It is believed that the increasing global impact of ischemia survivors, which brings serious burden to family and society. Stroke leads to varying degrees of functional impairment for and it is tending to encroach on younger adults. Moreover, modern stress, the rate of stroke has increased year by year, leading to an increased overall incidence, high disability, and high mortality [1, 2]. As reported, ischemia stroke is a major cause of global mortality and morbidity [3–5]. With the fast pace of modern life and the gradual increase of modern stress, the rate of stroke has increased year by year, and it is tending to encroach on younger adults. Moreover, stroke leads to varying degrees of functional impairment for survivors, which brings serious burden to family and society. It is believed that the increasing global impact of ischemia stroke in the few decades will certainly affect the healthcare in several developing countries, including China.

Cerebral ischemia is caused by cerebral vascular occlusion induced by many reasons. Cerebral vascular occlusion leads to cerebral ischemia, hypoxia, and a series of pathological damage to brain. The physiological of cerebral ischemia is generally thought as a rapid cascade reaction with multilink and multichannel characteristics [6, 7]. In this event, the local steady state is broken and the pathological change is produced with the mix of excitotoxicity, oxidative stress, intracellular calcium overload, inflammatory reaction, cellular swelling, and eventually apoptosis or necrosis. In particular, the injury of blood brain barrier (BBB) structure and function is the

### 1. Introduction

Cerebral ischemia is commonly known as ischemia stroke, accounting for more than 80% of stroke cases. It seriously harms people's health with high incidence, high disability, and high mortality [1, 2]. As reported, ischemia stroke is a major cause of global mortality and morbidity [3–5]. With the fast pace of modern life and the gradual increase of modern stress, the rate of stroke has increased year by year, and it is tending to encroach on younger adults. Moreover, stroke leads to varying degrees of functional impairment for survivors, which brings serious burden to family and society. It is believed that the increasing global impact of ischemia
key process. When in reperfusion, inflammatory factors could permeate through the damaged BBB into the brain. Moreover, many of the original harmless substances, such as oxygen molecules, will also be harmful via BBB. These factors lead to brain injury, and the brain injury became more serious during reperfusion. This situation causes great difficulty in the treatment of cerebral ischemia patients [8, 9].

Currently, the only effective drug for stroke which has been approved by Food and Drug Administration (FDA) is tissue-type plasminogen activator (t-PA), which is thrombolytic therapy by intravenous injection. It can achieve recanalization of blood flowing that is considered to be the most direct and effective treatment method. However, the drug must be used after a short period of limited stroke medication and secondary risk of bleeding; to a certain extent, it limits the clinical application of thrombolytic therapy [10]. Therefore, the new strategy treatment for stroke as well as long-term brain protection of new drugs is still the field of cerebral ischemia injury prevention and research focus and objectives [11]. And western medicine is increasingly recognized as failing to achieve the desired goals in the treatment of complex diseases, whereas traditional Chinese medicine wholism.

Xingnaojing injection (XNJI), an effective TCPM, is derived from a classic Chinese emergency prescription named An Gong Niu Huang pills. An Gong Niu Huang pills is from “Treatise on Differentiation and Treatment of Epidemic Febrile Diseases” written by Wu Tang in the Qing Dynasty, which is widely used to cure various acute cerebrovascular diseases with good effectiveness. XNJI is produced by the secondary distillation of steam from the following four herbs: artificial Moschus, synthetic Dryobalanops aromatica Gaertn. F., Gardenia jasminoides Ellis, and Radix Curcumae. Moschus. Radix Curcumae. Moschus is the preferred medicine to rescue with aromatics, and combination with Dryobalanops aromatica Gaertn. F. could enhance the effect of resuscitation [2, 12]. In recent research, it demonstrated the characteristics and advantages of multitarget, multicomponent and multichannel regulation [12]; XNJI could directly act on the BBB permeability in nerve center by inhibiting inflammatory factors effectively [13–17]. Moreover, it could regulate the effect on cognitive function and antioxidant free radicals [18, 19], alleviate encephalodema, and ameliorate the ischemia, anoxic state antiscell autophagy, and apoptosis in brain [16, 20–24].

At present, clinical meta-analysis demonstrates that XNJI could promote the recovery of neurological function in patients with cerebral ischemia and reduce the cerebral infarction area [25]. And, there are many studies reporting the mechanism of XNJI on cerebral ischemia; however, there is no publication to summarize the mechanism of Xingnaojing treatment of cerebral ischemia. Therefore, we performed a systematic review and meta-analysis of experimental animal studies to gain a better understanding of the effect and mechanism of XNJI on cerebral ischemia and to explore its mechanism further (Figure 1).

2. Methods

2.1. Literature Search. Literature filtering was conducted independently by two investigators (Rong Ma and Jianxia Wen), including Chinese National Knowledge Infrastructure (CNKI), Wanfang Database, VIP medicine information system (VMIS), PubMed, MEDLINE, Embase, and the Cochrane Library from the inception to June 2018. The following terms searched were used individually or in combination: “Xingnaojing injection” OR “XNJI” AND “stroke” OR “cerebral ischemia” OR “cerebral ischemia-reperfusion”.

2.2. Inclusion and Exclusion Criteria. The inclusion criteria are as follows: (i) the experiment is based on animal model of cerebral ischemia; (ii) treatment group receives the XNJI only; (iii) the included studies contain control group and XNJI treatment group; (iv) studies must include one of the defined outcome measures. The primary outcome measures are as follows: neurological deficit score, brain edema, cerebral infarction area, and neuronal apoptosis; the second outcome measures: tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-1β (IL-1β), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and malondialdehyde (MDA).

The studies were excluded, if they presented the following criteria: (i) clinical studies; (ii) treatment group without XNJI or combined with other agents; (iii) review and/or meta-analysis; (iv) the primary outcome measures and the second outcome measures which are not included in the literature; (v) duplicated publications; (vi) the article which has only an abstract.

2.3. Data Collection. The data extraction and quality assessment of the included studies were conducted independently by two investigators (Rong Ma and Jianxia Wen), and any disagreements were solved through discussion with corresponding author. We have extracted the following data from the included studies: (1) the first author's name and year of publication; (2) species of animals, animal sex, animal weight, numbers of animals in XNJI treatment group, and control group; (3) the model of cerebral ischemia (transient or permanent), the time of cerebral ischemia and reperfusion, XNJI dosage, and intervention duration; (4) primary and second outcome measures. And if the experimental group of animals in the study received various doses of XNJI, only the data of highest dose of XNJI was included.

2.4. Assessment of Methodological Quality. The methodological quality of the included studies was assessed based on the Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies (CAMARADES) with 10-item quality checklist [26]: (1) publication in a peer-reviewed journal; (2) statement of temperature control; (3) random allocation to groups; (4) allocation concealment; (5) blinded assessment of outcome; (6) use of anesthetic without significant internal protection of blood vessel; (7) appropriate animal model (aged, healthy, diabetic, or hypertensive); (8) sample size calculation; (9) compliance with animal welfare...
regulations; (10) statement of potential conflict of interests. Each study was assessed and scored on a scale from 0 (lowest) to 10 (highest) points.

2.5. Statistical Analysis. All values of neurological deficit score, cerebral infarction area, brain edema, neuronal cell apoptosis, and the level of TNF-α, IL-6, IL-1β, SOD, GSH-Px, and MDA are considered as continuous data and analysed by RevMan 5.3 (2008 The Nordic Cochrane Centre). Outcomes were presented as mean difference (MD) with 95% confidence interval (CI) and the I-square ($I^2$) statistic used to assess heterogeneity. If the $I^2 = 0$, which suggested that there is no heterogeneity, fixed effect model would be used to perform a meta-analysis. If the $I^2 \leq 50\%$ or $P \geq 0.1$, it is considered...
minor heterogeneity with fixed effect model. If the $I^2 > 50\%$ or $P < 0.1$, there is significant heterogeneity with random effect model.

3. Results

3.1. Study Identification and Selection. A flowchart of the study selection process is shown in Figure 2. The search has identified 392 relevant studies. However, we searched for specific studies from the literature search of the foreign language databases because XNJI is only used domestically in China currently. Ultimately, 23 studies with 578 animals were screened by title, abstract and full-text for further quality assessment [13,16,17,20–24,27–41].

3.2. Study Characteristics. A total of 578 animals (290 in the trial group; 288 in the control group) were included in the 23 studies. Sprague-Dawley (SD) rats or Wistar rats were used in most of the animal experiments; other animals such as mongolian gerbil, mice, and rabbits were used in a few experiment. Most of the research projects were male rats, both male and female, were also included. In the selected studies, the experimental animals were predominantly using intravenous or intraperitoneal injection in the dosage of XNJI 0.5 ~ 50 mL/kg and the same volume of normal saline as a control, and most of the dosing methods were administered in a single dose. Additionally, outcomes included neurological deficit score, brain edema, cerebral infarction area, neuronal apoptosis, serum levels of inflammatory factors (TNF-α, IL-6, and IL-1β), and the antioxidant level of body (SOD, MDA, and GSH-Px). There were also three articles which explored the impact of XNJI on BBB damage [20,29,34]. The detailed characteristics of the 23 articles are shown in Table 1.

3.3. Methodological Quality. All studies were published in a peer-reviewed journal. Seven studies described the temperature control [13, 29, 30, 32, 33, 37, 39]; eighteen studies described random allocation [13, 16, 20–24, 27–30, 32–36, 38, 40], and four studies reported the random sequence was generated by a random number table [29–31, 33]. None of the studies used either allocation concealment or blinded assessment of outcome. As for the use of anesthetics, chloral hydrate was used as anesthetic in nine studies [13, 20–22, 29–31, 33, 38], pentobarbital sodium was used as anesthetic in three studies [16, 32, 40], ethyl ether was used as anesthetic in two studies [23, 39], and iso-mo pentobarbital sodium, ethyl carbamate, and thiophene sodium were used as anesthetic in one study respectively [28, 36, 41]. Six articles did not report the detail of anesthetics [17,24,27,34,35,37]. One study chooses rats with hypertensive [32], and others choose the healthy mouse, rats, or rabbits. Fifteen studies described a sample size calculation [16,17,20,21,24,27–31,33,34,36,40,41]. And, no studies reported compliance with animal welfare regulations or a statement of potential conflict of interests. Details of each experiment are shown in Table 2.
Table 1: The characteristics of the included studies.

| Study (year)     | Special/strain | Sex | Weight (g) | N(T/C) | Model | Index | Intervention | Outcome measures |
|------------------|----------------|-----|-------------|--------|-------|-------|--------------|------------------|
| Yan et al. 2017  | Rat/W          | M   | 250±20      | 24(12/12) | P     | 2/24  | i.p. NS      | i.p. XNJ 5 mL kg⁻¹ d⁻¹ (1d) | NDS, NCA          |
| Li et al. 2016   | Rat/W          | M   | NR          | 20(10/10) | P     | 1.5/72 | i.p. NS      | i.p. XNJ 20 mL kg⁻¹ d⁻¹ (7d) | NDS, TNF-α, CIA   |
| Chen et al. 2015 | Rat/W          | M   | 200~250     | 36(18/18) | P     | 0.16/48 | i.p. NS      | i.p. XNJ 10 mL kg⁻¹ d⁻¹ (1d) | BE, BBB           |
| Wu 2015          | Rat/W          | M   | 250±50      | 24(12/12) | P     | 2/70  | i.p. NS      | i.p. XNJ 50 mL kg⁻¹ d⁻¹ (5d) | NDS               |
| Zhong et al. 2015| Rat/W          | M   | 200~250     | 108(54/54) | P     | 0.16/72 | NR           | i.p. XNJ 10 mL kg⁻¹ d⁻¹ (3d) | BE, BBB           |
| Huang et al. 2014| Rat/W          | M   | 280~300     | 20(10/10) | P     | 0.3/0.3 | i.p. NS      | i.p. XNJ 2 mL kg⁻¹ d⁻¹ (1d) | CIA               |
| Ma 2014          | Rat/SD         | M   | 200±20      | 12(6/6)   | T     | 24/-  | i.p. NS      | i.p. XNJ 3 mL kg⁻¹ d⁻¹, 3 times (1d) | NDS, GSH-Px |
| Zeng 2013        | Rat/SD         | M   | 280~300     | 20(10/10) | P     | 2/24  | c.i.v NS    | c.i.v. XNJ 2 mL kg⁻¹ d⁻¹ (1d) | CIA, NCA |
| Zhu 2012         | Rat/SD         | M   | 200~200     | 40(20/20) | P     | 2/168 | c.i.v. NS   | c.i.v. XNJ 2 mL kg⁻¹ d⁻¹ (1d) | NDS, CIA, NCA |
| Huang 2012       | Mouse          | M   | 20~22       | 24(12/12) | P     | 2/NR  | i.p. NS     | i.p. XNJ 10 mL kg⁻¹ d⁻¹ (5d) | CIA, IL-6, IL-1β, TNF-α |
| Li and Xie 2011  | Rat/SD         | M   | 250~300     | 12(6/6)   | P     | 2/24  | i.v. NS     | i.v. XNJ 10 mL kg⁻¹ d⁻¹ (1d) | NDS, CIA, IL-6, IL-1β, BBB |
| Guo et al. 2010  | Rat/SD         | M   | 200~250     | 16(8/8)   | P     | 2/24  | i.v. NS     | i.v. XNJ 10 mL kg⁻¹ d⁻¹ (1d) | MDA, SOD, NCA |
| Wu 2007          | Rat/W          | M   | 260±10      | 43(23/20) | T     | 8/-   | i.p. NS     | i.p. XNJ 8 mL kg⁻¹ d⁻¹ (5d) | TNF-α, BE |
| Zhang et al. 2006| Mouse          | M&F | 50~80       | 18(9/9)   | P     | 0.16/4 | i.v. NS     | i.v. XNJ 0.685 mL kg⁻¹ d⁻¹ (1d) | SOD |
| Lu 2006          | Rat/SD         | M   | 200~250     | 16(8/8)   | P     | 2/48  | i.p. NS     | i.p. XNJ 10 mL kg⁻¹ d⁻¹ (1d) | SOD, MDA, NCA |
| Shen et al. 2004 | Rat/SD         | M   | 250±20      | 12(6/6)   | T     | 6/-   | NR          | i.p. 1.25 mL kg⁻¹ d⁻¹, 2 times (1d) | NDS |
| Wang et al. 2004 | Rabbit         | M&F | 2200~3000   | 20(10/10) | P     | 0.5/2 | i.v. NS     | i.v. XNJ 1 mL kg⁻¹ d⁻¹ (1d) | MDA, SOD |
| Zhou et al. 2002 | Mouse          | M   | 28~30       | 15(7/8)   | P     | 0.08/0.16 | i.p. NS   | i.p. XNJ 5 mL kg⁻¹ d⁻¹ (1d) | GSH-Px, SOD, LMF |
| Wan et al. 2001  | Rat/SD         | M   | 200~250     | 16(8/8)   | T     | 0.66/- | i.p. NS     | i.p. XNJ 3 mL kg⁻¹ d⁻¹ (1d) | GSH-Px |
| Cai et al. 2000  | Rat/W          | M   | 205±15      | 20(10/10) | T     | 3/-   | i.p. NS     | i.p. XNJ 2 mL kg⁻¹ d⁻¹ (1d) | NS |
| Fu et al. 2000   | Rat/W          | M   | 200~300     | 30(15/15) | P     | 3/3   | NR          | i.p. XNJ 20 mL kg⁻¹ d⁻¹ (7d) | BE, CIA, NCA |
| Chen et al 2000  | Rabbit         | M&F | 2200~3600   | 20(10/10) | P     | 0.5/2 | i.v. NS     | i.v. XNJ 1 mL kg⁻¹ d⁻¹ (1d) | TNF-α, IL-1β, IL-6, BUC |
| Zhang et al 1997 | Rabbit         | NR  | 2500~3000   | 12(6/6)   | P     | 0.5/0.5 | i.v. NS     | i.v. XNJ 40 mL kg⁻¹ d⁻¹ (1d) | MDA, GSH-Px |

Note: XNJ is Xingnaojing injection; SD is Sprague-Dawley; W is Wistar; M is male; F is female; P is permanent; T is transient; i.p. is intraperitoneal injection; i.v. is intravenous injection; c.i.v. is caudal intravenous injection; NR is not report; Index ischem/rep(h) is index ischemia and reperfusion in hours; - means no reperfusion; BE is brain edema; BBB is blood brain barrier; NDS is Neurological Deficit Score; CIA is cerebral infarction area; NCA is Neuronal cell apoptosis; TNF-α is brain tumor factor α; IL-6 is interleukin-6; IL-1β is interleukin-1β; SOD is superoxide dismutase; MDA is malondialdehyde; GSH-Px is glutathione peroxidase.
4. Effect of Interventions on Cerebral Ischemia

4.1. Primary Outcome Measures

4.1.1. Neurological Deficit Score. Neurological deficit score was measured in seven studies with 120 animals. Significant heterogeneity occurred in index of neurological deficit score \( (P < 0.00001, I^2 = 93\%) \). Therefore, random effect model was adopted for meta-analysis. The MD with 95\% CI of neurological deficit score was \(-1.25 \pm 1.25\) (Figure 3(a)). Subgroup analysis showed that XNJI got a remarkable effect on the models of ischemia-reperfusion \( (n=76, -1.35 \pm 2.36, -0.34), P=0.009 \) compared to permanent ischemia \( (n=44, -1.08 \pm 1.66, -0.51), P=0.0002 \) (Figure 3(b)).

4.1.2. Cerebral Infarction Area, Brain Edema, and Neuronal Cell Apoptosis. Cerebral infarction area, brain edema, and neuronal cell apoptosis were measured in six studies \([13, 21, 24, 27, 33, 35]\), four studies \([16, 20, 24, 29]\), and six studies \([21, 22, 24, 27, 33, 35]\) with 96, 145, and 106 animals, respectively. Significant heterogeneity appeared in cerebral infarction area, brain edema, and neuronal cell apoptosis \( (P < 0.00001, I^2 = 93\%; P = 0.004, I^2 = 78\%; P < 0.00001, I^2 = 96\%) \). Therefore, random effect model was adopted for meta-analysis. The MD with 95\% CI of cerebral infarction area, brain edema, and neuronal cell apoptosis were \(-14.98 \pm 21.36, -8.59\) (Figure 4(a)), \(-4.64 \pm 5.38, -3.90\) (Figure 4(b)), \(-12.21 \pm 18.05, -6.37\) (Figure 4(c)). The pooled analysis indicated that the cerebral ischemia area, brain edema, and the neuronal cell apoptosis could significantly alleviated by using XNJI compared with control group \( (P < 0.00001, P < 0.00001, P < 0.00001) \).

4.2. Second Outcome Measures

4.2.1. Inflammatory Factor. The effect of XNJI on TNF-\( \alpha \), IL-6, and IL-1\( \beta \) is summarized in Figure 5. Serum TNF-\( \alpha \), IL-6, and IL-1\( \beta \) level were measured in four \([13, 16, 29, 34]\), three \([13, 17, 34]\), and two articles \([17, 34]\) with 107, 56, and 32 animals, respectively. Significant heterogeneity
represented in index of TNF-α and IL-1β (P < 0.00001, \(I^2 = 98\%\), \(P < 0.00001\), \(I^2 = 99\%\)). Therefore, random effect model was adopted for meta-analysis. The MD with 95% CI and P of TNF-α and IL-1β was \(-4.13 (-6.68, -1.58)\), \(P = 0.001\); \(-228.69 (-586.20, -128.83)\), \(P = 0.21\) (Figures 5(a) and 5(c)). In addition, there were two experiments which assessed the changes in IL-1β. There is no heterogeneity displayed in the meta-analyses of IL-6 (\(P = 0.77\), \(I^2 = 0\%\)). Based on the statistical meta-analysis of fixed effect model, the MD with 95% CI and P of IL-6 was \(-119.23 (-138.04, -100.43)\), \(P < 0.00001\) (Figure 5(b)). It demonstrated that XNJI could significantly increase the level of SOD, GSH-Px and decrease the level of MDA (\(P = 0.002\), \(P = 0.01\), \(P < 0.00001\)).

5. Discussion

5.1. Preclinical Evidence and Mechanism of Xingnaojing Injection for Cerebral Ischemia. The rapid development of modern technology makes many oral formulations of Chinese medicine developing as injections to meet the needs of modern medicine. XNJI is refined based on the traditional Chinese prescription named An Gong Niu Huang pills [42], which is widely applied in clinic for a variety of coma and cerebrovascular accident patients [43, 44]. It could alleviate quickly and effectively the clinical symptoms of cerebral ischemia such as hemiplegia, partial body sensory disorder, aphasia vomiting, and ataxia [45].

The pathogenesis of cerebral ischemia and reperfusion is a rapid cascade reaction. The accumulation of inflammatory

\[\text{SOD, GSH-Px, and MDA level, the direct index of oxidation system of the body, were measured in five [22, 23, 35, 36, 38], three [32, 38, 39], and six articles [22, 23, 32, 35, 36, 41] with 77, 43, and 86 animals, respectively. Significant statistical heterogeneity was observed in all the three meta-analysis (}P < 0.00001, \(I^2 = 96\%\); P < 0.00001, \(I^2 = 92\%\); P < 0.00001, \(I^2 = 98\%\)). The MD with 95\% CI of SOD (Figure 6(a)), GSH-Px (Figure 6(b)), and MDA (Figure 6(c)) was 53.02 (20.25, 85.78), 8.65 (1.77, 15.54), and \(-4.16 (-5.50, -2.82)\), respectively. It indicated that the XNJI could significantly increase the level of SOD, GSH-Px and decrease the level of MDA (P = 0.002, P = 0.01, P < 0.00001).

4.2.2. Antioxidant Level. SOD, GSH-Px, and MDA level, the direct index of oxidation system of the body, were measured in five [22, 23, 35, 36, 38], three [32, 38, 39], and six articles [22, 23, 32, 35, 36, 41] with 77, 43, and 86 animals, respectively. Significant statistical heterogeneity was observed in all the three meta-analysis (P < 0.00001, \(I^2 = 96\%\); P < 0.00001, \(I^2 = 92\%\); P < 0.00001, \(I^2 = 98\%\)). The MD with 95\% CI of SOD (Figure 6(a)), GSH-Px (Figure 6(b)), and MDA (Figure 6(c)) was 53.02 (20.25, 85.78), 8.65 (1.77, 15.54), and \(-4.16 (-5.50, -2.82)\), respectively. It indicated that the XNJI could significantly increase the level of SOD, GSH-Px and decrease the level of MDA (P = 0.002, P = 0.01, P < 0.00001).
cytokines in ischemia tissue is an important factor to aggrava
tecerebral ischemia and hypoxia. When cerebral ischemia-
reperfusion occurs, cerebrovascular endothelial cells are ac-
tivated. Meanwhile, platelets and immune cells release a large
number of proinflammatory cytokines, including TNF-α, IL-
6, IL-1β, PAF (platelet activating factor), and complement
activation products substance. TNF-α is a vital role in the
inflammatory network of cytokines and is considered as
the trigger medium of a systemic inflammatory reaction
[46]. It can directly inhibit vascular endothelial cell function,
increase vascular permeability, decrease circulatory resis-
tance, and induce cytokines and adhesion molecules release
like the waterfall, resulting in inflammatory damage cascade
amplification effect, finally, resulting in wall thickening,
stenosis, and cerebral infarction [21, 22]. Through the meta-
analysis, we found XNJI had significant anti-inflammatory
effect. Compared with control group, the TNF-α, IL-6, and
IL-1β levels of XNJI group were lower by 4.13, 119.23, and
228.69 ng/L (Figure 5). In addition, the results showed that
the I² value of IL-6 was 0%, suggesting a relatively reliable
therapy.

Oxidative stress is another reaction after cerebral ischemia,
and the function of free radical scavenging system in the body decreased during cerebral ischemia.
The endogenous antioxidant systems are unbalanced and
produced large amounts of free radicals, leading to the
peroxidation of lipid, protein and nucleic acid, and the
biochemical alteration (SOD ↓, GSH-Px ↓, and MDA↑), and
further led to BBB disruption with secondary vasogenic
edema, activation of apoptosis, and brain infarction [47, 48].
Therefore, the production and release of oxygen free radicals
are the key steps that cause cerebral injury. Scavenging
oxygen free radicals is an important way to treat cerebral
ischemia-reperfusion injury. In theory, block oxidative stress
or act on the key molecules could reduce cerebral ischemia-
reperfusion induced oxidative damage. Our data provide
evidence that XNJI could improve the body’s antioxidant
function after cerebral ischemia-reperfusion (Figure 6),
suggesting that XNJI may reduce the damage of cerebral
ischemia by regulating inflammatory and oxidative stress.

The important outcomes of cerebral ischemia and reper-
fusion injury are neurological deficit score, cerebral infarc-
tion area, brain edema, and neuronal cell apoptosis. Inflam-
matory, oxidative stress, and destroyed BBB could be cause
and effect by each other and lead to cerebral edema, cell
necrosis and activation of apoptosis [49], and brain infarc-
tion, which were manifested as neurological dysfunction in clinic [9]. In the animal experiment, it was tested by
neurological deficit score. STAIR (2009) states that [50]
multiple indicators should be selected in the study of cerebral
ischemia drugs, which should include infarction area and
neurological function; this emphasized the importance of
behavioral outcomes due to its close relationship to late
survival rate clinically. Functional recovery of clinical stroke
patients is a major endpoint indicator [51, 52]. Evidence
showed the beneficial of XNJI on neurological function

| Study or Subgroup | Experimental | Control | Mean Difference | Mean Difference |
|-------------------|--------------|---------|----------------|----------------|
|                   | Mean | SD  | Total | Mean | SD  | Total | Weight | Mean Difference | IV, Random | 95% CI | Mean Difference | IV, Random | 95% CI |
| Chen et al 2000   | 2.1  | 0.79| 10    | 2.98 | 0.96| 10    | 26.3%  | -0.88 [-1.65, -0.11] | -0.88 [-1.65, -0.11] |
| Huang 2012       | 1.024| 0.089| 12 | 1.368 | 0.103| 12 | 26.9%  | -0.34 [-0.42, -0.27] | -0.34 [-0.42, -0.27] |
| Li et al 2016     | 7.84 | 0.89 | 10 | 9.62 | 1.24 | 10 | 26.0%  | -1.78 [-2.73, -0.83] | -1.78 [-2.73, -0.83] |
| Wu 2007          | 35.43 | 4.23 | 23 | 51.55 | 4.68 | 20 | 20.8%  | -16.12 [-18.80, -13.44] | -16.12 [-18.80, -13.44] |
| Total (95% CI)    | 55 | 52 | 100.0% | | | | | | | | 4.13 [-6.68, -1.58] | 4.13 [-6.68, -1.58] |

Heterogeneity: Tau² = 6.28; Chi² = 143.09, df = 3 (P < 0.00001); I² = 98%
Test for overall effect: Z = 3.18 (P = 0.001)

| Study or Subgroup | Experimental | Control | Mean Difference | Mean Difference |
|-------------------|--------------|---------|----------------|----------------|
|                   | Mean | SD  | Total | Mean | SD  | Total | Weight | Mean Difference | IV, Fixed | 95% CI | Mean Difference | IV, Fixed | 95% CI |
| Chen et al 2000   | 207.6 | 70.3 | 10 | 313.9 | 92.9 | 10 | 6.8% | -106.30 [-178.51, -34.09] | -106.30 [-178.51, -34.09] |
| Li and Xie 2011   | 117.29 | 19.12 | 6 | 241.38 | 21.36 | 6 | 67.2% | -124.07 [-147.01, -101.13] | -124.07 [-147.01, -101.13] |
| Huang 2012       | 124.5 | 35.5 | 12 | 234.6 | 54.7 | 12 | 26.0% | -110.10 [-147.00, -73.20] | -110.10 [-147.00, -73.20] |
| Total (95% CI)    | 28 | 28 | 100.0% | | | | | | | | -119.23 [-138.04, -100.43] | -119.23 [-138.04, -100.43] |

Heterogeneity: Chi² = 0.53, df = 2 (P = 0.77); I² = 0%
Test for overall effect: Z = 12.43 (P < 0.00001)

| Study or Subgroup | Experimental | Control | Mean Difference | Mean Difference |
|-------------------|--------------|---------|----------------|----------------|
|                   | Mean | SD  | Total | Mean | SD  | Total | Weight | Mean Difference | IV, Random | 95% CI | Mean Difference | IV, Random | 95% CI |
| Chen et al 2000   | 89.6 | 46.2 | 10 | 135.7 | 51.4 | 10 | 50.0% | -46.10 [-69.93, -3.27] | -46.10 [-69.93, -3.27] |
| Li and Xie 2011   | 268  | 34  | 6 | 698.92 | 50.71 | 6 | 50.0% | -410.92 [-447.58, -374.26] | -410.92 [-447.58, -374.26] |
| Total (95% CI)    | 16 | 16 | 100.0% | | | | | | | | -228.69 [-586.20, 128.83] | -228.69 [-586.20, 128.83] |

Heterogeneity: Tau² = 66133.07; Chi² = 160.84, df = 1 (P < 0.00001); I² = 99%
Test for overall effect: Z = 1.25 (P = 0.21)

Figure 5: Forest plot of comparison: (a) TNF-α; (b) IL-6; (c) IL-1β. I² and P are the criterion for the heterogeneity test, • pooled mean difference, — mean difference, and 95% CI.
Evidence-Based Complementary and Alternative Medicine 9

Figure 6: Forest plot of comparison: (a) SOD; (b) GSH-Px; (c) MDA. $I^2$ and $P$ are the criterion for the heterogeneity test, — pooled mean difference, — mean difference, and 95% CI.

(Figure 3) and cerebral infarction area (Figure 4(a)), which is consistent with clinical reports [25]. At the same time, subgroup analysis showed that XNJI had a better effect on the model of cerebral ischemia-reperfusion injury than the model of permanent cerebral ischemia. However, the heterogeneity still existed that may be related to different dose and duration of XNJI. Additionally, there were a study which had reported that XNJI have a significant effect on ultrastructural of brain when ischemia-reperfusion [17] and three studies reported the alleviation of XNJI on BBB damage [20, 29, 34]; however, we did not conduct a meta-analysis due to its quantitative limitations. The destruction of BBB plays an extremely important role in the process of cerebral ischemia. It is the destruction of BBB that causes the originally innocuous substance into the brain tissue to become harmful substances. Therefore, it is recommended that the BBB research should make a consideration in the further. Moreover, most of the studies included in this study are preventive one-time administration; however, cerebral ischemic stroke is mostly treated with XNJI after onset for one week, clinically. Therefore, it is recommended that study with therapeutic administration and longer administration may be considered in the further.

5.2. Strength. Preclinical efficacy experiments are typically cited to justify the initiation of clinical trials. Our findings contribute to the literature on preclinical design and reinforce our exploratory analysis for the mechanism of XNJI against cerebral ischemia. Moreover, they could eliminate unnecessary repetitive tests and contribute to further study in animal experiments to increase the likelihood of success in future clinical trials. Furthermore, as a traditional Chinese medicine, XNJI is a relatively safe drug. Therefore, it may play a potentially greater role in clinical practice in the future.

5.3. Limitations. The average quality score of studies was 4.5. Many studies have failed to describe their methods in detail, such as randomized trials, blind evaluation of results, and assignment of hidden. Therefore, we recommend that all research published in China should follow a guideline similar to the Consolidated Standards of Reporting Trials (CONSORT) Statement for clinical studies [53]. These strategies will promote the identification and use of many TCPM (e.g., XNJI) outside China. In addition, there are some deviations caused by the following reasons: first, different animal species, drug dose, duration of administration, and method of administration
Table 2: Quality assessment of included studies.

| Study (year) | (1) | (2) | (3) | (4) | (5) | (6) | (7) | (8) | (9) | (10) | score |
|--------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|-------|
| Yan et al. 2017 | √  | UN  | √  | UN  | UN  | √  | √  | √  | UN  | UN  | 4     |
| Li et al. 2016  | √  | UN  | √  | UN  | UN  | √  | √  | √  | UN  | UN  | 5     |
| Chen et al. 2015 | √  | √  | √  | UN  | UN  | √  | √  | √  | UN  | UN  | 6     |
| Wu 2015          | √  | √  | √  | UN  | UN  | √  | √  | √  | UN  | UN  | 6     |
| Zhong et al. 2015 | √  | UN  | √  | UN  | UN  | √  | √  | √  | UN  | UN  | 5     |
| Huang et al. 2014 | √  | UN  | √  | UN  | UN  | √  | √  | √  | UN  | UN  | 5     |
| Ma 2014          | √  | √  | √  | UN  | UN  | √  | √  | UN  | UN  | UN  | 5     |
| Zeng 2013        | √  | √  | √  | UN  | UN  | √  | √  | √  | UN  | UN  | 6     |
| Zhu 2012         | √  | UN  | √  | UN  | UN  | √  | √  | √  | UN  | UN  | 5     |
| Huang 2012       | √  | √  | UN  | UN  | UN  | √  | √  | UN  | UN  | 4     |
| Li and Xie 2011  | √  | √  | UN  | UN  | UN  | √  | √  | UN  | UN  | 4     |
| Guo et al. 2010  | √  | UN  | √  | UN  | UN  | √  | UN  | UN  | 3     |
| Wu 2007          | √  | UN  | √  | UN  | UN  | √  | √  | UN  | UN  | 5     |
| Zhang et al. 2006 | √  | UN  | √  | UN  | UN  | √  | √  | UN  | UN  | 4     |
| Lu 2006          | √  | UN  | √  | UN  | UN  | √  | √  | UN  | UN  | 4     |
| Shen et al. 2004 | √  | √  | UN  | UN  | UN  | √  | √  | UN  | UN  | 3     |
| Wang et al. 2004 | √  | UN  | √  | UN  | UN  | √  | √  | √  | UN  | 5     |
| Zhou et al. 2002 | √  | UN  | √  | UN  | UN  | √  | √  | UN  | UN  | 4     |
| Wan et al. 2001  | √  | √  | UN  | UN  | UN  | √  | √  | UN  | UN  | 4     |
| Cai et al. 2000  | √  | UN  | √  | UN  | UN  | √  | √  | √  | UN  | 5     |
| Fu et al. 2000   | √  | UN  | √  | UN  | UN  | √  | √  | √  | UN  | 4     |
| Chen et al. 2000 | √  | UN  | UN  | UN  | UN  | √  | √  | √  | UN  | 3     |
| Zhang et al. 1997 | √  | UN  | UN  | UN  | UN  | √  | √  | √  | UN  | 4     |

Note: (1) publication in a peer-reviewed journal; (2) statement of temperature control; (3) random allocation to groups; (4) allocation concealment; (5) blinded assessment of outcome; (6) use of anesthetic without significant internal protection of blood vessel; (7) appropriate animal model (aged, healthy, diabetic, or hypertensive); (8) sample size calculation; (9) compliance with animal welfare regulations; (10) statement of potential conflict of interests. UN is unclear.

resulted in some deviation. Second, animal models used in most studies are healthy; however, patients with cerebral ischemia are often associated with diabetes, high blood pressure, hyperlipidemia, and the like. Third, our search strategy includes only Chinese and English databases, leading to certain deviations. Thus, the results should be interpreted with caution.

6. Conclusions

Based on the results of this meta-analysis, the effect of XNJI on cerebral ischemia is encouraging. XNJI may be a promising method to alleviate ischemia-induced brain damage by regulating oxidative stress and inflammatory reaction. Considering being accepted far and wide by practitioners, the experiments with more rigorous experimental design and stronger quality control are required.

Abbreviations

XNJI: Xingnaojing injection
TCPM: Traditional Chinese patent medicine
CNKI: Chinese National Knowledge Infrastructure
VMIS: VIP medicine information system

ARRIVE: Animal Research: Reporting of In Vivo Experiments
MD: Mean difference
CIs: Confidence intervals
$\chi^2$: $\chi^2$-square
CONSORT: Consolidated Standards of Reporting Trials
PAF: Platelet activating factor
SD: Sprague-Dawley
W: Wistar
M: Male
F: Female
P: Permanent
T: Transient
i.p.: Intraperitoneal injection
i.v.: Intravenous injection
c.i.v.: Caudal intravenous injection
NR: Not report
Index ischem/rep(h): Index ischemia and reperfusion in hours
BE: Brain edema
BBB: Blood brain barrier
NDS: Neurological deficit score
CIA: Cerebral infarction area
NCA: Neuronal cell apoptosis
BUC: Brain ultrastructural changes
TNF-α: Brain tumor factor α
IL-6: Interleukin-6
IL-1β: Interleukin-1β
SOD: Superoxide dismutase
MDA: Malondialdehyde
GSH-Px: Glutathione peroxidase.

Conflicts of Interest
The authors declare that they have no conflicts of interest.

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