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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: Due to the poor methodological quality of most of the included trials, it is not possible to reach a definitive conclusion whether both Chinese herbal medicine granules and decoctions have the same degree of effectiveness and safety in clinical practice, but this preliminary evidence supports the continued use of granules in clinical practice and research. Standardization of granules and further more rigorous pharmacological, toxicological and clinical studies are needed to demonstrate the equivalence with decoctions.

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

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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 and regions. 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 and Nobuo, 2004). In South Korean, more than 300 kinds of concentrated granules have been developed and are now covered by health insurance (Zhang 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, 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 and Zhang, 2005; Li, 2006; Ltd, 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 (Zhao, 1996; Yuan, 1999; Cheng, 2000; Xia, 2000; Li and Chen, 2010). 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 (Yuan, 1999; Zhang and Jiang, 2005; Yu et al., 2010). 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 et al., 2006; Ma 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 (Zhang and Jiang, 2005; Li, 2006; Liu, 2008; Li and Chen, 2010). 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 and Li) 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 and Green, 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, 6–7 steps were carried on by Luo and Li independently. They also cross checked the results with each other. Disagreements were resolved by discussion or submitting to the third researcher (Liu).

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 and Li) 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 and Green, 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 and Li) 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 (Fig. 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 and Li, 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 (Pan et al., 2005; Lv et al., 2007; Zhou et al., 2009; Xie and Li, 2010). 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 (Liang and Li, 1995; Lv et al., 2003; Liu et al., 2005; Kuang et al., 2008; Lu et al., 2008; Wei et al., 2009a,b) described adequate randomization procedures (such as use of a random number table or computer generated random numbers), 2 of these (Lu et al., 2008; Wei et al., 2009b) reported allocation concealment; 10 trials (Xu et al., 1998; Liu et al., 2005; Lv et al., 2007; Lu et al., 2008; Kuang et al., 2008; Huang and Zhu, 2009; Liao et al., 2009; Wang et al., 2009; Wei et al., 2009b; Xie and Li, 2010) mentioned blinding, of which 5 (Liu et al., 2005; Lu et al., 2008; Wang et al., 2009; Wei et al., 2009a; Huang and Zhu, 2009) reported that they used a placebo control. Other than for Liu's trial, placebos made from granules and decoctions were provided by pharmaceutical companies in the other 5 trials. In Huang, Liu, Lu and Wei'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 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 et al., 2005; Lv et al., 2007; Lu et al., 2008; Zhou et al., 2008; Wei et al., 2009b) reported the number of dropouts, but none of them used an intention-to-treat analysis.

Only 3 trials (Huang and Zhu, 2009; Wang et al., 2009; Wei et al., 2009b) 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 et al., 2005; Lv et al., 2007; Lu et al., 2008; Zhou et al., 2008; Wei et al., 2009b). In addition, some trials reported disease specific outcomes. For example, an RCT on uterine fibroids (Yang 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

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 and Tan (2010)	CCT	N	150	PC (U)	Cervical spondylosis	3	Self-made formula (S)	U	U	ER, cost-effect analysis
Yang 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 (2010)	RCT	N	63	PC (U)	Essential hypertension	3	*tianma gouteng yin* (C)	U	U	blood pressure, symptoms of RCM, blood biochemistry
Xie and Li (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 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 et al. (2009b)	RCT	Y	153	PC (F)	Chronic gastritis, functional dyspepsia (stomach deficiency)	3	*liangfu wan* (S)	U	R	ER
Huang and Zhu (2009)	RCT	Y	116	PC (F)	Acute and chronic bronchitis (phlegm and heat)	2	Self-made formula (C)	U	R	ER
Zhou et al. (2009)	RCT	N	40	U	Chronic pelvic inflammation	2	Self-made formula (C)	=	R	ER
Chen et al. (2009)	RCT	N	105	PC (F)	Chronic gastritis	2	Self-made formula (S)	=	R	ER, symptoms score
Wei et al. (2009a)	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 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 et al. (2009)	CCT	Y	335	PD	Chronic hepatitis B	2	Self-made formula (S)	=	R	liver function, ER
Zhang and Cai (2009)	RCT	N	65	PC (F)	Acute sinusitis (gallbladder heat stagnation)	2	Self-made formula (S)	U	U	ER
Wang et al. (2009)	RCT	Y	88	PC (U)	Papular urticaria (wind-heat)	3	Self-made formula (S)	U	R	ER
Zhou 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 et al. (2008)	RCT	Y	150	PC (U)	Diarrhea (cold wetness)	3	*huoxiang zhengqi san* (S)	=	R	ER, improvement of TCM symptoms
Yang et al. (2008)	RCT	N	180	PC (U)	Hysteromyoma /fibroids	3	Self-made formula (S)	U	U	volume of uterine fibroids, ER
Li 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 et al. (2008)	RCT	Y	60	PC (F)	Genital herpes (damp-heat)	3	*longdan xiegan tang* (S)	U	R	score of symptoms, ER
Yang and Liu (2007)	CCT	N	68	PC (F)	Sinusitis	2	Self-made formula (S)	U	U	ER
Lv 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 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 et al. (2006)	RCT	N	173	PD	Angina pectoris (deficiency of *qi* and *yin*)	4	*zhigancao tang* (S)	=	R	ER, electrocardiogram
Feng 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 et al. (2005)	RCT	N	648	U	Pregnant women	3	Lithospermum (S)	=	R	rate of complete abortion, average time of bleeding

Table 1 (*Continued*)

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
Pan et al. (2005)	RCT	N	153	PC (U)	Chronic prostatitis	3	Self-made formula (S)	=	R	ER, TCM syndrome scores
Guo and Zhao (2004)	RCT	N	82	PD	Herpes zoster (damp-heat)	2	Self-made formula (S)	=	R	ER, time of recovery
Sun (2004)	RCT	N	195	PC (U)	Psoriasis vulgaris	3	Self-made formula (S)	<	R	ER
Li (2003)	RCT	N	120	U	Acute tonsillitis, upper respiratory tract infection (exogenous wind-heat)	2	Self-made formula (S)	=	R	ER
Peng 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 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 (2003)	RCT	N	100	PC (U)	Cold (wind-heat)	2	Self-made formula (S)	=	R	cure rate
Sun et al. (2003)	RCT	N	121	PC (U)	Primary gout hyperuricemia	2	Self-made formula (S)	=	R	ER, uric acid
Qian et al. (2003)	CCT	N	138	PC (U)	Post-chemotherapeutic leucopenia	3	Self-made formula (S)	=	U	cases of post-chemotherapeutic leukopenia
Zhang et al. (2002)	RCT	N	60	PC (U)	Influenza	2	Modified *chaihu guizhi tang* (S)	=	R	ER, symptoms improvement time
Yu 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 et al. (2001)	CCT	Y	187	U	Eczema	3	Self-made formula (S)	<	U	ER
Hu and Wang (2000)	CCT	N	1982	PC (U)	Headache, insomnia, nervous disorders, hyperthyroidism and breast fibrosis	2	Unclear (S)	1/2~2/3	P	ER
Bei and Xiong (2000)	RCT	N	132	PC (U)	Four syndromes of TCM	2	*pingwei san, sangju yin, sanren tang, xiaoyao san* (C)	=	U	ER
Hu and Zeng (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 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 and Zhu (1999)	RCT	N	60	U	Stomach pain (*qi* stagnation)	2	*chaihu shugan san* (S)	=	R	ER, improvement from gastroscope
Li et al. (1999)	CCT	N	200	PD	Cough (exogenous cold- retention of fluid)	2	*xiaoqinglong tang* (S)	=	U	ER, dates of cough remission
Zhou 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 (1998)	CCT	N	100	PC (F)	Non-acute cholecystitis	2	Self-made formula (S)	=	R	ER, time of symptoms improvement
Xu et al. (1998)	RCT	N	93	U	Peptic ulcer, chronic gastritis	3	*buzhong yiqi tang* (unclear)	U	U	ER
Du and Xie (1998)	RCT	N	90	PD	Exogenous fever	3	*yinqiao san* (S)	=	R	ER
Wang 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

Table 1 (*Continued*)

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
Qiu 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 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 and Huang (1996)	RCT	N	100	U	Damp stagnation	2	*huoxiang zhengqi san* (S)	=	R	ER
Shao (1996)	RCT	N	62	U	Stomach pain of qi stagnation	2	*chaihu shugan san* (S)	=	R	ER, improvement of symptoms, laboratory examination
Liang and Li (1995)	RCT	Y	60	PD	Acute cerebral hemorrhage of gan yang hua feng	2	Self-made formula (C)	=	R	ER, improvement of symptoms
Zhu et al. (1995)	CCT	N	373	PD	*yin* deficiency of kidney	3	Series of *liuwei dihuang wan* formula (C)	=	R	ER, laboratory examination
Tian et al. (1985)	CCT	N	167	PC (F)	Stomach pain	2	Self-made formula (C)	U	U	ER
Xu (1980)	CCT	N	135	U	Rheumatoid arthritis	5	Tripterygium (S)	<	U	ER

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.

(Xie and Li, 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 (Xu, 1980; Liang and Li, 1995; Shao, 1996; Zhang and Huang, 1996; Xu et al., 1998; Qi et al., 1999; Zhou et al., 1999; Hu and Zeng, 2000; Hu and Wang, 2000; Lin et al., 2001; Lv et al., 2003, 2007; Qian et al., 2003; Sun et al., 2003; Liu et al., 2005; Lu et al., 2008; Kuang et al., 2008; Liao et al., 2009; Wang et al., 2009; Wei et al., 2009a,b; Huang and Zhu, 2009; Xie and Li, 2010) 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.

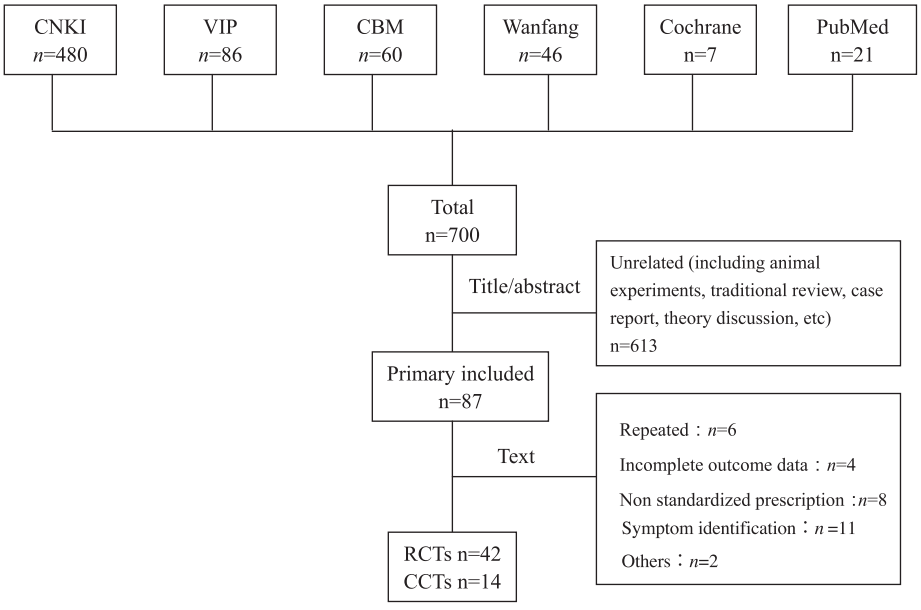

Fig. 1. Selection of clinical trials comparing granules and decoction. CNKI: China National Knowledge Infrastructure Databases; VIP: Chinese Science and Technology Periodical Database; CBM: Chinese Biomedical Literature Database; Wanfang: Wanfang database; RCTs: randomized controlled trials; CCTs: controlled clinical trials.

Table 2
Effect estimates of the included studies.

Study	Intervention (G vs D)	Effect index	RR/MD	95%CI
Tan and Tan (2010)	Self-made granules (n = 50) vs self-made decoction (n = 50)	Effective rate	0.98	[0.86, 1.11]
Yang et al. (2010)	Self-made granules (n = 19) vs self-made decoction (n = 18)	Effective rate	1.07	[0.83, 1.39]
Qin (2010)	*tianma gouteng yin* granules (n = 22) vs tianma gouteng yin decoction (n = 18)	Effective rate	0.98	[0.79, 1.21]
Xie and Li (2010)	*sishen wan* granules (n = 58) vs *sishen wan* decoction (n = 43)	Sutherland index	0.71 (MD)	[0.59, 0.83]
Liao 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 et al. (2009a)	*liangfu wan* granules (n = 52) vs *liangfu wan* decoction (n = 51)	Effective rate	1.02	[0.91, 1.15]
Huang and Zhu (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 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 et al. (2009)	Self-made granules (n = 55) vs self-made decoction (n = 50)	Effective rate	1.01	[0.90, 1.13]
Wei et al. (2009a)	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 et al. (2009)	Self-made granules (n = 43) vs self-made decoction (n = 43)	Effective rate	0.98	[0.89, 1.07]
Xiang 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 and Cai (2009)	Self-made granules (n = 35) vs self-made decoction (n = 30)	Effective rate	1.04	[0.93, 1.16]
Wang 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 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 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 et al. (2008)	Self-made granules (n = 40) vs self-made decoction (n = 100)	Volume of uterine fibroids (cm^3)	−0.66 (MD)	[−6.13, 4.81]
Li et al. (2008)	Self-made granules (n = 25) vs self-made decoction (n = 25)	Effective rate	1.16	[0.89, 1.51]
Kuang 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 and Liu (2007)	Self-made granules (n = 38) vs self-made decoction (n = 30)	Cure rate	1.04	[0.67, 1.61]
Lv 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 et al. (2006)	*xiaoqinglong tang* granules (n = 30) vs *xiaoqinglong tang* decoction (n = 30)	Cure rate	1.11	[0.53, 2.34]
Zhang et al. (2006)	*zhigancao tang* granules (n = 43) vs *zhigancao tang* decoction (n = 43)	ECG improvement rate	1.19	[0.88, 1.62]
Feng et al. (2005)	*bazheng san* granules (n = 42) vs *bazheng san* decoction (n = 38)	Effective rate	1.03	[0.92, 1.16]
Liu et al. (2005)	Lithospermum granules (n = 217) vs lithospermum decoction (n = 221)	Complete abortion rate	1.00	[0.97, 1.03]
Pan 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 and Zhao (2004)	Self-made granules (n = 42) vs self-made decoction (n = 40)	Cure rate	1.06	[0.78, 1.44]
Sun (2004)	Self-made granules (n = 104) vs self-made decoction (n = 35)	Effective rate	0.98	[0.89, 1.08]
Li (2003)	Self-made granules (n = 60) vs self-made decoction (n = 60)	Effective rate	1.00	[0.91, 1.10]

Table 2 (*Continued*)

Study	Intervention (G vs D)	Effect index	RR/MD	95%CI
Peng 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 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 (2003)	Self-made granules (n = 50) vs self-made decoction (n = 50)	Cure rate	1.02	[0.92, 1.14]
Sun 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 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 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 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 et al. (2001)	Self-made granules (n = 63) vs self-made decoction (n = 65)	Cure rate	0.88	[0.63, 1.25]
Hu and Wang (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 and Xiong (2000)	Self-made granules (n = 66) vs self-made decoction (n = 66)	Effective rate	0.98	[0.88, 1.10]
Hu and Zeng (2000)	*xiaochaihu tang* granules (n = 68) vs *xiaochaihu tang* decoction (n = 63)	Effective rate	0.99	[0.91, 1.07]
Qi 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 and Zhu (1999)	*chaihu shugan san* granules (n = 68) vs *chaihu shugan san* decoction (n = 63)	Effective rate	1.24	[0.94, 1.63]
Li 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 et al. (1999)	Self-made granules (n = 42) vs self-made decoction (n = 18)	Effective rate	1.01	[0.88, 1.15]
Zhang (1998)	Self-made granules (n = 50) vs self-made decoction (n = 50)	Effective rate	1.05	[0.89, 1.23]
Xu 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 and Xie (1998)	*yinqiao san* granules (n = 30) vs *yinqiao san* decoction (n = 30)	Effective rate	1.00	[0.91, 1.10]
Wang 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 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 et al. (1998)	Self-made granules (n = 31) vs self-made decoction (n = 31)	Cure rate	2.00	[0.19, 20.93]
Zhang and Huang (1996)	*huoxiang zhengqi san* granules (n = 50) vs *huoxiang zhengqi san* decoction (n = 50)	Effective rate	1.02	[0.93, 1.12]
Shao (1996)	*chaihu shugan san* granules (n = 31) vs *chaihu shugan san* decoction (n = 31)	Effective rate	1.07	[0.94, 1.22]
Liang and Li (1995)	Self-made granules (n = 30) vs self-made decoction (n = 30)	Hematoma absorption rate	0.99	[0.78, 1.25]
Zhu 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 et al. (1985)	Self-made granules (n = 101) vs self-made decoction (n = 66)	Effective rate	1.01	[0.97, 1.04]
Xu (1980)	Tripterygium granules (n = 5) vs tripterygium decoction (n = 75)	Effective rate	0.67	[0.33, 1.38]

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

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% (2/56) 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, 2010), *sishen wan* (Xie and Li, 2010), *buyang huanwu tang* (Liao et al., 2009), *liangfu wan* (Wei et al., 2009b), *huoxiang zhengqi san* (Zhang and Huang, 1996; Wang et al., 1998; Lu et al., 2008), *longdan xiegan tang* (Kuang et al., 2008), *xiaoqinglong tang* (Li et al., 1999; Zeng et al., 2006), *zhigancao tang* (Zhang et al., 2006), *bazheng san* (Feng et al., 2005), *chaihu guizhi tang* (Zhang et al., 2002), *xiangsha liujunzi tang* (Yu et al., 2002), *xiaochaihu tang* (Hu and Zeng, 2000), *chaihu Shugan san* (Shao, 1996; Cheng and Zhu, 1999), *buzhong yiqi tang* (Xu et al., 1998), *yinqiao san* (Du and Xie, 1998), and *liuwei dihuang wan* (Zhu et al., 1995). Another 38 trials researched self-made formulas, of which 2 trials were single herbs: lithospermum (*zicao*) (Liu et al., 2005) and tripterygium (*leigongteng*) (Xu, 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 (Liang and Li, 1995; Zhu et al., 1995; Shao, 1996; Zhang and Huang, 1996; Zhang, 1998; Du and Xie, 1998; Wang et al., 1998; Cheng and Zhu, 1999; Qi et al., 1999; Li et al., 1999, 2008; Bei and Xiong, 2000; Hu and Zeng, 2000; Zhang et al., 2002, 2006; Li, 2003; Lv et al., 2003; Qian et al., 2003; Sun et al., 2003; Zhai, 2003; Guo and Zhao, 2004; Liu et al., 2005; Feng et al., 2005; Pan et al., 2005; Lu et al., 2008; Zhou et al., 2008, 2009; Chen et al., 2009; Xiang et al., 2009; Zhao et al., 2009; Xie and Li, 2010; Yang et al., 2010), the dosage of granules was equivalent to the decoction; in 9 trials (Xu, 1980; Zhou et al., 1999; Hu and Wang, 2000; Lin et al., 2001; Yu et al., 2002; Sun, 2004; Lv et al., 2007; Liao et al., 2009; Wei et al., 2009a), the dosage of granules was 1/4–2/3 of that of the decoction; another 15 trials (Tian et al., 1985; Gao et al., 1998; Qiu et al., 1998; Xu et al., 1998; Peng et al., 2003; Zeng et al., 2006; Yang and Liu, 2007; Kuang et al., 2008; Yang et al., 2008; Zhang and Cai, 2009; Huang and Zhu, 2009; Wang et al., 2009; Wei et al., 2009b; Qin, 2010; Tan and Tan, 2010)did not reported whether the dosage of granules were equivalent to the decoction. Details on dosage are presented in Table 1.

2 trials (Qiu et al., 1998; Xu et al., 1998) did not report on the preparation of granules; granules in 9 trials (Tian et al., 1985; Liang and Li, 1995; Zhu et al., 1995; Qi et al., 1999; Bei and Xiong, 2000; Huang and Zhu, 2009; Liao et al., 2009; Zhou et al., 2009; Qin, 2010) 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 (Liang and Li, 1995; Hu and Zeng, 2000; Lin et al., 2001; Lv et al., 2003; Kuang et al., 2008; Lu et al., 2008; Huang and Zhu, 2009; Liao et al., 2009; Wang et al., 2009; Wei et al., 2009b; Xiang et al., 2009; Yang et al., 2010) reported that they were supported by research funding from central and local government. The other 44 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 (Hu and Wang, 2000; Feng et al., 2005; Tan and Tan, 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% and 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 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, 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 and Zhao, 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 (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 vs individualized treatments, and aggregated granules vs 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. We believe that further more rigorous and accurate pharmacological,

toxicological and clinical 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.

Disclosure statement

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

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