

Panax notoginseng saponins in the treatment of ischemic stroke—Meta-analysis and systematic review

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Article

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Abstract

Background

Panax notoginseng saponins(PNS)preparation is one of the most commonly used Chinese medicines for treating acute ischemic stroke(AIS)in China. However, compared with the traditional routine western medicine(WM)treatment, the effectiveness and safety of PNS as an auxiliary treatment need to be systematically reviewed.

Methods

The deadline for inclusion is before June 30, 2024. Comparing the randomized controlled trials(RCT)of PNSInclude Xuesaitong and Xueshuantongcombined with WM and WM alone in the treatment of AIS, the two researchers independently extracted the data, used Cochrane Bias Risk Scale to evaluate the quality of the included studies, and used RevMan5.3 for meta-analysis.

Results

In this study, 15 RCT involving 1499 participants were included, and the treatment of patients was evaluated by the National Institutes of Health Stroke Scale(NIHSS). Meta-analysis shows that adding PNS as an auxiliary treatment is more effective in clinical total efficiency [$RR = 1.22, 95\%CI 1.17-1.29$, $P < 0.00001$] compared with simple WM treatment. The included studies reported 49 cases of adverse reactions(ADR), of which 27 cases occurred in the experimental group.

Conclusion

PNS combined with WM is effective in treating AIS, which suggests that it may be a safe and effective alternative and can better improve neurological symptoms. However, due to the limitations of low methodological quality and small sample size, it is suggested that more high-quality RCT are still needed to verify the safety of PNS preparation.

Introduction

AIS is one of the most common cerebrovascular diseases at present, accounting for 70%-80% of all stroke types, which greatly increases the global disease burden^[1, 2]. At present, many achievements have been made in clinical routine treatment of blocked blood vessels and inhibition of platelet aggregation, but due to uncontrollable factors such as treatment time window and drug resistance, the treatment of ischemic stroke patients is limited^[3].

Panax notoginseng (Panax notoginseng [Burkill]) F.H.Chen extracted from the roots of Sanqi have good therapeutic effects on many systems, including nervous system^[4, 5]. According to pharmacological research, PNS preparation has many mechanisms, such as protecting vascular endothelial cells, inhibiting platelet adhesion and aggregation, dissolving thrombus, eliminating free radicals and alleviating edema caused by cerebral ischemia, which are beneficial to the treatment of AIS^[6, 7]. All herbal medicines in the text have been checked against MPNS [http://mpns.kew.org] with a final check date of August 5, 2024.

Methods

1. Literature resources

1.1 Criteria for inclusion

1.1.1 Research type: The types of included literature must be based on RCT, regardless of whether there is a blind method.

1.1.2 Research objects: The subjects met the diagnostic criteria of ischemic stroke formulated by the Fourth National Cerebrovascular Disease Conference, and were confirmed by brain computed tomography [CT] or magnetic resonance imaging [MRI]. There was no restriction on basic clinical conditions such as age, sex and severity of the disease.

1.1.3 Intervention measure: RCTs of PNS combined with conventional WM treatment and conventional WM alone were included. Patients in the control group were treated with conventional WM treatment, including mannitol, atorvastatin calcium, aspirin, clopidogrel, citicoline, etc. Patients in the experimental group were treated with PNS on the basis of control group treatment, including Xuesaitong and Xueshuantong. The drug dosage forms included injection and capsule.

1.1.4 Outcome indicator: All literatures used the total effective rate as the outcome measurement indicator, and the total effective rate $\% = \frac{\text{number of basically recovered patients} + \text{number of significantly improved patients}}{\text{total number of patients}} \times 100\%$. Changes in neurological deficit scores before and after treatment were assessed by the NIHSS. Specific indicators were, basic recovery: NIHSS decreased by more than 90%; significant improvement: NIHSS decreased by 46%-91%; improvement: NIHSS decreased by 18%-46%; no change: NIHSS changed within 18%; deterioration: NIHSS increased by more than 18% or death.

1.2 Criteria for exclusion

1.2.1 Duplicate publications; 1.2.2 The type of study was not clearly stated or the type of study was not a RCT; 1.2.3 The experimental group or control group was interfered by other treatment measures; 1.2.4 The data is incomplete and full text cannot be obtained.

2. Search strategy of literature

Search PubMed, Web of Science, Cochrane Library, Medline, Embase, EBSCO, China National Knowledge Infrastructure Database [CNKI], Wanfang Database, China Science and Technology Journal Database [VIP], Chinese Biomedical Literature Database [CBM]. All articles published up to June 30, 2024 were searched.

For the English databases, we used the combination of subject headings and text words to search, and the search subject headings were "PNS" and "stroke". For the Chinese databases, we used "Sanqi" or "panax notoginseng" or "PNS" or "panax notoginseng total soap" or "panax notoginseng extract" for preliminary search, on this basis, the second search was conducted by using "stroke" or "ischemic stroke" or "cerebrovascular accident" or "acute stroke" or "acute cerebrovascular accident" or "stroke acute stage". The search process did not limit the type of literature and publication time, nor did it limit the language.

After the search strategy was formulated, two investigators independently conducted the literature search. If there was a dispute in the process, they discussed it together and resolved it. If no agreement could be reached, the third investigator intervened.

3. Data extraction and quality evaluation of literatures

The following data were extracted from the included literatures: 1. Basic elements of the literatures [including the first author and the year of publication]. 2. Basic information of patients and whether there were differences between the baseline data of the two groups. 3. Intervention measures. 4. Evaluation indicators of treatment outcomes. 5. Occurrence of ADR.

The methodological quality of the included RCTs were evaluated using the Cochrane Risk Bias Assessment Tool, which included: 1. Randomization sequence generation. 2. Allocation scheme concealment. 3. Blinding of subjects and investigators. 4. Completeness of results data. 5. Whether study results were selectively reported. 6. Whether there were other sources of bias [such as selective reporting]. Each item was classified into low risk, unclear and high risk bias. The evaluation was done independently by two investigators and checked against each other. Any disagreements regarding data extraction and quality evaluation were resolved through discussion, or if agreement could not be reached, by the third investigator.

4. Data statistics

4.1 Selection of efficacy indicators

At present, meta-analysis can only carry out combined analysis of continuous variables and binary variables. According to clinical practice, basic recovery, significant improve and improve are combined as effective, and the rest are ineffective. The effective rates among the study groups are compared and combined.

4.2 Meta-analysis

RevMan5.3 software was used for data synthesis in this literature. Relative risk [RR] was used as analysis statistic for binary variables, mean difference [MD] was used as analysis statistic for continuous variables, and 95% confidence interval [95%CI] was used for each effect size. $P < 0.05$ was considered that the difference between experimental group and control group was statistically significant.

4.3 Heterogeneity test

Forest plots generated by RevMan5.3 software were used for heterogeneity test. The statistics of heterogeneity test within forest plots obeyed distribution. According to $\alpha = 0.1$ test level, if $P < 0.1$ was satisfied, heterogeneity existed among studies. At the same time, I^2 was used for quantitative analysis of heterogeneity, and its significance level was set at 50%, that is, $I^2 > 50\%$ was considered as large heterogeneity between studies, and fixed effect model was used for pooled effect size analysis between studies without heterogeneity, otherwise random effect model was used.

4.4 Sensitivity analysis

The stability of the results was tested by a sensitivity analysis between the random effects model and the fixed effects model.

4.5 Detection of publication bias

If the number of RCTs included is greater than 10, funnel plots will be drawn to assess potential publication bias.

Results

1. Searching result

We identified a total of 3698 search results by keywords, removed 656 duplicates, read titles and abstracts, removed 2592 articles unrelated to the content of this study. Through full-text reading and revalidation of the remaining 450 articles based on inclusion and exclusion criteria, 264 articles were excluded because the interventions in the control group did not meet the requirements (The control group was treated with unconventional WM, such as compound Danshen tablet, Chuanxiongine, Danhong and other traditional Chinese medicine), the outcome indicators of 105 articles did not meet the inclusion criteria, 52 articles were excluded as non-RCTs or unreasonable experimental design, 14 articles could not provide valid data or full text, and 15 eligible studies were included in the final meta-analysis. See Fig. 1 for the literature search flow chart.

2. Study characteristics

The studies included in this study were published in Chinese and published between 2011 and 2022. A total of 15 RCTs included 1499 patients, with 749 patients in the experimental group and 750 patients in

the control group. Most of the patients were middle-aged and elderly, with an average age of 63.37 years, ranging from 38 to 82 years old. There was no difference in clinical baseline data between the two groups in all items($P > 0.05$). In all RCTs, the intervention measures of the experimental group are PNS combined with the same routine WM treatment scheme as the control group. PNS preparation includes Xuesaitong and Xueshuantong, and the daily dosage ranges from 300 to 900mg. Each study includes NIHSS as the standard to evaluate the effect. See Table 1 and Table 2 for details.

Table 1
Characteristics of included trails on PNS for AIS

Study ID	Method	N(E/C)	Age	Intervention	Outcomes	ADR/ADE
Yu 2021 ^[8]	RCT	45/45	E 60–79(69.52 ± 1.48) C 60–78(69.39 ± 1.53)	E XST ¹ 400mg + WM C WM	NIHSS,Inflammatory factor levels,FIB,Blood lipid index	E 4 C 6
Zhang 2020 ^[9]	RCT	58/58	E 45–74(58.24 ± 5.66) C 48–80(62.45 ± 4.21)	E XST ¹ 400mg + WM C WM	NIHSS,Blood rheological index,rCBF,CRP	None
Zhang 2017 ^[10]	RCT	58/58	E 51–78(62.34 ± 10.85) C 51–77(62.19 ± 10.12)	E XST ¹ 400mg + WM C WM	NIHSS,MMSE,ADL,SF-36	Unclear
Chen 2014 ^[11]	RCT	80/80	E 41–79(63.89 ± 8.76) C 38–77(64.13 ± 9.02)	E XST ¹ 10ml + WM C WM	NIHSS	Unclear
Luo 2011 ^[12]	RCT	30/30	E 61.37 ± 2.24 C 62.35 ± 8.76	E XST ¹ 400mg + WM C WM	NIHSS,CRP	E 2 C 1
Qiu 2022 ^[13]	RCT	55/55	E 57–74(66.25 ± 4.24) C 56–76(66.74 ± 4.12)	E XST ² 600mg + WM C WM	NIHSS,BI,Hemodynamic index,Blood rheological index	Unclear
Notes: E represents experimental group; C represents control group; XST ¹ represents Xuesaitong; XST ² represents Xueshuantong; WM represents conventional western medicine treatment, such as Atorvastatin calcium, Mannitol, Aspirin et al.						

Study ID	Method	N(E/C)	Age	Intervention	Outcomes	ADR/ADE
Wang 2021 ^[14]	RCT	43/43	E 50–72(62.4 ± 4.8) C 52–71(62.4 ± 4.8)	E XST ² 300mg + WM C WM	NIHSS,Serological indicators	E 5 C 3
Kang 2021 ^[15]	RCT	57/57	E 52–81(67.35 ± 4.26) C 55–82(66.83 ± 4.45)	E XST ² 900mg + WM C WM	NIHSS,Blood rheological index,Inflammatory factor levels,Indicators of neural function	E 9 C 8
Luo 2021 ^[16]	RCT	50/50	E 52–79(62.8 ± 9.2) C 52–79(62.4 ± 9.4)	E XST ² 525mg + WM C WM	NIHSS,MMSE,ADL,WHO-QOL, Blood rheological index	E 6 C 4
Cui 2020 ^[17]	RCT	25/25	E 41–69(53.2 ± 4.9) C 42–67(52.6 ± 4.2)	E XST ² 500mg + WM C WM	NIHSS,Modified BI,Blood lipid index	None
Zhang 2014 ^[18]	RCT	43/43	E 66.5 ± 5.9 C 68.3 ± 8.1	E XST ² 500mg + WM C WM	NIHSS,NO,ET-1	E 1 C 0
Wei 2019 ^[19]	RCT	41/41	E 50–74(62.83 ± 4.17) C 50–75(62.79 ± 4.23)	E XST ² 500mg + WM C WM	NIHSS,Inflammatory factor levels	Unclear
Notes: E represents experimental group; C represents control group; XST ¹ represents Xuesaitong; XST ² represents Xueshuantong; WM represents conventional western medicine treatment, such as Atorvastatin calcium, Mannitol, Aspirin et al.						

Study ID	Method	N(E/C)	Age	Intervention	Outcomes	ADR/ADE
Chen 2018 ^[20]	RCT	50/50	E 53–72(60.3 ± 3.2) C 52–72(59.5 ± 3.7)	E XST ² 300mg + WM C WM	NIHSS	Unclear
Tan 2018 ^[21]	RCT	66/67	E 50–72(62.8 ± 5.2) C 52–71(63.41 ± 4.8)	E XST ² 500mg + WM C WM	NIHSS,Inflammatory factor levels	None
Zhang 2016 ^[22]	RCT	48/48	E 50–74(67.38 ± 3.17) C 51–76(68.52 ± 3.64)	E XST ² 300mg + WM C WM	NIHSS,BI,MRS,Blood rheological index	Unclear
Notes: E represents experimental group; C represents control group; XST ¹ represents Xuesaitong; XST ² represents Xueshuantong; WM represents conventional western medicine treatment, such as Atorvastatin calcium, Mannitol, Aspirin et al.						

Table 2
Clinical study effect

Study ID	Effective population of experimental group	Total population of experimental group	Effective population of control group	Total population of control group	Effective rate(E/C)‰
Yu 2021	42	45	34	45	93.33/75.56
Zhang 2020	55	58	46	58	94.83/79.31
Zhang 2017	56	58	49	58	96.55/84.48
Chen 2014	66	80	54	80	82.50/67.50
Luo 2011	28	30	21	30	93.33/70.00
Qiu 2022	49	55	40	55	89.09/72.73
Wang 2021	40	43	33	43	93.02/76.74
Kang 2021	49	57	38	57	85.96/66.67
Luo 2021	48	50	37	50	96.00/74.00
Cui 2020	23	25	17	25	92.00/68.00
Zhang 2014	38	43	30	43	88.37/69.77
Wei 2019	37	41	30	41	90.24/73.17
Chen 2018	47	50	41	50	94.00/82.00
Tan 2018	52	66	42	67	78.79/62.69
Zhang 2016	44	48	39	48	91.67/81.25

3. The methodological quality of the included studies

Cochrane risk bias tool was used for research and analysis. Among them, 9 studies showed that the generation of random sequence was low risk, using random number table method or coin toss method. 1 study showed that the generation of random sequence was high risk, and it was allocated according to the single and double numbers of admission. The rest studies did not elaborate on the generation method of random sequence. 8 studies explicitly mentioned that the subjects signed the informed consent form of patients and their families, so they were all assessed as high risk, and all the studies did not clarify the blindness of the researchers. In addition, no research shows whether the allocation scheme is hidden. The results and data of the experiments included in this meta-analysis are complete, and there is no selective report of the research results. More details about these studies are shown in Fig. 2 and Fig. 3.

4. Effects of interventions

4.1 Heterogeneity test

After the heterogeneity test, $I^2 = 0\% < 50\%$, and the $P = 0.99 > 0.1$ of the Q test, it is suggested that the heterogeneity among the selected literatures in this study is not statistically significant, and the fixed effect model can be selected for meta-analysis.

4.2 The result of the combination of effect values

The RR value of 15 studies was 1.22, and the $95\%CI$ was 1.17–1.29, which was statistically significant. The statistical significance test $Z = 8.15$, $P < 0.00001$, suggesting that the effective situation of combined PNS in treating AIS was better than that of the control group. See the following forest plot for details(Figure 4).

4.3 Sensitivity analysis

In order to confirm the stability of the total clinical effective rate, we eliminated the results with the maximum weight and the minimum weight respectively, and changed from the fixed effects model to the random effects model. After removing the most weighted item(Chen 2014), the result is $RR = 1.22$, $95\%CI$ is 1.16–1.29, $P < 0.00001$, and after removing the least weighted item[Cui 2020], the result is $RR = 1.22$, $95\%CI$ is 1.16–1.28, $P < 0.00001$, the result of changing the model is $RR = 1.21$, and the $95\%CI$ is 1.16–1.27, $P < 0.00001$. There is no obvious diversity in the results, so the sensitivity of this study is not high.

4.4 Funnel plot analysis

Meta-analysis is essentially an observational study, and bias may occur in every step of analysis, among which publication bias is the most common. Drawing a funnel plot can help to identify whether there is publication bias. In this study, the RR value of 15 studies is taken as the abscissa, and the differential coefficient of RR value is taken as the ordinate. The funnel plot analysis shows that publication bias is not detected from the symmetrical funnel plot, as shown in Fig. 5.

Discussion

Stroke has the characteristics of high incidence, high disability rate, high mortality rate, high recurrence rate and high economic burden, among which AIS accounts for about 70%-80% of the whole, belonging to the most common type of stroke^[1, 2]. AIS refers to the process of cerebral ischemia and hypoxia caused by arterial stenosis or occlusion, which leads to serious damage to the central nervous system(CNS). It is also called acute cerebral infarction“ACI”. It is very important to intervene in ACI early and actively. At present, based on the pathophysiological mechanism of ACI, the clinical treatments for ACI mainly include intravenous thrombolysis and mechanical embolectomy. Intravenous thrombolysis can improve microcirculation and restore blood supply in ischemic area through recanalization of blood vessels, which can significantly improve the prognosis of patients' nervous system. However, because the time window of intravenous thrombolysis is limited to 4.5 hours, less than 3% of patients can benefit from this method^[1, 23, 24]. Mechanical thrombectomy is mainly aimed at patients with large vascular occlusion, which has attracted wide attention because of its advantages of rapid vascular recanalization, low bleeding conversion rate and long treatment time window. However, this method belongs to invasive treatment, and it is inevitable to damage the vascular wall by minimally invasive surgery based on physical or mechanical principles^[25].

The application of antiplatelet drugs such as aspirin and clopidogrel is universal and extensive in clinic. By inhibiting platelet aggregation, the symptoms can be relieved and the condition can be prevented from getting worse. However, the use of these drugs will increase the incidence of cardiovascular and cerebrovascular events again, which is called aspirin resistance(AR)or clopidogrel resistance“CPGR”^[26, 27]. Therefore, it is necessary to find an effective and safe alternative therapy to further improve the prognosis of patients with ACI. With the modernization of traditional Chinese medicine“TCM”and the increasing research and development of TCM, the application of TCM in ACI has become a new choice.

PNS are the main bioactive components of Panax Notoginseng, which contain 20 different saponins such as ginsenoside Rb1, Rd, Rg1, Re and notoginsenoside R1. Different saponins have different neuroprotective mechanisms^[28]. Among them, ginsenoside Rg1 increases the speed of ATP production, improves the oxidative respiration function of cells and improves energy metabolism^[29].

Notoginsenoside R1 can prevent the generation of oxidative stress and reduce the generation of free radicals in ischemic areas, thus protecting brain tissue. At the same time, notoginsenoside R1 can also reduce the expression of inflammatory factors to inhibit inflammatory response^[30, 31]. In addition to the above effects, antithrombosis and inhibition of platelet aggregation are the most important clinical effects of PNS on ACI, which can improve the blood circulation and oxygen supply in the infarcted area and reduce nerve damage without increasing the risk of bleeding and other adverse reactions^[32–34]. The synergistic effect of many mechanisms may be the reason why PNS have obvious advantages in ACI.

Through systematic review, we have made clear the therapeutic effect of PNS on ACI, which can reduce the symptoms of neurological deficit and improve the total effective rate of drug treatment by promoting the repair of neurons, glial cells and microvessels after cerebral ischemia^[35, 36]. In this study, Xuesaitong and Xueshuantong, which are widely used in clinic at present, are used as auxiliary treatment methods to describe the positive role of PNS in ACI more comprehensively and scientifically, and provide supporting evidence for the application of PNS in the treatment of ACI patients. Adverse reactions caused by PNS have also been reported, including headache, dry throat, palpitation, itching, rash and even anaphylactic shock. At present, it is believed that large dose of PNS is the main cause of adverse reactions. According to the drug application instructions, the daily dosage of PNS should not exceed 400mg, and the continuous dosage should not exceed 15 days^[37]. Therefore, it is very important for clinical drug evaluation. Strictly grasp the usage and dosage, strengthen drug monitoring, closely observe drug reactions, and reduce joint drug use.

Although this study shows that PNS is effective as a treatment for ACI, the quality of the included research methodology is not ideal. None of the studies described the hidden situation of distribution scheme in detail, and the implementation of blind method was not exact. The number of patients included in various RCTs was small, so large-scale and well-designed RCTs were needed to provide high-quality evidence to further confirm the clinical efficacy and safety of PNS.

Conclusion

In this meta-analysis, PNS preparation combined with routine WM treatment has a significant effect on ACI patients, and does not increase the risk of adverse reactions. It is suggested that PNS preparation may be a safe and effective alternative therapy to improve the prognosis of ACI, which is worthy of clinical application.

Declarations

Competing interests:

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Author contribution statement:

Danjie Fan: Data acquisition and analysis; Draft the main content of the manuscript;

Shuyue Song: Data acquisition and analysis; Draw the figures and tables presented in the text;

Xiangyu Ji: Data collection and collation;

Dachuan Li: Data collection and collation;

Yuyang Zhao: Data collection and collation;

Kunming Xie: Study design and conception; Paper revision and guidance;

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Data Availability

The datasets used during the current study are available from the corresponding author on reasonable request.

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Figures

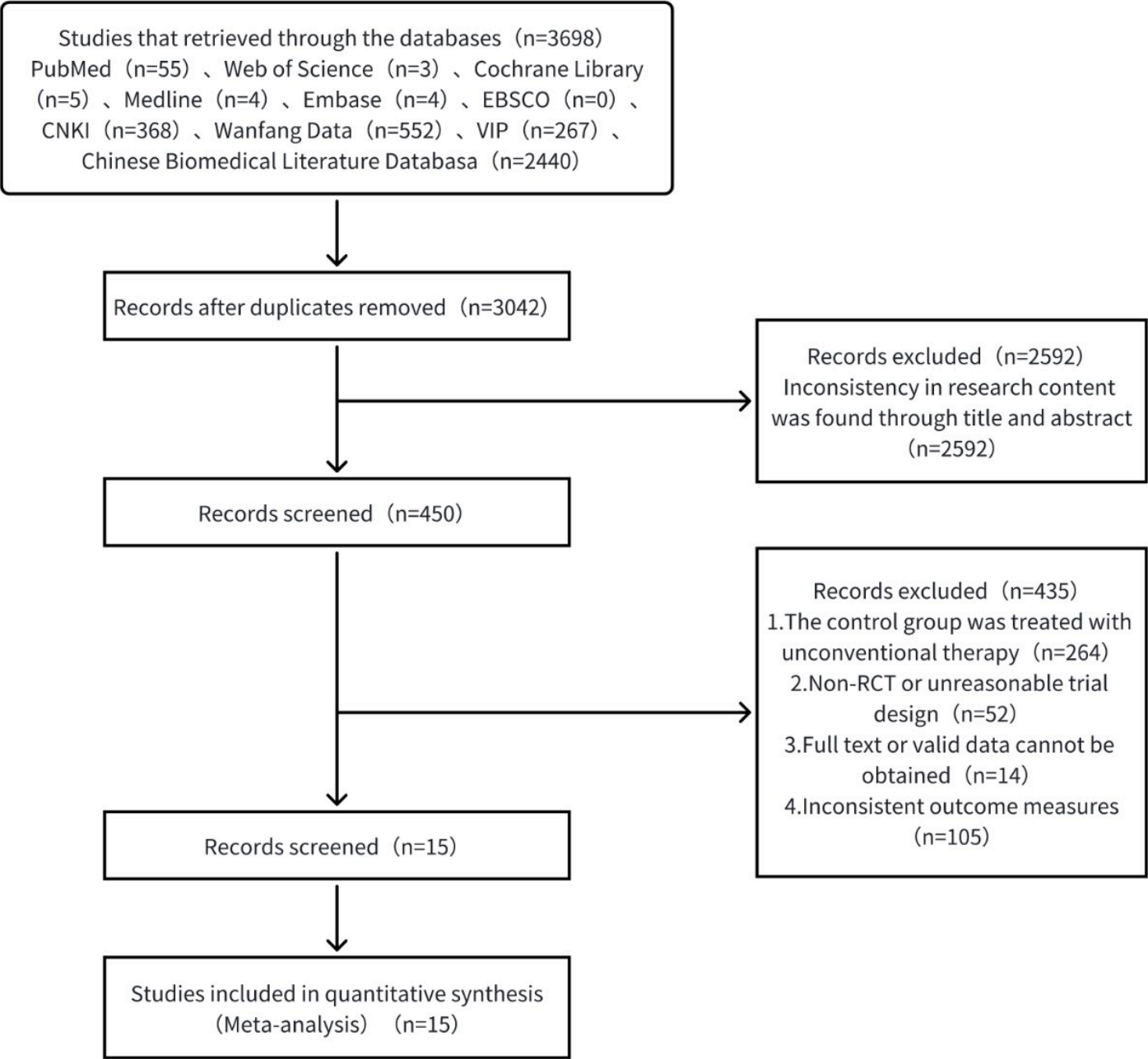


Figure 1

Literature Search Flow Chart

Chen 2014	?	?	?	?	+	+	+
Chen 2018	+	?	?	?	+	+	+
Cui 2020	?	?	?	?	+	+	+
Kang 2021	+	?	?	?	+	+	+
Luo 2011	+	?	?	?	+	+	+
Luo 2021	?	?	?	?	+	+	+
Qiu 2022	+	?	?	?	+	+	+
Tan 2018	+	?	?	?	+	+	+
Wang 2021	+	?	?	?	+	+	+
Wei 2019	+	?	?	?	+	+	+
Yu 2021	?	?	?	?	+	+	+
Zhang 2014	?	?	?	?	+	+	+
Zhang 2016	?	?	?	?	+	+	+
Zhang 2017	+	?	?	?	+	+	+
Zhang 2020	+	?	?	?	+	+	+
Random sequence generation (selection bias)							
Allocation concealment (selection bias)							
Blinding of participants and personnel (performance bias)							
Blinding of outcome assessment (detection bias)							
Incomplete outcome data (attrition bias)							
Selective reporting (reporting bias)							
Other bias							

Figure 2

Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

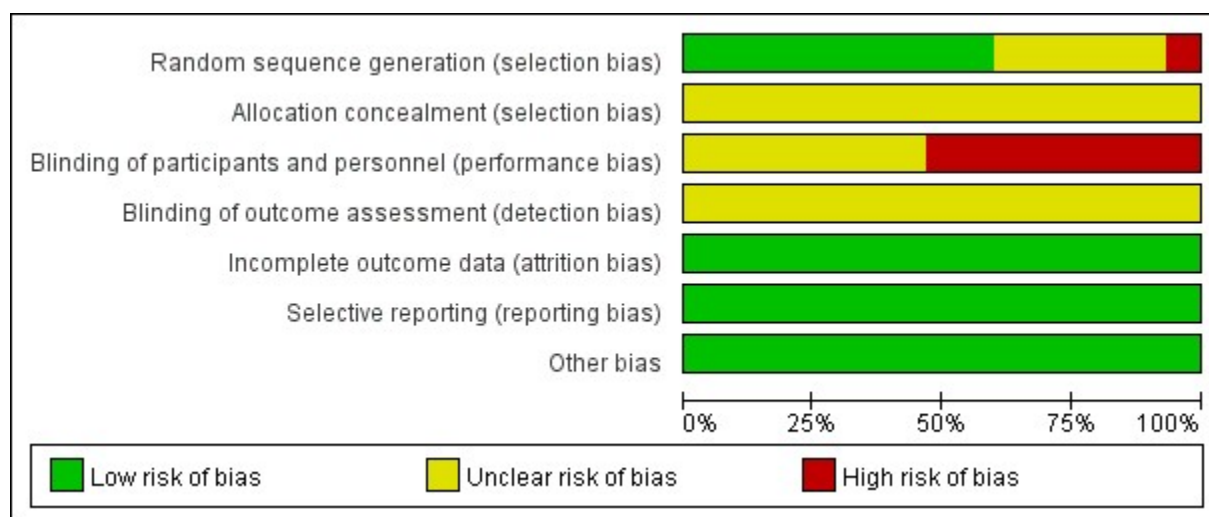


Figure 3

Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

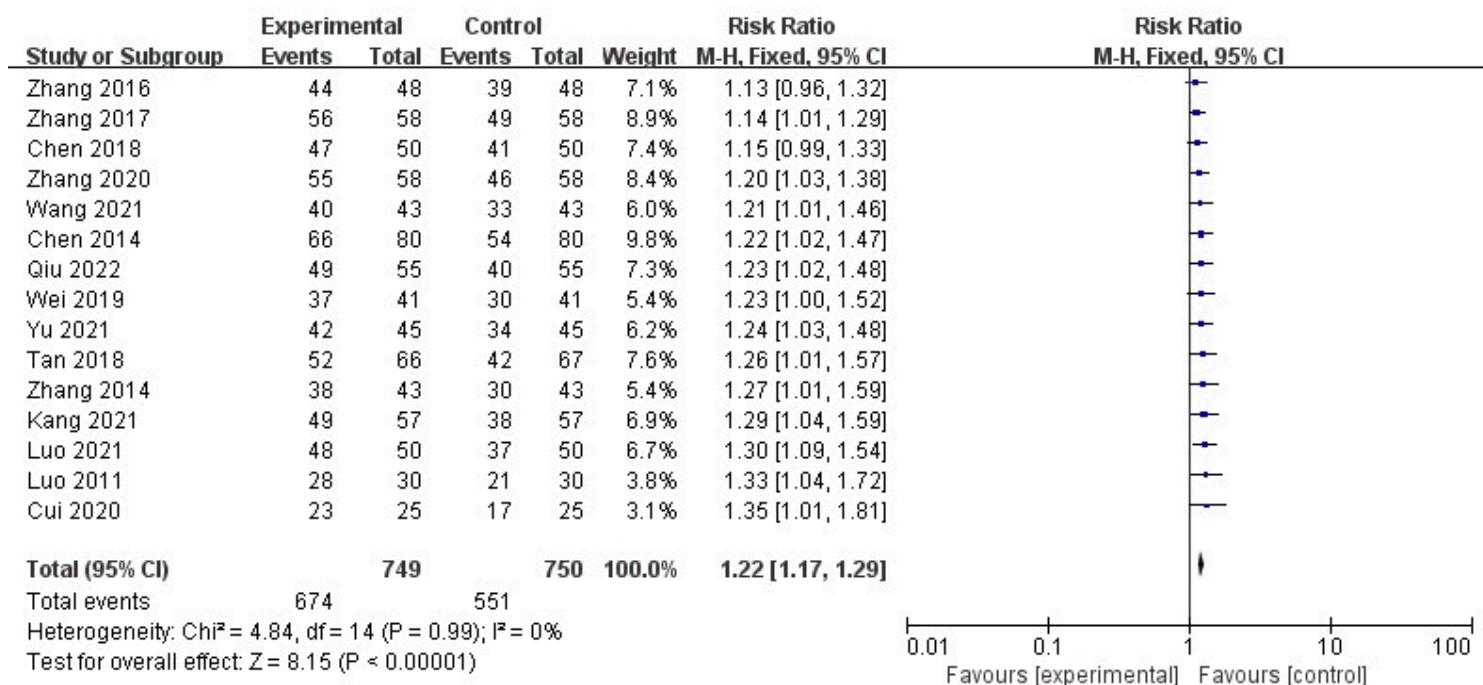


Figure 4

Results of the meta-analysis visualized in a forest plot. Forest plot adopted *RR* and its corresponding *95%CI* based on the fixed effects model.

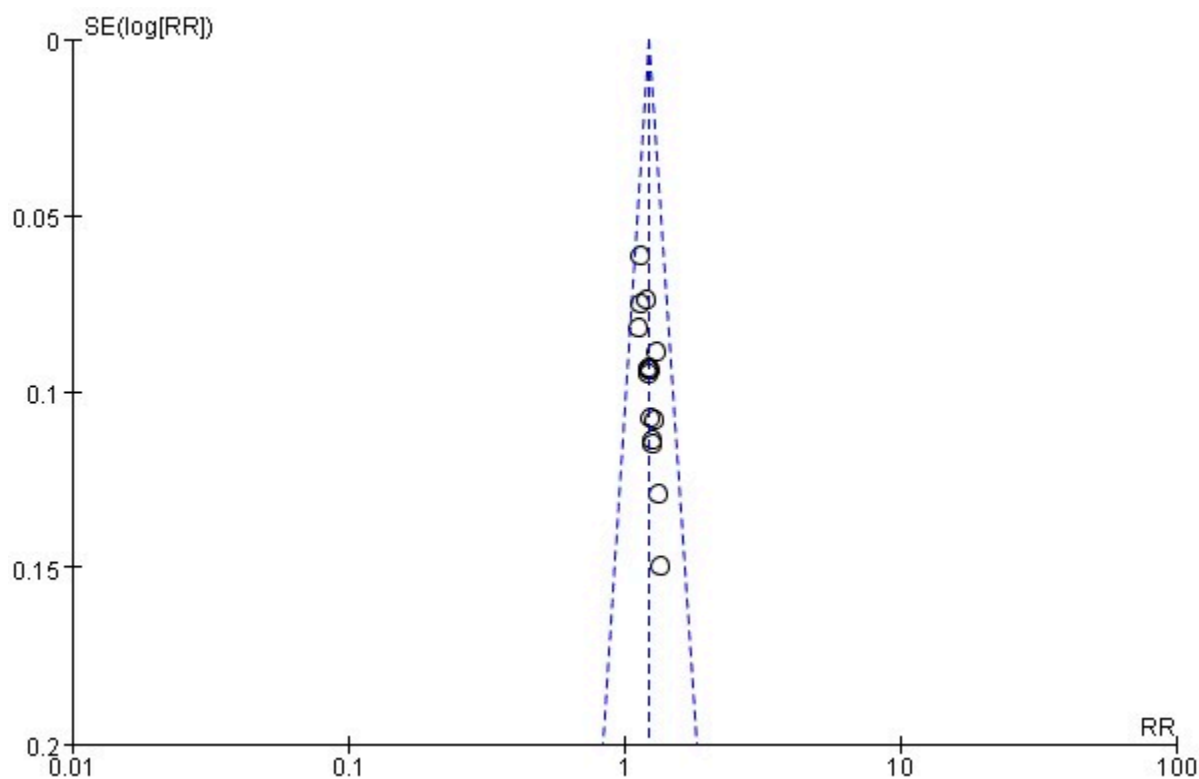


Figure 5

Assessing of publication bias in a funnel plot. No publication bias could be detected from the symmetrical funnel plot.