Uncovering the intension of *Alisma orientale* decoction for treating vertigo: a perspective from network analysis

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Abstract: *Alisma orientale decoction* (AOD), a traditional Chinese medicine composed of AO and AM, has a significant effect on the treatment of vertigo, improving the curative effect and reducing the likelihood of side effects with long-term stable medication. This manuscript established an interaction network between AOD and vertigo to explain, using network pharmacology, how AOD works to treat vertigo. Data mining of several databases yielded 12 candidate compounds, including eight components of AO and four components of AM, along with 331 potential targets. PPI analysis showed that the compounds acted mainly on key targets of MAPK1, EGFR, MAPK14, ERBB2, PIK3CA, MAPK8 and MTOR. In addition, GO and KEGG studies indicated that proteoglycans, ErbB signalling, HIF-1 signalling, chord metabolism, estrogen signalling, prolactin signalling and osteogenic class differentiation pathways were strongly involved in the signalling pathways of vertigo therapy. Data mining of the therapeutic targets and pathways provided new insights and considerations for drug development and clinical therapy of vertigo.

Keywords: network pharmacology; *Alisma orientale* decoction; AOD; vertigo; *Atractylodes macrocephala*.

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1 Introduction

Vertigo is a motor hallucination caused by lesions or excessive stimulation of the labyrinth semicircular canal ampullary crest nerve endings of the inner ear, its neuro-afferent pathway or cerebral cortex projection area (Johkura, 2021), which exceeds the body's ability to compensate, resulting in the body's own spatial orientation and balance dysfunction (Lamb and Davies, 2020; Chen et al., 2021; Cai et al., 2019; Byun et al., 2019). Currently, the incidence of vestibular disease is also increasing annually, with comorbidities in a variety of diseases in modern medicine, such as peripheral vertigo, hypertension, and cerebral atherosclerosis (Chen et al., 2021; Cai et al., 2019; Byun et al., 2019). The disease involves multisystem lesions with a complex pathophysiological mechanism that remains unclear.

Western medicine has always considered the cessation of vertigo episodes as the priority of treatment, and antihistamines are preferred to relieve symptoms (Sert et al., 2021; Deng et al., 2020; Ohle et al., 2020; Ercin et al., 2021; Dyhrfjeld-Johnsen and Attali, 2019; Hain and Uddin, 2003). There are also a variety of medications available for the clinical treatment of this condition, the effects of which vary depending on the cause or improve microcirculation (Ardouin, 1971), dilate blood vessels, antiplatelet aggregation (Noriko, 1997), improve brain metabolism, etc. (Becker-Bense et al., 2014), but they are only used to control vertigo symptoms as the primary goal. In addition to drug treatment, physiotherapy is also an important part of the treatment of vertigo (Brandt and Daroff, 1980; Nomura and Kobayashi, 2012; Svensson et al., 2020; Takeda, 2009). Their efficacy is remarkable, but their high cost and other problems limit their clinical application. Western medicine currently has limited treatment methods for residual symptoms and recurrence of some dizziness after manual reduction, while traditional Chinese medicine has certain advantages in this regard (Tsai et al., 2016; Jiang et al., 2012; Liu et al., 2014). Research survey data show that the treatment efficacy and vertigo recurrence rate of the study group using traditional Chinese medicine treatment are more ideal than those of Western medicine, and the data difference is significant ($P < 0.05$) (Nguyen-Huynh, 2012).

Compared with Western medicine for the treatment of related diseases, AOD not only improves efficacy, but also reduces the occurrence of side effects and achieves long-term stable administration (Lin et al., 2022). Network pharmacology is a disease-gene-target drug discovery model that addresses drug interventions and effects on disease pathways from a holistic and systematic perspective to unravel the complicated mechanistic

pathways of drugs in humans (Hopkins, 2007, 2008; Li and Zhang, 2013; Jafari et al., 2022; Hsieh et al., 2021; Wang et al., 2021). This study established an AOD-vertigo-target interaction network to elucidate the putative pathway of AOD action in the symptomatic treatment of vertigo.

2 Data mining methods

2.1 Rresearch process

The databases used in this study are listed in Table 1. The study flow chart is shown in Figure 1.

Figure 1 Flowchart of the main pathways of AOD in vertigo therapy

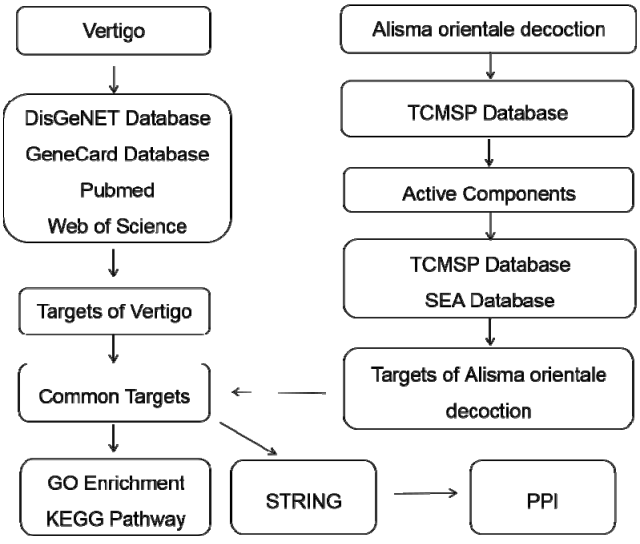


Table 1 Basic database information used to screen the effective targets of AOD for the treatment of vertigo

Categories	*The name of database*	*Reference or website*
Traditional Chinese medicine database	TCMSP Database	Ru et al. (2014)
	SEA Database	Keiser et al. (2007)
Genetic database	GeneCard Database	Safran et al. (2010)
	DisGeNET database	Piñero et al. (2021)
	OMIN database	Szklarczyk et al. (2019)
Bioinformatics database	STRING Database	Huang et al. (2009)
	DAVID 6.8 Database	Ashburner et al. (2000)
Literature database	Web of Science	www.webofscience.com
	PUBMED	www.PUBMED.ncbi.nlm.nih.gov

2.2 Data collection

To collect the active compounds of AOD, *Alisma orientale* and *Atractylodes macrocephala* were first used as keywords to search the TCMSP database. The OB parameter was set to be greater than 30% and 0.18 in the determination of the active compounds of AOD. Then, to obtain the compounds of AOD more comprehensively, the Web of Science and PUBMED databases were searched using the keywords *Alisma orientale* decoction (AOD), *Alisma orientale*, *Atractylodes macrocephala*, Compounds, Ingredients and Pharmacology, and the effective compounds of AO and AM were obtained.

The target protein information and target gene names were obtained from TCMSP (Ru et al., 2014) and SEA (Keiser et al., 2007). To collect disease targets for vertigo, vertigo keywords were selected from the MeSH term field of PUBMED and WOS. The GeneCards database (Safran et al., 2010) was used to identify vertigo-related target genes with correlation scores greater than 20. Similarly, the OMIN and DisGeNET databases (Piñero et al., 2021) were used to remove target genes with low weights. A Venn diagram of the targets of vertigo and AOD was then constructed, and the potential targets of AOD in the treatment of vertigo were obtained and imported into the STRING database (Huang et al., 2009). The species setting in the STRING database (Huang et al., 2009) was restricted to Homo sapiens with an interaction score greater than 0.9.

2.3 GO/KEGG analysis

The key target genes were introduced into the DAVID 6.8 database (Ashburner et al., 2020), the species was selected as Homo sapiens, and GO (Ashburner et al., 2020; Mi et al., 2019) and KEGG (Kanehisa et al., 2021) analyses were performed on the key target genes. The genes in the first 15 KEGG pathways were defined as therapeutic target genes. $P<0.01$ was used as the threshold in the KEGG pathway. Cytoscape 3. 7.2 (Shannon et al., 2003) and network analyser tools were considered to map the protein interaction network.

3 Result

3.1 Effective components and target genes of AOD

We screened eight active components from AO and four from AM on the TCMSP website. The molecular structures of the active compounds are shown in Figure 2. A total of 331 target gene names were associated with these 12 active components. In addition, we selected 2,480 vertigo-related genes from the literature database, GeneCard database and DisGeNET database by taking the first median of the relevance score, while 328 target genes of the 12 selected effective components were obtained after deduplication from the TCMSP and SEA databases. There were 139 overlapping target genes associated with AOD and vertigo. The overlap between disease targets and component targets is shown in a Venn diagram (Figure 3).

Figure 2 (a) The potential active compounds of AM (b) AO for the treatment of vertigo

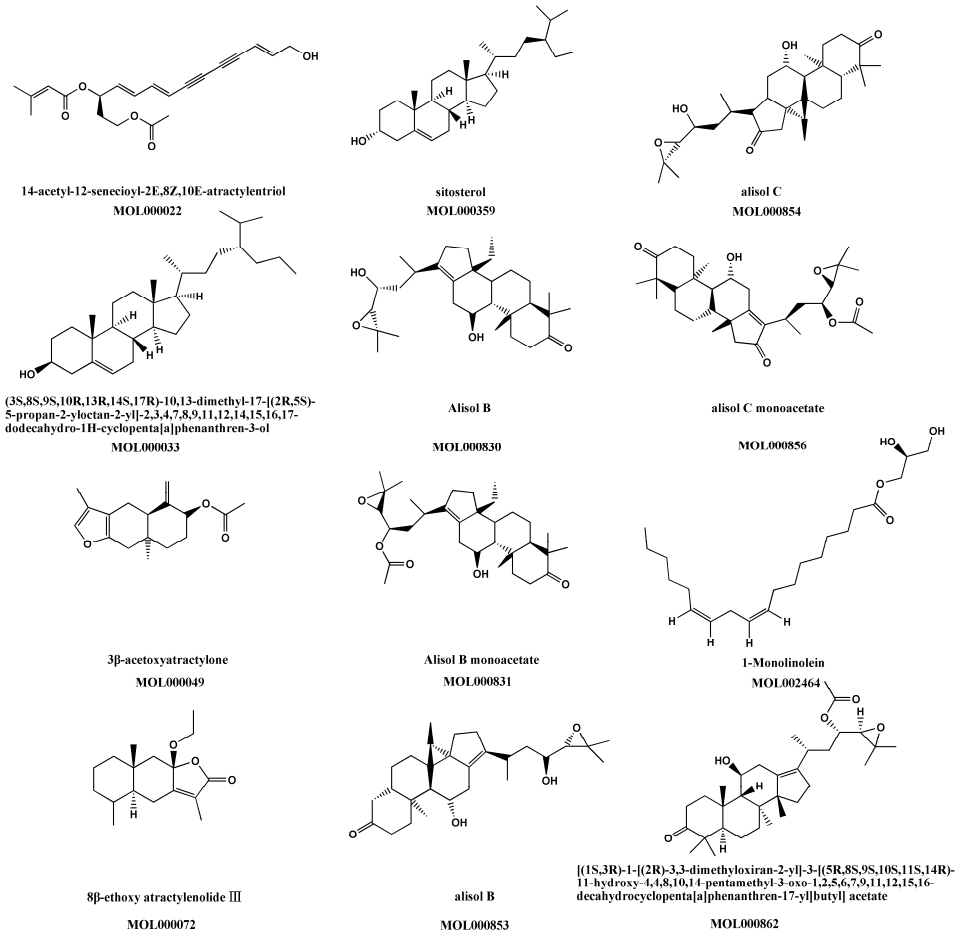
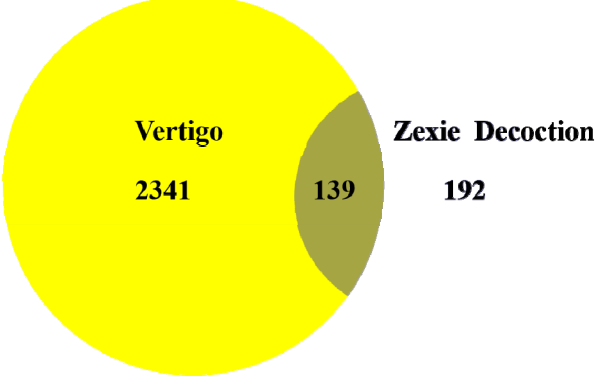


Figure 3 The number of target genes for vertigo and AOD are shown in the Venn diagram (see online version for colours)



3.2 PPI network analysis

The AOD-vertigo PPI interaction network is shown in Figure 4. There were 120 nodes and 1,196 edges in the graph, and the average degree of the target was 17.6. There were 49 targets with above average degree values. Table 2 shows the top 20 targets sorted by degree values from largest to smallest. The top targets sorted by degree values with a degree value two times higher than the average were SRC, FOS, JUN, MTOR, PIK3CA, MAPK14, MAPK1, ESR1, EGFR, MAPK3, NOS3, RPS6KB1, ERBB2, PPARG and PPARA. In addition, a high betweenness centrality value indicated that the target was critical to the drug's mechanism of action. The top ten targets sorted by betweenness centrality values were SRC, FOS, JUN, PIK3CA, PTGS2, PPARG, TRPV1, MAPK14, ESR1 and PPARA. Therefore, it can be concluded that SRC, FOS, JUN, MTOR, PIK3CA, MAPK14, MAPK1, ESR1, EGFR, MAPK3, NOS3, RPS6KB1, ERBB2, PPARG, PPARA, PIK3CA, PTGS2 and TRPV1 were the most important targets.

Figure 4 PPI network diagram of vertigo therapy by AOD (see online version for colours)

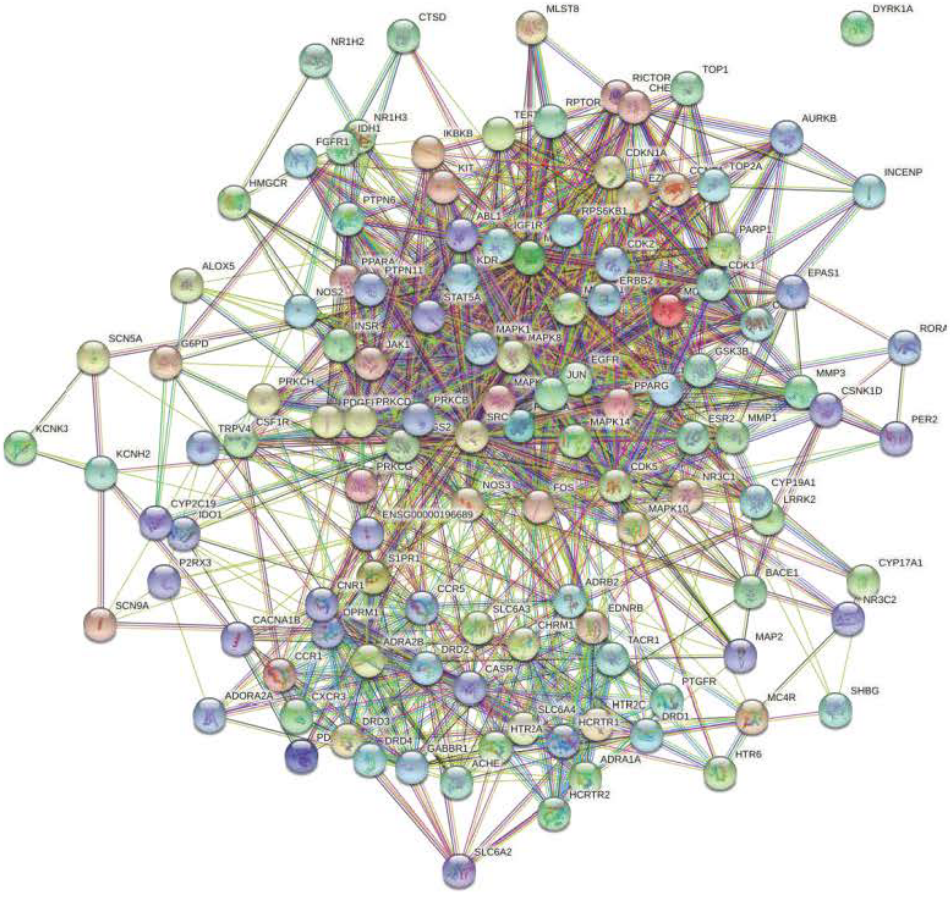


Table 2 The degree and betweenness centrality values of the top 20 targets, sorted by the degree of vertigo

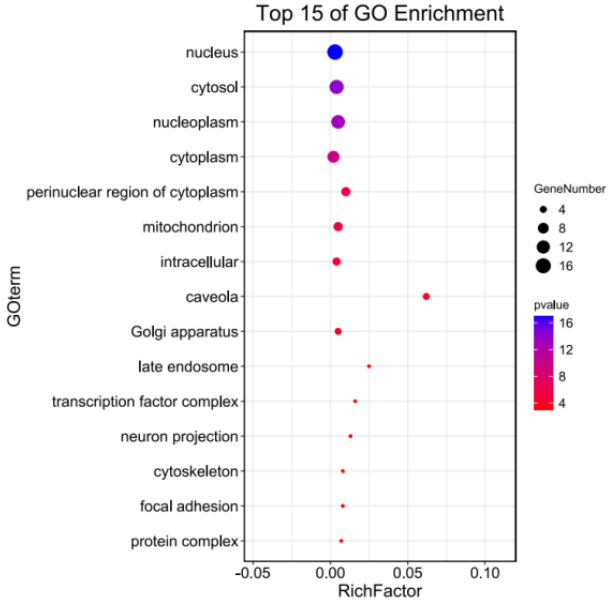
Targets	*Degree*	*Betweenness centrality*	*Targets*	*Degree*	*Betweenness centrality*
SRC	66	0.14384991	NOS3	38	0.56034483
FOS	63	0.11382402	RPS6KB1	37	0.54621849
JUN	60	0.06475833	ERBB2	37	0.55084746
MTOR	54	0.02667353	PPARG	37	0.55555556
PIK3CA	53	0.05756192	PPARA	36	0.55084746
MAPK14	50	0.03202276	HIF1A	35	0.54393305
MAPK1	50	0.01899392	STAT5A	34	0.54166667
ESR1	48	0.03134025	PTGS2	33	0.54621849
EGFR	46	0.02249606	PTPN11	32	0.53278689
MAPK3	44	0.01254261	GSK3B	32	0.53278689

3.3 GO biological process and KEGG pathway

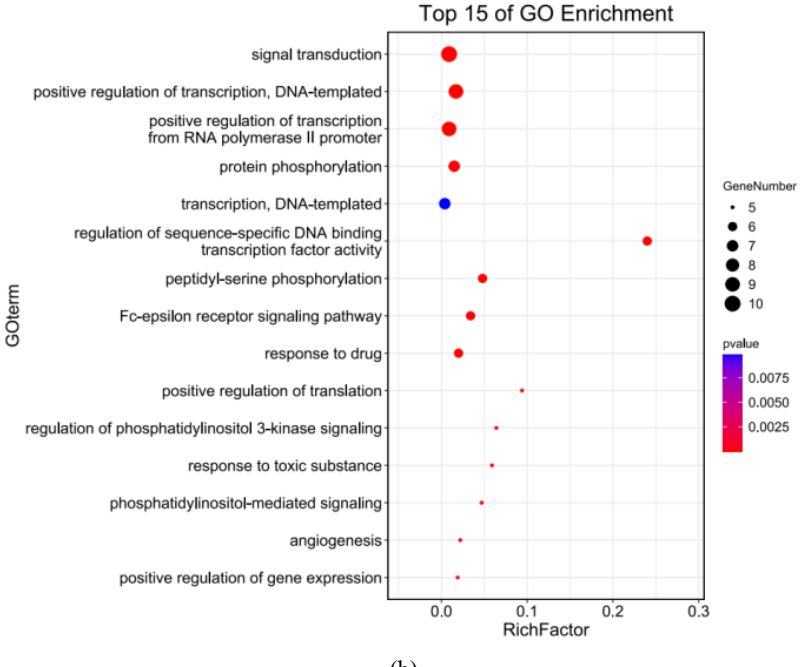
In the GO analysis, only the key targets with more than two times the average degree value (17.6) were selected. The first 15 terms in the biological process GO analysis are shown in Figure 5, containing 166 BP, 40 MF and 18 CC. As shown in Figure 5, nucleus, cytosol, nucleoplasm, cytoplasm, cytosol, perinuclear region of cytoplasm and mitochondria were enriched in CC. The MF enrichment mainly contained protein binding, adenosine triphosphate binding, kinase activity, enzyme binding, transcription factor binding and the same protein binding. BP had the most abundant enrichment area, including signal transduction, positive regulation of transcription, positive regulation of transcription by RNA polymerase II promoter, phosphorylation of peptidyl serine, Fc-epsilon receptor signalling pathway, response to drugs, positive regulation of translation, etc.

The genes in the first 15 KEGG pathways and 91 therapeutic target genes were selected as therapeutic target genes, active ingredients and Chinese medicines to construct the Chinese medicine-drug-target network diagram, as shown in Figure 6. The node values in the drug-target network diagram represented the correlation between the active components and the target genes. The compounds mainly targeted the genes MAPK1, EGFR, MAPK14, ERBB2, PIK3CA, MAPK8 and MTOR, and these genes had a large but not the largest degree and betweenness centrality. The active constituents 1-monolinolein (MOL002464), alisol B (MOL000853), sitosterol (MOL000359) and alisol C (MOL000854) were the key medical compounds with large node values with the target genes and were predicted to be potential drug precursors for the treatment of vertigo.

Figure 5 GO biological process enrichment analysis with (a) CC, (b) MF, and (c) BP enrichment (see online version for colours)



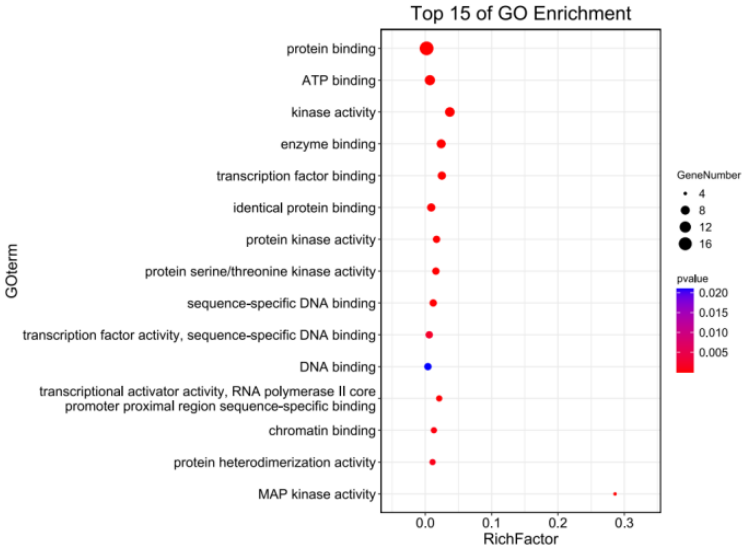
(a)



(b)

Notes: The red to blue colours in the cycles indicate the number of target genes. A more blue colour meant a higher level of importance.

Figure 5 GO biological process enrichment analysis with (a) CC, (b) MF, and (c) BP enrichment (continued) (see online version for colours)



(c)

Notes: The red to blue colours in the cycles indicate the number of target genes. A more blue colour meant a higher level of importance.

Figure 6 The network diagram among AO/AM, key effective components and target genes (see online version for colours)

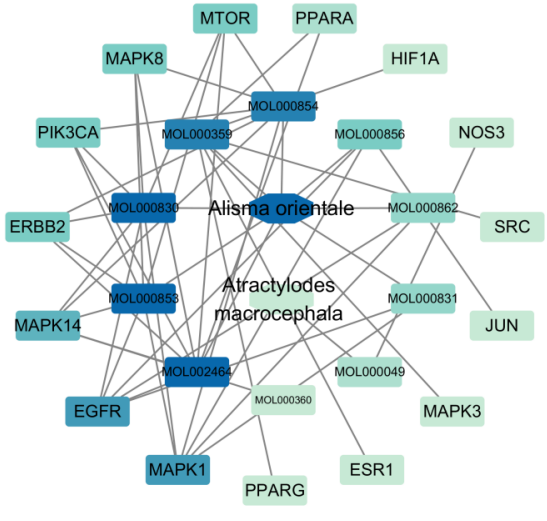
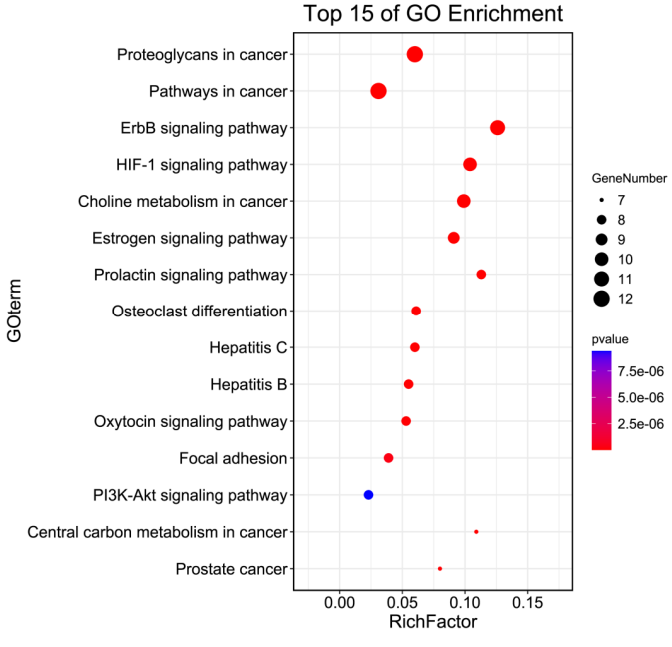


Table 3 The node values of the selected targets and active compounds

Targets	*Node values*	*Molecule*	*Node values(a)*
MAPK1	6	MOL002464	7
EGFR	6	MOL000853	6
MAPK14	5	MOL000830	6
ERBB2	4	MOL000359	6
PIK3CA	4	MOL000854	6
MAPK8	4	MOL000856	3
MTOR	4	MOL000862	2
PPARA	2	MOL000831	2
HIF1A	1	MOL000049	1
NOS3	1	MOL000360	1
SRC	1		
JUN	1		
MAPK3	1	(a)The node values from the compounds to target genes.	
ESR1	1		
MAPK1	1		

The corresponding KEGG pathways bubble diagram is shown in Figure 7. The pathways related to inflammation included proteoglycans in cancer, chondrocyte metabolism in cancer, osteoporosis class differentiation, estrogen, prolactin, ErbB and HIF-1 pathways, etc.

Figure 7 The main KEGG pathway of the active ingredient pointed to potential target genes (see online version for colours)



4 Discussion

In clinical practice, peripheral vertigo is treated with vestibular inhibitors, antihistamines, minimally invasive procedures, semicircular canal blocks, labyrinthine resections and neurotomies (Byun et al., 2019; Sert et al., 2021). A significant number of clinical trials have demonstrated that AOD has unique benefits in alleviating symptoms and improving prognosis in patients with vertigo (Deng et al., 2014; Tsai et al., 2016; Guo et al., 2017).

Proteoglycans (protein polysaccharides), including heparan sulphate and chondroitin sulphate proteoglycans, regulate many signalling pathways and cell-cell interactions. Protein glycans are abundant in the brain and play an important role in protecting against nervous system injury and disease. The alteration of protein glycans is also a normal response to central nervous system injury. Regulation of this response greatly promotes the improvement of disease. Protein polysaccharides are the main components of the external environment of brain cells and regulate cell signalling and cell migration. Some studies have summarised the support for linking specific proteoglycan changes to changes in the EGFR signalling pathway (Wade et al., 2013). The development of the nervous system and the ERBB pathway played a good role. Recent evidence has shown that the ErbB receptor is essential for nerve development and that the ERBB3 receptor in the brainstem is involved in motor function (Wang et al., 2020). Dizziness is a common disease of the nervous system, and research has shown that 10% of 600 patients in the neurology department suffered from dizziness with mid-vestibular peripheral vertigo, followed by central vestibular vertigo. Dizziness is an important accompanying symptom in neurology patients and has a major impact on patients (Lamb and Davies, 2020). ERBB signalling may be involved in radial glial specification and radial movement of neurons in the cortex (Patten et al., 2003). HIF-1α, a subunit of HIF-1, enters the nucleus and binds with HIF-1β to generate the potent translational factor HIF-1, which then binds to the hypoxia response element of the target gene, inducing the cell to modulate the expression of various target genes (Yan et al., 2012; Fillies et al., 2005). Recent studies have identified HIF-1α as one of the key regulatory targets of the ERK/MAPK pathway (Su et al., 2021), and the molecular biological mechanism has been little studied. Epidermal growth factor receptor (ErbB) signalling is critical in the nervous system, as activation of the ErbB signalling pathway has been found to reduce neuronal inflammation in brain tissue, reduce neuronal damage and then play a neuroprotective role (Weller and Reifenberger, 2020). As an important signalling molecule in the nervous system, oestrogen not only influences structural and functional changes in the nervous system, but also promotes neuronal survival, growth, repair, regeneration and synaptic plasticity. Cholinergic damage is an important basis for neuronal apoptosis. Recent studies have confirmed that cholinergic and estrogen form a network in the brain and interact through their respective signalling pathways (Janicki and Schupf, 2010). Oestrogen transported energy substances such as glucose by increasing blood supply to the brain, regulated apolipoprotein expression, protected brain-derived NT, promoted growth, development and differentiation of brain neurons, protected neurons and promoted repair of their injuries. MAPK is a type of signalling protease that can convert various extracellular stimuli into specific cellular responses in eukaryotic cells, acting as a signalling hub to regulate cell proliferation, differentiation, stress response, autophagy and apoptosis (Flores et al., 2019). Many organs are involved in the development of vertigo, but it is most commonly associated with the liver. The diagnosis and treatment of vertigo is a process of continuous recognition, understanding, development and

improvement. In many modern theories, the therapy of vertigo from the liver has played a prominent role, providing clinical ideas and forming a relatively complete clinical theoretical scheme. The first reports on the relationship between the liver and vertigo in dizziness disease came from HuangDiNeiJing, a famous ancient Chinese medical classic, which was consistent with the results of hepatitis C and B enriched by the KEGG pathway in this study. It was also suggested that the therapeutic target proteins of AOD in the treatment of vertigo were from the liver.

5 Conclusions

Our study showed that the eight compounds from AO and four compounds from AM were potentially effective components for the treatment of vertigo. 1-Monolinolein, alisol B, sitosterol and alisol C were selected and predicted to be potential drug precursors for the treatment of dizziness in strong correlation with the target genes of MAPK1, EGFR, MAPK14, ERBB2, PIK3CA, MAPK8 and MTOR by acting on the signalling pathways of proteoglycans in cancer, ErbB, HIF-1, etc. The results were consistent with recent basic research on dizziness and classical recipes, indicating a high reference value and providing ideas and methods for subsequent experimental design and further research.

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References

Ardouin, P. (1971) 'A new treatment of vertigo by cerebral microcirculation regulation and oxygenator action on the sensorial epithelium of vestibule', *Rev. Laryngol. Otol. Rhinol.*, Vol. 92, No. 9, pp.585–592.

Ashburner, M., Ball, C.A., Blake, J.A., Botstein, D., Butler, H., Cherry, J.M., Davis, A.P., Dolinski, K., Dwight, S.S., Eppig, J.T., Harris, M.A., Hill, D.P., Tarver, L.I., Kasarskis, A., Lewis, S., Matese, J.C., Richardson, J.E., Ringwald, M., Rubin, G.M. and Sherlock, G. (2000) 'Gene ontology: tool for the unification of biology', *Nat. Genet.*, Vol. 25, No. 1, pp.25–29.

Becker-Bense, S., Dieterich, M., Buchholz, H.G., Bartenstein, P., Schreckenberger, M. and Brandt, T. (2014) 'The differential effects of acute right- vs. left-sided vestibular failure on brain metabolism', *Brain Struct. Funct.*, Vol. 219, No. 4, pp.1355–1367.

Brandt, T. and Daroff, R.B. (1980) 'Physical therapy for benign paroxysmal positional vertigo', *Arch. Otolaryngol.*, Vol. 106, No. 8, pp.484–485.

Byun, H., Chung, J.H., Lee, S.H., Park, C.W., Kim, E.M. and Kim, I. (2019) 'Increased risk of benign paroxysmal positional vertigo in osteoporosis: a nationwide population-based cohort study', *Sci. Rep.*, Vol. 9, No. 1, p.3469.

Cai, H.B., Duan, L., Tian, T., Li, Z.C., Zhao, C.C. and Ge, Z.M. (2019) 'Elevated serum macrophage migration inhibitory factor levels correlate with benign paroxysmal positional vertigo and recurrence events', *Biosci. Rep.*, Vol. 39, No. 8, p.BSR20191831.

Chen, J., Zhang, S., Cui, K. and Liu, C. (2021) 'Risk factors for benign paroxysmal positional vertigo recurrence: a systematic review and meta-analysis', *J. Neurol.*, Vol. 268, No. 11, pp.4117–4127.

Deng, M., Liu, C., Jiang, W., Wang, F., Zhou, J., Wang, D. and Wang, Y. (2020) 'A novel genetic variant associated with benign paroxysmal positional vertigo within the LOXL1', *Mol. Genet. Genomic. Med.*, Vol. 8, No. 8, p.e1469.

Deng, W., Yang, C., Xiong, M., Fu, X., Lai, H. and Huang, W. (2014) 'Danhong enhances recovery from residual dizziness after successful repositioning treatment in patients with benign paroxysmal positional vertigo', *Am. J. Otolaryngol.*, Vol. 35, No. 10, pp.753–757.

Dyhrfjeld-Johnsen, J. and Attali, P. (2019) 'Management of peripheral vertigo with antihistamines: New options on the horizon', *Br. J. Clin. Pharmacol.*, Vol. 85, No. 6, pp.2255–2263.

Ercin, D., Erdur, B., Turkcuer, I., Seyit, M., Ozen, M., Yilmaz, A., Ozge, D. and Ercin Z. (2021) 'Comparison of efficacy dimenhydrinate and metoclopramide in the treatment of nausea due to vertigo; a randomized study', *Am. J. Emerg. Med.*, Vol. 40, No. 10, pp.77–82.

Fillies, T., Werkmeister, R., van Diest, P.J., Brandt, B., Joos, U. and Buerger, H. (2005) 'HIF1-alpha overexpression indicates a good prognosis in early stage squamous cell carcinomas of the oral floor', *BMC Cancer*, Vol. 5, No. 1, p.84.

Flores, K., Yadav, S.S., Katz, A.A. and Seger, R. (2019) 'The nuclear translocation of mitogen-activated protein kinases: molecular mechanisms and use as novel therapeutic target', *Neuroendocrinology*, Vol. 108, No. 2, pp.121–131.

Guo, Z., Su, Z., Wang, Z., Luo, X. and Lai, R. (2017) 'The effect of Chinese herbal medicine Banxia Baizhu Tianma decoction for the treatment of vertebrobasilar insufficiency vertigo: a systematic review and meta-analysis of randomized controlled trials', *Complement Ther. Med.*, Vol. 31, No. 1, pp.27–38.

Hain, T.C. and Uddin, M. (2003) 'Pharmacological treatment of vertigo', *CNS Drugs*, Vol. 17, No. 1, pp.85–100.

Hopkins, A.L. (2007) 'Network pharmacology', *Nat. Biotech.*, Vol. 25, No. 2, pp.1110–1111.

Hopkins, A.L. (2008) 'Network pharmacology: the next paradigm in drug discovery', *Nat. Chem. Biol.*, Vol. 4, No. 10, pp.682–690.

Hsieh, K., Wang, Y., Chen, L., Zhao, Z., Savitz, S., Jiang, X., Tang, J. and Kim, Y. (2021) 'Drug repurposing for COVID-19 using graph neural network and harmonizing multiple evidence', *Sci. Rep.*, Vol. 11, No. 11, p.23179.

Huang, D.W., Sherman, B.T. and Lempicki, R.A. (2009) 'Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources', *Nature Protoc.*, Vol. 4, No. 1, pp.44–57.

Jafari, M., Mirzaie, M., Bao, J., Barneh, F., Zheng, S., Eriksson, J., Heckman, C.A. and Tang, J. (2022) 'Bipartite network models to design combination therapies in acute myeloid leukaemia', *Nature Commun.*, Vol. 13, No. 1, p.2128.

Janicki, S.C. and Schupf, N. (2010) 'Hormonal influences on cognition and risk for Alzheimer's disease', *Curr. Neurol. Neurosci. Rep.*, Vol. 10, No. 1, pp.359–366.

Jiang, M., Lu, C., Zhang, C., Yang, J., Tan, Y., Lu, A. and Chan, K. (2012) 'Syndrome differentiation in modern research of traditional Chinese medicine', *J. Ethnopharmacol.*, Vol. 140, No. 5, pp.634–642.

Johkura, K. (2021). 'Vertigo and dizziness', *Rinsho shinkeigaku*, Vol. 61, No. 3, pp.279–287.

Kanehisa, M., Furumichi, M., Sato, Y., Ishiguro-Watanabe, M. and Tanabe, M. (2021) 'KEGG: integrating viruses and cellular organisms', *Nucleic Acids Res.*, Vol. 49, No. D1, pp.D545–D551.

Keiser, M.J., Roth, B.L., Armbruster, B.N., Ernsberger, P., Irwin, J.J., Shoichet, B.K. (2007) 'Relating protein pharmacology by ligand chemistry', *Nat. Biotech.*, Vol. 25, No. 5, pp.197–206.

Lamb, D. and Davies, D.P. (2020) 'Identifying stroke in the Dizzy ED patient: development of a vertigo assessment tool by literature review', *Physiotherapy*, Vol. 2020, No. 2, p.107.

Li, S. and Zhang, B. (2013) 'Traditional Chinese medicine network pharmacology: theory, methodology and application', *Chin J. Nat. Med.*, Vol. 11, No. 1, pp.110–120.

Lin, J., Wang, Q., Xu, S., Zhou, S., Zhong, D., Tan, M., Zhang, X. and Yao, K. (2022) 'Banxia baizhu tianma decoction, a Chinese herbal formula, for hypertension: integrating meta-analysis and network pharmacology', *Front Pharmacol.*, Vol. 13, No. 1, p.1025104.

Liu, H.M., Tao, L.I. and Neurology, D.O. (2014) 'Thinking about vertigo effectiveness evaluation methods in clinical research of Chinese medicine', *Chin. J. Integr. Med.*, Vol. 34, No. 10, pp.1256–1259.

Mermelstein, P.G. and Micevych, P.E. (2008) 'Nervous system physiology regulated by membrane estrogen receptors', *Rev. Neurosci.*, Vol. 19, No. 6, pp.413–424.

Mi, H., Muruganujan, A., Ebert, D., Huang, X. and Thomas, P.D. (2019) 'PANTHER version 14: more genomes, a new PANTHER GO-slim and improvements in enrichment analysis tools', *Nucleic Acids Res.*, Vol. 47, No. D1, pp.D419–D426.

Nguyen-Huynh, A.T. (2012) 'Evidence-based practice: management of vertigo', *Otolaryngol. Clin. North Am.*, Vol. 45, No. 5, pp.925–940.

Nomura, Y. and Kobayashi, H. (2012) 'Laser irradiation of the semicircular canal: occlusion of the canal or duct', *Acta oto-laryngol.*, Vol. 132, No. 1, pp.106–111.

Noriko, K. (1997) 'Clinical study of platelet aggregation in patients with vertigo and dizziness', *Equilib. Res.*, Vol. 56, No. 1, pp.284–295.

Ohle, R., Montpellier, R.A., Marchadier, V., Wharton, A., McIsaac, S., Anderson, M. and Savage, D. (2020). 'Can emergency physicians accurately rule out a central cause of vertigo using the HINTS examination? A systematic review and meta-analysis', *Acad. Emerg. Med.*, Vol. 27, No. 9, pp.887–896.

Patten, B.A., Peyrin, J.M., Weinmaster, G. and Corfas, G. (2003) 'Sequential signaling through Notch1 and erbB receptors mediates radial glia differentiation', *J. Neurosci.*, Vol. 23, No. 14, pp.6132–6140.

Piñero, J., Saüch, J., Sanz, F. and Furlong, L.I. (2021) 'The DisGeNET cytoscape app: exploring and visualizing disease genomics data', *Comput. Struct. Biotechnol. J.*, Vol. 19, No. 1, pp.2960–2967.

Ru, J., Li, P., Wang, J., Zhou, W., Li, B., Huang, C., Li, P., Guo, Z., Tao, W., Yang, Y., Xu, X., Li, Y., Wang, Y. and Yang, L. (2014) 'TCMSP: a database of systems pharmacology for drug discovery from herbal medicines', *J. Cheminform.*, Vol. 6, No. 1, p.13.

Safran, M., Dalah, I., Alexander, J., Rosen, N., Iny Stein, T., Shmoish, M., Nativ, N., Bahir, I., Doniger, T., Krug, H., Sirota-Madi, A., Olender, T., Golan, Y., Stelzer, G., Harel, A. and Lancet, D. (2010) 'GeneCards Version 3: the human gene integrator', *Database*, Vol. 2010, p.baq020.

Sert, E.T., Cayir, S., Mutlu, H. and Kokulu, K. (2021) 'Effectiveness of clinical risk factors in the detection of central pathology in patients with isolated vertigo', *J. Emerg. Med.*, Vol. 60, No. 6, pp.709–715.

Shannon, P., Markiel, A., Ozier, O., Baliga, N. S., Wang, J. T., Ramage, D., Amin, N., Schwikowski, B. and Ideker, T. (2003) 'Cytoscape: a software environment for integrated models of biomolecular interaction networks', *Genome Res*, Vol. 13, No. 11, pp.2498–2504.

Su, Q., Wang, J., Wu, Q., Ullah, A., Ghauri, M.A., Sarwar, A., Chen, L., Liu, F. and Zhang, Y. (2021) 'Sanguinarine combats hypoxia-induced activation of EphB4 and HIF-1α pathways in breast cancer', *Phytomedicine*, Vol. 84, No. 1, p.153503.

Svensson, J., Hermansen, A., Wibault, J., Löfgren, H., Dedering, Å., Öberg, B., Zsigmond, P. and Peolsson, A. (2020) 'Neck-related headache in patients with cervical disc disease after surgery and physiotherapy: a 1-year follow-up of a prospective randomized study', *Spine*, Vol. 45, No. 14, pp.952–959.

Szklarczyk, D., Gable, A.L., Lyon, D., Junge, A., Wyder, S., Huerta-Cepas, J., Simonovic, M., Doncheva, N.T., Morris, J.H., Bork, P., Jensen, L.J. and Mering, C.V. (2019) 'STRING v11: protein-protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets', *Nucleic Acids Res.*, Vol. 47, No. D1, pp.D607–D613.

Takeda, N. (2009) 'Pharmacological basis of drug therapy for vertigo', *Equilibrium Res.*, Vol. 59, No. 2, pp.93–102.

Tsai, T.Y., Li, C.Y., Livneh, H., Lin, I.H., Lu, M.C. and Yeh, C.C. (2016) 'Decreased risk of stroke in patients receiving traditional Chinese medicine for vertigo: a population-based cohort study', *J. Ethnopharmacol*., Vol. 184, No. 1, pp.138–143.

Wade, A., Robinson, A.E., Engler, J.R., Petritsch, C., James, C.D. and Phillips, J.J. (2013) 'Proteoglycans and their roles in brain cancer', *FEBS J*., Vol. 280, No. 10, pp.2399–2417.

Wang, Q., Ren, X., Zhang, X., Wang, G., Xu, H., Deng, N., Liu, T. and Peng, Z. (2020) 'Therapeutic effect of berberine on insomnia rats by ErbB signaling pathway', *Med. Sci. Monit.*, Vol. 26, No. 1, p.e921831.

Wang, Y., Yang, H., Chen, L., Jafari, M. and Tang, J. (2021) 'Network-based modeling of herb combinations in traditional Chinese medicine', *Brief Bioinform*. Vol. 22, No. 5, p.bbab106.

Weller, M. and Reifenberger, G. (2020) 'Beyond the World Health Organization classification of central nervous system tumors 2016: what are the new developments for gliomas from a clinician's perspective', *Curr. Opin. Neurol.*, Vol. 33, No. 6, pp.701–706.

Yan, J., Zhang, Z. and Shi, H. (2012) 'HIF-1 is involved in high glucose-induced paracellular permeability of brain endothelial cells', *Cell Mol. Life Sci.,* Vol. 69, No. 1, pp.115–128.

Nomenclature

AOD	*Alisma orientale* decoction
AO	*Alisma orientale*
AM	*Atractylodes macrocephala*
OMIN	online mendelian inheritance in man
WOS	Web of Science
OB	Oral bioavailability
DL	Drug-like property