RESEARCH ARTICLE

Neurological recovery and antioxidant effects of resveratrol in rats with spinal cord injury: a meta-analysis

Bao-Ping Xu[1, 2, #], Min Yao[1, 3, #], Zhen-Jun Li[1, 4], Zi-Rui Tian[1, 3], Jie Ye[5], Yong-Jun Wang[1, 3], Xue-Jun Cui[1, 3, *]

1 Spine Disease Institute, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China
2 Lu'an Hospital of Traditional Chinese Medicine, Lu'an, Anhui Province, China
3 Key Laboratory of Theory and Therapy of Muscles and Bones, Ministry of Education (Shanghai University of Traditional Chinese Medicine), Shanghai, China
4 Gansu Provincial Hospital of Traditional Chinese Medicine, Lanzhou, Gansu Province, China
5 Department of Orthopedics and Traumatology, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China

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Abstract

Objective: To critically assess the neurological recovery and antioxidant effects of resveratrol in rat models of spinal cord injury.

Data sources: Using "spinal cord injury", "resveratrol" and "animal experiment" as the main search terms, all studies on the treatment of spinal cord injury in rats by resveratrol were searched for in PubMed, EMBASE, MEDLINE, Web of Science, Science Direct, China National Knowledge Infrastructure, Wanfang, VIP, and SinoMed databases by computer. The search was conducted from their inception date to April 2017. No language restriction was used in the literature search.

Data selection: The methodological quality of each study was assessed by the initial Stroke Therapy Academic Industry Roundtable recommendations. Two reviewers independently selected studies according to the title, abstract and full text. The risk of bias in the included studies was also evaluated. Meta-analyses were performed with Review Manager 5.3 software.

Outcome measures: Neurological function was assessed by the Basso, Beattie, and Bresnahan scale score, inclined plane score and Gale's motor function score. Molecular-biological analysis of antioxidative effects was conducted to determine superoxide dismutase levels, malondialdehyde levels, nitric oxide synthase activity, nitric oxide levels, xanthine oxidase and glutathione levels in spinal cord tissues.

Results: The methodological quality of the 12 included studies was poor. The results of meta-analysis showed that compared with the control group, resveratrol significantly increased the Basso, Beattie, and Bresnahan scale scores after spinal cord injury (n = 300, mean difference (MD) = 3.85, 95% confidence interval (CI) [2.10, 5.59], $P < 0.0001$). Compared with the control group, superoxide dismutase levels were significantly elevated (n = 138, standardized mean difference (SMD) = 5.22, 95% CI [2.98, 7.45], $P < 0.00001$), but malondialdehyde levels were significantly diminished (n = 84, SMD = –3.64, 95% CI [–5.84, –1.43], $P = 0.001$) in the spinal cord of the resveratrol treatment group.

Conclusions: Resveratrol promoted neurological recovery and exerted antioxidative effects in rat models of spinal cord injury. The limited quality of the included studies reduces the application of this meta-analysis. Therefore, more high-quality studies are needed to provide more rigorous and objective evidence for the pre-clinical treatment of spinal cord injury.

Key Words: *antioxidation; meta-analysis; neurological recovery; pharmacotherapy; rats; resveratrol; spinal cord injury; systematic review*

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***Correspondence to:**
Xue-Jun Cui, PhD, 13917715524@139.com.

#Both authors contributed equally to this paper.

orcid:
0000-0002-9006-4547 (Xue-Jun Cui)
0000-0001-6257-2766 (Bao-Ping Xu)

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Introduction

Spinal cord injury (SCI) is a severe traumatic disease that causes motor and sensory deficits of the body below the damaged section of spinal cord and is associated with high morbidity and mortality (Rogers and Todd, 2016). The economic and psychological costs to patients with SCI can be enormous and their quality of life is often severely curtailed (Oyinbo, 2011). The total global incidence of SCI is approximately 750 per 1,000,000 people (Wyndaele and Wyndaele, 2006) with over 70% of patients undergoing surgical intervention, however, generally with very poor prognosis (Papadopoulos et al., 2002; McKinley et al., 2004). In the last few decades, studies have grappled with the challenge of developing effective agents for preventing or reversing the potentially devastating consequences of SCI. The main ones in current use are methylprednisolone, ganglioside 1, gastrodin and neurotrophic factors (Hollis and Tuszynski, 2011; Adamczak and Hoh, 2016; Caliskan et al., 2016; Du et al., 2016). However, there is an increased risk of respiratory tract infection after methylprednisolone treatment for

SCI because of its inhibition of immune function (Bydon et al., 2014), whereas allergies are a common adverse effect for ganglioside 1 (Ates et al., 2006). At present, there are no satisfactory pharmacological therapies for the treatment of SCI because of their side effects and inadequate effectiveness (Hollis and Tuszynski, 2011; Rogers and Todd, 2016). Thus, various other novel strategies for SCI repair have been explored and are the focus of much research.

Resveratrol (3,5,4-trihydroxystilbene), a polyphenol compound, is an abundant drug derived from various herbs (Rocha-Gonzalez et al., 2008). It has a long history in the treatment of cardiovascular and neurological diseases (Lopez et al., 2015). Some previous studies have shown that resveratrol can traverse the blood-brain barrier and provide potential neurological recovery, antioxidant effects and anti-inflammatory effects after SCI (Ates et al., 2006; Liu and Sun, 2009; Tang, 2010; Kesherwani et al., 2013; Du et al., 2016; Sawda et al., 2017; Lange and Li, 2018). Many animal experiments have been designed to evaluate the neurobehavioral recovery and antioxidative effects of resveratrol in SCI. However, there is still controversy about the effectiveness of resveratrol on neurobehavioral recovery in rats with SCI and whether it is due to its antioxidant properties.

Systematic reviews are secondary studies that attempt to collate all the evidence, using a methodical approach to minimize the risk of bias and combine the results of individual studies to produce a better estimate of the effects of a treatment. Therefore, we conducted a systematic review and meta-analysis to assess the neurological recovery and antioxidative effects of resveratrol in rat models of SCI.

Data and Methods

Search strategy

Literature retrieval was conducted from English and Chinese databases, including PubMed, EMBASE MEDLINE, Web of Science, Science Direct, China National Knowledge Infrastructure, Wanfang, VIP, and China Biology Medicine databases. Relevant studies were found using the following search terms "resveratrol-3-sulfate", "cis-resveratrol", "trans-resveratrol", "SRT-501", "SRT501", "SRT 501", "trans-resveratrol-3-O-sulfate", "3,5,4′-trihydroxystilbene", "3,4′,5-stilbenetriol", "resveratrol", "spinal cord injury", "spinal cord injuries", "traumatic spinal cord injury", "cervical myelopathy", "cervical spondylosis myelopathy", "cervical spondylomyelopathy", "multilevel cervical spondylotic myelopathy", "cervical spondylotic myelopathy", and "spinal cord repair". In addition, the bibliographies of all included articles and important conference papers were searched for additional relevant studies. Retrieval of literature was carried out from the inception dates of the databases to April 2017.

Study selection

Two reviewers (BPX and MY) evaluated each article separately for preliminary screening, according to the title and abstract, then read through the full text for secondary screening. Disagreements were resolved by agreement and discussion with a third party (XJC). No language restriction was used in the literature search, and the search was limited to studies in rats.

Inclusion criteria

Studies were included if they fulfilled all of the following criteria:

(1) Experimental rat studies that involved at any age or gender with traumatic SCI, including contusion, Allen's method induced injury, crush and compression injury.

(2) Controlled SCI experiments with intervention that involved *in vivo* administration of resveratrol, with no limitations on method of administration, formulation or dosage.

(3) Outcome of neurological function was evaluated and recorded.

(4) Biochemical examination of the peroxidation index was included in the analysis.

No language, publication date, or publication status restrictions were imposed.

Exclusion criteria

Studies with one or more of the following conditions were excluded:

(1) SCI models induced by other causes, such as complete transverse spinal cord injury and spinal cord ischemia/reperfusion injury.

(2) Conference papers and publications of abstracts only that lacked quantitative data information.

(3) Repeated publications.

Data extraction

The information was independently extracted from papers using a standardized data extraction tool by two authors (BPX and MY). The following data were extracted: first author, publication year, animal gender, strain and age of rats, number of rats per group treated with resveratrol, animal model of SCI, SCI level, type of intervention, timing of intervention, duration of intervention, daily dose of resveratrol and outcomes of significance to SCI. From these data, the mean ± standard deviation (SD) of every experimental outcome and the numbers of rats in the resveratrol treatment group and SCI group were extracted for meta-analysis. For experiments using multiple dosages of resveratrol compared with the SCI control group, we combined the multiple dosages of the resveratrol treatment groups into a single group for each of the experiments. If neural function evaluation was performed more than once, the last one was used. If the biochemical examinations were performed at different time points, the last outcome indicators that were conducted after SCI were adopted. Last measurements were taken no later than 1 week post SCI. If there were any controversies, we settled the problem by discussion or with the assistance of a third reviewer (XJC).

If the data were missing or incomplete for extraction and analysis, we contacted the authors and requested the additional information. If the data were represented as a graph without a numerical value, numerical values were requested from the authors via email; if a response was not received,

digital ruler software was used to estimate numerical values from the graphs with GetData Graph Digitizer 2.24 (http://getdata-graph-digitizer.com/download). If the required data were not presented or obtainable, the study was excluded from the meta-analysis.

Assessment of risk of bias in included studies

The methodological quality of individual studies was assessed according to the initial Stroke Therapy Academic Industry Roundtable (STAIR) recommendations (1999). The STAIR was updated by the STAIR group in 2009, according to the Recommendations for Ensuring Good Scientific Inquiry for America (Fisher et al., 2009). The initial STAIR list includes the following: (1) sample-size calculation, (2) inclusion and exclusion criteria, (3) randomization, (4) allocation concealment, (5) reporting of animals excluded from analysis, (6) blinded assessment of outcome and (7) reporting potential conflicts of interest and study funding. The risks of bias were assessed by two independent researchers (BPX and ZJL) for each study. Bias was assessed as a low or high risk of bias, and "unclear" indicated that the risk of bias was not clear.

Outcome measures

The primary outcomes were evaluation of function (Basso, Beattie, and Bresnahan scale (BBB) score, inclined plane score and Gale's motor function score) and molecular-biological analysis of antioxidative effects including superoxide dismutase (SOD) levels, malondialdehyde (MDA) levels, reactive oxygen species levels, nitric oxide synthase activity, nitric oxide levels, xanthine oxidase and glutathione levels in the spinal cord tissues.

Statistical analysis

Meta-analysis was conducted using Review Manager, version 5.3 (Cochrane Collaboration, http://community.cochrane.org/help/tools-and-software/revman-5/revman-5-download). Data from all resveratrol groups were pooled to compare with the SCI groups; data were pooled if outcomes were reported by at least three studies and continuous variables were expressed as mean difference (MD) or standardized mean difference (SMD), both with 95% CI. Outcomes including neurological behavior and antioxidative effects were analyzed. If the units of measurement were consistent, MD was used to assess effect size; when the units of measurement were different, SMD was used to assess the effect size. Heterogeneity was tested using chi-square tests: $P < 0.1$ means heterogeneity, while $P > 0.1$ means no heterogeneity. The I^2 statistic was also used to evaluate the heterogeneity: $0\% \leq I^2 < 25\%$ represents no heterogeneity; $25\% \leq I^2 < 50\%$ means low heterogeneity; $50\% \leq I^2 < 75\%$ reveals moderate heterogeneity; $75\% \leq I^2$ shows severe heterogeneity. Pooled effect size was estimated using fixed-effects models when there was a lower heterogeneity among the studies, otherwise random-effect models were used. A $P < 0.05$ was considered statistically significant and the publication biases were judged by funnel plots.

Results

Search results

Among the 212 articles found in the initial search strategy, 111 similar and duplicated studies were removed. Seventy-one articles were ruled out by the titles and abstracts; 30 studies were retained. One study was a conference paper without specific data information (Yang and Luo, 2009); ten did not report any outcome that met the inclusion criteria (Yang and Piao, 2002b, c; Liu et al., 2005, 2013a, b, 2015; Mei et al., 2007; Wang et al., 2012; Mei et al., 2013; Ciftci et al., 2016); and four studies duplicated data (Liu et al., 2011, 2013a; Mei et al., 2012, 2014). Finally, 15 articles (randomized controlled trial studies) met the inclusion criteria (Yang and Piao, 2002a, 2003; Yang, 2003; Mei, 2005; Ates et al., 2006; Liu and Sun, 2009; Liu and Yang, 2009; Zhao et al., 2010, 2017; Mei et al., 2011; Wang et al., 2011; Wang, 2012; Liu et al., 2014; Xiang, 2015; Li, 2016). Three articles from the same experimental study were conducted as independent experiments (Yang and Piao, 2002a, 2003; Yang, 2003). Therefore, 13 independent studies were included in this study, which contained 15 articles. Of the 15 articles, only one article reported nitric oxide synthase activity, and there were not enough articles to pool data for a meta-analysis (Zhao et al., 2010), so 12 independent studies including 14 articles were chosen for the final meta-analysis after evaluation (Yang and Piao, 2002a, 2003; Yang, 2003; Mei, 2005; Ates et al., 2006; Liu and Sun, 2009; Liu and Yang, 2009; Mei et al., 2011; Wang et al., 2011; Wang, 2012; Liu et al., 2014; Xiang, 2015; Li, 2016; Zhao et al., 2017). The flow chart of the study selection is summarized in **Figure 1**.

Characteristics of included studies

Characteristics of the studies included in this systematic review are shown in **Table 1**. Of the 14 articles that met the inclusion criteria, most were from China and three were published in English (Yang and Piao, 2002a; Ates et al., 2006; Zhao et al., 2017). All studies were randomized controlled experiments. Sprague-Dawley rats were used in 11 studies (Yang and Piao, 2002a, 2003; Yang, 2003; Mei, 2005; Liu and Sun, 2009; Liu and Yang, 2009; Mei et al., 2011; Wang et al., 2011; Wang, 2012; Liu et al., 2014; Xiang, 2015; Li, 2016; Zhao et al., 2017) and Wistar rats were used in one study (Ates et al., 2006). The total sample sizes for the studies ranged from 24 to 120 (Liu and Sun, 2009; Liu and Yang, 2009; Zhao et al., 2010) and the average sample size was 63. Four studies used only male rats, three studies were conducted using female rats and the other studies had no sex information.

All studies used a weight-drop model to induce SCI in rats. The spinal cords of rats in the included studies were exposed aseptically by laminectomy from T7 to T10. Seven studies performed SCI at T8 (Yang and Piao, 2002a, 2003; Yang, 2003; Mei, 2005; Liu and Sun, 2009; Liu and Yang, 2009; Zhao et al., 2010; Mei et al., 2011; Wang et al., 2011), and no study investigated a cervical or lumbar SCI model. The animals were subjected to an impact on the dorsal surface of the spinal cord, with a range of 25 to 50 g/cm, while two studies

Table 1 Characteristics of the included studies

Study	Country	Animals (body weight)	Model of SCI	Sectionalization and intervention Numbers of per group	Treatment timing of resveratrol	Sample processing	Outcome
Yang and Piao (2002a, 2003); Yang (2003)	China	SD rats (180–220 g)	T8 weight drop model (10 g × 2.5 cm)	A: Sham SCI (n = 6) B: SCI (n = 6) C: SCI + Res50 (50 mg/kg, i.p.) (n = 6) D: SCI + Res100 (100 mg/kg, i.p.) (n = 6) E: SCI + MPSS (100 mg/kg, i.p.) (n = 6)	1, 24, and 48 hour after SCI	1 h/1 d/2 d	Other: MDA, SOD, ROS, ultrastructural examination, western blotting (MAP2, NF, Tau protein)
Mei (2005)	China	Male SD rats (330 ± 25 g)	T8 weight drop model (10 g × 3 cm)	A: Blank (n = 2) B: Sham SCI (n = 6) C: SCI (n = 18) D: SCI + Res (100 mg/kg, i.p.) (n = 18) E: SCI + MPSS (100 mg/kg, i.p.) (n = 18)	Immediately after SCI	8 h/1 d/3 d	Other: SOD, Bcl-2, Bax
Ates et al. (2006)	Turkey	Male Wistar albino rats (200–250 g)	T7–10 weight drop model (5 g × 10 cm)	A: Sham SCI (n = 9) B: SCI (n = 9) C: SCI + Res (100 mg/kg, i.p.) (n = 9) D: SCI + MPSS (30 mg/kg, i.p.) (n = 9) E: SCI + Res (100 mg/kg, i.p.) + MPSS (30 mg/kg, i.p.) (n = 9) F: SCI + ethanol (2% ethanol 1 mL, i.p.) (n = 9)	Immediately after SCI	11 d /42 d	Behavioristics: inclined plane score, Gale's motor function score Other: H&E staining, MDA, GSH, NO, XO
Liu and Sun (2009)	China	SD rats (280–320 g)	T8 Allen's method (10 g × 2.5 cm)	A: Sham SCI (n = 8) B: SCI (n = 8) C: SCI + Res (100 mg/kg, i.p.) (n = 8)	Immediately after SCI	3 d	Behavioristics: BBB scale Other: H&E staining, MDA, SOD
Liu and Yang (2009)	China	SD rats (280–320 g)	T8 Allen's method (10 g × 2.5 cm)	A: Sham SCI (n = 8) B: SCI (n = 8) C: SCI + Res (200 mg/kg, i.p.) (n = 8)	Immediately after SCI	3 d	Behavioristics: BBB scale Other: H&E staining, Nissl staining, TUNEL staining
Mei et al. (2011)	China	Male SD rats (220 ±30 g)	T8 Allen's method	A: SCI (n = 18) B: SCI + MPSS (100 mg/kg, p.o.) (n = 18) C: SCI + Res (100 mg/kg, p.o.) (n = 18)	Immediately after SCI	8 h/1 d/3 d	Other: SOD
Wang et al. (2011)	China	Male SD rats (280–320 g)	T8 Allen's method (10 g × 2.5 cm)	A: Sham SCI (n = 16) B: SCI (n = 16) C: SCI + Res (200 mg/kg, i.p.) (n = 16)	Immediately after SCI	6/12 h	Behavioristics: BBB scale Other: MDA, SOD, IL-6, TNF-α
Wang (2012)	China	SD rats	T10 Allen's method	A: Sham SCI (n = 16) B: SCI (n = 32) C: SCI + SOL (100 mg/kg, i.p.) (n = 32) D: SCI + Res (100 mg/kg, i.p.) (n = 32)	Immediately after SCI	4 h /8 h /1 d/ 1.5 d	Behavioristics: BBB scale Other: H&E staining, TUNEL staining, SIRT1, IL-1β,IL-6, IL- 10, TNF-α
Liu et al. (2014)	China	SD rats (280–320 g)	T8 Allen's method (10 g × 2.5 cm)	A: Sham SCI (n = 10) B: SCI (n = 10) C: SCI + Res50 (50 mg/kg, i.p.) (n = 10) D: SCI + Res100 (100 mg/kg, i.p.) (n = 10) E: SCI + Res200 (200 mg/kg, i.p.) (n = 10) F: SCI + Res300 (300 mg/kg, i.p.) (n = 10)	Immediately after SCI	3 d	Behavioristics: BBB scale Other: H&E staining, Nissl staining
Xiang (2015)	China	Female SD rats (220–250 g)	T10 Allen's method (10 g × 2.5 cm)	A: Blank (n = 24) B: Sham SCI (n = 24) C: SCI (n = 24) D: SCI + Res (50 mg/kg, i.p.) (n = 24)	Immediately after SCI	3 d	Behavioristics: BBB scale Other: TUNEL staining, TTC staining, TNF-α, IL-6, IL-10, NCAM-L, ectrophysiological examination
Li (2016)	China	Female SD rats (200 g)	T9 weight drop model (10 g × 5 cm)	A: Sham SCI (n = 6) B: SCI (n = 20) C: SCI + Res (200 mg/kg, i.p.) (n = 20)	1 hour after SCI	7/28 d	Behavioristics: BBB scale Other: H&E staining, western bloting (GFAP, P-STAT3, BMP2) immunofluorescence assay (ISCA)
Zhao et al. (2017)	China	Female SD rats (220–240 g)	T9-10 Allen's method (10 g × 3 cm)	A: Sham SCI (n = 17) B: SCI (n = 17) C: Res (100 mg/kg, i.p.) (n = 17)	Immediately after SCI	7 d	Behavioristics: BBB scale Other: Nissl staining, H&E staining

Bax: Bcl-2 associated X protein; BBB scale: Basso, Beattie, and Bresnahan scale; Bcl-2: B-cell lymphoma-2; BMP2: bone morphogenetic protein 2; GFAP: glial fibrillary acidic protein; GSH: glutathione; H&E: hematoxylin-eosin; IL-1β: interleukin-1β; IL-6: interleukin-6; IL-10: interleukin-10; i.p: intraperitoneal; ISCA: injured spinal cord astrocyte; MAP2: microtubule associated protein 2; MDA: malondialdehyde; MPSS: methylprednisolone sodium succinate; NCAM-L: neural cell adhesion molecule-like protein; NF: neurofilament; NO: nitric oxide; NOS: nitric oxide synthase; po: per os; P-STAT3: phosphorylated signal transducers and activators of transcription-3; Res: resveratrol; ROS: reactive oxygen species; SCI: Spinal cord injury; SD: Sprague-Dawley; SIRT1: silent information regulator 1; SOD: superoxide dismutase; SOL: solutol; Tau protein: microtubule-associated protein tau; TNF-α: tumor necrosis factor-α; TTC staining: triphenyl-2H-tetrazolium chloride staining; TUNEL: transferase mediated dUTP nick end labeling; XO: xanthine oxidase.

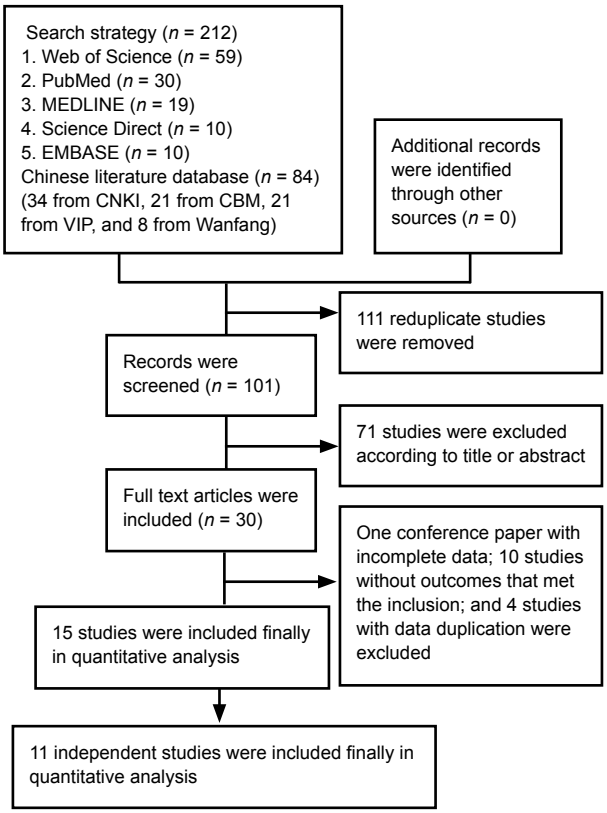

Figure 1 Summary of the literature identification and selection process.
CBM: China Biology Medicine; CNKI: China National Knowledge Infrastructure.

gave no detail regarding strike force parameters (Mei et al., 2011; Wang, 2012).

In most studies resveratrol was administered to SCI rats immediately afterwards, either intraperitoneally (Yang and Piao, 2002a, 2003; Yang, 2003; Mei, 2005; Ates et al., 2006; Liu and Sun, 2009; Liu and Yang, 2009; Wang et al., 2011; Wang, 2012; Liu et al., 2014; Xiang, 2015; Li, 2016; Zhao et al., 2017) or orally (Mei et al., 2011), at doses ranging from 50 to 300 mg/kg (Yang and Piao, 2002a, 2003; Yang, 2003; Mei, 2005; Ates et al., 2006; Liu and Sun, 2009; Liu and Yang, 2009; Mei et al., 2011; Wang et al., 2011; Wang, 2012; Liu et al., 2014; Xiang, 2015; Li, 2016; Zhao et al., 2017). The positive control medication was methylprednisolone sodium succinate (Yang and Piao, 2002a, 2003; Yang, 2003; Mei, 2005; Ates et al., 2006; Zhao et al., 2010; Mei et al., 2011; Liu et al., 2014; Xiang, 2015). All studies reported the outcomes by evaluation of function or biochemical analysis, and the BBB test was used in rats with traumatic SCI 12 hours to 28 days after injury. Some studies also used immunohistochemical analysis and electrophysiological examination to detect features of SCI (Yang and Piao, 2002a, 2003; Yang, 2003; Ates et al., 2006; Liu and Sun, 2009; Liu and Yang, 2009; Wang, 2012; Liu et al., 2014; Xiang, 2015; Li, 2016; Zhao et al., 2017).

Bias analysis of included studies

The risks of bias for all 12 independent studies, included in the 14 articles, are shown in **Table 2**. Overall, the methodological quality of the studies was not high. None of the studies described a sample-size calculation, randomization method, allocation concealment or potential conflicts of interest or study funding. Eight studies described the inclusion and exclusion criteria (Mei, 2005; Ates et al., 2006; Liu and Sun, 2009; Zhao et al., 2010; Wang et al., 2011; Wang, 2012; Liu et al., 2014; Li, 2016) and only one study described the animals excluded from analysis (Ates et al., 2006). Blinded assessment of the outcome was described in two studies (Wang et al., 2011; Liu et al., 2014). Only two studies contained a statement of potential conflicts of interest (Li, 2016; Zhao et al., 2017).

Meta-analysis of neurological recovery and antioxidative effects of resveratrol

Assessment of neurological recovery effect of resveratrol

The meta-analysis of BBB score data from eight studies showed a significant neurological recovery effect with resveratrol (Liu and Sun, 2009; Liu and Yang, 2009; Wang et

Table 2 Assessment of risk of bias in included studies

Study	Sample size calculation	Inclusion and exclusion criteria	Randomization	Allocation concealment	Reporting of animals excluded from analysis	Blinded assessment of outcome	Reporting potential conflicts of interest and study funding
Yang (2003); Yang and Piao (2002a, 2003)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Mei (2005)	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear
Ates et al.(2006)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Liu and Sun (2009)	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear
Liu and Yang (2009)	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear
Mei et al. (2011)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Wang et al. (2011)	Unclear	Low	Unclear	Unclear	Unclear	Low	Unclear
Wang (2012)	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear
Liu et al. (2014)	Unclear	Low	Unclear	Unclear	Unclear	Low	Unclear
Xiang (2015)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Li (2016)	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Low
Zhao et al. (2017)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low

al., 2011; Wang, 2012; Liu et al., 2014; Xiang, 2015; Li, 2016; Zhao et al., 2017). The BBB score significantly increased after resveratrol intervention (8 studies, n = 300, MD = 3.85, 95% CI [2.10 to 5.59], P < 0.0001; **Figure 2**) in a random-effects model because of the high heterogeneity (I^2 = 99%, P < 0.00001). In addition, dose subgroup analysis was not performed as fewer studies were included. Significant heterogeneities (I^2 > 90%) still existed in the sensitivity analysis, and there was no significant difference in the before and after the sensitivity analysis.

One study (Ates et al., 2006) measured neurological recovery using the inclined plane score and Gale's motor function score. Significant increases of the mean inclined plane test results and motor function scores were found compared with the SCI control group (P < 0.05). The resveratrol group also revealed a significantly greater improvement on the inclined plane test than the group that received methylprednisolone sodium succinate therapy (Ates et al., 2006).

Assessment of antioxidative effects of resveratrol

Antioxidative effects were measured in nine articles (Yang and Piao, 2002a, 2003; Yang, 2003; Mei, 2005; Ates et al., 2006; Liu and Sun, 2009; Zhao et al., 2010; Mei et al., 2011; Wang et al., 2011). Five studies measured SOD levels after SCI (Yang and Piao, 2002a, 2003; Yang, 2003; Mei, 2005; Liu and Sun, 2009; Mei et al., 2011; Wang et al., 2011). Heterogeneity was significantly high in this group of studies (heterogeneity χ^2 = 38.64, P < 0.0001, I^2 = 90%; **Figure 3**). SOD levels were significantly higher in the resveratrol group compared with the SCI group (five studies, n = 138, SMD = 5.22, 95% CI [2.98, 7.45], P < 0.00001; **Figure 3**) using a random-effects model.

Four studies measured MDA levels after SCI (Yang and Piao, 2002a, 2003; Yang, 2003; Ates et al., 2006; Liu and Sun, 2009; Wang et al., 2011) and found that MDA levels were significantly lower in the resveratrol group than in the SCI groups using a random-effects model (four studies, n = 84, SMD = −3.64, 95% CI [−5.84 to −1.43], P = 0.001; **Figure 4**).

Reactive oxygen species levels were measured in one study after SCI; the post-traumatic reactive oxygen species level in the injured cord was significantly lower in the resveratrol group compared with the SCI group (P < 0.05) (Yang and Piao, 2002a, 2003; Yang, 2003). Only one study (Ates et al., 2006) tested for other antioxidative measures and reported that nitric oxide and xanthine oxidase were significantly lower, and glutathione levels were higher in the resveratrol group than in the SCI group (P < 0.05).

Publication bias

Funnel plots of publication bias for BBB score, SOD levels and MDA levels are assessed (**Figure 5**). The asymmetries found in the funnel plots indicated the possibility of publication bias.

Discussion

Summary of main results

This is the first meta-analysis to evaluate the neurological recovery and antioxidative effects of resveratrol in rat models of SCI. Our study found that administration of resveratrol after SCI could provide a beneficial impact on the neurological recovery and the antioxidant activity in rats. Compared with SCI groups, a significant elevation in the BBB score was detected and resveratrol treatment significantly increased serum SOD levels and decreased serum MDA levels in rats after SCI in the resveratrol groups. Despite our selection criteria, the general quality of the included articles was not high; no study was considered to be of high quality as the sample-size calculation method, randomization and allocation concealment mechanisms were not all reported in every one of the included studies.

Strengths and limitation of evidence

The pathophysiological mechanism of secondary SCI is still not clear, but oxidative stress reactions play a significant role in the physiological pathology and subsequent functional neurological recovery. Our quantitative analysis of previous studies demonstrated improved neurological recovery and antioxidative effects of resveratrol in rats with SCI. A fundamental assumption is that the results of animal studies, if performed well enough, would be meaningful in humans and lead to promising neurological recovery drugs for clinical practice. However, there are several sources of bias in this systematic review.

A reliable conclusion of a meta-analysis is based on the quantity and quality of the included studies. Where we were able to obtain the STAIR assessment of quality from the included studies, it was judged to be of low quality. There are several limitations of this systematic review. First, among the 15 articles selected, only 3 articles were published in English, the rest were written in Chinese or from China and, more importantly, we did not know whether all the papers were widely peer-reviewed before publication. In addition, the limited number of articles was also a major limitation of this review. Many of the included studies were published some time ago. Nearly half of the included articles were published pre-2010. We found the quality of the included articles was poor, lacking adherence to applicable animal research guidelines. Second, none of the included studies mentioned the random allocation of rats to groups, and it has been shown that studies not using random allocation are more likely to report a positive effect than studies that do (Bebarta et al., 2003). The measurement methods for SOD and MDA levels were different in different studies and the measurement units also varied. Although we use standardized mean difference values to reduce the statistical effect size, the bias was still not completely eliminated and this is also an important factor influencing the quality of the research. None of the studies reported sample-size calculations and the number of included studies was relatively small, potentially producing large positive bias effects. Therefore, the confidence in our analysis is limited by the quality of the original studies; the true effect is likely to be substantially different from the estimated effect.

Resveratrol exists in two isoforms, cis-resveratrol and trans-resveratrol. Most recent studies focus on the trans-iso-

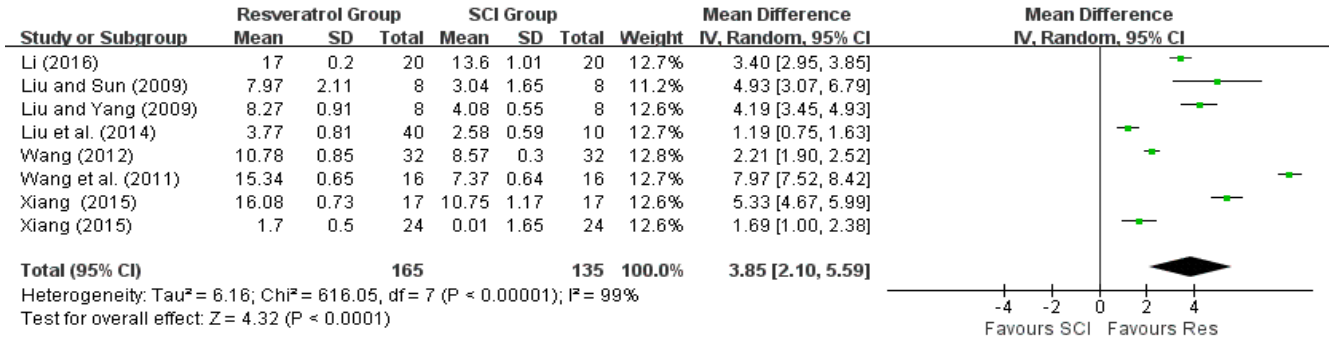

Figure 2 Forest plot for the effects of resveratrol intervention on Basso, Beattie, and Bresnahan scale scores in rats with SCI (random-effects model).
CI: Confidence interval; Res: resveratrol; SCI: spinal cord injury; SD: standard deviation.

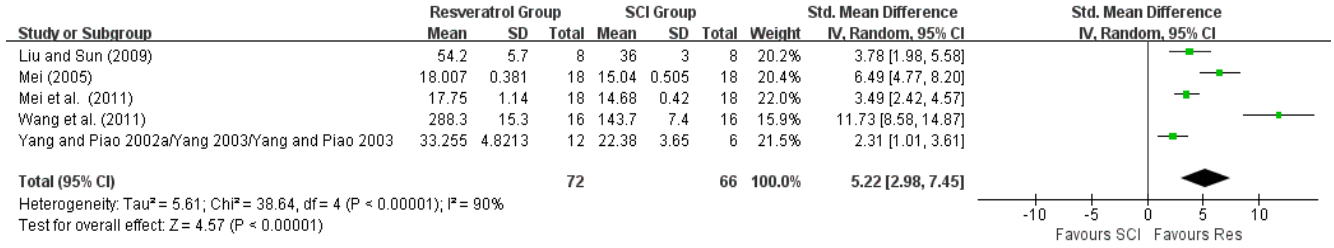

Figure 3 Forest plot for the effects of resveratrol intervention on superoxide dismutase levels in rats with SCI (random-effects model).
Superoxide dismutase meta-analysis after SCI. CI: Confidence interval; Res: resveratrol; SCI: spinal cord injury; SMD: standardized mean difference.

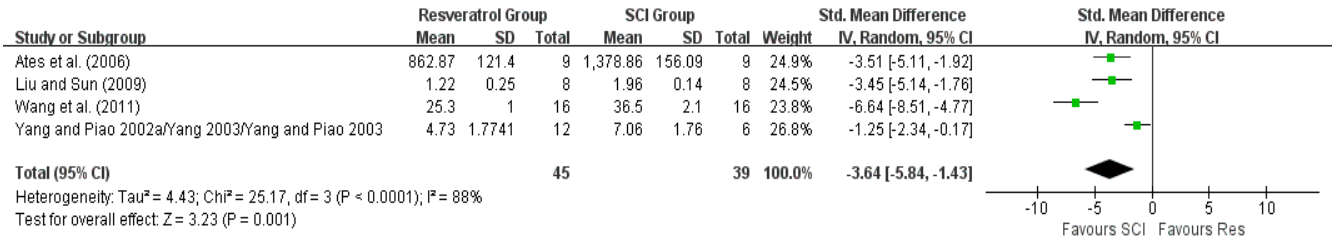

Figure 4 Forest plot for the effects of resveratrol intervention on malondialdehyde levels in SCI rats (random-effects model).
CI: Confidence interval; Res: resveratrol; SCI: spinal cord injury; SMD: standardized mean difference.

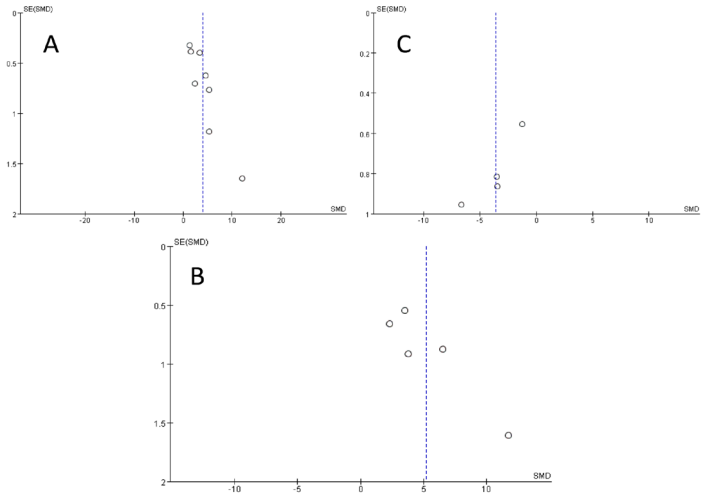

Figure 5 Asymmetries found in the funnel plots indicated the possibility of publication bias.
Funnel plots of publication bias for Basso, Beattie, and Bresnahan scale scores (A), superoxide dismutase (B) and malondialdehyde levels (C).

mer, which has been suggested to be the principal one responsible for the neurological recovery and antioxidative effects (Yanez et al., 2006; Mikulski et al., 2010; Wang and Chatterjee, 2017). Trans-resveratrol is readily converted to the cis- isoform under ultraviolet or light, and this conversion reduces the potency and therapeutic effects of resveratrol (Delmas et al., 2011). A parameter of cis- or trans-isoform of resveratrol usage in meta-analysis should be considered; however, none of the 15 articles included in this study mentioned isoforms of resveratrol. The administration of the resveratrol is also a critical factor because the bioavailability of oral resveratrol, hypodermic and intraperitoneal injection of resveratrol is poor (Rotches-Ribalta et al., 2012). Another important factor in determining heterogeneity is the source of financial support. The funded organization should be disclosed in the article; however, eight of the studies included in our analysis did not disclose detailed information of funding. The outcomes targeted in this review were specific to rat models that used a weight-drop model to induce SCI and did not include other animal models or other SCI models, thus the therapeutic effects of resveratrol by neurological recovery and antioxidation shown in this review may not apply to all species and SCI models. Although the SCI model is widely used by different labs, it can still vary and relies heavily on the technique of the surgeon. Furthermore, the BBB locomotor score is a subjective assessment method, and the results varied in the different studies, which will make it more difficult to interpret the conclusions. All these aspects suggest that there is a high risk of bias. Unfortunately it will inevitably affect the credibility of the conclusions for this paper.

Potential mechanism of neurological recovery and antioxidative effects

Secondary injury, including neuronal apoptosis and oxidative stress responses, occurs after the initial SCI and leads to further neurological damage (Liu et al., 2016; Kong and Gao, 2017; Simon et al., 2019). It plays an important role in secondary pathology following SCI (Cheng et al., 2019; Rodemer and Selzer, 2019; Sharma et al., 2019). Some studies found that expression of Bcl-2 genes, associated with the inhibition of apoptosis of neuronal cells rose significantly, and neuronal apoptosis were significantly inhibited, after treatment of SCI rats with resveratrol (Zhang et al., 2012; Kong and Gao, 2017; Zhao et al., 2017). In addition, BBB scores increased significantly after resveratrol intervention compared with the SCI group (Zhao et al., 2017); indicating that resveratrol administration significantly improved the recovery of locomotor function in rats with SCI. Many free radicals are produced after SCI (Bains and Hall, 2012; Hall et al., 2016) causing lipid oxidative degradation, thus SOD and MDA levels were used as indices of oxidative damage (Oumi et al., 2017). Previous studies found that resveratrol is a biological antioxidant that can reduce secondary oxidative stress-induced cell damage after SCI by increasing serum SOD levels and decreasing serum MDA levels (Ates et al., 2006; Fu et al., 2016). Resveratrol may act by removing free radicals. This potential mechanism of neurological recovery and antioxidative effects suggests that resveratrol could be a potential preventive and therapeutic agent for neurological disease.

Conclusions

Based on the results of this meta-analysis, we demonstrated that resveratrol intervention could improve neurological recovery and antioxidative effects in rat models of SCI. A possible mechanism is that it scavenges free radicals, decreasing the levels of MDA and increasing SOD levels, thereby inhibiting neuronal apoptosis.

The results of this meta-analysis must be interpreted and applied with an appropriate degree of caution because some factors such as the poor methodological quality of the studies and possible publication bias may undermine the validity of the positive findings. Even so, resveratrol could be a promising drug to treat SCI. In the future, it deserves a larger study that takes into account the design features recommended in the discussion of this meta-analysis.

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