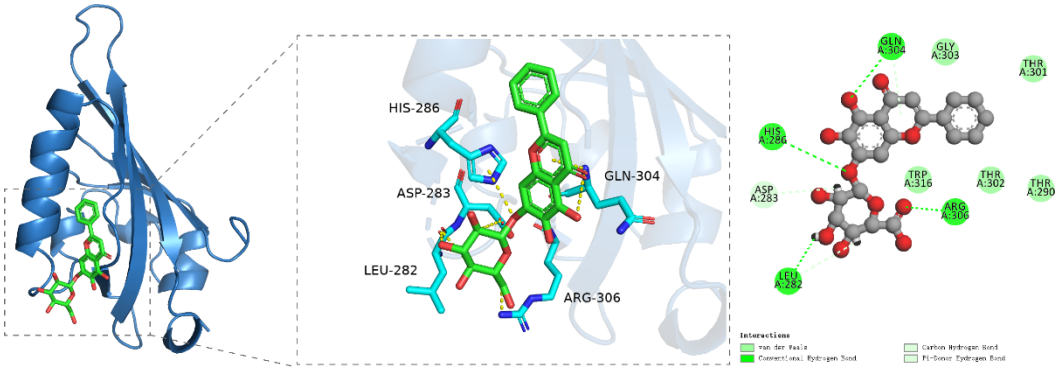

Figure 7 Binding of honeysuckle components in the blood bind to the HIF1A protein receptor.

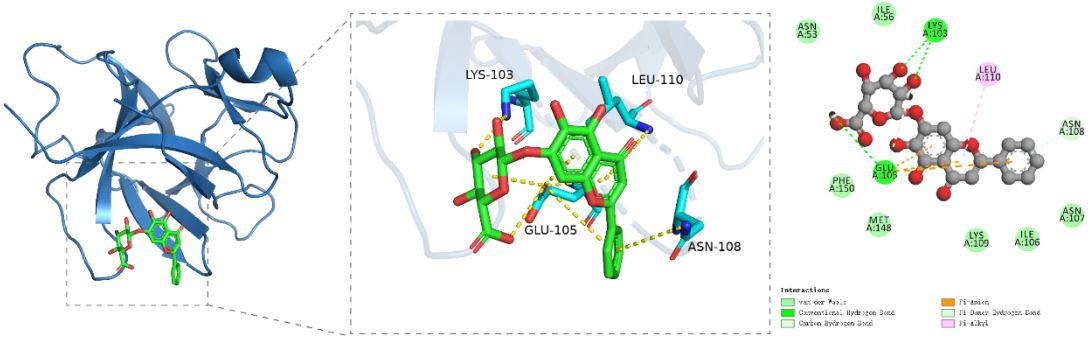

Figure 8 Binding of the blood component of honeysuckle binds to the IL-1β protein receptor.

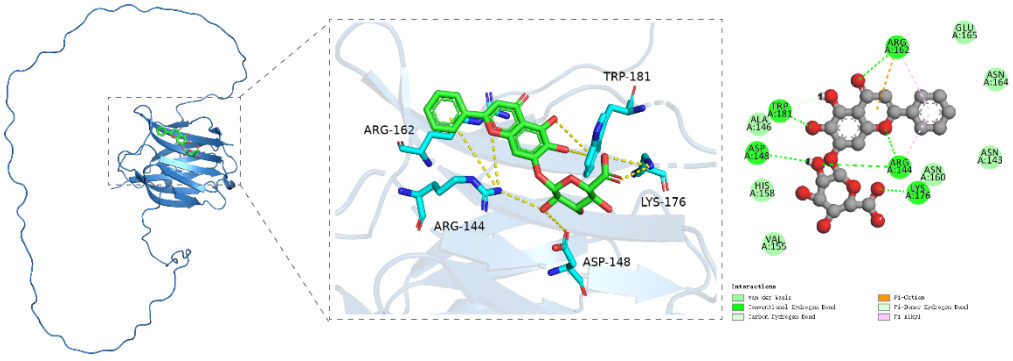

Figure 9 Binding of the blood component of honeysuckle to the LGALS3 protein receptor.

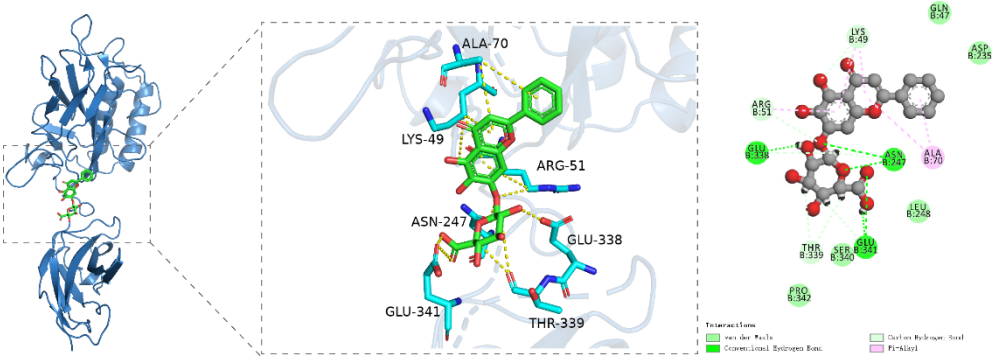

Figure 10 Binding of the blood components of honeysuckle to the NF-κB protein receptor.

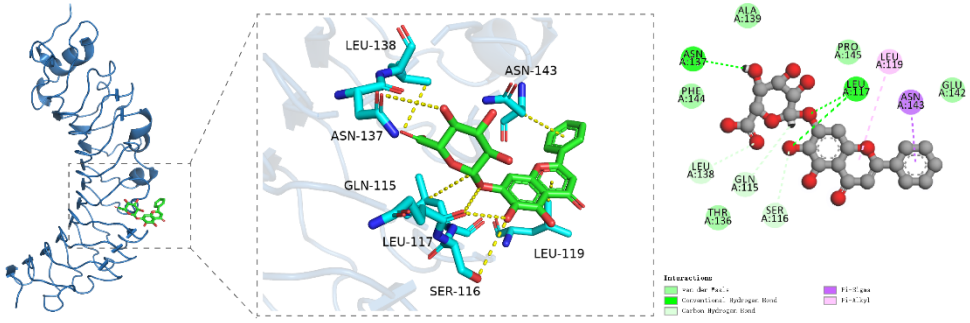

Figure 11 Binding of the blood component of honeysuckle to the TLR4 protein receptor.

Lys103 and Glu105 residues on the IL-1β protein receptor form hydrogen bond interactions with the blood components of honeysuckle, and Leu108 residues form hydrophobic interactions with these residues. The residues at Asn108 and Glu105 on the receptor interact with the blood components of honeysuckle. The Glu105 residue also forms electrostatic interactions with the compound.

The Arg162, Trp181, Asp148, Arg144, and Lys176 residues on the LGALS3 protein receptor form hydrogen bond interactions with the blood component of honeysuckle, with which the Arg162 residue also forms hydrophobic and electrostatic interactions. Additionally, the Arg144 residue on the receptor forms hydrophobic interactions with the blood component of honeysuckle. Residues Trp181 and Lys176 further form hydrocarbon interactions with the blood components of honeysuckle.

Residues of Asn247, Glu341 and Glu338 on the NF-κB protein receptor form hydrogen bond interactions with the blood components of Lonicerae, and residues Lys49, Arg51, Thr339, Glu341, Glu338 and Asn247 form hydrocarbon interactions with flos. The Ala70 and Lys49 residues on the receptor form hydrophobic interactions with the blood component of honeysuckle.

Residues Asn137 and Leu117 on the TLR4 protein receptor interact with the blood components of honeysuckle and with residues Leu138, Gln115 and Ser116. Residue Leu119 forms hydrophobic interactions with the blood components of honeysuckle, and residue Asn143 forms Pi-sigma interactions with the blood components of honeysuckle.

Discussion

In this study, 15 common targets of the blood components of honeysuckle and smoke inhalation-induced lung injury were identified through the combined application of network pharmacology-related databases. A total of 95 target points for the blood-entering components of honeysuckle and 960 disease targets associated with smoke inhalation-induced lung injury were identified, with 15 common targets shared between the two. Several of these targets are closely linked to immune regulation, emphasizing honeysuckle's potential to modulate the immune response in lung injury. Notably, NF-κB1, a key regulator of inflammation, plays a central role in immune and inflammatory pathways. By targeting NF-κB1, honeysuckle may help reduce inflammation and modulate immune responses, potentially mitigating the harmful effects of smoke exposure. Additionally, key targets such as TNF-α and the JAK/STAT signaling pathways were identified, both of which are crucial for regulating the inflammatory cascade and immune cell proliferation. Honeysuckle's active components may inhibit TNF-α, thereby reducing immune-mediated damage. Furthermore, the involvement of TLR2 suggests that honeysuckle could regulate immune responses and reduce secondary injuries, such as nerve damage. Together, these findings underscore the immunomodulatory potential of honeysuckle in smoke inhalation-induced lung injury, providing a promising foundation for future therapeutic interventions. The identified targets, including TNF-α, JAK/

STAT, and TLR2, play crucial roles in the immune response to smoke inhalation-induced lung injury. TNF-α mediates inflammation and immune activation, while JAK/STAT signaling regulates immune cell proliferation and survival. TLR2 is involved in pathogen recognition and immune modulation. The components of honeysuckle may regulate these pathways, reducing inflammation and immune damage, thereby protecting lung tissue. These common targets provide key insights for further understanding the mechanism of action of honeysuckle. Specific molecular targets were also analyzed, among which cathepsin D (CTSD) is a lysosomal protease that plays an important role in apoptosis and autophagy. In lung injury caused by smoke inhalation, the apoptotic and autophagic processes of cells may be disrupted. The regulation of CTSD by components of honeysuckle in the blood may help restore normal cell death and renewal mechanisms.[11] Kruppel-like factor 5 (KLF5) is a transcription factor involved in various biological processes, including cell proliferation, differentiation, and inflammatory responses. In an inflammatory environment, KLF5 may be abnormally activated, and its regulation by honeysuckle may help inhibit excessive inflammatory responses.[12] The transthyretin protein (TTR) plays a key role in maintaining the normal transport and metabolism of thyroid hormones. Smoke inhalation-induced damage may disrupt the body's metabolism, and the effect of honeysuckle on TTR may help restore metabolic balance.[13] Hypoxia-inducible factor-1 α (HIF-1A) is activated under hypoxic conditions, and the local hypoxic environment caused by smoke inhalation can alter HIF-1A expression. Honeysuckle's regulation of HIF-1A may be crucial for improving the hypoxic state and alleviating the related pathological processes.[14] Calpain 1 (CAPN1) is involved in cell signal transduction and cytoskeletal regulation, playing a role in the cellular stress response. Honeysuckle's regulation of CAPN1 may influence the adaptive response of cells to stress. N-methyl-D-aspartate receptor subunit 1 (GRIN1) is vital for the nervous system and may cause changes in nerve regulation following lung injury. The regulation of GRIN1 by honeysuckle could impact the neural repair mechanisms in lung injury.[15]

Network PPI analysis revealed that NF-κB1 was one of the core targets. The NF-κB signaling pathway plays a key regulatory role in the inflammatory response. In smoke inhalation-induced lung injury, inflammation is a core pathological process. The release of inflammatory factors and activation of inflammatory cells lead to the destruction and dysfunction of lung tissue. Activation of NF-κB1 promotes the transcription and expression of various inflammatory factors, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6). Regulation of NF-κB1 by the transport of honeysuckle components into the blood may reduce the production of these inflammatory factors, thereby inhibiting inflammation by suppressing NF-κB1 activation. This finding aligns with previous studies showing that many natural products exert anti-inflammatory effects by regulating the NF-κB signaling pathway.[16] GO enrichment analysis further revealed that the blood components of honeysuckle played a therapeutic role by modulating biological processes such as inflammation, apoptosis, and oxidative stress. The inflammatory response is an early and ongoing process in smoke inhalation-induced lung injury, and the infiltration of inflammatory cells and release of inflammatory factors contribute to disordered tissue injury and repair processes. Regulation of the inflammatory response by honeysuckle may occur through various mechanisms, including its influence on chemotaxis, adhesion, and activation of inflammatory cells, as well as the regulation of transcription, translation, and secretion of inflammatory factors.[17] Apoptosis plays a crucial role in tissue repair and remodeling after lung injury. In smoke inhalation-induced lung injury, apoptosis may be either overactivated or inhibited, resulting in tissue damage and impaired repair. Honeysuckle's regulation of apoptosis may help maintain the balance between apoptosis and cell survival, promoting normal tissue repair. Oxidative stress is another key mechanism of lung injury caused by smoke inhalation. The production of free radicals and an imbalance in the antioxidant system lead to oxidative damage to cells and tissues. The blood components of honeysuckle may alleviate oxidative stress by enhancing the activity of antioxidant enzymes or directly scavenging free radicals.[18] KEGG enrichment analysis revealed the involvement of the NF-κB signaling pathway, which further emphasizes honeysuckle's important role in regulating the inflammatory response. Additionally, other signaling pathways may be involved, with complex interactions occurring between them. For instance, the NF-κB signaling pathway can interact with the MAPK signaling pathway to jointly regulate biological processes such as inflammation and apoptosis.[19]

The molecular docking results revealed that the blood components of honeysuckle exhibited strong binding affinity to IL-1β, NF-κB, and other core targets. These findings provide molecular-level evidence of a direct interaction between the blood components of honeysuckle and its targets. IL-1β is a critical inflammatory factor that plays a central role in initiating and maintaining the inflammatory response. The strong binding affinity between honeysuckle's blood components and IL-1β supports the idea that it may reduce the inflammatory response, potentially by inhibiting IL-1β activity or its receptor binding. The strong binding affinity of honeysuckle with NF-κB further supports the mechanism of its anti-inflammatory effect through regulation of the NF-κB signaling pathway. This binding may alter the conformation, activity, and interactions of NF-κB with other molecules, inhibiting its transcriptional activity and the expression of downstream inflammatory factors. This finding aligns with network pharmacological analyses and similar reports,[20] suggesting that honeysuckle acts directly on key inflammatory targets at the molecular level.

Honeysuckle contains a variety of bioactive components that may work synergistically in treating smoke inhalation-induced lung injury. Components like chlorogenic acid and luteolin can target different molecules or signaling pathways individually, but their combined effects result in a synergistic regulation of key biological processes such as inflammation, apoptosis, and oxidative stress. This multicomponent synergistic effect is a hallmark of traditional Chinese medicine (TCM), allowing it to address the complex pathological processes of diseases at multiple levels. Using network pharmacology and molecular docking techniques, we have systematically explored how the blood components of honeysuckle influence lung injury caused by

smoke inhalation, both at the global and molecular levels. While previous research has primarily focused on individual components or targets, this study highlights the multicomponent, multitarget, and multisignaling characteristics of honeysuckle by integrating multiple databases and analytical tools. Future research will involve in vitro and in vivo experiments, such as treating LPS-stimulated RAW264.7 macrophages with honeysuckle extracts to assess NF-κB phosphorylation and IL-1β secretion, as well as using a murine smoke inhalation model to evaluate lung histopathology, inflammatory cytokine levels, and NF-κB pathway activation following honeysuckle intervention.

Conclusion

In this study, network pharmacology and molecular docking techniques were employed to investigate how the blood-entering components of honeysuckle influence smoke inhalation-induced lung injury. Through analysis of multiple databases, 15 common targets were identified, with NF-κB1 emerging as one of the core targets. GO and KEGG enrichment analyses indicated that the components of honeysuckle in the blood exert therapeutic effects by regulating biological processes such as inflammation, apoptosis, oxidative stress, and the NF-κB signaling pathway. Molecular docking studies revealed that the blood components of honeysuckle exhibited strong binding affinities to IL-1β, NF-κB, and other core targets. These findings highlight the multicomponent, multitarget, and multi-signaling pathway characteristics of honeysuckle, suggesting potential synergistic effects between its various components.

Author Contributions

All authors contributed equally to this article.

Conflict of Interest

The authors declare no conflict of interest.

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