Original Article

Investigating the multitarget pharmacological mechanism of *Rhodiola wallichiana* var. *cholaensis* acting on angina pectoris using combined network pharmacology and molecular docking

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Background: *Rhodiola wallichiana* var. *cholaensis* (RW) is one of the traditional Chinese medicinal materials, which is used to treat angina pectoris (AP). However, the possible underlying mechanisms remains unclear. The aim of this study was to explore RW in the treatment of AP and to identify the potential mechanism of the core compounds.

Methods: In this study, systematic and comprehensive network pharmacology and molecular docking were used for the first time to explore the potential pharmacological mechanisms of RW on AP. First, the relative compounds were obtained by mining the literature, and potential targets of these compounds using target prediction were collected. We then built the AP target database using the DigSee and GeneCards databases. Based on the data, overlapping targets and hub genes were identified with Maximal Clique Centrality (MCC) algorithm in Cytoscape, cytoHubba. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses and protein-protein interaction (PPI) analysis were performed to screen the hub targets by topology. Molecular docking was utilized to investigate the receptor-ligand interactions on Autodock Vina and visualized in PyMOL.

Results: A total of 218 known RW therapeutic targets were selected. Systematic analysis identified nine hub targets (*VEGFA*, *GAPDH*, *TP53*, *AKT1*, *CASP3*, *STAT3*, *TNF*, *MAPK1* and *JUN*) mainly involved in the complex treatment effects associated with the protection of the vascular endothelium, as well as the regulation of glucose metabolism, cellular processes, inflammatory responses, and cellular signal transduction. Molecular docking indicated that the core compounds had good affinity with the core targets.

Conclusions: The results of this study preliminarily identify the potential targets and signaling pathways of RW in AP therapy and lay a promising foundation for further experimental studies and clinical trials.

Keywords: *Rhodiola wallichiana* var. *cholaensis* (RW); network pharmacology; angina pectoris (AP); signaling pathway; molecular docking

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Introduction

Angina pectoris (AP) is a clinical syndrome with episodes of chest pain as the main symptoms due to temporary hypoxia and ischemia of the heart (1). The incidence of AP in China is about 3.6%, and the trend is increasing year by year (2). It is well known that AP is a typical symptom of myocardial ischemia. Therefore, conventional medicines for the treatment of AP, such as nitrates, beta-blockers, calcium channel blockers, are mainly used to alleviate the symptoms of AP (3).

Traditional Chinese medicine (TCM) is an integrated system of medicine with a history of thousands of years. It has potential application value in clinical practice (4). *Rhodiola wallichiana* var. *cholaensis* (RW) is a common species of the genus *Rhodiola*, which is one of the most popular medicinal plants in Asia (5). Clinical studies have shown that RW preparations can reduce the symptoms of AP, heart failure and other heart diseases, have antioxidant and anti-inflammatory effects, and reduce hypoxia-induced cellular oxidative stress (6,7). Moreover, modern pharmacological researches have revealed multiple bioactivities of RW plants, such as antioxidative (8,9), immunomodulatory (10), anti-Inflammatory (11), antidiabetic (12,13), antihypertensive and neuroprotective (14,15) antistress and antidepressant (16-18), anti-altitude sickness (19,20), antifatigue (21,22), and anticancer (23,24) activities. The relationship between the chemical profile and bioactivities of RW should be established. However, due to the multi-compound system of TCM, the material basis and molecular mechanisms involved in RW remain unclear. Therefore, it is important to develop modern and technical means to analyze the mechanism of RW in treating various diseases.

Network pharmacology is a new research method that integrates pharmacodynamics, pharmacokinetics, and network analysis. In recent years, it has been applied to elucidate the possible mechanism of TCM prescriptions in the treatment of various diseases from the perspective of proteomics systems (25-27). In particular, it has been used to characterize the interaction relationship of TCM in multi-components and multitargets, as well as to study the mechanism of multitarget compounds affecting the biological network of TCM (28,29). In this study, we explore the hub active ingredients and potential mechanisms of RW in AP based on network pharmacology and molecular docking. We present this article in accordance with the STREGA reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1891/rc).

Highlight box

Key findings

- The results of this study verify and predict the molecular mechanism of *Rhodiola wallichiana* var. *cholaensis* (RW) in angina pectoris (AP) at the system level, which may provide enlightenment for the mechanism of RW and other anti-AP Chinese medicines and promote the application of RW in the treatment of AP.

What is known and what is new?

- RW is a traditional Chinese medicine that activates blood circulation and removes blood stasis, which can effectively relieve patients' blood circulation disorders and improve the protective effect against cardiovascular diseases.
- We found that these hub targets (*VEGFA*, *GAPDH*, *TP53*, *AKT1*, *CASP3*, *STAT3*, *TNF*, *MAPK1* and *JUN*) ameliorated AP by participating in protecting the vascular endothelium, regulating glucose metabolism, regulating cellular processes, regulating the inflammatory response, and participating in cell signal transduction, among other processes.

What is the implication, and what should change now?

- The clinical application of RW in cardiovascular diseases has accurate efficacy, high safety, few adverse reactions, and can achieve rapid and effective treatment purposes. It is one of the ideal choices for the treatment of cardiovascular diseases.

Methods

Schematic diagram

In this study, network pharmacology strategies, including drug similarity assessment, oral bioavailability prediction, multiple drug target prediction, and other network pharmacology techniques, were used to study the potential role of RW against AP mechanisms. The gene target network of RW was analyzed through network pharmacology, starting with the identification of active substances and key target genes whose expression is altered in AP and whose protein products are predicted to interact with active compounds in RW. *Figure 1* presents the schematic diagram of the study design and workflow. We investigated the mechanism of action of RW using network pharmacology and molecular docking methods.

Chemical ingredient database building

A total of 83 RW compounds were collected through literature mining. Then, their biomolecular activities were

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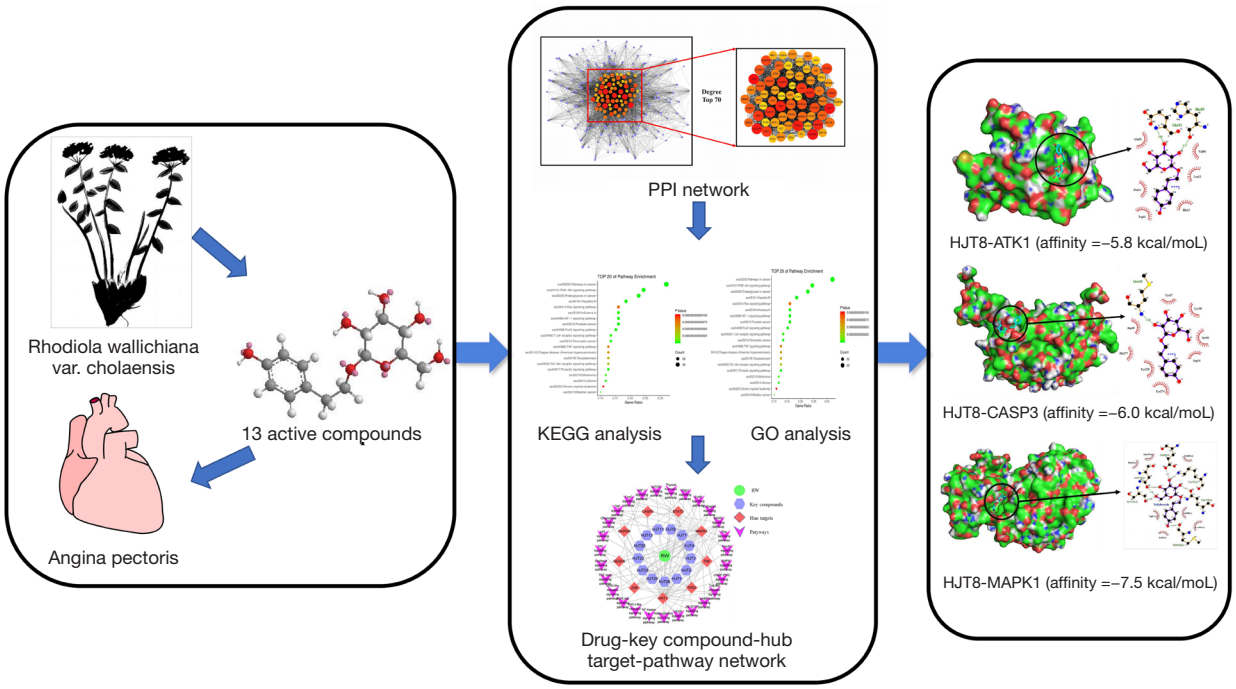

Figure 1 Flow chart showing the analysis of the mechanisms of action of RW based on data mining and network pharmacology. PPI, protein-protein interaction; KEGG, Kyoto Encyclopedia of Genes and Genomes; GO, Gene Ontology; RW, *Rhodiola wallichiana* var. *cholaensis*.

viewed using the PubChem database (https://pubchem.ncbi.nlm.nih.gov) (30). Finally, the standard simplified molecular-input standard delay format (SDF) and the structural information of 42 compounds were obtained, including that of salidroside, tyrosol, and quercetin, among others (31-33).

Screening of active compounds of RW

The SDF format file was uploaded under the item "Chemical Ingredients Database Building" to the Swiss ADME platform (http://www.swissadme.ch) (34,35), a platform for predicting the relevant parameters of the absorption and drug-like properties of candidate compounds. First, we set the gastrointestinal (GI) absorption as "High" for the conditions under which the drug can be absorbed to screen for active compounds with good oral bioavailability; second, we set five types of drug predictability (Lipinski, Ghose, Veber, Egan, Muegge), and there were three or more compounds that appeared with "Yes" in the results, which could be considered the active compounds.

Active compound target prediction

The SDF format file was imported into the Swiss Target Prediction (http://www.Swisstargetprediction.ch/) (36,37) and PharmMapper (http://www.lilab-ecust.cn/pharmmapper/) (38-40) platforms with the property set to "*Homo sapiens*", in order to collect all the predicted targets and removing duplication.

Prediction of known therapeutic targets

Genes associated with AP were collected and screened from the GeneCards database (http://www.genecards.org/) (41) and DigSee database (http://210.107.182.61/geneSearch/) (42). We searched GeneCards and DigSee for data using the keywords "angina pectoris" with the species limited to "*Homo sapiens*". Then, the top 1,000 target genes were selected from the GeneCards database, and 541 targets were obtained from the DigSee database. Finally, 1,297 genes were collected after removal of duplicates. To obtain the potential target genes of RW that played a major role in AP, the AP-related genes

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were compared with potential gene targets of the active components.

Network construction

A network analysis was performed to scientifically determine the complex relationship between AP-related compounds and targets. Subsequently, based on the protein-protein interactions (PPIs), we linked the putative targets of RW, the AP-related targets, and interactional proteins together. Then, to illustrate the relationship between the possible targets of RW and known targets of AP, a drug-compound-target-disease network was constructed and visualized using Cytoscape software (version 3.7.2) (26). The PPI network of the interaction between RW and AP was obtained via Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) software (http://string-db.org/cgi/input.pl), in which the limiting conditions were "*Homo sapiens*" and a confidence score ≥0.4. The subsequent results were saved in tab separated values (TSV) format and imported into Cytoscape software to visualize and analyze the interaction network. We used the style function from the statistics tool in Cytoscape to set the node size and color settings to reflect the size of the degree and the thickness of the edge of the comprehensive score to obtain the final protein interaction network. Degree refers to the number of links to node I and is usually used to describe the topological importance of proteins in the network. Therefore, we used cytoHubba to select the central gene with the degree value as the tangent point to analyze the pharmacological effects of key targets.

Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment

GO and KEGG pathway enrichment analyses were executed on the candidate targets using Database for Annotation, Visualization and Integrated Discovery (DAVID) 6.8 (43). GO gene enrichment analysis included 3 categories: biological process (BP), molecular function (MF), and cell component (CC). With $P \leq 0.05$ as the truncated value, the results were calculated using bilateral hypergeometric tests, including the identification of the enriched GO terms and the localization of the biological and MFs of these proteins. Finally, the bubble chart was plotted using the ImageGP platform (http://www.ehbio.com/ImageGP/index.php/Home/Index/index.html) (44).

Molecular docking simulation

Core targets were obtained from the PPI network for molecular docking. Initially, AutoDockTools 1.5.6 was employed to set the number of rotatable bonds for the 12 small molecule compounds. Subsequently, protein conformation was determined in the Protein Data Bank (PDB; https://www.rcsb.org/) (45-47) database. The screening conditions were set as follows: (I) the protein structure was obtained by X-crystal diffraction; (II) the crystal resolution of the protein was less than 2.5 Å; (III) the species was *Homo sapiens*; and (IV) association action models were constructed with the STRING and PDB databases. Based on the above conditions, a total of 11 core target protein PDB IDs were gathered. Additionally, PyMOL 2.7 (https://pymol.org/2/) and AutoDockTools were applied to not only remove water molecules and proligand small molecules but also to hydrogenate and charge them. Finally, molecular docking calculations were performed using AutoDock Vina 1.1.2, and PyMOL and LigPlot+ software was used to visualize the docking results.

Results

Target screening of RW and AP

A total of 83 chemical ingredients were obtained from the RW according to related literature studies. After removal of duplicates, 26 chemical ingredients (*Table 1*) and 671 corresponding targets of RW were acquired, and 1,297 therapeutic targets for AP were obtained from the GeneCards database and DigSee database (*Figure 2A*). Then, the ultimate gene targets of RW acting on AP were obtained by mapping these targets to the components of the disease targets. As shown in *Figure 2B*, 218 target genes corresponding to RW candidate compounds of AP were obtained for further research.

Network construction and result analysis

TCM exerts its therapeutic role mainly through the synergistic effect between compounds and targets. To illustrate the potential mechanism of this synergistic effect of RW on AP, it is necessary to understand the effects of each component in RW on its target proteins. Based on the network analysis of compounds and putative targets in Cytoscape 3.7.2, as shown in *Figure 2C*, our study showed that the network was composed of 1,754 edges and 697 nodes, among which 26 were component nodes and

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Table 1 Analysis of the 26 underlying compounds in RW

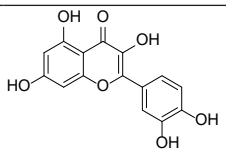
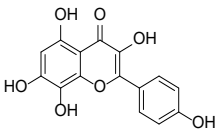
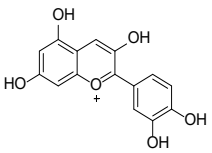
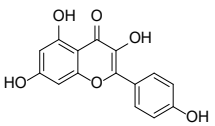
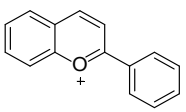
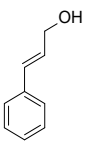
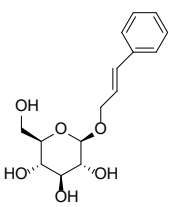
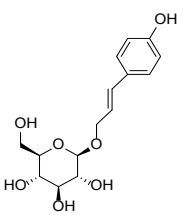
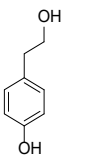
No.	Mol ID	Compound	Formula	Chemical structure
1	HJT1	Quercetin	$C_{15}H_{10}O_7$	
2	HJT2	Herbacetin	$C_{15}H_{10}O_7$	
3	HJT3	Cyanidin	$C_{15}H_{11}O_6^+$	
4	HJT4	Kaempferol	$C_{15}H_{10}O_6$	
5	HJT5	Anthocyanin	$C_{15}H_{11}O^+$	
6	HJT6	Cinnamic alcohol	$C_9H_{10}O$	
7	HJT7	Rosin	$C_{15}H_{20}O_6$	
8	HJT8	Salidroside	$C_{14}H_{20}O_7$	
9	HJT9	Tyrosol	$C_8H_{10}O_2$	

Table 1 *(continued)*

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Table 1 *(continued)*

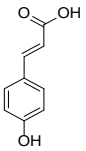
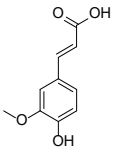
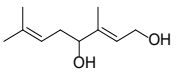
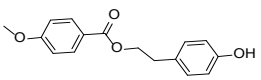
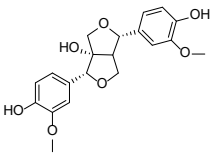
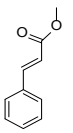
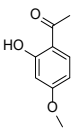
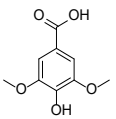
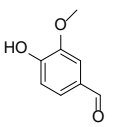
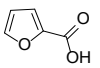
No.	Mol ID	Compound	Formula	Chemical structure
10	HJT10	p-Hydroxy-cinnamic acid	$C_9H_8O_3$	
11	HJT11	Ferulic acid	$C_{10}H_{10}O_4$	
12	HJT12	Rosiridol	$C_{10}H_{18}O_2$	
13	HJT13	p-hydroxyphenethyl anisate	$C_{16}H_{16}O_4$	
14	HJT14	8-hydroxypinoresinol	$C_{20}H_{22}O_7$	
15	HJT15	Methyl trans-cinnamate	$C_{10}H_{10}O_2$	
16	HJT16	Paeonol	$C_9H_{10}O_3$	
17	HJT17	Syringate	$C_9H_{10}O_5$	
18	HJT18	Vanillin	$C_8H_8O_3$	
19	HJT19	2-furoic acid	$C_5H_4O_3$	

Table 1 *(continued)*

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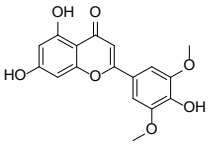
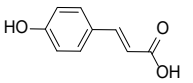
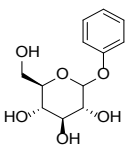
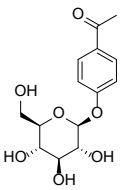
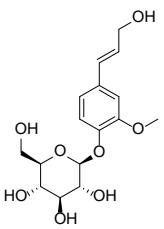
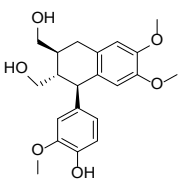
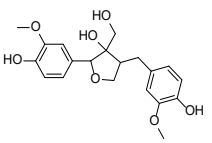
Table 1 *(continued)*

No.	Mol ID	Compound	Formula	Chemical structure
20	HJT20	Tricin	$C_{17}H_{14}O_7$	
21	HJT21	p-hydroxycinnamic acid	$C_9H_8O_3$	
22	HJT22	β-D-phenyl glucopyranoside	$C_{12}H_{16}O_6$	
23	HJT23	Picein	$C_{14}H_{18}O_7$	
24	HJT24	Coniferin	$C_{16}H_{22}O_8$	
25	HJT25	Scaphopetalone	$C_{21}H_{26}O_6$	
26	HJT26	Berchemol	$C_{20}H_{24}O_7$	

RW, *Rhodiola wallichiana* var. *cholaensis*; Mol, molecule.

671 were target nodes. It was clear that the target genes with high degree and mediated centrality were most important to the antianginal effect of RW in the network.

Construction and analysis of the PPI network

To further investigate the potential mechanism of action of RW in the treatment of AP, target genes acting on the corresponding components were submitted to the STRING database, a subsequent PPI network was constructed, and then highly reliable target protein interaction data sets with a score >0.7 were selected. A single protein is unlikely to perform a specific function, and proteins often interact with each other to form large molecular complexes that perform their biological functions. Thus, exploring and constructing a PPI network is key to understanding the BPs

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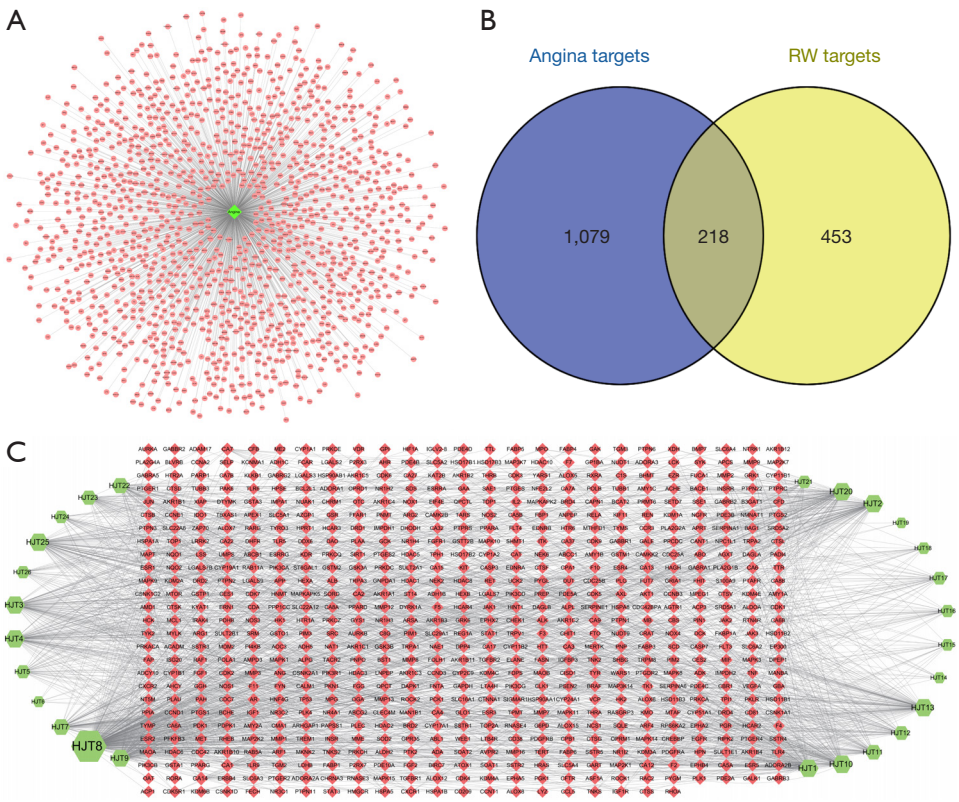

Figure 2 Analysis of the active compounds of RW and the putative RW antianginal effect. (A) Angina target network plotting. The red circle represented all the 1,297 genes of AP obtained from GeneCards and DisGeNET, while the green diamond represented the disease. (B) The Venn diagram showed the 218 overlapping targets of AP and compounds of RW. (C) The compound-predicted target network of RW. The green hexagon represented all the 26 compounds of RW, while red diamond represented the 671 targets. The size of the nodes is directly proportional to the degree of the nodes. Cytoscape 3.7.2 software was used to generate the figure. RW, *Rhodiola wallichiana* var. *cholaensis*; AP, angina pectoris.

and biological functions of cells. The PPI network (*Figure 3*) file obtained was imported into Cytoscape software. After adjusting the parameters, we selected 70 key genes that were related to the various pathogenic processes of AP according to the degree.

GO functional analysis

A total of 70 potential genes associated with AP were analyzed in the DAVID panel. We undertook GO enrichment analyses of 70 targets to explore their general functions. As shown in *Figure 4*, the GO analysis results showed the key predictive targets of RW acting on AP, and 20 GO items with low P values and more enrichment targets were enriched. Our results showed that these predictive targets were mainly involved in cell signal transduction, protein autophosphorylation, and positive regulation of cell proliferation, indicating that RW may regulate the biological function of AP through these pathways, thus playing a key role in treatment of AP.

KEGG signaling pathway analysis

To identify the relevant signaling pathways involved in the antianginal effect of RW, DAVID analysis was performed. A total of 34 KEGG signaling pathways were obtained, and 27 pathways were associated with AP. To show the results of the signaling pathways intuitively and explicitly, a bubble diagram was drawn, as seen in *Figure 4D*; here, the bubble scale represents the number of genes, and the depth of the bubble color represents the P value; the change in color from green to red represents the P value from low to high,

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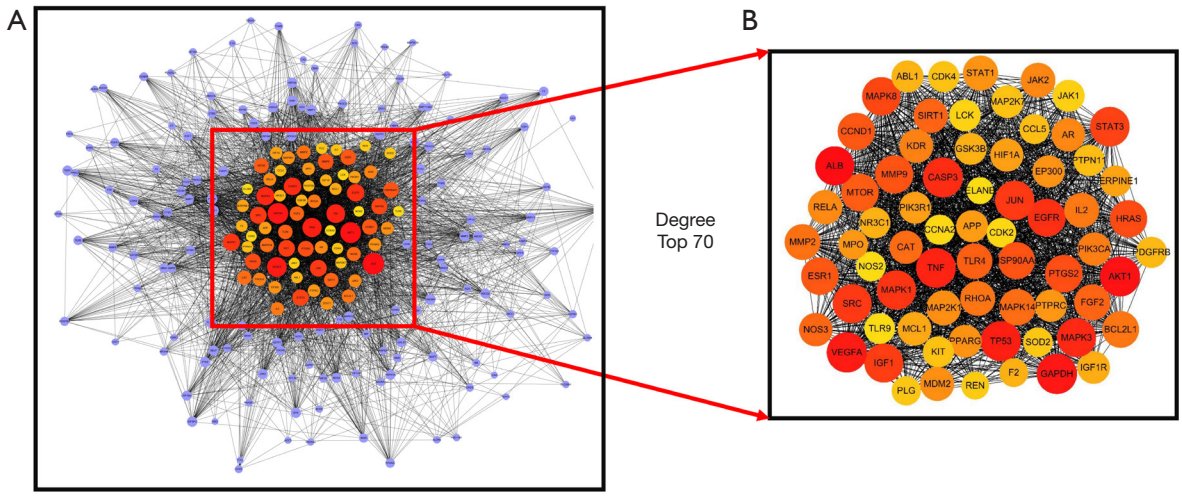

Figure 3 Identification of a core PPI network for RW against angina. (A) The interactive PPI network of RW and AP targets comprising 218 nodes and 4,456 edges are shown. (B) The PPI network of significant proteins extracted from this network comprises 70 nodes and 1,689 edges. PPI, protein-protein interaction; RW, *Rhodiola wallichiana* var. *cholaensis*; AP, angina pectoris.

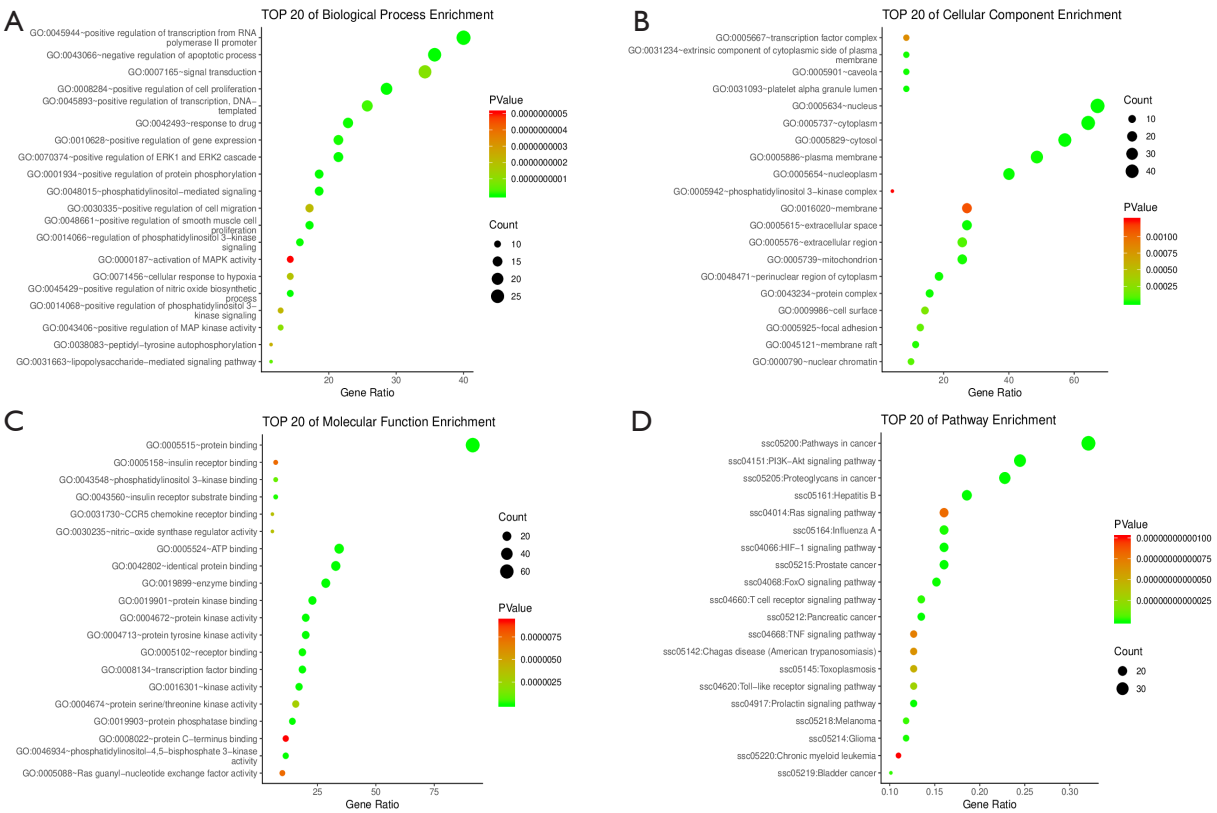

Figure 4 Enrichment analyses of overlapping genes between RW and AP, including KEGG pathway, GOBP, GOMF and GOCC. (A) Enriched Gene Ontology terms for biological processes of potential targets. (B) Enriched Gene Ontology terms for the cellular components of potential targets. (C) Enriched Gene Ontology terms for molecular functions of potential targets. (D) Enrichment analysis of the KEGG signaling pathways. GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; RW, *Rhodiola wallichiana* var. *cholaensis*; AP, angina pectoris; BP, biological process; MF, molecular function; CC, cellular component.

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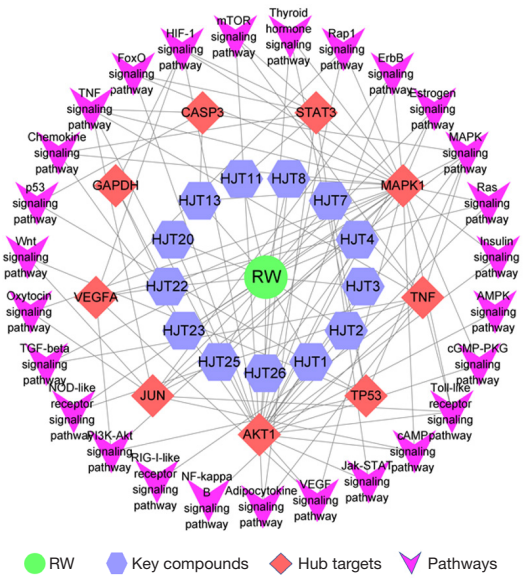

Figure 5 Drug-key compound-hub target-pathway network. The green circle represents the drug, the blue hexagons represent the key compounds, the red diamonds represent the hub targets, and the purple arrows represent the pathways. Cytoscape 3.7.2 software was used to generate the figure. RW, *Rhodiola wallichiana* var. *cholaensis*.

and the size of the nodes indicates how many target genes are associated.

The KEGG analysis results indicated multiple channels and mechanisms of action of RW against AP.

The top 20 pathways with lower P values and more gene enrichment are listed in *Figure 4D* and include the PI3K-Akt signaling pathway, HIF-1 signaling pathway, Ras signaling pathway, thyroid hormone signaling pathway, and Toll-like receptor signaling pathway. These signaling pathways are closely related to the anti-AP effects of RW. To elucidate their interactions, we established a graphical network containing the main chemical-target-signaling pathway of RW (*Figure 5*).

Molecular docking simulation

In this study, nine potential targets with 13 corresponding compounds were simulated with molecular docking, and the docking results were analyzed. The analysis revealed higher-affinity results for compound and hub targets (*Table 2*). Using PyMOL software, we found that 13 compounds could enter the active pocket of the protein. HJT8 (salidroside; *Figure 6A*) was used as an example for analysis. The salidroside small molecule forms four hydrogen bonds with Lys52, Asn152, Ser151, and Met106 residues and has a higher affinity (affinity =–7.5 kcal/mol) with MAPK1 (*Figure 6B*).

Discussion

TCM, a complex, mixed system of multiple ingredients and multiple targets, has traditionally been used to prevent and treat various cardiovascular diseases (CVDs) (33,48,49). RW has a high clinical value as a traditional Chinese medicine in relieving AP. Chu *et al.* (50) included seven randomized controlled trials in 662 patients with stable angina and found that the combination of oral/intravenous infusion of RW provided good relief of angina compared with conventional Western treatment. Man *et al.* (5) included 18 randomized controlled trials involving 1,679 patients and found that RW adjuvant therapy significantly reduced the frequency of angina attacks by ≥80%, the weekly frequency of angina attacks, and significantly improved abnormal electrocardiograms. In addition, it significantly reduced whole blood viscosity, plasma viscosity, and serum levels of fibrinogen. Although RW can effectively relieve AP, its pharmacological mechanism of action remains unclear. Consequently, in the present study, a pharmacology network method was used to identify bioactive compounds, potential targets, and the pathways modulated by these compounds in the RW treatment of AP.

Nine potential hub targets were identified based on selection and network topology analysis, including *VEGFA*, *GAPDH*, *TP53*, *AKT1*, *CASP3*, *STAT3*, *TNF*, *MAPK1* and *JUN*. Numerous studies have shown that the targets mentioned above are mainly involved in the protection of the vascular endothelium, as well as the regulation of glucose metabolism, cellular processes, inflammatory responses, and cellular signal transduction. Vascular endothelial growth factor (VEGF), a strong pro-angiogenesis cytokine, is secreted by vascular endothelial cells, which could increase the permeability of microvessels and venules and promote angiogenesis, thus improving myocardial hypoxia and relieving AP (51-53). A recent study has demonstrated that the inflammatory response is related to the occurrence of CVDs such as coronary heart disease, which may cause local endothelial activation, atherosclerotic plaque rupture, and then thrombosis formation or rupture, leading to AP and myocardial infarction (54). Tumor necrosis factor-alpha (TNF-α) usually appears in the early stage of inflammatory reaction, and plays an important role in cell function regulation, immunity and

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Table 2 Analysis of the target-compound docking simulation

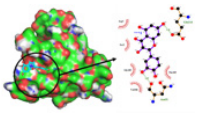
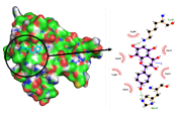
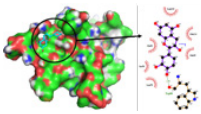
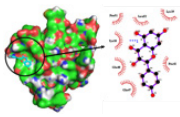
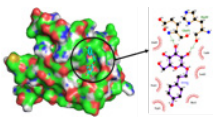
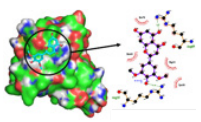
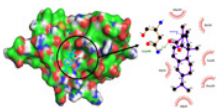
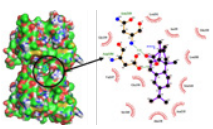
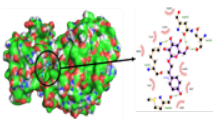
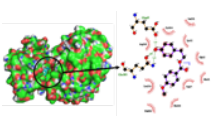
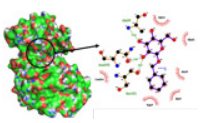
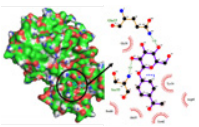
Target protein	PDB ID	Active ingredient	Docked complex of protein and ligand	Affinity (kcal/mol)
AKT1	1UNQ	Quercetin		−6.4
		Herbacetin		−6.2
		Anthocyanidins		−5.6
		Kaempferol		−6.2
		Salidroside		−5.8
		Tricin		−5.9
TNF	5UUI	Rosin		−6.8
TP53	6IUA	Rosin		−6.8
MAPK1	2OJJ	Salidroside		−7.5
		p-hydroxyphenethyl anisate		−6.9
		Benzyl alcohol-O-β-D-pyran glycosidase		−5.9
		l-picein		−6.4

Table 2 *(continued)*

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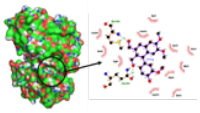
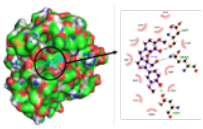
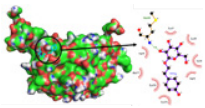
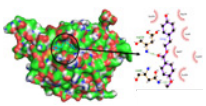
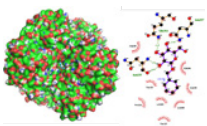
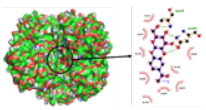
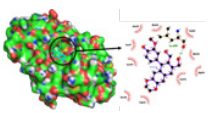
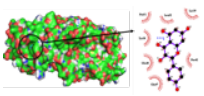
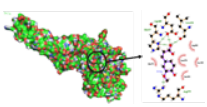
Table 2 *(continued)*

Target protein	PDB ID	Active ingredient	Docked complex of protein and ligand	Affinity (kcal/mol)
		Scaphopetalone		−7.5
		Berchemol		−7.1
CASP3	1RHM	Salidroside		−6.0
		p-hydroxyphenethyl anisate		−6.4
GAPDH	6YND	Benzyl alcohol-O-β-D-pyran glycosidase		−7.3
		l-picein		−7.8
c-JUN	5T01	Scaphopetalone		−5.8
VEGFA	4ZFF	Benzyl alcohol-O-β-D-pyran glycosidase		−6.7
STAT3	1BJ1	Ferulic acid		−5.8

PDB, Protein Data Bank.

inflammatory reaction. It can regulate atherosclerotic plaque and coronary heart disease by affecting vascular endothelial function and vascular remodeling (55). The study has shown that proinflammatory cytokines are significantly increased in patients with AP compared to healthy individuals. Meanwhile, it is important to note that this increased inflammatory activity may be related to the pathogenesis of AP. 1-Deoxynojirimycin (DNJ) significantly improves angina attack frequency by reducing the levels of inflammatory cytokines, including TNF-α (56). AKT1 is an important protein in the PI3K pathway that can regulate cell apoptosis, proliferation, and antioxidant activity (57,58). Han *et al.* (59) demonstrated that hypericin can reduce the inflammatory response by activating phosphorylated protein kinase B (PKB) and reducing TNF-α and interleukin (IL)-6 activity, thus alleviating myocardial ischemia-reperfusion injury. The *p53* gene is an important apoptosis-related gene can be divided into two types: wild type (wp53) and mutant type (mp53). The mutant *p53* gene can promote cell growth and participate in the occurrence of various tumors. The main function of the wild-type *p53* gene is to participate in the negative regulation of cell growth, limiting cell growth and division. In recent years, studies have found that the *p53* gene is not only associated with the occurrence and

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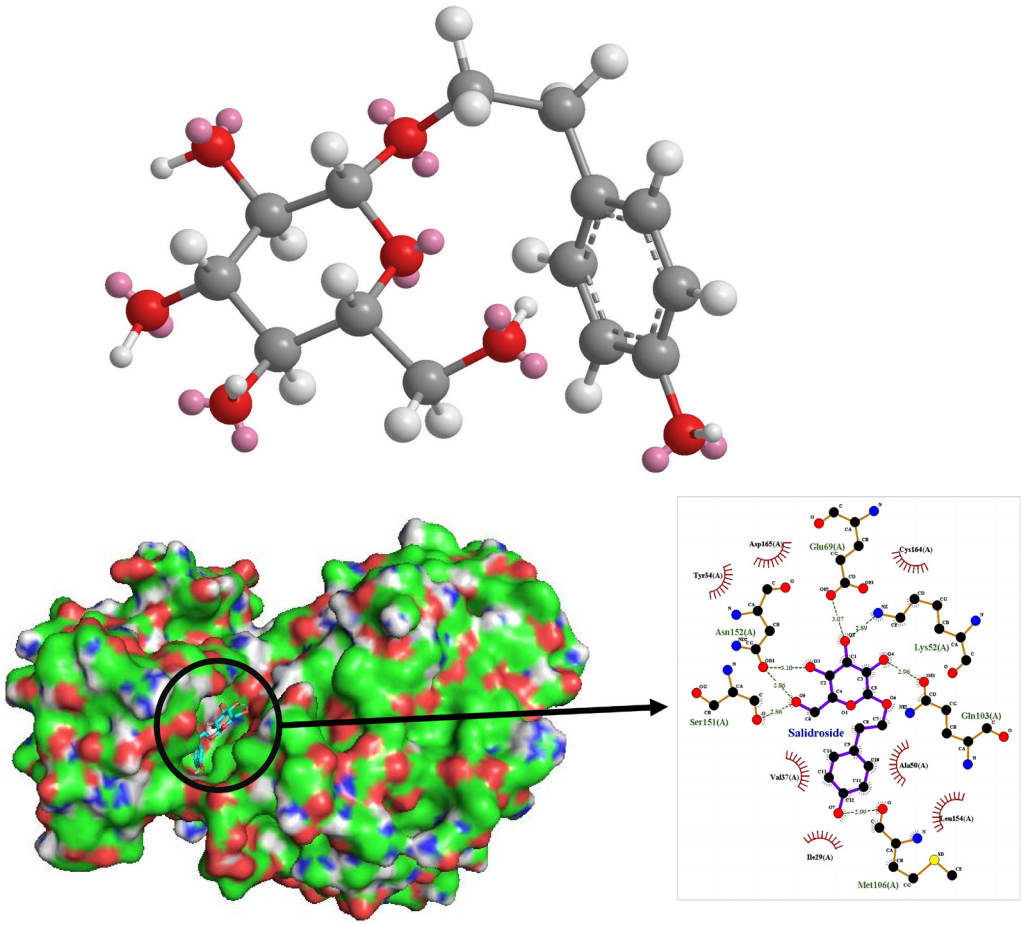

Figure 6 Analysis of the interaction between the salidroside and MAPK1 target proteins. (A) Three-dimensional structure of salidroside. (B) Analysis of the target-compound (HJT8) docking simulation. PyMOL 2.7 and LigPlot+ 1.4.5 software was used to generate the figure.

development of many tumors but also participates in the occurrence of apoptosis in the cardiovascular system (60,61). *JUN* is the heterodimer form of activating protein 1 (AP-1). Previous study has demonstrated that c-JUN can induce the production of adhesion factors in endothelial cells and increase the expression of chemokines and the formation of foam cells, thus promoting the formation and development of atherosclerosis (62). MAPK1 belongs to the Ser-Thr kinase protein family and has been previously reported in different features of cardiac modelling and regulation of inflammation, cell proliferation, and differentiation (63,64). STAT3 is a latent transcription factor that was initially identified as a cytokine signaling transductor and is involved in a variety of BPs, such as cell proliferation (65), differentiation (66), and survival (67).

To understand the potential biological mechanism of RW against AP, GO and KEGG functional enrichment analyses of DAVID and KEGG were applied. Through KEGG pathway analysis ($P<0.05$), we identified 21 AP-related signaling pathways, including HIF-1, PI3K-Akt, MAPK, FoXO, TNF, Ras, and Toll-like receptor signaling pathways. Accordingly, these pathways may be involved in the progression of AP. Based on the P value, we chose the HIF-1 signaling pathway as the most likely candidate for further study. Hypoxia-inducible factor (HIF) is a transcriptional complex that responds to changes in oxygen and provides a master regulator for cells to coordinate changes in gene transcription. HIF acts on all mammalian cell types and is ancient in evolutionary terms. At the molecular level, the HIF complex contains an α subunit and a β subunit, both of which can be selected from several options. HIF-β subunits are composed and participate in heterogeneous reactions.

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The α subunit is regulated and unique to hypoxic reactions. Under hypoxic conditions, HIF-1α is induced and highly expressed, transferring from the cytoplasm to the nucleus and initiating downstream gene expression, such as that of erythropoietin and VEGF. HIF-1α can increase myocardial glucose intake and transportation to continuously provide the compensatory energy supply by regulating myocardial *GLUT4* and *PKM2* gene expression (68). HIF-1α also facilitates the activation of PDK1 and PDK4 as well as UCP2 to enhance mitochondrial oxidative phosphorylation (69). Moreover, NRF1 and TFAM play distinct roles in mitochondrial biogenesis (70), and the upregulation of NRF1 and TFAM promotes mitochondrial DNA synthesis in infarcted cardiac muscle (71). Therefore, the HIF-1 signaling pathway is activated in cardiomyocytes to produce continuous adenosine triphosphate (ATP) in adaptation to hypoxia by shifting myocardial metabolism substrate to glucose intake and transportation (72).

In this study, GO enrichment analysis was adopted. The targets were connected with the regulation of protein phosphorylation, nitric oxide biosynthesis, cell membrane region, platelet alpha granule, protein kinase, and protein phosphatase. Therefore, the results suggest that RW treats AP by participating in BP, CC, and MF.

Molecular docking analysis simulation provided a visual interpretation of the interaction between key compounds and their potential protein targets. For example, salidroside mainly forms 4 hydrogen bonds with Lys52, Asn152, Ser151, and Met106 A residues on MAPK1. Salidroside exerts various pharmacological effects, such as antifatigue, antioxidation, immune regulation, and free radical scavenging activities. In recent years, *in vivo* and *in vitro* experiments have proven that the compound has positive anticancer, anti-inflammatory, antioxidative, neuroprotective, myocardial-protective, liver-protective, and kidney-protective effects (73,74). In addition, it has been reported that salidroside can inhibit the release of lactate dehydrogenase (LDH), creatine-kinase (CK) and aspartate aminotransferase (AST) from human cardiomyocytes by increasing the expression of HIF-1α, increasing the content of superoxide dismutase (SOD), increasing the activity of human cardiomyocytes, and reducing the death and apoptosis of cells (75). Overall, it was speculated that the main composition of RW may play a significant role in the treatment of AP through hub targets in these top-ranking signaling pathways. However, some limitations of our study should be considered. For instance, the results are only based on the screening of already known chemical constituents of RW, related targets, and signaling pathways from the literature and existing databases. Consequently, more in-depth research is required to characterize the underlying mechanisms of RW in the treatment of angina.

At present, network pharmacology is mostly used in the screening of drug active ingredients, prediction of the mechanism of action of specific drugs, analysis of targets of main active ingredients, and development of combination drugs. As a research idea, network pharmacology can also be used to explain the compatibility rules of traditional Chinese medicine compounds and discover new indications of traditional Chinese medicine. Network pharmacology is becoming a powerful and attractive tool to reflect the multi-component and multi-target characteristics of traditional Chinese medicine. Based on network pharmacology methods, it can help explain many difficult problems in the material basis of traditional Chinese medicine efficacy.

Conclusions

Via network pharmacology and molecular docking virtual computing, 26 ingredients of RW and putative known therapeutic targets were collected, and the underlying mechanism of RW in the treatment of AP was explored. RW exerted treatment effects on AP by regulating nine hub targets: *VEGFA*, *GAPDH*, *TP53*, *AKT1*, *CASP3*, *STAT3*, *TNF*, *MAPK1* and *JUN*. Based on the results of GO and KEGG pathway enrichment analysis, we found that these hub targets ameliorated AP by participating in protecting the vascular endothelium, regulating glucose metabolism, regulating cellular processes, regulating the inflammatory response, and participating in cell signal transduction, among other processes. In summary, this study used a network pharmacology approach to investigate the complex network relationships among multiple components, targets, and pathways of RW in the treatment of AP. The results of this study verify and predict the molecular mechanism of RW in AP at the system level, which may provide enlightenment for the mechanism of RW and other anti-AP Chinese medicines and promote the application of RW in the treatment of AP. However, our research results are based on computational analysis, and further experiments are needed to verify these hypotheses.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1891/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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