Send Orders for Reprints to reprints@benthamscience.net

Combinatorial Chemistry & High Throughput Screening, 2026, *29*, 2253-2266

RESEARCH ARTICLE

Baihe Dihuang Danshen Decoction Alleviates Myocardial Ischemia-Reperfusion Injury in Depression-Induced Rats by Inhibiting Ferroptosis

Ling Huang[1], Cuihua Liu[1], Yudan Liang[2], Wenquan Huang[1], Shizhong Zhang[3], Qiang Xu[4,*] and Kuncheng Qiu[1,*]

[1]Third-Grade Pharmacological Laboratory on Traditional Chinese Medicine, State Administration of Traditional Chinese Medicine, College of Medicine and Health Sciences, China Three Gorges University, Yichang, China; [2]Three Gorges Public Inspection and Testing Center, Yichang, China; [3]College of Basic Medical Sciences, Three Gorges University, Yichang, China; [4]Yichang City Hospital of Traditional Chinese Medicine, Yichang, China

© 2026 The Author(s). Published by Bentham Science Publisher. This is an open access article published under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/legalcode

ARTICLE HISTORY

Received: February 23, 2025
Revised: May 22, 2025
Accepted: May 22, 2025

DOI:
10.2174/0113862073387437250803043736

Abstract: ***Introduction*:** The comorbidity of myocardial ischemia reperfusion injury (MIRI) and depression (DEP) may worsen the prognosis of coronary heart disease surgery. Currently, research on medications and therapeutic mechanisms for MIRI combined with DEP is still insufficient. This study aims to explore the relationship between DEP and MIRI, and the therapeutic effects and mechanisms of Baihe Dihuang Danshen decoction (BDDSD) on DEP combined with MIRI.

***Methods*:** SD rats were assigned to a final experimental framework of six groups (Sham, MIRI, DEP+MIRI, BDDSD, DEP drug control, MIRI drug control). DEP was induced *via* 6-week chronic unpredictable mild stress (CUMS), with BDDSD administered during the final 2 weeks. MIRI was then induced by 30-minute coronary artery ligation and 2-hour reperfusion. DEP severity was assessed using behavioral tests (open field, elevated plus maze, sucrose preference, forced swimming). MIRI outcomes were evaluated *via* infarct size, histopathology, serum markers (LDH, IL-6, IL-1β), myocardial oxidative stress (MDA, GSH, SOD, Fe^{2+}), and NADPH/FSP1/CoQ10 pathway proteins (FSP1, CoQ10, FTL, NOX2, NOX4, COX2).

***Results*:** Compared with the MIRI group, DEP significantly exacerbated MIRI, manifested by increased serum IL-6 and IL-1β levels, enlarged infarction area, and aggravated oxidative damage (elevated MDA/Fe^{2+}, decreased SOD/GSH). Compared with the DEP+MIRI group, BDDSD intervention relieved DEP of rats, and subsequently reduced infarction area; decreased serum LDH, IL-6, and IL-1β; lowered myocardial MDA and Fe^{2+} while increasing SOD and GSH; upregulated FSP1/CoQ10/FTL; and downregulated NOX2/NOX4/COX2 expression.

***Discussion*:** DEP can aggravate inflammation and oxidative stress, promoting cardiac ferroptosis, thereby exacerbating MIRI. Our results demonstrate that BDDSD alleviates MIRI-DEP comorbidity through a dual mechanism, mitigating depressive symptoms and inhibiting myocardial ferroptosis *via* modulation of the NADPH/FSP1/CoQ10 pathway. Although the efficacy of BDDSD is encouraging, its dose-effect relationship and long-term safety require further study.

***Conclusion*:** BDDSD effectively treats DEP-MIRI comorbidity through its dual mechanism, mitigating DEP and protecting against myocardial ferroptosis. Our study not only offers a novel therapeutic strategy for patients with DEP requiring coronary heart disease surgery but also provides new targets for developing drugs to treat MIRI combined with DEP.

Keywords: Myocardial ischemia reperfusion injury, depression, baihe dihuang danshen decoction, NADPH/FSP1/CoQ10 pathway, myocardial, ferroptosis, chronic unpredictable mild stress (CUMS).

*Address correspondence to these authors at the Yichang City Hospital of Traditional Chinese Medicine, Yichang, China, E-mail: 9463488@qq.com; and Third-Grade Pharmacological Laboratory on Traditional Chinese Medicine, State Administration of Traditional Chinese Medicine, College of Medicine and Health Sciences, China Three Gorges University, Yichang, China; E-mail: qiukun108@126.com

1875-5402/26 2026 Bentham Science Publishers

Combinatorial Chemistry & High Throughput Screening

1. INTRODUCTION

Percutaneous coronary intervention and coronary artery bypass grafting are effective methods in the clinical treatment of severe coronary heart disease [1-3], but they often lead to myocardial ischemia-reperfusion injury (MIRI) [4], which impairs myocardial function. More seriously, depression (DEP) is prevalent among patients with coronary heart disease, with a prevalence rate as high as 40% [5-7], and patients with preoperative DEP have prolonged hospital stays [8] and significantly increased postoperative mortality [9, 10]. The key issue is that the combined effects of DEP and MIRI may increase the risk of adverse cardiovascular events. MIRI damages the myocardium through mechanisms such as oxidative stress [11, 12] and inflammatory responses[13, 14], while DEP exacerbates myocardial dysfunction by activating the hypothalamic-pituitary-adrenal axis, promoting platelet aggregation and so on [15-18]. This "double hit" effect can lead to more severe postoperative complications. However, research on the treatment of MIRI combined with DEP remains insufficient [19]. Therefore, exploring drugs to treat MIRI combined with DEP is of great clinical significance for improving the outcomes of coronary heart disease surgery.

However, the traditional clinical approach, such as treating DEP before surgical treatment for coronary heart disease, is not effective, because there is a complex bidirectional relationship between DEP and coronary heart disease [20]. DEP not only exacerbates the condition of patients with coronary heart disease [21-23], but the psychological and financial burden of coronary heart disease can also lead to DEP [23, 24]. Therefore, treating DEP before surgical treatment for coronary heart disease cannot avoid the occurrence of "MIRI combined with DEP". Treating DEP and MIRI simultaneously may be a good solution. However, there are no specific drugs that can treat MIRI and DEP simultaneously. Given side effects and drug interactions, the combination of antidepressants and drugs used to treat cardiovascular diseases also has potential therapeutic risks. As people pay more attention to natural botanicals, traditional Chinese medicine (TCM) has proven to be an effective means to prevent and treat MIRI [25, 26]. Depending on the patient's specific situation, TCM is suitable for treating some complex diseases by combining different botanical drugs. It is the advantage of TCM to treat complex diseases through multi-components and multi-targets [27, 28]. Thus, TCM has great potential in the treatment of MIRI combined with DEP.

It is known that the mechanism of comorbidity between DEP and cardiovascular diseases includes inflammation, autonomic imbalance, mitochondrial dysfunction, and so on [29]. But it is unclear how DEP affects MIRI and through what mechanism. Studies have shown that inflammation is closely related to oxidative stress and ferroptosis [30-32]. Ferroptosis is one of the important pathological mechanisms of MIRI [33, 34]. DEP can cause a significant release of inflammatory cytokines (such as TNF-α, IL-1, and IL-6) in the body [35]. These inflammatory cytokines trigger a cascade of effects that lead to myocardial ferroptosis [30, 36]. Therefore, we think that DEP-induced inflammation promoting myocardial ferroptosis may be an important way for DEP to affect MIRI. When MIRI is combined with DEP, the heightened levels of inflammatory cytokines exacerbate the systemic inflammatory response, activating the NOX system. This leads to the consumption of NAD(P)H and a substantial increase in the production of reactive oxygen species (ROS) [37]. Excessive ROS induce iron metabolism disorders, triggering lipid peroxidation reactions, which ultimately lead to myocardial ferroptosis [38-40]. FSP1, by using NADPH/H as an electron source, reduces lipid free radicals under the action of CoQ10 and inhibits ferroptosis [41, 42]. Therefore, the ferroptosis signaling pathway NADPH/FSP1/CoQ10 may play an important role in the prevention and treatment of MIRI combined with DEP.

In this study, we employed BaiheDihuang-Danshen decoction (BDDSD), a novel formulation combining two classical TCM prescriptions, to treat MIRI combined with DEP in rats. BDDSD integrates the therapeutic principles of Baihe Dihuang decoction (BDD) and Danshen decoction (DSD): BDD, composed of lily bulbus and Rehmanniae radix, originates from the classical text Jin Gui Yao Lue and has been historically used to alleviate DEP [43-45]; DSD, comprising Salviae miltiorrhizae radix et rhizom, Amomi fructu, and Santali albi lignu, is clinically recognized for its anti-inflammatory and antioxidant properties in ischemic heart disease [46-48], with bioactive tanshinones notably inhibiting ferroptosis [49]. On this basis, the formulation of BDDSD strategically combines BDD and DSD to create a multi-target therapeutic approach. Our study represents the first investigation of BDDSD for MIRI-DEP comorbidity, aiming to validate its dual-pathway efficacy compared to BDD (DEP-focused) and DSD (MIRI-focused) monotherapies. To elucidate the mechanisms underlying the therapeutic effects of BDDSD on MIRI combined with DEP, we investigated the role of the NADPH/FSP1/CoQ10 pathway. Furthermore, to ensure pharmacological consistency across experimental groups, we established an LC-MS-MS method to quantify seven characteristic bioactive compounds in BDDSD.

2. MATERIALS AND METHODS

2.1. Chemicals and Reagents

Malondialdehyde (MDA) and Superoxide dismutase (SOD) kits were purchased from Beijing Soleibao Technology Co., Ltd. Glutathione (GSH), Lactate dehydrogenase (LDH) and tissue Fe^{2+} kits were purchased from Nanjing Jiancheng Bioengineering Institute. IL-6, IL-1β ELISA assay kits were obtained from Shanghai Enzyme-linked Biotechnology Co., Ltd. BCA kit was supported by Beijing Applygen Technology Co., Ltd and 0.5% TTC staining solution was supported by Wuhan Saiweier Biotechnology Co., Ltd. FSP1 and β-Tubulin were purchased from Wuhan ABclonal Technology Co., Ltd. NOX2, NOX4, COX2, FTL, CoQ10, β-actin Antibodies were all obtained from Wuhan Proteintech Group, Inc. Acetonitrile, methanol, and formic acid were HPLC-grade and other reagents were of analytical grade. Reference Standards of Rehmannioside D, Tanshinol, Protocatechuic acid, Vanillic acid, regaloside A, regaloside B and Cryptotanshinone were purchased from the China National Institutes for Drug Control.

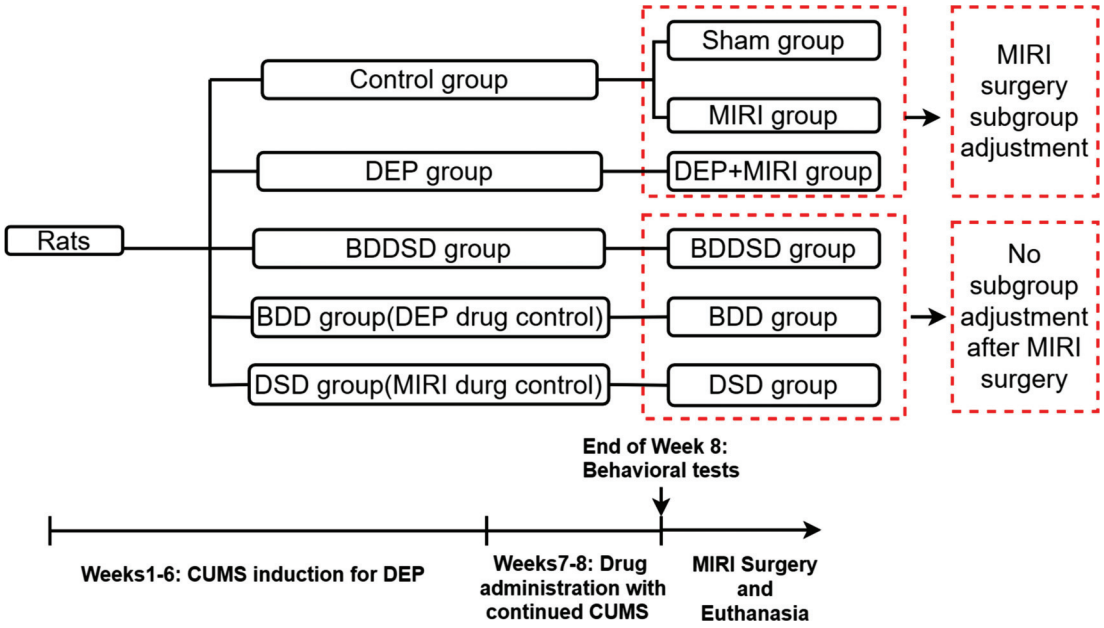


Fig. (1). Flowchart of MIRI combined with DEP model construction and experimental grouping.

2.2. Animals

Male SD rats (SPF grade, 6 weeks old, 180-200 g) were purchased from the Experimental Animal Center of China Three Gorges University (License No. SCXK(E) 2022-0012). Rats were housed at 22±2°C, 60±5% humidity, under a 12-hour light-dark cycle. All procedures complied with the ARRIVE guidelines and were approved by the Ethics Committee of China Three Gorges University (No. 2024020T). Detailed measures to ensure animal welfare (*e.g.*, anesthesia and humane endpoints) are described in Section 2.4.

2.3. Drug Preparation and Extraction

Lily bulbus (*Lilium lancifolium* Thunb.), Rehmanniae radix (*Rehmannia glutinosa* Libosch.), Salviae miltiorrhizae radix et rhizome (*Salvia miltiorrhiza* Bge.), Amomi fructus (*Amomum villosum* Lour.) and Santali albi lignum (*Santalum album* L.) were all supported by Affiliated Renhe Hospital of China Three Gorges University, and the quality of these Herbs conforms to the provisions of the Chinese Pharmacopoeia.

The BDDSD consists of 30 g of Lily, 25 g of Rehmanniae, 30 g of Salviae miltiorrhizae, 6 g of Amomi fructus and 6 g Santali albi lignum. BDD consists of 30g of Lily and 25 g of Rehmanniae. DSD consists of 30 g of Salviae miltiorrhizae, 6 g of Salviae miltiorrhizae and 6 g of Santali albi lignum. All of the above doses are for an adult in one day. The extraction methods of BDDSD, BDD and DSD were the same. Place the herbs in a round-bottomed flask and add distilled water in a ratio of 1:6 (*w:v*). Then, reflux extraction was carried out twice, each time, for 1 hour. The filtrate was combined and concentrated to 100 mL and stored at 4°C for later use. All the decoctions were prepared every 5 days, and the dosage was converted according to the body surface area method [50]. The final intragastric dose given to the rats was calculated based on the decoction equivalent corresponding to the weight of the crude herbs: BDDSD (10.1 g/kg/day), BDD (5.7 g/kg/day), and DSD (4.4 g/kg/day).

2.4. MIRI Combined with DEP Rat Model and Groups

The SD rats were randomly divided into five groups by weight, including the Control group, DEP group, BDDSD group, BDD group, and DSD group (Fig. **1**). The BDD and DSD were respectively used as the DEP control drug and the MIRI control drug. There were 24 rats in the Control group and only 12 in the other groups. Besides the Control group, we used the chronic unpredictable mild stress (CUMS) method to induce DEP in other groups for 6 weeks [51, 52]. The CUMS method included fasting (24 hours), water deprivation (24 hours), overnight lighting (12 hours), wet bedding (24 hours), ice water swimming (10 minutes), and tilting the rat cage for 12 hours. One of these methods is randomly applied each day, and the same method cannot be repeated every two days. In the 7th to 8th week, the Control group was given normal saline and the BDDSD, BDD, and DSD groups were administered with the corresponding decoction, during which CUMS stimulation was maintained. At the end of the 8th week, behavioral tests were conducted to assess the degree of DEP in each group [53]. After a 24-hour rest, the Control group was divided into the Sham group and the MIRI group, with 12 rats in each group. Except for the Sham group, we performed MIRI surgery in the MIRI group, DEP group, BDDSD group, BDD group, and DSD group. The method of MIRI surgery was as follows: the rats were anesthetized with an intraperitoneal injection of 1% pentobarbital sodium (40 mg/kg), and the left anterior descending branch of the coronary artery was ligated. If the ST segment of the rat's electrocardiogram was elevated, the ligation was considered successful. The ligation was maintained for 30 minutes, followed by 2 hours of reperfusion [54, 55]. During surgery, all rats were maintained at 37 ± 0.5°C with separate heated pads. At the end of ischemia-reperfusion, rats were given an intraperitoneal injection of pentobarbital sodium (20 mg/kg) to maintain anesthesia and were euthanized by exsanguination *via* the abdominal aorta. The chest was immediately opened, and the heart tissue was rapidly excised. The collected blood was separated into serum and stored at -80°C.

2.5. Effects of BDDSD, BDD and DSD on DEP in Rats

2.5.1. Open Field Test (OFT)

The OFT was performed in a quiet environment where each rat was gently placed in the center of an open-field arena (100 cm × 100 cm × 50 cm). The spontaneous activity of each rat, such as the duration of time spent in the central area, was observed and recorded using a video analysis system. After each test session, the open field area is thoroughly cleaned with 75% ethanol to remove any residual traces before proceeding with subsequent tests.

2.5.2. Elevated Plus Maze Test (EPMT)

Firstly, the rats were acclimated to the experimental environment for 2 hours. Subsequently, each rat was placed in the central square of the maze with its head oriented towards an open arm. Concurrently, a camera monitor was activated to record the duration of time spent in the open arms, measured in seconds. In each subsequent trial, the rat was consistently positioned in the same location. Following each test, the rat's feces were removed, and the maze was cleaned with 75% ethanol to eliminate any olfactory cues that may influence the behavior in subsequent trials.

2.5.3. Sucrose Preference Test (SPT)

Initially, two bottles of 1% sucrose solution were provided in each cage for a 24-hour acclimation period. A bottle of 1% sucrose solution was then replaced with distilled water, allowing the rats to acclimate for another 24 hours. After the acclimation phase, the rats were subjected to a 12-hour water deprivation period, after which the formal testing commenced. During the test, rats in each group were provided with ample amounts of both 1% sucrose solution and distilled water. After an hour, the water bottle was removed and the volume of the consumed sucrose solution and distilled water was measured. Notably, the positions of the two water bottles were switched 30 minutes after the start of the test to mitigate the effects of the rats' positional preferences [56, 57].

Sucrose preference (SP)% = sucrose consumption / [sucrose consumption + distilled water consumption] ×100.

2.5.4. Forced Swimming Test (FST)

The method of FST is improved based on the literature report [58]. Rats were sequentially placed into a transparent Plexiglas cylinder (60 cm in height × 30 cm in diameter), filled to two-thirds with water at 25°C. The rats were allowed a 1-minute acclimation period within the cylinder, followed by a 10-minute observation period during which their duration of immobility was recorded.

2.6. Effects of BDDSD, BDD and DSD on DEP+MIRI in Rats

2.6.1. Tetrazolium Chloride Staining (TTC staining)

TTC staining was used to evaluate the effect of BDDSD on myocardial infarct size [59]. MIRI surgery was performed on all rats from the MIRI, DEP, BDDSD, BDD and DSD groups. The sham group also had surgery but no coronary artery ligation. Five rats were randomly selected from each group. After MIRI surgery, the rats were killed and their hearts were fixed in an OTC embedding medium and frozen at -20°C for 30 minutes. The left ventricle was then sectioned along its longitudinal axis into five 1-2 mm transverse slices. These slices were placed in a brown bottle and covered completely with TTC staining solution, followed by a water bath at 37°C. After staining for 10-15 minutes, the staining condition was observed.

2.6.2. Hematoxylin and Eosin Staining (HE staining)

HE staining was used to observe the histopathological effects of BDDSD on MIRI in rats with DEP [60]. One rat was randomly selected from each group. The rat heart was fixed with a 4% paraformaldehyde solution, dehydrated, and embedded in paraffin. Then the area near the left ventricle was cut horizontally into 4 μm sections for HE staining. The dried myocardial tissue slices were soaked in xylene and a gradient of ethanol solutions in sequence. Then, the slices were stained with hematoxylin and eosin, and dehydrated with a gradient of ethanol solutions. Finally, the slices were sealed with neutral resin and observed under a microscope.

2.6.3. GSH, MDA, SOD, Fe^{2+} Levels in Rat Myocardium and IL-6, IL-1β, LDH Levels in Serum

After TTC staining and HE staining experiments, the remaining six rats in each group were subjected to abdominal aortic blood collection after MIRI surgery. The blood was allowed to clot at room temperature for 30 minutes, followed by centrifugation at 4°C at 3000 rpm for 15 minutes. The serum was collected and the levels of LDH, IL-6 and IL-1β in the serum were detected with kits. Additionally, tissue from the ligated cardiac regions of the rats was prepared into homogenates. And GSH, MDA, SOD and Fe^{2+} contents were detected with kits. IL-6 and IL-1β were primarily used to assess whether DEP affects MIRI through inflammatory factors. The MDA, SOD, LDH and GSH were used to evaluate oxidative damage of rat myocardium. The GSH and Fe^{2+} levels were used to preliminarily evaluate cardiac ferroptosis in rats.

2.6.4. Detection of Ferroptosis-related Protein Expression with Western Blot

Cardiac tissue samples were collected and lysed on ice with RIPA lysis buffer. Total protein was extracted from the tissue, and protein concentration was quantified using the BCA method. Proteins of interest, such as FSP1(1:10000), NOX2(1:5000), NOX4(1:4000), CoQ10(1:1000), COX2 (1:2000) and FTL(1:6000) were separated by SDS-PAGE. The gel was then transferred to a membrane, which was incubated with primary antibodies overnight at 4°C, followed by incubation with secondary antibodies for 1 hour at room temperature. The membrane was then treated with an ECL developing solution and imaged using an imaging system. The grayscale values were analyzed using ImageJ software.

2.7. Content Determination of the Seven Compounds in BDDSD

We established an LC-MS-MS method for the determination of main compounds in BDDSD for quality control, including Rehmannioside D, Tanshinol, Protocatechuic acid, Vanillic acid, regaloside A, regaloside B and Cryptotanshinone. Chromatographic separation was carried out on an ACQUITY UPLC ® BEH-C18 column (2.1 mm × 100

mm, 1.7 μm), with acetonitrile (solution A) and -0.1% formic acid (solution B) as the mobile phase for gradient elution. The quantification of the analytes was performed by mass spectrometry with electrospray ionization (ESI) under negative and positive ion multiple reaction monitoring (MRM) mode, the drying gas temperature was 250 °C, and the sheath gas temperature was 350°C. The ion pairs we used were Rehmannioside D (709.2→362.9), Tanshinol (197.1→122.9, Protocatechuic acid (153.0→107.0), Vanillic acid (167.0→151.9), Regaloside A (399.1→163.0), Regaloside B (441.1→381.0) and Cryptotanshinone (297.1→254.0). The column temperature was 30°C and the gradient duration was 10 min at a flow rate of 0.2 mL/min as following: 5–5% A (0–1 min), 5–50% A (1–3 min), 50–95% A (3–5 min),9 5–95% A (5–7 min), 95–5% A (7-8 min), and 5–5%A (8–10 min). The injection volume was 5 μL. Before injection, the drug extract was diluted 2000 times with water and methanol as a sample solution, so that the alcohol content was 50%. We weighed seven reference standards and dissolved each in 50% methanol to a concentration of 1μg/mL. Then, an appropriate amount of each of the seven reference standard solutions was mixed to a final volume of 10 mL to prepare the mixed standard reference solution. The standard solution and sample solution were filtered with a 0.22 syringe filter before analysis.

2.8. Statistical Analysis

Statistical analysis was performed using GraphPad Prism 8.0.1. The data were expressed as mean ± standard deviation. Normality and homogeneity of variances were verified using the D'Agostino-Pearson and Brown-Forsythe tests, respectively. For multiple group comparisons, one-way ANOVA followed by Tukey's post hoc test was applied. All tests were two-tailed, with statistical significance defined as $P < 0.05$. Effect sizes for post hoc comparisons were calculated as Cohen's d. Cohen's d values were classified as large ($d \geq 0.8$), medium ($d \geq 0.5$), or small ($d \geq 0.2$).

3. RESULTS

3.1. Effects of BDDSD on Behavior in Rats with DEP

Behavioral tests, including OFT, EPMT, SPT and FST, are often used to assess the effects of drugs on animals with DEP [61]. Since the Control group has not been further subdivided into subgroups at this point (n = 24), when conducting the tests, half of these 24 rats were randomly selected for testing to ensure that the number of rats in each group was equal ($n = 12$).

The OFT result is shown in Figs. (**2A-C**). Compared with the Control group, the DEP group had significantly reduced duration time in the central area (4.4±1.5 *vs.* 37.7 ± 1.9 s, $P < 0.001$, d=19.5) and total journey (373±61 *vs.* 1235±76 mm, $P < 0.001$, d=12.5), indicating that the depressed rats exhibited typical decreased exploratory behavior. Compared with the DEP group, both the BDD group and the BDDSD group significantly improved depressive behavior (both $P < 0.05$). Among them, the BDDSD group had significantly longer duration time in the central area (22.2±5.5 s) and greater total journey (1026 ± 87 mm) than the BDD group (15.2±4.0 s, 739±45 mm) ($P < 0.01$, duration time: d=1.5, total journey: d=4.1).

The EPMT result showed that the rats in the DEP group had significantly reduced duration time in the open arms (65 ± 12 *vs.* 216 ± 42 s, $P < 0.001$, d=4.9) and total journey (285 ± 78 *vs.* 1496 ± 257 mm, $P < 0.001$, d=6.4) compared with the Control group (Figs. **2D-F**), indicating that the depressed rats exhibited typical avoidance behavior. Compared with the DEP group, the BDDSD group had significantly increased duration time in the open arms (192 ± 27 *vs.* 65 ± 12 s, $P < 0.01$, d=6.1) and total journey (1033 ± 100 *vs.* 285 ± 78 mm, $P < 0.01$, d=8.34). The therapeutic effect of the BDDSD group was significantly better than that of the BDD group (192± 27 *vs.* 161 ± 21 s, 1033± 100 *vs.* 614 ± 125 mm) ($P < 0.05$, duration time: d=1.3, total journey: d=3.7). Although the DSD group showed a trend of improvement, there was no statistical difference. These results indicate that BDDSD can effectively enhance the rats' willingness to explore a novel environment.

Additionally, the results of the SPT and FST revealed that, compared with the Control group, the sucrose preference of the depressed rats was significantly reduced (50 ± 6% *vs.* 86 ± 5%, $P < 0.001$, d=6.5), and the immobility time in the FST was significantly increased (428 ± 28 *vs.* 324 ± 52 s, $P < 0.01$, d=2.5) (Figs. **2G, H**). In the SPT, compared with the DEP group, BDDSD intervention significantly increased the sucrose preference of the rats (69 ± 3% *vs.* 50 ± 6%, $P < 0.001$, d=4.0), and the BDD group also had a significant improvement (65 ± 10% *vs.* 50 ± 6%, $P < 0.01$, d=1.8), while the DSD group showed no significant change. In the FST, the BDDSD group significantly reduced the immobility time of the rats (319 ± 61 s *vs.* 428 ± 28 s, $P < 0.01$, d=2.3), and there was no significant difference compared with the Control group; the immobility time of the BDD group was shorter than that of the DEP group (338 ± 47 s *vs.* 428 ± 28 s, $P < 0.05$, d=2.8), while the DSD group showed no significant improvement.

These behavioral tests showed that BDDSD exhibited significant antidepressant effects, comparable to and even surpassing the DEP-positive control drug BDD. In contrast, the MIRI-positive drug DSD showed little improvement in DEP rats. .

3.2. Effect of BDDSD on Myocardial Tissue Injury in rats Suffering from MIRI Combined with DEP

To evaluate the effect of BDDSD on MIRI in rats with DEP, the myocardial infarct size was measured and HE staining was performed on the injured myocardium of the rats (Figs. **3A, B**). Compared to the Sham group, both the MIRI and DEP+MIRI groups had myocardial infarctions ($P<0.05$), and the infarct size in the DEP+MIRI group was 1.5 times that of the MIRI group ($P<0.05$). Compared with the DEP+MIRI group, the DSD group's infarct size dropped by 41%, BDDSD by 46%, and BDD by 22.3%. BDDSD had a smaller infarct size than BDD, likely due to its antidepressant effects, enhancing the treatment of MIRI in depressed rats. Compared with the DEP + MIRI group, the myocardial infarction area in the BDD group was reduced but showed no significant difference from the MIRI group, also confirming that alleviating DEP can reduce DEP's impact on MIRI.

Compared with the Sham group, HE staining showed that myocardial cells in the MIRI and DEP+MIRI groups had

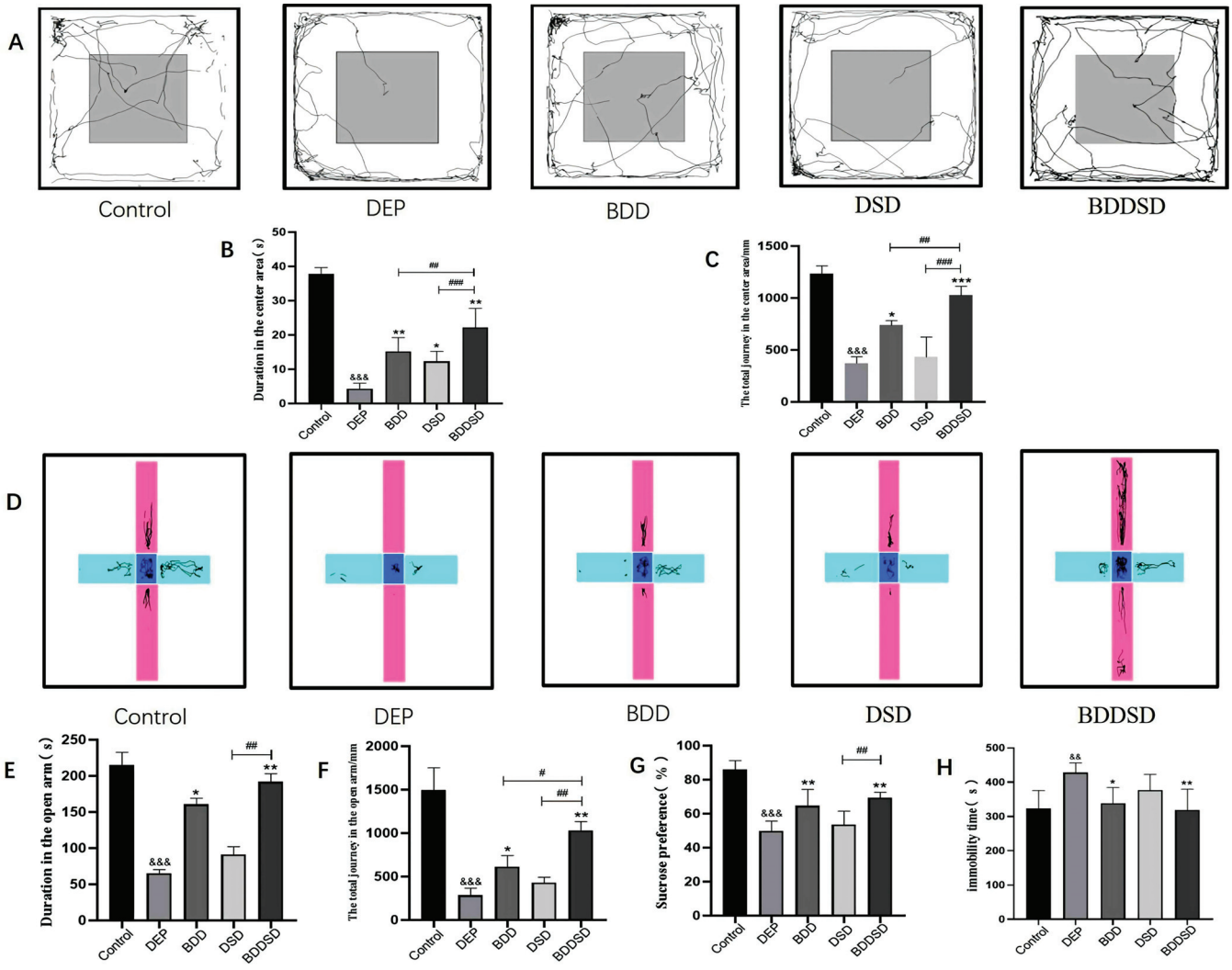


Fig. (2). Effects of BDDSD on the behavior of rats with DEP. **(A)** Motion track in the OFT. **(B)** Duration time in the central area. **(C)** Total journey in the central area. **(D)** Motion track in the EPMT. **(E)** Duration in the open arm. **(F)** Total journey in the open arm. **(G)** Changes in sucrose preference percentage. **(H)** Immobility time. Data are expressed as mean±SD, n=12. $^{\&\&}P<0.01$, $^{\&\&\&}P<0.001$ *vs.* Control group; $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, *vs.* DEP group. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

disrupted myofibrils, expanded interstitial spaces, and inflammatory infiltration, with more severe damage in the DEP+MIRI group (Fig. **3C**). Compared with the DEP+MIRI group, the BDDSD and DSD groups had more orderly myocardial fibers, clearer striations, and improved inflammatory infiltration, with BDDSD performing better than DSD. The BDD group also showed some improvement over the DEP+MIRI group, likely due to BDD's antidepressant effects.

3.3. Effects of BDDSD on Myocardial Oxidative Injury and Inflammation in Rats Suffering from MIRI Combined with DEP

Serum LDH levels are often used to evaluate the degree of myocardial injury [62]. The serum LDH levels in DEP+MIRI and MIRI groups were significantly higher than those in the sham group (Fig. **4A**). Compared with the DEP+MIRI group, BDDSD and DSD reduced the serum LDH levels, with BDDSD demonstrating a more pronounced effect than DSD. Then we assessed the myocardial oxidative injury in myocardial tissues of rats by measuring MDA, SOD, GSH, and Fe^{2+} content (Figs. **4B-E**). The results revealed that myocardial oxidative injury was more severe in the MIRI+DEP group than other groups. BDDSD effectively mitigated myocardial oxidative injury in MIRI rats suffering from MIRI combined with DEP. Although DSD exhibited similar effects, its efficacy was inferior to that of BDDSD. Given that GSH and Fe^{2+} content are key mediators of ferroptosis [63, 64], the regulatory effects of BDDSD on GSH and Fe^{2+} levels suggest its potential involvement in modulating myocardial ferroptosis.

We proposed that DEP exacerbated MIRI by promoting myocardial ferroptosis by activating inflammation. Clinical studies have reported elevated serum levels of inflammatory factors in depressed patients [65-67]. Therefore, we measured serum IL-6 and IL-1β levels in each group of rats (Figs. **4F, G**). Compared with other groups, the serum levels of IL-6 and IL-1β were significantly elevated in the DEP+MIRI

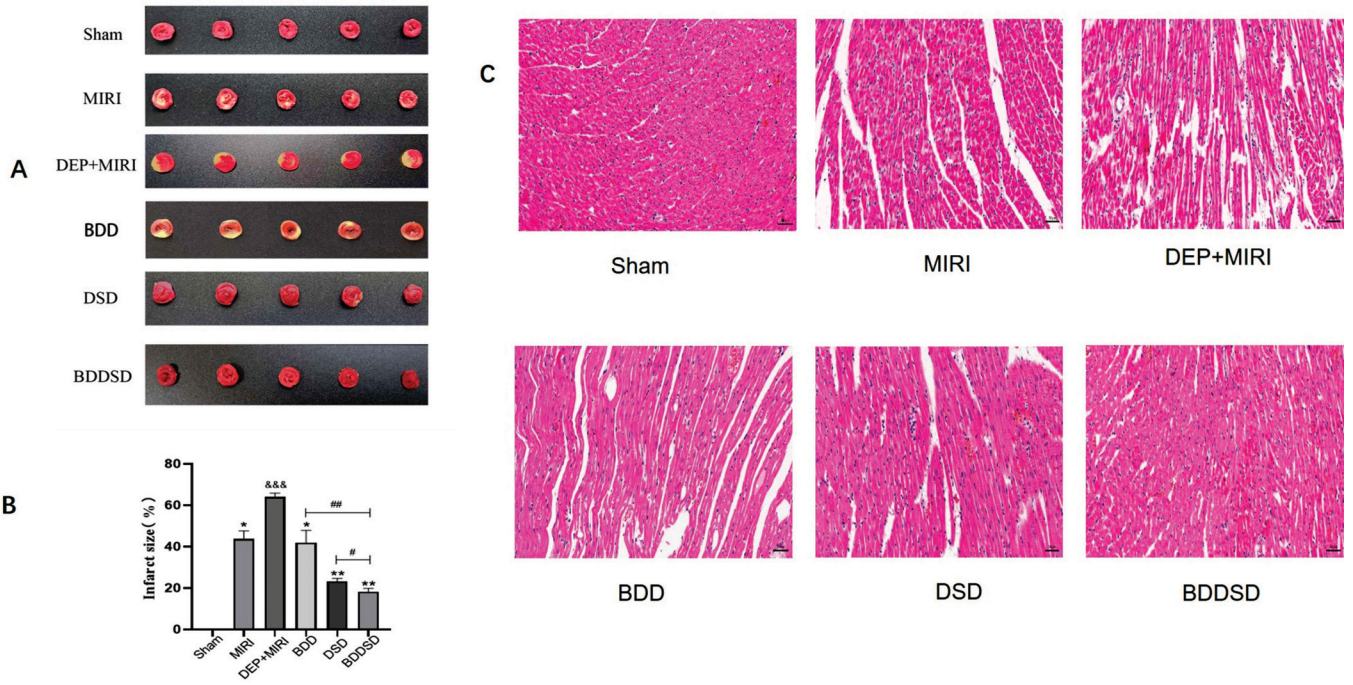


Fig. (3). Effects of BDDSD on myocardial tissue injury in MIRI rats with DEP. **(A, B)** myocardial tissue TTC staining (n=5). **(C)** myocardial tissue HE staining (×200). Data are expressed as mean±SD, $^{\&\&\&}P$<0.001 *vs.* Sham group; $^{*}P < 0.05$, $^{**}P < 0.01$, *vs.* DEP+MIRI group. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

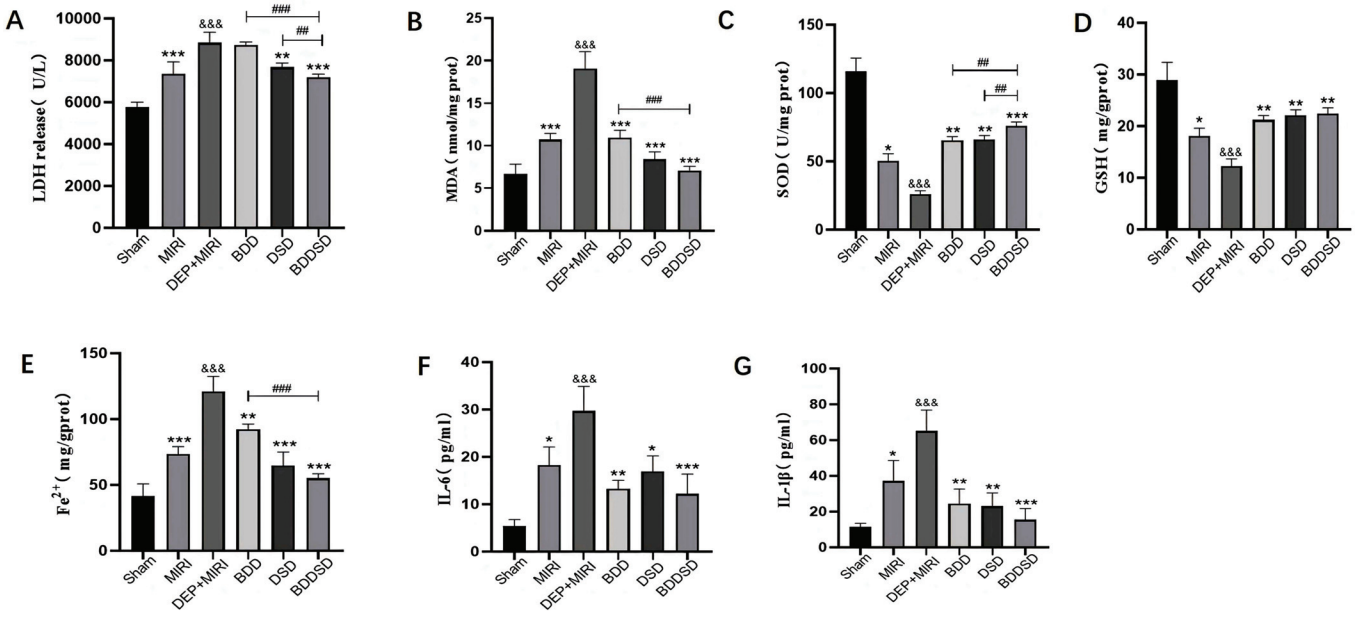


Fig. (4): Effects of BDDSD on myocardial oxidative injury and serum inflammatory factors. **(A)** Serum LDH level. **(B-E)** Levels of MDA, SOD, GSH, and Fe^{2+} in rat myocardial tissue. **(F, G)** Levels of IL-6 and IL-1β in rat serum. Data are expressed as mean ± SD, n = 6, $^{\&\&\&}$P<0.001 *vs.* Sham group; $^{*}P$ <0.05, $^{**}P < 0.01$, $^{***}P < 0.001$ *vs.* DEP+MIRI group. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

group, whereas treatment with BDDSD markedly reduced their serum concentrations. Notably, BDD exhibited regulatory effects on MDA, SOD, GSH, Fe^{2+} content, and serum IL-6 and IL-1β levels in rats, when compared with the DEP+MIRI group. These findings further substantiate our hypothesis that treating DEP may confer therapeutic benefits in managing MIRI combined with DEP.

3.4. Effects of BDDSD on Protein Expression Associated with NADPH/FSP1/CoQ10 Pathway

Emerging evidence suggests that the NADPH/FSP1/CoQ10 pathway plays a pivotal role in counteracting ferroptosis [42, 68]. Our previous findings demonstrated that DEP exacerbates MIRI through inflammatory activation and oxi-

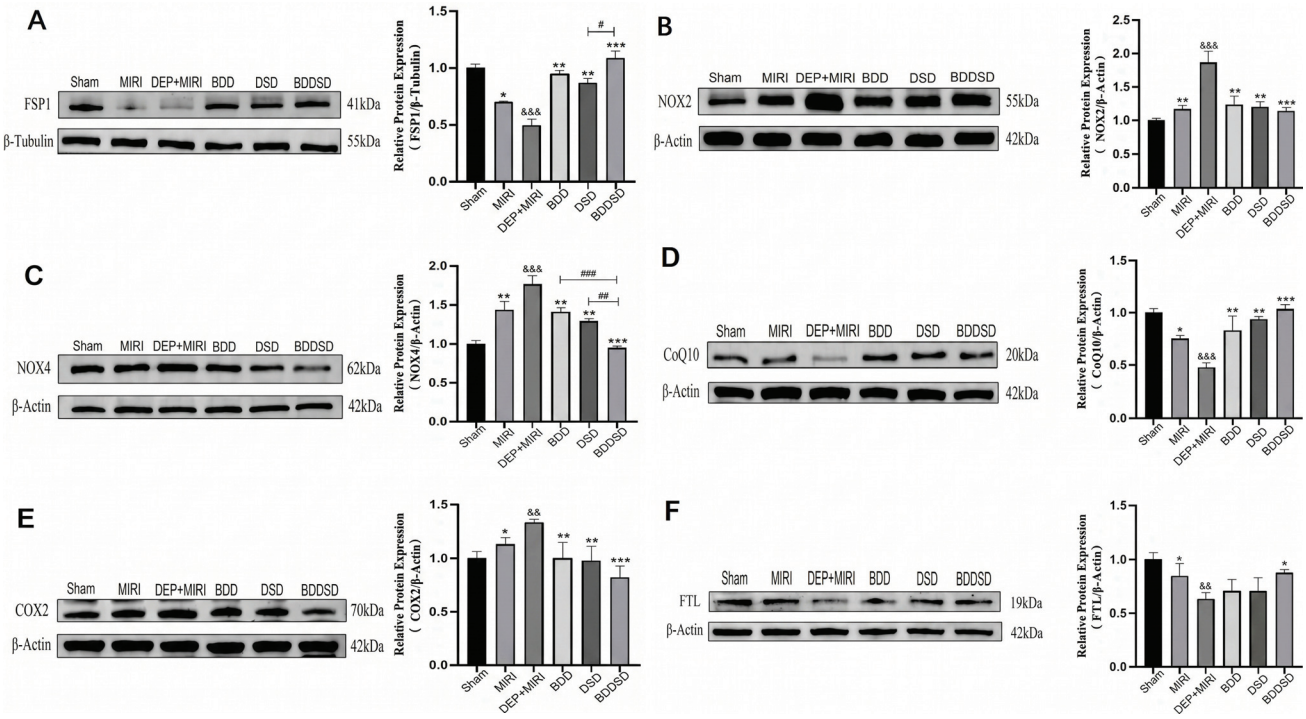


Fig. (5). Effects of BDDSD on protein expression on ferroptosis and NADPH/FSP1/CoQ10 pathway. **(A-F)** expression levels of myocardial FSP1, NOX2, NOX4, CoQ10, COX2, and FTL. Data are expressed as mean ± SD, $^{\&\&}P<0.01$, $^{\&\&\&}P<0.001$ *vs.* Sham group; $^{*}P<0.05$, $^{**}P<0.01$,$^{***}P<0.001$ *vs.* DEP+MIRI group;$^{\#}P<0.05$,$^{\#\#}P<0.01$,$^{\#\#\#}P<0.001$ *vs.* BDDSD group. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

dative stress (Fig. **4**), which are known to trigger NOX-mediated NADPH depletion and subsequent ROS overproduction. Crucially, FSP1 requires NADPH as an electron donor to reduce CoQ10, forming a key antioxidant system that prevents membrane lipid peroxidation - the hallmark of ferroptosis [69]. Therefore, we investigated the protein expression related to ferroptosis and NADPH/FSP1/CoQ10 pathway, including FSP1, CoQ10, NOX2, NOX4, FTL, and COX2.

FSP1, CoQ10, NOX2, and NOX4 are key proteins related to the FSP1 pathway. FTL reflects iron metabolism [70, 71], while COX2, a key marker of lipid peroxidation, indicates the degree of ferroptosis [72]. As shown in Fig. (**5**), the expression of FSP1, CoQ10, and FTL was decreased in the DEP+MIRI group (Figs. **5A, D, F**), while the expression of NOX2, NOX4 and COX2 was increased compared to the Sham group and MIRI group (Figs. **5B, C, E**). The BDD, DSD, and BDDSD groups exhibited elevated protein expression of FSP1 and CoQ10, with only the BDDSD group showing a significant increase in FTL expression compared to the DEP+MIRI group. Meanwhile, the expression of NOX2, NOX4, and COX2 was decreased in the BDD, DSD, and BDDSD groups. Compared with the BDD and DSD groups, the BDDSD group showed better regulatory effects on the expression of these related proteins. In our results, BDD also regulated the expression of these proteins. We believe that it exerted its effects on DEP+MIRI through the treatment of DEP. These results not only demonstrate that BDDSD can inhibit myocardial ferroptosis in rats by regulating the NADPH/FSP1/CoQ10 pathway, thereby alleviating MIRI, but also strongly support our hypothesis that a dual-target approach for DEP and MIRI provides better therapeutic effects for MIRI combined with DEP.

3.5. Content of Seven Compounds in BDDSD

Fig. (**6**) presents the chromatograms of the standard solution (Group 1) and sample solution (Group 2). Fig. (**6A**) shows the total ion chromatogram, while Fig. 6B-H displays the multiple reaction monitoring of the seven compounds: Rehmannioside D (Fig. **6B**), Tanshinol (Fig. **6C**), Protocatechuic acid (Fig. **6D**), Vanillic acid (Fig. **6E**), Regaloside A (Fig. **6F**), Regaloside B (Fig. **6G**), and Cryptotanshinone (Fig. **6H**). We measured the sample six times and recorded the peak area. The RSD values of the peak areas of Rehmannioside D, Tanshinol, Protocatechuic acid, Vanillic acid, regaloside A, regaloside B and Cryptotanshinone were 1.45%, 0.83%, 4.48%, 2.44%, 1.14%, 1.61% and 5.41%, respectively. The same sample was detected at 0 h, 2 h, 4 h, 6 h, 8h, 12 h and 24 h, the RSD values of the seven compounds were 1.59%, 2.64%, 1.82%, 0.04%, 0.01%, 0.15% and 0.23%, respectively. We used the peak area at different concentrations of the seven compounds to establish standard curves, as shown in Table **1**. Using the established standard curves, the concentration of Rehmannioside D, Tanshinol, Protocatechuic acid, Vanillic acid, regaloside A, regaloside B and Cryptotanshinone in the sample solution was 151.1±1.2, 173.0±1.6, 1.6±0.1, 8.3±0.1, 36.9±0.3, 71.1±0.6, and 4.0±0.0 μg/mL, respectively. The recovery rate was detected, as shown in Table **2**. It should be noted that the active compounds of Santali albi lignum were mainly volatile, and the proportion of Santali albi lignum in BDDSD was very low. Therefore, the active compounds in Santali albi lignum were difficult to detect, so we did not use Santali albi lignum's active compounds as quality control.

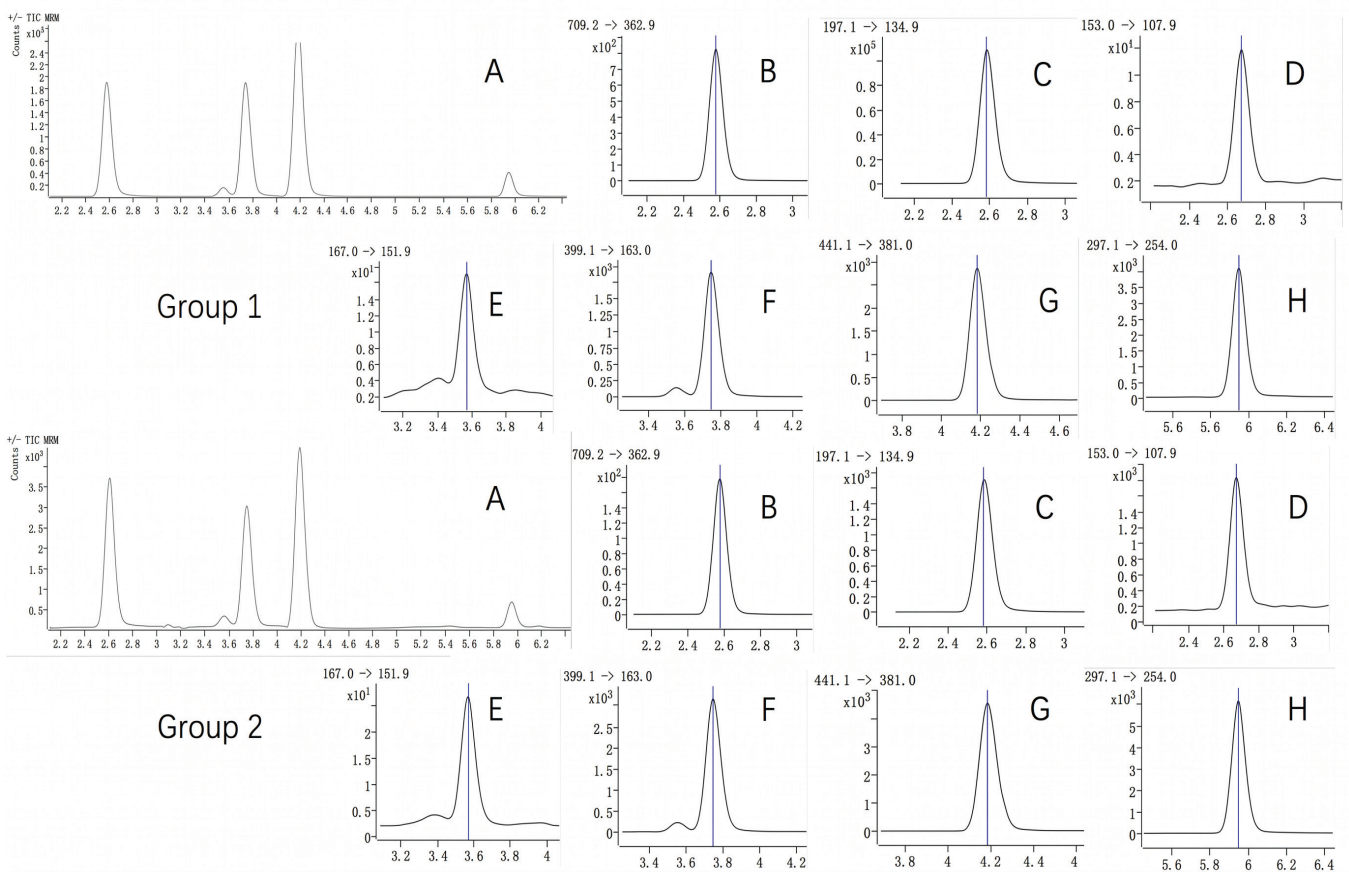


Fig. (6). Chromatograms of standard solution (Group 1) and sample solution (Group 2). (**A**) Total ion chromatogram, (B-H) Multiple reaction monitoring of the seven compounds. (**B**) Rehmannioside D, (**C**) Tanshinol, (**D**) Protocatechuic acid, (**E**) Vanillic acid, (**F**) Regaloside A, (**G**) Regaloside B, (**H**) Cryptotanshinone. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 1. Linear equations and correlation coefficients for seven compounds.

Reference Standard	Source	Regression equation	R	RT (min)	Linear Range (ng/mL)
Rehmannioside D	Rehmanniae radix	y= 26.782x-1060.4	0.9967	2.602	67.0-511.8
Tanshinol	Salviae miltiorrhizae radix et rhizoma	y=64.841x-67.665	0.9999	2.614	20.8-200.3
Protocatechuic acid	Amomi fructus	y=59.387x-1.58	0.9993	2.700	0.2-2.0
Vanillic acid	Amomi fructus	y= 17.499x-2.021	0.9995	3.577	1.0-10.1
Regaloside A	Lily bulbus	y=465.038x-421.969	0.9997	3.750	4.5-49.8
Regaloside B	Lily bulbus	y=337.932x-121.256	0.9990	4.192	8.4-101.0
Cryptotanshinone	Salviae miltiorrhizae radix et rhizoma	y=839.620x-41.790	0.9993	5.950	0.5-4.9

Table 2. Concentration in sample and recovery study.

Reference Standard	Concentration in Sample (ng/mL)	Standard Addition Concentration (ng/mL)	Detected Concentration (ng/mL)	Recovery (%)	Concentration in BDDSD (μg/mL)
Rehmannioside D	75.6±0.6	75.1	75.1±0.4	99.5±1.1	151.1±1.2
Tanshinol	86.5±0.8	86.3	85.6±0.5	98.4±0.8	173.0±1.6
Protocatechuic acid	0.8±0.0	0.8	0.8±0.0	104.6±1.5	1.6±0.1
Vanillic acid	4.1±0.1	4.1	4.1±0.1	102.5±2.5	8.3±0.1
Regaloside A	18.4±0.2	18.7	18.6±0.3	104.8±3.0	36.9±0.3
Regaloside B	35.5±0.3	35.5	35.0±0.5	98.4±2.1	71.1±0.6
Cryptotanshinone	2.0±0.3	2.0	2.1±0.1	104.5±5.4	4.0±0.0

Method: An equal volume of standard solution with the same concentration was added to the sample solution for analysis.
Recovery= (Detected concentration*2-concentration in sample)/Standard addition concentration (n = 6).
Since the measured sample is diluted 2000 times, the actual concentration of each component in BDDSD is calculated.

4. DISCUSSION

DEP combined with MIRI can raise the risk of adverse cardiovascular events after coronary heart disease surgery and may lead to more severe postoperative complications. As people pay more and more attention to the impact of DEP on cardiovascular diseases [73-75], we believe that research on MIRI combined with DEP and the search for therapeutic drugs are meaningful for the clinical surgical treatment of coronary heart disease. This study established an MIRI combined with DEP model and explored the therapeutic effects and mechanisms of BDDSD on MIRI combined with DEP, aiming to reveal the benefits of simultaneous treatment of DEP and MIRI in the process of treating "MIRI combined with DEP".

BDDSD is a novel formulation optimized based on BDD and DSD. Behavioral tests (OFT, EPMT, *etc*.) showed that BDDSD has significant antidepressant effects. Further research revealed that DEP could significantly exacerbate oxidative damage and inflammatory responses following MIRI (Fig. **4**). In a depressed state, the abnormal increase of IL-6/IL-1β activated the cardiac NOX2/4 system, causing NADPH depletion and a surge in ROS. This supports the relevant reports of the "DEP - Inflammation - Cardiovascular Injury" theory [76]. The breakthrough of this study lay in identifying ferroptosis as a bridge in this process: NADPH depletion weakened the FSP1/CoQ10 pathway's ability to suppress lipid peroxidation (as evidenced by elevated COX2, Fig. **5**), and the accumulation of free Fe^{2+} (Fig. **4E**) further worsened cardiac injury through the Fenton reaction [38, 77]. BDDSD offered a dual-regulatory treatment advantage: it alleviated DEP to reduce its impact on MIRI and inhibited cardiac ferroptosis by modulating key proteins such as FSP1. This multi-target synergistic intervention overcame the limitations of single-pathway ferroptosis inhibitors (*e.g.*, ferrostatin-1), providing a new strategy for the treatment of DEP combined with MIRI and a novel paradigm for treating complex comorbidities.

Studies show that DEP exacerbates cardiovascular diseases *via* inflammation-linked pathways, including HPA axis dysregulation, autonomic dysfunction and so on [15-18]. Our research indicates that DEP-induced inflammation promotes MIRI, but the roles of the hypothalamic-pituitary-adrenal axis and autonomic nervous system in this process require further study. In addition, we found that BDDSD can treat MIRI combined with DEP by regulating the NADPH/FSP1/CoQ10 pathway and inhibiting cardiac ferroptosis. However, the specific molecular mechanisms of this pathway remain poorly understood.

5. STUDY LIMITATIONS

This study explores how DEP affects MIRI and the role and mechanism of BDDSD in treating MIRI combined with DEP. Due to experimental challenges, we did not investigate the dose-efficacy relationship of BDDSD, limiting its clinical application guidance. Although we established a BDDSD quality control standard, the active components in traditional Chinese medicine are complex, and further research is needed to identify those effective for treating MIRI combined with DEP. Future research will focus on several areas. We will delve deeper into how DEP activates inflammation to promote cardiac ferroptosis and clarify the molecular mechanisms of regulating the NADPH/FSP1/CoQ10 pathway to inhibit cardiac ferroptosis. Additionally, we will screen the active components in BDDSD and conduct clinical trials on BDDSD for treating MIRI combined with DEP.

CONCLUSION

This study shows that DEP can worsen MIRI by enhancing inflammation-driven ferroptosis. DEP-induced overexpression of IL-6/IL-1β activates the NOX system, depletes NADPH and generates excessive ROS, which promote ferroptosis and aggravate MIRI. BDDSD alleviates this comorbidity by easing DEP and inhibiting cardiac ferroptosis *via* modulating the NADPH/FSP1/CoQ10 pathway. Our study not only offers a new molecular target for MIRI combined with DEP treatment but also enhances the understanding of ferroptosis in the context of DEP and MIRI comorbidity.

AUTHORS' CONTRIBUTIONS

The authors confirm their contribution to the paper as follows: study conception and design: KQ; data collection: LH; data analysis or interpretation: CL; methodology: YL; investigation: QX; draft manuscript: SZ, WH and KQ. All authors reviewed the results and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

BDD	=	Baihe Dihuang Decoction
BDDSD	=	Baihe Dihuang Danshen Decoction
DEP	=	Depression
DSD	=	Danshen Decoction
EPMT	=	Elevated Plus Maze Test
FST	=	Forced Swimming Test
HE	=	Hematoxylin and Eosin Staining
MIRI	=	Myocardial Ischemia-Reperfusion Injury
OFT	=	Open Field Test
SPT	=	Sucrose Preference Test
TTC	=	Tetrazolium Chloride Staining

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All animal experiments were approved by the Ethics Committee for Animal Experiments of China Three Gorges University, China (Ethics Approval No. 2024020T).

HUMAN AND ANIMAL RIGHTS

This study adheres to internationally accepted standards for animal research, following the 3Rs principle. The ARRIVE guidelines were employed for reporting experiments involving live animals, promoting ethical research practices.

All the animal experimentations were performed in accordance with the US National Research Council's Guide for the Care and Use of Laboratory Animals.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The data and supportive information are available within the article.

FUNDING

This work was supported by the Public Hospital Reform and High-Quality Development of Traditional Chinese Medicine Project of Yichang City (Grant # YWGZ24-35, YWGZ24-03), Special fund for Talents of Medicine and Health Sciences, Three Gorges University (Grant # 2023JKXK05), Yichang Municipal Natural Science Foundation Program (Grant # A24-3-040), and Scientific Research Project of Education Department of Hubei Province, China (Grant # Q20221213).

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

The authors would like to thank the Third-Grade Pharmacological Laboratory on Traditional Chinese Medicine, State Administration of Traditional Chinese Medicine, China Three Gorges University for providing the experimental platform.

REFERENCES

[1] Doenst, T.; Haverich, A.; Serruys, P.; Bonow, R.O.; Kappetein, P.; Falk, V.; Velazquez, E.; Diegeler, A.; Sigusch, H. PCI and CABG for treating stable coronary artery disease. *J. Am. Coll. Cardiol.,* **2019**, *73*(8), 964-976. http://dx.doi.org/10.1016/j.jacc.2018.11.053 PMID: 30819365

[2] Luo, Y.; Li, G.L.; Pan, Y.Z.; Zhou, S.F. Determinants and prognostic implications of reperfusion injury during primary percutaneous coronary intervention in Chinese patients with acute myocardial infarction. *Clin. Cardiol.,* **2009**, *32*(3), 148-153. http://dx.doi.org/10.1002/clc.20294 PMID: 19301290

[3] Tao, S.; Tang, X.; Yu, L.; Li, L.; Zhang, G.; Zhang, L.; Huang, L.; Wu, J. Prognosis of coronary heart disease after percutaneous coronary intervention: A bibliometric analysis over the period 2004–2022. *Eur. J. Med. Res.,* **2023**, *28*(1), 311. http://dx.doi.org/10.1186/s40001-023-01220-5 PMID: 37658418

[4] Dwaich, K.H.; Al-Amran, F.G.Y.; AL-Sheibani, B.I.M.; Al-Aubaidy, H.A. Melatonin effects on myocardial ischemia–reperfusion injury: Impact on the outcome in patients undergoing coronary artery bypass grafting surgery. *Int. J. Cardiol.,* **2016**, *221*, 977-986. http://dx.doi.org/10.1016/j.ijcard.2016.07.108 PMID: 27441478

[5] Ski, C.F.; Taylor, R.S.; McGuigan, K.; Long, L.; Lambert, J.D.; Richards, S.H.; Thompson, D.R. Psychological interventions for depression and anxiety in patients with coronary heart disease, heart failure or atrial fibrillation. *Cochrane Libr.,* **2024**, *2024*(5), CD013508. http://dx.doi.org/10.1002/14651858.CD013508.pub3 PMID: 38577875

[6] Hou, Q.L.; Liu, L.Y.; Wu, Y. The effects of mhealth interventions on quality of life, anxiety, and depression in patients with coronary heart disease: Meta-analysis of randomized controlled trials. *J. Med. Internet Res.,* **2024**, *26*, 52341. http://dx.doi.org/10.2196/52341 PMID: 38861710

[7] Carney, R.M.; Freedland, K.E.; Rich, M.W. Treating depression to improve survival in coronary heart disease. *J. Am. Coll. Cardiol.,* **2024**, *84*(5), 482-489. http://dx.doi.org/10.1016/j.jacc.2024.05.038 PMID: 39048281

[8] AbuRuz, M.E. Pre-operative depression predicted longer hospital length of stay among patients undergoing coronary artery bypass graft surgery. *Risk Manag. Healthc. Policy.,* **2019**, *12*, 75-83. http://dx.doi.org/10.2147/RMHP.S190511 PMID: 31191059

[9] Stenman, M.; Holzmann, M.J.; Sartipy, U. Association between preoperative depression and long-term survival following coronary artery bypass surgery — A systematic review and meta-analysis. *Int. J. Cardiol.,* **2016**, *222*, 462-466. http://dx.doi.org/10.1016/j.ijcard.2016.07.216 PMID: 27505334

[10] Poole, L.; Ronaldson, A.; Kidd, T.; Leigh, E.; Jahangiri, M.; Steptoe, A. Pre-surgical depression and anxiety and recovery following coronary artery bypass graft surgery. *J. Behav. Med.,* **2017**, *40*(2), 249-258. http://dx.doi.org/10.1007/s10865-016-9775-1 PMID: 27552993

[11] Zhai, P.; Ouyang, X.; Yang, M.; Lin, L.; Li, J.; Li, Y.; Cheng, X.; Zhu, R.; Hu, D. Luteolin protects against myocardial ischemia/reperfusion injury by reducing oxidative stress and apoptosis through the p53 pathway. *J. Integr. Med.,* **2024**, *22*(6), 652-664. http://dx.doi.org/10.1016/j.joim.2024.09.001 PMID: 39343710

[12] Su, Z.; Li, P.; Ding, W.; Gao, Y. Urolithin A improves myocardial ischemia–reperfusion injury by attenuating oxidative stress and ferroptosis through Nrf2 pathway. *Int. Immunopharmacol.,* **2024**, *143*(Pt 2), 113394. http://dx.doi.org/10.1016/j.intimp.2024.113394 PMID: 39437484

[13] Algoet, M.; Janssens, S.; Himmelreich, U.; Gsell, W.; Pusovnik, M.; Van den Eynde, J.; Oosterlinck, W. Myocardial ischemia-reperfusion injury and the influence of inflammation. *Trends Cardiovasc. Med.,* **2023**, *33*(6), 357-366. http://dx.doi.org/10.1016/j.tcm.2022.02.005 PMID: 35181472

[14] Yao, Y.; Li, F.; Zhang, M.; Jin, L.; Xie, P.; Liu, D.; Zhang, J.; Hu, X.; Lv, F.; Shang, H.; Zheng, W.; Sun, X.; Duanmu, J.; Wu, F.; Lan, F.; Xiao, R.P.; Zhang, Y. Targeting CaMKII-δ9 ameliorates cardiac ischemia/reperfusion injury by inhibiting myocardial inflammation. *Circ. Res.,* **2022**, *130*(6), 887-903. http://dx.doi.org/10.1161/CIRCRESAHA.121.319478 PMID: 35152717

[15] Xu, L.; Zhai, X.; Shi, D.; Zhang, Y. Depression and coronary heart disease: Mechanisms, interventions, and treatments. *Front. Psychiatry,* **2024**, *15*, 1328048. http://dx.doi.org/10.3389/fpsyt.2024.1328048 PMID: 38404466

[16] Bremner, J.D.; Campanella, C.; Khan, Z.; Shah, M.; Hammadah, M.; Wilmot, K.; Al Mheid, I.; Lima, B.B.; Garcia, E.V.; Nye, J.; Ward, L.; Kutner, M.H.; Raggi, P.; Pearce, B.D.; Shah, A.J.; Quyyumi, A.A.; Vaccarino, V. Brain correlates of mental stress-induced myocardial ischemia. *Psychosom. Med.,* **2018**, *80*(6), 515-525. http://dx.doi.org/10.1097/PSY.0000000000000597 PMID: 29794945

[17] Mason, J.C.; Libby, P. Cardiovascular disease in patients with chronic inflammation: Mechanisms underlying premature cardiovascular events in rheumatologic conditions. *Eur. Heart J.,* **2015**, *36*(8), 482-489. http://dx.doi.org/10.1093/eurheartj/ehu403 PMID: 25433021

[18] Lin, J.; Yang, R.; Zhang, Y.; Hou, Y.; Yang, H.; Zhou, X.; Liu, T.; Yang, Q.; Wang, Y. The mediation effects of metabolic and immune–inflammation factors on the depression–premature coronary heart disease association. *J. Affect Disord.,* **2023**, *331*, 434-441. http://dx.doi.org/10.1016/j.jad.2023.03.046 PMID: 36990287

[19] Wang, Y.; Zhang, H.; Chai, F.; Liu, X.; Berk, M. The effects of escitalopram on myocardial apoptosis and the expression of Bax and Bcl-2 during myocardial ischemia/reperfusion in a model of rats with depression. *BMC Psychiatry,* **2014**, *14*(1), 349. http://dx.doi.org/10.1186/s12888-014-0349-x PMID: 25471226

[20] Zhang, W.Y.; Nan, N.; Song, X.T.; Tian, J.F.; Yang, X.Y. Impact of depression on clinical outcomes following percutaneous coronary intervention: A systematic review and meta-analysis. *BMJ Open,* **2019**, *9*(8), 026445.

http://dx.doi.org/10.1136/bmjopen-2018-026445 PMID: 31434764

[21] Jha, M.K.; Qamar, A.; Vaduganathan, M.; Charney, D.S.; Murrough, J.W. Screening and management of depression in patients with cardiovascular disease. *J. Am. Coll. Cardiol.,* **2019**, *73*(14), 1827-1845.
http://dx.doi.org/10.1016/j.jacc.2019.01.041 PMID: 30975301

[22] Abdul Manan, H.; Mir, I.A.; Humayra, S.; Tee, R.Y.; Vasu, D.T. Effect of mindfulness-based interventions on anxiety, depression, and stress in patients with coronary artery disease: A systematic review and meta-analysis of randomized controlled trials. *Front. Psychol.,* **2024**, *15*, 1435243.
http://dx.doi.org/10.3389/fpsyg.2024.1435243 PMID: 39144586

[23] Daskalopoulou, M.; George, J.; Walters, K.; Osborn, D.P.; Batty, G.D.; Stogiannis, D.; Rapsomaniki, E.; Pujades-Rodriguez, M.; Denaxas, S.; Udumyan, R.; Kivimaki, M.; Hemingway, H. Depression as a risk factor for the initial presentation of twelve cardiac, cerebrovascular, and peripheral arterial diseases: Data linkage study of 1.9 million women and men. *PLoS One,* **2016**, *11*(4), 0153838.
http://dx.doi.org/10.1371/journal.pone.0153838 PMID: 27105076

[24] Gray, R. Review: Prevalence of depression and its associated factors in patients post-coronary artery bypass graft surgery. *J. Res. Nurs.,* **2018**, *23*(1), 89-90.
http://dx.doi.org/10.1177/1744987117730470 PMID: 34394411

[25] Xing, N.; Long, X.T.; Zhang, H.J.; Fu, L.D.; Huang, J.Y.; Chaurembo, A.I.; Chanda, F.; Xu, Y.J.; Shu, C.; Lin, K.X.; Yang, K.; Lin, H.B. Research progress on effects of traditional Chinese medicine on myocardial ischemia–reperfusion injury: A review. *Front. Pharmacol.,* **2022**, *13*, 1055248.
http://dx.doi.org/10.3389/fphar.2022.1055248 PMID: 36561346

[26] Li, Y.; Li, Y.; Li, B.; Liu, Y.; Zhang, J.; Kuang, W.; Lu, J.; Cao, Z.; Cui, J.; Fan, Z.; Guo, B.; Li, D. Antiplatelet therapy with integrated traditional chinese and western medicine for use in myocardial ischemia-reperfusion injury: A review of clinical applications and mechanisms. *Evid. Based Complement. Alternat. Med.,* **2021**, *2021*, 1-9.
http://dx.doi.org/10.1155/2021/7409094 PMID: 34335837

[27] Chen, J.; Wei, X.; Zhang, Q.; Wu, Y.; Xia, G.; Xia, H.; Wang, L.; Shang, H.; Lin, S. The traditional Chinese medicines treat chronic heart failure and their main bioactive constituents and mechanisms. *Acta. Pharm. Sin B,* **2023**, *13*(5), 1919-1955.
http://dx.doi.org/10.1016/j.apsb.2023.02.005 PMID: 37250151

[28] Wang, Y.; Fan, X.; Qu, H.; Gao, X.; Cheng, Y. Strategies and techniques for multi-component drug design from medicinal herbs and traditional Chinese medicine. *Curr. Top Med. Chem.,* **2012**, *12*(12), 1356-1362.
http://dx.doi.org/10.2174/156802612801319034 PMID: 22690682

[29] Pope, B.S.; Wood, S.K. Advances in understanding mechanisms and therapeutic targets to treat comorbid depression and cardiovascular disease. *Neurosci. Biobehav. Rev.,* **2020**, *116*, 337-349.
http://dx.doi.org/10.1016/j.neubiorev.2020.06.031 PMID: 32598982

[30] Liu, C.; Li, Z.; Li, B.; Liu, W.; Zhang, S.; Qiu, K.; Zhu, W. Relationship between ferroptosis and mitophagy in cardiac ischemia reperfusion injury: A mini-review. *PeerJ,* **2023**, *11*, 14952.
http://dx.doi.org/10.7717/peerj.14952 PMID: 36935924

[31] Yu, Y.; Yan, Y.; Niu, F.; Wang, Y.; Chen, X.; Su, G.; Liu, Y.; Zhao, X.; Qian, L.; Liu, P.; Xiong, Y. Ferroptosis: A cell death connecting oxidative stress, inflammation and cardiovascular diseases. *Cell. Death Discov.,* **2021**, *7*(1), 193.
http://dx.doi.org/10.1038/s41420-021-00579-w PMID: 34312370

[32] Xu, J.; Tao, L.; Jiang, L.; Lai, J.; Hu, J.; Tang, Z. Moderate hypothermia alleviates sepsis-associated acute lung injury by suppressing ferroptosis induced by excessive inflammation and oxidative stress *via* the Keap1/GSK3β/Nrf2/GPX4 signaling pathway. *J. Inflamm. Res.,* **2024**, *17*, 7687-7704.
http://dx.doi.org/10.2147/JIR.S491885 PMID: 39498104

[33] Cai, W.; Liu, L.; Shi, X.; Liu, Y.; Wang, J.; Fang, X.; Chen, Z.; Ai, D.; Zhu, Y.; Zhang, X. Alox15/15-HpETE aggravates myocardial ischemia-reperfusion injury by promoting cardiomyocyte ferroptosis. *Circulation,* **2023**, *147*(19), 1444-1460.
http://dx.doi.org/10.1161/CIRCULATIONAHA.122.060257 PMID: 36987924

[34] Jin, Y.; Tan, M.; Yin, Y.; Lin, C.; Zhao, Y.; Zhang, J.; Jiang, T.; Li, H.; He, M. Oroxylin A alleviates myocardial ischemia–reperfusion injury by quelling ferroptosis *via* activating the DUSP10 / MAPK -Nrf2 pathway. *Phytother. Res.,* **2024**, *38*(11), 5290-5308.
http://dx.doi.org/10.1002/ptr.8315 PMID: 39225191

[35] Fioranelli, M.; Bottaccioli, A.G.; Bottaccioli, F.; Bianchi, M.; Rovesti, M.; Roccia, M.G. Stress and inflammation in coronary artery disease: A review psychoneuroendocrineimmunology-based. *Front. Immunol.,* **2018**, *9*, 2031.
http://dx.doi.org/10.3389/fimmu.2018.02031 PMID: 30237802

[36] Chen, Y.; Fang, Z.M.; Yi, X.; Wei, X.; Jiang, D.S. The interaction between ferroptosis and inflammatory signaling pathways. *Cell. Death Dis.,* **2023**, *14*(3), 205.
http://dx.doi.org/10.1038/s41419-023-05716-0 PMID: 36944609

[37] Cadenas, S. ROS and redox signaling in myocardial ischemia-reperfusion injury and cardioprotection. *Free Radic. Biol. Med.,* **2018**, *117*, 76-89.
http://dx.doi.org/10.1016/j.freeradbiomed.2018.01.024 PMID: 29373843

[38] Deng, L.; He, S.; Guo, N.; Tian, W.; Zhang, W.; Luo, L. Molecular mechanisms of ferroptosis and relevance to inflammation. *Inflamm. Res.,* **2023**, *72*(2), 281-299.
http://dx.doi.org/10.1007/s00011-022-01672-1 PMID: 36536250

[39] Wang, B.; Wang, Y.; Zhang, J.; Hu, C.; Jiang, J.; Li, Y.; Peng, Z. ROS-induced lipid peroxidation modulates cell death outcome: Mechanisms behind apoptosis, autophagy, and ferroptosis. *Arch. Toxicol.,* **2023**, *97*(6), 1439-1451.
http://dx.doi.org/10.1007/s00204-023-03476-6 PMID: 37127681

[40] Liu, J.; Kang, R.; Tang, D. Signaling pathways and defense mechanisms of ferroptosis. *FEBS J.,* **2022**, *289*(22), 7038-7050.
http://dx.doi.org/10.1111/febs.16059 PMID: 34092035

[41] Zheng, J.; Conrad, M. The Metabolic Underpinnings of Ferroptosis. *Cell. Metab.,* **2020**, *32*(6), 920-937.
http://dx.doi.org/10.1016/j.cmet.2020.10.011 PMID: 33217331

[42] Doll, S.; Freitas, F.P.; Shah, R.; Aldrovandi, M.; da Silva, M.C.; Ingold, I.; Goya Grocin, A.; Xavier da Silva, T.N.; Panzilius, E.; Scheel, C.H.; Mourão, A.; Buday, K.; Sato, M.; Wanninger, J.; Vignane, T.; Mohana, V.; Rehberg, M.; Flatley, A.; Schepers, A.; Kurz, A.; White, D.; Sauer, M.; Sattler, M.; Tate, E.W.; Schmitz, W.; Schulze, A.; O'Donnell, V.; Proneth, B.; Popowicz, G.M.; Pratt, D.A.; Angeli, J.P.F.; Conrad, M. FSP1 is a glutathione-independent ferroptosis suppressor. *Nature,* **2019**, *575*(7784), 693-698.
http://dx.doi.org/10.1038/s41586-019-1707-0 PMID: 31634899

[43] Chi, X.; Wang, S.; Baloch, Z.; Zhang, H.; Li, X.; Zhang, Z.; Zhang, H.; Dong, Z.; Lu, Y.; Yu, H.; Ma, K. Research progress on classical traditional Chinese medicine formula Lily Bulb and Rehmannia Decoction in the treatment of depression. *Biomed. Pharmacother.,* **2019**, *112*, 108616.
http://dx.doi.org/10.1016/j.biopha.2019.108616 PMID: 30780102

[44] Gu, S.; Mou, T.; Chen, J.; Wang, J.; Zhang, Y.; Cui, M.; Hao, W.; Sun, Y.; Zhang, C.; Zhao, T.; Wei, B. Develop a stepwise integrated method to screen biomarkers of Baihe-Dihuang Tang on the treatment of depression in rats applying with composition screened, untargeted, and targeted metabolomics analysis. *J. Sep. Sci.,* **2022**, *45*(10), 1656-1671.
http://dx.doi.org/10.1002/jssc.202100841 PMID: 35234356

[45] Zhang, H.; Xue, X.; Pan, J.; Song, X.; Chang, X.; Mao, Q.; Lu, Y.; Zhao, H.; Wang, Y.; Chi, X.; Wang, S.; Ma, K. Integrated analysis of the chemical-material basis and molecular mechanisms for the classic herbal formula of Lily Bulb and Rehmannia Decoction in alleviating depression. *Chin. Med.,* **2021**, *16*(1), 107.
http://dx.doi.org/10.1186/s13020-021-00519-x PMID: 34674715

[46] Gong, D.; Yuan, T.; Wang, R.; Sun, S.; Dawuti, A.; Wang, S.; Du, G.; Fang, L. Network pharmacology approach and experimental verification of Dan-Shen Decoction in the treatment of ischemic heart disease. *Pharm. Biol.,* **2023**, *61*(1), 69-79.

http://dx.doi.org/10.1080/13880209.2022.2152059 PMID: 36546685

[47] Chen, M.; Wang, R.; Liao, L.; Li, Y.; Sun, X.; Wu, H.; Lan, Q.; Deng, Z.; Liu, P.; Xu, T.; Zhou, H.; Liu, M. DanShen Decoction targets miR-93-5p to provide protection against MI/RI by regulating the TXNIP/NLRP3/Caspase-1 signaling pathway. *Phytomedicine,* **2024**, *135*, 156225.
http://dx.doi.org/10.1016/j.phymed.2024.156225 PMID: 39547100

[48] Liu, M.; Li, Z.; Ouyang, Y.; Chen, M.; Guo, X.; Mazhar, M.; Kang, J.; Zhou, H.; Wu, Q.; Yang, S. Material basis and integrative pharmacology of danshen decoction in the treatment of cardiovascular diseases. *Phytomedicine,* **2023**, *108*, 154503.
http://dx.doi.org/10.1016/j.phymed.2022.154503 PMID: 36332387

[49] Wang, T.X.; Duan, K.L.; Huang, Z.X.; Xue, Z.A.; Liang, J.Y.; Dang, Y.; Zhang, A.; Xiong, Y.; Ding, C.; Guan, K.L.; Yuan, H.X. Tanshinone functions as a coenzyme that confers gain of function of NQO1 to suppress ferroptosis. *Life. Sci. Alliance,* **2023**, *6*(1), 202201667.
http://dx.doi.org/10.26508/lsa.202201667 PMID: 36319062

[50] Nair, A.; Jacob, S. A simple practice guide for dose conversion between animals and human. *J. Basic Clin. Pharm.,* **2016**, *7*(2), 27-31.
http://dx.doi.org/10.4103/0976-0105.177703 PMID: 27057123

[51] Bian, L.; Wang, S.; Li, W.; Li, J.; Yin, Y.; Ye, F.; Guo, J. Cryptotanshinone regulates gut microbiota and PI3K-AKT pathway in rats to alleviate CUMS induced depressive symptoms. *Biomed. Pharmacother.,* **2023**, *169*, 115921.
http://dx.doi.org/10.1016/j.biopha.2023.115921 PMID: 38011787

[52] Zhang, M.; Wu, W.; Huang, C.; Cai, T.; Zhao, N.; Liu, S.; Yang, S. Shuxie-1 Decoction Alleviated CUMS -Induced Liver Injury *via* IL-6/JAK2/STAT3 Signaling. *Front. Pharmacol.,* **2022**, *13*, 848355.
http://dx.doi.org/10.3389/fphar.2022.848355 PMID: 35462928

[53] Yue, N.; Huang, H.; Zhu, X.; Han, Q.; Wang, Y.; Li, B.; Liu, Q.; Wu, G.; Zhang, Y.; Yu, J. Activation of P2X7 receptor and NLRP3 inflammasome assembly in hippocampal glial cells mediates chronic stress-induced depressive-like behaviors. *J. Neuroinflammation,* **2017**, *14*(1), 102.
http://dx.doi.org/10.1186/s12974-017-0865-y PMID: 28486969

[54] Liu, Y.; Cheng, X.; Qi, B.; Wang, Y.; Zheng, Y.; Liang, X.; Chang, Y.; Ning, M.; Gao, W.; Li, T. Aucubin protects against myocardial ischemia-reperfusion injury by regulating STAT3/NF-κB/HMGB-1 pathway. *Int. J. Cardiol.,* **2024**, *400*, 131800.
http://dx.doi.org/10.1016/j.ijcard.2024.131800 PMID: 38244891

[55] Zhang, J.; Du, Y.; Xiong, Z.; Cheng, H.; Du, Y.; Xiong, Y.; Lv, J.; Huang, W.; Qiu, K.; Zhang, S. Bombesin protects myocardium against ischemia/reperfusion injury *via* activation of the Keap1-Nrf2-HO-1 signaling pathway. *Peptides,* **2024**, *180*, 171279.
http://dx.doi.org/10.1016/j.peptides.2024.171279 PMID: 39053647

[56] Zhang, S.; Hu, Y.; Zhao, Y.; Feng, Y.; Wang, X.; Miao, M.; Miao, J. Molecular mechanism of Chang Shen Hua volatile oil modulating brain cAMP-PKA-CREB pathway to improve depression-like behavior in rats. *Phytomedicine,* **2024**, *130*, 155729.
http://dx.doi.org/10.1016/j.phymed.2024.155729 PMID: 38772184

[57] Zhang, M.; Li, A.; Yang, Q.; Li, J.; Wang, L.; Liu, X.; Huang, Y.; Liu, L. Beneficial effect of alkaloids from *Sophora alopecuroides* L. on CUMS-induced depression model mice *via* modulating gut microbiota. *Front. Cell. Infect. Microbiol.,* **2021**, *11*, 665159.
http://dx.doi.org/10.3389/fcimb.2021.665159 PMID: 33954123

[58] Chang, J.; Yang, H.; Shan, X.; Zhao, L.; Li, Y.; Zhang, Z.; Abankwah, J.K.; Zhang, M.; Bian, Y.; Guo, Y. Bergamot essential oil improves CUMS-induced depression-like behaviour in rats by protecting the plasticity of hippocampal neurons. *J. Cell. Mol. Med.,* **2024**, *28*(8), 18178.
http://dx.doi.org/10.1111/jcmm.18178 PMID: 38553964

[59] Aisa, Z.; Liao, G.C.; Shen, X.L.; Chen, J.; Li, L.; Jiang, S.B. Effect of autophagy on myocardial infarction and its mechanism. *Eur. Rev. Med. Pharmacol. Sci.,* **2017**, *21*(16), 3705-3713.
PMID: 28925470

[60] An, Z.; Li, J.; Yu, J.; Wang, X.; Gao, H.; Zhang, W.; Wei, Z.; Zhang, J.; Zhang, Y.; Zhao, J.; Liang, X. Neutrophil extracellular traps induced by IL-8 aggravate atherosclerosis *via* activation NF-κB signaling in macrophages. *Cell. Cycle,* **2019**, *18*(21), 2928-2938.
http://dx.doi.org/10.1080/15384101.2019.1662678 PMID: 31496351

[61] Acikgoz, B.; Dalkiran, B.; Dayi, A. An overview of the currency and usefulness of behavioral tests used from past to present to assess anxiety, social behavior and depression in rats and mice. *Behav. Processes,* **2022**, *200*, 104670.
http://dx.doi.org/10.1016/j.beproc.2022.104670 PMID: 35667641

[62] Ashok, D.; Garbus, H.; Ebenebe, O.V. Mitochondrial membrane potential and lactate dehydrogenase activity in a model of acute *in vitro* ischemia/reperfusion injury. *Methods Mol. Biol.,* **2025**, *2894*, 35-42.
http://dx.doi.org/10.1007/978-1-0716-4342-6_4 PMID: 39699808

[63] Ursini, F.; Maiorino, M. Lipid peroxidation and ferroptosis: The role of GSH and GPx4. *Free Radic. Biol. Med.,* **2020**, *152*, 175-185.
http://dx.doi.org/10.1016/j.freeradbiomed.2020.02.027 PMID: 32165281

[64] Xing, G.; Meng, L.; Cao, S.; Liu, S.; Wu, J.; Li, Q.; Huang, W.; Zhang, L. PPARα alleviates iron overload-induced ferroptosis in mouse liver. *EMBO Rep.,* **2022**, *23*(8), 52280.
http://dx.doi.org/10.15252/embr.202052280 PMID: 35703725

[65] Vaccarino, V.; Johnson, B.D.; Sheps, D.S.; Reis, S.E.; Kelsey, S.F.; Bittner, V.; Rutledge, T.; Shaw, L.J.; Sopko, G.; Bairey Merz, C.N. Depression, inflammation, and incident cardiovascular disease in women with suspected coronary ischemia: The National Heart, Lung, and Blood Institute-sponsored WISE study. *J. Am. Coll. Cardiol.,* **2007**, *50*(21), 2044-2050.
http://dx.doi.org/10.1016/j.jacc.2007.07.069 PMID: 18021871

[66] Caruso, G.; Fresta, C.G.; Grasso, M.; Santangelo, R.; Lazzarino, G.; Lunte, S.M.; Caraci, F. Inflammation as the common biological link between depression and cardiovascular diseases: Can carnosine exert a protective role? *Curr. Med. Chem.,* **2020**, *27*(11), 1782-1800.
http://dx.doi.org/10.2174/0929867326666190712091515 PMID: 31296155

[67] Maes, M.; Nowak, G.; Caso, J.R.; Leza, J.C.; Song, C.; Kubera, M.; Klein, H.; Galecki, P.; Noto, C.; Glaab, E.; Balling, R.; Berk, M. Toward omics-based, systems biomedicine, and path and drug discovery methodologies for depression-inflammation research. *Mol. Neurobiol.,* **2016**, *53*(5), 2927-2935.
http://dx.doi.org/10.1007/s12035-015-9183-5 PMID: 25934103

[68] Fang, H.; Cavdar, O.; Yao, Z.; Zhu, X.; Shen, Y.; Liu, C. Angiotensin type 1 and type 2 receptors-induced mitochondrial dysfunction promotes ferroptosis in cardiomyocytes. *J. Hum. Hypertens.,* **2025**, *39*(3), 226-236.
http://dx.doi.org/10.1038/s41371-024-00982-7 PMID: 39789125

[69] Li, W.; Liang, L.; Liu, S.; Yi, H.; Zhou, Y. FSP1: A key regulator of ferroptosis. *Trends Mol. Med.,* **2023**, *29*(9), 753-764.
http://dx.doi.org/10.1016/j.molmed.2023.05.013 PMID: 37357101

[70] Tang, D.; Chen, X.; Kang, R.; Kroemer, G. Ferroptosis: Molecular mechanisms and health implications. *Cell. Res.,* **2021**, *31*(2), 107-125.
http://dx.doi.org/10.1038/s41422-020-00441-1 PMID: 33268902

[71] Xie, Y.; Hou, W.; Song, X.; Yu, Y.; Huang, J.; Sun, X.; Kang, R.; Tang, D. Ferroptosis: Process and function. *Cell. Death Differ.,* **2016**, *23*(3), 369-379.
http://dx.doi.org/10.1038/cdd.2015.158 PMID: 26794443

[72] Liu, C.; Liu, E.; Li, Z.; Li, W.; Jin, J.; Sui, H.; Chen, G.; Sun, Z.; Xi, H. Danlou tablet attenuates ischemic stroke injury and blood–brain barrier damage by inhibiting ferroptosis. *J. Ethnopharmacol.,* **2024**, *322*, 117657.
http://dx.doi.org/10.1016/j.jep.2023.117657 PMID: 38145861

[73] Kupper, N.; Denollet, J.; Type, D. Type D personality as a risk factor in coronary heart disease: A review of current evidence. *Curr. Cardiol. Rep.,* **2018**, *20*(11), 104.
http://dx.doi.org/10.1007/s11886-018-1048-x PMID: 30209683

[74] Krittanawong, C.; Maitra, N.S.; Qadeer, Y.K.; Wang, Z.; Fogg, S.; Storch, E.A.; Celano, C.M.; Huffman, J.C.; Jha, M.; Charney, D.S.;

Lavie, C.J. Association of depression and cardiovascular disease. *Am J. Med.,* **2023**, *136*(9), 881-895. http://dx.doi.org/10.1016/j.amjmed.2023.04.036 PMID: 37247751

[75] Yoshimura, R. Cardiovascular disease, and major depression: Study on both diseases and serum brain-derived neurotrophic factor (BDNF). *Psychiatry Clin. Neurosci.,* **2024**, *78*(8), 429. http://dx.doi.org/10.1111/pcn.13678 PMID: 38895990

[76] Perry, B.I.; Oltean, B.P.; Jones, P.B.; Khandaker, G.M. Cardiometabolic risk in young adults with depression and evidence of inflammation: A birth cohort study. *Psychoneuroendocrinology,* **2020**, *116*, 104682. http://dx.doi.org/10.1016/j.psyneuen.2020.104682 PMID: 32339985

[77] Jiang, X.; Stockwell, B.R.; Conrad, M. Ferroptosis: Mechanisms, biology and role in disease. *Nat. Rev. Mol. Cell. Biol.,* **2021**, *22*(4), 266-282. http://dx.doi.org/10.1038/s41580-020-00324-8 PMID: 33495651