Action Mechanism of Components from *Gardenia jasminoides* on Eye Skin Based on Network Pharmacology

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Abstract [**Objectives**] To explore the pharmacological effects of *Gardenia jasminoides* and its potential benefits on eye skin. [**Methods**] TCMSP and SymMap databases were used to screen the active components and corresponding targets of *G. jasminoides*. Human eye skin-related targets were screened, and the active component-target network and protein-protein interaction (PPI) network were established. Gene ontology (GO) analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis were performed. [**Results**] Twenty-six active compounds were screened out from *G. jasminoides*, and 277 targets were obtained. From the Gencards database, 26 652 disease targets were retrieved and 205 related gene targets were screened. The active component-action target network of *G. jasminoides* constructed by Cytoscape software revealed the potential of *G. jasminoides* to play a role in multiple biological pathways. In addition, PPI-network analysis, GO function analysis and KEGG pathway enrichment analysis revealed that the active components of *G. jasminoides* mainly regulate the biological processes such as inflammatory response, oxidative stress and apoptosis, involving MAPK, NF-κB and other important signaling pathways. [**Conclusions**] This study provides a theoretical basis for the eye skin protection of *G. jasminoides* and an important clue for future drug development.

Key words Network pharmacology, *Gardenia jasminoides* of Jiangxi Province, Effects on eye skin, Biological signaling pathways

1 Introduction

Gardenia jasminoides has a long history in Jiangxi Province. According to historical records, as early as the Tang Dynasty, it had been cultivated in Jiangxi and was a tribute to the royal family. With the changes of history, *G. jasminoides* has gradually become an important crop in Jiangxi, and is widely planted in camphor trees, Jingdezhen, Fuzhou, Ganzhou and *etc.* Jiangxi Province, located in the south of China, has a mild climate, abundant rainfall and fertile land, which provides unique advantages for the growth of *G. jasminoides*. In particular, Ganjiang River, Fuhe River and other rivers in Jiangxi provide sufficient water for *G. jasminoides*, making *G. jasminoides* grow stronger.

Gardeniae Fructus is the dried ripe fruit of *G. jasminoides*, and it was first recorded in *Shen Nong's Herbal Classic*. According to the record, it has effects of clearing heat and promoting diuresis, purging fire and relieving restlessness, cooling blood and detoxifying. In *Compendium of Materia Medica*, the efficacy of Gardeniae Fructus is recorded as quenching thirst, promoting urination and benefiting five strangury diseases (stone strangury, qi strangury, blood strangury, unctuous strangury, and fatigue strangury)[1]. Gardeniae Fructus is highly valued in the traditional Chinese Medicine (TCM). Flowers, leaves, and seeds of *G. jasminoides* are also valuable Chinese herbal medicines, which are commonly used in TCM prescriptions and have a variety of medicinal values[2]. *G. jasminoides* contains fatty acids, iridoids, phenolic acids, flavonoids, volatile oils, pigments and polysaccharides[3]. Among them, gardenia yellow pigment, as a natural and non-toxic food pigment, is widely used in food, cosmetics and other fields[4]; gardenia oil is rich in linoleic acid, squalene, phytosterol and crocin I[5], which has antidepressant, sedative and hypnotic, antioxidant and anti-tumor effects[6], and can be used as both food and medicine.

According to the TCM theory, *G. jasminoides* has that function of clearing away heat and toxic material, is used for treating various diseases cause by internal heat, such as fever, sore throat, furuncle and *etc.*, can promote the metabolism of water in the body, and has a certain effect on treating diseases caused by edema, such as nephritis and edema caused by heart disease. The components in *G. jasminoides* have obvious effects on reducing inflammation and redness, and are commonly used in the treatment of arthritis and some acute and chronic inflammation. Geniposide and crocin can participate in multiple signaling pathways to weaken the inflammatory response, reduce the level of oxidative stress, and jointly play an anti-inflammatory role. Some studies have shown that *G. jasminoides* has certain antibacterial effects and it can inhibit the growth of some bacteria and fungi, and is used to treat infections caused by these microorganisms. In traditional Chinese medicine, *G. jasminoides* is commonly used to treat hepatitis, jaundice and other liver diseases. *G. jasminoides* can promote bile secretion and excretion, and help improve liver function. The aqueous extract of *G. jasminoides* can weaken hepatic fibrosis by regulate multiple pathways and play a role in protect that liver; *G. jasminoides* is also helpful for lowering blood pressure. The active components in *G. jasminoides* have a positive effect on the prevention and treatment of heart disease by improving cardiovascular function. Geniposide, crocin and gardenia alcohol have protective effects on nervous system. Studies have found that it has a positive effect on the treatment of Parkinson's disease (PD) and Alzheimer's disease (AD)[7]. Geniposide and crocin in *G. jasminoides* have significant effects in protecting myocardial cells and reducing myocardial injury, especially in improving atherosclerosis by geniposide. *G. jasminoides* is also used to treat nervous system

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symptoms such as insomnia and dreaminess, and has the effect of calming the nerves. *G. jasminoides* contains natural antioxidants that can help resist free radicals and have certain anti-aging and health-promoting effects. *G. jasminoides* is used in some traditional applications to treat eye diseases, such as blurred vision and eye fatigue, which may be related to its anti-inflammatory and antioxidant properties. Geniposide can reduce blood glucose through multiple pathways. Geniposide is the main active component of *G. jasminoides* with immunomodulatory effect, and it plays a great role in inhibiting cancer cells. Iridoid glycosides are the main antidepressant components of *G. jasminoides* and can participate in the regulation of multiple signaling pathways to play an antidepressant role, and gardenia oil can also participate in the regulation of signaling pathways to treat depression; *G. jasminoides* and its carbonized product gardenia charcoal are often used to treat hematemesis, hematochezia and other diseases[8]. In ancient books of traditional Chinese medicine that *G. jasminoides* has the effect of treating eye skin diseases, and *Shennong's Herbal Classic* recorded that *G. jasminoides* has the effect of treating "white, red, urticaria and ulcers". It is also recorded in *Essentials of Materia Medica* that compound gardenia can be used to treat "tinea versicolor, blister sores and ulcers". Modern pharmacological studies have shown that *G. jasminoides* has good anti-inflammatory, analgesic[9], treatment of vitiligo[10], radiation protection and other effects[11], and gardenia oil has the effect of treating herpes zoster and other eye skin diseases[12].

Ultra-violet radiation (UVR) is roughly divided into three bands according to wavelength: UVA, UVB, and UVC. The ultraviolet components that can pass through the ozone layer and cause human eye skin damage are UVB (280 – 315 nm) and UVA (315 – 400 nm). The damage intensity of UVB to eye skin is 1 000 times greater than that of UVA[13]. Long-term and high-dose UVB radiation is the main environmental factor leading to eye skin photoaging and photodamage. Under ultraviolet radiation, the eye skin appears a large number of wrinkles, epidermis hyperplasia, basement membrane structure damage and collagen degradation. The main player in causing these changes was Mattlix Metaloprotenas (MMPs). which are a family of Zn^{2+}-dependent hydrolases with highly homologous structure and function, and they are considered to be the main enzymes of extracellular matrix (ECM) degradation and have a strong ability to degrade extracellular matrix. The MMP enzyme family encodes metalloproteinases including interstitial collagenase (MMP-1), gelatinase A (MMP-2), matrixlysin-I (MMP-3), and gelatinase B (MMP-9), with gelatinase A and gelatinase B digesting collagen types IV and VII[14]. The stimulation of UVB can induce the activation of mitogen-activated protein kinase (MAPK) signaling pathway, which leads to the overexpression of MMP-2 and MMP-9, the formation of epidermal hyperplasia, the decomposition of basement membrane at the junction of epidermis and dermis, the degradation of collagen, the increase of wrinkles, and the breakthrough of inflammatory cells into the epidermis.

2 Data and methods

2.1 Screening of active components and targets of *G. jasminoides* We used TCMSP database (https://tcmsp-e.com/tcmsp.php) and SymMap database (http://www.symmap.org/) to screen the reported active components of *G. jasminoides* and the corresponding targets. In order to improve the authenticity and reliability of the data, the screening conditions were set as oral bioavailability (OB) $\geqslant$ 30% and drug-likeness (DL) $\geqslant$0.18. The screened targets of *G. jasminoides* were input into UniProt database (https://www.uniprot.org) to obtain the standardized gene names of the corresponding targets. All targets were humanized and screened for duplicated genes.

2.2 Screening of human eye skin-related targets Taking "eye skin" as the key word, we screened the relevant targets in the Gencards database (https://www.genecards.org/), and the top 20% of the targets with score as the targets related to the occurrence and development of eye skin diseases. The target information was imported into Hiplot biomedical data online visualization tool (https://hiplot.cn) to plot the Venn diagram, and the related targets of *G. jasminoides* that may have therapeutic effects on eye skin were screened out.

2.3 Establishment of active component-target network With the aid of Cytoscape 3.10.1 software, we analyzed the active components of *G. jasminoides* and the related targets of human eye skin, and established active component-target network of *G. jasminoides*. The active components of *G. jasminoides* and their corresponding targets are represented by nodes, and the relationship between the two nodes is represented by "edges". According to the topology analysis of the established network graph, we evaluated the importance of the nodes in the network using the degree of the nodes.

2.4 Establishment of protein-protein interaction (PPI) network We imported the target genes of *G. jasminoides* in eye skin into String database (https://string-db.org) to establish PPI network. Then, we removed the single node without interaction in the network, so as to explore the pharmacological mechanism of *G. jasminoides* at the level of protein interaction.

2.5 Gene ontology (GO) analysis and pathway enrichment analysis (KEGG) We imported the target genes of *G. jasminoides* in the eye skin into the David database (https://david.ncifcrf.gov), and conducted the GO function analysis and KEGG pathway enrichment analysis under the condition of $P < 0.01$. The output analysis data was plotted by Hiplot biomedical data online visualization tool to obtain biological function and pathway information highly related to the pharmacological effects of *G. jasminoides*.

3 Results and analysis

3.1 Analysis of active components and targets of *G. jasminoides* Based on the screening conditions, a total of 26 effective active compounds were screened in the TCMSP database and SymMap database, as shown in Table 1. We imported the targets corresponding

to the active components into the UniProt database, and obtained 277 corresponding targets after the gene names were standardized and the non-human genes and duplicate genes were removed.

Table 1 Effective active compounds of *Gardenia jasminoides*

TCMSP No.	Name	*OB*//%	*DL*//%
MOL004561	Sudan III	84.07	0.59
MOL002341	Hesperetin	70.31	0.27
MOL000785	Palmatine	64.60	0.65
MOL007245	3-Methylkempferol	60.16	0.26
MOL004328	Naringenin	59.29	0.21
MOL003095	5-hydroxy-7-methoxy-2-(3,4,5-trimethoxyphenyl) chromone	51.96	0.41
MOL000098	Quercetin	46.43	0.28
MOL009038	GBGB	45.58	0.83
MOL001942	Isoimperatorin	45.46	0.23
MOL000449	Stigmasterol	43.83	0.76
MOL002897	Epiberberine	43.09	0.78
MOL001494	Mandenol	42.00	0.19
MOL000422	Kaempferol	41.88	0.24
MOL010228	Carotenoid	40.76	0.55
MOL002776	Baicalin	40.12	0.75
MOL000358	Beta-sitosterol	36.91	0.75
MOL000296	Hederagenin	36.91	0.75
MOL001454	Berberine	36.86	0.78
MOL001406	Crocetin	35.30	0.26
MOL001941	Ammidin	34.55	0.22
MOL001506	Supraene	33.55	0.42
MOL002714	Baicalein	33.52	0.21
MOL002883	Ethyl oleate (NF)	32.40	0.19
MOL001663	3-Epioleanolic acid	32.03	0.76
MOL000173	Wogonin	30.68	0.23
MOL006397	Jatrorrhizine	30.44	0.75

3.2 Components of *G. jasminoides* acting on the eye skin-disease targets Taking the word "eye skin" as the keyword, we searched the Gencards database, and obtained 26 652 disease targets. Next, we conducted the intersection analysis between the top 20% targets of the score and 277 targets of the active components of *G. jasminoides* (Fig. 1). Finally, we found that a total of 205 gene targets of *G. jasminoides* may have effects on eye skin, as shown in Table 2.

3.3 Active component-target network of *G. jasminoides* With the aid of Cytoscape 3.10.1 software, we established the active component-target network (Fig. 2). According to the analysis results, there are 231 nodes and 506 edges in the active component-target network of *G. jasminoides*. As shown in Fig. 2, the outermost three circles are the action targets, and the square nodes are the effective active components of *G. jasminoides* acting on the eye skin. According to the results of network topology analysis, the average value of the established network nodes is 4.31, and there are 44 nodes greater than the average value; the average value of betweenness is 0.008 7, and there are 34 nodes whose centrality is greater than the average value. There are 28 nodes meeting the requirements at the same time, and the screening results are shown in Table 3.

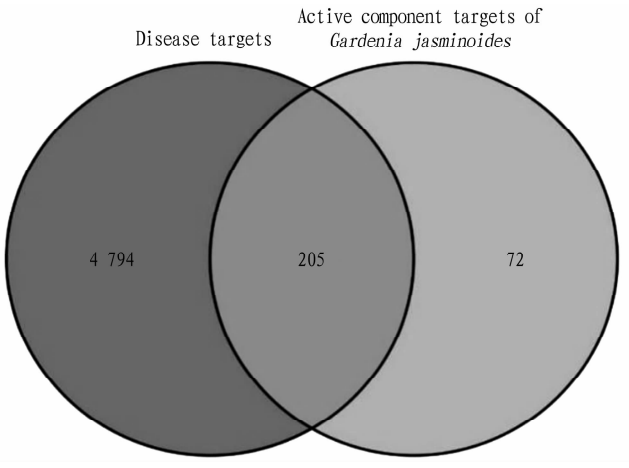

Fig. 1 Venn diagram for action targets of *Gardenia jasminoides* and eye skin gene targets

Table 2 Targets of active compounds from *Gardenia jasminoides*

No.	Target	No.	Target	No.	Target	No.	Target
1	FBN1	53	CASP8	105	ERBB3	157	GSR
2	TP53	54	CHEK2	106	APOB	158	TCF12
3	CDKN2A	55	CRP	107	HMGCR	159	ADH1C
4	PTEN	56	VCAM1	108	RXRA	160	CDK1
5	COL1A1	57	GSTM1	109	CYP1A1	161	HAS2
6	AKT1	58	CASP3	110	F3	162	AKR1C1
7	IFNG	59	CD40LG	111	CDK2	163	OPRM1
8	IL6	60	CXCL10	112	CYP3A4	164	PC
9	TNF	61	MMP3	113	ADRB2	165	PPP3CA
10	ERBB2	62	IGF2	114	LPL	166	F2R
11	RAF1	63	LDLR	115	RELA	167	ABCC1
12	COL3A1	64	PPARA	116	PLAT	168	PTGER3
13	MYC	65	GSTP1	117	CHRM3	169	DUOX2
14	IL10	66	MPO	118	NOS3	170	CHRNA7
15	MMP1	67	HMOX1	119	ESR2	171	F7
16	IL1B	68	SOD1	120	HSP90AA1	172	MAP2
17	TGFB1	69	MAPK14	121	ACHE	173	PRSS1
18	GJA1	70	NFKBIA	122	LYZ	174	FOSL1
19	CXCL8	71	IGFBP3	123	XDH	175	CLDN4
20	IL1A	72	NOS2	124	MAOA	176	LTA4H
21	CTSB	73	LEP	125	KCNMA1	177	NR3C2
22	MAPK1	74	MAPK8	126	STAR	178	CXCL2
23	MMP2	75	AHR	127	THBD	179	HSP90AB1
24	STAT1	76	SREBF1	128	MAPK10	180	SLC6A3
25	IL2	77	BAX	129	GSK3B	181	PTPN1
26	PPARG	78	DPP4	130	PGR	182	ADH1B
27	EGF	79	CTSA	131	MCL1	183	ACP3
28	MMP9	80	ADIPOQ	132	PROS1	184	BBC3
29	ICAM1	81	FABP5	133	PRKACA	185	RBL1
30	CCL2	82	PLAU	134	ALOX5	186	ABCA2
31	KDR	83	SERPINE1	135	IGHG1	187	FASN
32	BCL2	84	CXCL11	136	PTGS1	188	RASSF1
33	INS	85	IKBKB	137	CASP9	189	NFATC1
34	CAV1	86	CYP1B1	138	LDHA	190	MAP3K3
35	RASA1	87	BIRC5	139	CHEK1	191	NR1I2

(To be continued)

(Continued)

No.	Target	No.	Target	No.	Target	No.	Target
36	PPOX	88	PARP1	140	CYCS	192	BAD
37	GLA	89	HSPB1	141	NQO1	193	PRDX1
38	CHUK	90	PRKCD	142	TOP1	194	APOD
39	PTGS2	91	NCF2	143	CYP1A2	195	NCOA2
40	FOS	92	UGT1A1	144	SULT1E1	196	ACACA
41	JUN	93	ALOX12	145	TF	197	SPR
42	VEGFA	94	CYP19A1	146	CTSD	198	PON1
43	AR	95	CDKN1C	147	SCN5A	199	PRKCB
44	NFE2L2	96	SELP	148	F10	200	AKR1C3
45	FN1	97	PRKCA	149	PROCR	201	NCOA1
46	FBN2	98	TCF4	150	HTR2A	202	POR
47	INSR	99	PIK3CG	151	EIF6	203	CACNA2D1
48	ODC1	100	PPARD	152	BAK1	204	CCND3
49	ESR1	101	E2F1	153	IRF1	205	MGAM
50	SELE	102	TOP2A	154	SLC6A4		
51	CAT	103	SLPI	155	CCNB1		
52	SPP1	104	TFRC	156	CCNA2		

Table 3 Key nodes and their topological characteristics of *Gardenia jasminoides* effective compound-action target network

Node name	Node type	Node degree	Betweenness
Quercetin	Compound	130	0.593 1
Kaempferol	Compound	51	0.107 8
Wogonin	Compound	42	0.089 4
Baicalein	Compound	32	0.074 4
Carotenoid	Compound	30	0.181 4
Naringenin	Compound	28	0.125 4
G. jasminoides	Sample	26	0.160 8
5-hydroxy-7-methoxy-2-(3,4,5-trimethoxyphenyl) chromone	Compound	25	0.035 6
Beta-sitosterol	Compound	21	0.047 1
Stigmasterol	Compound	20	0.056 7
PTGS2	Action target	18	0.031 5
Palmatine	Compound	18	0.010 5
PRKACA	Action target	14	0.031 9
Sudan III	Compound	13	0.023 0
NCOA2	Action target	13	0.020 2
PTGS1	Action target	13	0.019 3
Hederagenin	Compound	12	0.026 4
HSP90AB1	Action target	11	0.019 2
HSP90AA1	Action target	11	0.019 2
PIK3CG	Action target	9	0.015 6
SCN5A	Action target	9	0.012 6
RXRA	Action target	8	0.009 4
DPP4	Action target	8	0.009 0
CASP3	Action target	7	0.041 9
PPARG	Action target	7	0.009 3
BCL2	Action target	6	0.012 5
RELA	Action target	5	0.009 5
AKT1	Action target	5	0.009 5

3.4 Analysis of PPI network for action targets of effective active compounds of *G. jasminoides* The PPI network for action targets of effective active compounds of *G. jasminoides* is shown in Fig. 3. The network contains 204 protein nodes and 4 437 edges, and the average value of the nodes is 43.5. The interaction between nodes is represented by edges. The more edges associated with a node, the more important the target point corresponding to the node, the higher the node value. The targets with the top 20 node values are listed in Table 4.

Table 4 Key nodes of PPI network for action targets of effective compounds of *Gardenia jasminoides*

No.	Node name	Node degree	No.	Node name	Node degree
1	AKT1	149	11	PTGS2	114
2	TNF	138	12	MYC	109
3	IL6	136	13	MMP9	108
4	TP53	134	14	PPARG	104
5	IL1B	131	15	TGFB1	99
6	INS	131	16	EGF	97
7	CASP3	121	17	FN1	97
8	JUN	120	18	HSP90AA1	96
9	ESR1	115	19	CCL2	93
10	BCL2	114	20	CYCS	93

3.4.1 GO functional analysis. We imported 205 targets of active compounds of *G. jasminoides* into the David database for GO functional analysis, and obtained 359 GO entries with significance ($P<0.01$). Among them, 280 were biological process (BP), 37 were molecular function (MF), and 42 were cell composition (CC). Taking the top 10 items of BP, MF and CC gene enrichment, we plotted a bar chart, as shown in Fig. 4.

3.4.2 KEGG pathway enrichment analysis. KEGG pathway enrichment analysis identified 61 pathways with significance ($P<0.01$). We imported the pathway data into the Hiplot biomedical data online visualization tool, and selected the top 20 pathways to plot a bubble diagram (Fig. 5) based on the P value and the number of gene enrichments.

4 Conclusions and prospects

4.1 Conclusions We systematically explored the mechanism of the effects of *G. jasminoides* produced in Jiangxi on the eye skin based on the network pharmacology. In this study, we first used TCMSP and SymMap databases to screen 26 effective active compounds of *G. jasminoides*, and standardized the targets of these compounds by UniProt database, and finally obtained 277 corresponding targets. In the process of screening eye skin-related targets, we retrieved a total of 26 652 disease targets from the Gencards database, and selected the top 20% of the scores of the targets to carry out intersection analysis with the targets of the active components of *G. jasminoides*, and finally screened 205 gene targets of *G. jasminoides* that may have effects on eye skin. The active component-target network of *G. jasminoides* was constructed by Cytoscape software, which contained 231 nodes and 506 edges, and further topological analysis showed that the degree of 44 nodes and the mediating centrality of 34 nodes were significantly higher than the average, which provided important clues for further study of the pharmacological effects of *G. jasminoides*. The results of PPI network analysis showed that the active components of *G. jasminoides*

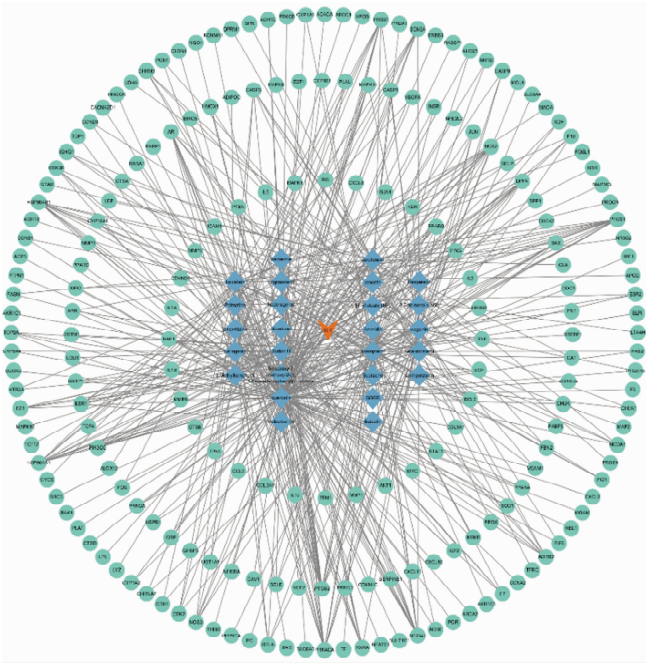

Fig. 2 Active component-target network of *Gardenia jasminoides*

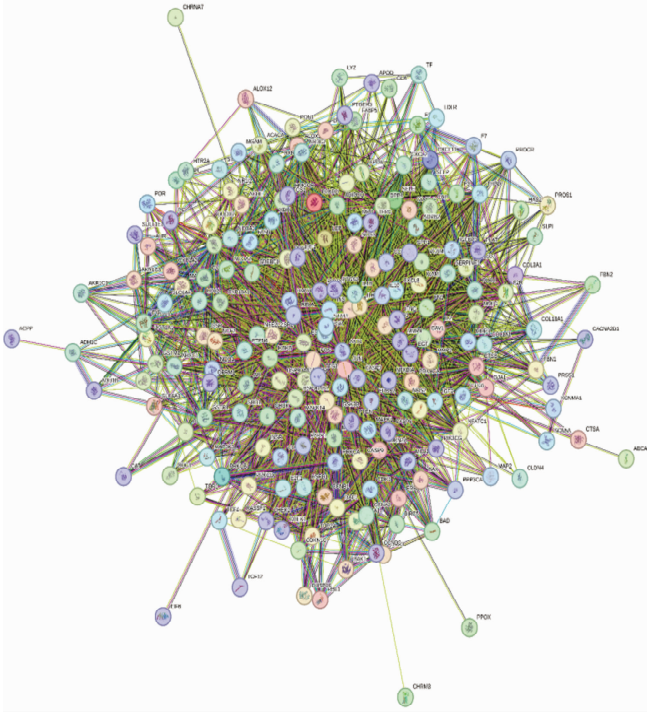

Fig. 3 PPI network for action targets of effective active compounds of *Gardenia jasminoides*

had a wide range of interactions at the protein interaction level, including 204 protein nodes and 4 437 edges, indicating that *G. jasminoides* played a role in multiple biological pathways. GO function analysis and KEGG pathway enrichment analysis further revealed that the active components of *G. jasminoides* play their pharmacological effects mainly by regulating biological processes such as inflammation, oxidative stress, apoptosis, and involving important signaling pathways such as MAPK and NF-κB.

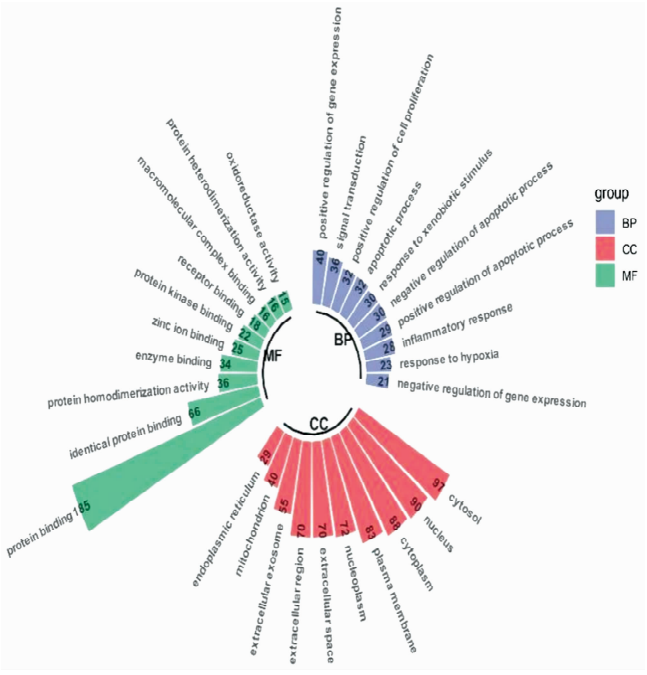

Fig. 4 GO functional analysis on action targets of active compounds of *Gardenia jasminoides*

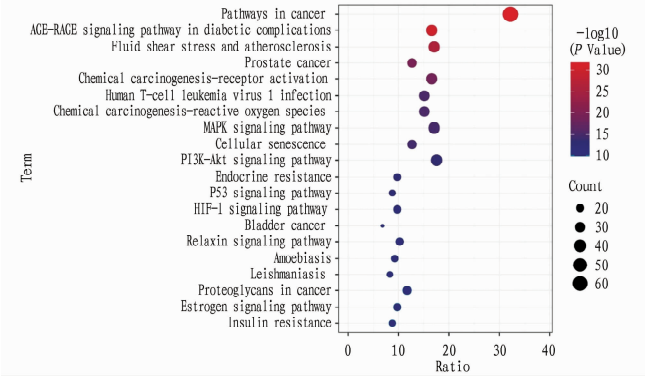

Fig. 5 KEGG pathway enrichment analysis on action targets of active compounds of *Gardenia jasminoides*

4.2 Prospects

4.2.1 Molecular docking research methods. In order to further study the interaction between the active components of *G. jasminoides* and its potential targets, further molecular docking analysis is needed in the future. Molecular docking techniques are used to predict the optimal mode of binding between a small molecule, such as the active components of *G. jasminoides*, and a large molecule, such as a protein target, and to assess its binding affinity. Following works are needed.

Target protein preparation: select key target proteins with significant roles in GO and KEGG analysis, and obtain their 3D structure data, usually from the Protein Data Bank (PDB) database.

Ligand molecule preparation: select the main active components of *G. jasminoides*, and use chemical software such as ChemBio Office to optimize the molecular structure and minimize the energy.

Docking process: use molecular docking software such as AutoDock Vina to dock the prepared ligand with the target protein

to generate multiple possible binding conformations.

Analysis of results: score the generated docking conformations, and select the conformation with the lowest binding free energy for analysis, and display the ligand-protein binding mode and key interactions by visualization software (such as PyMOL).

4.2.2 Molecular docking prediction results. The interaction between the main active components of *G. jasminoides* and its key target proteins was verified by molecular docking analysis. The following are the docking results of some important active components:

Quercetin and MMP-9: Quercetin stably bound to the active site of MMP-9 through hydrogen bonds and hydrophobic interactions, with a binding free energy of −8.5 kcal/mol, indicating that it has a high binding affinity, which helps to inhibit the enzymatic activity of MMP-9, thereby slowing down the eye skin photoaging process[15].

Kaempferol and NF-κB: Kaempferol bound to NF-κB mainly through hydrogen bonding and π-π stacking, and the binding free energy was −7.8 kcal/mol. This binding mode may contribute to the inhibition of the activation of NF-κB signaling pathway by kaempferol, thus exerting its anti-inflammatory effect.

Baicalin and ERK1/2: The binding between baicalin and ERK1/2 protein showed multiple hydrogen bond interactions with a binding free energy of −8.2 kcal/mol, suggesting that baicalin may play an antioxidant and anti-inflammatory role by interfering with ERK1/2 signaling pathway.

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