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Discussion on the Mechanism of Angelica Sinensis and Atractylodes Macrocephala on the Treatment of Depression Based on Network Pharmacology

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Abstract: To explore the mechanism of Angelica sinensis and Atractylodes macrocephala on the treatment of depression based on network pharmacology. the effective components of Angelica sinensis and Atractylodes macrocephala were obtained through TCMSP combined with literature retrieval; Predict drug component related targets in the database; Using online human Mendelian genetics (OMIM) database, Gene Cards, TTD, GRUGBANK database, and using “expression” as the keyword to obtain relevant disease targets; Draw Wayne diagram to get the potential target of Angelica Atractylodes macrocephala on the treatment of depression; Using String database and Cytoscape3 8.0 software to construct protein-protein interaction network and drug component disease target network of potential target; The biological process analysis and metabolic pathway analysis of Angelica Atractylodes macrocephala on the target of treating depression were carried out on metascape platform.

1. Introduction

Depression syndrome is the most common mental disease in clinic. It is mainly manifested by marked and persistent depression, often accompanied by the decline of thinking, will and cognitive function. According to the global disease survey and research, depression has become the third most common cause of disability in the world, next to back pain and headache. The pathogenesis of depression is complex, so far no clear cause has been found. Specifically, the causes of depression can be summarized as genetic factors, biochemical factors, neuroplasticity hypothesis, immune system activation, social factors, etc. Biochemical factors include abnormal metabolism of monoamine neurotransmitters, neuroendocrine disorders, dysregulation of serum total cholesterol level, increase of sex hormone level, and functional changes of hypothalamus pituitary adrenal axis[1]. Studies have shown that Atractylodes macrocephala polysaccharide can prevent nerve cell damage and repair the state of nerve function defect. Angelica sinensis can promote hippocampal regeneration, regulate neurotransmitters and regulate cytokines. Clinical experiments have also proved that it can inhibit depression and protect nerves[2]. According to the literature review, Atractylodes macrocephala and Angelica sinensis are often used in antidepressant compounds as

official drugs and adjuvants, such as Chaihu Shugan powder, Xiaoyao Powder and Danggui Shaoyao decoction. Therefore, the network pharmacology analysis of the two drugs is conducted here to explore the relationship and mechanism of the two drugs of Atractylodes macrocephala and Angelica sinensis with diseases from the perspective of drug target disease interaction and pathway.

2. Data and Methods

2.1 Collection of Active Ingredients and Targets of Angelica Sinensis and Atractylodes Macrocephala

In Tcmsp[3], “Angelica” and “Atractylodes macrocephala” were used as keywords to search for their chemical components,, Select to meet the bioavailability at the same time(OB) $\geqslant$ 30%, drug like property (DL) $\geqslant$ 0.18 Effective active ingredients of Guihe Atractylodes macrocephala,And then standardize in UniProt protein database.

2.2 Screening of Depression Related Gene Targets

“Depression” was used as the key word, and the databases (OMIM, http://omim.org/), grugbank and TTD were used (http://bidd.nus.edu.sg/group/cjttd) Genecards database(https://www.genecards.org)Taking relevancescore as the reference, the results of the four databases were combined, and the duplicate targets were screened and deleted to obtain the depression related gene targets.

2.3 Construction and Analysis of Compound Target Disease Network

The screened active ingredient target of Angelica Atractylodes and the depression disease target were intersected, and the venny2.1.0 tool was used(https://bioinfogp . CNB. CSIC. ES / tools / Venny /), and 38 drug disease common targets were obtained, as shown in Figure 1; Then the target was submitted to the string11.0 platform to obtain the target PPI network of Angelica Atractylodes, as shown in Figure 2.

2.4 Biological Process and Enrichment Analysis

Import the intersection targets of drugs and diseases into the metascape data platform, the species was defined as “homosapiens”, the p value $\leqslant$ 0.01, the minimum count was 3, and the enrichment factor $\geqslant$ 1.5 were set to obtain the Relevant results, and to study the biological process and key pathway of Atractylodes Angelica on the treatment of depression[4].

3. Results

3.1 Acquisition of Active Ingredient Targets

55 chemical constituents of Atractylodes macrocephala and 125 chemical constituents of Angelica sinensis were preliminarily extracted and 4 Chemical Constituents of Atractylodes macrocephala and 2 Chemical Constituents of Angelica sinensis were obtained after ADME screening, β- Sitosterol, stigmasterol, 3 β- Acetoxyatractylone, etc., see Table 1. 20 action targets of Atractylodes macrocephala and 65 action targets of Angelica sinensis were obtained, and a total of 54 action targets were obtained by deleting duplicate values after combination.

Table 1: Basic Information of Active Ingredients of Atractylodes Macrocephala and Angelica Sinensis

Name	MOLID	Sign	Molecular name	OB	DL
Atractylodes macrocephala	MOL000022	BZ1	14-acetyl-12-senecioyl-2E,8Z,10E-atractylentriol	63.37%	0.30
Atractylodes macrocephala	MOL000033	BZ2	(3S,8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-[(2R,5S)-5-propan-2-yloctan-2-yl]-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol	36.23%	0.78
Atractylodes macrocephala	MOL000049	BZ3	3β-acetoxyatractylone	54.07%	0.21
Atractylodes macrocephala	MOL000072	BZ4	8 β -ethoxyatractylenolideIII	35.95%	0.21
Chinses angelica	MOL000358	DG1	beta-sitosterol	36.91%	0.75
Chinses angelica	MOL000449	DG2	Stigmasterol	43.83%	0.76

3.2 Acquisition of Depression Related Targets

Disease targets were obtained from gene card, OMIM, TTD and drug library database, 12727, 76, 53 disease targets and 131 related targets in drug library were obtained respectively, all targets were merged and duplicate values were deleted, finally 1252 depression related targets were obtained.

3.3 Construction of PPI Network

Through venny2.1.0, the component targets and disease targets are intersected, and 38 common targets are obtained. These 38 common targets are considered as potential targets for Angelica sinensis and Atractylodes macrocephala in the auxiliary treatment of depression, as shown in Figure 1. Then submit the target to the string11.0 platform to obtain the PPI network as shown in Figure 2.

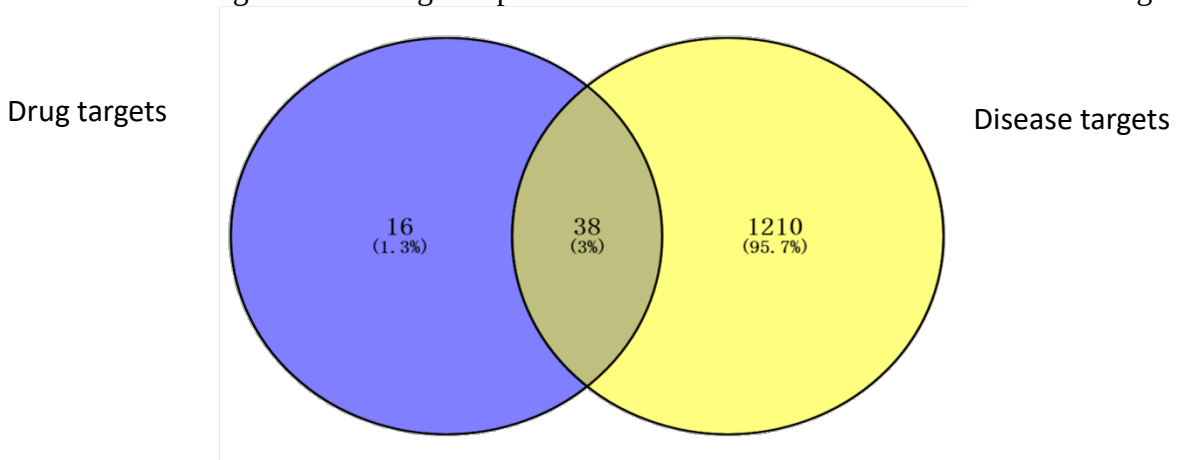

Figure 1: Wayne Diagram of the Components of Atractylodes Macrocephala Angelica Medicine Pair and the Target of Depression

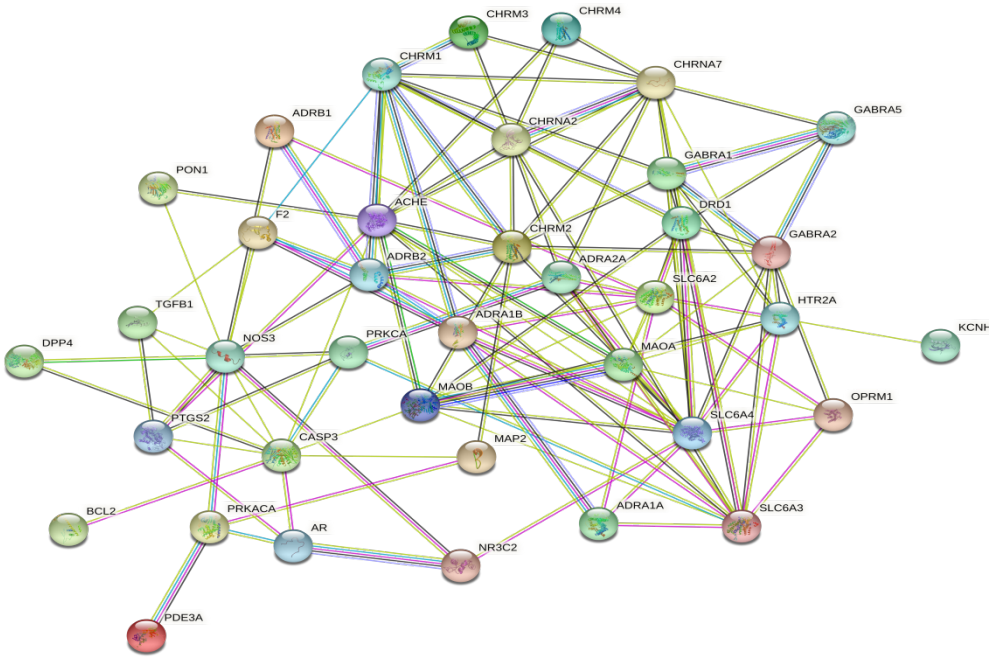

Figure 2: PPI Network Diagram of Abnormal Target

3.4 Angelica Sinensis and Atractylodes Macrocephala Target Disease Network

See Figure 3 for the compound targeted disease network of atractylodes macrocephala and angelica sinensis for intervention in depression. The network has 62 nodes and 91 edges. The blue prism represents the target, the yellow regular hexagon and the red regular hexagon represent the active components of Angelica sinensis and Atractylodes macrocephala, respectively, while the green circle and purple source represent Angelica sinensis and Atractylodes macrocephala. After topology analysis of the network, the highest content of active ingredients is β- Sitosterol, stigmasterol, 3 β- Atractylodes macrocephala acetyl.

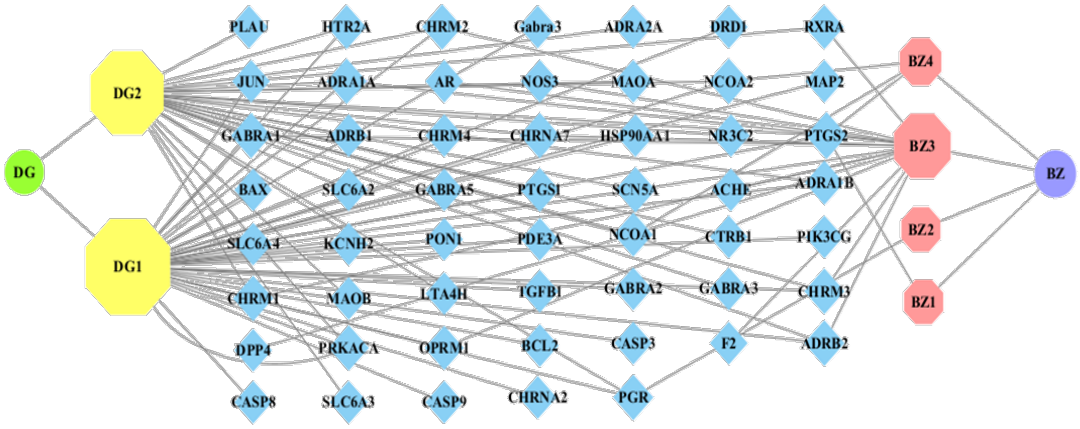

Figure 3: Danggui Baizhu Drug Pair Target Disease Network Diagram

3.5 PPI Network and Core Targets

See Figure 4 for the PPI network of Atractylodes macrocephala Angelica intervention in depression. The network includes 38 nodes and 126 edges. The node size and color are sorted

according to the degree value, and the sorting rule is proportional. According to the degree, the highest degree is 15, and the lowest degree is 1. The target proteins with degree ⩾ 10 are SLC6A4, SLC6A3, CHRNA7, ache, DRD1, NOS3, SLC6A2, MAOA, chrm1, chrm3 and CHRM2, which indicate that these core genes are the key targets of Angelica sinensis and Atractylodes macrocephala for the treatment of depression.

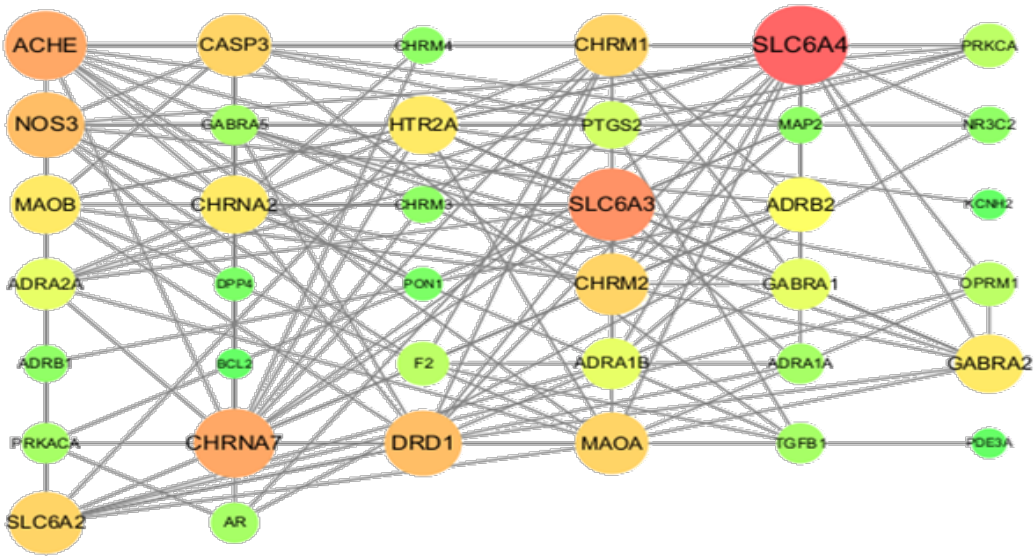

Figure 4: Core Target Map of PPI Network

3.6 Enrichment Analysis and Application of Target Function and Pathway

The obtained core genes of Angelica Atractylodes intersection were enriched and analyzed, and the genes were annotated and classified from biological pathway (BP), cellular component (CC) and molecular function (MF) to obtain a histogram of gene enrichment (see Fig. 5). Through the metascape data platform, gene function annotation and pathway enrichment analysis were performed on 38 targets, and 3053 go biological function entries were obtained, including 2428 BP related entries, 358 MF related entries, 267 CC related entries, and 183 signal pathways. With the help of originlab2018, the results were visualized and go biological function analysis and KEGG pathway enrichment analysis were carried out. With $P < 0.01$ as the main screening standard, BP screened 20 pathways, mainly involving chemical synaptic transmission, blood circulation, cell response to organic ring compounds, regulation of neurotransmitter level and regulation of ion transport; CC screened 10 related pathways, mainly involving postsynaptic membrane, membrane raft, dendrite, GABAergic synapse and dopaminergic synapse; MF screened 11 pathways, mainly related to the activity of postsynaptic neurotransmitter receptors, the activity of neurotransmitter receptors involved in postsynaptic membrane potential regulation, the activity of adrenergic receptors and catecholamine nodes. In addition, the first 10 paths of the visual path enrichment analysis results (see Figure 6 for the results) are highly related to the regulation of cerebral nerves and depression, mainly involving the interaction of nerve active ligand receptors, calcium signal pathways, cholinergic synapses, morphine addiction and 5-hydroxytryptamine synapses.

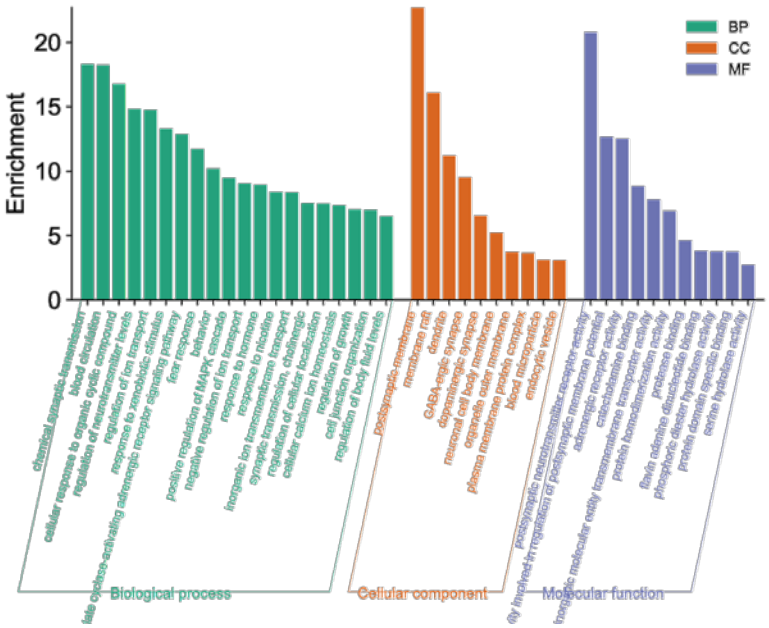

Figure 5: Histogram of Bp, Cc and Mf Gene Enrichment

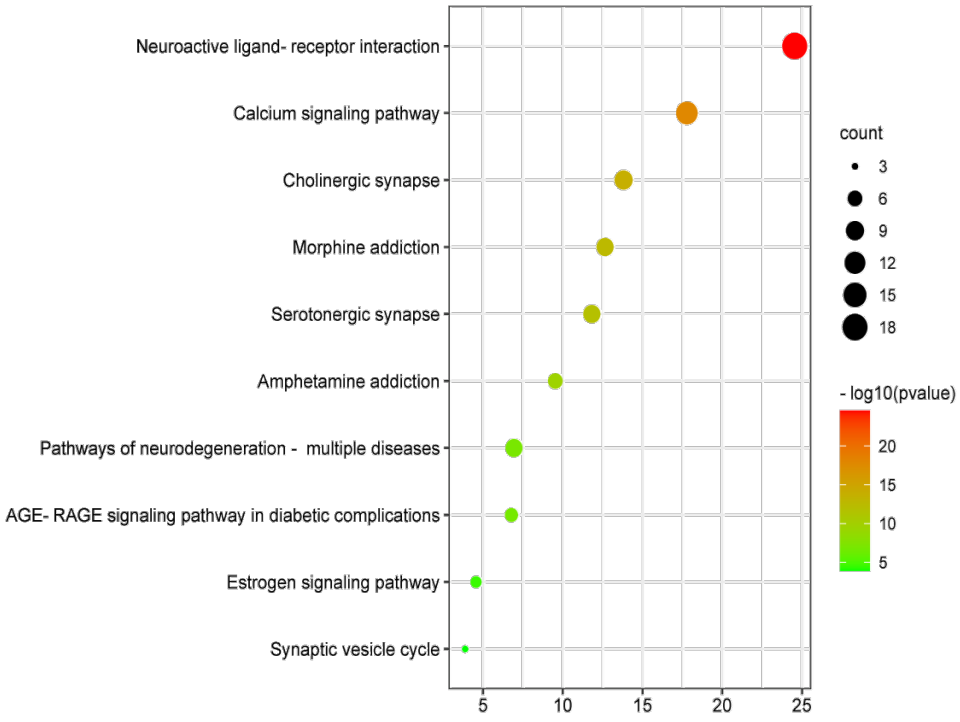

Figure 6: Bubble Diagram of KEGG pathway enrichment analysis

4. Discussion

In this study, 6 active ingredients, 54 potential drug targets, 1252 depression related targets and 38 common targets of “drug diseases” of Atractylodes macrocephala and Angelica sinensis were found. Among the active ingredients of Atractylodes macrocephala and Angelica sinensis, β-

Sitosterol, stigmasterol, 3 β- Acetoxy atractylone has many targets and plays a key role in PPI network, among which β- It has been found that sitosterol and stigmasterol can improve the activity of hippocampal neurons, reduce the impact of depression on hippocampal neurons, and thus fight against depression. Therefore, β- Sitosterol and its derivatives are often used in antidepressant research[5]. Other studies have shown that β- The expression of Notch1, hes - 1, Ki - 67 and NiCd proteins were significantly upregulated after treatment of embryonic neural stem cells with the seed oil of sitosterol (Alyssum homocarpum), indicating that it can promote the proliferation and differentiation of embryonic neural cells[6]. Stigmasterol has estrogen effect, which can effectively regulate GABAergic, dopaminergic, acetylcholine and other neurotransmitters, and can effectively improve memory and mental disorders. At present, the research on the active ingredients of Angelica sinensis antidepressant pharmacological action is limited, and there are still some antidepressant products to be developed.

According to the PPI network analysis, SLC6A4, SLC6A3, CHRNA7, ache, SLC6A2, MAOA, and other target proteins are the core targets of the PPI network of potential target proteins of Angelica Atractylodes on depression intervention, and also the connecting link between other nodes. SLC6A2 norepinephrine transporter, a gene that regulates norepinephrine homeostasis and norepinephrine reuptake to presynaptic nerve endings; SLC6A3, an important transporter in dopamine transmission, is highly expressed in presynaptic midbrain dopaminergic neurons and responsible for re uptake of dopamine from the synaptic space. This gene is considered to be related to the susceptibility to mood disorders; The low expression of SLC6A4 serotonin transporter, 5-HTT, is associated with an increased risk of depression and is considered to be a vulnerability marker of depression. This gene mediates depressive behavior and is associated with a variety of mental disorders[7].

KEGG analysis results show that the potential targets of Angelica sinensis and Atractylodes macrocephala are mainly concentrated in the signal pathways such as the calcium signal pathway, cholinergic synapse, morphine addiction, serotonergic synapse, amphetamine addiction, neurodegeneration, estrogen signal pathway, synaptic vesicle cycle and so on. It is suggested that the effective components of Angelica sinensis and Atractylodes macrocephala may act on these signal pathways to achieve the purpose of treating diseases. The neuroactive involved in promoting the development, differentiation and regeneration of neuronal cells, and is most closely related to neural function in physiology[8]; Experimental studies have shown that calcium ion signaling pathway is involved in regulating the activities of various enzymes, nervous system functions, glucose metabolism, etc. the dysregulation of calcium ion homeostasis directly leads to the disorder of neuronal structure and function and cell necrosis[9]. It can be seen that the angelica Atractylodes drug pair achieves the goal of multi-component, multi-target and multi-channel regulation of the disease network of depression by regulating the proteins in multiple signal pathways. Enrichment analysis showed that in the mechanism related to the treatment of depression, it reflected the characteristics of multi-target and multi-channel treatment of Atractylodes macrocephala and Angelica sinensis, and also reflected the synergistic effect of Angelica macrocephala on treatment.

To sum up, This paper studies the complex network relationship between Angelica and Atractylodes macrocephala,and found that Angelica Atractylodes and Atractylodes Atractylodes Atractylodes can effectively treat the depression of low mood and slow depression, reflecting the characteristics of the combined action of Angelica and Atractylodes Atractylodes on multiple channels and multiple targets. The research results preliminarily verified the basic pharmacological effects and related mechanisms of Angelica Atractylodes and Atractylodes Atractylodes Atractylodes Atractylodes, It also provides a new idea to explore the effect of atractylodes macrocephala angelica on the treatment of Mental illness.

5. Conclusion

Based on network pharmacology, this paper explains the mechanism of Angelica Atractylodes macrocephala on the treatment of depression from the molecular level, which may provide clues and basis for promoting neuronal development, regulating nervous system function, anti-inflammatory, anti-oxidation, participating in regulating blood circulation, etc.

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