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MEDICINAL CHEMISTRY RESEARCH

REVIEW ARTICLE

Research progress on the mechanism of anti-myocardial infarction effect and clinical application of effective components of *Salvia miltiorrhiza*

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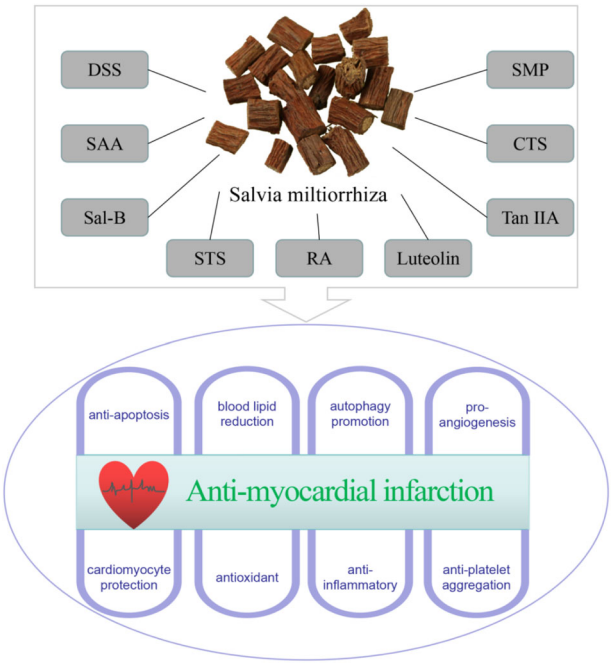
Abstract

Salvia miltiorrhiza, a plant in the Labiatae family, is a traditional Chinese herb. The small molecular components in *S. miltiorrhiza* can be divided into tanshinones and salvianolic acids, which have anti-inflammatory and anti-apoptotic effects by inhibiting the expression of inflammatory factors such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6) and some apoptosis factors. At the same time, these components can also play a protective effect on cardiomyocytes by activating Akt/ERK1/2/Nrf2 pathway, JAK2/STAT3 pathway, PI3K /Akt and Erk1/2 pathway. Moreover, polysaccharide is one of the main macromolecule active components of *S. miltiorrhiza*, which plays an antioxidant and myocardial protective role by reducing myocardial malondialdehyde, serum creatine kinase (CK) and lactate dehydrogenase (LDH) levels. Meanwhile, The above mechanisms are also the main way in which the clinical resistance of *S. miltiorrhiza* to cardiovascular disease. This study reviewed the mechanism and clinical application of the main medicinal components of *S. miltiorrhiza* in myocardial infarction.



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Keywords *Salvia miltiorrhiza* · Myocardial infarction · Active ingredients · Mechanism · Clinical

Introduction

Myocardial infarction (MI) is a common cardiovascular disease. Patients with myocardial infarction usually cause coronary atherosclerosis. Under the interference of certain factors, the atheromatous plaque ruptures, causing a large number of platelets to aggregate, thereby forming a thrombus. This can lead to reduced or even blocked blood flow in the coronary artery lumen, causing ischemic necrosis of the myocardium and eventually myocardial infarction [1, 2]. With the development of percutaneous coronary intervention (PCI) procedure [3], coronary thrombolytic therapy [4], and coronary bypass surgery [5, 6] in recent years, patients with MI can have their blood vessels opened and the infarct area reduced in a short time, allowing the ischemic myocardium to be perfused. However, patients are often troubled by complications after surgery, and there are no specific drugs that can completely prevent the occurrence of complications, so patients need to take long-term anti-platelet aggregation, lipid-lowering, beta-blockers, and other drugs. The long-term use of these drugs has a high probability of side effects such as liver and kidney damage, gastrointestinal reactions, and skin toxicity, which can seriously affect the prognosis of patients. Therefore, effective drugs for the treatment of myocardial infarction need to be clarified [7, 8].

There are numerous descriptions of myocardial infarction in the Chinese medical literature, which can be first seen in the Yellow Emperor's Classic of Internal Medicine - Ling Shu Jing. The book describes myocardial infarction as, "True heart pain, blue hands and feet to the elbow and knee joints, heart pain even." The cause of myocardial infarction is "deficiency of Yang in the chest and upward invasion of Yin" [9] according to Zhang Zhongjing. Therefore, the treatment of myocardial infarction should be done to invigorate blood and qi, resolve stasis and obstruction, expel evil and tonify yang, thus relieving the symptoms and allowing the disease to recover gradually.

Salvia miltiorrhiza (*S. miltiorrhiza*) Bunge belongs to the Labiatae family and is distributed in most of China and parts of Southeast Asia. *S. miltiorrhiza*, its dried rhizome, is a traditional Chinese medicine with thousands of years of history. Its main effects are invigorating blood stasis, nourishing Qi, calming the mind, cooling the blood, eliminating carbuncles, and is commonly used in the treatment of cardiovascular diseases such as MI, coronary heart disease, angina pectoris, etc. [10]. The active ingredients of *S. miltiorrhiza* include liposoluble ketones, water-soluble phenolic acids, and polysaccharides, among which lipid-soluble tanshinones have good anti-inflammatory [11] and apoptosis-inhibiting [12] effects. Water-soluble salvianolic acids mainly have antioxidant [13], cardiomyocyte protection [14], and anticoagulant [15] effects. *S.miltiorrhiza* polysaccharides, moreover, are primarily intended for treating myocardial protection [16], antioxidation [17], and anti-inflammation [18]. Compound Danshen Injection, Compound Danshen dropping pills and other preparations with *S. miltiorrhiza* as the main ingredient have been widely used in clinical practice for the treatment of cardiovascular diseases such as myocardial infarction and coronary heart disease [19]. A large number of studies have analyzed the effects and mechanisms of the active ingredients of *S. miltiorrhiza* in MI in previous reports, but there is a lack of systematic collation. We summarized the representative lipid-soluble components of Tanshinone IIA and cryptotanshinone, *the* water-soluble components salvianolic acid A, salvianolic acid B, danshensu, rosmarinic acid, and luteolin, and the water-soluble polysaccharide according to the previous related studies. In order to provide a basis for subsequent studies on *S. miltiorrhiza*, we summed up the effects and mechanisms of each active substance on MI and the clinical application of *S. miltiorrhiza*.

Lipid-soluble components

Tanshinone IIA

Tanshinone IIA (Tan IIA) has significant effects on MI. Its mechanism is closely related to the protection of cardiomyocytes, inhibition of apoptosis, and regulation of autophagy [20, 21]. Tan IIA can regulate microtubulin acetylation and inhibit Erk-2 phosphorylation, whose in vivo effect may be to significantly inhibit platelet aggregation by reducing the adhesion between platelets and the vessel wall [22]. The stimulation of insulin-like growth factor receptor II (IGF-IIR) expression levels can cause apoptosis, whereas Tan can counteract this phenomenon by regulating the expression of programmed cell death protein 4 (PDCD4) and activating the PI3K-Akt pathway [23, 24]. Tan can also regulate the expression levels of caspase-3, cytoplasmic cytochrome c (cyto c) and Apaf-1, which are related to mitochondrial signaling pathway, inhibiting apoptosis [25]. Myocardial infarction reperfusion injury (MI/RI) is one of the most common and difficult complications to manage in the treatment of MI. Apoptosis-inhibiting, apoptosis-inducing genes and their respective corresponding expression products are altered during MI/

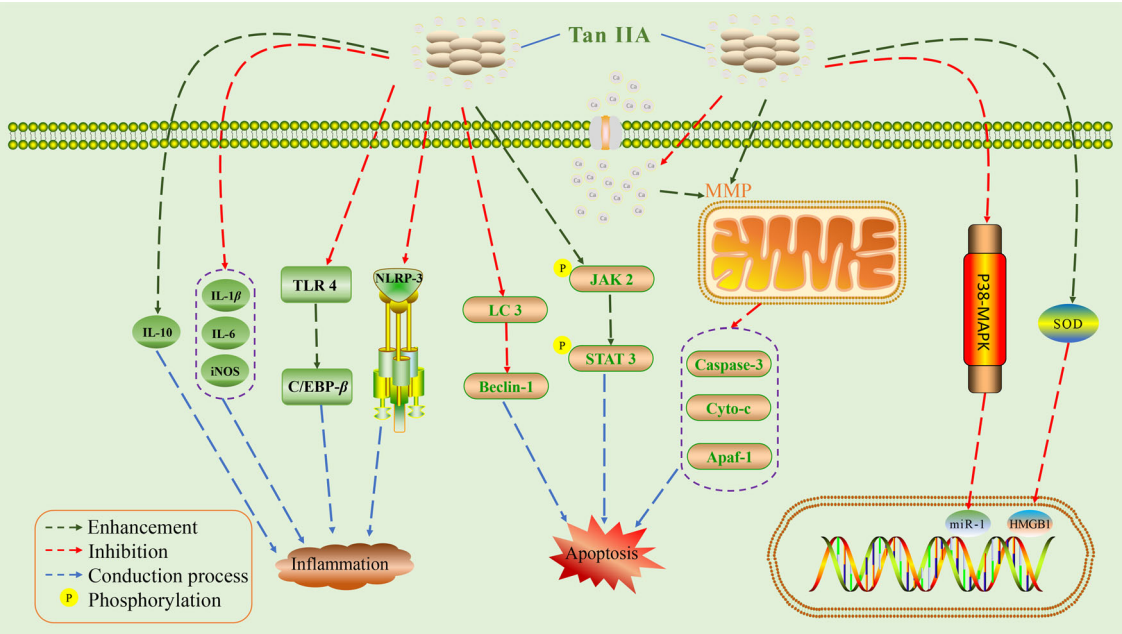


Fig. 1 The possible process of Tan IIA intervention in MI. Tan IIA Tanshinone IIA, IL-1β, IL-6, IL-10 interleukin-1β, interleukin-6, interleukin-10, iNOS inducible nitric oxide synthase, TLR4 Toll-like receptor 4, C/EBP-β CCAAT/enhancer binding protein β, LC3 light chain 3, NLRP3 NOD-like receptor family pyrin domain containing 3, LC3 light chain 3, JAK2 Janus kinase 2, STAT3 signal transducer and activator of transcription 3, MMP mitochondrial membrane potential, cyto c cytoplasmic cytochrome c, Apaf-1 Apoptotic protease activating factor-1, miR-1 microRNA-1, SOD superoxide dismutase, HMGB1 high mobility group protein B1

RI, resulting in apoptosis. It has been shown that Tan IIA can alleviate myocardial damage caused by MI/RI, restore myocardial function, and protect the heart. The mechanism is that Tan IIA could improve the symptoms associated with MI/RI by increasing SOD activity while decreasing high mobility group protein B1 (HMGB1) expression [26]. Tan IIA could also exert a protective effect by activating JAK2/STAT3 pathway [27]. In addition, the effect of Tan IIA on MI/RI may also be related to the activation of NLRP3 inflammasome and Th17 cell differentiation [21]. Interestingly, Tan IIA inhibited the expression of HMGB1 by suppressing reperfusion-induced oxidative stress and reduced inflammatory factor levels as well as a way to achieve cardioprotection [28]. Compared with individual drugs, the combination of Tan IIA and puerarin can better improve the expression of inflammatory factors such as IL-1β, IL-6, IL-10, and inducible nitric oxide synthase (iNOS), and the anti-inflammatory effects are achieved by inhibiting the expression of TLR4 protein and upregulating the expression of CCAAT/enhancer binding protein β (C/EBP-β) protein [29]. The combination of Tan IIA and cyclosporine A can improve mitochondrial function and protect cardiomyocytes by reducing the expression of PI3K/Akt/Bad pathway-related factors PPARγ coactivator-1-α, nucleo respiratory factor-1, and transcription factor A of mitochondrial [30]. Likewise, Tan IIA and Astragaloside IV showed great compatibility in the protection of cardiomyocytes, although their combination was unable to improve the effect achieved by any of the individual compounds [31].

Impaired cardiac pumping is likely to occur after a myocardial infarction, making the blood output of the heart unable to meet the basic metabolic demands of the bodies tissues, which can lead to heart failure [32]. Autophagy plays a key role in the development of heart failure [33]. Zhang et al. found that Tan IIA could significantly regulated various autophagy-related molecules such as protein 1 light chain 3 (LC3), p62 and Beclin1, and reduced cardiomyocyte apoptosis by decreasing the expression of related apoptotic proteins. It has been noted that Tan IIA has a significant effect on inhibiting microRNA (miR)-1 expression, and mechanistic studies have revealed that this effect is achieved through the P38 MAPK pathway [34].

Based on the above studies, Tan IIA could anti-MI by inhibiting platelet aggregation, reducing oxidative stress injury, improving mitochondrial function, and decreasing inflammatory factor levels. More importantly, reducing apoptosis through multiple signaling pathways such as JAK2/STAT3 pathway, PI3K-Akt pathway was the major way to anti-MI. The possible process of Tan IIA intervention in MI is shown in Fig. 1.

Tanshinone IIA sodium sulfonate

Tanshinone IIA sodium sulfonate (STS) is the product obtained by sulfonation of Tanshinone IIA, as shown in Fig. 2.

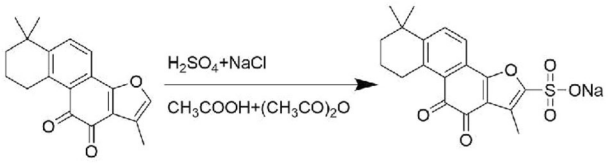


Fig. 2 Preparation of tanshinone IIA sodium sulfonate

Pyranodoxorubicin is a kind of antitumor drug which is prone to chronic cardiotoxicity in long-term use, and is often used in the establishment of myocardial injury model [20]. NF-κB is a classical pathway with a key role in the development of inflammation, and Sirt 1 is a gene with anti-inflammatory effects. It has been shown that STS can inhibit NF-κB translocation by upregulating Circ-sirt1 mRNA expression and alleviate the increase in LPS-induced TNF-α and IL-1β expression [35]. STS can also have a positive effect on MI/RI by reducing myocardial oxygen consumption and eliminating oxygen free radicals. Zhang et al. utilized MI/RI modeling in SD rats to investigate its mechanism. The results showed that STS significantly reduced the number of apoptotic cells, enhanced phosphorylation of Akt and FOXO3A, and inhibited the expression of BIM, indicating a better effect on the improvement of cardiac function [36].

Cryptotanshinone

Tan IIA has a significant effect on MI/RI among the active ingredients of *S. miltiorrhiza* divinorum mentioned previously, and cryptotanshinone (CTS) has a similar effect. Previous reports have demonstrated that MI/RI activates NF-κB to some extent and the response occurs prior to myocardial injury. Jin et al. explored the mechanism of CTS in reperfusion injury (RI) in terms of the effect of CTS on NF-κB. They found that injection of CTS could reduce infarct size in rats in a dose-dependent manner. After CTS treatment, The levels of inflammatory factors TNF-α and IL-1β were dramatically decreased, and MPO activity was inhibited. The inhibition of NF-κB luciflucifase activity induced by H_2O_2 was reduced, which may be due to the cardioprotective effect of CTS by inhibiting the activation of NF-κB signaling pathway [37]. CTS can also treat early atherosclerosis by reducing TNF-α-induced endothelial permeability, restoring NO production in venous endothelial cells, and inhibiting the expression of soluble intercellular adhesion molecule 1 (SICAM-1) [38]. Thus CTS can prevent the onset of MI and reduce the symptoms of early MI. In addition, the expression of caspase-12, C/EBP homologous protein (CHOP) and glucose-regulated protein 78 (GRP 78) was inhibited and the phosphorylation of JAK and STAT 3 was enhanced in MI/RI rats after intervention with CTS, suggesting that CTS exerts anti-apoptotic effects on cardiomyocytes by activating the JAK1/STAT3 signaling pathway [39]. However, there is a lack of research on other activities of CTS, and the literature on its anti-MI signaling pathway is scarce, which need to be filled in [40]. Related studies have shown that CTS has significant antioxidant activity, and oxidative stress is also one of the mechanisms of MI. Future studies can be conducted to investigate the role of this activity in MI.

Other components

Doxorubicin is an antibiotic drug used to treat acute leukemia and some malignancies. However, the cardiotoxicity caused by its long-term use limits its clinical usage. It was found that Tanshinone I (Tan I) could reduce oxidative stress, protect mitochondrial function and reduce apoptosis by regulating Nrf2 signaling pathway [41]. Tan I could also inhibite the expression of p-RIP 1, p-RIP 3, and p-MLKL, and promote the expression of nuclear factor erythroid 2 related factor 2 (Nrf2) and phosphorylation of Akt, showing a cardiovascular protective effect [42]. In addition, isotanshinone has been shown to have anti-inflammatory activity [43], and miltirone could modulate platelet function and inhibit oxidative stress [44]. However, no studies have been found that directly suggest the use of either of these components for MI treatment.

Water-soluble components

Salvianolic acid B

Salvianolic acid B (Sal-B) is a representative component of salvianolic acid, which has certain pharmacological effects on the heart, liver, kidney and brain. In recent years, the mechanism of Sal-B in the regulation of cardiovascular diseases has been revealed, which provides theoretical basis for the promotion of Sal-B in clinical applications [45]. As a member of the TRIM family of proteins, tripartite motif containing protein 8 (TRIM8) is involved in a variety of tissue I/R injury processes. The occurrence of MI/RI promotes the mRNA and protein expression of TRIM8, which makes the protein expression of glutathione peroxidase 1 (GPX 1) suppressed. Whereas low expression levels of GPX 1 can disrupt the protective effect of Sal-B on cardiomyocytes, and so it is necessary to downregulate the expression of TRIM8 during MI/RI [46]. Hu et al. showed that Sal-B had inhibitory effects on myocardial injury. In vitro studies showed that Sal-B could inhibit the TLR4/NF-κB signaling pathway and reduce the expression levels of IL-Iβ and NLRP3 inflammasome in LPS-induced H_9C_2 cells, suggesting that the attenuating effect of Sal-B on myocardial injury was achieved through the TLR4/NF-κB/

NLRP3 signaling pathway. Molecular docking showed that Sal-B could embed and bind to the hydrophobic pocket of myeloid differentiation protein 2 (MD2), so MD2 could be considered as a potential target of Sal-B [47]. In order to test the efficacy of the tested drug, we often set positive drugs for control in drug experiments. Benazepril is a common ACEI drug that reduces peripheral vascular resistance and cardiac load. It has been widely used in the clinical treatment of MI. To verify the therapeutic effect of Sal-B on MI, He et al. compared it with benazepril. The results showed that there were significant improvements in echocardiographic, hemodynamic, hemodynamic parameters and MI area reduction in both groups. The difference was that Sal-B showed better efficacy in angiogenesis. Analysis of the anti-MI mechanism of Sal-B showed that Sal-B could largely promote the expression of VEGF, demonstrating the unique effect of Sal-B in MI treatment [48]. Lin proved that Sal-B could more effectively reduce infarct size and the apoptosis of cardiomyocytes. The reason is that Sal-B could regulate the dysregulated expression of pro-apoptotic protein Bax and anti-apoptotic protein Bcl-2. Further, Sal-B has been found to promote the expression of the pro-angiogenic protein VEGF, promoting angiogenesis [49]. In addition to the above pathways, Sal-B also inhibits apoptosis by suppressing IL-6 and STAT3 expression, and increasing AMPK (Thr172) and Akt (Ser473) phosphorylation. Sal-B has endothelial cytoprotective effect, which is associated with the inhibition of HUVEC apoptosis. However, this effect is only effective in a certain concentration range [50].

Salvianolic acid A

Salvianolic acid A (SAA) has good anti-inflammatory and anti-myocardial ischemic effects. SAA can reduce the inflammatory response by inhibiting the release of IL-6 and TNF-α. It also has an anti-platelet aggregation effect by inhibiting the phosphorylation of Akt, a molecule downstream of PI3K signaling pathway. However, the gastrointestinal absorption of SAA had low bioavailability [51]. Li et al. revealed that the use of both intravenous SAA and oral SAA could greatly reduce the area of myocardial infarction and the levels of CK and LDH [52]. Nevertheless, intravenous administration had a more rapid onset and significant efficacy compared with oral administration. It indicates that SAA can effectively treat MI and the best mode of administration is intravenous injection. However, the focus of the article is on the choice of drug delivery method, and the mechanism of SAA is shallowly studied. The more important anti-inflammatory and anti-apoptotic effects of treating MI were also not investigated. A study by Zhou et al. bridged the former gap. They showed that SAA could exert significant anti-inflammatory and anti-apoptotic effects by reducing the levels of inflammatory factors TNF-α, IL-6 and IL-1β, and attenuating the expression of the pro-apoptotic factor Bax. SAA is similar to Sal-B in terms of its effects [53]. Lin et al. investigated the potency and dose-effect relationship between SAA and Sal-B during MI/RI and found that both components reduced MI in a dose-dependent manner. The difference is that the half-effective dose (ED50) of SAA is only 1/6 of Sal-B, suggesting that SAA may be more effective in MI/RI prevention and cure compared to Sal-B [54].

Danshensu

Danshensu (DSS) has been shown to have the effect of anti-inflammation and increasing blood flow, and its therapeutic effect on MI is mainly in cardioprotection. Li et al. found that DSS achieves cardioprotective function by promoting angiogenesis after MI. The mechanism may be to enhance the survival of endothelial progenitor cells (EPCs) through Akt phosphorylation and improve the pro-angiogenic effect of EPCs by the SDF-1α/CXCR4 axis [55]. Yu et al. demonstrated that DSS can exert antioxidant activity by activating the Akt/ERK1/2/Nrf2 pathway, which has a protective effect on the heart during MI/RI. DSS can also play a good role in inhibiting cardiomyocyte apoptosis by activating PI3K /Akt and Erk1/2 signaling pathways [56]. Zhang investigated the mechanism of DSS against arterial thrombosis and platelet aggregation. The results showed that DSS mainly inhibited platelet aggregation induced by adenosine diphosphate (ADP), 9,11-dideoxy-11α, 9α-epoxymethano-prostaglandin F2α (U46619), and tartrate-resistant acid phosphatase (TRAP)-6, which could inhibit thrombus formation without causing bleeding. DSS could also inhibit the activation of platelet by inhibiting the release of platelet DNA, which is used in the treatment of cardiovascular diseases [57]. In addition, DSS is generally made into Sodium danshensu for use due to its instability, which has the same effect as DSS.

Rosmarinic acid

Rosmarinic acid (RA), a water-soluble phenolic acid first isolated from rosemary, is found in high concentrations in *S. miltiorrhiza*. It has significant antioxidant and anti-inflammatory activities. RA can also exert anti-myocardial ischemic effects by inhibiting the expression of the p38 MAPK pathway in vivo [58]. Javidanpour et al. stated that the mechanism by which RA attenuates the damage caused by infarction is that RA enhances the expression of the RyR2 gene and promotes calcium stabilization [59]. The incidence of arrhythmias increases sharply after patients present with infarction, which becomes one of the major causes of high mortality after infarction. The subsequent study by Javidanpour et al. found that RA could inhibit the

Table 1 Information on anti-myocardial infarction components of *S. miltiorrhiza*

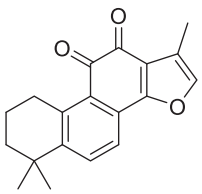
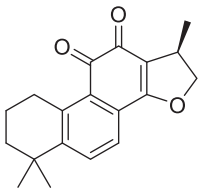
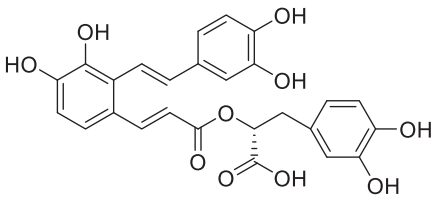
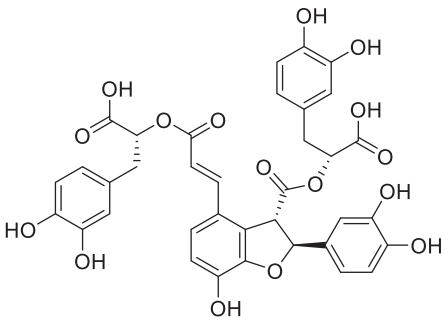
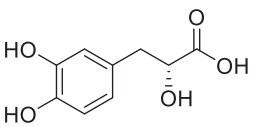
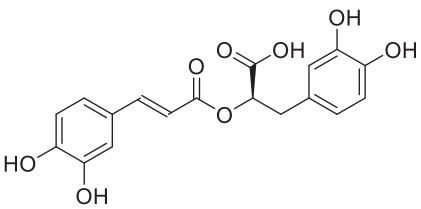
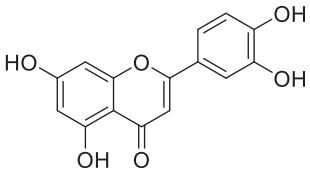
Name	Structural formula	Molecular formula	Molecular weight	Solubility
Tanshinone IIA		$C_{19}H_{18}O_3$	294.34	Liposoluble
Cryptotanshinone		$C_{19}H_{20}O_3$	296.36	Liposoluble
Salvianolic acid A		$C_{26}H_{22}O_{10}$	494.45	Water-soluble
Salvianolic acid B		$C_{36}H_{30}O_{16}$	718.61	Water-soluble
Danshensu		$C_9H_{10}O_5$	198.17	Water-soluble
Rosmarinic acid		$C_{18}H_{16}O_8$	360.34	Water-soluble

Table 1 (continued)

Name	Structural formula	Molecular formula	Molecular weight	Solubility
Luteolin		$C_{15}H_{10}O_6$	286.25	Water-soluble

overexpression of sodium calcium exchanger (NCX1) after AMI and suppress lipid peroxidation, preventing the occurrence of arrhythmias [60]. During recovery from MI, scarring of myocardial tissue self-repair can easily lead to myocardial fibrosis, which can seriously affect the prognostic outcome. Liu et al. [61] have shown that RA can reduce angiotensin type 1 receptor (AT1R) and phosphorylated-p38 mitogen-activated protein kinase (p38 MAPK) expression, preventing the development of cardiac fibrosis.

Luteolin

Luteolin is a traditional anti-inflammatory and antiviral component and one of the active ingredients of *S. miltiorrhiza*, which has positive effects on cardiovascular diseases [62]. Liu et al. found that luteolin could reduce infarct size, inhibit the expression of inflammatory factors, and reduce the rate of apoptosis significantly, acting as an anti-MI [61]. Hu et al. investigated the role of luteolin in post-infarction cardiac insufficiency, they showed that luteolin has the effect of improving prognosis after MI by inhibiting mammalian sterile 20-like kinase 1 (Mst1) upregulation to suppress cellular autophagy, reducing the release of myocardial enzymes after MI, and suppressing the expression of inflammatory factors [63].

Here in, we summarize the information of each component of *S. miltiorrhiza* against myocardial infarction, as shown in Table 1.

Combination of multiple components

From the above studies on the therapeutic effects and mechanisms of each component on MI, we can easily find that many components have similar medicinal effects. Therefore, some studies have combined multiple components to explore whether the therapeutic effect can be improved and the scope of application can be expanded, thus better exploiting the activity of each component. However, the mechanism of multicomponent synergism in traditional Chinese medicine is quite complex, and it is harder to reveal its mechanism on the basis of pharmacodynamics, which needs more in-depth research.

S. miltiorrhiza polyphenolic acid

S. miltiorrhiza polyphenolic acid is a water-soluble substance extracted from *S. miltiorrhiza* with small molecules such as salvianolic acid B, salvianolic acid Y, and purpureic acid, whose injections have been used in the treatment of cardiovascular diseases. Ma et al. showed that salvia polyphenolic acid from *S. miltiorrhiza* could improve myocardial fibrosis by increasing left ventricular ejection fraction (LVEF), left ventricular shortening fraction (LVFS), collagen volume fraction (CVF), decreasing left ventricular end-diastolic internal diameter (LVEDD), left ventricular end-systolic internal diameter (LVESD), and increasing the content of myocardial collagen and myocardial tissue hydroxyproline (HYP) in fibrosis [64]. Qin et al. found that *S. miltiorrhiza* polyphenolic acid could play an anti-myocardial injury and reduce the inflammatory response by decreasing the levels of two cardiac enzymes (CK and CK-MB) and two inflammatory factors (TNF-α and MPO) in rats with myocardial ischemic injury [65]. In addition, salvia polyphenolic acid also has a protective effect on liver, kidney, and lung, and can also be prescribed to treat diabetes, Parkinson's syndrome, tumor, and lumbar disc herniation [66].

Total tanshinone

We have reviewed the mechanism of each component of tanshinone, and it is not difficult to find that their efficacy is similar and there are many common pathways. For example, Tanshinone IIA, Cryptotanshinone, and Tanshinone I have been shown to have cardioprotective effects through the AKT signaling pathway. AKT is a central hub of signal transduction that regulates cellular functions, and the expression of its three family members, AKT1, AKT2, and AKT3, overlaps and varies in the myocardium. Among them, AKT2 is closely related to cardiomyocyte apoptosis,

while AKT1 and AKT3 are primarily associated with the function of cardiomyocytes. Among them, AKT2 is closely related to cardiomyocyte apoptosis, while AKT1 and AKT3 are primarily associated with the function of cardiomyocytes. AKT can promote cell growth through S6 kinase and increase positive inotropy through the function of Ca^{2+} handling proteins. Therefore the cardioprotective effect of Total tanshinone may be achieved through the activation of different AKT family members by the components. Calmodulin (CaM) is a signaling molecule that causes arrhythmias, and its protein level is an important cue for the development of arrhythmias after MI. Lu revealed that total tanshinone was effective in preventing arrhythmias after myocardial infarction through significant inhibition of the CaM signaling system [67]. The effect of tanshinone on the expression of mRNA and protein of Bcl-2 in MI/RI model rats was significantly promoted, while the effect on the expression of mRNA and protein of Bax was reversed, indicating that tanshinone could inhibit apoptosis, and the TUNEL staining results verified this conjecture [68]. Notably, Li et al. established a myocardial infarction model using isoprenaline-induced rabbits and found that Tanshinone had an inhibitory effect on the function of circulating neu [69]. Yan et al. established a nano-system with combined loading of calycosin (CAL) and tanshinone and co-modification of mitochondria-targeted tetrapeptide (MTP) and cyclic arginyl-glycyl-aspartic acid (RGD) peptide, and applied it to a rat model of MI. The results showed a significant reduction in infarct size [70]. Solid lipid nanoparticles (SLN) co-loaded with puerarin precursors synthesized by esterification and tanshinone were also shown to be suitable for MI area reduction [71]. Nano drug delivery systems have unique advantages in improving drug bioavailability, achieving targeting, slow and controlled release drug delivery, presenting new opportunities for MI therapy. Although the nano-system is not yet mature, its future as a new drug delivery system is immeasurable.

Others

Tan IIA and Sal-B are the representative components of the liposoluble and water-soluble substances of *S. miltiorrhiza*. Pan et al. investigated the efficacy of the combination of Tan IIA and Sal-B. The combination of both was shown to restore post-infarction cardiac function by stimulating eNOS phosphorylation, increasing CAT expression, and increasing L-arginine uptake of a series of targets related to NO production, in addition to the conventional effects of reducing infarct size and cardioprotection [72]. Sal-B has anti-inflammatory effects, but only Sal-B treatment is not effective enough to inhibit the levels of IL-6, TNF-α and other inflammatory factors in human umbilical vein endothelial cells (HUVEC) with hypoxic injury. Its inflammation inhibition is ideal when combined with salvianolic acid A, rosmarinic acid, and danshensu [73]. The experimental data from Wang et al. showed both total salvianolic acid and total tanshinone could/ reduce infarct size and improve recovery of post-infarct cardiac function, but the mechanism and time is different. Total salvianolic acid mainly plays a role in inhibiting apoptosis, G-protein coupled receptor activity and participating in oxidative stress in the later period after ischemic, while total tanshinone can stabilize the level of intracellular Ca^{2+} and inhibite cell adhesion molecules at the early stage post MI [74]. It is clear that the effects of the components on MI are not simply function individually, but complementary and interrelated.

Polysaccharide

Salvia miltiorrhiza polysaccharide (SMP), a water-soluble macromolecule, is one of the main active ingredientsin of *S. miltiorrhiza*. Previous studies on the cardioprotective effects of *S. miltiorrhiza* were mainly focused on small molecules such as tanshinones and salvianolic acids. In recent years, studies on the cardiovascular effects of *S. miltiorrhiza* polysaccharide have emerged one after another. It was found that SMP could eliminate H_2O_2-induced apoptosis by inhibiting mitochondrial dysfunction, improving antioxidant capacity and inactivation of caspase-3 cascade [75]. Song et al. used purified SMP1 to treat myocardial I/R injury and showed that SMP1 reduced I/R infarct-induced injury and inhibited apoptosis. The mechanism was related to the decrease in serum LDH and CK as well as myocardial MDA and SOD levels caused by SMP1 [76]. Prohibitin protein is closely associated with cell proliferation and apoptosis which is mainly present in mitochondria and nucleus. SMP could reduce H_2O_2-induced cardiomyocyte injury by upregulating prohibitin protein expression [77]. Geng et al. also used SMP1 to study the MI induced by ISO injection. The levels of six specific markers of MI degree, CK, creatine phosphokinase-MB (CK-MB), LDH, alkaline phosphate (ALP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT), were significantly decreased after SMP1 treatment, and the levels of SOD and CAT activities were increased, indicating that SMP1 can reduce the degree of MI and has a significant cardioprotective function [78]. Cyclooxygenase (COX), a membrane-bound protein, is associated with the inflammatory response. *S. miltiorrhiza* polysaccharide can inhibit the cardiac inflammatory response by reducing the expression of COX-2 [79]. SMP could also inhibit apoptosis and protect from damage caused by lipid peroxidation through activation of the Nrf2/HO-1 pathway [80]. Moreover, SMP could modulate the human immune system, inhibit cholesterol concentration, regulate serum protein concentration,

and have a protective effect against acute liver injury in mice.

Clinical application

S. miltiorrhiza is a classical traditional Chinese medicine that invigorates blood stasis. It can be used as medicine directly or made into injections such as Tanshinone injection, salvianolic acid for injection, etc. It can also be combined with other herbal species to make compound preparations, such as *S. miltiorrhiza* and Ligustrazine injection, Compound Danshen dropping pills, Compound Danshen Injection, etc. It is generally utilized for clinical treatment of cardiovascular diseases such as myocardial infarction, coronary heart disease and angina pectoris.

Simple recipe

Salvianolic acid for injection has the effects of promoting blood circulation, dredging collaterals, and removing blood stasis, which has a significant effect on the treatment of coronary heart disease and the recovery of ST segment after AMI. Dai et al. treated coronary heart disease patients with salvianolic acid for injection, showing that patients' cardiac diastolic function index (E/E') and left atrial volume index (LAVI) were significantly reduced, myocardial fibrosis indexes serum PCIII, HA and CTGF were improved, indicating that salvianolic acid for injection can reverse the degree of myocardial fibrosis and improve the diastolic function of the heart [81]. Salvianolic acid for injection is often used in combination with other drugs to provide better clinical effects or to enhance the efficacy of other drugs. The use of salvianolic acid for injection in combination with trimetazidine is a widely used treatment for patients with angina pectoris in coronary heart disease. Cai et al. pointed out that its mechanism is to reduce the levels of lipid indicators TC, TG, LDL-C and HDL-C, decrease the cardiac function index LVEF, increase LVESD and LVEDD, and decrease the platelet aggregation rate [82]. Zhang et al. analyzed the pharmacodynamics and pharmacokinetics of salvianolic acid for injection in vivo. They found that the combination of salvianolic acid for injection and aspirin can effectively inhibit platelet aggregation while reducing the risk of bleeding, which is primarily intended in the treatment of cardiovascular diseases [83].

Tanshinone injection is also known as Tanshinone IIA sodium sulfonate injection, is mainly composed of liposoluble small molecules extracted from *S. miltiorrhiza*, such as Tanshinone IIA, Tanshinone IIB, Tanshinone I and so on. It has a significant effect of antibacterial, activating blood circulation, and removing blood stasis, and is often used as an adjuvant treatment for heart function recovery. Shang et al. used tanshinone injection combined with noninvasive positive pressure ventilation in the treatment of patients with acute heart failure. The blood gas analysis showed that the mean arterial pressure (MAP), arterial partial pressure of oxygen, and arterial partial pressure of carbon dioxide were improved, and inflammatory factors such as high-sensitivity C-reactive protein (hs-CRP) and IL-6 were significantly reduced, and cardiac function was restored [84]. Zhao et al. showed that tanshinone injection could prevent restenosis after percutaneous coronary intervention (PCI) in patients with non-ST-segment elevation myocardial infarction (NSTEMI), and had an ameliorating effect on both the stress and inflammatory responses of patients [85]. The drug has the advantages of mild conditions, few side effects and high safety, and has been shown to be effective in related cardiovascular disease applications.

The main active ingredients of Lyophilized Salvia salt of lithospermic acid powder for injection (SSLA) are water-soluble substances such as salvianolic acid, rosmarinic acid, and tannic acid in *S. miltiorrhiza*. It has good stability and fast onset of action, and can be used as a therapeutic drug for diseases of the cardiovascular system, digestive system, endocrine system, and cerebrovascular system, mainly for the treatment of cardiovascular system diseases. Zhang et al. respectively administered SSLA and Danshen injection (DSI) to patients with coronary heart disease, and the results showed that the effects of the two were similar and there were no significant toxic side effects [86]. Wang et al. reported that SSLA could reduce the incidence of angina pectoris in patients with unstable angina pectoris, and the electrocardiogram was significantly improved, showing a good cardioprotective effect [87].

Compound prescription

S. miltiorrhiza and Ligustrazine injection (SLI) consists of *S. miltiorrhiza* aqueous extract and Ligustrazine hydrochloride, where *S. miltiorrhiza* aqueous extract mainly contains *S. miltiorrhiza* water-soluble substances. Ligustrazine is a characteristic component of Chuanxiong, which can be made into hydrochloride to improve the stability of the preparation. *S. miltiorrhiza* and Chuanxiong are traditional medicine pair, both of them enter the heart and liver meridian together, and have a stronger effect of activating blood circulation and removing blood stasis compared with unit medicine. It has been shown that SLI could reduce the inflammatory response and apoptosis rate by inhibiting the activation of caspase-3 and increasing the ratio of Bcl-2/Bax, and this effect may be achieved by activating the Akt-eNOS signaling pathway [88]. Zhu et al. found that SLI was effective in the treatment of angina pectoris, reducing the incidence of adverse effects and significantly improving

Table 2 Clinical drug related information of *S. miltiorrhiza*

Drug name	Chemical constituent/component	Efficiency	Major function
Salvianolic acid for injection	Salvianolic acid	Promote blood circulation, dredge collaterals, remove blood stasis	Coronary heart disease
Tanshinone injection	Sodium tanshinone IIA sulfonate	Antibiotic, activate blood circulation and removing blood stasis	Coronary heart disease, angina pectoris, myocardial infarction, premature ventricular contractions
Lyophilized Salvia salt of lithospermic acid powder for injection	*Salvia miltiorrhiza*	Promoting coronary circulation	Coronary heart disease, angina pectoris
Salvia miltiorrhiza and Ligustrazine injection	*Salvia miltiorrhiza*, Chuanxiong	Anti-platelet aggregation, dilate coronary arteries, reduce blood viscosity, improve microcirculation, anti-myocardial ischemia and myocardial infarction	Occlusive cardiovascular disease
Compound danshen dropping pills	*Salvia miltiorrhiza*, borneol, panax pseudo-ginseng	Activate blood circulation and removing blood stasis, regulate qi to alleviate pain	Chest paralysis due to Qi stagnation and blood stasis, with chest tightness and tingling in the precordial region
Compound danshen Injection	*Salvia miltiorrhiza*, Lignum Dalbergiae Odoriferae	Anti-myocardial ischemia, scavenging free radicals, reducing liver damage, sedation, improving blood rheology	Angina pectoris, acute myocardial infarction

three lipid levels, TC, TG, and LDL [89]. Research data of Ding et al. showed that SLI could alleviate myocardial injury in patients with severe burns by improving plasma cardiac troponin I (cTnI), creatine kinase isoenzyme MB (CK-MB) and atrial natriuretic peptide levels [90].

Compound Danshen dropping pills is a traditional Chinese medicine formula, which is included in the Pharmacopoeia of the People's Republic of China, 2020 edition. It consists of *S. miltiorrhiza*, borneol and panax pseudo-ginseng, which is widely used in cardiovascular diseases such as coronary heart disease and angina pectoris. Lv et al. retrieved the recovery of patients with coronary heart disease after PCI through statistical methods, showing that Compound Danshen dropping pills can reduce the incidence of postoperative adverse reactions in PCI, which has a positive significance for the prognosis of patients [91]. Huang et al. investigated the therapeutic effect of Compound Danshen dropping pills on patients with coronary heart disease. They indicated that the inflammatory response transmitters IL-6 and TNF-α were significantly reduced, the four lipid levels of TC, TG, LDL, and HDL were improved, and the hemodynamic indexes showed an increase in patients' hemodynamics, indicating significant efficacy [92].

Compound Danshen Injection is made of two kinds of Chinese herbal medicines, namely *S. miltiorrhiza* and Lignum Dalbergiae Odoriferae, in a ratio of 1:1. The main anticoagulant component in Lignum Dalbergiae Odoriferae is volatile oil that plays the role of antithrombotic. The combination of *S. miltiorrhiza* and Lignum Dalbergiae Odoriferae can activate blood circulation, remove blood stasis, reduce inflammation and pain, which has a significant effect on AMI and angina pectoris. Chen et al. showed good prognosis after PCI in patients with acute ST-segment elevation myocardial infarction with the application of Compound Danshen Injection, which resulted in improvement of three cardiac function indexes, LVEF, LVESD and LVEDD. Renal function indices showed low serum creatinine levels and good glomerular filtration, which could better prevent the occurrence of contrast-induced acute kidney injury (CIAKI) [93]. Compound Danshen Injection has a wide range of applications, and is also used for the sequelae of cerebral infarction, neurological deafness, neurasthenia, and some ophthalmic diseases in addition to the above cardiovascular diseases.

Other pharmacological effects

S. miltiorrhiza has a wide range of clinical applications and can be used in combination with a variety of herbs to bring out different medicinal effects, such as Dantian Lipid-Lowering Pill, a drug for lowering blood lipid; Dandeng Tongbao Capsules, a drug for stroke; Yangxin's Tablets, a

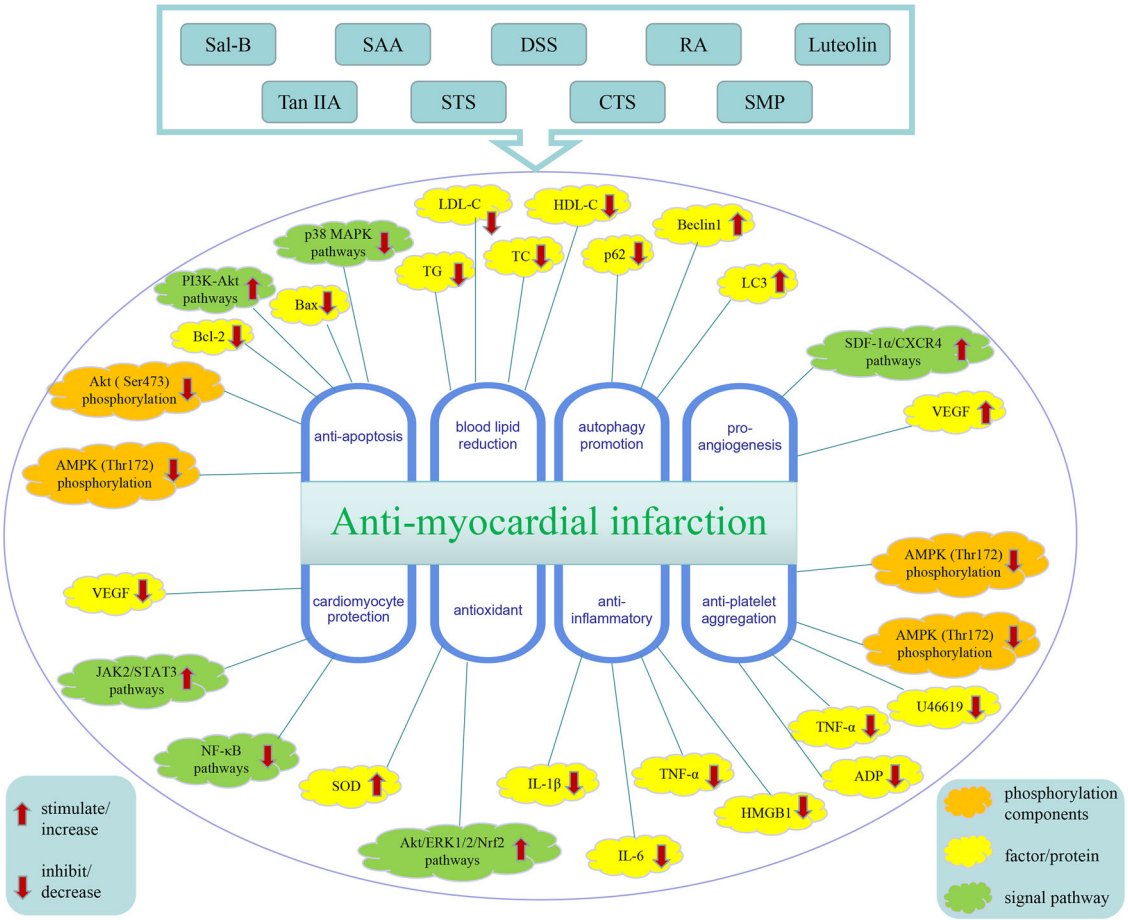


Fig. 3 Mechanism of anti-MI action of *S. miltiorrhiza*. Sal-B salvianolic acid B, SAA salvianolic acid A, DSS danshensu, RA rosmarinic acid, Tan IIA tanshinone IIA, STS sodium tanshinone IIA sulfonate, CTS cryptotanshinone, SMP *Salvia miltiorrhiza* polysaccharide

drug for cardiovascular diseases; Tianwang Tonic Heart Pill, a drug for tranquilizing the mind, etc. In this study, we select the drugs commonly used in the treatment of cardiovascular diseases among them to explore, and other drugs will not be discussed. The information related to the clinical drug of *S. miltiorrhiza* is shown in Table 2.

Discussions

S. miltiorrhiza is one of the earliest and most widely used traditional Chinese medicines in China, as it was first published in Sheng Nong's Herbal Classic. Its composition is complex, in addition to water-soluble salvianolic acid, liposoluble tanshinones, and polysaccharides mentioned in the text, there are also lactones, nitrogenous compounds, steroids, flavonoids, etc. The complex chemical composition of *S. miltiorrhiza* also directly leads to numerous pharmacological effects. *S. miltiorrhiza* has antitumor, anti-inflammatory, blood activation, and hypoglycemic effects, and can be used for cardiovascular diseases, gynecological diseases, and digestive system diseases, among which it is most commonly used for the treatment and prevention of cardiovascular diseases. In this article, we mainly summarized the mechanism of the active ingredients of *S. miltiorrhiza* against myocardial infarction. Previous studies on the mechanism of anti-myocardial infarction of *S. miltiorrhiza* have been limited by the relationship between single components and unilateral regulatory mechanisms [94, 95]. Therefore, we reviewed and summarized the articles on the anti-myocardial infarction of each active ingredient in recent years to provide a general interpretation of the mechanism (Fig. 3). According to Fig. 3, we found that the active ingredients of *S. miltiorrhiza* could exert multiple pharmacological effects through different pathways to achieve anti-MI effects.

The active ingredients of *S. miltiorrhiza* can exert anti-myocardial infarction effects at the overall and cellular levels. The effects of each ingredient on myocardial infarction can be exerted individually or can be intertwined through multicomponent combinations to protect the heart together. In clinical practice, besides being used alone, *S.*

miltiorrhiza can also be compounded with other traditional Chinese medicines, such as compound danshen drops and compound danshen injection, which have been applied in the treatment of cardiovascular diseases such as myocardial infarction and coronary heart disease. In this study, we summarized research articles on the activity of each active ingredient in *S. miltiorrhiza*, and organized the mechanism of each ingredient and clinical drugs to provide a reference for the subsequent research. We found that there are not enough studies related to the mechanism of small molecules such as cryptotanshinone and rosmarinic acid, and the literature on multicomponent combination is even scarcer. In addition, there is a lack of comprehensive analysis based on metabolomics and genomics in the mechanistic studies of *S. miltiorrhiza*, the application of each component mostly stays in animal and cellular experiments and has not been translated into clinical trials. Future research can be carried out in this direction. There are numerous components of *S. miltiorrhiza* and a vast research space, and there are certainly some undiscovered components with significant activity and undefined mechanisms waiting to be explored.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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