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COMPARISON OF RISKS FOR ADVERSE DRUG REACTIONS BETWEEN TRADITIONAL CHINESE MEDICINES AND WESTERN MEDICINES: A REVIEW OF CHINESE-LANGUAGE LITERATURES

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Abstract

Background: This study aimed to compare the risks for adverse drug reactions (ADRs) between traditional Chinese medicines (TCMs) and Western medicines (WMs).

Materials and Methods: A comprehensive review of ADR cases reported in the Chinese-language literatures from January 2006 to December 2011 was conducted to identify the frequency, severity and hazard of ADRs associated with TCMs and WMs. Sort ratio (SR) was employed to compare the ranking of TCMs and WMs. SR>1 when WMs ranked higher than TCMs. For group comparisons, nonparametric Mann-Whitney test was used whenever possible.

Results: A total of 5097 cases were induced by 212 TCMs and 908 WMs according to 3842 reports in the final full-text analysis. In the comparisons for the entire study group, as well as groups by pharmacology category and administration route, most WMs ranked higher than TCMs in occurring frequency, severity and hazard caused by ADRs. The results showed the adverse effects from Chinese medicines were comparatively rare and the risks caused by them were milder than by western medicine-related ADRs.

Conclusion: This study concluded by indicating that TCMs were safe in clinical practice compared with WMs, though not risk free. Improvements in quality control and in the training and regulation of practitioners could substantially reduce the already low incidence of problems involving TCMs.

Key words: Drug safety, Adverse drug reaction, Traditional Chinese medicines, Complementary medicines, Western medicines

Introduction

Traditional Chinese medicine (TCM) has been playing a very important role in health protection and disease control for thousands of years in China. Relying on natural products, mainly of herbal origin, used as raw materials for decoction, prepared herbal medicines or formulated traditional medicines, TCM is widely accepted and becomes a popular form of therapy (Zeng et al., 2010; Zhang et al., 2012). TCMs now amount to a global industry worth hundreds of millions of dollars a year, according to the study in PLoS Genetics (Facts and Details, 2012). The World Health Organization (WHO) has estimated that approximately 80% of the global population relies on traditional herbal medicines as part of standard healthcare (Foster et al., 2005) and, in the US, where herbal remedies are classified as dietary supplements, an estimated 1 in 5 adults regularly consume herbal products (Bent, 2008).

As Chinese herbal medicine becomes increasingly widely practiced in the West, reports of occasional adverse effects are appearing in the literature and questions are being asked about safety. Many consider that Chinese herbs are pure natural and with none adverse drug reactions (ADRs). Actually, TCM drugs, like other conventional drugs, can cause adverse reactions which are an inherent property that accompanies the therapeutic efficacy of drugs. Then how does the safety of TCMs compare with that of western medicines (WMs) in clinical therapy? Are the natural product-derived TCMs of a more benign nature in side-effects? There is considerable confusion and uncertainty in both herbal medicine practitioners and consumers in regard to these issues. However, there are still few published works systematically comparing the safety of TCMs with the more admitted method of WMs. Moreover, the prior studies tended to focus on a specific kind of drug. Their findings could not be

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extrapolated to all Chinese medicines and Western medicines. The absence of scientific understanding has resulted in skepticism and criticism about TCM. More research is needed to provide evidences.

In this article, we presented a wide-ranging, though not exhaustive, review of ADR cases reported in the Chinese-language literatures from January 2006 to December 2011, and aimed to systematically compare the risks for ADRs between TCMs and WMs by analyzing report frequency, severity and hazard. This approach could address the confusion as well as form a basis for scientific comparison**.**

Materials and Methods

Definition

According to the WHO definition, adverse drug reaction is any noxious, unintended, and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy (WHO, 1966). This definition excludes therapeutic failures, intentional and accidental poisoning (i.e., overdose), and drug abuse. Also, this does not include adverse events due to errors in drug administration or non-compliance (taking more or less of a drug than the prescribed amount). Using this conservative definition is to avoid overestimating the ADR incidence.

Search Strategies

The database we used was China National Knowledge Infrastructure (CNKI) spanning from January 2006 to December 2011. CNKI is a large-scale project to make Chinese scientific articles, dissertations, yearbooks, newspapers etc. digitally available through a few databases. It covers more than 8000 kinds of journals and is a must for everyone involved in research in and about China (China National Knowledge Infrastructure, 2013). In this study, CNKI was searched in Chinese by using the following keyword strategy: “adverse drug reaction” or “ADR” or “drug adverse effects” or “drug adverse events” or “drug adverse outcomes” or “drug side effects”. Articles were screened according to the titles and then selected after abstracts were read. The full text of the studies with potential relevance to the review was downloaded for further evaluation.

Study Selection

Inclusion criteria for each study were (a) the study was claimed as a research article; (b) the study described the ADR of conventional (Western and Chinese medicine) drugs; (c) The Western drugs and the formulated traditional medicines involved had registration numbers approved by the CFDA; the prepared herbal medicines should be contained in Chinese Pharmacopoeia (2010 edition); and the raw herbal medicines should be contained in Chinese Herbal Medicine Assembly.

The following kinds of studies were excluded: (a) the study was a duplicated or redundant publication; (b) reviews; (c) the ADR reported did not fit our strict definition; (d) combined use of drugs; and (e) lack of basic information on participants or ADRs.

Two reviewers (Z. Ruan and S. Yin) independently searched the database and selected studies according to the inclusion and exclusion criteria. Disagreements between reviewers were resolved by consensus after discussion. Figure.1 shows a flow diagram of study selection.

Data Extraction

A data extraction form was designed by all the authors. Two reviewers (Z. Ruan and S. Yin) independently extracted data items, including (a) citations (author, title, journal, and year); (b) characteristics of participants; (c) drugs involved in ADRs; (d) the distribution of administration routes; (e) time of the occurrence of ADRs; (f) types and clinical symptoms of ADRs; and (g) and the prognosis of ADRs. Disagreements were resolved by discussion or submitting to the third researcher (Y. Song).

Outcome Measures and Analysis

Frequency, severity, and hazard were considered during the comparison of adverse events (Li et al., 2008). For each of them, a lower value

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is better. The frequency is the number of ADR cases mentioned in the articles. The frequency of ADRs of one drugs group is the sum of ADR cases associated with each drug in this group. Severity is the point on an arbitrary scale of intensity of the adverse event in question. The existing literatures usually divided ADR into three levels: mild, moderate and serious (Li et al., 2008; Sun et al., 2003). For facilitating the quantitative

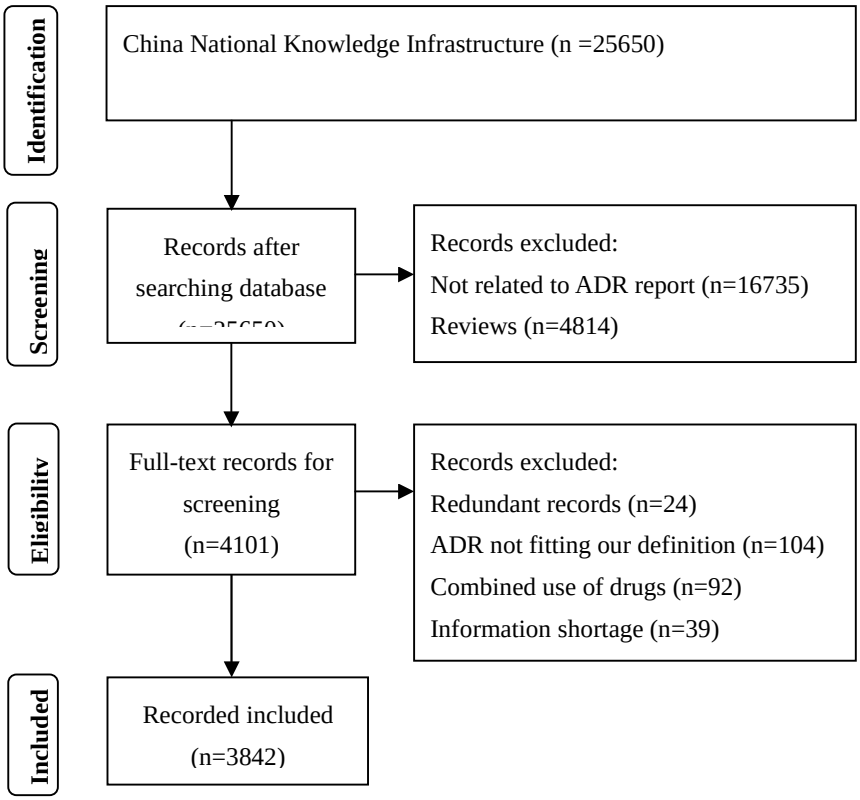

Figure1: Process of searching and screening studies

***ADR: Adverse Drug Reaction

analysis of ADR severity, this study refined the classification standard into seven levels and graded those on a scale of 1 to 7 (see table 1). The severity of ADRs of one drugs group was determined by summing the severity scoring of each ADR in this group and dividing this value by the total number of ADRs in this group. Hazard is to measure the damage caused by ADRs. The hazard of ADRs of one drugs group was determined by dividing the frequency of ADRs of this group by the total number of ADRs included in this review and multiplying this value by the severity of ADRs of this group. For group comparisons, whenever possible, we used nonparametric Mann-Whitney test.

For these three indicators, sort ratio (SR) was employed to compare the ranking of TCMs and WMs. First, we sorted frequency, severity and hazard in descending order respectively (if any values are equal, average their ranks), and then computed the SR of each indicator with the following formula.

$$SR = \frac{\sum R_c}{n_c} \Big/ \frac{\sum R_w}{n_w}$$

n_c is the number of TCMs that were ranked; n_w is the number of WMs that were ranked; $\sum R_c$ is the sum of the ranking number of each TCM; $\sum R_w$ is the sum of the ranking number of each WM. When the ranking number is big, the rank is low, vice versa. So SR>1 means the TCMs rank lower than WMs. SR=1 means TCMs and WMs have the same ranking. SR<1 means TCMs rank higher than WMs.

Table 1: New classification standard of adverse drug reactions

ADR	Definition	Grading		Score
Mild	Mild adverse effects. Patients do not take any medicine, ADRs may disappear naturally.	Level 1	Disappear after stopping taking medicine	1
Moderate	Patients with transient impairment do not need hospitalization (initial or prolonged). ADRs can disappear after treatment or intervention.	Level 2	Recovery time is less than or equal to 7 days	2
		Level 3	Recovery time is more than 7 days	3
Serious	A serious adverse effect is defined as one when the patient outcome is one of the following: a) death; b) life-threatening; c) Hospitalization (initial or prolonged); d) Disability; e) Congenital anomaly; f) Requires intervention to prevent permanent impairment or damage.	Level 4	Transient impairment and need hospitalization (initial or prolonged)	4
		Level 5	Significant, persistent, or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life	5
		Level 6	Life-threatening	6
		Level 7	Death	7

ADR: adverse drug reaction

Results

Overall Comparison

Figure 1 depicts the process of study selection. The search of bibliographical database identified 25650 potentially relevant articles. According to pre-specified selection criteria as described in Methods, 3842 studies were included for comparative analysis, which contained 5097 ADRs cases. Among them, the ADRs induced by WMs were 4374 (85.42%) and ADRs caused by TCMs were 723 (14.18%). The frequency of ADRs of WMs group was six times as high as that of TCMs group. The severity of western medicine-related ADRs (3.2850) was slightly greater than that of TCM-related ADRs (3.0845) with statistical significance (p=0.000). The hazard of ADRs of WMs group was 2.8197, 6.5 times as great as TCMs group.The 5097 cases of ADRs involved 1120 kinds of drugs in total, including 212 TCMs and 908 WMs. According to the frequency, severity and hazard of ADRs, the top 20 drugs involved in ADR are showed in table 2. The most commonly reported ADRs was to Levofloxacin injection, which had its ADRs mentioned in 123 articles. The Levofloxacin injection was also the most hazardous medicine. *Shuang Huang Lian* injection and *Xue Sai Tong* injection were the two most common Chinese medicines involved in ADRs, which were reported 50 ADR cases and 42 ADR cases respectively. Of the 1120 kinds of drugs, the SR of frequency, severity and hazard was 1.20, 1.14 and 1.27, respectively. This suggested that the western medicine-related ADRs were more intensive than Chinese medicine-related ADRs in occurring frequency, severity and hazard.

Comparisons by Pharmacology Category

According to the modern pharmacological classification, TCMs involved in this review can be divided into 14 categories. The corresponding categories of WMs were employed to make a comparison. Almost in every category, the frequency of ADRs of WMs group was high than that of TCMs group (see table 3). The most commonly reported TCMs leading to ADRs were cardiovascular medicines. Regarding WMs, the ADRs

Table 2: Top 20 drugs involved in ADRs according to frequency, severity and hazard

Frequency			**Severity**			**Hazard**		
Rank	Drug involved in ADR	Frequency score	**Rank**	Drug involved in ADR	Severity score	**Rank**	Drug involved in ADR	Hazard score
1	Levofloxacin injection	123	**1**	*Mu Xiang* [a]	7.00	**1**	Levofloxacin injection	0.1717
2	Ceftriaxone injection	89	**2**	*Huang Yao Zi* capsule [a]	7.00	**2**	Ceftriaxone injection	0.1222
3	Clindamycin injection	80	**3**	*Gua Di* [a]	7.00	**3**	Azithromycin injection	0.1099
4	Azithromycin injection	79	**4**	*Chan Su* [a]	7.00	**4**	Clindamycin injection	0.1085
5	Gatifloxacin injection	57	**5**	Micronomicin hydrochloride injection	7.00	**5**	Cefoperazone sodium and sulbactam sodium for injection	0.0783
6	Cefoperazone sodium and sulbactam sodium for injection	52	**6**	Bromisovale and procaine injection	7.00	**6**	Lidocaine injection	0.0714
7	*Shuang Huang Lian* injection [a]	50	**7**	Thymopentin injection	7.00	**7**	*Shuang Huang Lian* injection [a]	0.0687
8	Cefoperazone injection	47	**8**	Tegafur tablets	7.00	**8**	Cefoperazone injection	0.0645
9	Carbamazepine tablet	44	**9**	Huperzine-A tablets	7.00	**9**	Paclitaxel injection	0.0604
10	*Xue Sai Tong* injection [a]	42	**10**	Pravastatin sodium tablets	7.00	**10**	Gatifloxacin injection	0.0577
11	Benzylpenicillin injection	40	**11**	Meropenem injection	7.00	**11**	Carbamazepine tablet	0.0549
12	Oxaliplatin injection	37	**12**	Azathioprine tablets	7.00	**12**	Cefotaxime sodium injection	0.0508
13	Lidocaine injection	36	**13**	Protamine sulphate injection	7.00	**13**	Benzylpenicillin injection	0.0494
14	Cefotaxime sodium injection	36	**14**	Compound metamizole sodium tablets	7.00	**14**	Oxaliplatin injection	0.0494
15	Paclitaxel injection	35	**15**	Compound acpirin tablets	7.00	**15**	*Xue Sai Tong* injection [a]	0.0481
16	Ceftazidime injection	35	**16**	Bicalutamide tablets	7.00	**16**	Iohexol injection	0.0481
17	Dexamethasone injection	32	**17**	Aspirin capsules	7.00	**17**	Dexamethasone injection	0.0439
18	Clindamycin phosphate injection	32	**18**	Pirarubicin injection	6.75	**18**	Tiopronin injection	0.0424
19	Amiodarone injection	29	**19**	5-Fluorouracil injection	6.75	**19**	*Qing Kai Ling* injection [a]	0.0384
20	Fat emulsion injection	29	**20**	Propofol injection	6.67	**20**	Vitamin K1 injection	0.0379

ADR: adverse drug reaction

[a] Traditional Chinese medicines

were more associated with anti-infective medicines. Additionally, the severity and hazard of ADRs induced by WMs were also greater than TCMs in most categories, especially in antineoplastic and immunosuppressives, diuretics, ophthalmological preparations and medicines affecting the blood groups. In the comparisons by pharmacology category, the SR of frequency, severity and hazard of ADRs was 1.50, 1.45 and 1.74, respectively. This also indicated that most WMs ranked higher than TCMs in occurring frequency, severity and hazard.

Table 3: Adverse drug reactions by pharmacology category

Pharmacology category	Frequency		Severity		Hazard	
	TCMs	WMs	TCMs	WMs	TCMs	WMs
Ear, nose and throat medicines	10	9	2.40	2.33	0.0047	0.0041
Medicines for disease of joints	16	42	2.88	3.10	0.0090	0.0255
Medicines acting on the respiratory tract	26	95	3.00	2.98	0.0153	0.0555
Hormones, other endocrine medicines and contraceptives	1	171	2.00	3.18	0.0004	0.1065
Medicines for pain and palliative care	91	217	2.98	3.34	0.0532	0.1422
Anti-infective medicines	129	1628	3.51	3.24	0.0889	1.0334
Antineoplastic and immunosuppressives	53	363	2.60	3.82	0.0271	0.2721
Diuretics	5	40	1.80	2.95	0.0018	0.0232
Dermatological medicines	14	21	2.71	2.43	0.0075	0.0100
Gastrointestinal medicines	55	253	3.27	3.05	0.0353	0.1515
Cardiovascular medicines	146	355	3.08	3.23	0.0883	0.2250
Ophthalmological preparations	1	35	1.00	2.63	0.0002	0.0180
Medicines acting on central nervous system	138	344	3.20	3.15	0.0867	0.2127
Medicines affecting the blood	16	163	2.19	3.83	0.0069	0.1226
Sort ratio		**1.50**		**1.45**		**1.74**

TCMs: Traditional Chinese medicines; WMs: Western medicines

Table 4: Adverse drug reactions by administration route

Administration routes	Frequency		Severity		Hazard	
	TCMs	WMs	TCMs	WMs	TCMs	WMs
Oral administration	200	1167	2.56	2.90	0.1007	0.6655
Injection	480	3066	3.39	3.44	0.3200	2.0741
External use	16	35	3.31	2.43	0.0104	0.0167
Rectal administration	14	14	1.64	3.71	0.0045	0.0102
Inhaling	4	25	1.30	3.04	0.0010	0.0150
Others	12	52	1.50	2.93	0.0040	0.0300
Sort ratio		**1.66**		**1.60**		**1.69**

TCMs: Traditional Chinese medicines; WMs: Western medicines

Comparisons by Administration Route

Of 5097 ADR cases, 5085 reported the administration route. From the distribution of administration routes of the medicines inducing ADRs (see table 4), it can be easily found out that the cases caused by injections were the most, which was up to 3546 pieces and accounted for 69.73%

of the total. Among them, the number of reports of ADRs due to intravenous injection was the largest, about 2944 cases accounting for 57.90% of all. Moreover, the ADRs associated with injections were also the most hazardous. The severity of ADRs induced by injections scored more than 3 and these reactions were serious. This situation was found similar in both TCMs group and WMs group. Furthermore, other administration routes including oral, inhaling, external use, and rectal administration had 1539 ADR reported cases, 30.27% of the total, which indicated every administration route was possible to cause ADRs. Overall in the comparisons by administration routes, the SR of frequency, severity and hazard of ADRs was 1.66, 1.60 and 1.69, respectively. This also suggested that the risks and the number of ADRs caused by WMs were higher than TCMs.

Discussion

Drugs have the duality and could take some side-effects in the process of curing disease, Western medicines and TCMs are no exception (Zhang et al., 2005). Based on the sufficient evidence from ADR report and follow-up assessment**,** the regulatory actions taken in cooperation with the drug's sponsor in most countries including China may include: (a) adding the newly discovered adverse reaction to the drug's labeling; (b) sending letters to health professionals advising them of the adverse reaction; (c) restricting distribution and use of the drug; or (d) withdrawing the drug from the market (Zhang et al., 2012).

The results of this review suggested the hazard and the number of ADRs caused by Western medicines were about six times as high as TCMs. There was also significant difference in the severity of ADRs between them. In the comparisons by pharmacology category and administration route, the findings showed that most WMs ranked higher than TCMs in occurring frequency, severity and hazard of ADRs. So it demonstrated that the adverse effects from Chinese herbs were comparatively rare and the risks caused by TCMs were milder than WMs. Similar findings could be seen in Hong Kong, which showed that only 0.2% of the general medical admissions to the Prince of Wales Hospital were due to adverse reactions to Chinese medicine, as compared to 4.4% of admissions caused by Western pharmaceuticals (Chan et al., 1992). Therefore, the results of this review provide preliminary data to suggest that TCMs may be safe in comparison with WMs.

However, in some cases, herbs may also have safety issues that should be considered. Most of them were caused by injection, especially intravenous administration. It was reported that there were more than 100 kinds of TCM injections, accounting for less than 3% of 4000 kinds of TCM patent medicines, but adverse events of TCM injections accounted for more than 70% of all TCM adverse events (Luo, 2010). The preferred methods of use of TCM drugs in terms of safety are usually oral, intramuscular and then intravenous administration (Zhang et al., 2012). This statement is also confirmed by our findings. Table 5 lists frequently reported ADRs associated with TCM injections in the Chinese-language literatures (Cheng, 2006; Du et al., 2008; Gao, 2005; Gao et al., 2006; Han et al., 2006; Huang et al., 2006; Li et al., 2009; Li, 2005; Liang et al., 2006; Lin et al., 2009; Lin et al., 2005; Liu et al., 2005; Luo, 2005; Mo et al., 2006; Mo, 2008; Ouyang, 2008; Wang et al., 2010; Wang et al., 2005; Wang et al., 2008; Wang, 2009; Wu et al., 2008; Xun et al., 2007; Yang et al., 2005; Zeng et al., 2005; Zhang, 2005). TCM injection is an innovative and quick-acting dosage form. It has played a significant role in clinical treatment of acute and severe syndromes. The causes of TCM injection inducing ADRs might be the unstable quality of preparation; the irrational clinical use and operation; the sensitive physique of patient and the change of patients' primary illness, etc. Furthermore, although the ADRs of raw and prepared herbal medicines were rare, however some ADRs are sometimes even life-threatening, which should be drawn broad attention. For example, the *Gua Di Shui* which was mentioned in only one article caused death.

However, it is important to remember that these adverse events of TCMs are extremely unusual. The reported adverse events should not eclipse the importance of Chinese medicines. Chinese herbal medicine is generally both safe and effective, and there are many patients who have experienced dramatic benefits to their health from treatment (Blackwell, 1996; Yu et al., 2012). The vast majority of adverse events involving Chinese herbs which have been reported in the literature can be avoided by proper identification and quality control of herbs by manufacturers and suppliers, improvements to the training and regulation of both practitioners and dispensers, and enhancement of precautionary awareness of ADRs in medical units (Li, 2010; Wu et al., 2008). Furthermore, a handful of herbs traditionally known to be seriously toxic, such as Cao Wu and Wu Tao, should probably be restricted to use in hospital settings only. Herbs with some potential for toxicity, such as Fu Zi, should not be prescribed for patients who are also taking modem drugs. These improvements will assist greatly in establishing Chinese herbal medicine in the West as a safe and effective form of treatment. There are a number of limitations within the data that forms the bias of this review. The first is

Table 5: Most commonly reported ADRs associated with TCM injections

TCM injection	Adverse potential
Yu Xing Cao injection	Anaphylactic shock, hyperpyrexia, dyspnea, palpitation, fall of blood pressure, rash, and pruritus
Ge Gen Su injection	Rash, asthma, fever, hepatic lesion, hemolytic anemia, anaphylactic shock, and death
Qing Kai Ling injection	Allergic reaction, and death
Shuang Huang Lian injection	Anaphylactic shock, dyspnea, exfoliative dermatitis, and death
Fu Fang Dan Shen injection	Anaphylactic shock, cardiac arrest, sinus bradycardia, or sinus tachycardia, asthma, hepatorenal damage, urticaria, headache, chest congestion, dysphoria, eyes edema, and backache
Shen Mai injection	Anaphylactic shock, dyspnea, and death
Chuan Hu Ning injection	Rash, dyspnea, shiver, fever, thrombocytopenia, and anaphylactic shock
E Shu You injection	Rash, dyspnea, anaphylactic shock, and death
Yin Zhi Huang injection	Rash, anaphylactic shock, abdominal pain, diarrhea, backache, hemianesthesia, and death
Mai Luo Ning injection	Rash, anaphylactic shock, stenocardia, hematuresis, acute renal failure, and microcirculation disturbance
Ci Wu Jia injection	Rash, pruritus, headache, shiver, fever, nausea, vomiting, palpitation, allergic asthma, dyspnea, anaphylactic shock, and death
Deng zhai hua injection	Rapid atria fibrillation, chest congestion, nausea, vomiting, rash, diarrhea, and joint swelling
Huang Qi injection	Urticaria, phlebitis, anaphylactic shock, myalgia and gastrointestinal disorders

selective publication of positive cases. Serious ADRs usually tend to be published and mild adverse reactions are possible to be ignored. This publication bias might make ADR measures more severe. However, this potential bias existed in both literatures about ADRs of WMs and TCMs, which might not remarkably affect the results of the comparison. In addition, within the parameter of data sources, the collected cases did not reflect the whole situation. However, the data structure of adverse reactions is almost the same with the record by China National ADR Monitoring Center and other review results. Thus we believe this review can provide a rational argument for the safety of TCMs and continued investigation and use. However, further research is warranted to include studies not written in Chinese.

Conclusions

The adverse effects from Chinese herbs were comparatively rare and the risks caused by TCMs were milder than WMs based on the review of Chinese-language literatures from 2006 to 2011. It is possible to reach a conclusion in this study that Chinese herbal medicines are safe in clinical practice compared with Western medicines, though not risk free. Improvements in quality control and in the training and regulation of practitioners would substantially reduce the already low incidence of problems involving TCMs.

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