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Article

Research on Anti-inflammatory Targets and Mechanisms of alkaloids in *Picrasma quassioides* Benn Through Network Pharmacology

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This study aimed to investigate the molecular mechanism of *Picrasma quassioides* Benn against inflammation by means of network pharmacology. The paper will provide a reference for multi-target and multi-channel treatment of inflammation with traditional Chinese medicine. Through screening and analysis, 11 active ingredients and 109 anti-inflammation prediction targets were obtained and constructed a compound-target network. The targets such as VEGFA, TLR4 and STAT3 may play a crucial role. Network enrichment analysis showed that the 109 potential targets constitute a number of pathways or inflammatory reactions closely related to inflammation, including NF-κB signaling pathway and MAPK signaling pathway. The docking results indicated that the binding energy of Picrasidine Y and the inflammatory factors VEGFA is the highest. This study predicted the role of multiple active compounds in the alkaloids of Picrasma in the inflammatory response, and provided a theoretical basis for the anti-inflammatory mechanism of Picrasma.

Keywords: *Picrasma quassioides* (D.Don) Benn. Alkaloids. Inflammation. Network pharmacology. Molecular docking.

INTRODUCTION

As early as the early 1990s, inflammation has become one of the most interesting fields for biomedical researchers. Inflammation is a normal biological defense against infection and tissue damage. It can play a protective role by producing a series of physiological reactions to foreign organisms, including human pathogens, dust particles and viruses. Modern Western medicine divides inflammation into acute and chronic inflammation according to different inflammatory processes and cellular mechanisms. A lot of research evidence shows that acute inflammation usually develops gradually from chronic inflammation, and chronic inflammation can transform into various inflammatory diseases and even cause cancer. The results of some researchers suggest that inflammation-associated DNA damage in cancer stem-like cells leads to cancer development with aggressive clinical features (Murata, 2018). This study strongly reveals the relationship between inflammation and tumor formation and metastasis. Traditional Chinese medicine does not say that there is inflammation. Physicians associate "heat" with inflammation, and believe that inflammation originates from "heat" Studies have shown that inflammation is contained by heat clearing herbs (Lu *et al.,* 2020). According to the theory of Chinese medicine, the treatment of inflammation must start from changing the environment of the machine and improving the constitution. Through the multiple components of one traditional Chinese medicine or the collaborative treatment of multiple traditional Chinese medicine, it is not only aimed at the single place of the disease area, but from the whole person, which is omni-directional and diversified. Because of the complexity of the components of traditional Chinese medicine, its mechanism of action is not clear.

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Picrasma quassioides (D. Don) Benn is the dry branches, stems and leaves of the genus Picrasma in the family Simaroubaceae. It tastes bitter and is cold in nature. It has the effects of clearing away heat and toxin, removing dampness and swelling, and treating snake and insect bites. Alkaloids are the main anti-inflammatory components in Picrasma, among which indole alkaloids such as β-carboline alkaloids and canthinone alkaloids are the main ones (Jiao *et al.,* 2011). At present, there are few studies on the anti-inflammatory effect and related targets of Picrasma. Our research team measured the inhibition of β-carboline and canthinone alkaloids on NO and inflammatory factors (IL-6 and IκB-α) in the early stage, and found that some compounds had good inhibition and were closely related to the NF-κB pathway. However, the anti-inflammatory mechanism of the β-carboline alkaloids has not been known yet.

Network pharmacology is a new discipline based on the theory of system biology, which analyzes the network of biological system and selects specific signal nodes for multi-target drug molecular design. Traditional Chinese medicine has the characteristics of multi-component, multi-target and overall action, and various kinds of traditional Chinese medicine cooperate to produce therapeutic effect. Therefore, Network pharmacology is similar to traditional Chinese medicine, and we can have the aid of this tool to predict the way Chinese medicine works. It can reveal the network relationship of disease-target-drug interaction through computer simulation and network database retrieval technology, and can predict and analyze the drug action mechanism from the system level (Li, Zhang, 2013). In network pharmacology, a drug molecule can interact with multiple proteins. Through the visualized node network, the interaction between drugs and targets can be quickly analyzed, which is helpful to discover new candidate drugs, explore the mechanism of drug action, and determine whether the protein can be used as a drug targe (Hopkins, 2008).

Therefore, the purpose of this study is to use network pharmacology to find alkaloid related inflammatory targets, enrich biological processes and pathways related to targets, and explore the anti-inflammatory mechanism of Picrasma by constructing multiple alkaloid-target networks.

MATERIAL AND METHODS

Material

ChemOffice 2016, Swiss Target Prediction database (http://www.swisstargetprediction.ch/), Gene Cards database (https://www.genecards.org/), STRING database (https://string-db.org/), Venny 2.1.0 Online software mapping tool platform (https://bioinfogp.cnb.csic.es/tools/venny/), PDB database (https://www.rcsb.org/), Metascape database (http://metascape.org/), Cytoscape3.7.1, Moe2008.10 etc.

Methods

Construction of chemical composition library

Since the chemical components included in the Chinese medicine component database are not complete, the main anti-inflammatory chemical components of the alkaloids of Picrasma were found by searching relevant literatures (Lee J *et al.,* 2021). The molecular structure of alkaloids were drawn by ChemDraw software.

Prediction of the target of alkaloids

The Swiss target prediction database was used to predict the target, and "Homo sapiens" was selected as the target to predict the species. All the targets obtained were screened and sorted, and the potential targets of alkaloids could be obtained.

Acquisition of inflammatory targets

The Gene Cards (https://www.genecards.org/) knowledge base automatically integrates gene-centric data from approximately 150 online resources, including genome, transcriptome, proteome, genetic, clinical, and functional information. Using "inflammation" as a key word, a total of 10272 genes related to inflammatory factors were retrieved from the database. A total of 538 inflammatory factors with correlation scores greater than 10 were selected.

Obtaining potential targets

After the repeated values of alkaloids and inflammatory targets were removed and sorted by Excel software, Venny 2.1.0 mapping tool was used to get the intersection of the two targets, and the potential anti-inflammatory targets were obtained.

PPI network construction and analysis

The potential anti-inflammatory targets were input into string database for retrieval, and "Homo sapiens" was used as the protein category, with the minimum interaction threshold of 0.4. The protein interaction information was obtained, and then imported into Cytoscape 3.7.1 to draw PPI network. Among them, the compound and target are represented by nodes, and the interaction between compound and target is represented by edges. The size and color of nodes represent the degree value. The core targets were selected according to the degree value of nodes.

Biological process and pathway analysis

GO (Gene Ontology) is a database established by the Gene Ontology Federation. There are three categories of GO databases, namely, cellular component (CC), biological process (BP), and molecular function (MF), which describe the cellular environment in which the gene product is located, the biological processes involved, and the possible molecular functions, respectively. The Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway is a knowledge base including most of the known metabolic pathways and some of the known regulatory pathways. The metascape database (http://metascape.org/) is an online biological knowledge base and an analytic tool to extract biological information about gene functional classification, functional annotation, and enriched pathways. Metascape (http://metascape.org/) is a powerful tool for gene function annotation analysis, which can help people apply the current popular bioinformatics analysis methods to batch gene and protein analysis, so as to realize the cognition of gene or protein function. The results of Go and KEGG enrichment analysis were obtained by using metascape database to analyze the anti-inflammatory signal pathway of alkaloids in Picrasma.

Molecular docking

Select the target with the largest value in the PPI network as the receptor and the active ingredients of Picrasma having the number of gene targets >17 as the ligand for molecular docking verification. The alkaloid molecules found in the literature were drawn by ChemDraw software and the energy of alkaloid structural formula acting on the target of inflammatory pathway was minimized, 3D optimized and saved in mol format. The molecular docking study was performed using MOE 2008.10 to understand the ligandeprotein interactions in detail. The targetcompounds were built using the builder interface of the MOE program and subjected to energy minimization. The crystal structure of VEGFA protein (PDB ID: 5HHD), TLR4 protein (PDB ID: 5NAM) and STAT3 protein (PDB ID: 5U5S) were retrieved from Protein Data Bank. The edited crystal structure after removing water molecules was imported into MOE and chain A was considered for docking process as the protein is a dimer consisting of A and B chains. The structure is protonated, polar hydrogens were added and energy minimization was carried out till the gradient convergence 0.05 kcal/mol was reached to get the stabilized conformation. The active site was correlated with 'Site Finder' module of MOE to define the docking site for the ligands. Docking procedure was followed using the standard protocol implemented in MOE 2008.10 and the geometry of resulting complexes was studied using the MOE's Pose Viewer utility. The docking effects were evaluated by the affinity value. The affinity values ≤ -9, ≤ -7, and≤ -5 kcal/mol represent strong, good, and certain binding activity, respectively.

RESULTS

Alkaloids in Picrasma

Through literature review, a total of 29 β-carbolin alkaloids(1-20) and canthinone alkaloids(21-29) were obtained in Table I.

TABLE I - The name and chemical structure of alkaloids

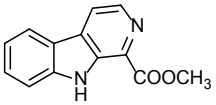
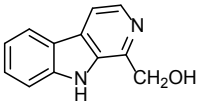
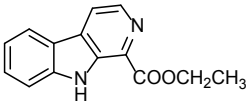
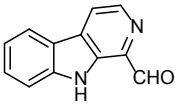
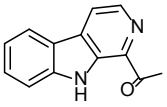
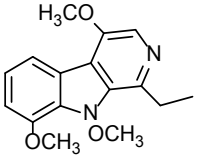
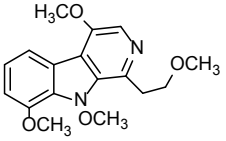
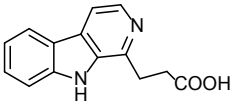
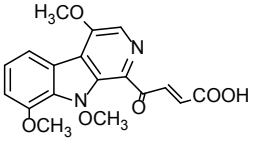
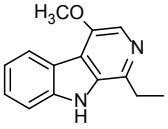
Alkaloids	Number	Name	Structure	Ref.
carboline	1	3-methxoycarbonyl-β-carboline		Lee J *et al*., 2021
	2	3-hydroxymethyl-β-carboline		Lee J *et al*., 2021
	3	3-ethxoycarbonyl-β-carboline		Lee J *et al*., 2021
	4	3-formyl-β-carboline		Lee J *et al*., 2021
	5	3-acetyl-β-carboline		Lee J *et al*., 2021
	6	6,12-dimethoxyl-3-ethyl-β-carboline		Lee J *et al*., 2021
	7	6,12-dimethoxy-3-(2-methoxylethyl)-β-carboline		Lee J *et al*., 2021
	8	β-carboline-3-propionic acid		Lee J *et al*., 2021
	9	Picrasidine E		Lee J *et al*., 2021
	10	6-methoxyl-3-ethyl-β-carboline		Lee J *et al*., 2021

TABLE I - The name and chemical structure of alkaloids

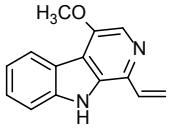
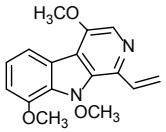
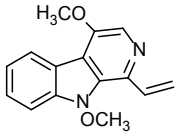
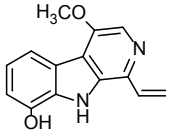
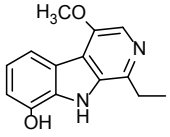
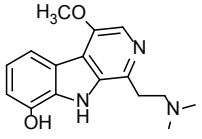
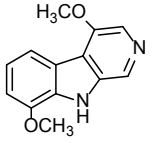
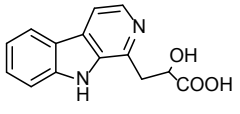
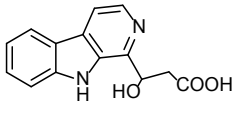
Alkaloids	Number	Name	Structure	Ref.
	11	6-methoxy-3-vinyl-β-carboline		Lee J *et al*., 2021
	12	6,12-dimethoxy-3-vinyl-,β-carboline		Lee J *et al*., 2021
	13	1,6-dimethoxy-3-vinyl-β-carboline		Lee J *et al*., 2021
	14	Picrasidine I		Lee J *et al*., 2021
	15	Picrasidine J		Lee J *et al*., 2021
	16	Picrasidine K		Lee J *et al*., 2021
	17	Picrasidine P		Lee J *et al*., 2021
	18	Picrasidine X		Lee J *et al*., 2021
	19	Picrasidine Y		Lee J *et al*., 2021

TABLE I - The name and chemical structure of alkaloids

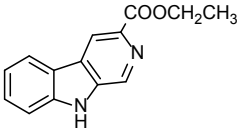
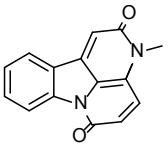
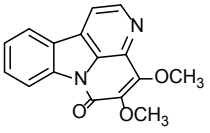
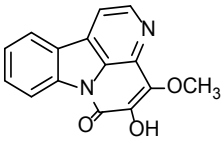
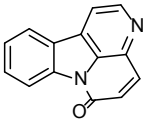
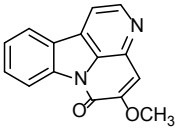
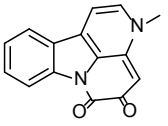
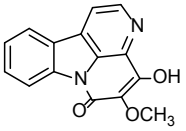
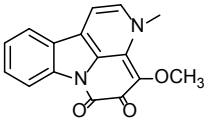
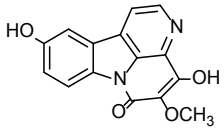
Alkaloids	Number	Name	Structure	Ref.
	20	5-ethxoycarbonyl-β-carboline		Lee J *et al*., 2021
canthinone	21	4-methyl-canthin-5,16-dione		Lee J *et al*., 2021
	22	14,15-dimethoxy-canthin-16-one		Lee J *et al*., 2021
	23	15-hydroxy-14-methoxy-canthin-16-one		Lee J *et al*., 2021
	24	canthin-16-one		Lee J *et al*., 2021
	25	15-methoxy-canthin-16-one		Lee J *et al*., 2021
	26	4-methyl-canthin-15,16-dione		Lee J *et al*., 2021
	27	14-hydroxy-15-methoxy-canthin-16-one		Lee J *et al*., 2021
	28	4-methyl-14-methoxy-canthin-15,16-dione		Lee J *et al*., 2021

TABLE I - The name and chemical structure of alkaloids

Alkaloids	Number	Name	Structure	Ref.
	29	11,14-dihydroxy-15-methoxy-canthin-16-one		Lee J *et al*., 2021

Prediction of potential targets

After deduplicating the predicted targets obtained in the Swiss database, there were 659 drug targets and 102 potential targets for β-carboline alkaloids; there were 468 drug targets and 70 potential targets for canthinone alkaloids. The 538 disease targets were obtained through the GeneCards database. Input drug and disease targets into Venny 2.1 online mapping tool platform to obtain pictures of compound targets related to inflammation. As shown in the figure (Figure 1), there are 109 closely related targets between alkaloids and inflammation. The results show that alkaloids in Picrasma may exert anti-inflammatory effect through multiple targets.

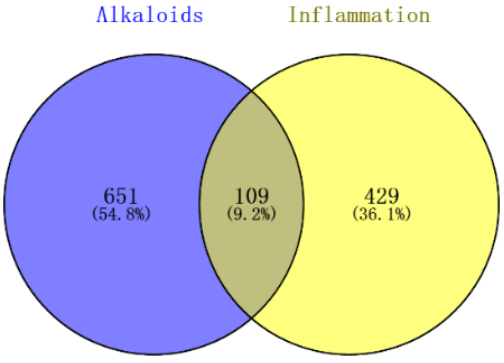


FIGURE 1 - Venn diagram of Picrasma alkaloids and inflammatory targets.

Compound-target network construction and analysis

Compounds, potential targets and other information were imported into Cytoscape software to draw alkaloid-potential targets network diagram (Figure 2). β-carbolin and canthinone alkaloids were marked in blue, and potential genes were marked in green. According to the compound-potential target point network analysis, NO.6, 9, 10, 14, 15, 17, 19, 21, 23, 26, 28 were the most ten compounds that can be linked with gene targets, and the number of targets associated with them was greater than the average of 17. It was speculated that these 11 compounds are the main anti-inflammatory components in alkaloids. The phenomenon that one component interacts with multiple targets, and multiple components can work together on the same target reflected the comprehensive regulation characteristics of alkaloids in Picrasma. The target number of the 11 active ingredients were 18, 22, 19, 19, 20, 19, 22, 19, 21, 19 and 21, respectively.

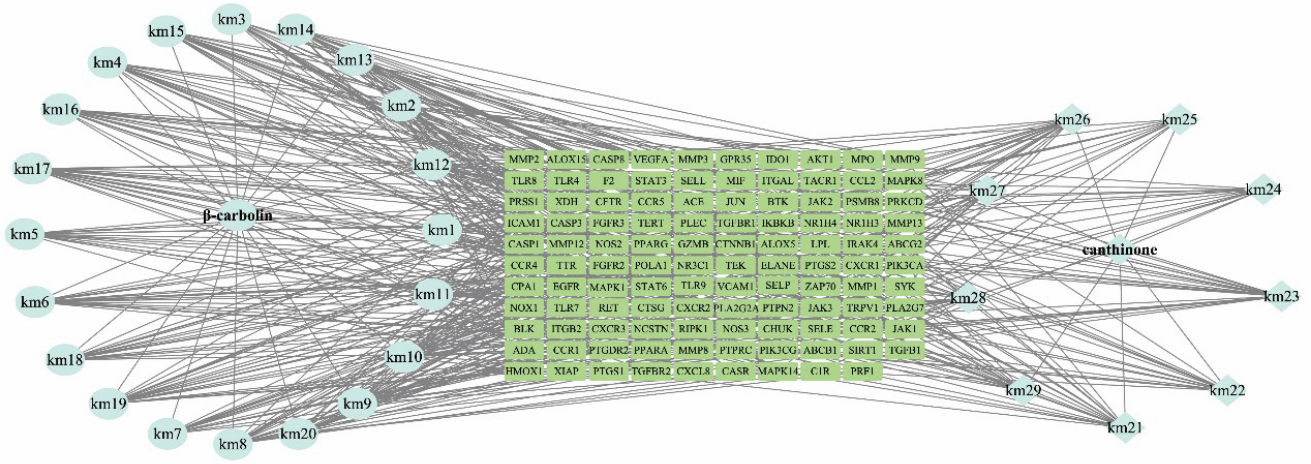


FIGURE 2 - The network diagram of active components and targets of alkaloids from Picrasma.

PPI network construction

By comparing the target of Picrasma active ingredient with the current clinical inflammatory target, we observed that the direct cross (same) target is shown in PPI network diagram (Figure 3). In the network, The three targets with the largest number of interactions between targets are vascular endothelial growth factor (VEGFA), Toll-like receptor 4 (TLR4) and Signal transducer and activator of transcription 3 (STAT3). It was speculated that these nodes may be the key anti-inflammation targets of Picrasma.

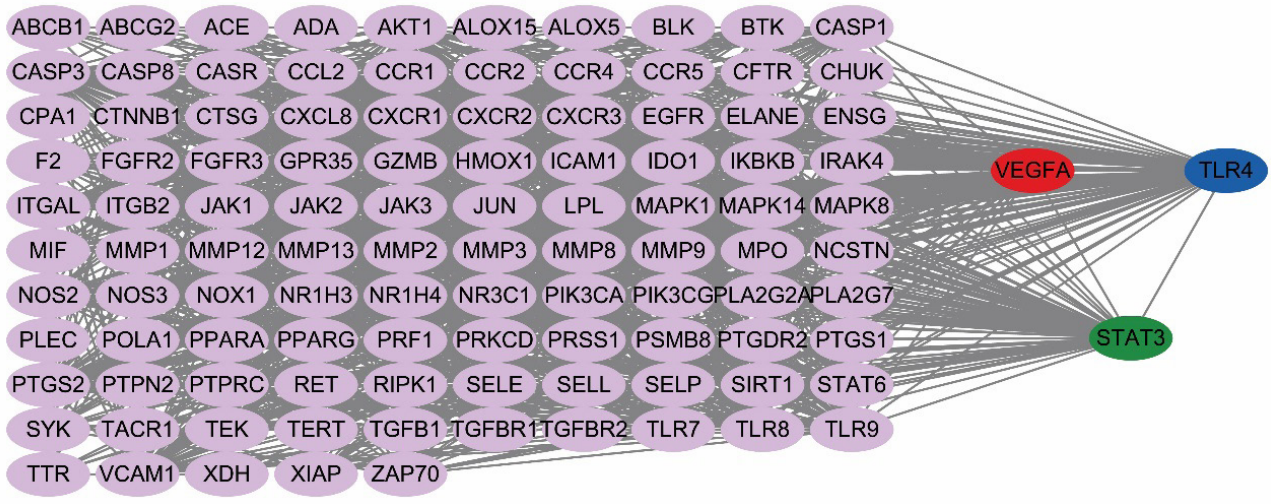


FIGURE 3 - The interaction network of Picrasma alkaloids and protein.

Enrichment analysis

The enrichment results are shown in Figure 4. In the GO biological function analysis, there are two enrichment pathways related to inflammation. There are many inflammatory pathways, including inflammatory response and regulation of MAPK cascade. As shown in Figure 5, in KEGG enrichment analysis, there are

three signaling pathways related to inflammation, namely, chemoking signaling pathway, NF-κB signaling pathway, and Inflammatory bowel disease. It was indicated that Picrasma may act on these signaling pathways in the treatment of inflammations.

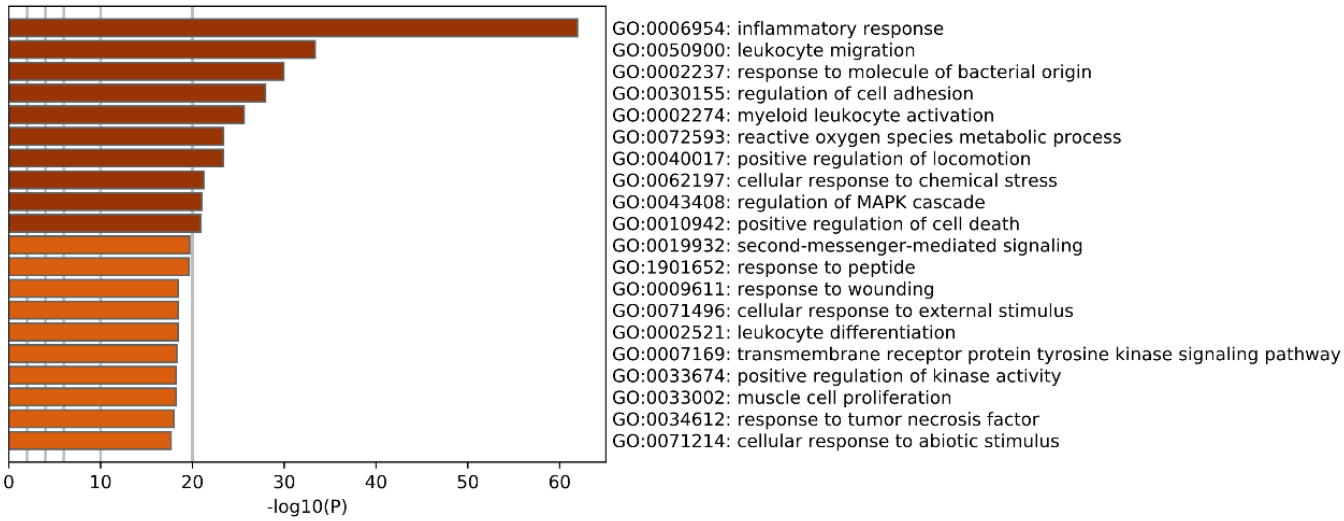


FIGURE 4 - GO biological function analysis results.

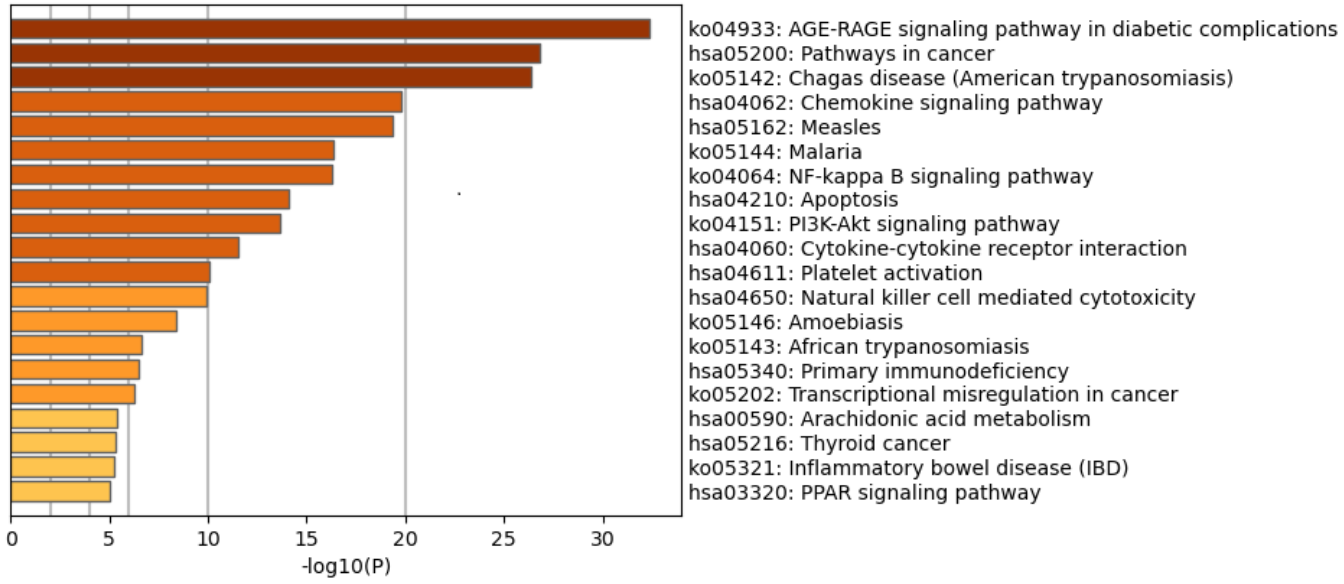


FIGURE 5 - KEGG enrichment analysis results.

Molecular docking

The active ingredients including 6,12-dimethoxyl-3-ethyl-β-carboline, Picrasidine E, 6-methoxyl-3-ethyl-β-carboline, Picrasidine I, Picrasidine J, Picrasidine P, Picrasidine Y, 4-methyl-canthin-5,16-dione, 15-hydroxy-14-methoxy-canthin-16-one, 4-methyl-canthin-15, 16-dione, and 4-methyl-14-methoxy-canthin-15, 16-dione

which have the number of gene targets >17, were used as ligands for molecular docking verification. The results are shown in Table II. The binding energy between these compounds and the targets was lower than −7.0 kcal/mol, indicating that the core active compounds of Picrasma had a good binding activity with the main target. The Picrasidine Y binding with VEGFA showed the highest binding energy (−10.9960 kcal/mol). The ligand compound 19 can form hydrogen bonds with O and N in the acceptor PHE-31 and PHE-37, which greatly increases the binding force. The lengths of these two hydrogen bonds are 2.50 and 3.07 Å respectively, which are indicated by green lines. Figure 6 shows the binding between Picrasidine Y and VEGFA. The amino acid residues LYS-11, LYS-58, PHE-34, PHE-38, PHE-60, TYR-10, TYR-53, VAL-28, VAL-30, VAL-36, ASP-29, ASP-32, ASP-35, ALA-27 and ALA-33 participated in the hydrophobic interactions (Figure 7).

TABLE II - Molecular docking scores of major active compound-main target molecular docking

		Binding energy (kcal/mol)		
Number	**Compound**	**VEGFA**	**TLR4**	**STAT3**
6	6,12-dimethoxyl-3-ethyl-β-carboline	-7.3059	-9.8275	-8.6935
9	Picrasidine E	-9.2866	-10.5901	-9.5611
10	6-methoxyl-3-ethyl-β-carboline	-8.2909	-9.3547	-9.1615
14	Picrasidine I	-9.4968	-9.8469	-10.2483
15	Picrasidine J	-9.1964	-10.0123	-9.4397
17	Picrasidine P	-8.5405	-9.2608	-8.6301
19	Picrasidine Y	-10.9960	-10.2953	-9.0778
21	4-methyl-canthin-5,16-dione	-8.2960	-9.0879	-10.5432
23	15-hydroxy-14-methoxy-canthin-16-one	-9.6817	-10.5843	-9.2025
26	4-methyl-canthin-15,16-dione	-7.6549	-9.0709	-7.9845
28	4-methyl-14-methoxy-canthin-15,16-dione	-8.3562	-9.4864	-8.9268

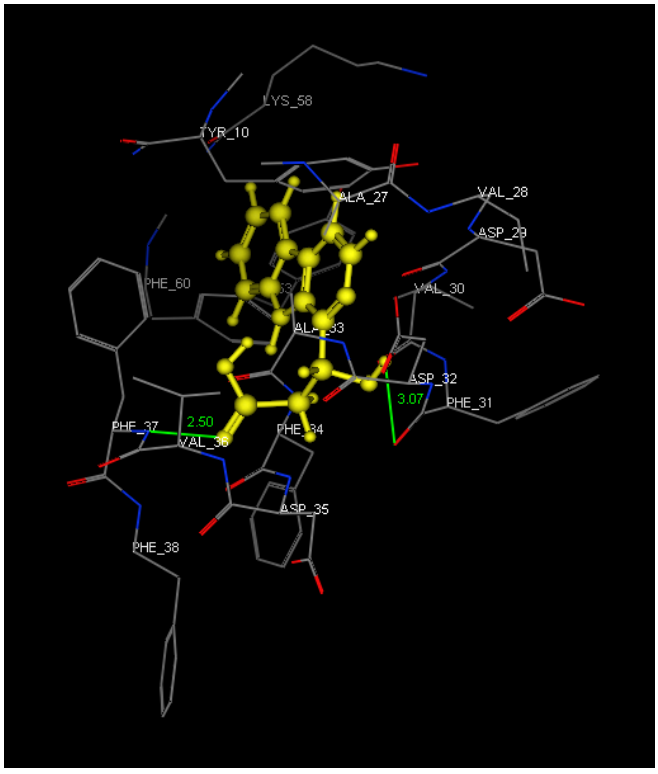


FIGURE 6 - Molecular docking diagram of Picrasidine Y and VEGFA.

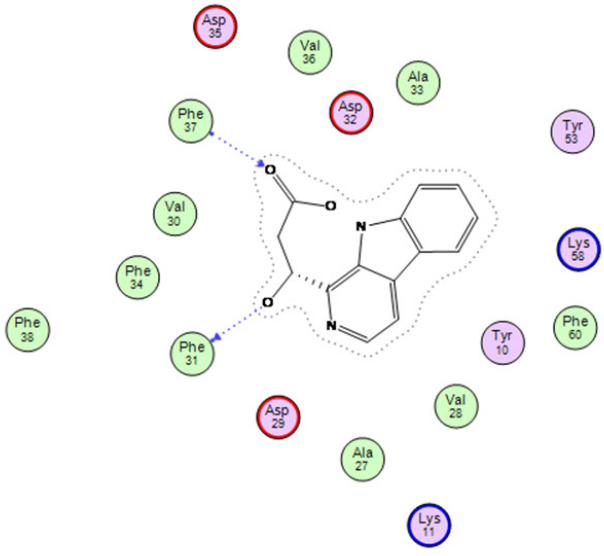


FIGURE 7 - Interaction diagram of Picrasidine Y and VEGFA.

DISCUSSION

As a traditional Chinese medicine, Picrasma has the heat-clearing and detoxifying effects that most traditional Chinese medicines have. Studies have shown that the extract of Picrasma has antibacterial effects, and its water decoction and fat-soluble total alkaloids can produce resistance to a variety of bacteria in vitro (Khan, Kihara, Omoloso, 2001). In addition, Picrasmaalso shows potential anti-inflammatory effect, and has also been developed into a traditional Chinese medicine preparation for the treatment of respiratory tract infections, enteritis and other diseases (Wang *et al.,* 2018). The active components in Picrasma has a complex chemical composition, including alkaloids, bitterin, triterpenoids, etc. The main alkaloid active components are β-carbolin and canthinone alkaloids. Literature studies have shown that Picrasma alkaloids can inhibit the body's inflammatory response and have a therapeutic effect on a variety of inflammatory diseases (Zhao *et al.,* 2012). Research by Shin showed that the extract of Picrasma can not only inhibit the production of inflammatory cells in mouse bronchoalveolar lavage fluid, but also reduce the levels of a variety of inflammatory factors, such as IL-4, IL-5 and so on (Shin *et al.,* 2014). In addition, Picrasma can inhibit airway inflammation by reducing the expression of inducible nitric oxide synthase (iNOS) and increasing the expression of heme oxygenase-1(HO-1). With the in-depth study of Picrasma, researchers found that after lipopolysaccharide induced acute lung injury model in mice, the content of reactive oxygen species and pro-inflammatory factors decreased significantly after Picrasma added (Lee *et al.,* 2016; Zhao *et al.,* 2013). More and more evidences show that Picrasma alkaloids play an important role in the treatment of inflammation. However, its mechanism of action is not yet clear.

In this study, 109 core targets were screened through multiple tools. With the help of compound-target network, we selected 11 compounds which are most closely related to potential targets as active ingredients. It reflects the anti-inflammation features of Picrasma with multiple components and multiple targets. The analysis of PPI makes the interactions of proteins clear. In the PPI network, VEGFA, TLR4 and STAT3 were the top 3 nodes in terms of degree value. It was speculated that they may be the major anti-inflammation targets of Picrasma. Most of these targets are well-known core targets related to inflammation. Take TLR4 as an example, the gene is expressed as Toll-like receptor 4 in humans. It acts

via MYD88, TIRAP and TRAF6, leading to NF-κB activation, cytokine secretion and the inflammatory response (Medzhitov, Preston-Hurlburt, Janeway, 1997; Arbour *et al.,* 2000; Arts *et al.,*2011).

From the enrichment analysis, the anti-inflammation pathways of the alkaloids of Picrasma mainly includes MAPK signaling pathway, chemoking signaling pathway, NF-κB signaling pathway and Inflammatory bowel disease.

Increasing studies have found that NF-κB signaling pathway can regulate inflammation and play an important role in inflammatory response. Inflammation is a major factor in the development of various chronic diseases, including cancer, inflammatory bowel disease, diabetes and cardiovascular disease (Galdiero, Marone, Mantovani, 2018; Li, 2019; Alolga *et al.,* 2020; Tu, Wan, Zeng, 2020). Among them, the NF-κB signaling pathway plays an important role in mediating the formation of inflammation. As an inducible transcription regulator, NF-κB plays an important role in regulating the expression of various inflammatory and immune genes by specifically binding to NF-κB binding sites in various cell enhancers. NF-κB is a complex and pleiotropic transcription factor. In addition to participating in cell proliferation, differentiation, apoptosis and other physiological activities, it is also involved in diabetes, lung injury, and atherosclerosis (Tao, Zhang, 2019; Shu, Liu, Jia, 2016; Zhang, Li, Qi, 2020). It plays a huge role in other diseases. These diseases often develop gradually from chronic inflammation, and the alkaloids of Picrasma may interact with this signal pathway to inhibit inflammation.

MAPK signaling pathway also plays an important role in the regulation of inflammatory factors. In inflammatory conditions, the expression of cytokines (IL-1) is tightly regulated by MAPK signaling pathways (Baldassare, Bi, Bellone, 1999). Studies have shown that MAPK signaling pathway can regulate inflammatory diseases such as lung injury and skin injury, which is closely related to inflammation (Li *et al.,* 2018; Li *et al.,* 2020).

Chemokine signaling pathway is composed of multiple chemokines, such as CCL2, CCl4 and CCR5. The researchers found that leukocyte migration, mediated in part by chemokines and chemokine receptors, plays an important role in the perpetuation of inflammation in rheumatoid synovium and macrophage inflammatory protein 1β/ CCL4 and CCR5 are key molecules involved in inflammation (Zhang *et al.,* 2015).

In this study, through network pharmacology method and network enrichment analysis, it was found that alkaloids of Picrasma are related to several inflammatory pathways, among which MAPK signaling pathway, chemoking signaling pathway and NF-κB signaling pathway may play crucial roles in inflammatory response. The active molecules of Picrasma had a good binding activity with key target proteins, indicating that the molecular docking results were consistent with the results of network pharmacology. The network pharmacology and molecular docking confirm each other, further explain the possible mechanism of anti-inflammatory effect of Picrasma.

CONCLUSION

In conclusion, the prediction results of network pharmacology demonstrate that alkaloids of Picrasma could act on multiple pathways closely related to inflammation, which was consistent with the results of anti-inflammatory activity experiments of some alkaloids of Picrasma conducted by our research group before. In the process of molecular docking, the binding effect of alkaloids with inflammatory targets VEGFA was the best, which further proved the fact that alkaloids interact with inflammatory proteins. This is consistent with the anti-inflammatory activity test results in the literature. On the basis of previous studies, we predicted the anti-inflammatory effects of other alkaloids on the basis of network pharmacology, studied the relationship between multiple inflammatory targets and alkaloids, further revealed the anti-inflammatory mechanism of alkaloids, and provided the basis for traditional Chinese medicine treatment of inflammation. The further experimental verification will be validated in our future studies.

DATA AVAILABILITY

The data sets used and/or analysed during the current study are available from the corresponding author on reasonable request.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHORS' CONTRIBUTIONS

Qijia Xu was responsible for obtaining and sorting out data and writing articles. Kai Wang, Yaoyao Xu, Yinhe Gao and Ge Wang helped with the arrangement of forms and pictures. Sheng Liu* and Feng Zhao* were engaged in the review of this article, correcting and guiding the author to correct the article.

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REFERENCES

Alolga RN, Nuer-Allornuvor GF, Kuugbee ED, Yin X, Ma G. Ginsenoside Rg1 and the control of inflammation implications for the therapy of type 2 diabetes: A review of scientific findings and call for further research. Pharmacol Res. 2020;152:104630.

Arbour NC, Lorenz E, Schutte BC, Zabner J, Kline JN, Jones M, et al. TLR4 mutations are associated with endotoxin hyporesponsiveness in humans. Nat Genet. 2000;25(2):187-191.

Arts RJ, Joosten LA, Dinarello CA, Kullberg BJ, van der Meer JW, Netea MG. TREM-1 interaction with the LPS/TLR4 receptor complex. Eur Cytokine Netw. 2011;22(1):11-14.

Baldassare JJ, Bi Y, Bellone CJ. The role of p38 mitogen-activated protein kinase in IL-1β transcription. J Immunol. 1999;162(9):5367.

Galdiero MR, Marone G, Mantovani A. Cancer inflammation and cytokines. Cold Spring Harb Perspect Biol. 2018;10(8):a028662.

Hopkins AL. Network pharmacology: the next paradigm in drug discovery. Nat Chem Biol. 2008;4(11):682-690.

Jiao WH, Gao H, Zhao F, Lin HW, Pan YM, Zhou GX, et al. Anti-inflammatory alkaloids from the stems of *Picrasma quassioides* BENNET. Chem Pharm Bull (Tokyo). 2011;59(3):359-364.

Khan MR, Kihara M, Omoloso AD. Antibacterial activity of Picrasma javanica. Fitoterapia. 2001;72(4):406-408.

Lee J, Gong YX, Jeong H, Seo H, Xie DP, Sun HN, et al. Pharmacological effects of *Picrasma quassioides* (D. Don) Benn for inflammation, cancer and neuroprotection (Review). Exp Ther Med. 2021;22(6):1357.

Lee JW, Park JW, Shin NR, Park SY, Kwon OK, Park HA, et al. *Picrasma quassiodes* (D.Don) Benn. attenuates lipopolysaccharide (LPS)-induced acute lung injury. Int J Mol Med. 2016;38(3):834-844.

Li D, Ren W, Jiang Z, Zhu L. Regulation of the NLRP3 inflammasome and macrophage pyroptosis by the p38 MAPK signaling pathway in a mouse model of acute lung injury. Mol Med Rep. 2018;18(5):4399-4409.

Li K, Fan Y, Xu Z, Xu C. Role of AhR and Foxo1 in skin inflammation in burn animal model via MAPK signaling pathway. Cell Mol Biol (Noisy-le-grand). 2020;66(2):53-58.

Li S, Zhang B. Traditional Chinese medicine network pharmacology: theory, methodology and application. Chin J Nat Med. 2013;11(2):110-120.

Lu ZB, Ou JY, Cao HH, Liu JS, Yu LZ. Heat-Clearing Chinese medicines in lipopolysaccharide-induced inflammation. Chin J Integr Med. 2020;26(7):552-559.

Medzhitov R, Preston-Hurlburt P, Janeway CA Jr. A human homologue of the Drosophila Toll protein signals activation of adaptive immunity. Nature. 1997;388(6640):394-397.

Murata M. Inflammation and cancer. Environ Health Prev Med. 2018;23(1):50.

Shin NR, Shin IS, Jeon CM, Hong JM, Oh SR, Hahn KW, et al. Inhibitory effects of *Picrasma quassioides* (D.Don) Benn. on airway inflammation in a murine model of allergic asthma. Mol Med Rep. 2014;10(3):1495-1500.

Shu B, Liu Z, Jia CY. Research progress on the relationship between acute lung injury/acute respiratory distress syndrome and NF-κB signal transduction. Chin J Injury and Repair (Electronic Edition). 2016;11(02):147-150.

Tao PY, Zhang Y. Bolus of six drugs including rehmannia alleviates inflammation and fibrosis of diabetic nephropathy by regulating NF-κB and TGF-β/Smad dual signaling pathway. J Guangzhou Univ Tradit Chin Med. 2019;36(02):245-250.

Tu C, Wan B, Zeng Y. Ginsenoside Rg3 alleviates inflammation in a rat model of myocardial infarction via the SIRT1/NF-κB pathway. Exp Ther Med. 2020;20(6):238.

Wang N, Li ZY, Zheng XL, Li Q, Yang X, Xu H. Quality assessment of picrasma injection, a traditional chinese medicine preparation, using HPLC combined with

chemometric methods and qualitative and quantitative analysis of multiple alkaloids by single marker. Molecules. 2018;23(4):856.

Zhang L, Yu M, Deng J, Lv X, Liu J, Xiao Y. Chemokine signaling pathway involved in CCL2 expression in patients with rheumatoid arthritis. Yonsei Med J. 2015;56(4):1134-1142.

Zhang WZ, Li GY, Qi Q. The regulatory effect of Dioscorea Panthaica Prain et Burkill on TLR4/MyD88/NF-κB signaling pathway in atherosclerotic rats. Chin J Tradit Chin Med. 2020;45(3):602-608.

Zhao F, Chen L, Bi C, Zhang M, Jiao W, Yao X. In vitro anti-inflammatory effect of picrasmalignan A by the inhibitionof iNOS and COX-2 expression in LPS-activated macrophage RAW 264.7 cells. Mol Med Rep. 2013;8(5):1575-1579.

Zhao F, Gao Z, Jiao W, Chen L, Chen L, Yao X. In vitro anti-inflammatory effects of beta-carbolinealkaloids, isolated from *Picrasma quassioides*, through inhibition of the iNOS pathway. Planta Med. 2012;78(18):1906-1911.

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