ORIGINAL RESEARCH

Investigating the Mechanism of Chinese Medicine Formula AACO Against Chronic Heart Failure by Network Pharmacology Analysis and Experimental Validation

Cheng Lu, MD; Huiling Li, MD; Xinting Wang, MD; Huiying Wang, MD; Lei Song, MD; Jingru Zhao, MD; Yongming Liu, MD, PhD

ABSTRACT

Background • A traditional Chinese medicine (TCM) formula, containing *Astragalus membranaceus (Fisch.) Bunge*, *Aconitum wilsonii Stapf ex Veitch*, *Curcuma longa L.,* and *Radix ophiopogonis* (AACO), has therapeutic value for the treatment of chronic heart failure (CHF).

Objective • This study intends to explore the pharmacological mechanism underlying the activity of the AACO formula against CHF.

Materials and Methods • Using the TCM Systems Pharmacology database and Bioinformatics Analysis Tool for Molecular Mechanism of TCM, the active ingredients contained in the herbs of the AACO formula were screened. Meanwhile, the target genes related to these active ingredients were identified and genes correlated with CHF were screened. Protein-protein interaction networks were built to elucidate the relationships between the AACO formula and CHF. Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) signal pathway enrichment analysis were carried out using the DAVID database. A "drug-component-target-disease" network was constructed with Cytoscape 3.7.0. The therapeutic effect of the AACO formula was proven by hemodynamic study, echocardiography evaluation, and histological analysis in transverse aortic constriction-induced CHF mice and was validated *in vitro*.

Results • A total of 105 active ingredients and 1026 related targets were screened and identified, and 240 related targets overlapping with CHF were selected. According to GO analysis, the enriched genes participated in gene expression and cardiac contraction regulation by Ca^{2+} regulation. From KEGG analysis, the calcium axis was identified as one of the main mechanisms through which the AACO formula exerts an anti-CHF effect. AACO was validated to significantly improve cardiac diastolic and systolic functions *in vivo* via an increase in the rate of Ca^{2+} reuptake of the myocardial sarcoplasmic reticulum and improved myocardial contractility *in vitro*.

Conclusions • Network pharmacology is a convenient method to study the complex pharmacological mechanisms of TCM. The calcium axis likely participates in the anti-CHF mechanism of AACO. (*Altern Ther Health Med.* [E-pub ahead of print.])

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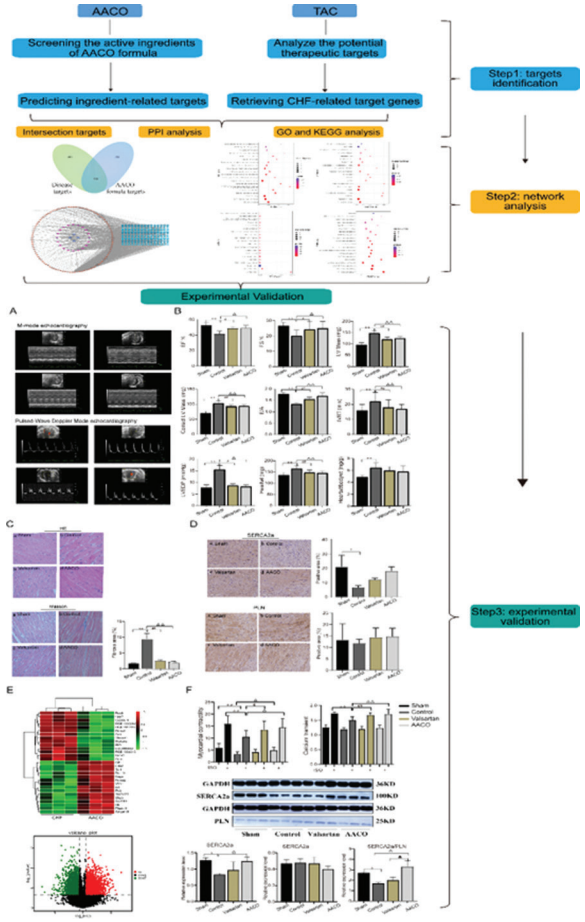
INTRODUCTION

Chronic heart failure (CHF) presents an increasing overall incidence owing to aging and an increase in the incidence of comorbidities.[1] Improvements in CHF treatment had increased the survival rate between 1980 and 2000, but since then, this positive trend has leveled off.[1] Considering the increasing incidence and undesired survival rate, the treatment of CHF remains challenging.

Chinese herbal formulas are a basic form of Chinese medicine. They have reliable therapeutic effects and have greatly contributed to the health of Chinese people for thousands of years. Chinese herbal formulas usually contain hundreds or thousands of active components and monomers. These active chemicals have synergistic pharmacological effects through different mechanisms, which enables Chinese herbal formulas to show superiority in treating complex diseases. However, the complexity of the active chemicals and their complicated mechanisms of action are difficult to determine. Network pharmacology analyzes data from gene, protein, disease, and medicine databases to clarify the synergistic pharmacological effects of Chinese herbal

Figure 1. Flowchart of a Network Pharmacology Approach for Showing the Mechanisms Involved in the Activity of the AACO Formula Against CHF



Abbreviations: AACO, *Astragalus membranaceus (Fisch.) Bunge*, *Aconitum wilsonii Stapf ex Veitch*, *Curcuma longa L.*, *Radix ophiopogonis*; CHF, chronic heart failure; GO, gene ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; PPI, protein-protein interaction.

formulas. The network construction of "Chinese herbal formula-components-pharmacological effects-diseases" helps clarify the correlations among components, targets, pathways, and diseases.

Chinese herbal formulas have shown notable curative effects in patients with CHF. The formula, which comprises *Astragalus membranaceus (Fisch.) Bunge*, *Aconitum wilsonii Stapf ex Veitch*, *Curcuma longa L.*, and *Radix ophiopogonis* (AACO), is effective in treating CHF.[2,3] This paper aims to elucidate the pharmacological mechanisms of AACO for CHF using network pharmacology analysis and experimental validation as shown in Figure 1.

MATERIALS AND METHODS

Active Ingredient Screening of AACO

We screened the active ingredients contained in the AACO formula from the Traditional Chinese Medicine Systems Pharmacology database (TCMSP; URL: https://www.ncbi.nlm.nih.gov) and the Bioinformatics Analysis Tool for Molecular Mechanism of Traditional Chinese Medicine (BATMAN-TCM; URL: http://bionet.ncpsb.org/batman-tcm).[4,5] The pharmacokinetic parameters and the corresponding criteria of active compounds, including oral bioavailability (≥ 30%), drug-likeness (≥ 0.18), and Caco-2 permeability (≥ -0.4), were identified by Absorption, Distribution, Metabolism, and Excretion (ADME) data.

Ingredient-Related Target Gene (TG) Prediction

Active ingredient-associated TGs were identified as mentioned in "2.1 Active Ingredient Screening of AACO". We transformed various ID forms of the TGs into UniProt (URL: https://www.uniprot.org/) IDs with the limitation of "*Homo sapiens*" as the species and obtained the official gene names.

Prediction of transverse aortic constriction-induced CHF Genes

Mouse total RNA was isolated with TRIzol regents. The RNA-seq data can be accessed through the Gene Expression Omnibus (GEO) database (URL: https://www.ncbi.nlm.nih.gov/geo), an open functional genomics data repository of the National Center for Biotechnology Information (NCBI), using accession number GSE217747. Using mouse genome microarray data, we analyzed candidate treatment targets for AACO and AACO-free in transverse aortic coarctation (TAC) model by using the LIMMA package, for the R programming language. Differentially expressed genes (DEGs) referred to those genes with a Q-value and a fold change < .05 and >1.5, respectively.

Retrieving CHF-Related TGs

CHF-related genes were identified by using the Therapeutic Target Database (TTD; URL: https://db.idrblab.org/ttd), Online Mendelian Inheritance in Man (OMIM; URL: http://www.omim.org/), and DisGeNET (URL: http://www.disgenet.org).[6-8] We transformed various ID forms of the targets into UniProt IDs, with the limitation of "*Homo sapiens*" as the species.

Constructing the Protein-Protein Interaction (PPI) Networks

PPI networks were constructed to illuminate the correlation of AACO with CHF by analyzing their overlapping targets. The relationships were analyzed by the application of STRING,[9] and visualized using Cytoscape (version 3.7.0), in which the node size was in direct proportion to the degree of centrality acquired from topology analysis.

Gene Function Analysis

We used the DAVID 6.8 database[10] (URL: https://david.ncifcrf.gov/) for gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) signal pathway enrichment analyses. Based on the p-value, the first 20 entries were chosen to create a bubble chart, which was completed using the OmicShare platform (URL: https://www.omicshare.com/).

Table 1. The Composition of TCM

Formula	Herbal Components Latin name	Herbal Components English name	Traditional Use	Amount (g)	Clinical Manifestations	Function
AACO	*Astragalus membranaceus (Fisch.) Bunge*	Radix Astragali	To treat qi deficiency syndrome	30	Deficiency of qi and yang marked by cardiac palpitation, shortness of breath, scarcely perceptible pulse, and spontaneous sweating	To replenish qi, restore the normal pulse, nourish yang, and promote the excretion of body fluid
	Aconitum wilsonii Stapf ex Veitch	Monkshood	To revive the yang for resuscitation	10		
	Curcuma longa L.	Turmeric	To promote the flow of qi and eliminate blood stasis	10		
	Radix Ophiopogonis	Dwarf lilyturf	To nourish yin and promote the production of body fluid, to moisten the lungs, and to ease the mind	10		

Abbreviations: AACO, *Astragalus membranaceus (Fisch.) Bunge*, *Aconitum wilsonii Stapf ex Veitch*, *Curcuma longa L.*, *Radix ophiopogonis*; TCM, Traditional Chinese medicine.

Constructing a "Drug-Component-Target-Disease" Network

We built a "drug-component-target-disease" network to obtain considerable insight into the complex correlations among the herbs contained in the AACO formula, the active ingredients, targets, and diseases using Cytoscape 3.7.0.[9]

Topology Analysis

Topology analysis was performed using the "network analyzer" tool in Cytoscape 3.7.0, which yielded betweenness centrality and degree value. We marked the node size and color based on the degree values, from largest to smallest.[9]

Experimental Validation

Ethical Approval. All experiments and animal care procedures were reviewed by the Institutional Animal Care and Use Committee and approved by the Shanghai Medical Experimental Animal Care Commission. The study followed the provisions and general recommendations of the Chinese Experimental Animals Administration Legislation. This study was approved by the ethics committee of the Shanghai University of Traditional Chinese Medicine (No. PZSHUTCM2302040001).

Experimental Animals. C57BL/6 mice (8–12 weeks old) were ordered from Lingchang BioTech, Shanghai, China (license no. SCXK 2018-0003) and reared in a specific-pathogen-free animal facility.

Model Construction and Drug Intervention. The mice underwent intraperitoneal anesthesia with 2% pentobarbital (35 mg/kg). Mouse breathing was controlled by tracheal intubation and ventilation. The tidal volume was 1.5 ml and the breathing frequency was 90–110 times/min. The surgical area was cleaned, the chest was opened to the second rib through a median thoracic incision, the thymus was separated, and the aortic arch was exposed. According to the diameter of the aortic arch (approximately 1.0–1.1 mm), a 27 G padding needle was used to pad the aorta. The aorta was separated and constricted 0.3 cm after the right common carotid artery. Two-dimensional ultrasound revealed that the diameter of the aorta was reduced by 50–55%, resulting in approximately 70% stenosis. The padding needle was extracted after ligation. The mediastinum was sutured in layers and the tracheal intubation was withdrawn after the mice resumed spontaneous breathing. The mice were housed in cages. The sham operation group did not undergo aortic arch ligation; the remaining procedures were the same as described.

After one week of feeding, all mice were administered AACO solution at 0.386 μg/g (TCM group), valsartan at 1.029 μg/g (valsartan group), or an equivalent amount of double-distilled water (sham group), once daily for 8 weeks. The dosages administered were chosen according to the "Human and Animal Body Surface Area Dose Equivalent Conversion Ratio Table".[11] The animals were sacrificed 24 hours after the last administration.

AACO Preparation and Identification. After purchasing the TCM from Tong Ren Tang, Shanghai, China, we prepared the AACO extract as follows: Using the reflux heating method, AACO (1000 g) was reacted with 90% ethanol for 1.5 hours, followed by filtering with a 120-mesh sieve. After concentrating the filtrate, the residue was decocted with water for 1 h and the sample was re-filtered. Finally, the filtrates obtained from the two steps were mixed and concentrated at 50°C. The mixture was lyophilized and subjected to AACO extraction (110 g). The AACO extract was confirmed by Dr. Cheng Lu per the Pharmacopoeia of the People's Republic of China 2015 Edition. The voucher specimen (No. 20200428) was placed at Shuguang Hospital affiliated with the Shanghai University of Traditional Chinese Medicine, Shanghai, China (Table 1).

UHPLC-Q-Orbitrap High-Resolution Mass Spectrometry (HRMS) Analysis. The AACO extract quality was confirmed by qualitative and quantitative analysis of the major bioactive components through chromatography-quadrupole/electrostatic field orbitrap HRMS (UHPLC-Q/Exactive; Thermo Fisher Scientific, San Jose, CA, USA). This was followed by the elution of the components with a gradient system composed of aqueous 0.1% formic acid (I) and acetonitrile (II) (0–2 min, 10% II; 2–9 min, 10–95% II).

Hemodynamic Study. The mice were anesthetized with 2% pentobarbital. We inserted a catheter (SPR-839; Millar Instruments, Houston, TX, USA) into the carotid artery and then into the left ventricle. After maintaining stability for several minutes, we used AD Instruments Power-Lab4/30 with Lab Chart Pro 7.0 software (MPVS-300; AD Instruments, Colorado Springs, CO, USA) to collect data on the pressure in the aorta and left ventricle.

Echocardiography. Mice were anesthetized with 2% pentobarbital. During the evaluation of cardiac function, the heart rate of the mice was maintained at approximately 450 bpm to diminish variation. Systolic function parameters, such as ejection fraction and fractional shortening, and diastolic function parameters, such as E and A waves, E/A ratio, and isovolumic relaxation time (IVRT), were measured using a Vevo 2100 imaging system (Toronto, ON, Canada) with the use of a 22–55 MHz MS450D transducer.

Histological Analysis. Mouse hearts were formaldehyde-fixed for 24 h, paraffin-embedded, and serially sectioned to 5 μm slices. Heart morphology and myocardial fibrosis were analyzed by hematoxylin-eosin and Masson's trichrome staining, respectively.

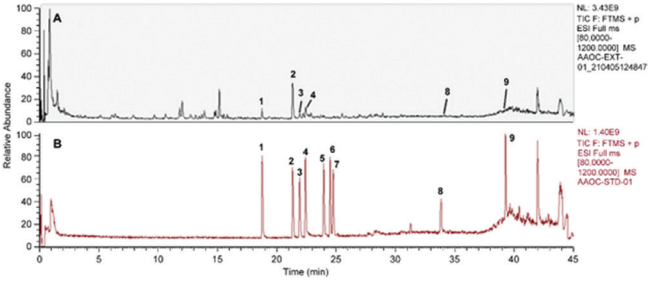
Immunohistochemistry. Following 30 min of blocking with 10% sheep serum in 0.3% Triton X-100-supplemented phosphate-buffered saline, heart slices were immersed in anti-SERCA2a (#9580 Cell Signaling Technology) and -phospholamban (PLN #14562 Cell Signaling Technology) primary antibodies for overnight incubation (4°C). After incubation with a secondary antibody conjugated with diaminobenzidine, the sections were mounted on slides.

Primary Adult Cardiomyocyte (CM) Isolation. Mice were anesthetized with 2% pentobarbital, and the hearts were cut and placed in a buffer consisting of the following materials (volume): NaCl (120 mM), KCl (5.4 mM), NaH_2PO_4 (1.2 mM), $NaHCO_3$ (20 mM), $MgSO_4$ (1.2 mM), glucose (5.6 mM), 2,3-butanedione monoxime (10 mM), taurine (20 mM), pH 7.33.[12] The solution was made by bubbling 95% O_2 and 5% CO_2 for 10 min using and then filtered through a 0.22-micron filter. Meanwhile, gentle cannulation of the heart via the aorta was performed using a small cannula, followed by a 5-minute perfusion with a buffer (2.5 ml/min). The heart was continuously perfused with a fresh collagenase solution (containing 12.5 mg of type II collagenase, 2.5 mg of type XIV protease, 50 μM $CaCl_2$, 0.1% BSA, filtered) for approximately 15 minutes until becoming soft. After cutting below the atria, the heart was transferred to a dish containing 5 ml of collagenase solution with calcium, sheared, and the myocardial tissue was transferred to a tube. The supernatant was transferred into a fresh tube containing 5 ml of stopping buffer (12.5 μM $CaCl_2$ and 2 ml of FBS) for a 1-minute centrifugation (500 rpm). The resuspended cells were gradually recovered to physiological calcium concentration (1 mM).

Adult Cardiomyocyte Contractility and Calcium Transient. According to the protocol published by Wang and others,[12] freshly isolated adult CMs were treated with 30 min of cultivation with Fluo-4 AM (5 μM; Molecular Probes, Grand Island, NY). Next, the CMs were placed in the dish center as close to the electrodes as possible (NaCl 120 mM, KCl 5.4 mM, NaH_2PO_4 1.2 mM, $MgSO_4$ 1.2 mM, HEPES 20 mM, glucose 5.5 mM, $CaCl_2$ 1 mM, pH 7.1, filtered). The cells were then settled with 2 ml of beating buffer for 5 minutes. The cells were electrically stimulated at 1 Hz and 30 V. We observed the calcium transients and contractile of the CMs–5–10 rod-shaped CMs per field coverage using an inverted microscope. The following settings were applied: time interval, 1 min; duration, 10 min; exposure time, 25 ms; 200 frames per movie. CM FS was calculated as the percentage of the difference between the maximal and minimal cell length in the maximal cell length. Calcium transients were recorded at 488 nm excitation and 505 nm emission. The analysis was performed using MetaMorph.

Western Blot Analysis. Heart tissue specimen homogenization was performed with a radioimmunoprecipitation lysate buffer supplemented with phosphatase and protease inhibitor cocktails, followed by supernatant collection. After separation on 10% sodium dodecyl sulfate–polyacrylamide gel electrophoresis gels, protein specimens were transferred onto membranes made of polyvinylidene difluoride (Millipore) for 2 h of room temperature sealing with 5% non-fat milk and the subsequent blotting with antibodies (all from Cell Signaling Technology) against SERCA, phospholamban, and GAPDH. Then came 1 h of room temperature incubation of the membranes by adding a horseradish peroxidase-labeled goat anti-rabbit IgG (Beyotime, Shanghai, China) secondary antibody (1:5000 dilution). Protein band visualization and quantification using BeyoECL Star (Beyotime, Shanghai, China) and ImageJ software, respectively.

Figure 2. The Fingerprint chromatograms of AACO Decoction



Abbreviations: AACO, *Astragalus membranaceus (Fisch.) Bunge*, *Aconitum wilsonii Stapf ex Veitch*, *Curcuma longa L.*, *Radix ophiopogonis*

Table 2. Sequences of Mouse Primers for Quantitative PCR

Gene	Forward primer	Reverse primer
SERCA	5'-GAGAACGCTCACACAAAGACC-3'	5'-CAATTCGTTGGAGCCCCAT-3'
PLN	5'-AAAGTGCAATACCTCACTCGC-3'	5'-GGCATTTCAATAGTGGAGGCTC-3'
GAPDH	5'-AGGTCGGTGTGAACGGATTTG-3'	5'-TGTAGACCATGTAGTTGAGGTCA-3'

Abbreviations: PCR, polymerase chain reaction

Quantitative Real-Time Polymerase Chain Reaction Analysis. We used a TRIzol reagent to separate tissue total RNA and transcribed it into cDNA with the use of a Revert Aid First Strand cDNA Synthesis Kit (Life Technologies), after which a TaqMan SYBR kit (Life Technologies) was used for real-time polymerase chain reaction. Primer sequences are listed in Table 2.

Statistical Analyses

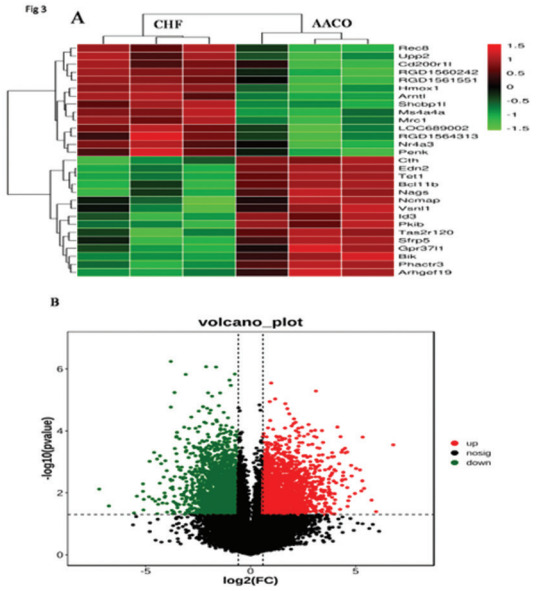
All experimental data are statistically processed by SPSS (version 20.0; SPSS Inc., Chicago, IL, USA) and presented as mean ± standard deviation. Variance homogeneity was analyzed using Levene's test, and data analyses were made with one-way analysis of variance and least significant difference t-tests, with the minimum significance level set at $P < .05$.

RESULTS

Screening and Collecting the Active Ingredients of the AACO Formula

The contents of calycosin-7-O-β-D-glucoside, benzoylnesaconine, benzoylaconine, benzoylhypaconine, astragaloside IV, and ruscogenin were determined by the

Figure 3. (A) The Heatmap Comparing Gene Expressions Between CHF and AACO Groups (n = 3). (B) The Volcano Plot of p Values of mRNA Weighted Fold Changes in Myocardial Tissue in CHF and AACO Groups. The Perpendicular Line Delimits Up- and Down-Regulation, with Red and Green Plots Representing Significantly Up-Regulated and Down-Regulated mRNAs (Fold Change >1.5, corrected $P < .05$), Respectively.



Abbreviations: AACO, *Astragalus membranaceus (Fisch.) Bunge*, *Aconitum wilsonii Stapf ex Veitch*, *Curcuma longa L.*, *Radix ophiopogonis*; CHF, chronic heart failure

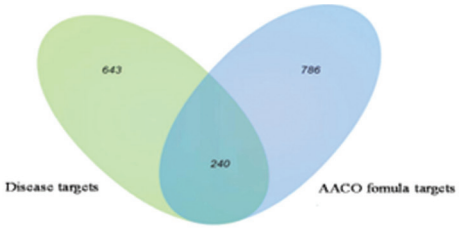
UHPLC-Q/Exactive method as 22.41, 129.59, 14.60, 5.12, 3.20, and 0.0080 μg/ml, respectively (Figure 2).

One hundred and five active compounds were acquired from the TCMSP and BATMAN-TCM databases for the four herbs of AACO, based on chemical similarity. From the TCMSP database, 16 active compounds were obtained from *Astragalus membranaceus (Fisch.) Bunge*, 14 from *Aconitum wilsonii* Stapf ex Veitch, and three from *Curcuma longa L.* From the BATMAN-TCM database, 35 active compounds from *Astragalus membranaceus (Fisch.) Bunge*, 58 from *Aconitum wilsonii* Stapf ex Veitch, 11 from *Curcuma longa L.*, and 22 from *Radix ophiopogonis* were collected. The repetitive active compounds were removed. Eventually, 105 active compounds were obtained, including astragaloside IV, calycosin, benzoylnesaconine, benzoylhypaconine, and benzoylaconine, et al. (Supplementary Table 1).

DEGs in TAC With and Without AACO

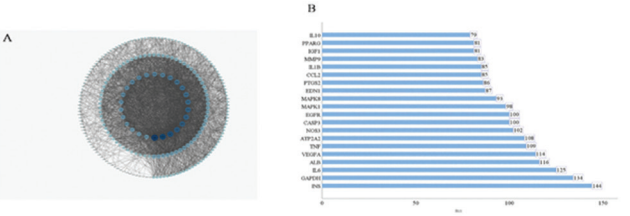
TAC mice treated with and without AACO were analyzed to identify mRNA expression profiles. See Figure 3A for the heatmap of the top 20 genes in TAC with and without AACO. Through volcano plot filtering, 867 DEGs ($P < .05$, FC > 1.5, Figure 3B), including 494 upregulated and 373 downregulated genes, were identified.

Figure 4. Prediction of Shared TGs Between the AACO Formula and CHF



Abbreviations: AACO, *Astragalus membranaceus (Fisch.) Bunge*, *Aconitum wilsonii Stapf ex Veitch*, *Curcuma longa L.*, *Radix ophiopogonis*; CHF, chronic heart failure

Figure 5. (A–B): A Protein-Protein Interaction (PPI) Network was Built to Illuminate the Relationships Among the Shared Target Genes



Abbreviations: AACO, *Astragalus membranaceus (Fisch.) Bunge*, *Aconitum wilsonii Stapf ex Veitch*, *Curcuma longa L.*, *Radix ophiopogonis*; CHF, chronic heart failure

Prediction of Compound-Related TGs

In total, 492 and 887 predicted targets of the AACO active constituents were acquired from the TCMSP and BATMAN-TCM, respectively. We obtained 1026 targets after deleting the duplicates. Among these, *Astragalus membranaceus (Fisch.) Bunge* had 540, *Aconitum wilsonii* Stapf ex Veitch 274, *Curcuma longa L.* 396, and *Radix ophiopogonis* 244 targets. We identified 12 common targets for the four herbs, namely MAOB, NOS1, OPRK1, PGR, ATP1A1, ADORA2B, RAPGEF2, DRD2, TACR2, IL1B, ESR1, and SCN5A.

Prediction of CHF-Related TGs

We obtained 883 TGs related to CHF from the TTD, OMIM, and DisGeNET (Figure 4).

Prediction of Shared TGs Between the AACO Formula and CHF

We mapped 1026 compound-related TGs and 883 CHF-related TGs to obtain 240 shared TGs by constructing a Venn diagram, which might elucidate the potential mechanisms of action underlying the anti-CHF effect of AACO (Figure 4, Supplementary Table 2).

Finally, a PPI network was constructed to elucidate the relationships between AACO and CHF by analyzing their overlapping targets (Figure 4). This network was composed of 237 nodes and 3,878 edges (Figure 5A). The degree values of the first 20 genes are shown in Figure 5B; the top 10 shared targets were INS, GAPDH, IL6, ALB, VEGFA, TNF, ATP2A2, NOS3, CASP3, and EGFR (Figure 5B).

Figure 6. (A–C): GO Analysis of the AACO Targets Involved in the Activity Against CHF. (A) Related Biological Processes, (B) Cell Structures, and (C) Part of Molecular Functions. The Dot Size in the Figure Represents the Gene Number, and the Color Represents the *P*-value. (D) KEGG Analysis of the AACO Targets Involved in the Activity Against CHF. (E) The "Drug-Compound-Target-Disease" Network was Built According to the Screened Compounds, Predicted Targets, and GO/KEGG Analysis. The Dot Size in the Figure Indicates the Gene Number, and the Color Represents the *P* value.

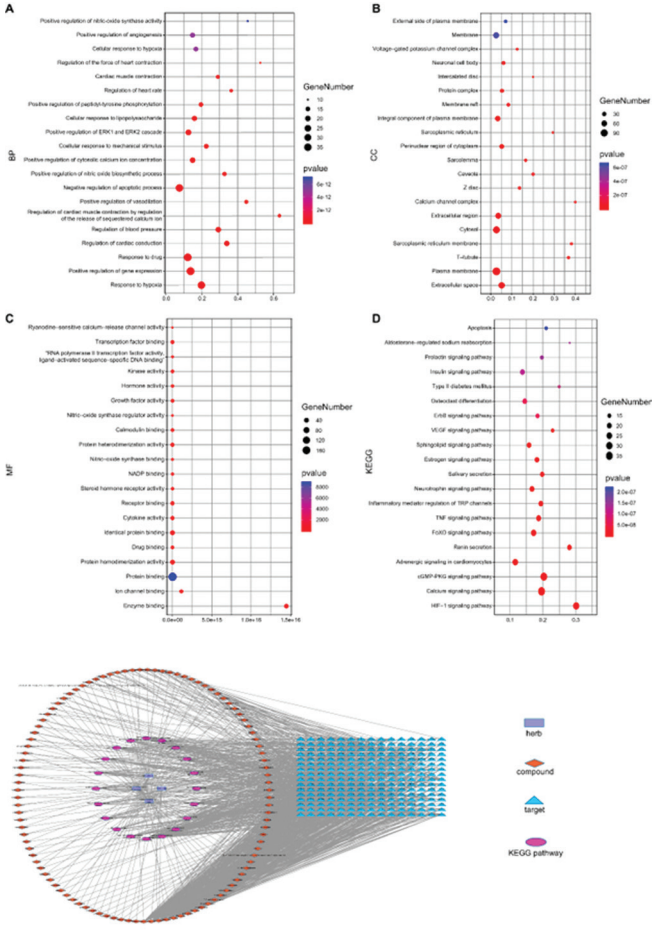


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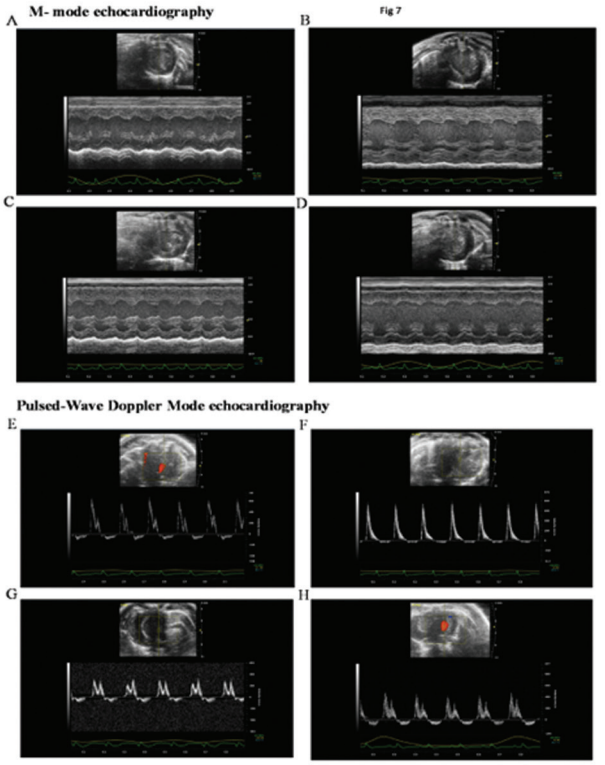
Figure 7. The AACO Formula Improved Cardiac Function in CHF Mice. (A–D) M-Mode Echocardiography Results of the Mice in the Four Groups. (E–H) Pulsed-Wave Doppler Mode Echocardiography Results of the Mice in the Four Groups.



Abbreviations: AACO, *Astragalus membranaceus (Fisch.) Bunge*, *Aconitum wilsonii Stapf ex Veitch*, *Curcuma longa L.*, *Radix ophiopogonis*; CHF, chronic heart failure.

GO and KEGG Enrichment Analyses of the TGs

GO and KEGG analyses of the 240 TGs were performed using the DAVID database. According to GO analysis, the enriched genes related to the biological process were involved in hypoxia, positive gene expression regulation, blood pressure modulation, positive modulation of cytosolic calcium ion concentration, and cardiac muscle contraction regulation by regulating the sequestered calcium ions release (Figure 6A). The enriched genes related to cell structure were involved in the plasma membrane, extracellular space, cytosol, extracellular region, and the calcium channel complex (Figure 6B). Finally, regarding molecular functions, the enriched genes were involved in enzyme binding, ion channel binding, protein binding, protein homodimerization activity, and drug binding (Figure 6C). KEGG analysis revealed that the TGs were enriched in HIF-1, calcium, cGMP-PKG, adrenergic signaling pathways, and renin secretion (Figure 6D, Supplementary Table 3). Collectively, the calcium axis is one of the main axes involved in the anti-CHF activity of the AACO formula.

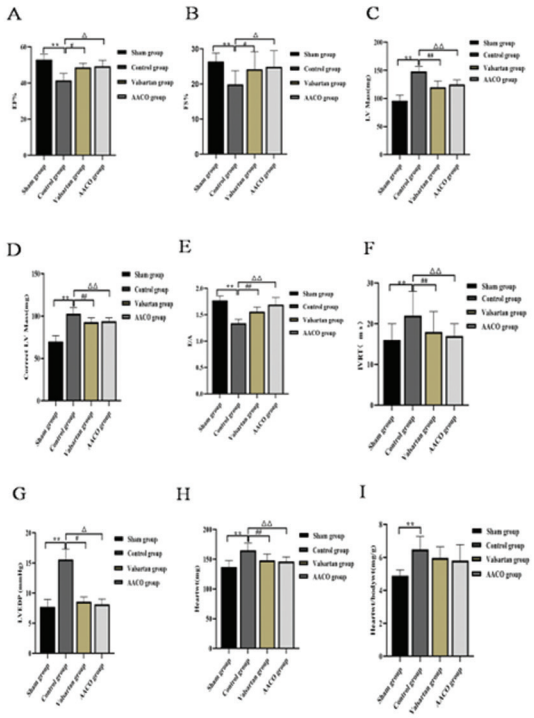
Network Construction

The "drug-compound-target-disease" network was built based on the screened compounds, predicted targets, and GO/KEGG analysis (Figure 6E).

The AACO Formula Improved Cardiac Function in CHF Mice

To test the efficacy of AACO in CHF treatment, we generated CHF mice via transverse aortic constriction. Echocardiography revealed that the ejection fraction, fractional shortening, and E/A ratio were statistically reduced in control mice versus sham mice, and the left ventricle mass and IVRT were markedly enhanced, suggesting that the model was successfully established (Figure 7A-H; Figure 8A–F). The ejection fraction, fractional shortening, E/A

Figure 8. The AACO Formula Improved Cardiac Function in CHF Mice. (A–F) Echocardiography Results of the Mice in the Four Groups. (A) EF %, (B) FS%, (C) LV Mass, (D) Correct LV Mass, (E) E/A, and (F) IVRT. (G) Hemodynamic Test Results and the LVEDP of the Mice in the Four Groups. (H) Heart Weight. (I) Heart Weight/Body Weight. *$P < .05$ and **$P < .01$: Control Group vs. Other Groups; #$P < .05$ and ##$P < .01$: Valsartan Group vs. Control Group; $^{\triangle}P < .05$ and $^{\triangle\triangle}P < .01$: AACO Group vs. Control Group; (n = 10).



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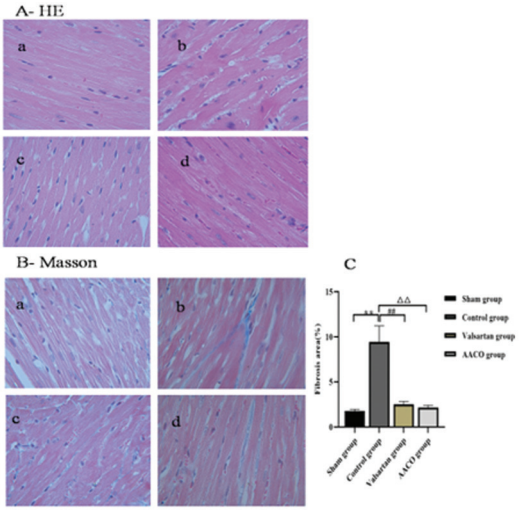
ratio, left ventricle mass, and IVRT were similar between the AACO and valsartan groups, which were improved compared to control mice (Figure 7A-H; Figure 8A–F). In the hemodynamic test, the control mice showed enhanced left ventricular end-diastolic pressure than sham, AACO, and valsartan groups (Figure 8G). Furthermore, a higher heart weight/body weight ratio was determined in the control group as compared to the other three groups (Figure 8H, I).

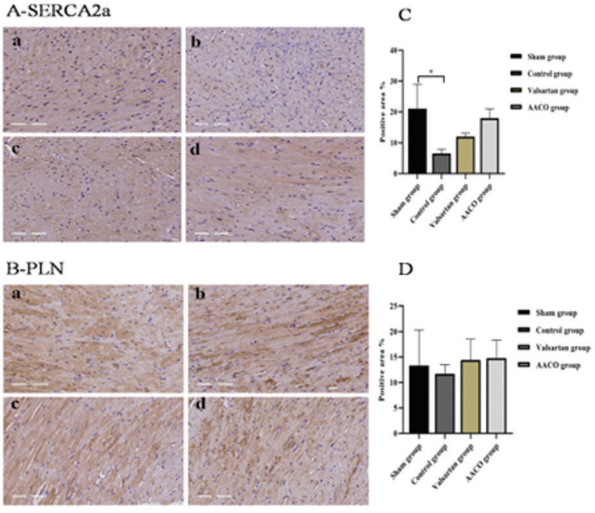
The CHF CMs were morphologically abnormal, accompanied by hypertrophy, which was in line with the heart function observed (Figure 9A). Masson's trichrome staining showed more severe myocardial fibrosis in control mice compared with sham mice and alleviated myocardial fibrosis in AACO and valsartan groups versus the control group (Figure 9B). Immunohistochemistry showed that the positive staining for SERCA2a and PLN was mainly concentrated in the cytoplasm, showing brown-yellow granules. The staining of SERCA2a was weaker in the control group than in the sham

Figure 9. The AACO Formula Inhibited Myocardial Fibrosis. (A) HE Staining. (B) Masson's Trichrome Staining. Scale Bar = 100 μm. a: Sham Group, b: Control Group, c: Valsartan Group, and d: AACO Group. *$P < .05$ and **$P < .01$: Control Group vs. Other Groups; #$P < .05$ and ##$P < .01$: Valsartan Group vs. Control Group; $^{\triangle}P < .05$ and $^{\triangle\triangle}P < .01$: AACO Group vs. Control Group (n = 10).



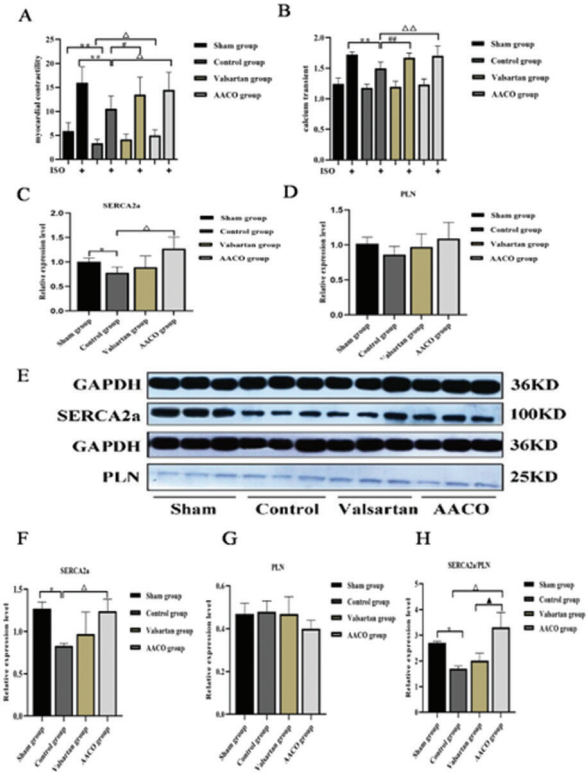
Abbreviations: AACO, *Astragalus membranaceus (Fisch.) Bunge*, *Aconitum wilsonii Stapf ex Veitch*, *Curcuma longa L.*, *Radix ophiopogonis*; HE, Hematoxylin and eosin

Figure 10. The AACO Formula Increased SERCA2a Expression and Promoted Calcium Transient and Myocardial Contractility. A–B: The Results of Immunohistochemistry Showed that the Positive Staining of SERCA2a and PLN was Mainly Concentrated in the Cytoplasm, Showing Brown-Yellow Granules. *$P < .05$ and **$P < .01$: Control Group vs. Other Groups; #$P < .05$ and ##$P < .01$: Valsartan Group vs. Control Group; $^{\triangle}P < .05$ and $^{\triangle\triangle}P < .01$: AACO Group vs. Control Group (n = 10).



Abbreviations: AACO, *Astragalus membranaceus (Fisch.) Bunge*, *Aconitum wilsonii Stapf ex Veitch*, *Curcuma longa L.*, *Radix ophiopogonis*, PLN, Phospholamban; SERCA2a, Sarcoplasmic reticulum calcium ATPase2a

Figure 11. (A) Therapeutic Effects of the Drugs on Cardiomyocyte Shortening. ISO, Isoproterenol, a β-Adrenergic Receptor Agonist (100 nM for AVM stimulation). (B) Therapeutic Effects of the Drugs on Cardiomyocyte Ca^{2+} Handling. ISO, Isoproterenol, a β-Adrenergic Receptor Agonist (100 nM for AVM stimulation). (C–D) SERCA2a and PLN mRNA Expression in the Calcium Signaling Pathway in the Hearts of the Four Groups. (E–H) SERCA2a and PLN Protein Expression in the Calcium Axis in the Hearts of the Four Groups. $^{*}P < .05$ and $^{**}P < .01$: Control Group vs. Other Groups; $\#P < .05$ and $\#\#P < .01$: Valsartan Group vs. Control Group; $^{\triangle}P < 0.05$ and $^{\triangle\triangle}P < .01$: AACO Group vs. Control Group; (n = 10).



Abbreviations: AACO, *Astragalus membranaceus (Fisch.) Bunge*, *Aconitum wilsonii Stapf ex Veitch*, *Curcuma longa L.*, *Radix ophiopogonis*; AVM, arteriovenous malformation; PLN, Phospholamban; SERCA2a, Sarcoplasmic reticulum calcium ATPase2a

group, whereas comparable positivity was observed for the control, AACO, and valsartan groups. PLN staining was similar among the four groups (Figure 10A–D).

Verification of the Mechanism Identified by Network Pharmacology Analysis

To validate the network pharmacology results, we isolated CMs from transverse aortic constriction mice who were treated with drugs for 8 weeks. The CM contractility test revealed significantly diminished CM contractility in control mice compared to sham mice, with a lower response to isoproterenol, a β-adrenergic receptor agonist (Figure 11A). Besides, significantly reduced CM calcium transients were determined in the control group as compared to the sham group (Figure 11B). After 8 weeks of AACO administration, CM contractility was significantly enhanced with a higher response to the β-adrenergic receptor agonist compared to the control group (Figure 11A). Significantly improved calcium transients were also found in the AACO group versus the control group (Figure 11B). While AACO and valsartan groups had similar CM contractility or calcium transients (Figure 11A, B). The control group showed reduced SERCA2a gene expression in the myocardium than the sham group, while the AACO group had markedly elevated SERCA2a gene expression than the control group (Figure 11C). PLN gene expression was similar among groups (Figure 11D). Furthermore, the myocardium SERCA2a protein expression was significantly decreased in the control group compared to the sham group, and it was greatly increased in the AACO group compared to the control group. No statistical difference was identified in PLN protein expression among the groups. The SERCA2a/PLN ratio was significantly lower in the control group than sham group and was significantly increased in the AACO group than control and valsartan groups (Figure 11E–F).

DISCUSSION

CHF has become the most important global public health issue and is the only cardiovascular disease with increasing incidence and high mortality. TCM can treat complex diseases by regulating the interaction of various factors in the human body to maintain the balance of the whole organism. However, the complexities of TCMs have restricted their development. Network pharmacology has been used to investigate the pharmacological mechanisms of TCM treatment of various complex diseases through the analysis of medicine, gene, protein, and disease information databases building an interaction network of "drug-component-target-disease".[13,14]

The AACO formula is a clinically proven prescription to treat CHF. This study confirmed that AACO could improve heart function, reduce heart mass, reduce left ventricular end-diastolic pressure, inhibit myocardial fibrosis in transverse aortic constriction mice, and enhance the contractility of CMs and CM calcium transients at the cellular level.

However, the four TCMs in the formula contain hundreds of active ingredients that exert synergistic pharmacological effects at different levels on multiple targets. We applied the network pharmacology method to investigate the mechanism of AACO in CHF treatment, obtained AACO active constituents, and predicted CHF-associated TGs by searching the databases. Through bioinformatic analysis, we found that the calcium axis might be one of the main signaling pathways involved in the activity of AACO against CHF.

The calcium axis is critical in modulating myocardial diastolic and systolic functions[15,16] and includes SERCA2a, PLN, and RyR2. SERCA2a is a myocardial sarcoplasmic reticulum (SR) calcium pump, and disorders in its expression and activity are key pathologies in CHF.[17] Protein kinase A phosphorylates PLN, resulting in the dissociation of PLN

from the binding site of SERCA2a, leading to its inhibitory effects on SERCA2a being reversed. SERCA2a reuptakes Ca^{2+} from the cytoplasm into the SR, causing CMs to relax and reserve Ca^{2+} for subsequent contraction. Pathological changes in any of these steps can cause a decline in myocardial diastolic and systolic functions. Several studies have shown that SERCA2a, PLN, and other calcium regulatory proteins play an extremely crucial role in patients with CHF and animal models.[15,18,19] The significantly reduced expression level and activity of SERCA2a in failed myocardial tissue and disorders in the regulation of PLN all lead to reduced Ca^{2+} reuptake into the SR in the diastolic period, reduced SR load, increased intracytoplasmic Ca^{2+} concentration, and decreased SR Ca^{2+} release during the systolic period, resulting in impaired systolic and diastolic functions, which is a characteristic of failed CMs and suggests a poor prognosis.[20,21]

Here, we confirmed that AACO promoted gene expression and protein levels of SERCA2a, while it exerted little influence on PLN expression. Furthermore, we speculated that AACO might affect the phosphorylation of PLN, but this requires further verification.

CONCLUSION

Network pharmacology, a practical means for studying the complicated pharmacological mechanisms underlying TCM treatment of various complex conditions, was used in this study to reveal that the calcium axis was the main pathway underlying the effect of AACO against CHF. Further investigations of the key steps in the calcium axis and the application of molecular biology, cell function, morphology, and other technical methods have proven the predicted results of network pharmacology, providing an important basis for TCM treatment of heart failure.

AUTHOR DISCLOSURE STATEMENT

All authors have read and approved the final manuscript. The authors declare that they have no conflict of interest. There are no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Cheng Lu as the first author helped with validation, writing, and original draft preparation; Huiling Li helped with software, visualization, and original draft preparation; Xinting Wang helped with validation; Huiying Wang assisted with writing-reviewing and editing; Lei Song helped with validation; Jingru Zhao helped with software; and Yongming Liu as the corresponding author provided supervision and helped with the conceptualization, validation, reviewing, and editing.

DATA AVAILABILITY STATEMENT

All data generated or used during the study are available from the corresponding author by request.

REFERENCES

1. McDonagh TA, Metra M, Adamo M, et al; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42(36):3599-3726. doi:10.1093/eurheartj/ehab368
2. Liu YM, Xu YY, Wang XL, Jiang MX. Hemodynamic research of Tonifying qi and warming Yang medicine in diastolic heart failure rats induced by pressure overload. *J. Shanghai Univ. Trad. Chin. Med*. 2012;26:71-75.
3. Lu C, Song L, Jiang M, Shen R, Liu Y. MPWD is a useful tool for evaluation of cardiac diastolic function in a rat model of pressure overload and the therapeutic effect of Tonifying qi and warming Yang medicine. *Liaoning J Trad Chin Med*. 2017;44:1978-1982.
4. Ru J, Li P, Wang J, et al. TCMSP: a database of systems pharmacology for drug discovery from herbal medicines. *J Cheminform*. 2014;6(1):13. doi:10.1186/1758-2946-6-13
5. Liu Z, Guo F, Wang Y, et al. BATMAN-TCM: a Bioinformatics Analysis Tool for Molecular mechANism of Traditional Chinese Medicine. *Sci Rep*. 2016;6(1):21146. doi:10.1038/srep21146
6. Amberger JS, Hamosh A. Searching Online Mendelian Inheritance in Man (OMIM): A Knowledgebase of Human Genes and Genetic Phenotypes. *Curr Protoc Bioinformatics*. 2017;58:1.2.1-1.2.12. doi:10.1002/cpbi.27
7. Piñero J, Bravo À, Queralt-Rosinach N, et al. DisGeNET: a comprehensive platform integrating information on human disease-associated genes and variants. *Nucleic Acids Res*. 2017;45(D1):D833-D839. doi:10.1093/nar/gkw943
8. Li YH, Yu CY, Li XX, et al. Therapeutic target database update 2018: enriched resource for facilitating bench-to-clinic research of targeted therapeutics. *Nucleic Acids Res*. 2018;46(D1):D1121-D1127. doi:10.1093/nar/gkx1076
9. von Mering C, Jensen LJ, Snel B, et al. STRING: known and predicted protein-protein associations, integrated and transferred across organisms. *Nucleic Acids Res*. 2005;33(Database issue):D433-D437. doi:10.1093/nar/gki005
10. Jiao X, Sherman BT, Huang W, et al. DAVID-WS: a stateful web service to facilitate gene/protein list analysis. *Bioinformatics*. 2012;28(13):1805-1806. doi:10.1093/bioinformatics/bts251
11. Wojcikowski K, Gobe G. Animal studies on medicinal herbs: predictability, dose conversion and potential value. *Phytother Res*. 2014;28(1):22-27. doi:10.1002/ptr.4966
12. Wang Q, Liu Y, Fu Q, et al. Inhibiting Insulin-Mediated β2-Adrenergic Receptor Activation Prevents Diabetes-Associated Cardiac Dysfunction. *Circulation*. 2017;135(1):73-88. doi:10.1161/CIRCULATIONAHA.116.022281
13. Yue SJ, Xin LT, Fan YC, et al. Herb pair Danggui-Honghua: mechanisms underlying blood stasis syndrome by system pharmacology approach. *Sci Rep*. 2017;7(1):40318. doi:10.1038/srep40318
14. Zhang R, Zhu X, Bai H, Ning K. Network Pharmacology Databases for Traditional Chinese Medicine: review and Assessment. *Front Pharmacol*. 2019;10:123. doi:10.3389/fphar.2019.00123
15. Kumarswamy R, Lyon AR, Volkmann I, et al. SERCA2a gene therapy restores microRNA-1 expression in heart failure via an Akt/FoxO3A-dependent pathway. *Eur Heart J*. 2012;33(9):1067-1075. doi:10.1093/eurheartj/ehs043
16. McCrink KA, Maning J, Vu A, et al. β-Arrestin2 Improves Post-Myocardial Infarction Heart Failure via Sarco(endo)plasmic Reticulum Ca^{2+}-ATPase-Dependent Positive Inotropy in Cardiomyocytes. *Hypertension*. 2017;70(5):972-981. doi:10.1161/HYPERTENSIONAHA.117.09817
17. Quan C, Li M, Du Q, et al. SPEG Controls Calcium Reuptake Into the Sarcoplasmic Reticulum Through Regulating SERCA2a by Its Second Kinase-Domain. *Circ Res*. 2019;124(5):712-726. doi:10.1161/CIRCRESAHA.118.313916
18. MacLennan DH, Kranias EG. Phospholamban: a crucial regulator of cardiac contractility. *Nat Rev Mol Cell Biol*. 2003;4(7):566-577. doi:10.1038/nrm1151
19. Soller KJ, Yang J, Veglia G, Bowser MT. Reversal of Phospholamban Inhibition of the Sarco(endo)plasmic Reticulum Ca2+-ATPase (SERCA) Using Short, Protein-interacting RNAs and Oligonucleotide Analogs. *J Biol Chem*. 2016;291(41):21510-21518. doi:10.1074/jbc.M116.738807
20. Mora MT, Ferrero JM, Romero L, Trenor B. Sensitivity analysis revealing the effect of modulating ionic mechanisms on calcium dynamics in simulated human heart failure. *PLoS One*. 2017;12(11):e0187739. doi:10.1371/journal.pone.0187739
21. Silveira CFSMP, Campos DHS, Freire PP, et al. Importance of SERCA2a on early isolated diastolic dysfunction induced by supravalvular aortic stenosis in rats. *Braz J Med Biol Res*. 2017;50(5):e5742. doi:10.1590/1414-431x20175742

Supplementary Table 1. The active ingredients of the AACO formula the herbs of the AACO formula

Curcuma zedoaria
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Aconitum carmichaeli Debx	Delphamine
Aconitum carmichaeli Debx	Delphatine
Aconitum carmichaeli Debx	Delsoline
Aconitum carmichaeli Debx	Deltaline
Aconitum carmichaeli Debx	Deltoin
Aconitum carmichaeli Debx	Deoxyaconitine
Aconitum carmichaeli Debx	Deoxyandrographolide
Aconitum carmichaeli Debx	Higenamine
Aconitum carmichaeli Debx	Hypaconitine
Aconitum carmichaeli Debx	Hypaphorine
Aconitum carmichaeli Debx	Ignavine
Astragalus membranaceus	Isotalatizidine
Astragalus membranaceus	kaempferol
Astragalus membranaceus	Karakoline
Astragalus membranaceus	Karanjin
Astragalus membranaceus	M-Aminophenol
Astragalus membranaceus	Mesaconitine
Astragalus membranaceus	Mescaline
Astragalus membranaceus	Neojiangyouaconitine
Astragalus membranaceus	Neokadsuranic Acid B
Astragalus membranaceus	Neoline
Astragalus membranaceus	Ortho-Aminophenol
Astragalus membranaceus	P-Aminophenol
Astragalus membranaceus	Para-Aminophenol
Astragalus membranaceus	SalsolinolSitosterol
Astragalus membranaceus	Talatisamine
Astragalus membranaceus	Vilmorrianine C
Astragalus membranaceus	Bifendate
Astragalus membranaceus	(3S,8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-[(2R,5S)-5-propan-2-yloctan-2-yl]-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol
Astragalus membranaceus	(6aR,11aR)-9,10-dimethoxy-6a,11a-dihydro-6H-benzofurano[3,2-c]chromen-3-ol
Astragalus membranaceus	20-Hexadecanoylingenol
Astragalus membranaceus	3,5-Dimethoxystilbene
Astragalus membranaceus	3,9-di-O-methylnissolin
Astragalus membranaceus	7-O-methylisomucronulatol
Astragalus membranaceus	Acetic Acid
Astragalus membranaceus	Adenine
Astragalus membranaceus	Astragaloside I
Astragalus membranaceus	Astragaloside II
Astragalus membranaceus	Astragaloside III
Astragalus membranaceus	Astragaloside IV
Astragalus membranaceus	Astragaloside V
Astragalus membranaceus	Astragaloside VI
Astragalus membranaceus	Astragaloside VII
Astragalus membranaceus	Astramembrannin I
Astragalus membranaceus	Betaine
Astragalus membranaceus	Beta-Sitosterol
Astragalus membranaceus	Calycosin
Ophiopogon japonicus	Canavanine
Ophiopogon japonicus	Choline
Ophiopogon japonicus	Chrysanthemaxanthin
Ophiopogon japonicus	Foliosidine
Ophiopogon japonicus	Formononetin
Ophiopogon japonicus	Gamma-Sitosterol
Ophiopogon japonicus	Guanosine
Ophiopogon japonicus	Hederagenin
Ophiopogon japonicus	Isorhamnetin
Ophiopogon japonicus	Kumatakenin
Ophiopogon japonicus	Lupeol
Ophiopogon japonicus	Mairin
Ophiopogon japonicus	Quercetin
Ophiopogon japonicus	Rhamnocitrin
Ophiopogon japonicus	Soyasapogenol B
Ophiopogon japonicus	Soyasaponin 1
Ophiopogon japonicus	Sucrose
Ophiopogon japonicus	Uridine
	6-Aldehydo-Isoophipogonone B
Molecule Name (the active compounds in the herbs)	Guanosine
Isocurcumenol	Methyl Ophiopogonanone A
Neocurdione	Methyl Ophiopogonanone B
Beta-Elemene	Ophiopogon A
Curcumin	Ophiopogon B
Curcumol	Ophiopogonanone A
Curdione	Ophiopogonanone C
Curzerene	Ophiopogonanone EOphiopogonin A
Hederagenin	Ophiopogonin B
Procurcumenol	Ophiopogonin C
Wenjine	Ophiopogonin D
11,14-eicosadienoic acid	Ophiopogonone B
3-Acetylaconitine	Orchinol
8-Deoxy-14-Dehydro-Aconosine	Stigmasterol
Aconine	Uridine
Aconitine	
Benzoylaconine	The active ingredients of the AACO formula. 105 active compounds were obtained, including astragaloside IV, calycosin, benzoylnesaconine, benzoylhypaconine, and benzoylaconine, et al.
Benzoylhypaconine	
Benzoylmesaconine	
Bullatine B	
Bullatine C	
Carnosifloside I	
Coryneine	
Crassicauline A	
Delavaconitine	
Delgrandine	

Supplementary Table 2. The compound-related target genes.

The active compounds of the AACO formula	**compound-related target genes**
(3S,8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-[(2R,5S)-5-propan-2-yloctan-2-yl]-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol	AR
(3S,8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-[(2R,5S)-5-propan-2-yloctan-2-yl]-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol	ESR1
(6aR,11aR)-9,10-dimethoxy-6a,11a-dihydro-6H-benzofurano[3,2-c]chromen-3-ol	ADRA1B
(6aR,11aR)-9,10-dimethoxy-6a,11a-dihydro-6H-benzofurano[3,2-c]chromen-3-ol	ADRA1D
(6aR,11aR)-9,10-dimethoxy-6a,11a-dihydro-6H-benzofurano[3,2-c]chromen-3-ol	ADRB2
(6aR,11aR)-9,10-dimethoxy-6a,11a-dihydro-6H-benzofurano[3,2-c]chromen-3-ol	AR
(6aR,11aR)-9,10-dimethoxy-6a,11a-dihydro-6H-benzofurano[3,2-c]chromen-3-ol	CA2
(6aR,11aR)-9,10-dimethoxy-6a,11a-dihydro-6H-benzofurano[3,2-c]chromen-3-ol	CALM1
(6aR,11aR)-9,10-dimethoxy-6a,11a-dihydro-6H-benzofurano[3,2-c]chromen-3-ol	CALM2
(6aR,11aR)-9,10-dimethoxy-6a,11a-dihydro-6H-benzofurano[3,2-c]chromen-3-ol	CALM3
(6aR,11aR)-9,10-dimethoxy-6a,11a-dihydro-6H-benzofurano[3,2-c]chromen-3-ol	CHRM4
(6aR,11aR)-9,10-dimethoxy-6a,11a-dihydro-6H-benzofurano[3,2-c]chromen-3-ol	ESR1
(6aR,11aR)-9,10-dimethoxy-6a,11a-dihydro-6H-benzofurano[3,2-c]chromen-3-ol	ESR2
(6aR,11aR)-9,10-dimethoxy-6a,11a-dihydro-6H-benzofurano[3,2-c]chromen-3-ol	GSK3B
(6aR,11aR)-9,10-dimethoxy-6a,11a-dihydro-6H-benzofurano[3,2-c]chromen-3-ol	NOS2
(6aR,11aR)-9,10-dimethoxy-6a,11a-dihydro-6H-benzofurano[3,2-c]chromen-3-ol	PPARD
(6aR,11aR)-9,10-dimethoxy-6a,11a-dihydro-6H-benzofurano[3,2-c]chromen-3-ol	PTGER4
(6aR,11aR)-9,10-dimethoxy-6a,11a-dihydro-6H-benzofurano[3,2-c]chromen-3-ol	PTGS1
(6aR,11aR)-9,10-dimethoxy-6a,11a-dihydro-6H-benzofurano[3,2-c]chromen-3-ol	PTK2B
11,14-eicosadienoic acid	CA2
11,14-eicosadienoic acid	NOS3
11,14-eicosadienoic acid	PPARD
20-Hexadecanoylingenol	CHGA
20-Hexadecanoylingenol	NR3C2
20-Hexadecanoylingenol	PRKCA
3,5-Dimethoxystilbene	ABCC2
3,5-Dimethoxystilbene	CDKN1A
3,5-Dimethoxystilbene	DNMT1
3,5-Dimethoxystilbene	DPYD
3,5-Dimethoxystilbene	DPYS
3,5-Dimethoxystilbene	HCN2
3,5-Dimethoxystilbene	HIF1A
3,5-Dimethoxystilbene	HTR2A
3,5-Dimethoxystilbene	IL1B
3,5-Dimethoxystilbene	PDE3A
3,5-Dimethoxystilbene	PDE3B
3,5-Dimethoxystilbene	SIRT1
3,9-di-O-methylnissolin	ADRA1B
3,9-di-O-methylnissolin	ADRA1D
3,9-di-O-methylnissolin	ADRA2C
3,9-di-O-methylnissolin	ADRB13,9-di-O-methylnissolin
ADRB2	3,9-di-O-methylnissolin
AR	3,9-di-O-methylnissolin
CA2	3,9-di-O-methylnissolin
CALM1	3,9-di-O-methylnissolin
CALM2	3,9-di-O-methylnissolin
CALM3	3,9-di-O-methylnissolin
ESR1	3,9-di-O-methylnissolin
ESR2	3,9-di-O-methylnissolin
GSK3B	3,9-di-O-methylnissolin
NOS2	3,9-di-O-methylnissolin
NOS3	3,9-di-O-methylnissolin
PPARD	3,9-di-O-methylnissolin
PTGER4	3,9-di-O-methylnissolin
PTGS1	3,9-di-O-methylnissolin
PTK2B	3-Acetylaconitine
CHRM2	6-Aldehydo-Isoophipogonone B
CRYZ	6-Aldehydo-Isoophipogonone B
NQO1	6-Aldehydo-Isoophipogonone B
VEGFA	7-O-methylisomucronulatol
ADRA1A	7-O-methylisomucronulatol
ADRA1B	7-O-methylisomucronulatol
ADRA1D	7-O-methylisomucronulatol
ADRA2C	7-O-methylisomucronulatol
ADRB1	7-O-methylisomucronulatol
ADRB2	7-O-methylisomucronulatol
AR	7-O-methylisomucronulatol
CA2	7-O-methylisomucronulatol
CALM1	7-O-methylisomucronulatol
CALM2	7-O-methylisomucronulatol
CALM3	7-O-methylisomucronulatol
CHRM2	7-O-methylisomucronulatol
CHRM4	7-O-methylisomucronulatol
ESR1	7-O-methylisomucronulatol
ESR2	7-O-methylisomucronulatol
GSK3B	7-O-methylisomucronulatol
HTR2A	7-O-methylisomucronulatol
KCNH2	7-O-methylisomucronulatol
NOS2	7-O-methylisomucronulatol
NOS3	7-O-methylisomucronulatol
PPARD	7-O-methylisomucronulatol
PTGER4	7-O-methylisomucronulatol
PTGS1	7-O-methylisomucronulatol
PTK2B	7-O-methylisomucronulatol
SLC6A2	8-Deoxy-14-Dehydro-Aconosine
CD34	8-Deoxy-14-Dehydro-Aconosine
CHRM2	8-Deoxy-14-Dehydro-Aconosine
HTR2AAcetic Acid	ACE
Acetic Acid	AKR1B1
Acetic Acid	ALAS2
Acetic Acid	ALDH2
Acetic Acid	APRT
Acetic Acid	ARG1
Acetic Acid	CAD
Acetic Acid	CAT
Acetic Acid	CHDH
Acetic Acid	CTSB
Acetic Acid	EPHX2
Acetic Acid	FASN
Acetic Acid	G6PD
Acetic Acid	GAPDH
Acetic Acid	GATM
Acetic Acid	GLB1
Acetic Acid	GPT
Acetic Acid	GSR
Acetic Acid	HDC
Acetic Acid	HMOX1
Acetic Acid	IL10
Acetic Acid	MMP12
Acetic Acid	MMP3
Acetic Acid	MMP8
Acetic Acid	MPO
Acetic Acid	NOS1
Acetic Acid	PNMT
Acetic Acid	PTGS1
Acetic Acid	PTGS2
Acetic Acid	RELA
Acetic Acid	REN
Acetic Acid	SDS
Acetic Acid	SELP
Acetic Acid	SERPINE1
Acetic Acid	SOD1
Acetic Acid	TNF
Acetic Acid	TPI1
Acetic Acid	XDH
Aconine	ATP2A2
Aconine	UCN2
Aconitine	CHRM2
Aconitine	CHRM4
Aconitine	PTGER4
Aconitine	PTGS1
Aconitine	SLC6A2
Adenine	ADORA1
Adenine	ADORA2AAdenine
ADORA2B	Astragaloside I
ABCB1	Astragaloside I
ALB	Astragaloside I
ATP1A1	Astragaloside I
KCNH2	Astragaloside II
ABCB1	Astragaloside II
ALB	Astragaloside II
ATP1A1	Astragaloside II
KCNH2	Astragaloside III
CXCR4	Astragaloside IV
ATP2A2	Astragaloside V
CXCR4	Astragaloside VI
CXCR4	Astragaloside VII
CXCR4	Astramembrannin I
CXCR4	Benzoylaconine
CHRM2	Benzoylaconine
SLC6A2	Benzoylhypaconine
CHRM2	Benzoylhypaconine
SLC6A2	Benzoylmesaconine
CHRM2	Benzoylmesaconine
SLC6A2	Beta-Elemene
ADORA1	Beta-Elemene
ADRA1A	Beta-Elemene
ALDH2	Beta-Elemene
APOE	Beta-Elemene
BCL2	Beta-Elemene
CAT	Beta-Elemene
CDKN1A	Beta-Elemene
CHRM2	Beta-Elemene
CYP2E1	Beta-Elemene
EDN1	Beta-Elemene
GATM	Beta-Elemene
IGF1	Beta-Elemene
IL1B	Beta-Elemene
KCNA3	Beta-Elemene
KCNIP2	Beta-Elemene
KCNQ1	Beta-Elemene
LEP	Beta-Elemene
MIP	Beta-Elemene
NPPA	Beta-Elemene
PTGS1	Beta-Elemene
PTGS2	Beta-Elemene
RHOA	Beta-Elemene
RYR2	Beta-Elemene
SLC6A2	Beta-Elemene
SOD1	Beta-Elemene
TP53Beta-Elemene	TPM1
Betaine	AKR1B1
Betaine	CAD
Betaine	GATM
Betaine	NOS1
Betaine	NOS3
Betaine	PIK3CG
Betaine	PPARG
Betaine	PTGS1
Betaine	PTGS2
Betaine	SLC18A3
Betaine	TGFB2
Betaine	TP53
Betaine	TPI1
Betaine	UCN2
Betaine	UTS2R
Beta-Sitosterol	AR
Beta-Sitosterol	BAX
Beta-Sitosterol	CYP27B1
Beta-Sitosterol	ESR1
Beta-Sitosterol	GC
Beta-Sitosterol	NFKB1
Beta-Sitosterol	NR3C1
Beta-Sitosterol	NR3C2
Beta-Sitosterol	PLN
Beta-Sitosterol	TBPL1
Bifendate	AR
Bifendate	ESR1
Bifendate	GSK3B
Bifendate	NOS2
Bifendate	PTGER4
Bifendate	PTGS1
Bullatine B	UCN2
Bullatine C	CHRM2
Calycosin	ADRB2
Calycosin	AR
Calycosin	CA2
Calycosin	CALM1
Calycosin	CALM2

Calycosin
CALM3
Calycosin
ESR1
Calycosin
ESR2
Calycosin
GSK3B
Calycosin
NOS2
Calycosin
PDE3A
Calycosin
PIM1
Calycosin
PPARDCalycosin
PPARG
Calycosin
PTGER4
Calycosin
PTGS1
Calycosin
PTGS2
Calycosin
PTK2B
Canavanine
ALAS2
Canavanine
ARG1
Canavanine
BAD
Canavanine
CAD
Canavanine
ECE1
Canavanine
EDN1
Canavanine
F2RL1
Canavanine
GATM
Canavanine
GPT
Canavanine
HMOX1
Canavanine
HTR2B
Canavanine
IFNG
Canavanine
IL1B
Canavanine
LCN2
Canavanine
NOS1
Canavanine
NOS2
Canavanine
NOS3
Canavanine
OPRM1
Canavanine
PIM1
Canavanine
PON1
Canavanine
PPARG
Canavanine
SLC18A3
Canavanine
SLC6A4
Canavanine
SLC7A1
Canavanine
TGFB2
Canavanine
TP53
Canavanine
UTS2R
Carnosifloside I
ATP1A1
Carnosifloside I
NR3C1
Choline
CHDH
Choline
CRP
Choline
FSCN1
Choline
HMOX1
Choline
NRG1
Chrysanthemaxanthin
ADA
Chrysanthemaxanthin
ADORA1
Coryneine
ADRA1A
Coryneine
ADRA1B
Coryneine
ADRA1D
Coryneine
ADRA2C
Coryneine
ADRB1
Coryneine
ADRB2Coryneine
ADRB3
Coryneine
DBH
Coryneine
MAPK1
Coryneine
PIK3CG
Coryneine
SLC6A2
Crassicauline A
CHRM2
Crassicauline A
SLC6A2
Curcumin
ATP2A2
Curcumol
CHRM2
Curcumol
NR3C1
Curdione
ABCC4
Curdione
ADA
Curdione
ADORA1
Curdione
ADORA2A
Curdione
ADORA2B
Curdione
ADRA1B
Curdione
ADRB1
Curdione
AGT
Curdione
ARID1A
Curdione
ATM
Curdione
ATP1A1
Curdione
ATP1A2
Curdione
ATP2A1
Curdione
ATP2B4
Curdione
AVPR2
Curdione
BCL2
Curdione
BNIP3
Curdione
CAMK2D
Curdione
CD34
Curdione
CRHR2
Curdione
CRP
Curdione
CSF2
Curdione
CX3CR1
Curdione
EDN1
Curdione
ESR1
Curdione
ESR2
Curdione
FKBP1B
Curdione
FOXP3
Curdione
G6PD
Curdione
GHRL
Curdione
GRK2
Curdione
HCN2
Curdione
HIF1A
Curdione
HRC
Curdione
IGF2
Curdione
IL10
Curdione
IL4Curdione
INS
Curdione
ITPR1
Curdione
ITPR2
Curdione
KCNH2
Curdione
LONP1
Curdione
LTA
Curdione
MTOR
Curdione
NOS1
Curdione
NOS1AP
Curdione
NR3C2
Curdione
PDE3A
Curdione
PDE3B
Curdione
PDE5A
Curdione
PDE9A
Curdione
PIK3CA
Curdione
PIK3CB
Curdione
PIK3CD
Curdione
PIK3CG
Curdione
PPP3CA
Curdione
PTGS2
Curdione
RYR1
Curdione
RYR2
Curdione
SEMA4D
Curdione
SIRT1
Curdione
SLC8A1
Curdione
SOD1
Curdione
SUMO1
Curdione
TBPL1
Curdione
TNF
Curdione
TOP2B
Curdione
TPH2
Curdione
UTS2
Curdione
VKORC1
Curdione
XDH
Curzerene
ADRA1A
Curzerene
ADRA1B
Curzerene
ADRB1
Curzerene
ADRB2
Curzerene
HTR2A
Curzerene
NOS3
Curzerene
NR3C1
Curzerene
PDE3A
Curzerene
SLC6A2
Curzerene
SLC6A4
Delavaconitine
CHRM2
Delavaconitine
CHRM4
Delavaconitine
SLC6A2Delgrandine
ADRA2C
Delgrandine
CHRM2
Delgrandine
HTR2A
Delgrandine
HTR2B
Delgrandine
KCNJ11
Delgrandine
SLC6A2
Delphamine
UCN2
Delphatine
UCN2
Delsoline
UCN2
Deltaline
ABCB1
Deltaline
ALB
Deltaline
KCNH2
Deltoin
ADRA1B
Deltoin
ADRB2
Deltoin
AR
Deltoin
CA2
Deltoin
CALM1
Deltoin
CALM2
Deltoin
CALM3
Deltoin
ESR1
Deltoin
ESR2
Deltoin
NOS3
Deltoin
NOS2
Deltoin
NR3C1
Deltoin
PPARD
Deltoin
PTGER4
Deltoin
PTGS1
Deoxyaconitine
CHRM2
Deoxyaconitine
CHRM4
Deoxyaconitine
SLC6A2
Deoxyandrographolide
AR
Deoxyandrographolide
ESR1
Deoxyandrographolide
NOS2
Deoxyandrographolide
NR3C1
Deoxyandrographolide
NR3C2
Deoxyandrographolide
PTGS1
Foliosidine
NQO1
Formononetin
ADRA1A
Formononetin
ADRB2
Formononetin
AR
Formononetin
CA2
Formononetin
CALM1
Formononetin
CALM2
Formononetin
CALM3
Formononetin
ESR1
Formononetin
ESR2
Formononetin
GSK3B
Formononetin
MAPK14
Formononetin
NOS2Formononetin
NOS3
Formononetin
PIM1
Formononetin
PPARD
Formononetin
PPARG
Formononetin
PTGER4
Formononetin
PTGS1
Formononetin
PTGS2
Formononetin
PTK2B
Formononetin
SLC6A2
Formononetin
SLC6A4
Gamma-Sitosterol
AR
Gamma-Sitosterol
BAX
Gamma-Sitosterol
CYP27B1
Gamma-Sitosterol
ESR1
Gamma-Sitosterol
GC
Gamma-Sitosterol
NFKB1
Gamma-Sitosterol
NR3C1
Gamma-Sitosterol
PLN
Gamma-Sitosterol
TBPL1
Guanosine
ADORA1
Guanosine
ADORA2A
Guanosine
ADORA2B
Guanosine
BRCA1
Guanosine
DNMT1
Guanosine
TBPL1
Hederagenin
ADRA1B
Hederagenin
AR
Hederagenin
CA2
Hederagenin
CHRM2
Hederagenin
ESR1
Hederagenin
NOS3
Hederagenin
NR3C1
Hederagenin
PPARD
Hederagenin
PTGER4
Hederagenin
PTGS1
Hederagenin
PTGS2
Higenamine
ADRA2C
Higenamine
ADRB1
Higenamine
ADRB2
Higenamine
ARRB2
Higenamine
CHRM2
Higenamine
HTR2A
Higenamine
HTR2B
Hypaconitine
CHRM2
Hypaconitine
SLC6A2
Hypaphorine
ADRB2
Hypaphorine
AR
Hypaphorine
PDE3AHypaphorine
PTGS1
Hypaphorine
PTGS2
Hypaphorine
SLC6A4
Ignavine
ABCC9
Ignavine
ADRA2C
Ignavine
APLN
Ignavine
ARRB1
Ignavine
ARRB2
Ignavine
ATP2B4
Ignavine
CD34
Ignavine
CHRM2
Ignavine
HTR2A
Ignavine
HTR2B
Ignavine
KCNJ11
Ignavine
NOS1
Ignavine
SLC6A2
Ignavine
SLC8A1
Isocurcumenol
CHRM2
Isocurcumenol
PTGS2
Isorhamnetin
AKR1B1
Isorhamnetin
AR
Isorhamnetin
CA2
Isorhamnetin
CYP27B1
Isorhamnetin
CALM1
Isorhamnetin
CALM2
Isorhamnetin
CALM3
Isorhamnetin
ESR1
Isorhamnetin
ESR2
Isorhamnetin
GSK3B
Isorhamnetin
MAPK14
Isorhamnetin
NCF1
Isorhamnetin
NOS2
Isorhamnetin
NOS3
Isorhamnetin
OLR1
Isorhamnetin
PIK3CD
Isorhamnetin
PIK3CG
Isorhamnetin
PIM1
Isorhamnetin
PPARD
Isorhamnetin
PTGS1
Isorhamnetin
PTGS2
Isorhamnetin
RELA
Isorhamnetin
XDH
Isotalatizidine
CHRM2
Kaempferol
ADRA1B
Kaempferol
AHSA1
Kaempferol
AKT1
Kaempferol
ARKaempferol
AR
Kaempferol
BAX
Kaempferol
BCL2
Kaempferol
CA2
Kaempferol
CA2
Kaempferol
CALM1
Kaempferol
CALM1
Kaempferol
CALM2
Kaempferol
CALM2
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CALM3
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CALM3
Kaempferol
CASP3
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CHRM2
Kaempferol
CRYZ
Kaempferol
ESR1
Kaempferol
ESR1
Kaempferol
ESR2
Kaempferol
ESR2
Kaempferol
GSK3B
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GSK3B
Kaempferol
HMOX1
Kaempferol
MAPK14
Kaempferol
MAPK14
Kaempferol
MAPK8
Kaempferol
MMP1
Kaempferol
NOS2
Kaempferol
NOS2
Kaempferol
NOS3
Kaempferol
NR1I2
Kaempferol
PIK3CG
Kaempferol
PPARD
Kaempferol
PPARD
Kaempferol
PPARG
Kaempferol
PPP3CA
Kaempferol
PTGER4
Kaempferol
PTGER4
Kaempferol
PTGS1
Kaempferol
PTGS2
Kaempferol
PTGS2
Kaempferol
PTK2B
Kaempferol
PTK2B
Kaempferol
RELA
Kaempferol
SCN5A
Kaempferol
SLC2A4
Kaempferol
SLC6A2
Kaempferol
TNF
Kaempferol
TOP2BKaempferol
VEGFA
Kaempferol
XDH
Kaempferol
PIK3CD

Karakoline
UCN2
Karanjin
ESR1
Karanjin
PIK3CD
Karanjin
PTGER4
Karanjin
PTGS1
Quercetin
NOS3
Kumatakenin
PTGS1
Lupeol
BAX
Lupeol
BCL2
Lupeol
CASP3
Lupeol
CYP27B1
Lupeol
ESR1
Lupeol
GC
Lupeol
NFKB1
Lupeol
PLN
Lupeol
SOD1
Lupeol
TBPL1
Mairin
AR
Mairin
ESR1
Mairin
NR3C1
M-Aminophenol
ADORA2B
M-Aminophenol
ANGPT1
M-Aminophenol
APOA1
M-Aminophenol
BMP4
M-Aminophenol
CAMK2D
M-Aminophenol
CHDH
M-Aminophenol
CRP
M-Aminophenol
EPO
M-Aminophenol
FASLG
M-Aminophenol
HCN2
M-Aminophenol
HRC
M-Aminophenol
IFNG
M-Aminophenol
IL10
M-Aminophenol
IL1B
M-Aminophenol
IL4
M-Aminophenol
IL6
M-Aminophenol
LGALS3
M-Aminophenol
LILRB1
M-Aminophenol
LTA
M-Aminophenol
NRG1
M-Aminophenol
PDE3A
M-Aminophenol
ROCK1
M-Aminophenol
SELP
M-Aminophenol
SIRT1M-Aminophenol
TGFB1
Mesaconitine
CHRM2
Mescaline
ADRA1A
Mescaline
ADRA1B
Mescaline
ADRA1D
Mescaline
ADRA2C
Mescaline
ADRB1
Mescaline
ADRB2
Mescaline
ADRB3
Mescaline
ANK2
Mescaline
CASQ2
Mescaline
CAV3
Mescaline
DBH
Mescaline
GPD1L
Mescaline
HTR2A
Mescaline
KCNQ1
Mescaline
NPPA
Mescaline
PDE3A
Mescaline
PTGS2
Mescaline
RYR1
Mescaline
SLC6A2
Mescaline
SLC6A4
Methyl Ophiopogonanone A
CNR2
Methyl Ophiopogonanone A
SOAT1
Methyl Ophiopogonanone B
AKT1
Methyl Ophiopogonanone B
CAV3
Methyl Ophiopogonanone B
CCR7
Methyl Ophiopogonanone B
CD36
Methyl Ophiopogonanone B
CNR2
Methyl Ophiopogonanone B
SOAT1
Neocurdione
ABCC4
Neocurdione
ADA
Neocurdione
ADORA1
Neocurdione
ADORA2A
Neocurdione
ADORA2B
Neocurdione
ADRA1B
Neocurdione
ADRB1
Neocurdione
AGT
Neocurdione
ARID1A
Neocurdione
ATM
Neocurdione
ATP1A1
Neocurdione
ATP1A2
Neocurdione
ATP2A1
Neocurdione
ATP2B4
Neocurdione
AVPR2
Neocurdione
BCL2
Neocurdione
BNIP3Neocurdione
CAMK2D
Neocurdione
CD34
Neocurdione
CRHR2
Neocurdione
CRP
Neocurdione
CSF2
Neocurdione
CX3CR1
Neocurdione
EDN1
Neocurdione
ESR1
Neocurdione
ESR2
Neocurdione
FKBP1B
Neocurdione
FOXP3
Neocurdione
G6PD
Neocurdione
GHRL
Neocurdione
GRK2
Neocurdione
HCN2
Neocurdione
HIF1A
Neocurdione
HRC
Neocurdione
IGF2
Neocurdione
IL10
Neocurdione
INS
Neocurdione
ITPR1
Neocurdione
ITPR2
Neocurdione
KCNH2
Neocurdione
LONP1
Neocurdione
LTA
Neocurdione
MTOR
Neocurdione
NOS1
Neocurdione
NOS1AP
Neocurdione
NR3C2
Neocurdione
PDE3A
Neocurdione
PDE3B
Neocurdione
PDE5A
Neocurdione
PDE9A
Neocurdione
PIK3CA
Neocurdione
PIK3CB
Neocurdione
PIK3CD
Neocurdione
PIK3CG
Neocurdione
PPP3CA
Neocurdione
PTGS2
Neocurdione
RYR1
Neocurdione
RYR2
Neocurdione
SEMA4D
Neocurdione
SIRT1
Neocurdione
SLC8A1
Neocurdione
SOD1
Neocurdione
SUMO1
Neocurdione
TNFNeocurdione
TOP2B
Neocurdione
TPH2
Neocurdione
UCN2
Neocurdione
UTS2
Neocurdione
VKORC1
Neocurdione
XDH
Neojiangyouaconitine
CHRM2
Neojiangyouaconitine
SLC6A2
Neokadsuranic Acid B
AGTR1
Neokadsuranic Acid B
AR
Neokadsuranic Acid B
ESR1
Neokadsuranic Acid B
NR3C1
Neokadsuranic Acid B
NR3C2
Neokadsuranic Acid B
PTGER4
Neoline
UCN2
Ophiopogon A
ATP1A1
Ophiopogon B
ATP1A1
Ophiopogonanone A
CNR2
Ophiopogonanone A
SOAT1
Ophiopogonanone C
CNR2
Ophiopogonanone C
SOAT1
Ophiopogonanone E
AKT1
Ophiopogonanone E
CAV3
Ophiopogonanone E
CCR7
Ophiopogonanone E
CD36
Ophiopogonanone E
CNR2
Ophiopogonanone E
SOAT1
Ophiopogonin A
ATP1A1
Ophiopogonin B
ATP1A1
Ophiopogonin C
ATP1A1
Ophiopogonin D
ATP1A1
Ophiopogonone B
CRYZ
Ophiopogonone B
NQO1
Ophiopogonone B
VEGFA
Orchinol
NR1I2
Orchinol
PRKCA
Orchinol
SCN5A
Ortho-Aminophenol
ADORA2B
Ortho-Aminophenol
ANGPT1
Ortho-Aminophenol
BMP4
Ortho-Aminophenol
CAMK2D
Ortho-Aminophenol
CHDH
Ortho-Aminophenol
CRP
Ortho-Aminophenol
EPO
Ortho-Aminophenol
FASLG
Ortho-Aminophenol
HCN2
Ortho-Aminophenol
HRCOrtho-Aminophenol
IFNG
Ortho-Aminophenol
IL10
Ortho-Aminophenol
IL1B
Ortho-Aminophenol
IL4
Ortho-Aminophenol
IL6
Ortho-Aminophenol
LGALS3
Ortho-Aminophenol
LILRB1
Ortho-Aminophenol
LTA
Ortho-Aminophenol
NRG1
Ortho-Aminophenol
PDE3A
Ortho-Aminophenol
ROCK1
Ortho-Aminophenol
SELP
Ortho-Aminophenol
SIRT1
Ortho-Aminophenol
TGFB1
P-Aminophenol
ADORA2B
P-Aminophenol
ANGPT1
P-Aminophenol
BMP4
P-Aminophenol
CAMK2D
P-Aminophenol
CHDH
P-Aminophenol
CRP
P-Aminophenol
EPO
P-Aminophenol
FASLG
P-Aminophenol
HCN2
P-Aminophenol
HRC
P-Aminophenol
IFNG
P-Aminophenol
IL10
P-Aminophenol
IL1B
P-Aminophenol
IL4
P-Aminophenol
IL6
P-Aminophenol
LGALS3
P-Aminophenol
LILRB1
P-Aminophenol
LTA
P-Aminophenol
NRG1
P-Aminophenol
PDE3A
P-Aminophenol
PTGER4
P-Aminophenol
PTGS1
P-Aminophenol
ROCK1
P-Aminophenol
SELP
P-Aminophenol
SIRT1
P-Aminophenol
TGFB1
Para-Aminophenol
ADORA2B
Para-Aminophenol
ANGPT1
Para-Aminophenol
BMP4
Para-Aminophenol
CAMK2D
Para-Aminophenol
CHDH
Para-Aminophenol
CRP
Para-Aminophenol
EPOPara-Aminophenol
FASLG
Para-Aminophenol
HCN2
Para-Aminophenol
HRC
Para-Aminophenol
IFNG
Para-Aminophenol
IL10
Para-Aminophenol
IL1B
Para-Aminophenol
IL4
Para-Aminophenol
IL6
Para-Aminophenol
LGALS3
Para-Aminophenol
LILRB1
Para-Aminophenol
LTA
Para-Aminophenol
NRG1
Para-Aminophenol
PDE3A
Para-Aminophenol
PTGER4
Para-Aminophenol
PTGS1
Para-Aminophenol
ROCK1
Para-Aminophenol
SELP
Para-Aminophenol
SIRT1
Para-Aminophenol
TGFB1
Procurcumenol
AR
Procurcumenol
ESR1
Procurcumenol
NOX1
Procurcumenol
NR3C1
Procurcumenol
PTGER4
Procurcumenol
PTGS1
Procurcumenol
RYR3
Procurcumenol
TGFB1
Quercetin
ACACA
Quercetin
ADRA2C
Quercetin
ADRB2
Quercetin
AHSA1
Quercetin
AKR1B1
Quercetin
AKT1
Quercetin
AR
Quercetin
BAX
Quercetin
BCL2
Quercetin
CA2
Quercetin
CASP3
Quercetin
CCL2
Quercetin
CDKN1A
Quercetin
CHEK2
Quercetin
COL1A1
Quercetin
COL3A1
Quercetin
CRP
Quercetin
CXCL2
Quercetin
DUOX2
Quercetin
EGFRQuercetin
ERBB2
Quercetin
ESR1
Quercetin
ESR2
Quercetin
GJA1
Quercetin
GSK3B
Quercetin
HIF1A
Quercetin
HK2
Quercetin
HMOX1
Quercetin
HSF1
Quercetin
HSPB1
Quercetin
HTR2A
Quercetin
HTR2B
Quercetin
IFNG
Quercetin
IGF2
Quercetin
IL10
Quercetin
IL1A
Quercetin
IL1B
Quercetin
IL6
Quercetin
IRF1
Quercetin
KCNH2
Quercetin
MAPK1
Quercetin
MAPK14
Quercetin
MMP1
Quercetin
MMP2
Quercetin
MMP3
Quercetin
MMP9
Quercetin
MPO
Quercetin
NCF1
Quercetin
NFE2L2
Quercetin
NOS2
Quercetin
NQO1
Quercetin
NR1I2
Quercetin
PARP1
Quercetin
PIK3CD
Quercetin
PIK3CG
Quercetin
PLAT
Quercetin
PON1
Quercetin
PPARA
Quercetin
PPARD
Quercetin
PPARG
Quercetin
PRKCA
Quercetin
PTEN
Quercetin
PTGER4
Quercetin
PTGS1
Quercetin
PTGS2
Quercetin
PTK2B
Quercetin
RAF1Quercetin
RELA
Quercetin
SCN5A
Quercetin
SERPINE1
Quercetin
SLC2A4
Quercetin
SOD1
Quercetin
SPP1
Quercetin
TGFB1
Quercetin
TNF
Quercetin
TP53
Quercetin
VDR
Quercetin
VEGFA

Quercetin	Soyasapogenol B	NR3C2
XDH	AR	Stigmasterol
Rhamnocitrin	Soyasapogenol B	PTGS1
AKR1B1	ESR1	Stigmasterol
Rhamnocitrin	Soyasapogenol B	PTGS2
AR	NR3C1	Stigmasterol
Rhamnocitrin	Soyasaponin 1	RYR2
CALM2	ATP1A1	Stigmasterol
Rhamnocitrin	Soyasaponin 1	SCN5A
CALM3	NR3C1	Stigmasterol
Rhamnocitrin	Stigmasterol	SLC6A2
ESR1	ADORA1	Stigmasterol
Rhamnocitrin	Stigmasterol	SOD1
ESR2	ADRA1A	Stigmasterol
Rhamnocitrin	Stigmasterol	TPM1
GSK3B	ADRA1BStigmasterol	Sucrose
Rhamnocitrin	ADRB1	AKR1B1
MAPK14	Stigmasterol	Sucrose
Rhamnocitrin	ADRB2	COL1A1
NOS2	Stigmasterol	Sucrose
Rhamnocitrin	AKR1B1	CXCR4
PIK3CG	Stigmasterol	Sucrose
Rhamnocitrin	ALDH2	IFNG
PPARG	Stigmasterol	Sucrose
Rhamnocitrin	APOE	MMP9
PTGS1	Stigmasterol	Sucrose
Rhamnocitrin	CAT	PPARG
PTGS2	Stigmasterol	Talatisamine
Salsolinol	CHRM2	CHRM2
ADRA1A	Stigmasterol	Uridine
Salsolinol	CYP2E1	APRT
ADRA1B	Stigmasterol	Uridine
Salsolinol	EDN1	DNMT1
ADRA1D	Stigmasterol	Uridine
Salsolinol	ESR1	DPYD
ADRA2C	Stigmasterol	Uridine
Salsolinol	GATM	ENPP1
ADRB1	Stigmasterol	Uridine
Salsolinol	HTR2A	NOS1
ADRB2	Stigmasterol	Uridine
Salsolinol	IGF1	NQO1
ARRB2	Stigmasterol	Uridine
Salsolinol	IL1B	PON1
ESR1	Stigmasterol	Vilmorrianine C
Salsolinol	KCNA3	ABCB1
NR3C1	Stigmasterol	Vilmorrianine C
Salsolinol	KCNIP2	ACE
NR3C2	Stigmasterol	Vilmorrianine C
Salsolinol	KCNQ1	CHRM2
PTGS1	Stigmasterol	Vilmorrianine C
Salsolinol	LEP	NOS1AP
PTGS2	Stigmasterol	Vilmorrianine C
Salsolinol	MIP	SLC6A2Wenjine
SLC6A2	Stigmasterol	AR
Sitosterol	NPPA	
AR	Stigmasterol	hsa04012:ErbB signaling pathway

The compound-related target genes. We mapped 1026 compound-related target genes and 883 CHF-related target genes to obtain 240 shared target genes which might elucidate the potential mechanisms of action underlying the anti-CHF effect of AACO.

Supplementary Table 3. KEGG analysis of the AACO targets involved in the activity against CHF signaling pathways the target genes

BAD	hsa04022:cGMP-PKG signaling pathway	CDKN1A
hsa04012:ErbB signaling pathway	ADORA1	hsa04066:HIF-1 signaling pathway
CAMK2D	hsa04022:cGMP-PKG signaling pathway	EDN1
hsa04012:ErbB signaling pathway	ADRA1A	hsa04066:HIF-1 signaling pathway
CDKN1A	hsa04022:cGMP-PKG signaling pathway	EGFR
hsa04012:ErbB signaling pathway	ADRA1B	hsa04066:HIF-1 signaling pathway
EGFR	hsa04022:cGMP-PKG signaling pathway	EPO
hsa04012:ErbB signaling pathway	ADRA1D	hsa04066:HIF-1 signaling pathway
ERBB2	hsa04022:cGMP-PKG signaling pathway	ERBB2hsa04066:HIF-1 signaling pathway
hsa04012:ErbB signaling pathway	ADRA2C	GAPDH
GSK3B	hsa04022:cGMP-PKG signaling pathway	hsa04066:HIF-1 signaling pathway
hsa04012:ErbB signaling pathway	ADRB1	HIF1A
MAPK1	hsa04022:cGMP-PKG signaling pathway	hsa04066:HIF-1 signaling pathway
hsa04012:ErbB signaling pathway	ADRB2	HK2
MAPK8	hsa04022:cGMP-PKG signaling pathway	hsa04066:HIF-1 signaling pathway
hsa04012:ErbB signaling pathway	ADRB3	HMOX1
MTOR	hsa04022:cGMP-PKG signaling pathway	hsa04066:HIF-1 signaling pathway
hsa04012:ErbB signaling pathway	AGTR1	IFNG
NRG1	hsa04022:cGMP-PKG signaling pathway	hsa04066:HIF-1 signaling pathway
hsa04012:ErbB signaling pathway	ATP1A1	IGF1
PIK3CA	hsa04022:cGMP-PKG signaling pathway	hsa04066:HIF-1 signaling pathway
hsa04012:ErbB signaling pathway	ATP1A2	IL6
PIK3CB	hsa04022:cGMP-PKG signaling pathway	hsa04066:HIF-1 signaling pathway
hsa04012:ErbB signaling pathway	ATP2A1	INS
PIK3CD	hsa04022:cGMP-PKG signaling pathway	hsa04066:HIF-1 signaling pathway
hsa04012:ErbB signaling pathway	ATP2A2	MAPK1
PIK3CG	hsa04022:cGMP-PKG signaling pathway	hsa04066:HIF-1 signaling pathway
hsa04012:ErbB signaling pathway	ATP2B4	MTOR
PRKCA	hsa04022:cGMP-PKG signaling pathway	hsa04066:HIF-1 signaling pathway
hsa04012:ErbB signaling pathway	BAD	NFKB1
RAF1	hsa04022:cGMP-PKG signaling pathway	hsa04066:HIF-1 signaling pathway
hsa04020:Calcium signaling pathway	CALM1	NOS2
ADORA2A	hsa04022:cGMP-PKG signaling pathway	hsa04066:HIF-1 signaling pathway
hsa04020:Calcium signaling pathway	CALM2	NOS3
ADORA2B	hsa04022:cGMP-PKG signaling pathway	hsa04066:HIF-1 signaling pathway
hsa04020:Calcium signaling pathway	CALM3	NPPA
ADRA1A	hsa04022:cGMP-PKG signaling pathway	hsa04066:HIF-1 signaling pathway
hsa04020:Calcium signaling pathway	INS	PIK3CA
ADRA1B	hsa04022:cGMP-PKG signaling pathway	hsa04066:HIF-1 signaling pathway
hsa04020:Calcium signaling pathway	ITPR1	PIK3CB
ADRA1D	hsa04022:cGMP-PKG signaling pathway	hsa04066:HIF-1 signaling pathway
hsa04020:Calcium signaling pathway	ITPR2	PIK3CD
ADRB1	hsa04022:cGMP-PKG signaling pathway	hsa04066:HIF-1 signaling pathway
hsa04020:Calcium signaling pathway	MAPK1	PIK3CG
ADRB2	hsa04022:cGMP-PKG signaling pathway	hsa04066:HIF-1 signaling pathway
hsa04020:Calcium signaling pathway	NOS3	PRKCA
ADRB3	hsa04022:cGMP-PKG signaling pathway	hsa04066:HIF-1 signaling pathway
hsa04020:Calcium signaling pathway	PDE3A	SERPINE1
AGTR1	hsa04022:cGMP-PKG signaling pathway	hsa04066:HIF-1 signaling pathway
hsa04020:Calcium signaling pathway	PDE3B	VEGFA
ATP2A1	hsa04022:cGMP-PKG signaling pathway	hsa04068:FoxO signaling pathway
hsa04020:Calcium signaling pathway	PDE5A	ATM
ATP2A2	hsa04022:cGMP-PKG signaling pathway	hsa04068:FoxO signaling pathway
hsa04020:Calcium signaling pathway	PLN	BNIP3
ATP2B4	hsa04022:cGMP-PKG signaling pathway	hsa04068:FoxO signaling pathway
hsa04020:Calcium signaling pathway	PPP3CA	CAT
CALM1	hsa04022:cGMP-PKG signaling pathway	hsa04068:FoxO signaling pathway
hsa04020:Calcium signaling pathway	RAF1	CDKN1A
CALM2	hsa04022:cGMP-PKG signaling pathway	hsa04068:FoxO signaling pathway
hsa04020:Calcium signaling pathway	RHOA	EGFR
CALM3	hsa04022:cGMP-PKG signaling pathway	hsa04068:FoxO signaling pathway
hsa04020:Calcium signaling pathway	ROCK1	FASLG
CAMK2D	hsa04022:cGMP-PKG signaling pathway	hsa04068:FoxO signaling pathway
hsa04020:Calcium signaling pathway	SLC8A1	IGF1
CHRM2	hsa04066:HIF-1 signaling pathway	hsa04068:FoxO signaling pathway
hsa04020:Calcium signaling pathway	ANGPT1	IL10
EGFR	hsa04066:HIF-1 signaling pathway	hsa04068:FoxO signaling pathway
hsa04020:Calcium signaling pathway	BCL2	IL6
ERBB2	hsa04066:HIF-1 signaling pathway	hsa04068:FoxO signaling pathway
hsa04020:Calcium signaling pathway	CAMK2D	INS
HTR2A	hsa04066:HIF-1 signaling pathway	hsa04068:FoxO signaling pathway
hsa04020:Calcium signaling pathway	CDKN1A	MAPK1
HTR2B	hsa04066:HIF-1 signaling pathway	hsa04068:FoxO signaling pathway
hsa04020:Calcium signaling pathway	EDN1	MAPK14
ITPR1	hsa04066:HIF-1 signaling pathway	hsa04068:FoxO signaling pathway
hsa04020:Calcium signaling pathway	EGFR	MAPK8
ITPR2	hsa04066:HIF-1 signaling pathway	hsa04068:FoxO signaling pathway
hsa04020:Calcium signaling pathway	EPO	PIK3CA
NOS1	hsa04066:HIF-1 signaling pathway	hsa04068:FoxO signaling pathway
hsa04020:Calcium signaling pathway	ERBB2hsa04066:HIF-1 signaling pathway	PIK3CB
NOS2	GAPDH	hsa04068:FoxO signaling pathway
hsa04020:Calcium signaling pathway	hsa04066:HIF-1 signaling pathway	PIK3CD
NOS3	HIF1A	hsa04068:FoxO signaling pathway
hsa04020:Calcium signaling pathway	hsa04066:HIF-1 signaling pathway	PIK3CG
PLN	HK2	hsa04068:FoxO signaling pathway
hsa04020:Calcium signaling pathway	hsa04066:HIF-1 signaling pathway	PTEN
PPP3CA	HMOX1	hsa04068:FoxO signaling pathway
hsa04020:Calcium signaling pathway	hsa04066:HIF-1 signaling pathway	RAF1
PRKCAhsa04020:Calcium signaling pathway	IFNG	hsa04068:FoxO signaling pathway
PTK2B	hsa04066:HIF-1 signaling pathway	SIRT1
hsa04020:Calcium signaling pathway	IGF1	hsa04068:FoxO signaling pathway
RYR1	hsa04066:HIF-1 signaling pathway	SLC2A4
hsa04020:Calcium signaling pathway	IL6	hsa04068:FoxO signaling pathway
RYR2	hsa04066:HIF-1 signaling pathway	TGFB1
hsa04020:Calcium signaling pathway	INS	hsa04068:FoxO signaling pathway
RYR3	hsa04066:HIF-1 signaling pathway	TGFB2
hsa04020:Calcium signaling pathway	MAPK1	hsa04071:Sphingolipid signaling pathway
SLC8A1	hsa04066:HIF-1 signaling pathway	ADORA1
hsa04020:Calcium signaling pathway	MTOR	hsa04071:Sphingolipid signaling pathway
TNNC1	hsa04066:HIF-1 signaling pathway	BAX
hsa04020:Calcium signaling pathway	NFKB1	
TNNC1	hsa04066:HIF-1 signaling pathway	

hsa04071:Sphingolipid signaling pathway
BCL2hsa04071:Sphingolipid signaling pathway
MAPK1
hsa04071:Sphingolipid signaling pathway
MAPK14
hsa04071:Sphingolipid signaling pathway
MAPK8
hsa04071:Sphingolipid signaling pathway
NFKB1
hsa04071:Sphingolipid signaling pathway
NOS3
hsa04071:Sphingolipid signaling pathway
PIK3CA
hsa04071:Sphingolipid signaling pathway
PIK3CB
hsa04071:Sphingolipid signaling pathway
PIK3CD
hsa04071:Sphingolipid signaling pathway
PIK3CG
hsa04071:Sphingolipid signaling pathway
PRKCA
hsa04071:Sphingolipid signaling pathway
PTEN
hsa04071:Sphingolipid signaling pathway
RAF1
hsa04071:Sphingolipid signaling pathway
RHOA
hsa04071:Sphingolipid signaling pathway
ROCK1
hsa04071:Sphingolipid signaling pathway
TNF
hsa04071:Sphingolipid signaling pathway
TP53
hsa04210:Apoptosis
ATM
hsa04210:Apoptosis
BAD
hsa04210:Apoptosis
BAX
hsa04210:Apoptosis
BCL2
hsa04210:Apoptosis
CASP3
hsa04210:Apoptosis
FASLG
hsa04210:Apoptosis
NFKB1
hsa04210:Apoptosis
PIK3CA
hsa04210:Apoptosis
PIK3CB
hsa04210:Apoptosis
PIK3CD
hsa04210:Apoptosis
PIK3CG
hsa04210:Apoptosis
TNF
hsa04210:Apoptosis
TP53
hsa04261:Adrenergic signaling in cardiomyocytes
ABCC4
hsa04261:Adrenergic signaling in cardiomyocytes
ADORA1
hsa04261:Adrenergic signaling in cardiomyocytes
ADORA2A
hsa04261:Adrenergic signaling in cardiomyocytes
ADRA1A
hsa04261:Adrenergic signaling in cardiomyocytes
ADRA1B
hsa04261:Adrenergic signaling in cardiomyocytes
ADRA1D
hsa04261:Adrenergic signaling in cardiomyocytes
ADRB1
hsa04261:Adrenergic signaling in cardiomyocytes
ADRB2
hsa04261:Adrenergic signaling in cardiomyocytes
AGTR1
hsa04261:Adrenergic signaling in cardiomyocytes
ATP1A1
hsa04261:Adrenergic signaling in cardiomyocytes
ATP1A2
hsa04261:Adrenergic signaling in cardiomyocytes
ATP2B4
hsa04261:Adrenergic signaling in cardiomyocytes
BAD
hsa04261:Adrenergic signaling in cardiomyocytes
BCL2
hsa04261:Adrenergic signaling in cardiomyocytes
CALM1
hsa04261:Adrenergic signaling in cardiomyocytes
CALM2
hsa04261:Adrenergic signaling in cardiomyocytes
CALM3
hsa04261:Adrenergic signaling in cardiomyocytes
CAMK2Dhsa04261:Adrenergic signaling in cardiomyocytes
CHRM2
hsa04261:Adrenergic signaling in cardiomyocytes
GHRL
hsa04261:Adrenergic signaling in cardiomyocytes
HCN2
hsa04261:Adrenergic signaling in cardiomyocytes
KCNQ1
hsa04261:Adrenergic signaling in cardiomyocytes
MAPK1
hsa04261:Adrenergic signaling in cardiomyocytes
MAPK14
hsa04261:Adrenergic signaling in cardiomyocytes
MAPK8
hsa04261:Adrenergic signaling in cardiomyocytes
NFKB1
hsa04261:Adrenergic signaling in cardiomyocytes
PDE3A
hsa04261:Adrenergic signaling in cardiomyocytes
PDE3B
hsa04261:Adrenergic signaling in cardiomyocytes
PIK3CA
hsa04261:Adrenergic signaling in cardiomyocytes
PIK3CB
hsa04261:Adrenergic signaling in cardiomyocytes
PIK3CD
hsa04261:Adrenergic signaling in cardiomyocytes
PIK3CG
hsa04261:Adrenergic signaling in cardiomyocytes
PLN
hsa04261:Adrenergic signaling in cardiomyocytes
PPARA
hsa04261:Adrenergic signaling in cardiomyocytes
PRKCA
hsa04261:Adrenergic signaling in cardiomyocytes
RAF1
hsa04261:Adrenergic signaling in cardiomyocytes
RHOA
hsa04261:Adrenergic signaling in cardiomyocytes
ROCK1
hsa04261:Adrenergic signaling in cardiomyocytes
RYR2
hsa04261:Adrenergic signaling in cardiomyocytes
SCN5A
hsa04261:Adrenergic signaling in cardiomyocytes
TNNC1
hsa04261:Adrenergic signaling in cardiomyocytes
TPM1
hsa04370:VEGF signaling pathway
BAD
hsa04370:VEGF signaling pathway
HSPB1
hsa04370:VEGF signaling pathway
MAPK1
hsa04370:VEGF signaling pathway
MAPK14
hsa04370:VEGF signaling pathway
NOS3
hsa04370:VEGF signaling pathway
PIK3CA
hsa04370:VEGF signaling pathway
PIK3CB
hsa04370:VEGF signaling pathway
PIK3CD
hsa04370:VEGF signaling pathway
PIK3CG
hsa04370:VEGF signaling pathway
PPP3CA
hsa04370:VEGF signaling pathway
PRKCA
hsa04370:VEGF signaling pathway
PTGS2
hsa04370:VEGF signaling pathway
RAF1
hsa04370:VEGF signaling pathway
VEGFA
hsa04380:Osteoclast differentiation
IFNG
hsa04380:Osteoclast differentiation
IL1A
hsa04380:Osteoclast differentiation
IL1B
hsa04380:Osteoclast differentiation
LILRB1
hsa04380:Osteoclast differentiation
MAPK1
hsa04380:Osteoclast differentiation
MAPK14
hsa04380:Osteoclast differentiation
MAPK8
hsa04380:Osteoclast differentiation
NCF1
hsa04380:Osteoclast differentiation
NFKB1hsa04380:Osteoclast differentiation
NOX1
hsa04380:Osteoclast differentiation
PIK3CA
hsa04380:Osteoclast differentiation
PIK3CB
hsa04380:Osteoclast differentiation
PIK3CD
hsa04380:Osteoclast differentiation
PIK3CG
hsa04380:Osteoclast differentiation
PPARG
hsa04380:Osteoclast differentiation
PPP3CA
hsa04380:Osteoclast differentiation
TGFB1
hsa04380:Osteoclast differentiation
TGFB2
hsa04380:Osteoclast differentiation
TNF
hsa04668:TNF signaling pathway
CASP3
hsa04668:TNF signaling pathway
CCL2
hsa04668:TNF signaling pathway
CSF2
hsa04668:TNF signaling pathway
CXCL2
hsa04668:TNF signaling pathway
EDN1
hsa04668:TNF signaling pathway
IL1B
hsa04668:TNF signaling pathway
IL6
hsa04668:TNF signaling pathway
MAPK1
hsa04668:TNF signaling pathway
MAPK14
hsa04668:TNF signaling pathway
MAPK8
hsa04668:TNF signaling pathway
MMP3
hsa04668:TNF signaling pathway
MMP9
hsa04668:TNF signaling pathway
NFKB1
hsa04668:TNF signaling pathway
PIK3CA
hsa04668:TNF signaling pathway
PIK3CB
hsa04668:TNF signaling pathway
PIK3CD
hsa04668:TNF signaling pathway
PIK3CG
hsa04668:TNF signaling pathway
PTGS2
hsa04668:TNF signaling pathway
TNF
hsa04668:TNF signaling pathway
LTA
hsa04722:Neurotrophin signaling pathway
BAX
hsa04722:Neurotrophin signaling pathway
BCL2
hsa04722:Neurotrophin signaling pathway
CALM1
hsa04722:Neurotrophin signaling pathway
CALM2
hsa04722:Neurotrophin signaling pathway
CALM3
hsa04722:Neurotrophin signaling pathway
CAMK2D
hsa04722:Neurotrophin signaling pathway
FASLG
hsa04722:Neurotrophin signaling pathway
GSK3B
hsa04722:Neurotrophin signaling pathway
MAPK1
hsa04722:Neurotrophin signaling pathway
MAPK14
hsa04722:Neurotrophin signaling pathway
MAPK8
hsa04722:Neurotrophin signaling pathway
NFKB1
hsa04722:Neurotrophin signaling pathway
NGFhsa04722:Neurotrophin signaling pathway
NOS3
hsa04722:Neurotrophin signaling pathway
PIK3CA
hsa04722:Neurotrophin signaling pathway
PIK3CB
hsa04722:Neurotrophin signaling pathway
PIK3CD
hsa04722:Neurotrophin signaling pathway
PIK3CG
hsa04722:Neurotrophin signaling pathway
PLCG1
hsa04722:Neurotrophin signaling pathway
PRKCA
hsa04722:Neurotrophin signaling pathway
RAF1hsa04722:Neurotrophin signaling pathway
RHOA
hsa04722:Neurotrophin signaling pathway
TP53
hsa04750:Inflammatory mediator regulation of TRP channelsCALM1
hsa04750:Inflammatory mediator regulation of TRP channelsCALM2
hsa04750:Inflammatory mediator regulation of TRP channelsCALM3
hsa04750:Inflammatory mediator regulation of TRP channelsCAMK2D
hsa04750:Inflammatory mediator regulation of TRP channelsF2RL1
hsa04750:Inflammatory mediator regulation of TRP channelsHTR2A
hsa04750:Inflammatory mediator regulation of TRP channelsHTR2B
hsa04750:Inflammatory mediator regulation of TRP channelsIGF1
hsa04750:Inflammatory mediator regulation of TRP channelsIL1B
hsa04750:Inflammatory mediator regulation of TRP channelsITPR1
hsa04750:Inflammatory mediator regulation of TRP channelsITPR2
hsa04750:Inflammatory mediator regulation of TRP channelsMAPK14
hsa04750:Inflammatory mediator regulation of TRP channelsMAPK8
hsa04750:Inflammatory mediator regulation of TRP channelsPIK3CA
hsa04750:Inflammatory mediator regulation of TRP channelsPIK3CB
hsa04750:Inflammatory mediator regulation of TRP channelsPIK3CD
hsa04750:Inflammatory mediator regulation of TRP channelsPIK3CG
hsa04750:Inflammatory mediator regulation of TRP channelsPRKCA
hsa04750:Inflammatory mediator regulation of TRP channelsPTGER4
hsa04910:Insulin signaling pathway
ACACA
hsa04910:Insulin signaling pathway
BAD
hsa04910:Insulin signaling pathway
CALM1
hsa04910:Insulin signaling pathway
CALM2
hsa04910:Insulin signaling pathway
CALM3
hsa04910:Insulin signaling pathway
FASN
hsa04910:Insulin signaling pathway
GSK3B
hsa04910:Insulin signaling pathway
HK2
hsa04910:Insulin signaling pathway
INS
hsa04910:Insulin signaling pathway
MAPK1
hsa04910:Insulin signaling pathway
MAPK8
hsa04910:Insulin signaling pathway
MTOR
hsa04910:Insulin signaling pathway
PDE3B
hsa04910:Insulin signaling pathway
PIK3CA
hsa04910:Insulin signaling pathway
PIK3CB
hsa04910:Insulin signaling pathway
PIK3CD
hsa04910:Insulin signaling pathway
PIK3CG
hsa04910:Insulin signaling pathway
RAF1
hsa04910:Insulin signaling pathway
SLC2A4
hsa04915:Estrogen signaling pathway
CALM1
hsa04915:Estrogen signaling pathway
CALM2
hsa04915:Estrogen signaling pathway
CALM3
hsa04915:Estrogen signaling pathway
EGFR
hsa04915:Estrogen signaling pathway
ESR1
hsa04915:Estrogen signaling pathway
ESR2
hsa04915:Estrogen signaling pathway
ITPR1hsa04915:Estrogen signaling pathway
ITPR2
hsa04915:Estrogen signaling pathway
MAPK1
hsa04915:Estrogen signaling pathway
MMP2
hsa04915:Estrogen signaling pathway
MMP9
hsa04915:Estrogen signaling pathway
NOS3
hsa04915:Estrogen signaling pathway
OPRM1
hsa04915:Estrogen signaling pathway
PIK3CA
hsa04915:Estrogen signaling pathway
PIK3CB
hsa04915:Estrogen signaling pathway
PIK3CD
hsa04915:Estrogen signaling pathway
PIK3CG
hsa04915:Estrogen signaling pathway
RAF1
hsa04917:Prolactin signaling pathway
ESR1
hsa04917:Prolactin signaling pathway
ESR2
hsa04917:Prolactin signaling pathway
GSK3B
hsa04917:Prolactin signaling pathway
INS
hsa04917:Prolactin signaling pathway
IRF1
hsa04917:Prolactin signaling pathway
MAPK1
hsa04917:Prolactin signaling pathway
MAPK14
hsa04917:Prolactin signaling pathway
MAPK8
hsa04917:Prolactin signaling pathway
NFKB1
hsa04917:Prolactin signaling pathway
PIK3CA
hsa04917:Prolactin signaling pathway
PIK3CB
hsa04917:Prolactin signaling pathway
PIK3CD
hsa04917:Prolactin signaling pathway
PIK3CG
hsa04917:Prolactin signaling pathway
RAF1
hsa04924:Renin secretion
ACE
hsa04924:Renin secretion
ADORA1
hsa04924:Renin secretion
ADRB1
hsa04924:Renin secretion
ADRB2
hsa04924:Renin secretion
ADRB3
hsa04924:Renin secretion
AGT
hsa04924:Renin secretion
AGTR1
hsa04924:Renin secretion
CALM1
hsa04924:Renin secretion
CALM2
hsa04924:Renin secretion
CALM3
hsa04924:Renin secretion
CTSB
hsa04924:Renin secretion
ITPR1
hsa04924:Renin secretion
ITPR2
hsa04924:Renin secretion
PDE3A
hsa04924:Renin secretion
PDE3B
hsa04924:Renin secretion
PPP3CA
hsa04924:Renin secretion
PTGER4
hsa04924:Renin secretion
REN
hsa04930:Type II diabetes mellitus
HK2
hsa04930:Type II diabetes mellitus
INS
hsa04930:Type II diabetes mellitus
KCNJ11
hsa04930:Type II diabetes mellitus
MAPK1hsa04930:Type II diabetes mellitus
MAPK8
hsa04930:Type II diabetes mellitus
MTOR
hsa04930:Type II diabetes mellitus
PIK3CA
hsa04930:Type II diabetes mellitus
PIK3CB
hsa04930:Type II diabetes mellitus
PIK3CD
hsa04930:Type II diabetes mellitus
PIK3CG
hsa04930:Type II diabetes mellitus
SLC2A4
hsa04930:Type II diabetes mellitus
TNF
hsa04960:Aldosterone-regulated sodium reabsorption
ATP1A1
hsa04960:Aldosterone-regulated sodium reabsorption
ATP1A2
hsa04960:Aldosterone-regulated sodium reabsorption
IGF1
hsa04960:Aldosterone-regulated sodium reabsorption
INS
hsa04960:Aldosterone-regulated sodium reabsorption
MAPK1
hsa04960:Aldosterone-regulated sodium reabsorption
NR3C2
hsa04960:Aldosterone-regulated sodium reabsorption
PIK3CA
hsa04960:Aldosterone-regulated sodium reabsorption
PIK3CB
hsa04960:Aldosterone-regulated sodium reabsorption
PIK3CD
hsa04960:Aldosterone-regulated sodium reabsorption
PIK3CG
hsa04960:Aldosterone-regulated sodium reabsorption
PRKCA
hsa04970:Salivary secretion
ADRA1A
hsa04970:Salivary secretion
ADRA1B
hsa04970:Salivary secretion
ADRA1D
hsa04970:Salivary secretion
ADRB1
hsa04970:Salivary secretion
ADRB2
hsa04970:Salivary secretion
ADRB3
hsa04970:Salivary secretion
ATP1A1
hsa04970:Salivary secretion
ATP1A2
hsa04970:Salivary secretion
ATP2B4
hsa04970:Salivary secretion
CALM1
hsa04970:Salivary secretion
CALM2
hsa04970:Salivary secretion
CALM3
hsa04970:Salivary secretion
ITPR1
hsa04970:Salivary secretion
ITPR2
hsa04970:Salivary secretion
NOS1
hsa04970:Salivary secretion
PRKCA
hsa04970:Salivary secretion
RYR3

KEGG analysis of the AACO targets involved in the activity against CHF.