Received: 22 January 2020 | Revised: 17 February 2021 | Accepted: 25 February 2021

DOI: 10.1002/emp2.12411

JACEP OPEN
JOURNAL OF THE AMERICAN COLLEGE OF EMERGENCY PHYSICIANS OPEN
A GLOBAL JOURNAL OF EMERGENCY MEDICINE
Open Access
WILEY

REVIEW ARTICLE

Toxicology

Toxicity of herbal medications suggested as treatment for COVID-19: A narrative review

Michael A. DiPietro MD | **Christopher Mondie DO**

Department of Emergency Medicine, Newark Beth Israel Medical Center, Newark, New Jersey, USA

Correspondence
Christopher Mondie DO, Department of Emergency Medicine, Associate Professor, Newark Beth Israel Medical Center, 201 Lyons Avenue, Newark, NJ 07112, USA.
Email: christopher.mondie@rwjbh.org

Funding and support: By *JACEP Open* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that no such relationships exist.

Abstract

Objectives: In the absence of a definitive cure, herbal medications are gaining increasing popularity in the general public for treatment of coronavirus disease 2019 (COVID-19). Although many herbal preparations are safe and can be used without complication, serious toxicities do occur. This article focuses on the major characteristics and toxicities of herbal preparations that have been proposed as treatments for COVID-19.

Methods: A review was performed focusing on herbal preparations that have gained popularity as potential treatments for COVID-19. Some of these preparations have been directly recommended by government agencies, whereas others have gained popularity through various other news sources.

Results: The herbal preparations covered in this paper include the cardiac glycoside oleandrin, plants of the *Datura* genus, and herbs commonly used in traditional Chinese Medicine including plants of the *Aconitum* genus, bitter apricot seeds, ephedra, and licorice root.

Conclusion: Although herbal preparations have been reported to aid in the treatment of COVID-19 with success, few clinical trials have been performed to evaluate their efficacy and instead rely mainly on *in vitro* studies and anecdotal reports. Furthermore, many of the herbal preparations suggested carry significant toxicities, and frontline healthcare workers should be aware of the common symptoms and toxidromes that result from these poisonings.

KEYWORDS
Chinese traditional, complementary therapies, coronavirus, herbal, herbal medicine, medicine, plant poisoning, toxicity

1 | INTRODUCTION

In December 2019, a new infectious disease was identified, coronavirus disease 2019 (COVID-19). This contagion is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and by the middle of March 2020, the World Health Organization classified COVID-19 as a pandemic. In response to the outbreak, various treatment modalities have been considered, with little efficacy shown in many promising medication candidates, including antivirals and immunomodulators.[1] At this time, there is no specific cure for patients infected with COVID-19, and reaction to this news has led portions of the population to turn to herbal supplementation in hopes of

Supervising Editor: Juan March, MD.

curing or preventing this disease.[2] Although few studies have been performed examining the efficacy of different herbal preparations, it has not stopped practitioners,[3] or even government agencies,[4–6] from suggesting herbal supplements as treatment.

The idea of using plants for healing purposes has been around since the beginning of recorded human history and forms the origin of much of modern medicine.[7] In 400 BC, Hippocrates described the use of salicylic tea to reduce fevers, and willow bark preparations were used regularly throughout the Middle Ages.[8] In the 1800s, the active components of this bark were isolated and sold under the brand name, Aspirin.[8] Even in current times, plant preparations are important sources for pharmacologic drug research and development. A recent success story involves the derivation of artemisinin from the sweet wormwood plant for the treatment of resistant Plasmodium falciparum malaria.[9] The herbal and dietary supplement market in the United States is a multibillion-dollar industry, with around 1 in 5 Americans admitting to using an herbal supplement in the past 12 months.[10] One of the first medications proposed as treatment of COVID-19, hydroxychloroquine, is itself derived from the plant species *Cinchona*. Despite being used regularly and in a variety of modern medicines, herbs and botanical products often carry an intrinsic toxicity.[11,12] Furthermore, many herbal products are subject to a variety of contaminants, whether from the environment, the cultivation practices, or in the manufacturing and processing of said products.[12]

Although herbal supplements are regulated by the Food and Drug Administration (FDA), they are not regulated in the same capacity as most medications and instead fall under the category of "dietary supplements."[12] In 1994, the Dietary Supplement Health and Education Act, defined dietary supplements as a category of food, which means they do not need premarket approval by the FDA.[12,13] Federal law does not require dietary supplements to be proven safe before they are marketed,[13] and for most claims made in the labeling of the supplement, the law does not require the manufacturer or seller to prove that the claim is accurate or truthful.[13] The FDA's main role in monitoring supplements occurs after the supplement is on the market and includes monitoring for severe adverse effects or product adulteration.[13] However, there are currently > 1000 companies producing medicinal plant products in North America and herbal products are available in a variety of mainstream outlets such as supermarkets, health food stores, and pharmacies or can be ordered online from around the world. Because of this poor regulation, it is not always clear what specific herbs are in the products being sold. One study[14] performed in 2013 looked at 44 different herbal preparations on the market and found that 59% of them contained DNA from plant species not listed on the label, and another 33% contained contaminants or fillers also not listed on the label. Although contamination or mislabeling is a grave concern, even preparations that contain only the intended herbs can cause significant toxicity, especially if they are self-prescribed or misused.

A review of the scant literature available has shown several common herbal preparations repeatedly being suggested as potential treatments for COVID-19. The focus of this article is to identify several of these herbal preparations and review the toxicity that results from misuse of these products. With the wealth of information available to the general public, both on the Internet and in the news, it is becoming much more common for patients to self-medicate with herbal supplements without the knowledge of their primary practitioners. Frontline healthcare workers, especially emergency medicine practitioners, should be aware of these common herbal preparations and be on the lookout for their associated toxidromes.

2 | OLEANDRIN

In August 2020, US president Donald Trump met in the Oval Office with Andrew Whitney, vice chairman and director of Phoenix Biotechnology, to discuss a new potential treatment for COVID-19.[6] The therapy being discussed was oleandrin, and the theory behind this supplement being used in the treatment of COVID-19 was based on a non-peer reviewed study[15] showing the inhibition of *in vitro* SARS-CoV-2 replication in the presence of oleandrin. Although the authors recommended further testing in animal models,[15] the study became national news when Dr. Ben Carson, the Secretary of Housing and Urban Development and a retired pediatric neurosurgeon, reported that he took the supplement when he was infected with COVID-19 and had complete relief of his symptoms.[3]

Oleandrin is a derivative of the plant *Nerium oleander*, an ornamental shrub native to Northern Africa, the Eastern Mediterranean Basin, and Southeast Asia.[16,17] Oleandrin is a cardiac glycoside with structures and action similar to those of digoxin.[18–21] Cardiac glycosides work by inhibiting the enzyme, Na+/K+ ATPase, in the membrane of cardiac myocytes.[17–21] This ultimately leads to an accumulation of intracellular calcium, and these changes in calcium concentration result in increased cardiac inotropy and decreased chronotropy.[20,21] Poisoning by ingestion of this plant is a common toxicological emergency in tropical and subtropical parts of the world and intentional self-harm following ingestion is prevalent in South Asian countries.[20,23]

Acute poisoning with oleandrin typically begins with an asymptomatic period of several minutes to several hours, with the first symptoms commonly being nausea, vomiting, and abdominal pain.[20,21] The absence of these initial symptoms within several hours following exposure makes severe acute poisoning unlikely. Other predominant features include drowsiness, generalized weakness, hyperkalemia, and most important, cardiotoxicity.[19–21] Alterations in cardiac rate and rhythm may result in nearly any dysrhythmia, with the exception of a rapidly conducted supraventricular tachyarrhythmia owing to the prominent atrioventricular nodal depressive effect of cardiac glycosides. The first rhythm often seen with toxicity is an ectopic ventricular rhythm and bidirectional ventricular tachycardia is nearly diagnostic although not always present.[21] The effects exhibited vary with the dose of cardiac glycoside ingested and the type of cardiac tissue involved; however, atrioventricular junctional blocks with associated increased ventricular automaticity are the most common cardiac manifestations. Chronic toxicities are often difficult to diagnose given their insidious onset; however, they may also include the same symptoms seen in acute poisonings.[21]

Oftentimes, measuring serum digoxin concentration is the only way to estimate levels of non-digoxin cardiac glycosides following ingestion, and in the correct clinical setting may assist in making a presumptive diagnosis of oleandrin toxicity. However, a low digoxin level does not rule out non-digoxin cardiac glycoside toxicity, and in the correct setting, treatment should still be initiated.[20,21,24] Acute management should follow a similar course as digoxin toxicity. This includes general measures, such as gastrointestinal decontamination, measuring electrolyte concentrations, and monitoring for dysrhythmias. Hyperkalemia caused by cardiac glycoside toxicity should be managed similarly to that of other etiologies, except for administration of calcium as a cardiac membrane stabilizer. This exception is based on the theory that calcium administration in the presence of excess cardiac glycoside levels can lead to an irreversible non-contractile state of the heart.[20,21,24] Definitive treatment is with administration of digoxin-specific antibody fragments.[20,21]

The FDA rejected approval of oleandrin as a dietary supplement and sent Phoenix Biotechnology a warning letter demanding the removal of claims that oleandrin can cure COVID-19. However, *Nerium oleander* can be purchased easily, and oleandrin tablets are available in diluted forms as a homeopathic medication.

3 | DATURA

In April 2020, 12 people in the Chittoor District in India were hospitalized after drinking a homemade concoction containing seeds from a plant from the *Datura* genus.[25] These 12 people came up with the idea to ingest this home remedy after watching a video posted on the popular social media app TikTok in which the creator shared tips and home remedies for how to keep oneself safe from the novel coronavirus.[25] The theory behind the use of *Datura* seeds for treatment of COVID-19 has roots in the earliest forms of medicine. Ancient Greek philosophers developed a concept titled the "Doctrine of Signatures," which suggested the shape of a plant, or its parts, provides a clue as to the medical condition the plant can treat.[25] The seeds of the plants in the *Datura* genus grossly resemble models of the SARS-CoV-2 virion, prompting suggestions that they may be a treatment for the disease.[25]

The genus *Datura* contains about 9 species of flowering plants in the nightshade family and are found all over the world.[20,26,27] These plants contain potent alkaloids, including atropine, scopolamine, and hyoscyamine, also known as the belladonna alkaloids.[22,27,28] The belladonna alkaloids are competitive, reversible antagonists of the muscarinic acetylcholine receptors.[20,22]

Symptoms of *Datura* poisoning resemble a classic anticholinergic toxidrome with symptoms typically occurring within 30 to 60 minutes after ingestion.[20,26,27] Initial symptoms include hallucinations, dry mucous membranes, thirst, dilated pupils, blurred vision, and difficulty speaking/swallowing.[21,27] Late symptoms include tachycardia, urinary retention, hyperthermia, respiratory arrest, and seizures.[20,27] The diagnosis of acute intoxication can be difficult, as it is typically a clinical diagnosis, so prompt recognition of the anticholinergic toxidrome is important.[26,27] Treatment involves supportive measures (airway, breathing, circulation, benzodiazepines for agitation) followed by definitive treatment with intravenous physostigmine.[20,26,27] Physostigmine is a reversible acetylcholinesterase inhibitor and results in decreased metabolism of acetylcholine. Of the available acetylcholinesterase inhibitors, physostigmine is the only one that crosses the blood–brain barrier, thus improving the neurologic symptoms seen with *Datura* poisoning.

The plants in the *Datura* genus are purchased easily both online and at different home and garden stores and also can be readily found in nature. There are currently no FDA-approved *Datura* containing supplements available for purchase.

4 | TRADITIONAL CHINESE MEDICINE

Traditional Chinese Medicine (TCM) uses have been documented since 200 AD to prevent, treat, and cure disease and to promote health.[12] Before the introduction of Western medicine to China in the 19th century, TCM had been the major treatment for most diseases in Chinese communities.[12] Althouh the United States has become the epicenter of cases of COVID-19, the pandemic had its origins in the Wuhan region of China.[2] Throughout the initial stages of the pandemic, practitioners in China used a unique medical guideline for disease management, which combined TCM and Western medicine together.[29,30] The government of China announced that 91.5% of COVID-19 cases were treated with a combined regimen of conventional medicine and TCM with promising results.[29] Many herbs used in TCM have an intrinsic toxicity, which is often negated through various processing techniques.[12] Millions of people around the world regularly use TCM and very few experience significant toxicities. The challenge for most TCM consumers is ensuring that the product they are consuming has been processed appropriately and is free of toxic components and environmental contaminants.[12] This can become a major problem when the herbs are not handled by experienced TCM practitioners.[12]

A systematic review published in June 2020, found 28 government-issued traditional medicine guidelines that provide treatment measures for COVID-19.[5] Of these 28 guidelines, 26 were issued by the Chinese government and 2 were Korean government issued.[5] These guidelines included recommendations for mild, moderate, severe, and recovery stages of the disease.[5] Multiple herbs found in these guidelines possess severe toxicity if not handled and processed correctly.

4.1 | Radix aconiti lateralis preparata (Fuzi)

The processed lateral root of *Aconitum carmichaelii* (radix aconiti lateralis preparata, or Fuzi as it is known in TCM[29]) is a famous traditional Chinese medicinal herb used extensively in the treatments of cardiovascular diseases, rheumatoid arthritis, bronchitis, and hypothyroidism.[31] In the 28 government-issued guidelines for treating COVID-19 mentioned previously, herbal preparations containing Fuzi were recommended 13 times.[5] *A. carmichaelii* belongs to the genus

Aconitum, which consists of over 300 species of plants distributed throughout the temperate regions of the northern hemisphere and throughout China.[12,31] Species of plants belonging to the *Aconitum* genus contain potent alkaloids, including aconitine, which are powerful cardiotoxins and neurotoxins.[19,22,31] In Europe and the United States, aconitine is found in *A. napellus*, commonly known as monkshood or wolfsbane.[22] In TCM, this herb is used only after a process of soaking and boiling the roots to hydrolyze aconite alkaloids into less toxic and non-toxic derivatives.[29,31,32] Poisonings may arise when there is inadequate processing of the roots or a larger than recommended dose of the herb is used.[12,32,33]

The toxicity of aconitine and related alkaloids result from their actions on voltage-gated sodium channels in the cell membranes of the myocardium, nervous system, and muscles.[22,32] Aconitine binds with high affinity to the open state of the voltage-sensitive sodium channels, causing persistent activation of these channels and a continuous influx of sodium.[22] This increases inotropy while delaying the final repolarization phase of the action potential and promotes premature excitation.[22,32] Fatalities may occur with as little as 5 mL of an aconitine tincture or 1 gram of the dried root.[22]

Patients suffering from aconitine poisoning present predominantly with a combination of neurological, gastrointestinal, and cardiovascular features.[19,22,32] The neurologic symptoms are typically both sensory and motor, including paresthesias and numbness of the face and perioral area, as well as skeletal muscle weakness in the limbs.[22,32] Gastrointestinal effects include nausea, vomiting, abdominal pain, and diarrhea.[22,32] The fatalities seen from aconitine poisoning are typically secondary to the cardiovascular features, which include hypotension, sinus bradycardia, and ventricular dysrhythmias.[19,22,32] Diagnosis of acute aconitine poisoning is clinical, and treatment is mainly supportive, including pressor support and antiarrhythmic medications.[22] Available clinical evidence suggests sodium channel blockers, such as amiodarone, flecainide, lidocaine, and procainamide as first-line therapy for dysrhythmias.[22,32]

Both Fuzi and *Aconitum* root are purchased easily on online stores, and the flowering plant monkshood (*A. napellus*) is commonly available at home and garden stores.

4.2 | Semen armeniacae amarum (Xing Ren)

Semen armeniacae amarum, or Xing Ren[29,30] as it is otherwise known, is used commonly in TCM for treatment of dry cough, wheezing, and difficulty breathing.[34] It is for this reason that it was one of the most used herbal preparations in combatting COVID-19 in China.[5,30] The previously mentioned guidelines issued by the Chinese and Korean governments recommend using preparations containing Xing Ren over 70 different times,[5] and a systematic review published in June 2020 found that 32% of COVID-19 patients treated with TCM received this herb.[6] A more common name for semen armeniacae amarum is bitter apricot seeds,[29,30] a controversial product that has gained popularity in recent times as an alternative cancer treatment.[35–37]

Apricot seeds toxicity stems from the chemical compound amygdalin,[35,37,38] which is naturally occurring in many plants, but most notably in the seeds of apricots, bitter almonds, plums, apples, and peaches.[35,37,38] Amygdalin is often sold under the name "Vitamin B17," despite not being a vitamin, and a semisynthetic form known as laetrile[36,37] was used as an alternative cancer therapy before being banned by the FDA in 1978.[36] Amygdalin is toxic because when ingested, it is readily metabolized by the enzyme beta-glucosidase to hydrocyanic acid, or cyanide.[37]

Cyanide is a potent inhibitor of many enzymes, including cytochrome oxidase, which functions in the electron transport chain in the mitochondria. Inhibition of cytochrome oxidase by cyanide results in inhibited aerobic metabolism and profound cellular hypoxia. Ingestion of large amounts of apricot seeds can result in cyanide toxicity and may present in a more insidious manner because of the duration of metabolism required.[35] Early signs of cyanide toxicity are typical of progressive hypoxia and include headache, confusion, tachycardia, and tachypnea.[35,37,38] Later signs include nausea, vomiting, arrythmias, coma, pulmonary edema, and renal failure.[35,37,38] The diagnosis is often made clinically, but a profound lactic acidosis is often seen on laboratory values and may aid in making the diagnosis.[37,38] Serum cyanide levels can be drawn but typically will not result in sufficient time to aid in treatment of the patient. Management involves supportive care (oxygen and pressor support) and definitive treatment is with hydroxycobalamin, which converts cyanide to the much less toxic cyanocobalamin and is excreted in the urine.[35,37,38]

Apricot seeds, kernels, and powder are all readily available for purchase on multiple online sites, vitamin stores, and large chain retailers.

4.3 | Ephedra herba (ma huang)

Ephedra herba, referred to as ma huang in TCM,[29,30] has been used for centuries for the treatment of flu-like symptoms, including fever, chills, headache, nasal congestion, and bronchospasm.[40,41] According to the *Chinese Herbal Medicine: Materia Medica*,[42] ma huang "facilitates the opening of the lungs and controls wheezing for those patients suffering from cough with wheezing due to the lungs being obstructed."[42,43] It was recommended in a total of 56 different herbal preparations for the treatment of patients infected with COVID-19, according to the 28 government-issued guidelines[5] and also was found to be the 6th most common herb used for treatment of COVID-19 patients in China.[29] Ma huang commonly is cooked first before ingestion, and the raw plant sometimes is rubbed externally on the body to help treat symptoms of asthma.[43]

Ephedra is prepared from the aerial parts of plants belonging to the genus *Ephedra*, which are widespread, being found in North America, southern Europe, northern Africa, and southwest and central Asia.[40] The toxicity of this herb stems from the presence of the alkaloids ephedrine and pseudoephedrine, which are found in many species of plants in this genus.[40,44] These alkaloids activate adrenergic alpha and beta receptors, inhibit norepinephrine reuptake, and increase the

release of norepinephrine into synapses, all of which result in a marked stimulant effect.[40]

Symptoms of acute ephedra intoxication include nervousness, headache, insomnia, dizziness, palpitations, skin flushing, vomiting, mania, and psychosis, with severe presentations including hypertension, seizures, stroke, and myocardial infarction.[22,41] There are no definitive diagnostic tests, and prompt diagnosis depends on recognizing the central nervous syndrome stimulant toxidrome.[22] Acute management is like that of other stimulants and includes benzodiazepines for agitation and seizures, external cooling for management of hyperthermia, and controlling hypertension.[44] Initial blood pressure management should involve an initial alpha blockade before beta blockade to prevent a potential unopposed alpha agonism, which would result in further elevation of the blood pressure. This is commonly achieved using the alpha receptor antagonist, phentolamine, after which virtually any other antihypertensive may be used.

In 2002, the FDA banned the sale of ephedra-containing dietary supplements after severe disability and multiple deaths were reported following use of these supplements.[22] However, other herbal preparations, such as bitter orange, which contain alkaloids similar in structure to ephedra (synephrine),[19,22] are widely available for purchase both online and in retail stores.

4.4 | Glycyrrhizin (Gan Cao)

Glycyrrhizin (Gan Cao in TCM[29,30]) is known commonly as licorice root and has been used for centuries in TCM to control coughing and stop phlegm production. In 2003, there were reports that glycyrrhizin inhibited the replication of 2 clinical isolates of SARS-associated coronavirus,[45,46] prompting the belief that it would be effective against COVID-19. It was the most used herbal supplement for treatment of patients infected with COVID-19[29] and was recommended in 72 different herbal preparations by the Chinese and Korean governments.[5] In another systematic review, it was found to have been used in 48.39% of patients treated for COVID-19 in China.[30] Glycyrrhizin is the sweet-tasting component of the roots of the plant *Glycyrrhiza glabra*, a flowering plant native to Asia and Southern Europe.[47]

Licorice is also a popular sweetener in many soft drinks and food products and the traditional belief that licorice is a healthy, natural substance has driven its increased consumption,[47] occasionally with hazardous side effects. The main difficulty with licorice dosing is that it is available in various forms that contain different amounts of the active components of licorice. The suggested upper limit of daily licorice consumption varies between different government bureaus; it typically ranges from 100 to 200 mg/d.[47]

The toxicity of licorice root is secondary to glycyrrhizin, which can lead to a syndrome known as apparent mineralocorticoid excess resulting from glycyrrhizin's inhibition of the enzyme 11-beta-hydroxysteroid dehydrogenase and subsequent increase in the activity of cortisol.[47,48] Glycyrrhizin also inhibits hepatic metabolism of aldosterone through suppression of 5-beta reductase activity, further contributing to the excess mineralocorticoid effect.[47] Licorice root extract typically contains between 200 and 800 mg of glycyrrhizin in every 2–4 mL.[47]

Clinical manifestations of licorice root overconsumption are like those of hyperaldosteronism, mainly hypertension, hypokalemia, hypernatremia, and muscle weakness.[47,48] Although there is no diagnostic test to confirm licorice root overconsumption, laboratory values may aid in the diagnosis. Unlike in primary hyperaldosteronism, licorice overconsumption will result in low levels of renin and aldosterone but will still show typical mineralocorticoid effects, with hypokalemia and hypernatremia still being present.[47] Treatment involves supportive therapy, including correction of the electrolyte abnormalities and management of the resultant hypertension, as well as prompt cessation of further licorice root consumption.[47] Mineralocorticoid receptor antagonists, such as spironolactone and eplerenone, may also be used to counteract many of the symptoms caused by excess mineralocorticoids seen with licorice toxicity and should be the first line of antihypertensive medications used.

Supplements containing licorice root or licorice root extract are purchased easily on multiple online sites, health food stores, and large chain retailers around the country.

5 | CONCLUSION

With the outbreak of the COVID-19 pandemic, health care experts and government agencies have been continuously searching for a cure for this disease. During the early stages of the pandemic, Chinese government officials recommended a treatment strategy combining traditional Chinese medicine with modern Western medicine techniques, with reported success. Since then, practitioners, as well as the general public, have turned toward herbal medicine preparations as a possible treatment modality for COVID-19. Many of the herbal supplements used in this treatment strategy have severe toxicities, especially when self-prescribed, misused, or prepared by untrained persons. Frontline healthcare workers, particularly those who work in the emergency department, should be aware of the associated symptoms and toxidromes that arise from poisonings by these common herbal preparations. Practitioners who have encountered significant toxicities secondary to herbal preparations, or who have concerns about the manufacturing of certain products, can report these concerns to the FDA via MedWatch, the Safety Information and Adverse Event Reporting Program.

CONFLICTS OF INTEREST

None.

AUTHOR CONTRIBUTIONS

MAD: primary author, CM: review/editing.

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How to cite this article: DiPietro MA, Mondie C. Toxicity of herbal medications suggested as treatment for COVID-19: A narrative review. *JACEP Open*. 2021;2:e12411.
https://doi.org/10.1002/emp2.12411