Mechanism of Bacteriostatic Effects of Snow Lotus: Insights from Network Pharmacology

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Abstract [**Objectives**] To investigate the potential applications and mechanisms of action of medicinal plants as bacteriostatic agents, utilizing snow lotus as a case study through network pharmacology. [**Methods**] The TCMSP and HIT 2.0 databases were employed to screen and obtain the active components and corresponding targets of snow lotus. The identified targets were subsequently intersected with the antibacterial and bacteriostatic targets sourced from the GeneCards and OMIM databases, resulting in the identification of the antibacterial and bacteriostatic targets associated with snow lotus. Cytoscape software was employed to construct the network diagram illustrating the active components and their corresponding action targets for snow lotus, as well as to analyze the network's topology. Additionally, GO enrichment analysis of the action targets was conducted utilizing the DAVID database. [**Results**] A total of 12 active components of snow lotus were identified through screening, which corresponded to 294 action targets. Subsequent analysis revealed 117 core action targets of snow lotus that exhibit antibacterial and bacteriostatic properties. The results from the network diagram suggested that snow lotus may exert its antibacterial and bacteriostatic effects through active components such as quercetin, apigenin, and luteolin. Additionally, it appeared to activate the immunomodulatory functions of the human body by interacting with targets such as CASP3, TNF, and IL-6. [**Conclusions**] Snow lotus may demonstrate antibacterial and bacteriostatic properties through mechanisms of action that involve multiple components, targets, and pathways, from *in vivo* and *in vitro* multiple pathways. The integration of botanical bacteriostatic agents with chemical disinfectants that possess broad-spectrum bactericidal effects is advantageous for broadening the bactericidal spectrum and minimizing irritation, in order to facilitate the development of more environmentally friendly and low-toxicity disinfection and bacteriostatic products.

Key words Snow lotus, Bacteriostatic agent, Bacteriostatic activity, Mechanism of action, Network pharmacology

1 Introduction

Chlorhexidine is a cationic biguanide chemical disinfectant that is widely utilized for the disinfection of skin, mucous membranes, and wounds, and demonstrates broad-spectrum antibacterial activity against both gram-negative and gram-positive bacteria[1-2]. Chlorhexidine binds to negatively charged bacterial cell membranes, thereby inhibiting various physiological activities of bacteria[3]. At elevated concentrations, chlorhexidine can cause significant damage to cytoplasmic membranes, resulting in the lysis of bacterial cells[4]. Although it exhibits a strong antibacterial effect against pathogenic microorganisms, the use of chlorhexidine at high concentrations may lead to skin irritation and exhibit cytotoxic effects when applied locally[5].

Natural plant extracts derived from herbs are receiving increasing attention from researchers across various countries due to their numerous advantages, including reduced toxicity, minimized skin irritation, a lower likelihood of inducing bacterial resistance, and their environmentally friendly nature[6-7]. The snow lotus is the flowering plant of *Saussurea involucrata* (Kar. et Kir.) Sch. Bip., belonging to the Asteraceae family. The snow lotus, referred to as Tianshan snow lotus, is found in rock crevices, gravel, and sandy riverbanks at altitudes exceeding 3 000 m in the Tianshan and Kunlun Mountains, specifically in the provinces of Gansu, Qinghai, and Xinjiang in China[8]. Historically, the snow lotus has been utilized in traditional herbal medicine for an extended period[9]. Modern phytopharmacological studies have demonstrated that snow lotus possesses antibacterial activity against pathogenic microorganisms, including *Staphylococcus aureus*, *Escherichia coli*, *Candida albicans*, and *Pseudomonas aeruginosa*[10-11]. However, the specific active components and the mechanisms by which snow lotus exerts its antibacterial and bacteriostatic effects remain unclear. Therefore, in this study, we employed network pharmacology to investigate the material basis and potential mechanisms underlying the antibacterial and bacteriostatic effects of snow lotus. Additionally, we aimed to explore the bacteriostatic pathways of botanical agents when used in conjunction with chemical disinfectants.

2 Information and methods

2.1 Screening of active components and action targets

Known compounds of snow lotus were collected using the Herbal Ingredients' Targets Platform (HIT 2.0). These compounds were then searched in the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) and were screened based on a drug-likeness (*DL*) score of ≥0.18, indicating potential pharmacological activity. Additionally, active components with a Topological Polar Surface Area (TPSA) of ≤140 may possess the ability to penetrate the skin or mucous membranes, allowing for the identification of corresponding action targets.

2.2 Screening of antibacterial and bacteriostatic action targets

The GenCards database and the Online Mendelian Inheritance in Man (OMIM) database were searched for relevant targets using the keywords "Antibacterial" and "Bacteriostasis". The identified antibacterial and bacteriostatic targets were summarized

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and de-duplicated, and then imported into the Hiplot Biomedical Data Visualization Tool (https://hiplot.cn/) along with the target information for snow lotus to create a Venn diagram. This process aimed to identify potential targets of snow lotus that may exhibit antibacterial and bacteriostatic effects.

2.3 Construction and analysis of active component-action target network The effective active components associated with the antibacterial and bacteriostatic efficacy of snow lotus, along with their action targets identified in Section **2.2**, were visualized and analyzed using Cytoscape 3.10.3 software. A network diagram illustrating the relationships among traditional Chinese medicine, effective active components, and action targets was established. The active compounds and their corresponding targets of snow lotus were represented as nodes, while the relationships between them were depicted as edges. A topological analysis was conducted based on the established network diagram, and the significance of the nodes within the network was assessed using degree and betweenness centrality.

2.4 Construction and analysis of PPI networks The antibacterial and bacteriostatic target genes of snow lotus, identified in Section **2.2**, were entered into the STRING database (https://string-db.org) to construct a PPI network. Single protein nodes in the network that exhibited no interaction relationships were removed to investigate the pharmacological action mechanism of snow lotus at the protein interaction level. The established PPI network information was imported into Cytoscape software, where the node degree value was utilized as an index for visualization and analysis.

2.5 GO enrichment analysis The coding gene information of snow lotus related to antibacterial and bacteriostatic effects, as obtained in Section **2.2**, was entered into the DAVID database (https://david.ncifcrf.gov). Gene Ontology (GO) analysis was conducted with a significance threshold of $P < 0.01$, using "human" as the analyzed species. The output data were plotted using Hiplot to extract functional information highly relevant to the antibacterial and bacteriostatic effects produced by snow lotus.

3 Results and discussion

3.1 Active components and action targets Based on the screening conditions, a total of 7 effective active compounds from snow lotus (Table 1) and 285 corresponding action targets were identified in the TCMSP and HIT 2.0 databases.

Table 1 Active components of snow lotus (*DL*≥0.18, TPSA≤140)

Mol ID	Compound name	*DL*	TPSA
MOL001986	Beta – Sitosterol	0.71	20.23
MOL000008	Apigenin	0.21	90.90
MOL000006	Luteolin	0.24	111.12
MOL001735	Hispidulin	0.27	100.12
MOL000347	Syringin	0.32	138.07
MOL009297	Jaceosidine	0.34	109.36
MOL000098	Quercetin	0.28	131.36

3.2 Antibacterial and bacteriostatic action targets Using "Antibacterial" and "Bacteriostasis" as the keywords, the GenCards and OMIM databases were searched for relevant targets. After summarizing and removing duplicate findings, the results were subsequently intersected with the target information related to snow lotus. In total, 113 potential targets through which snow lotus may exert antibacterial and bacteriostatic effects were identified (Fig.1).

3.3 Analysis of active component-action target network The active components of snow lotus that contribute to its antibacterial and bacteriostatic efficacy, along with their targets of action, were visualized and analyzed using Cytoscape software. A network diagram illustrating the relationships between the plant, active components and their action targets was established (Fig.2).

From the results of the topological analysis, it was evident that there were 121 nodes and 196 edges in the effective active component-action target network of snow lotus. As illustrated in Fig.2, the outermost two circles represented the action targets, while the central circle denoted the effective active components of snow lotus. The findings from the network topology analysis indicated that the average degree of the established network nodes was 3.24, with 7 nodes exceeding this average. Additionally, the average betweenness centrality was calculated to be 0.012 1, with 5 nodes surpassing this average. Based on the rankings of degree and betweenness centrality, the top three effective active components and the top five targets for action were identified. As illustrated in Table 2, quercetin, apigenin, and luteolin appear to be the primary active components of snow lotus that contribute to its antibacterial and bacteriostatic effects. Additionally, CASP3, BCL2, MAPK14, TNF, and IL6 may serve as the principal targets through which snow lotus exerts these effects.

Table 2 Key nodes of the effective compound-action target network of snow lotus and their topological characteristics

Node name	Node type	Degree	Betweenness centrality	Node name	Node type	Degree	Betweenness centrality
Quercetin	Compound	90	0.708 20	BCL2	Action target	4	0.010 43
Apigenin	Compound	48	0.267 14	MAPK14	Action target	3	0.006 88
Luteolin	Compound	48	0.205 41	TNF	Action target	3	0.006 88
CASP3	Action target	5	0.018 55	IL6	Action target	3	0.006 88

Existing research has demonstrated that quercetin exerts a beneficial inhibitory effect on *S. aureus*, *E. coli*, and *C. albicans*[12–13]. The antibacterial mechanisms of quercetin primarily involve the disruption of the bacterial cell wall, alterations in cell permeability, modulation of protein synthesis and expression, reduction of enzyme activity, and inhibition of nucleic acid synthesis[14]. Apigenin is a flavonoid compound that exhibits distinctive antibacterial activity against *S. aureus*, a significant human pathogen, and is effective in inhibiting quinolone-resistant strains of *S. aureus*[15]. Furthermore, apigenin demonstrates antibacterial activity against molds, specifically *C. albicans*, through a mechanism that induces membrane perturbation, resulting in the contraction of mold cells and subsequent leakage of cellular contents[16]. Several studies have indicated that apigenin also exhibits inhibitory effects on *Helicobacter pylori* and *C. albicans*[17-18]. Luteolin induces morphological structural degeneration characterized by content leakage, damage to cell walls and membranes, reduced ATP synthesis, and down-regulation of mRNA expression levels of genes associated with sulfonamide and quinolone resistance in multidrug-resistant *E. coli*[19]. It is hypothesized that the extracts of snow lotus may exhibit antibacterial and bacteriostatic properties due to the presence of three primary active components. The multi-component and multi-pathway mechanisms of action associated with snow lotus enhance its bacteriostatic efficacy, particularly when used in conjunction with the broad-spectrum fungicide chlorhexidine.

Caspase 3 (CASP3) is a critical component in the downstream signaling of caspase cascade activation and serves as a central protein in the execution of apoptosis[20]. Research has demonstrated that chemical agents targeting CASP3 and inhibiting its protein expression can significantly reduce the physiological activity of *E. coli*[21]. B-cell lymphoma-2 (BCL2) is known to play a critical role in the inhibition of apoptosis[22]. Recent studies have demonstrated that moscatilin influences the expression of the apoptosis-promoting gene *CASP3* as well as the anti-apoptotic gene *BCL2*, thereby modulating apoptotic processes. Additionally, moscatilin exhibits antibacterial activity against clinically significant gram-negative and gram-positive bacteria[23]. The mitogen-activated protein kinase 14 (MAPK14) can be activated by pro-inflammatory cytokines, which subsequently play an immunomodulatory role in local inflammation induced by bacterial pathogen infection[24]. Tumor necrosis factor (TNF) is a multifunctional cytokine that enhances the expression of the inflammatory factor IL-8 within the immune system and promotes inflammation[25]. IL-6 is a multifunctional cytokine that facilitates the local accumulation of immune cells, including T cells, B cells, and neutrophils, during inflammatory responses, and it also promotes the production of antibodies[26]. Numerous studies have demonstrated that host cells infected by pathogens secrete a variety of cytokines, including IL-6 and TNF, which are crucial in both promoting and regulating immune responses to bacterial infections[27-28]. Specifically, the active components found in snow lotus may inhibit bacterial activity and enhance the body's immunoregulatory functions by targeting these cytokines, thereby facilitating the clearance of bacterial pathogens from the body.

3.4 Analysis of PPI network The PPI network of antibacterial and bacteriostatic targets associated with snow lotus is illustrated in Fig. 3. This network comprised 113 protein nodes and 2 649 edges, with each edge representing an interaction between the nodes. Each edge signifies the interaction relationship between the respective nodes. A greater number of edges correlates with a larger node size, signifying a more critical role of the corresponding target protein. The results of the topological analysis reveal that the key target proteins responsible for the antibacterial and bacteriostatic effects of snow lotus include TNF, IL6, TP53, IL-1β, and AKT1.

TNF is a pivotal target protein for the antibacterial and bacteriostatic activities of snow lotus. As a cytokine, TNF plays a significant role in the human immune response by binding to various receptor types, and it possesses the capability to induce apoptosis in transformed cells and certain virus-infected cells[29]. Research has indicated that cytokines, including TNF-α, IL-6, and IL-1β, are associated with infections caused by *C. albicans*[30]. The application of natural medicines has the potential to modulate the expression levels of cytokines, thereby facilitating the treatment of vaginal *C. albicans* infections[30]. Tumor protein P53 (TP53) serves as a critical regulator of cell growth, apoptosis, and damage repair[31]. The P53 pathway plays a significant role in the management of viral infections by improving immune dysfunction and inhibiting both viral replication and transcription[32]. Macrophage polarization is intricately associated with the host's defense mechanisms against pathogens and harmful agents, while the dysregulation of macrophage differentiation is linked to infections and inflammatory diseases[33]. Research indicates that protein kinase B/Akt1 signaling plays a critical role in regulating pathogen-induced macrophage polarization, thereby influencing the host's response to bacterial infections[33].

3.5 GO enrichment analysis The 113 action targets of effective active compounds associated with the antibacterial and bacteriostatic activities of snow lotus were entered into the DAVID database for GO analysis, resulting in the identification of 845 GO entries at a significance level of $P<0.01$. Among these, 665 entries pertained to biological processes (BP), 122 entries to molecular functions (MF), and 58 entries to cellular components (CC). The analyzed data were subsequently imported into Hiplot, where they were filtered based on the P value, Q value ($Q<0.05$), and the number of enriched genes. The top 10 entries, ranked according to BP, MF, and CC, were utilized to create corresponding bar graphs (Fig. 4).

The results of GO analysis indicate that the effective active compounds derived from snow lotus may play a role in various biological processes within the vesicular lumen, Bcl-2 family protein complex, secretory granule lumen, and other anatomical regions. These compounds appear to modulate biological processes, including cellular responses to bacterial molecules, reactions to lipopolysaccharides, and responses to biostimuli. Consequently, they may influence molecular functions such as cytokine activity, transcription factor activity, protein binding, and enzyme binding, thereby exerting both antibacterial and bacteriostatic effects.

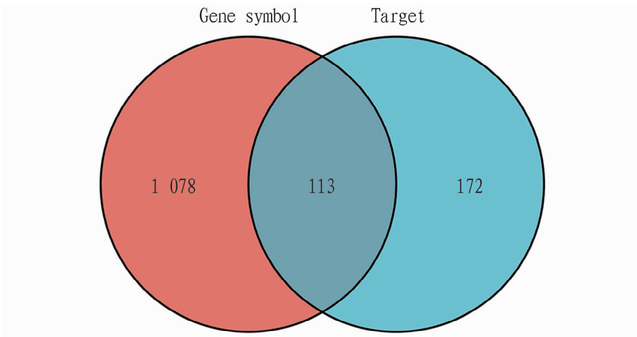


Fig. 1 Venn diagram of antibacterial and bacteriostatic gene targets and action targets of snow lotus

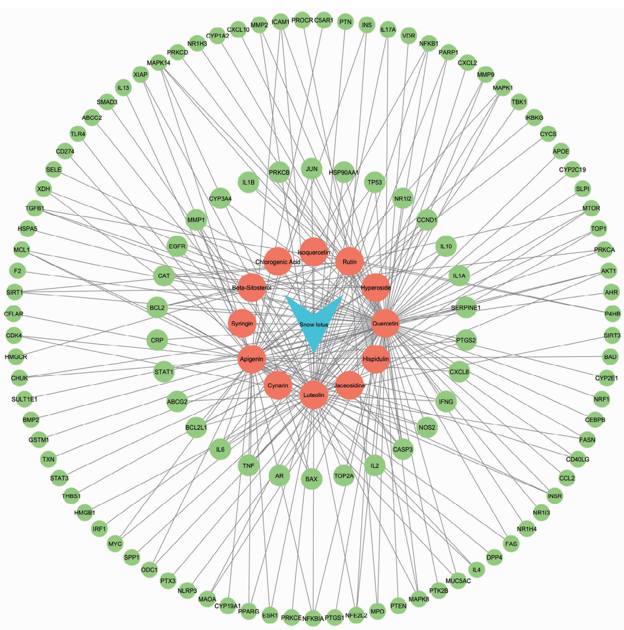


Fig. 2 Active component-action target network of snow lotus

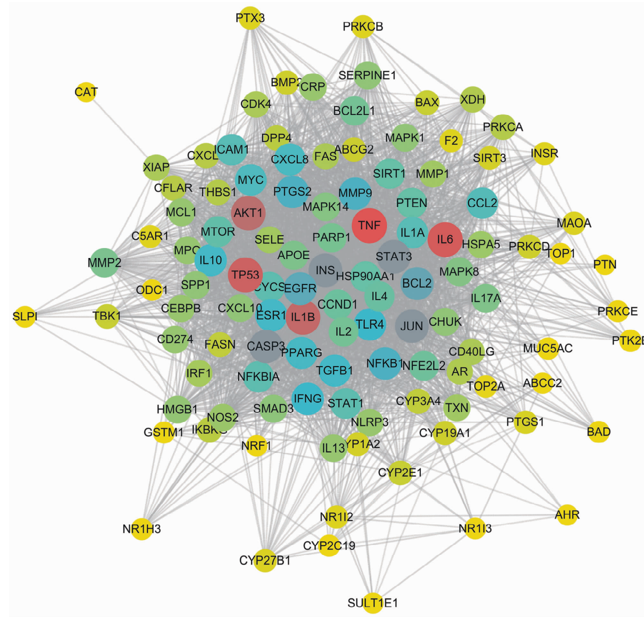
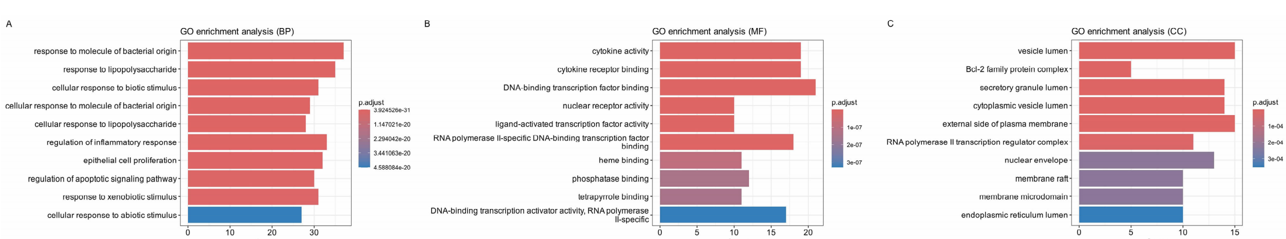


Fig. 3 PPI network of antibacterial and bacteriostatic targets of snow lotus

4 Conclusions and prospects

Contemporary research has consistently demonstrated that traditional Chinese medicines can exhibit bacteriostatic activity through the synergization of multiple components and targets. Furthermore, these medicines have been shown to mitigate bacterial drug resistance, enhance the efficacy of bacterial inhibition, and possess the notable capability of reversing certain drug resistance phenomena[34]. Although China is abundant in medicinal plant resources, the potential for developing natural products into effective bacteriostatic agents remains underexploited[35]. Additionally, botanical bacteriostatic components are generally mild and exhibit



NOTE A. BP enrichment results; B. MF enrichment results; C. CC enrichment results.

Fig. 4 GO enrichment analysis of action targets of effective active compounds from snow lotus

low irritancy, allowing for the direct application of many derived products on damaged skin or mucous membranes.

In this study, the snow lotus, a medicinal plant known for its antibacterial properties, was analyzed using a network pharmacology approach. The findings suggest that snow lotus may inhibit bacterial activity, modulate cellular responses to bacterial-derived molecules, and activate the body's immunomodulatory functions. This action is mediated through interactions with targets such as CASP3, TNF, and IL-6, facilitated by active components including quercetin, apigenin, and luteolin. Theoretical investigations indicate that snow lotus possesses the potential to be developed as a source of botanical bacteriostatic agents. However, its antibacterial and bacteriostatic mechanisms require validation through further comprehensive studies. It is important to acknowledge that the utilization of botanical bacteriostatic agents is associated with certain limitations, including restricted bactericidal efficacy and spectrum, as well as challenges in formulation[36]. Consequently, the consideration of synergistic inhibition in conjunction with broad-spectrum chemical disinfectants may be advantageous in the development and application of related disinfection products, with the objective of formulating novel compound antibacterial and bacteriostatic preparations.

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