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Investigation of the Mechanism of Traditional Chinese Medicines in Angiogenesis through Network Pharmacology and Data Mining

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Abstract

Background: Although traditional Chinese medicine is safe for the clinical treatment of angiogenesis, the *in vivo* intervention mechanism is diverse, complex, and largely unknown. Therefore, we aimed to explore the active ingredients of traditional Chinese medicine and their mechanisms for the treatment of angiogenesis.

Methods: Data on angiogenesis-related targets were collected from the GeneCards, Therapeutic Target Database, Online Mendelian Inheritance in Man, DrugBank, and DisGeNET databases. These were matched to related molecular compounds and ingredients in the traditional Chinese medicine system pharmacology platform. The data were integrated; based on the condition of Degree >1 and relevant literature, a target-compound network as well as compound-medicine and target-compound-medicine networks were constructed using Cytoscape. Molecular docking was used to predict the predominant binding combination of core targets and components.

Results: We obtained a total of 79 targets for angiogenesis, and 41 targets were matched to 3839

compounds. Then, 110 compounds were selected owing to their high correlation with angiogenesis. Fifty-five combinations in the network were obtained by molecular docking, among which PTGS2-Astragalin (-9.18 kcal/mol), KDR-Astragalin (-7.94 kcal/mol), PTGS2-quercetin (-7.41 kcal/mol), and PTGS2-myricetin (-7.21 kcal/mol) were the top combinations. These results indicated that the selected potential core compounds may have good binding activity with the core targets. Eighty new combinations were obtained from the network, and the top combinations based on affinity were KDR-beta-carotene (-10.13 kcal/mol), MMP9-beta-Sitosterol (-8.04 kcal/mol), MMP9-Astragalin (-7.82 kcal/mol), and MMP9-Diosgenin (-7.51 kcal/mol). The core targets included PTGS2, KDR, VEGFA, and MMP9. The essential components identified were astragalin, kaempferol, myricetin, quercetin, and β-sitosterol. The crucial Chinese medicines identified included Polygoni Cuspidati Rhizoma et Radix, Morus alba Root Bark, and Forsythia Fructus.

Conclusions: By systematically analysing the essential ingredients of traditional Chinese medicine and their targets, it is possible to determine their potential mechanism of action in the treatment of pathological angiogenesis. Our study provides a basis for further research and development of new therapeutics for angiogenesis.

Keywords: angiogenesis; mechanism research; network pharmacology

Background

John Hunter provided the first recorded scientific insights into the field of angiogenesis and coined the term angiogenesis in 1787[1]. Folkman[2-6] proposed the role of angiogenesis in tumour

45 growth in 1971. He hypothesised that tumour growth depends on angiogenesis to increase blood
46 supply and proposed stopping the blood supply to inhibit tumour growth, which subsequently
47 initiated the field of research on the relationship between angiogenesis and diseases. Angiogenesis
48 is the process of capillary sprouting from pre-existing vasculature, and it is highly induced by
49 hypoxia and other biological processes[5, 7]. The mechanism of angiogenesis can be divided into
50 two types. The first is sprouting angiogenesis, wherein vascular endothelial cell growth factor
51 (VEGF) can stimulate tip cells in the original blood vessel network to induce vascular sprouting[8,
52 9]. The second is intussusceptive angiogenesis, which proceeds through transluminal tissue pillar
53 formation and subsequent vascular splitting to expansion and remodelling of microvascular
54 networks[9-11].
55
56 Under normal circumstances, angiogenesis is the balance between the inhibiting factor and
57 growth factor. If the functions of either the inhibiting or growth factors are abnormal, it presents
58 as overgrowth, defect, or malformation. Angiogenesis is essential for nutrition and oxygen for the
59 growth and development of tumour cells. Under hypoxic conditions, tumours stimulate
60 neovascularization via the expression of growth factors such as VEGF[12]. Thus, exploring the
61 inhibition of angiogenesis for the treatment of tumours has gained increasing attention. However,
62 some studies have shown that using anti-angiogenic agents can induce potential resistance
63 mechanisms such as autophagy, VEGF-dependent alterations, non-VEGF pathways, and stromal
64 cell interactions[13-17]. Tumour cells may become accustomed to hypoxia or nutrient deprivation, or
65 they may induce angiogenesis via other growth factors[18, 19]. Such events can lead to higher
66 survival levels of the tumour cells. Moreover, some anti-angiogenic agents can cause side effects

such as acne-like rash, hypertension, and diarrhoea[20, 21].

Traditional Chinese medicine is valuable for the treatment of various diseases, especially refractory diseases. Previously, we found that many herbal extracts such as *Epimedium brevicornu* Maxim, *Dalbergia odorifera* T. Chen, and *Trichosanthes kirilowii* Maxim can regulate angiogenesis[22]. Cucurbitacin E, a compound in herbal extracts, can inhibit tumour angiogenesis by inhibiting vascular endothelial growth factor receptor 2 (KDR/VEGFR2)-mediated Jak-STAT3 and mitogen-activated protein kinase (MAPK) signalling pathways[23]. Astragaloside IV and curcumin can suppress the expression of fibroblast growth factor-2, matrix metalloproteinase 2, VEGF, hepatocyte growth factor, thrombosis-related factor tissue factor, and coagulation factor VII, thereby reducing the microvessel count[24]. The above herbal studies focused on single or several compounds related to angiogenesis. Nevertheless, during treatment, multiple herbal compounds interact or cross-react to regulate different targets and pathways. Thus, even though traditional Chinese medicine is safe for clinical treatment, the *in vivo* intervention mechanism is diverse, complex, and largely unknown.

In this study, the targets of angiogenesis were explored through network pharmacology, and the corresponding compound and herbs were matched. Furthermore, the effect of herbal compounds on angiogenesis and the intervention mechanism were demonstrated. The findings of this study are expected to provide insights for the development of novel therapeutics for angiogenesis. The detailed workflow of investigation is shown in Figure 1.

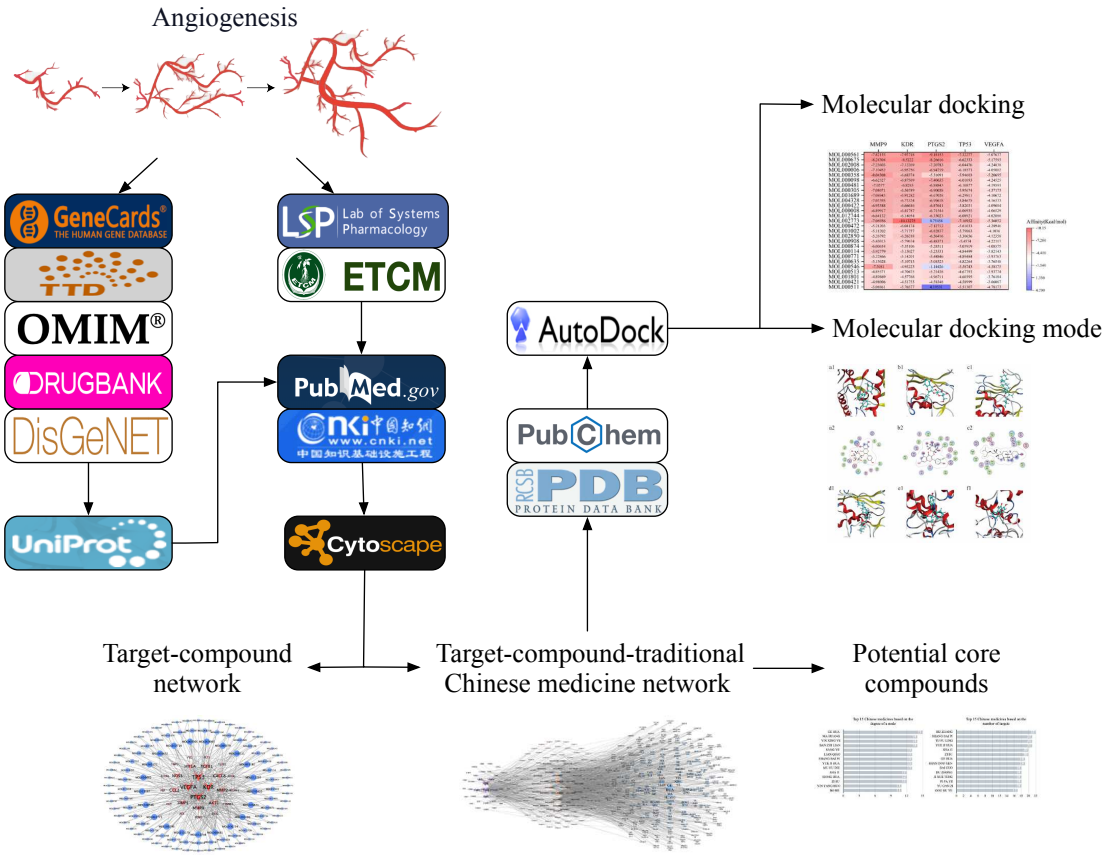


Figure 1. The workflow of the investigation

Methods

Collection of data regarding angiogenesis-related targets

Data were collected from GeneCards (https://www.genecards.org/)[25], Therapeutic Target Database (TTD; http://db.idrblab.net/ttd/)[26], Online Mendelian Inheritance in Man (OMIM, omim.org)[27], DrugBank (www.drugbank.ca)[28], and DisGeNET (www.disgenet.org)[29]. The keyword used to search these databases was 'angiogenesis'. After sorting and removing repeated targets, the full name of the matching targets was established using the UniProt database (https://www.uniprot.org/)[30].

Screening of related herbal compounds

The targets were used to match the compounds related to angiogenesis in the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP; http://tcmspw.com/)[31] and Encyclopedia of Traditional Chinese Medicine (ETCM; http://www.tcmip.cn/ETCM/index.php/Home/Index/)[32]. The compounds and targets were imported to Cytoscape version 3.8.1 (Institute for Systems Biology, Seattle, WA, USA)[33] to construct a 'target-compound' network. After preliminary screening, the related compounds were verified through a literature review, and the compounds closely related to diseases under the current generation research were screened as related compounds.

Collection of related traditional Chinese medicines and construction of a target-compound-traditional Chinese medicine network

By collecting the traditional Chinese medicines related to compounds and constructing the 'compound-traditional Chinese medicine' network combined with the 'compound-target' network, the 'target-compound-traditional Chinese medicine' network was constructed using Cytoscape 3.8.1 to explore and mine the relationships within the network. Key nodes were found by calculating the topological parameters of each node in the network using NetworkAnalyzer to preliminarily evaluate the effectiveness of traditional Chinese medicine and compounds on angiogenesis.

Molecular docking for targets and compounds

To define the reliability of the interaction relationship between the core targets and core components in the 'target-compound-traditional Chinese medicine network' and explore new drug–target combinations, the top five targets with a moderate value for target-compound-traditional Chinese medicine were selected as receptors. The crystal structures of these proteins were selected and preserved in PDB format from Biological Macromolecular Structures Enabling Breakthroughs in Research and Education (RCSB; http://www.rcsb.org/pdb/). The 3D structures of the candidate compounds were downloaded and saved in SDF format from PubChem (https://pubchem.ncbi.nlm.nih.gov/). These SDF files were converted to PDB format using Open Babel. The water molecules in the ligands were removed using AutoDock Tools 1.5.6 (Molecular Graphics Lab, La Jolla, CA, USA). After dispersing the ligands and receptors, non-polar hydrogen bonds were added, and Gasteiger charges were calibrated and stored as pdbqt files. The selected potential core ligands were treated with energy minimisation, and the ligand atom type and calculated charge were saved in the pdbqt format. AutoDock Vina 1.1.2[34] was used to calculate the docking score between the target and ligand to evaluate its matching degree and docking activity. A docking score of less than -4.25 was considered to indicate a binding between the ligand and target, a score of less than -5.0 was considered to indicate better binding activity, and a score of less than -7.0 indicated vigorous docking activity. The ideal combinations were selected according to the affinity value, and the molecular docking pattern was displayed by MOE2019.

Results

Target acquisition

We obtained 4609 targets related to angiogenesis from the GeneCards database and identified the targets with strong correlation by calculating the median of their correlation coefficients, because of the large number of targets. After six calculations, the medians were 0.65, 1.39, 3.25, 4.96, 7.47, and 10.52 and 74 targets with higher correlation coefficients were obtained. Furthermore, 5, 1, 0, and 0 related targets were separately obtained from the TTD, OMIM, DrugBank, and DisGeNET databases, respectively. After removing duplicate values and standardising these using the UniProt database, 79 angiogenesis targets were finally acquired. The TCMSP database contained information on 49 targets. However, eight targets did not match any compound because the database did not have information on related ingredients. Thus, only 41 targets were matched with small-molecule compounds and became potential targets. Table 1 shows the targets with over 10 corresponding compounds.

Table 1 Targets information

Number	Gene	Uniport number	Protein
1	PTGS2	P35354	Prostaglandin G/H synthase 2
2	KDR	P35968	Vascular endothelial growth factor receptor 2
3	VEGFA	P15692	Vascular endothelial growth factor A
4	FGF1	P05230	Acidic fibroblast growth factor
5	TP53	P04637	Cellular tumor antigen p53
6	MMP9	P14780	Matrix metalloproteinase-9
7	AKT1	P31749	RAC-alpha serine/threonine-protein kinase
8	MMP2	P08253	72 kDa type IV collagenase
9	CXCL8	P10145	Interleukin-8
10	FGF2	P09038	Basic fibroblast growth factor

11	HIF1A	Q16665	Hypoxia-inducible factor 1-alpha
12	TGFB1	P01137	Transforming growth factor beta-1
13	CCL2	P13500	C-C motif chemokine 2
14	NOS3	P29474	Nitric oxide synthase, endothelial

Identification of candidate compounds and target-compound network construction

A total of 3839 small-molecule compounds were matched with 41 potential targets to construct a target-compound network consisting of 3440 nodes and 3839 edges. Although many small-molecule compounds showed a match, some of them were less related to the target or were associated with fewer studies. Hence, under the condition of 'Degree >1', the targets and compounds with a greater degree of interaction were screened out, resulting in 28 targets and 264 candidate compounds. These were then screened through a literature review for *in vivo* and *in vitro* activities. Finally, 110 compounds with research significance and 26 related targets were determined; these were used to construct the 'target-compound' network (Figure 2), which contained 136 nodes and 370 edges.

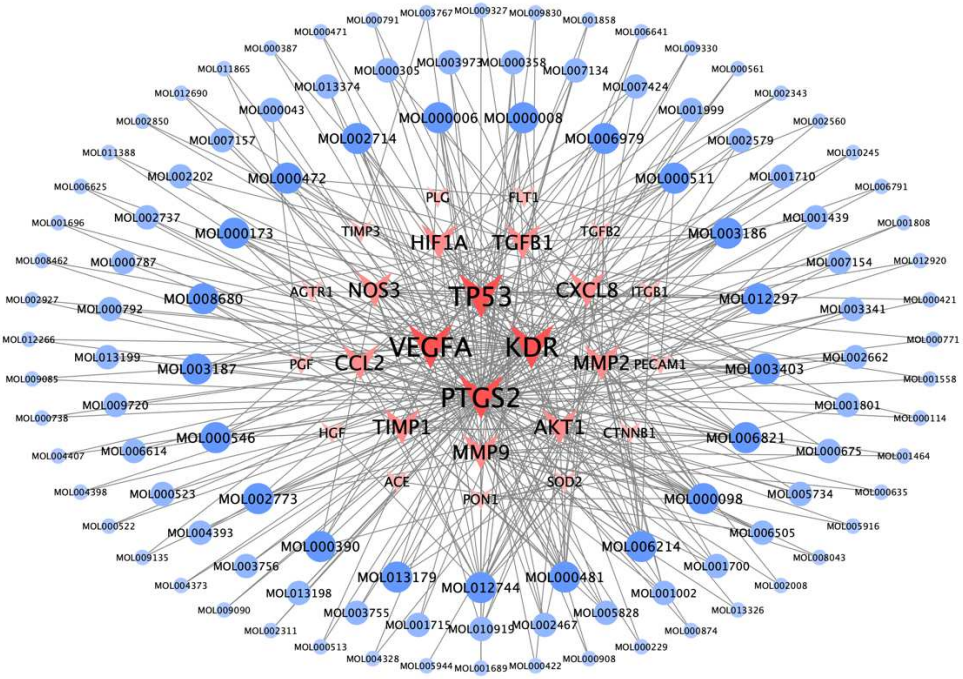


Figure 2. Target-compound network

Identification of traditional Chinese medicines and target-compound-Chinese medicine network construction

A total of 447 Chinese medicines were obtained from 110 candidate compounds through database and literature matching. A compound-Chinese medicine network was first constructed according to the relationship between the compounds and Chinese medicines, and it contained 594 nodes and 2240 edges. Based on the connections of the node, the top nine Chinese medicines were Puerariae Flos, Ephedra Herba, Ginkgo Folium, Scutellariae Barbatae Herba, Mori Follum, Forsythiae Fructus, *Morus alba* Root Bark, Mori Cortex, and Oroxyli Semen, which contain the candidate compounds 15, 14, 14, 14, 13, 13, 13, 13, and 13, respectively. Through the bridging effect of candidate compounds, the targets of various Chinese medicines were obtained. The top six Chinese

medicines were Polygoni Cuspidati Rhizoma et Radix, *Morus alba* Root Bark, Smilacis Glabrae Rhizoma, Mori Cortex, Hippophae Fructus, and Perilla Frutescens, which contain compounds 22, 21, 21, 21, 20, and 20, respectively. Therefore, it can be inferred that these six Chinese medicines have a strong regulatory effect on the development of angiogenesis. Figure 3 shows the top 15 candidate compounds of traditional Chinese medicines based on the number of related targets and the degree of a node in the compound-Chinese medicine network. The median compound degree value of the network was 7 according to a previous study[35]. According to the three conditions of closeness centrality, betweenness centrality, and compound degree value greater than 20, there were 27 potential core compounds, among which the top five ingredients were quercetin, β-sitosterol, kaempferol, luteolin, and ursolic acid. The remaining potential core compounds are shown in Table 2.

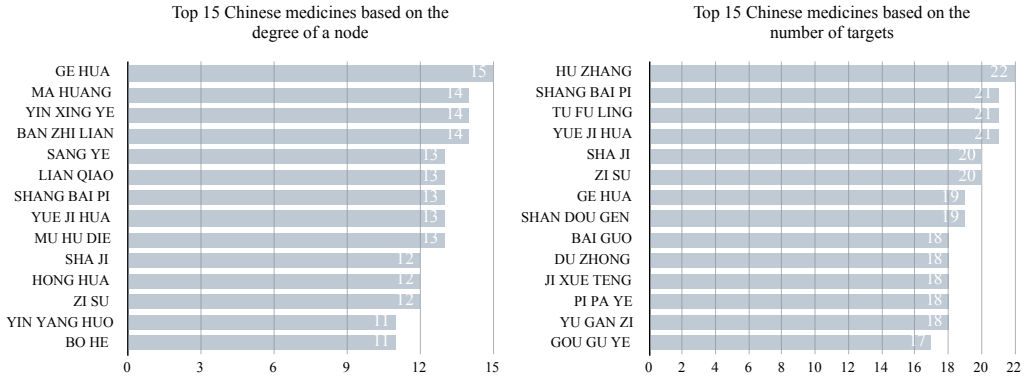


Figure 3. Number of candidate compounds and targets related to the traditional Chinese medicines

Table 2 Candidate compounds and targets information (degree > 20)

MoLID	CAS	MolName	Degree	OB	DL
MOL000098	117-39-5	quercetin	201	46.43	0.28
MOL000358	83-46-5	beta-sitosterol	192	36.91	0.75

MOL000422	520-18-3	kaempferol	136	41.88	0.24
MOL000675	112-80-1	oleic acid	120	33.13	0.14
MOL000006	491-70-3	luteolin	99	36.16	0.25
MOL000511	77-52-1	ursolic acid	88	16.77	0.75
MOL000008	520-36-5	apigenin	87	23.06	0.21
MOL000114	121-34-6	vanillic acid	86	35.47	0.04
MOL000305	143-07-7	lauric acid	69	23.59	0.04
MOL000513	149-91-7	3,4,5-trihydroxybenzoic acid(Gallic acid)	57	31.69	0.04
MOL000908	515-13-9	beta-elemene	51	25.63	0.06
MOL000771	501-98-4	p-coumaric acid	48	43.29	0.04
MOL000635	121-33-5	vanillin	48	52.00	0.03
MOL000561	480-10-4	Astragalin	39	14.03	0.74
MOL000472	518-82-1	emodin	37	24.40	0.24
MOL002850	128-37-0	butylated hydroxytoluene	35	40.0	0.07
MOL002773	7235-40-7	beta-carotene	34	37.18	0.58
MOL001801	69-72-7	salicylic acid	30	32.13	0.03
MOL000874	552-41-0	paeonol	30	28.79	0.04
MOL000481	446-72-0	genistein	26	17.93	0.21
MOL000421	59-67-6	nicotinic acid	25	47.65	0.02
MOL002008	529-44-2	myricetin	25	13.75	0.31
MOL004328	67604-48-2	naringenin	24	59.29	0.21
MOL001689	480-44-4	acacetin	23	34.97	0.24
MOL012744	501-36-0	resveratrol	23	19.07	0.11
MOL001002	476-66-4	ellagic acid	21	43.06	0.43
MOL000546	512-04-9	diosgenin	20	80.88	0.81

199

The target-compound-traditional Chinese medicine network was reconstructed by selecting traditional Chinese medicines with a degree >4 and their associated compounds and targets to display the relationship between angiogenesis-related targets, compounds, and traditional Chinese medicines more intuitively (Figure 4).

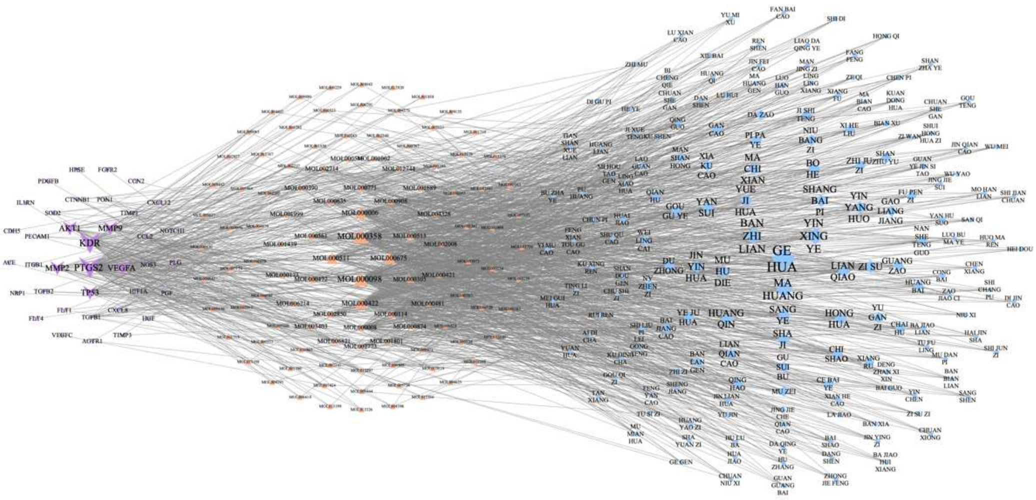


Figure 4.Target-compound-traditional Chinese medicine network. The diamond-shaped nodes represent the Chinese medicine, the triangular nodes represent the ingredients, and the V-shaped nodes represent the target. The icon size of each node is positively correlated with its degree value.

Molecular docking

The 27 core potential compounds were molecularly docked with five core targets, namely matrix metallopeptidase 9 (MMP9), VEGFR2, prostaglandin-endoperoxide synthase 2 (PTGS2), TP53,

and vascular endothelial growth factor A (VEGFA), and 135 sets of receptor-ligand docking results were obtained. Among the 135 receptor-ligand groups, 94 groups (69.63%) showed affinity <-5 and 22 groups (16.30%) showed affinity <-7.

Among the 135 combinations, 55 combinations were present in the target-compound network. Among these 55 combinations, the highest score for docking was observed for PTGS2-Astragalin (-9.18 kcal/mol), and the lowest docking score was observed for PTGS2-ursolic acid (4.20 kcal/mol). The average of the above combinations is -5.56 kcal/mol. This result indicates that the screened potential core compounds may have better binding activity with the core target and supports the reliability of drug–target interactions in the target-compound network to a certain extent.

In the molecular docking result, 80 new combinations outside the target-compound network were discovered. The more ideal combinations outside the target-compound network were KDR-beta-carotene (-10.13 kcal/mol), MMP9-beta-Sitosterol (-8.04 kcal/mol), MMP9-Astragalin (-7.82 kcal/mol), and MMP9-Diosgenin (-7.51 kcal/mol). There were 52 new combinations with affinity <-5 kcal/mol, suggesting that they all have good docking activity. The docking activity of these four combinations exceeded that of most combinations in the target-compound network; therefore, these are more likely to have a strong drug–target relationship. These docking results can provide data for further development of the experimental screening design of related Chinese medicines and ingredients in the future. The results are shown in Figure 5.

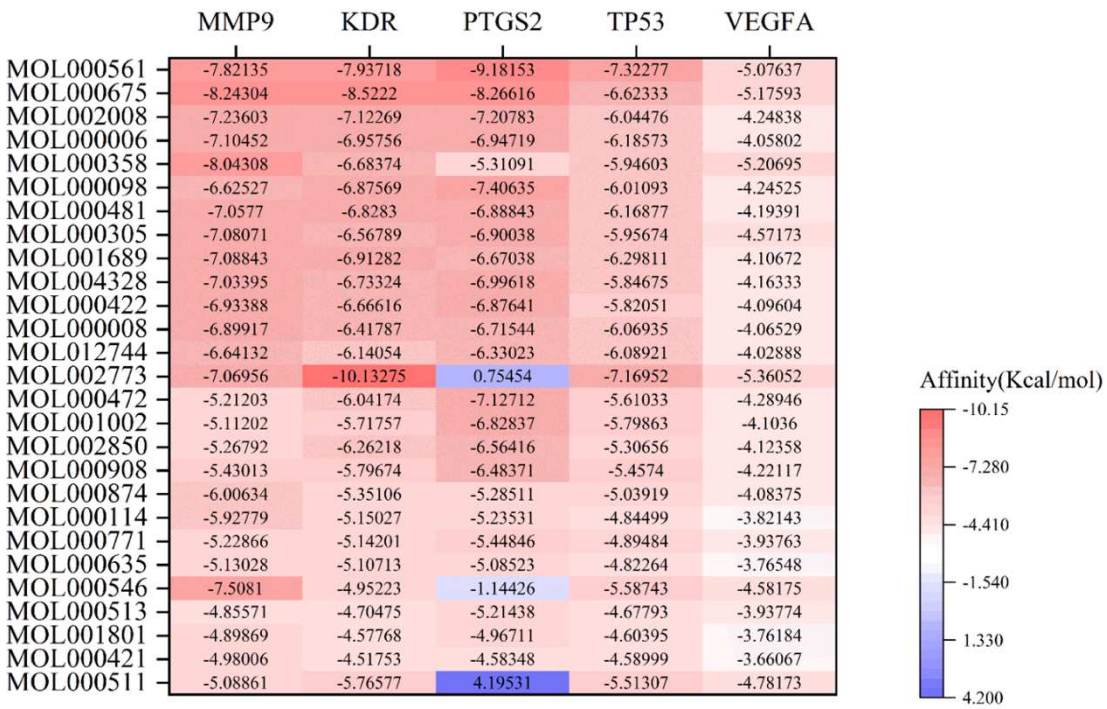
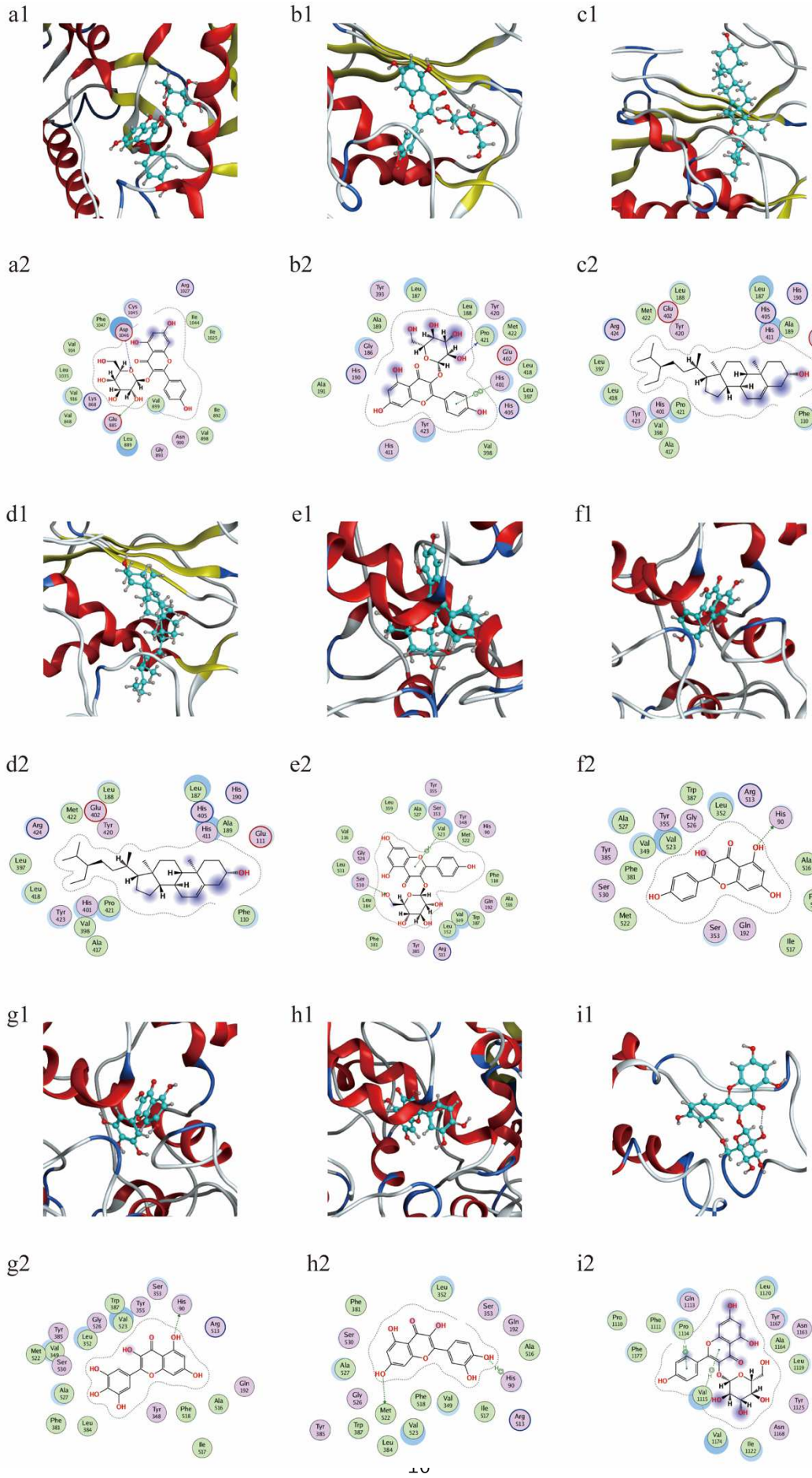


Figure 5. Molecular docking results

Considering the ideal combination of the affinity value of molecular docking and degree value of the target-compound-drug network, nine more ideal combinations were selected, and their docking conditions were displayed in three-dimensional and two-dimensional molecular docking patterns (Figure 6). As shown in Figure 6, each ligand was embedded in the active pocket of the target and interacted with multiple residues of the target through hydrophobic interaction and hydrogen bond formation.


a1
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h2
i2

Figure 6. Molecular docking model. In the 3D structure of ligand–protein complexes, protein scaffolds of the protein skeleton are displayed as tube shape, different peptide chains are coloured differently, and ligands are displayed as a blue bar. The 2D interaction model shows protein residues coloured by its property in a circle; green: hydrophobicity residues; purple: polarity residues. a: KDR-6gqq-Astragalin; b: MMP9-1gkc-Astragalin; c: MMP9-1gkc-beta-Diosgenin; d: MMP9-1gkc-beta-Sitosterol; e: PTGS2-5ikq-Astragalin; f: PTGS2-5ikq-Kaempferol; g: PTGS2-5ikq-Myricetin; h: PTGS2-5ikq-Quercetin; i: tp53-1jsp-Astragalin.

Discussion

Angiogenesis is a complex process that requires the coordinated regulation of several activating and inhibitory pathways. It participates in the development of many diseases, such as cancers, atherosclerosis, rheumatoid arthritis, hepatitis, and inflammation. There are many factors involved in the regulation of angiogenesis. As traditional Chinese medicines, which have a curative effect in clinical treatment, are applied in combination, the treatment contains multiple components and targets. Therefore, elucidating the mechanism and exploring the potential components of traditional Chinese medicines are of great significance in the development of novel drugs.

Target

According to the results of the target-compound network screening, the top scores were obtained for PTGS2, KDR, VEGFA, and MMP9. The primary role of PTGS2 in angiogenesis is to induce

the synthesis of individual prostanoids such as PGD2, PGE2, PGF2a, PGI2, and TXA2. Prostaglandin (PG) can boost VEGF production in a paracrine, intracrine, or autocrine manner. Moreover, VEGF stimulates PTGS2 expression, thereby triggering PG production. This in turn increases the levels of PGs and stimulates the expression of angiogenic factors such as VEGF and bFGF[36]. VEGF expression is regulated by many factors such as epidermal growth factor, hypoxia-inducible factor (HIF), and platelet-derived growth factor (PDGF). During angiogenesis, VEGF signalling regulates the activities of several kinases through VEGFR2 and guides the proliferation, migration, and survival of cells. An increased number of endothelial cells, both tip and stalk cells, is a significant feature of vascular proliferation. Endothelial tip cells are induced by VEGF gradients and promote the formation of filopodia. The molecular regulation of these events occurs via the activation of Notch signalling and increased expression of Notch ligands on endothelial cells. A high level of Notch signalling can decrease VEGFR2 expression. Physiological homeostasis requires this negative feedback loop[37]. One crucial event implicated in the migration and proliferation of vascular endothelial cells is the proteolytic degradation of basement membranes and extracellular matrix (ECM) components by matrix metalloproteinases (MMPs)[38]. The secretion of MMPs allows endothelial cells to penetrate their underlying basement membrane and eliminate the contact inhibition that blocks endothelial cell proliferation[39]. The gene expression of MMPs may stimulate the production and secretion of major proangiogenic factors such as VEGF and fibroblast growth factor-2, which promote angiogenesis[39-41]. MMP-9 cleaves ECM proteins and activates cytokines and chemokines to regulate tissue remodeling[42]. In the intracardiac injection experiment, the injected ECM-derived substance promoted cell attachment, migration, and proliferation; induced extracellular signal-regulated kinase (Erk) 1/2 activation;

and promoted angiogenesis and arteriogenesis[41]. In summary, the above targets play an essential role in the regulation of angiogenesis, and they are the preferred targets for traditional Chinese medicine intervention in angiogenesis.

Ingredients

Molecular docking results showed that the components that bind well to the targets are astragaloside, kaempferol, myricetin, quercetin, and β-sitosterol. Astragalin suppresses interleukin (IL)-1β-induced inflammatory mediators by activating peroxisome proliferator-activated receptor-γ, which subsequently inhibits IL-1β-induced nuclear factor (NF)-κB and MAPK activation[43]. NF-κB subunit p65 activates the transcription of HIF-1α and its target gene VEGF-A. Regulating HIF-1α via NF-κB activation can contribute to angiogenesis[44]. Kaempferol is an antioxidant that reduces reactive oxygen species (ROS) metabolism through its inhibition of the NF-κB pathway and upregulation of the associated transcriptional pathway[45]. ROS regulate angiogenesis via two different mechanisms: the HIF-VEGF/VEGFR2 signalling pathway and VEGF-independent mechanism involving the generation of lipid oxidation products[46]. Endothelial nitric oxide synthase (eNOS) plays an essential role in regulating cell migration activities and vascular permeability[47]. Myricetin and quercetin inhibit thioredoxin reductase (TrxR) in an NADPH- and concentration-dependent manner[48]. TrxR is a part of the thioredoxin (Trx) system, which includes Trx and NADPH[49]. This system plays essential roles in regulating cellular redox signalling and contributes to the regulation of VEGF-mediated signalling[50-52]. For example, TRX1, in endothelial cells, prevents von Hippel-Lindau-mediated degradation of the transcription factor HIF1, leading

312 to the induction of VEGF expression[53]. The action mechanism of myricetin and quercetin in
313 angiogenesis is not yet well understood, but it may be related to the Trx system. β-sitosterol
314 administration was reported to reduce the expression of chemokines and activity of MMP-2 and
315 MMP-9[54]. In summary, the above components of traditional Chinese medicine can be investigated
316 for intervention in angiogenesis.
317
318 **Chinese medicine**
319
320 An experiment using umbilical vein endothelial cells demonstrated that angiogenesis can be
321 regulated by the extract of Polygoni Cuspidati Rhizoma et Radix via the inhibition of the
322 phosphorylation of downstream signalling molecules such as Erk, Akt, and eNOS by
323 VEGF/VEGFR2[55]. These molecules can regulate endothelial cell survival, proliferation, and
324 migration[56, 57]. The extract of *Morus alba* Root Bark inhibits the proliferation and migration of
325 vascular smooth muscle cells induced by PDGF and stimulates the formation of nitric oxide (NO)
326 in endothelial cells[58]. NO is a vital gaseous signalling molecule that participates in the growth and
327 remodelling of essential biochemical and molecular reactions necessary for regulating
328 angiogenesis. The NO-induced activation of soluble guanylate cyclase increases cyclic guanosine
329 monophosphate formation and protein kinase G activity to modulate signalling cascades by the
330 phosphorylation of MAPKs, which successively phosphorylate and activate downstream proteins
331 such as ERK1/2[59, 60]. These events regulate the proliferation and migration of endothelial cells,
332 resulting in angiogenesis. Forsythiae Fructus aqueous extract triggers the inhibition of oxidative
333 stress and inflammation via the MAPKs/Nrf2/HO-1 signalling pathway and inhibits cancer cell

proliferation and angiogenesis[61].

Conclusions

In this study, we used network pharmacology to identify proteins related to angiogenesis through databases and documentation. In addition, we constructed a target-compound-traditional Chinese medicine network, which was explored and analysed for the potential compounds and mechanism of traditional Chinese medicine that participated in angiogenesis. The findings of this study can effectively narrow the scope of screening, improve scientific research efficiency, and reduce economic costs. However, this study was preliminary and based on database analysis; therefore, it does not fully demonstrate the real situation or verify the participation of traditional Chinese medicine in angiogenesis *in vivo*. The specific molecular mechanism still needs to be explored through subsequent experimental research.

List of abbreviations

ECM	Extracellular matrix
ETCM	Encyclopedia of Traditional Chinese Medicine
HIF	Hypoxia-inducible factor
OMIM	Online Mendelian Inheritance in Man
PDGF	Platelet-derived growth factor
ROS	Reactive oxygen species
TTD	Therapeutic Target Database

VEGF	Vascular endothelial cell growth factor

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

WD conceived and designed the study. WY, JL, XG, and ML collected the related targets of angiogenesis and related molecular compounds. WY and WD performed the network pharmacology analysis and molecular docking, and WY wrote the manuscript. WD and QH revised the manuscript. All authors were responsible for reviewing data. All authors read and approved the final manuscript.

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Authors' information

Not applicable.

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Figure Legends

Figure 1. The workflow of the investigation

Figure 2. Target-compound network

Figure 3. Number of candidate compounds and targets related to the traditional Chinese medicines

Figure 4.Target-compound-traditional Chinese medicine network. The diamond-shaped nodes represent the Chinese medicine, the triangular nodes represent the ingredients, and the V-shaped nodes represent the target. The icon size of each node is positively correlated with its degree value.

Figure 5. Molecular docking results

Figure 6. Molecular docking model. In the 3D structure of ligand–protein complexes, protein scaffolds of the protein skeleton are displayed as tube shape, different peptide chains are coloured differently, and ligands are displayed as a blue bar. The 2D interaction model shows protein residues coloured by its property in a circle; green: hydrophobicity residues; purple: polarity residues. a: KDR-6gqq-Astragalin; b: MMP9-1gkc-Astragalin; c: MMP9-1gkc-beta-Diosgenin; d: MMP9-1gkc-beta-Sitosterol; e: PTGS2-5ikq-Astragalin; f: PTGS2-5ikq-Kaempferol; g: PTGS2-5ikq-Myricetin; h: PTGS2-5ikq-Quercetin; i: tp53-1jsp-Astragalin.

Figures

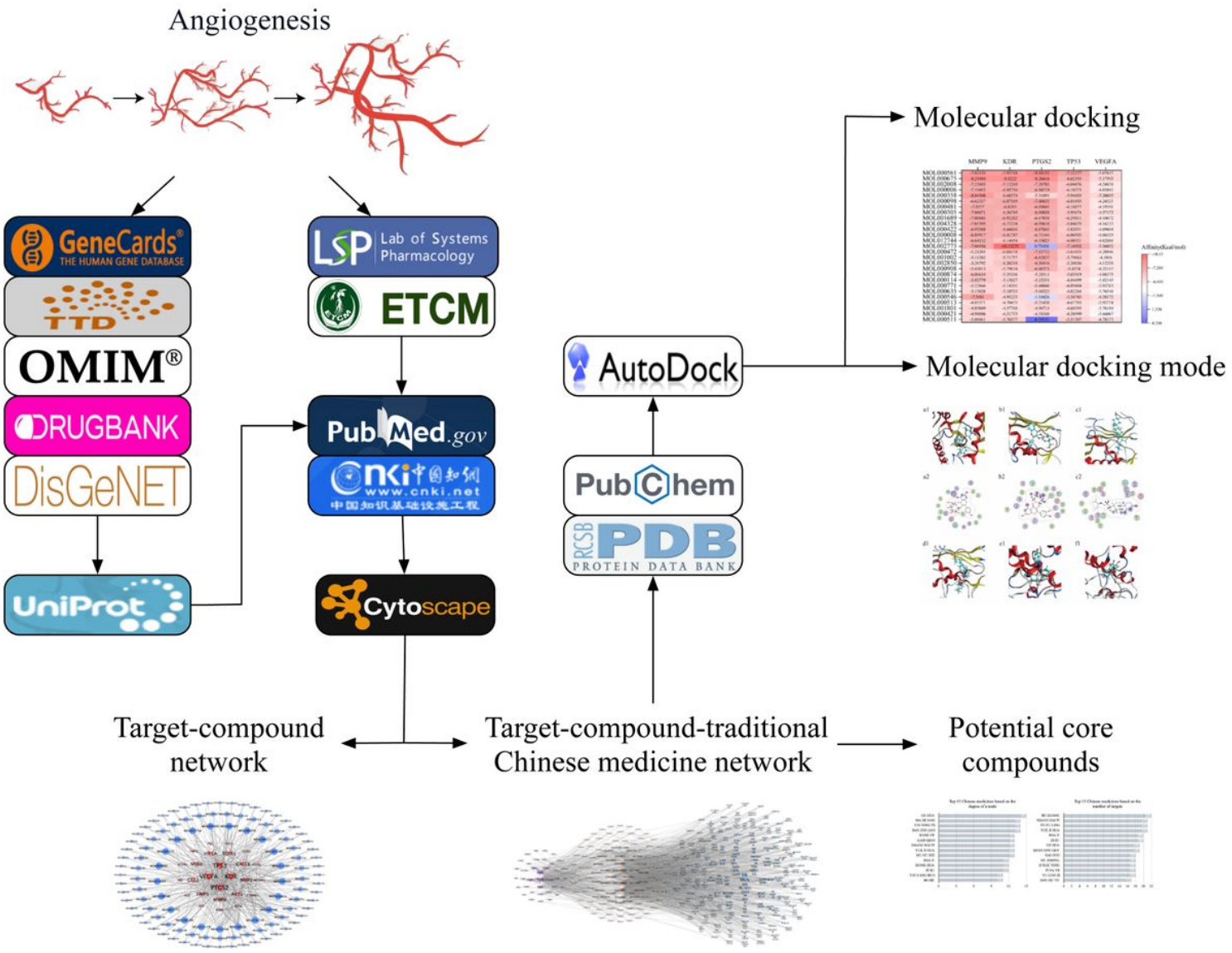
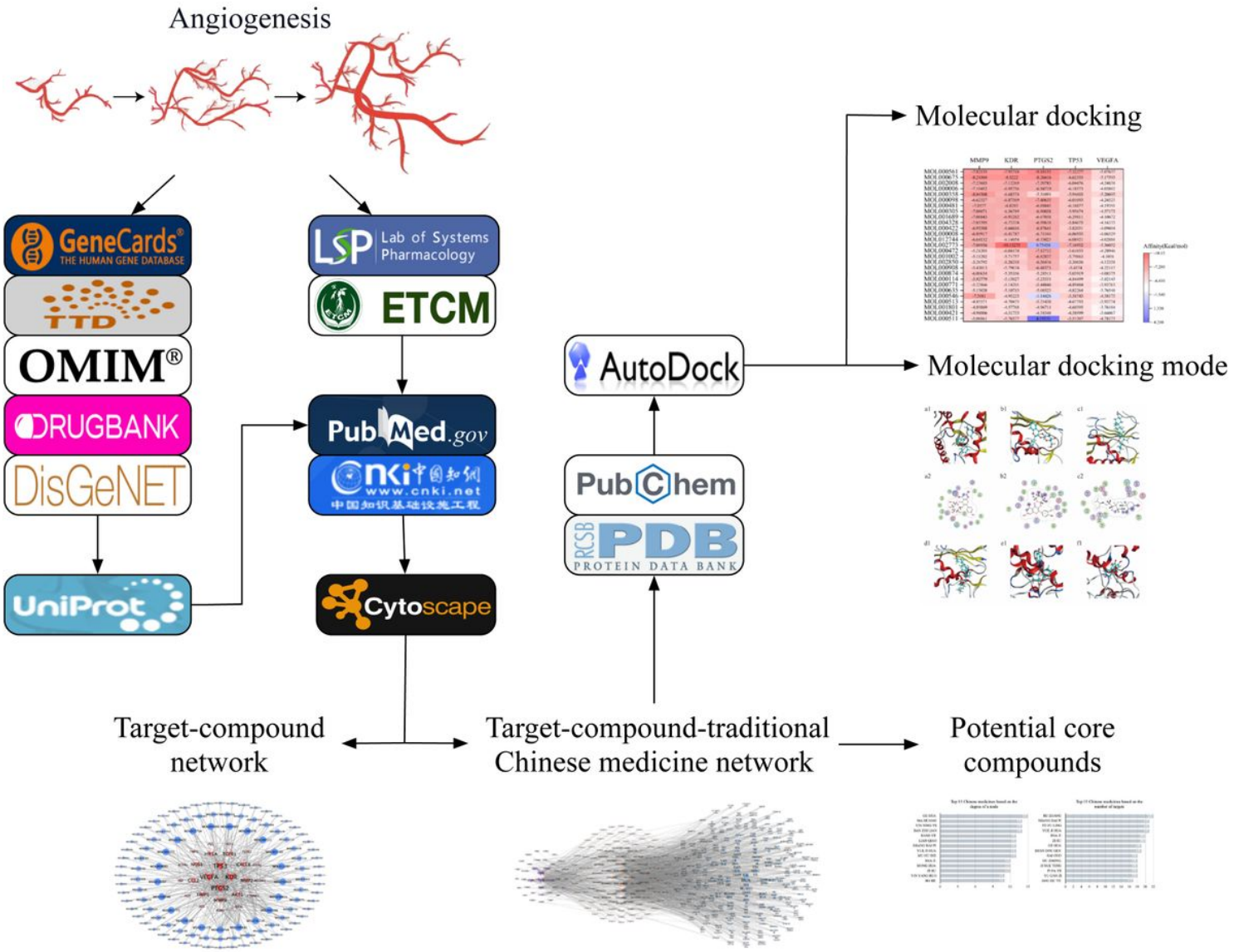


Figure 1

The workflow of the investigation



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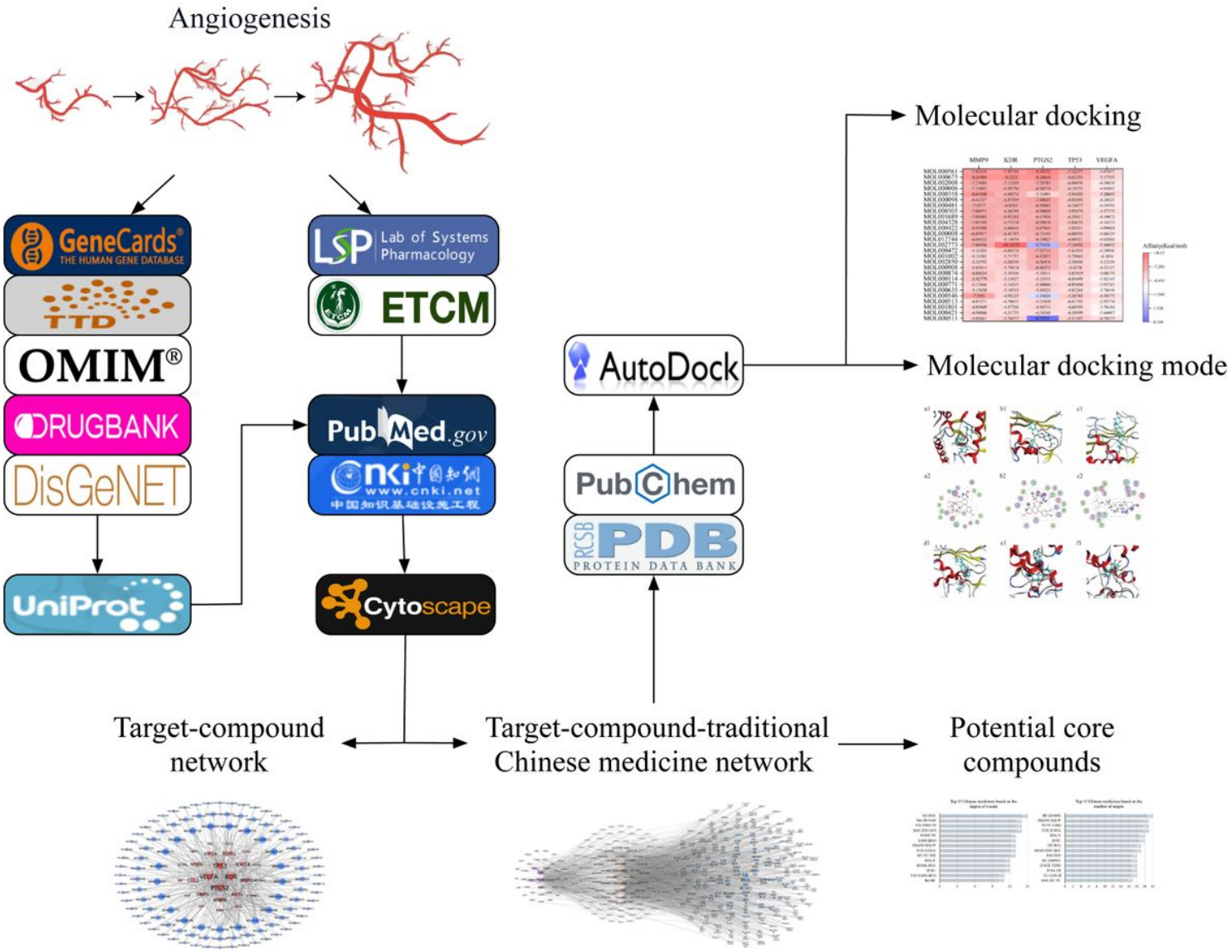

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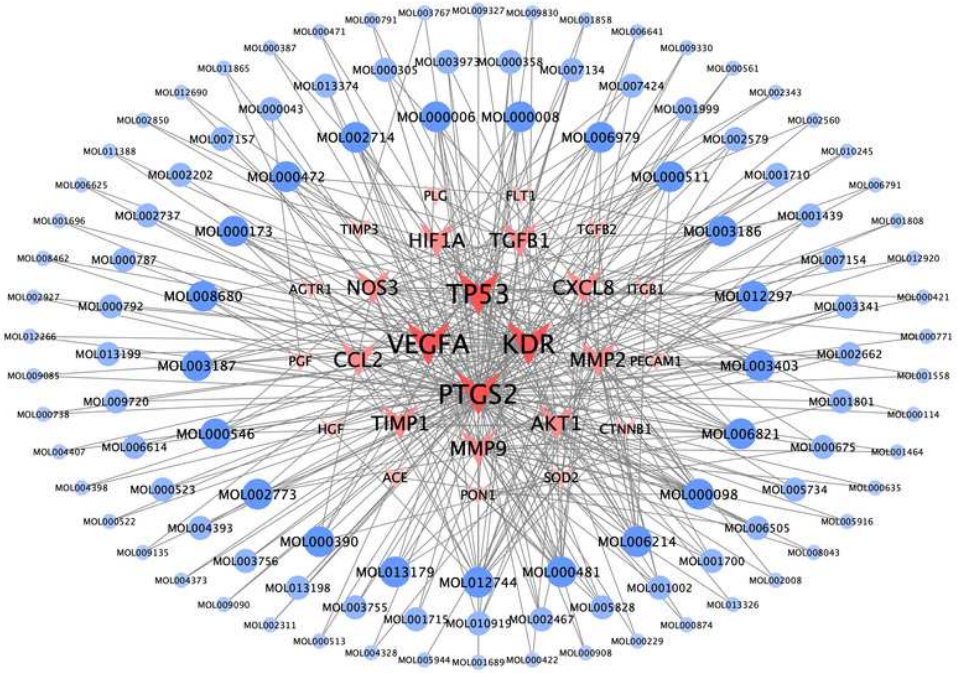

Figure 2

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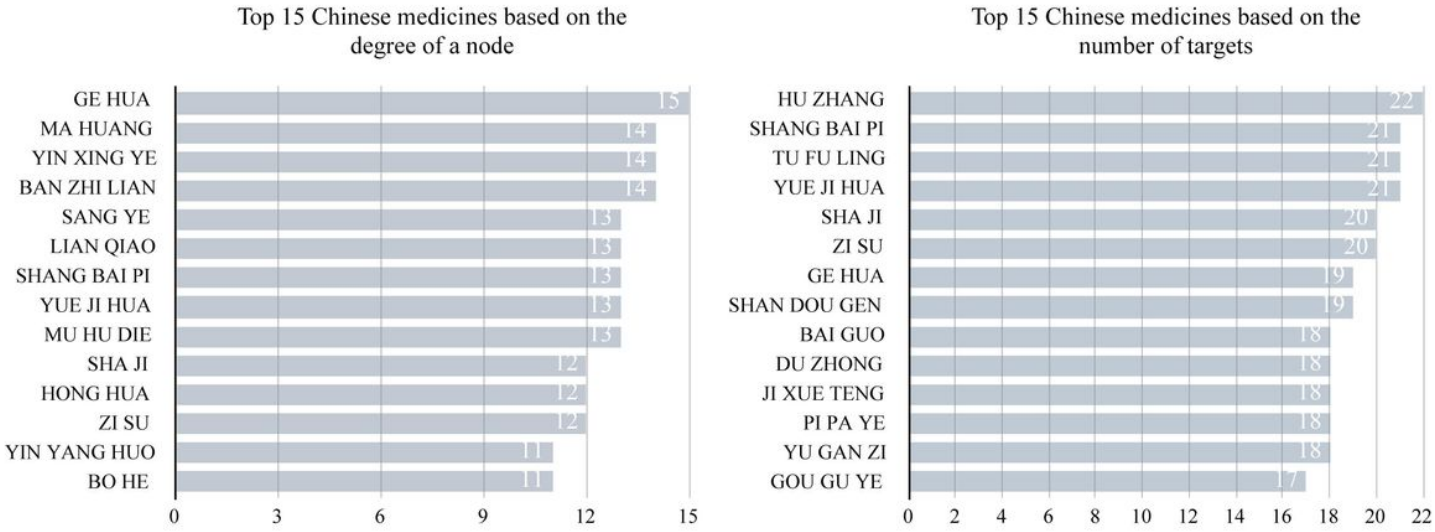

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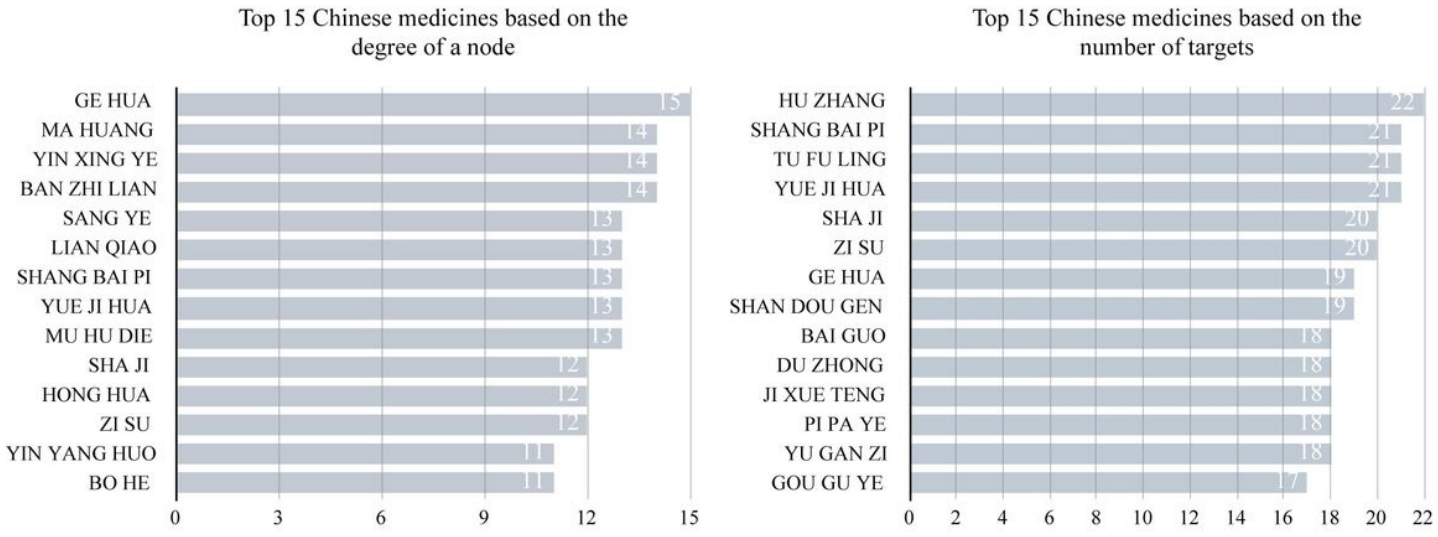
Number of candidate compounds and targets related to the traditional Chinese medicines



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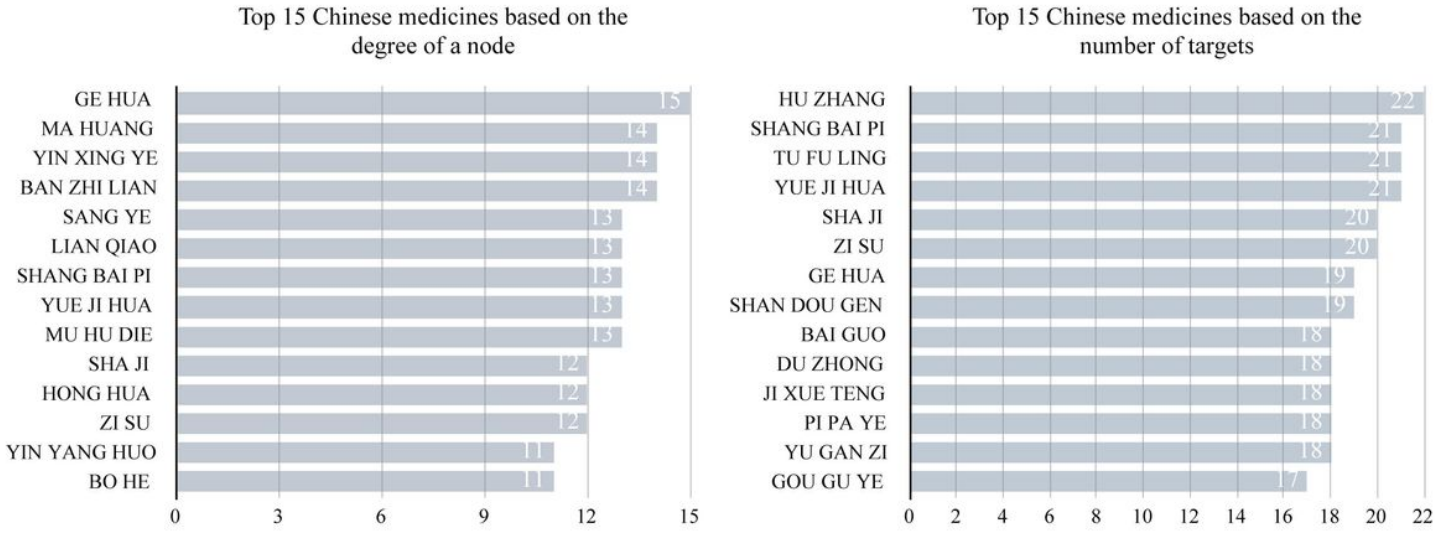

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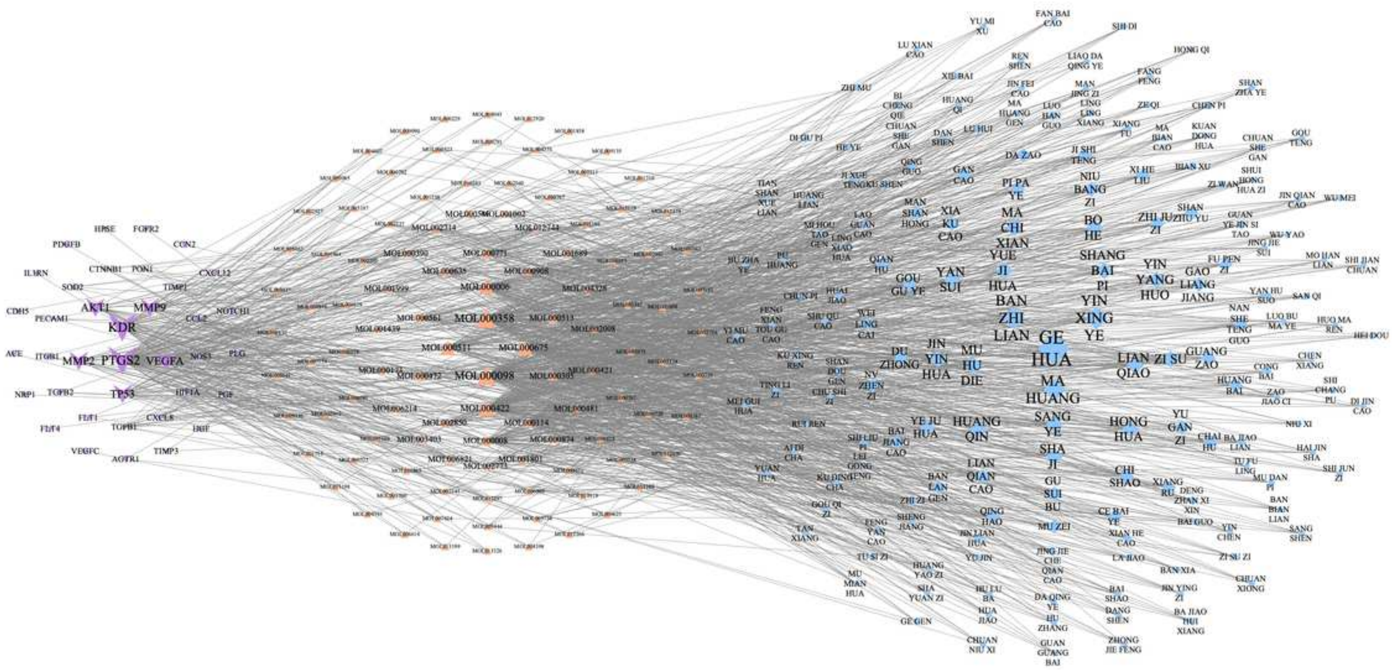

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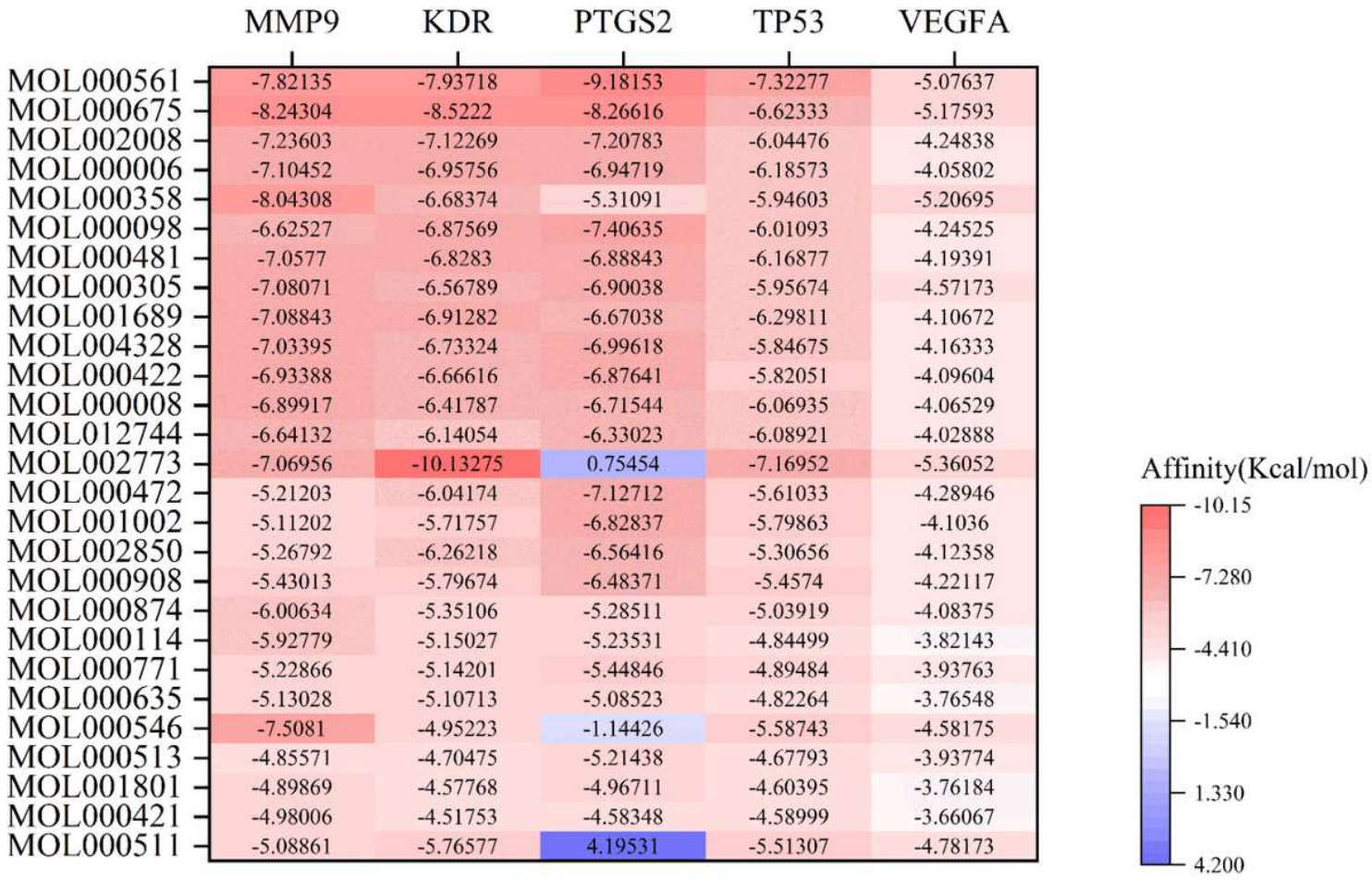
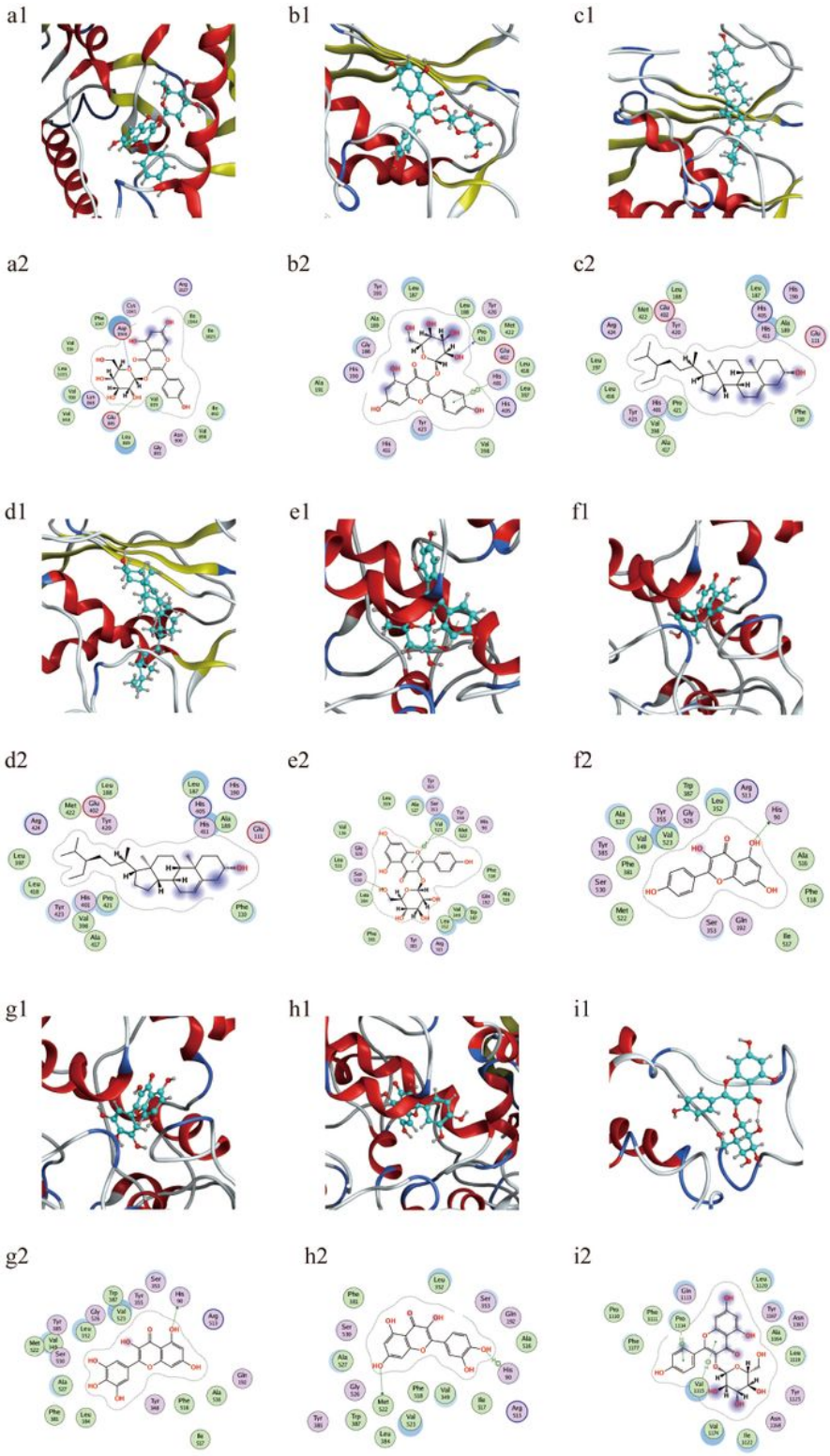


Figure 5

Molecular docking results



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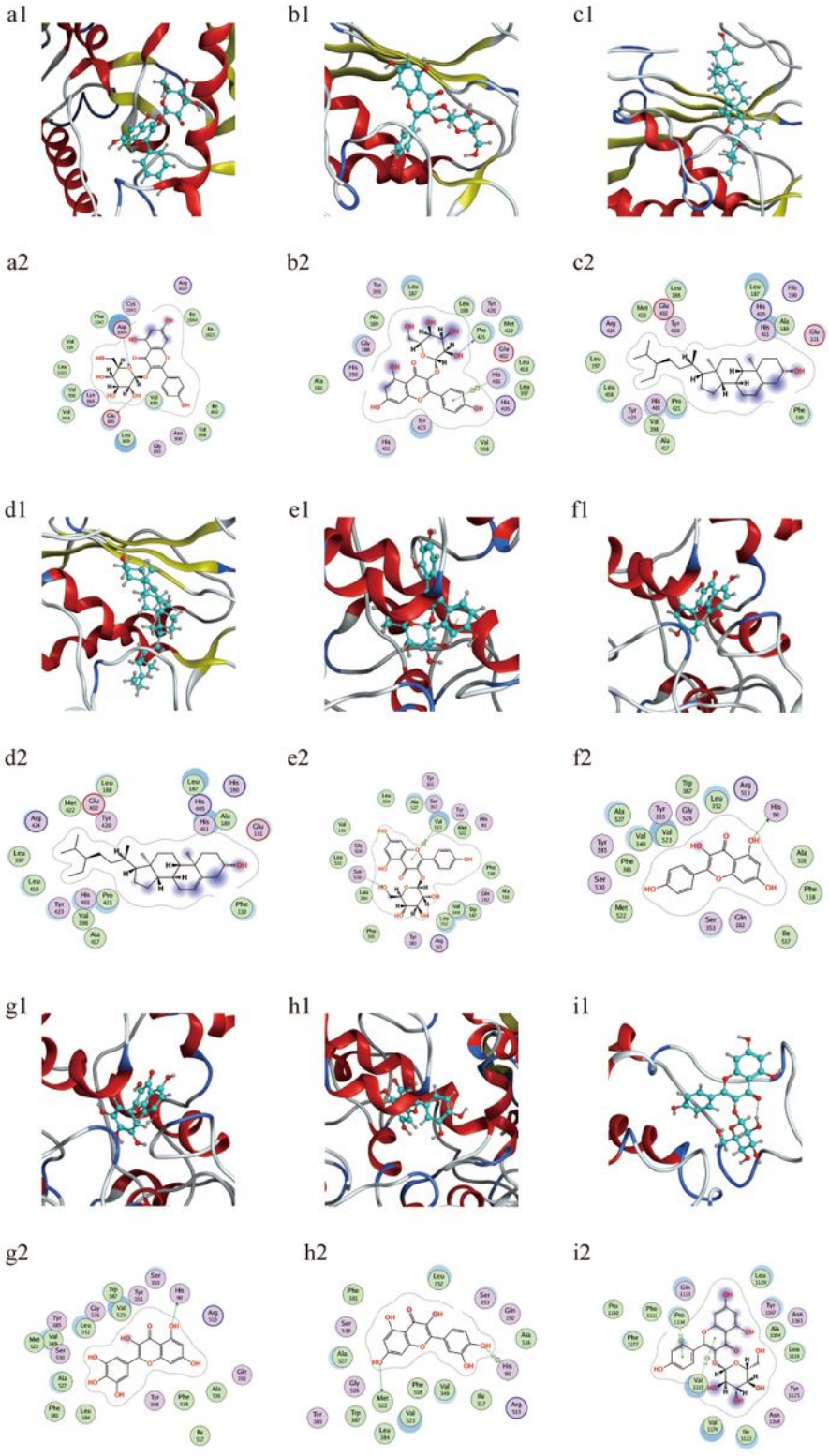

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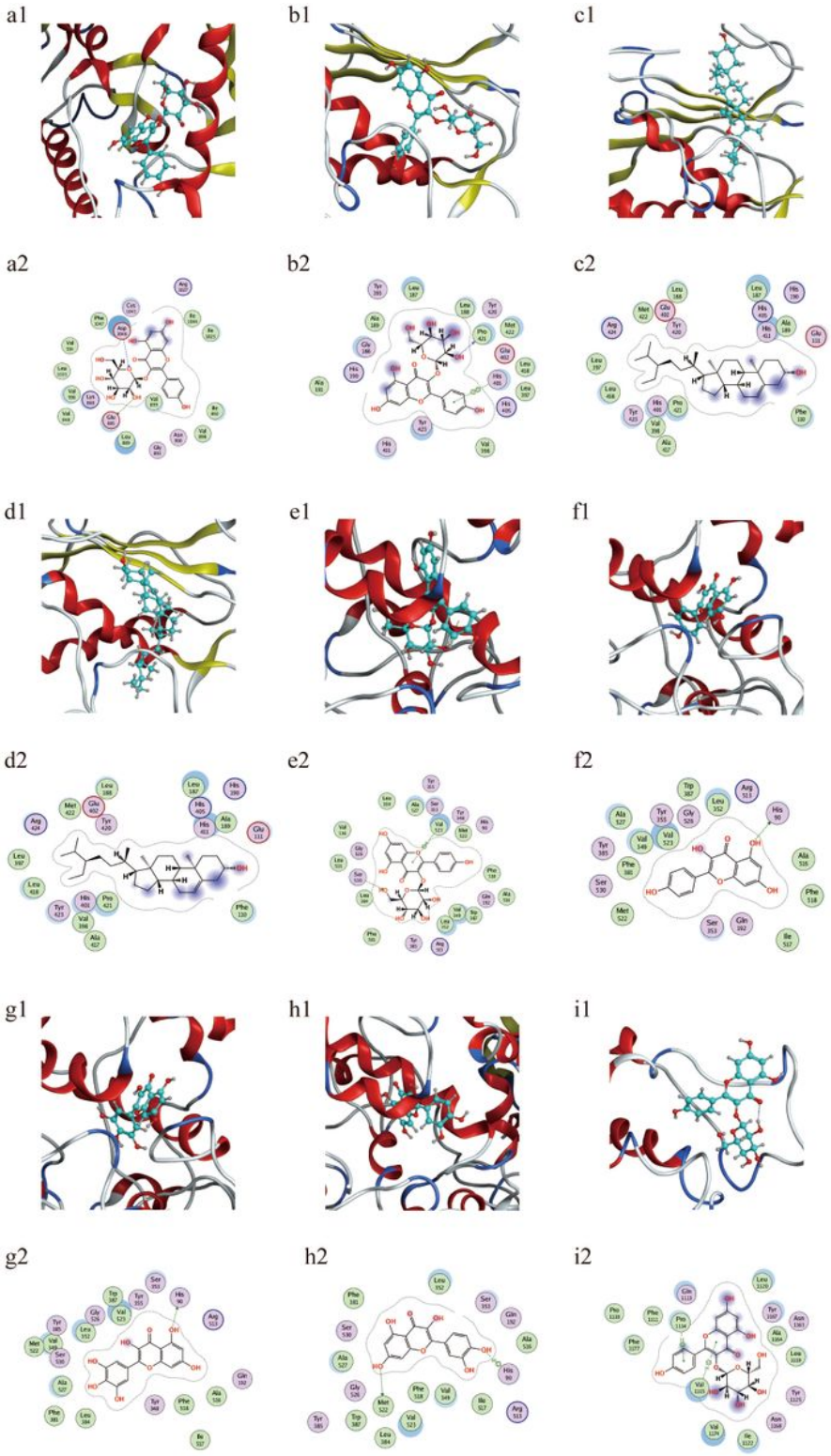

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