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Original Research Article

Utilizing network pharmacology to investigate the probable mechanism of Danshen chuanxiong drug pair in Kawasaki disease

Aiyuan Cai[1], Siting Xu[1], Jie He[2], Meiping Shi[1], Lanlin You[1], Zhongbin Pan[1], Yanxia Zheng[3]*

[1]Second Clinical Medical College, Guangzhou University of Chinese Medicine, Guangzhou City, Guangdong Province 510410, [2]School of Biomedical Engineering, Guangdong Medical University, Dongguan City, Guangdong Province 523808, [3]Department of Pediatrics, Guangdong Provincial Hospital of Chinese Medicine, Guangzhou City, Guangdong Province 510120, China

For correspondence: **Email: zhengyanxiamed@outlook.com*

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Abstract

Purpose: *To investigate the primary components and effect of Danshen-Chuanxiong (DS-CX) in the treatment of Kawasaki disease.*

Methods: *Active ingredients of DS-CX and targets of action were screened via the Traditional Chinese Medicine Systematic Pharmacology (TCMSP) and SwissTargetPrediction databases. Targets of Kawasaki disease were queried in OMIM, GeneCards, DRUGBANK, and Disgenet databases, and intersected with drug targets. Protein-protein interaction maps (PPIs) were constructed using STRING database and Cytoscape software, and core genes of Kawasaki disease were screened. Pathway enrichment analyses (DAVID database, Gene Ontology (GO) function and Kyoto Encyclopedia of Genes and Genomes (KEGG)) were conducted for DS-CX targeting Kawasaki disease crossover targets.*

Results: *A total of 64 active ingredients and corresponding potential target genes of DS-CX were obtained. Also, 928 human genes related to Kawasaki disease were obtained from OMIM, DRUGBANK, GeneCards and Disgenet databases. Potential target genes of DS-CX was intersected with 928 human Kawasaki disease-related genes, and a total of 55 genes were screened. The PPI network was built using STRING database and Cytoscape software, and overlapping genes were further screened. A total of 61 active ingredients were screened for their effects on Kawasaki disease-related targets. GO-function analysis revealed that DS-CX affected Kawasaki disease by positively regulating gene expression. Also, KEGG enrichment analysis found that DS-CX and Kawasaki disease was mainly enriched in pathways involved in cancer.*

Conclusion: *DS-CX regulates core genes (AKT1, IL6, and TP53) and other genes through active ingredients which in turn act on cancer pathway. Thus, DS-CX demonstrates anti-inflammatory and anti-platelet activities and helps blood vessel repair and remodeling in Kawasaki disease. Further studies to validate Danshen and Chuanxiong for the treatment of Kawasaki disease are needed to determine its mechanism of action.*

Keywords: *Danshen-Chuanxiong drug pair, Kawasaki disease, Anti-inflammatory, Antiplatelet, Network pharmacology*

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INTRODUCTION

Kawasaki disease predominantly affects children < 5, and it is primarily characterized by immune vasculitis, with coronary artery damage being a significant pathological alteration. Approximately 25 % of Kawasaki disease patients without treatment suffer from coronary artery damage, making it a leading cause of heart disease in children. In extreme cases, it may progress to coronary aneurysms and myocardial infarction [1]. Nonetheless, the development of Kawasaki disease is still not fully understood.

The consensus is that in genetically predisposed children, immune vasculitis arises from heightened immune reactions and unusual activation of T-cells in the bloodstream. This leads to elevated levels of cytokines and inflammatory agents, causing atypical platelet activation [2]. As a result, aspirin in combination with intravenous immunoglobulin is the standard treatment for Kawasaki disease due to its anti-inflammatory and anti-platelet properties. However, 15 - 25 % of patients with Kawasaki disease exhibited resistance to intravenous immunoglobulin, which develops into coronary artery damage [3]. Furthermore, prolonged use of aspirin results in the distortion of the stomach lining and bleeding. As a result, it is imperative to examine the origin of Kawasaki disease and investigate different treatment options.

Herbal medicine has its unique advantages in Kawasaki disease, acting not only on the immune and inflammatory mechanisms but also on susceptibility genes of Kawasaki disease. The dehydrated rhizome root of *Salvia miltiorrhiza* Burge, known as Danshen, is extensively utilized for the treatment of heart-related ailments, such as coronary artery disease, heart attacks, angina pectoris, and atherosclerosis [4]. The dry root and rhizome of *Ligusticum chuanxiong* Hort also known as Chuanxiong is used in traditional Chinese medicine. Chuanxiong has garnered significant interest as a key ingredient in treating heart-related illnesses, cancer conditions, and inflammatory conditions [5].

Danshen is frequently used in combination with various traditional Chinese medicines, among which Danshen-Chuanxiong (DS-CX) stands out as a commonly utilized herbal blend (a blend of plant substances) in top-selling herbal formulas [6]. The therapeutic role of DS-CX in Kawasaki disease has been studied [7]. However, no literature explains the rationale for their use as a drug pair in Kawasaki disease. Network pharmacology studies were standardized in 2021 with the publication of Guidelines on the Evaluation Methods of Network Pharmacology by Tsinghua University and the Professional Committee of the World Federation of Chinese Medicine Societies [8].

This study was the first to investigate the active ingredients and action of DS-CX in Kawasaki disease through network pharmacology (a discipline that integrates network analysis, systems biology and pharmacology to study the interaction between drugs and organisms, and reveals the mechanism of action, target and efficacy of drugs by constructing and analyzing drug-target-disease and other multi-level biological networks).

EXPERIMENTAL

Screening for the main active ingredients and targets of DS-CX

The chemical composition of Danshen and Chuanxiong was collected from the Traditional Chinese Medicine Systematic Pharmacology Database (TCMSP, http://lsp.nwu.edu.cn/tcmsp.php). Based on analysis of the pharmacokinetic parameters (absorption, distribution, metabolism, and efflux) of the compounds, combined with quantitative analysis, two thresholds were set (oral bioavailability (≥ 30 %) and drug-likeness (≥ 0.18)) to screen out the main active ingredient and corresponding potential protein targets. If no target information was available in the TCMSP database, the compounds were identified by the Canonical SMILES sequences in the PubChem database. Protein target prediction was then supplemented with the SwissTargetPrediction database (http://www.swisstargetprediction.ch/). The above-screened target proteins were queried through the UniProt database (https://www.uniprot.org/) for the corresponding human target genes.

Screening of Kawasaki disease-related targets

The Online Mendelian Inheritance in Man (OMIM) database (http:// www.omim.org), DRUGBANK database (http://www. drugbank.ca), GeneCards database (http: // www.genecards.org), and Disgenet database (http://www. disgenet.org) were used to search for Kawasaki disease-related targets, with the keywords "Kawasaki Disease" or "Mucocutaneous Lymph Node Syndrome". Targets with a relevance score greater than 10 were screened using GeneCards database, and the above targets were screened, and integrated, while overlapping targets were removed to create a Kawasaki disease-related target set. This study was approved by the Ethics Committee of the Second Clinical Medical College, Guangzhou University of Chinese Medicine (approval No. 2018C-16), and conducted in accordance with the Declaration of Helsinki [9].

Venn diagram of potential targets of DS-CX

Venn diagram analysis (https://bioinfogp.cnb.csic.es/tools/venny/index.html) was performed by combining target sets related to Kawasaki disease with target sets of the main active ingredients of DS-CX, and intersection targets of DS-CX-Kawasaki disease were extracted. Thereafter, the network diagram of DS-CX pair-active ingredient-target Kawasaki disease was constructed.

Protein-protein interaction (PPI) network of DS-CX

The intersection target of DS-CX-Kawasaki disease was uploaded to the STRING 11.5 online database (http: //string-db.org), and the gene genus was limited to *Homo sapiens*. The interaction threshold was set to medium confidence (0.400), and the protein-protein interaction information was obtained and imported into Cytoscape 3.9.2 software for PPI network mapping. Topological analysis of the PPI network was performed by CytoHubba, a plug-in in Cytoscape 3.9.2 software, and included maximal clique centrality (MCC), maximum neighborhood component (MNC), Degree, and edge percolated component (EPC). Topological analysis included MCC, MNC, EPC, and the top 10 nodes in each

topological analysis method were selected and tentatively defined as core genes.

Gene Ontology (GO) function and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis of DS-CX-Kawasaki disease crossover target

The DS-CX-Kawasaki disease crossover target was imported into DAVID 6.8 database (https://david.ncifcrf.gov/), and *Homo sapiens* GO and KEGG pathway enrichment analyses were performed. False discovery rate (FDR) of each enrichment result was calculated, and the FDRs were sorted in ascending order. Results were visualized with the Microbiology Letter (http://bioinformatics.com.cn/), and network diagram of DS-CX active ingredient -Kawasaki disease target – pathway was then constructed.

RESULTS

Active ingredient screening and potential target prediction

A total of 64 active ingredients were obtained, of which 5 were Chuanxiong and 59 were Danshen, and no common ingredient was detected. Through TCMSP platform and SwissTargetPrediction database, potential targets corresponding to 64 active ingredients were obtained, and only one target was retained in the repeated targets. Among these 64 active ingredients, 5 active ingredients of Chuanxiong had 25 potential targets of action, while the 59 active ingredients of Danshen had 130 potential targets of action (Figure 1). This suggests that DS-CX is used in the treatment of Kawasaki disease through multiple targets of multiple components.

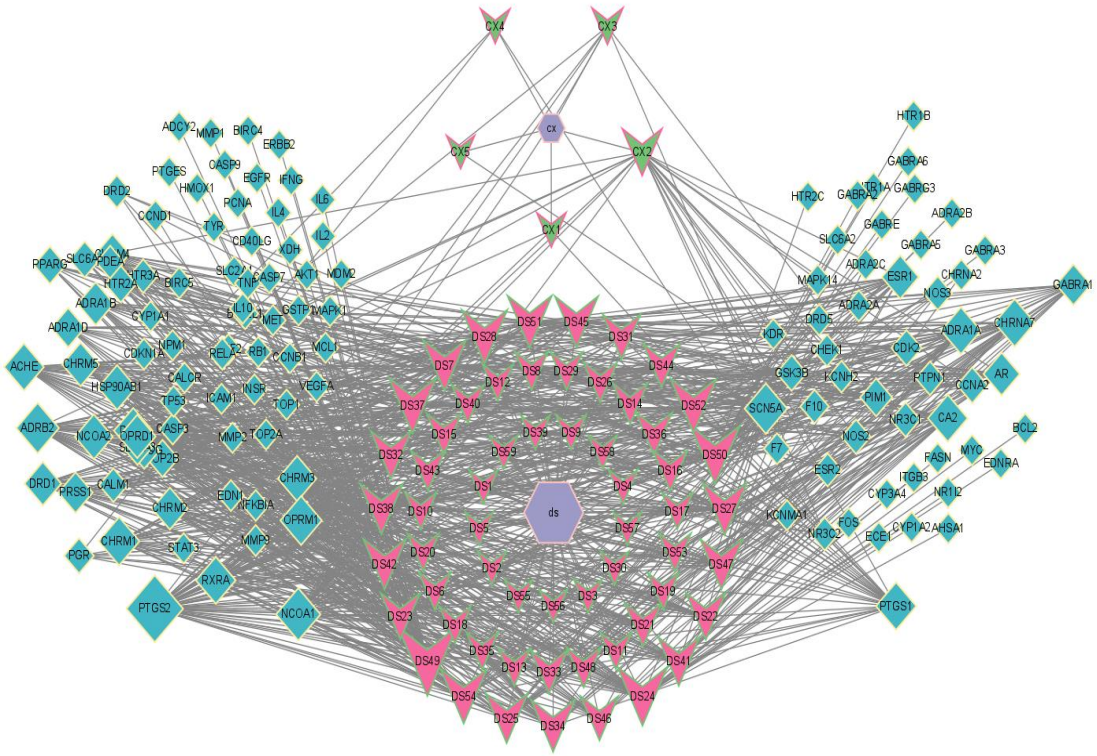

Figure 1: Active ingredient-target network for DS-CX

Identification of intersection target of DS-CX-Kawasaki disease

A total of 928 human genes related to Kawasaki disease were obtained from OMIM, DRUGBANK, GeneCards and Disgenet databases. Potential targets of DS-CX were intersected with 928 human genes related to Kawasaki disease, and a total of 55 genes were screened, indicating that 55 of the potential targets of the 64 active ingredients of the DS-CX combination are associated with Kawasaki disease (Figure 2; Table 1).

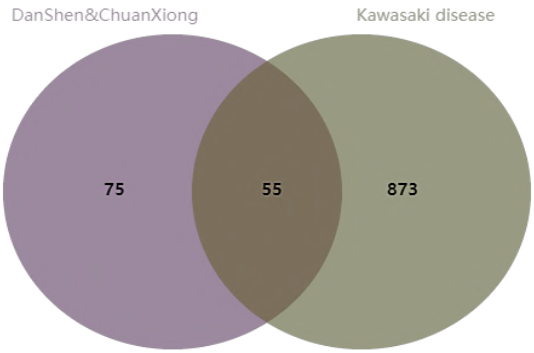

Figure 2: Venn diagram of potential targets of active ingredients in DS-CX and Kawasaki disease-related targets

Construction of DS-CX-Kawasaki disease intersection target PPI network map and screening of key targets

The PPI network map was obtained by network construction between DS-CX and 55 common target genes of Kawasaki disease through the STRING database (Figure 3 A). The network contains 55 nodes and 696 edges (Figure 3 B), the target interaction strength is expressed in degree, and the higher the interaction strength, the higher the value. According to MCC, MNC, Degree, and EPC topology analysis methods of the Cytohubba plugin in Cytoscape, a total of 10 overlapping core genes were identified (AKT1, IL6, TP53, CASP3, PTGS2, VEGFA, STAT3, TNF, EGFR, and ESR1; Table 2). These targets correlated with DS-CX in Kawasaki disease (KD; Figure 3 C).

Construction of DS-CX-active ingredient-target gene-Kawasaki disease network diagram

Active ingredients of DS-CX and its targets related to Kawasaki disease were introduced into Cytoscape to construct a network diagram (Figure 4). The network diagram of DS-CX active ingredient-target-Kawasaki disease contains 121 nodes and 374 edges with 61 selected active ingredients acting on Kawasaki disease-related targets and luteolin, tanshinone iia with myricanone being the top 3 chemical components in the drug pair of DS-CX (considered potential core compounds for Kawasaki disease treatment with DS-CX).

Table 1: The 55 targets associated with Kawasaki disease

No	Targets	No	Targets	No	Targets	No	Targets	No	Targets
1	PTGS1	12	NCOA1	23	TP53	34	DRD2	45	PCNA
2	PTGS2	13	NR3C2	24	NFKBIA	35	NOS3	46	ERBB2
3	NOS2	14	NR3C1	25	EDNRA	36	EGFR	47	HMOX1
4	ESR1	15	F10	26	EDN1	37	AKT1	48	ICAM1
5	AR	16	ACHE	27	CYP3A4	38	VEGFA	49	IL2
6	SCN5A	17	RELA	28	MYC	39	MMP2	50	IFNG
7	PPARG	18	BCL2	29	NR1I2	40	MAPK1	51	IL4
8	F7	19	FOS	30	ECE1	41	IL10	52	GSTP1
9	KDR	20	CDKN1A	31	STAT3	42	IL6	53	INSR
10	ESR2	21	MMP9	32	CCND1	43	MDM2	54	CD40LG
11	MAPK14	22	CASP3	33	TNF	44	MMP1	55	MET

Table 2: Topological property parameters of key targets in Kawasaki disease by DS-CX drug pair

Target	Key Action Genes	Degree	CytoHubb -EPC Score	CytoHubb -MCC Score	CytoHubb -MNC Score
RAC-alpha serine/threonine-protein kinase	AKT1	92	28.077	3.77E+18	46
Interleukin-6	IL6	90	27.984	3.77E+18	45
Tumor necrosis factor	TNF	88	27.381	3.77E+18	44
Cellular tumor antigen p53	TP53	88	27.936	3.77E+18	44
Vascular endothelial growth factor A	VEGFA	86	27.543	3.77E+18	43
Signal transducer and activator of transcription 3	STAT3	82	27.499	3.77E+18	41
Prostaglandin G/H synthase 2	PTGS2	82	27.642	3.77E+18	41
Caspase-3	CASP3	80	27.346	3.77E+18	40
Epidermal growth factor receptor	EGFR	80	27.647	3.45E+18	40
Estrogen receptor	ESR1	74	26.151	1.58E+17	37

EPC: edge percolated component, MCC: maximal clique centrality, MNC: maximum neighborhood component

GO and pathway enrichment analysis

According to FDR results, positive regulation of transcription from RNA polymerase II ranked high in the biological process of DS-CX and Kawasaki disease. Responses to the drug and positive regulation of gene expression indicated that DS-CX affects Kawasaki disease through biological processes (Figure 5 A). Cellular components mainly include macromolecular complex, caveola, and chromatin (Figure 5 B) while molecular functions include enzyme binding, activity of transcription factor RNA polymerase II, and ligand-induced sequence-specific DNA binding (Figure 6 A). The KEGG pathway analysis showed that DS-CX drug pair and Kawasaki disease were enriched in pathways of atherosclerosis, fluid shear stress, cancer, and hypoxia-inducible factor-1 (HIF-1; Figure 6 B).

Construction of DS-CX-active ingredient-Kawasaki disease target-pathway network diagram

The KEGG analysis reported that pathways in cancer and fluid shear stress, atherosclerosis, HIF-1 pathway, Proteoglycans in cancer, and Bladder cancer were the top 5 pathways enriched in the intersection targets of DS-CX and Kawasaki disease. Furthermore, active molecules and potential targets of DS-CX pathway correspond to the potential targets, and vice versa. Relevant data were entered into Cytoscape software to construct the component-target-pathway network of DS-CX in Kawasaki disease (Figure 6). The network map contained 113 nodes and 367 edges. The DS-CX drug pair was related to 55 active ingredients which include luteolin, tanshinone iia, myricanone, and 41 targets in the treatment of Kawasaki disease. The 10 core genes were all enriched in pathways in cancer except tumor necrosis factor (TNF; Figure 7). Enrichment of other Pathways was not as good as pathways in cancer, so the remaining 9 core genes were finally screened (AKT1, IL6, TP53, CASP3, PTGS2, VEGFA, STAT3, EGFR, and ESR1). The enriched pathway was selected as a pathway in cancer.

DISCUSSION

Pathogenesis of Kawasaki disease is unclear, and Western treatment has been relatively challenging. Chinese herbal medicine is efficient, has fewer side effects, and is suitable for diseases with complex mechanisms.

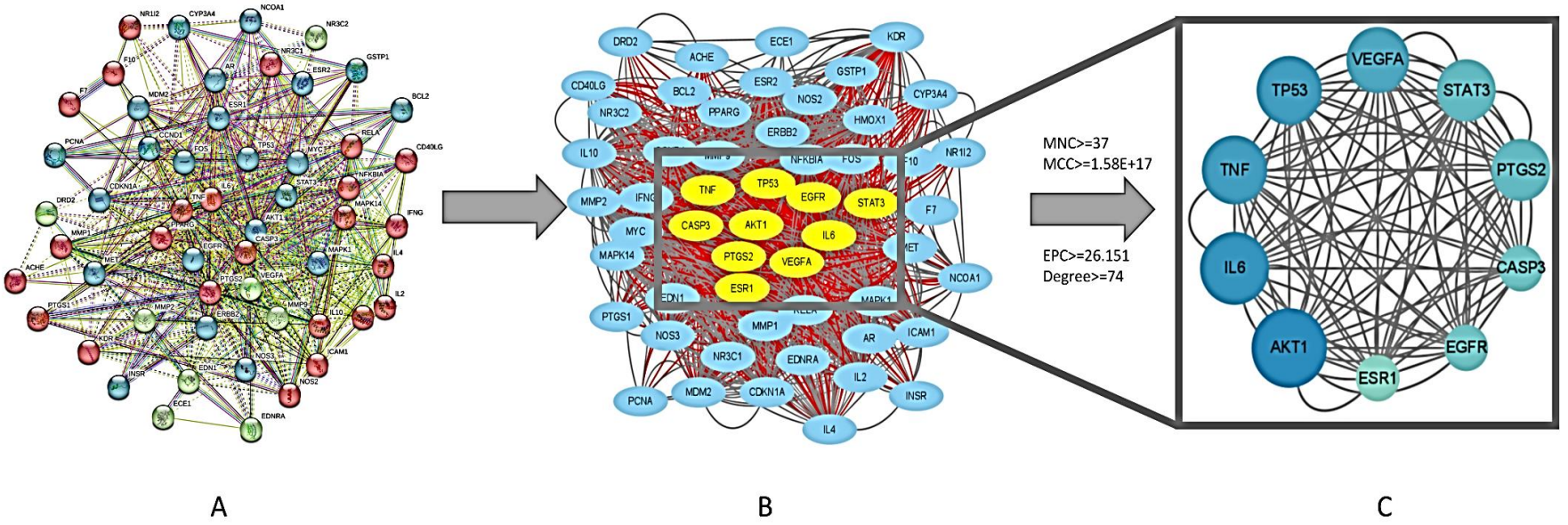

Figure 3: The PPI network of DS-CX targets for the treatment of KD. (A): The 55 common target genes through the STRING database. (B): The network contains 55 nodes and 696 edges. (C): The top 10 overlapping core target

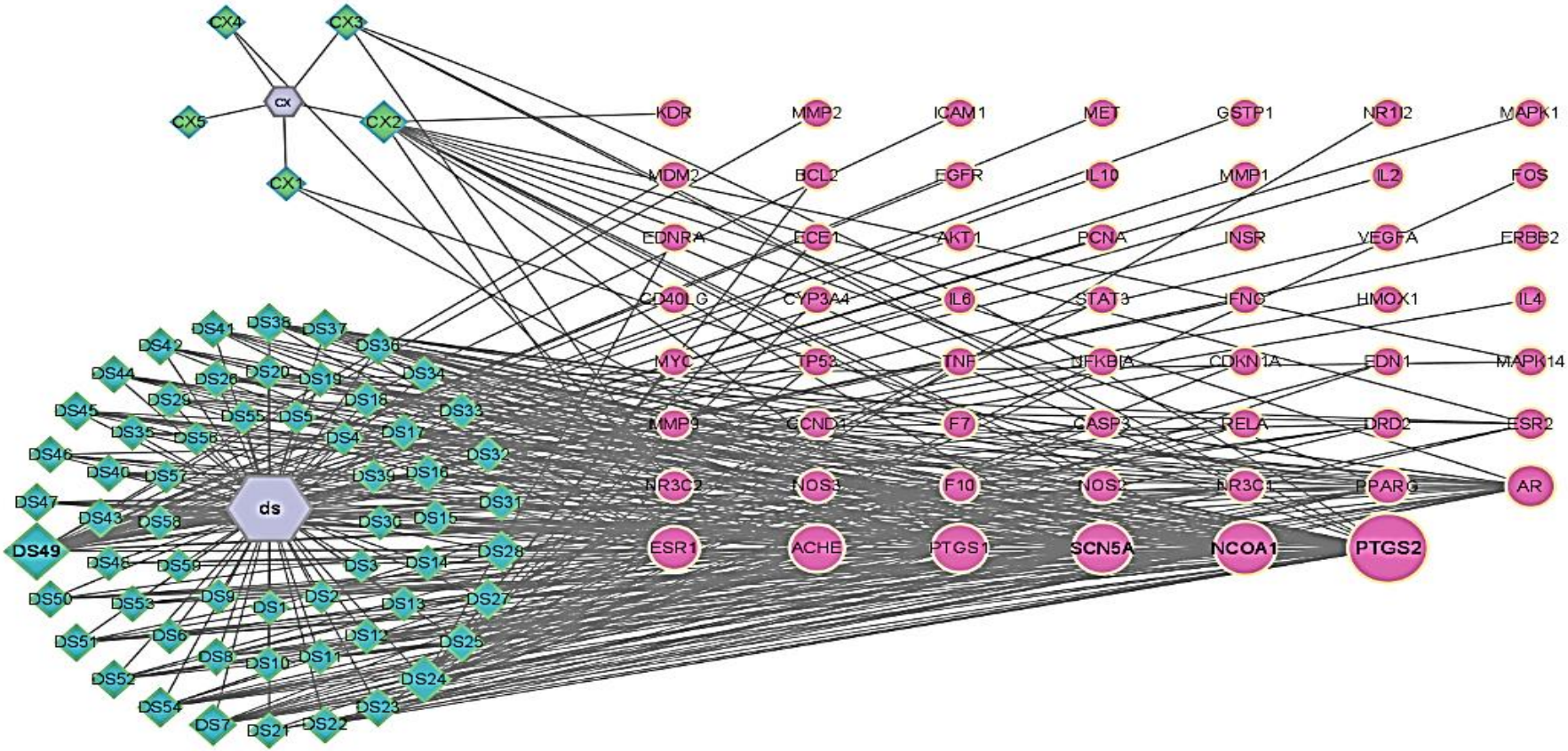

Figure 4: Network of DS-CX drug pair-active ingredients-targets-Kawasaki disease

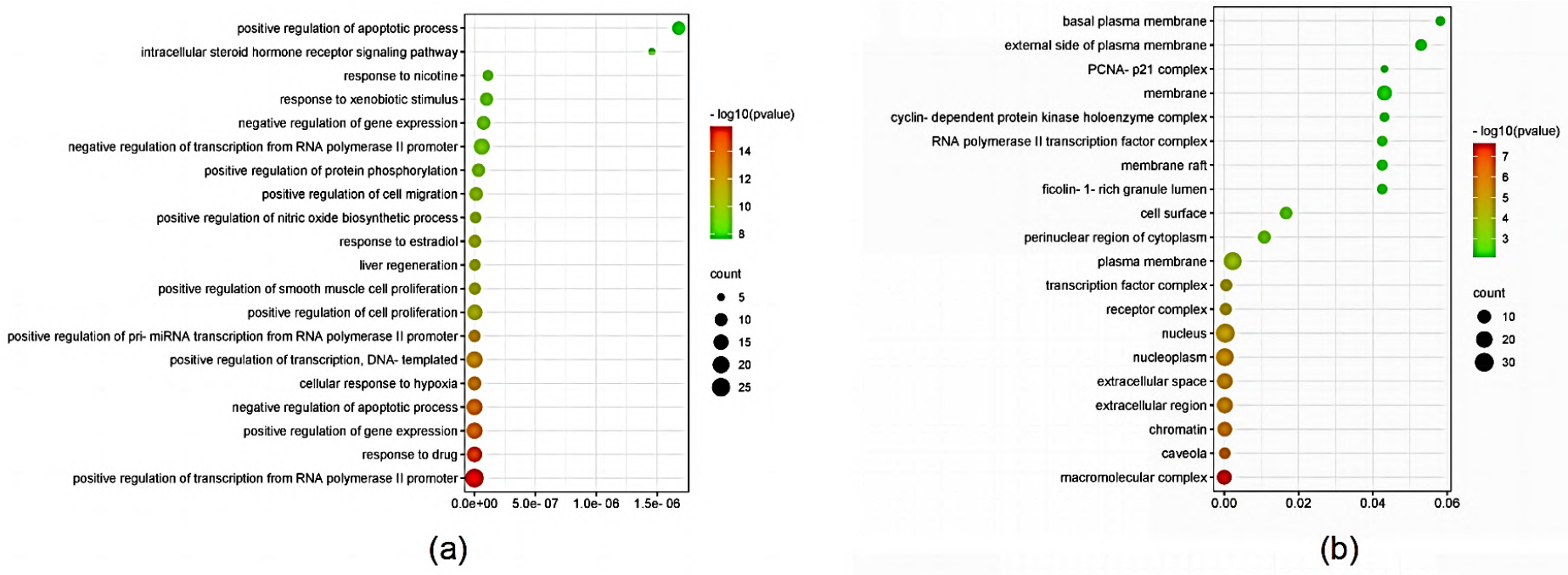

Figure 5: Bubble diagram of GO functional and KEGG pathways enrichment analysis of intersection targets of DS-CX drug pair-Kawasaki disease. (a): Biological process (b): Cellular component

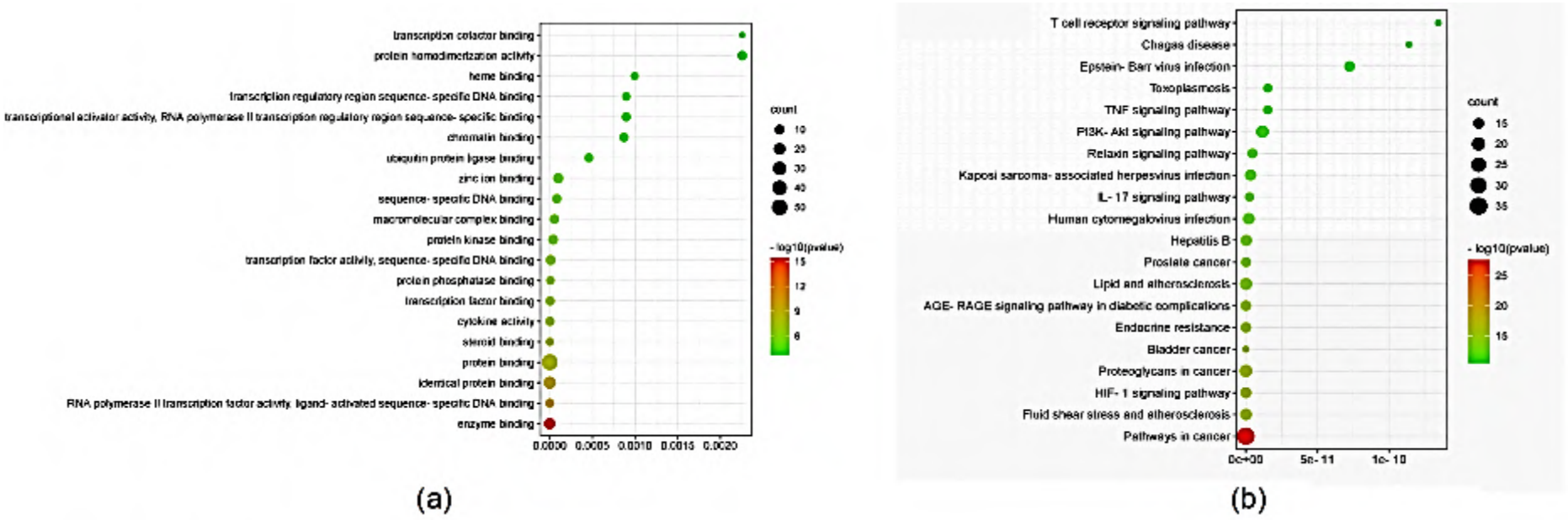

Figure 6: Bubble diagram of GO functional and KEGG pathways enrichment analysis of intersection targets of DS-CX-Kawasaki disease. (a): Molecular function (b): KEGG pathways

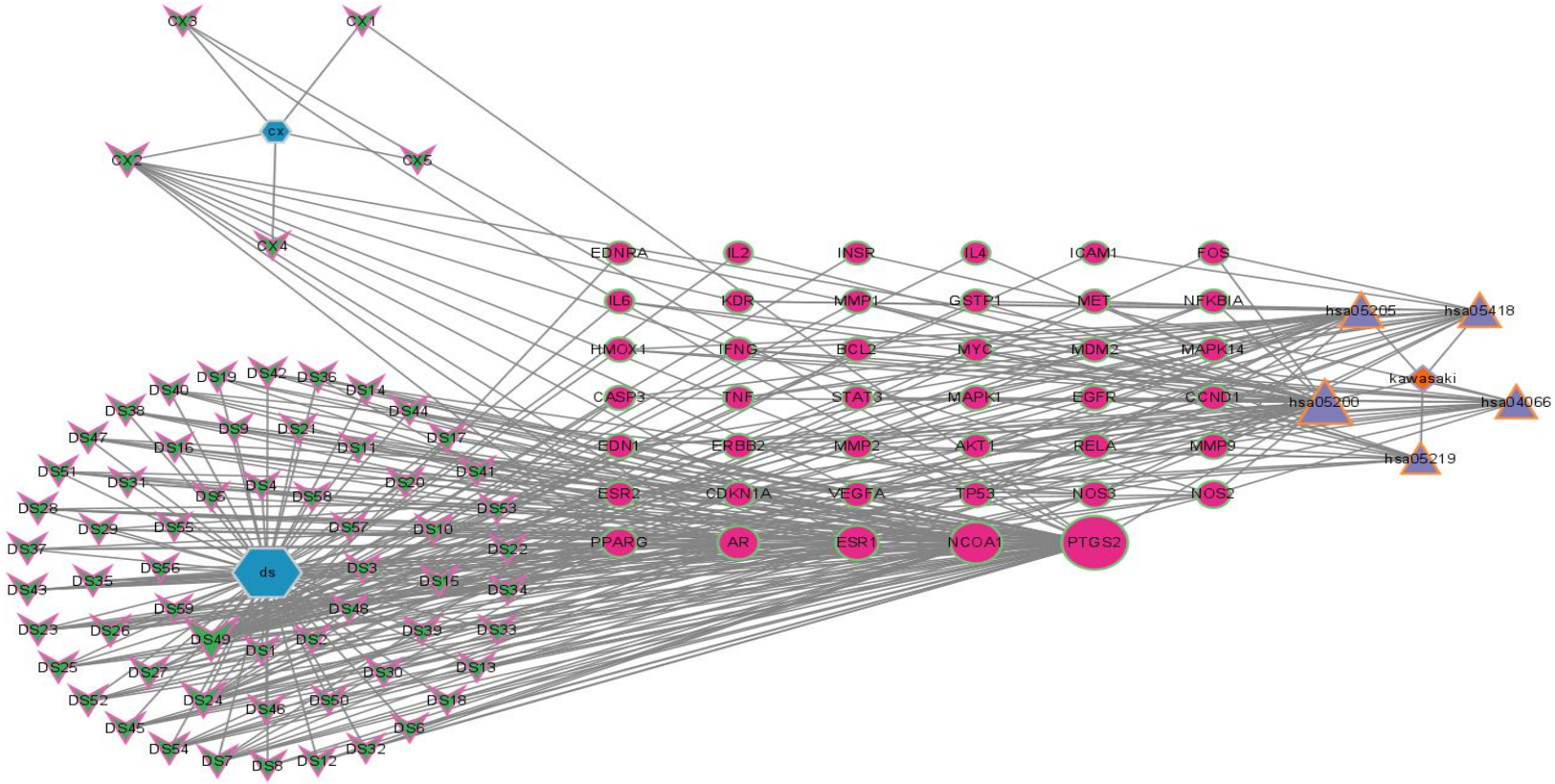

Figure 7: Components-target-pathways network for DS-CX drug pair

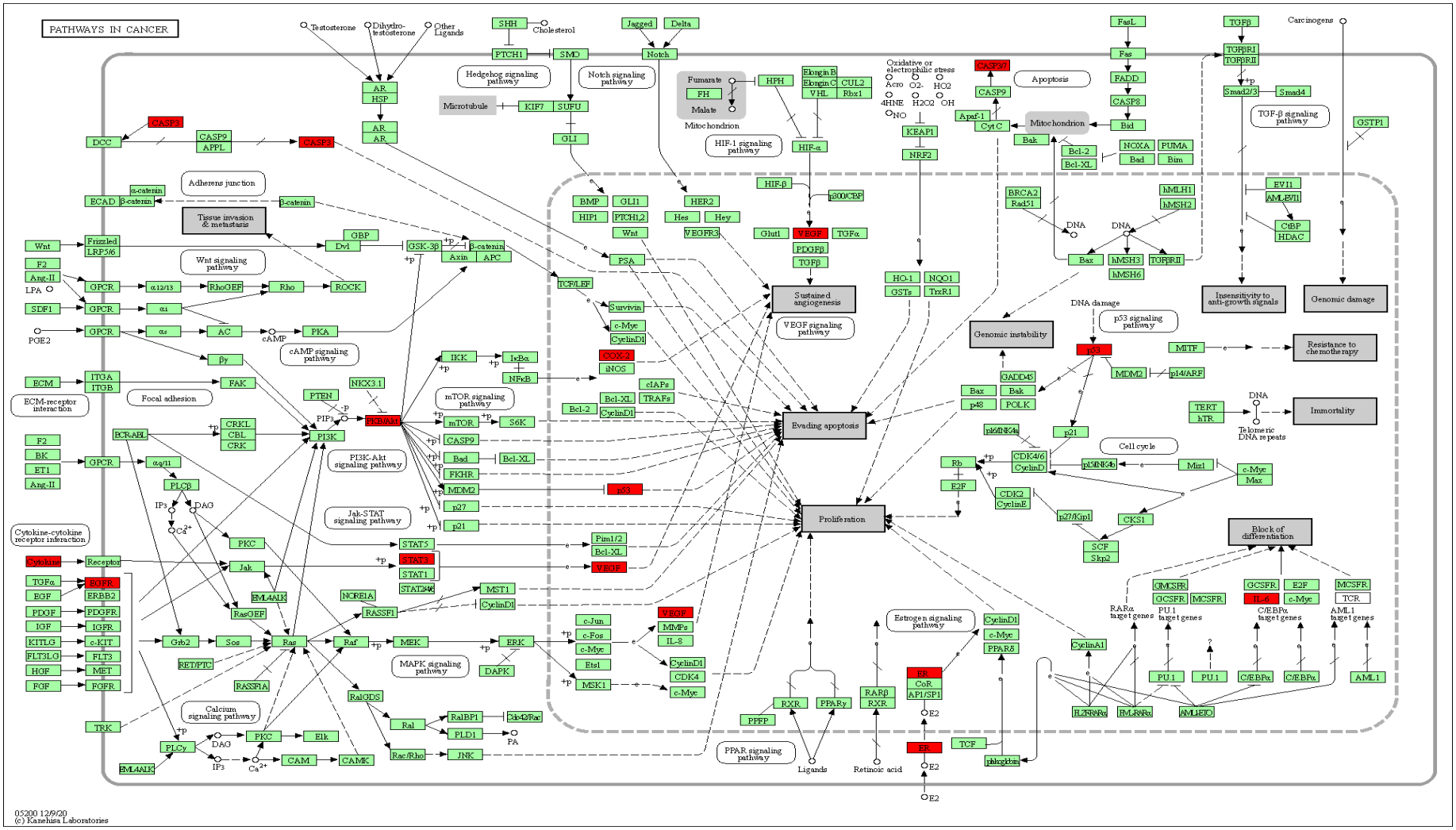

Figure 8: Intersection targets of DS-CX drug pair-Kawasaki disease in cancer pathways

Network pharmacology investigates the network of biological systems to create multi-target therapeutic compounds and selects particular nodes based on the idea of systems biology. This study screened key active ingredients and potential mechanisms of DS-CX, to provide reference for Kawasaki disease treatment with traditional Chinese medicine. The drug-component-disease-target interaction network analysis revealed that the main active ingredients of DS-CX were luteolin, tanshinone iia and myricetin.

Luteolin is a natural flavonoid, that is found in many plants and has antioxidant and pro-oxidant effects, as well as anti-microbial, anti-inflammatory and cancer-preventive properties. In addition, myricanone, which is mainly found in Chuanxiong, also has significant anti-inflammatory activity. Experimental data showed that tanshinone iia significantly reduces serum pro-inflammatory cytokine levels and exerts potential therapeutic effect on Kawasaki disease by inhibiting the production and activity of megakaryocytes in immune vasculitis [10]. Also, KEGG pathway enrichment analysis revealed that DS-CX for Kawasaki disease primarily engaged pathways in cancer which is in tandem with previous studies [11]. All of the genes enriched on cancer pathways (AKT1, IL6, TP53, CASP3, PTGS2, VEGFA, STAT3, EGFR, and ESR1) in this study were strongly correlated with Kawasaki disease.

Enhancing nitric oxide levels and maintaining vascular endothelial function by specifically activating AKT1 may lessen the damage following carotid ligation in vascular endothelial cells [12]. In a prospective study [13], serum interleukin-6 (IL6) levels were shown to be associated with coronary artery changes in patients with Kawasaki disease. Tumor protein p53 (TP53; a key gene) plays a crucial role in tumor suppression, influencing cell cycle, DNA repair, apoptosis, signaling, transcription, autophagy, and controlling cell growth, differentiation, and senescence [14]. Since genetic variants also lead to vascular structural damage and remodeling, Kawasaki disease may be related to TP53 in this regard. Furthermore, a change in the expression of CASP3 in immune effector cells affects Kawasaki disease susceptibility and activates external and endogenous cell death pathways, which collectively play a crucial role in apoptosis [15].

The PTGS2 contains the gene for cyclooxygenase 2 (Cox-2), a key inflammatory mediator in the atherosclerotic process that has been demonstrated to be expressed in vascular smooth muscle, monocytes, and fibroblasts [16]. The VEGFA interacts with tyrosine-protein kinase receptors on vascular endothelial cells to increase cell survival and vasodilation and is a susceptibility gene for Kawasaki disease [17]. Degree of vascular inflammation in Kawasaki is correlated with STAT3 gene expression, and this study has shown that STAT3 protects the vasculature by down-regulating pathways following the administration of STAT3 inhibitors [18].

The EGFR is an epidermal growth factor receptor that, when activated, promotes epidermal cell proliferation and epidermal repair [19]. Also, ESR1 is a hub of OLFM4-induced keratinocytes that promotes wound healing by regulating dermal and epidermal cell spacing in the skin [20]. Cutaneous signs of Kawasaki disease may be related to either of these targets. The results also showed that some core genes and active ingredients in DS-CX-active ingredient-target gene Kawasaki disease network were related to platelets.

Limitations of this study

This study has some limitations. This study investigated the active ingredients and possible targets of DS-CX through network pharmacology and did not further validate the findings following *in vitro* or *in vivo* experiments. It is hoped that with the advancement of modern pharmacological techniques and novel therapeutic approaches targeting specific clinical markers, new ideas may be available for precise diagnosis and treatment of Kawasaki disease.

CONCLUSION

Danshen Chuanxiong (DS-CX) regulates core genes such as AKT1, IL6, and TP53 through luteolin, tanshinone iia, and myricanone, exerts anti-inflammatory, anti-platelet, and helps vascular repair and remodeling, and also acts on cancer pathways. Further studies to validate Danshen and Chuanxiong for the treatment of Kawasaki disease are needed to determine its mechanism of action.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Aiyuan Cai and Siting Xu conceived and designed the study, and drafted the manuscript. Aiyuan Cai, Siting Xu, Jie He, Meiping Shi, Lanlin You, Zhongbin Pan and Yanxia Zheng collected, analyzed and interpreted the experimental data. Jie He and Meiping Shi revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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