

Mechanism research of Salvia miltiorrhiza on treating myocardial ischemia reperfusion injury according to network pharmacology combined with molecular docking technique

Zhiyan Jiang, PhD^{a,b,c,*}

Abstract

Myocardial ischemia reperfusion injury (MIRI) is a kind of complicated disease with an increasing incidence all over the world. Danshen was shown to exert therapeutic effect on MIRI. However, its chemical and pharmacological profiles remain to be elucidated. Network pharmacology was applied to characterize the mechanisms of Danshen on MIRI.

The active compounds were screened from the online database according to their oral bioavailability and drug-likeness. The potential proteins of Danshen were collected from the TCMSP database, whereas the potential genes of MIRI were obtained from Gene Card database. The function of gene and pathways involved were researched by GO and KEGG enrichment analysis. The compounds-targets and protein–protein interaction networks were constructed by Cytoscape software. The affinity between active components and potential targets was detected by molecular docking simulation.

A total of 202 compounds in Danshen were obtained, and 65 were further selected as active components for which conforming to criteria. Combined the network analysis and molecular docking simulation, the results firstly demonstrated that the effect of Danshen on MIRI may be realized through the targeting of vascular endothelial growth factor A, interleukin-6, and AKT1 by its active components tanshinone IIA, cryptotanshinone, and luteolin. The main regulatory pathways involved may include PI3K/ Akt signaling pathway, HIF-1 signaling pathway, and interleukin-17 signaling pathway. The present study firstly researched the mechanism of Danshen on MIRI based on network pharmacology.

The results revealed the multicomponents and multi-targets effects of Danshen in the treatment of MIRI. Importantly, the study provides objective basis for further experimental research.

Abbreviations: CAHD = coronary atherosclerotic heart disease, CHD = coronary heart disease, CPT = cryptotanshinone, DS = Danshen, GO = Gene Ontology, MIRI = myocardial ischemia reperfusion injury, PPI = protein–protein interaction, TSA = tanshinone IIA.

Keywords: Danshen, molecular docking, molecular mechanisms, myocardial ischemia reperfusion injury, network pharmacology

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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1. Introduction

Cardiovascular diseases have an accumulating incidence worldwide caused mainly by the change of people's lifestyle. High fat diet and less exercise often increase the burden of heart, which leads to the occurrence of cardiovascular disease.^[1-3] Notably, cardiovascular diseases, especially the coronary heart disease (CHD), have a high mortality rate in urban population.^[4,5] It is generally realized that the pathogenesis of CHD is closely related to coronary atherosclerosis. In pathological condition, the blocked coronary blood flow will lead to myocardial ischemia, resulting in myocardial tissue damage or dysfunction, further inducing acute myocardial infarction and endangering life. Prompt restoration of blood flow to the ischemic myocardium can limit the infarct size, reduce mortality, and avoid further myocardial injury. Actually, thrombolytic therapy and coronary intervention are indeed the most effective treatment for reducing the size of a myocardial infarct and improving the clinical outcome. Unfortunately, reconstructing blood flow to the heart can also cause cardiovascular damage, which is called myocardial ischemia/reperfusion injury (MIRI).^[6-8] Coping with adverse outcomes caused by MIRI, there is no effective treatment at present, and reducing the abnormal apoptosis of myocardial cells caused by ischemia/reperfusion and preventing from myocardial infarction are the main purposes of treatment.

Salvia miltiorrhiza (Danshen in Chinese) is the dried root and rhizome of the labiaceae plant Salvia miltiorrhiza Bge. Studies have shown that Danshen (DS) is the most widely used Chinese herbal medicine for the treatment of ischemic heart disease and ischemic stroke.^[9,10] DS is a kind of multi-targets herbal medicine, which can be used alone or combined with other herbal medicine for the treatment of cardiovascular and cerebrovascular diseases.^[11–13] Especially, DS and its compound preparation have been reported that take crucial part in the improvement of symptoms of MIRI in vivo and invitro experiments.^[14,15] Indeed, >200 compounds have been identified from DS, demonstrating its multi-target pharmacological action; however, it is pretty difficult to clarify these complex pharmacological mechanisms by the conventional research strategies.

For the view of chemistry, traditional Chinese herbal medicine are complicate systems with multiple targets as well as interactions among their substances.^[16] Different from western medicine of "one target, one drug," herbal medicines always exert multi-targets. This trait is a double-edged sword. Studies have shown that multi-target drugs can avoid the shortcomings of single-target drugs, such as single targeting and easy drug resistance.^[17,18] However, due to the complex characteristics of multi-target drugs, it is difficult to clarify the mechanism of action. Network pharmacology combines the systems biology with pharmacokinetic and pharmacodynamics to research medicines, targets and their pharmacological activities.^[19] Systematically, network pharmacology is on the basis of the interactions of disease-gene-targets-drug networks to observe the effect of herbs on diseases. Therefore, network pharmacology is realized as a promising method to cast light upon traditional Chinese herbs or formulas.^[20]

In the present study, I used computational tools and resources to investigate the pharmacological network of DS on MIRI to predict the active compounds and potential protein targets. Molecular docking approach was applied to detect the interactions between activated compounds and protein targets. The detailed technical strategy of the present study was shown in Figure 1.

2. Methods

2.1. Screening of active compounds and targets

Based on the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP, https://tcmspw. com/tcmsp.php),^[21] the chemical components of DS were searched, and the compounds with oral bioavailability (OB) \geq 30% and drug-likeness (DL) \geq 0.18 were collected. Oral bioavailability (OB), which is the relative amount of a drug entering the bloodstream in prototype form after oral administration, is a key indicator of drug bioactivity and can be used as a screening value of \geq 30%. DL is based on the similarity principle that generally similar molecules should have similar biological activity and DL ≥0.18 is the selection criteria for compounds.^[22,23] At the same time, their action targets were screened in TCMSP. And then, the targets were transformed into the official gene symbols using R software according to the Uniprot (https://www.uniprot.org/), one of the most informative and resourceful protein databases.

2.2. Collection of overlapping genes of "MIRI-DS"

MIRI-related genes of homo-sapiens were collected from online database: Gene Cards is a searchable, integrative database that provides comprehensive information on all annotated and predicted human genes (https://www.genecards.org). The overlapping genes between MIRI-related genes and targets of active compounds were obtained using R software. A venn diagram was drew by R software to show the association between MIRI and active compounds related genes.

2.3. Creating a protein-protein interaction network and screening of hub genes

Importing the overlapping genes of "MIRI-DS" into the STRING online database (www.string-db.org/), a well-known database for protein–protein interaction (PPI) analysis,^[24] to get the interactions between proteins. The results were then visualizing



Table 1

Information of active compounds in Danshen with OB $\geq\!\!30\%$ and DL $\geq\!\!0.18.$

| MA.20.0101 1.2,8-1-Parkprotensitione 220.34 8,76 0.85 MA.20.01058 Parkfarsker 41.77 45.85 0.76 MA.20.0171 Parkfarsker 300.34 8,51 0.75 MA.20.01727 Stabili 300.34 8,51 0.75 MA.20.01727 Stabili 300.34 8,51 0.75 MA.20.01727 Stabili 300.34 8,51 0.75 MA.20.01600 Distabili 300.34 8,51 0.76 MA.20.01600 Distabili 300.35 0.76 0.75 MA.20.01600 Distabili 30.76 0.83 0.77 MA.20.01600 Distabili 30.77 0.78 <th>Mol ID</th> <th>Mol Name</th> <th>MW</th> <th>OB (%)</th> <th>DL (%)</th> | Mol ID | Mol Name | MW | OB (%) | DL (%) |
|--|-----------|--|--------|--------|--------|
| MEDD0169 Professtelsel 412.77 43.83 0.76 MED00171 Professt-59-resolution 414.79 85.81 0.75 MED00182 Exploit 270.3 45.46 0.23 MED001825 Darly transmission 12.0 45.46 0.23 MED002551 Darly transmission 12.0 45.76 0.47 MED00565 Darly transmission 226.25 98.16 0.25 MED005056 Landorin 226.25 98.16 0.25 MED007056 5.6 Ulty drowy - Aspray - Adve 0.25 0.42 0.4 | MOL001601 | 1,2,5,6-Tetrahydrotanshinone | 280.34 | 38.75 | 0.36 |
| MD.00171 Porfarst 5-on-Stells d. 414.79 36.91 0.75 MD.002222 Supplit 300.48 301.48 301.48 0.28 MD.002225 Supplit 300.48 301.48 301.48 0.28 MD.002276 Baralin 446.39 446.39 0.16 0.25 MD.002078 Baralin 446.39 0.16 0.25 MD.002078 Baralin 446.39 0.16 0.25 MD.002078 Baralin 301.43 0.24 0.26 0.23 0.26 MD.0020708 C.4.Maryor Synthistone 16 310.37 44.33 0.04 MD.0020708 C.4.Maryor Synthistone 16 310.37 44.33 0.24 MD.0020708 C.4.Maryor Synthistone 16 312.29 44.02 0.24 MD.0020708 C.4.Maryor Synthistone 16 0.31 0.26 0.24 0.24 MD.0020708 C.4.Maryor Synthistone 16 312.29 0.44 0.24 0.24 0.24 0.24 0.24 0.24 0.24 | MOL001659 | Poriferasterol | 412.77 | 43.83 | 0.76 |
| M0L001942 bioingreation 270.3 45.46 0.23 M0L00292 Suppl 300.48 35.11 0.28 M0L00291 Darlydicatistione II A 292.25 43.76 0.4 M0L00292 Darlydicatistione II A 292.25 35.16 0.26 M0L002060 Landin 242.3 35.16 0.26 M0L002064 Sp.61/mixerup * tecrnyl+11-dimethyl 2.3-dingkrophreamthren-4-one 298.41 40.66 0.23 M0L007056 Sp.61/mixerup * tecrnyl+1-dimethyl 2.3-dingkrophreamthren-4-one 298.41 44.93 0.43 M0L007056 Sa-Hydroxylestimume IIn 310.37 44.93 0.44 M0L007058 Sa-Hydroxylestimume IIn 310.37 44.93 0.44 M0L007059 Cy-14-Mixeryl-3-mitoxylestimylestimume 296.23 73.44 0.23 M0L007051 General Hydroxynehylestimume 294.23 23.16 0.44 M0L007051 General Hydroxynehylestimume 294.23 23.16 0.44 M0L007052 General Hydroxynehylestimume 294.24 2 | MOL001771 | Poriferast-5-en-3beta-ol | 414.79 | 36.91 | 0.75 |
| M0.00222 Supid 300.48 36.11 0.28 M0.002275 Bacalin 446.39 447.3 0.25 M0.002075 Bacalin 446.39 0.25 61.8 0.25 M0.002075 Bacalin 261.3 0.25 0.16 0.25 M0.002076 Latentin 261.3 0.25 0.16 0.25 M0.002076 S.5.Dhydaxy-Praporph_11-dimethy 4.3.dhydaphenarthren-4-one 268.41 0.37 4.43 0.44 M0.002076 S.4.Hydrotoghamy 7-tydroxy-bronzhan-4-ylacnylc acid 312.29 48.24 0.23 M0.002075 S.4.Hydrotydarthrone 16 0.31 0.44 0.42 0.4 M0.002075 S.4.Hydrotydarthrone 16 27.4 44.64 0.12 0.44 M0.002075 S.4.Hydrotydarthrone 16 284.32 30.16 0.4 M0.002075 S.4.Hydrotydarthrone 16 284.32 30.16 0.4 M0.002075 Prawadistin a 388.49 10.3 2.6 0.4 M0.002075 Prawadistin a <td>MOL001942</td> <td>Isoimperatorin</td> <td>270.3</td> <td>45.46</td> <td>0.23</td> | MOL001942 | Isoimperatorin | 270.3 | 45.46 | 0.23 |
| M40.00251 Dehydrotanshinore II.A 292.3 4.3.76 0.4.3 M40.00276 Baicalin 282.4 61.85 0.2.6 M40.00276 Baicalin 282.5 36.16 0.2.5 M40.00276 Camping in any Action and Action a | M0L002222 | Sugiol | 300.48 | 36.11 | 0.28 |
| ML0.02776 Bascalin 446.3 9 0.12 0.75 ML0.00060 Lunchin 282.24 61.85 0.26 ML0.00060 Lunchin 282.52 36.16 0.25 ML0.00076 5.6-Unprices/-recorp.1.1Gimethyl-2.3-dihydrophernerthren-4-one 286.31 0.35 0.37 0.43 ML0.00716 5.2-Unprices/-recorp.1.1Gimethyl-2.3-dihydrophernerthren-4-one 286.34 0.43 0.44 0.44 ML0.007164 G.5.32(2): A.4-Unprices/-France/op/1recorp.1-rec | MOL002651 | Dehydrotanshinone II A | 292.35 | 43.76 | 0.4 |
| MLD.00569 Digalate 228.25 95.16 0.26 MLD.00824 n=amrth 426.8 39.51 0.76 MLD.001704 2-legringl-5-methylphenanthrens, 3/-doine 296.41 33.77 0.23 MLD.001704 2-legringl-5-methylphenanthrens, 3/-doine 296.41 33.77 0.23 MLD.001704 2-legringl-5-methylphenanthrens, 3/-doine 296.41 33.74 44.83 0.44 MLD.001704 2-legringl-5-methylphengl-6-phenoduran-4-fylacylic acid 310.37 44.84 0.37 MLD.001705 5-ohythyl-6-soekyl shardshigel methyl celer 36.84 46.78 0.41 MLD.001705 5-ohythyl-6-soekyl shardshigel methyl celer 278.32 37.07 0.36 MLD.001705 7-soekyl shardshigel methyl celer 298.34 65.74 0.41 MLD.001705 7-soekyl shardshigel methyl celer 330.46 11.32 0.44 MLD.001706 7-methylphenathylphen | MOL002776 | Baicalin | 446.39 | 40.12 | 0.75 |
| ML0.00006 Lutabin 286.25 36.16 0.25 ML0.000764 5.6-Ditytcov-7-isopropl-1, finithly-2,3-ditytcophenanthren-4-one 296.41 33.17 0.29 ML0.000764 5.6-Ditytcov-7-isopropl-1, finithly-2,3-ditytcophenanthren-4-one 296.41 33.17 4.49 0.44 ML0.00705 5.6-Ditytcov-1-isopropl-1, finithly-2,3-ditytcov-benzofuran-4-ylacytic acid 310.17 4.49 0.44 ML0.007050 2.4-Hybrany-3-methoophenyl-5-G-hytrosopropl-7-methooy-3-benzofuran-cahoacidehyde 36.4 42.6 0.43 ML0.007050 2.4-Hybrany-3-methoophenyl-5-G-hytrosopropl-7-methooy-3-benzofuran-cahoacidehyde 326.4 42.6 0.43 ML0.007050 3.5-Debt-hydroxoprople/strainside methyl ester 296.3 23.1 0.64 ML0.007051 Methylanotrashing innone 273.2 37.07 0.86 ML0.007051 Praxwalakin b 330.46 110.32 0.44 ML0.007054 Praxwalakin b 330.41 16.6 7.4 0.46 ML0.007054 Praxwalakin b 330.41 6.6 7.4 0.45 ML0.0070705 | MOL000569 | Digallate | 322.24 | 61.85 | 0.26 |
| M0.00824 - arannin 426.5 G-Dhytony-7-iscoropy-1, 1-cimethyl-2,3-dthytophenanthren-4-one 286.41 4377 428 408 4023 4000704 2-locoropy-1-4-methylehendrum-4-one 286.41 437.27 4.493 0.444 40007048 [C-3-2,2-4-Dhytophytopy-7-backfuran-4-ylacrylic add 312.29 4.624 0.31 40007048 [C-3-2,2-4-Dhytophytopy-1-7-methog-hendrum-4-ylacrylic add 312.29 4.624 0.31 40007051 2-4-bitytopy-methog-line hybropy-1-7-methog-3-benzofuran-arboaddehyde 286.39 4.46 4.69 0.71 4.70 4.70 4.70 4.70 4.70 4.70 4.70 4.70 | M0L000006 | Luteolin | 286.25 | 36.16 | 0.25 |
| MAL002036 5.6.019ydrowy3-reporpsyl1.1-dimethy2-3.4-done 284.34 40.86 0.23 30.000704 3.6-4ydroxy4rashinone lia 34.000 7.4.4.9(acytory4 5.4.4.9)(acytory4 5.4. | MOL006824 | α-amyrin | 426.8 | 39.51 | 0.76 |
| MULD07041 2-biograph-6-methylphenathrene 3-4-done 24434 40.86 0.23 MULD07048 E3-4-biographenthylb-6-fahydroxyberxoluran-4-yllacrylic acid 310.37 44.83 0.44 MULD07049 E3-4-biographenthylb-6-f3-hydroxyberxoluran-4-yllacrylic acid 326.78 0.44 MULD07050 2-(4-hydroxy3-methoxybertylb-6-f3-hydroxypropl/5-methoxy-3-berxoluran-carboxaldehyde 366.4 62.78 0.4 MULD07050 2-(4-hydroxy3-methoxybertylb-f8-f3-hydroxypropl/5-methox-3-berxoluran-carboxaldehyde 366.4 62.78 0.4 MULD07051 Ferrystatisninione 294.52 37.17 0.36 MULD07054 Ferrystatisninione 294.52 37.17 0.36 MULD07054 Persentalistin 37.17 0.36 57.4 0.44 MULD07054 Persentalistin 37.17 0.36 57.4 0.44 MULD07058 Persentalistin 37.17 0.36 57.4 0.44 MULD07059 Persentalistin 37.17 0.36 57.4 0.44 MULD07070 Restanelinone 39.14 9.4 <td>M0L007036</td> <td>5,6-Dihydroxy-7-isopropyl-1,1-dimethyl-2,3-dihydrophenanthren-4-one</td> <td>298.41</td> <td>33.77</td> <td>0.29</td> | M0L007036 | 5,6-Dihydroxy-7-isopropyl-1,1-dimethyl-2,3-dihydrophenanthren-4-one | 298.41 | 33.77 | 0.29 |
| MULLU/145 36-r-BytacyArabition is 310.37 44.33 0.14 MULD/145 C3-12 (2.4) 48.24 0.31 MULD/145 C3-12 (2.4) 48.24 0.31 MULD/145 C4-Hytdrox-prophyto-PhytocybercyU-7-methoxy-3-berzofurancarbocaldehyde 656.4 6.6 MULD/145 C4-Hytdrox-sherzofuran-4-yflacryfic acid 286.24 0.4 MULD/145 C4-Hytdrox-sherzofuran-4-yflacryfic acid 280.24 7.3.4 MULD/145 C4-Hytdrox-sherzofuran-4-yflacryfic acid 280.24 7.3.4 MULD/145 C4-Hytdrox-sherzofuran-10, 11-dione 280.24 0.4 MULD/145 C4-Hytdrox-sherzofuran-10, 11-dione 280.24 0.4 MULD/145 Przewiajkin b 280.24 0.4 1.0 2.4 MULD/145 Przewiajkin b 280.44 1.0 4.6 0.6 MULD/145 Przewiajkin b 280.44 1.0 4.6 0.6 MULD/145 Przewiajkin b 280.44 1.0 4.6 0.6 MULD/145 Przewiajkin b 280.44 <td>MOL007041</td> <td>2-Isopropyl-8-methylphenanthrene-3,4-dione</td> <td>264.34</td> <td>40.86</td> <td>0.23</td> | MOL007041 | 2-Isopropyl-8-methylphenanthrene-3,4-dione | 264.34 | 40.86 | 0.23 |
| MULD/1048 [E]-3 (2-13, 3-11)/(trio)/performance/provide 200 312.29 48.24 0.31 MULD/1048 [E]-3 (2-13, 3-11)/(trio)/(tri)/(trio)/(trio)/(trio)/(tri)/(trio)/(trio)/(trio)/(trio | MOL007045 | 3α -Hydroxytansninone lla | 310.37 | 44.93 | 0.44 |
| MILLD/149 4-Methylenemintrine 28-35 U.23 MULD0705 E-o-Syring/-E-o-actely stanchised methyle ster 622.64 42.64 0.4 MULD07051 E-o-Syring/-E-o-actely stanchised methyle ster 229.12 23.4 0.4 MULD07058 3-beta-hydroxymethylinetanshiquinone 278.32 37.10 0.36 MULD07068 Praxwaginone 278.32 35.70 0.45 MULD07068 Praxwaginone I 330.46 11.0.12 0.44 MULD07068 Praxwaginone I 280.3 55.7 0.4 MULD07070 (S.YPe, F.7 bhydroxy-1, 6-dimethyl-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-dione 312.34 43.13 10.45 MULD07070 (S.YPe, F.7 bhydroxy-1, 6-dimethyl-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-dione 312.34 43.13 10.45 MULD07070 Sareod 398.45 50.7 0.45 MULD07070 Sareod 398.45 50.7 0.45 MULD07071 Sareod 398.45 50.7 0.45 MULD07078 Caphydroxy-1, 6-dimethyl-8,9-dihydro-7H-naphtho[8,7-g | MOL007048 | (E)-3-[2-(3,4-Dinydroxypnenyi)-7-nydroxy-benzoturan-4-yijacrylic acid | 312.29 | 48.24 | 0.31 |
| MCLD070b1 24+6+70/dxy3-5+10e1000/gb00/gb1-7+10e100y-5-bet/2010a1catubadeby0e 626.64 66.69 07.71 MCLD07051 Furmyfarshinone 294.32 23.16 0.41 MCLD07051 Furmyfarshinone 294.32 37.07 0.36 MCLD07051 Methyfuendarshinquinone 294.32 37.07 0.36 MCLD07051 Methyfuendarshinquinone 294.32 30.46 110.32 0.44 MCLD07064 Przevasikin a 393.46 110.32 0.44 MCLD070768 Przevagilione e 292.3 62.24 0.41 MCLD070768 Przevagilione e 296.34 65.74 0.4 MCLD070771 Przevagilione e 308.35 62.47 0.45 MCLD07078 Salared 308.48 57.95 0.56 MCLD07078 Salared 308.44 59.97 0.52 MCLD07078 Salarend 306.41 59.97 0.52 MCLD07078 Salarend 308.41 59.97 0.52 MCLD070780 Captidars | MOL007049 | 4-Methylenemiltirone | 266.36 | 34.35 | 0.23 |
| MILLD/ICII b-b-synthyle-b-datagy statistication in the statistin the statistication in the statistication in the s | MOL007050 | 2-(4-Hydroxy-3-methoxyphenyl)-5-(3-hydroxypropyl)-7-methoxy-3-benzolurancarboxaldenyde | 300.4 | 02.78 | 0.4 |
| MILLOURDS PUILIPIARE SINUALE 240.23 7.3.44 0.42 MILLOURDS Select - jointy converting line learneshing income 248.22 22.16 0.41 MILLOURDS Select - jointy converting line learneshing income 248.22 32.16 0.41 MILLOURDS Prawaksion a 398.44 37.11 0.65 MILLOURDS Prawaksion b 230.44 110.32 0.44 MILLOURDS CS.74 0.71 0.75 0.74 0.41 MILLOURDS CS.74 0.71 Prawaksion b 249.23 62.24 0.41 MILLOURDS CS.74 0.75 C.70 0.45 0.45 0.41 MILLOURDS CS.74 0.41 0.45 0.44 0.45 0.44 MILLOURDS CS.74 0.43 306.35 52.47 0.45 0.44 0.41 MILLOURDS Darsheen 0 304.44 0.75 0.56 0.45 0.42 0.38 0.38 MILLOURDS Darsheen 0 304.51 | MOL007051 | 6-0-Synngyl-8-0-acetyl snanzniside metnyl ester | 028.04 | 40.09 | 0.71 |
| microlitobs 296.22 32.10 0.31 MCL07063 Przewalskin a 338.49 37.11 0.65 MCL07063 Przewalskin b 300.46 11.32 0.44 MCL07064 Przewalskin b 300.46 11.32 0.44 MCL070766 Przewalunne b 296.34 55.74 0.41 MCL07070 (RS,7R+6,7-20hydroxy-1.6-dimethyl-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-dione 312.34 40.31 0.46 MCL007071 Sclarend 308.56 43.67 0.21 MCL007072 Sclarend 308.56 43.67 0.52 MCL007071 Darshenol B 306.41 56.97 0.52 MCL007081 Darshenol A 36.41 58.24 0.48 MCL007085 Salvienne 292.4 30.88 0.55 MCL007095 Darshenol A 36.41 58.84 0.49 MCL007096 Darshenol A 36.41 58.84 0.52 MCL007097 Darshenol A 36.86 0.32 48.68 | MOL007050 | FUTTI yildi ishinone 2. Pata budrow mathullanatanabiguinana | 290.20 | 73.44 | 0.42 |
| miclosoft 216.22 37.01 0.36 MICLOSOFGE Przewalskin a 386.49 37.11 0.66 MICLOSOFGE Przewalskin b 292.3 62.24 0.41 MICLOSOFGE Przewalskin b 292.3 62.24 0.41 MICLOSOFGE Przewalurione B 292.3 62.24 0.41 MICLOSOFGE Przewalurione B 292.3 62.24 0.41 MICLOSOFGE Przewalurione B 292.4 40.31 0.45 MICLOSOFGE Przewalurione F 308.55 52.47 0.45 MICLOSOFOF Tashinaldehyde 308.35 52.47 0.45 MICLOSOFOF Tashinaldehyde 306.41 36.88 0.55 MICLOSOFOR Salvienone 296.39 52.34 0.4 MICLOSOFOR Desoynecorpotranshinone 298.41 49.4 0.29 MICLOSOFOR Desoynecorpotranshinone 298.43 64.67 0.21 MICLOSOFOR Desoynecorpotranshinone 298.45 36.61 0.38 <td>MOL007059</td> <td>S-Dela-HyuloxyHeliiyilellelalisiilquilloile Mathulanatanchinauinana</td> <td>294.32</td> <td>32.10</td> <td>0.41</td> | MOL007059 | S-Dela-HyuloxyHeliiyilellelalisiilquilloile Mathulanatanchinauinana | 294.32 | 32.10 | 0.41 |
| mLcorobac Parenasis no 360 16 370 222 052 MLD07068 Przewaquirone B 296 34 55 74 0.41 MLD07070 (65, 7R)-6, 7-Uhytrov-1,6-dimethyl-8,9-dihytro-7H-naphtho[8,7-g]benzofuran-10,11-dione 312.34 41.31 0.45 MLD07077 Sclared 306.86 43.37 0.21 MLD07077 Sclared 306.86 43.37 0.21 MLD07077 Sclared 306.86 43.37 0.21 MLD07078 Darshenol B 364.48 57.95 0.56 MLD07078 Darshenol A 336.41 38.88 0.55 MLD07026 Salvilenone 292.4 30.38 0.38 MLD07028 Darshenol A 336.41 38.88 0.55 MLD07029 Darshenol A 336.41 38.88 0.55 MLD07029 Darshenol A 38.61 38.88 0.55 MLD07029 Darshenol A 38.61 38.88 0.52 MLD07010 Dil | MOL007001 | Przewalckin a | 270.32 | 37.07 | 0.30 |
| Inductors 1.52 0.14 0.14 MICL00706 Preveaujurone B 296.3 65.24 0.4 MICL007076 Preveaujurone C 296.3 55.74 0.4 MICL007071 Preveaujurone C 312.34 40.31 0.46 MICL007071 Preveaujurone C 312.34 40.31 0.46 MICL007079 Tanshinatichyde 308.35 52.47 0.45 MICL007079 Tanshinatichyde 308.35 52.47 0.45 MICL007079 Tanshinatichyde 336.41 56.87 0.52 MICL007082 Danshenol A 336.41 56.87 0.52 MICL007084 Cryptotarshinone 296.39 52.34 0.4 MICL007094 Danshenspiroketallactone 282.36 50.43 0.31 MICL007095 Deoxynecoryptanshinone 284.38 68.27 0.31 MICL007010 Dhydranshinactone 284.38 68.27 0.31 MICL007015 Epidanshenspiroketallactone 284.3 64.9 | MOL007003 | FIZEWalskill a Przewalskih h | 330.49 | 110 32 | 0.05 |
| MILL00706 Preventuinone f 296.34 55.74 0.4 MILL007070 (BS, TR) 6, 7- Dhydroxy-1, 6-dimethyl-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-dione 312.34 41.31 0.45 MILL007077 Sclareel 308.36 43.67 0.21 MUL007077 Sclareel 308.36 43.67 0.21 MUL007078 Sclareel 308.36 43.67 0.21 MUL007078 Darshennol A 354.48 57.95 0.56 MUL007085 Salvilenone 292.34 0.38 0.38 MUL007086 Cryptotarshinone 292.4 0.38 0.38 MUL007080 Dens-shexinkum d 336.41 38.68 0.55 MUL007080 Densyneocryptotanshinone 296.31 38.68 0.32 MUL007010 Dihydrotanshinone I 278.32 45.04 0.32 MUL007010 Dihydrotanshinone I 296.33 54.98 0.39 MUL007010 Dihydrotanshinone I 296.33 54.98 0.39 MUL0070110 Dihy | MOL007068 | Przewacijinone R | 292.3 | 62 24 | 0.44 |
| Million Cost Att 31 Other MOL007070 (65,776,67-Dihydroxy-1,6-dimethyl-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-dione 312,34 40,31 0.46 MOL007071 Przewaquinone f 312,34 40,31 0.46 MOL007079 Tanshinaldehyde 308,55 43,67 0.25 MOL007079 Tanshinaldehyde 308,41 55,95 0.56 MOL007082 Danshenol B 336,41 56,97 0.52 MOL007088 Caylotianshinone 292,4 30,88 0.38 MOL007088 Caylotianshinone 286,39 52,34 0.4 MOL007089 Deoxyneoxyptotanshinone 288,41 49,4 0.29 MOL007010 Dihydrotanshinone I 278,32 45,64 0.36 MOL007101 Dihydrotanshinone I 278,32 45,64 0.36 MOL007107 C09092 286,5 36,07 0.25 MOL007111 Isotanshinone II 294,37 49,82 0.4 MOL007111 Isotanshinone II 31 | MOL007069 | Przewagulinone c | 296 34 | 55 74 | 0.41 |
| WDLD07071 Provequinone f State of Molece (Molece (Mol | MOL007070 | (6S 7R)-6 7-Dibydroxy-1 6-dimethyl-8 9-dibydro-7H-nanbtho[8 7-a]benzofuran-10 11-dione | 312.34 | 41.31 | 0.45 |
| MDL007077 Selared 308.56 43.87 0.21 MDL007079 Transhinaldehyde 308.35 52.47 0.45 MDL007082 Danshenol B 336.41 56.87 0.52 MDL007082 Danshenol A 336.41 56.87 0.52 MDL007088 Cryptolanshinone 292.4 30.38 0.38 MDL007094 Danshenshinum d 336.41 38.86 0.55 MDL007094 Danshenspirokefallactone 282.36 50.43 0.31 MDL007100 Dihydrotanshinaetone 286.31 38.68 0.32 MDL007101 Dihydrotanshinaetone 286.31 38.68 0.32 MDL007107 C90902 286.5 36.07 0.25 MDL007111 Isotanshinone I 294.37 49.92 0.4 MDL007118 Macrospitotanshinone 296.39 51.84 0.32 MDL007118 Macrospitotanshinone I 294.37 49.92 0.4 MDL007118 Macrostaginone 312.39 71.03 | MOL007071 | Przewanujnone f | 312.34 | 40.31 | 0.46 |
| MCL007079 Tanshinaldehyde 308.35 52.47 0.46 MOL007081 Danshenol A 354.48 57.95 0.56 MOL007085 Salvilenone 292.4 30.38 0.38 MOL007085 Salvilenone 296.3 9.52.34 0.4 MOL007083 Captotanshinone 286.36 50.43 0.31 MOL007084 Danshexinkum d 336.41 49.4 0.29 MOL007089 Deaxhexinkum d 336.41 49.4 0.29 MOL007080 Deaxynexpiroketallactone 286.31 49.04 0.29 MOL007100 Dihydrotanshinatone I 276.32 45.04 0.36 MOL007105 Epidanshenspiroketallactone 286.43 66.27 0.25 MOL007116 Isocryptotanshinone I 294.37 49.92 0.4 MOL007117 Manool 304.57 45.04 0.2 MOL007118 Isocryptotanshinone I 294.46 39.61 0.28 MOL007118 Mitinone I 312.39 71.03 <td>MOL007077</td> <td>Sclareol</td> <td>308.56</td> <td>43.67</td> <td>0.21</td> | MOL007077 | Sclareol | 308.56 | 43.67 | 0.21 |
| MOLOO7081 MOLOO7082 Darshend B 354.48 57.96 0.56 MOLOO7082 Darshend A 336.41 56.97 0.52 MOLOO7082 Darshend A 336.41 36.84 0.53 MOLOO7088 Cryptotanshinone 296.39 52.34 0.4 MOLO07094 Darshenspiroketallactone 282.36 50.43 0.31 MOLO07095 Deoxyneocryptotanshinone 286.31 38.68 0.32 MOLO07096 Deoxyneocryptotanshinone I 276.32 45.04 0.36 MOLO07101 Dihydrotanshinone I 276.32 45.04 0.36 MOLO07107 C09092 286.5 36.07 0.25 MOLO07111 Isotanshinone I 294.37 49.92 0.4 MOL007115 Manool 304.57 45.04 0.28 MOL007118 Mitrionone I 294.36 38.66 0.37 MOL007119 Mitrionone I 312.39 71.03 0.44 MOL007111 Isotanshinone I 272.32 49.95 | M0L007079 | Tanshinaldehvde | 308.35 | 52.47 | 0.45 |
| MOL007082 Danshenol A 336.41 56.97 0.52 MOL007085 Salvilenone 292.4 30.38 0.38 MOL007083 Dan-shexinkum d 336.41 38.88 0.55 MOL007093 Dan-shexinkum d 336.41 38.88 0.55 MOL007094 Denshenspiroketallactone 282.36 50.43 0.31 MOL007095 Deoxyneocryptotanshinone 286.31 38.68 0.32 MOL007101 Dihydrotanshinone I 278.32 45.04 0.36 MOL007105 Epidanshenspiroketallactone 286.3 36.07 0.25 MOL007105 Ibidanshinone I 294.37 49.92 0.4 MOL007115 Manol 304.57 45.04 0.28 MOL007115 Manol 304.57 45.04 0.28 MOL007118 Mitrione I 312.39 71.03 0.44 MOL00712 Mitrione I 312.39 71.03 0.44 MOL00712 Mitrione I 272.3 39.46 0.28 <td>MOL007081</td> <td>Danshenol B</td> <td>354.48</td> <td>57.95</td> <td>0.56</td> | MOL007081 | Danshenol B | 354.48 | 57.95 | 0.56 |
| MOL007086 Salvilenone 292.4 30.38 0.38 MOL007086 Cryptotanshinone 296.39 52.34 0.4 MOL007094 Dansheskrinkum d 36.64 38.88 0.55 MOL007094 Danshespiroketallactone 282.36 50.43 0.31 MOL007100 Dihydrotanshinone I 286.31 38.68 0.32 MOL007105 Epidarshenspiroketallactone 246.33 662.77 0.31 MOL007107 C09092 286.5 36.07 0.25 MOL007107 C09092 296.45 30.41 49.92 0.4 MOL007118 Isotanshinone I 296.39 54.98 0.39 MOL007118 Marcostegiol 296.46 39.61 0.28 MOL007118 Marcostegiol 296.46 39.61 0.28 MOL007118 Marcostegiol 304.37 45.04 0.28 MOL007121 Mitirone I 312.39 71.03 0.44 MOL007121 Mitirone I 30.43 36.56 | M0L007082 | Danshenol A | 336.41 | 56.97 | 0.52 |
| MOL007088 Cyptotanshinone 296.39 52.34 0.4 MOL007093 Dan-shexinkum d 336.41 38.88 0.55 MOL007098 Deoxyneocryptotarshinone 282.36 50.43 0.31 MOL007098 Deoxyneocryptotarshinone 298.41 49.4 0.29 MOL007101 Dihydrotanshinachene 278.32 45.04 0.36 MOL007105 Epidanshensprioketallactone 286.5 36.07 0.25 MOL007105 Epidanshensprioketallactone 296.39 54.38 0.39 MOL007118 Iscoryptotanshinone II 294.37 49.92 0.4 MOL007115 Manool 304.57 45.04 0.2 MOL007118 Iscoryptotanshinone II 298.46 39.61 0.28 MOL007119 Mitinone I 312.39 71.03 0.44 MOL007120 Mitinone I 312.39 70.35 39.46 0.23 MOL007121 Mitinone I 277.35 39.46 0.23 MOL007121 Mitinone I | M0L007085 | Salvilenone | 292.4 | 30.38 | 0.38 |
| MOL007093 Dan-sheexinkum d 336.41 38.88 0.55 MOL007094 Danshenspiroketallactone 282.36 50.43 0.31 MOL007100 Dihydrotanshinatone 298.41 49.4 0.29 MOL007101 Dihydrotanshinatone 278.32 45.04 0.36 MOL007105 Epidanshenspiroketallactone 284.38 68.27 0.31 MOL007107 C09092 286.5 36.07 0.25 MOL007111 Isotanshinone I 294.37 49.92 0.4 MOL007111 Isotanshinone I 304.457 45.04 0.2 MOL007115 Manool 304.57 45.04 0.2 MOL007118 Microstegiol 298.46 39.61 0.28 MOL00712 Miltinone I 312.39 49.68 0.32 MOL00712 Miltinone I 312.39 71.03 0.44 MOL00712 Miltinone I 312.39 71.03 0.44 MOL00712 Miltinone I 312.39 71.03 0.44 <td>MOL007088</td> <td>Cryptotanshinone</td> <td>296.39</td> <td>52.34</td> <td>0.4</td> | MOL007088 | Cryptotanshinone | 296.39 | 52.34 | 0.4 |
| MOL007094 Danshenspirokkallactone 282 36 50.43 0.31 MOL007098 Deoxyneocryptotanshinone 298 41 49.4 0.29 MOL007101 Dihydrotanshinone I 278.32 45.04 0.36 MOL007107 C09092 286.5 36.07 0.25 MOL007108 Iscoryptatanshinone I 294.33 54.98 0.39 MOL007111 Istanshinone II 294.37 49.92 0.4 MOL007115 Manol 304.57 45.04 0.28 MOL007116 Mitronne I 312.39 49.68 0.32 MOL007112 Mitronne I 312.39 71.03 0.44 MOL00712 Mitronne I 312.39 71.03 0.44 MOL00712 Mitronne I 312.39 71.03 0.44 MOL00712 Mitronne I 32.39 71.03 0.44 MOL00712 Mitrone I 32.39 71.03 0.44 0.23 MOL007121 Mitrone I 314.31 < | MOL007093 | Dan-shexinkum d | 336.41 | 38.88 | 0.55 |
| MOL007098 Deoxyneocryptotanshinone 288 41 49.4 0.29 MOL007100 Dihydrotanshinactone 266.31 38.68 0.32 MOL007101 Dihydrotanshinactone 278.32 45.04 0.36 MOL007105 Epidanshenspiroketallactone 284.33 68.27 0.31 MOL007107 C09092 286.5 36.07 0.25 MOL007111 Isotanshinone I 294.37 49.92 0.4 MOL007115 Manol 304.57 45.04 0.28 MOL007118 Microstegiol 298.46 39.61 0.28 MOL007118 Microstegiol 312.39 71.03 0.44 MOL007121 Miltionone I 312.39 71.03 0.44 MOL007121 Miltirone 30.04 38.66 0.37 MOL007122 Miltirone I 270.35 39.46 0.22 MOL007124 Neocryptotanshinone ii 270.35 39.46 0.32 MOL007130 Prolitospermic acid 314.31 64.37 | MOL007094 | Danshenspiroketallactone | 282.36 | 50.43 | 0.31 |
| MOL007100 Dihydrotanshinactone 266.31 38.68 0.32 MOL007110 Dihydrotanshinone I 278.32 45.04 0.36 MOL007107 C09092 284.38 68.27 0.31 MOL007117 C09092 286.5 36.07 0.25 MOL007116 Isocryptolanshi-none 296.3 54.98 0.39 MOL007111 Isotanshinone II 294.37 49.92 0.4 MOL007115 Manool 304.57 45.04 0.28 MOL007118 Mitorone I 312.39 49.68 0.32 MOL007120 Mittionone II 312.39 71.03 0.44 MOL007121 Mittione II 300.43 36.56 0.37 MOL007122 Mittione I 277.35 39.46 0.23 MOL007124 Neocryptotanshinone ii 270.35 39.46 0.23 MOL007132 Vittore II-MetryL-8,9-dihydro-7H-naphtho[5,6-g]benzofuran-6,10,11-trione 280.29 34.72 0.37 MOL007132 VittoryL-8,9-dihydro-7H-naphtho[5,0-g]b | MOL007098 | Deoxyneocryptotanshinone | 298.41 | 49.4 | 0.29 |
| MOL007101 Ditydratanshinone I 278.32 45.04 0.36 MOL007105 Epidanshenspiroketallactone 284.38 68.27 0.31 MOL007107 C09092 286.5 36.07 0.25 MOL007118 Isocryptotanshi-none 294.37 49.92 0.4 MOL007111 Isotrashinone I 294.37 49.92 0.4 MOL007115 Manool 304.57 45.04 0.2 MOL007118 Mitronstainone II 312.39 49.68 0.32 MOL007120 Mitronne II 312.39 71.03 0.44 MOL007121 Mitronne II 272.32 44.95 0.24 MOL007122 Mitrone II 272.32 44.95 0.24 MOL007123 Mitrone II 272.32 44.95 0.24 MOL007124 Necoryptotanshinone ii 270.35 39.46 0.33 MOL007130 Prolithospermic acid 314.31 64.37 0.31 MOL007141 Salvianolic acid J 360.34 109.38 | MOL007100 | Dihydrotanshinlactone | 266.31 | 38.68 | 0.32 |
| MOL007105 Epidamshenspirokettallactone 284.38 68.27 0.31 MOL007107 C09092 286.5 36.07 0.25 MOL0071108 Isocryptotanshi-none 296.39 54.98 0.39 MOL007111 Isotanshinone II 294.37 49.92 0.4 MOL007115 Marool 304.57 45.04 0.2 MOL007118 Microstegiol 298.46 39.61 0.28 MOL007119 Miltionone I 312.39 71.03 0.44 MOL007122 Miltirone I 300.43 36.56 0.37 MOL007123 Miltirone I 270.35 39.46 0.25 MOL007124 Neocryptotanshinone ii 270.35 39.46 0.32 MOL007125 Neocryptotanshinone 314.41 52.49 0.32 MOL007132 (2R)-3-(3,4-Dihydroxyphenyl)explanes/uran-6,10,11-trione 314.31 64.37 0.31 MOL007142 Neocryptotanshinone 314.31 64.37 0.31 MOL007132 (2R)-3-(3,4-Dihydroxyphenyl)exp | MOL007101 | Dihydrotanshinone I | 278.32 | 45.04 | 0.36 |
| MOL007107 C09092 286.5 36.07 0.25 MOL007108 Isocryptotanshinone 296.33 54.98 0.39 MOL007111 Isotanshinone II 294.37 49.92 0.4 MOL007115 Manool 304.57 45.04 0.28 MOL007118 Microstegiol 298.46 39.61 0.28 MOL007120 Miltionone I 312.39 49.68 0.32 MOL007121 Miltionone II 300.43 36.65 0.37 MOL007122 Miltione 300.43 36.66 0.37 MOL007124 Mecryptotanshinone ii 272.32 44.95 0.24 MOL007125 Neocryptotanshinone ii 270.35 39.46 0.23 MOL007126 Neocryptotanshinone ii 270.35 39.44 0.23 MOL007127 1-Methyl-8.9-dihydro-7H-naphtho[5.6-g]benzofuran-6,10,11-trione 314.31 64.37 0.31 MOL007132 (2R)-3-(3,4-Dihydroxyphenyl)-2-[(Z)-3-(3,4-dihydroxyphenyl)acyloylyoxy-propionic acid 360.34 109.38 0.35 | MOL007105 | Epidanshenspiroketallactone | 284.38 | 68.27 | 0.31 |
| MULL007108 Isocryptotanshin-none 296 39 54.98 0.39 MOLL007111 Isotanshinone II 294.37 49.92 0.4 MOL007115 Manool 304.57 45.04 0.2 MOL007118 Microstegiol 298.46 39.61 0.28 MOL007119 Mitionone I 312.39 49.68 0.32 MOL007120 Mitionone I 300.43 36.56 0.37 MOL007121 Mitionone II 300.43 36.56 0.37 MOL007122 Mitione II 272.32 44.95 0.24 MOL007123 Mitione II 270.35 39.46 0.23 MOL007124 Neocryptotanshinone ii 270.35 39.46 0.23 MOL007130 Prolithospermic acid 314.31 64.37 0.31 MOL007140 (2)-3-(3, 4-dihydroxyhenyl)acryloylow-propionic acid 300.34 109.38 0.35 MOL007140 Salvianolic acid g 340.3 45.56 0.61 MOL007141 Salvianolic acid g 30.45 | MOL007107 | C09092 | 286.5 | 36.07 | 0.25 |
| MULL07111 Isotanshinone II 294.37 49.92 0.4 MOLL007115 Manool 304.57 45.04 0.2 MOL007118 Microstegiol 298.46 39.61 0.28 MOL007119 Mittionne I 312.39 71.03 0.44 MOL007120 Mittionne II 300.43 36.56 0.37 MOL007121 Mittionne II 282.41 38.76 0.25 MOL007122 Mittione 270.35 39.46 0.23 MOL007123 Necryptotanshinone 314.41 52.49 0.32 MOL007125 Necryptotanshinone 314.41 52.49 0.32 MOL007130 Prolithospermic acid 314.31 64.37 0.31 MOL007132 (2)-3-(2, (2)-3-(3, 4-dihydroxy-phenyl)acrylor/propionic acid 314.31 84.54 0.26 MOL007140 (2)-3-12-(E)-2-(3, 4-Dihydroxyphenyl)acrylor/phenylacrylic acid 314.31 84.54 0.26 MOL007141 Salvianolic acid g 34.41 52.49 0.32 MOL007142 | MOL007108 | Isocryptotanshi-none | 296.39 | 54.98 | 0.39 |
| MULLOV/115 Manool 304.57 45.04 0.2 MULLOV/115 Microstegiol 298.46 39.61 0.28 MULLOV7119 Miltionone I 312.39 49.68 0.32 MULLOV7120 Miltionone II 312.39 71.03 0.44 MULLOV7121 Miltirone II 300.43 36.56 0.37 MULLOV7122 Miltirone II 272.32 44.95 0.28 MULLOV7124 Neccryptotanshinone ii 270.35 39.46 0.23 MULLOV7125 Neccryptotanshinone 314.41 52.49 0.32 MULLOV7125 Neccryptotanshinone 314.41 52.49 0.32 MULLOV7130 Prolithospermic acid 314.31 64.37 0.31 MULLOV7130 Prolithospermic acid g 340.3 45.56 0.61 MULLOV7140 (2)-3-(2-1(E)-2-(3, 4-Dihydroxyphenyl)var)(2-7(Z)-3-(3, 4-dihydroxy-phenyl]acryloyloxy-phenyl]acryloyloxy-phenylacrylox 340.3 45.56 0.61 MULLOV7140 Salvianolic acid g 340.3 45.56 0.61 | MOL007111 | Isotanshinone II | 294.37 | 49.92 | 0.4 |
| MULCUOY 118 Microstegiol 298.4b 39.61 0.28 MOLL007119 Miltionne I 312.39 49.68 0.32 MOL007120 Miltionne II 312.39 71.03 0.44 MOL007121 Miltipolone 300.43 36.56 0.37 MOL007122 Miltirone II 300.43 36.56 0.37 MOL007123 Miltirone II 272.32 44.95 0.24 MOL007124 Neocryptotanshinone II 270.35 39.46 0.23 MOL007125 Neocryptotanshinone 270.35 39.46 0.32 MOL007130 Prolithospermic acid 314.41 52.49 0.32 MOL007130 Prolithospermic acid 314.31 64.37 0.31 MOL007140 (2)-3-[2[C)-2-3(.4-dihydroxy-phenyl)acryloyloy-propionic acid 360.34 109.38 0.35 MOL007141 Salvianolic acid g 340.3 45.56 0.61 MOL007142 Salvianolic acid g 300.48 34.49 0.23 MOL007143 Salvianolic ac | MOL007115 | Manool | 304.57 | 45.04 | 0.2 |
| MOLL007119 Millidinitie I 312.39 49.06 0.32 MOLL007120 Millitionone II 312.39 71.03 0.44 MOLL007121 Miltipolone 300.43 36.56 0.37 MOL007122 Miltirone II 300.43 36.56 0.25 MOL007123 Miltirone II 272.32 44.95 0.24 MOL007124 Neocryptotanshinone Ii 270.35 39.46 0.23 MOL007125 Neocryptotanshinone 314.41 52.49 0.32 MOL007127 1-Methyl-8,9-dihydro-7H-naphtho[5,6-g]benzofuran-6,10,11-trione 280.29 34.72 0.37 MOL007130 Prolithospermic acid 314.31 64.37 0.31 MOL007140 (Z)-3-[2-[(E)-2-(3, 4-Dihydroxyphenyl)acryloyl]oxy-propionic acid 360.34 109.38 0.35 MOL007141 Salvianolic acid g 340.3 45.56 0.61 MOL007142 Salvianolic acid j 340.3 45.56 0.61 MOL007143 Salvianone I 270.4 32.43 0.23 | MOL007118 | Miltianana I | 298.46 | 39.61 | 0.28 |
| MOLL07120 Millipolone 312.39 71.03 0.444 MOLL07121 Milipolone 300.43 36.56 0.37 MOLL07121 Milipolone 300.43 36.56 0.37 MOL007123 Militrone II 272.32 44.95 0.24 MOL007124 Neocryptotanshinone ii 270.35 39.46 0.23 MOL007127 1-Methyl-8,9-dihydro-7H-naphtho[5,6-g]benzofuran-6,10,11-trione 280.29 34.72 0.32 MOL007130 Prolithospermic acid 314.31 64.37 0.31 MOL007132 (2R)-3-(3,4-Dihydroxyphenyl)-2-[(Z)-3-(3,4-dihydroxyphenyl]acryloyl]oxy-propionic acid 360.34 109.38 0.35 MOL007140 (2)-3-[2-[(E)-2-(3,4-Dihydroxyphenyl)oxy-phenyl]acrylic acid 314.31 64.37 0.31 MOL007141 Salvianolic acid j 340.3 45.56 0.61 MOL007142 Salvianolic acid j 340.3 45.56 0.61 MOL007143 Salvianolic acid j 300.48 34.49 0.23 MOL007145 Salvianolic acid j 300.48 | MOL007119 | Miltionone II | 312.39 | 49.00 | 0.32 |
| MOLLOD7121 Miltipone 30.45 30.50 0.37 MOLL007122 Miltirone 282.41 38.76 0.23 MOL007123 Miltirone II 272.32 44.95 0.24 MOL007124 Neocryptotanshinone ii 270.35 39.46 0.23 MOL007125 Neocryptotanshinone 314.41 52.49 0.32 MOL007127 1-Methyl-8,9-dihydro-7H-naphtho[5,6-g]benzofuran-6,10,11-trione 280.29 34.72 0.37 MOL007130 Prolithospermic acid 360.34 109.38 0.35 MOL007140 (2/-3-[2-[(E)-2-(3,4-Dihydroxyphenyl)/2-[(Z)-3-(3,4-dihydroxy-phenyl]acrylic acid 314.31 88.54 0.26 MOL007140 (2/-3-[2-[(E)-2-(3,4-Dihydroxyphenyl)/2-1,[(Z)-3-(3,4-dihydroxy-phenyl]acrylic acid 340.3 45.56 0.61 MOL007141 Salvianolic acid g 340.3 45.56 0.61 MOL007142 Salvianolic acid j 340.3 45.56 0.61 MOL007143 Salvialone 270.4 32.43 0.23 MOL007145 Salvialone 28.8 | MOL007120 | Millionone II Miltipologo | 312.39 | 71.03 | 0.44 |
| MOLDO7122 Miltione Z02-41 S0.70 0.25 MOLD07123 Miltione II 272.32 44.95 0.24 MOLD07124 Neocryptotanshinone Ii 270.35 39.46 0.23 MOL007125 Neocryptotanshinone 314.41 52.49 0.32 MOL007127 1-Methyl-8.9-dihydro-7H-naphtho[5,6-g]benzofuran-6,10,11-trione 280.29 34.72 0.37 MOL007130 Prolithospermic acid 360.34 109.38 0.35 MOL007142 (2H)-3-(3,4-Dihydroxyphenyl)-2-[(Z)-3-(3,4-dihydroxy-phenyl)acryloyl]oxy-propionic acid 360.34 109.38 0.35 MOL007140 (2)-3-[2-(E)-2-(3,4-Dihydroxyphenyl)inyl]-3,4-dihydroxy-phenyl]acrylic acid 314.31 88.54 0.26 MOL007141 Salvianolic acid g 340.3 45.56 0.61 MOL007142 Salvianolic acid j 270.4 32.43 0.23 MOL007143 Salviolone 286.38 31.72 0.24 MOL007145 Salviolone 286.38 31.72 0.24 MOL007150 (6S)-6-Hydroxy-1-methyl-6-methylol-8,9- | MOL007121 | Miltirone | 282 /1 | 38.76 | 0.37 |
| Molecon 123 Ministrian 212.32 14.33 0.24 MOL007124 Neocryptotanshinone ii 270.35 39.46 0.23 MOL007125 Neocryptotanshinone 314.41 52.49 0.32 MOL007127 1-Methyl-8,9-dihydro-7H-naphtho[5,6-g]benzofuran-6,10,11-trione 280.29 34.72 0.37 MOL007130 Prolithospermic acid 314.31 64.37 0.31 MOL007142 (2R)-3-(3,4-Dihydroxyphenyl)-2-[(Z)-3-(3,4-dihydroxyphenyl)acryloyl]oxy-propionic acid 360.34 109.38 0.35 MOL007140 (Z)-2-[(E)-2-(3,4-Dihydroxyphenyl)acryloyl]oxy-propionic acid 340.3 45.56 0.61 MOL007141 Salvianolic acid g 340.3 45.56 0.61 MOL007142 Salvianolic acid j 340.3 45.36 0.61 MOL007143 Salvienone I 270.4 32.43 0.23 MOL007145 Salviolone 268.38 31.72 0.24 MOL007149 NSC 122421 300.48 34.49 0.28 MOL007150 (6S)-6-Hydroxy-1-methyl-6-methylol-8,9-dihydro-7H-na | MOL007122 | Millione II | 202.41 | 11 95 | 0.23 |
| MOLD07125 Neocryptotanshinone 210.05 05.10 0120 MOLD07125 Neocryptotanshinone 314.41 52.49 0.32 MOLD07127 1-Methyl-8,9-dihydro-7H-naphtho[5,6-g]benzofuran-6,10,11-trione 280.29 34.72 0.37 MOL007130 Prolithospermic acid 314.41 64.37 0.31 MOL007132 (2R)-3-(3,4-Dihydroxyphenyl)-2-[(Z)-3-(3,4-dihydroxyphenyl)acryloyl]oxy-propionic acid 360.34 109.38 0.35 MOL007140 (Z)-3-[C-](E)-2-(3,4-Dihydroxyphenyl)-3,4-dihydroxy-phenyl]acrylic acid 314.31 88.54 0.26 MOL007141 Salvianolic acid g 340.3 45.56 0.61 MOL007142 Salvianolic acid j 340.3 45.56 0.61 MOL007142 Salvianolic acid j 270.4 32.43 0.23 MOL007143 Salvilenone I 270.4 32.43 0.23 MOL007145 Salviolone 268.38 31.72 0.24 MOL007150 (6S)-6-Hydroxy-1-methylo-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-quinone 312.34 42.67 0.45 < | MOL007123 | Neocryntotanshinone ii | 270.35 | 39.46 | 0.24 |
| MOLD07127 1-Methyl-8,9-dihydro-7H-naphtho[5,6-g]benzofuran-6,10,11-trione 280.29 34.72 0.37 MOLD07130 Prolithospermic acid 314.31 64.37 0.31 MOL007132 (2R)-3-(3,4-Dihydroxyphenyl)-2-[(Z)-3-(3,4-dihydroxyphenyl)acryloyl]oxy-propionic acid 360.34 109.38 0.35 MOL007140 (Z)-3-[2-[(E)-2-(3,4-Dihydroxyphenyl)vinyl]-3,4-dihydroxy-phenyl]acrylic acid 314.31 88.54 0.26 MOL007141 Salvianolic acid g 340.3 45.56 0.61 MOL007142 Salvianolic acid j 538.49 43.38 0.72 MOL007143 Salvianolic acid j 538.49 43.38 0.72 MOL007145 Salviolone 270.4 32.43 0.23 MOL007145 Salviolone 268.38 31.72 0.24 MOL007149 NSC 122421 300.48 34.49 0.28 MOL007150 (6S)-6-Hydroxy-1-methyl-6-methylol-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-quinone 312.34 42.67 0.45 MOL007151 Tanshindiol B 312.34 42.85 0.45 MOL007152 Przewaquinone E 312.34 42.85 0.45 | MOL007125 | Neocryptotanshinone | 314 41 | 52 49 | 0.20 |
| MOL007130 Prolithospermic acid 314.31 64.37 0.31 MOL007132 (2R)-3-(3,4-Dihydroxyphenyl)-2-[(Z)-3-(3,4-dihydroxyphenyl)acryloyl]oxy-propionic acid 360.34 109.38 0.35 MOL007140 (Z)-3-[2-[(E)-2-(3,4-Dihydroxyphenyl)vinyl]-3,4-dihydroxy-phenyl]acrylic acid 314.31 88.54 0.26 MOL007141 Salvianolic acid g 340.3 45.56 0.61 MOL007142 Salvianolic acid j 538.49 43.38 0.72 MOL007143 Salvilenone I 270.4 32.43 0.23 MOL007145 Salviolone 268.38 31.72 0.24 MOL007150 (6S)-6-Hydroxy-1-methyl-6-methylol-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-quinone 312.34 42.67 0.45 MOL007151 Tanshindiol B 312.34 42.67 0.45 MOL007152 Przewaquinone E 312.34 42.85 0.45 MOL007154 Tanshinone iia 294.37 49.89 0.4 MOL007155 (6S)-6-(Hydroxymethyl)-1,6-dimethyl-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-dione 310.37 65.26 0.45 | M0L007127 | 1-Methyl-8.9-dihydro-7H-naphtho[5.6-g]benzofuran-6.10.11-trione | 280.29 | 34.72 | 0.37 |
| MOL007132 (2R)-3-(3,4-Dihydroxyphenyl)-2-[(Z)-3-(3,4-dihydroxyphenyl)acryloyl]oxy-propionic acid 360.34 109.38 0.35 MOL007140 (Z)-3-[2-[(E)-2-(3,4-Dihydroxyphenyl)vinyl]-3,4-dihydroxy-phenyl]acrylic acid 314.31 88.54 0.26 MOL007141 Salvianolic acid g 340.3 45.56 0.61 MOL007142 Salvianolic acid j 538.49 43.38 0.72 MOL007143 Salvienone I 270.4 32.43 0.23 MOL007145 Salviolone 268.38 31.72 0.24 MOL007149 NSC 122421 300.48 34.49 0.28 MOL007150 (6S)-6-Hydroxy-1-methyl-6-methylol-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-quinone 312.34 75.39 0.46 MOL007151 Tanshindiol B 312.34 42.67 0.45 MOL007152 Przewaquinone E 312.34 42.85 0.45 MOL007154 Tanshinone iia 294.37 49.89 0.4 MOL007155 (6S)-6-(Hydroxymethyl)-1,6-dimethyl-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-dione 310.37 65.26 0.45 | M0L007130 | Prolithospermic acid | 314.31 | 64.37 | 0.31 |
| MOL007140 (Z)-3-[2-[(E)-2-(3,4-Dihydroxyphenyl)vinyl]-3,4-dihydroxy-phenyl]acrylic acid 314.31 88.54 0.26 MOL007141 Salvianolic acid g 340.3 45.56 0.61 MOL007142 Salvianolic acid j 538.49 43.38 0.72 MOL007143 Salvienone I 270.4 32.43 0.23 MOL007145 Salviolone 268.38 31.72 0.24 MOL007149 NSC 122421 300.48 34.49 0.28 MOL007150 (6S)-6-Hydroxy-1-methyl-6-methylol-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-quinone 312.34 75.39 0.46 MOL007152 Przewaquinone E 312.34 42.67 0.45 MOL007154 Tanshindiol B 312.34 42.85 0.45 MOL007152 Przewaquinone E 312.34 42.85 0.45 MOL007154 Tanshinone iia 294.37 49.89 0.4 MOL007155 (6S)-6-(Hydroxymethyl)-1,6-dimethyl-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-dione 310.37 65.26 0.45 MOL007156 Tanshinone VI | M0L007132 | (2R)-3-(3,4-Dihydroxyphenyl)-2-[(Z)-3-(3,4-dihydroxyphenyl)acryloyl]oxy-propionic acid | 360.34 | 109.38 | 0.35 |
| MOL007141 Salvianolic acid g 340.3 45.56 0.61 MOL007142 Salvianolic acid j 538.49 43.38 0.72 MOL007143 Salvianolic acid j 538.49 43.38 0.72 MOL007143 Salvianolic acid j 270.4 32.43 0.23 MOL007145 Salviolone 268.38 31.72 0.24 MOL007149 NSC 122421 300.48 34.49 0.28 MOL007150 (6S)-6-Hydroxy-1-methyl-6-methylol-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-quinone 312.34 75.39 0.46 MOL007151 Tanshindiol B 312.34 42.67 0.45 MOL007152 Przewaquinone E 312.34 42.85 0.45 MOL007154 Tanshinone iia 294.37 49.89 0.4 MOL007155 (6S)-6-(Hydroxymethyl)-1,6-dimethyl-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-dione 310.37 65.26 0.45 MOL007155 Tanshinone VI 296.34 45.64 0.3 | MOL007140 | (Z)-3-[2-[(E)-2-(3,4-Dihydroxyphenyl)vinyl]-3,4-dihydroxy-phenyl]acrylic acid | 314.31 | 88.54 | 0.26 |
| MOL007142 Salvianolic acid j 538.49 43.38 0.72 MOL007143 Salvilenone I 270.4 32.43 0.23 MOL007145 Salviolone 268.38 31.72 0.24 MOL007149 NSC 122421 300.48 34.49 0.28 MOL007150 (6S)-6-Hydroxy-1-methyl-6-methylol-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-quinone 312.34 75.39 0.46 MOL007151 Tanshindio B 312.34 42.67 0.45 MOL007152 Przewaquinone E 312.34 42.85 0.45 MOL007154 Tanshinone iia 294.37 49.89 0.4 MOL007155 (6S)-6-(Hydroxymethyl)-1,6-dimethyl-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-dione 310.37 65.26 0.45 MOL007155 Tanshinone VI 296.34 45.64 0.3 | MOL007141 | Salvianolic acid g | 340.3 | 45.56 | 0.61 |
| MOL007143 Salvilenone I 270.4 32.43 0.23 MOL007145 Salviolone 268.38 31.72 0.24 MOL007149 NSC 122421 300.48 34.49 0.28 MOL007150 (6S)-6-Hydroxy-1-methyl-6-methylol-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-quinone 312.34 75.39 0.46 MOL007151 Tanshindiol B 312.34 42.67 0.45 MOL007152 Przewaquinone E 312.34 42.85 0.45 MOL007154 Tanshinone iia 294.37 49.89 0.4 MOL007155 (6S)-6-(Hydroxymethyl)-1,6-dimethyl-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-dione 310.37 65.26 0.45 MOL007155 Tanshinone VI 296.34 45.64 0.3 | MOL007142 | Salvianolic acid j | 538.49 | 43.38 | 0.72 |
| MOL007145 Salviolone 268.38 31.72 0.24 MOL007149 NSC 122421 300.48 34.49 0.28 MOL007150 (6S)-6-Hydroxy-1-methyl-6-methylol-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-quinone 312.34 75.39 0.46 MOL007151 Tanshindiol B 312.34 42.67 0.45 MOL007152 Przewaquinone E 312.34 42.85 0.45 MOL007154 Tanshinone iia 294.37 49.89 0.4 MOL007155 (6S)-6-(Hydroxymethyl)-1,6-dimethyl-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-dione 310.37 65.26 0.45 MOL007155 Tanshinone VI 296.34 45.64 0.3 | MOL007143 | Salvilenone I | 270.4 | 32.43 | 0.23 |
| MOL007149 NSC 122421 300.48 34.49 0.28 MOL007150 (6S)-6-Hydroxy-1-methyl-6-methylol-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-quinone 312.34 75.39 0.46 MOL007151 Tanshindiol B 312.34 42.67 0.45 MOL007152 Przewaquinone E 312.34 42.85 0.45 MOL007154 Tanshinone iia 294.37 49.89 0.4 MOL007155 (6S)-6-(Hydroxymethyl)-1,6-dimethyl-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-dione 310.37 65.26 0.45 MOL007156 Tanshinone VI 296.34 45.64 0.3 | MOL007145 | Salviolone | 268.38 | 31.72 | 0.24 |
| MOL007150 (6S)-6-Hydroxy-1-methyl-6-methylol-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-quinone 312.34 75.39 0.46 MOL007151 Tanshindiol B 312.34 42.67 0.45 MOL007152 Przewaquinone E 312.34 42.85 0.45 MOL007154 Tanshinone iia 294.37 49.89 0.4 MOL007155 (6S)-6-(Hydroxymethyl)-1,6-dimethyl-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-dione 310.37 65.26 0.45 MOL007156 Tanshinone VI 296.34 45.64 0.3 | MOL007149 | NSC 122421 | 300.48 | 34.49 | 0.28 |
| MOL007151 Tanshindiol B 312.34 42.67 0.45 MOL007152 Przewaquinone E 312.34 42.85 0.45 MOL007154 Tanshinone iia 294.37 49.89 0.4 MOL007155 (6S)-6-(Hydroxymethyl)-1,6-dimethyl-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-dione 310.37 65.26 0.45 MOL007156 Tanshinone VI 296.34 45.64 0.3 | MOL007150 | (6S)-6-Hydroxy-1-methyl-6-methylol-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-quinone | 312.34 | 75.39 | 0.46 |
| MOL007152 Przewaquinone E 312.34 42.85 0.45 MOL007154 Tanshinone iia 294.37 49.89 0.4 MOL007155 (6S)-6-(Hydroxymethyl)-1,6-dimethyl-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-dione 310.37 65.26 0.45 MOL007156 Tanshinone VI 296.34 45.64 0.3 | MOL007151 | Tanshindiol B | 312.34 | 42.67 | 0.45 |
| MUL007154 Ianshinone iia 294.37 49.89 0.4 M0L007155 (6S)-6-(Hydroxymethyl)-1,6-dimethyl-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-dione 310.37 65.26 0.45 M0L007156 Tanshinone VI 296.34 45.64 0.3 | MUL007152 | Przewaquinone E | 312.34 | 42.85 | 0.45 |
| MULUU/155 (65)-6-(Hydroxymethyl)-1,6-dimethyl-8,9-dihydro-/H-naphtho[8,7-g]benzofuran-10,11-dione 310.37 65.26 0.45 MOL007156 Tanshinone VI 296.34 45.64 0.3 | MUL007154 | | 294.37 | 49.89 | 0.4 |
| VIULUU7156 IARSNINONE VI 296.34 45.64 0.3 | MUL00/155 | (65)-6-(Hydroxymethyl)-1,6-dimethyl-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-dione | 310.37 | 65.26 | 0.45 |
| | WULUU/156 | I ansninone VI | 296.34 | 45.64 | 0.3 |

DL = drug-likeness, MW = molecular weight, OB = oral bioavailability.

by Cytoscape 3.6.1. Cytohubba was applied to analyze the degree of interactions between proteins and obtained the hub genes based on the degree values.

2.4. Gene ontology and kyoto encyclopedia of genes and genomes analysis

In order to further analyze the biological function process and signal transduction involved in the DS on MIRI, R software was used to annotate the gene ontology (GO) biological function of the "drug-disease" intersection genes. Moreover, ClueGo plug-in in Cytoscape software was used to enrich the kyoto encyclopedia of genes and genomes (KEGG) pathway of the overlapping genes, and the enrichment results were screened with P < .01, kappa score=0.4 as the standard for clustering and visualization analysis.

2.5. Interaction network construction and analysis

To investigate the in-depth molecular mechanism of DS on MIRI, the DS—compound – MIRI—targets (DCMT) network was constructed by Cytoscape software (Version. 3.6.1). In this network, the components and proteins were represented as nodes, whereas the interactions between nodes were represented as edges.

2.6. Molecular docking

To study the association between active compounds and hub genes in the network, molecular docking approach was applied to analyzed the strength and mode of interactions between active compounds screened form networks and hub genes from PPI. The protein crystal structures were obtained from Protein Data Bank database (PDB, http:// www. rcsb.org/). The protein structures were screened based on the criteria as follows: the protein structure must be from Homo sapiens; the structure is obtained by X-crystal diffraction; the resolution is <3 Å; priority is given to protein structures that have been previously reported in molecular docking study. The process is simply described as follows: The structures of active compounds were obtained from TCMSP database. Autodock Tools and autodock vina (version: 1.1.2)^[25] were applied for molecular docking. Pymol and Discovery Studio were used to analyze the results of docking and presented as final figures.

3. Results

3.1. Identification of bioactive compounds in Danshen

Screening through TCMSP database, a total of 202 components of Danshen were obtained. As shown in Table 1, there were 65 active ingredients that met the criteria of OB \geq 30% and DL \geq 0.18. The molecular IDs of these 65 active compounds were input into TCMSP to obtain their potential protein targets. A total of 932 protein targets were obtained and after removing duplicate; 108 targets were screened to the further study.

3.2. Acquisition of MIRI related targets and "disease-drug" overlapping targets

Through the GeneCard database, a total of 1239 human related genes were retrieved with the key word "Myocardial ischemia reperfusion injury." The targets of DS were intersected with MIRI



related genes, and a total of 61 "disease-drug" intersection genes were obtained (Fig. 2), which were the potential targets of DS acting on MIRI. The detailed contents of the overlapping genes are shown in Table 2.

3.3. Construction and analysis of protein interaction (PPI) network

The PPI network of 61 overlapping genes was constructed through the String database. Analysis showed that there were a total of 61 nodes and 624 edges in this network (Supplementary figure 1, http://links.lww.com/MD/G514). The PPI network was imported into Cytoscape 3.6.1 software and Cytohubba plug-in was used to analyze the key nodes of the above 61 genes. As shown in Figure 3, AKT1, IL-6, vascular endothelial growth factor A (VEGFA), MAPK1, STAT3, CASP3, PTGS2, FOS, MYC, JUN, MAPK14, and BCL2L1 interacted with the other proteins in the highest frequency, and the interaction between targets was stronger and the degree value was larger, which indicated to play an important role in the PPI network. The results revealed that these targets might be potential targets of active components of DS in the treatment of MIRI, which were worthy of further discussion.

3.4. Construction and analysis of DS-compounds-MIRItargets network

The obtained active compounds-MIRI-targets and the interactions between them were analyzed by R software, and the results were visualized by Cytoscape 3.6.1 to get the network of "DS compounds - MIRI - targets" (DCMT) as shown in Figure 4. The network consisted of 118 nodes, including 1 traditional Chinese medicine—Danshen, 55 active compounds, 61 targets and 1 disease—MIRI. The results indicated the multitarget action of active components in DS on MIRI. Through the analysis of the network, the top 3 active components with the highest correlation with the treatment of MIRI were: luteolin, tanshinone IIA, cryptotanshinone.

3.5. GO and KEGG Pathway Enrichment Analysis

In order to further clarify the biological characteristics of the potential targets of Danshen on MIRI, GO, and KEGG pathway enrichment analysis were performed by R/Bio-conductor platform. All of 142 pathways shown in supplementary Table 1,

| Table | 2 | | | | |
|---------|----|---------|--------|----|-------|
| Targets | of | Danshen | action | on | MIRI. |

| No. | Target Symbol | Target Name | ID | Degree |
|----------|------------------|--|-------|----------|
| 1 | | PAC alpha soring/throoping protoin kingso | 207 | 19 |
| 1 | | Interfaultin 6 | 207 | 40 |
| 2 | | Vaccular and the lial growth factor A | 7400 | 43 |
| 3 | MADIZ1 | Mitegen activated protein kinege 14 | 1422 | 42 |
| 4 | | Signal transducer and estimator of transcription 2 | 6774 | 40 |
| 0 | SIAIS | | 0774 | 30 |
| 0 | | Udspase-3 Drostaglandin C//Laurthaga 1 | 030 | 30 |
| / | PIGSZ | Prostagiandin G/H synthase i | 5742 | 38 |
| 8 | FUS | Proto-oncogene c-Fos | 2353 | 37 |
| 9 | MYC | Myc proto-oncogene protein | 4609 | 37 |
| 10 | JUN | Transcription factor AP-1 | 3725 | 35 |
| 11 | MAPK14 | Mitogen-activated protein kinase 14 | 1432 | 34 |
| 12 | BCL2L1 | Bcl-2-like protein 1 | 598 | 33 |
| 13 | CCND1 | G1/S-specific cyclin-D1 | 595 | 33 |
| 14 | IL-10 | Interleukin-10 | 3586 | 32 |
| 15 | MMP9 | Matrix metalloproteinase-9 | 4318 | 32 |
| 16 | RELA | Transcription factor p65 | 5970 | 31 |
| 17 | PPARG | Peroxisome proliferator activated receptor gamma | 5468 | 31 |
| 18 | ICAM1 | Intercellular adhesion molecule 1 | 3383 | 29 |
| 19 | IL-4 | Interleukin-4 | 3565 | 28 |
| 20 | MMP2 | 72 kDa type IV collagenase | 4313 | 28 |
| 21 | ESR1 | Estrogen receptor | 2099 | 28 |
| 22 | IL-2 | Interleukin-2 | 3558 | 27 |
| 23 | HMOX1 | Heme oxygenase 1 | 3162 | 27 |
| 24 | CASP9 | Caspase-9 | 842 | 27 |
| 25 | NB3C1 | Glucocorticoid receptor | 2908 | 26 |
| 26 | IFNG | Interferon gamma | 3458 | 25 |
| 27 | APP | Amvloid beta A4 protein | 351 | 25 |
| 28 | NEKBIA | NE-kanna-B inhihitor alnha | 4792 | 25 |
| 20 | | Cyclin_dependent kinase inhibitor 1 | 1026 | 25 |
| 30 | MDM2 | E3 ubiquitin_protein ligace Mdm2 | /1020 | 20 |
| 31 | NOS2 | Nitric ovide synthese, inducible | 4133 | 24 |
| 20 | MMD1 | | 4040 | 22 |
| 32 22 | | CD40 ligand | 4312 | 21 |
| 33 | | Chuagan authora kingga 2 hata | 909 | 20 |
| 34 | | Glycogen synthase kinase-s bela | 2932 | 19 |
| 30 | UPRIMI CASERZ | | 4900 | CI 14 |
| 30 | | Caspase-7 | 840 | 14 |
| 37 | ADRB2 | Beta-2 adrenergic receptor | 154 | 14 |
| 38 | BIRCS | Baculoviral IAP repeat-containing protein 5 | 332 | 12 |
| 39 | ACHE | Acetylcholinesterase | 43 | 12 |
| 40 | OPRD1 | Delta-type opioid receptor | 4985 | 11 |
| 41 | BCL2 | Apoptosis regulator Bcl-2 | 596 | 10 |
| 42 | PTGS1 | Prostaglandin G/H synthase 1 | 5742 | 10 |
| 43 | GSTP1 | Glutathione S-transferase P | 2950 | 9 |
| 44 | SLC6A4 | Sodium-dependent serotonin transporter | 6532 | 9 |
| 45 | HTR3A | 5-hydroxytryptamine receptor 3A | 3359 | 9 |
| 46 | ITGB3 | Integrin beta-3 | 3690 | 8 |
| 47 | EDNRA | Endothelin-1 receptor | 1909 | 7 |
| 48 | PTGES | Prostaglandin E synthase | 9536 | 7 |
| 49 | AKR1B1 | Aldose reductase | 231 | 7 |
| 50 | TYR | Tyrosinase | 7299 | 6 |
| 51 | SLC6A3 | Sodium-dependent dopamine transporter | 6531 | 6 |
| 52 | INSR | Insulin receptor | 3643 | 5 |
| 53 | PCNA | Proliferating cell nuclear antigen | 5111 | 5 |
| 54 | CHRM2 | Muscarinic acetvlcholine receptor M2 | 1129 | 5 |
| 55 | FASN | Fatty acid synthase | 2194 | 4 |
| 56 | ECE1 | Endothelin-converting enzyme 1 | 1889 | 4 |
| 57 | SI C6A2 | Sodium-dependent noradrenaline transporter | 6530 | 3 |
| 58 | NB3C2 | Nuclear Recentor Subfamily 3 Group C Member 2 | 4306 | 3 |
| 59 | KCNH2 | Potassium voltage-rated channel subfamily H member 2 | 3757 | 2 |
| 60 | CHBM3 | Muscarinic acetulcholine recentor M3 | 1121 | 2 |
| 61 | SCN54 | Sodium channel protein type 5 subunit aloba | 6221 | ے 1 |
| 01 | | ooulum onalmer protein type o Subuliit alpha | 0001 | 1 |



http://links.lww.com/MD/G515 were enriched. The top 20 (Count ≥2 and P < .05) significantly enriched terms in functions of these targets were shown in Figure 5A and B, which indicated that DS may regulate the development of MIRI via amide binding, cytokine receptor binding and peptide binding to exert its therapeutic effect on MIRI. To explore the underlying involved pathways of DS on MIRI, KEGG analysis was conducted. As results, the top 20 significantly enriched pathways of DS on MIRI were shown in Figure 6A and B. Among these pathways enriched, PI3K-Akt signaling pathway, interleukin (IL)-17 signaling pathway, AGE-RAGE signaling pathway in diabetic complica-

tions, T cell receptor signaling pathway, tumor necrosis factor signaling pathway, and HIF-1 signaling pathway were mostly associated with MIRI, which have been reported in number of studies. Furthermore, a cluster analysis by using ClueGo indicated that pathways enriched from KEGG were mainly classified in IL-17 signaling pathway, apoptosis, and fluid shear stress atherosclerosis (Fig. 7).

3.6. Molecular docking between active compounds and potential targets

Because 61 potential targets were obtained, the top 3 targets (AKT1, IL6, and VEGFA), which had higher degree, were selected for molecular docking with top 3 active components screened from "DS-MIRI" network. The ranking of the affinity of the 3 molecule components was achieved, as shown in Table 3. The results revealed that TSA and CPT have the higher affinity to VEGFA. The details of docking were performed in Figure 8A–I. I observe that the molecule could bind with the protein by H-bong or π - π accumulation, respectively. For instance, the analysis of TSA indicated that TSA bound to the active pocket of VEGFA and interacted with the H-bond of the amino group on CYS-54, ASP-56, and ASN-55. Besides, it has Pi-Alkyl with amino group of ILE-39 and PHE-29 (Fig. 8I).

4. Discussion

MIRI belongs to the category of coronary atherosclerotic heart disease (CAHD). When the blood supply from the coronary artery is contradictory to the blood demand of the myocardium, the coronary blood flow is insufficient to supply the myocardial tissue to complete the normal metabolic function, which will lead to the occurrence of myocardial ischemia and hypoxia.^[26] Sudden short-term ischemia and hypoxia can induce angina pectoris, whereas long-term severe ischemia and hypoxia can lead to critical cardiovascular diseases such as acute myocardial



Figure 4. "DS-compounds-MIRI-targets" (DCMT) network.





infarction.^[27] In recent years, the incidence of CAHD has been increasing, following with high mortality. Interventional therapy is one of the main methods for the treatment of CAHD, but MIRI is the main complication after thrombolysis and coronary interventional therapy in clinical patients with CHD.^[7,28] The occurrence of MIRI usually results in poor prognosis and even

endangers the life of the patients. Therefore, it is crucial to find safe and effective methods to prevent the occurrence of MIRI.

Traditional Chinese herbal medicine Danshen (DS) is the dried root of *Salvia miltiorrhiza* Bunge, a kind of labiaceae plants. It is a famous herbal medicine in China. Due to the diversity and effectiveness of its pharmacological activities, DS has become one



Figure 6. KEGG pathway enrichment analysis. (A) Top 20 pathways from KEGG (*P*-adjust value <.01). (B) A bubble plot to describe *p*-adjust value range of to 20 pathways.



Figure 7. Clustering analysis of signal pathways. The pathways were presented by circles. The main clusters are shown in bold labels.

of the visiting cards of Chinese medicines in contemporary China.^[9,11] At present, DS is mainly used in the prevention and treatment of metabolic disorders such as cardiovascular and cerebrovascular diseases and hyperlipidemia, and plays important roles in the prevention and adjuvant treatment of MIRI.^[29,30] With the deepening research of its pharmacology and molecular biology, researchers have found that the mechanism of DS's clinical therapeutic effect is varied. To clarify the multi-targets effects of herbal medicines, network pharmacology provides a new method for the study of explaining the pharmacological mechanisms of traditional Chinese herbal medicine.

Based on the network pharmacology, the present study systematically elaborated the pharmacological mechanism of DS in the treatment of MIRI. At first, through the analysis of the DCMT network, it was suggested that the main components of DS in the treatment of MIRI might be tanshinone IIA (TSA),

| Table 3 | | | | | |
|--|-------------|------------|--------------|--|--|
| Affinity of 3 active compounds of Danshen. | | | | | |
| Affinity, kcal/mol | AKT1 (1UNQ) | IL6 (1ALU) | VEGFA (3QTK) | | |
| Luteolin | -6.3 | -6.6 | -8.1 | | |
| Cryptotanshinone | -7.7 | -6.6 | -9.6 | | |
| Tanshinone IIA | -7.3 | -6.3 | -9.8 | | |

cryptotanshinone (CPT) and luteolin. Tanshinone IIA, a kind of fat-soluble diterpenoids extracted from Danshen, has been widely applied in adjunctively treating cardiovascular diseases in China for a long time.^[9,31] Accumulating evidence have shown the protective effects of TSA in ischemic myocardium. For instance, study of Yuan et al indicated that TSA protects the MIRI through PI3K/Akt-eNOS signaling pathway and blocking the expression of mitochondrial permeability transition pore in rats.^[32] Moreover, Hu et al demonstrated that TSA could prevent myocardial tissue from ischemia reperfusion injury by inhibiting the expression of high mobility group box-B1 (HMGB1) and inducing the inflammatory reaction.^[33] By whatever mechanism of action, TSA plays crucial role in the improvement of the outcomes of MIRI. As a natural quinone component, the medicinal value of CPT has received increasing attentions. In previous study, Jin et al detected the cardiovascular protective effects of CPT in vivo experiments. The results revealed that CPT reduced myocardial infarct size and improved cardiac function after ischemia and reperfusion injury. Importantly, their study suggested that CPT could protect myocardial injury from ischemia and reperfusion by inhibiting the NF-KB activation, cytokine production and adhesion molecules.^[34] The disruption of calcium homeostasis is one of the important factors leading to myocardial injury. Calcium overload can occur in cardiomyocytes as a result of myocardial infarction or other stress, such as hypoxia and reoxygenation, leading to myocardial systolic dysfunction. Study of Liu et al have shown that CPT can suppress calcium overload in vitro cell experiments, and in vivo animal experiments have further verified that CPT plays a protective role in myocardium through antioxidant and anti-inflammatory



Figure 8. Molecular docking between active compounds and main potential targets. (A) CPT act on AKT1; (B) Luteolin act on AKT1; (C) TSA act on AKT1; (D) CPT act on IL6; (E) Luteolin act on IL6; (F) TSA act on IL6; (G) CPT act on VEGFA; (H) Luteolin act on VEGFA; (I) TSA act on VEGFA. In every figure of molecular docking: a. holistic view of docking model; b. enlarged view of the docking section; c. 2D diagram of docking results. CPT = cryptotanshinone, TSA = tanshinone IIA, VEGFA = vascular endothelial growth factor A.

activities.^[35] Luteolin is a flavonoid with molecular formula of $C_{15}H_{10}O_6$ and relative molecular weight of 286.23. Luteolin is found in many medicinal plants, which has reported to play important roles in myocardial protection. Kim et al studied the protective effect of flavonoids on H92C cardiomyocytes in the simulation of MIRI, and the experimental results showed that luteolin could significantly increase the expression of anti-apoptotic protein Bcl-2 and inhibit the expression of pro-apoptotic protein Bax.^[36] In addition, luteolin can reduce the frequency and duration of ventricular tachycardia and ventricular fibrillation during ischemia and reperfusion in rat model of MIRI, and significantly reduce the size of myocardial infarction.^[37]

Protein interactions play important roles in important biological processes such as cell cycle control, metabolism and signaling pathways, and disease pathways. Therefore, the systematic mapping of protein interactions is essential for the interpretation of protein function and the understanding of complex cellular processes.^[38,39] In the present study, after analysis of PPI network, the top 3 proteins calculated by degrees were obtained. Respectively, they are AKT1 (RAC-alpha serine/ threonine-protein kinase), IL-6, and VEGFA. AKT1 can mediate PI3K-dependent cell adhesion, invasion, metastasis, and regulate cell apoptosis. AKT cascading activation is central to a variety of conditioning strategies and plays a related cardioprotective role in the reperfusion injury saving kinase pathway, which is blocked by inhibitors of upstream kinase PI3K.^[40,41] Inflammatory is closely related to the pathogenesis of MIRI. IL-6 is one of the common inflammatory cytokines. Studies have shown that IL-6 can cause neutrophils to adhere to vascular endothelial cells, and thus induce neutrophils to exude and infiltrate, and make cardiomyocytes damaged. Suppressing the production of inflammatory cytokines such as IL-6 could protect against the MIRI.^[42,43] If the role of paracrine mechanisms is taken as a starting point, the administration of growth factors to promote tissue revascularization represents an attractive option that has been explored in animal models of limb ischemia or myocardial infarction. Proangiogenic cytokines such as VEGF.^[44] VEGFA is a member of the VEGF growth factor family. The VEGF family play an important role in the regulation of angiogenesis networks. VEGF directly affects vascular endothelial cells by promoting the proliferation and migration of vascular endothelial cells.^[45] Ai et al indicated that upregulation of VEGFA could accelerate cardiac angiogenesis and improves cardia function.[46] Similarly, Guo et al also demonstrated that myocardial protective effect could be exerted via upregulating the VEGFA.^[47]

The results of enrichment analysis of GO and KEGG pathways showed that the significant enrichment pathways were mainly concentrated in PI3K/ Akt signaling pathway, hepatitis B, cancer related pathway, tumor necrosis factor signaling pathway, IL-17 signaling pathway, fluid shear stress and atherosclerosis, virus infection and HIF-1 signaling pathway, among others. Among them, PI3K/Akt signaling pathway can regulate the activation of inflammatory cells, release of inflammatory mediators, and play a regulatory role in chronic inflammation.^[48] HIF-1 is a hypoxiainducible factor that activates genes encoding proteins involved in hypoxic homeostasis response and induces the expression of proteins controlling glucose metabolism, cell proliferation, and angiogenesis, playing a key role in ischemic and hypoxic mvocardium.^[49] Cluster analysis by using ClueGO showed that the pathways mainly classified in IL-17 signaling pathway, apoptosis, fluid shear stress, and atherosclerosis. IL-17 is an

inflammation-related cytokine. Studies have shown that the activation of IL17 and its mediated signaling pathway leads to end-stage myocardial cell necrosis and loss of apoptosis.^[50-52] Therefore, inhibiting the apoptosis of myocardial cells after ischemia reperfusion can effectively protect the myocardium from the injury. Endothelial cells transduce the frictional force from blood flow (fluid shear stress) into biochemical signals that regulate gene expression and cell behavior via specialized mechanisms and pathways. These pathways shape the vascular system during development and during postnatal and adult life to optimize flow to tissues.^[53,54] This fluid shear stress is closely related to the occurrence and development of atherosclerosis.[55] A study in vivo revealed this association between alignment and atherosclerosis, which ECs fail to align in flow; under the condition of hypercholesterolemic, these syndecan4-/- mice show increased atherosclerosis, including lesions in regions of laminar flow that are normally protected.^[56] Furthermore. the results of molecular docking suggested that the vina scores of TSA, CPT, and VEGFA were -9, 8 and -9.6 kcal/mol, respectively. It is generally believed that when the vina score is >-7 kcal/mol, there is a strong binding force between molecules. As active components contenting more in Danshen, the role of TSA and CPT in the treatment of MIRI deserves further study.

5. Conclusion

To be summarized, the present study suggests that luteolin, TSA, CPT might be the crucial active compounds in DS on MIRI. AKT1, IL6, VEGFA, MAPK1, STAT3, CASP3, PTGS2, FOS, MYC, JUN, MAPK14, and BCL2L1 might be the potential targets. Moreover, the effect of DS on MIRI might be achieved by regulating the IL-17 signaling pathway, PI3K/Akt signaling pathway or HIF-1 signaling pathway. Molecular docking indicated that the better affinity between TSA and potential target VEGFA, which was worthy to be further researched.

The present study based on network pharmacology and molecular docking simulation could provide a systematic analysis for the research of DS on MIRI. But nevertheless, it is noted that there were limitations in the present study. First, focusing on proven target genes may preclude potential targets that have not been experimentally validated. Secondly, the verification analyses which lack of in the present study will be completed in the further study to elucidate the molecular mechanism in the treatment of Danshen on MIRI.

Author contributions

Zhiyan Jiang contributed to the study conception and design. Zhiyan Jiang collected the data and performed the data analysis. Zhiyan Jiang contributed to the interpretation of the data and the completion of figures and tables. Zhiyan Jiang contributed to the drafting of the article and final approval of the submitted version. **Conceptualization:** Zhiyan Jiang.

Data curation: Zhiyan Jiang.

Formal analysis: Zhiyan Jiang.

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