

Risk of Using Traditional Herbal Medicine against COVID-19

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Abstract: COVID-19 is a serious pandemic since spring 2020. Numbers of traditional herbal medicines have been applied to conquer the virus. Here, we underline the potential risk of using the herbal medicines, by reviewing the chemical properties and toxicology of carcinogenicity chemical entities, e.g. aristolochic acids, glycyrrhizinic acid, in the herbal remedies. We stress here that although traditional herbal remedies are beneficial to relieve the COVID-19 symptoms, they should not be considered as preventive medicine or overdosing.

Key words: Aristolochic acids, COVID-19, chrysophanol, ephedrine, glycyrrhizic acid, TCM.

1. Introduction

COVID-19 is an ongoing global pandemic, caused by β -coronavirus called SARS-CoV-2, which can cause mild to severe lower respiratory diseases [1]. Most people infected with COVID-19 have mild to moderate symptoms. Patients who are older or have other underlying conditions are prone to severe symptoms. Medicines and therapies for the treatment of COVID-19 can be divided into three categories: a) antiviral drugs, e.g. Remdesivir, Ribavirin; b) symptomatic treatment, i.e. dexamethasone, hydroxychloroquine, oxygen support; and c) traditional and alternative medicine, including Traditional Chinese Medicine. To our best knowledge, there are currently no medicines or treatments that can be used as specific drugs for COVID-19.

2. Potential Risk of Using the Herbal Medicines

Several traditional herbal medicine-based remedies have been widely applied in the treatment against COVID-19 symptoms [2]-[5]. However, it has been noticed that some of those herbal-based medicine prescriptions contain *Asarum heterotropoides*, *Glycyrrhiza uralensis*, *Ephedra sinica*, *Rhizoma rheii*, etc., which may contain carcinogenic and nephrotoxic chemical entities. Here, we take the examples of two remedies *Qingfei Paidu* and *Lianhua Qinwen* to analyse the potential risk of using herbal medicines for the COVID-19 treatment.

According to the "TCM Prevention and Treatment Plan for COVID-19 Infection" released by the Chinese authority [6], *Qingfei Paidu* and *Lianhua Qinwen* are used to treat COVID-19 pneumonia patients. Both of the formulas contain herbs from the Aristolochiaceae family. The former contains *Asarum heterotropoides* while the latter contains *Houttuynia cordata*. When misuse or overdose, these two herbs may show strong nephrotoxicity [7] as they contain aristolochic acids (AAs), which lead to interstitial fibrosis, renal tubule atrophy, complete disappearance of renal tubules, and renal tumour formation.

Since the 1990s, researchers have discovered potential side effects of aristolochic acids. In 1992, Belgian researchers reported that local women who took weight-loss pills containing aristolochic acids suffered from related nephropathies such as kidney failure and kidney carcinoma [8]. Subsequently, clinicians worldwide have claimed cases of its toxicity and aristolochic acids rapidly became the focus of public concern and aroused widespread attention. In 2002, aristolochic acids have been classified as a Class I carcinogen by the International Agency for Research on Cancer (IARC) [9]. The US Food and Drug Administration (USFDA) and many other countries have banned the sale of herbal medicines which contain aristolochic acids. However, some Asian countries enjoy a long history of traditional herbal medicine treatment and AA-containing herbs are still used in many Chinese patent medicines.

Table 1 summarizes Chinese herbal medicines known to contain aristolochic acids. Among them, aristolochic acids exist in considerable quantities in the plants of genus *Aristolochia* and *Asarum* [10]. Aristolochic acids are carboxylic acids with nitrophenanthrene moiety. Some typical entities from the aristolochic acids family are shown in Fig 1a. Among aristolochic acids, the most toxic compounds are aristolochic acid I (8-methoxy-6-nitrophenanthro-(3,4-d)-1,3-dioxolo-5-carboxylic acid, AAI) and aristolochic acid II (6-nitrophenanthro-(3,4-d)-1,3-dioxolo-5-carboxylic acid, AAII). Aristolochic acids are first isolated from *Aristolochia kankauensis* [11] and were found in at least seven species of *Aristolochia* [12].

Table 1. Chinese Herbal Medicines Known to Contain AAs

Latin Name	English name
<i>Aristolochiaceae</i>	Aristolochic
<i>Aristolochia cathcartii</i>	Aristolochia
<i>Aristolochia cinnabarinus</i>	Root of Kaempfer Dutchmans pipe
<i>Aristolochia debilis</i>	Radix aristolochiae
<i>Asarum heterotropoides</i>	Asarum sieboldii
<i>Aristolochia manshuriensis</i>	Manshuriensis
<i>Aristolochia mollissima</i>	Aristolochia
<i>Aristolochia obliqua</i>	Fangchi
<i>Clematis Chinensis</i>	Radix clematidis

After being administrated, AAI and AAII are metabolized to *N*-hydroxyaristolactam with the catalysis of NQO1, CYP1A2, CYP1A1 in the liver and NQO1, CRP, COX in the kidney [13], [14] (Fig. 1b), forming the reactive intermediates, aristolactam nitrenium ion. *N*-Hydroxyaristolactam can also be metabolized to aristolactam-*N*-sulfate by sulfotransferase in the liver [14], resulting in an aristolactam nitrenium ion. The electrophilic nitrenium ions covalently bind purine nucleobases, cause adenine to thymine transversion, potentially mutating tumour suppressor genes, e.g. H-ras and TP53, thus initiating carcinogenicity.

Apart from the carcinogenicity, aristolochic acids are tightly linked to chronic kidney injury. Vanherweghem *et al.* first identified aristolochic acids as the causative agent for progressive chronic interstitial fibrosis and advanced kidney failure [15]. Therefore, the condition is also named aristolochic acid nephropathy, or Chinese herbal nephropathy. The pathologic mechanism of aristolochic acid nephropathy has been ascertained by *in vitro* and *in vivo* experiments. In brief, four reasons contribute to nephropathy: 1) endoplasmic reticulum stress injury [16]; 2) oxidative stress injury [17]; 3) immune-mediated inflammatory [18]; 4) tubular epithelial cell transdifferentiation [19].

When talking about toxicity, we have to consider the dose as *dosis sola facit venenum*. *Qingfei Paidu* remedy contains 3.1% *Asarum heterotropoides* [20] (Table 2) by weight whilst *Lianhua Qinwen* remedy contains 13% *Houttuynia cordata* [21] (Table 3). Although the root of *Asarum* has a repressed level of aristolochic acids (< 0.5 ppm) [22] and is commonly utilized in remedies, the whole plant of *Asarum* has a high concentration of aristolochic acids (1-100 ppm). The whole plant can be mislabeled and misused as the root. As both *Qingfei*

Paidu and *Lianhua Qinwen* are over-the-counter (OTC) drugs that can be accessed by the general public. The general public is likely to intake these remedies in excess amount and extended period as self-protective measurement under the pandemic panic [23]. Seniors who meanwhile take other medications for chronic disease, either herbal remedies or chemical medicines, make the situation even more complicated. Further detailed contents of aristolochic acids in Chinese patent medicines are summarized in reference [24].

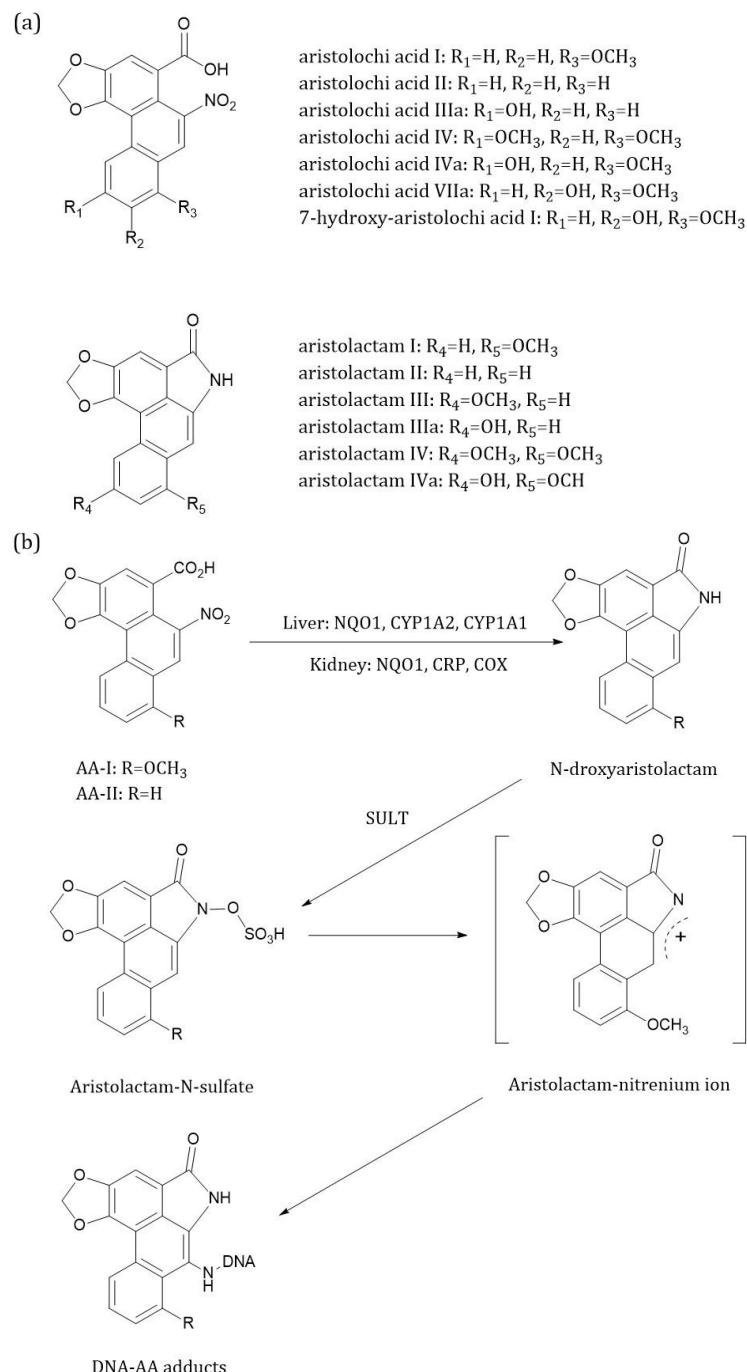


Fig. 1. (a) Typical entities from the aristolochic acids family; (b) pathway for metabolic of AAI and AAII.

Aside from *Asarum heterotropoides*, *Glycyrrhiza uralensis*, *Ephedra sinica*, and *Rhizoma rheii* are likewise frequently applied in anti-COVID-19 remedies. *Qingfei Paidu* comprises 3.1% *Glycyrrhiza uralensis* and 4.6% *Ephedra sinica* whereas *Lianhua Qinwen* contains 4.3% *Glycyrrhiza glabra*, 4.3% *Ephedra sinica*, and 2.6% *Rhizoma rheii*.

Table 2. Formula of *Qingfei Paidu*

Latin name	Dosage (g)
<i>Radix bupleuri</i>	16
<i>Gypsum fibrosum</i>	15
<i>Poria cocos</i>	15
<i>Dioscorea oppositifolia</i>	12
<i>Atractylodes macrocephala</i>	9
<i>Alisma plantago-aquatica</i>	9
<i>Agastache rugosa</i>	9
<i>Aster tataricus</i>	9
<i>Belamcanda chinensis</i>	9
<i>Cinnamomum cassia</i>	9
<i>Ephedra sinica</i>	9
<i>Prunus armeniaca</i>	9
<i>Pinellia ternata</i>	9
<i>Polyporus umbellatus</i>	9
<i>Tussilago farfara</i>	9
<i>Zingiber officinale</i>	9
<i>Asarum heterotropoides</i>	6
<i>Citrus aurantium</i>	6
<i>Camellia japonica</i>	6
<i>Citrus reticulata</i>	6
<i>Radix glycyrrhizae Preparata.</i>	6

Table 3. Formula of *Lianhua Qinwen*

Latin name	Dosage (g)
<i>Dryopteris crassirhizoma</i>	255
<i>Forsythia suspensa</i>	255
<i>Gypsum fibrosum</i>	255
<i>Houttuynia cordata</i>	255
<i>Isatis indigotica</i>	255
<i>Lonicera japonica</i>	255
<i>Armeniacae amarum</i>	85
<i>Ephedra sinica</i>	85
<i>Glycyrrhiza uralensis</i>	85
<i>Pogostemon cablin</i>	85
<i>Rhodiola rosea</i>	85
<i>Rheum palmatum</i>	51
<i>Mentha canadensis</i>	7.5

Glycyrrhiza uralensis and *Glycyrrhiza glabra* are the most commonly used *Glycyrrhiza* species in traditional Chinese medicine [25]. The dried root and the underground stem of the *Glycyrrhiza* species, also known as licorice, have been used to suppress cough and asthma for centuries in China and the world. Recent studies demonstrated evidences of licorice and its extraction, i.e. liquorice, in detoxification, anti-inflammatory [26], and anti-viral activities [27]. Other than COVID-19, liquorice is documented to be effective against herpes simplex, Japanese encephalitis, influenza, and vesicular stomatitis virus [28]. The major ingredient of licorice extraction, glycyrrhetic acid, plays the key role in the pharmaceutical effects. Glycyrrhetic acid (Fig. 2a), i.e. glycyrrizic acid, is a triterpenoid saponin that represents 10% of the licorice dry weight [29]. Cases have been reported the association between intake of glycyrrhetic acid and chronic hypokalemic nephropathy [30]. Licorice-induced rhabdomyolysis has also been reported. In a rare and extreme case, a 49-year-old male who consumed 16% licorice root powder (i.e. 600 ppm glycyrrhetic acid) b.i.d. for 1.5 years to treat gastric complaints was hospitalized for hypokalemic rhabdomyolysis and acute renal failure [31]. Meanwhile, uptake of high dose of glycyrrhetic acid can lead to hypertension, hypokalaemia, or fluid retention [32].

Ephedra sinica, an Ephedra species native to Mongolia, Russia, and northeastern China, is a revailing herb to treat respiratory conditions such as nasal congestion, bronchospasm, asthma, and bronchitis. Active ingredient in Ephedra extactions, ephedrine (Fig. 2b), is also applied for weight loss and obesity and to enhance athletic performance [33]. Cases have been reported that overdosage of Ephedra supplement results to elevations of creatine phosphokinase, acute kidney injury [34] as well as kidney stones [35].

As a universal traditional herbal medicine, *Radix et Rhizoma Rhei* is used as a purgative and anti-inflammatory, anti-bacterial agent in clinic remedies and health care for a long history [36]. In traditional Korean medicines *Rhizoma Rhei*-contained Ganweiqitong tablet is used for obesity [37]. Its active ingredient, chrysophanol, is a natural anthraquinone derivative with 1,8-dihydroxy and 3-methyl groups [38] (Fig. 2c). Varies studies on the pharmacology of chrysophanol have been published. In an anti-inflammatory study, chrysophanol was proved to suppress LPS-induced NF- κ B activation and inhibit the production of tumor necrosis factor α , interleukin-6, which is possibly beneficial to relieve the symptom of COVID-19. The antiviral activity of chrysophanol were also investigated on poliovirus II/III, human rhinovirus II, and herpes simplex virus I [39]. In the meantime, attention have to be paid on the side effect of chrysophanol and *Rhizoma Rhei*-containing remedies. Chronic interstitial nephritis and tubular atrophy are claimed to associated with prolonged usage of *Rhizoma Rhei* extraction [40]. Furthermore, studies on the interaction of chrysophanol with DNA demonstrated that chrysophanol is able to bind DNA in a similar manner as ethidium bromide but with less toxicity [41]. But still, the side effect and reverse reactions to chrysophanol and *Rhizoma Rhei*-containing remedies in clinical and health care application should be underlined.

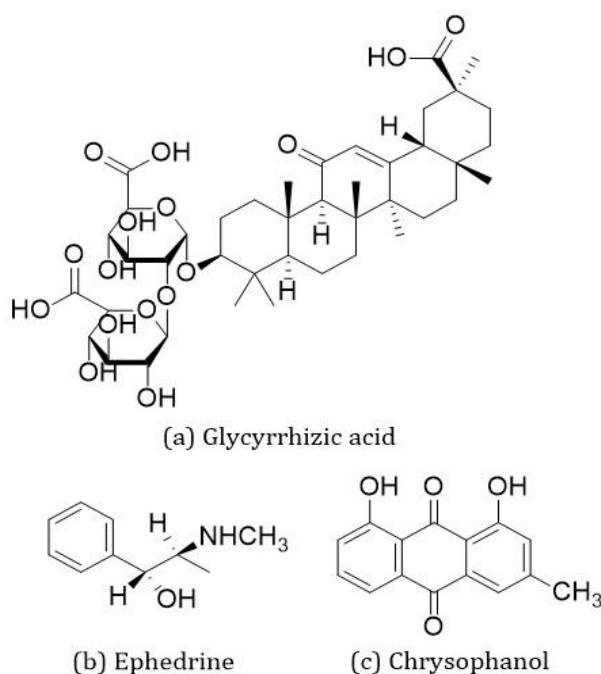


Fig. 2. Structure of (a) glycyrrhetic acid; (b) ephedrine; (c) chrysophanol.

3. Conclusion

In conclusion, the benefit of using traditional herbal remedies containing *Asarum heterotropoides*, *Glycyrrhiza uralensis*, *Ephedra sinica*, and *Rhizoma rheii*, for COVID-19 treatment is documented. The formulations have been cautiously designed and tested by patients. The side effects have been managed to the minimum. However, due to the accessibility of the over-the-counter traditional herbal medicines, the pandemic panic, and inevitable large-scale consumption by the general public, these remedies can only be

considered as therapy for patients with clear evidence of COVID-19 infection. Doses and duration have to be adjusted individually according to the clinical condition, gender and age of the patients. The herbal remedies can not be used as preventive medication, overdosage, longer than the required duration of use.

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Rui Zhao conducted the research, analyzed the data, wrote the paper.

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