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**Traditional Chinese Medicines in the management of cardiovascular diseases: a comprehensive
systematic review**

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Short title: Traditional Chinese Medicines and cardiovascular diseases

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What is already known about this subject:

- Traditional Chinese Medicines encompass a wide range of treatments which have been claimed to have therapeutic benefits in different diseases.
- Individual studies have generally been too small to allow reliable conclusions to be drawn.

What this study adds:

- We performed a systematic review of the efficacy of Traditional Chinese Medicines in cardiovascular diseases.
- Our results suggest some efficacy in blood pressure lowering but no consistent therapeutic benefit in stroke, heart failure, coronary heart disease or type 2 diabetes mellitus.

Abstract:

Aims: The aim was to perform a systematic review of the efficacy of Traditional Chinese Medicines (TCM) in cardiovascular disease.

Methods: Electronic databases were searched up to 11th November 2015 for all randomised-controlled trials evaluating the effect of TCM in hypertension, ischaemic stroke, heart failure, coronary heart disease and type 2 diabetes mellitus. Pooled odds ratios (ORs) were calculated using a fixed-effects model.

Results: Four hypertension studies were eligible for statistical analysis and included 133 patients receiving TCM and 130 control patients. There were significant reductions in systolic blood pressure in patients receiving TCM, comparable to results achieved with pharmaceutical medicines. An OR of 3.781 (95% confidence interval 2.392, 5.977; $p = 0.000$) was observed for the anti-hypertensive effect of TCM. Significant heterogeneity was present ($p = 0.011$), with a tendency towards publication bias that did not reach significance ($p = 0.05275$). Outcome measures for other cardiovascular diseases were inconsistent.

Conclusions: Certain TCM compounds appear to have significant anti-hypertensive effects, and although some are associated in some studies with improved outcomes in coronary heart disease, heart failure and type 2 diabetes mellitus the data are inconsistent and will require large-scale randomised-controlled trials to allow full evaluation of any potential therapeutic benefit in these areas.

Introduction:

Cardiovascular diseases account for over 17.5 million deaths per year, predominantly due to myocardial infarction and stroke [1], making them the leading causes of mortality worldwide. As a result of both growth and aging of populations, the prevalence of cardiovascular morbidity and mortality continues to rise [2]. New therapies are therefore constantly being sought to both prevent and to treat cardiovascular diseases.

Traditional Chinese medicine (TCM) encompasses a broad range of holistic therapies, originally developed in ancient China, which are used globally to treat a multitude of pathologies, including cardiovascular diseases. The key principle underlying TCM is 'qi', a vital life force that is said to circulate within the body and to lead to the development of illnesses when its flow is obstructed. TCM is used in various forms, including herbology, acupuncture, and physical exercises, such as t'ai chi, in an attempt to improve the circulation of qi and thus relieve symptoms of disease. Other aspects may include the manipulation of 'yin' and 'yang', two complementary yet contrary forces that are said to lead to health and well-being when in harmony, and to illness when they are unbalanced. These concepts are not recognised in pharmaceutical medicine (PM), where there is a greater focus on achieving physiological and symptomatic targets with the use of pharmacological agents that have regulatory quality controls.

Up to 75% of the world's population rely on traditional or herbal medications as part of their basic healthcare, and safety control measures are variable [3]. Indeed, there are numerous reports of hepatotoxicity [4], renal failure [5], and cardiotoxicity [6] resulting from herbal medicine use, as well as potential drug interactions. To date, relatively few studies have been performed to evaluate the efficacy of TCM in the treatment of cardiovascular diseases. Here we systematically review the

available data on TCM in the management of some of the most important cardiovascular diseases: hypertension, acute ischaemic stroke, heart failure, coronary heart disease, and type 2 diabetes

Methods:

Search strategy and inclusion criteria

Electronic databases (PUBMED, MEDLINE and EMBASE) were searched up to 11th November 2015 for all studies evaluating the effect of TCM on hypertension, ischaemic stroke, heart failure and coronary heart disease. All languages were searched, but only those where the results sections were in English were included. The Medical Subject Headings text words or key words used in the search were 'traditional Chinese', or 'Chinese herbal', or 'acupuncture' in combination with each of the following terms: 'coronary artery', 'coronary heart', 'angina', 'myocardial infarction', 'acute coronary', 'hypertension', 'hypertensive', 'antihypertensive', 'blood pressure', 'heart failure', 'BNP', 'systolic function', 'diastolic function', 'left ventricular', 'stroke', 'cerebrovascular', 'ischaemia', 'ischaemic', and 'diabetes'. Studies were required to be randomised-controlled trials with adult human subjects, comparing the effect of TCM with placebo therapy or PM on clinical parameters for at least 2 weeks. Hard end-points, such as systolic blood pressure data, and inclusion of the standard deviation or standard error of mean for data points were required. Figure 1 shows a breakdown of the search.

Statistical analysis

Data were analysed using Comprehensive Meta-analysis version 3 software (Biostat, USA). A meta-analysis was conducted for hypertension only, as this was the only condition with the use of

consistent outcomes and measures of efficacy. A pooled odds ratio (OR) was calculated using a fixed-effect model, and 95% confidence intervals (CIs) were calculated to assess the strength of the association. Heterogeneity testing was performed and publication bias was assessed using a funnel plot and Egger's regression asymmetry test.

Results:

Hypertension

Patients enrolled in the studies were required to meet at least one of the current or past guidelines for definitions of hypertension according to the National Institute of Health and Care Excellence [7]. Studies that either compared TCM to PM or compared TCM to placebo or no treatment were included. 2254 results were accessed, of which 312 were trials. Of these, 304 trials were excluded for failing to meet the inclusion criteria. As the most data was available for systolic blood pressure (SBP) recordings, this was the parameter used to assess efficacy of treatment (Table 1).

Seven randomised controlled trials were identified, 4 of which compared TCM to placebo or no treatment [8-11] and were subsequently included in the meta-analysis (Figure 2). One of the larger studies compared two formulations of the same TCM therapy, with both producing statistically similar results [8]; therefore, to avoid introducing bias, only one of the formulations (Bushen Qinggan granules) was included within the meta-analysis. Three of the 4 studies showed a significant reduction in SBP in patients treated with TCM compared with placebo or no treatment, as measured by 24 hour ambulatory blood pressure monitoring (ABPM). An odds ratio of 3.781 (95% confidence interval 2.392, 5.977; $p = 0.000$) was observed for the anti-hypertensive effect of TCM. Significant heterogeneity was present ($p = 0.011$), with a tendency towards publication bias that did not reach significance ($p = 0.05275$).

Among the remaining studies, two compared TCM to standard PM. The first, a study by Zhong et al, assessed the efficacy of a TCM decoction for calming Gan and suppressing hyperactive yang (GSHY) compared with enalapril. There were no significant differences in ABPM parameters between the two groups, the TCM decoction demonstrating a similar antihypertensive effect to enalapril in this setting [12]. The second study comprised three groups of elderly patients with isolated systolic hypertension: 1 taking both TCM (Jiangya capsule) and PM (nimodipine tablet), 1 taking TCM and a simulated PM tablet, and 1 taking PM and a simulated TCM capsule [13]. The TCM therapy was once again found to be of similar efficacy to PM, and the reduction in SBP was amplified when both TCM and PM were used in combination. Lastly, Flachshampf et al assessed TCM acupuncture as a potential treatment for essential hypertension [14]. They found that this significantly lowered SBP immediately following the procedure when compared with sham acupuncture, but blood pressure returned to baseline post-intervention. The components of commonly used TCMs for the treatment of hypertension and other cardiovascular diseases are summarised in Table 2 [15-29].

Overall, it appears that targeted TCM can cause significant reductions in SBP and may be comparable with PM in certain cases, based on the results from these small-to-medium studies. Larger multi-centre trials are required, however, to allow firm conclusions to be drawn regarding the anti-hypertensive effects of TCM.

Stroke

TCM has been extensively studied in the treatment of ischaemic stroke (apoplexy syndromes in TCM) and of post-stroke morbidities. However, studies have tended to recruit small numbers of participants over variable time courses, for example, any time up to 12 weeks post-stroke, and have included heterogeneous groups of patients with strokes of varying severity. Randomisation techniques were rarely described; and where they were, often the methods used, such as

randomising to treatment or control groups based on gender, rendered the trial data inappropriate for further assessment. Due to the multiple modalities of assessing neurological function with no consistency in the use of functional scoring systems, such as the Barthel Index, Fugl-Meyer Assessment (FMA) scores and National Institutes of Health Stroke Scale (NIHSS), meta-analysis was not possible. Studies assessing motor function post-stroke were included in this review.

Danqi Piantang Jiaonang / NeuroAid therapy

Danqi Piantang Jiaonang (DPJ), marketed across the world as 'NeuroAid', is the most commonly used TCM for the treatment of ischaemic stroke (Table 2). When applied to murine models of cerebral ischaemia, DPJ has been shown to stimulate neurogenesis and improve cognitive and motor outcomes [18]. The results of re-analysed data obtained from two unpublished randomised-controlled trials from 2000, involving a total of 605 participants, demonstrated improved neurological function post-stroke in those taking DPJ compared with another TCM approved for stroke therapy [30]. A multitude of small placebo-controlled trials followed this, showing variable degrees of mild motor function recovery with DPJ [31 32], potentially due to increased cerebral arterial blood flow in those taking DPJ [33].

In 2013, the initial results from the multicentre 'CHinese Medicine neuroaid Efficacy on Stroke recovery (CHIMES)' trial were published, following recruitment of 1100 participants who had suffered an ischaemic stroke within the preceding 72 hours. Patients were treated for 12 weeks and the primary outcome was a change in the modified Rankin Scale (mRS), indicating functional improvement. The data showed that DPJ was no better than placebo at improving neurological outcomes in patients with acute or subacute ischaemic stroke [34]. Subsequent post-hoc analyses have postulated that certain patient groups, such as those with more severe strokes, may respond

better to DPJ than others, but no convincing statistics are available to support this postulate robustly [35-38].

Acupuncture

Stroke is the condition that is most commonly treated by acupuncture in the Chinese inpatient setting [39]. Chinese traditional acupuncture utilises a series of around 400 acupoints to manipulate the flow of qi through twelve principal meridian channels, which are divided into yin and yang groups and correspond to hollow or solid organs within the body. Electroacupuncture, laser acupuncture and dry needling, which are relatively modern techniques, have not been reviewed. While acupuncture has repeatedly proven to be safe and well-tolerated, there is limited evidence of efficacy in improving neurological function post-stroke. Trials to date have tended to involve low patient numbers, and the use of blinding of placebo or control therapies is understandably challenging.

When acupuncture is compared with physiotherapy and conventional rehabilitation, results from larger-scale multicentre studies have generally either found that it either provides no significant improvements in terms of motor function or that it is less effective than physiotherapy in improving functional assessment scores, without any additive / synergistic effects when used in combination with standard rehabilitation [40-44].

Studies that demonstrate potential benefits of acupuncture include one small trial where acupuncture paired with massage showed significant improvement in functional scores in FMA and NIHSS, but not mRS, compared with those undergoing conventional rehabilitation [45]. An additional, larger study identified improved outcomes in patients receiving acupuncture compared with a control group, with 6 cases of stroke recurrence in the acupuncture group (n = 144) compared

with 34 in the control group (n = 143) [46]. This study, however, lacked detailed patient characteristics to allow further interpretation of this finding.

To summarise, despite a large number of randomised-controlled trials investigating potential benefits in neurological recovery in those taking TCM, no effective TCM treatments for ischaemic stroke have been identified to date.

Heart failure

Although there are a variety of TCM drugs used to treat symptoms of heart failure, there is very little consistency in the use of end-point markers, such as N-terminal fragment brain natriuretic peptide (BNP) levels or left ventricular ejection fraction (LVEF). Meta-analysis was therefore not performed. Despite several trials having low numbers of participants, the overall quality of the data was high, with randomisation techniques described, and a relatively homogenous pool of patients, of similar age (50 – 65 years) who all had chronic heart failure graded as mild-moderate according to the scales used. The results of the selected heart failure studies are included in Table 3. All patients were on optimal PM, including an ACE-inhibitor (ACE-I), β -blocker, diuretic and digitalis preparation if appropriate.

The signs of heart failure, such as peripheral oedema and shortness of breath, may be considered to represent Xin-Shen Yang deficiency or fluid retention syndromes in TCM. Jiang et al treated a group of patients with dual TCM and PM diagnoses of fluid overload with Kanlijian TCM and compared this to a control group [47]. They identified that, in addition to improving TCM symptoms, there was a significant increase in LVEF in patients taking Kanlijian. Closer inspection reveals that the baseline LVEF was markedly lower in this cohort compared with the control group (43% vs 52%), which may account for the difference observed.

Other small studies have identified that, in those taking TCM, measures including average movement velocity of the mitral ring (a marker of haemodynamic function) [48], 6 minute walking distance [49], and left ventricular mass index scores [50] were improved compared with the control groups. A study of 102 patients randomised to TCM or control found that LVEF increased whilst BNP levels fell in patients allocated to receive TCM [51]. The largest study included in this review recruited around 500 patients with heart failure to receive a TCM mixture or placebo, and identified a significant reduction in BNP levels in the treatment group, indicating improved cardiac function [52].

Whilst there are some promising results for the treatment of heart failure with TCM, the majority of the studies recruited small numbers of participants, making it challenging to extrapolate results reliably. Further large-scale and well-designed studies to evaluate fixed outcomes, such as BNP levels and LVEF, would be useful to better evaluate the place of TCM in heart failure.

Coronary heart disease

Coronary heart disease encompasses a spectrum of clinical presentations, with patients ranging from having no symptoms to those presenting with stable angina or acute coronary syndromes. Of the 310 clinical studies accessed, 12 were included in this review. Outcome measures were diverse and thus not suitable for meta-analysis.

Acupuncture was evaluated as a possible treatment for stable ischaemic heart disease in several small studies, with variable results. One trial compared genuine and sham acupuncture and found no difference in improvement of angina frequency or severity of attacks between the two groups, although there was a median reduction of 50% in anginal attack rate in both groups, implying a potentially beneficial effect from both genuine and sham acupuncture treatments [53]. A similar

study conducted in patients with stable ischaemic heart disease found a significant increase in heart rate variability, which has positive prognostic value, in patients receiving genuine acupuncture compared with sham treatment [54]. T'ai chi has also been evaluated as a potential therapy and, whilst it does not modify measures such as heart rate variability, it has been demonstrated to improve baroreflex sensitivity [55]. Herbal therapy with Shenshao tablets [56] and Quyu Xiaoban capsules [57] have been shown to reduce the frequency of angina attacks compared with control treatments.

In patients with a history of previous myocardial infarction (MI), a multicentre study involving 2704 patients with ongoing hypertension compared Xuezhikang TCM with a control group, and found that those receiving treatment had a 43% reduction in coronary events [58].

A study evaluating Tongxunluo herbal therapy in patients undergoing percutaneous coronary intervention (PCI) for ST-elevation MI identified a significant reduction in ST-elevation compared with the control group at multiple time points, alongside increased myocardial perfusion scores, indicating a potential therapeutic role for TCM alongside PM [59]. A subsequent study evaluated the use of Compound Chuanxiong capsule with Xinyue capsule in the PCI setting and found a significant reduction in the incidence of major cardiac events compared with the placebo group. These data, however, appear to have been obtained by pooling the sums of all adverse events, including the development of heart failure, angina and recurrent MI, and therefore likely overestimate the effect of a small number of unwell patients with multiple clinical problems [60].

With such a wide range of possible clinical presentations and a lack of consistent outcomes, it is difficult to arrive at definitive conclusions when evaluating the effect of TCM in this group of patients. Individual trials suggest potential benefits, but reproducible data in larger studies are required before definitive conclusions can be reached.

Type 2 diabetes mellitus

A multitude of clinical studies have been carried out looking at the relationship between TCM and glycaemic control, however, there have been relatively few randomised-controlled trials in patients with T2DM. Whilst a meta-analysis was not possible, primarily due to both the variety of biomarkers of glycaemic control that have been assessed, including glycated haemoglobin (HbA1c), plasma glucose, fasting plasma glucose, and C-peptide levels, and the heterogeneity of patients recruited for studies, there was ample literature available for review.

Tong et al conducted one of the larger randomised-controlled trials, using TM81 (Tang-Min-Ling-Wan), a formula based on a classic combination of TCM herbs, including *Rhizoma coptidis* and *Radix paeoniae alba*. They found a significant reduction in HbA1c and fasting plasma glucose levels in those who received TM81, compared with those who received placebo [61]. Similarly, positive results were found in a multicentre randomised-controlled trial administering either Tianqi (a mixture of 10 herbal medicines, including *Astragali radix* and *Ginseng radix*) or placebo to patients with impaired glucose tolerance. They found that those taking the Tianqi capsule were more likely to develop normal glucose tolerance over the 12 month treatment period, and fewer subjects in this group progressed to developing T2DM compared with the placebo group. Overall, there was a 32% reduction in risk of progressing to T2DM in those taking Tianqi compared with placebo [62].

Interestingly, a number of studies evaluate both the symptom-based and physiology-based approaches of TCM and PM respectively, and explore the value of combining the two. Zhang et al assessed parameters of glycaemic control in 109 patients with pharmacologically treated T2DM who fell into one of three TCM syndromes: intrinsic damp syndrome, internal heat with yin deficiency, and dual qi and yin deficiency. They found that the latter group had comparatively more stable blood glucose profiles, whilst those with internal heat with yin deficiency had significantly higher HbA1c percentage values and higher fasting blood glucose levels [63]. Luo et al divided T2DM into 6

TCM syndrome groups and found that those with qi deficiency syndrome had higher levels of triglycerides and leptin, and additionally had higher body mass index values. The authors postulate that, according to TCM practice, qi deficiency syndrome leads to chronic fatigue and a general lack of energy, meaning that patients become less active and are prone to weight gain [64]. Dual qi and yin deficiency syndrome has also been associated with late-stage diabetes, where the heat from fire pathogens consumes yin and reduces qi, leading to symptoms of a dry mouth and intense thirst (polydipsia) and treatment aims to restore the balance of qi and yin [65].

Several studies have gone on to assess the benefit of adding TCM to PM treatment. Lian et al recruited a group of patients with T2DM (based on World Health Organisation criteria), who had achieved poor glycaemic control with metformin alone. They treated half of the patients by adding in Jinlinda therapy (a compound of 17 Chinese medicinal herbs) in addition to their regular metformin dose, whilst the other half received a placebo in addition to metformin. The Jinlinda group had a significant reduction in HbA1c percentage values compared to the placebo group [66], indicating that the compound may have hypoglycaemic properties, or possibly improves sensitivity to endogenous insulin.

Rather than adding TCM separately to standard PM diabetic treatment, one group recently published data from a placebo-controlled randomised trial, where Xiaoke, a compound preparation of glibenclamide (0.25 micrograms per pill) and TCM herbs, including *Radix astralgi* and *Rhizoma disease* (Chinese yam), was produced using modern pharmaceutical techniques to ensure that precise doses of the components were present. Two groups of T2DM patients were recruited – those who were drug-naïve and those on metformin monotherapy. Patients were randomised to receive either Xiaoke tablets or standard glibenclamide for 48 weeks, with doses of both treatments adjusted every 4 weeks to optimise markers of glycaemic control or to improve tolerability of the drug. Treatment with Xiaoke was reported to produce similar improvements in glycaemic control with a lower risk of hypoglycaemia compared to standard glibenclamide therapy [67]. Although the

results of this trial are somewhat challenging to interpret, as patients were on varying doses of the drugs, which were up- or down-titrated on a monthly basis at the discretion of the investigators, it appears that in this case, a combination of PM and TCM is efficacious in terms of achieving target physiological control of T2DM whilst addressing TCM syndrome symptoms.

The heterogeneity of patients recruited, without uniform criteria for a diagnosis of T2DM, and the range of outcomes measured, makes it challenging to draw firm conclusions on the efficacy of current TCM compounds in the treatment of this metabolic disorder. There are ongoing clinical trials assessing the combination of PM and TCM for the treatment of T2DM, which may further elucidate the role of TCM compounds in achieving glycaemic control. Indeed, additional ventures, such as the Xiaoke trial, may allow for modernisation and standardisation of TCM, whilst utilising a more holistic, symptom-based approach in PM.

Discussion:

The enduring popularity of TCM is likely due in part to the high value society places on continuing tradition and routine practices; but evidence also shows that, in some areas of Asia, younger and more affluent groups of people favour TCM compared with older people who work in so-called blue-collar occupations [68]. One of the perceived advantages of TCM compared with PM is that it focuses on relieving symptoms rather than improving clinical signs of disease, and typically involves a holistic approach that considers the most appropriate therapy for multiple co-morbidities.

There were many limitations to this review, which have generated challenges when evaluating and summarising data. Firstly, only studies with at least their abstract and results section published in English were considered for conclusion, which diminishes the pool of available studies. Secondly, although the selected studies were randomised-controlled trials, the overall methodological quality

was poor with essential information regarding randomisation methods, patient demographics and reasons for participant withdrawal frequently missing from the reports.

Many studies were unable to be blinded, due to the fact that TCM is frequently administered as a highly-scented liquid decoction several times per day, in contrast to the standard tablet or capsule containing PM. Acupuncture also represented a challenge in terms of blinding, and whilst some studies did utilise sham acupuncture procedures as a control measure, patients are generally able to discern the difference and report feeling less pressure compared with genuine acupuncture needles (43), with the distinct sensation of pressure (De Qi) from a genuine acupuncture needle inducing greater cutaneous and muscular blood flow (44). Additionally, using genuine needles with sham acupoints as a control measure may induce similar cutaneous afferent nerve responses to those of acupuncture (44), thus masking potential benefits, or perhaps identifying that the overall process of acupuncture is efficacious in improving particular disease symptoms, regardless of whether the traditional acupoints are used.

Data from studies assessing potential anti-hypertensive effects were promising, but basic experimental studies, utilising animal models to identify pharmacological pathways and mechanisms of drug action, followed by pharmacokinetic / pharmacodynamics and drug safety studies, in addition to large, high-quality randomised-controlled trials are required to confirm these preliminary findings. Indeed, for the other cardiovascular diseases assessed, there has been very little convincing data to support the recommendation of TCM for treatment of ischaemic stroke, coronary heart disease and heart failure. TCM was generally very well tolerated in the majority of studies, and its use in the context of cardiovascular disease – notwithstanding the lack of robust evidence of efficacy – may be appropriate alongside PM. .

There is currently a pressing demand for studies using animal models to investigate the observed physiological responses with human TCM use (see Table 2), and it is hoped that such studies will help

to elucidate pharmacological mechanisms of action and thus also facilitate the development of future therapies based on such mechanisms.

Conclusion:

Certain TCM compounds appear to have significant anti-hypertensive effects, and some may possibly improve outcomes in coronary heart disease and heart failure, but in all cardiovascular disease states discussed in this review there is a clear need for well-designed large-scale randomised-controlled trials to allow proper evaluation of any potential therapeutic benefit of such therapies.

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All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work .

Figure legends:

Figure 1: Search strategy

Summary of the search strategy used to identify eligible studies for the systematic review.

Figure 2: Meta-analysis of hypertension studies

Forest plot of four hypertension studies in which the anti-hypertensive effect of TCM was compared with control groups. OR: odds ratio; CI: confidence interval.