Action Mechanism of Radix Aucklandiae against Gastric Ulcer Based on Network Pharmacology

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Abstract [**Objectives**] To explore the potential targets and action mechanism of radix aucklandiae (RA) in the treatment of gastric ulcer (GU) by network pharmacology. [**Methods**] Gene targets were obtained through TCMSP, DisGeNet, OMIM, GeneCards databases, which related to GU and the active components of RA. The mutual potential functional targets were selected through Venny to constitute the PPI protein interaction network. The DAVID database was applied for GO and KEGG enrichment analysis of the common targets to construct the "Active component - Target - Pathway" network and analyze the relationship between them. [**Results**] There are 31 active components, 82 related targets and 16 common targets in the treatment of GU. The active components in Ra may exert anti-ulcer effects through six signaling pathways, including NF-κB, Toll-like receptors, VEGF and HIF-1. In addition, PTGS2, TNF, TLR4, JUN, IL2, SRC, RELA, KDR, NOS2 and PLAU may be the 10 key targets of Ra in the treatment of GU. [**Conclusions**] Ra controls GU through the synergies of multiple components, targets and pathways. It can provide a theoretical basis for further study on the mechanism of RA in treating GU.

Key words Network pharmacology, Radix Aucklandiae, Gastric ulcer

1 Introduction

Gastric ulcer (GU) is one of the most common clinical digestive system diseases. Approximately 10% of people suffers from GU around the world[1]. GU has three major clinical manifestations: high incidence, high recurrence and high canceration. It is listed as one of the leading precancerous lesions by the WHO and seriously threatens people's lives and health[2]. The formation of GU is associated with an imbalance between attack and defense factors in the stomach[3]. GU is caused by many etiologies, including stress, alcohol abuse, increased gastric acid/pepsin secretion, long-term heavy use of non-steroidal anti-inflammatory drugs and Helicobacter pylori infection[4]. There are a lot of clinical drugs available for the treatment of GU and short-term cure of GU is no longer a problem. However, what still plague us are the adverse effects of anti-ulcer drugs and the high recurrence rate after drug withdrawal. China enjoys a long history in applying Chinese medicine to treat GU with definite effect. Therefore, it is practically significant to find useful anti-ulcer drugs from Chinese medicine.

Radix Aucklandiae (RA) is the dry root of the plant *Akolia lappa* Decne. It is warm in nature, pungent and bitter in taste, and is a member of the spleen, stomach, large intestine and triple energizer meridian. With the effects of moving Qi and relieving pain, strengthening the spleen and eliminating food, it is commonly used to treat symptoms such as spleen and stomach qi stagnation, abdominal distension and pain, and severe diarrhea. Modern research has shown that the main chemical components of RA include alkaloids, terpenoids, flavonoids, anthraquinones, *etc.*[5]. The pharmacological effects of RA include anti-inflammatory[6], antibacterial[7], anti-tumor[8], anti-GU[9], antioxidant[10]. Through literature review, it was found that Aucklandia odora extracts had protective effects on rats with water-stressed, hydrochloric acid-ethanolic and reserpine induced acute gastric mucosa injury models[11-12]. Most of the existing studies have focused on the pharmacodynamic observation of the anti-GU effects of RA and its effects of inhibition of gastric acid and antioxidant. However, little attention was paid to the role of RA and its main active components in the treatment of GU and its related mechanisms.

Network pharmacology has become a new tool and instrument to evaluate the pharmacological basis and mechanism of action of herbal medicines. This study applied network pharmacology to investigate the main active components of RA in the treatment of GU and the potential mechanism of action against GU. It will lay a theoretical basis for future studies.

2 Materials and methods

2.1 Database and software Databases, software, and online tools used in this study are shown in Table 1.

Table 1 Databases, software, and online tools used in this study

Database/software	Website	Functions
TCMSP	http://tcmspw.com/tcmsp.php	Screening components and predicting targets
Dis GENET	https://www.disgenet.org/	Predicting disease targets
OMIM	https://www.omim.org/	Predicting disease targets
GeneCards	https://www.genecards.org/	Predicting disease targets
UniProt	https://www.uniprot.org/	Coding protein correcting gene
Venny	http://bioinfogp.cnb.csic.es/tools/venny	Drawing a common target map
STRING	https://string-bd.org/	Protein network interactions
Cotyscape 3.7.2	N/A	PPI perspective
DAVID	https://david.ncifcrf.gov/	Function enrichment analysis

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2.2 Collection of active components and potential targets of RA We retrieved "Radix Aucklandiae" in the TCMSP database[13], with a screening condition of $OB \geqslant 30\%$, collected eligible Active components of RA, and obtained potential targets. The UniProt database[14] was applied to limit "Homo sapiens" to species conditions and collect the gene names of the corresponding targets for the active components of RA.

2.3 Collection of potential targets for GU In databases such as DisGeNet[15], OMIM[16], and GeneCards[17], the relevant targets for GU were retrieved by the keyword "Gastric Ulcer". The relevant targets for GU were obtained after deleting the duplicates.

2.4 Screening of common targets and construction of Component – Target Networks In this paper, we adopted Venny software to visually demonstrate the active components and targets of the drug through Venny diagrams. Then the "component-target" network diagram was constructed by Cytoscape.

2.5 Construction of Protein – Protein Interaction (PPI) Network The common targets of drugs and diseases obtained in Section **2.4** was import into the STRING database[18] to get a PPI network by obtaining protein interactions with common targets.

2.6 Annotation of biological process and pathway enrichment analysis The intersection targets were imported into the DAVID database[19-20]. "Homo sapiens" was selected to perform GO and KEGG enrichment analysis[21]. Then the common targets of the drug and disease, and KEGG pathways obtained from Section **2.4** were used to construct the "component-target-pathway" network of RA by Cytoscape 3.7.2 software. As a result, it clarified the potential material basis and related action mechanism of RA in treating GU.

3 Results and analysis

3.1 Collection of active components and targets of RA First, 106 effective components of RA were acquired through database screening, and 31 effective components were obtained with the screening indicator $OB \geqslant 30\%$ (Table 2). Based on the target genes corresponding to these 31 active components, this paper further organized and enriched the target genes related to GU. Eventually, 82 targets were obtained after deleting duplicate and invalid targets.

3.2 Collection of potential targets in GU A total of 515 targets related to GU were collected by combining and taking the intersection of DisGeNet database (136), OMIM database (77) and GeneCards database (301). 434 targets related to GU were obtained after collation.

3.3 Construction of active drug component-target network Matching analysis was conducted between the 82 potential targets of RA collected through screening and 434 related targets of GU that met the screening criteria. After taking the intersection to remove duplicate values, 16 common targets of RA and GU were finally obtained for subsequent analysis (Table 3). The result was demonstrated in the form of Venn diagrams by Venny 2.1 software (Fig. 1).

Table 2 Main active component of RA

Molecule ID	Component
MOL000019	D-camphene
MOL000118	(L)-α-Terpineol
MOL000131	EIC
MOL000175	Cyclopentene
MOL000193	(Z)-Caryophyllene
MOL000198	(R)-Linalool
MOL000202	Shepherene
MOL000244	borneol
MOL000267	β-Citronellol
MOL000348	4-[(Z) -3-hydroxypropyl-1-enyl] -2,6-dimethoxyphenol
MOL000449	Stigmasterol
MOL000475	Anethole
MOL000612	(−)-α-Cedarene
MOL000666	Hexanal
MOL000922	(R)-p-Menth-1-en-4-ol
MOL000991	Cinnamaldehyde
MOL001390	Nitropropane
MOL001732	IFP
MOL002003	(−)-Caryophyllene oxide
MOL002122	(Z)-Ligustilide
MOL002361	Tarragon
MOL002850	Butyl hydroxytoluene
MOL010813	Benzocarbazole
MOL010817	7-methyl-4-(1-methylethylidene)-bicyclic [5.3.1]
MOL010826	Muxiang lactone
MOL010828	Cauliflower extract
MOL010832	Eremophilene
MOL010834	Acetyl eugenol
MOL010843	Balchanin

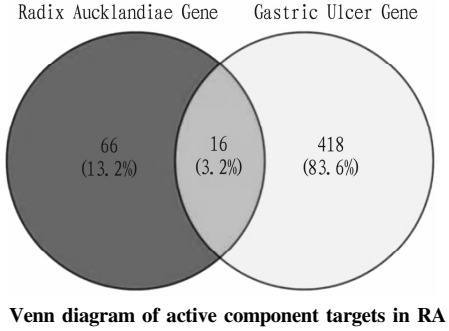


Fig. 1 Venn diagram of active component targets in RA and GU

3.4 PPI network construction for common targets in RA and GU Common targets in Section **3.3** were imported into STRING data to obtain protein-protein interaction. Then a PPI graph was plotted by Cytoscape 3.7.2. It was found that the larger the nodes and darker the colors in the graph, the higher the representativeness value (Fig. 2).

Table 3 Common targets

Sequence No.	Target protein	Encoding gene	Degree value
1	Cyclooxygenase 2	*PTGS2*	14
2	Tumor necrosis factor	*TNF*	14
3	AP-1 transcription factor subunit	*JUN*	12
4	Toll like receptor 4	*TLR4*	12
5	Non receptor tyrosine kinase	*SRC*	12
6	Heme oxygenase 1	*HMOX1*	9
7	Interleukin-2	*IL2*	12
8	Kinase insertion domain receptor	*KDR*	8
9	Inducible nitric oxide synthase	*NOS2*	9
10	NF-κB subunit	*RELA*	7
11	Plasmin Activator, Urokinase	*PLAU*	11
12	Coagulation factor III, tissue factor	*F3*	6
13	Nuclear factor E2 related factor 2	*NFE2L2*	6
14	Cyclooxygenase 1	*PTGS1*	4
15	Cathepsin D	*CTSD*	2
16	Glutathione sulfur transferase P1	*GSTP1*	4

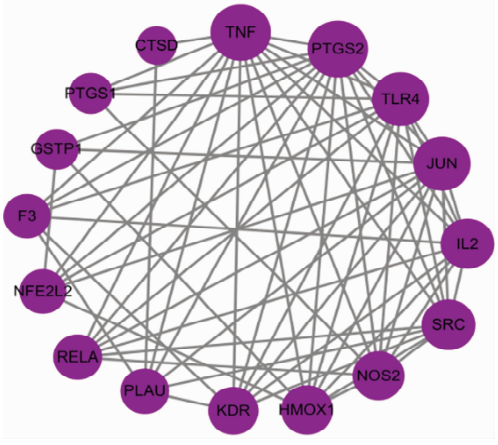


Fig. 2 Core target interaction of RA in treating GU

3.5 GO function enrichment analysis of interaction targets between Ra and GU It was found from GO analysis that the anti-GU effects of RA were mainly concentrated in the regulation of cell proliferation, inflammation, positive regulation of endothelial cell proliferation, regulation of protein kinase B signaling, cyclooxygenase pathway, oxidative stress response, positive regulation of ERK1 and ERK2 cascade, positive regulation of NF-κB. Cell groups were mainly enriched in the extracellular space, cytoplasm, nucleus and cytoplasm. Besides, molecular functions were mainly enriched in heme binding, prostaglandin endoperoxide synthase activity, peroxidase activity, and RNA polymerase II distal enhancer sequence-specific DNA binding (Fig. 3).

3.6 KEGG pathway enrichment analysis of the interaction targets between RA and GU The KEGG analysis revealed that the smaller the *P* value, the more significant the enrichment. The bubble diagram of the first 24 significantly enriched KEGG pathways is shown in Fig. 4. It can be seen that the pathways related to the anti-GU of RA are NF-κB, Toll-like receptor, TNF, VEGF, HIF-1, PI3K-Akt, *etc.* (Table 4). This suggests that RA may exert its anti-GU effect by regulating the 6 pathways.

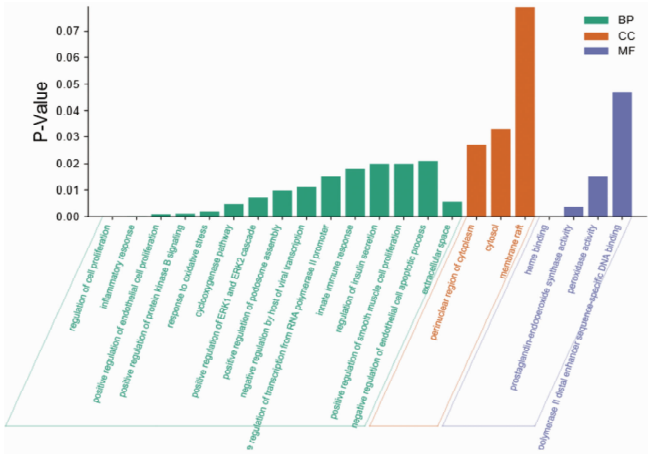


Fig. 3 GO biofunctional enrichment analysis of the key anti-GU targets of the active components in RA

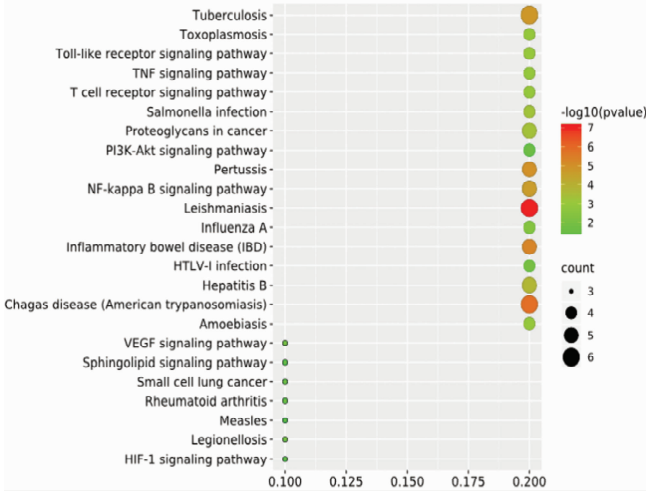


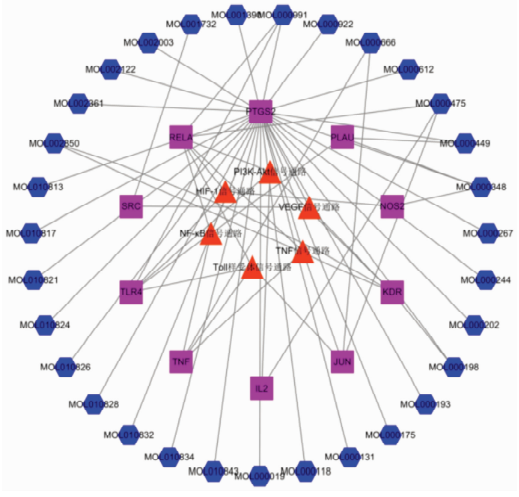
Fig. 4 KEGG bubble diagram of common targets

Table 4 KEGG pathway enrichment analysis of key targets in the active components of RA in anti-GU

Pathway name	*P*	Number of genes	Enriched gene
NF-κB	2.2×10^{-5}	5	*PLAU*, *RELA*, *PTGS2*, *TLR4*, *TNF*
Toll-like receptor	9.5×10^{-4}	4	*JUN*, *RELA*, *TRIA*, *TNF*
TNF	1.1×10^{-3}	4	*JUN*, *RELA*, *PTGS2*, *TNF*
VEGF	5.8×10^{-3}	3	*SRC*, *KDR*, *PTGS2*
HIF-1	1.6×10^{-2}	3	*RELA*, *NOS2*, *TLR4*
PI3K-Akt	2.5×10^{-2}	4	*RELA*, *IL2*, *KDR*, *TLR4*

3.7 "Active component-target gene-pathway" network analysis The Cytoscape 3.7.2 software was used to construct the "active component-target-pathway" network of RA (Fig. 5). In this network, there are a total of 48 nodes, including 31 active components (blue triangles), 10 common targets between RA and GU (purple red), and the top 6 KEGG signaling pathways (red triangles). The active components with more targets include cinnamaldehyde, anethole, (R)-linalool, stigmasterol, and costunolide. This indicates that these components may be the material basis of aucklandia for treating GU. *PTGS2*, *TNF*, *TLR4*, *JUN*, *IL2*, *SRC*, *RELA*, *KDR*, *NOS2*, and *PLAU* are the targets that

connect more active components and pathways. It shows that these targets may be the key ones of RA in treating GU. The essential active components of RA may regulate NF-κB, Toll-like receptors, VEGF, TNF, PI3K-Akt, and HIF-1 signaling pathways through these targets to exert anti-ulcer effects.



Note: The blue outer circle represents the active component, the purple middle circle represents the target, and the red inner circle represents the signal pathway.

Fig. 5 "Active components – Target – Pathway" Network of Ra

4 Discussion

In this study, we used network pharmacology to construct networks of "drug-active component-target" and "core target interactions". It thoroughly investigated the effective active components, potential targets and action mechanisms of RA in treating GU from multiple aspects and at multiple levels. We also established a PPI network of active components and common targets. The results showed that *PTGS*2, *TNF*, *TLR*4, *JUN*, *IL2*, *SRC*, *RELA*, *KDR*, *NOS*2 and *PLAU* were the key targets. Moreover, the GO functional analysis revealed that the common targets were enriched in inflammation, cyclooxygenase pathway, oxidative stress response and positive regulation of NF-κB.

KEGG enrichment results identified six pathways associated with GU, namely NF-κB, Toll-like receptor, TNF, VEGF, HIF-1, and PI3K-Akt. NF-κB is an essential intracellular nuclear transcription factor involved in the regulation of apoptosis, oxidative stress response, and inflammation. Normally, NF-κB binds to IκB to form an inactive NF-κB/IκB complex present in the cytoplasm. When stimulated by injury, the complex is dissociated and moved to the nucleus by activated NF-κB to regulate the expression of inflammation-related factors (such as TNF, IL-6, IL-1β, *etc.*), causing Inflammation[22]. Inflammation can damage mucosal tissue and disrupt angiogenesis, and is the main reason why ulcers are difficult to heal and recur[23]. TNF is the initiator of the inflammation. Thus, the increase in TNF expression can promote the release of other inflammatory factors and aggravate the inflammation of the organism or tissues. Additionally, TNF can also act on vascular endothelial cells, causing vascular damage, resulting in local tissue, hemorrhage or necrosis, and further aggravating tissue damage[24]. The HIF-1 signaling pathway is a core transcription factor that regulates oxygen homeostasis. HIF-1 protein expression is significantly increased during acute gastric mucosal injury, indicating the occurrence of ulcers accompanied by a hypoxic environment[25]. In contrast, VEGF is one of the target genes regulated by the HIF-1 signaling pathway and is the most potent cytokine promoting neoangiogenesis in the organism[26]. The increase in VEGF expression can promote local blood circulation and nutrient metabolism in the ulcerated surface.

In summary, we analyzed the potential targets of RA in treating GU and its related mechanisms through the network pharmacology. It was found that RA has the characteristics of multi-ingredient, multi-target, and multi-pathway in treating GU. It is expected to provide a theoretical basis for further research on the action mechanism of RA in against the GU.

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Individuals were small, and the length of mature individuals was 5 – 7 cm; the longitudinal stripes on both sides of the body were lighter in color ····· 4

4. The yellow longitudinal stripes on the back were continuous and thick, and the middle one was the most prominent; the prostate gland was obvious ····· *H. tianjinensis* Liu
The yellow longitudinal stripes on the back were discontinuous, thin and spotted, and the longitudinal stripes where a2 ring was located were dark or missing; the prostate gland was not obvious ····· *H. nipponia* Whitman

3.2 Dry samples of medicinal leeches Molecular taxonomy of 4 dry samples of medicinal leeches was studied. DNA was successfully extracted from 4 samples and COI fragment sequences were obtained. The sequence alignment results are shown in Table 2.

Table 2 Sequence alignment results of dry samples of medicinal leeches

No.	Name	Refer to Genbank ID	Identification results
1	*Eisenia andrei*	LC006116	*Eisenia andrei*
2	*Barbronia weberi*	KU553102	*Barbronia weberi*
3	Northeast *Hirudo*	MF358688	*Erpobdella* (morphological identification is needed for species in accordance with living samples)
5	Unknown	KU553102	Barbronia weberi

3 Conclusion

There are many species of Hirudo circulating in the market at present, such as "Northeast *Hirudo*", "*E. andrei*", "*B. weberi*" and "*W. laevis*". In addition, some wild counterfeits including *Erpobdella*, *Hameadipsa* and non-*Hirudo* species are circulated and used as Hirudo in the market, and there is a problem that Hirudoof different origins are mixed with each other for medication. Moreover, these related species are difficult to distinguish and identify only by the current standards, which affects the quality and safety of genuine medicinal materials.

The current *Pharmacopoeia* standard has only a morphological description for the species control of Hirudo. When the medicinal materials are presented in dry state or processed in powder, they can hardly be identified by naked eyes. At the same time, it is found in practice that TLC identification method can not be used to distinguish genuine Hirudo from some counterfeit ones. To a certain extent, the lack of quality control indicators for qualitative identification and testing of this kind of standard Chinese herbal medicines brings difficulties to drug control, and makes the production enterprises or inspection departments unable to identify the species of Hirudo used, which may lead to the use of uncontrolled medicinal materials from unknown sources for drug production, and even affect the safety of clinical medication. Therefore, the next step will be to study and design primer pairs based on amplification of small fragments of genes, in order to quickly and accurately identify the sources of Hirudo in medicinal materials and traditional Chinese medicine prescriptions, and provide a reference for molecular biological identification of Hirudo.

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