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Systematic review on the adverse reactions of oral administration of *Indigo Naturalis* and its preparations

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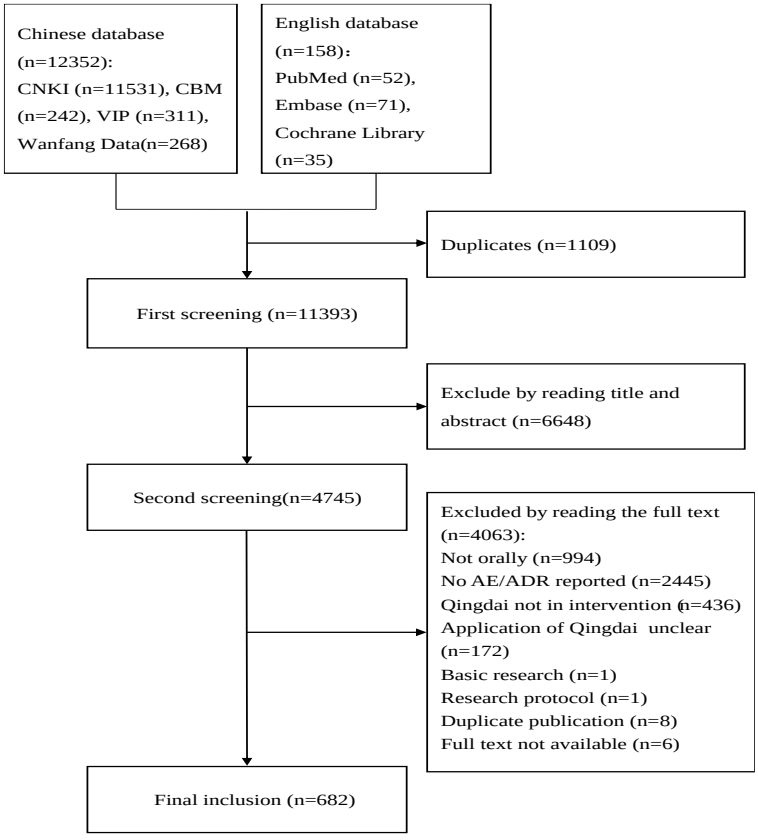
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Highlights

This paper investigated the ADE/ADR of oral *Indigo Naturalis* (Qingdai) preparation by a systematic review of published papers, and estimated the maximum possible incidence rate of ADE/ADR incidence was 14.99%, which provided useful reference for the clinical rational application of Qingdai oral preparation.

Traditionality

Indigo Naturalis (Qingdai) is extracted from the leaves or stems of Strobilanthes cusia, Polygonum tinctorium and Isatis tinctoria, which has been widely used through histroy for inflammatory diseases with “heat” syndrome in ENT, ophthalmology, dermatology, gastroenterology, etc.



Abstract

Objective: This article systematically analyses the effects of adverse drug events/adverse drug reactions (ADEs/ADRs) of oral *Indigo Naturalis* (Qingdai) preparations in order to provide references for its rational clinical application.

Methods: All clinical studies reporting ADE/ADR related to the oral administration of Qingdai preparations were searched through electronic databases, including PubMed, the Cochrane Library, Embase, China National Knowledge Infrastructure (CNKI), China Biology Medicine disc (CBM), VIP Information Chinese Journal Service Platform (VIP), and Wanfang database, from inception to September 27, 2020. Information were extracted from these literatures, including primary disease, type of adverse reactions, dose, treatment, outcomes and so on. Incidence of ADE/ADR was estimated, as well as distribution of primary diseases and victim organs and systems were analyzed.

Results: A total of 682 articles were included, with 651 clinical population studies and 31 case reports. Among them, 604 detailed ADR/AE involving 33459 patients using oral Qingdai preparations, and a total of 5061 cases were found to present adverse events, including 2827 cases of digestive system (abdominal pain, diarrhea, etc.), 469 cases of blood system damage (thrombocytopenia, leukopenia, anemia, etc.), 313 cases of liver damage (abnormal liver function, liver toxicity, elevated liver enzymes, etc.), 327 cases of nervous system reactions (headache, dizziness, poor sleep, etc.) and 1186 cases of other systems and organs. Severe adverse events (SAEs) mainly were liver damage, and could be relived after symptomatic treatment.

Conclusion: From the systematic information retrieval and analysis, it is found that oral Qingdai preparations application may clinically cause ADEs/ADRs in terms of gastrointestinal tract and liver damage. Therefore, when using oral Qingdai preparations, liver and stomach protection should be done. At the same time, pay close attention to various biochemical indicators and the patient's drug response during the treatment process, and, if necessary, deal with it in time so as not to deteriorate the condition. Moreover, active surveillance system should be conducted to monitor ADE/ADR, so as to establish a clearer causal relationship between the drug and the adverse event.

Keywords: Qingdai, *Indigo Naturalis*, Oral preparations, Adverse drug reactions, Adverse drug events, Systematic review

Abbreviations: AE, adverse drug event; ADR, adverse drug reaction; SAR, severe drug reaction.

Funding: This research was financially supported by The National Key R&D Program of China（Grant No. 2019YFC1709802）.

Competing interests: The authors declare that there is no conflict of interests regarding the publication of this paper.

Citation: Deng XY, Lan R, Xie QW, et al. Systematic review on the adverse reactions of oral administration of *Indigo Naturalis* and its preparations. TMR Modern Herbal Medicine 2021; 4(1):5.

Executive Editor: Chaoyong Wu

Submitted: 17 January 2021, **Accepted**: 28 January 2021, **Online**: 29 January 2021.

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doi: 10.12032/MHM2021B0117001

Introduction

Indigo Naturalis (Qingdai) is a kind of dry powder, lump or granule made by processing the leaves or stems of *Strobilanthes cusia*, *Polygonum tinctorium* and *Isatis tinctorial* [1]. Modern pharmacological studies show that the main active components of Qingdai are indigo and indigo jade red, which have many pharmacological effects such as anti-cancer, anti-pathogenic microorganisms, anti-inflammatory analgesia and liver protection [2], and can be used for the treatment of skin diseases, digestive system, gynecological diseases, cancer and other diseases [3]. With the widespread use of Qingdai preparations in clinical practice, adverse drug events / adverse drug reactions (ADEs/ADRs) have become increasingly prominent, especially oral drugs. In 2013, the National Center for ADR Monitoring reported 344 cases of ADE/ADR related to compound Qingdai preparations from 2004 to June 2012, of which 23 cases were severe drug reaction (SAR), like drug-induced liver damage, gastrointestinal bleeding, etc. [4]. The adverse reactions reported in the past were mostly gastrointestinal reactions such as nausea, vomiting and liver dysfunction. However, in recent years, some new SARs have been reported frequently. In 2016, the European Heart Journal published the first case report of fatal pulmonary hypertension caused by oral Qingdai [5]. After the report was published, the Ministry of Health and Labour of Japan issued a warning about oral Qingdai drugs [6]. Later in August 2018, Kondo S et al. [7] reported 2 cases of conjunctivitis with colon wall thicking and edematous changes after taking Qingdai. Soon in November, Yanai S et al. [8] reported 1 case of ulcerative colitis patient who suffers thickening of the right colon after increasing the dose of *Indigo Naturalis*. This suggests that we should pay attention to the adverse reactions caused by Qingdai preparations. Although a few reports reviewed the adverse reactions of oral Qingdai preparations, they did not systematically search all clinical trials, observational studies and case reports, and they only focused on several common ADRs, such as gastrointestinal damage [9-11]. Moreover, the data is out of date, which were not likely to include the new SARs, such as above mentioned cases reported in recent years. And also the incidence of ADE/ADR has not been estimated. Hence, the purpose of this study is to comprehensively included clinical reports on ADE/ADR related to the application of oral Qingdai Preparations, and systematically summarize, analyze all ADEs/ADRs, in order to provide reference for the clinical rational application of the drug.

Methods

Data sources

Seven major English and Chinese biomedical database were searched, including PubMed, the Cochrane Library, Embase, China National Knowledge Infrastructure (CNKI), China Biology Medicine disc (CBM), VIP Information Chinese Journal Service Platform (VIP), and Wanfang database, from their inception to September 27, 2020. Key words and MeSH terms included Qing Dai, indigo, *Indigo Naturalis*, clinical observation, clinical trial, clinical study, case report, adverse event, adverse effect, side effect, safety, etc. Search strategy were tailored to each database by professional librarian. Detailed search strategies are presented in the supplementary materials.

Inclusion criteria

(1) Research types include all clinical reports, such as randomized controlled trials, non-randomized controlled trials, cohort studies, case-control studies, case series reports, case reports, etc.; (2) Intervention was oral Qingdai preparations; and (3) The literature which details the specific situation of ADR/AE.

Exclusion criteria

(1) Not related with clinical application of Qingdai preparation (e.g. Qingdai was conditional added into herb formula); (2) Duplicate publication; (3) Literature unable to access their full text.

Literature screening

After the literature retrieval is completed, all documents were imported into the EndNoteX7 software for management and screening. According to the above inclusion and exclusion criteria, the documents were screened by reading of title and abstract. If the documents were still uncertain, the full text was read for further screening.

Data extraction

Data was extracted and managed by Epi Data3.1, The extracted information includes: (1) Basic information (author, publication time, publication journal); (2) Type of literature research; (3) The original disease studied; (4) Combined medication; (5) Drug dosage; (6) ADE/ADR manifestation and number of cases; (7) management and outcome, etc. Two researchers independently extracted data, with a third researcher to verify in case of disagreements.

Statistical Methods

Descriptive statistical analysis was the main method by SPSS 22.0 statistical software, to calculate the proportion of diseases distribution, the proportion of ADR/AE involving organ systems or SAEs, etc.

Results

General information

Document Retrieval Results A total of 12510 Chinese and English literature (12352 Chinese records and 158 English records respectively) were retrieved with 682 articles finally included (Literature screening flow is shown in Figure 1). The process involved a wide range of Qingdai preparations, including compound Huangdai tablets, compound Qingdai tablets, classic recipes such as Daige powder, Shengma Biejia decoction and a large number of self-made decoctions based on Qingdai.

Disease distribution This study included 682 articles, of which 2 cases reported involving 2 original disease types. The results showed that the clinical diseases with ADE were mainly concerning dermatological, digestive and hematological diseases. Dermatological diseases were the most, including psoriasis, eczema, pityriasis roseus, urticaria, psoriasis and so on. Since children are special drug users, a separate analysis of pediatric drugs will be conducted. See Table 1 for details.

ADE/ADR reporting There were 682 records finally included, including 31 case reports and 651 clinical population studies (with number of cases with or without ADE/ADR, and could be used for estimation of incidence), in which 604 clearly reported the number of specific cases of ADE/ADR. Among them, 5016 cases involving 33459 patients of oral Qingdai preparations were reported, and the estimated incidence rate of ADE was 14.99%. See Table 2 for details.

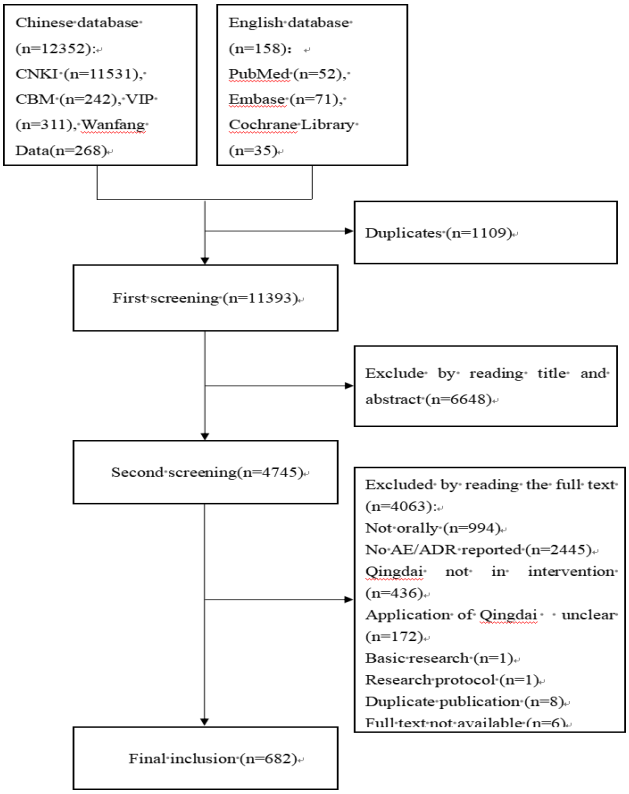


Figure 1 Flowchart of Literature Screening

Table 1. Disease distribution

Category	Quantity	Percentage (%)
Dermatological diseases (including psoriasis, eczema, pityriasis rosea, psoriasis, facial hormone-dependent dermatitis, acne, urticaria, herpes zoster, etc.)	309	45.18
Digestive system diseases (including ulcerative colitis, reflux esophagitis, indigestion, hepatitis, jaundice, fatty liver, gastritis, constipation, etc.)	137	20.03
Hematopathy (including acute promyelocytic leukemia, chronic myeloid leukemia, primary thrombocytopenia, multiple myeloma, myelodysplastic syndrome, etc.)	95	13.89
Respiratory diseases (including upper respiratory infections, chronic bronchitis, chronic obstructive pulmonary disease, bronchiectasis, pharyngitis, tonsillitis, cough, asthma, etc.)	40	5.85
Immune diseases (including primary or idiopathic thrombocytopenic purpura, Henoch-Schonlein purpura, systemic lupus erythematosus, lymphadenitis, etc.)	21	3.07
Tumor (including lung, rectum and other tumors and chemoradiotherapy patients, etc.)	22	3.22
Cardiovascular-cerebrovascular diseases (including stroke, epilepsy, arrhythmia, hyperlipidemia and so on)	8	1.17
Others (including cancer pain, periodontitis, genital herpes, goiter, prostatitis, renal and ureteral colic, oral ulcers, etc.)	20	2.92
Pediatrics (including acute promyelocytic leukemia, peptic ulcer, cytomegalovirus hepatitis, hand, foot and mouth disease, pneumonia, idiopathic thrombocytopenic purpura, acute tonsillitis, nephritis, etc.)	32	4.68
Total	684	100

doi: 10.12032/MHM2021B0117001

Table 2. The description of ADE/ADR in the included literature

Included literature	Description of ADE/ADR	Number of articles	Composition (%)
Clinical population studies	Clearly reported the number of ADE/ADR cases	379	55.57
	No obvious ADE/ADR or no ADE/ADR	225	32.99
	Mention of ADR/AE, but no specific number of cases	47	6.89
Case reports		31	4.55
Total		682	100

Table 3. ADE/ADR System relating to organ systems and clinical manifestations

Types of organ systems involved in ADE/ADR	Main clinical manifestations	Example	Composition (%)
Gastrointestinal damage	Abdominal pain, diarrhea, increased defecation, nausea, vomiting, gastrointestinal bleeding, anorexia, loss of appetite, etc.	2827	55.19
Blood system damage	thrombocytopenia, leukopenia, purpura, bone marrow suppression, anemia, etc.	469	9.16
Neurological impairment	Headache, vertigo, poor sleep, irritability, fatigue, limb numbness, peripheral nerve abnormalities, attention loss, etc.	327	6.38
Liver damage	Liver damage, drug-induced hepatitis, etc.	313	6.11
Dry reaction	Dry mouth, dry lips, dry pharynx, dry skin and mucous membrane, etc.	274	5.35
Skin and its appendages damage	Pruritus, erythema, blister, flushing, desquamation, etc.	268	5.23
Immune dysfunction and infection	Infection, impairment of immune function, etc.	103	2.01
Respiratory system damage	Cough, pulmonary toxicity, etc.	69	1.35
Systemic damage	Fever, sepsis, inflammation, etc.	67	1.31
Cardiovascular system damage	Arrhythmia, panic, palpitation, abnormal electrocardiogram, abnormal blood pressure, abnormal cardiac function, cardiotoxicity, etc.	75	1.46
Urinary system damage	Abnormal renal function, abnormal urine, etc.	69	1.35
Vascular, bleeding and clotting disorders	Bleeding tendency, thrombus, etc.	49	0.96
Others	Abnormal blood lipids, abnormal menstruation, alopecia, abnormal blood sugar, etc.	212	4.14

Adverse drug events/Adverse drug reactions

Types of organ systems and clinical manifestations involved in ADE/ADR Among all ADE/ADR damages, more than half of cases were gastrointestinal damage (55.19%), followed by blood system damage and liver damage. See Table 3 for details.

Management and outcome Most of the clinical studies did not elaborate management and outcome of ADEs/ADRs. Some commonly used management were drug withdrawal, dose reduction or symptomatic treatment, and most ADE/ADR symptoms of patients could be improved. Some patients can improve without specific treatment because of the drug tolerance.

Serious adverse events Most clinical reports included only briefly described the symptoms of ADE/ADR, and did not report the severity of adverse reactions. Meanwhile, they did not specify the management and outcome of ADEs/ADRs in detail. So the study failed to give an accurate ratio of SAEs.

Dosage relationship with ADR There were 9 studies, which related to compound Qingdai preparations in the treatment of acute promyelocytic leukemia and chronic myeloid leukemia, reported that the maximum doses of 36-45 tablets per day that exceeded dose limits (30 tablets per day). The dosages of the remaining studies varied greatly due to different oral dosage forms, but they are all within the prescribed range. Therefore, it cannot be claimed that there is an absolute relationship between the dosage and the occurrence of ADE/ADR.

Combined medication Among the 457 articles with ADE/ADR observation, there were 224 studies had combined medication use. It can be seen that about half of the oral Qingdai preparations were combined. Since there is no clear drug contraindication in the instructions of Chinese patent medicines or other

dosage forms containing Qingdai ingredients, it is unknown yet whether the occurrence of ADE/ADR is related to the possible drug interactions during the combined use. Therefore, when determining the causality of adverse reactions, it is difficult to rule out the effect of combination medication.

Characteristics of case reports There were 66 cases (22 males, 43 women, one did not specified) in 31 included case reports, 28 patients over 50 years old, 29 under 50 years old, and 9 unknown. The time of occurrence of ADE/ADR were between 2 hours and 6 months after drug taken.

A total of 27 serious adverse events were recorded, including 16 cases of acute liver damage and 1 case of death. The rest were improved after withdrawal and symptomatic treatment. One patient died of retinoic acid syndrome. There were 3 patients developed circulatory system reactions, 4 patients developed gastrointestinal damage, 1 patient developed aplastic anemia, and 1 patient developed ischemic colitis, all of which resolved after symptomatic treatment. One patient was observed to be 3-hour medication shock, but improved after symptomatic treatment. Of them 15 cases were judged as causal [12], after excluding the influence factors such as comedication and disease progression. 11 cases were of psoriasis, 1 of constipation, 1of pityriasis rosea, 1 of eczema, 1 ulcerative colitis. The most common adverse reactions involved organ system was gastrointestinal system (abdominal pain, diarrhea, blood stool, 10 cases).

Discussion

The estimated maximum possible incidence rate found in this study is relatively much higher than most Chinese herbs, partly because the incidence number calculated in this study was based on event, not patient level. One patient usually encounters two or three gastrointestinal reactions at the same time, so an incidence rate of patients who suffered ADE might be two or three times smaller.

Moreover, confirmed causality is required to calculate the real incidence rate. Several causality methods are widely used to assess the causal relationship, such as Naranjo ADR probability scale, WHO–UMC causality categories. All these scales take account comedication, drug withdrawal, management, outcome of ADEs, and other confoundings like disease natural progression, etc. However, limited information was provided in included studies, which makes it difficult to clarify causal relationship [13, 14].

More than half of ADE were gastrointestinal damages. Indirubin, the main component of *Indigo Naturalis*, may be the cause of digestive system toxicity, but the specific mechanism needs be further study [13-14]. Another indication for rationale use of Qingdai from this study is to change oral taken to topical use like enema. One of our previous study showed that ADE incidence of Qingdai enema was not higher than that of conventional therapies for UC patients [15]. Although clinical studies can calculate the incidence of ADE, few report the management and outcome of ADE/ADR in publication. Compared with this, case reports provide more detailed information. The recorded adverse event treatment and outcome indicate that the serious adverse events are mostly related to acute liver damage. Therefore, in the clinical application of Qingdai preparation, we should be prepared to protect the liver, pay close attention to various biochemical indicators and drug reactions of patients and deal with potential ADE/ADR in time. In case reports, the proportion of ADE/ADR in women was more than that in men (43:22). Women may be more sensitive to drugs than men, and are more likely to suffer ADE/ADR [16].

China has established a comprehensive ADR monitoring network. Like other countries, ADR is collected and reported mainly through spontaneous reporting system, which inevitably has the limitations like low reporting rate, low quality and high randomness. This requires doctors to collect information and report it consciously according to ADE/ADR report form when they find suspicious ADE/ADR in clinical work. In addition, physicians should be encouraged to publish ADE/ADR reports in journals after reporting ADE/ADR information to the national monitoring center, especially new and serious adverse events, with standardize and detailed reporting of gender, age, allergy history and other diseases of patients with ADE/ADR, provide specific information of combined medication, and use international causal standards [17].

Clinical studies aimed at evaluating the efficacy of intervention measures account for the vast majority of the literature, but they are generally less active in monitoring and following-up of ADE/ADR, also there is no consensus on how to comprehensively evaluate the quality of ADE/ADR reports of different research types [18]. The secondary analysis method, like systematic review, is not well developed by now, so the study of adverse reactions should pay attention to active monitoring. Active monitoring is different from the passive monitoring of spontaneous reporting. It is necessary to develop a detailed monitoring plan in advance, including the data collection plan of adverse events, to comprehensively and completely collect adverse reactions and their influencing factors through the implementation of the studies [19]. Novel active monitoring methods facilitated by electronic surveillance system emerge, which links multi data

sources including electronic health data, social media, literature and drug labels [20]. So it is suggested that well-designed large sample post marketing reevaluation, centralized hospital monitoring, registry studies and other research designs should be carried out to monitor ADE/ADR, so as to further clarify the relationship between drugs and AEs, as well as comprehensively understand the influencing factors of adverse reactions.

Conclusion

Our study found that the estimated maximum possible incidence rate of ADE/ADR incidence for *Indigo Naturalis*(Qingdai) oral preparations was 14.99%. More than half of the cases were liver and gastrointestinal damage, therefore, corresponding protection should be scheduled, while close attentions of biochemical indicators to be paid as well as the patient's drug response during the treatment process for timely ADE management. Moreover, active surveillance should be conducted to monitor ADE/ADR, so as to establish a clearer causal relationship between the drug and the adverse event.

Supplementary materials

Search Strategies

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