Mining potential adverse drug reactions of Houttuynia cordata Thunb from "real world" cases

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Abstract

Objective: Search the "real world" case reports of Houttuynia cordata Thunb (HCT)-associated adverse drug reactions (ADRs) to systematically mine potential ADRs of HCT and further investigate whether HCT contained preparations could cause aristolochic acid nephropathy or cancer.

Methods: PubMed, EMBASE, Science Direct, Scopus, Web of Science, and CNKI, Wanfang, VIP, Sinomed databases were searched from databases setup to 1st January 2019. All case reports using HCT contained preparations were pooled according to inclusion and exclusion criteria. 15 items in case reportes including basic informations of studies/patients, characters/treaments of ADRs were extracted and analyzed.

Results: A total of 346 case reports (441 patients) on the use of different preparations of HCT were finally pooled, among which 89 articles (117 patients) just presented efficacy reports without ADRs and 257 articles (324 patients) on the HCT-related ADRs were further analyzed. ① HCT in vivo injections were recorded in 265 articles (338 patients) including 249 ADR reports (315 patients) and 16 efficacy reports (23 patients). As for the ADRs reports, allergic reaction was the major ADRs with different symptoms and onset time. The worst consequences were anaphylactic shock (116/315) and death (11/315), followed by dyspnea (228/315), change of complexion (181/315), heart of abnormality (180/315), chest tightness (147/315), cyanosis (142/315) and so on. The fast onset time was 10 seconds and the most ADRs happened in 30 minutes. Dexamethasone was the mainly medication to treat ADRs. ② Oral HCT agents were descripted in 75 articles (94 patients) including 8 ADR reports (9 patients) and 67 efficacy reports (85 patients). Among the 8 ADR reports, 8 patients used Chinese patent medications contained HCT and only 1 patient used HCT decoction. The ADRs almost manifested as skin symptoms, including rubella, macula, rash and urticaria. ③ HCT external preparations reported in 6 articles (9 patients), none of those presented any ADRs symptoms. ④ No case was found to develop cancer, aristolochic acid nephropathy, interstitial nephritis, renal interstitial fibrosis or renal failure due to HCT preparations.

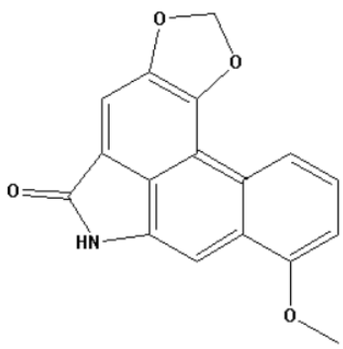
Conclusion: The HCT-related ADRs were mostly caused by its processed preparations, including HCT injections and patent preparation. The oral HCT agents as docoction rearly caused ADRs. There were no reports of aristolochic acid nephropathy or cancer cases caused by HCT.

Key words: Houttuynia Cordata, *In vivo* injections, Oral agents, Adverse drug reactions

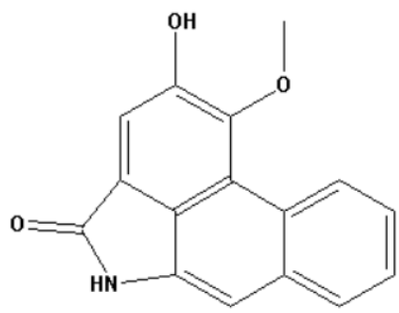
Introduction

Houttuynia cordata Thunb (HCT), the sole species in the genus Houttuynia that belongs to the Saururaceae family, is an important medicinal plant widely used in traditional Chinese medicine. The perennial herb has bitter tasete and sight cold meridian tropism. According to Li Shi-zhen's Ben Cao Gang Mu, it has the functions of relieving fever, resolving toxin, reducing swelling, draining pus and promoting urination. With the development of modern medical technology, Chinese patent medicine containing HCT has been widely used in the treatment of tonsillitis, pharyngitis, urinary tract infection, acute bronchitis, endometritis, lung abscess, etc. And the preparations of HCT developed from single oral preparation to a variety of preparations, such as injections and eye drops.

Besides medicinal value, HCT has become a kind of "delicious vegetable" in all parts of China, especially in southwestern China for more than 2,000 years. However, nowadays, it has attracted attention due to the ingredient of aristolochic lactam A II (First report by German in 1992) [1], as a research published in 2017 argued that there was a relationship between Aristolochic acid (AAs) and hepatocellular carcinoma [2]. The metabolited of AAs is aristolochic lactam I, and it can form DNA adduct with the nucleus of renal cortex cells, which has irreversible and permanent carcinogenicity. but aristolochic lactam I and A II are two different molecules with different structures (Figure 1). As a medicine-food homology plant, HCT has been used in China for thousands of years. Whether there is any link between it and cancer is related to the health of millions of people. The real world case reports are the first references of the thesis of medical research. Therefore, we intend to verify the efficacy or side effects of HCT from the real world case reports, in order to find evidence of the toxic side effects of HCT.



Aristolochic lactam I, from Aristolochic acid



Aristolochic lactam A II, from Houttuynia cordata Thunb

Figure 1: The structures of Aristolochic lactam I and A II

1 Materials and methods

1.1 Search strategies

PubMed, EMBASE, Science Direct, Scopus, Web of Science, and CNKI, Wanfang, VIP, Sinomed databases were searched from databases setup to 1st January 2019 with the terms "Houttuynia AND case report".

1.2 Inclusion criteria:

① Only case reports were pooled, with the basic information about the patients, such as age, gender, primary diseases, therapeutic schedule, or clinical symptoms of ADRs, treatments for ADRs. ② No limitation in the dosage forms. ③ The incidence of side effects was related to HCT.

1.3 Exclusion criteria

Repeated publications; Literature was not available; Non-Chinese and English literature; Systematic evaluation and meta-analysis literature; Summary of case reports; Animal research literature; Clinical observation literature; Clinical controlled research literature; Cell and virus research literature; Production and preparation of preparations research literature.

1.4 Data extraction and data analysis

Two researchers independently screened the studies and extracted data. Any discrepancies was discussed and solved by two researchers.

Following informations were extracted: ① The basic information of the reports (eg. author, title, years, journal. 4 items); ② The basic information of the patients (eg. age,

gender, primary diseases, allergic history. 4 items); ③ The characters of ADRs case reports (eg. therapeutic schedule, the onset time, the clinical symptoms, the inproving time and the improvement. 5 items); ④ Treatments for ADRs (eg. therapeutic schedule and improvement, 2 items). Totally, 15 items of the above four aspects were gotten from the original text of each case reports, and conducted a descriptive analysis for the items.

2 Results

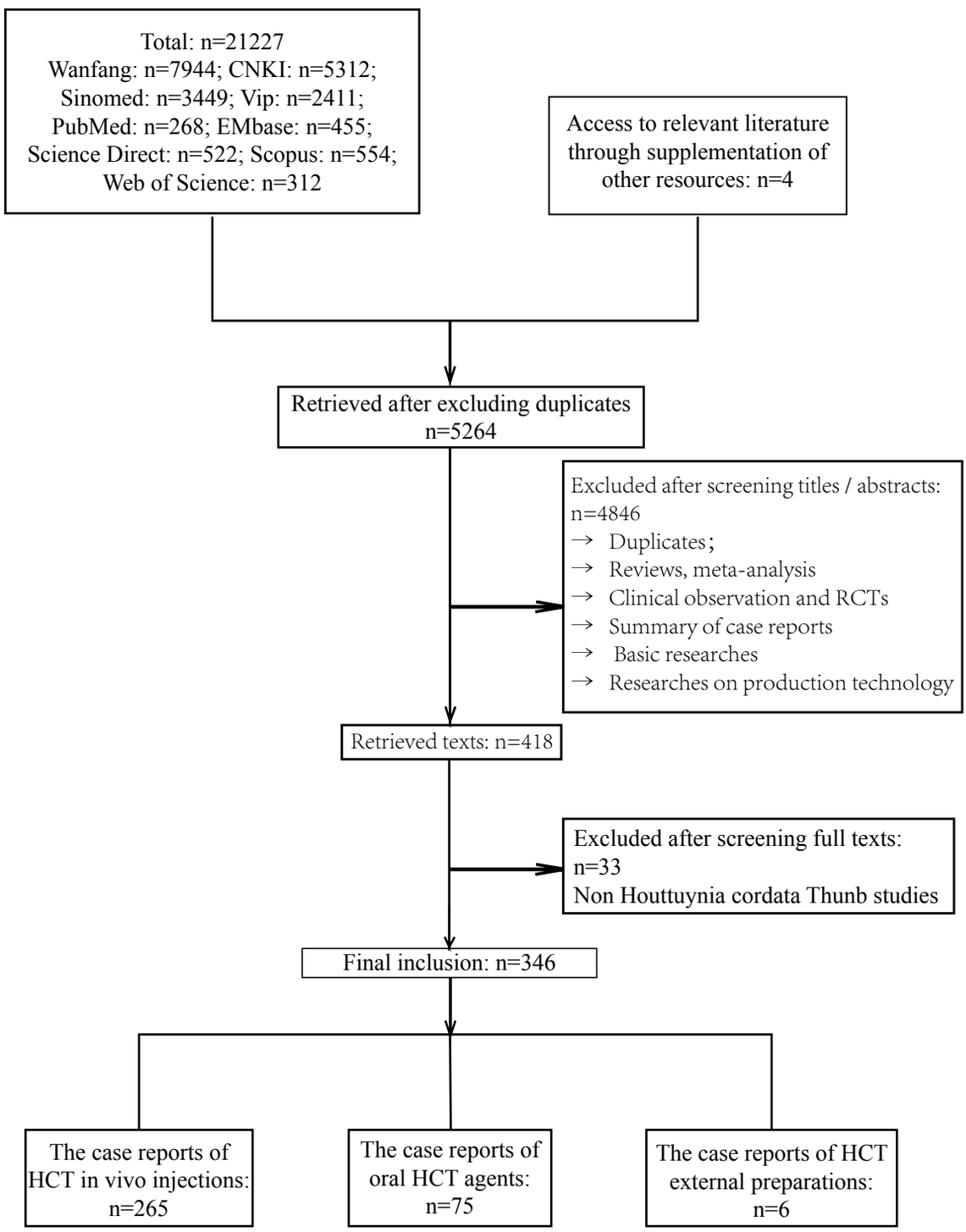


Figure 2: The flow chart of study screening

Based on inclusion and exclusion criteria, a total of 346 case reports of different preparations of HCT were finally included with a tatal of 441 patients (Figure 2). Of the 346 included studies, 265 were case reports about HCT in vivo injections with 338 patients, 75 were case reports about HCT oral agents with 94 patients, 6 were case reports about HCT external preparations with 9 patients.

2.1 The pooled analysis for case reports of HCT *in vivo* injections

There were 265 case reports (338 patients) of HCT *in vivo* injections incluing 144 males and 189 females with 5 gender unknown, of which, 16 articles with 23 patients reported the effects, and 249 articles with 315 patients were HCT injections-related ADRs case reports. The age of patients ranged from nine-month to 84-year-old, with the median age at 28-year-old or the average age at 28.08-year-old (Figure 3). There were 5 patients whose age was unknown.

2.1.1 The basic information of the patients

Allergic history: In the 338 patients (265 case reports), 60 of them reported no allergic histories and 116 reported allergic histories. Other 162 patients did not describe allergic history at all.

Primary diseases: Respiratory diseases were the most common diseases for the treatment of HCT *in vivo* injections; and followed by fever, urinary diseases (Table 1).

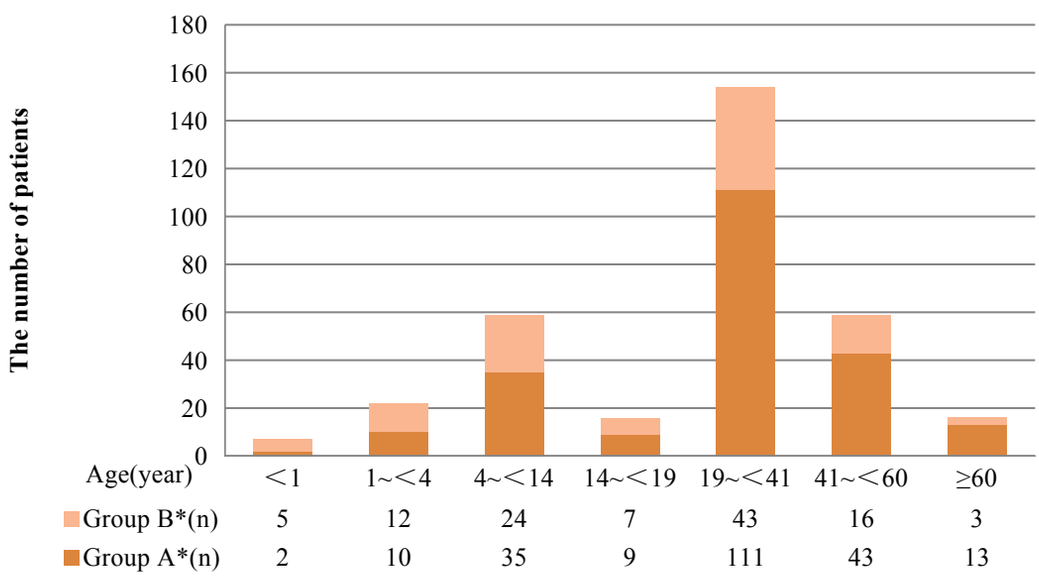


Figure 3: The age distribution for pooled case reports of HCT *in vivo* injection（n=333）

Note: Group A: the patients only treated by HCT *in vivo* injections
Group B:the patients treated with combined medications including HCT *in vivo* injection

Table 1: Primary diseases treated by HCT *in vivo* injection in the cases

Protopathies	Total (n)	Group A (n)	Group B (n)	Protopathies	Total (n)	Group A (n)	Group B (n)
Upper respiratory tract infection				Urinary system infection			
Common cold	50	38	12	Urinary infection	11	6	5
Tonsillitis	20	11	9	Others	3	3	---
Pharyngitis	7	4	3	Acute cystitis	2	1	1
Pharyngolaryngitis	1	-	1	Gynecological inflammation			
Others	109	76	33	Pelvic infection	9	5	4
Lower respiratory infection				Others	5	2	3
Pneumonia	22	12	10	Vaginitis	3	2	1
Bronchitis	18	12	6	Digestive system disease			

Acute bronchitis	16	9	7	Bellyac and Diarrhoea	5	5	-
Chronic bronchitis	7	5	2	Appendicitis	3	2	1
Others	7	2	5	Gastroenteritis	2	1	1
Pulmonary infection	5	4	1	Enteritis	2	-	2
Tuberculosis	3	3	-	Cholecystitis	1	1	-
Bronchial asthma	1	1	-	Others	2	0	2
Tracheitis	1	1	-	Ceratitis	2	1	1
Other respiratory tract Infections	4	3	1	Others	22	16	6
Fever	172	110	62	Unknown	2	2	-

The route of administration: The most common route of administration for HCT injection was intravenous drip (85.0%, 272/320), followed by intramuscular injection (10.3%, 33/320). Houttuynine sodium injection was all administered by intravenous drip (18/18).

The dosage and solvent: When the injections was administered by intervenous drop, the dose of HCT injection ranged from 4ml to 100mL. And it was mainly diluted by 5% glucose injection. 58 patients were administered directly by intravenous drip without dilution. The dose of Houttuynine sodium injection ranged from 2mg to 20mg, and it was mainly diluted by 5% glucose injection. When the injections was administered by intramuscular injection, the dose of HCT injection ranges from 1ml to 16ml. (Table 2)

Table 2: The solvent and route of administration for houttuynia *in vivo* injections

Route of administration	HCT injection (320 patients) (n)	Houttuynine sodium injection (18 patients) (n)
Travenous drip		
50~500ml 5% glucose injection	141	16
50~500ml 10% glucose injection	31	1
100~250ml 5% sodium chloride and glucose injection	5	-
100~250ml 0.9% sodium chloride injection	6	1
Undiluted	58	-
Unknown	31	-
Intramuscular injection	33	-
Acupoint injection	4	-
Intravenous injection	2	-
Subconjunctival injection	2	-
Enema	2	-
Oral (keep in the mouth for 10 min)	1	-
Unknown	4	-

Drug combination: HCT *in vivo* injections were used alone in 227 patients. 111 patients were treated with combined medications including HCT *in vivo* injections. The most common drugs combined with HCT *in vivo* injections in the cases were antibacterial agents (77.5%, 86/111) (Table 3).

Table 3: Other medications combined with HCT *in vivo* injection

Medications	Numbers	Medications	Numbers
Antibacterial agents		Other medications	
Cephalosporins	28	Dexamethasone	6
Penicillins	21	Antipyrine	3
Azitromycin	7	Daqing Root Injection	3
Floxacins	6	Aminopyrine Injection	2
Lincomycin	5	Solcoseryl	1
Erythromycin	4	Vitamin C	1
Fosfomycin	4	Recombinant Human Interferon	1
Clindamycin	3	Ribavirin	1
Metronidazole	3	Shilexin	1
Gentamicin	2	Danshen Injection	1
Amikacin	1	Bolus of Six Drugs Including Rehmannia	1
Tinidazole	1	Decoction of Gentiana for Purging the Liver-Fire	1
Netilmicin	1	Shenmai Injection	1
Fu Fang Zi Xin You	1	Bupleurum Injection	1

2.1.2 The symptoms of the HCT *in vivo* injections-related ADRs

A total of 265 case reports with 338 patients accepted HCT *in vivo* injections treatment. Among them, there were 23 cases without ADRs (6.8%, 23/338) occurred during the treatment and 315 patients experienced ADRs (93.2%, 315/338) (Figure 4). The common clinical symptoms of ADR cases after HCT in vivo injections was dyspnea (72.4 %, 228/315), change of complexion (57.5 %, 181/315), heart of abnormality (57.1 %, 180/315), chest tightness (46.7 %, 147/315), cyanosis (45.1 %, 142/315) and so on. There were 11 patients even presenting other symptoms, including hematuria, oliguria, hemolysis, neuritis, multiple organ failure, instant amaurosis, convulsion in childhood, acute cellulitis, urogenital abnormalities and infusion reaction, respectively. Of 315 patients with ADRs, 281 patients were diagnosed with allergic reaction, other 32 patients can be classified as allergic reaction according to their symptoms and onset/ improving time, remained 2 patients could not be classified as allergic reaction. There were 116 patients presented with anaphylactic shock. 11 patients died due to HCT *in vivo* injections (the dosage of HCT *in vivo* injections ranged from 1.33mL ~ 100mL).

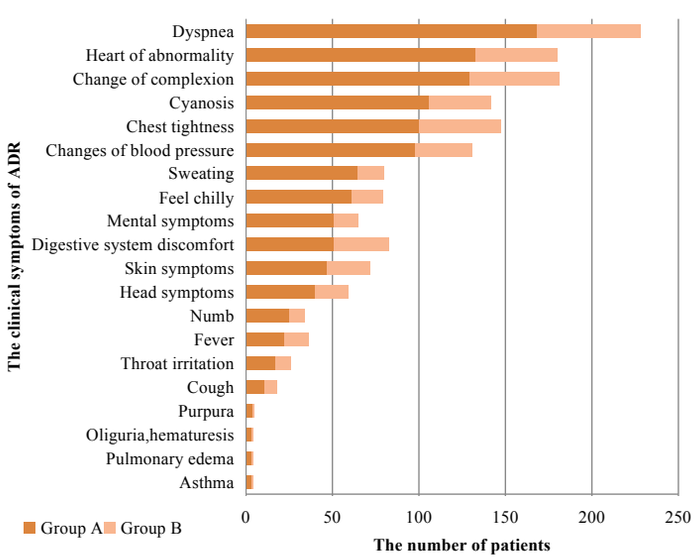


Figure 4: The clinical symptoms of ADRs cases after HCT *in vivo* injection（n=315）

Note: Group A: the patients only treated by HCT *in vivo* injections
Group B: the patients treated with combined medications including HCT *in vivo* injections

2.1.3 The onset time/ taken dosage of the ADRs cases

After using HCT *in vivo* injections, 251 of the 315 patients reported the onset time of ADRs, with the shortest in 10 seconds and the longest at 10 days (the median time less than 10 minutes). Most of the ADRs (65.8%, 231/315) happened in 30 minutes (Figure 5a); while, 44 of the 315 patients reported the dosage at ADRs, with the minimum dosage at 3mL and the maximum dosage at 400 mL (the median at 30mL) (Figure 5b). Other 20 patients with ADRs did not describe the onset time or taken dosage.

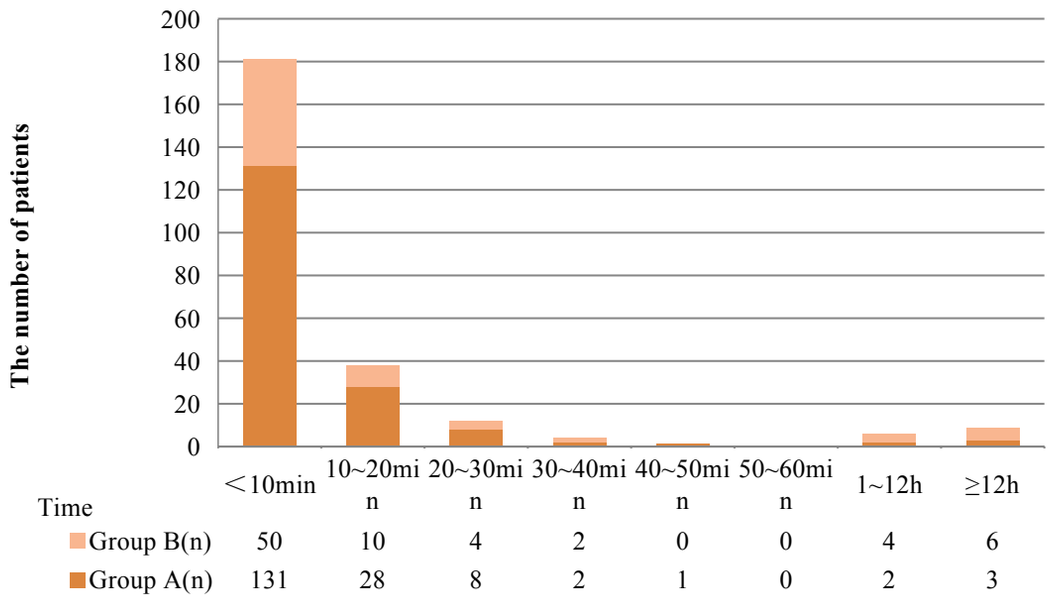


Figure 5a: The onset time of ADRs in cases after using HCT *in vivo* injections (n=251)

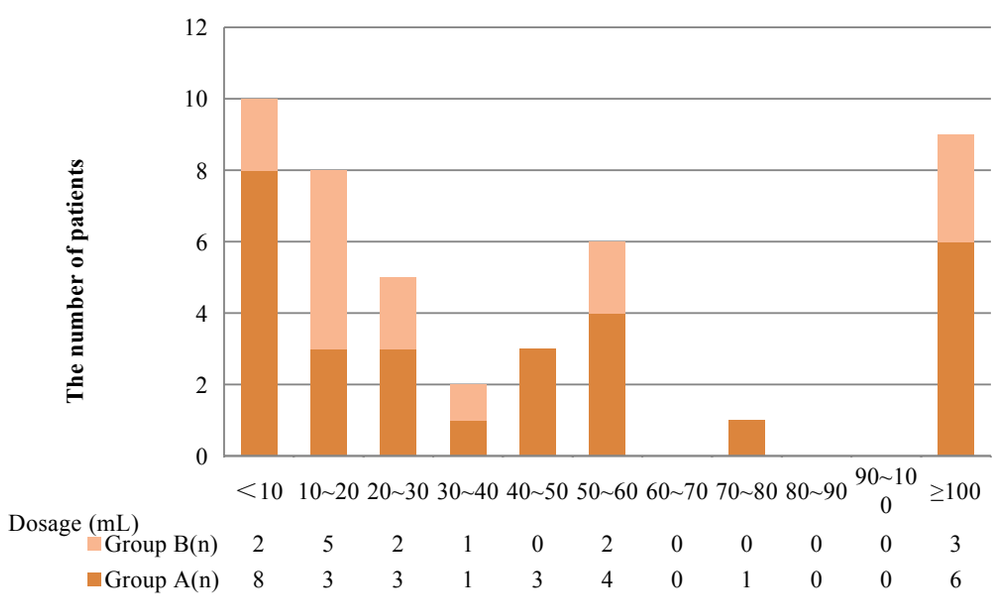


Figure 5b: The taken dosage of HCT *in vivo* injections in ADRs cases (n=44)

2.1.4 The treatment to the ADRs cases

Non-drug therapy: 242 patients in 184 articles discontinued HCT *in vivo* injections after ADRs appeared, 189 patients were given oxygen inhalation and 63 patients were ordered to lie flat.

Drug therapy: 271 patients in 221 articles were given relative medications to treat the ADRs symptoms, such as glucocorticoids (86.3 %, 234/271), vasoconstrictors (47.9 %, 130/271) and antihistamines (44.7 %, 121/271). The major agents were dexamethasone, adrenaline, promethazine and calcium gluconate (Figure 6).

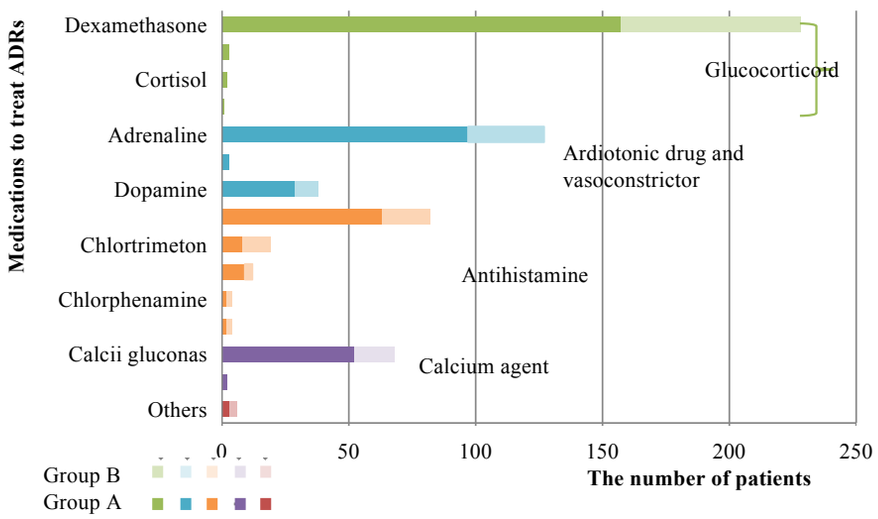


Figure 6: Medications to treat ADRs of HCT *in vivo* injections in the cases (n=282)

2.1.5 The improvement time:

In the 315 patients with HCT injections-related ADRs, 254 of them reported improving time after ADRs, with the shortest in 10 seconds and the longest at 5 days (the median at 20 minutes). 50 patients did not describe the improving time after ADRs and 11 patients died without improving time. (Figure 7).

The improvement of the ADRs cases: After treatment for the 315 ADRs cases, 304 patients improved and 11 patients died.

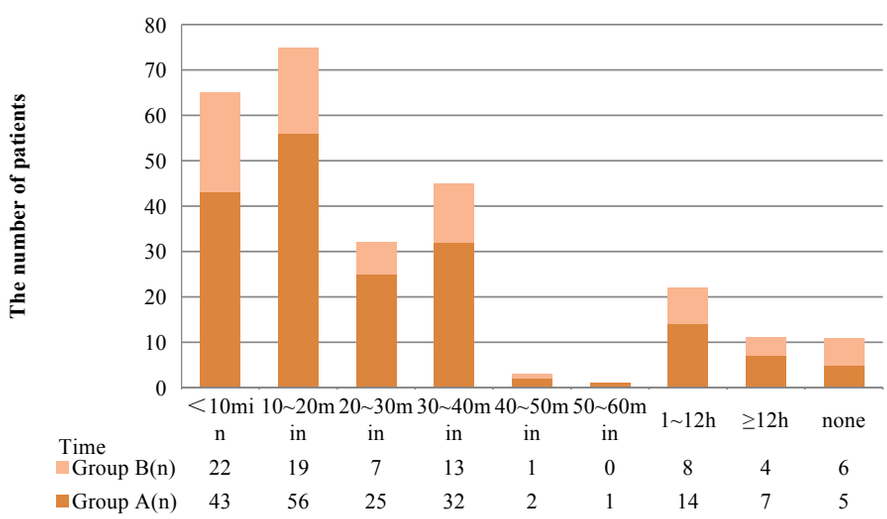


Figure 7: The improving time after ADR of HCT *in vivo* injections (n=265)

2.2 The pooled analysis for case reports of oral HCT agents

There were 75 case reports with 94 patients using oral HCT agents for treatment, including 44 males and 50 females. The aged of the 94 patients were from eight-month to 74-year-old, with the median age at 34-year-old (Figure 8). All the patients did not describe allergic history. The 75 case reports included 8 ADR reports (9 patients) and 67 efficacy reports (85 patients).

Primary diseases: The most common diseases treated by oral HCT agents were respiratory infections (56.4%, 53/94), followed by cancer (9.6%, 9/94), nephritis (5.3%, 5/94), urinary tract infection (5.3%, 5/94), gynecological inflammation (4.2%, 4/94), skin inflammation (2.1%, 2/94), tuberculosis (2.1%, 2/94) and digestive system discomfort (2.1%, 2/94), etc. (Figure 9)

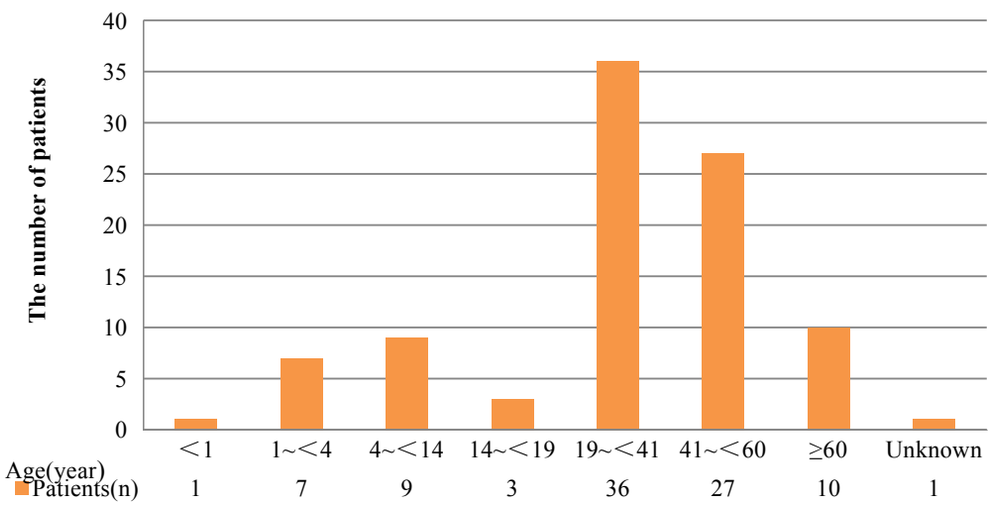


Figure 8: The age distribution for pooled case reports of oral HCT agents (n=94)

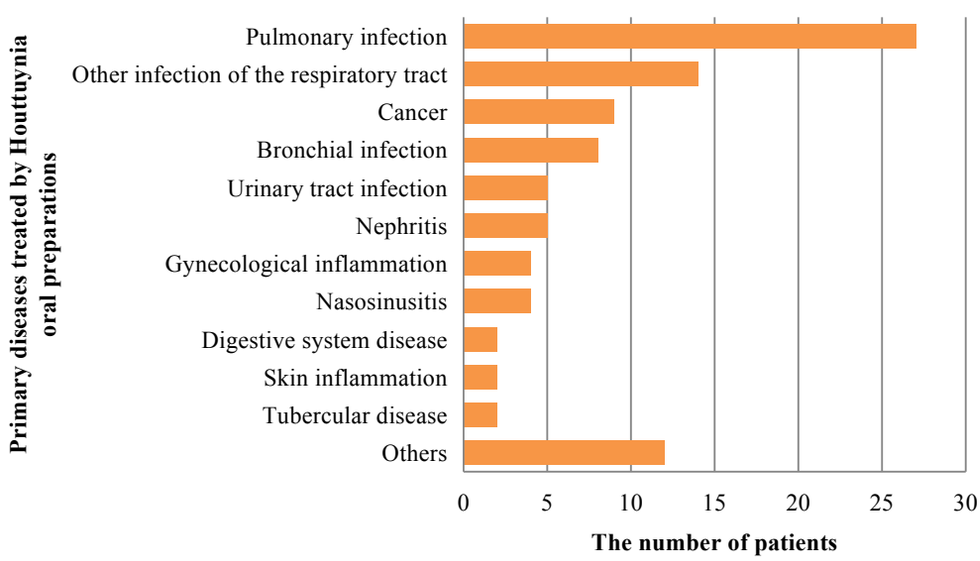


Figure 9: Primary diseases treated by oral HCT agents in the cases (n=94)

The dosage forms of administration: Of the 94 patients, 82 patients uesd HCT decoction, 2 used HCT chewable tablets, 2 used Xian Zhu Li Oral Liquid. Other 8 patients used HCT powder, HCT granules, HCT syrup, Zhi Tong Hua Zheng capsule, Lian Hua Qing Wen capsule, Huang Long Ke Chuan granules, Rhinitis or Anti-virus granule, respectively.

The dosage of administration: For HCT decoction, the dosage of dry HCT was between 8g and 60g, the dosage of fresh HCT was between 20g and 250g.

The improvement of the ADRs cases and the treatment overment of the efficacy cases: 85 of the 94 patients reported the efficacy of oral HCT agents without ADRs, while 9 of the 94 patients reported the ADRs of oral HCT agents. The major ADRs of the 9 patients were skin symptoms, such as rubella, maculopapule, exanthema, urticaria. In the 9 patients, 8 of them used HCT patent drugs and only 1 used HCT decoction. For the ADRs after using oral HCT agents, the shortest onset time was 10 minutes and the longest was 3 days. All the patients got better after treatment for the ADR cases.

2.3 The pooled analysis for case reports of HCT external preparations.

There were 6 case reports with 9 patients for HCT external preparations, including 7 males and 2 females, age ranking from seven-month to 65-year-old. The HCT external preparation most from fresh HCT were used to treat erysipelas, skin pustules, chronic abscesses, carbuncle and acute mastitis. All the patients recovered after 3 to 10 days of treatment by external application of HCT and no ADRs were reported. All the patients did not describe allergic history.

3 Discussion

By the end of 2018, there were more than 10,000 articles discribing HCT from China or other contries, including 30% clinical studies, 17% review, 13% ingredient-identifical studies, 11% laboratory studies, 3.4% case reports and 25.6% other articles. Present study just focus on case reports and intend to clarify HCT related ADRs in the real world, and further to make clear wether HCT have any relevant with interstitial nephritis, renal interstitial fibrosis, even aristolochic acid nephropathy or cancer. We finally reviewed 346 case reports of 441 patients using different preparations of HCT, of which 1/4 cases just reported efficacy without ADRs and 3/4 articles reported the HCT-related ADRs. We found no case in the 441 patients reporting interstitial nephritis or renal interstitial fibrosis. Not to mention aristolochic acid nephropathy or cancer although HCT was suspected due to containing Aristolochiaceae lactam, a potential carcinogen.

In the systematic review, it was noteworthy that the HCT-related ADRs were mainly (96.9%) caused by HCT *in vivo* injections and rarely (3.1%) caused by oral HCT agents. As for the the HCT *in vivo* injections-related ADRs, the vast majority was allergic reaction with diffierent symptoms, such as dyspnea, heart of abnormality, change of complexion, chest tightness, cyanosis. The worst consequences were anaphylactic shock (36.8%) and death (3.5%). About 72.1% ADRs happened in 10 minutes after HCT in vivo injections, which was irrelevant to the dosage of HCT. And most of them (81.9 %) can relief quickly within 40 minutes after treatment according to symptoms. Wu [3], Shan [4] *et al.* reached the same conclusions based on ADR data of HCT injection (2554 cases) recorded in National ADR Center before 2008, and Wu [5] *et al.* also arrivaled at the same conclusions. Interestely, we found that the number of adult patients was more than that of the juveniles and elders as well as ADRs' onset time in most case reports was so quick that was in 10 minutes after HCT *in vivo* injections. These results was consistent with the reports by Wu [3], Wu [5], Li [6-8], and Li [9] *et al*. We paid more attention to the ADRs relating to the kidney lesion, and found that only 1.6% of the patients experienced hematuria and oliguria, and all of them got better after treatment.

Differently, most ADR cases (67.3%) were caused by HCT *in vivo* injections alone, and 76% of anaphylactic shock were also caused by HCT *in vivo* injections alone. It's different from the previous point of view, like "severe ADR rarely occurs when used alone, and allergic reactions easily occur when combined with other injections" [6-9].

For the first time, medications for the treatment of ADRs by HCT *in vivo* injections were summarized systematically. The resultes showed that more than 3/4 of the patients were treated by glucocorticoids, and more than 1/2 were treated by vasoconstrictors or antihistamines to alleviate allergic symptoms and rescue anaphylactic shock. All of these further clarify that most HCT injection related ADRs were just allergic reactioon.

In addition, in the case reports of oral HCT agents, most cases (89.3%) were to report the efficacy of HCT on the treatment for respiratory tract infection or cancer. Only 10.7% cases were to report ADRs of oral HCT agents, of which 88.9% patients used HCT Chinese patent drugs in stead of docoction.

Combining above results, the HCT-related ADRs were mainly caused by its in vivo injections and Chinese patent medicines. Both of them are manufacture preparations and various excipients and impurities may bring allergens in to injection or oral HCT agents. Li [7] *et al.* run a study on HCT injection, and found that the main reason of sensitization of HCT injection was that excessive Tween 80 concentration in the production of HCT injection. It was also pointed out that the causes of ADRs of HCT injection also include the nonstandard production process [6,8], the unstable property of the active component decanoyl acetaldehyde [10]. It is clear that most HCT-related ADRs are

irrelevant to HCT itself. That is why that the HCT-related ADRs rarely occur in decoction treatment, but mainly caused by processed preparations.

Furthermore, we also systematically analyzed the clinical controlled trials (168 articles, 19464 patients) and cohort studies (144 articles, 12515 patients), that were mainly to observe the efficacy and safety of oral HCT agents in the treatment for infectious diseases, such as respiratory system, urinary system and digestive system (unpublished). The results showed that a few patients (63 patients) experienced medium rather than serious ADRs, such as abdominal pain, diarrhea and rashes. No anaphylactic shock, various kidney diseases, cancer or death were reported in these trials and studies. It is supporting that oral HCT agent is relatively safety.

In present study, we just analyzed case reports related to HCT and some articles were not published on high quality journal. Some of them did not give more explanation and there may be some bias. However, these cases are all from the real world without any designs or interventions, and the results based on real cases are more reliable and more clinical reference value.

4 Conclusion

As for HCT-related ADRs, the marjor cases manifested as allergic symptoms and was meanly caused by processed preparations, including HCT injections and patent preparation. The oral HCT agents as docoction rearly caused ADRs. No ADRs of nephritis, renal interstitial fibrosis, aristolochic acid nephropathy or cancer was caused by HCT.

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Competing interests

The authors declare no competing financial interests. Readers are welcome to comment on the online version of this article at https:// www.tmrjournals.com/ fthc

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