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Therapeutic effect of angelica and its compound formulas for hypertension and the complications: Evidence mapping

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ABSTRACT

Background: Hypertension is one of the common diseases, which brings heavy burden to human race. Currently, western medication is in absolutely dominant position in the treatment of hypertension, but it maintains for a short time and there are various side effects and drug tolerance. Therefore, Chinese medicine has attracted great attention in the treatment field of hypertension, and angelica is one of the most frequently used herbs.
Objectives: In order to give some inspiration to researches in these fields, this article presents the current research status of angelica and its compound formulas treating hypertension and its complications with evidence mapping.
Methods: Main databases were systematically searched, and researches about angelica or its compound formulas containing angelica treating hypertension or its complications were included. EXCEL 2013 was used to integrate and process the data, and the result is showed intuitively with the bubble diagram.
Results: 49 RCTs were included after screening. The articles recruited were published with a rising trend along with time. Of the 49 RCTs, there is the outcome measure of general the efficacy in the result part in 34 RCTs (69.4%), and all the clinical effective rate in the angelica intervention group is significantly higher than the control group. There is the outcome measure of reduction of MAP in the result part in 28 RCTs, and 27 RCTs (96.4%) showed that the angelica intervention group is significantly improved than the control group while 1 (3.6%) showed no significant differences. There is the outcome measure of efficacy of target organ protection in the result part in 26 RCTs, and 25 RCTs (96.2%) showed that there is significant difference between the angelica intervention group and the control group. Of the 49 RCTs, there is the outcome measure of adverse effects in the result part in 17 RCTs. 14 RCTs (82.4%) reported no adverse effects, 2 RCTs (11.8%) reported adverse effects rate as lower than 10%, and 1 RCT (7.1%) reported adverse effects rate as higher than 40%.
Conclusion: Current research with low quality has revealed that angelica is effective in reduction of MAP and target organ protection and the adverse effects rate is low, and the effectiveness and safety of angelica needs to be proved by further researches with high quality. Researches of high quality are needed to provide scientific evidence for angelica in treating hypertension and its complications.

Abbreviations: CBM, Chinese biomedical literature database; CNKI, Chinese national knowledge infrastructure; AMSTAR, a measurement tool to assess systematic reviews; MAP, mean artery pressure; ROB, risk of bias; RCTs, randomized controlled trials

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Introduction

Hypertension is one of the common diseases and an important reason of death and disability in human race (Houston, 2015). Meanwhile, it is the main risk factor of ischemic heart disease, stroke, heart failure, chronic renal disease, cognitive decline and premature death (Linden, 2011). Currently, western medications for hypertension include diuretics, α-receptor antagonist, angiotensin II receptor blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, which is in absolutely dominant position (Editor, 2016; Jiaojiao, 2016; Yuan, 2018). Despite of the obvious effects, western medications maintains for a short time and there are various side effects and drug tolerance (Ran et al., 2014). Therefore, it's necessary to explore and search for a new drug for hypertension. Many experts carried out active exploration in the field of complementary and alternative medicine. It was showed that, among the Chinese herbs treating hypertension, angelica is one of the most frequently used herbs (Yongmin et al., 2014), which is widely used in the clinic in the forms of extraction or compound ingredients.

Derived from systematic evaluations for complementary and alternative medicine in Yale University, evidence mapping is a research method consisting of comprehensive lookup, scientific analysis, systematic summary and high generalization, which is able to accurately show the whole picture of the study (Katz et al., 2003). Because of the unique advantage in presenting the status of evidence system (Pgcerthsc et al., 2011), evidence mapping is currently used in related researches (Headspace, 2011; Lun et al., 2011). Some evidence mapping articles have been published in chinese medicine fields like acupuncture, Taiji and massage (Hempel et al., 2014; Miake-Lye et al., 2016), but there's none evidence mapping researches about Chinese herbs. In order to give some inspiration to researches in these fields, this article presents the current research status of angelica and its compound formulas treating hypertension and its complications with evidence mapping.

Method

Literature resources

Cochrane, Web of science, PubMed, Embase, CBM (Chinese Biomedical Literature Database), WanFang Database, CNKI (Chinese National Knowledge Infrastructure) were systematically searched. Some complementary search was done with Google Scholar. The time limit of retrieval is from the foundation time of the databases till February 2018. Search strategy can be seen in Appendix A.

Inclusive and exclusive criteria

Inclusive criteria: researches about angelica or compounds containing angelica treating hypertension or its complications, mainly systematic reviews and randomized controlled trials.

Exclusive criteria: redundant publication, fundamental researches, mix researches with multiple intervention measures, meeting abstracts.

Literature screening and quality evaluation

Two researchers carry out primary literature screening independently before a face to face confirmation. When there's disagreement, consult third party to an ultimate agreement. Basic information was extracted in the same way. Recruited systematic reviews were evaluated with AMSTAR (Shea et al., 2007), and randomized controlled trials were evaluated with bias risk assessment toll of Cochrane (Higgins, 2009).

Outcome measures

The main outcome measures are: clinical efficacy, efficacy of target organ protection, reduction of MAP (mean artery pressure), adverse effects rate.

Clinical efficacy is defined differently in each research. When the clinical effective rate in the angelica intervention group is higher than the control group and there's significant difference, the angelica intervention is effective, or else, it's ineffective.

Efficacy of target organ protection is determined by the changes of the organ related biochemical indicators before and after the interventions. When the target organ protection values in the angelica intervention group are superior to the control group and there's significant difference, the angelica intervention is effective, or else, it's ineffective.

Definition of MAP: mean artery pressure of a whole cardiac cycle. For researches in which there's no MAP but systolic and diastolic pressure, calculate the MAP with the following formula. MAP = diastolic pressure + 1/3(systolic pressure-diastolic pressure) (Gengying, 1989).

Definition of adverse effects rate: percentage of patients with adverse effects in the whole group.

Statistic analysis

EXCEL 2013 was used to integrate and process the data, and the result is showed intuitively with the bubble diagram.

Result

Basic characteristics of included researchers

Till February 2018, 3968 articles were found and 49 RCTs were included after screening. None systematic review or Meta analysis were included. The screening process can be seen in Fig. 1. The articles recruited were published from 1999 to 2017. The number of studies published in 2014 (7 studies), 2015 (7 studies), 2016 (7 studies) is the most, 2.6 studies published in a year on average, which can be seen in Fig. 2. Basic characteristics of included researchers can be seen in Table 1.

18 Chinese medicine treatment principles were covered in the included researchers, such as supplementing qi and activating blood, supplementing qi and nourishing blood, *etc.* 18 principles and number of corresponding research can be seen in Fig. 3.

Evidence mapping

Each bubble corresponds to one included RCT research. The size, color and position of the bubbles were used to indicate the current research status of angelica and its compound formulas treating hypertension. The size of the bubbles indicates the sample size, and the color of the bubbles indicates the quality of the researches. There are 6 items in the standards of ROB, and in each item, there're three evaluation results: ‘low bias’, ‘unclear’, ‘high bias’. In order to quantify the risk of bias evaluation results, we calculate ‘low bias’ as ‘1 point’, and add up the total score of all the items for each article. Articles with total score of 1 or 2 are categorized as researches of low quality and revealed as red color, articles with total score of 3 or 4 are categorized as researches of middle quality and revealed as yellow color, articles with total score of 5 or 6 are categorized as researches of high quality and revealed as green color. In the included researchers, according to the Chinese medicine properties, the intervention principles are divided into 18 types: supplementing qi and activating blood; supplementing qi and nourishing blood; supplementing qi, nourishing yin and activating blood; supplementing kidney and activating blood; supplementing and activating blood; angelica alone, dissolving phlegm and activating

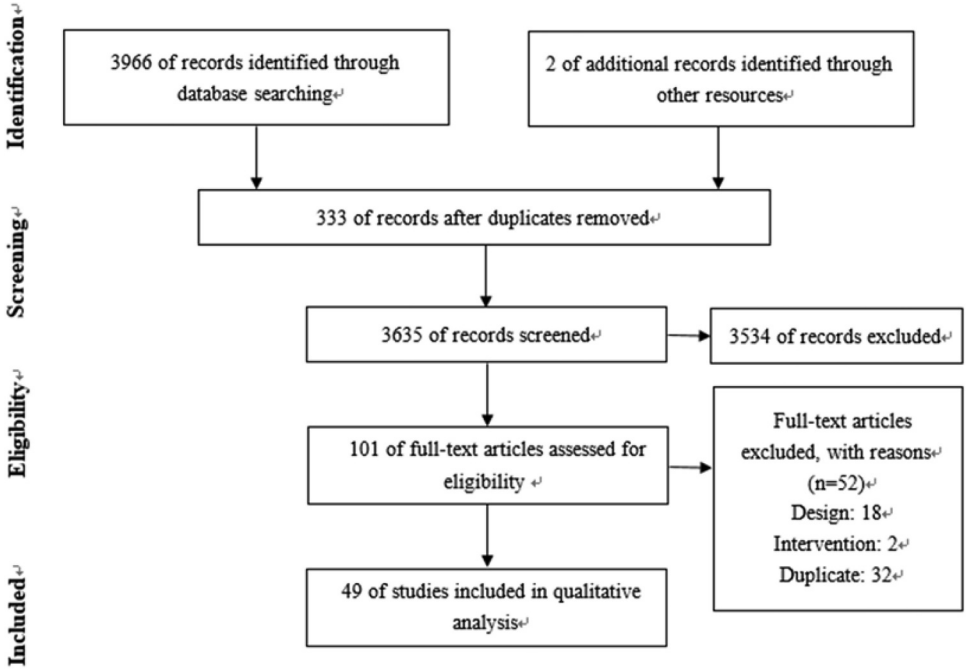

Fig. 1. Screening process.

blood; activating blood; activating blood and dissolving stasis; activating blood and draining dampness and clearing heat; regulating qi and activating blood; regulating qi, nourishing yin and activating blood; calming liver and activating blood; dispelling stasis and dissolving phlegm, dispelling wind and unblocking the collaterals; warming yang and activating blood; warming yang, regulating qi and activating blood; nourishing yin and activating blood. In the bubble diagram, the vertical coordinate corresponds to Chinese medicine properties in the researches, and the horizontal coordinate corresponds to intervention measures (in Fig. 3) or the efficacy score of angelica treating hypertension (in Figs. 4–6). In Fig. 4, it corresponds to reduction of MAP, adverse effects rate in Fig. 5, and efficacy of target organ protection in Fig. 6. The coordinate of each bubble corresponds to its research information.

Clinical efficacy

Of the 49 RCTs, there is the outcome measure of general the efficacy in the result part in 34 RCTs (69.4%), and all the clinical effective rate in the angelica intervention group is significantly higher than the control group. In the 34 researches, most of the intervention measures are compound preparation combined with western medicine (25, 73.5%), and most of the Chinese medicine property type are activating blood and dissolving stasis (7, 20.1%). (Seen in Fig. 4)

Reduction of MAP (mean artery pressure)

Of the 49 RCTs, there is the outcome measure of reduction of MAP in the result part in 28 RCTs, and 27 RCTs (96.4%) showed that the angelica intervention group is significantly improved than the control group while 1 (3.6%) showed no significant differences. In the 28 researches, the MAP reduction results are: in 3 (10.7%) researches, the MAP was reduced by 8–10 mmHg; in 23 (82.1%) researches, the MAP was reduced by 10–30 mmHg, and in 2 (7.1%) researches, the MAP was reduced by 30–50 mmHg. (Seen in Fig. 5)

Efficacy of target organ protection

There is the outcome measure of efficacy of target organ protection

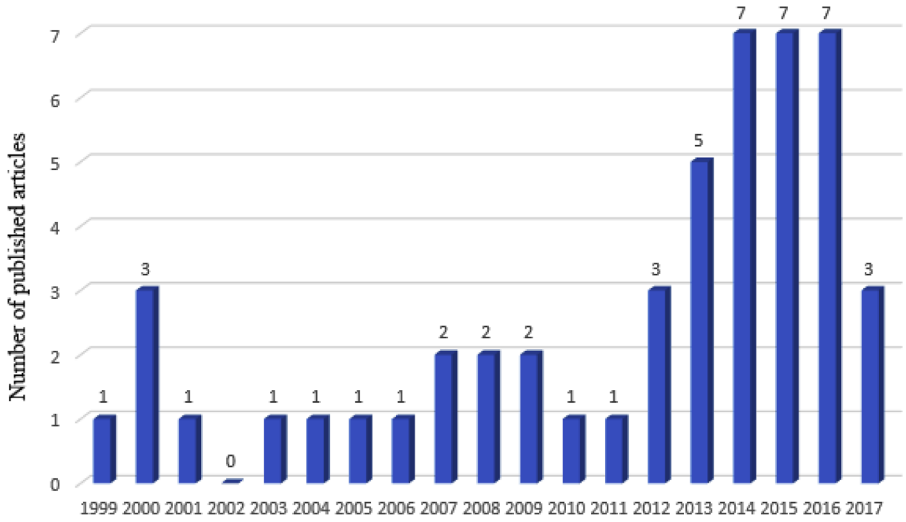

Fig. 2. Published articles in each year.

Table 1
Published years of the included articles.

Main characteristics of the included RCTs	RCTs (n)	Percentage (%)
Main outcome index		
Effectiveness	34	69
Adverse reaction rate	17	35
Target organ protection	26	53
Mean arterial pressure reduction	28	57
Hypertension type		
Primary hypertension	7	14
Secondary hypertension	4	8
Unclear	30	61
Hypertension complications		
Premonitory Symptom of Apoplexy	1	2
Hypertension with depression	1	2
Hypertensive kidney injury	1	2
Chronic obstructive pulmonary disease with pulmonary hypertension	1	2
Hypertensive cerebral hemorrhage	1	2
Chronic nephritis	1	2
Chronic kidney disease	1	2
Diabetic hypertension	1	2
Hypertension with hyperuricemia	1	2
Diabetes mellitus with hypertension	1	2
Hypertensive headache	1	2
Primary hypertension with anxiety	1	2
Interventions		
Compound preparation	12	24
Angelica injection	5	10
Compound preparation combined with western medicine	31	63
Compound preparation combined with acupuncture therapy	1	2
The quality of RCT		
0 point	1	2
1 point	30	61
2 points	18	37

in the result part in 26 RCTs, and 25 RCTs(96.2%) showed that there is significant difference between the angelica intervention group and the control group, while 1 (3.8%) showed no significant differences. The target organs in the researches are: brain (4,15.4%), kidney (9, 34.6%), cardio-vascular (12, 46.2%) and kidney and cardio-vascular (1, 3.8%). (Seen in Fig. 6)

Adverse effects rate

Of the 49 RCTs, there is the outcome measure of adverse effects in the result part in 17 RCTs. 14 RCTs (82.4%) reported no adverse effects, 2 RCTs (11.8%) reported adverse effects rate as lower than 10%, and 1 RCT (7.1%) reported adverse effects rate as higher than 40%. (Seen in Fig. 7)

Discussion

The result of this article has showed the characteristics of angelica and its compound formulas in the treatment field of hypertension and its complications. In the aspect of clinical efficacy, despite of the obvious effect, most of the intervention measures are compound preparations of angelica; in most researches, angelica and its compound preparations were used combined with western medicine in the treatment of hypertension and its complications, and in a few researches, acupuncture was combined as an intervention measure. In the aspect of reduction of MAP (mean artery pressure), angelica and its compound preparations combined with western medicine showed prominent advantage over western medicine alone for 10–30 mmHg, but angelica or its compound preparation alone showed limited effect. In the aspect of target organ protection, angelica and its compound preparations showed great protection for brain, kidney and cardio-vascular. There were big samples in the researches of renal and cardio-vascular protection. In the aspect of adverse effects, angelica and its compound preparations have few adverse effects. To sum it up, angelica and its compound preparations have great effects in MAP reduction and target organ protection, and there are few adverse effects. However, the mechanism is still unclear, which is a big barrier for further spreading in the clinic. In further researches, we should work on the fundamental exploration of the mechanism, for example, the protection mechanism for organs like brain and kidney.

The quality evaluation of the researches has showed that, all the researches are of low quality, mainly caused by design defects and insufficient sample. All the researches in the future should be designed scientifically and multi-centered and big- sample researches are needed to confirm the efficacy and safety.

According to the result of our study, although there are no serious adverse reactions in the current study, the sample size of studies included are small. Thus, large-scale studies are needed to investigate possible serious adverse reactions. There is still a lack of research on comparison between compound preparations or a comparison between

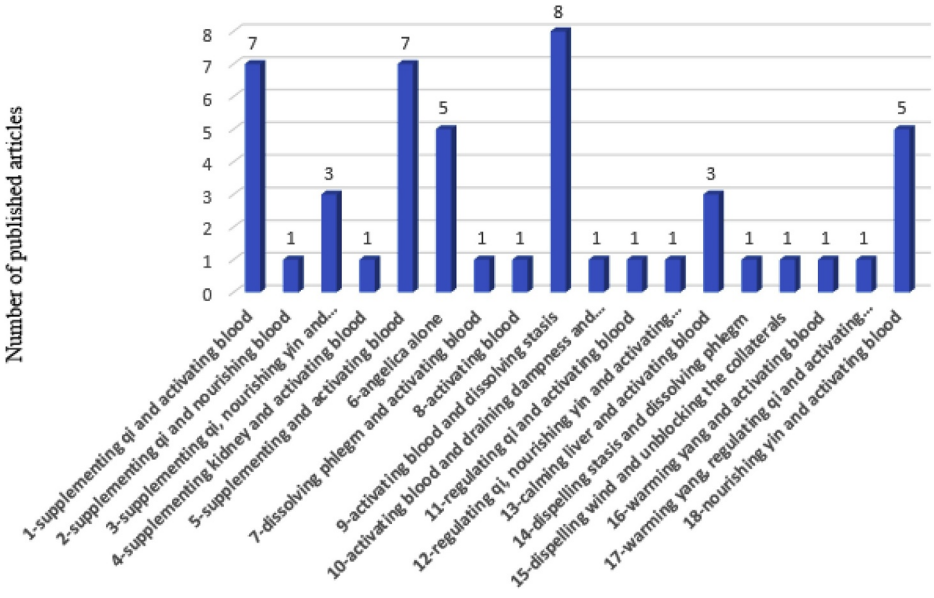

Fig. 3. Intervention principles and number of corresponding research.

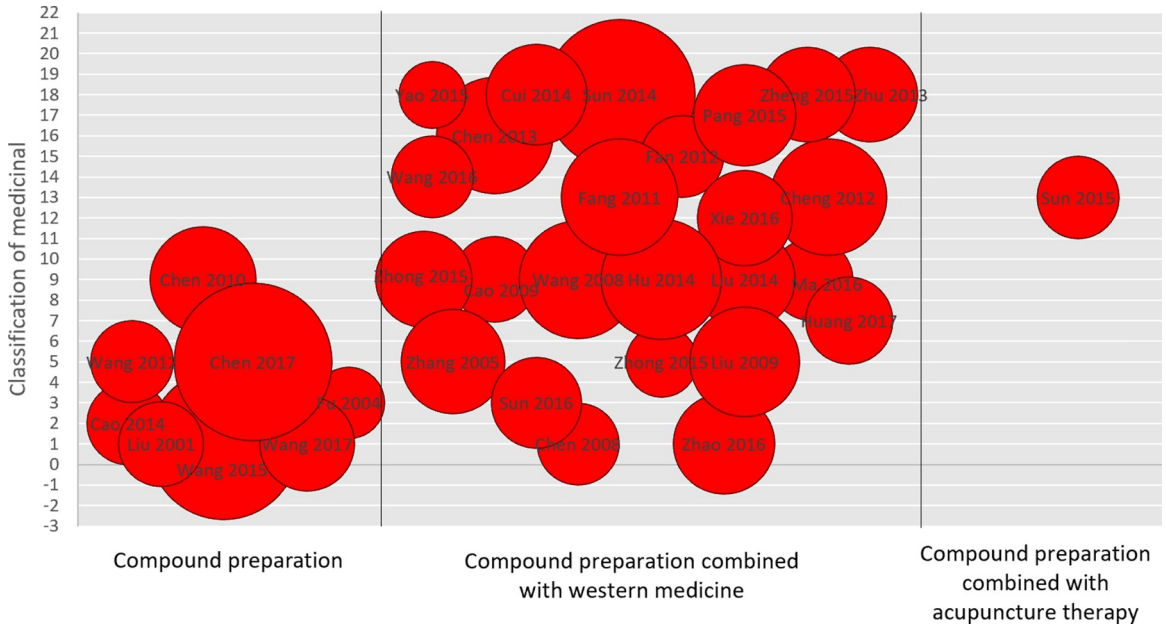

Fig. 4. Clinical efficacy.

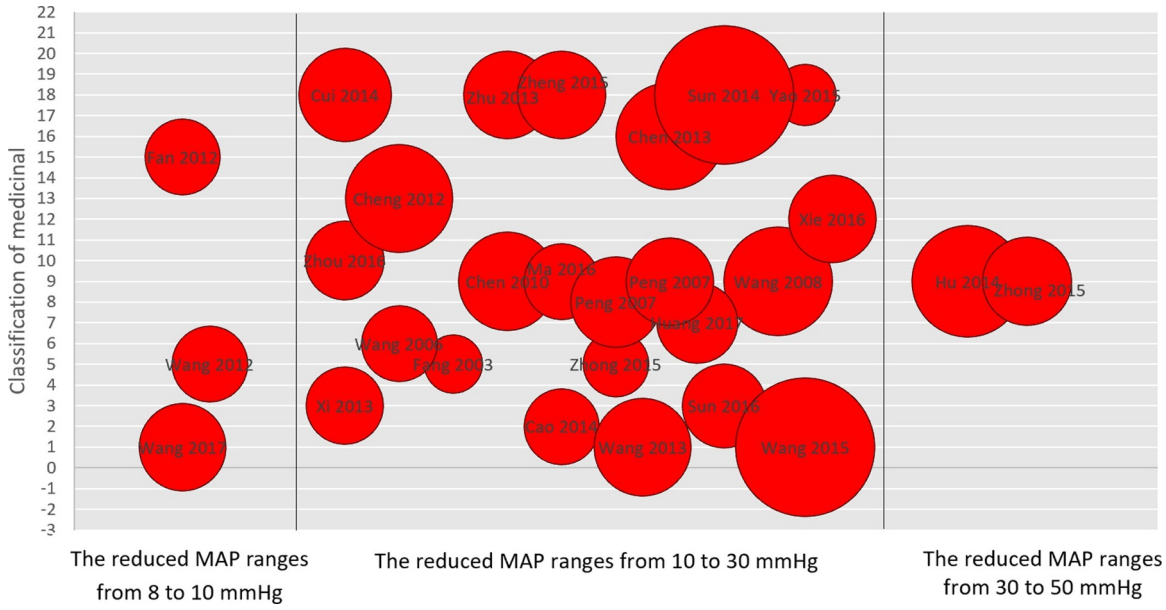

Fig. 5. Reduction of MAP (mean artery pressure).

compound preparations of angelica with angelica itself. Thus, based on current research results, we still cannot rank them according to their effectiveness and safety, so it is still difficult to make the best clinical decision.

Besides, there are some researches about the efficacy and safety of angelica injections treating hypertension and its complications. Chinese medicine injections are unique in China, which is a new invention of Chinese medicine preparations, but there're arguments about the application in the clinic all the time. According to the 2014 national annual report about drug adverse effects, there were 1,270,000 cases of adverse effect caused by Chinese medicine preparations, 6.7% of which were very severe. The adverse effects rate of Chinese medicine preparations in 2014 was higher than 2013, which was a bad sign (State Food and Drug Administration website, 2015). Therefore, when we are using angelica injections treating hypertension and its complications in the clinic, adverse effects should be carefully monitored.

Along with the development of complementary and alternative medicine, many relevant researches and evidences were published. As a new intervention measure for hypertension, angelica and its compound preparations has a great expectation in the clinical applications. On one aspect, researches about the efficacy in this article have proved the potential advantage in treating hypertension and its complications, which is the precondition of clinical applications. On the other aspect, the huge production scale of angelica in our country has guaranteed firm fundament for further clinical applications. Some investigation showed that the cultivation area of angelica was as high as 560,000 mu (1/15 of a hectare), and the export of angelica was 20,000 tons which was a very big portion of the market (https://wenku.baidu.com/view/bad3e4dca300a6c30d229f79.html). In 2011, the diagnostic and treatment guide of Chinese medicine for hypertension published by China Association of Chinese Medicine recommended angelica compound preparations (Chinese Medicine Association, 2011). The guide pointed

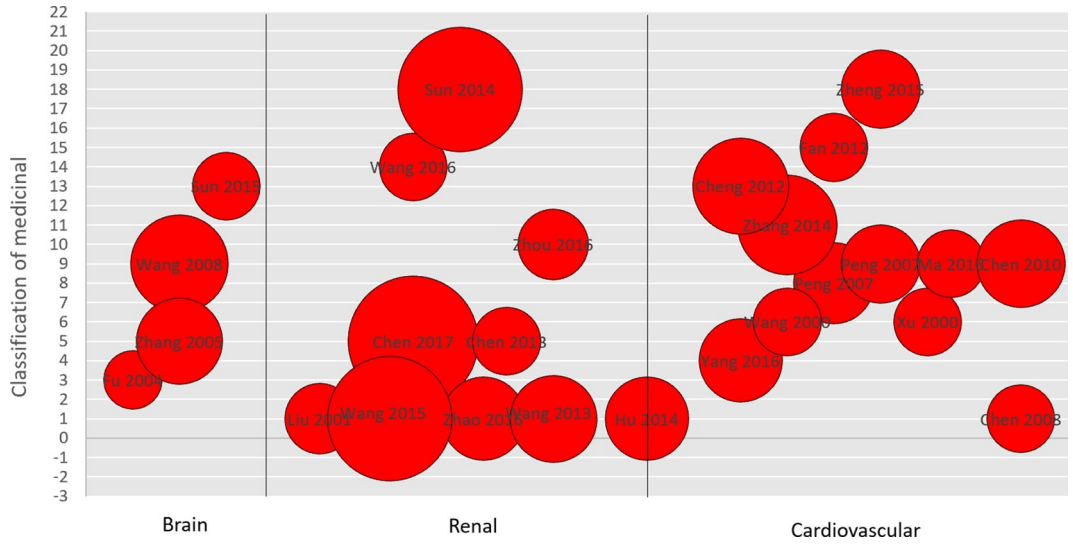

Fig. 6. Efficacy of target organ protection.

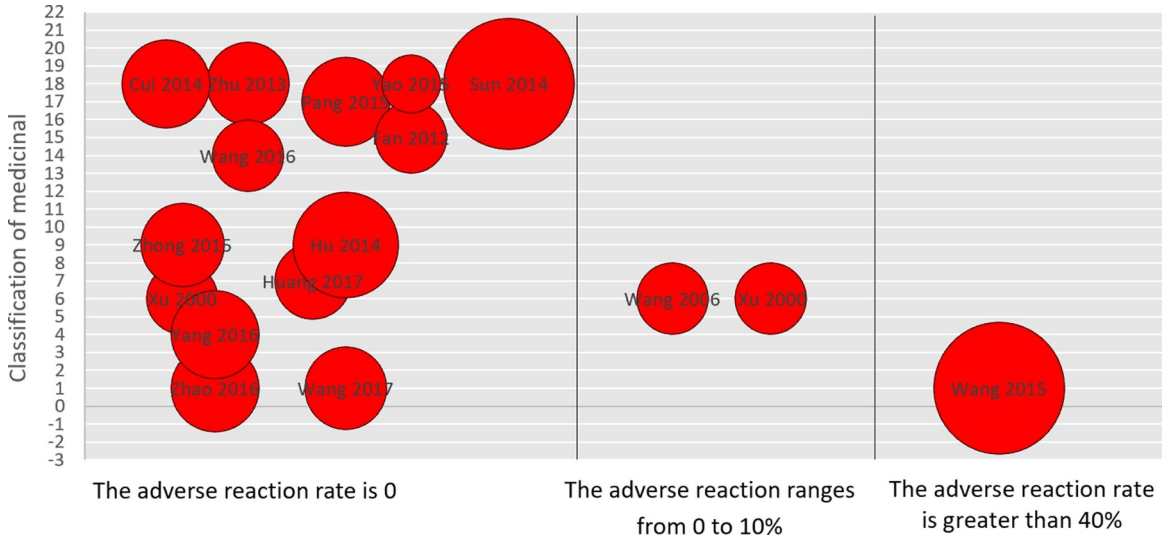

Fig. 7. Adverse effects rate

out that, modified Gentian Liver-Draining Decoction (Lóng Dǎn Xiè Gān Tāng), Chinese Angelica Gentian Aloe Pill (Dāng Guī Lóng Huì Wán) and modified Two Fairy Decoction (Èr Xiān Tāng) can be used to treat hypertension, which promoted the application of angelica in hypertension treatment. However, the guide also pointed out that, the recommendations were supported by limited evidences. Therefore, the application of angelica in hypertension treatment still relies on further development of evidence based medicine and perfection of more evidence.

After systematic searching of the databases, this article has presented the current research status of angelica and its compound preparations treating hypertension and its complications with evidence mapping. And there're still limitations in this research. First, all the included researches are of low quality, which directly influenced the reliability of the result. Second, heterogeneity and complex intervention measures in the included researches made it impossible to find efficacy and safety of single herbs. Third, in most of the researches, the intervention measures are compound preparations of angelica, and it's hard to tell the interactions among different ingredients.

Current research with low quality has revealed that angelica is effective in reduction of MAP and target organ protection and the adverse effects rate is low, and the effectiveness and safety of angelica needs to be proved by further researches with high quality. Researches of high quality are needed to provide scientific evidence for angelica in treating hypertension and its complications.

Contributors

Huiping Wei, Yingdong Li and Yaolong Chen were responsible for the design of the subject. Xufei Luo, Yujie Xiao and Yajing Tong were responsible for literature search, screening of documents, evaluation of literature, and drafting of the first draft. Yu Wang, Pei Jin, Chengxu Ma, Zhaoyuan Fu, Huan Guo were responsible for the interpretation of the basic theory of Chinese medicine; Huiping Wei and Xinke Zhao were responsible for translation; Yaolong Chen and Xufei Luo were responsible for assessing the risk of bias; Huiping Wei and Yingdong Li were responsible for the revision of the manuscript.

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The authors apologize to colleagues whose work was not cited due to space limitations or our oversight.

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Conflict of interest

None.

Financial disclosure

We wish to confirm that there are no known conflicts of interest associated with this publication and that there has been no significant financial support for this work that could have influenced its outcome.

Appendix A

Search strategies (set the strategy of PubMed as an example)
PubMed
#1. “Hypertension” [Mesh]
#2. “hypertension” [Title/Abstract]
#3. “hypertensive” [Title/Abstract]
#4. “hyperpietic” [Title/Abstract]
#5. “high blood pressure” [Title/Abstract]
#6. “feritin” [Title/Abstract]
#7. “HTN” [Title/Abstract]
#8. “cerebral hemorrhage” [Title/Abstract]
#9. “cerebral thrombosis” [Title/Abstract]
#10. “cerebral infarction” [Title/Abstract]
#11. “cerebral edema” [Title/Abstract]
#12. “stroke” [Title/Abstract]
#13. “heart failure” [Title/Abstract]
#14. “coronary heart disease” [Title/Abstract]
#15. “myocardial infarction” [Title/Abstract]
#16. “myocardial hypertrophy” [Title/Abstract]
#17. “renal failure” [Title/Abstract]
#18. “fundus hemorrhage” [Title/Abstract]
#19. “diabetes” [Title/Abstract]
#20. OR/#1- #19
#21. “Angelica sinensis” [Mesh]
#22. “Angelica sinensis” [Title/Abstract]
#23. “Danggui” [Title/Abstract]
#24. “Dang gui” [Title/Abstract]
#25. “Chinese angelica” [Title/Abstract]
#26. OR/#21- #25
#27. #20 AND #26

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