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Exploration of the mechanism of pattern-specific treatments in coronary heart disease with network pharmacology approach[☆]

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ABSTRACT

Traditional Chinese medicine (TCM) pattern is a valuable classification method in the treatment of complex disease such as coronary heart disease (CHD). In accordance to TCM patterns, our ancestors created many pertinent TCM formulae, which have been used in China for thousands of years and are still playing an important role in China today. However, the biological mechanism of TCM pattern-specific formulae remains elusive. In this paper, we chose CHD patterns (Qi-stagnation induced blood-stasis syndrome, abbreviated as QSB; Qi-deficiency induced blood-stasis syndrome, abbreviated as QDB) as examples to illustrate the mechanism of their pattern-specific formulae. Using entity grammar systems (EGS) formalism, we built two pharmacologic networks of the formulae and obtained the intersection and difference networks by network comparison. Then we analyzed their common and different mechanisms for treating CHD by GO enrichment analysis. The results indicate that QDB-specific formula takes more special molecular paths to treat CHD, which contribute to more severe pathological changes in comparison with QSB. In this paper, we achieved a better understanding of the pharmacological characteristics of CHD patterns-specific formulae, which is beneficial to explore different therapies for a disease to enhance the effectiveness and pertinence of treatment.

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1. Introduction

TCM pattern has been proven to be an effective classification method in patient stratification integrated with biomedical diagnostic method [1,2]. In accordance to TCM patterns, our ancestors created many pertinent TCM formulae, which have been used in China for thousands of years and are still playing an important role in China today especially in the treatment of chronic diseases [3] and miscellaneous diseases, such as coronary heart disease(CHD). According to the feature of the patterns, proper therapeutic strategies such as pertinent formulae are adopted in clinics. It is valuable to explore the mechanism of different pattern-specific formulae to enhance the effectiveness and pertinence of treatment for a disease, especially for the complex disease with personalized conditions.

Abbreviations: TCM, traditional Chinese medicine; CHD, coronary heart disease; EGS, entity grammar systems; QSB, Qi-stagnation induced blood-stasis syndrome; QDB, Qi-deficiency induced blood-stasis syndrome; DS, Dan-Shen decoction for QSB; BYHW, Bu-Yang-Huan-Wu decoction for QDB; PIN, protein-protein interaction network

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Chinese medicine holds that blood-stasis syndrome is a common reason responsible for CHD in clinic of Chinese medicine due to Qi-stagnation (QSB) and Qi-deficiency (QDB). Modern TCM researches believe that QSB is the primary stage of CHD, while QDB is advanced [4]. In this work, we use QSB-specific formula (DS) and QSB-specific formula (BYHW) as the probe to explore the common and different mechanism of QSB and QDB treatments, respectively.

In the field of network pharmacology [5], network-based approaches are promptly used to interpret the mechanism of TCM at molecular network level [6-9]. Some research linked the component targets to disease targets in protein interaction network (PIN) to understand therapeutic action of TCM on patterns. For examples, Jiang et al. linked TCM targets with disease targets of cold and hot patterns based on PIN [10]. Li S proposed a map of "Phenotype network-biological network-herb network" with an attempt to uncover the network systems underlying TCM syndrome and Herb formula [11]. Their works demonstrated that the interventions in treating some diseases with TCM pattern-specific formulae could be more effective than treatments without TCM pattern classification from the perspective of network pharmacology.

Protein-protein interaction network (PIN) is typically deduced directly from systematic two-hybrid [12,13] and affinity purification-mass spectrometry data [14]. So the interaction between

proteins in PIN means binding, which is an edge with no directions. As PIN is an undirected and unsigned network (lacking positive or negative labels) [15], it cannot be used to depict the biological delivery effect of drugs through signal transduction of network. In other words, even if we know the proteins affected by TCM components, it would still be limited to illuminate the related therapeutic effects for specific disease.

So in this paper we used the signalling transduction network from pathway interaction database (PID) as background, which is signed and directed. We not only focused on the targets hit by chemical components in a formula directly, but also disease proteins influenced by these targets through network delivery. To fulfil this task, entity grammar systems (EGS) as a system modelling theory was used, which has already been successfully used in biological network construction [16]. And based on EGS a new concept, TCM grammar system (TGS) [17] was proposed, which is a universal method applied to uncover the molecular mechanism of TCM. So by EGS we inferred the relationship between component targets and disease proteins, and then built the pharmacologic networks of DS and BYHW to uncover the mechanism of QSB and QDB, respectively. Then we compared the two networks of DS and BYHW to obtain the intersection and difference networks. By Gene Ontology (GO) enrichment analysis, we discovered the common and different pharmacological effects of two pattern-specific formulae.

2. Method

2.1. Data sources

As two empirical prescriptions in clinic, Dan-Shen decoction (DS) and Bu-Yang-Huan-Wu decoction (BYHW) have been used to treat CHD with Qi-stagnation induced blood-stasis syndrome and Qi-deficiency induced blood-stasis syndrome, respectively, for thousands of years.

DS consists of three herbs, including *Radix et Rhizoma Salviae Miltiorrhizae*, *Lignum Santali Albi*, *Fructus Amomi*. BYHW consists of six herbs, including *Flos Carthami*, *Radix Angelicae Sinensis*, *Rhizoma Chuanxiong*, *Radix Paeoniae Rubra*, *Radix Astragali*, *Pheretima*.

The components of nine herbs are from Traditional Chinese Medicines Database (TCMD) [18] Traditional Chinese Medicine Basic Information Database of State Administration of Traditional Chinese Medicine of People's Republic of China (<http://dbshare.cintcm.com/ZhongYaoJiChu/>) and A Handbook on Analysis of the Active Composition in Traditional Chinese Medicine [19]. Totally, 118 components of DS and 226 components of BYHW were collected from the database and literature (Additional file 3).

The component targeting proteins were derived from the database of STITCH1.0 (http://stitch1.embl.de/cgi/show_input_page.pl?UserId=8xW_ofqsp9Hs&sessionId=1J1OYwhxclvB).

STITCH [20] is a search tool for interactions of chemicals, integrating information about interactions from metabolic pathways, crystal structures, binding experiments and drug-target relationships. When inputting the chemical name into STITCH, "Homo sapiens" species should be select from the organism drop-down box. In order to obtain the more overall results, the parameter of required confidence score was set higher than 0 and the interacting entity number was set with 500. More information about the chemicals involved in this paper, such as chemical structure information, could be obtained from STITCH or PubChem (<http://www.ncbi.nlm.nih.gov/pccompound>). In DS, totally 46 components with 765 targets were collected from STITCH1.0, and 132 components with 3691 targets for BYHW (Additional file 4).

Human signalling pathways are connected with each other in cells. In other words, if one node was perturbed by a drug, many other nodes in the network will be influenced as well. TCM

formulae treat disease not only by acting on disease targets directly but also affecting the related proteins which can regulate the disease targets by the network signalling delivery. In this paper, we are aimed to find how chemical constitutes influence CHD proteins by network delivery in a background bionetwork.

For constructing a comprehensive network of human cells, we integrated 136 human signalling pathways retrieved from PID (pathway interaction database, <http://pid.nci.nih.gov/index.shtml>). Fifty-seven disease targets of CHD were collected from Sciclips (<http://www.sciclips.com/>).

In the network, the interactions between nodes were represented with positive direction and negative direction only. In order to deduce the effect of chemical constitutes to CHD, the end nodes of the network were marked with disease targets of CHD. The networks were visualized with Cytoscape [21].

2.2. Network model construction by entity grammar systems

Entity grammar systems is a formal grammar system that aims at complex biological system modelling [16]. Because of the scalability features of EGS, it has already been used to establish the regulating flow graph of chemical processes [22] and illustrate the mechanism of TCM [17].

An entity grammar system G is a quintuple, $G=(V_N, V_T, F, P, S)$, where, $V_N \cup V_T = V$. V_N is finite set of non-terminal symbols, V_T is the finite set of terminal symbols, and $V_N \cap V_T = \emptyset$. F is the finite set of operations. The entities in the system were expressed as $E(V, F)$. P is a set of inference rules for deducing relationships between entities, S is the start entities. The details for establishing a definite entity grammar system were described in Ref. [16].

Identification of the TCM effective component combinations need the explicit relationship between components and disease. The model was established using EGS for predicting signal transduction effect and extracting sub-network. In this model, set V contains different types of nodes, set F contains the distinctive types of relationships between the adjacent nodes prepared before deduction, and set P contains the rules used for inferring the new relations of nodes. The concrete content was described as follows:

- (1) $V = V_1 \cup V_2 \cup V_3 \cup V_4$
 V_1 is the set of proteins on which the TCM chemical components act. V_2 is the set of the disease targets of CHD. V_3 and V_4 represent the sets of proteins and non-proteins in the pathway interaction network, respectively.
- (2) $F = \{\text{link}(X,Y,Z,W), \text{left}(X,Y,Z,W), \text{right}(X,Y,Z,W), \text{road}(X,Y,Z,W), \text{tnet}(X,Y,Z,W), \text{minnet}(X,Y,Z,W), \text{in}(X), \text{out}(Y)\}$
 $\text{Link}(X,Y,Z,W)$ represents biomolecular interactions. In $\text{link}(X,Y,Z,W)$, $X, Y \in V_3 \cup V_4$, $Z \in \{\text{pos}, \text{neg}\}$, $W \in Z^*$. The value of W means the number of interactions through which X transforms into Y . In $\text{left}(X,Y,Z,W)$, $X \in V_1, Y \notin V_2, Z \in \{\text{pos}, \text{neg}\}$, $W \in Z^*$. In $\text{road}(X,Y,Z,W)$, $X \notin V_1, Y \notin V_2, Z \in \{\text{pos}, \text{neg}\}$, $W \in Z^*$. In $\text{right}(X,Y,Z,W)$, $X \notin V_1, Y \in V_2, Z \in \{\text{pos}, \text{neg}\}$, $W \in Z^*$. In $\text{tnet}(X,Y,Z,W)$ and $\text{minnet}(X,Y,Z,W)$, $X \in V_1, Y \in V_2, Z \in \{\text{pos}, \text{neg}\}$, $W \in Z^*$. In $\text{in}(X)$, $X \in V_1 \cap V_3$, in $\text{out}(Y)$, $Y \in V_2 \cap V_3$.
- (3) $P = P_1 \cup P_2 \cup P_3 \cup P_4 \cup P_5 \cup P_6 \cup P_7 \cup P_8 \cup P_9 \cup P_{10} \cup P_{11} \cup P_{12} \cup P_{13}$
 $P_1 = \{\text{link}(A,B,C,1), \text{not in}(A), \text{not out}(B) \Rightarrow \text{road}(A,B,C,1)\}$,
 $P_2 = \{\text{link}(A,B,C,1), \text{in}(A), \text{not out}(B) \Rightarrow \text{left}(A,B,C,1)\}$,
 $P_3 = \{\text{link}(A,B,C,1), \text{not in}(A), \text{out}(B) \Rightarrow \text{right}(A,B,C,1)\}$,
 $P_4 = \{\text{left}(A,B,\text{pos},D), \text{road}(B,C,\text{pos},E), F = E + D, F < = 14 \Rightarrow \text{left}(A,C,\text{pos},F)\}$,
 $P_5 = \{\text{left}(A,B,\text{pos},D), \text{road}(B,C,\text{neg},E), F = E + D, F < = 14 \Rightarrow \text{left}(A,C,\text{neg},F)\}$,
 $P_6 = \{\text{left}(A,B,\text{neg},D), \text{road}(B,C,\text{neg},E), F = E + D, F < = 14 \Rightarrow \text{left}(A,C,\text{pos},F)\}$,
 $P_7 = \{\text{left}(A,B,\text{neg},D), \text{road}(B,C,\text{pos},E), F = E + D, F < = 14 \Rightarrow \text{left}(A,C,\text{neg},F)\}$,

$P_8 = \{\text{link}(A,B,X,Y), \text{in}(A), \text{out}(B) \Rightarrow \text{tnet}(A,B,X,Y)\},$
 $P_9 = \{\text{left}(A,B,\text{pos},D), \text{right}(B,C,\text{pos},E), F = E + D, F < = 15$
 $\Rightarrow \text{tnet}(A,C,\text{pos},F)\},$
 $P_{10} = \{\text{left}(A,B,\text{neg},D), \text{right}(B,C,\text{neg},E), F = E + D, F < = 15$
 $\Rightarrow \text{tnet}(A,C,\text{pos},F)\},$
 $P_{11} = \{\text{left}(A,B,\text{pos},D), \text{right}(B,C,\text{neg},E), F = E + D, F < = 15$
 $\Rightarrow \text{tnet}(A,C,\text{neg},F)\},$
 $P_{12} = \{\text{left}(A,B,\text{neg},D), \text{right}(B,C,\text{pos},E), F = E + D, F < = 15$
 $\Rightarrow \text{tnet}(A,C,\text{neg},F)\},$
 $P_{13} = \{\# \min\{D : \text{tnet}(A,B, _ , D)\} = X, \text{tnet}(A,B,C,X) \Rightarrow \text{minnet}(A,B,C,X)\}$

In this definition, $\text{link}(X,Y,Z,W)$ represents a biochemical reaction, which is a function with four variables. The variable X ranked first is the reactant or catalyst of a reaction. The second is the product of the reaction Y . Z is the positive or negative relations between A and B . The last variable W means the number of reactions through which X transforms into Y . In all links, W equals 1 because X and Y belong to one reaction. $\text{In}(A)$ represents the set of chemical component targets that TCM components act on. $\text{Out}(B)$ represents the set of disease targets.

$P_1 \cup P_2 \cup P_3$ is the set of rules to mark the chemical component targets that will be deduced from, and the disease targets that will be deduced to. Taken P_1 for instance, P_1 means that if a component target A is not the reactant of $\text{link}(A,B,C,D)$ and a disease target B is not the product of $\text{link}(A,B,C,D)$, then we mark $\text{link}(A,B,C,D)$ with a new function of $\text{road}(A,B,C,1)$.

$P_4 \cup P_5 \cup P_6 \cup P_7$ is the set of rules to infer the downstream of the component targets by the network dynamic delivery. For example, if a target protein A is activated by a component, next B will be activated as $\text{left}(A,B,\text{pos},D)$. If we have also known $\text{road}(B,C,\text{pos},E)$, then $\text{left}(A,C,\text{pos},F)$ can be derived according to P_4 . The number of reactions from molecule A to C called F , equals D plus E .

$P_8 \cup P_9 \cup P_{10} \cup P_{11} \cup P_{12}$ is the set of rules to deduce the effects and distances of chemical component targets to the disease targets. P_{13} is the rule for identifying the shortest path from component targets to disease targets. In this work, we only consider the paths of no more than 15 steps.

The mode of action between proteins in the background network contains two types of effects, the positive direction (pos) and the negative direction (neg). The components affect disease by acting on the disease targets directly or on proteins that can ultimately influence the disease targets in the entire signal transduction pathway. The ultimate impact of intervention will depend on the product of each step in transduction. In some situation, the influence of components to disease is bidirectional through different pathways.

In summary, by EGS we integrated the 136 signalling pathways from PID to construct a directed background network. Next we marked component targets and disease targets in the background network, respectively, and then inferred the relationship between them based on P rules in the context of the background network previously built. At last, we identified a series of active components for CHD from DS and BYHW by the network dynamic transduction, and built two mechanism networks of DS and BYHW formulae (shown in Fig. 1) to explain how they influence the disease targets of CHD.

2.3. Network analysis

Cytoscape has implemented a plugin of merge networks, which allows the user to find the union, intersection and difference of networks based on node identifiers. We used Merge to compare the mechanism networks of DS and BYHW and got one intersection network (shown in Fig. 2) and two difference networks (shown in Fig. 3).

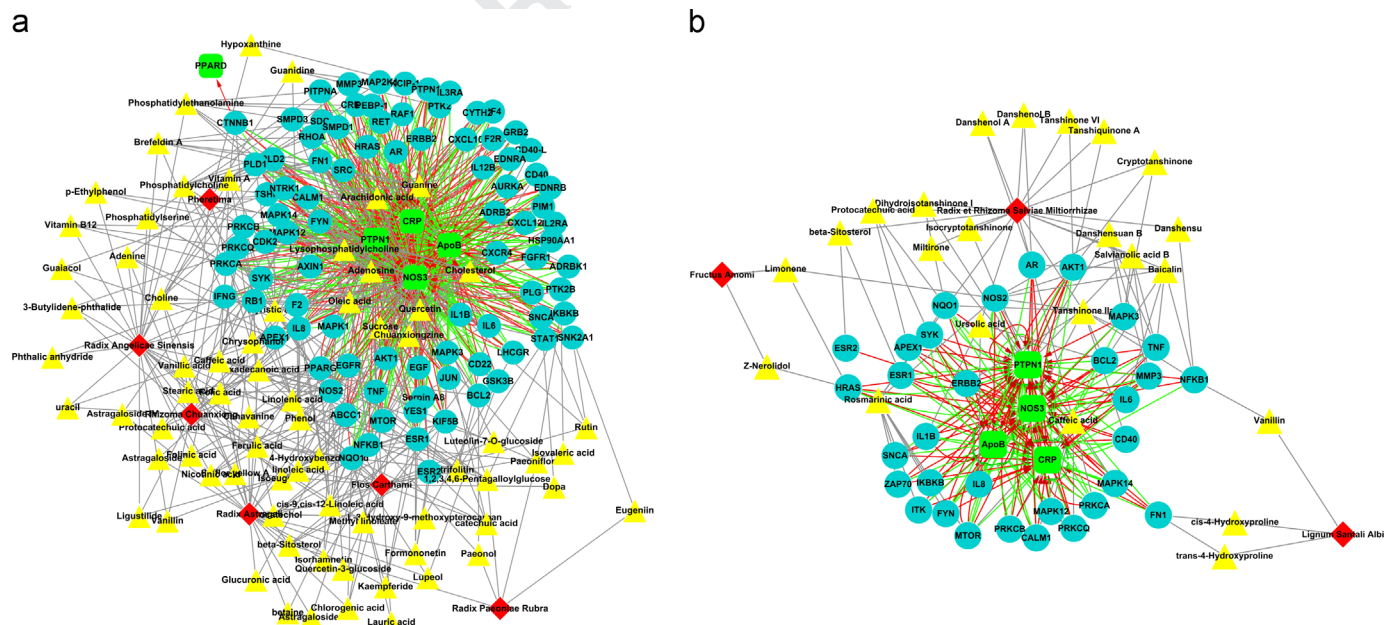


Fig. 1. Mechanism networks of BYHW and DS in treating CHD. (a) The mechanism network of BYHW: BYHW consists of 6 herbs (red diamonds), which include 71 effective components (yellow triangles) to CHD. The 71 components act on 91 proteins (blue circles), which can ultimately influence 5 disease targets (green rectangles) by signalling transduction of the bionetwork. Positive direction '→' (red edges) represents that one protein promotes the expression or enhances the activity of the next protein. Negative direction '→' (green edges) represents that one protein inhibits the expression or weakens the activity of the next protein. Herbs and their components are linked by undirected edges '—' (grey edges), so as to the components and proteins they act on. (b) The mechanism network of DS: DS consists of 3 herbs (red diamonds), which include 23 effective components (yellow triangles) to CHD. The 23 components act on 34 proteins (blue circles), which can ultimately influence 4 disease targets (green rectangles) by signalling transduction of the bionetwork. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

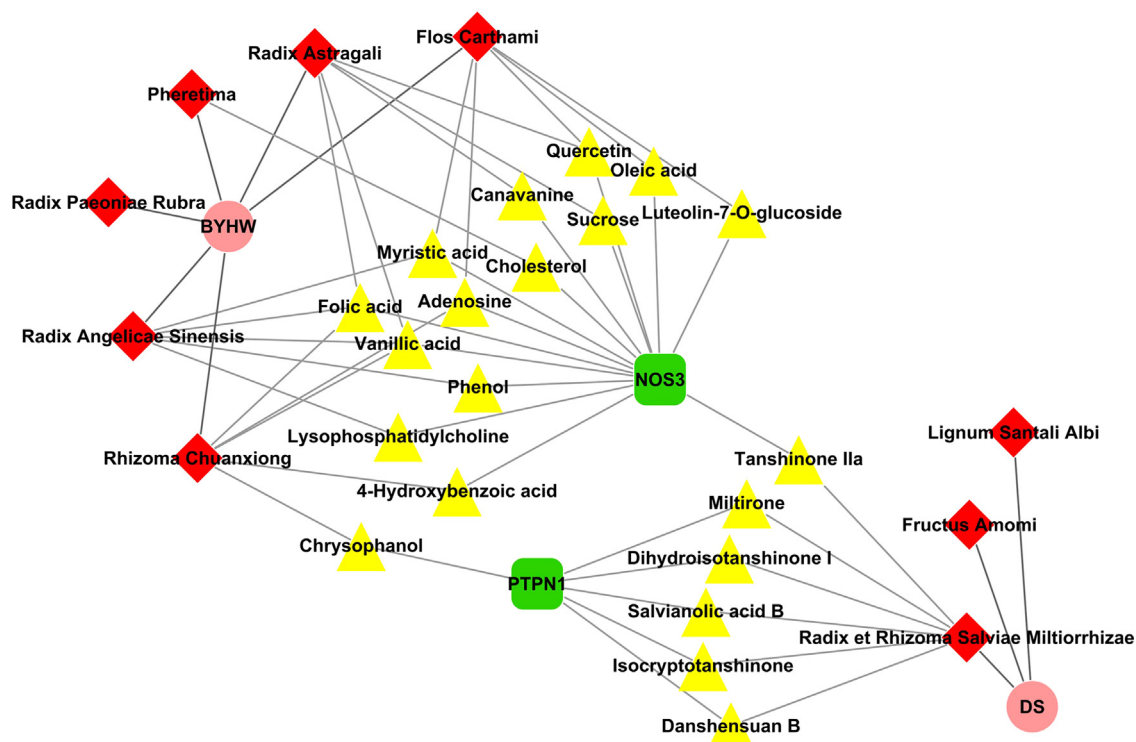


Fig. 2. Partial intersection network of BYHW and DS.

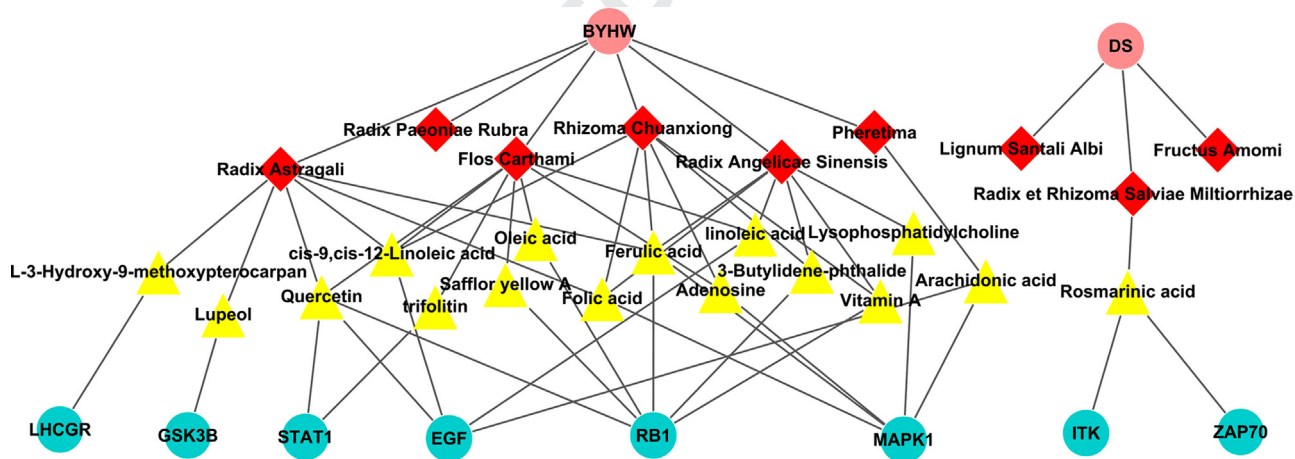


Fig. 3. Difference networks of BYHW and DS.

Based on the intersection and difference of networks, gene ontology (GO) enrichment analysis was utilized to predict possible functions by evaluating the involved biological processes by BinGO [43], a plugin for Cytoscape. Component targets and related disease targets in the networks were analyzed by BinGO, in which hypergeometric test was performed.

3. Results/discussion

In this paper, we compared molecular networks of two pattern-specific formulae and analyzed their common and different mechanisms for treating CHD by GO enrichment analysis. And we achieved a better understanding of the pharmacological characteristics of CHD patterns-specific formulae, which is beneficial to explore different

therapies for a disease to enhance the effectiveness and pertinence of treatment.

3.1. Construction of mechanism networks of two pattern-specific formulae for treating CHD

Compounds of TCM formula act on numerous proteins according to the data mining of STITCH. Nevertheless, how to elucidate the biological delivery effect between these proteins and the disease targets remains a challenge. As the intensive study of system biology and network pharmacology, it is possible to uncover the links between components and disease targets in the context of human cellular networks or signalling transduction pathways.

In this paper, we use TGS to build pharmacological networks of DS and BYHW, which can affect CHD targets by signal transduction. As a result, we derived 71 active components (Additional file 1) from

BYHW (Fig. 1(a), and 23 active components (Additional file 2) from DS (Fig. 1(b)).

The active components, chlorogenic acid [23], quercetin [24], folic acid [25], paeoniflorin and paeonol [26], astragaloside IV [27] are identified from BYHW. And ursolic acid [28], baicalin [29], cryptotanshinone [30], dihydroisotanshinone I [31], rosmarinic acid [32] are identified from DS. All the active components have been proved to contribute to the CHD treatment. This indicates that the mechanism networks we built are reliable to some extent.

3.2. GO enrichment analysis of mechanism networks of two pattern-specific formulae for treating CHD

3.2.1. The GO processes of the intersection network of BYHW and DS

It has been shown that functional enrichment analysis is conducive to gain insights into the shared underlying biological function of the proteins in a network [33]. Functional enrichment was carried out using BinGO. For each formula, the most significant GO biological processes were assigned based on its mechanism network. The common processes of two pattern-specific formulae (DS and BYHWT) are shown in Table 1.

The result indicates that DS and BYHWT both play a pharmacodynamics with the biological processes, such as regulation of immune system process, wound healing, blood coagulation, inflammatory response, response to organic nitrogen, regulation of cell proliferation, regulation of apoptotic process and so on. To illustrate the common mechanism for details, we built the intersection network of DS and BYHW, and totally 32 targets were involved in the intersection network.

The GO processes of blood coagulation and response to organic nitrogen are to be discussed as examples in the partial intersection network of BYHW and DS (Fig. 2). Two CHD targets, endothelial nitric oxide synthase (NOS3) and tyrosine-protein phosphatase non-receptor type 1 (PTPN1), are related to blood coagulation and response to organic nitrogen processes. From BYHW and DS, we find 14 and 6 components, respectively, acting on NOS3 and PTPN1. For example, chrysophanol from BYHW and salvianolic acid B from DS both act on PTPN1, which dephosphorylates and inactivates a number of CHD-related receptor protein tyrosine kinases, including the epidermal growth factor (EGF) and platelet-derived growth factor (PDGF) receptors [34]. So they can decrease the risk of coronary artery disease [35]. Moreover, tanshinone IIa from *Radix et Rhizoma Salviae Miltiorrhizae* and luteolin-7-O-glucoside from *Flos Carthami* both can affect NOS3 and contribute to CHD treatment [36]. As we know, endothelial cell apoptosis is one of CHD risk factors. As shown in Table 1, both BYHW and DS

Table 1
The GO processes of the intersection network display partially.

Common processes(GO terms)	P-value
Regulation of immune system process	4.59E-24
Response to stress	6.04E-22
Wound healing	9.89E-22
Blood coagulation	7.45E-21
Inflammatory response	5.29E-15
Response to organic nitrogen	3.38E-14
Regulation of oxidoreductase activity	5.12E-14
Nerve growth factor receptor signalling pathway	6.68E-14
Regulation of cell proliferation	1.62E-13
Positive regulation of NF-kappaB transcription factor activity	1.58E-12
Regulation of apoptotic process	3.36E-12
Positive regulation of MAPK cascade	4.30E-12
Cellular response to fibroblast growth factor stimulus	1.03E-11

Notes: P-value is the probability of obtaining the observed effect, a very small P-value indicates that the observed effect is very unlikely to have arisen purely by chance, and therefore provides evidence against the null hypothesis.

can regulate cell proliferation, which could improve angiogenesis and vasculogenesis and be beneficial to myocardial revascularization in CHD.

In a word, the shared processes clarify the pathological mechanism of QSB and QDB both related to inflammatory reaction, hyp immunity, oxidative stress injury, arrhythmia and high cholesterol and so on.

3.2.2. The GO processes of the difference networks of BYHW and DS

The difference processes of DS and BYHWT are shown in Table 2. The result indicates that DS plays a pharmacodynamics with the specific biological processes, such as positive regulation of calcium-mediated signalling, homotypic cell-cell adhesion, T cell aggregation, lymphocyte aggregation, regulation of ion transmembrane transporter activity, cellular response to oxygen levels, regulation of exocytosis, interleukin-4 production. These processes are still related to anti-inflammatory mechanism of DS. On the other hand, BYHW plays a pharmacodynamics with the specific biological processes, such as positive regulation of adenylate cyclase activity, brain development, regulation of kidney development, central nervous system development and so on. Emerging evidence suggests that brain development is similar with aging in the pattern of lateral cortical changes [37]. The result indicates that some effective components in BYHWT may be of value in ensuring good cognitive function during aging.

BYHW hits 59 specific targets by some active components, such as ferulic acid from *Rhizoma Chuanxiong*, quercetin and L-3-hydroxy-9-methoxypterocarpan from *Radix Astragali*, trifolitin from *Flos Carthami*. Partial difference network of BYHW are shown on the left of Fig. 3. Studies had shown that GSK3B polymorphisms were associated with grey matter and intracranial volume in healthy individuals, which are related to brain development and cognitive function [38].

DS only hits two specific targets, tyrosine-protein kinase (ITK/TSK) and tyrosine-protein kinase ZAP-70 (ZAP70) by rosmarinic acid. The special network of DS are shown on the right of Fig. 3. The evidence suggests that ZAP-70 can mediate T-cell adhesion and migration [39], and ITK is of crucial importance for B and T cell development, which are both related to inflammatory process [40].

Overall, the QDB-specific formula (BYHW) shows several special therapeutic actions, such as promoting blood circulation, ensuring good cognitive function, promoting kidney development

Table 2
The difference GO processes of BYHW and DS display partially.

Formula	GO terms	P-value	
DS	Positive regulation of calcium-mediated signalling	5.82E-04	
	Homotypic cell-cell adhesion	8.87E-04	
	T cell aggregation	1.19E-03	
	Lymphocyte aggregation	2.37E-03	
	Regulation of ion transmembrane transporter activity	6.17E-03	
	Cellular response to oxygen levels	7.30E-03	
	Regulation of exocytosis	8.10E-03	
	Interleukin-4 production	8.27E-03	
	BYHWT	Positive regulation of adenylate cyclase activity	8.83E-10
		Developmental maturation	3.66E-09
Mesenchymal cell differentiation		1.94E-08	
Positive regulation of phosphatidylinositol 3-kinase cascade		3.96E-07	
Cascular process in circulatory system		1.08E-06	
Brain development		1.43E-06	
Myoblast differentiation		1.64E-06	
Regulation of kidney development		1.73E-06	
Positive regulation of calcium ion transport into cytosol		2.16E-06	
Central nervous system development		6.11E-06	

and so on. These therapeutic actions are related to severe pathological changes in CHD [41,42].

4. Conclusion

In this paper, we (1) built the mechanism networks of two pattern-specific formulae by EGS formalism and find out the active component groups in them; (2) compared two networks by Merge and obtained the intersection and difference networks; (3) discovered common and different mechanisms of QDB and QSB pattern-specific formulae in CHD by GO analysis.

All together, we discovered common and different mechanisms of two pattern-specific formulae for treating CHD. The shared processes clarify the pathological mechanism of QSB and QDB both related to inflammatory reaction, hypimmunity, oxidative stress injury, arrhythmia and high cholesterol. Furthermore, the QDB-specific formula (BYHW) shows several special therapeutic actions, such as promoting blood circulation, ensuring good cognitive function, promoting kidney development and so on. These therapeutic actions are related to severe pathological changes in CHD. According to the Chinese medicine theory, QSB is considered as the primary stage of CHD, QDB the advanced stage. In certain degree, our results proved that pattern-specific treatments can be illustrated by mechanism networks of corresponding formulae for CHD, which may provide new therapeutic ideas for disease treatment.

Conflict of interest statement

None declared.

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled, "Exploration of the Mechanism of Pattern-Specific Treatments in Coronary Heart Disease with Network Pharmacology Approach".

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.compbimed.2014.05.003>.

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