The Synergistic Effects of *Astragalus mongholicus* and *Salvia miltiorrhiza* on Coronary Heart Disease Identified by Network Pharmacology and Experiment

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**Background and Purpose:** Two Chinese herbal medicines Huang Qi (HQ, *Astragalus mongholicus*) and Dan Shen (DS, *Salvia miltiorrhiza*) are often combined to treat coronary heart disease (CHD). The purpose of this study was to identify the underlying synergistic effects and mechanisms of HQ and DS against CHD.

**Methods:** The active components and targets of HQ and DS, CHD-related genes, and the biological progression were analysed by network pharmacology. The myocardial infarction (MI) rat model was established by ligating the left anterior descending coronary artery. Cardiac function was detected by ultrasonic electrocardiography. The MI size, fibrosis, cardiac hypertrophy, lipid metabolism, blood viscosity, and coagulation indexes were analysed by histological staining or chemical methods, respectively.

**Results:** A total of 170 shared and specific seed genes of HQ and DS against CHD were identified. The shared and specific biological processes of HQ and DS against CHD were obtained. The LVEF and LVFS values significantly increased, the myocardium infarct size and fibrosis significantly decreased, the values of lipid metabolism indexes and blood viscosity indexes significantly reduced in the HQ + DS treatment group vs HQ or DS single treatment \((P < 0.05)\); the LVEDd, LVEDs, and the CSA values significantly reduced in HQ single and HQ + DS treatment groups vs MI group \((P < 0.05)\); the coagulation index (APTT, PT, TT, and FIB) values decreased significantly in the DS single and HQ + DS treatment groups vs MI group \((P < 0.05)\).

**Conclusion:** In MI rats, HQ and DS exhibited synergistic effects on improving cardiac function, reducing MI size, fibrosis, regulating hyperlipidaemia, and maintaining circulatory system homeostasis; HQ had the specific advantage of alleviating cardiac remodelling; DS had the specific advantage of regulating hypercoagulability. This study revealed that HQ and DS not only exerted synergistic effects but also exhibited complementary effects on CHD.

**Keywords:** coronary heart disease, *Astragalus mongholicus*, *Salvia miltiorrhiza*, synergistic effects, network pharmacology, myocardial infarction

**Introduction**

Cardiovascular disease (CVD) remains the leading cause of death and disability worldwide, with increased hospitalisation and discharge rates, causing serious public health issues and economic burden. In 2010, the estimated global cost of CVD was US$863 billion, which is expected to increase to US$1044 billion by 2030. Therefore, safe and effective treatments are urgently needed to tackle this major health threat.
Traditional Chinese medicine (TCM) has attracted significant attention due to its integrative efficacy and fewer side effects, especially on chronic intractable diseases.\(^3\) Two Chinese herbal medicines Huang Qi (HQ) and Dan Shen (DS), or specifically Astragalus mongholicus and Salvia miltiorrhiza, respectively, in Latin have been used to treat coronary heart disease (CHD) clinically in China for thousands of years.\(^4,5\) According to TCM, patients with CHD often have symptoms of Qi deficiency and blood stasis.\(^6\) CHD patients with Qi deficiency often have symptoms of chest tightness, chest pain, palpitation, shortness of breath, fatigue, and pale complexion.\(^7\) CHD patients with blood stasis often have symptoms of cyanosis, purple or bruised tongue, fixed chest pain, and sublingual varices.\(^8\) Compared with CHD patients without Qi deficiency and blood stasis, larger left ventricular end-diastolic diameter (LVEDd) and left ventricular end-systolic diameter (LVEDs), less left ventricular ejection fraction (LVEF) and left ventricular fractional shortening (LVFS), and higher blood lipids concentration are present in CHD patients with Qi deficiency and blood stasis.\(^9\) Supplementing Qi and promoting blood circulation are the main treatment methods. Invigorating Qi could significantly improve the LVEF, LVEDd, and NTproBNP indexes in chronic heart failure of coronary heart disease.\(^10\) Promoting blood circulation treatment can effectively reduce the incidence of angina pectoris and nitroglycerin use, improve heart function, and improve the quality of life of CHD patients.\(^11\) HQ has the functions of invigorating Qi, diuresis, detoxification, and regenerating muscles.\(^12\) Astragaloside IV (AST), one active component of HQ can protect the heart against MI by improving cardiac histology and ventricular contractility.\(^13\) DS has the effects of relieving itching, removing carbuncle, regulating menstruation, stopping bleeding, stabilizing foetus, promoting blood circulation, calming the mind, clearing heat, and avoiding pestilence.\(^14\) HQ combined with DS could accelerate blood circulation, prevent thrombosis, eliminate congestion, and remove excess fluid and phlegm. Recently, HQ combined with DS has been applied to treat CVD, type 2 diabetes, pulmonary fibrosis, cirrhosis, and cancer.\(^15-18\)

Our previous study identified a Chinese herbal formulation Huoxue Anxin recipe (HAR), containing HQ and DS as the monarch herbs, having multi-effects on CHD.\(^19,20\) However, the synergistic effects and possible mechanisms of HQ and DS against CHD are not well understood. Identifying the synergistic effects and mechanism of HQ and DS against CHD via modern science and technology would help to clarify these aspects, promote a more extensive clinical application, and benefit individuals who experiencing CHD.

In this study, we identified the specific and shared seed genes of HQ and DS with activity against CHD, and the biological processes of HQ and DS against CHD using network pharmacology. We also verified the synergistic and specific effects and mechanisms of HQ and DS against CHD using experimental evidence (Figure 1).

**Materials and Methods**

**Network Pharmacology**

**Active Components Screening of HQ and DS**

Chemical components of HQ and DS were retrieved from the Traditional Chinese Medicine Systems Pharmacology Database, a unique pharmacology platform that captures the relationships between herbal ingredients, targets, and diseases (TCMSP, \(\text{http://lsp.nwu.edu.cn/tcmsp.php}\), the TCM integrated pharmacology database (TCMID, \(\text{https://omictools.com/tcmid-tool}\)), and literature mining. The components were filtered by integrating oral bioavailability (OB ≥ 30%) and drug-likeness (DL ≥ 0.18) as suggested by the TCMSP database.\(^21\)

**Target Fishing of the Active Components**

Verified targets of the candidate components were retrieved from PubChem (\(\text{https://pubchem.ncbi.nlm.nih.gov/}\)) using the criteria of active activity. Predictive targets were retrieved from the SEA database (\(\text{http://sea.bkslab.org/}\)) using the criteria of Max Tc score ≥ 0.5, and from the Swiss Target Prediction database (\(\text{http://www.swisstargetprediction.ch/}\)) using the criteria of probability ≥ 0.5.\(^22\) In simple terms, the candidate components were uploaded to an online database, the species were restricted to human sources, and potential targets were identified through high-throughput screening. The targets of each component from the different databases were combined and the repeated targets were deleted. The C-T network was visualized using Cytoscape 3.2 software.

**The Shared and Specific Seed Genes of HQ and DS Against CHD**

CHD-related and differentially expressed (DE) genes were collected using the keywords “coronary heart disease” in the Therapeutic Target Database (\(\text{https://db.idrblab.org/ttd/}\)), DrugBank (\(\text{https://www.drugbank.ca/}\)), and DisGeNET (\(\text{http://www.disgenet.org/search}\)) databases which contain collections of genes and variants associated with human diseases.\(^23\) The shared and specific seed genes HQ and
DS against CHD were obtained by overlapping the shared and specific targets of the HQ and DS with CHD-related DE genes, respectively, using an online Draw Venn Diagram tool (http://bioinformatics.psb.ugent.be/webtools/Venn/).

Metascape GO Enrichment Based on the Shared and Specific Seed Genes of HQ and DS Against CHD, Respectively
Metascape (http://metascape.org/gp/index.html) enables the automated meta-analysis of gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways. The three lists of genes were retrieved from the latest version of the Metascape database (last updated on 2019-08-14). In the GO Biological Processes (BPs), the highest-level terms in the BP GO graph structure, and pathways with a term ≥3 counts, enrichment factors > 1.5, and a false discovery rate (FDR) < 0.01 were specific biological progress for genes in the network. GO analysis was based on the specific and shared seed genes of HQ and DS against CHD, respectively.

Experimental Evidence
Hyperlipidaemia Combined with MI Model in Rats
Male Sprague-Dawley rats (150, bodyweight 180 ± 20 g) were provided by Beijing Vital River Laboratory Animal Technology Co., Ltd. (Animal license: SCXK [Beijing] 2012–0001). The animals were maintained under 12-h light/12-h dark cycles, at a temperature of 22 ± 2°C, and humidity of 50 ± 2%. MI was induced by ligation of the left anterior descending artery, after being given a high-fat forage (cholesterol 1%, egg-yolk powder 10%, lard oil 10%, bile salts 0.2%, and the basic ingredients 78.8%) for 28 days. The protocol was followed as described in our previous report.19,20 Briefly, after the administration of anaesthetics by intraperitoneal injections of 40 mg/kg sodium pentobarbital (Lot. No. 200-323-9, Shanghai Sinopharm Chemical Reagent Co., Ltd, China), the animals were preoperatively subjected to 12-lead electrocardiography (ECG). For the surgical procedure, the rats were subjected to endotracheal intubation with the ventilator set to provide positive pressure ventilation (SAR-830/A, CWE Inc., USA). Following disinfection and opening of the chest, the left anterior descending coronary artery was ligatured 2-mm below the branch point. MI was confirmed with S-T segment elevation of the ECG. The rats in the sham group were similarly operated without the ligation. The 90 surviving rats were randomly assigned into six groups (n = 15): Sham, MI (model), Atorvastatin, HQ, DS, and HQ combined with DS treatment groups. Animals were continuously fed with a high-fat forage diet except for the Sham group. All procedures were carried out following the recommendations of Laboratory Animal Management and Use Regulations from the Beijing Laboratory Animal Management Committee. The protocol was also approved by the Animal Ethics Committee of Guang’anmen hospital, China Academy of Chinese Medical Sciences (approval number: EC_AF_055).
Medical Intervention

Atorvastatin calcium tablets were provided by Pfizer Pharmaceuticals Limited (Lot. No. EG 6081). The tablets were dissolved in distilled water and intragastrically administered at a dose of 7.3 mg/kg/day. The herbal medicines of HQ (Lot. No. 20082311) and DS (Lot. No. 20091081) were provided by Sichuan New Green Pharmaceutical Science and Technology Development Co., Ltd. The granules were dissolved in distilled water. HQ single treatment was administered 5 g/kg/day, DS single treatment was administered 5 g/kg/day, and HQ combined DS treatment was administered with HQ 2.5 g/kg/day + DS 2.5 g/kg/day. The rats were treated intragastrically once a day for four weeks. An equal volume of distilled water was intragastrically administered to the sham and MI groups.

Non-Invasive Transthoracic Echocardiography Measurement

After four weeks of treatment, a non-invasive trans thoracic echocardiography method was used to evaluate cardiac function using a small animal ultrasonic machine (VEVO 3100, VisualSonics, Canada). This method consisted of a two-dimensional mode, a time-motion mode, and blood-flow measurement in the pulsed Doppler mode. The LVEF, LVFS, LVEDd, and LVEDs were calculated from the M-mode.

Anaesthesia, Blood Sample, and Heart Sample Collection

After four weeks of treatment, the rats were anaesthetised by intraperitoneal injections of 40 mg/kg sodium pentobarbital (Lot. No. 200-323-9, Shanghai Sinopharm Chemical Reagent Co., Ltd, China). The abdominal cavity was opened and 9 mL blood samples were collected from the abdominal venous (3 mL for the blood lipid measurements, 4 mL for the blood viscosity measurements, and 2 mL for the blood coagulation measurements). Next, the thoracic cavity was opened and the whole hearts were isolated. In each group, three hearts were quantitatively detected for myocardial infarct size by triphenyltetrazolium chloride (TTC) staining (Lot. No. 20200516, Shanghai Zeye Biotechnology Co., Ltd, China), and five hearts were fixed in 4% paraformaldehyde (Lot. No. 20200713, Solarbio, Beijing, China) for histological analysis.

Determination of Myocardial Infarct Size

Myocardial infarct size was quantitatively detected by TTC staining. The hearts were rapidly frozen (~20 °C for 1 h), cut into 4-mm thick slices (total of three), and each slice was incubated at 37°C in 1 mL of 1% TTC (dissolved in pH 7.4 phosphate buffer) for 10 min. The TTC entered the normal cells and bound to dehydrogenase in red, while dead cells were not stained by TTC due to the lack of dehydrogenase. Slices were then transferred to 4% paraformaldehyde for 10 min. Finally, digital photos of the heart slices were obtained (Canon, SX60 HS). The differently stained areas of the heart images (white: infarct region; red: non-infarct region) were quantified by Image-Pro Plus 6.0 (Media Cybernetics, USA). The myocardial infarct size was quantified by measuring the white myocardial area/total white and red myocardial area of the left ventricular×100%. An evaluation of all images was carried out in a blinded manner throughout the study.

Histological Analysis

The rat hearts were fixed for 24 h in 4% paraformaldehyde (Lot. No. 20200713, Solarbio, Beijing, China) at room temperature, embedded in paraffin, and sectioned into 3-μm thick slices from the portion approximately 400-μm distal to the ligation point. Heart sections were deparaffinized using xylene at room temperature and rehydrated in serial dilutions of alcohol. Samples were stained with Masson’s trichrome for the detection of myocardium fibrosis, and wheat germ agglutinin (WGA) for the detection of myocardial cell size. Peroxidase conjugated WGA (VECTOR, Catalogue No. PL-1026, USA) 40 mg/mL was diluted in 10 mM phosphate buffer (pH 7.5) and 0.15 M NaCl to produce a working solution of 5 μg/mL. The slides were incubated for 1 hour, then coloured with DAB (Zhongshan Company, Beijing, China) for 10 sec. Each specimen was examined three to four times, and photomicrographs were obtained under a bright field microscope (Olympus IX 70, Japan). The myocardium fibrosis was quantified by measuring the blue myocardium area/total red and blue myocardium area×100%. For the WGA staining, suitable cross-sections, with nearly circular to oval cardiomyocytes, were selected. The outlines of the cardiomyocytes were traced to determine the cross-sectional area (CSA) which was calculated by measuring 400–600 cells distant from the infarct region of each heart. The percentage of myocardium fibrosis, and myocardial cell size were observed and imaged under.
a microscope (Olympus IX 73, Japan), and measured using Image-Pro Plus 6.0 software (Media Cybernetics, USA).

Blood Lipid Measurements
The serum was used to analyse blood lipid indexes. The concentrations of triglycerides (TG, A110-1), total cholesterol (Chol, A111-1), low-density lipoprotein cholesterol (LDL-C, A113-1), and high-density lipoprotein-cholesterol (HDL-C, A112-1) were measured using assay kits from Nanjing Jiancheng Bioengineering (Nanjing, China) according to the kit manufacturer’s instructions.

Blood Viscosity and Coagulation Measurements
A venous blood sample (approximately 4 mL) was collected and mixed well in a 5 mL of heparin vacuum anticoagulation tube. Whole blood viscosity (WBC) and plasma viscosity (PV) at high shear rates (200/s) were measured using a rotational viscometer (LVDV-II+P, CP40, Brookfield Engineering Labs Inc., USA). Haematocrit (HCT) was measured by a gravimetric technique by centrifuging blood samples at 650 ×g for 20 min. The ratio of HCT to whole blood viscosity (OTE) at high shear rates (200/s) was used as a measure of oxygen availability for tissues.28

A venous blood sample (approximately 2 mL) was collected and placed in a 5 mL vacuum anticoagulant tube containing sodium citrate. The mixture was then centrifuged at 1608 ×g for 10 minutes to separate plasma. Activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), and fibrinogen (FIB) content were measured using an LG-PABER-I coagulometer (Beijing Steellex Scientific Instrument Company, China) using an automatic coagulation analyser (ACL-TOP700; Instrumentation Laboratory, Milan, Italy) within 24 hours at room temperature. During the measurement, matched calibration products, quality control products, and reagents were used following the manufacturer’s instructions.

Statistical Analysis
Data are presented as the mean ± SD. Statistical comparison of the data was performed using one-way analysis of variance followed by Dunnett’s post hoc test for multiple comparisons using GraphPad Prism 6.0 (GraphPad, Inc., La Jolla, CA, USA). A P value < 0.05 was considered significant.

Results
Network Pharmacology
The Active Components of HQ and DS
A total of 20 active components from HQ and 62 active components from DS were obtained (Table 1). All satisfied the criteria of OB ≥ 30% and DL ≥ 0.18.

The Shared and Specific Targets of the Active Components of HQ and DS
A total of 408 targets from 14 active components of HQ and 423 targets from 40 active components of DS were obtained, whereas 6 active components of HQ and 22 active components of DS were no targets reached the set criteria. Among the selective targets, HQ and DS shared 254 targets, HQ had 154 specific targets, and DS had 169 specific targets. The Venn diagram of the shared and specific targets of HQ and DS is exhibited in Supplemental materials (Figure S1). The C-T network was visualized by Cytoscape software (Figure 2).

The Specific and Shared Seed Genes of HQ and DS Against CHD
A total of 1650 CHD-related DE of genes were collected (1574 from DisGeNET, 68 from Drugbank, and 8 from TTD database). By overlapping the shared and specific targets of HQ and DS with CHD-related DE of genes, HQ and DS shared 83 seed genes against CHD. HQ had 52 specific seed genes against CHD, and DS had 35 specific seed genes against CHD (Figure 3). The UniProt ID, gene name, and protein name of the shared and specific seed genes are listed in the Supplemental materials (Table S1).

Metascape Gene Ontology (GO) Enrichment Analysis Based on the Shared and Specific Seed Genes of HQ and DS Against CHD
The shared biological process of HQ and DS focused on four areas: (1) nutrient metabolism: response to nutrient levels, response to an inorganic substance, metabolism of lipids, lipid biosynthetic process, steroid metabolic process; (2) cell proliferation: genes involved in male infertility, cellular response to organic cyclic compounds, positive regulation of cell migration, positive regulation of ion transport, cellular response to nitrogen, compound Phase 1 - functionalization of compounds; (3) circulatory system homeostasis: fluid shear stress and atherosclerosis, regulation of hormone levels, circulatory system process; and (4) inflammatory response and oxidative stress: interleukin-4 and interleukin-13 signalling, response to oxidative stress, reactive oxygen species biosynthetic process (Figure 4A). The specific
### Table 1 The Active Components of HQ and DS

#### HQ

| Mol ID | Molecule Name                                                                 | OB (%) | DL    |
|--------|-------------------------------------------------------------------------------|--------|-------|
| M438   | (3R)-3-(2-hydroxy-3,4-dimethoxyphenyl)chroman-7-ol                            | 67.67  | 0.26  |
| M33    | 17-dodecahydro-1H-cyclopenta[a]phenanthen-3-ol                                | 36.23  | 0.78  |
| M380   | (6αR,11αR)-9,10-dimethoxy-6α,11-dihydro-6H-benzofuran-[3,2-c]chromen-3-ol     | 64.26  | 0.42  |
| M442   | 1,7-Dihydroxy-3,9-dimethoxypterocarpene                                       | 39.05  | 0.48  |
| M371   | 3,9-di-O-methyllissolin                                                        | 53.74  | 0.48  |
| M374   | 5’-hydroxyiso-muronutol-2',5’-di-O-glucoside                                  | 41.72  | 0.69  |
| M378   | 7-O-methylisomuronutol                                                        | 74.69  | 0.30  |
| M379   | 9,10-dimethoxypterocarpan-3-O-β-D-glucoside                                  | 36.74  | 0.92  |
| M387   | Bifendate                                                                    | 31.10  | 0.67  |
| M417   | Calycosin                                                                    | 47.75  | 0.24  |
| M433   | FA                                                                            | 68.96  | 0.71  |
| M392   | Formononetin                                                                 | 69.67  | 0.21  |
| M296   | Hederagenin                                                                  | 36.91  | 0.75  |
| M398   | Isoflavanone                                                                  | 109.99 | 0.30  |
| M439   | Isomuronutol-7,2'-di-O-glucosiole                                             | 49.28  | 0.62  |
| M354   | Isorhamnetin                                                                 | 49.60  | 0.31  |
| M239   | Jaranol                                                                      | 50.83  | 0.29  |
| M422   | Kaempferol                                                                   | 41.88  | 0.24  |
| M211   | Mairin                                                                       | 55.38  | 0.78  |
| M98    | Quercetin                                                                    | 46.43  | 0.28  |

#### DS

| Mol ID | Molecule Name                                                                 | OB (%) | DL    |
|--------|-------------------------------------------------------------------------------|--------|-------|
| M7132  | (3,4-dihydroxyphenyl)acryloyl]-oxypropanoic acid                             | 109.38 | 0.35  |
| M7155  | 1,6-dimethyl-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-dione              | 65.26  | 0.45  |
| M7150  | (6S,7R)-6,7-dihydroxy-1,6-dimethyl-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-dione | 75.39  | 0.46  |

(Continued)
The specific biological process of DS focused on three areas: (1) lipid and glucose metabolism: lipid catabolic process, cellular response to lipid, response to lipopolysaccharide, glucose homeostasis, cellular response to lipoprotein particle stimulus, monocarboxylic acid transport and metabolic process; (2) circulation system homeostasis: circulatory system process; wound healing; Eicosanoid metabolism via Cyclooxygenases (COX); (3) mood stability: regulation of behaviour, endocrine process (Figure 4C). The detailed information (GO ID, biological process description, gene count, and Log10 P-value) of the GO enrichment is reported in the Supplemental materials (Table S2).

Experimental Evidence

The Synergistic Effects of HQ and DS on Improving Cardiac Function in MI Rats

The LVEF and LVFS values decreased significantly in the MI group, whereas the LVEDd and LVEDs values increased significantly compared to the values of the sham group (P < 0.01). The LVEF and LVFS values increased in the four treatment groups (Atorvastatin, HQ single, DS single, and HQ + DS), whereas the LVEDd and LVEDs values decreased in two treatment groups (HQ single and HQ + DS) compared to those of the MI group (P < 0.05).

Compared to the HQ or DS single treatment group, the values of LVEF and LVFS further increased (P < 0.05) in the HQ + DS treatment group (Table 2 and Figure 5).

The Synergistic Effects of HQ and DS on Reducing Left Ventricular Myocardial Infarct Size

Compared with the sham group, the percentage of infarct size increased significantly (49.51 ± 8.30 vs 0.00 ± 0.00, P < 0.001) in the left ventricle in the MI group. Compared with the MI group, the percentage of infarct size decreased significantly in the left ventricle in four treatment groups (Atorvastatin, HQ single, DS single, and HQ + DS, P < 0.05 or P < 0.01).

Compared with the DS single treatment group, the percentage

Table 1 (Continued).

| MolID  | Molecule_Name                  | OB (%) | DL   |
|-------|--------------------------------|--------|------|
| M7061 | Methylene-tanshinquinone       | 37.07  | 0.36 |
| M7118 | Microstegiol                  | 39.61  | 0.28 |
| M7119 | Miltionone I                  | 49.68  | 0.32 |
| M7120 | Miltionone II                 | 71.03  | 0.44 |
| M7121 | Miltipolone                   | 36.56  | 0.37 |
| M7122 | Miltirone                     | 38.76  | 0.25 |
| M7123 | Miltirone II                  | 44.95  | 0.24 |
| M7125 | Neocryptotanshinone           | 52.49  | 0.32 |
| M7124 | Neocryptotanshinone ii        | 39.46  | 0.23 |
| M7149 | NSC 122421                    | 34.49  | 0.28 |
| M1771 | Poriferast-5-en-3beta-ol      | 36.91  | 0.75 |
| M1659 | Poriferasterol                | 43.83  | 0.76 |
| M7130 | Prothrombinic acid            | 64.37  | 0.31 |
| M7063 | Przewalskin a                 | 37.11  | 0.65 |
| M7064 | Przewalskin b                 | 110.32 | 0.44 |
| M7068 | Przewaquinone B               | 62.24  | 0.41 |
| M7069 | Przewaquinone c               | 55.74  | 0.40 |
| M7152 | Przewaquinone E               | 42.85  | 0.45 |
| M7071 | Przewaquinone f               | 40.31  | 0.46 |
| M7141 | Salvianolic acid g            | 45.56  | 0.61 |
| M7142 | Salvianolic acid j            | 43.38  | 0.72 |
| M7085 | Salvilenone                   | 30.38  | 0.38 |
| M7143 | Salvilenone I                 | 32.43  | 0.23 |
| M7145 | Salviolone                    | 31.72  | 0.24 |
| M7077 | Sclareol                      | 43.67  | 0.21 |
| M2222 | Sugiol                        | 36.11  | 0.28 |
| M7079 | Tanshinaldehyde              | 52.47  | 0.45 |
| M7151 | Tanshidiol B                 | 42.67  | 0.45 |
| M7156 | Tanshinone VI                 | 45.64  | 0.30 |
| M6824 | α-amyrin                      | 39.51  | 0.76 |

Notes: The Mol ID, Molecule_name, OB (%), and DL of the active components of HQ and DS were listed.
Abbreviations: OB, oral bioavailability; DL, drug-like.
of infarct size decreased significantly in the HQ + DS treatment group (P < 0.05, Figure 6).

The Synergistic Effects of HQ and DS on Alleviating Myocardium Fibrosis and Cardiac Hypertrophy in MI Rats

Compared with the sham group, the number of myocardial cells decreased and collagen accumulation increased significantly (64.26 ± 12.5 vs 2.06 ± 0.86, P < 0.001) in the left ventricular myocardium area in the MI group. Compared with the MI group, the number of myocardial cells increased and collagen decreased significantly in the myocardium area in four treatment groups (Atorvastatin, HQ single, DS single, and HQ + DS, P < 0.05 or P < 0.01). Compared with the MI group, the CSA of left ventricular myocardial cells increased significantly in the MI group (569.33 ± 109.05 vs 280.37 ± 44.06, P < 0.001). Compared with the MI group, the myocardial cell size decreased significantly in two treatment groups (HQ single and HQ + DS, P < 0.05). Compared with the DS single treatment group, the collagen accumulation reduced and CSA of left ventricular myocardial cell size decreased significantly in the HQ + DS treatment group (P < 0.05, Figure 7).

The Synergistic Effects of HQ and DS on Improving the Survival Rate

During the experiment, none of the rats died in the sham group; four rats in the MI group died on days 1, 2, 9 and 14 after surgery; six rats in the Atorvastatin group died on days 1, 4, 4, 8, 9, and 12 after surgery; three rats in HQ group died on days 15, 19, and 23 after surgery; three rats in DS group died on days 12, 16, and 21 after surgery; two rats in the HQ + DS group died on days 15 and 18 after surgery. HQ combined with DS treatment significantly increased the survival rate of rats when compared to that...
WP2882: Nuclear Receptors Meta-Pathway
R-HSA-556833: Metabolism of lipids
GO:0008202: steroid metabolic process
GO:0072593: reactive oxygen species metabolic process
R-HSA-6785807: Interleukin-4 and Interleukin-13 signaling
GO:0003013: circulatory system process
GO:0071497: cellular response to organic cyclic compound
GO:0008610: lipid biosynthetic process
GO:0006954: inflammatory response
WP4673: Genes involved in male infertility
GO:0006979: response to oxidative stress
ko05418: Fluid shear stress and atherosclerosis
GO:0010817: regulation of hormone levels
GO:0010035: response to inorganic substance
GO:0030335: positive regulation of cell migration
GO:1903409: reactive oxygen species biosynthetic process
GO:0043270: positive regulation of ion transport
GO:0031667: response to nutrient levels
R-HSA-211945: Phase I - Functionalization of compounds
GO:1901699: cellular response to nitrogen compound

ko05418: Fluid shear stress and atherosclerosis
ko04933: AGE-RAGE signaling pathway in diabetic complications
WP1533: Vitamin B12 Metabolism
GO:0044283: small molecule biosynthetic process
R-HSA-109582: Hemostasis
GO:0006954: inflammatory response
GO:0006066: alcohol metabolic process
GO:00030302: response to reactive oxygen species
GO:0030335: positive regulation of cell migration
GO:0071497: cellular response to organic cyclic compound
WP3624: Lung fibrosis
GO:0031667: response to nutrient levels
GO:0050900: leukocyte migration
GO:0001819: positive regulation of cytokine production
GO:0014074: response to purine-containing compound
R-HSA-9006934: Signaling by Receptor Tyrosine Kinases
WP4747: Netrin-UNC5B signaling Pathway
GO:199074B: cellular detoxification
GO:1903409: reactive oxygen species biosynthetic process
GO:0008202: steroid metabolic process

GO:0001819: positive regulation of cytokine production
GO:0032787: monounsaturated fatty acid metabolic process
GO:0032496: response to lipopolysaccharide
GO:0016042: lipid catabolic process
GO:0071396: cellular response to lipid
GO:0031347: regulation of defense response
GO:0042593: glucose homeostasis
GO:0003013: circulatory system process
WP697: Estrogen metabolism
GO:0042060: wound healing
WP4719: Eicosanoid metabolism via Cyclo Oxynogenases (COX)
R-HSA-211859: Biological oxidations
GO:0071402: cellular response to lipoprotein particle stimulus
GO:2000273: positive regulation of signaling receptor activity
GO:0015718: monounsaturated fatty acid transport
GO:0042493: response to drug
GO:0050795: regulation of behavior
GO:0050886: endocrine process
GO:2000106: regulation of leukocyte apoptotic process
GO:0010035: response to inorganic substance

Figure 4 GO analysis of the shared and specific biological processes of HQ and DS against CHD. (A) The shared biological processes or pathways of HQ and DS against CHD. (B) The specific biological processes or pathways of HQ against CHD. (C) The specific biological processes or pathways of DS against CHD. The values of the x-axis represent $-\log_{10} P$ values. The higher the value the more significant the biological processes or pathways.
of the MI or Atorvastatin group ($P < 0.05$), but was not considered statistically significant when compared with HQ or DS single treatments ($P > 0.05$, Figure 8).

### The Synergistic Effects of HQ and DS on Lipid Metabolism in MI Rats

Compared with the sham group, the serum TG, Chol, and LDL-C concentrations increased significantly in the MI group ($P < 0.01$). Compared with the MI group, the serum TG, Chol, and LDL-C concentrations decreased significantly in four treatment groups (Atorvastatin, HQ single, DS single, and HQ + DS, $P < 0.05$ or $P < 0.01$). Compared with the HQ single or DS single treatment group, the serum TG, Chol, and LDL-C concentrations further decreased in the Atorvastatin and the HQ + DS treatment groups ($P < 0.05$, Table 3).

### Table 2 Effect of HQ and DS on Cardiac Functional Parameters

| Groups         | n  | LVEF (%) | LVFS (%) | LVEDd (mm) | LVEDs (mm) |
|----------------|----|----------|-----------|------------|------------|
| Sham           | 15 | 90.53 ± 9.14 | 49.90 ± 7.98 | 6.42 ± 0.41 | 4.01 ± 0.30 |
| MI             | 11 | 41.31 ± 6.82** | 17.49 ± 4.27** | 8.43 ± 0.62** | 6.63 ± 0.65** |
| Atorvastatin   | 9  | 51.93 ± 9.75*  | 22.33 ± 4.69*  | 3.96 ± 0.56*  | 5.82 ± 0.71  |
| HQ             | 12 | 59.66 ± 7.42** | 14.61 ± 6.31** | 7.68 ± 0.57** | 5.58 ± 0.43** |
| DS             | 12 | 56.41 ± 5.31** | 22.98 ± 6.44** | 8.05 ± 0.94** | 5.79 ± 0.86** |
| HQ + DS        | 13 | 67.52 ± 7.89** | 32.81 ± 6.12** | 7.62 ± 0.72** | 5.24 ± 0.63** |

Notes: Values are presented as mean ± SD. **$P < 0.01$ vs the sham group; *$P < 0.05$, **$P < 0.01$ vs MI group; #$P < 0.05$ vs HQ single treatment group; $\Delta P < 0.05$ vs DS single treatment group.

Abbreviations: LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening; LVEDd, left ventricular end-diastolic diameter; LVEDs, left ventricular end-systolic diameter.

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Figure 5 The noninvasive trans-thoracic echo images of different groups. The echo images were taken by VEVO 3100, the most advanced equipment for small animal cardiac function detecting: (A), Sham group; (B), MI group; (C), Atorvastatin group; (D), HQ group; (E), DS group; and (F), HQ + DS group. Measurements of the left ventricle dimensions by M-mode tracing of the left ventricle are used for the calculation of LVEF, LVFS, LVEDd, and LVEDs.
The Synergistic Effects of HQ and DS on Blood Viscosity and Coagulation Indexes in MI Rats

The results of blood viscosity indexes (WBV, PV, HCT, and OTE) and the coagulation indexes (APTT, PT, TT, and FIB) are shown in Table 4. Compared with the sham group, the values of WBV, PV, and OTE were significantly increased ($P < 0.01$); the values of APTT, PT, and TT were significantly shortened ($P < 0.01$), and the FIB value was significantly increased ($P < 0.01$) in the MI group. Compared with the MI group, the values of WBV, PV, and OTE were significantly decreased in four treatment groups (Atorvastatin, HQ single, DS single, and HQ + DS, $P < 0.05$ or $P < 0.01$); the values of APTT, PT, and TT were significantly prolonged, and FIB value was significantly increased ($P < 0.01$).
decreased in two treatment groups (DS single and DS + HQ, \( P < 0.05 \)). Compared with the HQ or DS single treatment group, the values of PV were significantly decreased in the Atorvastatin and HQ + DS treatment groups \( (P < 0.05) \); the values of WBV and OTE were significantly decreased in the HQ + DS treatment group \( (P < 0.05) \).

**Discussion**

CHD is a major public health concern worldwide. Patients with CHD often experience both physical and mental distress. Repeated MI and long-term hypoxia can induce arrhythmia, cardiac remodelling, myocardial asthenia, heart failure, and eventually endanger life.\(^{29}\) Even during
In this study, through network analysis, we determined that HQ and DS share the biological processes of nutrient metabolism, cell proliferation, circulatory system homeostasis, inflammatory response, and oxidative stress. The specific biological processes of HQ include metabolism, cell proliferation, fibrosis, inflammatory response, and oxidative stress. The specific biological processes of DS involve lipid and glucose metabolism, circulation system homeostasis, and mood stability. The experimental evidence indicated that HQ and DS exert synergistic effects on improving cardiac function, alleviating myocardial fibrosis, regulating hyperlipidaemia, and hyperviscosity syndrome. HQ exhibits specific advantages on preventing cardiac remodelling after MI, such as reducing left ventricular dilatation and myocardial cell hypertrophy. DS had specific advantage effects on regulating hypercoagulable and maintain hemodynamic homeostasis.

Hyperlipidaemia, along with hypertension, diabetes, and smoking is a major risk factor of CHD. Lipid accumulation, inflammatory response, oxidative injury, and fibrosis in the arterial wall is the major pathological basis for CHD. Following MI, the modification of the ventricular structure and shape is defined ventricular remodelling (VR). MI induces an intense injury response that ultimately generates a collagen-dominated scar. The excessive fibrotic process is often sustained in a manner detrimental to optimal recovery, resulting in adverse remodelling and impaired cardiac function after MI. Excessive collagen proliferation and deposition in both the infarct and non-infarct zone, myocardial apoptosis in the MI zone, myocardial hypertrophy in the non-infarct zone, and the gradual enlargement of the ventricular chamber leads to haemodynamic changes, generating heart failure. Hypercoagulable status and hyperviscosity syndrome of acute coronary syndromes (ACS) also contributed to hemodynamic changes. The heightened levels
of tissue factor and fibrinogen are related with a “hypercoagulable status” and present a higher incidence of ischemic complications after ACS. Cytokines, particularly circulating IL-1β, IL-6, and IL-8 are upregulated in systemic and chronic inflammatory conditions. Hypercoagulability is an important hallmark of inflammation, and these cytokines are critically involved in abnormal clot formation, erythrocyte pathology, and platelet hyperactivation, and these three cytokines have known receptors on platelets. Drugs of anti-coagulants, anti-hyperviscosity, anti-platelet, and anti-thrombotic should be considered as haemorheological due to the activities in maintaining blood fluidity. The herbal anti-coagulant drugs exhibit fewer side effects and better tolerability and, probably, their selected use in patients with a “hypercoagulable status” may improve the clinical outcome after MI. Plasma and blood viscosities significantly increase in hyperlipidaemic patients. The hyperviscosity syndrome caused by chylomicronaemia is considered the underlying reason for some of the symptoms. Hyperviscosity syndrome is prone to a lower capacity for oxygen delivery to tissues and reduced the efficiency of triglyceride (TG) clearance rate in hyperlipidaemia patients. Therefore, regulating hyperlipidaemia, preventing VR, or improving haemodynamics are critical factors for preventing heart failure after MI.

Our findings indicate that HQ combined with DS had synergistic effects on regulating hyperlipidaemia, preventing VR, improving hemodynamic, and thus preventing heart failure after MI. The synergistic effects of HQ and DS may result from their shared biological processes of improving tissue energy metabolism, promoting myocardial cell proliferation, maintaining circulatory system homeostasis, and inhibiting the inflammatory response and oxidative stress. Compared with Atorvastatin, which exerts significant effects on regulating hyperlipidaemia, HQ combined with DS significantly increased the survival rate of MI rats. Data from clinical trials have demonstrated the efficacy of pharmacologic interventions using statins in reducing the risk of CVD events and total mortality in the ever-growing pool of patients as secondary prevention. However, statins have been associated with many serious side effects and are unable to lower CVD or total mortality. In this study, the mortality rate in the Atorvastatin group was higher than in the untreated MI group. We deduce this may be attributed to the side effects of statins, eg, muscle injury, liver injury, and hyperglycaemia, which might be fatal in the acute phase of MI rats because of the left ventricular myocardium under the infarction and hypoxia conditions.

HQ had specific advantage effects on alleviating cardiac remodelling in terms of cardiac hypertrophy and left ventricular enlargement after MI. This may result from its specific function on promoting cardiac metabolism and myocardial cell proliferation, and inhibiting fibrosis, the inflammatory response, and oxidative stress. Metabolic pathways integrate to support tissue homeostasis and to prompt changes in the cell phenotype. The heart consumes

### Table 4 Blood Viscosity and Coagulation Index Among Groups

| Groups     | n  | WBV (mpa/s) | PV (mpa/s) | HCT (%)   | OTE (Ratio) |
|------------|----|------------|------------|-----------|-------------|
| Sham       | 15 | 4.37 ± 0.35| 1.02 ± 0.47| 46.36 ± 0.31| 0.094 ± 0.007|
| MI         | 11 | 9.57 ± 1.52| 2.19 ± 0.53| 47.09 ± 1.43| 0.203 ± 0.0094|
| Atorvastatin| 9  | 6.28 ± 0.53| 1.21 ± 0.41| 47.52 ± 12.16| 0.132 ± 0.0035|
| HQ         | 12 | 6.39 ± 0.51| 1.69 ± 0.36| 48.74 ± 12.56| 0.131 ± 0.0053|
| DS         | 12 | 6.86 ± 0.58| 1.61 ± 0.42| 46.31 ± 14.12| 0.148 ± 0.0065|
| HQ + DS    | 13 | 5.86 ± 0.41| 1.15 ± 0.38| 47.33 ± 11.27| 0.124 ± 0.0041|
| Groups     | n  | PT (s)     | APTT (s)   | TT (s)    |   | HCT, hematocrit; OTE: oxygen transport efficiency or oxygen delivery index of whole blood = WBV/HCT. APTT, activated partial thromboplastin time; PT, prothrombin time; TT, thrombin time; FIB, fibrinogen. Notes: Values are presented as mean ± SD. **p < 0.01 vs sham group; *p < 0.05, **p < 0.01 vs MI group; *p < 0.05 vs HQ single treatment group; *P < 0.05 vs DS single treatment group.
relatively large amounts of substrate not only to regenerate ATP for contraction but also to sustain biosynthetic reactions for the replacement of cellular building blocks. The cardiac metabolic inefficiency and loss of coordinated anabolic activity metabolism that occurs during pathological stress (eg, MI, pressure overload) are emerging as proximal causes of pathological VR.37 Oxidative stress due to reactive oxygen species (ROS) and the inflammatory molecules IL-1β, IL-6, TNF-α, and NF-kB, participates in several aspects of cardiac remodelling after infarction that includes cardiomyocyte apoptosis, fibrogenic responses, and hypertrophy.48

DS had the specific advantage in maintaining circulation system homeostasis and mood stability. In this study, DS significantly reduced fibrinogen levels, and prolonged PT, TT, and APTT time with specific beneficial effects on regulating hypercoagulable status after MI. Nowadays antithrombotic therapy in the form of antiplatelet plus anticoagulant drugs, represents the main treatment of ACS, and the prognosis of ACS patients is significantly improved, which is particularly helpful in the acute phase of ACS.39 Most cardiovascular events result from a thrombotic complication of atherosclerotic lesions. In arterial vessels such as the coronary bed, an interrelationship of haemostatic, coagulation, and fibrinolytic factors is implicated. Fibrinogen circulates in plasma as a dimer and plays an important role in coagulation and haemostasis as well as inflammation, and is a well-established risk factor/ marker for cardiovascular diseases.49

The limitations of this study can be attributed to three aspects. Firstly, patients with CHD often experience both physical and mental distress. According to the network analysis, DS had the biological process of maintaining mood stability. It would be meaningful if the concentration of serotonin, dopamine, and melatonin in the serum or brain would be studied in the future. Secondly, conventional doses of HQ and DS were used in this study. Herbal medicine often has a positive dose-effect relationship.50 A high dose, conventional dose, and low dose of HQ and DS on treating CHD should be defined in the future. Thirdly, some signalling pathways, such as transforming growth factor β/Smad pathways, which are closely associated with myocardial hypertrophy, remodelling, and fibrosis should be further studied.51,52 This would help to clarify the underlying mechanism of HQ and DS activity on CHD.

**Conclusion**

HQ combined with DS exerted synergistic effects on regulating hyperlipidaemia, preventing VR, improving haemodynamics, and thus preventing heart failure after MI. HQ had the specific advantage of alleviating cardiac remodelling after MI, while DS specifically alleviated hypercoagulability status after MI. Our results show that HQ and DS not only achieve synergistic effects but also exert complementary effects on MI. We recommend the combination of HQ and DS in treating CHD.

**Abbreviations**

HQ, Huang Qi, *Astragalus mongholicus*; DS, Dan Shen, *Salvia miltiorrhiza*; CHD, coronary heart disease; MI, myocardial infarction; LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening; LVEDd, left ventricular end-diastolic diameter; LVEDs, left ventricular end-systolic diameter; CSA, cross-sectional area; CVD, cardiovascular disease; VR, ventricular remodelling; TCM, traditional Chinese medicine; TG, triglycerides; Chol, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein-cholesterol; WBC, whole blood viscosity; PV, plasma viscosity; HCT, hematocrit; OTE, whole blood viscosity; APTT, activated partial thromboplastin time; PT, prothrombin time; TT, thrombin time; FIB, fibrinogen; ACS, acute coronary syndromes; WGA, wheat germ agglutinin.

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**Disclosure**

The authors declare that there are no conflicts of interest regarding the publication of this paper.

**References**

1. Panagiotakos DB, Notara V, Kouvari M, Pitsavos C. The Mediterranean and other dietary patterns in secondary cardiovascular disease prevention: a review. *Curr Vasc Pharmacol*. 2016;14(5):442–451. doi:10.2174/15701611499160719104731

2. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. *Circulation*. 2017;135(10):e146–e603. doi:10.1161/CIR.0000000000000485
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1. Wu H, Tian J, Dai D, et al. Efficacy and safety assessment of traditional Chinese medicine for metabolic syndrome. BMJ Open Diabetes Res Care. 2020;8(1):e001181. doi:10.1136/bmjdrce-2020-001181

2. Wang Q. Clinical efficacy evaluation of Radix astragali in the treatment of coronary heart disease patients with angina pectoris. J Zhejiang Med Coll. 2000;23(2):147–148.

3. Li YF, Du YW, Wu SX, Ma JJ, Li M. A multi-center randomized controlled clinical study of the efficacy and safety of danshen injectable powder in treating patients with coronary artery disease and angina pectoris/syndrome of blood stasis. China Foreign Med Treat. 2014;11:131–132.

4. Zhang WQ, Luy SC, Zhu YP, Zhang JP. Review of researches on Radix astragali in treating patients with coronary artery disease and blood stasis syndrome. J Traditional Chin Med. 2021;62(12):1092–1096. doi:10.13288/j.j-11626-r.2021.12.015

5. Lv YH, He YC, Yang J, Xu L, Liu HX, Zheng QS. Study of the symptoms scale for evaluating changes in patients with coronary angina pectoris and qi-deficiency combined with stagnation of blood in traditional Chinese medicine. Chin J Clin Pharmacol Ther. 2008;13(7):786–791.

6. Chen KJ, Shi DZ, Fu CG, et al. Diagnostic criteria of blood stasis syndrome of coronary heart disease. Chin J Integr Med. 2016;36(10):1162. doi:10.7661/CJIM.2016.10.1162

7. Wang WQ, Zhao GY, Huang Z. Correlation analysis between angiography and blood stasis syndrome. J Zhejiang Med Coll. 2021;53(12):62–66. doi:10.13457/j.cnki.jzmc.2021.12.016

8. Yang J, Tian X, Zhang Q, Wang X, Song WL. Observation on curative effects of conventional treatment combined with Qishen Yiqi dropping pill in treating chronic heart failure of coronary heart disease. Tianjin TCM. 2021;38(07):863–867. doi:10.11656/j.issn.1672-1519.2021.07.11

9. Zhu ZF. The Clinical observation on 62 cases of coronary heart disease treated by Warming Yang and promoting blood circulation. J Anhui Health Vocational Tech Coll. 2017;16(2):37–39.

10. Han LL, Lu ZW, Meng XL, Yu J, Guo WX. To talk about the effect of coronary artery disease by Astragalus. CJGTMTC. 2007;22(2):53–55.

11. Fathiazad F, Tamarzadeh N, Alsos D, Garjani A, Vaez H. The effect of ginsenoside Rb1 against gastric cancer based on network pharmacology. Drug Des Devel Ther. 2019;13:5109–5118. doi:10.2147/DDDT.S270757

12. Fu QW, Zhu J, Wang B, et al. LINC02288 promotes chondrocyte apoptosis and inflammation through miR-374a-3p targeting RTN3. J Gene Med. 2021;23(5):e3314. doi:10.1002/jgm.3314

13. Gömöri K, Szabados T, Kenyeres É, et al. Cardioproteective effect of novel matrix metalloproteinase inhibitors. Int J Mol Sci. 2020;21(9):1690. doi:10.3390/ijms21091690

14. Merino H, Singla DK, Tang YL. Notch-1 mediated cardiac protection following embryonic and induced pluripotent stem cell transplantation in doxorubicin-induced heart failure. PLoS One. 2014;9(7):e101024. doi:10.1371/journal.pone.0101024

15. Liu KM, Zhang HH, Wang YN, et al. Wild-type p53-induced phosphatase 1 deficiency exacerbates myocardial infarction-induced ischemic injury. Chin Med J. 2017;130(11):1333–1341. doi:10.4103/0366-9999.206533

16. Nemeth N, Alexy T, Furka A, et al. Inter-species differences in hematocrit to blood viscosity ratio. Biochemistry. 2009;46(2):155–165. doi:10.2332/BIR.2009-0533

17. Xia Y, Zhang F, Zhao S, et al. Adiponectin determines farnesoid X receptor agonism-mediated cardioprotection against post-infarction remodelling and dysfunction. Cardiovasc Res. 2018;114(10):1335–1349. doi:10.1093/cvr/cvy093

18. Ma Y, Lv W, Gu Y, Yu S. 1-Deoxyxojirimycin in Mulberry (Morus indica L.) Leaves ameliorates stable angina pectoris in patients with coronary heart disease by improving antioxidant and anti-inflammatory capacities. Front Pharmacol. 2019;10:569. doi:10.3389/fphar.2019.00569

19. Fukushima K, Tominaga K, Nagashima K, et al. Gastroduodenal ulcer bleeding in elderly patients on low dose aspirin therapy. World J Gastroenterol. 2018;24(34):3908–3918. doi:10.3748/wjg.v24.i34.3908

20. Tournadre A, Statins, myalgia, and rhabdomyolysis. Joint Bone Spine. 2020;87(1):37–42. doi:10.1016/j.jbspin.2019.01.018

21. Xu Y, Hu H, Li Y, et al. Effects of hufuxin formula on the arterial functions of patients with coronary heart disease. Pharm Biol. 2019;57(1):13–20. doi:10.1080/13880209.2018.1561726

22. Venkatesh K, Deepak DC, Venkatesha VT. Escalation of coronary atherosclerosis in younger people by comparison of two autopsy studies conducted a decade apart. Heart Views. 2018;19(4):128–136. doi:10.4103/HEARTVIEWS.HEARTVIEWS_49_17

23. Wang HH, Garruti G, Liu M, Portincasa P, Wang DQ. Cholesterol and lipoprotein metabolism and atherosclerosis: recent advances in reverse cholesterol transport. Ann Hepatol. 2017;16(Suppl.1):s3–105. doi:10.5604/01.3001.0010.5495

24. Snider JC, Riley LA, Mallory NT, et al. Targeting 5-HT(2B) receptor signaling prevents border zone expansion and improves microstructural remodeling after myocardial infarction. Circulation. 2021;143(13):1317–1330. doi:10.1161/CIRCULATIONAHA.120.051517

25. Chistjakov DA, Orekhov AN, Bobryshev YV. The role of cardiac fibroblasts in post-myocardial heart tissue repair. Exp Mol Pathol. 2016;101(2):231–240. doi:10.1016/j.yexmp.2016.09.002

26. Chen H, Dong Y, He X, Li J, Wang J. Paeoniflorin improves cardiac function and decreases adverse postinfarction left ventricular remodeling in a rat model of acute myocardial infarction. Drug Des Devel Ther. 2018;12:823–836. doi:10.2147/DDDT.S163405
39. Campo G, Pavasini R, Pollina A, TEBaldi M, Ferrari R. Coagulation factors and recurrence of ischemic and bleeding adverse events in patients with acute coronary syndromes. *Thromb Res.* 2013;132(2):151–157. doi:10.1016/j.thromres.2013.06.007

40. Bester J, Pretorius E. Effects of IL-1β, IL-6 and IL-8 on erythrocytes, platelets and clot viscoelasticity. *Sci Rep.* 2016;6:32188. doi:10.1038/srep32188

41. Liao F. Herbs of activating blood circulation to remove blood stasis. *Clin Hemorheol Microcirc.* 2000;23(2–4):127–131. PMID: 11321431.

42. Kassner U, Dippel M, Steinhagen-Thiessen E. Severe hypertriglyceridemia: diagnostics and new treatment principles. *Internist (Berl).* 2017;58(8):866–876. doi:10.1007/s00108-017-0234-z

43. Wu HC, Lee LC, Wang WJ. Plasmapheresis for hypertriglyceridemia: the association between blood viscosity and triglyceride clearance rate. *J Clin Lab Anal.* 2019;33(2):e22688. doi:10.1002/jcla.22688

44. Ward S, Lloyd Jones M, Pandor A, et al. A systematic review and economic evaluation of statins for the prevention of coronary events. *Health Technol Assess.* 2007;11(14):1–160, iii–iv. doi:10.3310/hta11140

45. Fung BM, Heinzle ER, Wong AL. Statin-associated necrotizing autoimmune myositis complicated by an uncommon adverse effect to treatment. *Case Rep Med.* 2019;2019:4601304. doi:10.1155/2019/4601304

46. Ravnokov U, Alahbudgaela A, De Lorgeril M, et al. The new European guidelines for prevention of cardiovascular disease are misleading. *Expert Rev Clin Pharmacol.* 2020;13(12):1289–1294. doi:10.1080/17512433.2020.1841635

47. Gibb AA, Hill BG. Metabolic coordination of physiological and pathological cardiac remodeling. *Circ Res.* 2018;123(1):107–128. doi:10.1161/CIRCRESAHA.118.312017

48. Hori M, Nishida K. Oxidative stress and left ventricular remodelling after myocardial infarction. *Cardiovasc Res.* 2009;81(3):457–464. doi:10.1093/cvr/cvn335

49. Drouet L, Bal Dit Sollier C. Besides fibrinogen, are haemostatic, coagulation and/or fibrinolytic parameters predictors or markers of the risk of cardiovascular events? *Therapie.* 2005;60(2):137–147. doi:10.2515/therapie:2005018

50. Luo R, Sun X, Shen F, Hong B, Wang Z. Effects of high-dose rosuvastatin on ventricular remodelling and cardiac function in ST-segment elevation myocardial infarction. *Drug Des Devel Ther.* 2020;14:3891–3898. doi:10.2147/DDDT.S254948.eCollection.

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