Potential Mechanisms of Yanghe Decoction in the Treatment of Soft Tissue Sarcoma and Arteriosclerosis Obliterans Based on Network Pharmacology

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Abstract

Objective The objective of this study was to investigate potential mechanisms of Yanghe Decoction (YHD) in treating soft tissue sarcoma (STS) and arteriosclerosis obliterans (ASO) based on the use of network pharmacology.

Methods Candidate compounds and potential targets were identified through the TCM Systems Pharmacology database and a comprehensive literature search. Related targets of STS and ASO were collected in the GeneCards database, DisGeNET database, and Drugbank database. Furthermore, The STRING 11.0 database was used to determine protein–protein interaction (PPI) networks; common targets were obtained and imported into Cytoscape 3.7.2. Then, a PPI network comprising common targets was drawn, and network topology analysis was performed to screen for key shared targets. Gene ontology functional enrichment analysis and Kyoto Encyclopedia of Genes and Genomes pathway enrichment analysis of key shared targets were performed by using Metascape software. Subsequently, a compound–target–pathway network was constructed via Cytoscape 3.7.2.

Results The following signaling pathways were found to be associated with the mechanisms of YHD in treating STS and ASO: AGE-RAGE signaling pathway, IL-17 signaling pathway; HIF-1 signaling pathway, TNF signaling pathway, interactions between cytokines and cytokine receptors, Th17 cell differentiation, and NOD-like receptor signaling pathway. Among the compounds and targets involved in these pathways, quercetin, luteolin, and kaempferol were found to be core compounds, and TNF, IL-6, and MAPK1 were found to be core targets.

Conclusion Taken together, our findings elucidated that potential mechanisms of YHD in treating STS and ASO involved cellular proliferation/differentiation, angiogenesis, inflammation, immune responses, oxidative stress, and other related signaling pathways.

Keywords
- soft tissue sarcoma
- arteriosclerosis obliterans
- network pharmacology
- Traditional Chinese medicine
- Yanghe Decoction

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Introduction

Soft tissue sarcoma (STS) is a malignant solid tumor derived from fat, fascia, muscle, fibers, lymph, and blood vessels. The incidence rate of STS in China is approximately 2.38/100,000 individuals per year, and this rate continues to increase.[1] Arteriosclerosis obliterans (ASO) involves chronic occlusion of peripheral arteries caused by long-term atherosclerosis, which mostly occurs in the lower extremities. The prevalence of ASO in the elderly is particularly high. Due to the increase in the proportion of the aging population in China, the incidence of ASO is also increasing each year, and it has become an urgent public health and medical problem in China.[2]

Traditional Chinese medicine (TCM) posits that STS belongs to the categories of "sarcoma" and "stone gangrene." The occurrence of STS is related to a lack of vital qi and attack by cold pathogen, which leads to qi stagnation, blood stasis, and phlegm resistance. Yanghe Decoction (YHD), used as a treatment in STS patients, has been shown to significantly improve clinical symptoms and extend survival time.[3,4] ASO belongs to the category of "necrosis" in TCM and is mostly the result of yang deficiency in spleen and kidney, with coldness and wetness as external manifestations, which leads to qi and blood stagnation, and obstruction of channels. YHD has the function of warming yang and tonifying blood, dispersing cold and dredging stagnation. Therefore, it is commonly used in the treatment of ASO.[5,6]

Although the above findings suggest that YHD may be efficacious in treating both STS and ASO, its underlying mechanisms in this therapeutic process remain unknown. Unfortunately, traditional pharmacological research methods alone are not sufficient to fully elucidate the mechanisms of action of YHD. In contrast, network pharmacology is a powerful tool for investigating the mechanisms of action of TCM compounds. In particular, network pharmacology assesses multilevel relationships of compounds, targets, and pathways to provide insights into the mechanisms of action of TCM compounds.[7,8] In the present study, we have used network pharmacology to investigate the mechanisms of action of YHD in treating both STS and ASO, which may provide useful findings for further experimental research and clinical applications.

Materials and Methods

Screening of Chemical Components of YHD

We used the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) database and analysis platform[9] and an extensive literature search to identify candidate compounds and targets of the following six key components in YHD: Shudihuang (Rehmannia glutinosa, SD), Rougui (Cinnamomum cassia Presl, RG), Mahuang (Ephedra sinica Stapf, MH), Jiezi (Semen sinapis, JZ), Sheng jiang (Zingiber officinale Rosc, SJ), and Gancao (Glycyrrhiza uralensis Fisch, GC). Lujiao Jiao (Colla Corni Cervi) was excluded since it was not suitable for our present pharmacological study. According to the absorption, distribution, metabolism, and excretion parameters in the TCMSP database, Chinese medicinal compounds with oral bioavailability $\geq$30% and with a drug-like-index (DL) $\geq$0.18 were selected as candidate compounds.

Collection and Treatment of Targets in YHD

We obtained potential targets of the candidate compounds through the TCMSP database, uploaded them into the UniProt database (https://www.uniprot.org/), limited the species to "human," and obtained the genetic information corresponding to each protein target. Then, we imported these data into Cytoscape 3.7.2 to build a compound–target–pathway network diagram.

Acquisition of Common Targets of YHD in the Treatment of STS and ASO

We used "soft tissue sarcoma" and "arteriosclerosis obliterans" as search terms in the GeneCards database (https://www. genecards.org), DisGeNET database (https://www.disgenet.org/), and Drugbank database (https: //www.drugbank.ca) to collect disease targets related to STS and ASO. If there were too many disease targets in the database, we defined targets with scores greater than the median score as potential targets. Then, we merged potential targets obtained from each database and removed any duplicates. Subsequently, we determined cross targets, and the cross targets were displayed via a Venn diagram through OmicShare (https://omicshare.com/index.php).

Screening of Key Shared Targets

We entered the obtained common targets into the STRING 11.0 database (https://string-db.org/). The organism category was set to Homo sapiens. We obtained protein–protein interaction networks of the common targets via a combined score $>$0.4 as the screening criterion. Then, we imported the screened information into Cytoscape 3.7.2 to plot the protein–protein interaction network between the common targets and performed network topology analysis. Key shared targets were selected according to values greater than the median.

GO Function Enrichment and KEGG Signal Pathway Enrichment Analysis

We uploaded the key common targets to Metascape (https://metascape.org/) and set the parameter to H species to obtain the gene ontology (GO) function enrichment analysis results and Kyoto Encyclopedia of Genes and Genomes (KEGG) signal pathway enrichment analysis results. GO functional enrichment analysis includes biological process (BP), cell composition (CC), and molecular function (MF). According to the value of log (10)p, we used the bioinformatics online mapping tool to visualize various top-ranked GO items and filtered out the top 20 signaling pathways according to theirs. OmicShare was used to visualize the results of enrichment analysis of the top 20 KEGG pathways. Finally, we imported these data into Cytoscape 3.7.2 to construct a compound–target–pathway interaction network.

Results

Screening of Chemical Components of YHD

We identified a total of 76 chemical constituents of SD, 103 chemical constituents of RG, 363 chemical constituents of MH, 37 chemical constituents of JZ, 265 chemical constituents of SJ, and 280 chemical constituents of GC. A total of 129 candidate chemical constituents were obtained after screening, including two chemical constituents of SD, three chemical constituents of RG, 23 chemical constituents of MH, three chemical constituents of JZ, five chemical constituents of SJ, and 92 chemical constituents of GC. After deleting duplicates, a total of 118 chemical components were obtained (►**Table 1**).

Collection and Treatment of Targets in YHD

We obtained 28 targets of SD, 153 targets of RG, 209 targets of MH, 17 targets of JZ, 49 targets of SJ, and 213 targets of GC. After deleting duplicates, a total of 233 drug targets were obtained, which were imported into Cytoscape 3.7.2 to construct a drug–compound–target interaction network (►**Fig. 1**).

Acquisition of Common YHD Targets in the Treatment of STS and ASO

We obtained 1,615 STS disease targets and 223 ASO disease targets. The above two groups of disease targets were intersected with 233 compound targets in YHD (►**Fig. 2**), which yielded a total of 43 common targets, as follows: MMP2, PLAU, NOS2, UGT1A1, GJA1, CRP, CXCL8, SELE, THBD, TNF, IL1A, LDLR, MPO, STAT3, SLPI, CTSD, VEGFA, TGF-1β, CCL2, MMP1, STAT1, IL-6, GSR, HMOX1, MMP3, IL-10, MAPK1, PLAT, SOD1, IL-2, IFNG, IL-4, ICAM1, HIF1A, NOS3, CXCL10, SERPINE1, VCAM1, IL-1β, PTGS1, F3, CYP3A4, and MMP9.

Screening and Analysis of Key Shared Targets

The interaction network between common target proteins is shown in ►**Fig. 3**. Through network topology analysis, 20 key common targets were screened out. The specific key common targets were as follows: TNF, IL-6, IL-1β, VEGFA, MMP9, CCL2, IL-10, CXCL8, VCAM1, ICAM1, MMP2, SERPINE1, MPO, IL-4, MAPK1, NOS3, CRP, HMOX1, STAT3, and IFNG.

GO and KEGG Analyses

A total of 745 BPs were obtained and were mainly related to cell migration, cell apoptosis, cytokine metabolism, and cell response to biological stimuli. A total of 12 CCs were obtained and involved membrane rafts, membrane microdomains, membrane domains, and the extracellular matrix. A total of 14 MFs were obtained and involved cytokine activity, receptor ligand activity, growth factor activity, and chemokine receptor binding. The top-ranked items included cytokine-mediated signaling pathways, positive regulation of cell migration, positive regulation of cell motility, positive regulation of cellular-component movement, positive regulation of locomotion, and other matters (►**Fig. 4**). KEGG pathway enrichment analysis yielded 65 signaling pathways, among which the top 20 pathways included the AGE-RAGE signaling pathway (related to diabetic complications), IL-17 signaling pathway, and HIF-1 signaling pathway and other matters (►**Table 2**). The results of KEGG pathway enrichment analysis of the top 20 KEGG pathways were visualized using OmicShare (►**Fig. 5**) and were then imported into Cytoscape 3.7.2 to build a compound–target–pathways interaction network (►**Fig. 6**).

Discussion

YHD is derived from the *Waike Zhengzhi Quansheng Ji*.[10] SD can nourish yin and blood. RG and SJ can warm the yang and dissolve the cold. MH can open the sweat pores of the skin and release pathogens. JZ can dredge collaterals and resolve phlegm. GC can nourish qi and detoxify and harmonize medicines. STS is a type of malignant solid tumor. The formation of STS is due to an imbalance of yin and yang. Yang deficiency leads to cold coagulation, phlegm obstruction, blood stasis, and eventually leads to tumors. Cold dampness pathogen is the superficial reason of ASO, while yang deficiency of spleen and kidney is the root cause. Most of the patients are middle aged and elderly people, who often have the syndromes of deficiency, blood stasis, and phlegm. It can be seen that the above two diseases have yang deficiency, phlegm dampness, and blood stasis in varying degrees. YHD can warm yang to regenerate qi and blood and remove cold to dredge collaterals and disperse accumulation. Therefore, it theoretically explains the reason why YHD can treat STS and ASO.

In the present study, we used network pharmacology to identify signaling pathways involved in the effects of YHD in treating STS and ASO, which included the following: the AGE-RAGE signaling pathway, IL-17 signaling pathway, HIF-1 signaling pathway, TNF signaling pathway, interactions of cytokines and cytokine receptors, Th17 cell differentiation, and NOD-like receptor pathway. The topological properties were analyzed based on the degree values and corresponding intermediary values in the two networks of drug–compound–targets and compound–target–pathways. The most important compounds were determined to be quercetin, luteolin, and kaempferol. Additionally, the most critical targets were found to be TNF, IL-6, and MAPK1. To corroborate these findings, we performed an extensive literature search and further explored the mechanisms of YHD in the treatment of STS and ASO.

Quercetin[11] and luteolin[12] exhibit proteasome inhibitory activity and have significant effects in overcoming multidrug resistances of various tumors such as sarcomas. Quercetin[12] and kaempferol[13] can inhibit tumor invasion and metastasis by inhibiting the activity of MMP-9 in human fibrosarcoma HT1080 cells. Quercetin can induce apoptosis of human liposarcoma SW 872 cells by down-regulating Bcl-2, cleaving PARP, and activating caspase-3, Bax, and Bak.[14] Luteolin can down-regulate β-catenin expression, inhibit Wnt signaling, and reduce the formation of fibromatosis, sarcoma, and

Table 1 Basic information of 118 candidate compounds of YHD

Drud	Mol ID	Molecule Name	OB (%)	DL
SD	MOL000359	Sitosterol	36.91	0.75
	MOL000449	Stigmasterol	43.83	0.76
RG	MOL000004	procyanidin B1	67.87	0.66
	MOL000422	Kaempferol	41.88	0.24
	MOL000098	Quercetin	46.43	0.28
MH	MOL010788	Leucopelargonidin	57.97	0.24
	MOL002823	Herbacetin	36.07	0.27
	MOL010489	Resivit	30.84	0.27
	MOL004798	Delphinidin	40.63	0.28
	MOL000006	Luteolin	36.16	0.25
	MOL000492	(+)-catechin	54.83	0.24
	MOL001494	Mandenol	42	0.19
	MOL001506	Supraene	33.55	0.42
	MOL001755	24-Ethylcholest-4-en-3-one	36.08	0.76
	MOL002881	Diosmetin	31.14	0.27
	MOL004328	Naringenin	59.29	0.21
	MOL004576	Taxifolin	57.84	0.27
	MOL005043	Campest-5-en-3β-ol	37.58	0.71
	MOL005190	Eriodictyol	71.79	0.24
	MOL005573	Genkwanin	37.13	0.24
	MOL005842	Pectolinarigenin	41.17	0.3
	MOL007214	(+)-Leucocyanidin	37.61	0.27
	MOL011319	Truflex OBP	43.74	0.24
JZ	MOL010690	Uniflex BYO	30.13	0.25
	MOL013037	2-(2-phenylethyl)-6-[[(5S,6R,7R,8S)-5,6,7-trihydroxy-4-keto-2-(2-phenylethyl)-5,6,7,8-tetrahydrochromen-8-yl]oxy]chromone	31.31	0.61
	MOL001697	Sinoacutine	63.39	0.53
SJ	MOL000358	β-sitosterol	36.91	0.75
	MOL006129	6-methylgingediacetate2	48.73	0.32
	MOL001771	Poriferast-5-en-3β-ol	36.91	0.75
	MOL008698	Dihydrocapsaicin	47.07	0.19
GC	MOL001484	Inermine	75.18	0.54
	MOL001792	DFV	32.76	0.18
	MOL000211	Mairin	55.38	0.78
	MOL002311	Glycyrol	90.78	0.67
	MOL000239	Jaranol	50.83	0.29
	MOL002565	Medicarpin	49.22	0.34
	MOL000354	Isorhamnetin	49.6	0.31
	MOL003656	Lupiwighteone	51.64	0.37
	MOL003896	7-Methoxy-2-methyl isoflavone	42.56	0.2
	MOL000392	Formononetin	69.67	0.21
	MOL000417	Calycosin	47.75	0.24
	MOL004805	(2S)-2-[4-hydroxy-3-(3-methylbut-2-enyl) phenyl]-8,8-dimethyl-2,3-dihydropyrano [2,3-f]chromen -4-one	31.79	0.72

Table 1 (*Continued*)

Drud	Mol ID	Molecule Name	OB (%)	DL
	MOL004806	Euchrenone	30.29	0.57
	MOL004808	Glyasperin B	65.22	0.44
	MOL004810	Glyasperin F	75.84	0.54
	MOL004811	Glyasperin C	45.56	0.4
	MOL004814	Isotrifoliol	31.94	0.42
	MOL004815	(E)-1-(2,4-dihydroxyphenyl)-3-(2,2-dimethylchromen-6-yl) prop-2-en-1-one	39.62	0.35
	MOL004820	Kanzonols W	50.48	0.52
	MOL004824	(2S)-6-(2,4-dihydroxyphenyl)-2-(2-hydroxypropan-2-yl)-4-methoxy-2,3-dihydrofuro[3,2-g]chromen-7-one	60.25	0.63
	MOL004827	Semilicoisoflavone B	48.78	0.55
	MOL004828	Glepidotin A	44.72	0.35
	MOL004829	Glepidotin B	64.46	0.34
	MOL004833	Phaseolinisoflavan	32.01	0.45
	MOL004835	Glypallichalcone	61.6	0.19
	MOL004838	8-(6-hydroxy-2-benzofuranyl)-2,2-dimethyl-5-chromenol	58.44	0.38
	MOL004841	Licochalcone B	76.76	0.19
	MOL004848	Licochalcone G	49.25	0.32
	MOL004849	3-(2,4-dihydroxyphenyl)-8-(1,1-dimethylprop-2-enyl)-7-hydroxy-5-methoxy-coumarin	59.62	0.43
	MOL004855	Licoricone	63.58	0.47
	MOL004856	Gancaonin A	51.08	0.4
	MOL004857	Gancaonin B	48.79	0.45
	MOL004860	Glycyrrhiza uralensis Fisch glycoside E	32.89	0.27
	MOL004863	3-(3,4-dihydroxyphenyl)-5,7-dihydroxy-8-(3-methylbut-2-enyl) chromone	66.37	0.41
	MOL004864	5,7-dihydroxy-3-(4-methoxyphenyl)-8-(3-methylbut-2-enyl) chromone	30.49	0.41
	MOL004866	2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-6-(3-methylbut-2-enyl) chromone	44.15	0.41
	MOL004879	Glycyrin	52.61	0.47
	MOL004882	Licocoumarone	33.21	0.36
	MOL004883	Licoisoflavone	41.61	0.42
	MOL004884	Licoisoflavone B	38.93	0.55
	MOL004885	Licoisoflavanone	52.47	0.54
	MOL004891	Shinpterocarpin	80.3	0.73
	MOL004898	(E)-3-[3,4-dihydroxy-5-(3-methylbut-2-enyl)phenyl]-1-(2,4-dihydroxyphenyl)prop-2-en-1-one	46.27	0.31
	MOL004903	Liquiritin	65.69	0.74
	MOL004904	Licopyranocoumarin	80.36	0.65
	MOL004905	3,22-Dihydroxy-11-oxo-delta(12)-oleanene-27-α-methoxycarbonyl-29-oic acid	34.32	0.55
	MOL004907	Glyzaglabrin	61.07	0.35
	MOL004908	Glabridin	53.25	0.47
	MOL004910	Glabranin	52.9	0.31
	MOL004911	Glabrene	46.27	0.44

(*Continued*)

Table 1 (*Continued*)

Drud	Mol ID	Molecule Name	OB (%)	DL
	MOL004912	Glabrone	52.51	0.5
	MOL004913	1,3-dihydroxy-9-methoxy-6-benzofurano[3,2-c]chromenone	48.14	0.43
	MOL004914	1,3-dihydroxy-8,9-dimethoxy-6-benzofurano[3,2-c]chromenone	62.9	0.53
	MOL004915	Eurycarpin A	43.28	0.37
	MOL004917	Glycyroside	37.25	0.79
	MOL004924	(-)-Medicocarpin	40.99	0.95
	MOL004935	Sigmoidin-B	34.88	0.41
	MOL004941	(2R)-7-hydroxy-2-(4-hydroxyphenyl) chroman-4–one	71.12	0.18
	MOL004945	(2S)-7-hydroxy-2-(4-hydrox yphenyl)-8-(3-methylbut-2-enyl) chroman-4-one	36.57	0.32
	MOL004948	Isoglycyrol	44.7	0.84
	MOL004949	Isolicoflavonol	45.17	0.42
	MOL004957	HMO	38.37	0.21
	MOL004959	1-Methoxyphaseollidin	69.98	0.64
	MOL004961	Quercetin der	46.45	0.33
	MOL004966	3′-Hydroxy-4’-O-Methylglabridin	43.71	0.57
	MOL000497	Licochalcone A	40.79	0.29
	MOL004974	3′-Methoxyglabridin	46.16	0.57
	MOL004978	2-[(3R)-8,8-dimethyl-3,4-dihydro-2H-pyrano[6,5-f]chromen-3-yl]-5-methoxyphenol	36.21	0.52
	MOL004980	Inflacoumarin A	39.71	0.33
	MOL004985	Icos-5-enoic acid	30.7	0.2
	MOL004988	Kanzonol F	32.47	0.89
	MOL004989	6-prenylated eriodictyol	39.22	0.41
	MOL004990	7,2’,4’-trihydroxy-5-methoxy-3-arylcoumarin	83.71	0.27
	MOL004991	7-Acetoxy-2-methylisoflavone	38.92	0.26
	MOL004993	8-prenylated eriodictyol	53.79	0.4
	MOL004996	Gadelaidic acid	30.7	0.2
	MOL000500	Vestitol	74.66	0.21
	MOL005000	Gancaonin G	60.44	0.39
	MOL005001	Gancaonin H	50.1	0.78
	MOL005003	Licoagrocarpin	58.81	0.58
	MOL005007	Glyasperins M	72.67	0.59
	MOL005008	Glycyrrhiza flavonol A	41.28	0.6
	MOL005012	Licoagroisoflavone	57.28	0.49
	MOL005013	18α-hydroxyglycyrrhetic acid	41.16	0.71
	MOL005016	Odoratin	49.95	0.3
	MOL005017	Phaseol	78.77	0.58
	MOL005018	Xambioona	54.85	0.87
	MOL005020	dehydroglyasperins C	53.82	0.37

Abbreviation: DL, drug-like-index; GC, Gancao; JZ, Jiezi; MH, Mahuang; OB, oral bioavailability; RG, Rougui; SD, Shudihuang; SJ, Sheng jiang; YHD, Yanghe Decoction.

Table 2 Enrichment analysis of KEGG signaling pathway (top 20)

ID	Term	p-Value	Genes
hsa04933	AGE-RAGE signaling pathway in diabetic complications	3.06987E-27	ICAM1, IL-1β, IL-6, CXCL8, MMP2, NOS3, SERPINE1, MAPK1, CCL2, STAT3, TNF, VCAM1, VEGFA
hsa05418	Fluid shear stress and atherosclerosis	3.1339E-20	HMOX1, ICAM1, IFNG, IL-1β, MMP2, MMP9, NOS3, CCL2, TNF, VCAM1, VEGFA
hsa05144	Malaria	4.40514E-20	ICAM1, IFNG, IL-1β, IL-6, CXCL8, IL-10, CCL2, TNF, VCAM1
hsa04657	IL-17 signaling pathway	2.0254E-17	IFNG, IL-1β, IL-4, IL-6, CXCL8, MMP9, MAPK1, CCL2, TNF
hsa05142	Chagas disease (American trypanosomiasis)	4.80526E-17	IFNG, IL-1β, IL-6, CXCL8, IL-10, SERPINE1, MAPK1, CCL2, TNF
hsa05143	African trypanosomiasis	5.40725E-16	ICAM1, IFNG, IL-1β, IL-6, IL-10, TNF, VCAM1
hsa05323	Rheumatoid arthritis	3.27888E-15	ICAM1, IFNG, IL-1β, IL-6, CXCL8, CCL2, TNF, VEGFA
hsa04066	HIF-1 signaling pathway	8.507E-15	HMOX1, IFNG, IL-6, NOS3, SERPINE1, MAPK1, STAT3, VEGFA
hsa04668	TNF signaling pathway	1.47723E-14	ICAM1, IL-1β, IL-6, MMP9, MAPK1, CCL2, TNF, VCAM1
hsa05321	Inflammatory bowel disease	5.51947E-14	IFNG, IL-1β, IL-4, IL-6, IL-10, STAT3, TNF
hsa04060	Cytokine-cytokine receptor interaction	3.59495E-13	IFNG, IL-1β, IL-4, IL-6, CXCL8, IL-10, CCL2, TNF, VEGFA
hsa05164	Influenza A	6.88443E-13	ICAM1, IFNG, IL-1β, IL-6, CXCL8, MAPK1, CCL2, TNF
hsa05140	Leishmaniasis	2.31419E-11	IFNG, IL-1β, IL-4, IL-10, MAPK1, TNF
hsa05133	Pertussis	2.96757E-11	IL-1B, IL-6, CXCL8, IL-10, MAPK1, TNF
hsa05146	Amoebiasis	1.24592E-10	IFNG, IL-1β, IL-6, CXCL8, IL-10, TNF
hsa05219	Bladder cancer	1.66454E-10	CXCL8, MMP2, MMP9, MAPK1, VEGFA
hsa04659	Th17 cell differentiation	2.41559E-10	IFNG, IL-1β, IL-4, IL-6, MAPK1, STAT3
hsa05161	Hepatitis B	1.46222E-09	IL-6, CXCL8, MMP9, MAPK1, STAT3, TNF
hsa04621	NOD-like receptor signaling pathway	3.97175E-09	IL-1β, IL-6, CXCL8, MAPK1, CCL2, TNF
hsa05152	Tuberculosis	5.41283E-09	IFNG, IL-1β, IL-6, IL-10, MAPK1, TNF

Abbreviation: KEGG, Kyoto Encyclopedia of Genes and Genomes.

mesenchymal tumors.[15] Quercetin,[16] luteolin,[17] and kaempferol[18] all have anticoagulant, antithrombotic, antiplatelet-aggregation, and defibrillating effects. Quercetin can also exert antiarterial effects by inhibiting the expression of SDF-1 and CXCR4 in the sera of APOE mice, regulating blood lipid levels in atherosclerotic rats and interfering with the activities of key proteins in the PI3K/Akt/NF-κb pathway.[19,20] In addition, luteolin also can reduce atherosclerosis by reducing inflammation in APOE mice.[21]

TNF is a cytokine that can directly kill tumor cells and exerts antitumor effects by activating the immune system. Ubiquitin-specific protease 20 can inhibit smooth-muscle cell inflammation caused by TNF overexpression by deubiquitinating β and relieving atherosclerosis.[22] IL-6 is a pleiotropic cytokine expressed by immune cells and various tumor cells. IL-6 induces inflammation, promotes cancer cell proliferation, and inhibits apoptosis, thereby promoting chemotherapy resistance. Studies have shown that IL-6 promotes the progression of Ewing's sarcoma by increasing resistance to apoptosis and promoting metastasis under cellular stress.[23] Inflammation is a major factor leading to atherosclerosis. IL-6 is an upstream inflammatory cytokine that plays a central role in downstream inflammatory responses leading to atherosclerosis.[24] MAPK1 is a member of the MAP kinase family and is also known as ERK2. MAPK1/ERK2 is involved in processes such as cellular proliferation, differentiation, and transcriptional regulation. Most patients with angiosarcoma have obvious genetic changes related to the MAPK signaling pathway, which activates the MAPK pathway and increases tumor cell proliferation. In the occurrence and development of alveolar rhabdomyosarcoma, HGF/MET signaling (mainly through ERK2 signaling)

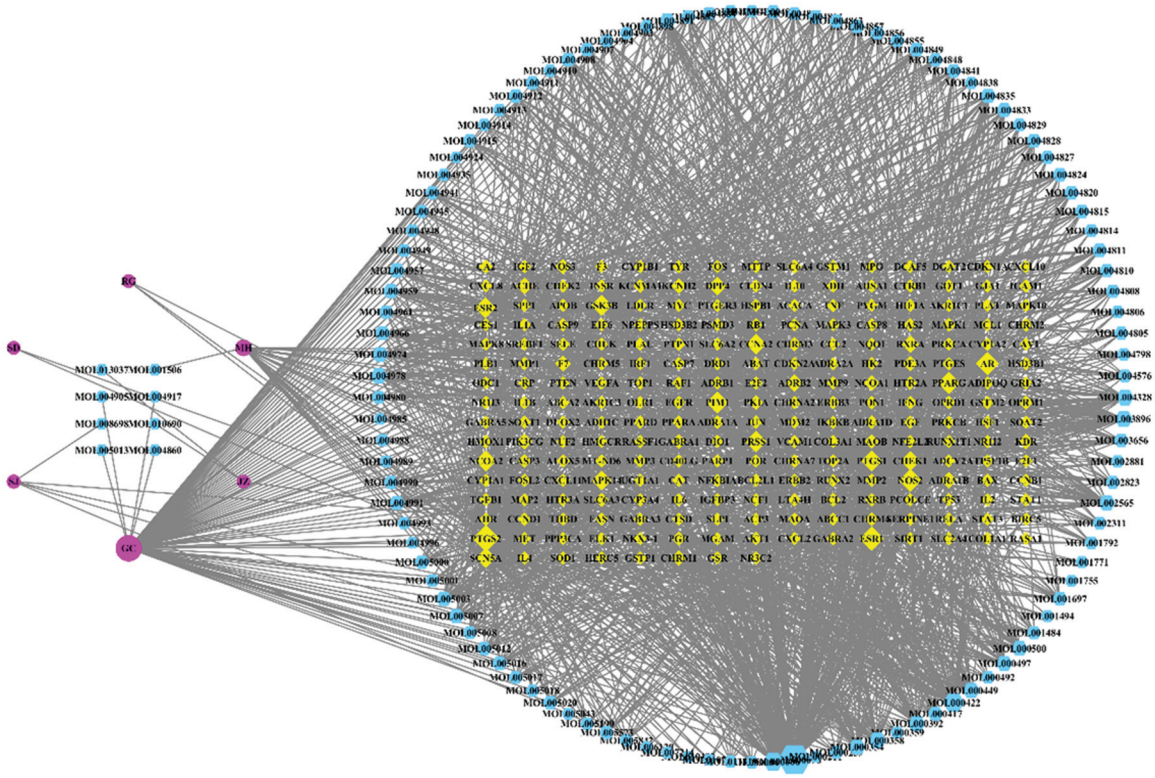

Fig. 1 Network of drugs–compounds–targets related to YHD in the treatment of STS/ASO.
Notes: The regulatory network was constructed by 357 nodes (six Chinese herbs, 118 candidate compound nodes, and 233 target nodes) and 1,769 edges; among the 118 candidate compounds, eight compounds had no corresponding targets found in the database; purplish-red represents Chinese herbs, blue represents compound, yellow represents target,and the size of node is directly proportional to the Degree value of node.

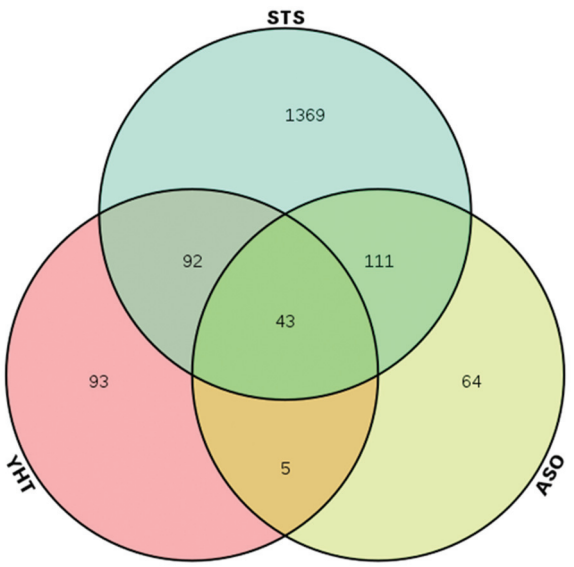

Fig. 2 Venn diagram of YHD targets in the treatment of STS and ASO.

promotes the cellular motility and participates in the occurrence, invasion, and metastasis of tumor cells.[25,26] MAPK1 is expressed in platelets and is activated by various agonists. Agonist-induced phosphorylation of MAPK1 can inhibit platelet aggregation; furthermore, loss or down-regulation of MAPK1 up-regulates VCAM-1 expression stimulated by insulin and TNF-α, leading to vascular disease.[27,28]

The AGE-RAGE signaling pathway not only causes oxidative stress, inflammation, thrombosis, and fibrosis in a variety of cells but also activates a variety of signal transduction pathways related to cellular proliferation and apoptosis. Furthermore, the AGE-RAGE signaling pathway plays an important role in the occurrence, development, and metastasis of tumors.[29,30] The IL-17 signaling pathway not only participates in autoimmune diseases and chronic inflammatory diseases but also participates in tumor cell survival, angiogenesis, chemokine production, tissue remodeling, and immune modification of the tumor microenvironment, thereby affecting the occurrence and development of STS and ASO.[31–34] The HIF-1 signaling pathway participates in the regulation of angiogenesis, cellular metabolism, and autophagy, as well as in the occurrence or development of malignant tumors and inflammatory responses. Some studies have shown that the HIF-1 signaling pathway affects cellular metabolism, differentiation, angiogenesis, proliferation, and metastasis and this pathway is related to the prognosis of patients with STS and chondrosarcoma.[35,36] The HIF-1 signaling pathway can also cause endothelial cell dysfunction, angiogenesis, and inflammation by up-regulating VEGF, NO, ROS and PDGF. Moreover, these responses play a role in the development of ASO.[37] Cytokines are small polypeptides or glycoproteins that are synthesized and secreted by a variety of cells and include interleukins, interferons,

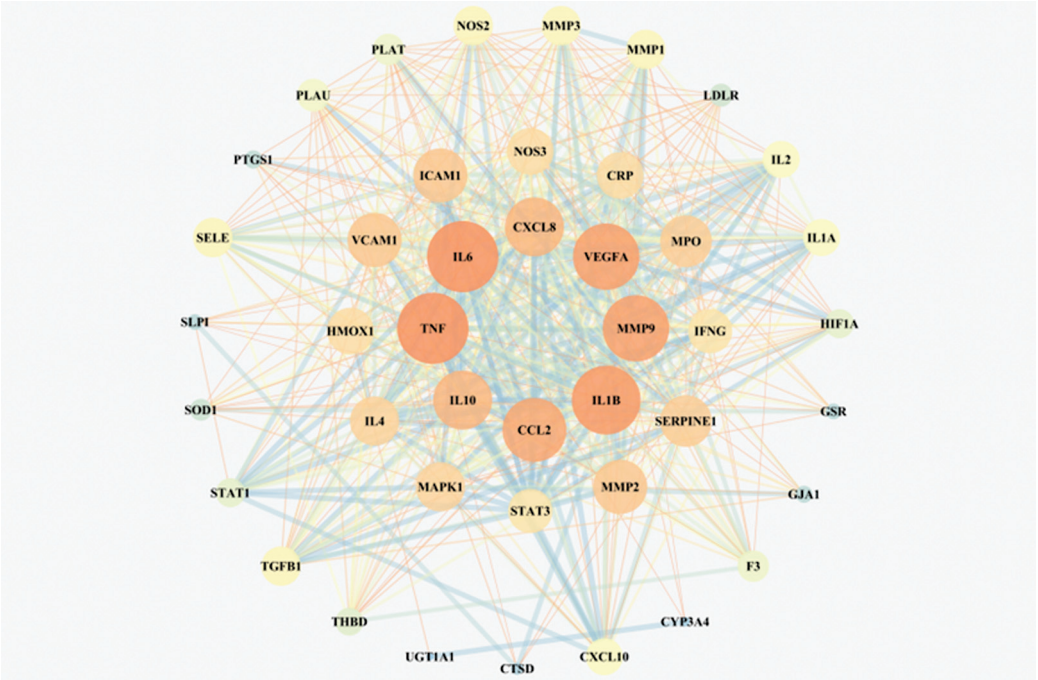

Fig. 3 Protein–protein interaction network of the common targets of YHD and STS/ASO.

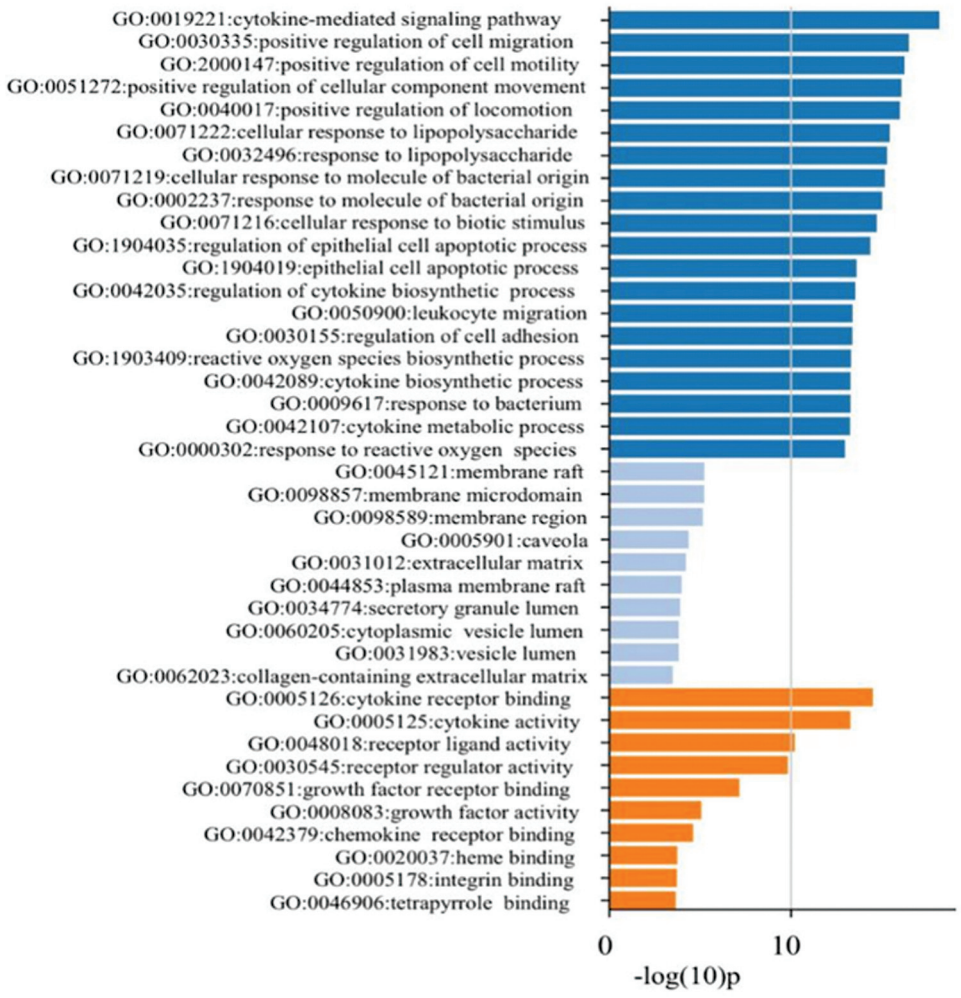

Fig. 4 GO enrichment analysis.

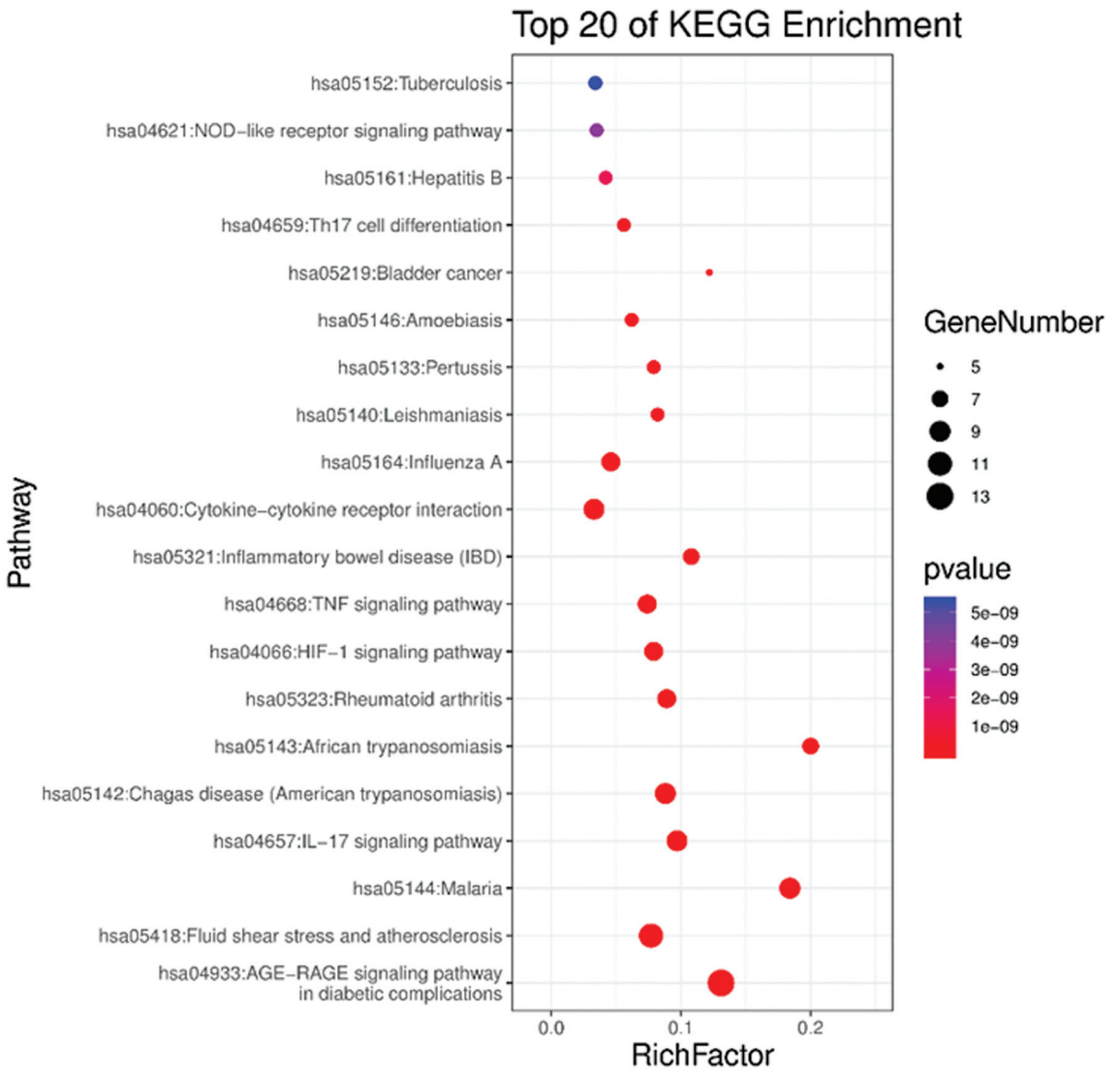

Fig. 5 KEGG signaling pathway enrichment analysis (top 20).

chemokines, growth factors, the tumor necrosis factor superfamily and colony-stimulating factors. Interactions between cytokines and cytokine receptors can regulate the growth and differentiation of cells, regulate immune responses, participate in inflammatory responses, repair damaged tissues, and have regulatory effects on STS and ASO.[38–41] In addition, TNF signaling pathway, Th17 cell differentiation, and NOD-like receptor signaling pathway are all signal pathways related to immunity and inflammation, which can activate NF-κB, MAPK, and endoplasmic reticulum emergency pathway and promote the release of inflammatory factors such as IL-6 and mediate inflammatory response, which is closely related to tumors, inflammatory diseases, and autoimmune diseases.[42,43]

Conclusions

In summary, this study reveals that the mechanism of YHD in the treatment of STS and ASO mainly involves cell proliferation, differentiation, angiogenesis, inflammation, immune response, oxidative stress, and other related signal pathways, which is consistent with the current research on the mechanism of STS and ASO. To some extent, it is proved that the results predicted by the network pharmacology method are reliable, but further experimental verification is still needed. This study can not only guide the experimental research in the next stage but can also provide a reliable basis for clinical application and new drug development.

Credit Authorship Contribution Statement

Yiran Zhai: Conceptualization, methodology, data curation, formal analysis, and writing original draft. **Binyi Li** and **Lili Miao**: Writing - review & editing. **Shanshan Li and Jie Wang**: Formal analysis. **Shiqing Jiang**: Conceptualization, methodology, and supervision.

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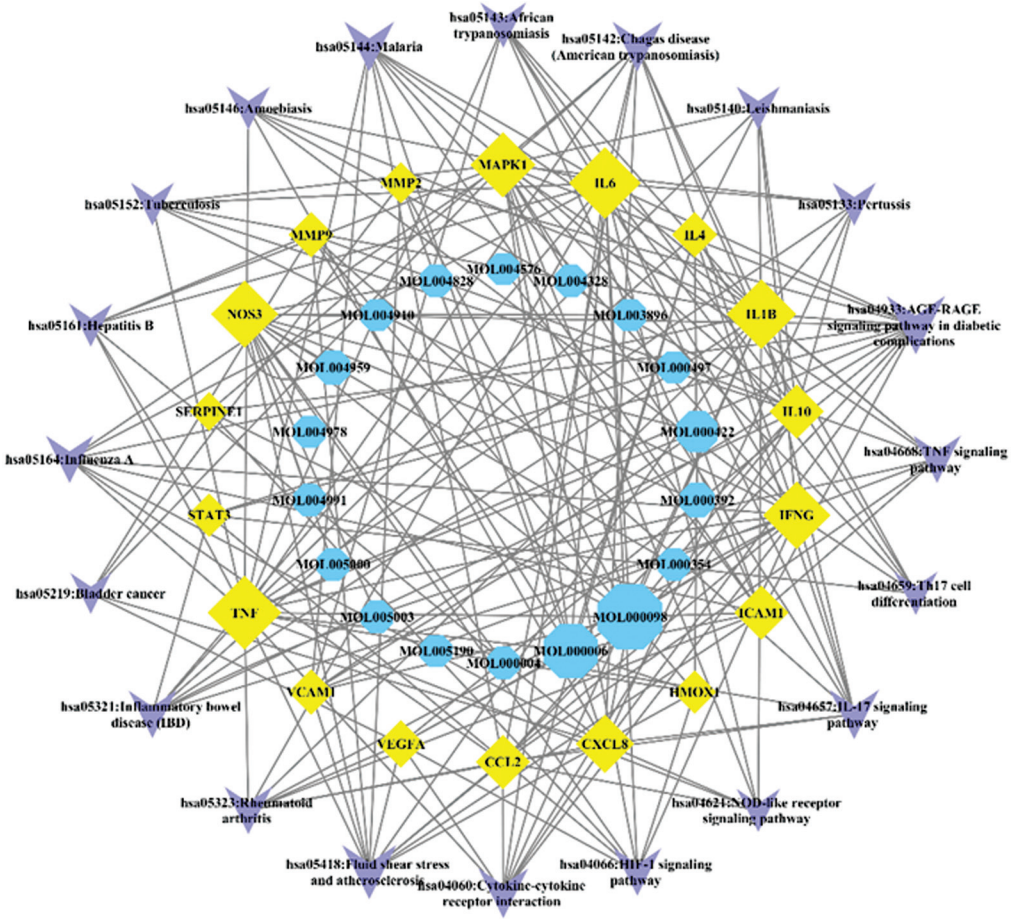

Fig. 6 Network of compounds–*targets*–pathways related to YHD in the treatment of STS/ASO.
Notes: The network consists of 56 nodes (18 compounds,18 key common targets, and 20 pathway nodes) and 203 edges; purple represents the pathway, blue represents the compound, yellow represents the target, and the size of the node is directly proportional to the degree value of the node.

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Conflict of Interest

The authors declare no conflict of interest.

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