The Mechanism of Aidi Injection on Breast Cancer Based on Network Pharmacologyanalysis

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Abstract

Background: Aidi injection (ADI)is a Chinese patent medicine with anti-cancer effect, which has been used to treat breast cancer (BC) in China for many years, but its potential pharmacological mechanism is still indeterminacy. In this resaearch, network pharmacology, a systematic and comprehensive approach, was used to reveal ADI's potential pharmacological mechanism in treating BC for the first time.

Methods: Databases were used to collect targets related to the bioactive components of ADI and BC. the relevant networks were established by the string database, and were screened potential bioactive components and core targets. Eventually, core targets and pathway enrichment were analyzed by DAVID database.

Results: As the results showed, we collected 99 bioactive ingredients,345 ADI-related targets after deduplication and 368 BC-related targets. Of these, 108 common targets were overlapped. We then performed an enrichment analysis on the common target network and the protein-protein interaction (PPI) network.

Conclusion: The results showed that ADI may inhibit breast cancer through seven important signal pathways involved in the "regulation of vascular endothelial function", "inflammatory response" and "apoptosis" biological processes. Through further clustering and enrichment analysis of the PPI network of ADI's bioactive component targets and BC-related targets, we found that cancer, ErbB, MAPK, TLR, chemokine, p53 and cell cycle signaling pathway, mainly contributed to the effects of ADI in treating BC. In conclusion, this study reveals the possible mechanism of ADI in treating BC, and provides a new direction for drug development for ADI in treating BC.

1. Background

The incidence and mortality of cancer have increased year by year, and cancer has become the leading cause of death [1]. Among women, BC have the highest incidence in recent years and are on the rise, which seriously threatening their health[2].Worldwide, there are about 2.1 million newly diagnosed female BC cases in 2018, accounting for almost 1 in 4 cancer cases among women[3]. The disease is the most frequently diagnosed cancer in the vast majority of the countries (154 of 185) and is also the leading cause of cancer death in over 100 countries[4].In clinic, radiation therapy, chemotherapy, endocrine therapy, photodynamic therapy and targeted therapy are commonly used. However, they have some disadvantages [5]. For example, radiotherapy will induce large gastrointestinal reactions, obvious decline in blood imageradiation dermatitis, radiation pneumonia, and so on [6]. Another example is that in neoadjuvant chemotherapy, patients who are not sensitive to chemotherapy, which will expand the scope of surgery, increase the difficulty of surgery, and may even lose the opportunity of surgery.

Chinese Herbal Medicine has been one of the most frequently used alternative treatments for different types of cancer. Chinese medicine has been paid more and more attention by doctors and patients. For

patients who have received systemic adjuvant chemotherapy, traditional Chinese medicine treatment can effectively combine with western medicine to alleviate toxic side effects caused by chemotherapy drugs, such as blood cell reduction, nausea, vomiting, diarrhea, rash, hair loss, fatigue, etc[7-8]. Many laboratory studies have shown that crude extracts of Chinese herbal medicines and active ingredients can inhibit BC cell proliferation and migration, induce apoptosis of breast cancer cells in vitro, and reduce the side effects of chemotherapy drugs[9-11] .

Aidi injection (ADI, Z52020236, China food and Drug Administration) includes *Mylabrisphalerata Pallas* (Ban Mao), *Acanthopanax senticosus*(Ci Wu Jia),*Astragalus membranaceus*(Huang Qi) and *Panax ginseng* (Ren Shen)，which has the effects of clearing away heat, detoxifying, eliminating phlegm and dispersing stasis. Their main active ingredients are cantharidin, astragaloside, ginsenoside, elentheroside E, isofraxidin, syringin, coniferin and so on. ADI has been used to treat the cancers, including gynecological malignancies, primary liver cancer, lung cancer, BC etc[12-14].Studies have shown that ADI can inhibit proliferation, promote apoptosis and necrosis of BC cells, and significantly reduce cell diameter[15].In addition, it can reduce the serum VEGF level in BC patients, and inhibit tumor angiogenesis, thereby inhibiting tumor cell proliferation, invasion and metastasis[16]. However, its mechanism is largely unknown to us.

It can also be seen that Chinese medicine has the characteristics of multiple components and multiple targets, and in previous studies, comprehensive data could not be obtained. In recent years, network pharmacology has integrated the multidisciplinary technologies and contents of systems biology, multi-directional pharmacology, bioinformatics and computer science to carry out "disease phenotype-gene-target-drug". By establishing a multi-level network, we explored the relationship between drugs and diseases, clarified the mechanism of drug action, and studied its integrity, systemi city, and complexity. The results may guide the development of new drugs. This research method is consistent with the characteristics of traditional Chinese medicine [13]. To construct the "drug component-target" multi-level biological network of ADI, network pharmacology method was used in this study.

2. Methods

2.1. Collecting drug molecular information and screening for active molecules

Chemical compounds in ADI were mainly obtained from the TCM systems pharmacology database (TCMSP, http://tcmspw.com/tcmsp.php) and the TCM database@Taiwan (TCM@Taiwan, http://tcm.cmu.edu.tw), the two largest pharmacological data platforms for Traditional Chinese Medicine. They contain all herbs, chemical components and pharmacokinetic properties (namely, absorption, distribution, metabolism and excretion or ADME) information in the Pharmacopoeia of the *People's Republic of China* (2010 edition)[17]. In addition, the databases of the China National Knowledge Infrastructure were also used to supply any omitted components. Finally,313 components from ADI were

collected, including 190, 87, 9 and 27 from Renshen, Huangqi, Ciwujia, and Banmao, respectively (Supplementary Table S1)

2.2 Pharmacokinetics ADME Assessment

The recommended standard refers to the TCMSP database (TCMSP, http://ibts.hkbu.edu.hk/LSP/tcmsp.php), which includes only predicting the octanol-water partition coefficient (AlogP) and drug similarity (DL). If AlogP<5 and DL≥0.18 is satisfied, when the compound is retained, the compound that didn't not conform to the standard compound would be removed from the list. The final compound was obtained. (Supplementary Table S2).

The screened compound molecules were then searched in the Pubchem database (https://pubchem.ncbi.nlm.nih.gov/) and the found compounds in the PubchemCID number and SMILES format were recorded with molecular SDF file is saved. The molecules which were not found in Pubchem, in the Swiss Target Prediction database (http://www.swisstargetprediction.ch/), drew the same structure according to the formula in the TCMSP database, then recorded the SMILES format and saved the SDF file of the molecule.

2.3 Prediction of compound-related target genes

We upload the SDF file saved in the previous step to the pharmmapper database (http://www.lilab-ecust.cn/pharmmapper/), and fill in the mailbox, then continue to select "Human protein targets only", and finally get all predictions molecularly related targets. We then found the official name of the predicted gene on the UniProt website (http://www.uniprot.org/) and selected "Search / ID Mapping", selecting the type as "Homo sapiens". Finally, our various ID forms will be converted to UniProt ID. This data is arranged into the ADI's drug component-target relationship data set (SupplementaryTable3).

2.4 Obtaining genetic data related to BC

BC-related genes are available from two official databases: Gene Cards database (https://www.genecards.org/), online Mendelian inheritance (OMIM, http ://www.omim.org/) and the simple "Homo sapiens" chose the protein linked to BC (SupplementaryTable4).

2.5 Network construction

We followed the method of Li et al to continue the following work according to the previous work in our laboratory [18], and we used Cytoscape (http://www.cytoscape.org, version 3.7.1) [19] to construct the common-target network selected from ADI and BC (Supplementary Table5).

PPI network construction. Protein is a biological macromolecule. Organisms have the synergistic effect of protein to complete various life activities and achieve various life functions. The various functions of an organism are manifested by the interaction of many proteins under specific conditions rather than by individual proteins. Establishment of PPI networks can make the link between prediction targets and other human proteins closer, which has become a promising target for drug discovery [20]. Using Cytoscape plug-in Bisogenet to build and visually analyze at different detail levels, the network contains six main PPI databases, including the biomolecular interaction network database (BIND), the complete molecular interaction database (complete), the human protein reference database (HPRD), the molecular interaction database (MINT), and the biological interaction database master database (Biogrid) [21]. We define the identifier as "Homo sapiens, protein identifier only" in the Bisogenet program, select the PPI data sources, set the distance from the input set to the new nodes as "1", and represent the output as "proteins". We establish PPI networks with BC related goals and ADI related goals.

Central network evaluation. Along with the rapid development of bioinformatics technology, the evaluation of the central network of PPI networks containing a large number of gene combinations and proteomics data becomes the main method to screen the core proteins. The PPI network BC related goals and ADI related goals is merged and then intersected. Then we use the plug-in of the CytoNCA evaluate intersection. Cytonca includes six centriality measures, such as degree centrality (DC), closed centrality (CC), network centrality (NC), Betweenness centrality (BC), method based on local average connectivity (LAC) and eigenvector centrality (EC) [22], to filter the data. We take the “DC ≥ 2 × median DC” as the screening criteria for preliminary processing of data, and the criterion used for secondary screening is "DC、BC、EC、CC、LAC、NC greater than or equal to their median"[23] (Supplementary Table 6) for data screening as the core target.

Cluster analysis. Clustering analysis can be performed by extracting nodes with the same or similar attributes as clusters for sub-regional analysis of complex PPI networks.The core-target PPI network (Supplementary Table 7) conducted cluster analysis by MCODE, a cluster analysis algorithm in Cytoscape in this research [24,25] .

2.6 Enrichment analysis

Annotated Visualization Database and Integrated Discovery Database (DAVID, https://david.nicifcrf.gov/, version 6.8) with P≤0.05 as screening criteria were used for gene ontology (GO) enrichment analysis[26, 27]. We used the DAVID database to apply for Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis with p≤0.05 as screening criteria[28] to reveal the gene pathway annotation network for functional groupings. Furthermore, a collection of tools for "Search Pathway" and "Color Pathway ", KEGG Mapper (https://www.genome.jp/kegg/mapper.html) which is used to analyze the connections between upstream and downstream in main signaling pathways[29]. The mechanism of ADI therapeutic BC (Supplementary Table S8, 9, 10) is revealed by enrichment analysis of common target networks and PPI networks.

3. Results

3.1 ADI component-target network

We collected 313 ADI components from the TCMSP and TCM@Taiwan natural products database, of which 190 were from Renshen,87 from Huangqi and 9 from Ciwujia,27 from Banmao. The components were screened with the criteria of AlogP<5 and DL ≥ 0.18, and 99 bioactive components of ADI were included, of which 47.5% (47/99) were from renshen,40.4% (40/99) from Huangqi,9.1% (9/99) from Ciwujia and 3.0% (3/99) from Banmao. (Fig.1A,B). Of these 99 bioactive components, three groups from Renshen, Huangqi, and Ciwujia overlapped significantly, indicating that different herbs in a formula could share the same or similar components and targets with synergistic effects. Generally speaking, the therapeutic and preventive effects of a compound formula rely on the synergies among the multiple components, targets and pathways[30].Subsequently, the structure information of bioactive components such as molecular structures, canonical smiles and their "sdf" files is obtained from Pubchem and ZINC product databases. After removing duplicate samples, 351 potential targets were explored from 99 bioactive ingredients. Then, we used Cytoscape to build a visual ADI target network with 443 nodes and 863 edges (Fig. 1C).

3.2 Common-target network

We input the 108 common targets into the DAVID for GO and KEGG analysis to obtain 71 biological processes (BP),12 cellular components (CC), 22 molecular functions (MF), and 81 KEGG pathways(P<0.05) to understand the mechanism of ADI treatment BC (Fig. 2A, B).

We found that the enrichment pathways were cancer pathways, ErbB signaling pathways, and MAPK signaling, which are closely related to the occurrence of BC. In addition, we found that ADI inhibited tumorigenesis by regulating the biological processes of nitric oxide, controlling cell proliferation and apoptosis, and inhibiting angiogenesis. In addition, the positive regulation of the ERK1 and ERK2 cascades is also considered to be closely related to cell proliferation, transformation, and differentiation, etc., and is of great significance to elucidate the pathogenesis of BC.

3.3 ADI-BC PPI network

Bisogenet established a PPI network ADI related objectives and BC related objectives (Fig. 3A, B). Then the same nodes and edges in two PPI networks will obtain an intersection point (Fig. 3C). Next, the intersection of the PPI network is evaluated CytoN selecting topology analysis. The significant target of ADI on BCPPI network is selected by the "DC>=44"" screening criterion (Fig. 3D). Six screening criteria were selected for further screening, and a core target PPI network containing 423 ADI candidate targets was obtained.

3.4 Enrichment analysis of the 422 key targets.

We elucidated the biological functions of 422 major targets by dividing the final central PPI network into eight clusters and selecting GO and KEGG pathways for enrichment analysis, respectively. A total of 379 BPs, 67 CCs, and 92 MFs were obtained. Based on the results of these GO terms, it could be seen that the development of BC was closely related to various biological processes, such as angiogenesis, cell proliferation, apoptosis, inflammatory response, ubiquitinated proteins, etc. The KEGG enrichment results of these eight clusters overlapped with the KEGG enrichment results of 108 common targets.It was found that the ADI enrichment pathway mainly focused on the cancer, ErbB, MAPK, TLR, chemokine, p53 and cell cycle signaling pathway.(Fig.4)

4. Discussion

BC is one of the most common diseases in the female population [31]. It poses a serious threat to human health, especially women's health. Facing this complex disease, traditional Chinese medicine (TCM) with multiple components and multiple targets is an important and commonly used adjuvant therapy in China. TCM can not only relieve the discomfort of cancer, but also can be used throughout the treatment process. Studies have shown encouraging results with traditional Chinese medicine for breast cancer[32,33].The ADI we studied was composed by Renshen,Huangqi,Ciwujia and Banmao. In 2000, it was identified as a secondary protection Chinese medicine and a National Medical Insurance Class B drug[34]. In clinical, ADI has been used to treat various malignant tumors, including BC. However, its biologically active ingredients and mechanism are still unclear, which greatly limits its clinical application. With the rapid development of bioinformatics, network pharmacology has become an effective method to study the relationship between biologically active ingredients and the mechanism of TCM.

In this study, we focused on three aspects of network pharmacology (Fig.5). First the occurrence of cancer and some other diseases were found in the enrichment analysis of 108 common targets. Second, exhibited a refined detail of ADI on BC compared to the common-target analysis. Third, at the gene level, cancer pathway, ErbB, MAPK, TLR, chemokine, p53 and cell cycle signaling pathway are considered to be the key pathways for treating BC.

We then searched for seven key signaling pathways of ADI related to BC treatment. Cancer pathways can be found to be directly related to cancer. Many studies have found that breast cancer may be caused by regulating the ErBb signaling pathway [35]. By reducing the phosphorylation of the receptor tyrosine kinases ErbB1, ErbB2, and ErbB3, the ErbB signaling pathway can be inhibited, thereby suppressing the occurrence of breast cancer [36]. The core genes involved in this pathway are EGRF and Akt1. EGRF is one of the ErBbs receptor tyrosine kinases. Studies have shown that tumor growth and metastasis can be inhibited by inhibiting EGF-induced EGFR signaling pathway and its downstream targets [37]. Akt plays important biological roles, such as participating in cell survival, apoptosis, proliferation, angiogenesis and

other physiological processes and tumorigenesis[38].Studies have found that down-regulating Akt phosphorylation inhibits tumor development. After ErbB2 and ErbB2 receptors bind in the ErBb signaling pathway, they activate intracellular phosphatase activity, then phosphorylate PIP2 to generate PIP3, and recruit Akt proteins to the inner surface of the cell membrane. In our research, we also found that chemokines are closely related to tumorigenesis and growth. Through targeted MAPK signaling pathways and chemokine signaling pathways, It could be seen that they were abnormally expressed in many malignancies and played a vital role in the process of metastasis. Chemokines regulate tumor growth by affecting tumor stromal cells, inducing cell growth in the tumor microenvironment, and releasing angiogenic factors [39,40].The AKT signaling pathway is an intracellular mechanism of chemokine-mediated VEGF-C secretion in human breast cancer cells [41]. In promoting tumorigenesis and development, chronic infection and inflammation are considered the most important acquisition and environmental factors. The Toll-like receptor signal transduction pathway is related to inflammation. It can be considered that inflammation is also one of the mechanisms leading to breast cancer. The P53 signaling pathway is the major pathway in cell cycle control, and account for about 50% of human malignancies[42].

The polymorphism of human genetic genes determines the human body's sensitivity and response to diseases and drugs, and the diversity of clinical manifestations. This is similar to the concept of “Zheng” (pattern) in TCM-a summary of pathological characteristics at a certain stage of disease development, and it is a functional state in which the body responds to pathogenic factors. Based on this, we speculate that one of the theoretical foundations of TCM is natural polygenes [43, 44]. We believe that ADI is effective for breast cancer from the level of gene repair and expression to the level of signal transduction and cascade activation in the pathway. Meanwhile, the relationship between human genetic polymorphism and TCM model type/treatment effect was emphasized by some researchers from the perspective of clinical and experimental trials [45]. Therefore, a new research method to verify the effectiveness of TCM may be polygenic analysis. However, our study still has some limitations. First, our collection of bioactive components and targets is not comprehensive enough. we modified it by new detection methods such as liquid chromatography, mass spectrometry, two-dimensional liquid chromatography or quadrupole time-of-flight mass spectrometry. Second, our online pharmacology lacks validation of animal and clinical trials. In the future, the relationship between TCM model type and genetic polymorphism will be verified in animal experiments and clinical trials.

5. Conclusions

According to the results, the therapeutic effects of ADI were mainly through seven important signaling pathways in three biological processes, namely"regulating vascular endothelial function","inflammatory response" and "apoptosis". Among them, ErbB signaling pathway, chemokine signaling pathway, p53 signaling pathway, and cell cycle can be considered as the main pathways for ADI to treat breast cancer. This study reveals the potential mechanism of action of ADI on in treating BC to some extent. It also provides a new direction for drug development for ADI in treating BC.

6. Abbreviations

ADI: Aidi injection, BC: Breast Cancer, TCM: traditional Chinese medicine, TCMSP: Traditional Chinese Medicine Systems Pharmacology, AlogP: the octanol-water partition coefficient, DL: drug-likeness, BPs: biological processes, CCs: cell compositions, MFs: molecular functions, ADME: absorption, distribution, metabolism and excretion, OMIM: online Mendelian inheritance, PPI: protein protein interaction, BIND: biomolecular interaction network database, HPRD: the human protein reference database, MINT: the molecular interaction database, DC: degree centrality, CC: closed centrality, NC: network centrality, BC: Betweenness centrality, LAC: local average connectivity, EC: eigenvector centrality, GO: gene ontology, KEGG: Kyoto Encyclopedia of Genes and Genomes,PI3K: phospholipid phthalinositol kinase, MAPK: mitogen-activated protein kinase, AKT: protein kinase B, MMP2: matrix metalloproteinase 2, MMP9: matrix metalloproteinase 9,TLR: Toll like receptors.

7. Declarations

7.1. Ethics approval and consent to participate

Not applicable.

7.2. Consent for publication

Not applicable.

7.3. Availability of data and materials

The data used to support the results of this study can be obtained from the first author upon reasonable request.

7.4. Competing interests

The authors declare that they have no conflict of interest.

7.5. Funding

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7.6. Authors' contributions

Jing Su: Investigation, Methodology, Writing - original draft; Kedi Liu: Investigation, Methodology, Writing-original draft; Xingru Tao: Investigation, Methodology, Writing - original draft; Fei Li: Resources, Software; Shi Zhao: Resources, Software; Yang Bai: Resources, Software; Xinming Lu: Data curation; Jing Li: Data curation; Sha Chen: Data curation; Jialin Duan: Writing - review & editing; Peifeng Wei: Writing - review & editing; Miaomiao Xi: Funding acquisition, Project administration, Writing - review & editing.

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Figures

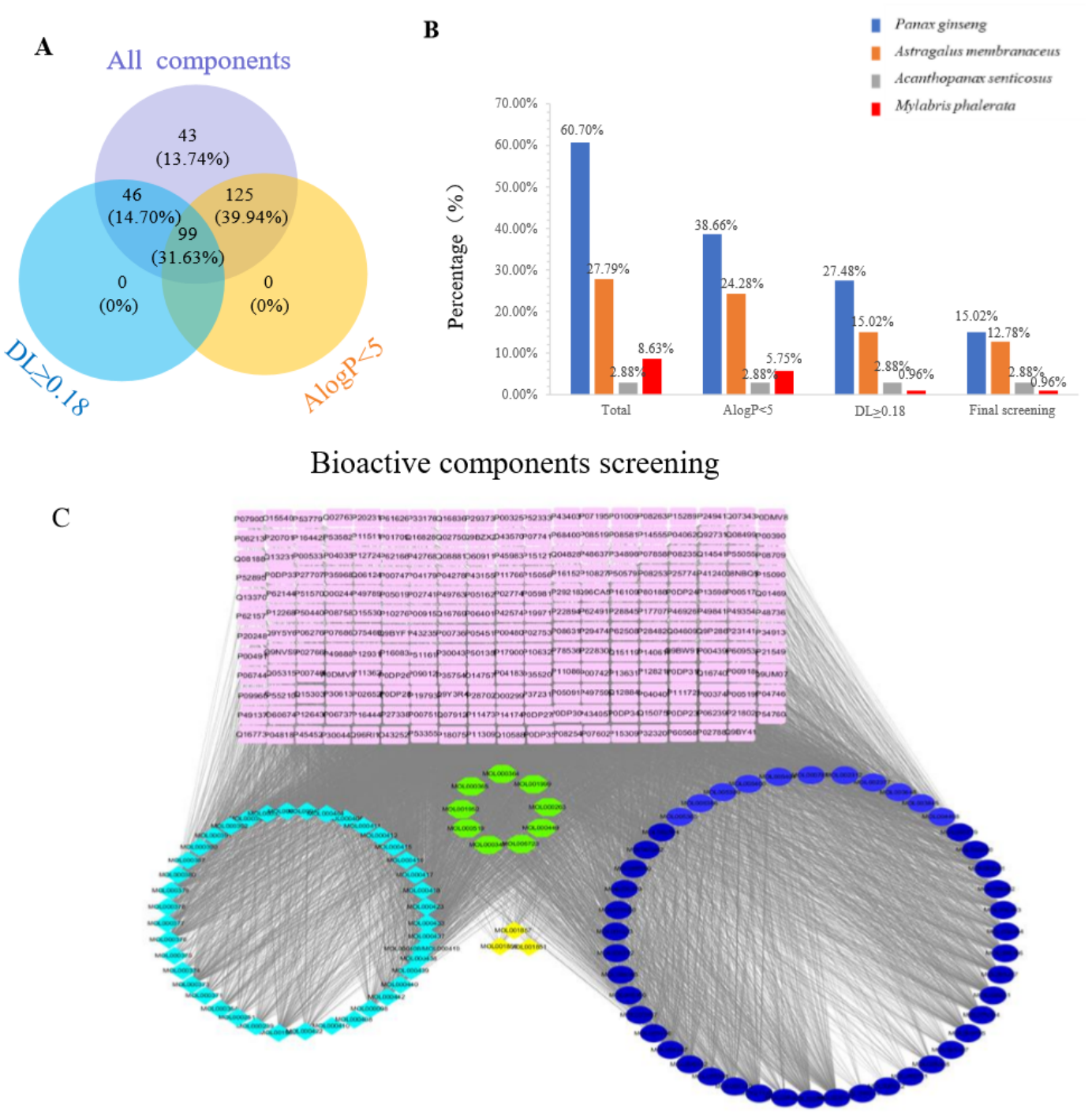

Figure 1

ADI component-target network. (A) Venn diagram: two ADME related models screen 99 bioactive components (blue section indicates AlogP<5 components, yellow section represents DL≥0.18). (B)Distributions of different herbs. (C)Establishing a visual network of ADI components including 443 nodes and 863 edges. The blue, yellow, green and orange nodes represent bioactive components from renshen, astragalus, ciwujia and banmao, respectively. The pink nodes represent the target.

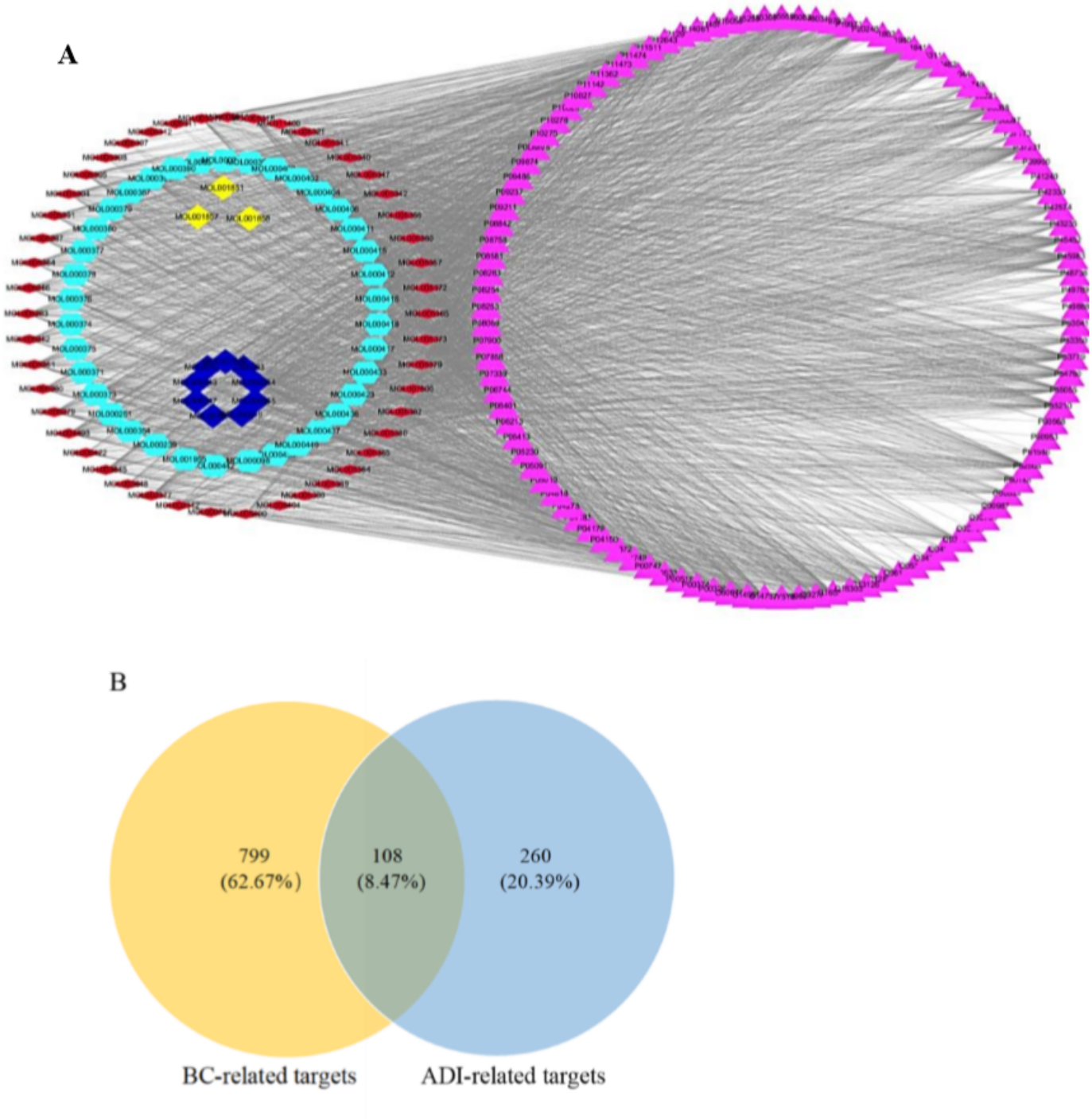

Figure 2

Common-target network. (A) The commom target network consists of 204 nodes and 3213 edges. The red, sky blue, blue and yellow nodes repre sent the bioactive components of Renshen, Huangqi, Ciwujia and Banmao, respectively, and the pink nodes represent the target. (B) ADI and BC have 108 common targets.

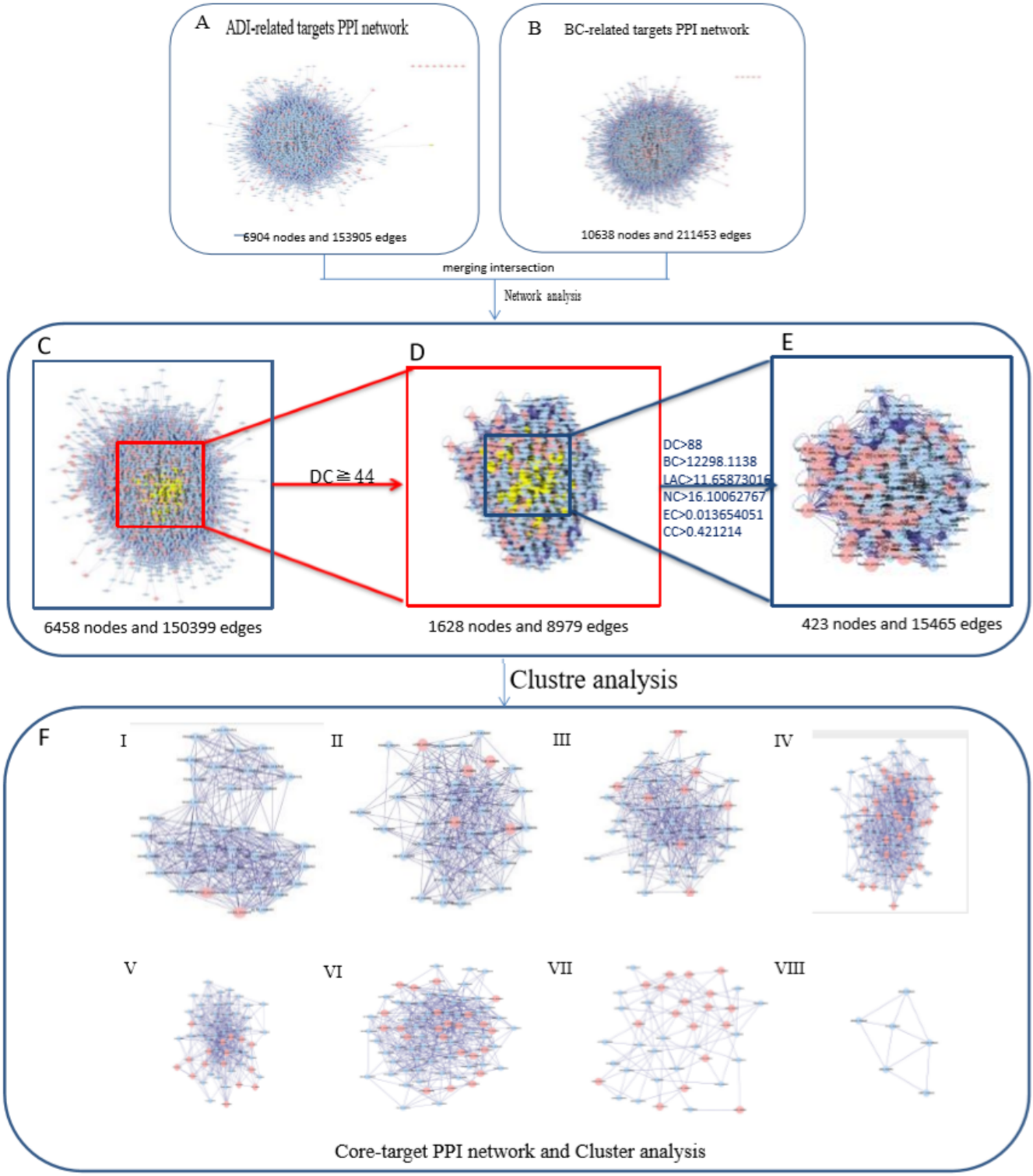

Figure 3

ADI-BC PPI network. (A) Targets PPI network related to ADI (6,904 nodes and 153,905edges). (B) Targets PPI network related to BC (10,638 nodes and 211,453 edges). (C) PPI networks intersection(6,458 nodes and 150,399 edges). (D) PPI networks using DC >44" as screening criteria (1,628 nodes and 18,966 edges). (E) Network with "DC">88"EC">0.013654051"LAC">1165873016"BC">11298.1138"CC">0.421214 and"

NC">1610062767 as the core goal PPI screening criteria (423 nodes and 15,465,465 edges) .(F) Clusters of core-target PPI network. Pink indicates ADI related target and BC related target. yellow and blue indicate the selected target of screening criteria and other human proteins, respectively.

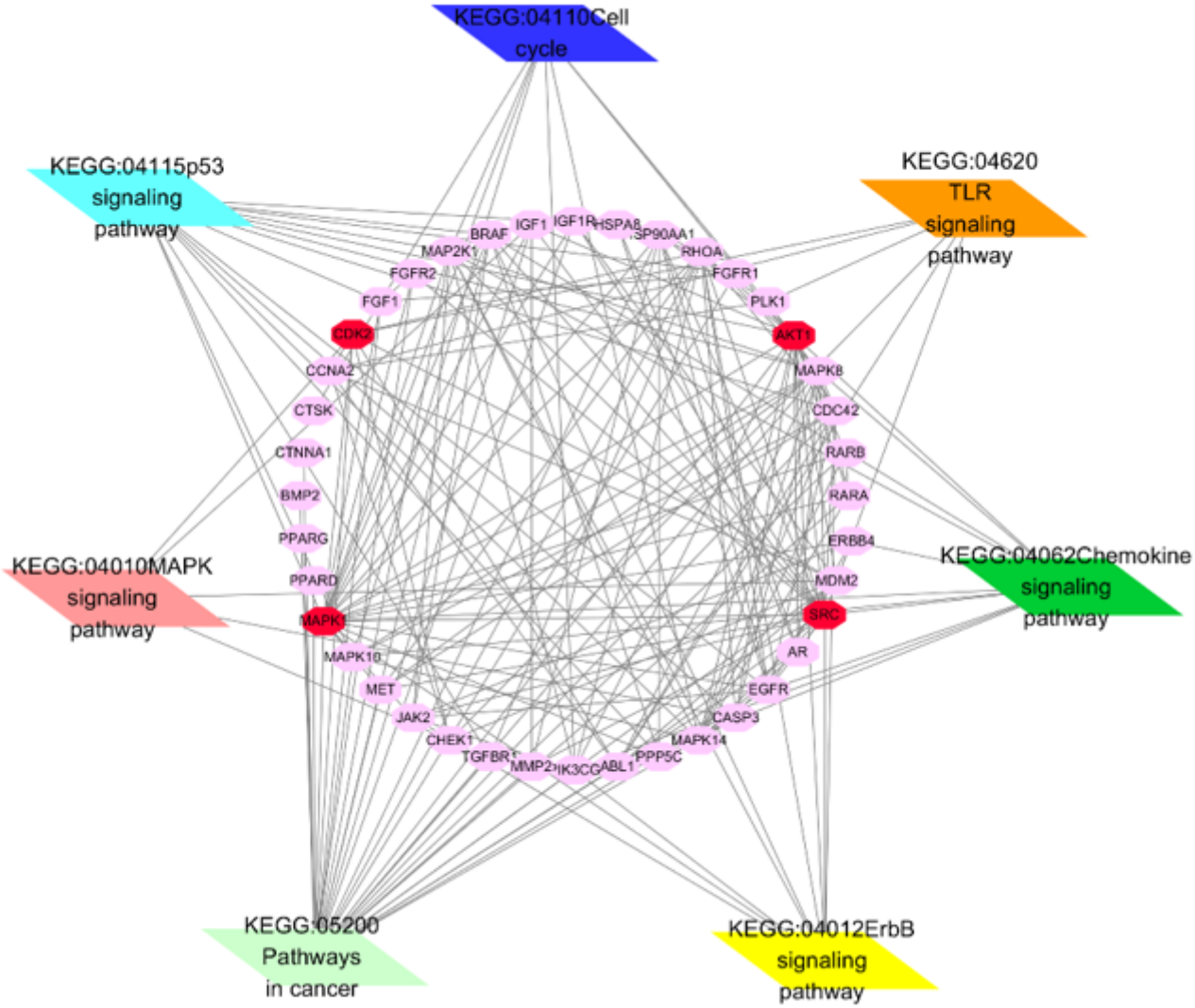

Figure 4

Core target path network. Sky blue, dark blue, purple, light green, yellow, dark green and orange nodes represent the seven signal paths of the main targets in the enrichment analysis; pink nodes represent the important common goals of ADI and BC; red nodes represent the core common goals screened by the PPI network.

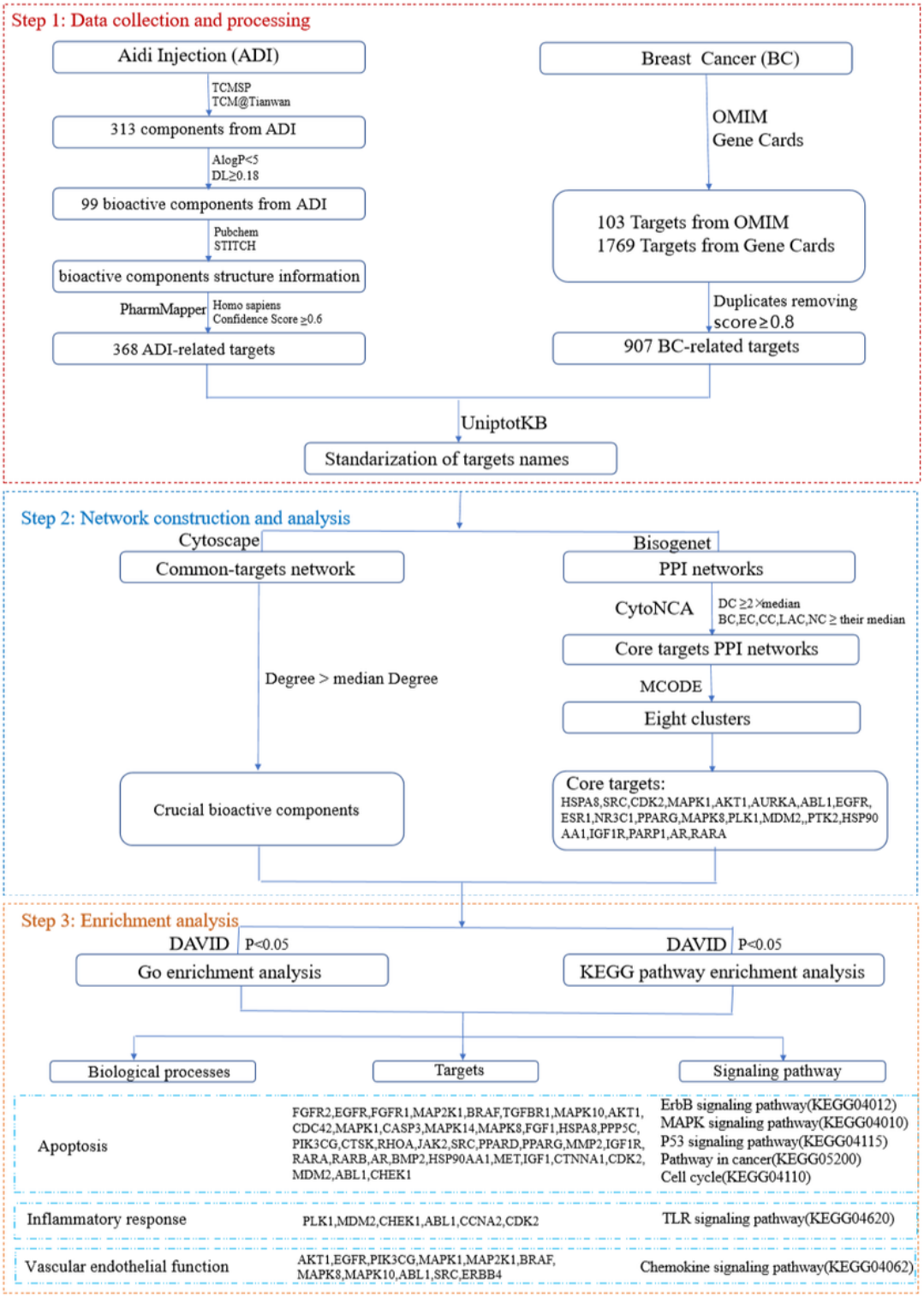

Figure 5

Diagram of the study design.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- S1.ComponentsofeachherbinADI.xlsx
- S2.BioactivecomponentsofeachherbinADI.xlsx
- S3.PotentialtargetsofbioactivecomponentsinADI.xlsx
- S4.KnownBCrelatedtargets.xlsx
- S5.108commontargetsbetweenADIandBC.xlsx
- S6.Networkcentralityanalysisandevaluation.xlsx
- S7.GOandKEGGpathwayanalysisforthe108commontargets.xlsx
- S8.TheClusterofthecoretargetPPInetwork.xlsx
- S9.GOanalysisforeachcluster.xlsx
- S10.KEGGpathwayanalysisforeachcluster.xlsx