How reliable is the reporting of current studies on adverse effects of combining drug-herb in the treatment of cardiovascular diseases

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Introduction and objectives

- In recent years, a large amount of money has been spent annually on Chinese herbal products in the UK; £6 million on ginkgo each year since 2004; £8.3 million on ginseng-related products in 2009 [1]. Heart disease is the leading cause of death in England and Wales [2]. Cardiovascular patients often consume seven prescribed medications and two herbal, vitamin or mineral products daily[3] yet the understanding of drug-herb interactions (DHIs) is poor in both the Biomedical and Chinese medicine communities [4,5].
- Traditional Chinese herbs have been used for the past two thousand years [6] but in modern times many heart disease patients take both Chinese herbs and cardiovascular drugs concurrently and more evidence is merging of adverse effects [7]. For example, Dan shen, which has 50 compounds, interacts with warfarin and causes bleeding [8]. Current evidence of drug-herb interaction for heart conditions is mixed so further research is needed in this area.
- Hence, the intention of this poster project is to present clear and up-to-date knowledge on this matter for practitioners and the public. It is worth noting that there is a reluctance among some patients to report adverse interactions because they don't want to tell their GP that they are taking Chinese Medicine (CM) [7].

Objectives: to provide the current and reliable evidence of drug-herb interactions in patients who are also taking conventional cardiovascular drugs.

Three steps for this project:

1. Identify the current available evidence
2. Evaluation
3. Provide reliable information for the medical community & public

Methods, search strategy and selection criteria

Qualitative research method was used. A search of the PubMed, Medline and Google scholar databases was performed from October to December 2012 using search terms "herb and drug interaction", "cardiovascular drugs and herbs", "RCT in heart diseases and Chinese herbal medicine", and "adverse effects of Chinese herbal medicine in cardiovascular patients" to identify articles, statistics and abstracts on herb-cardiovascular drug interactions. All the data was written in English, published in peer reviews for the inclusive criteria. Paper sources were also used.

The current evidence in CM and cardiovascular drugs (CD)

- Nine reviews and two open-label three-way crossover randomised studies were chosen for contrast (see the numbered articles in which agree the interaction below).
- Bai guo (in studies 1,2, 3, 6, 8,9,11), ren shen (studies 1,2,3,6,7,10,11), ma huang (1,2), dan shen (1,2,3,4,5) and dang gui (1,2,3,5) are among the most frequently reported herbs for DHIs but not all the five herbs are covered by all the articles.
- Most of these studies report adverse DHIs but the findings of two 3-way crossover studies (9 &10) are different; they did not find adverse interaction between Bai guo and warfarin or Ren shen and warfarin. See the table 1 below:

Drugs/herbs	Bai guo (1,2, 3, 6, 8,9,11)	Ren shen (1,2,3,6,7,10,11)	Dan shen (1,2,3,4,5)	Dang gui (1,2,3,5)	Ma huang (1,2)
Warfarin	1,2,3, 6,11	1,2,3,6,7	1,2,3,4,5	1,2,3,5	
Aspirin	1,3, 6,8 (possibly)	6	4	5	
digoxin		1,3	1,3,4	3	
Beta-blockers					1

Reviews: 1. Tachjian, A. et al., (2010) [7]; 2. Valli, G., et al., (2002) [33]; 3. Fugh-Berman, A. and Ernst, E., (2001) [34]; 4. Lin, T.H. and Hsieh, C.L., (2010) [35]; 5. Chan, E. et al., (2010) [8]; 6. Elmer, G.W. et al., (2007) [36]; 7. Qi, L.W., et al., (2011) [13]; 8. Bent, S. et al., (2005) [37]; 11. Izzo and Ernst, (2001) [29]. Three-way crossover randomize studies: 9. Jiang, X. et al., (2005) [38]; 10. Jiang X. et al., (2004) [39].

Questions

The current available evidence shows:

- the evidence is contradictory; the results of studies 9 and 10 are different from 1,2,3,6,7,8 and 11 (baiguo)
- insufficient qualitative trials and lack of a unified study design
- little knowledge of the Chinese herbs and their application when taken with heart drugs, hence the three questions needed to be asked:

1. Which evidence is most reliable?
2. Do aspects such as recipients' age and dosages matter?
3. Is a randomised trial workable for this subject?

Literature review

This literature review will examine the background information and the quality of these reports and the peer-journals in order to reach a balanced conclusion.

1. Background information: drug-drug/herb interactions and regulations
2. The quality of these 11 studies
3. Quality of journals and authors' stances

1. Background information

1.1 drug-drug interactions (DDIs) of cardiovascular diseases in Biomedical area

- DDIs are familiar in the medical community; aspirin has the ability of inhibiting the synthesis of vasodilating postaglands, whereas angiotensin converting enzyme inhibitors (ACEi) increase prostaglandin production. Co-adminstration could reduce the prostaglandin mediated decrease in arterial pressure associated with ACEi and potential depression of renal function, therefore, patients who have heart failure and ischaemic heart disease would be exposed to risk if they take both of these drugs [9].
- Little information about the adverse effects of DDIs is given to patients, although the NHS has produced a basic information booklet for patients about oral anticoagulant therapy [10,31].
- Old people or those with multiple long-term diseases are more susceptible to adverse drug reactions (ADRs); the concurrent prescription of more than four drugs is seen more frequently in older patients [11].
- A report from a teaching hospital in India revealed that DDIs occurred in 14.66% of the patients in a cardiology department. Patients with more than 10 prescribed drugs developed DDIs more frequently (65.91%) and DDIs were observed more in patients who are over 60 years [12].

1.2 drug-herb interactions (DHIs)

- There is little knowledge about DHIs; scientific understanding is incomplete and it is often confusing for health care professionals and patients [13].
- Recommendations to avoid DHIs are often based on in vitro observations (a scientific experience in a controlled environment outside of a living organism), [14]), animal studies and case reports [13].

1.3 Regulations

- The MHRA (The Medicines and Healthcare products Regulatory Agency) is the regulatory agency for medicine.

2. The quality of these studies

In this section, methodologies of the nine reviews and two trials will be measured by AMSTAR (assessment of multiple systematic reviews) by Shea, B.J. et al., (2007) [15] and CONCORT 2010 [30].

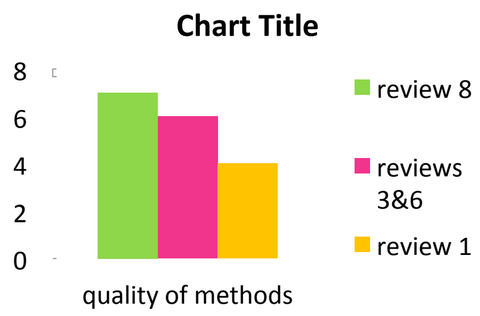
2.1 Findings among these studies:

- the reviews are mixed sources from randomized trials to case reports.
- AMSTAR -a pioneering measurement tool for systematic review:

In order to assess the methodological quality of the night reviews, the test of AMSTAR will be a guide to follow. A score will be given if the answer is yes, so a total score at the end of each review will be a rough guide for readers to get a sense of the best scored reviews. See the table 2 below:

AMSTAR/reviews	1	2	3	4	5	6	7	8	11
1. A prior design provided?	No,	No	No	No	No	Yes	No	No	No
2. Duplicate study selection/data extraction?	Not mentioned	No	No	No	No	No	No	Yes	Yes
3. Comprehensive literature search?	Yes	No,	Yes	Yes	No	Yes	No	Yes	Yes
4. The status of publication (e.g grey literature)?	No	No	Yes	No	Not stated	No	No	Yes	Yes
5. A list of studies provided?	No	No	No	No	No	Yes	No	Yes	No
6. Characteristics of included studies provided?	Yes	No	Yes	No	No	Yes	No	Yes	No
7. Quality of included studies assessed?	No	No	Yes	No	No	Not apply, only one type	No	No	No
8. Scientific quality of the included studies used appropriately in formulating conclusions?	No	No,	Yes	No	Yes	No	No	No	No
9. The methods used to combined the findings of studies are appropriate?	Yes	No	Yes	No	Yes	Yes	No	Yes	No
10. The likelihood of publication bias assessed?	No	No	No	No	No	No	No	No	No
11. Conflict of interest stated?	Yes	No	No	Yes	No	Yes	Yes	Yes	No
Scores	4	0	6	2	2	6	1	7	3

Best scores of the qualitative reviews:



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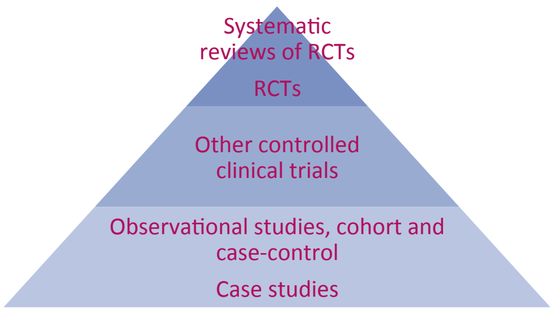
2.2 The gold standard for contemporary medical research:

Randomized Controlled trials (RCTs) is the contemporary gold standard for medicine research to achieve unbiased results. The pyramid graph below shows the hierarchy of evidence to assess the quality of trial design [16]. Hence, bias is more likely in the case reports, whereas systematic reviews of RCTs or RCTs will be the least biased. Among these articles, the two open label, three-way crossover randomized studies (studies 9 &10) would belong to the middle section: controlled clinical trials.



3. Quality of these journals and stances of authors

See table 3 below for details of these journals and authors.

Studies & reviews	journals	authors	Rating
1	Journal of the American College of Cardiology (JACC) JACC is described as "the best read cardiovascular journal worldwide, with an international reputation for excellence" [17].	Ara Tachjian and others: Tachjian holds a title of Clinic Fellow Medicine at the Harvard Catalyst Profile. He specialises in drug-herb interactions in cardiovascular conditions [18].	high
2	Journal of the American College of Cardiology (see above)	Georgianne Valli: Valli studied at Columbia College of Physicians and Surgeons, she works at Berkshire Health System, USA. She is a cardiologist doctor with 7 years experience [32].	Relatively low
3	Blackwell Science Ltd Br J Clin Pharmacol The British Journal of Clinical Pharmacology was first published bimonthly in 1974. It is for 'Promoting the disciplines of pharmacology and therapeutics and providing advice on standards of teaching and practice to policy makers' [19] .	Adriane Fugh-Berman: Fugh-Berman is an Associate Professor in the Department of Pharmacology and Physiology and in the Department of Family Medicine at Georgetown University Medical Center. She co-directs a master's program in natural products within the Department of Pharmacology and Physiology [20].	high
4	Lin and Hsieh Chinese Medicine; licensed BioMed Central Ltd: It is an "open access, online journal publishing evidence-based, scientifically justified, and ethical research into all aspects of Chinese medicine" [21].	Ching-Liang Hsieh, MD, PhD: Hsieh is a director, International Society of Oriental Medicine and an editor. He was awarded outstanding intellectuals of 21st century, integration of Chinese and Western Medicine [22].	high
5	Thomson Reuters (Scientific) Ltd: A global company which provides data and advanced analytics that hospitals and health systems use to improve performance and lower costs [23].	Elena Chan: She comes from a Pharmacology background and publishes articles of drug-herb interactions and "Insulin and Human (rDNA Origin) Inhalation Powder" online.	low
6	NIH Public Access: National Institutes of Health Public Access is USA Department of Health and Service. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Center upon acceptance for publication [24].	Gary W Elmer: 60 articles related to pharmacology are published on the website of University of Washington [25].	high
7	NIH Public Access: (see above)	Lian-Wen Qi: He has published various articles about the metabolism and interactions of Ginseng and other drugs.	high
8	JGIM (Journal of General Internal Medicine): "It promotes improved patient care, research, and education in primary care, general internal medicine, and hospital medicine" [26].	Stephen Bent: Associate Professor of Medicine, Psychiatry, Epidemiology & Biostatistics [27].	Relatively high
9	British Journal of Clinical Pharmacology (see above 3)	Xuemin Jiang, PhD works at Faculty of Pharmacy, the University of Sydney.	high
10	British Journal of Clinical Pharmacology (see above)	Xuemin Jiang (see above).	high
11	NHS: National Institute for Health Research: Is a large, multi-faceted and national organisation and "it has increased the volume of applied health research for the benefit of patients and the public" [28].	Izzo AA: the author works at the department of Experimental Pharmacology, University of Naples, Italy and has been actively publishing articles related to herb-drug interactions [29].	high

Summary: studies 1, 3, 4, 6, 7, 9, 10 and 11 are judged to come from the better quality peer journals and authors of the highest reputation.

Results

Table 4 below is a summary table to compare methodologies (M), journals and authors (JA) of these studies and assesses the reliability of drug-herb interactions in cardiovascular diseases found in these studies (the results are derived from the analysis).

Study	Strengths/weaknesses	Bias	Results
3-way crossover studies, study 9 & 10	**S**: Inclusive/exclusive criteria (trial approved, well thought through analysed material, scientific data collection and analytical techniques. Good quality of journal and experienced authors. **W**: Short trial period, small sized study, age group (not representative), no mention about follow-up period, the nature of open label trial does not qualify for unbiased study based on the CONCORT statement 2010 [30].	More weaknesses than strengthens, the key deciding points are: bias and unrepresentative age group (most heart patients are over 35 years [2].	M: unreliable JA: high
Reviews, 1, 2, 3, 4, 5, 6, 7, 8, 11	1 **S:** A wide range of resources used, very informative, plenty of data and charts. Good quality of journal and experienced authors. **W**: There is no rigorous study method, evidence from second sources and case reports. No charts for the combined findings.	This review aims to inform public, not strictly a systematic review. Evidence based on case reports.	M: 4 JA: high
2	**S:** Drawn from 200 references. High quality of journal but the author's experience is weak. **W**: It scores the lowest mark-0. It gives unfiltered information and relies on secondary sources.	It highlights the existing data on efficacy and adverse effects, not systematic review. Bias based on unchallenged view.	M: 0 JA: low
3	**S:** A systematic review which states its methods, sources, a comprehensive table to provide clear data and a report reliability scale is developed to assess the degree of the interactions. Author has rich experience. **W:** There are no 'a priori design', no duplicated study selection and data extraction, no list conflict of interest stated.	A systematic review which includes good methods and a report reliability test, but lack of scientific rigour.	M: 6 JA: high
4	**S:** A very detailed study of pharmacological effects of danshen, a comprehensive literature research has been performed. Authors have rich knowledge of both Chinese Medicine and Biomedicine. **W:** Lack of scientific trials, secondary evidence, no indication of included and excluded criteria provided.	This review evaluates Danshen in its details of pharmacology and possible adverse effects, but insufficient qualitative methodology.	M: 2 JA: high
5	**S:** In depth scientific study on danshen and dang gui molecules and their targets & reactions with cardiovascular drugs. Tables to display the detailed herb-drug interactions with specific enzymes. **W:** Lack of rigorous systematic review criteria on basic study method statement, e.g a priori design, or duplicate study selection. The journal has its commercial set up.	It focuses on Danshen and dang gui's molecular targets and metabolic pathways and is a systematic review, but low quality methodology.	M: 2 JA: low
6	**S:** A good review of retrospective analysis on interview data. It includes a proven study and a long period of recorded data. A good peer-journal. **W:** Lack of scientific rigour for unbiased tests, only subjective interviews were taken.	It is a retrospective analysis on interview data, which is debatable for its subjective view.	M: 6 JA: high
7	**S:** In depth explanation of pharmacokinetic data of Ginseng and its interactions with drugs. **W:** Lack of comparison with other studies within this area, no data and inclusive and exclusive criteria provided.	This review aims to explain pharmacokinetic data of Ginseng and its interactions with drugs. It acknowledges the problem of lack of RCTs in this area. Bias based on unchallenged view.	M: 1 JA: high
8	**S:** It includes most wanted criteria by the standard of a systematic review compared to the others. **W:** Lack of RCTs and deficient in assessing the quality of the chosen cases and trials.	It is a systematic review which is rigorous in its method compared to the others.	M: 7 JA: relatively high
11	**S:** A comprehensive literature research and duplicate study data was applied. **W:** No details of methods used to select the studies, the validity of inclusive studies was not assessed, low qualitative studies such as case reports were used in baiguo.	A systematic review but low quality studies e.g case reports.	M: 3 JA: high

Summary: Articles 6, 8,3,1 (in order of quality) and possibly 11are judged to be the best reviews so reliability is higher in these studies.

Result: The reliability of DHIs in cardiovascular diseases:

Drugs/herbs	Bai guo (1,2, 3, 6, 8,9,11)	Ren shen (1,2,3,6,7,10,11)	Dan shen (1,2,3,4,5)	Dang gui (1,2,3,5)	Ma huang (1,2)
Warfarin	3, 6,11	1,3,6	1,3	1,3	
Aspirin	1,3, 6,8 (possibly)	6			
Digoxin	1,3	1,3	3		
Beta-blockers					1

Yes interactions (from the available sources):

- ✖ Baiguo: warfarin, aspirin
- ✖ Renshen: warfarin, aspirin, digoxin
- ✖ Danshen: warfarin, digoxin
- ✖ Danggui: warfarin, digoxin
- ✖ Ma huang: beta-blockers

Discussion

The current evidence of DHIs in cardiovascular diseases is largely based upon case studies, reports and poorly designed trials. Some of the authors come from a biomedical background while others are from the CM tradition. They make an attempt to understand each other's viewpoints but there are still large areas of uncertainty. Aspects such as patients' age and dosage were raised in some of these articles. On the other hand, trials which test DHIs in heart patients could lead to some ethical issues. Perhaps future studies need to focus initially on in vitro studies (cellular biology, outside of a living organism) which could later be followed by in vivo studies (animals and human).

Conclusion

Information about DHIs in cardiovascular diseases needs to be transparent so that practitioners in both biomedicine and CM can be made aware of the adverse effects. The available evidence shows that interactions occur in patients who are taking warfarin with either baiguo, renshen or danggui; aspirin with either baiguo, or renshen; digoxin with either renshen, danshen or dang gui; beta-blockers with ma huang. Current evidence shows that these combinations should be avoided but there may well be others that have not yet been identified.

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