Investigation of Possible Herb-Drug Interactions for the Treatment of Cardiovascular Diseases

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This correspondence is intended as a brief report of an investigation that furthers the data in previous reports published in this journal by McEwen[1] and Maione.[2]

Cardiovascular diseases (CVDs) are the leading cause of mortality and mainly account for thrombotic events.[3] Herbal medicines are widely used for the treatment of CVDs due to traditional and cultural beliefs and have so for many years. However, in several countries, herbal medicines have relatively loose regulatory requirements and can be considered self-prescribed medications.[1,4,5] In numerous experimental studies, herbal medicines have been found to have an effect on biological mechanisms related to the cardiovascular system.[6,7] Hence, increasingly greater attention has been paid to potential risk of interactions between conventional drugs and widespread active herbs.[4,8]

The article by McEwen[1] reviewed herbal efficacy and noted their potential to modify progression of CVD via the modification of platelet function. Furthermore, Maione[2] investigated two single compounds of danshen (*Salvia miltiorrhiza*) and reported their underlying mechanism on platelet function and hemostasis. McEwen[1,9] also suggested that the herb – drug interactions are not fully understood and outlined underlying mechanisms of action and, in particular, potential risks that herbal medicine create by affecting concomitant anticoagulant therapy. In terms of the complexity and wide prevalence of herbal medicines, it is of great importance to explore the biological mechanism of herb – drug interactions for reasons of safety. This correspondence explains the possible biological mechanism of herb – drug interaction at the drug targets of action.[10] To our knowledge, this issue has not been fully described in the existing literature.

In clinical practice, both *Salviae miltiorrhizae radix et rhizoma* (Danshen in Mandarin, DS) and Chuanxiong Rhizome (Chuanxiong in Mandarin, CX) are herbs frequently used for invigorating blood circulation and eliminating stasis.[11,12] A pairing (a basic unit of complex herbal formulae) of the two herbs was one of the most frequently compatible herbal pairs in best-selling herbal formulae released by the China Association of Chinese Medicine in 2017.[13] Therefore, our investigation employs the herbal pair (DS – CX) to analyze the mechanism of action and possible interaction with Western drugs. Moreover, to understand the intrinsic herb – drug interaction on the molecular level, this investigation uses the network of pharmacological approach[14] to integrate the abundant data which have accumulated from previous research on herbal medicines and current approved anti-CVD drugs. For detailed methods, please refer to the Appendix (also refer to ►**Fig. 1** and ►**Tables 1**, **2**).

In this investigation, the "target – (pathway) – target" network clearly shows that DS – CX interacts with the targets of anti-CVD Western drugs. DS – CX may interact with 56 (33.9%) of targets of anti-CVD Western drugs. Totally, DS – CX's 384 compounds may affect 567 biological molecules. Meanwhile, it is of significance to specify the kind of interactions in the specific pathways, especially the main thrombotic pathways. Our investigation found that two (prostaglandin-endoperoxide synthase 1 [PTGS1], integrin subunit alpha 2b [ITGA2B]; 22.2%) out of nine Western medicine targets on platelet activation are involved in target sets of DS – CX. Similarly, for the pathway of vascular smooth muscle contraction, there are 6 of 17 drug targets (adenosine A2a receptor [ADORA2A], ADORA2B, adrenoceptor alpha 1A [ADRA1A], ADRA1B, ADRA1D, potassium calcium-activated channel subfamily M alpha 1 [KCNMA1]; 35.3%) are relevant to DS – CX. In addition, for the pathway of complement and coagulation cascades, the corresponding number is 4 (F2, F10, Serpin [serine protease inhibitors] family E member 1 [SERPINE1], plasminogen activator, urokinase [PLAU]; 36.4%) out of 11. Refer to the Appendix for

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more detailed results of network analysis. Higher overlapping intensity between pharmaceutical and herbal targets may mean higher risk in clinical practice of Western drugs.

For example, the verified corresponding targets of aspirin include prostaglandin G/H synthase 1 (COX-1 [Cyclooxygenase-1]; gene name: *PTGS1*) and prostaglandin G/H synthase 2 (COX-2; gene name: *PTGS2*).[15,16] COX-1 mainly contributes to the arachidonic acid metabolism pathway and the platelet activation pathway. COX-2 is mainly involved in the arachidonic acid metabolism pathway directly relevant to thrombosis and the vascular endothelial growth factor (VEGF) signaling pathway relevant to thrombosis indirectly. COX-1 and COX-2 might be targeted by senkyunolide B, senkyunolide C, and senkyunolide E from CX, and phenanthraquinones from DS, including tanshinone I, 1-dehydrotanshinone IIA, neocryptotanshinone, przewaquinone A, isotanshinone I, nortanshinone, etc. Previous studies have partially supported the potential effects of DS and CX on COX-1 and COX-2.[11,12,17]

With the wide prevalence of active herbal medicines, it is necessary to add an understanding of the biological mechanism of herb – drug interaction. In general, this

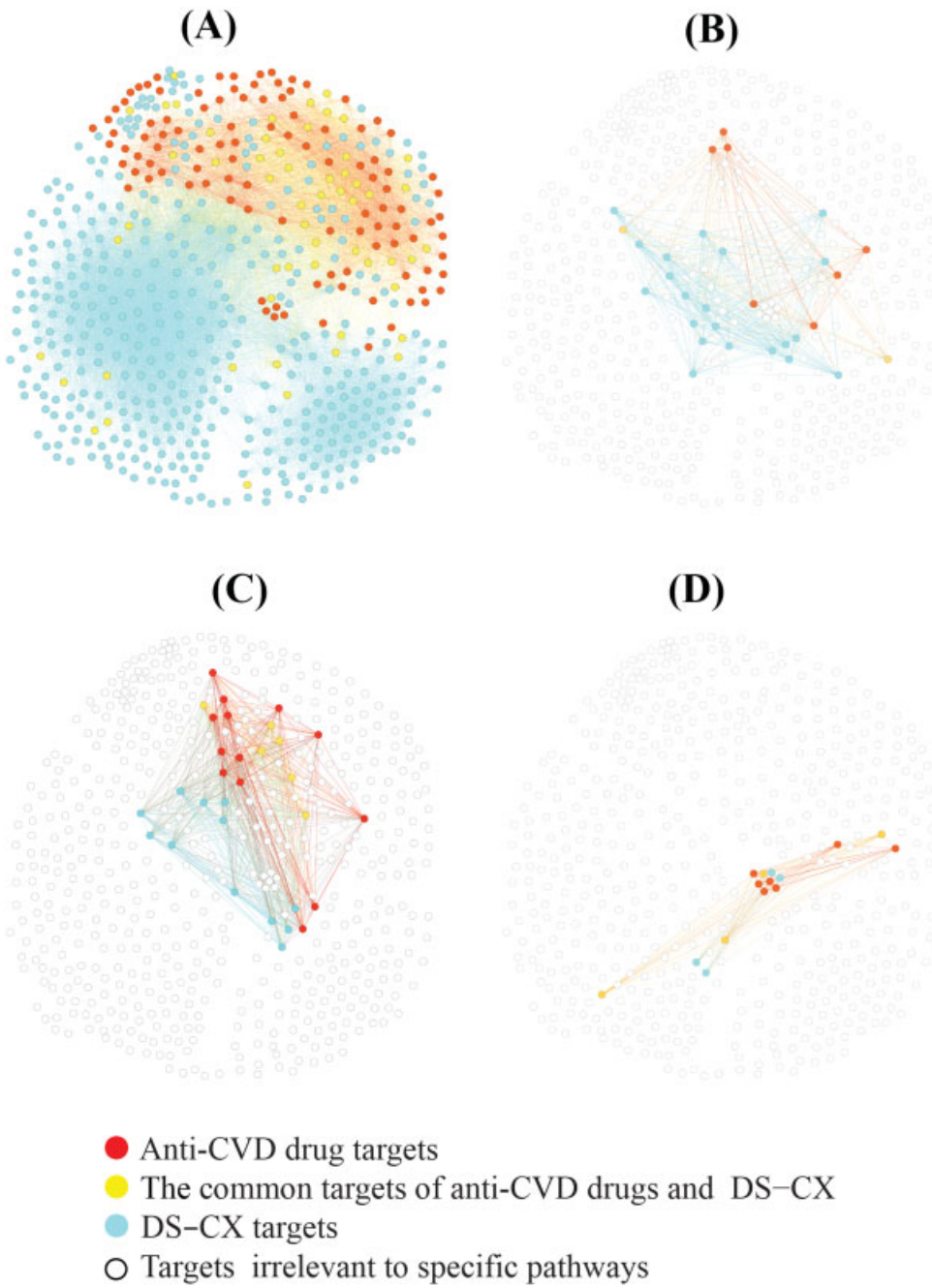

Fig. 1 The TPT (target – [pathway] – target) networks; (**A**) whole network, (**B**) subnetwork in the platelet activation pathway, (**C**) subnetwork in the vascular smooth muscle contraction pathway, (**D**) subnetwork in the complement and coagulation cascades pathway. CVD, cardiovascular disease; DS–CX, danshen–chuanxiong.

Table 1 A general comparison of conventional anti-CVD drugs and DS – CX

	Western drugs (W)	Danshen (DS)	Chuanxiong (CX)	DS – CX	JI
Compounds	217	188	220	384	0.005[a]
Targets	165	439	339	567	0.339

Abbreviations: CVD, cardiovascular disease; DS–CX, danshen–chuanxiong; FDA, Food and Drug Administration; JI, Jaccard's index.
[a]Adenosine is the only common compound of anti-CVD drugs and DS – CX. It was approved in 1989 by FDA for cardiac therapy.

Table 2 Target-based interaction between anti-CVD drugs and DS – CX

	Anti-CVD drug targets	Common targets	JI
Whole network ►**Fig. 1A**	165	56	0.339
Subnetwork ►**Fig. 1B**	9	2	0.222
Subnetwork ►**Fig. 1C**	17	6	0.353
Subnetwork ►**Fig. 1D**	11	4	0.364

Abbreviations: CVD, cardiovascular disease; JI, Jaccard's index.

kind of herb – drug interaction implies that patients simultaneously taking anti-CVD Western drugs and DS – CX may be exposed to additional risks caused by accumulated effects on common herb – drug targets. More importantly, this kind of risk is not usually visible and difficult for clinical physicians to observe due to wide herbal utilization as undisclosed self-medication. In this context, herb – drug relationships are worthy of further exploration in the future, especially from experimental and clinical perspectives.

Authors' Contributions

Y.J.H. and F.Q.Y. conceived and designed the study; H.L.Z. analyzed data, performed the network analysis, and drafted the manuscript; Y.J.H. and F.Q.Y. revised the manuscript. All authors have read and approved the final manuscript.

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Conflicts of Interest

The authors have no conflicts of interest to declare.

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Appendix—Methods and Results

Network pharmacology has been widely used to explain complex biological system and herbal medications.[18,19] This investigation employed the approach of network pharmacology to explain the possible biological mechanism of herb – drug interaction at the drug targets of action. First, the data of compounds of danshen–chuanxiong (DS – CX) were preliminarily collected from chemical databases, including TCM database@Taiwan,[20] traditional Chinese medicine-information database (TCM-ID),[21] Herbal Ingredients' Targets Database (HIT),[22] and traditional Chinese medicine systems pharmacology database (TCMSP),[23] together with the supplements from PubMed literature. The data of targets or putative targets of DS – CX compounds were obtained from PubChem,[24] TCMSP,[23] and similarity ensemble approach (SEA).[25] Moreover, we collected information around drugs used for the treatment of cardiovascular diseases (CVDs), mainly including anti-CVD small molecules and biological products approved by the U.S. Food and Drug Administration (FDA) by September 2017.[26] The data of targets of these conventional drugs were extracted from the databases of Drugbank[15] and Drugcentral.[16] The enrichment analysis of targets of DS – CX and conventional drugs was carried out by STRING[27] to acquire the target – pathway associations.

Based on the target – pathway associations, a "target – (pathway) – target" (TPT) network was constructed with the reference to our previous work.[14] In this TPT network, a node represents a DS – CX's or pharmaceutical target distinguished by different colors, and an edge indicates that both of connected nodes are involved in at least one of the same pathways. By highlighting targets relevant to specific pathways and neglecting irrelevant ones, the TPT network can be shown as various subnetworks specific to different pathways.

►**Fig. 1A** shows the whole TPT network and various TPT subnetworks specific to different anti-thrombotic pathways, that is, the platelet activation pathway (►**Fig. 1B**), the vascular smooth muscle contraction pathway (►**Fig. 1C**), and the complement and coagulation cascades pathway (►**Fig. 1D**).

As identified in ►**Fig. 1A**, there exists a large number of biological molecules relevant to DS – CX; more importantly, many of them are also targets of conventional anti-CVD drugs. This type of overlap seems to be more distinct in the vascular smooth muscle contraction pathway and the complement and coagulation cascades pathway in comparison with the platelet activation pathway, as identified in ►**Fig. 1B–D**. In order to measure quantitatively, we established an adjusted Jaccard's index (JI) which denotes how many percentages of compounds or targets of anti-CVD drugs are covered by DS – CX. In ►**Table 1**, values in columns "W," "DS," "CX," and "DS–CX" represent the number of corresponding compounds or targets. As ►**Table 1** shows, there is only one common compound of anti-CVD drugs and DS – CX, but targets between them have a high overlap.

Moreover, ►**Table 2** shows target-based interaction between anti-CVD drugs and DS – CX in different thrombotic pathways. Values in the middle of the two columns indicate the corresponding number of anti-CVD drug targets or common targets, which are used to calculate the JI. The relatively higher JI values in ►**Fig. 1C, D** further demonstrate the observation in ►**Fig. 1** that herb – drug interaction between anti-CVD drugs and DS – CX may be more serious in the vascular smooth muscle contraction pathway and the complement and coagulation cascades pathway.