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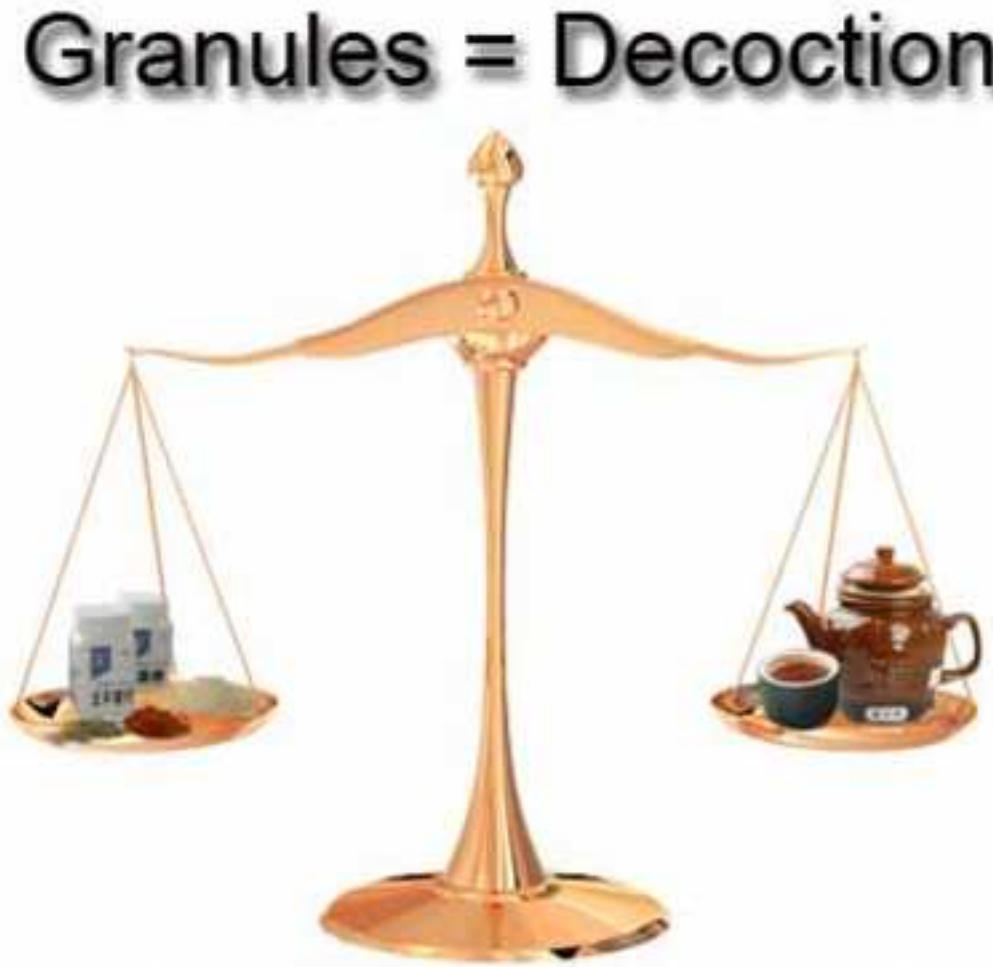
*Graphical Abstract



Chinese herbal medicine granules show the same effectiveness as decoctions in this systematic review.

Comparison of effectiveness and safety between granules and decoction of Chinese herbal medicine: a systematic review of randomized clinical trials

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Abstract:

Background: The clinical use of Chinese herbal medicine granules is gradually increasing. However, there is still no systematic review comparing the effectiveness and safety of granules with the more traditional method of herbal decoctions.

Method: A literature search was conducted using China National Knowledge Infrastructure Databases (CNKI), Chinese Science and Technology Periodical Database (VIP), China Biomedical Database web (CBM), Wanfang Database, PubMed, and the Cochrane Library until March 10, 2011. Clinical controlled trials (CCTs) including randomized trials (RCTs) comparing the effectiveness and safety between Chinese herbal medicine granules and decoction were included. Two authors conducted the literature searches, and extracted data independently. The assessment of methodological quality of RCTs was based on the risk of bias from the Cochrane Handbook, and the main outcome data of trials were analyzed by using RevMan 5.0 software. Risk ratio (RR) or mean difference (MD) with a 95% confidence interval (CI) were used as effect measure.

Results: 56 clinical trials (n=9748) including 42 RCTs and 14 CCTs were included, and all trials were conducted in China and published in Chinese literature. 40 types of diseases and 15 syndromes of traditional Chinese medicine (TCM) were reported. Granules were provided by pharmaceutical companies in 13 trials. The included RCTs were of generally low methodological quality: 7 trials reported adequate randomization methods, and 2 of these reported allocation concealment. 10 trials used blinding, of which 5 trials used placebo which were delivered double blind (blinded participants and practitioners). 98.2% (55/56) of studies showed that there was no significant statistical difference between granules and decoctions of Chinese herbal medicine for their effectiveness. No severe adverse effects in either group were reported.

Conclusions: Although our results suggest there was no difference between Chinese herbal medicine granules and decoctions in their effectiveness and safety, the poor methodological quality of most of the included trials means that we are unable to reach a definitive conclusion that both Chinese herbal medicine granules and decoctions have the same degree of effectiveness and safety in clinical practice. Further more rigorous research comparing granules with herbal

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decoctions is required but this preliminary evidence supports the continued use of granules in clinical practice and research.

Keywords: Chinese herbal medicine, granules, decoction, comparison, systematic review, clinical trials

1. Background

Prolonged boiling or 'decocting' is the earliest and most popular method of preparing herbal medicines in the practice of traditional Chinese medicine (TCM). The composition of herbs within a decoction is flexible and can be revised according to the condition of a patient, defined according to TCM syndrome differentiation and treatment principles. However, decoctions have some disadvantages, such as the difficulties in ensuring quality control of the herbal ingredients, the time and inconvenience they required to prepare, the practical problems relating to their transportation and storage, the difficulty in ensuring adequate quality control of the herbal ingredients, and the requirement to consume a large volume of unpleasant tasting medicine. These obstacles can reduce compliance and may interfere with Chinese herbal medicine (CHM) treatment. Historically different kinds of formulation have been developed in response to these shortcomings. These include traditional preparations of *wan* (pills), *san* (powder), *gao* (ointment), *dan* (another type of pill used in TCM) and the modern formulations of granules (*ke li ji*), oral liquids, capsules, tablets, and even injections.

Since granules may retain the advantages of decoctions and also address the problems of quality control, preparation, and administration that occur with decoctions, their use has increased dramatically both within China and other Asian countries. In Taiwan, Japan and South Korea research into granules began in the 1970s, and has led to rapid growth in this sector of the herbal market. In Japan, more than 400 kinds of granules have been developed, 148 Kampo granule herbal drugs were covered by National Health Insurance Fund, and 86% of Japanese medical doctors use granules in their clinical practice (Edwin Lowell Cooper and Nobuo Yamaguchi, 2004). In South Korean, more than 300 kinds of concentrated granules have been developed and are now covered by health insurance (Zhang BG et al., 2000). Compared with Taiwan, Japan and South Korean, the mainland of China's research and development in this field has been relatively slower. Although Chinese herbal medicine granules were first included in the 1977 edition of Chinese Pharmacopoeia (zhong guo yao dian) (Yuan ST, 1999), these 'granules' were developed from patent medicine formulations and did not include single herbal granules that could be used for individualized prescriptions. Until 1987, the Chinese Ministry of Health required the reform of TCM formulations in order to improve their effectiveness and to ensure adequate protection for endangered Chinese medicinal plants. Therefore, after their initial production and a period of evaluation about 4 years, Chinese manufactured granules for individualized prescriptions were first produced in 1992, and the first group of herbal pharmaceutical companies producing granules were officially approved by the Chinese State Administration of TCM in 1993. Currently, Chinese pharmaceutical companies have developed more than 600 kinds of individual herb granules and 200 kinds of herbal formulae, which have been widely used in clinical practice (Jia Wei and Zhang Lixin, 2005; Li Q, 2006; Ltd Jiangyin Tianjiang Pharmaceutical Co., 2011). Granules were covered by basic medical insurance in Beijing in April, 2009.

With the development and wide use of granules, their effectiveness and safety have become

an increasing focus for research. How do the effectiveness and safety of granules' compare with decoctions? Can granules be used as a substitute to traditional decoctions? There is considerable confusion and uncertainty in both herbal medicine producers and consumers in regard to these issues (Cheng H, 2000; Li AJ and Chen X, 2010; Xia JG, 2000; Yuan ST, 1999; Zhao CL, 1996). Within a complex Chinese herbal formula, a variety of chemical reactions may occur during preparation. Differences in the detail of manufacture (boiling, desiccation and granulation) may affect dissolution rates and change the proportion of available compounds within a formula (Yu LN et al., 2010; Yuan ST, 1999; Zhang XX and Jiang ZY, 2005). There is some chromatographic evidence that contents of constituents and active components in a herbal decoction may exhibit a different high-performance liquid chromatography (HPLC) fingerprint chromatogram to those found in an identical mixture of granules dissolved in boiling water (Chen LH et al., 2006; Ma YP et al., 2006). In addition, in China the price of granules is higher than dried Chinese herbs used in decoctions and this has limited the use of granules (Li AJ and Chen X, 2010; Li Q, 2006; Liu KJ, 2008; Zhang XX and Jiang ZY, 2005). In the West the converse is true and powders are considerably cheaper to use than decocted herbs.

In response to this confusion clinical studies comparing the effectiveness and safety of decoctions and granules have been published over the previous 3 decades, but no systematic review of these studies has been published. The aim of this current review is to examine these data to evaluate the effectiveness and safety of granules in comparison with decoctions, in order to address this confusion.

2. Materials and methods

2.1. Search strategy

A search strategy was designed to search all the available literature. We searched the Chinese National Knowledge Infrastructure Databases (CNKI) (1979-2011), the Chinese Science and Technology Periodical Database (VIP) (1989-2011), the Chinese Biomedical Database web (CBM) (1978-2011), the Wanfang Database (1985-2011), PubMed (1966-2011), and the Cochrane Library (Issue 3, 2011). All the searches ended at 10th March, 2011. There was no limitation on language or publication type. The search terms included "decoction" and "granules". Two authors (Luo H and Li Q) conducted the literature search independently. Articles were screened according to the title and then selected after abstracts were read. The full text was downloaded if the study met the inclusion criteria.

2.2. Inclusion criteria

Studies meeting the following three criteria were included in this review: (1) Type of studies: randomized controlled trials (RCTs), clinical controlled trials (CCTs). (2) Type of interventions: the study was designed to compare the effectiveness and safety of granules and decoctions, or if the clinical trial included more than two kinds of interventions, at least of which one was a decoction group and the other one was granule group. (3) The proportions of herbal medicine composition in the decoction and granules were the same.

2.3. Exclusion criteria

The following kinds of studies were excluded: (1) Multiple publications reporting the same data of patients. (2) Lack of basic information on participants or interventions. (3) Inconsistency in intervention between treatment and control group. (4) Interventions for external use.

2.4. Assessment methods

2.4.1. Searching for studies

Searching for studies was carried out by using criteria from the Cochrane Reviewers' Handbook 5.0.2 (Higgins JPT and Green S, 2009): (1) Search results from different databases were imported into the document management software Note Express 2.0; (2) Repeated and non-relevant studies were rejected by screening the title and abstract; (3) The full text of studies of potential relevance to the review were downloaded. (4) Repeated studies and publications were removed. (5) In instances of missing information the main researcher of the study was contacted for clarification. (6) Studies for inclusion were identified according to the inclusion criteria. (7) Finally a decision was made whether or not to include the study. Steps 1~5 were carried on by Luo H, 6~7 steps were carried on by Luo H and Li Q independently. They also cross checked the results with each other. Disagreements were resolved by discussion or submitting to the third researcher (Liu JP).

2.4.2. Methodological quality assessment

Evidence from an RCT is considered as the gold standard for therapeutic evaluation, so we specifically evaluated the methodological quality of RCTs in this review. Two authors (Luo H and Li Q) evaluated the quality of included RCTs. Assessment of the methodological quality of RCTs was conducted in accordance with criteria from the Cochrane Reviewers' Handbook 5.0.2 (Higgins JPT and Green S, 2009). We assessed studies according to the risk of bias for each important outcome within the included trials, taking into account the adequacy of the generation of the allocation sequence, allocation concealment, blinding and outcome reporting. The quality of all the included trials was categorized as low / unclear / high risk of bias. Trials that met all the criteria were categorized as low risk of bias, those that met none of the criteria were categorized as high risk of bias, and the others were categorized as unclear risk of bias if insufficient information was available to make a judgment. Disagreements were submitted to JP Liu to resolve.

2.4.3. Data extraction and analysis

A data extraction form was designed by all the authors. Two authors (Luo H and Li Q) extracted the data independently. Data was inputted into Microsoft Excel. Items in the form included (1) citations (author, title, journal, year, issue, volume, and page); (2) methodological character of trials; (3) participants (sample size, disease); (4) the nature of the interventions; (5) outcome measures; (6) a summary of results; (7) adverse effects; and (8) health economic outcomes.

The main outcomes data of the trials were analyzed by using RevMan 5.0 software. The efficacy measure was risk ratio (RR) with a 95% confidence interval (CI) for dichotomous data or mean difference (MD) with a 95% CI for continuous data. Meta-analysis was to be used if the trials had a good homogeneity of study design, participants, interventions, control, and outcome measures.

3. Results

3.1. Basic information of studies

After a primary search of 6 electronic databases, 700 citations were identified, 28 of which were identified from PubMed and Cochrane Library. However the majority of these were excluded due to their obvious ineligibility after reading the title/abstract or their repeated mention in different databases. 87 studies were included in the initial analysis. After reading the full text of each article, 56 trials met the inclusion criteria and were included in the final review, including 42 RCTs, 14 CCTs (**Figure 1**). All the included studies were published in Chinese. A

study identified in the Cochrane Library met the inclusion criteria but the full text was not available, therefore, the full article was downloaded from a Chinese Journal database according to its' citation (Liang QH and Li XQ, 1995).

9748 patients were involved in the included 56 trials. The mean sample size of trials was 174, the minimum was 30 and maximum was 1982. All the trials were carried out in China. There was a diverse distribution of diseases or TCM syndromes, with 40 diseases diagnosed according to modern medicine and 15 syndromes diagnosed according to TCM. Participants in some trials were diagnosed by a combination of modern medicine and TCM. The majority of interventions (52/56) were oral use; interventions in 4 trials used enemas (Lv CS et al., 2007; Pan PG et al., 2005; Xie S and Li JJ, 2010; Zhou B et al., 2009). More details of the trials are presented in **Table 1**.

According to our pre-defined methodological quality criteria, no trial could be considered as having a low risk of bias, and the majority (76.2%, 32/42) of the included RCTs were evaluated as having a high risk of bias. None of the trials reported sample size calculation; 7 trials (Kuang L et al., 2008; Liang QH and Li XQ, 1995; Liu JH et al., 2005; Lu M et al., 2008; Lv ZH et al., 2003; Wei LB et al., 2009; Wei LF et al., 2009) described adequate randomization procedures (such as use of a random number table or computer generated random numbers), 2 of these (Lu M et al., 2008; Wei LF et al., 2009) reported allocation concealment; 10 trials (Huang YJ and Zhu QY, 2009; Kuang L et al., 2008; Liao LY et al., 2009; Liu JH et al., 2005; Lu M et al., 2008; Lv CS et al., 2007; Wang PJ et al., 2009; Wei LF et al., 2009; Xie S and Li JJ, 2010; Xu JL et al., 1998) mentioned blinding, of which 5 (Huang YJ and Zhu QY, 2009; Liu JH et al., 2005; Lu M et al., 2008;Wang PJ et al., 2009; Wei LF et al., 2009) reported that they used a placebo control. Other than for Liu JH's trial, placebos made from granules and decoctions were provided by pharmaceutical companies in the other 5 trials. In Huang YJ, Liu JH, Lu M and Wei LF's trials, matched placebos were used to blind participants and practitioners; that is, in intervention group, patients received both real granules and placebo decoctions, while patients in control group received both real decoctions and placebo granules, which made the blind feasible. Moreover, both placebo decoction and granules were indistinguishable from the real treatment with respect to color, smell and packaging. In Lv's trial (Lv CS et al., 2007), granules and decoction were prepared using the same packaging in the form of dark liquid ,for which the color and smell were the same. All the packaging work was prepared in the hospital pharmacy. When these packages arrived at participants and practitioners location, they were blind to the intervention. So there was no need to use a placebo in this study. The other 4 trials did not report any details on how blinding was achieved. None of trials included a blinded assessor. Five trials (Liu JH et al., 2005; Lu M et al., 2008; Lv CS et al., 2007; Wei LF et al., 2009; Zhou P et al., 2008) reported the number of dropouts, but none of them used an intention-to-treat analysis.

Only 3 trials (Huang YJ and Zhu QY, 2009; Wang PJ et al., 2009; Wei LF et al., 2009) mentioned that their research used a non-inferiority study design to compare the effectiveness of decoction and granules.

3.2. Effectiveness and safety evaluation

3.2.1. Selection of outcome measure

Due to the diversity of diseases in the included trials, the outcomes measures were similarly diverse. The majority of trials used complex outcomes measures containing symptoms, signs,

and laboratory indexes, to evaluate the effectiveness of interventions. However the outcomes were also frequently aggregated and divided into four basic categories of therapeutic response: clinical remission (or clinical completely remission), marked effect, effective, and ineffective. The definitions of these were similar in all the trials. For example, ineffective was defined as "there is no significant difference or deterioration in symptoms, signs, or laboratory indices before and after treatment"; the effective was defined as "there is an improvement in symptoms, signs, or laboratory indices after treatment". Marked effective was defined as "there is a significant improvement in symptoms, signs, or laboratory indices after treatment"; and the clinical remission was defined as "the clinical symptoms and signs disappeared, and laboratory indices return to normal after treatment" (Liu JH et al., 2005; Lu M et al., 2008; Lv CS et al., 2007; Wei LF et al., 2009; Zhou P et al., 2008) . In addition, some trials reported disease specific outcomes. For example, an RCT on uterine fibroids (Yang H et al., 2008) reported the change of uterine volume.

3.2.2. Estimate effect of decoction and granules

45 trials reported outcomes as dichotomous data, so RR was used in their evaluation. 11 trials reported laboratory outcomes or outcomes providing continuous data, so MD with a 95% CI was used. The results showed that, with the exception of 1 RCT (Xie S and Li JJ, 2010) that reported the superiority of granules over a decoction when *sishen wan* was used as an enema for moderate colitis (MD: 0.71; 95% CI: [0.59, 0.83]), the results in all the trials showed no significant difference between the decoction and granule using groups. These results are presented in **Table 2**.

3.2.3. Adverse effects

23 trials (Hu BL and Zeng XJ, 2000; Hu SR and Wang HJ, 2000; Huang YJ and Zhu QY, 2009; Kuang L et al., 2008; Liang QH and Li XQ, 1995; Liao LY et al., 2009; Lin XR et al., 2001; Liu JH et al., 2005; Lu M et al., 2008; Lv CS et al., 2007; Lv ZH et al., 2003; Qi DM et al., 1999; Qian SY et al., 2003; Shao M, 1996; Sun WF et al., 2003; Wang PJ et al., 2009; Wei LB et al., 2009; Wei LF et al., 2009; Xie S and Li JJ, 2010; Xu JL et al., 1998; Xu XY, 1980; Zhang DA and Huang AJ, 1996; Zhou CY et al., 1999) reported mild adverse effects; no severe adverse effects were reported in the studies. No statistical differences were found in the rate of mild adverse effects occurring between decoction and granule groups. The review demonstrated that Chinese herbal medicine granules were safe.

3.3. Characteristic of interventions

3.3.1. Arms of interventions

The numbers of treatment arms in the trials can be seen in **Table 1**. 62.5% (35/56) of the trials had two arms (granules and decoction); 33.9% (19/56) had three arms; 3.5% (1/56) had four or five arms. Besides granules and decoction, the interventions included placebo, western medicine, other Chinese herbal medicines, and waiting list controls. In some trials, all the participants used conventional western medicines.

3.3.2. Formulae used in interventions

20 trials researched traditional CHM formulas, including *tianma gouteng yin*(Qin FL, 2010), *sishen wan*(Xie S and Li JJ, 2010), *buyang huanwu tang*(Liao LY et al., 2009), *liangfu wan*(Wei LF et al., 2009), *huoxiang zhengqi san*(Lu M et al., 2008; Wang YS et al., 1998; Zhang DA and Huang AJ, 1996), *longdan xiegan tang*(Kuang L et al., 2008), *xiaoqinglong tang*(Li CH et al., 1999; Zeng R et al., 2006), *zhigancao tang*(Zhang BZ et al., 2006), *bazheng san*(Feng L et al.,

2005), *chaihu guizhi tang*(Zhang XM et al., 2002), *xiangsha liujunzi tang*(Yu YL et al., 2002), *xiaochaihu tang*(Hu BL and Zeng XJ, 2000), *chaihu Shugan san*(Cheng XR and Zhu Y, 1999; Shao M, 1996), *buzhong yiqi tang*(Xu JL et al., 1998), *yinqiao san*(Du SH and Xie ZM, 1998), and *liuwei dihuang wan*(Zhu XY et al., 1995).. Another 38 trials researched self-made formulas, of which 2 trials were single herbs: lithospermum (*zicao*) (Liu JH et al., 2005) and tripterygium (*leigongteng*) (Xu XY, 1980).

3.3.3. Sources of granules

According to the studies, granules were mainly sourced from pharmaceutical companies and pharmacy departments in hospitals. Sources of granules in 33 trials were pharmaceutical manufacturers in China, all of whom were authorized to produce granules. 13 trials stated that granules were provided by pharmaceutical companies free of charge, while 20 trials reported their granules were from pharmaceutical companies, but the authors did not specify whether their granules were free of charge. To evaluate whether granules provided and funded by pharmaceutical companies could be an important source of bias in this review, we analyzed the results of the 13 relevant trials, and found that there were no significant differences in mean outcome related to the provider or funder of the products being evaluated. The data from this subgroup was consistent with the overall results of the 56 included trials. 9 trials reported that their granules were made by the pharmacy departments in their own hospitals. 14 trials did not report the source of granules. Details on sources of granules are presented in **Table 1**.

3.3.4. Dosage and preparation of granules and decoction

In 32 trials, the dosage of granules was equivalent to the decoction; in 9 trials , the dosage of granules was 1/4 ~2/3 of that of the decoction; another 15 trials did not reported whether the dosage of granules were equivalent to the decoction. Details on dosage are presented in **Table 1**.

2 trials did not report on the preparation of granules; granules in 9 trials were patent medicine granules, which involved the preparation of a traditional decoction of a formula of individual herbs that was then concentrated, dried and extracted to produce herbal granules (Ltd Jiangyin Tianjiang Pharmaceutical Co., 2011); In another 45 trials, the preparation of granules comprised aggregated mixtures of different single herbal granules for individualized prescription. All the individual granules had been prepared in advance by pharmaceutical companies or pharmacy departments of hospitals. In the trials, individual herb granules were formulated to match the decoction, and then mixed with boiling water for a few minutes, without the protracted boiling process that characterizes decoctions. Details on this issue are presented in **Table 1**.

Standardization of interventions is usually required in clinical trials. The method of CHM preparation in the decoction group (control group) should also be identical for each participant in a TCM clinical trial in order to reduce the performance bias and to compare and evaluate the effect between the decoction and other control treatments. In this review, 35 included trials used standardized methods of preparation reported by researchers, 1 trial reported that the decoction was prepared by the patients themselves, 20 trials did not report any information about preparation of the decoction (**Table 1**).

3.4. Sources of Funding

12 trials reported that they were supported by research funding from central and local government. The other 43 trials did not mention sources of funding. None of the trials reported funding from other organizations or pharmaceutical companies.

3.5. Health economic evaluation

3 trials (Feng L et al., 2005; Hu SR and Wang HJ, 2000; Tan BS and Tan DG, 2010) reported health economic outcomes; all the trials showed that the price of granules in China is currently higher than that of decoctions by between 16.61%~312%.

4. Discussion

4.1. Analysis of effectiveness and safety

The results of this review suggest that there is no significant difference in effectiveness and safety between Chinese herbal medicine granules and decoctions.

Meta-analysis could not be employed due to the inconsistency and heterogeneity of study design, participants, diseases, interventions, controls, and outcome measures; nearly all the trials (98.2%) reported no difference in outcomes between granules and decoctions, and the remaining single trial's results showed the superiority of granules over decoction. We evaluated the safety reports from the granules: no serious adverse effects were reported in the studies. No statistical differences were found in the rate of mild adverse effects occurring between the decoction and granule groups.

4.2. Limitation of the systematic review

4.2.1. Methodological quality and design style of included studies

The methodological quality of the included RCTs was poor. The designs of the majority of trials were also problematic. Only 3 trials mentioned that their research used a non-inferiority study designs to compare the effectiveness of decoction and granules. It seemed that most researchers lacked knowledge of the appropriate clinical research methodology. This was particularly apparent when comparing the effectiveness of a new herbal drug versus a controlled herbal drug of known and proven effectiveness. In this situation most researchers publishing in this field were still using a conventional clinical trial design and inappropriate statistical methods for significance testing. They did not apply methods used for non-inferiority, equivalence and superiority within their trial designs. This means the results of this systematic review should be interpreted with caution.

4.2.2. Potentially publication bias

None of the trials reported negative or non equivalence outcome. A greater than 98% rate of equivalence seems a little too good to be true and may be a reflection of publication bias in this systematic review. Although we searched the trials as systematically and comprehensively as possible, it seemed such publication bias was inevitable. This phenomenon maybe related to a reluctance to publish negative or conflicting data.

4.2.3. Declaring potential conflicts of Interest

78.6% (44/56) of trials did not report exactly how their trials had been funded; 30.4% (17/56) of trials did not report the source of granules. 58.9% (33/56) of trials mentioned that they used granules from pharmaceutical companies, of which 60.6% (20/33) failed to report whether the granules were provided free by pharmaceutical companies. The publication of a trial has a direct relationship with trial funding and trials supported by companies are more likely to report positive results than those supported by government or other academic organizations (Liu JP, 2009). Consequently there maybe some risk of bias for some included trials in this review which did not report these potential conflicts of interest.

4.2.4. Inconsistency of dosages between granules and decoction

The dosages between granules and decoction were the same in 57.1% (32/56) of trials; the dosages of granules was lower than those of decoction in 16.1% (9/56) of trials; 26.8% (15/56)

of trials did not reported information on this issue. It seemed that there was some inconsistency of dosages in clinical research when comparing granules and decoctions concurrently that raises additional questions about the rigor and validity of these findings. However trials that used a lower dose for granules than decoction also reported equivalent clinical outcomes for the two approaches. In addition, in 9 trials, granules were manufactured by the hospitals themselves without any details on preparation, which were questionable. Such heterogeneities should be avoided in future trials.

4.2.5. Inconsistency of prescription methods among granules

As reported in section 3.3.4, there was an inconsistency with respect to how the granules were formulated in the included trials (2 trials did not report on the preparation of granules, granules in 9 trials were derived from decoctions of standardized herbal formulae, 45 trials used granules comprising aggregated mixtures of different single herbal granules). In the trials that used mixtures of different single herbal granules prescriptions were individualized for each patient. Since there is currently no formal definition of 'granules for prescription' from the Chinese government's pharmacopoeia (SATCM of China Editorial Committee of Chinese Materia Medica, 1999), we would encourage the next edition of the pharmacopoeia (in 2015) to add a general chapter on granules for prescription, so as to avoid this inconsistency.

4.3. Clinical implications for Chinese practitioners using Chinese herbal medicine granules

The data from this review suggests that the aggregated mixtures of different single herb granules were just as effective as the granules derived from decoctions of complex herbal formulae in their respective trials. This has significant clinical and research implications because the CM clinician could, without any diminution of therapeutic effect, individualize therapy by combining single herbal granules rather than using the fixed, generic formulae available via granules from complex decoctions. However, the poor methodological quality of these trials means that we should be very circumspect about how we interpret these data. Once again more rigorous research is required to confirm or refute these preliminary findings.

5. Conclusion and recommendations

There are a number of limitations within the data that forms the basis of this review. The main problems with the included studies were related to their scientific quality, design and reporting all of which may create bias. Our initial and tentative conclusions will certainly require further research involving better study design, methodology and transparency, in particular the use of non-inferiority or equivalence designs (Huang Q and Zhao M, 2007). We also suggest that researchers must pay attention to the dose of granules and decoctions, improve the quality of trials, and report the study and its funding in the normal manner within a CONSORT statement (D. Moher et al., 2010).

The results of this review provide preliminary data suggesting that CHM granules may have the same effectiveness and safety as decoctions. However, the poor methodological quality of most of the included trials means that we are unable to reach a definitive conclusion that both Chinese herbal medicine granules and decoctions have the same degree of effectiveness and safety in clinical practice.. We suggest that, subject to more and better research, studies should focus on using quality controlled granules manufactured by well regulated pharmaceutical companies to treat clearly defined syndromes or diseases. Comparisons of standardized versus individualized treatments, and aggregated granules versus granules derived from complex decoctions are important secondary questions for CHM that need to be addressed as a matter of

some urgency.

Granular preparations can be recommended for clinical use as they are safe and certainly simpler to control, produce and manage as a consistent medical product than decoctions. . If granules are to be used more widely in China, then pharmaceutical companies and hospitals must reduce their production and distribution costs to lower the price of granules and make them a more realistic and competitive option for clinicians and patients. Furthermore the government should consider including the use of granule based herbal preparations as part of Chinese medical health insurance if they wish them to be more widely used. In the West, granules are considerably cheaper to dispense than the dried herbs used for decoctions so these obstacles to the wider use of granules do not arise.

We believe this review provides a rational argument for the continued investigation and use of granules. They can provide a more consistent herbal product that will improve our ability to regulate and research Chinese Herbal Medicines internationally. However, given the limitations of the current research, we are not able to reach a definitive conclusion that both Chinese herbal medicine granules and decoctions have the same effectiveness and safety in clinical practice. We believe that further more rigorous and accurate studies are required to confirm or refute these preliminary findings. It is only by clearly demonstrating equivalence that we can be certain of combining any therapeutic benefits from the long tradition of CHM with the practical advantages of more modern means of herbal medicine production.

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Disclosure statement

The authors state that no competing financial interests exist in this systematic review.

Appendix A.

Figure 1; Table 1 and 2.

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Table 1-characteristics of studies

study	design	fund	sample size	granule source	Disease and TCM diagnosis	groups	formula and its component	medicine dosage (G vs D)	decoction preparation	outcome measure
Tan BS and Tan DG, 2010	CCT	N	150	PC(U)	cervical spondylosis	3	self-made formula(S)	U	U	ER, cost-effect analysis
Yang JM et al., 2010	RCT	Y	58	U	chronic atrophic gastritis(deficiency of stomach *yin*)	3	self-made formula(S)	=	U	ER, improvement from gastroscopy and pathology
Qin FL, 2010	RCT	N	63	PC(U)	essential hypertension	3	*tianma gouteng yin*(C)	U	U	blood pressure, symptoms of RCM, blood biochemistry
Xie S and Li JJ, 2010	RCT	N	101	PC(U)	ulcerative colitis (*yang* deficiency of spleen and kidney)	2	*sishen wan*(S)	=	R	ER, TCM syndrome scores, Sutherland index
Liao LY et al., 2009	RCT	Y	60	PC(F)	stroke recovery (*qi* deficiency and blood stasis)	2	*buyang huanwu tang*(C)	1/3	R	ER,TCM syndrome scores
Wei LF et al., 2009	RCT	Y	153	PC(F)	Chronic gastritis, functional dyspepsia (stomach deficiency)	3	*liangfu wan*(S)	U	R	ER
Huang YJ and Zhu QY, 2009	RCT	Y	116	PC(F)	acute and chronic bronchitis (phlegm and heat)	2	self-made formula(C)	U	R	ER
Zhou B et al., 2009	RCT	N	40	U	chronic pelvic inflammation	2	self-made formula(C)	=	R	ER
Chen RF et al., 2009	RCT	N	105	PC(F)	chronic gastritis	2	self-made formula(S)	=	R	ER, symptoms score

Wei LB et al., 2009	RCT	N	130	PC(F)	chronic kidney disease stage of 4 or 5 (deficiency of *qi* and blood, wetness internal)	3	self-made formula(S)	<	R	scores of symptoms and SGA, function indexes of nutritional, renal and hematopoietic
Zhao L et al., 2009	RCT	N	100	PC(U)	acute bronchitis children (wind-heat invading lung)	2	self-made formula(S)	=	U	ER, TCM syndrome
Xiang LL et al., 2009	CCT	Y	335	PD	chronic hepatitis B	2	self-made formula(S)	=	R	liver function, ER
Zhang XY and Cai PP, 2009	RCT	N	65	PC(F)	acute sinusitis (gallbladder heat stagnation)	2	self-made formula(S)	U	U	ER
Wang PJ et al., 2009	RCT	Y	88	PC(U)	papular urticaria (wind-heat)	3	self-made formula(S)	U	R	ER
Zhou P et al., 2008	RCT	N	80	PC(F)	insomnia	2	self-made formula(S)	=	R	ER, Pittsburgh Sleep Quality Index (PSQI), TCM syndrome scores
Lu M et al., 2008	RCT	Y	150	PC(U)	diarrhea (cold wetness)	3	*huoxiang zhengqi san*(S)	=	R	ER, improvement of TCM symptoms
Yang H et al., 2008	RCT	N	180	PC(U)	Hysteromyoma /fibroids	3	self-made formula(S)	U	U	volume of uterine fibroids, ER
Li C et al., 2008	RCT	N	50	PC(U)	infantile anorexia (spleen-stomach disharmony)	2	unclear(S)	=	U	ER, symptoms score, weight, intake per date, urinary excretion rate of xylose
Kuang L et al., 2008	RCT	Y	60	PC(F)	genital herpes (damp-heat)	3	*longdan xiegan tang*(S)	U	R	score of symptoms, ER
Yang JF and Liu YL, 2007	CCT	N	68	PC(F)	sinusitis	2	self-made formula(S)	U	U	ER

Lv CS et al., 2007	RCT	N	60	PC(F)	end stage liver failure	2	self-made formula(S)	1/3	R	ER,TCM syndrome scores, blood ammonia, Endotoxin
Zeng R et al., 2006	RCT	N	60	U	Acute bronchitis (lung qi obstruction, retention of fluid)	2	*xiaoqinglong tang*(S)	U	R	ER, improvement of TCM symptoms
Zhang BZ et al., 2006	RCT	N	173	PD	angina pectoris (deficiency of *qi* and *yin*)	4	*zhigancao tang*(S)	=	R	ER, electrocardiogram
Feng L et al., 2005	RCT	N	80	PC(F)	acute urinary tract infection (damp-heat)	2	*bazheng san*(S)	=	R	ER, average time of take effect, daily cost
Liu JH et al., 2005	RCT	N	648	U	pregnant women	3	lithospermum(S)	=	R	rate of complete abortion, average time of bleeding
Pan PG et al., 2005	RCT	N	153	PC(U)	chronic prostatitis	3	self-made formula(S)	=	R	ER, TCM syndrome scores
Guo H and Zhao ZY, 2004	RCT	N	82	PD	herpes zoster (damp-heat)	2	self-made formula(S)	=	R	ER, time of recovery
Sun RZ, 2004	RCT	N	195	PC(U)	psoriasis vulgaris	3	self-made formula(S)	<	R	ER
Li AH, 2003	RCT	N	120	U	acute tonsillitis, upper respiratory tract infection (exogenous wind-heat)	2	self-made formula(S)	=	R	ER
Peng LS et al., 2003	RCT	N	30	PD	viral hepatitis A (damp-heat)	2	self-made formula(S)	U	R	recovery dates of disease, recovery dates of ALT and TBIL(d)
Lv ZH et al., 2003	RCT	Y	120	PC(U)	primary osteoporosis	2	self-made formula(S)	=	U	ER, bone mineral density, improvement and remission of low back pain

Zhai H, 2003	RCT	N	100	PC(U)	cold (wind-heat)	2	self-made formula(S)	=	R	cure rate
Sun WF et al., 2003	RCT	N	121	PC(U)	primary gout hyperuricemia	2	self-made formula(S)	=	R	ER, uric acid
Qian SY et al., 2003	CCT	N	138	PC(U)	post-chemotherapeutic leucopenia	3	self-made formula(S)	=	U	cases of post-chemotherapeutic leukopenia
Zhang XM et al., 2002	RCT	N	60	PC(U)	influenza	2	modified *chaihu guizhi tang*(S)	=	R	ER, symptoms improvement time
Yu YL et al., 2002	RCT	N	100	PC(U)	deficiency of spleen *qi*	2	*xiangsha liujunzi tang*(S)	1/2	U	ER, TCM syndrome scores
Lin XR et al., 2001	CCT	Y	187	U	eczema	3	self-made formula(S)	<	U	ER
Hu SR and Wang HJ, 2000	CCT	N	1982	PC(U)	Headache, insomnia, nervous disorders, hyperthyroidism and breast fibrosis	2	unclear(S)	1/2~2/3	P	ER
Bei LM and Xiong YX, 2000	RCT	N	132	PC(U)	four syndromes of TCM	2	*pingwei san, sangju yin, sanren tang, xiaoyao san*(C)	=	U	ER
Hu BL and Zeng XJ, 2000	CCT	Y	131	PC(U)	*shaoyang* syndrome(upper respiratory tract infection, acute and chronic gastritis, gastric ulcer, hepatitis)	2	*xiaochaihu tang*(S)	=	R	ER
Qi DM et al., 1999	RCT	N	1200	U	coronary heart disease, hypertension, type 2 diabetes	2	self-made formula(C)	=	U	ER, TCM syndrome scores, electrocardiogram, blood glucose, urine glucose, blood lipid and hematological indexes
Cheng XR and	RCT	N	60	U	stomach pain (*qi* stagnation)	2	*chaihu shugan san*(S)	=	R	ER, improvement from gastroscope

Zhu Y, 1999										
Li CH et al., 1999	CCT	N	200	PD	cough(exogenous cold- retention of fluid)	2	*xiaoqinglong tang*(S)	=	U	ER, dates of cough remission
Zhou CY et al., 1999	RCT	N	80	PD	ankylosing spondylitis	3	self-made formula(S)	1/4	R	ER, symptoms, signs and laboratory examination indexes
Zhang DA, 1998	CCT	N	100	PC(F)	non-acute cholecystitis	2	self-made formula(S)	=	R	ER, time of symptoms improvement
Xu JL et al., 1998	RCT	N	93	U	peptic ulcer, chronic gastritis	3	*buzhong yiqi tang*(unclear)	U	U	ER
Du SH and Xie ZM, 1998	RCT	N	90	PD	exogenous fever	3	*yinqiao san*(S)	=	R	ER
Wang YS et al., 1998	CCT	N	60	PC(U)	wind-cold-wet syndrome(cold, vomiting, diarrhea)	2	*huoxiang zhengqi san*(S)	=	R	ER, improvement of vomiting, abdominal pain, diarrhea and fever, blood, stool
Qiu M et al., 1998	CCT	N	82	U	chronic hepatitis B (spleen deficiency and dampness-heat with blood stasis)	3	self-made formula(unclear)	U	U	ER, negative conversion rate of HBsAg and HBV-DNA, liver function
Gao H et al., 1998	CCT	N	62	U	acute hepatitis E	2	self-made formula(S)	U	U	ER, improvement of symptoms and signs, liver function, serum viral markers
Zhang DA and Huang AJ, 1996	RCT	N	100	U	damp stagnation	2	*huoxiang zhengqi san*(S)	=	R	ER
Shao M, 1996	RCT	N	62	U	stomach pain of qi stagnation	2	*chaihu shugan san*(S)	=	R	ER, improvement of symptoms, laboratory examination

Liang QH and Li XQ, 1995	RCT	Y	60	PD	acute cerebral hemorrhage of gan yang hua feng	2	self-made formula(C)	=	R	ER, improvement of symptoms
Zhu XY et al., 1995	CCT	N	373	PD	*yin* deficiency of kidney	3	series of *liuwei dihuang wan* formula(C)	=	R	ER, laboratory examination
Tian DY et al., 1985	CCT	N	167	PC(F)	stomach pain	2	self-made formula(C)	U	U	ER
Xu XY, 1980	CCT	N	135	U	rheumatoid arthritis	5	tripterygium(S)	<	U	ER

Abbreviations: G: granule; D: decoction; RCT: randomized controlled trial; CCT: control clinical trial; Y: yes; N: no; PC: pharmaceutical company; PD: pharmacy department of setting hospital; U: unclear; F: free of charge; S: single; C: compound; R: prepared by researchers; P: prepared by patients; ER: effective rate; TCM: traditional Chinese medicine.

Table 2- Effect estimates of the included studies

study	intervention(G *vs* D)	effect index	RR / MD	95%CI
Tan BS and Tan DG, 2010	self-made granules(n=50) *vs* self-made decoction(n=50)	effective rate	0.98	[0.86, 1.11]
Yang JM et al., 2010	self-made granules(n=19) vs self-made decoction(n=18)	effective rate	1.07	[0.83, 1.39]
Qin FL, 2010	*tianma gouteng yin* granules(n=22) vs tianma gouteng yin decoction(n=18)	effective rate	0.98	[0.79, 1.21]
Xie S and Li JJ, 2010	*sishen wan* granules(n=58) vs *sishen wan* decoction(n=43)	Sutherland index	0.71(MD)	[0.59, 0.83]
Liao LY et al., 2009	*buyang huanwu tang* granules(n=30) vs *buyang huanwu tang* decoction(n=30)	effective rate	1.14	[0.87, 1.49]
Wei LF et al., 2009	*liangfu wan* granules(n=52) vs *liangfu wan* decoction(n=51)	effective rate	1.02	[0.91, 1.15]
Huang YJ and Zhu QY, 2009	*qingjin tangjiang* granules + placebo of decoction(n=58) vs *qingjin tangjiang* decoction + placebo of granules(n=58)	effective rate	1.00	[0.89, 1.12]

Zhou B et al., 2009	self-made granules enema(n=20) vs self-made decoction enema(n=20)	effective rate	1.11	[0.93, 1.31]
Chen RF et al., 2009	self-made granules(n=55) vs self-made decoction(n=50)	effective rate	1.01	[0.90, 1.13]
Wei LB et al., 2009	self-made granules(n=50) vs self-made decoction(n=38)	SCr(umol/L); BUN(mmol/L)	SCr: -13.64(MD); BUN: 0.34(MD)	SCr:[-41.80, 14.52]; BUN:[-1.49, 2.17]
Zhao L et al., 2009	self-made granules(n=43) vs self-made decoction(n=43)	effective rate	0.98	[0.89, 1.07]
Xiang LL et al., 2009	self-made granules(n=105) vs self-made decoction(n=127)	ALT(U/L), AST(U/L), TBil(μmol/L)	ALT:1.07(MD); AST:-1.67(MD); TBil:-0.81(MD)	ALT:[-4.82, 6.96]; AST:[-8.36, 5.02] TBil:[-8.04, 6.42]
Zhang XY and Cai PP, 2009	self-made granules(n=35) vs self-made decoction(n=30)	effective rate	1.04	[0.93, 1.16]
Wang PJ et al., 2009	self-made granules + placebo of decoction(n=26) vs self-made decoction+ placebo of granules(n=27)	effective rate	1.08	[0.95, 1.22]
Zhou P et al., 2008	self-made granules(n=36) vs self-made decoction(n=36)	Pittsburgh Sleep Quality Index (PSQI)	-0.24(MD)	[-1.85, 1.37]

Lu M et al., 2008	*huoxiang zhengqi san* granules+ placebo of decoction(n=36) vs *huoxiang zhengqi san* decoction+ placebo of granules(n=36)	effective rate	1.00	[0.89, 1.13]
Yang H et al., 2008	self-made granules(n=40) vs self-made decoction(n=100)	volume of uterine fibroids(cm3)	-0.66(MD)	[-6.13, 4.81]
Li C et al., 2008	self-made granules(n=25) vs self-made decoction(n=25)	effective rate	1.16	[0.89, 1.51]
Kuang L et al., 2008	*longdan xiegan tang* granules(n=20) vs *longdan xiegan tang* decoction(n=20)	effective rate	1.00	[0.81, 1.23]
Yang JF and Liu YL, 2007	self-made granules(n=38) vs self-made decoction(n=30)	cure rate	1.04	[0.67, 1.61]
Lv CS et al., 2007	self-made granules(n=20) vs self-made decoction(n=22)	blood ammonia, Endotoxin	NH3:3.19(MD); ETM:-0.00(MD).	NH3:[-9.92, 16.30]; ETM:[-0.02, 0.02]
Zeng R et al., 2006	*xiaoqinglong tang* granules(n=30) vs *xiaoqinglong tang* decoction(n=30)	cure rate	1.11	[0.53, 2.34]
Zhang BZ et al., 2006	*zhigancao tang* granules(n=43) vs *zhigancao tang* decoction(n=43)	ECG improvement rate	1.19	[0.88, 1.62]

Feng L et al., 2005	*bazheng san* granules(n=42) vs *bazheng san* decoction(n=38)	effective rate	1.03	[0.92, 1.16]
Liu JH et al., 2005	lithospermum granules(n=217) vs lithospermum decoction(n=221)	complete abortion rate	1.00	[0.97, 1.03]
Pan PG et al., 2005	self-made granules enema(n=50) vs self-made decoction enema(n=53)	effective rate	1.03	[0.91, 1.16]
Guo H and Zhao ZY, 2004	self-made granules(n=42) vs self-made decoction(n=40)	cure rate	1.06	[0.78, 1.44]
Sun RZ, 2004	self-made granules(n=104) vs self-made decoction(n=35)	effective rate	0.98	[0.89, 1.08]
Li AH, 2003	self-made granules(n=60) vs self-made decoction(n=60)	effective rate	1.00	[0.91, 1.10]
Peng LS et al., 2003	self-made granules(n=30) vs self-made decoction(n=30)	recovery dates of ALT and TBIL(d)	ALT:1.01(MD); TBIL:-0.48(MD)	ALT:[-36.74, 38.76]; TBIL:[-37.52, 36.56]
Lv ZH et al., 2003	self-made granules(n=64) vs self-made decoction(n=56)	bone mineral density (g/cm^2)	0.01(MD)	[-0.04, 0.06]
Zhai H, 2003	self-made granules(n=50) vs self-made decoction(n=50)	cure rate	1.02	[0.92, 1.14]

Sun WF et al., 2003	self-made granules(n=40) vs self-made decoction(n=41)	uric acid(μmol/L)	3.85(MD)	[-33.46, 41.16]
Qian SY et al., 2003	self-made granules(n=50) vs self-made decoction(n=46)	rate of post-chemotherapeutic leukopenia	0.95	[0.69, 1.31]
Zhang XM et al., 2002	modified *chaihu guizhi tang* granules(n=30) vs modified *chaihu guizhi tang* decoction(n=30)	defervescence time(h)	1.64(MD)	[-1.80, 5.08]
Yu YL et al., 2002	*xiangsha liujunzi tang* granules(n=50) vs *xiangsha liujunzi tang* decoction(n=50)	effective rate	1.04	[0.93, 1.17]
Lin XR et al., 2001	self-made granules(n=63) vs self-made decoction(n=65)	cure rate	0.88	[0.63, 1.25]
Hu SR and Wang HJ, 2000	self-made granules(n=803) vs self-made decoction(n=1179)	effective rate	headache: 0.99 insomnia: 0.98 nervous disorders: 0.99 hyperthyroidism: 1.02 breast fibroids: 1.00	headache: [0.96, 1.03] insomnia: [0.94, 1.02] nervous disorders: [0.95, 1.02] hyperthyroidism: [0.97, 1.09] breast fibroids: [0.95, 1.07]
Bei LM and Xiong YX, 2000	self-made granules(n=66) vs self-made decoction(n=66)	effective rate	0.98	[0.88, 1.10]

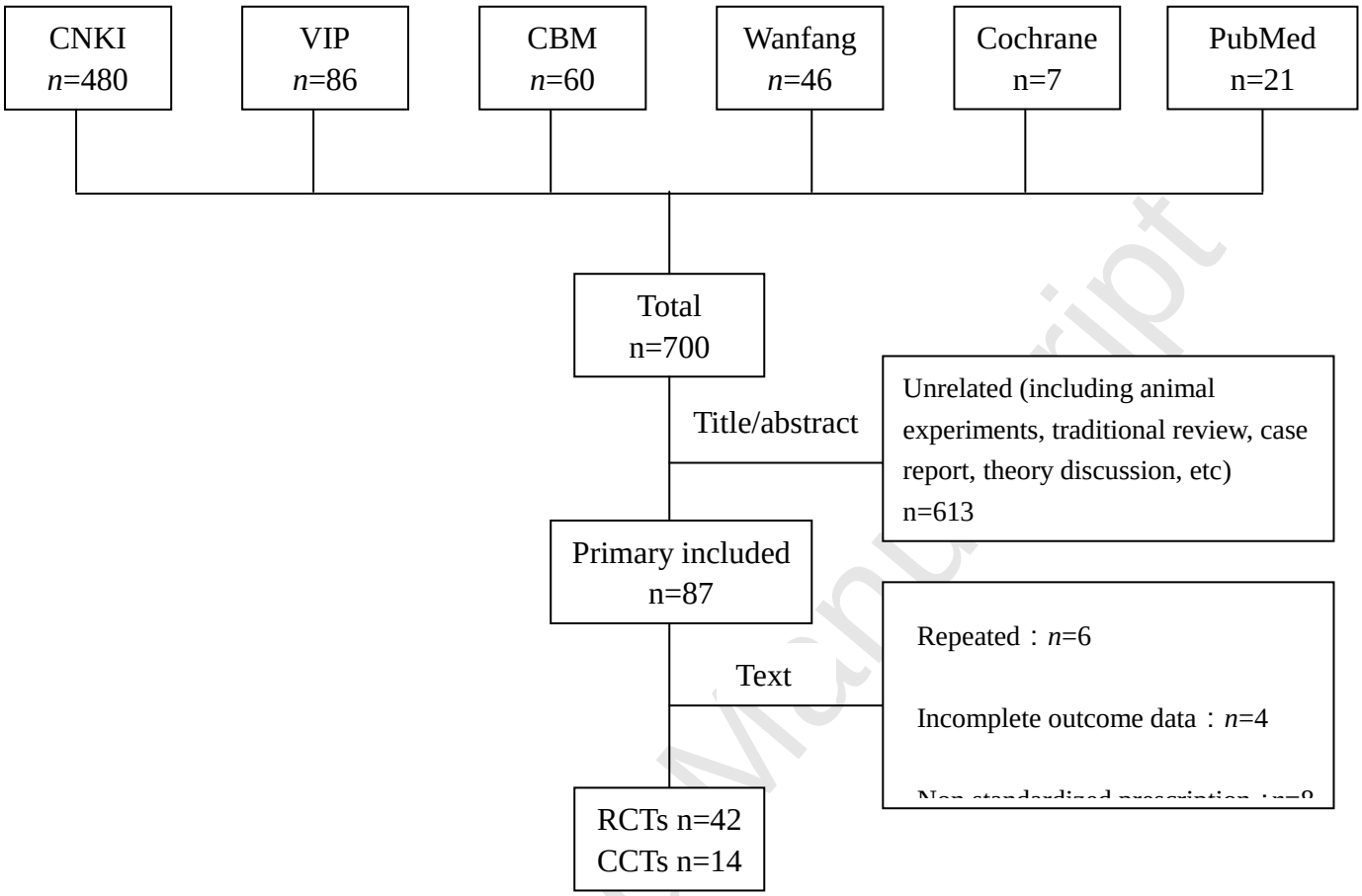
Hu BL and Zeng XJ, 2000	*xiaochaihu tang* granules(n=68) vs *xiaochaihu tang* decoction(n=63)	effective rate	0.99	[0.91, 1.07]
Qi DM et al., 1999	self-made granules(n=800) vs self-made decoction(n=400)	effective rate	coronary heart disease: 1.03 hypertension: 1.02 type 2 diabetes: 1.02	coronary heart disease: [0.97, 1.10] hypertension: [0.96, 1.08] type 2 diabetes: [0.97, 1.08]
Cheng XR and Zhu Y, 1999	*chaihu shugan san* granules(n=68) vs *chaihu shugan san* decoction(n=63)	effective rate	1.24	[0.94, 1.63]
Li CH et al., 1999	*xiaoqinglong tang* granules(n=100) vs *xiaoqinglong tang* decoction(n=100)	cough remission time (d)	-0.10(MD)	[-0.33, 0.13]
Zhou CY et al., 1999	self-made granules(n=42) vs self-made decoction(n=18)	effective rate	1.01	[0.88, 1.15]
Zhang DA, 1998	self-made granules(n=50) vs self-made decoction(n=50)	effective rate	1.05	[0.89, 1.23]
Xu JL et al., 1998	*buzhong yiqi tang* granules(n=33) vs *buzhong yiqi tang* decoction(n=32)	effective rate	1.01	[0.82, 1.24]
Du SH and Xie ZM, 1998	*yinqiao san* granules(n=30) vs *yinqiao san* decoction(n=30)	effective rate	1.00	[0.91, 1.10]

Wang YS et al., 1998	*huoxiang zhengqi san* granules(n=30) vs *huoxiang zhengqi san* decoction(n=30)	effective rate	1.00	[0.94, 1.07]
Qiu M et al., 1998	self-made granules(n=33) vs self-made decoction(n=34)	negative conversion rate of HBsAg and HBV-DNA	HBsAg: 0.92 HBV-DNA: 1.04	HBsAg: [0.53, 1.60] HBV-DNA: [0.59, 1.83]
Gao H et al., 1998	self-made granules(n=31) vs self-made decoction(n=31)	cure rate	2.00	[0.19, 20.93]
Zhang DA and Huang AJ, 1996	*huoxiang zhengqi san* granules(n=50) vs *huoxiang zhengqi san* decoction(n=50)	effective rate	1.02	[0.93, 1.12]
Shao M, 1996	*chaihu shugan san* granules(n=31) vs *chaihu shugan san* decoction(n=31)	effective rate	1.07	[0.94, 1.22]
Liang QH and Li XQ, 1995	self-made granules(n=30) vs self-made decoction(n=30)	hematoma absorption rate	0.99	[0.78, 1.25]
Zhu XY et al., 1995	*liuwei dihuang wan* granules(n=41) vs *liuwei dihuang wan* decoction(n=41)	effective rate	1.00	[0.95, 1.05]
Tian DY et al., 1985	self-made granules(n=101) vs self-made decoction(n=66)	effective rate	1.01	[0.97, 1.04]

Xu XY, 1980	tripterygium granules(n=5) vs tripterygium decoction(n=75)	effective rate	0.67	[0.33, 1.38]

Abbreviations: G: granule; D: decoction; RR: risk ratio; MD: mean difference; CI: confidence interval.

Figure 1 Selection of clinical trials comparing granules and decoction



Abbreviations:
CNKI: China National Knowledge Infrastructure Databases; VIP: Chinese Science and Technology Periodical Database; CBM: Chinese Biomedical Literature Database; Wanfang: Wanfang database; RCTs: randomized controlled trials; CCTs: controlled clinical trials.