Efficacy of tanshinone IIA in rat models with myocardial ischemia–reperfusion injury: a systematic mini-review and meta-analysis

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ABSTRACT

Background. Myocardial ischemia–reperfusion injury (MIRI) refers to severe damage to the ischemic myocardium following the restoration of blood flow, and it is a major complication of reperfusion therapy for myocardial infarction. Notably, drugs such as metoprolol have been utilized to reduce ischemia–reperfusion injury. Tanshinone IIA is a major constituent extracted from *Salvia miltiorrhiza* Bunge. Recently, tanshinone IIA has been studied extensively in animal models for controlling MIRI. Therefore, we conducted a meta-analysis on the application of tanshinone IIA in rat models with MIRI to evaluate the therapeutic effects of tanshinone IIA.

Methods. A comprehensive search was conducted across PubMed, Web of Science, Embase, the Cochrane Library, the China National Knowledge Infrastructure database, the Wanfang database, and the Chinese Scientific Journal Database to gather studies on tanshinone IIA intervention in rat models with MIRI. We employed SYRCLE's risk of bias tool to assess study quality. The primary outcome indicators were superoxide dismutase (SOD) and malondialdehyde (MDA). Myocardial infarction area was a secondary outcome indicator. This study was registered at PROSPERO (registration number CRD 42022344447).

Results. According to the inclusion and exclusion criteria, 15 eligible studies were selected from 295 initially identified studies. In rat models with MIRI, tanshinone IIA significantly increased SOD levels while reducing MDA levels and myocardial infarction area. Moreover, the duration of myocardial ischemia influenced the effectiveness of tanshinone IIA. However, additional high-quality research studies are needed to establish the efficacy and definitive guidelines for the use of tanshinone IIA. Animal studies demonstrated that tanshinone IIA exerted a significant therapeutic effect when the ischemia duration was less than 40 minutes. Tanshinone IIA was found to be more effective when administered via intravenous, intraperitoneal, and intragastric routes at doses above 5 mg/kg. Additionally, treatment with tanshinone IIA at all stages—prior to myocardial ischemia, after ischemia but before reperfusion, prior to ischemia and after reperfusion, and after reperfusion—showed satisfactory results.

Conclusions. Tanshinone IIA enhanced SOD activity and reduced MDA levels, thereby ameliorating oxidative stress damage during MIRI. Additionally, it reduced the myocardial infarction area, indicating its effectiveness in mitigating MIRI-induced damage in rats and demonstrating a myocardial protective effect. These findings contribute valuable insights for developing MIRI treatment strategies.

INTRODUCTION

According to the World Health Organization, ischemic heart disease remains the primary cause of death worldwide, accounting for 16% of all deaths (*Wang et al., 2022*). As the world's population ages, the incidence of acute myocardial infarction rises annually (*Reynolds et al., 2017*). Therapies for acute myocardial infarction significantly impact the global population's economic burdens (*Pasala et al., 2022*). The prompt restoration of coronary blood supply is the most effective method for preventing myocardial cell death caused by myocardial ischemic injury. This is achieved primarily through percutaneous coronary intervention, coronary artery bypass grafting operations, and thrombolytic technology (*Biscaglia et al., 2022*).

Myocardial ischemia–reperfusion injury (MIRI) is a secondary complication of ischemic heart disease. It occurs when blood flow is suddenly restored to the ischemic myocardium, potentially resulting in cardiac myocyte dysfunction, structural damage to cardiac cells, and cell death, all of which contribute to the deterioration of cardiac function (*Evans et al., 2020*; *Liu et al., 2018*). The cellular and molecular events involved in MIRI are complex and mediated through multiple pathways, including oxygen free radicals, energy metabolism disruption, calcium overload, autophagy, apoptosis, mitochondrial dysfunction, and microvascular injury (*Chen et al., 2023*; *He et al., 2022*). The exact mechanism of MIRI remains incompletely understood, and there is currently no comprehensive treatment available for it.

Tanshinone IIA is a lipid-soluble diterpenoid isolated from the traditional Chinese medicine *Salvia miltiorrhiza* Bunge (*Huang et al., 2022*). Owing to its anti-inflammatory, lipid-regulating, antioxidant, and anti-apoptotic effects, tanshinone IIA can prevent various cardiovascular disorders (*Li, Xu & Liu, 2018*). Consequently, it is commonly used in the treatment of cardiovascular diseases (*Ren et al., 2019*).

MIRI can impact markers such as oxidative stress and the extent of myocardial infarction. The size of the myocardial infarction area directly correlates with the severity of MIRI. During ischemia, reactive oxygen species and reactive nitrogen species, such as superoxide anions and nitric oxide, are overproduced, disrupting redox balance and leading to oxidative stress (*Chen, Shi & Guo, 2021*). Superoxide dismutase (SOD) and malondialdehyde (MDA) are crucial markers of oxidative stress (*Tian et al., 2019*).

In this study, an extensive literature review on the intervention of tanshinone IIA in MIRI rats was conducted. The therapeutic effects of tanshinone IIA were systematically evaluated in rat models with MIRI, to provide medical evidence for the clinical application of tanshinone IIA.

MATERIALS AND METHODS

Protocol and registration

This article is a meta-analysis following the Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (*Page et al., 2021*). The review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42022344447.

Search strategy

Computers were employed to search databases such as PubMed, Web of Science, Cochrane Library, Embase, the China National Knowledge Infrastructure (CNKI), the Wanfang Database, and the Chinese Scientific Journals Database (VIP). The search period extended from the inception of each database until June 10, 2024. Both subject terms and free-text words were utilized in the searches. The search phrase included three components: intervention strategy, illness, and animal species. The permitted languages were English and Chinese. Two authors (XB Zhang, and HH Jiang) separately searched English and Chinese databases for all relevant articles using the following terms: "Myocardial Reperfusion Injury", "Injuries, Myocardial Reperfusion", "Myocardial Reperfusion Injuries", "Reperfusion Injuries, Myocardial", "Myocardial Ischemic Reperfusion Injury", "Reperfusion Injury, Myocardial", "Injury, Myocardial Reperfusion", "Rats", "Rat", "Rattus", "Rattus norvegicus", "Rats, Norway", "Rats, Laboratory", "Laboratory Rat", "Laboratory Rats", "Rat, Laboratory", and "Tanshinone IIA". The detailed search strategy is provided in Table S1.

Inclusion and exclusion criteria

The included studies met the following criteria: (1) Rat models with MIRI, specifically induced by ligation of the left anterior descending coronary artery to cause ischemia and reperfusion; (2) tanshinone IIA as an intervention, with no restrictions on dosage, route of administration, or duration of treatment; (3) randomized controlled trials; (4) SOD, methane dicarboxylic aldehyde (MDA), and myocardial infarct area as outcome measures.

The following criteria were used to exclude studies: (1) Animal species were not rats; (2) tanshinone IIA was combined with other intervention therapies; (3) studies were in the form of clinical case reports, duplicates, reviews; (4) studies were not in English or Chinese or published after June 10, 2024.

Study selection and data extraction

Two researchers (XB Zhang and LL Zhang) independently conducted the literature search, data extraction, and cross-checking. Contentious matters were discussed and resolved with the assistance of a third party (CJ Li). Duplicate material was filtered out using EndNote

X9 software to begin the screening process. The second phase involved reading the titles and abstracts of the literature to eliminate unrelated works. Finally, the full texts of the remaining articles were reviewed and evaluated against the inclusion criteria to identify those that met them.

Assessment of risk of bias in individual studies

The SYRCLE's risk of bias tool was employed to evaluate the risk of bias in experimental animal research (*Sun et al., 2020*). Two authors (XB Zhang, and C Chen) independently assessed the quality of the included studies using this tool, analyzing sequence generation, baseline characteristics, allocation concealment, random housing, blinding, random outcome assessments, incomplete outcome data, selective outcome reporting, and other sources of bias. Disagreements on quality assessment were resolved through discussion and consensus. A "yes" indicated a low risk of bias in the study, a "no" suggested a high risk of bias, and "unclear" meant that there were insufficient details to determine the study's risk of bias.

Statistical analysis

The meta-analysis was conducted using RevMan 5.4 (Cochrane Collaboration, London, UK) and Stata 16.0 software (Stata Corp, College Station, TX, USA). Data were compiled based on relative risk (RR) with a 95% confidence interval (CI). For measurement data, the standard mean difference or mean difference (MD) with a 95% CI was used. Under minimal heterogeneity ($p > 0.1$, $I^2 < 50\%$), a fixed-effect model was used to combine statistics, while under substantial heterogeneity ($p \leq 0.1$, $I^2 \geq 50\%$), a random-effect model was employed. Meta-analysis was conducted using the random-effects model to aggregate RR. To identify the sources of heterogeneity, subgroup and sensitivity analyses were performed. Publication bias was assessed using Egger's test and funnel plots.

RESULTS

Study selection

Based on the specified article search strategy, 295 articles were initially identified. Using EndNote X9 software, 90 duplicates were removed. Subsequently, after the review of titles and abstracts, 153 articles were excluded. Upon full-text review, an additional 37 articles were eliminated. Ultimately, 15 articles were included in the meta-analysis (Fig. 1).

Study characteristics

This meta-analysis included 15 articles: eight written in Chinese (*Yang, 2010*; *Hu et al., 2015*; *Ma et al., 2017*; *Jiao, 2016*; *Dai et al., 2013*; *Ding, Wang & Huang, 2020*; *Tang et al., 2017*; *Zhang & Zhang, 2010*) and seven written in English (*Li et al., 2016*; *Yuan et al., 2014*; *Zhai et al., 2024*; *Fu et al., 2007*; *Wei et al., 2014*; *Li et al., 2022*; *Shen et al., 2018*). All studies were from China. The meta-analysis involved 488 rats: 168 in the control group and 320 in the experimental group. In the experimental group, tanshinone IIA was administered, while the control group received normal saline, blank, or carboxymethyl cellulose sodium. The method used in the included articles to induce rat models with MIRI involved ligation
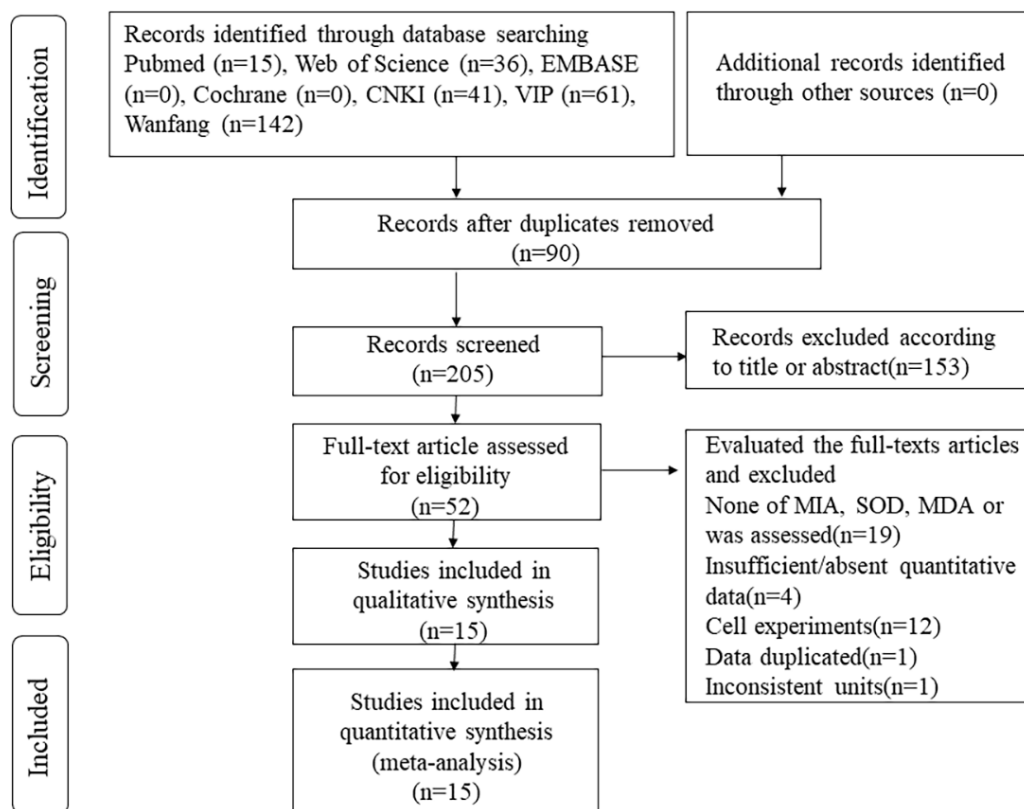
Figure 1 Flow diagram of the literature selection process.

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and subsequent release of the left anterior descending coronary artery. SOD was assessed as an outcome measure in nine studies, MDA in eight studies, and myocardial infarct area in 10 studies. Detailed characteristics of the included articles are provided in Table 1.

Quality evaluation

The SYRCLE's risk of bias tool was used to assess bias risk in 15 articles. *Tang et al. (2017)* detailed the randomization method, while others mentioned randomization without specifying the method. Both the experimental and control groups had similar baseline characteristics. Each study reported its findings clearly and comprehensively. None of the studies indicated any other biases, so they were all classified as "low risk". However, none of the studies provided information on allocation concealment, random housing of animals during the experiment, blinding of caregivers or investigators, random outcome assessment, or blinding of outcome assessment, resulting in all studies being categorized as "unclear" (Fig. 2). Overall, the included articles were not of particularly high quality. There are notable flaws in the design and implementation of animal experimental methodology in these studies that need to be addressed to facilitate the translation of basic research into clinically feasible investigations.

Table 1 Summary of characteristics of the included studies.

Study	Species	Sex	Age	Weight	Ischemia duration	Reperfusion duration	Groups (n)	Dose	Route	Treatment time	Outcome measure
Ding, Wang & Huang (2020)	SD	Male	?	210~270 g	40 min	120 min	Control ($n = 13$) TSA II A-L ($n = 13$) TSA II A-H ($n = 13$)	NS 4 ml kg^{-1} d^{-1} 8 mg kg^{-1} d^{-1} 16 mg kg^{-1} d^{-1}	i.p i.p i.p	Prior to ischemia	MIA, SOD
Ma et al. (2017)	SD	Male	8~12 W	180~220 g	30 min	180 min	Control ($n = 16$) TSA II A ($n = 16$)	NS 20 mg kg^{-1} d^{-1}	i.g i.g	Prior to ischemia	MIA
Tang et al. (2017)	SD	Male	8W	260~280 g	30 min	480 min	Control ($n = 10$) TSA II A ($n = 10$)	NS 30 mg kg^{-1} d^{-1}	i.g i.p	Prior to ischemia	SOD
Jiao (2016)	SD	Male	7~8 W	250~280 g	30 min	120 min	Control ($n = 10$) TSA II A ($n = 10$)	not intervene 15 mg kg^{-1} d^{-1}	- i.g	Prior to ischemia	MDA, SOD
Li et al. (2016)	SD	Male	?	210~250 g	30 min	120 min	Control ($n = 13$) TSA II A-L ($n = 13$) TSA II A-H ($n = 13$)	not intervene 10 mg kg^{-1} d^{-1} 20 mg kg^{-1} d^{-1}	- i.v i.v	Prior to ischemia	MIA
Hu et al. (2015)	Wistar	Male	20~32 W	260~300 g	20 min	60 min	Control ($n = 10$) TSA II A-L ($n = 10$) TSA II A-M ($n = 10$) TSA II A-H ($n = 10$)	not intervene 10 mg kg^{-1} d^{-1} 20 mg kg^{-1} d^{-1} 40 mg kg^{-1} d^{-1}	- i.p i.p i.p	Prior to ischemia	MIA, SOD, MDA
Yuan et al. (2014)	SD	Male	?	250~300 g	30 min	120 min	Control ($n = 16$) TSA II A-L ($n = 8$) TSA II A-M ($n = 16$) TSA II A-H ($n = 8$)	not intervene 5 mg kg^{-1} d^{-1} 10 mg kg^{-1} d^{-1} 20 mg kg^{-1} d^{-1}	- i.v i.v i.v	Prior to ischemia	MIA
Dai et al. (2013)	SD	Male	?	240~320 g	30 min	120 min	Control ($n = 8$) TSA II A-L ($n = 8$)	not intervene 30 mg kg^{-1} d^{-1}	- i.v	Prior to ischemia	SOD
Zhang & Zhang (2010)	Wistar	?	?	?	30 min	120 min	Control ($n = 20$) TSA II A ($n = 20$)	NS 15 mg kg^{-1} d^{-1}	i.g i.g	Prior to ischemia	MDA
Yang (2010)	Wistar	Male	?	250~300 g	15 min	30 min	Control ($n = 8$) TSA II A-L ($n = 8$) TSA II A-M ($n = 8$) TSA II A-H ($n = 8$)	NS 5 mg kg^{-1} d^{-1} 10 mg kg^{-1} d^{-1} 20 mg kg^{-1} d^{-1}	i.g i.g i.g i.g	Prior to ischemia	MIA, MDA
Fu et al. (2007)	SD	Male	?	280~300 g	45 min	120 min	Control ($n = 13$) TSA II A-L ($n = 13$) TSA II A-M ($n = 13$) TSA II A-H ($n = 13$)	0.5% CMC-Na 15 mg kg^{-1} d^{-1} 30 mg kg^{-1} d^{-1} 60 mg kg^{-1} d^{-1}	i.g i.g i.g i.g	Prior to ischemia	SOD, MDA
Wei et al. (2014)	SD	Male	?	250~300 g	30 min	24 h	Control ($n = 8$) TSA II A ($n = 8$)	NS 8 mg kg^{-1} d^{-1}	i.p i.p	Before reperfusion and after reperfusion	MIA, SOD, MDA
Shen et al. (2018)	SD	Male	?	200–210 g	45 min	120 min	Control ($n = 7$) TSA II A ($n = 7$)	NS 7.912 mg kg^{-1} d^{-1}	i.g i.g	Prior to ischemia	MIA, SOD, MDA
Zhai et al. (2024)	SD	Male	8~9 W	23–25 g	30 min	3d	Control ($n = 6$) TSA II A ($n = 6$)	PBS 10 mg kg^{-1} d^{-1}	i.p i.p	Prior to ischemia and after reperfusion	MIA, SOD, MDA
Li et al. (2022)	SD	Male	?	?	30 min	120 min	Control ($n = 10$) TSA II A ($n = 10$)	0.5% CMC-Na 15 mg kg^{-1} d^{-1} 15 mg kg^{-1} d^{-1}	i.g i.g	Prior to ischemia	MIA

Notes.

Abbreviations: TSA II A, Tanshinone IIA; TSA II A-L, Tanshinone IIA low-dose group; TSA II A-M, Tanshinone IIA medium-dose group; TSA II A-H, Tanshinone IIA high-dose group; Control, receiving either normal saline, blank, or carboxymethylcellulose sodium group; i.p, intraperitoneal injection; i.g, intragastric; i.v, intravenous injection; NS, normal saline; MIA, myocardial infarction area; SOD, superoxide dismutase; MDA, methane dicarboxylic aldehyde; CMC-Na, Carboxymethylcellulose sodium; ?, not recorded.

Figure 2 Evaluation of literature quality outcomes derived from SYRCLE's Risk of Bias utilizing the Cochrane tool. (A) Risk of bias summary: the review authors' assessments of each risk of bias item for each included study. (B) Risk of bias graph: review authors' judgments about each risk of bias item displayed as a percentage for all included studies.

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Meta-analysis of primary outcomes
Superoxide dismutase

Nine of the included studies (*Ding, Wang & Huang, 2020*; *Tang et al., 2017*; *Jiao, 2016*; *Hu et al., 2015*; *Dai et al., 2013*; *Fu et al., 2007*; *Wei et al., 2014*; *Shen et al., 2018*; *Zhai et al., 2024*) examined the effect of tanshinone IIA on SOD levels (unit: U/mol) in rat models with MIRI (experimental group, $n = 192$; control group, $n = 85$). Owing to significant heterogeneity among the articles ($p < 0.00001$, $I^2 = 99\%$), we conducted subgroup analyses to explore the sources of this heterogeneity. Subgroups were categorized based on ischemia duration (15 min $\leq$ time $<$ 30 min, 30 min $\leq$ time $<$ 40 min, or 40 min $\leq$ time $\leq$ 45 min), reperfusion duration (30 min $\leq$ time $<$ 120 min, 120 min $\leq$ time $<$ 180 min, or 180 min $\leq$ time $\leq$ 480 min), dosage (5 mg kg^{-1} d^{-1} $\leq$ dosage $<$ 20 mg kg^{-1} d^{-1}, 20 mg kg^{-1} d^{-1} $\leq$ dosage $<$ 30 mg kg^{-1} d^{-1}, or 30 mg kg^{-1} d^{-1} $\leq$ dosage $\leq$ 60 mg kg^{-1} d^{-1}), route of administration (i.v., i.g., or i.p.), and timing of treatment (prior to ischemia, after ischemia and before reperfusion, after reperfusion, prior to ischemia and after reperfusion). The results indicated significantly lower heterogeneity in the subgroup with an ischemic duration of 40–45 min (Table 2) (Figs. S1–S5), suggesting that this factor might be contributing to the heterogeneity. However, substantial heterogeneity persisted in the other subgroups (Table 2) (Figs. S1–S5), indicating that other factors could also be influencing the heterogeneity. SOD levels can be influenced by various factors. Differences in testing instruments and methodologies used across various studies may have been a primary contributing factor. Additionally, regional variations in the technique of left anterior descending coronary artery ligation for inducing ischemia and reperfusion during the modeling process could also be responsible. Apart from these factors, no other significant methodological differences were identified among the nine studies. Therefore, a random-effects model was utilized to combine data from the nine studies. According to this meta-analysis, the tanshinone IIA group demonstrated a significant increase in SOD levels compared with the control group (MD = 5.25, 95% CI [4.27–6.23], $p < 0.00001$) (Fig. 3).

Methane dicarboxylic aldehyde

Eight studies (*Jiao, 2016*; *Hu et al., 2015*; *Zhang & Zhang, 2010*; *Yang, 2010*; *Fu et al., 2007*; *Wei et al., 2014*; *Shen et al., 2018*; *Zhai et al., 2024*) examined the effect of tanshinone IIA on MDA levels (unit: nmol/mL) following intervention in rat models with MIRI (experimental group, $n = 192$; control group, $n = 82$). Owing to significant result heterogeneity ($p < 0.00001$, $I^2 = 1.0\%$), a subgroup analysis was conducted to identify the sources of heterogeneity based on ischemia duration (15 min $\leq$ time $<$ 30 min, 30 min $\leq$ time $<$ 40 min, or 40 min $\leq$ time $\leq$ 45 min), reperfusion duration (30 min $\leq$ time $<$ 120 min, 120 min $\leq$ time $<$ 180 min, or 180 min $\leq$ time $\leq$ 480 min), dosage (5 mg kg^{-1} d^{-1} $\leq$ dosage $<$ 20 mg kg^{-1} d^{-1}, 20 mg kg^{-1} d^{-1} $\leq$ dosage $<$30 mg kg^{-1} d^{-1}, or 30 mg kg^{-1} d^{-1} $\leq$ dosage $\leq$ 60 mg kg^{-1} d^{-1}), route of administration (i.v., i.g., or i.p.), and treatment timing (prior to ischemia, after ischemia and before reperfusion, after reperfusion, prior to ischemia and after reperfusion). The results indicated a reduction in heterogeneity in the subgroup with dosages of 30–60 mg/kg (Table 3) (Figs. S6–S10),

Table 2 Subgroup analysis of SOD based on ischemia duration, reperfusion duration, dosage, route and treatment time.

| Criteria for grouping	Subgroup	n	Mean difference (MD)	I^2 (%)	Z	P
Ischemia duration	15 min ≤ Time < 30 min	3	48.32 (21.61, 75.03)	85	3.55	0.0004
	30 min ≤ Time < 40 min	11	3.94 (2.97, 4.92)	99	7.92	<0.00001
	40 min ≤ Time ≤ 45 min	6	13.60 (9.90, 17.31)	26	7.19	<0.00001
Reperfusion duration	30 min ≤ Time < 120 min	3	48.32 (21.61, 75.03)	85	3.55	0.0004
	120 min ≤ Time < 180 min	8	16.05 (10.20, 21.90)	83	5.38	<0.00001
	Time ≥ 180 min	9	2.19 (1.32, 3.05)	99	4.96	<0.00001
Dosage	5 mg kg^{-1} d^{-1} ≤ Dosage < 20 mg kg^{-1} d^{-1}	14	4.43 (3.46, 5.40)	99	8.93	<0.00001
	20 mg kg^{-1} d^{-1} ≤ Dosage < 30 mg kg^{-1} d^{-1}	1	44.94 (23.48, 66.40)	—	4.11	<0.0001
	30 mg kg^{-1} d^{-1} ≤ Dosage ≤ 60 mg kg^{-1} d^{-1}	5	23.11 (8.75, 37.46)	92	3.15	0.002
Route	i.v	1	15.30 (2.34, 28.26)	—	2.31	0.02
	i.g	5	15.89 (8.28, 23.49)	89	4.09	<0.0001
	i.p	14	2.78 (1.87, 3.68)	99	6.02	<0.00001
Treatment time	Prior to ischemia	12	20.70 (13.92, 27.48)	89	5.98	<0.00001
	After ischemia and before reperfusion	1	2.48 (2.28, 2.68)	—	23.74	<0.00001
	After reperfusion	6	1.71 (0.82, 2.61)	99	3.76	0.0002
	Prior to ischemia and after reperfusion	1	112.39 (96.00, 128.87)	—	13.44	<0.00001
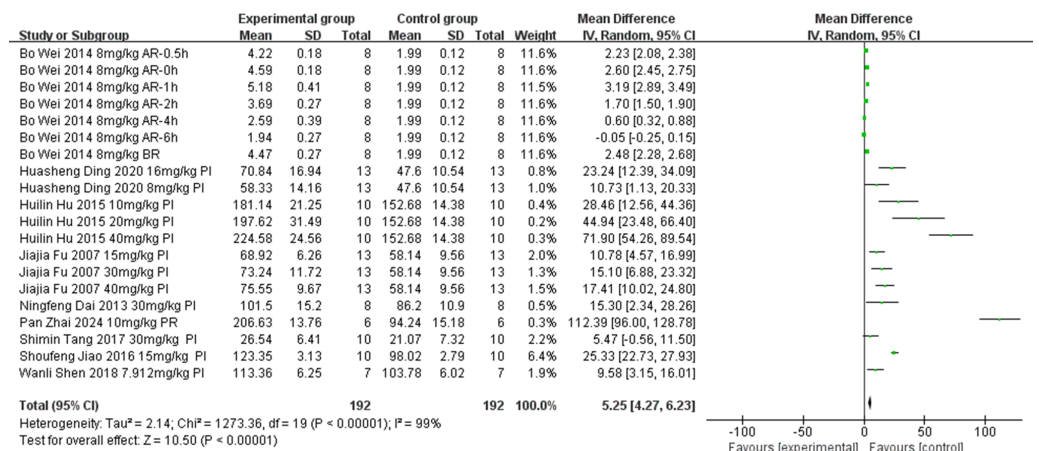
Figure 3 Forest plot of SOD. PI, prior to ischemia; BR, after ischemia and before reperfusion; AR, after reperfusion; PR, prior to ischemia and after reperfusion.

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suggesting that dosage contributed to the observed heterogeneity. However, significant heterogeneity persisted in the other subgroups (Table 3) (Figs. S6–S10), suggesting that the heterogeneity had other causes. Variations in the test kit employed and the location of the ligated left anterior descending coronary artery among studies possibly contributed to the observed heterogeneity. We employed a random-effects model. The meta-analysis showed that the tanshinone IIA group significantly reduced MDA levels compared with the control group (MD = −1.48, 95% CI [−1.82 to −1.14], p < 0.00001) (Fig. 4).

Table 3 Subgroup analysis of MDA based on ischemia duration, reperfusion duration, dosage, route and treatment time.

Criteria for grouping	Subgroup	n	Mean difference (MD)	I^2 (%)	Z	P
Ischemia duration	15 min $\leq$ Time < 30 min	6	−1.59 (−2.48, −0.70)	99	3.49	0.0005
	30 min $\leq$ Time < 40 min	10	−0.96 (−1.20, −0.72)	98	7.85	<0.00001
	40 min $\leq$ Time $\leq$ 45 min	4	−0.82 (−1.77, 0.12)	92	1.70	0.09
Reperfusion duration	30 min $\leq$ Time < 120 min	6	−1.59 (−2.48, −0.70)	99	3.49	0.0005
	120 min $\leq$ Time < 180 min	6	−1.04 (−1.91, −0.17)	98	2.34	0.02
	Time $\geq$ 180 min	8	−0.84 (−1.09, −0.59)	98	6.54	<0.00001
Dosage	5 mg kg^{-1} d^{-1} $\leq$ Dosage < 20 mg kg^{-1} d^{-1}	15	−0.91 (−1.22, −0.60)	100	5.78	<0.00001
	20 mg kg^{-1} d^{-1} $\leq$ Dosage < 30 mg kg^{-1} d^{-1}	2	−2.37 (−3.92, −0.81)	96	2.98	0.003
	30 mg kg^{-1} d^{-1} $\leq$ Dosage $\leq$ 60 mg kg^{-1} d^{-1}	3	−1.65 (−2.38, −0.92)	72	4.44	<0.00001
Route	i.v	9	−1.32 (−2.12, −0.51)	100	3.20	0.001
	i.g	11	−0.93 (−1.16, −0.70)	98	7.92	<0.00001
Treatment time	Prior to ischemia	12	−1.31 (−2.01, −0.620)	100	3.69	0.0002
	After ischemia and before reperfusion	1	−0.71 (−0.77, −0.65)	—	22.45	<0.00001
	After reperfusio	6	−0.59 (−0.89, −0.30)	99	3.93	<0.0001
	Prior to ischemia and after reperfusion	1	−3.52 (−4.10, −2.94)	—	11.94	<0.00001
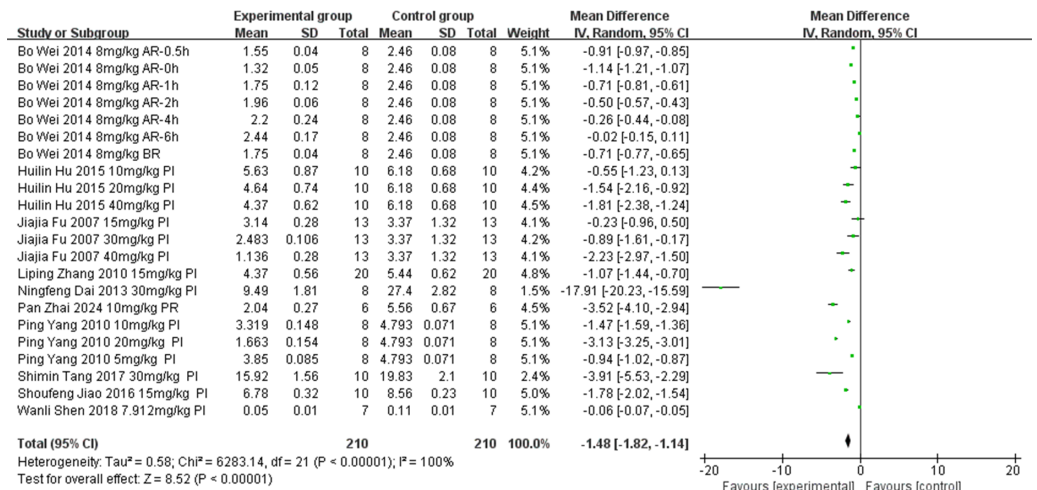
Figure 4 Forest plot of MDA. PI, prior to ischemia; BR, after ischemia and before reperfusion; AR, after reperfusion; PR, prior to ischemia and after reperfusion.

Full-size 🖼 DOI: 10.7717/peerj.17885/fig-4

Meta-analysis of secondary outcomes
Myocardial infarction area

Ten of the included studies (*Ding, Wang & Huang, 2020*; *Ma et al., 2017*; *Li et al., 2016*; *Hu et al., 2015*; *Yuan et al., 2014*; *Yang, 2010*; *Wei et al., 2014*; *Shen et al., 2018*; *Zhai et al., 2024*; *Li et al., 2022*) investigated the effect of tanshinone IIA on myocardial infarction area in rat models with MIRI (experimental group, $n = 249$; control group, $n = 107$). Units: %. We conducted a subgroup analysis to identify the sources of heterogeneity based on ischemia duration (15 min $\leq$ time < 30 min, 30 min $\leq$ time < 40 min, or 40 min $\leq$ time $\leq$ 45 min), reperfusion duration (30 min $\leq$ time < 120 min, 120 min $\leq$ time < 180 min, or 180 min

Table 4 Subgroup analysis of myocardial infarction area based on ischemia duration, reperfusion duration, dosage, route and treatment time.

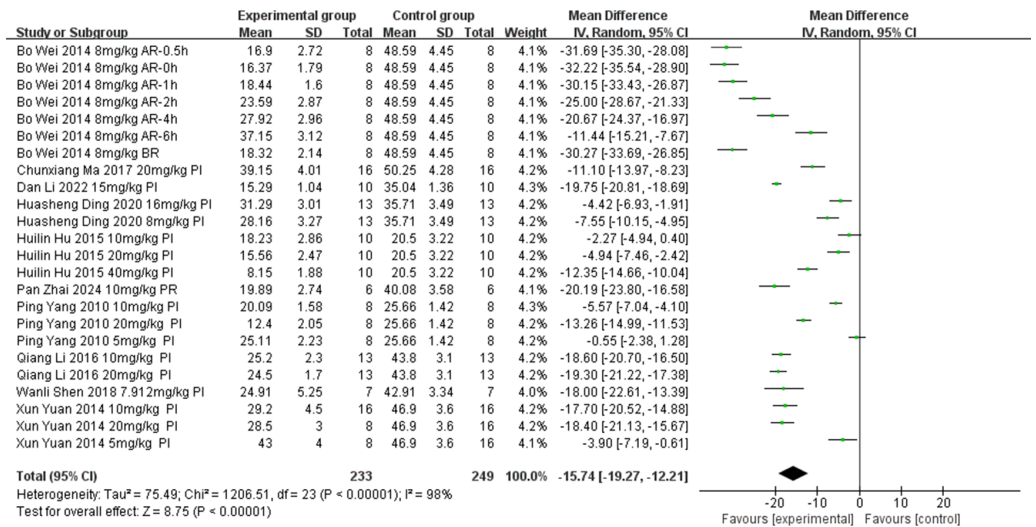| Criteria for grouping	Subgroup	n	Mean difference (MD)	I^2 (%)	Z	P
Ischemia duration	15 min $\leq$ Time < 30 min	6	−6.51 (−10.75, −2.26)	96	3.00	0.003
	30 min $\leq$ Time < 40 min	15	−21.29 (−24.62, −17.97)	96	12.55	<0.00001
	40min $\leq$ Time $\leq$ 45 min	3	−9.68 (−16.05, −3.31)	92	2.98	0.003
Reperfusion duration	30 min $\leq$ Time < 120 min	6	−6.51 (−10.75, −2.26)	96	3.00	0.003
	120 min $\leq$ Time < 180 min	9	−14.21 (−18.33, −10.09)	97	6.76	<0.00001
	180 min $\leq$ Time $\leq$ 480 min	9	−23.63 (−29.29, −17.98)	96	8.19	<0.00001
Dosage	5 mg kg^{-1} d^{-1} $\leq$ Dosage < 20 mg kg^{-1} d^{-1}	18	−16.61 (−21.30, −11.92)	98	6.94	<0.00001
	20 mg kg^{-1} d^{-1} $\leq$ Dosage < 30 mg kg^{-1} d^{-1}	5	−13.42 (−18.33, −8.51)	96	5.36	<0.00001
	30 mg kg^{-1} d^{-1} $\leq$ Dosage $\leq$ 60 mg kg^{-1} d^{-1}	1	−12.35 (−14.66, −10.04)	—	10.47	<0.00001
Route	i.v	5	−15.69 (−20.34, −11.05)	94	6.62	<0.00001
	i.g	6	−11.31 (−18.12, −4.51)	99	3.26	0.001
	i.p	13	−17.89 (−24.06, −11.72)	98	5.68	<0.00001
Treatment time	Prior to ischemia	16	−11.09 (−14.74, −7.44)	98	5.95	<0.00001
	After ischemia and before reperfusion	1	−30.27 (−33.69, −26.85)	—	17.34	<0.00001
	After reperfusio	6	−25.23 (−31.53, −18.92)	95	7.84	<0.00001
	Prior to ischemia and after reperfusion	1	−20.19 (−23.80, −16.58)	—	10.97	<0.00001

$\leq$ time $\leq$ 480 min), dosage (5 mg kg^{-1} d^{-1} $\leq$ dosage < 20 mg kg^{-1} d^{-1}, 20 mg kg^{-1} d^{-1} $\leq$ dosage < 30 mg kg^{-1} d^{-1}, or 30 mg kg^{-1} d^{-1} $\leq$ dosage $\leq$ 60 mg kg^{-1} d^{-1}), route of administration (i.v., i.g., or i.p.), and treatment timing (prior to ischemia, after ischemia and before reperfusion, after reperfusion, prior to ischemia and after reperfusion), considering the significant heterogeneity in the results ($p < 0.00001$, $I^2 = 98\%$). The results indicated lower heterogeneity in the group with ischemia duration of 40–45 min compared with other groups (Table 4) (Figs. S9–S12), suggesting that ischemia duration was a source of heterogeneity. However, substantial heterogeneity persisted in the remaining subgroups (Table 4) (Figs. S9–S12), suggesting that additional sources of heterogeneity existed. A random-effects model was employed. The tanshinone IIA group significantly reduced myocardial infarction area compared with the control group (MD = −15.74, 95% CI [−19.27 to −12.21], $p < 0.00001$) (Fig. 5).

Publication bias analysis

Publication bias in the meta-analysis of SOD, MDA, and myocardial infarction area was assessed using Egger's test and funnel plots. The results showed asymmetry in the funnel plots and Egger's tests for each SOD, MDA, and myocardial infarction area, indicating potential publication bias. This bias could be influenced by factors such as the overall poor quality of the included articles (Fig. 6).

Sensitivity analysis

To assess the consistency and reliability of the meta-analysis results, sensitivity analyses were conducted for SOD, MDA, and myocardial infarction area outcomes included in this study. Each meta-analysis was systematically recalculated after the exclusion of one study at a time, and the results were combined for the remaining studies. The sensitivity analysis indicated that excluding individual studies did not significantly alter the combined effect

Study or Subgroup	Experimental group			Control group			Weight	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Bo Wei 2014 8mg/kg AR-0.5h	16.9	2.72	8	48.59	4.45	8	4.1%	-31.69 [-35.30, -28.08]
Bo Wei 2014 8mg/kg AR-0h	16.37	1.79	8	48.59	4.45	8	4.1%	-32.22 [-35.54, -28.90]
Bo Wei 2014 8mg/kg AR-1h	18.44	1.6	8	48.59	4.45	8	4.1%	-30.15 [-33.43, -26.87]
Bo Wei 2014 8mg/kg AR-2h	23.59	2.87	8	48.59	4.45	8	4.1%	-25.00 [-28.67, -21.33]
Bo Wei 2014 8mg/kg AR-4h	27.92	2.96	8	48.59	4.45	8	4.1%	-20.67 [-24.37, -16.97]
Bo Wei 2014 8mg/kg AR-6h	37.15	3.12	8	48.59	4.45	8	4.1%	-11.44 [-15.21, -7.67]
Bo Wei 2014 8mg/kg BR	18.32	2.14	8	48.59	4.45	8	4.1%	-30.27 [-33.69, -26.85]
Chunxiang Ma 2017 20mg/kg PI	39.15	4.01	16	50.25	4.28	16	4.2%	-11.10 [-13.97, -8.23]
Dan Li 2022 15mg/kg PI	15.29	1.04	10	35.04	1.36	10	4.3%	-19.75 [-20.81, -18.69]
Huasheng Ding 2020 16mg/kg PI	31.29	3.01	13	35.71	3.49	13	4.2%	-4.42 [-6.93, -1.91]
Huasheng Ding 2020 8mg/kg PI	28.16	3.27	13	35.71	3.49	13	4.2%	-7.55 [-10.15, -4.95]
Huilin Hu 2015 10mg/kg PI	18.23	2.86	10	20.5	3.22	10	4.2%	-2.27 [-4.94, 0.40]
Huilin Hu 2015 20mg/kg PI	15.56	2.47	10	20.5	3.22	10	4.2%	-4.94 [-7.46, -2.42]
Huilin Hu 2015 40mg/kg PI	8.15	1.88	10	20.5	3.22	10	4.2%	-12.35 [-14.66, -10.04]
Pan Zhai 2024 10mg/kg PR	19.89	2.74	6	40.08	3.58	6	4.1%	-20.19 [-23.80, -16.58]
Ping Yang 2010 10mg/kg PI	20.09	1.58	8	25.66	1.42	8	4.3%	-5.57 [-7.04, -4.10]
Ping Yang 2010 20mg/kg PI	12.4	2.05	8	25.66	1.42	8	4.2%	-13.26 [-14.99, -11.53]
Ping Yang 2010 5mg/kg PI	25.11	2.23	8	25.66	1.42	8	4.2%	-0.55 [-2.38, 1.28]
Qiang Li 2016 10mg/kg PI	25.2	2.3	13	43.8	3.1	13	4.2%	-18.60 [-20.70, -16.50]
Qiang Li 2016 20mg/kg PI	24.5	1.7	13	43.8	3.1	13	4.2%	-19.30 [-21.22, -17.38]
Wanli Shen 2018 7.912mg/kg PI	24.91	5.25	7	42.91	3.34	7	4.0%	-18.00 [-22.61, -13.39]
Xun Yuan 2014 10mg/kg PI	29.2	4.5	16	46.9	3.6	16	4.2%	-17.70 [-20.52, -14.88]
Xun Yuan 2014 20mg/kg PI	28.5	3	8	46.9	3.6	16	4.2%	-18.40 [-21.13, -15.67]
Xun Yuan 2014 5mg/kg PI	43	4	8	46.9	3.6	16	4.1%	-3.90 [-7.19, -0.61]
Total (95% CI)			233			249	100.0%	-15.74 [-19.27, -12.21]

Heterogeneity: Tau² = 75.49; Chi² = 1206.51, df = 23 (P < 0.00001); I² = 98%
Test for overall effect: Z = 8.75 (P < 0.00001)

Figure 5 Forest plot of myocardial infarction area. PI, prior to ischemia; BR, after ischemia and before reperfusion; AR, after reperfusion; PR, prior to ischemia and after reperfusion.

Full-size DOI: 10.7717/peerj.17885/fig-5
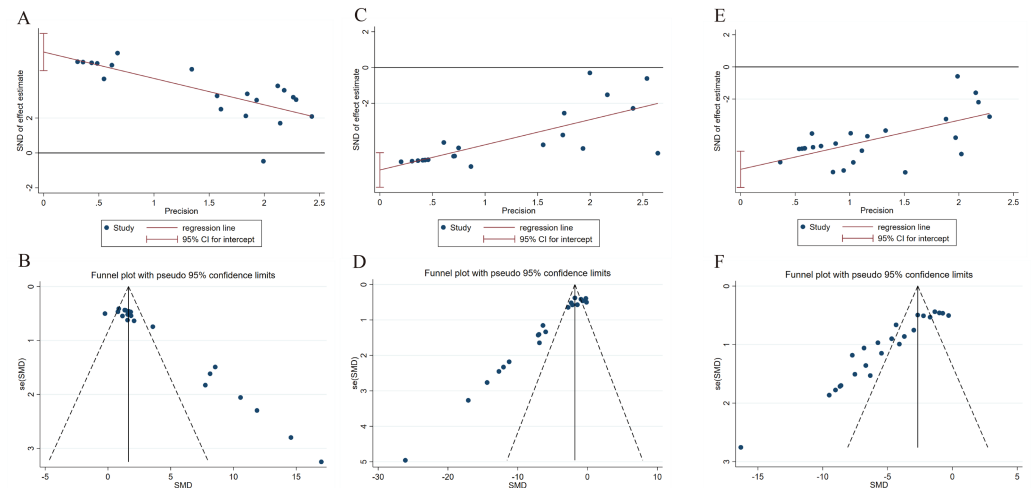
Figure 6 Egger's tests and funnel plots for evaluating publication bias. (A, B) Egger's test and funnel plot for publication bias in SOD. (C, D) Egger's test and funnel plot for publication bias in MDA. (E, F) Egger's test and funnel plot for publication bias in myocardial infarction area.

Full-size DOI: 10.7717/peerj.17885/fig-6

sizes for SOD, MDA, and myocardial infarction area. This underscores the robustness of the conclusions drawn from this meta-analysis (Fig. 7).

DISCUSSION

This systematic review and meta-analysis investigated the efficacy and utility of tanshinone IIA in treating MIRI in rat studies, aiming to identify success factors and provide robust evidence for future treatments of MIRI. The left anterior descending coronary artery was

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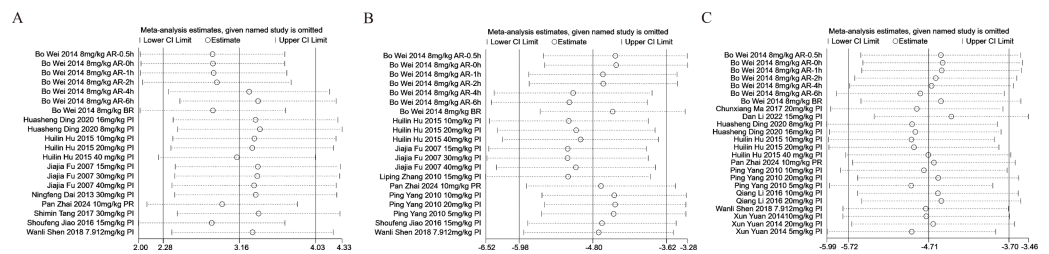
Figure 7 Sensitivity analysis chart for SOD, MDA, and myocardial infarction area. (A) Sensitivity analysis chart for SOD. (B) Sensitivity analysis chart for MDA. (C) Sensitivity analysis chart for myocardial infarction area.

Full-size 🖼 DOI: 10.7717/peerj.17885/fig-7

consistently used as the site for ligation and release in the rat models of MIRI included in this systematic review and meta-analysis, ensuring the validity and reliability of the data input and minimizing bias. SOD serves as the primary oxygen radical scavenging enzyme in organisms, while MDA is a critical indicator of the severity of free radical injury. In MIRI, disruption of cellular oxidative stress equilibrium occurs, and both SOD and MDA levels serve as markers of this imbalance in the body (*Zhang et al., 2022*). The myocardial infarction area directly reflects the severity of MIRI. Therefore, we conducted a systematic review and meta-analysis to compile data on tanshinone IIA therapy in rat models of MIRI.

Oxidative stress plays a crucial role in the pathogenesis of myocardial injury. During myocardial ischemia and hypoxia, significant amounts of oxygen radicals are generated, leading to increased permeability of cardiac cell membranes and potential necrosis (*Petrosillo et al., 2005*). SOD neutralizes free radicals and suppresses the formation of highly reactive hydroxyl radicals (*Fujii, Homma & Osaki, 2022*). Elevated SOD levels enhance the body's antioxidant capacity, thereby mitigating myocardial injury. Consequently, SOD was selected as one of the primary endpoints. The findings showed that tanshinone IIA treatment in rat models with MIRI resulted in increased serum SOD levels. Similar outcomes were observed across subgroups based on ischemia duration, reperfusion duration, dosage, route, and treatment time. Furthermore, we identified ischemia duration as a potential source of heterogeneity and noted that subgroup analysis only partially reduced this heterogeneity. This heterogeneity is attributable to factors such as measurement discrepancies between research institutions and variations in the site of ligation of the left anterior descending coronary artery during the experiments.

MDA is the end product of lipid peroxidation by oxygen radicals. MDA can induce cell membrane degeneration and alter membrane fluidity and permeability, thereby indicating the extent of oxidative damage to cardiac myocytes (*Nehra et al., 2022*; *Tawfik, Makary & Keshawy, 2021*). SOD serves as an indicator of the body's antioxidant capacity, while MDA levels reflect the presence of free radicals. Therefore, MDA was selected as one of the primary outcomes of this study. The results demonstrated that tanshinone IIA reduced MDA levels in the serum of rat models with MIRI, with consistent findings across subgroups based on reperfusion duration, dosage, route, and treatment time. However, subgroup analysis revealed that tanshinone IIA did not significantly reduce MDA levels in the subgroup

with ischemia duration between 40 and 45 min (MD $= -0.82$, 95% CI [-1.77–0.12], $p =$ 0.09). These results suggest that tanshinone IIA was less effective in mitigating MIRI under conditions of longer ischemic durations. However, the subgroup comprised only four studies, necessitating further research to validate this conclusion. Despite the reduction in subgroup heterogeneity achieved through subgroup analysis, significant heterogeneity persisted in other subgroups. Differences in measurement techniques across studies and variations in the site of ligation of the left anterior descending coronary artery possibly contributed to this heterogeneity.

The myocardial infarction area serves as a direct measure of MIRI severity and visually depicts the therapeutic impact of tanshinone IIA. The results showed that tanshinone IIA reduced the myocardial infarction area in rat models with MIRI, with consistent findings across subgroups based on ischemia duration, reperfusion duration, dosage, route, and treatment time. Moreover, we identified ischemia duration as a potential source of heterogeneity. However, there remained unexplained variation, which is attributable to differences in detection equipment and methodologies used across studies.

This systematic review represents the first comprehensive examination of the effects of tanshinone IIA on rat models with MIRI. The included articles underwent rigorous filtering and inspection processes. It can be inferred that the overall quality of the included articles was not particularly high. Despite the rigorous evaluation of the tanshinone IIA intervention in rat models with MIRI, this study had several limitations: First, only articles written in Chinese and English were included. The search for grey articles and conference articles was inadequate owing to challenges in accessing these sources. Second, some results exhibited high heterogeneity, with a few included publications and outcome indicators demonstrating publication bias. Third, this article represents a meta-analysis of animal experiments, which may have been influenced by the quality of the original study design, resulting in a lower quality overall and potentially affecting the accuracy of the results. This study was limited to rat models with left anterior descending coronary artery ligation to induce ischemia and reperfusion. All studies included were conducted in China, with no representation from other geographical regions, which constitutes a limitation in the scope of the research. Fourth, the included studies lacked descriptions regarding allocation concealment, blinding of caregivers and investigators, random housing, and blinding of outcome assessment. Furthermore, this meta-analysis was limited to 15 articles, of which seven were in English and eight in Chinese, with a greater number of Chinese articles than English articles, suggesting a potential language bias. Consequently, the included studies were categorized as having uncertain risks. To enhance the validity of the study's conclusions, larger sample sizes and higher-quality studies are necessary.

CONCLUSION

In this meta-analysis, 15 articles were included to provide more reliable preclinical evidence concerning SOD, MDA, and myocardial infarction area. A comprehensive analysis of tanshinone IIA use in rat models with MIRI revealed significant efficacy when the ischemia duration was less than 40 min. Tanshinone IIA demonstrated a notable therapeutic effect

through intraperitoneal, intragastric, and intravenous administrations at doses exceeding 5 mg/kg. Additionally, treatment with tanshinone IIA at all stages—prior to myocardial ischemia, after ischemia but before reperfusion, prior to ischemia and after reperfusion, and after reperfusion—showed satisfactory results. Therefore, the potential translation of tanshinone IIA from laboratory research to clinical treatment for MIRI holds considerable promise.

ADDITIONAL INFORMATION AND DECLARATIONS

Competing Interests

The authors declare there are no competing interests.

Author Contributions

- Xiaobin Zhang conceived and designed the experiments, performed the experiments, prepared figures and/or tables, and approved the final draft.
- Hehe Jiang performed the experiments, prepared figures and/or tables, and approved the final draft.
- Linlin Zhang performed the experiments, authored or reviewed drafts of the article, and approved the final draft.
- Chen Chen performed the experiments, authored or reviewed drafts of the article, and approved the final draft.

- Mengzhen Xing analyzed the data, prepared figures and/or tables, and approved the final draft.
- Dongqing Du analyzed the data, authored or reviewed drafts of the article, and approved the final draft.
- Yujie Li analyzed the data, prepared figures and/or tables, and approved the final draft.
- Yuning Ma analyzed the data, prepared figures and/or tables, and approved the final draft.
- Yuxia Ma conceived and designed the experiments, prepared figures and/or tables, and approved the final draft.
- Chunjing Li conceived and designed the experiments, prepared figures and/or tables, and approved the final draft.

Data Availability

The following information was supplied regarding data availability:

Raw data are available in the Supplemental Files.

Supplemental Information

Supplemental information for this article can be found online at http://dx.doi.org/10.7717/peerj.17885#supplemental-information.

REFERENCES

Biscaglia S, Uretsky BF, Tebaldi M, Erriquez A, Brugaletta S, Cerrato E, Quadri G, Spitaleri G, Colaiori I, Di Girolamo D, Scoccia A, Zucchetti O, D'Aniello E, Manfrini M, Pavasini R, Barbato E, Campo G. 2022. Angio-based fractional flow reserve, functional pattern of coronary artery disease, and prediction of percutaneous coronary intervention result: a proof-of-concept study. *Cardiocasular Drugs and Therapy* **36**:645–653 DOI 10.1007/s10557-021-07162-6.

Chen J, Huang Q, Li J, Yao Y, Sun W, Zhang Z, Qi H, Chen Z, Liu J, Zhao D, Mi J, Li X. 2023. Panax ginseng against myocardial ischemia/reperfusion injury: A review of preclinical evidence and potential mechanisms. *Journal of Ethnopharmacology* **300**:115715 DOI 10.1016/j.jep.2022.115715.

Chen L, Shi D, Guo M. 2021. The roles of PKC-δ and PKC-ε in myocardial ischemia/reperfusion injury. *Pharmacological Research* **170**:105716 DOI 10.1016/j.phrs.2021.105716.

Dai NF, Chen W, Zheng ZF, Zang QW. 2013. The protective effect of tanshinon II A postconditioning on myocardial ischemica/reperfusion injury in rats. *Chinese Journal of Cardiovascular Research* **11**:549–551 DOI 10.3969/j.issn.1672-5301.2013.07.020.

Ding HS, Wang YJ, Huang ZY. 2020. Effects of tanshinone IIA on the expressions of HMGB1, IL-1β and SOD in myocardial ischemia-reperfusion injury in rats. *Journal of Emergency in Traditional Chinese Medicine* **29**:776–778 DOI 10.3969/j.issn.1004-745X.2020.05.008.

Evans S, Weinheimer CJ, Kovacs A, Williams JW, Randolph GJ, Jiang W, Barger PM, Mann DL. 2020. Ischemia reperfusion injury provokes adverse left ventricular

remodeling in dysferlin-deficient hearts through a pathway that involves TIRAP dependent signaling. *Scientific Reports* **10**:14129 DOI 10.1038/s41598-020-71079-7.

Fu JJ, Huang HQ, Liu JJ, Pi RB, Chen JW, Liu PQ. 2007. Tanshinone IIA protects cardiac myocytes against oxidative stress-triggered damage and apoptosis. *European Journal of Pharmacology* **568**:213–221 DOI 10.1016/j.ejphar.2007.04.031.

Fujii J, Homma T, Osaki T. 2022. Superoxide radicals in the execution of cell death. *Antioxidants* **11(3)**:501 DOI 10.3390/antiox11030501.

He J, Liu D, Zhao L, Zhou D, Rong J, Zhang L, Xia Z. 2022. Myocardial ischemia/reperfusion injury: mechanisms of injury and implications for management (review). *Experimental and Therapeutic Medicine* **23**:430 DOI 10.3892/etm.2022.11357.

Hu HL, Qian G, Tang GM, Zhou BQ. 2015. Effect of tanshinone IIA on HMGB1 in rats after myocardial ischemia and reperfusion. *Chinese Journal of Gerontology* **35**:4185–4187 DOI 10.3969/j.issn.1005-9202.2015.15.033.

Huang X, Deng H, Shen QK, Quan ZS. 2022. Tanshinone IIA: pharmacology, total synthesis, and progress in structure-modifications. *Current Medicinal Chemistry* **29**:1959–1989 DOI 10.2174/0929867328666211108110025.

Jiao SF. 2016. The mechanism of AMPKa2 mediating tanshinone IIA against myocardial ischemia/reperfusion injury. Master's thesis, Nanchang University, Nanchang, China. *Available at https://kns.cnki.net/KCMS/detail/detail.aspx?dbname=CMFD201901&filename=1016195491.nh.*

Li Q, Shen L, Wang Z, Jiang HP, Liu LX. 2016. Tanshinone IIA protects against myocardial ischemia reperfusion injury by activating the PI3K/Akt/mTOR signaling pathway. *Biomedicine and Pharmacotherapy* **84**:106–114 DOI 10.1016/j.biopha.2016.09.014.

Li ZM, Xu SW, Liu PQ. 2018. Salvia miltiorrhizaBurge (Danshen): a golden herbal medicine in cardiovascular therapeutics. *Acta Pharmacologica Sinica* **39**:802–824 DOI 10.1038/aps.2017.193.

Li D, Yang ZH, Gao S, Zhang H, Fan GW. 2022. Tanshinone IIA ameliorates myocardial ischemia/reperfusion injury in rats by regulation of NLRP3 inflammasome activation and Th17 cells differentiation. *Acta Cirúrgica Brasileira* **37**:e370701 DOI 10.1590/acb370701.

Liu Q, Li Z, Liu Y, Xiao Q, Peng X, Chen Q, Deng R, Gao Z, Yu F, Zhang Y. 2018. Hydromorphine postconditioning protects isolated rat heart against ischemia-reperfusion injury via activating P13K/Akt/eNOS signaling. *Cardiovascular Therapeutics* **36**:e12481 DOI 10.1111/1755-5922.12481.

Ma CX, Sun Y, Chen XB, Zhang L. 2017. Study on the protective effect of tanshinone IIA pretreatment on myocardial ischemia-reperfusion injury. *Shaanxi Medical Journal* **46**:1358–1359 DOI 10.3969/j.issn.1000-7377.2017.10.014.

Nehra S, Bhardwaj V, Kalra N, Ganju L, Bansal A, Saxena S, Saraswat D. 2022. Correction to: nanocurcumin protects cardiomyoblasts H9c2 from hypoxia-induced hypertrophy and apoptosis by improving oxidative balance. *Journal of Physiology and Biochemistry* **78**:707 DOI 10.1007/s13105-022-00886-5.

Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* **372**:n71 DOI 10.1136/bmj.n71.

Pasala S, Cooper LB, Psotka MA, Sinha SS, De Filippi CR, Tran H, Tehrani B, Sherwood M, Epps K, Batchelor W, Damluji AA. 2022. The influence of heart failure on clinical and economic outcomes among older adults ≥75 years of age with acute myocardial infarction. *American Heart Journal* **246**:65–73 DOI 10.1016/j.ahj.2021.11.021.

Petrosillo G, Di Venosa N, Ruggiero FM, Pistolese M, D'Agostino D, Tiravanti E, Fiore T, Paradies G. 2005. Mitochondrial dysfunction associated with cardiac ischemia/reperfusion can be attenuated by oxygen tension control. Role of oxygen-free radicals and cardiolipin. *Biochimica et Biophysica Acta/General Subjects* **1710**:78–86 DOI 10.1016/j.bbabio.2005.10.003.

Ren J, Fu L, Nile SH, Zhang J, Kai G. 2019. Salvia miltiorrhiza in treating cardiovascular diseases: a review on its pharmacological and clinical applications. *Frontiers in Pharmacology* **10**:753 DOI 10.3389/fphar.2019.00753.

Reynolds K, Go AS, Leong TK, Boudreau DM, Cassidy-Bushrow AE, Fortmann SP, Goldberg RJ, Gurwitz JH, Magid DJ, Margolis KL, McNeal CJ, Newton KM, Novotny R, Quesenberry Jr. CP, Rosamond WD, Smith DH, Van Wormer JJ, Vupputuri S, Waring SC, Williams MS, Sidney S. 2017. Trends in incidence of hospitalized acute myocardial infarction in the cardiovascular research network (CVRN). *American Journal of Medicine* **130**:317–327 DOI 10.1016/j.amjmed.2016.09.014.

Shen WL, Yu F, Xu L, Chen C, Cao YN, Liu S, Han NY, Wang C, Qi R. 2018. Protective effects of tanshinone IIA derivative on myocardial ischemia/reperfusion injury in rats. *Journal of Chinese Pharmaceutical Sciences* **27**:1–13 DOI 10.5246/jcps.2018.01.001.

Sun T, Wang P, Deng T, Tao X, Li B, Xu Y. 2020. Effect of panax notoginseng saponins on focal cerebral ischemia-reperfusion in rat models: a meta-analysis. *Frontiers in Pharmacology* **11**:572304 DOI 10.3389/fphar.2020.572304.

Tang SM, Wu YM, Zhou TY, Li XY, Meng XB, Zhang H. 2017. The protective effect of Tanshinone IIA on oxidative stress induced by myocardial ischemia reperfusion injury of rats. *China Medical Herald* **14**:8–11.

Tawfik MK, Makary S, Keshawy MM. 2021. Upregulation of antioxidant nuclear factor erythroid 2-related factor 2 and its dependent genes associated with enhancing renal ischemic preconditioning renoprotection using levosimendan and cilostazol in an ischemia/reperfusion rat model. *Archives of Medical Science* **17**:1783–1796 DOI 10.5114/aoms/111373.

Tian L, Cao W, Yue R, Yuan Y, Guo X, Qin D, Xing J, Wang X. 2019. Pretreatment with Tilianin improves mitochondrial energy metabolism and oxidative stress

in rats with myocardial ischemia/reperfusion injury via AMPK/SIRT1/PGC-1 alpha signaling pathway. *Journal of Pharmacological Sciences* **139**:352–360 DOI 10.1016/j.jphs.2019.02.008.

Wang Z, Yao M, Jiang L, Wang L, Yang Y, Wang Q, Qian X, Zhao Y, Qian J. 2022. Dexmedetomidine attenuates myocardial ischemia/reperfusion-induced ferroptosis via AMPK/GSK-3beta/Nrf2 axis. *Biomedicine and Pharmacotherapy* **154**:113572 DOI 10.1016/j.biopha.2022.113572.

Wei B, Li WW, Ji J, Hu QH, Ji H. 2014. The cardioprotective effect of sodium tanshinone IIA sulfonate and the optimizing of therapeutic time window in myocardial ischemia/reperfusion injury in rats. *Atherosclerosis* **235**:318–327 DOI 10.1016/j.atherosclerosis.2014.05.924.

Yang P. 2010. Study on mechanism and the protective effect of tanshinone II A and prohibitin against myocardial ischemia/reperfusion injury. PhD thesis, Southern Medical University, Guangzhou, China.

Yuan X, Jing S, Wu L, Chen L, Fang J. 2014. Pharmacological postconditioning with tanshinone IIA attenuates myocardial ischemia-reperfusion injury in rats by activating the phosphatidylinositol 3-kinase pathway. *Experimental and Therapeutic Medicine* **8**:973–977 DOI 10.3892/etm.2014.1820.

Zhai P, Chen QY, Wang XX, Ouyang XH, Yang ML, Dong YL, Li JY, Li YM, Luo SS, Liu Y, Cheng X, Zhu R, Hu DS. 2024. The combination of Tanshinone IIA and Astragaloside IV attenuates myocardial ischemia-reperfusion injury by inhibiting the STING pathway. *Chinese Medicine* **19**:34 DOI 10.1186/s13020-024-00908-y.

Zhang YJ, Wu SS, Chen XM, Pi JK, Cheng YF, Zhang Y, Wang XJ, Luo D, Zhou JH, Xu JY, Li X, Wu Z, Jiang W, Wang XX. 2022. Saikosaponin D alleviates DOX-induced cardiac injury in vivo and in vitro. *Journal of Cardiovascular Pharmacology* **79**:558–567 DOI 10.1097/fjc.0000000000001206.

Zhang LP, Zhang J. 2010. Effects of tanshinone IIA on myocardial ischemia-reperfusion injury in rats. *Chinese Community Doctors* **12**:28 DOI 10.3969/j.issn.1007-614x.2010.27.026.