

C-C,N,S treats atrial fibrillation through regulating inflammatory procession: a study of network pharmacology research and gene set enrichment analysis validation

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Abstract

Triangle drug combination of *Citrus medica L.var.sarcodactylis Swingle*, *Naradostachys jatamansi DC.* and *Salvia miltiorrhiza Bge.* (C-C,N,S) is usually appeared in atrial fibrillation-treating (AF) decoction and has good clinical effects. However, the core pathological process and mechanism of C-C,N,S intervening AF is unclear. So we intend to use network pharmacology and gene set enrichment analysis to explore the potential mechanism. We detected all compounds of C-C,N,S from CNKI database, predicted its bioactive compounds and potential anti-AF targets from related online platforms and databases. Then through PPI network, gene expression analyses, GO and KEGG pathway enrichment analysis on anti-AF targets, we determined the potential mechanism of C-C,N,S treating AF. Finally we used gene set enrichment analysis (GSEA) to validate the therapeutic effect of C-C,N,S. In conclusion, the therapeutic effect of C-C,N,S treating AF was focused on anti-inflammation. C-C,N,S can regulate inflammatory process and inhibit atrial remodeling and fibrosis through regulating TNF signaling pathway, IL-17 signaling pathway (MAPK signaling involved in) and PI3K-Akt signaling pathway. Some genes regulated by specific herbal medicine explained reason of the combination.

Introduction

Atrial fibrillation (AF), a common type of cardiac arrhythmia, is characterized by disordered ventricular rate, impaired cardiac function and atrial mural thrombosis. According to statistics, there are 8 million years lived with disability due to AF in 2019¹. With population living longer and chronic risk factor increasing, the number would rise. AF pathogenesis is complex, and mainstream theory consider that it is related to electrophysiology remodeling, inflammation, fibrosis and neural mechanisms²⁻⁴. In addition, modifiable risk factors such as obesity, diabetes, high blood pressure and so on has been confirmed to be involved in the development of AF⁵⁻⁷. With AF continuous development, stroke, heart failure, myocardial infarction, even death would be happen⁷⁻¹⁰. So there are calling for ideal pharmacologic approaches to treat AF¹¹.

Traditional Chinese medicine (TCM) has been existing over two thousand years, hundreds of medical practitioners accumulated rich experience in treating AF using herbal medicine decoction¹²⁻¹⁴. In clinical practice, doctors prescribe herbal medicine decoction based on the actual situation of AF patients. But no matter how prescribing, some herbal medicines are always kept as an indispensable presence in AF-treating decoction. The concept of triangle drug derives from *the Yellow Emperor's Classic of Internal Medicine*¹⁵, which means three core Chinese herbal medicine, like the three sides of a triangle, are combined to treat the core pathogenesis of a certain disease under guideline by TCM theory. Triangle drug combination of *Citrus medica L.var.sarcodactylis Swingle*, *Naradostachys jatamansi DC.* and *Salvia miltiorrhiza Bge.* (C-C,N,S) (Fig. 1, Table 1) is usually appeared in AF-treating decoction and has good clinical effects proven by patients. However, the core pathological process and mechanism of C-C,N,S intervening AF is unclear. This is appeal to explore.

Table 1. The Latin and Chinese Pinyin names of three herbal medicine.

	Latin	Chinese Pinyin (Abbreviation)
A	<i>Citrus medica L.var.sarcodactylis Swingle</i>	FO SHOU (FS)
B	<i>Naradostachys jatamansi DC.</i>	GAN SONG (GS)
C	<i>Salvia miltiorrhiza Bge.</i>	DAN SHEN (DS)

After professor Li proposing TCM network pharmacology in 1999¹⁶, this method develops rapidly and applies widely¹⁷⁻¹⁹. Network pharmacology can explain effectiveness of herbal medicine through multi-compound, multi-target, multi-pathway pattern from systematic and holistic perspective²⁰. Gene set enrichment analysis (GSEA) is used to interpret micro-array data at the level of gene sets²¹. This is helpful for distinguishing up-regulated and down-regulated genes²² which can analyze potential mechanism further. These are commonly used tools in bioinformatics.

In this study, we used approach of network pharmacology and GSEA to explore the mechanism of C-C,N,S treating AF and find the core pathogenesis of AF that can be intervened by C-C,N,S. And the flow diagram is in Fig. 2.

Materials and methods

Screening of C-C,N,S bioactive compounds and predicted targets

We conducted a comprehensive search on CNKI database (<https://www.cnki.net/>) to ensure the integrity of chemical compounds present in FS, GS, and DS with a deadline of May 18, 2023. We then compiled the individual components of each herb. Subsequently, we obtained the SMILES number for each chemical component from PubChem database (<https://pubchem.ncbi.nlm.nih.gov/>) and inputted them into ADMET lab 2.0 database²³⁻²⁴ to retrieve physicochemical properties and medicinal chemistry information. Bioactive compounds were filtered based on a quantitative estimate of drug-likeness (QED) above 0.67 and the permeability of human colon adenocarcinoma cell lines (Caco-2) above -5.15 ²³⁻²⁵. Finally, the SMILES number of each bioactive component was submitted to Swiss Target Prediction online platform (<http://www.swisstargetprediction.ch/>) to obtain predicted targets.

Screening of potential targets related to AF in C-C,N,S

We performed a search in DrugBank database (<https://go.drugbank.com/>), Therapeutic Target Database (TTD, <http://db.idrblab.net/ttd/>), GeneCards databases (<http://www.genecards.org/>), OMIM database (<http://www.omim.org/>) and DisGeNET database (<https://www.disgenet.org/>) using the keyword “atrial fibrillation” with a deadline of May 18, 2023. Subsequently, we elected the genes that appeared at least twice in the aforementioned databases as the targets relevant to human AF. Finally, we determined the

common targets between C-C,N,S and AF by using Venn diagram. These common targets were identified as potential targets for treating AF with C-C,N,S.

Protein-protein interaction (PPI) network construction

We inputted a total of 129 potential targets into STRING database (<http://string-db.org>) to obtain protein-protein interaction information. The minimum required interaction score was set to high confidence (0.700). To visualize the PPI network, we used Cytoscape_3.9.1. Additionally, we employed the CytoNCA, cytoHubba and MCODE plug-ins to extract topological parameters, identify hub genes and detect potential functional modules for further analysis.

Gene expression analysis

We obtained mRNA levels of 129 targets from BioGPS database²⁶ (<https://biogps.org>). The default datasets was GeneAtlas U133A, gcrma. We selected organ/tissue/cell that were observed to be present at least 10 times over the median level as targets specific expression. Then we constructed target-specific expression network and visualized it using Cytoscape_3.9.1.

GO and KEGG enrichment analysis

We used the clusterProfiler R package to perform GO and KEGG enrichment analysis of 129 targets. The results were filtered using a significant threshold of $P < 0.01$ and visualized using the ggplot2 R package. GO enrichment analysis results selected top 20 and they were classified from biological process (BP), molecular function (MF) and cellular component (CC). KEGG enrichment analysis results selected top 50. They were categorized and summarized based on the six classifications in the KEGG PATHWAY Database (<https://www.genome.jp/kegg/>). Pathways that were not directly associated with AF were excluded from the KEGG enrichment results. Conversely, pathways that were clearly related to AF were used to construct target-pathway network. We used Cytoscape_3.9.1 to visualize it.

Gene set enrichment analysis (GSEA) validation

We retrieved GEO database (<https://www.ncbi.nlm.nih.gov/geo/>) using keyword atrial fibrillation to find suitable gene chips of AF patients. Subsequently, we used Limma R packages to filter differentially expressed genes, followed by GSEA analysis using GSEABase R package. The criteria for differential expression were set as $|\log FC| > 1$ and $P\text{-}Val < 0.05$. Finally, based on the enrichment results of pathways that showed up-regulated and down-regulated genes, we further analyzed the potential genes related to AF in C-C,N,S, and validated the functional role of C-C,N,S in treating AF.

Results

C-C,N,S bioactive compounds and predicted targets

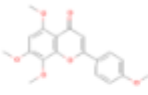
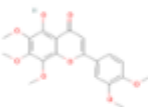
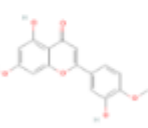
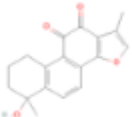
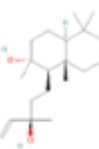
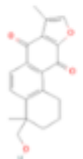
The chemical compounds of FS were found to be 138²⁷, GS were 143^{28–30}, and DS were 148³¹ (Supplementary Table 1). Following filtration, a total of 87 bioactive compounds of C-C,N,S were obtained

with 21 from FS, 27 from GS, and 40 from DS, where one compound was co-existing between GS and DS (Supplementary Table 2). In total, 810 targets of 87 bioactive compounds were obtained after removing duplicate targets (Supplementary Table 3).

Potential targets related to AF in C-C,N,S

The targets of AF from DrugBank database were 7, TTD database were 22, GeneCards database were 4941, OMIM database were 111 and DisGeNET database were 939 (Supplementary Table 4). We selected 674 targets that presented at least two above databases as AF targets (Fig. 3A-B). By intersecting, we obtained a total of 129 targets anti-AF of C-C,N,S (Supplementary Table 5, Fig. 3C). Cytoscape_3.9.1 was applied to build a network of bioactive compounds and anti-AF targets of C-C,N,S (Fig. 4). We found that some targets were regulated by three herbal medicines commonly, while another targets were regulated by one herbal medicine specifically. In addition, the top 3 compounds with the highest degree in each herbal medicine were analyzed in Cytoscape, they were 6-Demethoxytangeretin, Demethylnobiletin, Diosmetin, nardoguaianone A, nardoperoxide, nardoguaianone B, tanshinol B, sclareol and isotanshinone B (Table 2).

Table 2 The 3 core compounds of each herb in C-C₂N₂S.

ID	Compound Name	Structure	Caco-2	QDE	Degree
FS3	6-Demethoxytangeretin		-4.549	0.707	28
FS1	Demethylnobiletin		-4.609	0.688	25
FS14	Diosmetin		-4.916	0.672	24
GS5	nardoguaianone A		-4.616	0.683	27
GS3	nardoperoxide		-4.616	0.683	27
GS6	nardoguaianone B		-4.571	0.683	23
DS15	tanshinol B		-4.807	0.758	25
DS28	sclareol		-4.53	0.739	20
DS23	isotanshinone IIB		-4.905	0.75	18

PPI network

Using String 12.0 database, we constructed a PPI network comprising 123 nodes and 1216 edges (Fig. 5A-B). Figure 5C displayed the ranking of top 20 targets based on Degree (The topology properties of the network were presented in Supplementary Table 6). Top 10 hub genes were identified by the MCC algorithm in cytoHubba plug-in, and the first (TNF) and second (IL6) hub genes were regulated by GS specifically, forth (AKT1) were regulated by FS specifically, fifth (CTNNB1) were regulated by DS specifically (Fig. 5D-E). Protein clusters were generated based on MCODE plug-in, and the highest-scoring cluster (19 genes, score of 15.889) was selected for analysis (Fig. 5F). Almost hub genes were included in the highest-scoring cluster. The result of GO function analysis revealed that cellular response to chemical

stress, response to oxidative stress, cellular response to oxidative stress, response to reactive oxygen species and response to metal ion were significantly enriched (Fig. 5G).

Gene expression

Using BioGPS database, we obtained the specific expression of each gene (Supplementary Table 7). And we visualized it using Cytoscape (Fig. 6), the network showed that the highest expressed organ were liver, then were heart, kidney and lung; the highest expressed tissue were smooth muscle, then were whole blood, prefrontal cortex and adrenal cortex; the highest expressed cell were CD33⁺ myeloid, then were cardiac myocytes, adipocyte and CD105⁺ endothelial.

GO and KEGG enrichment analysis

GO enrichment analysis revealed the enrichment results of biological process, cellular compound and molecular function (Fig. 7A). The enrichment in biological process mainly included muscle system process, response to reactive oxygen species, response to oxidative stress and regulation of blood circulation. The enrichment in cellular compounds included membrane raft, membrane microdomain, focal adhesion and cell-substrate junction. The enrichment in molecular function included in voltage-gated monoatomic cation channel activity, protein serine/threonine kinase activity, endopeptidase activity and heme binding.

KEGG enrichment analysis showed that 129 genes were enriched in lipid and atherosclerosis, fluid shear stress and atherosclerosis, AGE-RAGE signaling pathway in diabetic complications, HIF-1 signaling pathway, TNF signaling pathway, IL-17 signaling pathway, Focal adhesion and so on (Fig. 7B). We categorized the top 50 pathways, and it is obviously that signal transduction was key point of C-C,N,S treating AF (Fig. 7C-D). We selected AF-related pathway to construct target-pathway network (Fig. 7E), in which MAPK1, MAPK3, AKT1, PIK3CA, PRKCA, MAPK9, MAP2K1, RAF1, TNF and IL6 gene targets were top ranked. MAPK and PI3K-Akt signaling pathway maybe the key pathways for C-C,N,S treating AF.

Gene set enrichment analysis validation

Through searching, we found a suitable gene chip set. GSE143924 were divided into two groups based on whether patient have AF or not after surgery. A total of 15 post-operative atrial fibrillation (POAF) gene chips and 15 sinus rhythm (SR) gene chips were obtained. We filtered significant genes using limma R packages, then used GSEABase R package to perform GSEA and obtained 74 significant pathways (Supplementary Table 8). There were 5 pathways which echoed the result of KEGG enrichment analysis from network pharmacology including IL-17 signaling pathway, TNF signaling pathway, PI3K-AKT signaling pathway, lipid and atherosclerosis and focal adhesion (Fig. 8, Table 3). That validated that C-C,N,S could treat persistent AF through above pathways. Further analysis, we concluded that MAPK1, MAPK3, MAPK9, CASP3, CASP8, PI3KCA, IL6, PTGS2 were high-expression in AF patients comparing with SR patients, while VEGFA, IGF1R, PDGFRB, EGFR, KIT and MET were low-expression.

Table 3. Gene targets connection between GSEA and network pharmacology.

Pathway	Gene (protein/enzyme)	Status in AF patient	Regulating by
TNF signaling pathway	MAPK9(JNK)	high	FS/GS/DS
	CASP8(CASP8/10)	high	DS
	PI3KCA(PI3K)	high	FS/GS/DS
	IL6(IL6)	high	GS
	PTGS2(Ptgs2)	high	FS/GS/DS
	MAP2K4(MKK4/7)	unchange	DS
	MAP2K1(MEK1)	unchange	GS/DS
	CASP3(CASP3)	unchange	FS/DS
	MMP9(Mmp9)	unchange	FS/GS/DS
	ICAM1(Icam1)	unchange	FS
	VCAM1(Vcam1)	unchange	FS
IL-17 signaling pathway	CASP3/CASP8(Casp)	high	FS/DS
	HSP90B1(Hsp90)	unchange	FS
	MAPK1/MAPK3(MAPKs)	high	GS/DS
	IL6(IL6)	high	GS
	PTGS2(COX2)	high	FS/GS/DS
	MMP9(MMP9)	unchange	FS/GS/DS
PI3K-AKT signaling pathway	VEGFA(GF)	low	FS/GS
	IGF1R/PDGFRB/EGFR/KIT/MET(RTK)	low	FS/GS/DS
	IL6(Cytokine)	unchange	GS
	PI3KCA(PI3K Class IA)	high	FS/GS/DS
	F2R/CHRM2(GPCR)	high	FS/GS/DS
	PIK3CG(PI3K Class IB)	high	FS/GS/DS
	PRKCA(PKCs)	high	FS/GS/DS
	MAP2K1(MEK)	unchange	GS/DS
	BCL2(Bcl-2)	unchange	FS/GS
	HSP90B1(HSP90)	unchange	FS

Discussion

Atrium high-frequency excitation is the feature of AF. The occurrence of AF is due to triggering rapidly in a vulnerable atrial substrate caused by repetitive focal ectopic firings, while the maintenance is not only related to triggers as well as vulnerable substrate but various risk factors⁵⁻⁷. These non-modifiable and modifiable risk factors work together to cause inflammation, atrium remodeling, atrium fibrosis and so on²⁻⁴. Inflammasome and inflammatory signaling pathways involve in the atrial electrical change, calcium handling and structural remodeling³²⁻³³. In addition, enhancement of inflammation will exacerbate fibrosis of cardiac fibroblasts and apoptosis of cardiac myocytes³⁴⁻³⁵. It is clearly that inflammation is key pathology of AF, and anti inflammation can delay the development of AF.

Citrus medica L.var.*sarcodactylis* Swingle (FS), *Nardostachys jatamansi* DC. (GS) and *Salvia miltiorrhiza* Bge.(DS) are general Chinese herbal medicine treating different disease, while combination of the three herbal medicine is often an essential existing in the AF-treating decoction. *Citrus medica* L.var.*sarcodactylis* Swingle had anti-inflammatory effect³⁶. 6-Demethoxytangeretin, Demethylnobiletin and Diosmetin, maybe important compounds treating AF, are all belong to citrus flavonoid. 6-Demethoxytangeretin can regulate inflammatory response mediated by mast cell through suppressing production and gene expression of IL6³⁷. Demethylnobiletin, also known as 5-Demethylnobiletin, has anti-inflammatory effect which can inhibit lipopolysaccharide-induced NO production and reduce inflammation-related cytokines (IL6, IL-1 β , TNF- α) elevation through regulating JAK2/STAT3 pathway³⁸⁻³⁹; 5-Demethylnobiletin also can counteract the production of ROS accelerated by CCL₄ and enhance the antioxidant enzymes⁴⁰. Diosmetin can reduce the levels of inflammatory mediators just like 5-Demethylnobiletin⁴¹; specially, Diosmetin can exert cardioprotective effect on myocardial ischaemia injury in neonatal rats by decreasing oxidative stress and myocardial apoptosis which maybe related to AMPK signaling activation⁴²⁻⁴³. *Nardostachys jatamansi* DC. is a commonly used herbal medicine treating arrhythmia, which had anti-cholinesterases, anti-hyperglycemic anti-inflammatory, anti-hypertensive and anti-tyrosinase effects⁴⁴; it also has antiproliferative potential and can prevent cell death of cardiomyocyte⁴⁵⁻⁴⁶. Nardoguaianone A, nardoperoxide and nardoguaianone B as potential anti AF compounds need further research. *Salvia miltiorrhiza* Bge., widely known in internationally, had anti-inflammation, anti-oxidation, anti-atherogenesis and anti-diabetes effects⁴⁷. Study showed that tanshinol can protect human umbilical vein endothelial cells against hydrogen peroxide-induced apoptosis through enhancing antioxidant defense and preserving mitochondrial function of cells⁴⁸; Sclareol can protect hearts against Ang II-induced injuries through inhibiting MAPK-mediated inflammation⁴⁹; and isotanshinone can mediate neutrophil to anti inflammation⁵⁰. These potential anti AF compounds play a role through intervening inflammation.

In this study, we found 87 bioactive compounds and 129 AF-related targets of C-C,N,S. Through analyzing for the 129 targets, we determined that C-C,N,S, has the anti inflammatory effect and can treating AF through controlling inflammation as well as further controlling atrial remodeling and fibrosis. The PPI

network analysis indicated that TNF and IL6 were key genes, cellular response to chemical stress and response to oxidative stress were key biological processes. The relationship between IL6, TNF and AF had been validated^{51–52} and that pointed that the mechanism of C-C,N,S treating AF maybe related to inflammation. Then the gene specific expression analysis provided a possibilities that C-C,N,S can regulate the inflammation occurred in cardiac myocytes, adipocytes and endothelial which maybe generated by liver diseases and heart diseases^{53–55}. Subsequently, GO function and KEGG pathways analysis further explained the anti inflammation mechanism of C-C,N,S. The main targets from target-pathway network (Fig. 7E) focused on mitogen activated protein kinase (MAPK) family. MAPK signaling pathway plays an important roles in biological processes such as cell growth, differentiation, apoptosis, and inflammation^{56–57}. Studies showed that the activation of phosphorylated MAPK signifcantly increased the susceptibility to AF⁵⁸. and AF atrial structural remodeling could be reversed by decreasing MAPK expression⁵⁹. In addition, AKT1 as a key genes from PI3K-Akt signaling pathway, plays a role in the regulation of cell proliferation, survival and metabolism^{60–61}. Studies showed that activated PI3K-Akt signaling pathway could protect the atrial myocytes from excessive oxidative stress and inflammatory processes to resist atrial remodeling⁶² and also could affect pulmonary fibrosis through involving in the expression of collagen and cell proliferation in lung fibroblasts⁶³. Finally, we validated the conclusion using the gene chip sets of POAF and SR patients. C-C,N,S could indeed mediate the inflammatory-related signaling pathway to regulate inflammatory process and further alleviate atrium remodeling as well as fibrosis. As as an endogenous mediator of inflammation, TNF- α involves in atrial fibrosis⁶⁴. In addition, the activation of TNF- α signaling promote atrial remodeling³³. FS, GS and DS maybe down-regulate JNK1/2 to reduce the expression of inflammasome such as IL6; GS maybe also down-regulate TNF directly to inhibit activation of TNF signaling pathway (Fig. 8A). Studies have found that IL-17 signaling pathway stimulates the release of proinflammatory cytokines, which promote myocardial fibrosis and thus induce the development of AF^{65–66}. GS and DS maybe down-regulate MAPKs to reduce the expression of inflammasome such as IL6 (Fig. 8B). In POAF patients, PI3K-Akt signaling pathway is down-regulated, which is in accordance with Zhao's research⁶². FS maybe mediate AKT1 directly to affect signal transduction of downstream (Fig. 8C). These needed to further confirmed by experiments.

Conclusion

Based on network pharmacology, the study determined the core bioactive compounds and AF-related targets of C-C,N,S, specific expression of 129 gene targets, as well as the main signaling pathways (MAPK signaling pathway and PI3K-Akt signaling pathway), and revealed the potential mechanism of C-C,N,S treating AF. In the triangle drug combination of *Citrus medica* L.var.*sarcodactylis* Swingle (FS), *Nardostachys jatamansi* DC. (GS) and *Salvia miltiorrhiza* Bge.(DS), some targets were regulated by three herbal medicines commonly, while some targets were regulated by one herbal medicine specifically, which indicating the essential of each herbal medicine. In addition, we demonstrated the potential therapeutic effect of C-C,N,S through POAF gene chip sets and validated that C-C,N,S can regulate

inflammatory process and inhibit atrial remodeling and fibrosis through TNF signaling pathway, IL-17 signaling pathway (MAPK signaling involved) and PI3K-Akt signaling pathway.

Declarations

Data availability

The gene chip set for this study can be found in the GEO database
<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE143924>.

Author contributions

H Y conceived the study; W L designed the study; Y S completed the study and manuscript. H Y and W L reviewed the manuscript. All authors have read and approved the final manuscript.

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Competing interests

The authors declare no competing interest.

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Figures



A



B



C



Figure 1

Triangle drug combination of *Citrus medica* L. var. *sarcodactylis* Swingle, *Naradostachys jatamansi* DC. and *Salvia miltiorrhiza* Bge. Above represents untreated wild plant and below represents herbal medicine through processing.

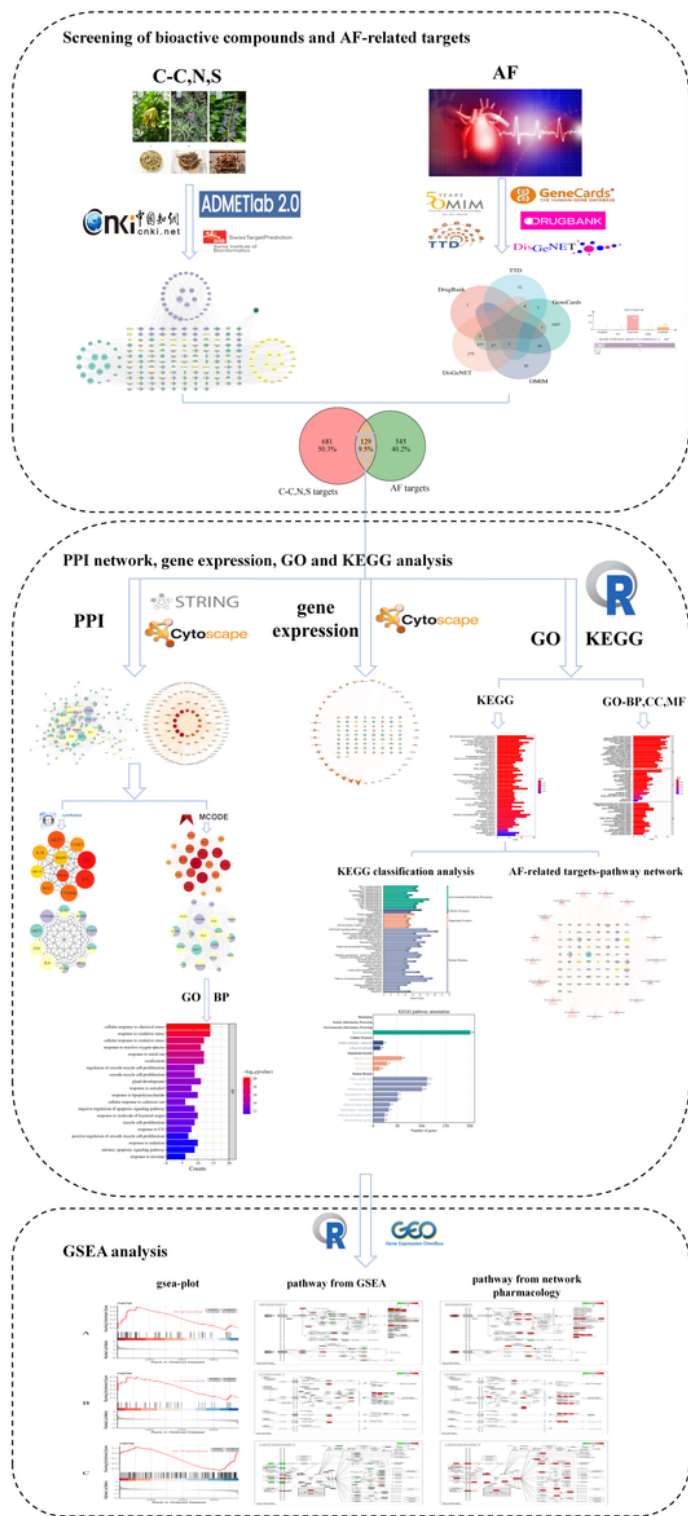
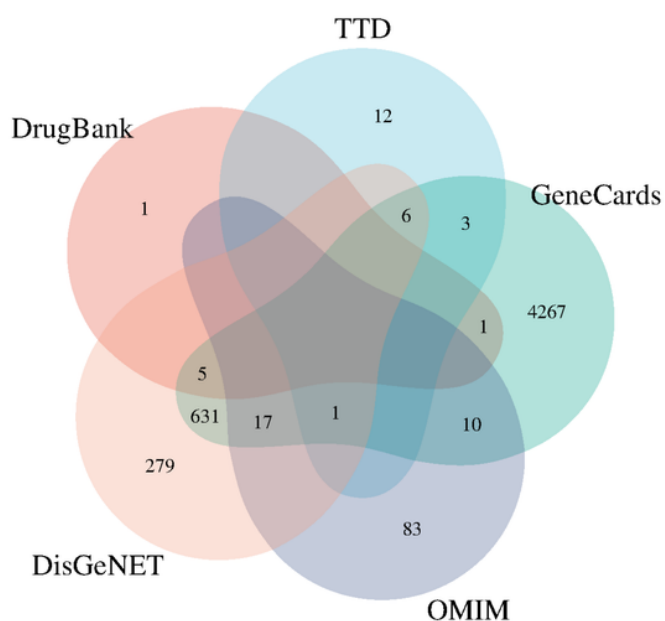
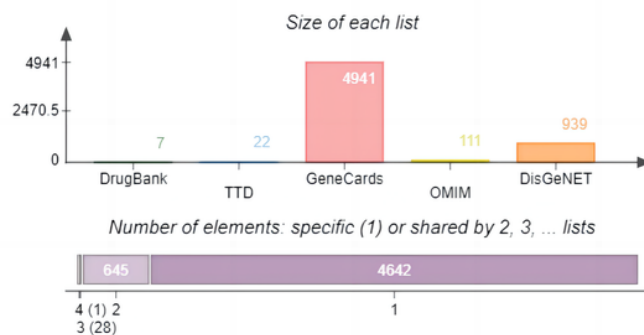


Figure 2

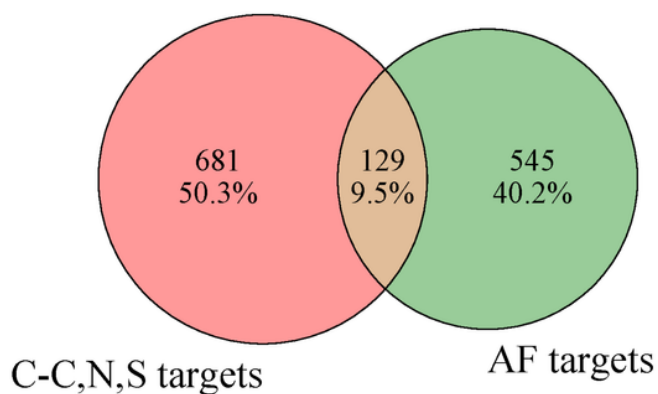
Flow diagram.



A



B



C

Figure 3

A: Venn diagram of AF-related targets in 5 disease databases. B: Duplicated AF-related targets situation. C: Venn diagram of 674 AF-related targets and 810 C-C,N,S bioactive compounds targets.

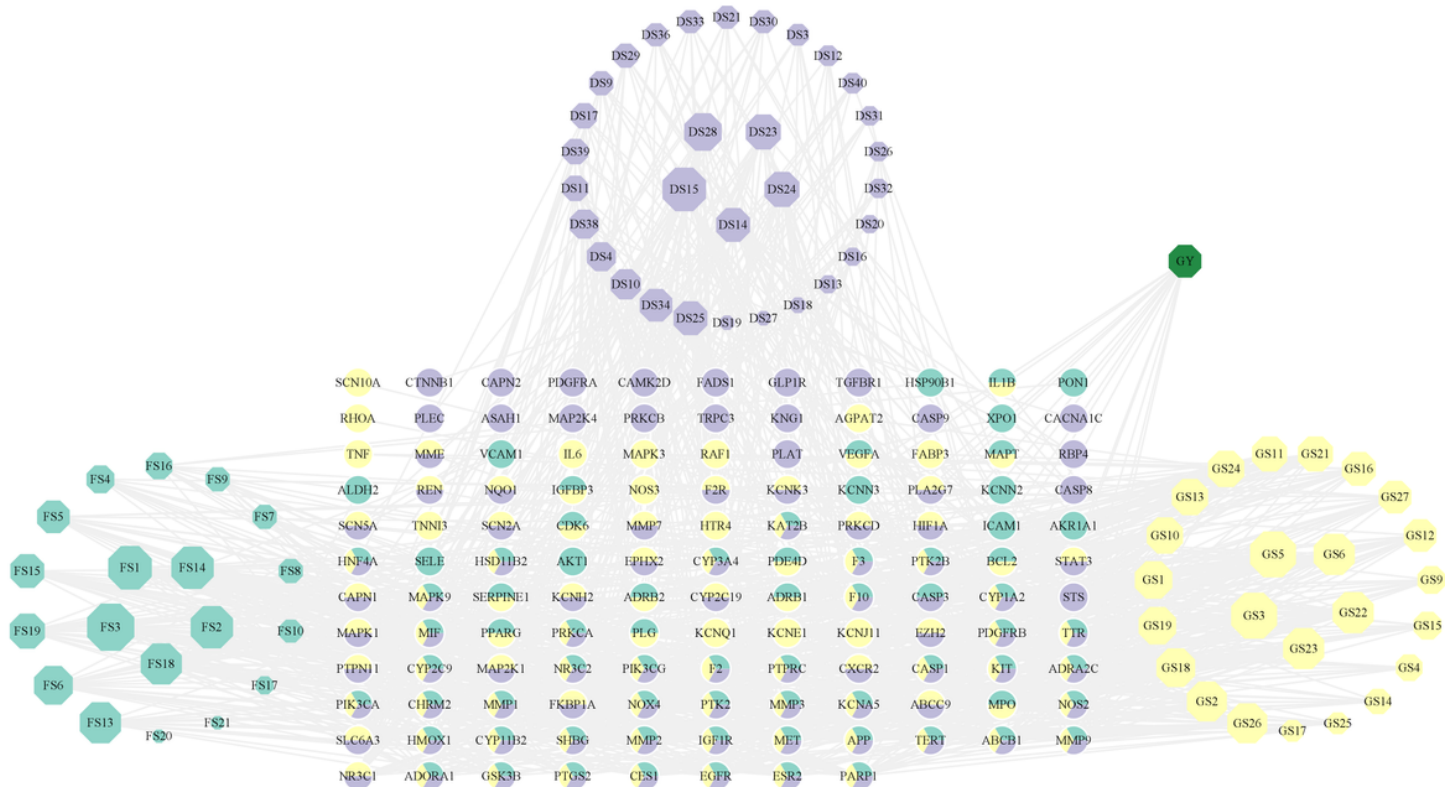
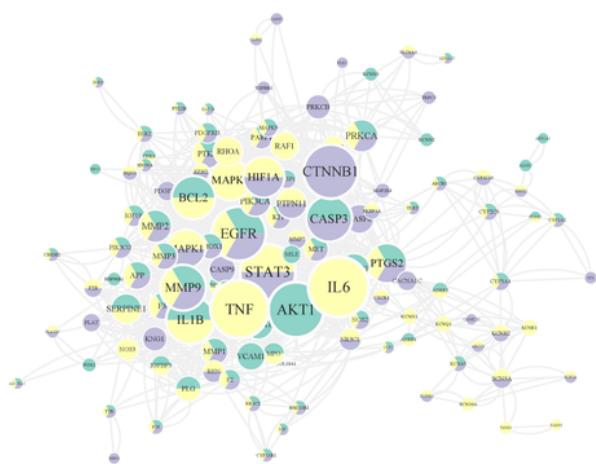
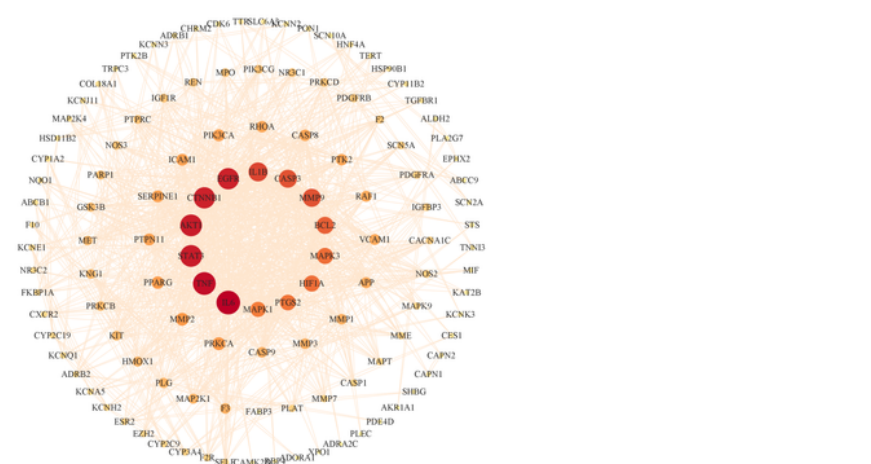


Figure 4

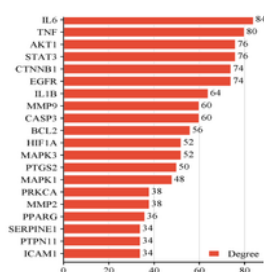
Network on bioactive compounds and potential anti-AF targets of C-C,N,S. Hexagons represent the bioactive compounds with light green representing FS, yellow representing GS, purple representing DS, and dark green representing co-existing between GS and DS. Circulars represent anti-AF targets of C-C,N,S, and we used corresponding colors to indicate the regulation situation of each target. Bioactive compounds and anti-AF targets of C-C.N.S are arranged according to degree values.



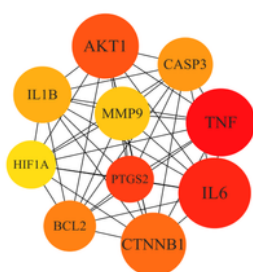
A PPI network



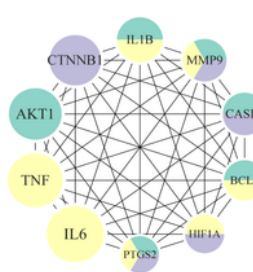
B PPI network



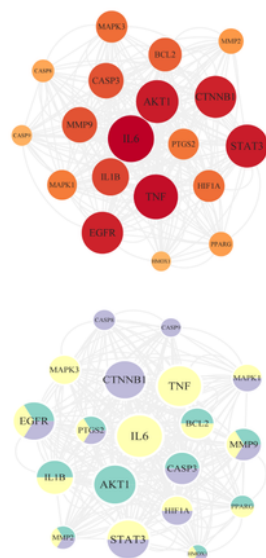
C Degree of top 20 genes



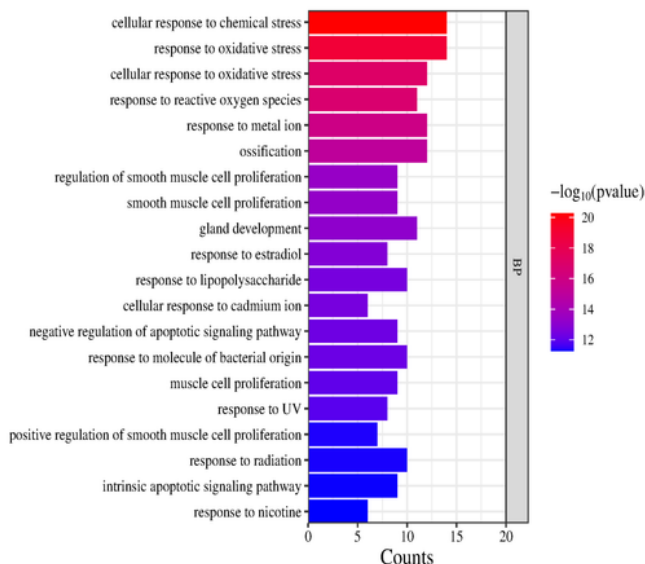
D Hub genes



E Hub genes



F Cluster 1 19 genes, Score:15.889



G GO function analysis of 19 genes

Figure 5

A: PPI network, indicated the regulation situation of C-C,N,S on targets, light green represents FS, yellow represents GS, purple represents DS. B: PPI network, ranking based on Degree, the larger area the node, the darker the color, the significance the gene. C: The ranking of top 20 targets based on Degree. D-E: The top 10 hub genes. F: The highest-scoring cluster. G: GO function analysis of 19 genes.

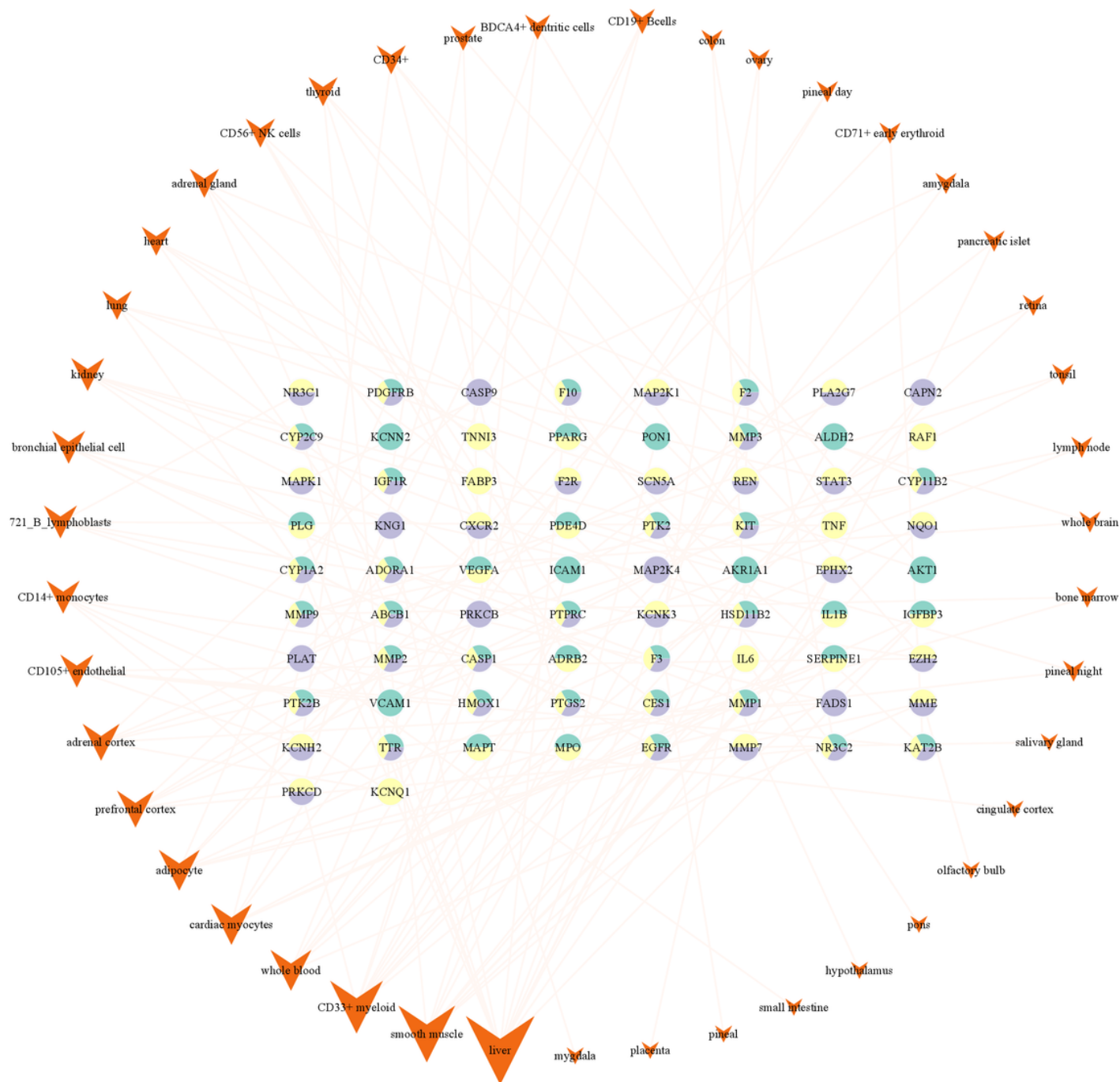


Figure 6

Network on genes specific expression of C-C,N,S. Orange represents organ/tissue/cell.

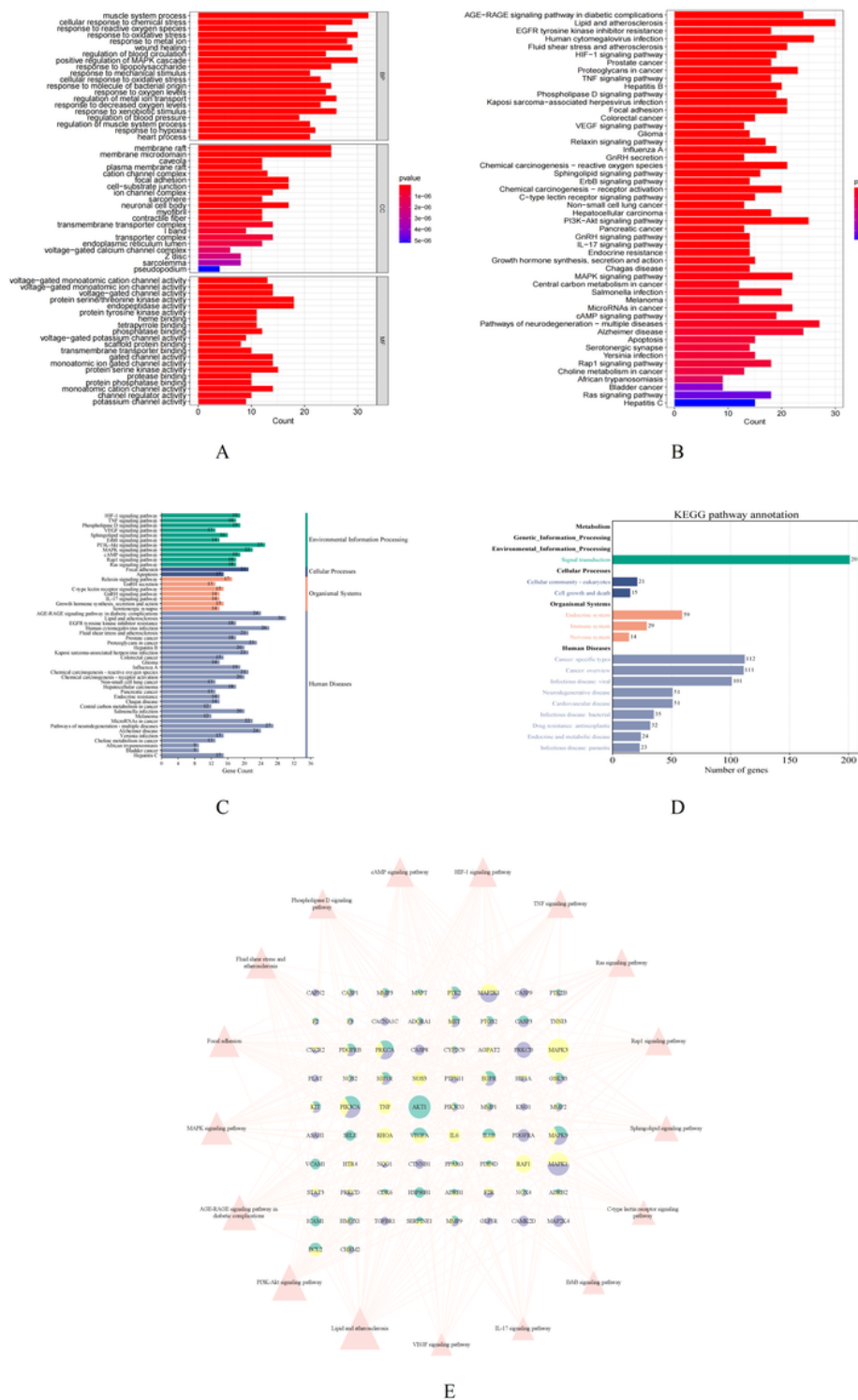


Figure 7

A: Top 20 results of GO enrichment analysis including biological process (BP), cellular compound (CC) and molecular function (MF). B: Top 50 results of KEGG enrichment analysis. C-D: Taxonomic analysis of top 50 KEGG enrichment results. E: Target-pathway network of C-C,N,S. Pink represents pathways. They ranked based on Degree value.



Figure 8

Results of GSEA analysis. Left represent the gsea-plot. Middle represents the pathway-plot from GSEA. In the figures, color red represents the high-expression gene in AF patients, color green is the opposite. Right represents the pathway-plot from network pharmacology. In the figures, color red represents genes regulated by C-C,N,S.

Supplementary Files

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