ISSN 2706-6819 Vol.5, Issue 9: 64-72, DOI: 10.25236/IJFM.2023.050911

Bioinformatics study of active substances and disease targets of atractylodes macrocephala based on network pharmacology

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Abstract: *Atractylodes macrocephala, as a common Chinese traditional medicine, plays an important role in the treatment of digestive tract diseases and many kinds of tumors, showing great medicinal value. However, due to the complexity of Chinese traditional medicine of compounding, information on the main active ingredients of Atractylodes macrocephala are not clear. In this study, the main active ingredients, drug targets and the relationship with diseases of Atractylodes macrocephala were investigated by using Chinese traditional medicine network pharmacology and bioinformatics, with a view to providing theoretical basis for clinical experiments. The results showed that seven active substances were retrieved from TCMSP (https://old.tcmsp-e.com/tcmsp.php) database, and 44 target genes were predicted by Pharmmaper. Eight core proteins, including ALB, EGFR, MAPK1, AR, MAPK14, PGR, MAPK8, and ANXA5, were obtained from String Protein Interaction Database. Further analysis by KEGG and GO pathway enrichment indicated that the above proteins were involved in metabolic pathways such as inflammatory response and cancer. Meanwhile, disease association analysis showed that Atractylodes macrocephala could treat inflammation, Alzheimer's disease and various tumors. The present study demonstrated the efficacy of Atractylodes macrocephala in treating different diseases from its active ingredients, drug targets and pathways, which suggests that Atractylodes macrocephala has potential multiple medicinal values in the future.*

Keywords: *Atractylodes macrocephala, active compounds, target genes, network pharmacology*

1. Introduction

Atractylodes macrocephala has rich medicinal and economic value as an ancient Chinese herb. It has been recorded in ancient Chinese medical texts that *Atractylodes macrocephala* has the effects of tonifying qi and strengthening the spleen, drying dampness and inducing diuresis, stopping sweating, and settling the foetus, and can treat foetal restlessness, oedema, abdominal distension and diarrhoea [1]. *Atractylodes macrocephala* is often used in Chinese traditional medicine as a gastrointestinal regulator, laxative, spleen tonic and qi enhancer, which is closely related to intestinal regulation [1].

Modern clinical studies have shown that *Atractylodes macrocephala* can effectively enhance immunity, resist inflammation as well as reduce the risk of tumour development [2]. Studies have shown that atractylenolide components (atractylenolide I, atractylenolide III) are the effective components of *Atractylodes macrocephala* for anti-inflammation and anti-cancer [3]. Atractylenolide I can promote gastrointestinal digestion and absorption in spleen-deficient rats, and can significantly improve appetite, upper arm muscle circumference, wasting and physical strength in patients with cachexia, and can significantly reduce the levels of cytokines IL-1, TNF-α, and urinary protein hydrolysis-inducing factor PIF [4]. For example, clinical use of larger doses of *Atractylodes macrocephala* can enhance ileal contraction, promote gastrointestinal peristalsis and gastric emptying, and significantly improve patients' digestive system function [1]. In addition, atractylenolide substances can also inhibit the reproduction of tumour cells and induce apoptosis of tumour cells [5]. For example, when human cancer cell lines (Du145, HepG2 and HL-60) were acted on with atractylenolide substances, all cell lines were inhibited and showed good anticancer activity [4]. Meanwhile, atractylenolide also has a role in the treatment of Alzheimer's disease. For example, bis-atractylenolide can effectively improve the learning and memory ability of demented rats, suggesting that bis-atractylenolide can alleviate the intellectual impairment of dementia model rats to a certain extent. Although *Atractylodes macrocephala* has applications in the treatment of many diseases, there are few chemical drugs based on *Atractylodes macrocephala*'s active

ISSN 2706-6819 Vol.5, Issue 9: 64-72, DOI: 10.25236/IJFM.2023.050911

substances. Because the active substances of *Atractylodes macrocephala* are diverse, while acting on a wide variety of potential target genes, which leads to the mechanism of *Atractylodes macrocephala* with the treatment of various diseases is not clear. The design of multi-target drug molecules for the purpose of comprehensive analysis of biological networks, which is consistent with the multi-molecule, multi-target and multi-target modulation of Chinese traditional medicine, and has been applied more in the study of single-flavour Chinese traditional medicine and compounding, which has provided a new paradigm for the development of new Chinese traditional medicine.

In this study, we investigated the relationship among the active ingredients, targets and metabolic pathways of *Atractylodes macrocephala*, and made extensive predictions on the possible efficacy of *Atractylodes macrocephala* as well as the mechanism to provide reference for the subsequent experiments.

2. Methods

2.1. Screening of active compounds

By searching the the Chinese traditional medicine Systems Pharmacology Database and Analysis Platform (TCMSP) [10] for the keyword "*Atractylodes macrocephala*", 55 active substances were obtained. The oral bioavailability (OB) > 30% and drug-likeness (DL) > 0.18 were used as the screening criteria, and 7 active substances that met the criteria were obtained, along with their structural, pharmacological and molecular properties data.

2.2. Target prediction of active comprounds

Seven relevant active substance files were downloaded from TCMSP and uploaded one by one into Pharmapper (http://www.lilab-ecust.cn/pharmmapper/submitfile.html) database, initially 1757 pairs of active substance-target gene pairs were obtained, and then the data were screened with the threshold value of Norm Fit > 0.8 & zscore > 0.5. Further, the target gene names were converted to official gene symbol via the Universal Protein Resource (Uniprot, https://www.uniprot.org/).

2.3. Protein-Protein Interaction (PPI) network map of target genes with screening of key genes

The screened potential target genes of active compounds in *Atractylodes macrocephala* were imported into the String database (https://cn.string-db.org/) and restricted to "*homo sapiens*" to exclude non-human corresponding genes. After research, the PPI network graph and the degree of each node were obtained. The genes were ranked according to the degree, and retained genes with the highest degree as the hub genes. Further, the nodes were divided into three clusters by kmeans method and the network graph was organized by placing the hub genes in the central position.

2.4. Enrichment analysis of Gene Ontology (GO) and KEGG pathway

The WebGestalt Gene functional enrichment platform (https://www.webgestalt.org/) was used for the GO (Biological Process, Cellular Component, and Molecular Function) and the KEGG pathway enrichment analysis. *Homo sapiens* was chosen in the organism of interest option, and genome was selected in the reference set. The FDR less than 0.05 was used as the selection criterion of both GO and KEGG.

2.5. Protein-disease relationships

The GeneCards data base was used to query the relationship between the above core proteins and diseases. The target genes were import GeneCards database with default parameters. Finally, the GeneCards results of the interactions between chemicals, genes, functional phenotypes, and diseases, and provides information about the disease-associated environment, exposure factors, and potential mechanisms of drug action were downloaded for further analysis and visualization.

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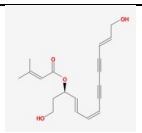
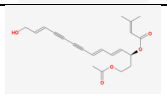
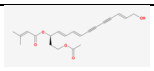
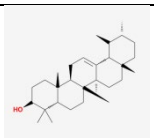
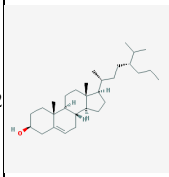
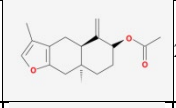
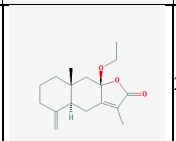
3. Results

3.1. Screening of active compounds of Atractylodes macrocephala

A total of 55 active substances of *Atractylodes macrocephala* were obtained by TCMSP query, and 7 active substances were obtained by threshold screening, which were MOL000020, MOL000021, MOL000022, MOL000033, MOL000049, and MOL000072, respectively.The oral bioavailability (OB) values of these 7 active substances ranged from 35.95%-62.40% and the drug likeness (DL) values ranged from 0.21-0.78 (Table 1).

Table 1: Pharmacologic information of seven active ingredients in Atractylodes macrocephala by using the CTMSP database.

Active ingredients of *Atractylodes macrocephala*														
Molecule ID	Molecule name	Download structure	Pharmacological and molecular properties data											
			MW	AlogP	Hdon	Hacc	OB (%)	Caco-2	BBB	DL	FASA-	TPSA	RBN	HL
MOL000020	12-senecioyl-2E,8E,10E-atractylentriol		312.39	2.50	0	4	62.40	0.01	-1.37	0.22	0.12	72.42	8	6.07
MOL000021	14-acetyl-12-senecioyl-2E,8E,10E-atractylentriol		355.44	3.21	0	5	60.31	0.33	-1.09	0.31	0.05	75.66	10	5.32
MOL000022	14-acetyl-12-senecioyl-2E,8Z,10E-atractylentriol		356.45	3.54	1	5	63.37	0.42	-1.14	0.30	0.00	72.83	10	6.43
MOL000028	α-Amyrin		426.80	7.35	1	1	39.51	1.42	1.28	0.76	0.00	20.23	0	3.83
MOL000033	(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		428.82	8.54	1	1	36.23	1.45	1.09	0.78	0	20.23	7	5.22
MOL000049	3β-acetoxyatractylone		274.39	3.39	0	3	54.07	1.13	1.08	0.22	0	39.44	2	-1.31
MOL000072	8β-ethoxy atractylenolide III		276.41	3.68	0	3	35.95	1.08	1.12	0.21	0	35.53	2	8.34

MOL000033 has a megawatt value (MW) of 428.82, which is 72.37-154.43 higher than the remaining six actives.Its AlogP value of 8.54, as the highest of the above seven actives, is more than three times as high as the AlogP value of MOL000020.MOL000020's FASA value of 0.12 is the highest of these highest value among the seven actives. In addition, the FASA of MOL000021 was 0.05, while the values of MOL000033, MOL000049, MOL000028, MOL000072, and MOL000022 were 0. Meanwhile, the Caco-2 value of MOL000020 was 0.01 and the BBB value was -1.37, which were the smallest values under all data. Similar to MOL000020, the BBB values were negative for MOL000021 and MOL000022, which were -1.09 and -1.14, respectively, while the Hdon values of the five actives, MOL000020, MOL000021, MOL000028, MOL000049, and MOL000072, were all 0, and the values of MOL000022, MOL000033 have Hdon value of 1. Meanwhile, the OB value of MOL000022 is the maximum value of these seven actives, and the RBN values of MOL000022 and MOL000021 are 10, which is the highest value of these

ISSN 2706-6819 Vol.5, Issue 9: 64-72, DOI: 10.25236/IJFM.2023.050911

seven actives, while the RBN value of MOL000021 is the minimum value of 0.

3.2. Identification of potential drug target

Table 2: Seven active substances were extracted from Pharmmaper database, and the corresponding target genes and target gene functions were obtained by eliminating redundancy.

Target Genes	*Amino Acid*	*Function*
PTPN1	435	
CA2	1150	It is essential for bone resorption and osteoclast differentiation. Reversible hydration of carbon dioxide.
PPIA	165	
TTR	147	
TREM1	234	
AKR1C3	323	
GSTP1	210	
AR	920	
MMP13	471	
KIF11	1056	
MAPK14	360	
ANXA5	320	
MCR	359	
Alb	609	Serum albumin is the main protein of plasma, which has good binding ability to water, Ca(2+), Na(+), K(+), fatty acids, hormones, bilirubin, drugs and so on. Its main function is to regulate the colloid osmotic pressure of blood.
ADAM17	824	
TGFBR1	567	
GC	474	An adaptable protein is present in various bodily fluids such as plasma, ascitic fluid, cerebrospinal fluid, and urine. It can also be found on the surface of numerous cell types. Within plasma, this protein acts as a carrier for vitamin D sterols and plays a role in preventing actin polymerization by binding to its individual units.
CFD	253	
EGFR	1210	
Braf	751	
RORA	523	
ESRRG	458	
MIF	115	Pro-inflammatory cytokines play a role in the innate immune response to bacterial pathogens. The expression of MIF in inflamed regions indicates its participation as a mediator in regulating macrophage function in the host's defense mechanism.
DHODH	395	
SHBG	402	By controlling the concentration of steroid hormones in the blood, it manages their plasma metabolic clearance rate.
ITGAL	1170	
AKR1C2	323	
STS	583	
BMP2	396	
CASP7	303	
APOA2	100	
MAPKAPK2	400	
PIM1	313	
PGR	933	The regulation of gene expression in eukaryotes and the modulation of cellular proliferation and differentiation in target tissues are influenced by the presence of steroid hormones and their corresponding receptors.
MAOB	520	
NR1H4	486	
HSD17B1	328	
EPHB4	987	
MAPK10	464	
MAPK1	360	
PIK3CG	1102	
MAPK8	427	
PDE4D	809	
PDE4B	736	
median	456.5	
average	533.4318182	
minimum	100	
maximum	1210	

We utilized the PharmMapper database to convert the 7 active substances of Atractylodes macrocephala, with the aim of achieving a preliminary prediction of the target genes of the active substances. A total of 1757 pairs of target genes and active substances were obtained after conversion. After screening the 7 different active substances under certain conditions, we obtained 76 pairs of target proteins and active ingredients. To summarize, the 7 active ingredients finally corresponded to 44

ISSN 2706-6819 Vol.5, Issue 9: 64-72, DOI: 10.25236/IJFM.2023.050911

different target genes, and the average length of amino acids of all target genes was 533, with a minimum value of 100 and a maximum value of 1,210 (Table 2).

3.3. Protein-Protein Interaction (PPI) network construction and hub gene screening

In order to identify the hub genes among the 44 target genes corresponding to *Atractylodes macrocephala*, these 44 target genes were import to the String database and constructed a PPI network graph (Figure 1). The results revealed the presence of 119 links among the 44 nodes, with an average node degree of 5.41 and an average local clustering coefficient of 0.62. Furthermore, the three most central genes were ALB, EGFR, and MAPK1, exhibiting linkage degrees of 26, 19, and 15, respectively. ALB encodes one of the pivotal proteins in plasma, known as serum albumin, which is highly abundant in blood and participates in numerous blood-related functions, and pertaines to blood regulation. On the other hand, MAPK1 encodes the mitogen-activated protein kinase, which orchestrates a range of biological processes including cell growth, adhesion, survival, and differentiation. Moreover, it exerts influence over the initiation and regulation of mitosis and postmitotic functions. All three genes are closely intertwined with cellular physiological processes, frequently associating them with cancer and somatic mutation events. In addition, the 44 nodes were clustered into three different groups by the k-means algorithm. The first cluster (red) encompassed 21 nodes, including ALB, ANXA5, APOA2, and others; the second cluster (green) comprised 16 nodes, featuring ADAM17, BRAF, CASP7, and others; and the third cluster (blue) encompassed 7 nodes, containing AKR1C2, AKR1C3, DHODH, and others.

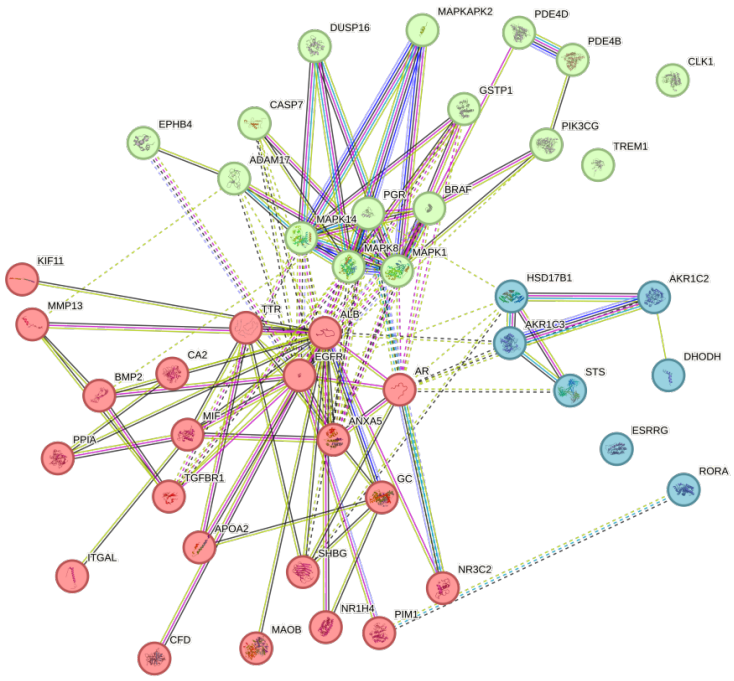


Figure 1: PPI internet diagram of forty-four target genes corresponding to Atractylodis Macrocephalae.

3.4. Gene Ontology (GO) analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment

In the GO enrichment analysis of potential targets of *Atractylodes macrocephala*, 19 GO terms were obtained from WebGestalt by thresholding FDR<0.05, of which 9 were molecular functions, 8 were biological functions, and 2 were cellular components (Figure 2). The molecular function was primarily included the cellular response to biotic stimulus, response to molecule of bacterial origin, stress-activated protein kinase signaling cascade. The biology function was mainly involved with direct ligand regulated sequence-specific DNA binding, transcription factor activity, steroid binding and steroid hormone receptor activity. Addationally, the cellular components was contained ficolin-1-rich granule and vesicle lumen.

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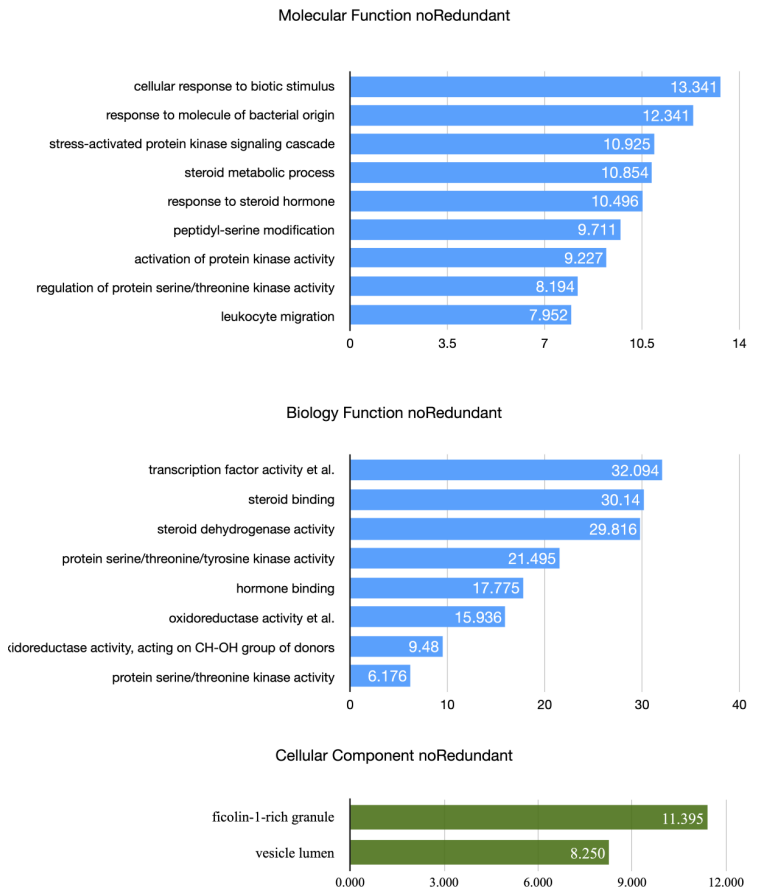

(A) Molecular Function noRedundant. (B) Biology Function noRedundent. (C) Cellular Component noRedundent.

Figure 2: GO enrichment diagram of target genes corresponding to Atractylodis Macrocephalae.

For the KEGG enrichment analysis of the *Atractylodes macrocephala*'s potential targets, 10 KEGG bio-entries with threshold FDR<0.05 were obtained from WebGestalt (Figure 3).The target genes were mainly enriched in the epithelial cell signaling in helicobacter pylori infection,pancreatic cancer, pertussis, AGE-RAGE signaling pathway in diabetic complications, colorectal cancer and Th17 cell differentiatio.

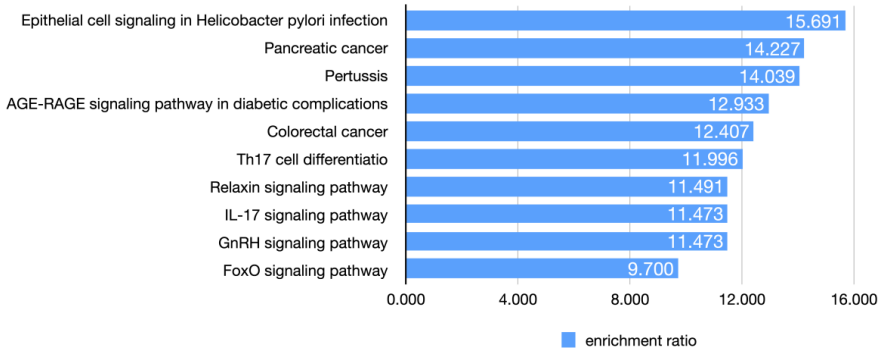

Figure 3: KEGG enrichment result diagram of target genes corresponding to Atractylosid Macrocephalae.

3.5. Enrichment of disease and drugs

GeneCards were used to screen 13 cancers with matching genes in the components of *Atractylodes macrocephala*. The graphical tool was used to explore the association of genes with diseases and to rank the number of associated genes, which included 30 matches for breast cancer, 25 matches for prostate

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cancer, 20 matches for lung cancer, 13 matches for digestive system cancers, 14 matches for ovarian cancer, and 13 matches for liver cancer. Among the above diseases, breast cancer, lung cancer and digestive system cancer had the highest number of matching genes with *Atractylodes macrocephala*, which indicated that *Atractylodes macrocephala* had a certain degree of efficacy against prostate cancer, breast cancer, and digestive system cancers such as lung cancer, pancreatic cancer, and colon cancer.

By using WebGestalt website, 6 drugs related to the target genes of Atractylodes macrocephala were found, they are Gestrinone, Levonorgestrel, Mitotane, Danazol, Stanolone and Stanolone acetate (Figure 4). The Gestrinone exhibited the highest enrichment ratio, while Mitotane, Danazol, and Stanolone shared the same enrichment ratio, thereby ranking equally. Notably, both Stanolone and Stanolone acetate held the third position, with an equivalent enrichment ratio.

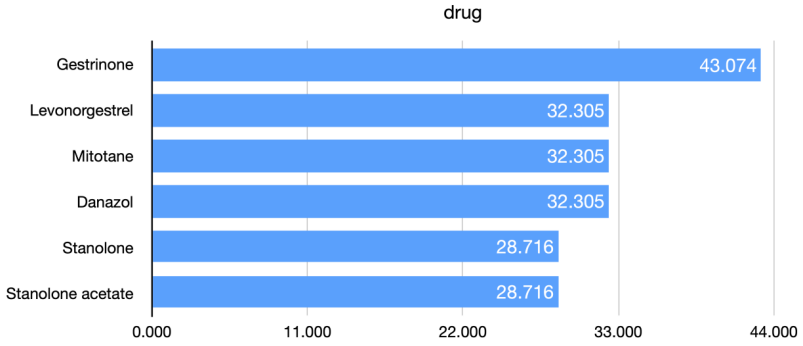

Figure 4: Drug enrichment distribution of target genes by using Webgestalt database.

4. Discussion

Atractylodes macrocephala, as an ancient Chinese herb with rich medicinal value, has the efficacy of tonifying qi and inducing diuresis, stopping sweating, and tranquilizing the fetus, which can treat fetal restlessness, edema, abdominal distension and diarrhea. In addition, studies have shown that *Atractylodes macrocephala* also has the efficacy of regulating the gastrointestinal tract, anti-tumor, anti-inflammatory, and immune-enhancing, which demonstrates the great value of *Atractylodes macrocephala*'s application in medicine [1]. However, since Chinese traditional medicine compounding is characterized by multi-components and multi-targets, and the mechanism of action is more complex, therefore, this paper uses Chinese traditional medicine network pharmacology and bioinformatics to explore the main active ingredients, drug action targets, and the relationship with diseases of *Atractylodes macrocephala*, with a view to providing theoretical basis for experimental validation.

In this paper, a total of 55 active components of *Atractylodes macrocephala* were obtained by searching TCMSP, and seven standardized active substances, such as *Atractylodes macrocephala* lactone I, Acetylammonia caryophyllanthus ketone, and 8β-ethoxy *Atractylodes macrocephala* lactone III, were obtained by screening. Previously, Yang et al selected 77 candidate active substances of *Atractylodes macrocephala* from TCMSP and TCM database, and 27 active substances were obtained through screening [6]. In comparison, the seven active substances identified in this study were included. Studies have shown that atractylenolide is the main component of *Atractylodes macrocephala* that exerts medicinal effects, and has anti-inflammatory and anti-tumor effects both in vivo and in vitro [1]. For example, five different sesquiterpenoids in *Atractylodes macrocephala* were found to inhibit acute inflammation in mice induced by xylene and acetic acid, which are foreign irritants [7]. In addition, the volatile oil in *Atractylodes macrocephala* have the function of regulating gastrointestinal metabolism and promoting nutrient absorption. The above suggests that multiple active components in *Atractylodes macrocephala* can be synergistically involved in the treatment of digestive disorders as well as other cancers, showing multiple medicinal values.

Target gene analysis revealed that the active ingredients of *Atractylodes macrocephala* exert functional efficacy mainly through the core targets of ALB, EGFR, MAPK1 and AR. Among them, the close association of EGFR with malignant tumours has been reported in several papers, especially with non-small cell lung cancer [8]. Genetic testing based on patients with non-small cell lung cancers worldwide has shown that approximately 10-15% of patients have concomitant EGFR driver mutations,

ISSN 2706-6819 Vol.5, Issue 9: 64-72, DOI: 10.25236/IJFM.2023.050911

which have been identified as the most common driver of non-small cell lung cancer [8]. In addition, whole exome sequencing, transcriptome sequencing, and whole genome sequencing of 115 paired cervical cancer-normal samples by Mexican and Norwegian researchers showed that somatic mutations in %8 of primary squamous cell carcinomas included recurrent substitutions of E322K in the MAPK1 gene [9]. Another study of AR mutations in prostate cancer showed that AR gene mutations may increase with tumour progression. The above studies suggest that C. alba actives can correspond to multiple targets. Further, KEGG enrichment analysis was performed to obtain metabolic pathways including diabetic complications, Helicobacter pylori infection, hepatocyte signalling pathway, pancreatic cancer, and AGE-RAGE in colorectal cancer. The production of advanced glycation end products (AGEs) associated with hyperglycaemia was found to play a central role in the pathophysiology of the disease, which may be a central drug target for the action of the active substances of *Atractylodes macrocephala* [10]. In addition, the FoxO protein can contribute to the development of breast cancer, the second most common cancer in women, suggesting that the active ingredient in *Atractylodes macrocephala* may be beneficial in inhibiting the effects of this protein. Overall, the active constituents of *Atractylodes macrocephala* have a positive effect on the resistance to inflammatory responses as well as inhibiting the development of a wide range of tumours.

By analyzing the association between drug targets and diseases, the present study demonstrated that the active substances in *Atractylodes macrocephala* have therapeutic effects in the treatment of gastric cancer, Alzheimer's disease, lung cancer and cervical tumor. Previously, it was shown that *Atractylodis Macrocephalae* Lactones could improve the memory and learning ability of demented rats, and to a certain extent, could alleviate the mental retardation of dementia model rats [11]. Thus, we expect that *Atractylodes macrocephala* will be put into dementia drugs in the future and play a positive therapeutic role in the treatment and alleviation of dementia. In addition, polysaccharide components in *Atractylodes macrocephala* were found to stimulate macrophage proliferation and significantly inhibit the activity of hepatocellular carcinoma cell lines and cervical cancer cell lines in an experiment by Qin et al [12]. Another study showed that a 4-course treatment of *Atractylodes macrocephala* with Radix et Rhizoma Polygoni Multiflori Soup was given to patients with breast cancer bone metastases, and the results showed that there was no significant difference in the efficacy group of *Atractylodes macrocephala* as compared to that of the control group [13]. Therefore, the treatment of breast cancer bone metastatic disease with *Atractylodes macrocephala* remains controversial [13]. The above results suggest that *Atractylodes macrocephala* plays an important role in human inflammation, intestinal diseases, and tumor treatment, but due to the complexity of its active ingredients and the variety of drug targets, the mechanism of interaction with diseases remains to be further investigated in the future.

5. Conclusion

In summary, we explore the active substances and target genes of *Atractylodes macrocephala* by the network pharmacology and bioinformatics. Our results imply that the target genes' pathways of *Atractylodes macrocephala*, and they were associated with cancer and other diseases. In additional, we found hub genes ALB, EDFR, MAPK1 and AR of the PPI network. I hope that our findings will provide a theoretical basis for the use of *Atractylodes ma*crocephala in the treatment of cancer and other diseases.

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