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Exploring the Antibacterial and Antiviral Mechanisms of Baiyaozi Via Network Pharmacology

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Abstract: *This paper aims to analyze the antibacterial and antiviral active components of Baiyaozi and predict its molecular mechanisms via network pharmacology. The Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) and literature were used to screen active components of Baiyaozi (Radix Stephania cepharantha), and Pubchem and Swiss Target Prediction were used to collect the targets of the active components. The GeneCards database was used to search and screen the antibacterial and antiviral targets, intersecting with the practical components' targets to obtain the antibacterial and antiviral core targets of Baiyaozi. Then, the active ingredients and target genes were introduced into Cytoscape to construct the active component-target network regulation map of Baiyaozi. The STRING database was used for protein-protein interaction (PPI) network analysis, and the DAVID platform was used to conduct GO functional and KEGG pathway enrichment analyses of common targets. Eight active ingredients of Baiyaozi acted on 67 antibacterial targets and 130 antiviral targets. Cepharanthine, isocorydine, and berberine might be the main antibacterial and antiviral components of Baiyaozi. The GO function and KEGG pathway enrichment analyses of common targets suggested that the antibacterial and antiviral pathways of Baiyao might focus on apoptosis, autophagy, tumor necrosis factor signaling pathway, HIF-1 signaling pathway, and the PI3K-Akt pathway. Also, the comprehensive PPI, GO, and KEGG analysis indicated that HSP90AA1, SRC, and AKT1 might be the main targets. Conclusion: Baiyaozi has multi-component, multi-target, multi-pathway antibacterial and antiviral molecular mechanisms, providing a theoretical reference for further interpretation.*

Keywords: *Baiyaozi; Traditional Chinese medicine antibiotics; Antiviral; Immune regulation; Network pharmacology*

1. Introduction

Baiyaozi is the dry tuber of *Stephania Cepharantha hayata* [1], a plant of the Menispermaceae family. The chemical composition of Baiyaozi mainly includes luteanin, cepharanthine, isotetrandrine, cepharamine, homoaromoline, berberine cepharanone A, berberine cepharanone B, berberine, and crebanine. Baiyaozi has various functions, including clearing heat and detoxifying, cooling blood and stopping bleeding, dispersing stasis, and reducing swelling, which can be used for acute hepatitis, bacillary dysentery, and acute appendicitis. Topical application can treat mumps, lymphadenitis, and neurodermatitis [2]. Recent studies have shown that Baiyaozi has anti-cancer, analgesic, sedative, antibacterial, anti-inflammatory, immune enhancement, drug resistance reversal, and anti-arrhythmia pharmacological effects [3]. Moreover, by mixing Baiyaozi extract with antibiotics, such as β-lactam, aminoglycoside, and macrolide, the antibacterial activity can be significantly enhanced, and the mixtures have a strong inhibitory effect on bacterial drug resistance [4]. However, the mechanisms underlying Baiyaozi's effects remain unclear.

Antibiotics have been widely used to treat bacterial infections since their discovery in the 1930s [5]. Nevertheless, antibiotic overuse and abuse greatly promote the emergence of antibiotic-resistant bacteria (ARBs) and accelerate the spread of multi-drug-resistant bacteria and antibiotic-resistance genes (ARGs) worldwide, such as vancomycin-resistant *Enterococcus* [6] and methicillin-resistant *Staphylococcus aureus* [7]. ARBs have a very low cure rate and the second-highest death rate after

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malignant tumors [8]. Traditional Chinese medicine (TCM), such as andrographitis [9] and Houttuynia isatidis [10], have many effective ingredients that can inhibit and kill some bacteria and viruses, as well as modulate immunity and improve drug resistance [11]. Hence, studying TCM antibacterial and antiviral mechanisms is significant for delaying bacterial drug resistance and expanding its clinical application range.

Network pharmacology uses histology, high-throughput screening, and network visualization and analysis techniques to elucidate the underlying molecular mechanisms of diseases from a multidimensional perspective [12]. However, the mechanisms of Baiyaozi in treating infections have multi-targets; thus, unilateral factors and single targets cannot explain these mechanisms. Therefore, this study constructed a "drug-ingredient-target" network using network pharmacology approaches and focused on analyzing the active ingredients, potential targets, and signaling pathways of Baiyaozi to explore its possible antibacterial and antiviral mechanisms.

2. Methods

2.1. Collection of potential Baiyaozi constituents and targets

Potential Baiyaozi constituents were collected using the Traditional Chinese Medicine Systematic Pharmacology Database and Analysis Platform (TCMSP), with oral bioavailability (OB) ≥ 30% and drug-like properties (DL) ≥ 0.18 as the screening conditions for the constituents, supplemented by literature search. Their chemical structure and properties, such as MW, BBB, HL, OB, and DL, were retrieved from TCMSP. Finally, Pubchem and Swiss Target Prediction were used to collect the targets of compounds, set the species as *Homo sapiens*, and establish their target database.

2.2. Antibacterial and antiviral target screening and active compound-target network diagram construction

Targets related to antibacterial and antiviral were searched using "antibacterial" and "antiviral" keywords in the GeneCards database. The screening condition was set to relevance > 0.5, and the Venn diagram was drawn to analyze overlapping genes and obtain potential targets of compounds against bacteria and viruses. The overlapping genes were imported into Cytoscape software to construct a "drug-ingredient-target" network.

2.3. Protein interaction analysis of overlapping genes

The antibacterial and antiviral overlapping gene data were entered into the STRING website to construct the protein-protein interaction (PPI) network. The species "*Homo sapiens*" was selected on the website, with high confidence (0.700), while free proteins were hidden to obtain the PPI interaction network relationship map.

2.4. Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichments

Furthermore, to analyze the potential targets of antibacterial and antiviral active ingredients of Baiyaozi in biological processes (BP), molecular functions (MF), cellular components (CC), and KEGG pathways, the collected gene data were imported into the DAVID database, with the species set as "*Homo sapiens*." GO and KEGG pathway enrichment analyses were performed for the two gene sets. The top 10 GO terms and KEGG pathways were selected and imported into the Microbiology Letter website (www.bioinformatics.com.cn) to obtain GO histograms and KEGG enrichment maps.

3. Results

3.1. Main Baiyaozi constituents and their targets

Using OB ≥ 30% and DL ≥ 0.18 as screening conditions, 25 Baiyaozi chemical constituents were retrieved from TCMSP. At the same time, the literature review revealed that some compounds, such as cepharanthine [13] and homoaromoline [14], although having low DL values, were present at high levels in Baiyaozi and were associated with antibacterial and antiviral activities. Therefore, eight major constituents were finally selected for subsequent analysis. The compounds and their biochemical

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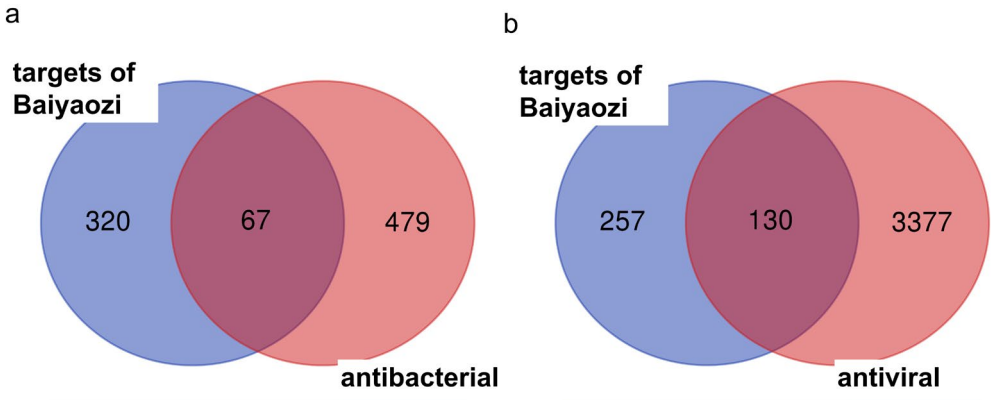
properties are summarized in Table 1, where OB is the oral bioavailability, and drug-like (DL) refers to the similarity of a compound to a known drug, an important indicator to evaluate whether a compound can be used as a drug or not [15]. The BBB is an indicator to assess the ability of a compound to enter the central nervous system; compounds with BBB < -0.3 are considered non-penetrating (BBB-), from -0.3 to +0.3 moderately penetrating (BBB±), and > 0.3 strongly penetrating (BBB+) [16]. Finally, 387 targets of active ingredients were collected by the Swiss Target Prediction.

Table 1: Information of potential constituents of Baiyaozi.

name	MW	OB (%)	BBB	DL	Half-life
cepharanthine	606.77	77.42	0.29	0.06	10.74
papaverine	339.42	64.04	0.57	0.38	4.14
Luteanin	341.44	55.63	0.7	0.55	1.3
codeine	299.4	45.48	0.87	0.56	10.06
homoaromoline	608.79	44.56	0.12	0.11	3.96
(S)-(6-methoxy-4-quinolyl)-[(2S,4S,5 S)-5-vinylquinuclidin-2-yl]methanol	324.46	38.06	0.25	0.4	3.88
berberine	336.39	36.86	0.57	0.78	6.57
CREBANINE	339.42	34.64	0.62	0.75	5.27

3.2. Active ingredient-target network diagrams for Baiyaozi

By searching with "antibacterial" and "antiviral" keywords, 1912 antibacterial and 8897 antiviral potential targets were identified in the GeneCards database. Considering a Relevance score > 0.5, 546 antibacterial and 3507 antiviral potential targets were obtained. The targets of Baiyaozi active ingredients were compared with antibacterial and antiviral-related genes, and 67 antibacterial (Figure 1a) and 130 antiviral (Figure 1b) targets were obtained. Cytoscape was used to establish a schematic diagram of the active ingredient-target regulatory network by connecting the eight active ingredients with antibacterial (Figure 2a) or antiviral (Figure 2b) target genes. In the antibacterial target network, several components acted together on the targets such as CDK2, SRC, JAK2, PIK3CG, ADRB2, NOS2, MAPK14, KCNH2, F3, and MTOR. Meanwhile, the top two components in the degree ranking were luteanin and cepharanthine, suggesting that these two components might play a key role in antibacterial processes. Several components acted together on the targets in the antiviral target network, such as PIK3CD, CDK2, PIK3CA, SRC, JAK2, HTR1A, PRKCA, PIK3CG, LCK, and NOS2. The top two components in the degree ranking were cepharanthine and berberine, suggesting that these two components might play a key role in the antiviral processes. The eight active ingredients acted synergistically on 67 antibacterial and 130 antiviral target genes, reflecting the multi-component and multi-target mechanisms of Baiyaozi.



a: antibacterial; b: antiviral.

Figure 1: Screening of potential antibacterial and antiviral action targets of Baiyaozi

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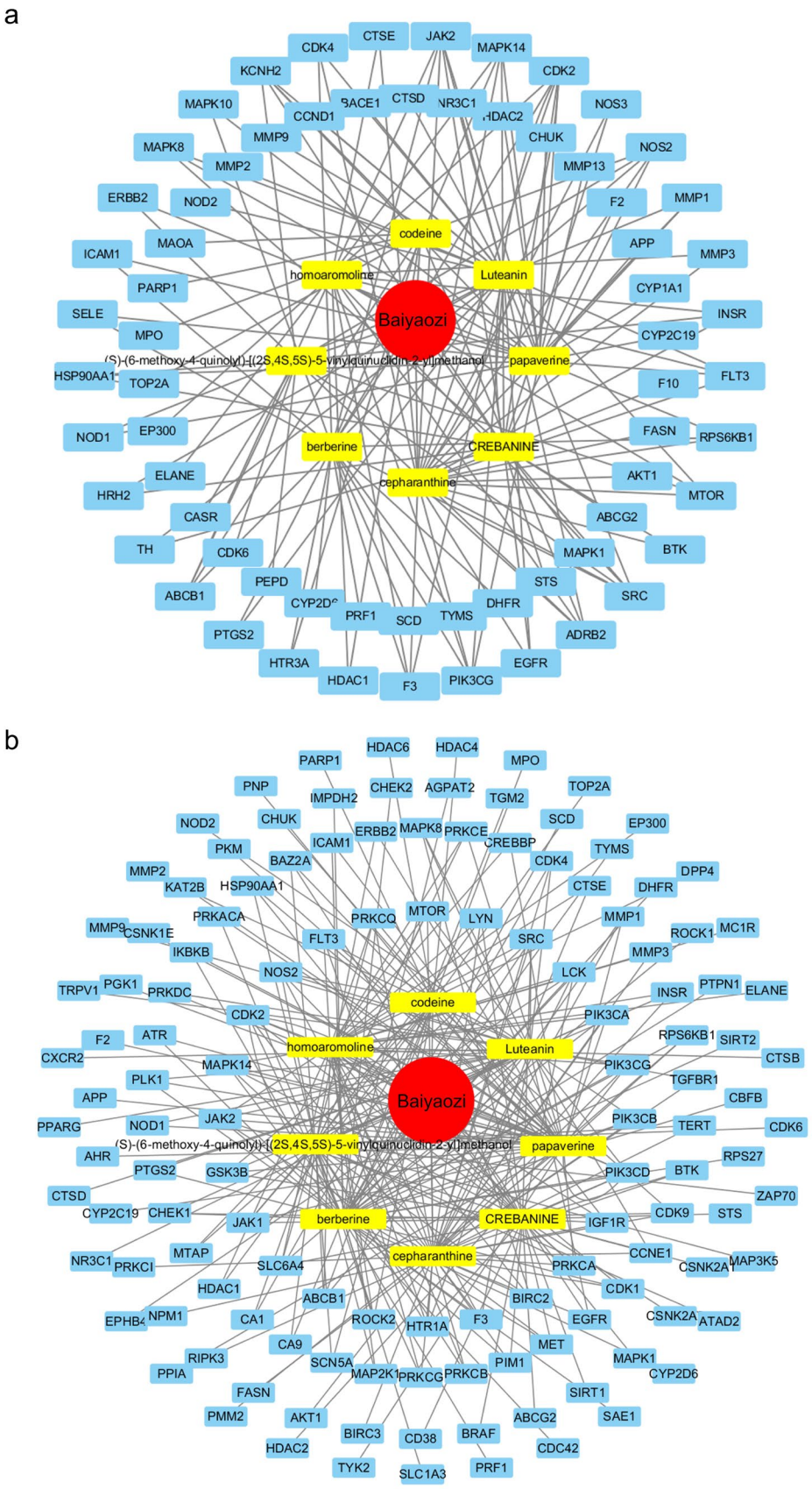

a: antibacterial; b: antiviral.

Figure 2: Network of "drugs-components-potential targets" of Baiyaozi

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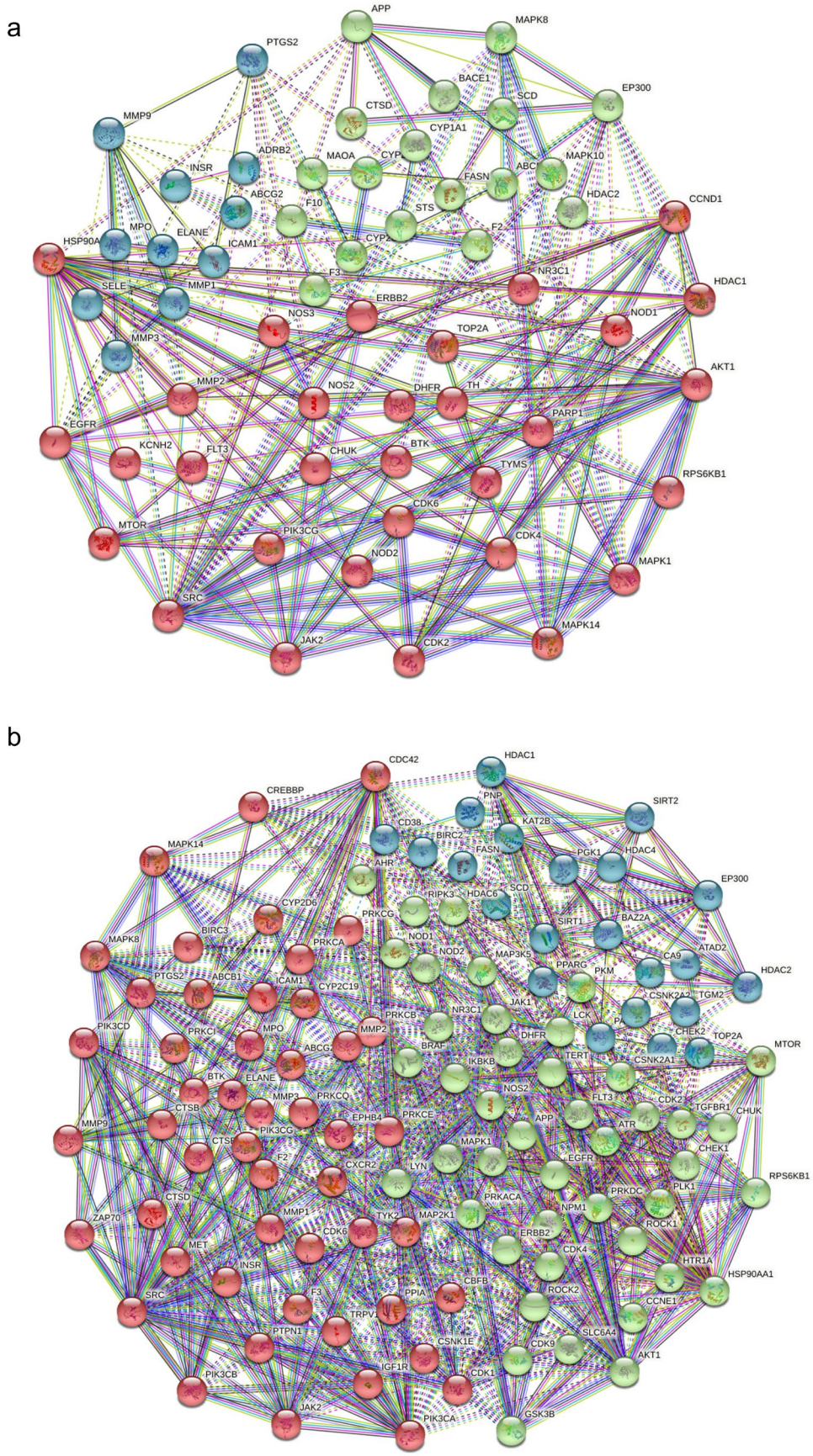

a: antibacterial; b: antiviral.

Figure 3: Protein-protein interaction (PPI) network screening of common targets

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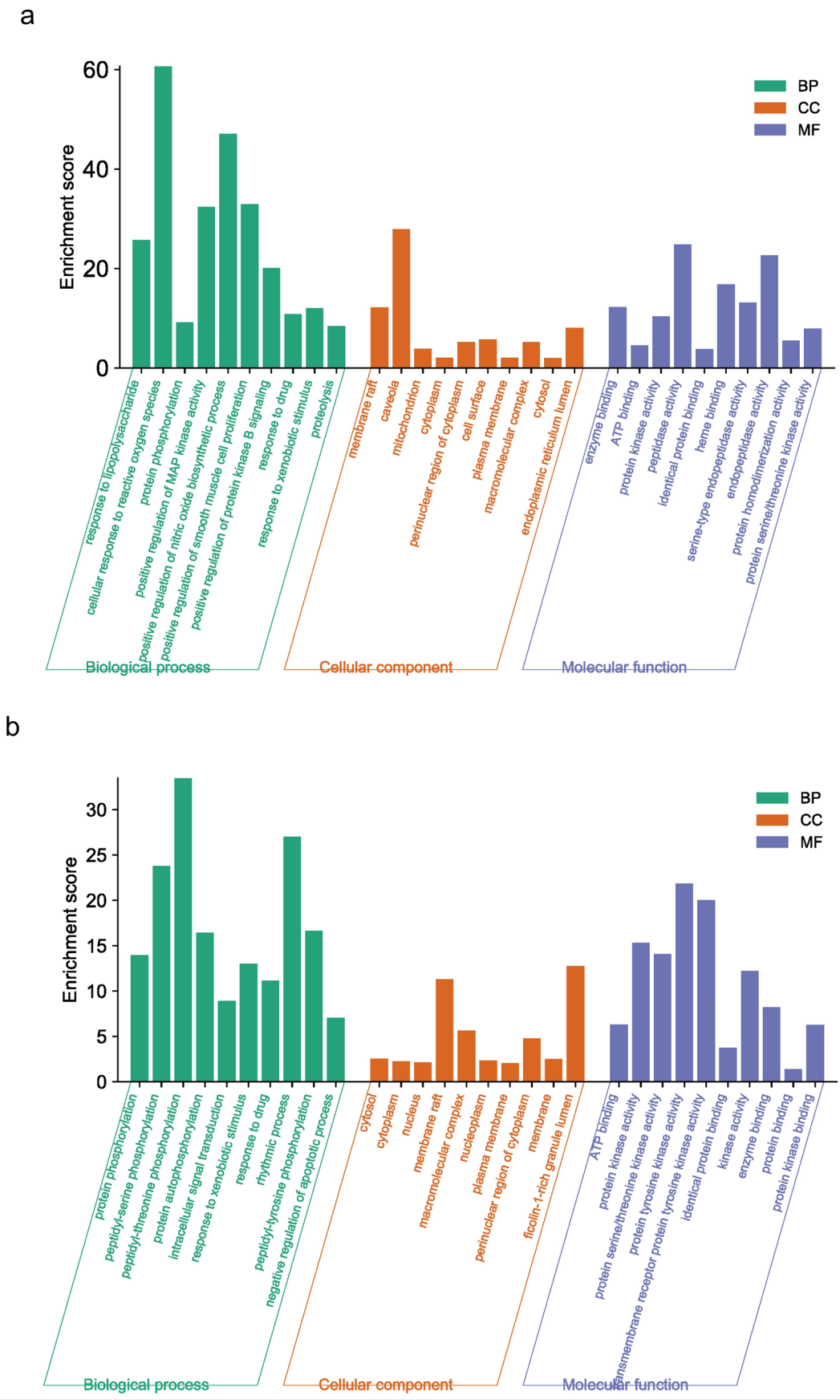

a: antibacterial; b: antiviral.

Figure 4: GO enrichment of core targets

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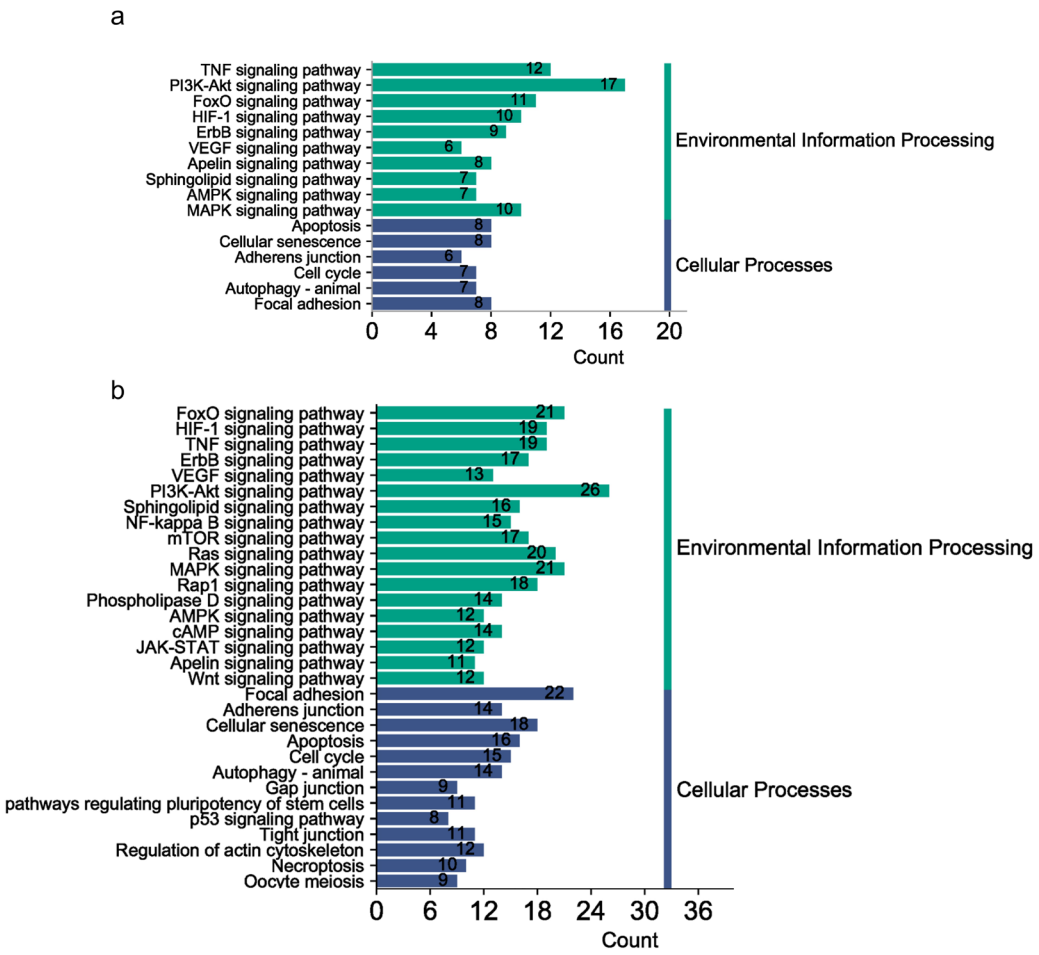

a: antibacterial; b: antiviral.

Figure 5. KEGG enrichment of core targets:

3.3. PPI network analysis

The STRING database is an online tool for searching the interaction relationships of known proteins. The antibacterial and antiviral targets of Baiyaozo were separately imported into the STRING database to obtain the PPI network (Figure 3). More than one link was detected between two proteins, indicating multiple interaction relationships between proteins. The PPI network of antibacterial targets contains 67 protein nodes and 189 interaction relationships, and the top ten genes ranked by linkage are HSP90AA1, SRC, AKT1, EGFR, and EP300, followed by MAPK1, CCND1, MMP9, MAPK8, and ERBB2 (Figure 3a). The PPI network of antiviral targets contains 130 protein nodes and 632 interactions (linkages), and the top ten genes in the linkage ranking were SRC, HSP90AA1, PIK3R1, AKT1, PIK3CA, MAPK1, LCK, JAK2, EGFR, and EP300 (Figure 3b). The higher the number of genes linked to neighboring genes, the more likely they are to be the core genes of network regulation, suggesting a greater role in the network and likely to be the main target of Baiyaozi.

3.4. GO enrichment

The GO enrichment analysis was performed for the potential antibacterial and antiviral targets of Baiyaozi using the DAVID database, respectively. With $p < 0.001$ and FDR < 0.05 as screening conditions, in the biological process category, the antibacterial target proteins were mainly involved in the positive regulation of nitric oxide biosynthetic processes, positive regulation of MAP kinase activity, and cellular response to reactive oxygen species, the antiviral target proteins were mainly involved in peptidyl-threonine phosphorylation, rhythmic process, and peptidyl-serine phosphorylation. In the MF category, the antibacterial target proteins were mainly involved in peptidase activity, the caveola, membrane raft, and endoplasmic reticulum lumen. The antiviral target proteins were mainly positioned

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in the ficolin-1-rich granule lumen, macromolecular complex, endopeptidase activity, and heme binding. The antiviral target proteins were mainly involved in the protein tyrosine kinase activity, transmembrane receptor protein tyrosine kinase activity, and protein kinase activity. The antibacterial target proteins were mainly positioned in the membrane raft in the CC category. The first 10 related enrichment results of antibacterial (Figure 4a) and antiviral (Figure 4b) were visualized based on the GO enrichment.

3.5. KEGG pathway enrichment

The KEGG pathway enrichment analysis was performed for the potential antibacterial and antiviral targets of Baiyaozi using the DAVID database. The results showed that 131 pathways were involved in the antibacterial targets, and 166 were involved in the antiviral targets. With $p < 0.001$ as the screening condition, 16 pathways were obtained for the antibacterial targets of Baiyaozi after removing specific diseases and other irrelevant entries (Figure 5a), mainly including PI3K-Akt, TNF, autophagy-animal, and apoptosis signaling pathways. The screened antiviral targets involved 31 pathways (Figure 5b). Besides the same pathways enriched with antibacterial targets, the unique pathways of the antiviral targets of Baiyaozi included necrosis, JAK-STAT, mTOR, and NF-κB signaling pathways. These results suggested that the active ingredients of Baiyaozi might exert antibacterial and antiviral effects through multiple signaling pathways, and the antibacterial and antiviral pathways might be shared.

4. Discussion

The misuse of antibiotics can lead to bacterial resistance and ultimately promote the emergence of resistant bacteria [5]. The declining efficacy of antibiotics and the lack of new antibiotic development have prompted "herbal antibiotics" as a hot research topic, which refers to a large class of herbs that can inhibit and kill some bacteria and viruses, regulate immune function, analgesia, anti-inflammation, and has other comprehensive therapeutic effects. Therefore, it has unique advantages and broad development prospects in preventing and treating infectious diseases [17]. The results of *in vitro* experiments showed that Baiyaozi has significant synergistic effects combined with antibiotics at 8:1, which can be applied to treat bacterial infectious diseases, reverse multiple drug resistance, and expand the antibacterial spectrum [4]. However, the research on the anti-infective mechanisms of herbal medicine is not deep enough. Herein, we used network pharmacology to screen the antibacterial and antiviral targets of Baiyaozi and explored the possible mechanisms underlying its antibacterial and antiviral effects.

The screening results revealed that eight Baiyaozi ingredients acted on 67 antibacterial and 130 antiviral targets. The target network diagram of active ingredients suggested that cepharanthine might be the main compound responsible for the antibacterial and antiviral efficacy of Baiyaozi. Additionally, luteanin and berberine were important compounds for Baiyaozi efficacy. Cepharanthine is a naturally occurring isoquinoline alkaloid, and available studies have shown that it has many biological activities, such as anti-inflammatory, anti-tumor, antiviral, and immune-enhancing effects. For example, Ershun et al. used a mastitis mouse model to demonstrate the anti-inflammatory properties of cepharanthine by reducing TNF-α, IL-1β, and IL-6 levels [18]. Moreover, *in vitro* and *in vivo* experiments have shown that cepharanthine can prevent cell death by inhibiting endotoxin-induced NO in macrophages, thereby preventing extensive endotoxin damage in septic shock [19]. Preclinical studies have revealed significant effects of cepharanthine against HIV, human T-cell leukemia virus, hepatitis B virus, SARS-CoV, and other viruses. Besides, *in vitro* results have shown that cepharanthine degrades viral particles and cellular components through STING-mediated interferon-independent autophagy [13]. Yao Liu's study showed that cepharanthine indirectly inhibited the phosphorylation levels of targets in the PI3K/Akt and p38 MAPK signaling pathways and induced apoptosis in infected cells, reducing herpes simplex virus type 1 infection and subsequent multiplication [20]. Notably, cepharanthine has been reported to have broad-spectrum antiviral capabilities, including SARS-CoV-2 and related variants, and is considered a promising candidate for COVID-19 treatment [21]. Studies have reported various pharmacological effects of luteanin, such as anti-arrhythmic, vasodilatory, anti-tumor, and anti-inflammatory effects [22]. Luteanin derivatives have antioxidant, antibacterial, and antiproliferative effects *in vitro*, with significantly higher inhibitory effects against *Salmonella typhi* and *Escherichia coli* than other common bacteria [23]. Meanwhile, recent studies suggest that luteanin has strong anti-sepsis effects by upregulating VDR expression and inhibiting NF-κB p65 translocation into the nucleus, thereby reducing LPS-mediated inflammatory storm [24]. Chin et al. showed that berberine could inhibit viral DNA synthesis [25]. Meanwhile, berberine exerted anti-inflammatory effects by

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downregulating pro-inflammatory cytokine expression and inhibiting the NF-κB p65 signaling pathway. Based on the above studies, cepharanthine, luteanin, and berberine in Baiyaozi might exert antibacterial and antiviral effects through multiple pathways.

Furthermore, the PPI network analysis identified six strongly associated proteins involved in antibacterial and antiviral processes: HSP90AA1, SRC, AKT1, EGFR, EP300, and MAPK1, possible core targets for anti-infection effects in Baiyaozi. Heat shock proteins (HSPs) are highly conserved and widely found in prokaryotes and eukaryotes [26]. HSPs are important molecular chaperones and stress response biomarkers in cells and are critical for maintaining the correct protein folding [27]. HSP90 is an HSP. Hsp90-α (Hsp90AA1) belongs to the cytoplasmic class of isoforms and is encoded by the HSP90aa1 gene [28]. Proteins are degraded through the ubiquitin-protease pathway when the function of HSP90AA1 is inhibited [29], which is closely related to immune regulation, apoptosis, autophagy, and tumor development [30, 31]. HSP90AA1 is also considered an important regulator of inflammation. It is secreted extracellularly during wound healing and inflammation and activates the NF-κB and STAT3 transcriptional programs to induce inflammation [32]. Meanwhile, SRC proteins belong to the SRC family of kinases, specific tyrosine protein kinases in the cytoplasm. SRC proteins play a key role in the transcription and expression of various immune factors and are involved in the progression of lung cancer and HBV and HIV infections. Together with the topological analysis results, it is hypothesized that SRC plays an important role in anti-tumor and antiviral infection therapy [33]. AKT1 is a serine/threonine protein kinase with apoptosis-inhibiting and metabolism-regulating effects. Studies have shown that AKT1 is associated with several bacterial infection pathways. For example, by activating the PI3K/Akt1/mTOR signaling pathway, *Mycobacterium tuberculosis* can induce M2 polarisation in macrophages and interfere with the host immune response [34]. EGFR, EP300, and MAPK1 are associated with tumor development, immune regulation, and apoptosis [35]. It is speculated that these targets might be the key action targets for the active ingredients of Baiyaozi to exert antibacterial and antiviral effects.

The GO and KEGG pathway enrichment analyses of the common targets suggested that the antibacterial and antiviral targets shared some pathways, mainly involving cell death and inflammatory signaling pathways, such as apoptosis, autophagy, tumor necrosis factor, HIF-1, PI3K-Akt, AMPK, and MAPK signaling pathways, which were roughly the same as the antibacterial pathway screened by Nan Xu et al. [36, 37]. Infection is the process of body dysfunction caused by the invasion of pathogenic bacteria. Apoptosis, autophagy, and tumor necrosis factor signaling pathways play a general role in inflammation caused by pathogenic bacterial infections [36]. Activation of the HIF-1 pathway enhances macrophages' killing of *Mycobacterium tuberculosis* [38]. Various pathogenic bacteria have been shown to activate the PI3K/Akt signaling pathway to increase bacterial invasion [37, 39]. Additionally, the cAMP, JAK-STAT, mTOR, and NF-κB signaling pathways and other pathways enriched in antiviral targets have important roles in regulating inflammation. Upregulation of intracellular cAMP inhibits anti-inflammatory activity by inhibiting the release of free radicals [40]. As a cytokine signaling pathway of great interest in recent years, the JAK-STAT signaling pathway plays an important regulatory role in cell proliferation, apoptosis, differentiation, and immune response, especially in regulating macrophage polarization typing and inflammation. Besides, mTOR has a strong immunosuppressive effect and is involved in various biological processes such as apoptosis, autophagy, and tumorigenesis. Viral infection activates the mTOR pathway to promote the translation of proteins that cause the organism to assume a pathological state [41]. In summary, Baiyaozi can exert anti-infective effects through multiple signaling pathways, particularly cell death and inflammatory and immunomodulatory pathways.

5. Conclusion

The anti-infective effects of TCM are multi-linked and multi-pathway, mobilizing favorable factors and improving the resistance and self-healing ability of the organism. Herein, we analyzed the active ingredients, related targets, and signaling pathways of Baiyaozi via network pharmacology and found that cepharanthine, luteanin, and berberinei might be important components of the antibacterial and antiviral effects of Baiyaozi. The main targets included HSP90AA1, SRC, and AKT1, and the mechanisms were mainly related to apoptosis, autophagy, tumor necrosis factor signaling pathway, HIF-1 signaling pathway, and PI3K-Akt pathway. Therefore, we provided a direction for later in-depth research and a scientific basis for the further development and application of Baiyaozi.

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