Study on the Mechanism of Allergic Rhinitis Treated by Centipeda Minima from Different Geographic Areas

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Background: To study the effect of volatile oils of Centipeda minima (C. minima) from Sichuan, Henan, Guangdong, Jiangxi, Hubei, Guangxi, and Shanxi on allergic rhinitis. The study also explores the mechanism of the oil's therapeutic effects using animal experimental models.

Material and Methods: C. minima was collected in seven different geographic areas. Steam distillation was used to extract the volatile oil components of C. minima. Using network pharmacology and molecular docking methods for target protein and biological pathway analysis. Furthermore, a rat model of allergic rhinitis was used to assess the in vivo effects of C. minima components. Hematoxylin-eosin staining was used to evaluate the tissue-related therapeutic effect of C. Minima.

Results: We extracted 15 common C. minima components from seven geographic regions of China and identified 343 of their molecular targets. Our data analysis indicated that 34 of these targets are related to allergic rhinitis and participate in 49 metabolic pathways. The molecular docking analysis showed that the identified target proteins can better bind the extracted drug components. Animal experiments confirmed that C. minima-extracted volatile oil can effectively treat allergic rhinitis.

Conclusion: Small differences were observed between the volatile components of C. minima collected in different geographic regions. The mechanism of C. minima component effects on allergic rhinitis is complex, multi-targeted, and associated with multi-pathway regulation. Considering that the effectiveness of the oil was confirmed in vivo, the volatile components of C. minima can be recommended for further testing and for the treatment of allergic rhinitis.

Keywords: allergic rhinitis; volatile oil; molecular docking simulation; network pharmacology

Background:

Centipeda minima (C. minima) is an aliases coriander, also known as chickweed. The plant is drought-resistant and grown in most provinces of China. C. minima has a spicy taste and has been shown to minimize nasal secretions and cough associated with colds and other respiratory complications[1]. It has been demonstrated that the main medicinal chemical components of C. minima include volatile oils, flavonoids, and polysaccharides [2]. Notably, the volatile oil components in C. minima were suggested to be the main anti-inflammatory effectors of this medicinal plant [3]. Accordingly, those components were traditionally used for the treatment of allergic rhinitis and associated headache, although the underlying therapeutic mechanism of these medicinal effects remains unclear.

Allergic rhinitis is a non-infectious inflammatory disease that affects the nasal mucosa. It has been marked by paroxysmal sneezing, runny and itchy nose, and nasal congestion. These health complications can impact work and other daily activities. Studies have shown that C. minima can significantly inhibit the activation of eosinophils and mast cells, reduce pathological changes in nasal mucosal tissues, reduce histamine levels, and lessen nasal obstruction[4,5].

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In this experimental study, volatile oil components were extracted from C. minima collected in seven different geographic areas of China. The best extraction conditions were experimentally determined using steam distillation. Following extraction, gas chromatography–mass spectrometry (GC–MS) was used to analyze the volatile oil composition of C. minima. Network pharmacology analysis was used to explore component–related molecular targets. The overall level of protein–disease correlation was assessed and the main pathways and key targets of C. minima components were determined. Molecular docking tests were done using the identified target proteins. The C. minima was used in in vivo animal experiments to evaluate drug efficacy and provide a reference for further clinical experiments.

Material and Methods:

1.1 Extraction of volatile oil from C. minima

C. minima medicinal materials were collected in seven producing areas of China including Guangdong, Henan, Sichuan, Jiangxi, Guangxi, Hubei, and Shanxi. Firstly, the best oil extraction process was determined using steam distillation, to obtain the optimal extraction parameters, the extraction protocol was developed using variable amount of the medicinal material and added water, and the extraction temperature as described previously [6]. Following this, volatile oils and other components were collected from different C. minima plants obtained in seven geographic locations for further analysis.

1.2 Determination of chemical composition of Volatile oils from C. minima

The chemical composition of the extracted volatile oil from C. minima was estimated using GC–MS. The GC–MS included Agilent HP–5ms (30m × 250μm × 0.25μm) capillary column. The used carrier gas was high purity He. The used injection volume was 3μL. The split ratio was 50:1. The flow rate was set at 1 ml/min. Temperature program was set as following: initial temperature was 55 ℃ with gradual temperature change set as 8 ℃/min; reaching 80 ℃ hold for 1 min; the following gradual temperature change was set as 6 ℃ /min; reaching 200 ℃ hold for 3 min; the following gradual temperature change was set as 3℃ /min; reaching 250℃ hold for 3 min. Mass spectrometry conditions were set as following: EI was used as an ion source; electron energy was 70 eV; ion source temperature was 230 ℃, MS quadrupole temperature was 150 ℃; multiplier voltage was 1.5 kV; scan mass range was 28 ~ 555 m/z; scanning interval was 0.5 s; and scan speed was 781 amu/s as described previously [7,8].

1.3 Fingerprint and cluster analysis

The GC–MS data was processed using Data Analysis software. For similarity analysis, the data was imported into the similarity evaluation system of chromatographic fingerprint for traditional Chinese medicine as described previously [9,10]. To detect the differences between the ingredients from plants collected in different geographic areas, SIMCA software was used to perform a cluster analysis on the content of ingredients.

1.4 Acquisition and comparison of C. Minima Component target with the targets of allergic Rhinitis

Processed by Data Analysis, get the common components of the seven geographic regions using Venny 2.1.0 (https://bioinfogp.cnb.csic.es/tools/venny/index.html). Then using Pubchem (https://pubchem.ncbi.nlm.nih.gov/) search for the English name. To find the relevant targets of identified ingredients, the Canonical SMILES numbers were copied and pasted on the Swiss Target Prediction (http://www.swisstargetprediction.ch/) website tool. To obtain the disease–related target , we searched for allergic rhinitis–related key–words using DisGeNET (http://www.disgenet.org/), OMIM (https://omim.org/), TTD (https://db.idrblab.org/ttd/)as described previously [11,12].

1.5 C. minima component–related targets and Associated allergic rhinitis target mapping

To obtain intersection targets of the volatile oil components and rhinitis, the identified C. minima component targets and allergic rhinitis–related targets

were imported into Venny 2.1.0 software. The intersection target was regarded as the effective protein–target of C. minima component linked to allergic rhinitis. Using the Merge function of Cytoscape 3.7.1 software, the component–target–disease network map was constructed. On the map, nodes represent components, targets, and diseases; edges were used to connect components, targets, and diseases. The C. minima protein–targets in allergic rhinitis were analyzed using the constructed network.

1.6 Protein Interaction Network

As described above, the identified intersection genes/proteins were uploaded to the STRING platform (https://string–db.org)[13]. Within this software tool, the data were uploaded as Multiple proteins and the selected organism was defined as Homo sapiens to obtain the protein interaction network figure. The output result was set in TSV format, saved as the node1, node2 data, and uploaded to Cytoscape 3.7.1 software. Cytoscape analysis was conducted to get the topology characteristics of the network, and adjust the node size according to the Degree value.

1.7 GO analysis and KEGG analysis

Using R language, we analyzed the intersection genes associated with of C. minima and allergic rhinitis using GO (GeneOntology) and KEGG (Kyoto Encyclopedia of Genes and Genomes) tools. Pathway enrichment data was collected to reflect the biological effect of C. minima on allergic rhinitis.

1.8 Molecular docking

According to the protein degree value identified as described above, we selected the top three proteins ranked by the degree value, and downloaded the PDB format of their 3D structure provided by the PDB (http://www.rcsb.org/pdb/home/home.do) website. Following this, we detected the corresponding ligands of these proteins and downloaded their 2D structures from Pubchem (https://pubchem.ncbi.nlm.nih.gov/) website. The protein structure was saved in SDF format. Using DrugBank database, find positive drug and download as 2D structures and used to perform molecular docking analysis with Discovery Studio 4.0 software. Firstly, the 3D structure of the protein was imported into the software and water groups were deleted. Following this, conventional procedures were performed to complete the incomplete residues, delete the excess protein conformation, hydrogenate, and distribute the relevant charges. The complete ligand 2D structures were imported into the software. After basic preprocessing, the software was used to identify the protein active centers, select the (Libdock) docking mode, define default docking parameters, and analyze the data [14].

1.9 Allergic Rhinitis animal models in vivo

Sprague Dawley SPF grade male rats (180 ± 20g) were purchased from Chengdu Dashuo Experimental Animal Co., Ltd. (production license certificate number SYXK (Chuan) 2015–030). The study protocol was approved by the animal ethics committee for Shaanxi University of Chinese Medicine. Before the experiment, the rats had free access to food and drink under the circadian rhythm light conditions for 7 days. Thirty rats were randomly divided into 3 groups. All groups, except the blank control group, were injected with ovalbumin OVA (purchased from Sigma) and aluminum–containing adjuvant to initiate allergic rhinitis model according to the previously described method [15,16]. After successful administration, nasal saline was administered to the control group rats every day. The model group rats were administered 100 μl/well of 0.1% C. minima volatile oil. To observe the pathological changes after 15 days treatment, the animals were humanely euthanized, their nasal mucosa tissues were cut out, fixed with 4% paraformaldehyde for 24 h, and processed using conventional dehydration method, paraffin embedding, sectioning, and hematoxylin–eosin (H&E) staining.

Results:

2.1 Volatile oil extraction and GC–MS analysis

Through the experiment, the extraction condition is passing a 10–mesh sieve, 9 times the amount of water is added, and the oil yield of the C. minima is the highest when the heating temperature is 300° C. The C. minima

from seven geographic regions were used to extract volatile oil according to this process, absorb 100 μl of volatile oil obtained from each production area, and constant volume 10 ml with ether, add anhydrous sodium sulfate to remove water and prepare samples for GC–MS detection.

2.2 Fingerprint and cluster analysis

C. minima–extracted volatile oil–related GC–MS data was imported into the similarity evaluation system of chromatographic fingerprints of traditional Chinese medicine. The obtained fingerprints are shown in Figure 1. The similarity analysis data is shown in Table 1. The data shows small differences between C. minima composition samples collected from seven geographic areas. Notably, Shanxi and Hubei, Shanxi and Sichuan, Jiangxi and Guangxi, Shanxi and Guangdong samples were found as similar in composition (similarity from 0.90 to 0.98). Shanxi and Henan, Henan and Guangdong, Hubei and Guangxi were found similar in composition (similarity from 0.82 to 0.90 range). The C. minima component cluster analysis data is shown in Figure 2. The results indicate that the content of plants collected in Jiangxi and Hubei, Shanxi and Sichuan, is relatively similar.

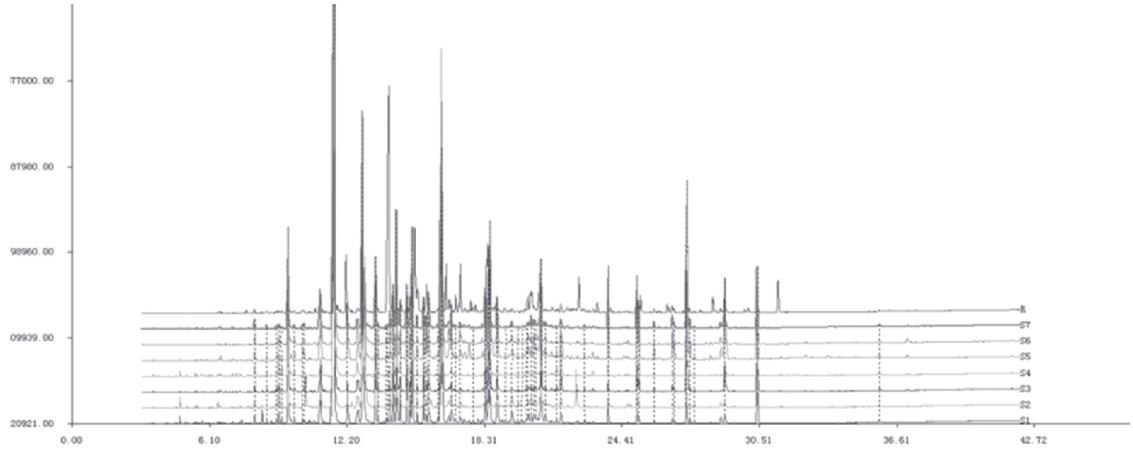

Figure 1. Fingerprints of volatile oil of C. minima from different producing areas
(S1 Shanxi; S2 Hubei; S3 Jiangxi; S4 Guangxi; S5 Henan; S6 Sichuan; S7 Guangdong)

Table 1 Fingerprints of volatile oil of C. minima from different producing areas

	S1	S2	S3	S4	S5	S6	S7	Comparison fingerprint
S1	1.000	0.973	0.926	0.898	0.825	0.981	0.977	0.976
S2	0.973	1.000	0.910	0.888	0.805	0.964	0.958	0.964
S3	0.926	0.910	1.000	0.981	0.927	0.920	0.905	0.980
S4	0.898	0.888	0.981	1.000	0.859	0.898	0.861	0.952
S5	0.825	0.805	0.927	0.859	1.000	0.808	0.852	0.909
S6	0.981	0.964	0.920	0.898	0.808	1.000	0.952	0.969
S7	0.977	0.958	0.905	0.861	0.852	0.952	1.000	0.965
Comparison fingerprint	0.976	0.964	0.980	0.952	0.909	0.969	0.965	1.000

Table note: S1 Shanxi; S2 Hubei; S3 Jiangxi; S4 Guangxi; S5 Henan; S6 Sichuan; S7 Guangdong

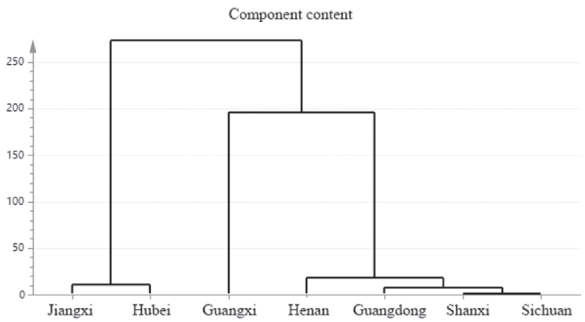

Figure 2. Cluster analysis diagram

2.3 Plants, collected in seven different areas, share the common composition and disease–related Targets

We extracted 15 volatile oil constituents from C. minima specimens collected in seven geographic areas using Venny software tool. The 15 constituents and their total percentages (Pct Total) detected for each geographic region is shown in Table 2. Furthermore, the

components were analyzed using Pubchem and Swiss Target Prediction databases. The obtained targets were integrated in the table. Duplicate values were deleted. A total of 343 targets were identified and component–target map was constructed using Cytoscape software as shown in Figure 3. Using "allergic rhinitis" as a search phrase, we identified the disease–related targets. DisGeNE, OMIM, and TTD were used to collect the data which was integrated in the table. Deleting duplicate values, we determined 323 disease targets.

Table 2 Ingredients and Pct Total in each production area

NO.	compound	RT	Sichuan	Henan	Guangdong	Jiangxi	Hubei	Guangxi	Shanxi
1	cis–Chrysanthenol	1092.16	4.516	0.834	1.538	4.232	3.484	4.141	5.889
2	8,9–Dehydrothymol	1103.209	1.389	1.986	2.185	1.786	1.721	1.017	1.989
3	Bicyclo[3.1.1]hept–2–en–6–ol, 2,7,7–trimethyl–, acetate, [1S–(1.alpha.,5.alpha.,6.beta.)]–	1234.799	34.797	16.547	23.552	31.082	28.231	39.184	27.953
4	Modephene	1393.533	0.937	1.155	1.536	0.881	1.513	0.899	1.343
5	Petasitene	1401.937	0.475	0.719	0.944	0.663	0.653	0.657	0.805
6	.beta.–isocomene	1414.405	1.051	1.235	1.728	0.961	1.083	0.94	1.525
7	Caryophyllene	1417.262	3.31	3.101	3.763	3.482	3.214	3.299	3.28
8	trans–.alpha.–Bergamotene	1438.626	0.328	0.341	0.486	0.266	0.328	0.22	0.403
9	.alpha.–Humulene	1452.529	0.561	0.994	1.889	0.751	0.851	0.669	0.863
10	10s,11s–Himachala–3(12),4–diene	1426.106	2.341	3.723	5.028	4.36	3.707	3.097	3.665
11	Copaene	1574.242	1.191	0.417	0.722	0.457	0.714	0.339	0.732
12	Butanoic acid, 2–methyl–, 3,7–dimethyl–2,6–octadienyl ester, (Z)–	1583.259	0.516	6.33	5.351	1.405	2.647	1.282	3.153
13	Cyclododecane	1678.479	3.096	2.289	3.51	3.043	3.592	3.324	3.388
14	2–Pentadecanone, 6,10,14–trimethyl–	1866.45	2.482	1.208	0.718	0.348	0.141	0.434	0.702
15	Docosane	2494.165	2.627	1.791	2.87	3.048	2.987	2.078	3.323

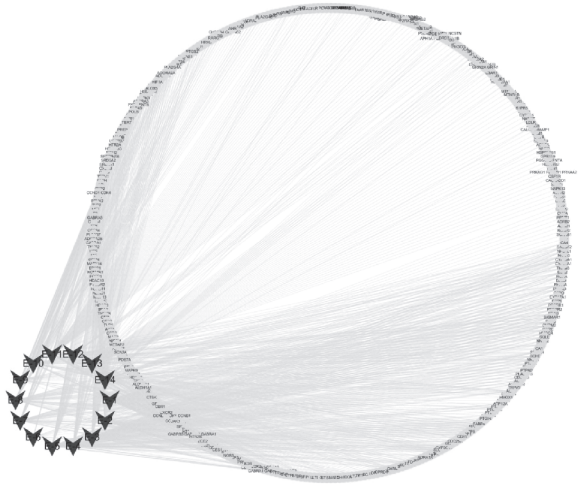

Figure 3. The common components of seven producing areas–target map

2.4 Volatile oil components and disease–related Target mapping

The obtained component targets and disease–related targets were introduced into Veeny software. Consequently, 34 intersecting genes were obtained as shown in Figure 4. The constructed intersection diagram between various components and the target proteins is shown in the Figure 5.

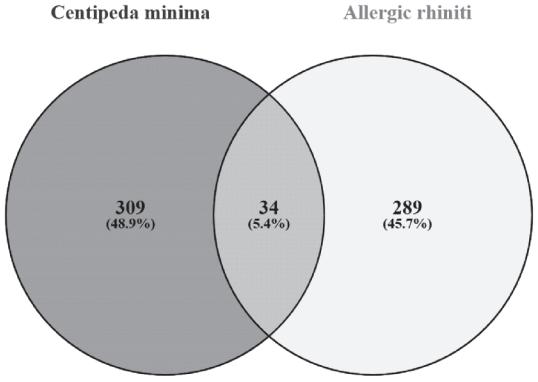

Figure 4. Composition target and disease target Venny diagram

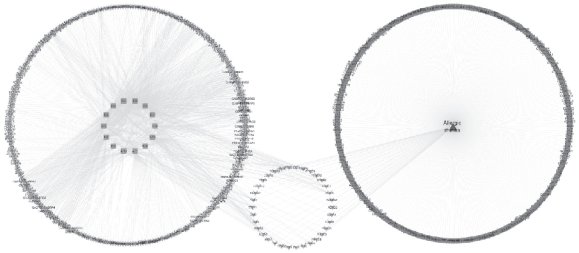

Figure 5. Ingredient–target–disease (The blue on the left represents the component, the green is the target of the component, the red on the right is the disease name, the purple is the disease target, and the orange in the middle represents the component target and the disease common target)

2.5 Protein interaction network

To analyze protein interactions, 34 intersection targets were imported into the STRING platform as shown in Figure 6(a). Red color indicates an evidence of fusion, green – an evidence of proximity, yellow – an evidence collected via text mining, light blue– an evidence collected via database search, blue–an evidence of coexistence, black – an evidence of co–expression, and purple – experimental evidence. The analysis results were imported into STRING and Cytoscape 3.7.1. The resulting protein interaction diagram is shown on Figure 6(b). In this figure, the size of the circle changes according to the degree value of each protein, higher degree value indicates that a protein participates in more pathway interactions. According to the degree values, the three proteins, including tumor necrosis factor (TNF), Prostaglandin–endoperoxide synthase (PTGS) PTGS2, and cannabinoid receptor (CNR) CNR1, were selected.

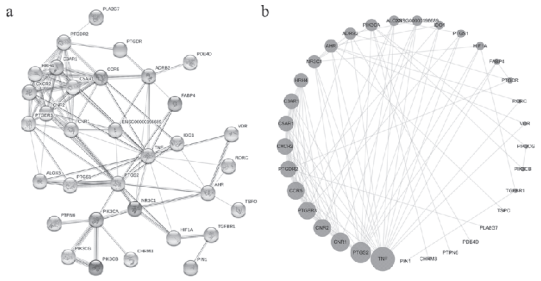

Figure 6. Protein interaction

2.6 GO analysis and KEGG analysis

ClusterProfiler package in R language was used to perform GO and KEGG analysis on the intersection targets. The GO analysis results show that the biological process (BP) was associated with 567 pathways, including cellular calcium homeostasis and acute inflammation. The enrichment analysis of the top 20 pathways and corresponding p–value are shown in Figure 7(a). The horizontal axis indicates the number of genes in the BP term. The vertical axis describes the used terms. The color changes from blue to red according to p values adjusted from smaller to larger. Figure 7(b), each node represents an enriched BP entry and the node size corresponds to the rich number of genes under the entry. Indicating various relationship between entries (core pathway) as shown in Figure 7(c). The gray dots represent genes and the yellow – entry names. The figure demonstrates enriched targets in each pathway and shows that C. minima is involved in multiple biological processes associated with allergic rhinitis.

Our data analysis detected 8 cellular component (CC) pathways liked to phosphatidylinositol 3 kinase complex, mast cell granulation, transferase complex and transport of phosphorus–containing groups, external components of plasma membrane, membrane rafts, and others pathways involved in the pathology of allergic rhinitis. Figure 8 shows the enrichment analysis results of each pathway according to its significance (p value).

Molecular function (MF) analysis defined 51 pathways including 1–phosphatidylinositol–3–kinase, prostate–like receptor, nuclear receptors, and various transcription factors pathways. It has been shown that regulated sequence–specific DNA binding is involved in the occurrence of allergic rhinitis. Figure 9 shows the enrichment analysis results for the top 20 pathways with the significant differences according to their p–values.

KEGG analysis identified 49 related pathways including neuroactive ligand–receptor interaction, regulation of lipolysis in adipocytes, human cytomegalovirus infection, and others. The analysis data shows that C. minima active ingredients are associated with activation of multiple pathways that can be potentially linked to treatment of allergic rhinitis. Figure 10 shows the top 10 pathways according to their p values.

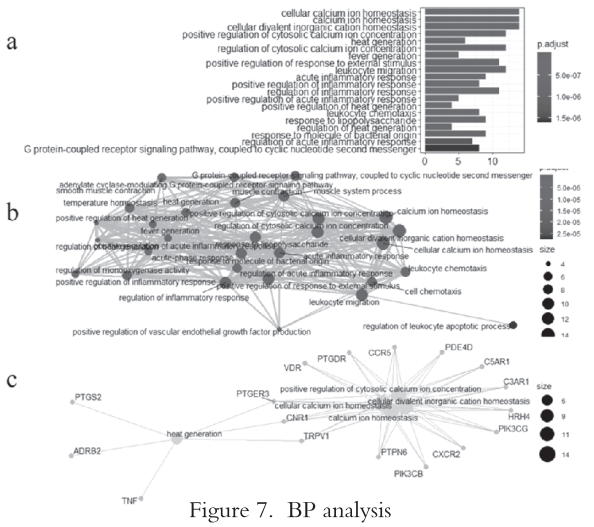

Figure 7. BP analysis

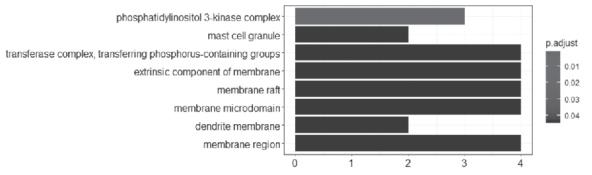

Figure 8. CC analysis

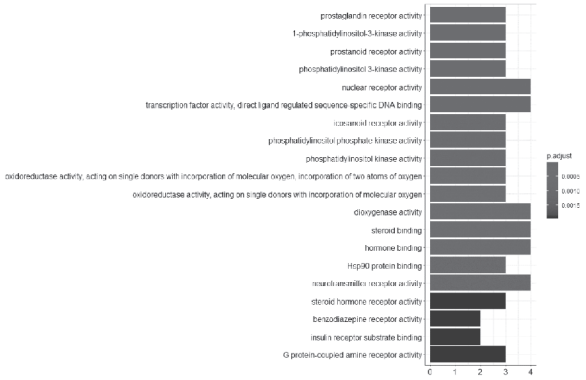

Figure 9. MF analysis

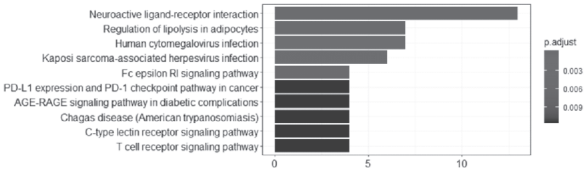

Figure 10. KEGG pathway

2.7 Results of molecular docking analysis

TNF, PTGS2, and CNR1 were identified as top three proteins with the highest median value of protein interaction degree. Molecular docking analysis was conducted with C. minima components. The docking analysis results for each protein were compared with its corresponding positive control drug. The docking analysis showed that these three proteins can be stably docked with the C. minima components. Notably, CNR1 protein docking score was higher than that of the positive control drug. TNF protein docking score was lower than that of the positive control drug. The docking scores are shown in Table 3, and the docking analysis results are shown in Figure 11. The figure shows the relationship between key amino acid residues and molecular functional groups. Amino acid residues are represented by small discs. Amino acid names are abbreviated on the discs. Dark green represents hydrogen bonds; light green – carbon–hydrogen bonds; and purple – alkyl groups. Dark purple indicates π –π stacking; orange – electron–withdrawing; and the dotted line – the interaction between the acceptor residue and the ligand atom.

Table 3 Molecular docking scores

Protein	Ligand	PubChem CID	LibDock Score
TNF	Thalidomide（Positive drug）	5426	86.6862
	Copaene	19725	80.7849
	Petasitene	636697	71.3039
	10s,11s–Himachala–3(12),4–diene	14038471	64.6302
PTGS2	Dihomo–gamma–linolenic acid （Positive drug）	5280581	127.277
	2–Pentadecanone, 6,10,14–trimethyl–	10408	111.073
CNR1	Dronabinol（Positive drug）	16078	96.6223
	Docosane	12405	114.553
	2–Pentadecanone, 6,10,14–trimethyl–	10408	90.2531
	trans–.alpha.–Bergamotene	6429302	72.2785

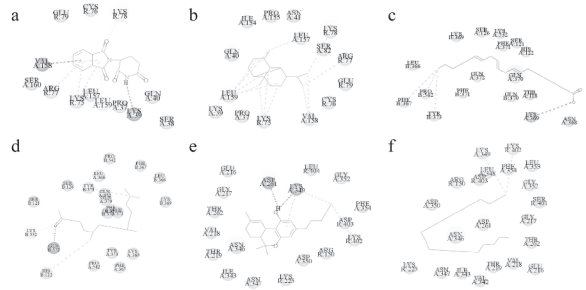

Figure 11. Molecular docking (a).5426(Thalidomide) with TNF 2D diagram (b).19725(Copaene) with TNF 2D diagram. (c). 5280581(Dihomo–gamma–linolenic acid) with PTGS2 2D diagram. (d). 10408(2–Pentadecanone, 6,10,14–trimethyl–) with PTGS2 2D diagram. (e).16078(Dronabinol) with CNR1 2D diagram. (f).12405(Docosane) with CNR1 2D diagram.

2.8 H&E staining results

Histopathological rat tissues analysis demonstrated that nasal mucosa epithelium in the control group was not damaged. No inflammatory cell infiltration was observed in the submucosa of control rats. Alternatively, in the disease model group, a large amount of nasal mucous cilia fell off and nasal epithelium was damaged. Tissues samples indicated gland hyperplasia and swelling, interstitial edema, and interstitial inflammatory cell infiltration in the affected animals. In the C. minima

extract-treated rats, the nasal mucosal damage was significantly lower, with lower glandular hyperplasia, and lower level of inflammatory cells infiltration in the interstitial cell layers. The results are shown in Figure 12.

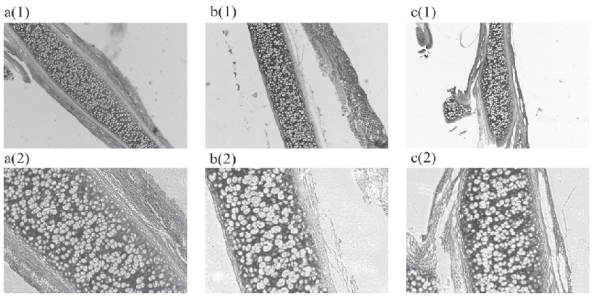

Figure 12. Hematoxylin-eosin stain (a (1)(2) is the blank group 4 × 10 and 10 × 10, b (1)(2) is the model group 4 × 10 and 10 × 10, c (1)(2) is the therapy group 4 × 10 and 10 × 10)

Discussion:

Allergic rhinitis is a common type of allergic inflammatory disease triggered by environmental allergens and mediated by immunoglobulin E (IgE) [17]. Globally, the pathology is marked by an upward trend. Allergic rhinitis affects daily activities and represents a significant health problem [18]. C. minima is a known medicinal herb used to treat allergic rhinitis [19]. However, the mechanisms of C. minima' s effects remain unclear.

In this experimental study, pharmacological network analysis was used to determine the protein interactions and activation of pathways associated with allergic rhinitis and triggered by the volatile components of C. minima from seven different geographic areas. The main pathways associated with allergic rhinitis and C. minima were linked to neuroactive ligand-receptor interaction. Screening for the key target proteins that act on the disease indicated that these proteins are TNF, PTGS2, and CNR1. It is known from the literature that TNF is a multi-effect proinflammatory cytokine, which can participate in the activation of chemotaxis in neutrophils and eosinophils to vascular endothelial cells and induce the production of pro-inflammatory factors in vascular endothelial cells and fibroblasts in allergies. TNF plays an important role in the occurrence and development of disease response and treatment outcome [20,21]. PTGS2 is a prostaglandin, an inflammatory mediator. PTGS2 regulates eosinophil leukocyte migration during inflammatory responses [22]. CNR is a G protein-coupled receptor, of which CNR1 and CNR2 are important subtypes. CNR1 and CNR2 are members of an endogenous cannabinoid system that plays an important role in the normal physiological metabolism in epithelial cells and during inflammatory response in skin diseases. CNRs play an important role in regulating the various physiological and pathological processes involved in the endocannabinoid system. This system plays a role in the regulation of stress, pain, immunity, cognition, oncogenesis, and other physiological processes. It also plays an important role in maintaining skin homeostasis and regulating cell proliferation, differentiation, and apoptosis. This system is involved in regulating the body's inflammation levels [23,24]. Molecular docking analysis was performed on the above key proteins. The docking analysis results show that the target protein can bind the C. minima components, and the docking score is better or slightly lower than that of the positive drug control.

Through animal experiments we also found that C. minima can significantly improve the proliferation of eosinophils and other inflammatory cells, as well as reducing the pathological changes of nasal mucosa. We speculate that the mechanism of C. minima in the treatment of allergic rhinitis is mainly through the neuroactive ligand-receptor interaction involved in the development of the disease, the regulation of lipolysis in adipocytes, and human cytomegalovirus infection pathway. TNF, PTGS2, and CNR1 were identified in this experiment as the main C. minima target proteins that can mediate its therapeutic effects in treating allergic rhinitis. C. minima oils appear to coordinate reduction of rhinitis through multiple targets and multiple pathways, which can provide a basis for the further development and medicinal utilization of these components. However, the continuous improvement of network technology and the real-time update of the database indicate the necessity for further testing. Therefore, the targets of C. minima treatment for allergic rhinitis should be verified

in future research.

Conclusion:

In this study, the optimal conditions for extracting C. minima by steam distillation were obtained. Using network pharmacology analysis combined with molecular docking tools, the target proteins in allergic rhinitis were obtained from the common components of volatile C. minima oil from 7 different geographic areas of China. C. minima mainly regulates the target proteins TNF, PTGS2, and CNR1. Simultaneously, it participates in the activation of biological pathways involved in neuroactive ligand–receptor interaction, regulation of lipolysis in adipocytes, and human cytomegalovirus infection pathway. Animal model experiments further confirmed the remarkable therapeutic effect of C. minima for the treatment of allergic rhinitis.

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References

[1]Jia X, Zhang Y. Research Progress On Essential Oils of Cenpiteda Minima(L.)A.Br.et Aschers. Shandong Chemical Industry 2018;47:66–8.

[2]Cao J, Li G. Chemical constituents of Centipeda minima. China Journal of Chinese Materia Medica 2012;37:2301–3.

[3]Zhang H, Lin Y, Liu X, Huo M, Wu J. The anti–inflammatory and analgesic activities of the essential oil from Centipeda minima. Chinese Journal of Spectroscopy Laboratory 2013;30:1913–21.

[4]Gao Y, Mei Q. Research progress on the pharmacological and clinical study of Centipeda. Global Traditional Chinese Medicine 2010;3:307–9.

[5]Liu Z, Yu H, Wen S, Liu Y. Histopathological study on allergic rhinitis treated with Centipeda minima. China Journal of Chinese Materia Medica 2005:53–5.

[6]Li C, You H, Song X, Zhang Z, Fu Q. Optimization of extraction technology of essential oil in Biyuanling granules by orthogonal experiment. Lishizhen Medicine and Materia Medica Research 2006:1264.

[7]Liu J, Hou H, Tu W. GC–MS analysis of the essential oil components of Centipeda minima. Chinese Traditional and Herbal Drugs 2002:20–1.

[8]Tang X, Mao H, Zou D. GC–MS Analysis of Chloroform Extraction of Centipeda Minima. Guangdong Chemical Industry 2019;46:34–5.

[9]Lin X, Zhang Z, Wang S, Yan M, Chen Y, Zhang J. Establishment of HPLC Fingerprints of Paeonia tactilora Decoction Pieces and Its Cluster Analysis and Principal Component Analysis. China Pharmacy 2019;30:3375–82.

[10]Liu P, Lie S, Tang P, Tian J. Establishment of GC fingerprints of Citrus medica and determination of four constituents. Chinese Traditional Patent Medicine 2018;40:2491–6.

[11]Nong J, Zeng P, Li J, Liu J, Li J. Immunoinflammatory mechanism of Panax notoginseng in the treatment of osteonecrosis of the femoral head based on network pharmacology. Chinese Journal of Tissue Engineering Research 2020;24:4613–9.

[12]Xiaoxiao X, Rong L, Jian C. Prediction of anti–pancreatic cancer targets and molecular mechanisms of resveratrol through the assays of network Pharmacology. Sichuan Journal of Physiological Sciences 2019;41:1–4+17.

[13]YG T, XF H, JY W, MR K, LJ W, SX X. Exploring Molecular Mechanism of Huangqi in Treating Heart Failure Using Network Pharmacology. Evidence–based complementary and alternative medicine :

eCAM 2020;2020:6473745.
[14]Yao X, Xiao X, Huang B, Xu Z. Molecular docking and in vitro screening of active anti-hepatitis B virus components from Abruscantoniensis. The Chinese Journal of Clinical Pharmacology 2019;35:439-41+48.
[15]M S, S G, M Z, et al. Distraction of olfactory bulb-medial prefrontal cortex circuit may induce anxiety-like behavior in allergic rhinitis. PloS one 2019;14:e0221978.
[16]Liu M, Zhang D, Li X, Zhang F, Wang X, Zhang Q. The Effect of Ovalbumin Nasal Strengthening Stimulate for Rat Model of Allergic Rhinitis. Chinese Journal of Otorhinolaryngology in Integrative Medicine 2013;21:325-8.
[17]JJ K, JH L, CH J, et al. Chemokine RANTES promoter polymorphisms in allergic rhinitis. The Laryngoscope 2004;114:666-9.
[18]Huang H, Wan S, Hu J. Research of Allergic Rhinitis Drugs. Pharmaceutical Biotechnology 2019;26:186-8.
[19]Yu H, Wen S, Liu Z, Fang Y, Wang H. An experimental study on the therapeutic effeels of herba centipeda on allergic rhinitis. Chinese Journal of Otorhinolaryngology in Integrative Medicine 2001:220-4.
[20]Zhou Y, Tai H, Zheng H, Huang Y. Effect of acupuncture at Xiaguan point on serum levels of interleukin-6 and tumor necrosis factor-α in rats with allergic rhinitis. Hunan Journal of Traditional Chinese Medicine 2019;35:134-6.
[21]Zhang Z, Zhong L, Ling B, Yuan M. Effect of Yupingfeng Powder on activity of IL-6 and TNF-α in rats with allergic rhinitis. Chinese Traditional Patent Medicine 2014;36:1804-8.
[22]Zhe J, Jiaan R, Shanlun Q. Human bone mesenchymal stem cells-derived exosomes overexpressing microRNA-26a-5p alleviate osteoarthritis via down-regulation of PTGS2. International immunopharmacology 2020;78.
[23]Chen Y, Chen G, Yu H, Wu B, Xu G. Effect of cannabinoid receptor 2 on body weight,blood lipids and inflammatory factor in obese mice. Chinese Journal of Biochemical and Pharmaceuticals 2014;34:96-8.
[24]Wang L, Wan M, An J. Expression of CNR1 and CNR2 in serum and lesions of patients with psoriasis vulgaris. Chinese Journal of Laboratory Diagnosis 2018;22:1250-2.

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探索，取得了令人满意的效果，不仅提高了学生的专业理论知识和实践操作技能，而且实现了培养学生立德树人的根本任务，为学生今后走上工作岗位，走进社会奠定了坚实的基础。

参考文献

[1]潘宏波,黄大志.对高校公共体育课开展课程思政同向育人的探讨[J].当代体育科技,2018(17):71-73.
[2]王海威,王伯承.论高校课程思政的核心要义与实践路径[J].学校党建与思想教育,2018(14):32-34.
[3]陆道坤.课程思政推行中若干核心问题及解决思路—基于专业课程思政的探讨[J].思想理论教育,2018,(03):64-69.
[4]习近平.把思想政治工作贯穿教育教学全过程开创我国高等教育事业发展新局面[N].人民日报,2016-12-09(001).
[5]陈晓华.牛羊生产技术[M].2版.北京：中国农业科学技术出版社,2015年.