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Review

A network-based analysis of the types of coronary artery disease from traditional Chinese medicine perspective: Potential for therapeutics and drug discovery

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ABSTRACT

Ethnopharmacological relevance: Coronary heart disease (CAD) is one of the most dangerous threats to human health due to its high incidence and high mortality. CAD has several major types, such as blood stasis and qi deficiency according to the syndromes of diagnosis in traditional Chinese medicine (TCM), which are treated with different herbs or compound prescriptions. However, up to now a deep analysis of the relationship between CAD and its types both at molecular or systems levels is still unavailable, which greatly limits the combination of TCMS with Western drugs to form an integrative/alternative medicine for treatment of the complex disease.

Materials and methods: In this review, we attempt to decipher the underlying mechanisms of major types of CAD by connecting the drugs, targets and diseases to obtain the compound-target-disease associations for reconstructing the biologically-meaningful networks based on systems pharmacology method.

Results: The results indicate that the herbs for eliminating blood stasis have pharmacological activity of dilating blood vessel, improving the microcirculation, reducing blood viscosity and regulating blood lipid, while qi-enhancing herbs have the potential for enhancing energy metabolism and anti-inflammation.

Conclusions: A systematic exploration of types of CAD may bring out the best between research on drug molecules and TCM phenotypic information, so as to accelerate development of network-based drug discovery as well as to facilitate the therapy of this disease.

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1. Introduction

Coronary artery disease (CAD), also called coronary heart disease, is the result of the accumulation of atheromatous plaques within the walls of the coronary arteries (Liu et al., 2010), leading to atherosclerosis of the coronary arteries, which gradually narrow and block blood flow to the heart muscle and finally causing heart attack. CAD is the most frequent cause of death worldwide, which is manifested by different clinical types such as chest tight, shortness of breath, chest pain, angina pectoris, heart attack, and cardiac infarction, etc.

CAD is often caused by the complicated interactions between individual genetic background and environmental factors, and the symptoms are presented in more than one organ or tissue and spread to the whole body (Gibson, 2009). In Western medicine, CAD is often treated by surgical operations, pharmaceutical drugs, physical activities, and other interventional therapies. As Western medicine generally focuses on the structure and function of heart, it ignores differences in systematic function, curative reaction, and the individual. For example, unstable angina pectoris might be diagnosed as CAD, but normally, about 80% of typical chest pains have no influence on the heart (Wikipedia, 2013). However, it has become clear that diagnostic accuracy of CAD could be reflected according to different symptoms in order for the treatments to be of maximal benefit.

TCM, often seen as one of the most important parts in complementary and alternative medicine (CAM), has fought against such diseases with a long history and also has accumulated thousands of prescriptions as well as clinical practices (Shang et al., 2011). TCM is mainly based on the overall observation of human symptoms, which is totally different from the reductionism thinking mode of Western medicine. Syndrome (“ZHENG” in Chinese Mandarin) is the basic unit and key term in TCM theory. A syndrome represents an observable indicator of abnormality. It is the outcome after a careful analysis of all signs that can be regarded as a profile of symptom combinations and clinical phenotypes (Li et al., 2006). Nowadays, as the core of diagnosis and target of herbal remedy in TCM, the syndrome has always been studied in the context of a specific disease or biomedical condition, and many reports have demonstrated that syndromes are significantly associated with various diseases (Kang et al., 2008).

In TCM, CAD belongs to the scope of chest heartache and cardiodynia, which mainly contains blood stasis, qi deficiency, phlegm-turbidness, cold coagulation, Yin deficiency, Yang deficiency, etc. (Ren et al., 2012). A recent large-scale investigation of 5284 hospitalized patients with CAD showed that the top three TCM patterns were blood stasis (79.3%), qi deficiency (56.5%), phlegm-turbidness in turn (41.1%) (Gao et al., 2012). In addition, another comprehensive retrieval of the TCM syndromes of CAD from year 1970–2010 also showed the similar distributions (Mao et al., 2011). Fortunately, thousands of years' clinical practices have accumulated a considerable number of single herbs or herbal formulas that exhibit safety and efficacy in treating the CAD with different types (Chen et al., 2006).

However, how to understand CAD based on different types at the molecular/systems level remains unclear. The clarification of this issue is significantly critical since it not only establishes a diagnosis avenue in microcosmic level, but also divides the disease into several types and provides a biological basis investigation for individual syndrome. And also, the lack of disease-syndrome correlation limited the combination of Chinese herbal medicine with Western medicine so as to form the integrative medicine for treating diseases.

Therefore, the current review aims to decipher the underlying connections between the major types and CAD in the TCM framework. Our work takes the known herbs as the probe to uncover the potential mechanism between the major types and CAD by connecting the drugs, targets and diseases so as to obtain compound-target-disease associations for reconstructing the biologically-meaningful networks. A systematic exploration of the types of CAD based on TCM theory may not only facilitate systems-level understanding between molecular mechanism and TCM phenotypic information, but also contribute new opportunities to the process of drug discovery and therapeutics for complex chronic disease.

2. Types of syndromes of CAD according to TCM

2.1. Blood stasis

(Chinese: Xue Yu): Blood stasis is the major syndrome, accounting for 79.3% in CAD (Gao et al., 2012). It is a severe pathological process caused by disturbance of blood circulation. Blood stasis is often understood in the biomedical filed in terms of hematological disorders such as hemorrhage, congestion, thrombosis, local ischemia and tissue changes. The clinical manifestations are unstable angina pectoris or chest twinge accompanied by chest stuffiness. The main method in TCM for blood stasis is to administer with TCM preparations that promote blood circulation and dissolve blood stasis.

2.2. Qi deficiency

(Chinese: Qi Xu): In TCM, qi refers to the energy which flows within our body, to support a variety of biological functions such as movement, digesting food, as well as fight against diseases. Qi deficiency is the second leading syndrome, accounting for 56.5% in CAD (Gao et al., 2012). Qi deficiency could be distinguished from the symptoms of patients, such as dizziness, vertigo, spiritlessness, hypodynamia, short breath, light colored tongue, thin and fatty tongue as well as deep and thread pulse. According to the TCM, except for the herbs which increase qi efficiency, it is also important to keep the mind calm to maintain the qi balance in body.

2.3. Phlegm-turbidness

(Chinese: Tan Zhuo): Phlegm-turbidness is the third syndrome, accounting for 41.1% in CAD (Gao et al., 2012). The patients with

turbid-phlegm syndrome have the main characteristics such as chest distress with suffocating pain, shortness of breath, dyspnea, heavy limbs, corpulent body, much phlegm, high blood fat, high blood viscosity and sympathetic nerve hyper-function. In TCM, the therapeutic method of this syndrome is purging turbidity, expelling phlegm and dissipating masses.

In addition to the above main syndromes, CAD also includes cold coagulation, yin deficiency, yang deficiency et al. Presently, it is still impossible to comprehensively retrieve enough pharmacological information and clinical data about these types. Therefore, in this work we are mainly concentrating on CAD with blood stasis and qi deficiency, as well as their medicinal herbs and treatment methods.

3. Herbal medicines for CAD

In order to summarize and analyze the relationships of herbs and different types of CAD, we extracted the available information about the herbs with a text mining approach, which is based on the four different types of CAD via the PubMed and CNKI (from 2000–2012) using the retrieval words, such as 'herbal medicine', 'blood stasis/xue yu', 'qi deficiency/qi xu', 'phlegm-turbidness/tan zhuo' and 'cold coagulation/han zheng'. In Table 1, we choose the top 3 well studied herbs that exhibit pharmacological effects when used alone in human and/or animal trials for each types of CAD, respectively. From literature, it can be seen that different herbs have been studied to different extent. For example, articles for *Radix Salviae Miltiorrhizae* (*Salviae miltiorrhizae*) to blood stasis are the most abundant (475), due to the extensive study of this herb in history for treatment of many syndromes (21985 articles). This herb is also the first TCM product approved for phase II and III clinical trials by FDA presently (Zhou et al., 2005). Many studies have demonstrated that *Salviae miltiorrhizae* can improve blood microcirculation, dilate coronary arteries, increase blood flow, and prevent myocardial ischemia.

In addition, we have also considered the compounds in different species, and the most widely used TCMs are shown in Table 1. It is seen that, although the herbs are different, the main active components are the same. Due to the degree of research of different herbs, the statistical index is calculated as the (CAD-herbs-related articles)/(herbs-related articles) ratio to balance the bias and further evaluate the association between them and CAD. The *p*-value is applied to measure the significance of relevance between each herb and CAD reported in literature (Erhardt et al.,

2006) (significant when *p*-value < 0.01):

$$P = 1 - \sum_{i=0}^{k-1} f(i) = 1 - \sum_{i=0}^{k-1} \frac{(K_i)(N-Kn-i)}{(Nn)} \quad (1)$$

here, *N* is the total number of articles in PubMed and CNKI, *K* is the number of articles related to CAD, *n* is the number of articles about one single herb and *k* is the number of articles about the effects of corresponding herbs on CAD. All the results are summarized in Table 1.

In Table 1, for blood stasis syndrome, *Ligusticum chuanxiong* Hort (*Ligusticum chuanxiong*), *Salviae miltiorrhizae* and *Panax Notoginseng* (*Panax notoginseng*) are the top well studied herbs in the large number of blood stasis-related articles. Among them, *Ligusticum chuanxiong* obtained the highest ratio (5.03%; with *p*<0.01), indicating that *Ligusticum chuanxiong* is one of the most effective herb to treat blood stasis. The second one is *Salviae miltiorrhizae* (2.16%; with *p*<0.01), and then followed by *Panax notoginseng* (2.00%; with *p*<0.01). For the qi deficiency type of CAD, the first three well studied herbs are *Radix Codonopsis* (*Radix codonopsis*) with the ratio of 4.52% (*p*<0.01), *Radix Glycyrrhizae* (*Radix glycyrrhizae*) with the ratio of 3.80% (*p*<0.01) and *Radix Astragali* (*Radix astragali*) with the ratio of 3.29% (*p*<0.01). The third syndrome of CAD is phlegm-turbidness, the widely-used herbs are *Allium macrostemon* Bunge (*Allium macrostemon*; 5.63%; with *p*<0.01), *Trichosanthes kirilowii* Maxim (*T. kirilowii*; 3.75%; with *p*<0.01), *Pinellia ternata* (Thunb.) Breit. (*Pinellia ternata*; 2.72%; with *p*<0.01). For the last syndrome cold coagulation, *Radix Aconiti Lateralis Preparata* (*Radix radix preparata*) has the highest ratio of 4.83%, with *p*<0.01. *Cinnamomi Ramulus* (*Cinnamomi ramulus*) is the second with the ratio of 3.76%, with *p*<0.01, then followed by *Ephedra Herba* (*Ephedra herba*) with the ratio of 3.08%, with *p*<0.01.

4. TCM for Blood stasis

Blood stasis, one of the major oriental medicine diagnosis types of CAD, is characterized by the decrease of in blood flow velocity and the disturbance of the normal blood flow (Mchedlishvili, 1998). In the classic theory of TCM, it was stated that "when blockage is opened, pain is relieved; when blockage exists, pain persists" (Cheng, 2006). For CAD patients, there is often an increased activation of coagulation and inflammation, leading to the increasing morbidity of blood in the whole body. According to Table 1, some traditional herbs such as *Salviae miltiorrhizae*, *Panax notoginseng* and *Ligusticum chuanxiong* have been demonstrated to be effective in improving blood stasis, promoting blood circulation, resolving swelling and tranquillizing the mind. Therefore, in this

Table 1
Correlations between herbs with four types of CAD.

Herb name	Number of articles	
	Total (n)	Relevant to blood stasis (k; Ratio; p-value)
<i>Ligusticum chuanxiong</i> Hort (<i>Ligusticum chuanxiong</i> , Umbelliferae)	4649	234 (5.03%; <i>p</i> <0.01)
<i>Radix Salviae Miltiorrhizae</i> (<i>Salviae miltiorrhizae</i> , Lamiaceae)	21985	475 (2.16%; <i>p</i> <0.01)
<i>Panax Notoginseng</i> (<i>Panax notoginseng</i> , Araliaceae)	4724	93 (2.00%; <i>p</i> <0.01)
<i>Radix Codonopsis</i> (<i>Radix codonopsis</i> , Codonopsis)	2476	Relevant to qi deficiency (k; Ratio; p -value) 112 (4.52%; <i>p</i> <0.01)
<i>Radix Glycyrrhizae</i> (<i>Radix glycyrrhizae</i> , Leguminosae)	1476	56 (3.80%; <i>p</i> <0.01)
<i>Radix Astragali</i> (<i>Radix astragali</i> , Fabaceae)	13607	448 (3.29%; <i>p</i> <0.01)
<i>Allium macrostemon</i> Bunge (<i>Allium macrostemon</i> , Liliaceae)	444	Relevant to phlegm-turbidness (k; Ratio; p -value) 25(5.63%; <i>p</i> <0.01)
<i>Trichosanthes kirilowii</i> Maxim (<i>Trichosanthes kirilowii</i> , Cucurbitaceae)	720	27(3.75%; <i>p</i> <0.01)
<i>Pinellia ternata</i> (Thunb.) Breit. (<i>Pinellia ternata</i> , Araceae)	4116	112(2.72%; <i>p</i> <0.01)
<i>Radix Aconiti Lateralis Preparata</i> (<i>Radix radix preparata</i> , Ranunculaceae)	2627	Relevant to cold coagulation (k; Ratio; p -value) 127 (4.83%; <i>p</i> <0.01)
<i>Cinnamomi Ramulus</i> (<i>Cinnamomi ramulus</i> , Lauraceae)	3961	149 (3.76%; <i>p</i> <0.01)
<i>Ephedrae Herba</i> (<i>Ephedrae herba</i> , Ephedraceae)	3800	117 (3.08%; <i>p</i> <0.01)

The total number of articles (*N*) in PubMed and CNKI is 27648357. The number of articles related to blood stasis, qi deficiency, phlegm-turbidness and cold coagulation (*K*) are 10833, 7132, 2348 and 1580 respectively.

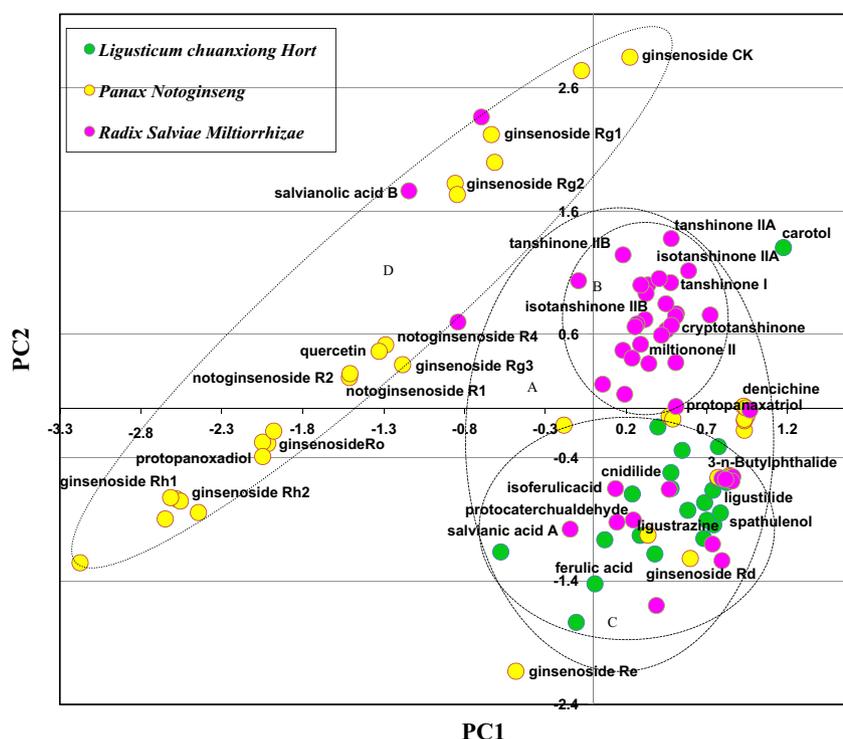


Fig. 1. Chemical space distribution of the active components present in *Ligusticum chuanxiong*, *Salvia miltiorrhizae* and *Panax notoginseng* based on their drug-related physicochemical properties.

part, we take the three key herbs for blood stasis treatment as an example to explore the pharmacological mechanism of treatment of blood stasis of CAD. We gathered 101 active compounds and their 67 targets for the three herbs from the previous work (B. Li et al., 2012; X. Li et al., 2012) (Table S1), and the details of the related pathways and disease types are given as follows.

4.1. Active components

Ligusticum chuanxiong, Family Umbelliferae, is one of the most important herbs for the treatment of cardiovascular diseases (CVD) (Commission, 2005). The rhizome of which is warm in property and pungent in flavor, with significant effects of “facilitation of blood circulation” and “removal of blood stasis” (Zhu, 1998). The oral administration of *Ligusticum chuanxiong* at an equivalent dosage of 30 times to patients for 90 days significantly lowered serum total cholesterol (TC) and triglyceride (TG) levels (Mei et al., 2000). In the recent research, X. Li et al. (2012) reported that the primary components of *Ligusticum chuanxiong* are ferulic acid, carotol, cnidilide, spathulenol, 3-n-butylphthalide, ligustilide and so on (Fig. 1), and some have been shown effective on the treatment of blood stasis. For example, ferulic acid can inhibit platelet aggregation and improve blood fluidity (Hou et al., 2004). Given at an oral dosage of 50 mg/kg/day for 30 days, it significantly lowered serum TC and low-density lipoprotein cholesterol (LDL-C) levels in rats fed by a high-fat diet (Ji and Gong, 2007). And 3-n-butylphthalide is able to inhibit platelet aggregation and enhance microcirculation, thus benefiting patients with ischemic stroke (Huang et al., 2010). Compound lactone (ligustrazine), may play an important role in promoting blood circulation and removing blood stasis (Liu et al., 2012). And the most abundant compound ligustilide also shows many pharmacological activities in cerebral blood vessels and general circulatory system (Teng et al., 1987).

Another versatile herb, *Salvia miltiorrhizae*, is derived from the root and rhizome of *Salvia miltiorrhiza* Bge. (Lamiaceae) (Lam et al., 2006). It has been widely used to treat patients with CAD by improving microcirculation, inducing coronary vasodilatation, and by suppressing thromboxane formation (Cheng, 2007). The oral administration of 12 *Salvia miltiorrhizae* tablets (0.27 g/tablet) for 24 weeks prominently lowered serum TC, TG, and LDL-C levels and increased HDL-C levels in 92 hypertensive and hyperlipidemic patients in China (Bei et al., 2010). The aqueous extracts of *Salvia miltiorrhizae* administered at oral dosages of 50, 100, and 150 mg/kg/day for 4 weeks distinctly decreased TC and TG levels and increased HDL-C serum levels in hyperlipidemic rats. According to Zhou et al. (2005), no evident side effects of *Salvia miltiorrhizae* have been found in different clinical practices.

In our previous work (X. Li et al., 2012), we discovered 43 major active components from *Salvia miltiorrhizae* that are related to CVD, which mainly include salvianic acid A, salvianolic acid B, cryptotanshinone, protocatechuicaldehyde, tanshinone IIB, isotanshinone IIA, isotanshinone IIB, miltionone II, tanshinone I, tanshinone IIA (IIA, S.C.G.ft.S.o.T, 1984) and so on (Fig. 1). Interestingly, some of them have been well demonstrated related to blood stasis. For instance, salvianic acid A can dilate the isolated coronary artery, increase the coronary flow rate and expand the blood vessel (Zhao et al., 1996). Salvianolic acids from *Salvia miltiorrhizae* increase cerebral blood flow after ischemia and inhibit thrombosis, thromboxane B2 formation and platelet aggregation (Jiang et al., 2005). Tanshinone IIA has been observed to possess antioxidant and anti-inflammatory activities (Zhao et al., 1996). Salvianolic acid B, one of the most abundant constituents in *Salvia* species, shows good pharmacological effects on atherosclerosis (Shi et al., 2007), obstruction of regional cerebral blood flow and platelet aggregation. It can increase NO production by endothelial cells and inhibit Angiotensin-converting enzyme (ACE) (Kang et al., 2003).

As a highly-valued herb, *Panax notoginseng* is derived from the dried root and rhizome of *Panax pseudoginseng* var. *notoginseng* Wall. (Araliaceae) (Committee, 2005). It is able to modulate vascular tone such as dilation blood vessels, activation of blood circulation, removal of blood stasis, and inhibiting platelet aggregation (Ma and Xiao, 1998). *Panax notoginseng* administered at oral dosages of 30, 60, and 100 mg/kg/day for 4 weeks largely decreased serum TC, TG, and LDL-C levels in rats fed a high-fat/high-cholesterol diet (Xia et al., 2011). According to X. Li et al. (2012), 36 major active constituents from *Panax notoginseng* were found, which include two types of documented bioactive molecules: dencichine and quercetin, which have been reported to have good hemostatic and antithrombotic effects (Formica and Regelson, 1995). In addition, triterpene saponins notoginsenosides and ginsenosides (Dong et al., 2003), the main ingredients in *Panax notoginseng*, ginsenoside Rf and other 18 saponins, and their metabolites, such as PPT (protopanaxatriol), PPD

(protopanaxadiol), ginsenoside CK and F1 also showed significant effectiveness on treating CAD (Fig. 1) (Li et al., 2004).

4.2. Feature comparisons of the three herbs based on active chemicals

To investigate whether the three herbs of similar pharmacological activity (treatment of blood stasis) have the chemicals with similar structural features, eight representative drug-related physicochemical properties including octanol-water partition coefficients (AlogP), molecular weight (MW), hydrogen bond donors/acceptors (nHDon and nHAcc), human colon adenocarcinoma (Caco-2), blood-brain barrier (BBB), oral bioavailability (OB), druglikeness (DL) were selected to carry out the analysis. The distribution of these active components in chemical space can be visualized by principal components analysis (PCA) using R software (Team, 2005), which could translate the high-dimensional data to a low-dimensional space, allowing for direct visualization of the compounds distributions (Table S2). The descriptor matrix was modeled by the first two principal components (PC) which explain 87.387% of the descriptor data variance (Table 2). The first PC (PC1) explains 70.688% of the total variance, and each component is expected to contribute in an equal manner to PC1. The second PC (PC2) accounts for about 16.698% of the total variance.

Table 2
Statistical results of the PCA.

Component	Initial eigenvalues		
1	Total 5.665	% of Variance 70.688	Cumulative % 70.688
2	1.336	16.698	87.387

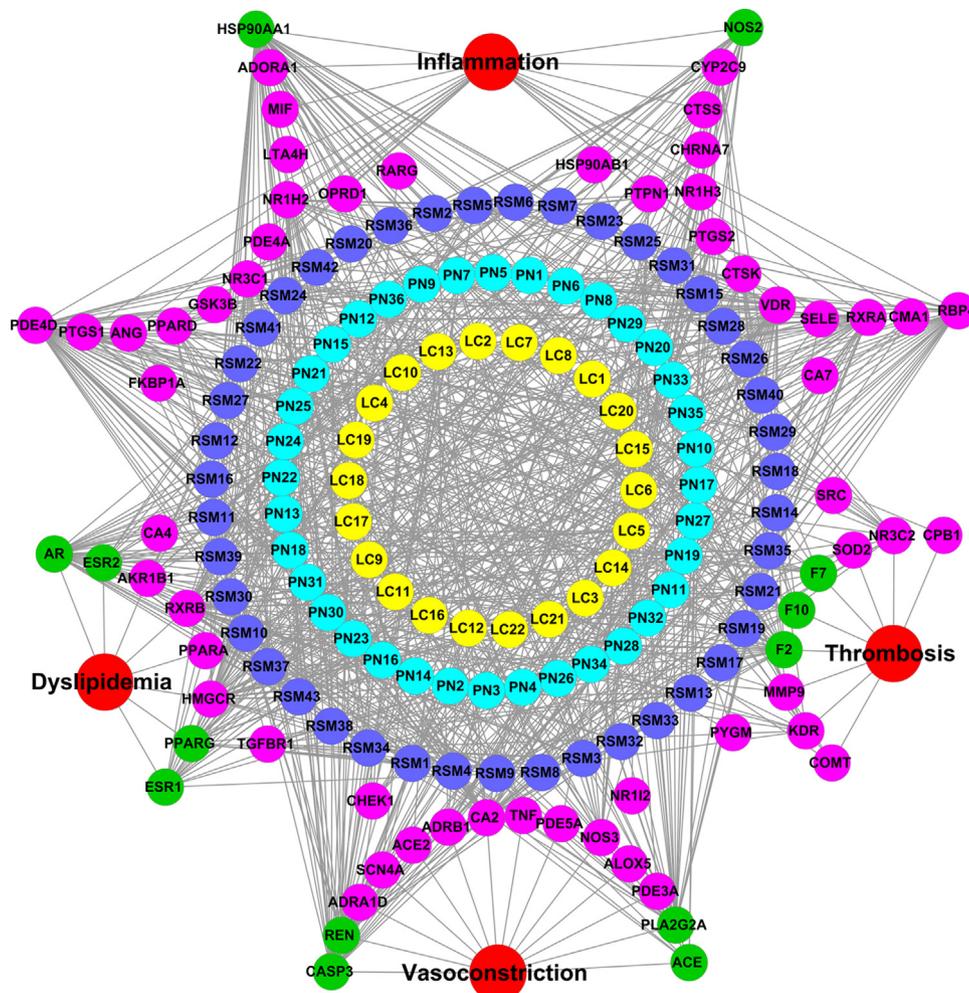


Fig. 2. Drug-target-disease network. The yellow, blue and purple circles represent the *Ligusticum chuanxiong*, *Panax notoginseng* and *Salviae miltiorrhizae*, respectively. The pink circles represent the targets of the three Chinese herbs, while the green circles are the common targets of the three herbs. The red circles represent the disease types of blood stasis.

As seen in Fig. 1, the areas of overlap (region A) may show that some compounds (for example, cnidilide in *Ligusticum chuanxiong*, salvianic acid A in *Salviae miltiorrhizae* and dencichine in *Panax notoginseng*) are physicochemical property similar, resulting in similar pharmacological actions on blood stasis. That is to say the features of target proteins of the ingredients from different herbs may be overlapped. For instance, the target protein Coagulation factor X (F10) which is related to thrombosis is hit by the following three active compounds cnidilide, salvianic acid A and dencichine. In addition, the compounds are also clustered in three independent areas (region B, C and D), indicating that the active components may be structurally/pharmacologically different in the three herbs. For example, the compounds in *Salviae miltiorrhizae* occupy two independent sub-clusters (region B and C). The ingredient tanshinone I in *Salviae miltiorrhizae* (region B) which target the estrogen receptor protein is related to dyslipidemia, while the compounds protocatechualdehyde (region C) that target the Coagulation factor VII (F7) is relevant to thrombosis. Interestingly, saponins as the primary active components responsible for the hypolipidemic effects of *Panax notoginseng* mainly concentrate in the region D. This indicates that each separated cluster may have similar mechanisms of action but affect different pathological processes or stages of the disease. Generally speaking, all these results show that the overlap dots of three herbs may have similar pharmacological roles, while the active components in the scattered region suggest that the three herbs may also have substantially different physicochemical properties. However, it is particularly mentioned that the very small differences may result in totally opposite pharmacological activities, such as agonists and antagonists which have totally opposite pharmacological activities are often so structurally similar. In this case, the extracting pharmacological implication from structural analysis is inapplicable if the data do not actually include the pharmacological activity against a common target.

4.3. Target networks

The herbs which contain many active compounds might target at one or multiple proteins in the biological network and then the biological system would attain new equilibrium in order to reduce the harmful impacts (Janga and Tzakos, 2009). Typically, the drug-target-disease network which links drugs and protein targets was used to interpret the mechanism of drug action, explore poly-pharmacology and predict new targets for drugs. The network was visualized by using Cytoscape 2.8.1 (Smoot et al., 2011) (Fig. 2). Blood stasis is considered to be closely related to thrombosis, dyslipidemia, vasodilatation and inflammation in modern medicine. According to our previous work (B. Li et al., 2012; X. Li et al., 2012), a total of 67-proteins were identified as the targets of the above three herbs (Table S1). Among these targets, 39 and 42 proteins were recognized as targets of *Salviae miltiorrhizae* and *Ligusticum chuanxiong*, respectively. *Panax notoginseng* has 36 potential protein targets, 34 of which are overlapped with those of *Salviae miltiorrhizae*.

Interestingly, the three herbs share 13 common targets (accounting for 19.1% of the total targets), which are associated with thrombosis, dyslipidemia and inflammation (Fig. 2). For example, prothrombin (F2), F7 and F10 play important roles in the thrombosis process. Injury to the vessel wall in general and to the endothelial lining specifically may be the major event that precipitates the thrombotic process (Slauson and Cooper, 2002). The injured vessels along with circulating coagulation factors and platelets combine in a series of interlacing reactions, resulting in vasoconstriction and the formation of a coagulum consisting of platelets and fibrin so as to form thrombosis. Androgen receptor (AR), Peroxisome proliferator-activated receptor gamma (PPARG),

and estrogen receptor alpha and beta (ERs) are closely related with the dyslipidemia. Dyslipidemia is considered to be responsible for the development of atherosclerosis through blood lipid accumulation and oxidation so as to cause blood vessel pathological changes, circulatory disorder, blood stream dynamics change which finally result in CAD (Assmann et al., 1998). The proteins concerned with vasoconstriction are rennin, ACE, Caspase-3 (CASP3) and phospholipase A2 membrane associated (PLA2G2A). And the regulation of them may cause hemangiectasis, and then lower blood pressure by inhibiting the proliferation of vascular smooth muscle cells. Nitric oxide synthase, inducible (eNOS) and heat shock protein HSP 90-alpha (HSP90- α) are well related to the vasodilatation and inflammation, the control of which can not only contribute to the improvement of endothelial and vasomotor dysfunction, but also prevent the inflammatory factor from damaging the blood vessel and cardiac muscle. Inflammation injury is mainly the result of damage of endothelial cell function, and the initial damage to the endothelial cells leads to degeneration and increased vascular permeability and platelet aggregation (Shihhan et al., 2010). These results explain why the three herbs exhibit similar pharmacological effects on CAD in the clinical practices.

In addition, we have also found that the three herbs possess their own specific targets. For instance, the chemical ligustilide in *Ligusticum chuanxiong* identifies the protein neuronal acetylcholine receptor subunit alpha-7 (nAChR- α -7) as its target, regulating the release of macrophage TNF thus reducing morbidity in CVD (B. Li et al., 2012). Moreover, this protein is also found to suppress mechanical pain responses associated with peripheral neuropathy and to accelerate functional recovery of the injured neurons, which has implications for the application of *Ligusticum chuanxiong* in treatment of pain. *Salviae miltiorrhizae* has the heat shock protein HSP 90-beta (HSP90- β) and macrophage migration inhibitory factor (MIF) as its specific targets concerned with vasodilatation and inflammation, which regulate the endothelial and vasomotor dysfunction and prevent damage of the inflammatory factor to the blood vessel and cardiac muscle. As for *Panax notoginseng*, the protein Angiotensin-converting enzyme 2 (ACE2) is the only specific target of this herb. The ACE2 can catalyze the conversion of angiotensin I to the nonapeptide angiotensins, or the conversion of angiotensin II to angiotensin, so the regulation of ACE2 may have an effect on hypertension or ischemic cardiovascular disease. These findings suggest that three herbs have similar effectiveness on treating blood stasis by generating and identifying both their active ingredients and targets specifically related to blood stasis.

5. TCM for qi deficiency

"Qi" is the term used in TCM to describe the vital energy that flows around our body. qi deficiency indicates that the energy is not flowing properly as a result of the malfunction of organs in body. qi deficiency, as the second most common syndrome of CAD, is characterized by short breath, light tongue, hemorheological disorders, heart-throb, spiritlessness, hypodynamia, weak pulse and so on (Wang et al., 2012). In traditional medicine, qi-enriching herbs/formulations have been widely used for treatment of CAD (Committee, 2005). According to Table 1, herbs *Radix codonopsis*, *Radix glycyrrhizae* and *Radix astragali* are the top three reinforcing "qi" herbs, which are used traditionally to enhance physical strength and endurance, strengthen the immune system and restore normal well-being. Here, these three herbs were selected as a combinatorial probe for elucidating why these herbs could be used in treatment of CAD and restore proper balance and harmony inside the body, which is based on the identification of the active compounds, drug targets and network analysis of CAD (Table S3).

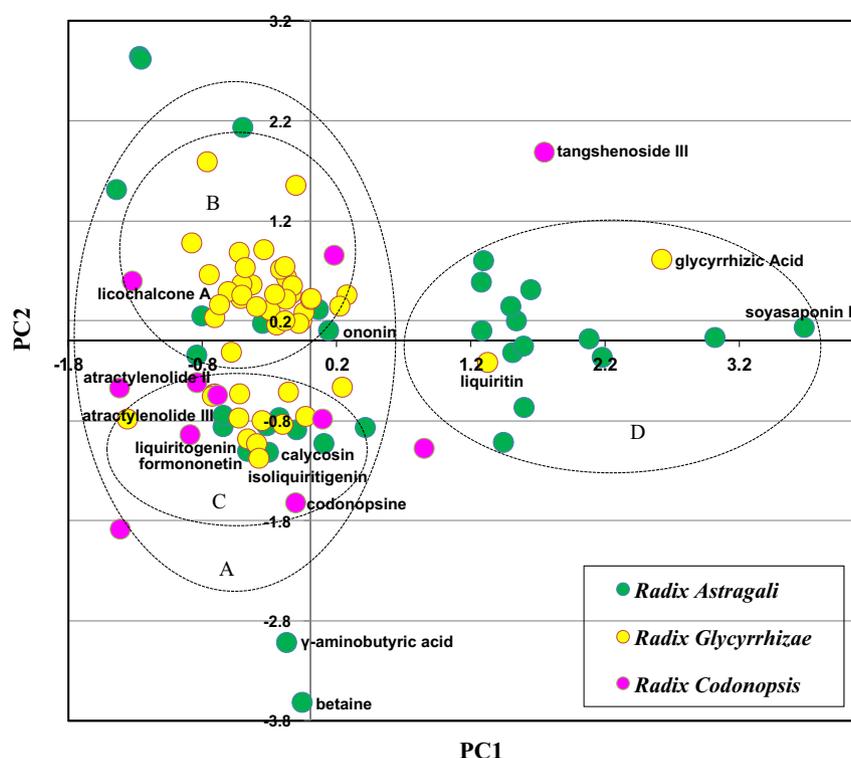


Fig. 3. Chemical space distribution of the active components present in *Radix codonopsis*, *Radix glycyrrhizae* and *Radix astragali* based on their drug-related physicochemical properties.

5.1. Active components

Radix codonopsis is the root of *Codonopsis pilosula* (Franch.) Nannf., *Codonopsis pilosula* Nannf. var. *modesta* (Nannf.) L.T. Shen and *Codonopsis tangshen Oliv* (Pharmacopoeia, 2010). It is a famous herb that has been used in TCM for thousands of years for its vital-energy tonifying. The modern research indicated that it has the functions of antioxidant, antimicrobial, anti-inflammatory effects and improving cellular immunity (Liu et al., 1988). The oral administration of water extracts of *Radix codonopsis* at a dosage of 2.5 g/kg/day for 4 weeks was proven to significantly reduce serum blood levels of cholesterol, while slightly decreased TG and enhance the ratio of HDL-C to various degrees in rats with experimental hyperlipidemia (Li, 1994). *Radix codonopsis* contains various biologically active components including tannins, triterpenes, atractylenolides, alkaloids, and steroids (Fig. 3) (Ichikawa et al., 2009). Saponins from *Radix codonopsis* have been reported to produce anti-inflammatory effect in a xylene-induced model of ear edema in mouse (Xu et al., 2008). Codonopsine as the major compound of alkaloids possesses antibiotic activity and hypotensive activity (Iida et al., 1986). Atractylenolide II and III as the major bioactive components of atractylenolides also showed well documented anti-inflammation and anticancer activities (Tang et al., 1984).

In both traditional Chinese and modern medicine, *Radix glycyrrhizae* has been most widely used in herb preparations. Being the rhizome of *Glycyrrhiza uralensis* Fisch., *Glycyrrhiza inflata* Bat. or *Glycyrrhiza glabra* L (Leguminosae), *Glycyrrhizae radix* belongs to the family of galegeae and genus glycyrrhiza (Hayashi et al., 1990). *Radix glycyrrhizae* has desirable pharmacological effects on preventing atherosclerosis, increasing resistance of low-density lipoprotein (LDL) to atherogenic modifications, reducing plasma lipid levels, and decreasing systolic blood pressure (Fuhrman et al., 2002), and even show certain impacts on antiarrhythmic disorder, and brain ischemia etc. (Zhan and Yang, 2006). The oral

Table 3

Statistical results of the PCA.

Component	Initial eigenvalues		
1	Total 4.973	% of Variance 62.162	Cumulative % 62.162
2	1.287	16.089	78.251

administrations of *Radix glycyrrhizae* extract to the animals for one month at three different doses, 0.2, 0.7 and 1 mg/mL/day show significant decrease in TC and TG, and a significant increase in HDL-C concentration compared with the untreated group (Saleem et al., 2011). Phytochemical investigations have demonstrated that the major bioactive components are flavonoids and pentacyclic triterpene saponin, including liquiritin, liquiritigenin, isoliquiritigenin, liquiritin apioside, glycyrrhizin and glycyrrhizic acid (Fig. 3) (Kamei et al., 2003). Among these phytoconstituents, flavonoids, as the secondary metabolites of the plant, show significant effects of anti-oxidative, anti-inflammation, and skin-whitening properties (Kim et al., 2008). Triterpenes, Glycyrrhizic acid and Licochalcone A, also the main active compounds, have anticancer, antiviral, anti-inflammatory and immunoregulative bioactivities, and even have chemo-preventive activity against AIDS (Meffert et al., 2003).

Radix astragali is the dried root of *Astragalus propinquus* (Fisch.) Bge. var. *mongholicus* (Bge.) Hsiao (Fabaceae) or *Astragalus membranaceus* (Fish.) Bge. (Fabaceae) (Sinclair, 1998). It is one of the best-known traditional herbs to reinforce body energy, which is demonstrated in possession of many biological functions, such as antioxidative, antihypertensive, antiaging activities. It can strengthen the superficial resistance and promote the discharge of pus and the growth of new tissues. Aqueous extracts of *Radix astragali* administered at oral dosages of 4.5, 9, and 18 g/kg/day for four weeks significantly lowered serum TC, TG and LDL-C levels, while increased HDL-C level in mice fed a fat emulsion diet (Liu and Zhang, 2007). No significant adverse effects have been reported for this TCM, except for certain allergic responses

(Xia, 2005). The main bioactive compounds associated with effects on human health are isoflavonoids, triterpene saponins, r-amino butyric acids, kumatakenin, betaine, traces of folic acid and astraisoflavanin (Lin et al., 2000). In general, isoflavonoids are most important, which include calycosin, formononetin and ononin (Fig. 3) (Wu et al., 2005). The isoflavonoids, considered 'marker compounds' for the quality control of *Radix astragali*, also show strong antioxidant activity, immunoregulation, and anti-inflammatory properties, and the capacity for treating cardiovascular diseases (Ying et al., 1996). Triterpenoid saponins, such as soyasaponin I also represent the major beneficial compounds responsible for the bioactivities of *Radix astragali* to human health (Qi et al., 2009).

5.2. Comparisons of three herbs based on active components

PCA was performed to obtain a visual representation of the molecular features of the three herbs, which is based on the eight chemical descriptors as mentioned above (Table S4). The first two PCs explain a major part of the variance (78.251%, Table 3). PC1 explains 62.162% of the total variance, while PC2 accounts for about 16.089% of the total variance. The distribution of the compounds from three herbs on the first two latent variables derived by PCA is shown in Fig. 3.

These herbal ingredients are widely distributed in the chemical space. The superposed dots suggest that the physicochemical features of different herbs are overlapped (region A), which indicate that these compounds may have similar mechanisms of action and may target the same targets. For example, the compounds calycosin in *Radix astragali*, Codonopsine in *Radix codonopsis* and liquiritin in *Radix glycyrrhizae* all target the AR protein which is related to energy metabolism. Moreover, the herbal ingredients can be separated into three independent clusters according to the physicochemical feature which may have similar mechanisms of action in each well-separated cluster. The compounds from *Radix glycyrrhizae* can be divided into two individual concentrated clusters (region B and C), suggesting that the physicochemical features of the ingredients may have different pharmacological effects. For instance, the dopamine receptor D2 (DRD2) hit by licochalcone A in *Radix glycyrrhizae* is also related to respiratory system disease (Liu et al., 2013), except for CVD. The active components from *Radix astragali* (region A and D) and *Radix codonopsis* (region B and C) are widely distributed in the chemical space, though they also distributed two independent sub-clusters, respectively. For example, soyasaponin I in *Radix astragali* (region D) have been proven to exhibit anti-tumorigenic activities in both colon cancer cells and tumor xenografts (Tin et al., 2007). These results may explain that the three herbs have widely pharmacological activities, which may not only have an important effect on CAD, but also play a role in other diseases. Together, all these findings demonstrate why the three herbs show similar energy-tonifying effects to some extent without the close evolutionary relationship. Here, it's also specific to note that the pharmacological information from structural analysis is unsuitable under special circumstances (for example, stereoisomers).

5.3. Targets network

The herbal medicine which targets multiple proteins is encouraged to explore the comprehensive relationships of a disease and botanic drugs. In this section, 138 proteins were identified as the targets of the three herbs for the qi deficiency. Among these targets, 59, 62 and 89 proteins were recognized as targets of *Radix codonopsis*, *Radix astragali* and *Radix glycyrrhizae* respectively (TcmSP™, <http://tcmSPnw.com/>, SEA, <http://sea.bkslab.org/>). Particularly, the three herbs possess 17 common targets, which have

been annotated to have significant relationships with the CAD. Detailed information is given below.

5.3.1. Targets related to anti-inflammation

CAD often begins with inflammatory changes in the endothelium, which expresses the adhesion molecule VCAM-1. We find that four targets for these herbs have relationships with the inflammatory processes. For instance, peroxisome proliferator activated receptor gamma (PPARG) (Park et al., 2001), which is hit by 8 active compounds (Table S3). In these compounds, isoliquiritigenin (ISL, liquorice) induces HO-1 expression, leading to inhibit macrophage-derived inflammation. Calycosin (*Radix astragali*) can reduce AGEs-induced macrophage migration and adhesion to endothelial cells to achieve anti-inflammation effect (Xu et al., 2011). In addition, arachidonate 15-lipoxygenase (ALOX15) also plays an important role in inflammation process by initiating the transformation of arachidonic acid into many potent bioactive chemical mediators such as leukotrienes and lipoxins (Vance et al., 2004). Prostaglandin G/H synthase 2 (PTGS2), a key enzyme leading to the formation of prostaglandins, is the target of nonsteroidal anti-inflammatory drugs (Kargman et al., 1995), which is hit by 9 compounds (Table S3). Among these compounds, licochalcone A has been reported to inhibit prostaglandin biosynthesis in lipopolysaccharide (LPS)-induced mouse macrophage cells to achieve anti-inflammation effect (Cui et al., 2008). In a word, regulation of those targets will lead to the improvement of inflammatory process and treatment of cardiovascular disease.

In addition, we also find that the three herbs possess their own specific targets. For instance, as a cell adhesion molecule, P-selectin hit by codonopsine (*Radix codonopsis*) can activate platelets and endothelium, which plays an essential role in the initial recruitment of leukocytes to the injury during inflammation. Thrombin identified as the target of the chemicals codonopsine, tangshenoside III, atractylenolide II and atractylenolide III in *Radix codonopsis* can amplify inflammation induced by other stimuli, either through ischemia (consequent upon thrombosis), directly via signals through protease activated receptors (PAR), or indirectly through generation of downstream mediators such as activated protein C. Moreover, telomerase reverse transcriptase (*Radix astragali*) hit by calycosin and formononetin has been demonstrated to prevent macrophage senescence and may have important implications for the development of atherosclerosis (Gizard et al., 2011). Phosphatidylinositol 3-kinase related to isoliquiritigenin and licochalcone A plays key roles in regulating the host inflammatory response. The net effect can either be pro- or anti-inflammatory depending on the system and cellular context studied (Cahill et al., 2012). As for *Radix Glycyrrhizae*, prothrombin targeted by isoliquiritigenin, licochalcone A, liquiritigenin, liquiritin can affect the dynamic process of thrombus formation, which may influence the onset and progression of atherosclerosis (Flick et al., 2011).

5.3.2. Targets related to energy metabolism

Heart failure is a syndrome resulting from the inability of the cardiac pump to meet the energy requirements of the body. Factors that lead to abnormal contraction and relaxation in the failing heart include metabolic abnormalities that result in decreased energy production, energy transfer and energy utilization. Patients suffering from heart failure always complain of early muscular fatigue and exercise intolerance. Alterations in energy metabolism that affect both cardiac and skeletal muscles argue for a generalized metabolic myopathy in heart failure (Ventura-Clapier et al., 2004).

Here we find four common drug targets of these herbs are related to energy metabolism. For example, beta-2 adrenergic receptor (ADRB2) is activated by hormone ligands like adrenaline and noradrenaline and plays a critical role in cardiovascular disease (Witter et al., 2009). Calmodulin (CAM) is a ubiquitous, calcium-binding protein that can bind to and regulate a multitude of different protein targets, thereby mediating many different biology processes such as metabolism. And sodium/glucose cotransporters (SGLT1 and SGLT2) are known as symporters involved in energy transportation (Isaji, 2007).

6. CVD pathway

From a system aspect, target proteins do not always perform their functions in isolation but may interact with other cellular components underlie different biological pathways, processes or cellular localizations (Barabási and Oltvai, 2004). Disease, as a complex disorder, is usually related to abnormalities in several pathways (Barabási et al., 2011). It is reasonable to infer that drug action is not only by targeting the disease-associated protein(s) directly, but also by modulating various metabolic enzymes, transporter proteins and the pathways involved in the specific pathological process. With the knowledge of drug targets and disease-associated proteins accumulating rapidly, a more detailed characterization of these relationships may offer a viable strategy to investigate the therapeutic mechanisms of a drug at the pathway level.

To get insight into the integral regulation of the herbs for blood stasis and qi deficiency types, we first collected the related pathways associated with CVD in KEGG (www.genome.jp/kegg). The human protein-protein interaction (PPI) networks were used to as a comprehensive background, in which the data come from BIND (Bader et al., 2003), BioGRID (Stark et al., 2006), DIP (Salwinski et al., 2004), HPRD (Peri et al., 2003), IntAct (Aranda et al., 2010), MINT (Zanzoni et al., 2002), MIPS (Pagel et al., 2005), PDZBase (Beuming et al., 2005) and Reactome databases (Vastrik et al., 2007). Finally, the proteins in CVD pathway were mapped to the PPIs and the closeness between herbal medicine targets p and CVD pathway related proteins p' on the basis of the PPI network:

$$\varphi_{pp'} = \frac{1}{nm} \sum_{i=1}^n \sum_{j=1}^m e^{-D^2_{p_i p'_j}} \quad (2)$$

where n and m respectively represent the number of herbal target p and CVD pathway-related protein p' which can be mapped on the PPI network. p_i is the known target of the herbal medicine. p'_j is the CVD pathway related protein, $D_{p_i p'_j}$ is the shortest distance between p_i and p'_j in the PPI network. The $D_{p_i p'_j}$ is defined as ∞ in case two proteins are unconnected on the PPI network. $e^{-D^2_{p_i p'_j}}$ is used to convert protein-protein distance to protein-protein closeness.

6.1. The targets of blood stasis type connecting with CVD pathway

According to the above formula, the obtained nearness of each time is generally quite similar of the 10,000 times of randomization. And the ultimate nearness between the two proteins is 0.0114. In order to evaluate the statistical significance between the actual distance and those of random counterpart, Z test is carried out and the significance is defined as $p < 0.01$. Comparing to the randomly-selected 13 proteins related to blood stasis (nearness=0.0024) from the background network, the 13 herbal targets show significantly ($p < 0.01$) close functional linkage relevance (ultimate nearness=0.0114) to the 150 CVD-related proteins. Of 13 target proteins, 12 can be plotted on the pathways. These proteins can be categorized as direct and indirect

interactions, which are mainly referred to the renin-angiotensin system pathway, apoptotic pathway, Wnt- β -catenin signaling pathway, hypertrophic cardiomyopathy. Fig. 4 shows that the 12 targets of the three herbs acting on different pathways respectively.

For direct interaction, the chemical bornyl-acetate in *Ligusticum chuanxiong*, dencichine in *Panax notoginseng* and phenylalanine in *Salviae miltiorrhizae* bind to ACE, located at the upstream of renin-angiotensin system pathway. The renin-angiotensin system pathway plays a significant role in regulating the blood volume and systemic vascular resistance, which together influence cardiac output and arterial pressure (Ferrario and Strawn, 2006) ACE inhibitors are often used to prevent angiotensin I and angiotensin II from binding to blood vessels and causing vasoconstriction, since angiotensin II is a strong hormone in renin-angiotensin system pathway, and can act directly on blood vessels to cause blood pressure increases. Besides, the caspase-3 hit by folic-acid (*Ligusticum chuanxiong*), quercetin (*Panax notoginseng*) and salvia-nolic acid B (*Salviae miltiorrhizae*) is found to perturb the apoptosis pathway. The modulation of the activity of caspase-3 suggests a potential therapeutic way to CVD (Hishikawa et al., 2000).

For indirect interaction, it is interesting to find that AR identified as the indirect/direct target of 31 active compounds is related with the CVD pathway by a bridge protein like cadherin-associated protein (CTNNB1). CTNNB1, a downstream effector of the Wnt signaling pathway, is shown to be a coactivator of the AR signaling in the presence of androgens. AR over-expression can potentiate the transcriptional activities of Wnt/ β -Catenin signaling, and then regulates the platelet function by canonical and non-canonical, finally plays a crucial role in hemostasis and thrombosis. ER α activity deficiency is associated with an accumulation of nuclear β -catenin, which is known to be involved in hypertrophic cardiomyopathy. Moreover, MYL3 encodes myosin light chain 3, which is identified to have relevance to mid-left ventricular chamber type hypertrophic cardiomyopathy (Maglott et al., 2007). The MYL3 cleaved by active caspase-3 may contribute to the activation of apoptotic pathways in heart, leading to contractile dysfunction before cell death. All these results indicate that these herbs are potential drugs for dealing with CVD through indirect actions on this pathway.

6.2. The targets of qi deficiency type connecting with CVD pathway

For qi deficiency pathway, the ultimate nearness between the two proteins is 0.0069 based on the above formula 2. Z test is also carried out to evaluate the statistical significance between the actual distance and those of the random counterpart. The 17 herbal targets related to qi deficiency exhibit significantly ($p < 0.01$) close functional linkage relevance (ultimate nearness=0.0069) to the 150 CVD-related proteins comparing to the randomly-selected 17 proteins (nearness=0.0065) from the background PPI network. Among the 17 target proteins, 14 are successfully mapped on the pathways. These proteins are mainly involved in the apoptotic pathway, NF-kappa B signaling pathway, and dilated cardiomyopathy, respectively (Fig. 4).

Tumor necrosis factor- α (TNF- α) can induce apoptosis and activates NF-kappa B through signaling cascades emanating from TNF receptor 1 (TNFR1). It may be considered as a major factor in the pathophysiological processes of CVD, acting both by contributing to hypertriglyceridaemia and by promoting atherosclerosis-related inflammation (Svenungsson et al., 2003). Because the stability of TNF mRNA depends on mitogen-activated protein kinase (MAPK14), which acts by blocking AU-rich elements-directed deadenylation, inhibiting MAPK14 (hit by 8 active components) (Cronin et al., 2012). In addition, the Peroxisome proliferator activated receptor gamma-depleted (PPARG) cells displayed enhanced inflammatory

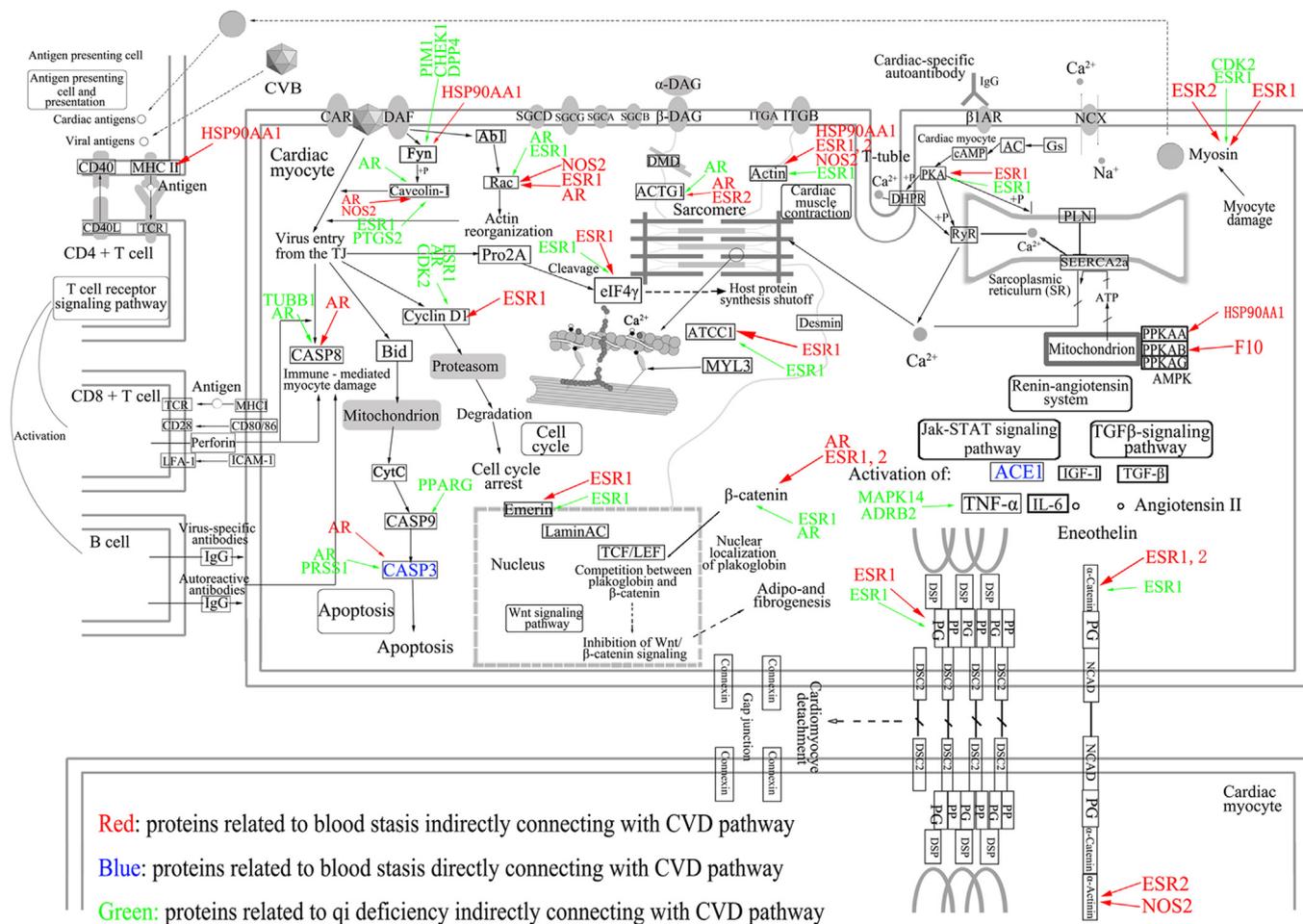


Fig. 4. Distribution of target proteins of herbs on the compressed CVD pathway.

responses to TNF- α stimulation, which is consistent with a chronic anti-inflammatory effect of endogenous PPARG. For instance, it is proved that TNF- α -secreting B cells are involved in myocardial fibrosis, which revealed a new pathogenic mechanism of B cells in dilated cardiomyopathy (DCM), which might be novel drug target (Yu et al., 2013). It has been reported that the serine/threonine-protein kinase Chk1 (CHEK1) can suppress a caspase-3-dependent apoptosis in response to DNA structural alterations induced by replication stress (Myers et al., 2009), since caspase-3 is primarily activated in CHEK1-depleted cells treated by the replication inhibitors (Rodriguez and Meuth, 2006). All these results reveal that it is critical to identify the targets in the signal pathways and then understand the therapeutic mechanisms of a drug at the pathway level.

7. Conclusion

Thousands of years' clinic practices in TCM have accumulated a considerable number of herbal medicines that exhibit reliable efficacy and safety in treating CAD, which is mainly based on the diagnosis of syndromes of diseases. However, how to set up the relationships between CAD and TCM syndromes at the systems level are extremely difficult. In this review, we have attempted to dissect the types of CAD according to TCM theory by means of the systems pharmacology method, which might provide new insights into heart diseases and drug treatment.

According to different types of CAD, we extract the available herbal medicines by the text mining approach, which is effective

for the blood stasis and qi deficiency types in CAD. The obtained herbs are introduced to an integrated system framework of microscopic "omics" information and macroscopic clinical symptoms. With the structural feature comparisons of active compounds in *Ligusticum chuani*, *Salvia miltiorrhiza* and *Panax notoginseng*, the three herbs are shown to possess the similar pharmacological characteristic for blood stasis. All the targets of these herbs are mainly involved in the process of anti-thrombosis, promoting vasodilatation, regulating dyslipidemia and anti-inflammation.

The qi-enhancing herbs (*Radix codonopsis*, *Radix glycyrrhizae* and *Radix astragalii*) are also shown to have similar pharmacological characteristic, which indicates that TCM is the combination therapy of multiple active compounds in essence. The prediction of the targets indicates that the three qi-enhancing herbs have potential in the aspects of energy metabolism enhancement and anti-inflammatory effects. This suggests TCM does not focus solely on the disease defined by specific pathological changes, but instead of concentrating on the overall functional state of the patient. Moreover, synergic effect of the active compounds can be observed when they are taken together based on the network analysis. Finally, the mapping of the targets to the CVD signal pathway further facilitates our understanding of the blood stasis and qi deficiency types at the systems level. In a word, the present work provides a systemic thinking of the relationships between the molecular mechanism of herbs with different CAD types, which facilitates the understanding of the holistic, complementary and synergic essence for TCM, and thus benefiting the process of drug discovery and the therapy of complex diseases.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.jep.2013.11.007>.

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