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# Complementary and alternative medicine

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## SEARCH STRATEGY

Methods: A review of PubMed, EMBASE, Google Scholar, grey literature and the wider Internet was conducted with an emphasis on English-language case studies, case reports and meta-analyses published January 1, 2020 through January 1, 2021. The following terms were included in the search: CAM therapies, Chinese herbal drugs, COVID-19 virus, SARS-CoV-2, dietary supplements, food economics, food sociology, nutrieconomics, homeopathy, medicinal plants, phytotherapy, plant extracts, traditional Chinese medicine, and adverse effects (AEs) (psychiatric, cardiac, endocrine, gastrointestinal, pulmonary, neurotoxic, nephrotoxicity, hepatotoxicity), contaminants, and SEs (side effects). Specific products searched for in the literature included: *Amorphophallus konjac* (Glucomanan), *Angelica sinensis* (dong quai), *Camellia sinensis*, *Citrus aurantium* (Bitter Orange), *Curcuma longa* (Curcumin or Turmeric), fish oils, *Garcinia cambogia*, *Ginkgo biloba*, *Glycyrrhiza glabra* (Licorice), mushrooms, *Piper methysticum* (kava), cinnamon, guarana, probiotics, soybean, *Withania somnifera* (Ashwagandha), *Pausinystalia johimbe* (Yohimbine), and *Zingiber officinale* (ginger). Cases presented in this document are in alphabetic listing by plant genus.

## INTRODUCTION

Complementary and alternative medicine (CAM) practices may cause adverse events (AEs). Mind/body therapies AEs are usually related to mechanical injury

or misapplication. Although historically considered natural, thus “safe,” the lack of standardization and oversight of herbal dietary supplements (HDS) remains problematic. Standardization includes documentation of material sourcing and handling and controls as needed to maintain a consistent product. Consistency is achieved through various quality assurance practices applied to agricultural and manufacturing processes to minimize the inherent variation of natural product composition (Eisner, 2001) [R]. In the United States (U.S.), manufacturers are required to include ingredients and formulations on the Supplement Facts label, but that information is not always correct, and the contents may be inconsistent with the label. Public health education on mislabeling, misbranding, false claims, and adulteration is required to minimize the risk to consumers while the U.S. Food and Drug Administration works to update the current regulations for dietary supplements (Crawford et al., 2020) [E]. Studies have shown that adverse drug reactions (ADRs) of herbal products are vastly underreported globally; however, serious ADRs have been found in 26–41% of available reports, primarily skin and appendage disorders followed by liver and biliary disorders (Shaikh Abdul Rahman & Aziz, 2020) [R]. This high incidence of serious ADRs which often implies death, a life-threatening reaction, hospitalization, prolonged hospital course, or significant disability should lead to increased vigilance (World Health Organization, 2002) [S]. Patients with comorbidities, chronic illness, and/or requirements for polypharmacy make it difficult to pinpoint which substance is responsible for the ADR (Eisner, 2001 [R]; Shaikh Abdul Rahman & Aziz, 2020 [R]).

All chemical substances have the potential to cause severe AEs depending on the dosage supplied.

The natural inconsistency of medicinal plant material is based on environmental and collection conditions, the age and part of plant, seasonal variation and even the preservation processes employed (van Wyk & Prinsloo, 2020) [R]. That inconsistency may affect the safety and efficacy of herbal medications, as may soil contaminants and adulterants added through the manufacturing process (van Wyk & Prinsloo, 2020) [R]. While there are guidelines, such as Good Manufacturing Practices (GMP) and good agriculture and collection practices (GACP), the global lack of governmental testing and oversight for HDS create the potential for ineffective and unsafe product use (van Wyk & Prinsloo, 2020) [R].

Pharmacovigilance has a role in educating the public about both the misperception of absolute safety of HDS and the importance of reporting ADRs attributed to them. WHO has long suggested the inclusion of herbal and traditional medicine monitoring in national pharmacovigilance systems (World Health Organization, South East Asia Region, 2017) [S]. Those systems rely on spontaneous reporting, and WHO is working on a system to gather those reports of adverse events to make available globally (VigiAccess.org) (WHO Collaborating Centre for International Drug Monitoring, 2021) [S]. The difference in laws, guidelines, herb nomenclature, and categorization among countries can make this task challenging (Kim et al., 2021) [R]. There is a growing consensus that systematic inclusion of herbal and traditional medicine in pharmacovigilance reporting, including a universal standardized classification system, is needed to facilitate global information sharing and safety tracking. However, the current spontaneous reporting systems (SRS) are designed for synthetic medications and would require modifications to address HDS, especially in countries that use the theory of Traditional Chinese Medicine (Bhimaneni et al., 2021) [R]; Kim et al., 2021) [R]. Even the most robust SRS face the challenge of underreporting herbal product usage, the complexity of herbal mixtures, and incomplete or misleading product labelling, making both safety concerns and patient education all the more important as global use of HDS continues to rise. WHO has reported that about 80% of the world population relies on traditional medicine for their primary healthcare needs. While developing countries account for the majority of that use, herbal supplement use in developing countries has been gaining popularity creating a wide number of health concerns (Parveen et al., 2015) [R].

### **Nutrieconomics (the economics and sociology of food)**

*Research in medicine, sociology, and economics has shown that what—and how well—humans eat impacts not only their individual health outcomes for conditions like obesity, diabetes,*

*and other chronic illnesses, but also affects the global public health, economy, and environment. This interdependence of the consumer, foods, and the industries that produce and supply them has introduced the concept of “nutrieconomics” (Drewnowski, 2010 [r]; Thomas et al., 2020 [R]; White et al., 2020 [R]).*

*The economics and sociology of food, or nutrieconomics, has many components that combine to provide potential food security and better nutrition to people. Sustainable food systems are connected by health, economics, society, and the environment (Drewnowski et al., 2020 [R]). Economic models for nutrition in the U.S, Nutrient Rich Foods Index (Drewnowski, 2010 [r]), and the European Union (Primavesi et al., 2015) [E] identify healthy low-cost foods to inform healthcare providers and to move consumers towards better food choices for improved health outcomes. Education to consumers on these more affordable “market baskets” is needed to get communities involved in supporting sustainable healthier eating. This information can also move governments towards sustainable policies and regulations on the food industry. The environmental impact included in food production, availability, access, utilization, and disposal should also be addressed (Drewnowski et al., 2020 [R]; Hirvonen et al., 2020 [S]; Marette & Réquillart, 2020 [R]). Economic models for nutrition in the U.S, Nutrient Rich Foods Index (Drewnowski, 2010) [r], and the European Union (Primavesi et al., 2015) [E] identify healthy low-cost foods to inform healthcare providers and to move consumers towards better food choices for improved health outcomes. Education to consumers on these more affordable “market baskets” is needed to get communities involved in supporting sustainable healthier eating. This information can also move governments towards sustainable policies and regulations on the food industry. The environmental impact included in food production, availability, access, utilization, and disposal should also be addressed (Drewnowski et al., 2020 [R]; Hirvonen et al., 2020 [S]; Marette & Réquillart, 2020 [R]).*

*Nutrieconomic models based on economics, sociology, and policy vary in focus and include elements that could combine to help alleviate the important sociological problem of food insecurity (Marette & Réquillart, 2020 [R]; Meunier, 2019 [r]; Thomas et al., 2020 [R]). Food or nutrient insecurity, where available and affordable food is low in nutritional value, can be local or regional. The spectrum of food insecurity flows from lack of access to consistent, sufficient, or affordable food supply due to pandemic, drought, or war, (usually a regional effect) to more local “food deserts” where there is limited access to nutrient-rich foods that can lead to better health due to supply or cost. Food products rich in nutritional value are often considered by local suppliers or the consumer to be too perishable, costly, and/or not easily obtainable. Highly processed foods that are high in energy density, but low in nutritional value, containing preservatives, added sugars, saturated fats and excess sodium, are readily available and consumed in many countries due to perception of long shelf-life, low cost, and convenience. Programs aimed at providing local access to healthier food*

choices at affordable or subsidized prices in neighbourhoods or villages are working to reduce chronic illnesses and malnutrition. Sustainable food policies and systems can be created to deliver healthier foods to local populations (Drewnowski et al., 2020 [R]; Hirvonen et al., 2020 [S]). Educating consumers on nutrient-dense foods that are affordable and derived locally has been the focus of several government and non-governmental agencies. Local programs such as neighbourhood gardens, mobile vendors selling fruits and vegetables, adding nutrient-rich staples and perishable foods to bodegas or local shops can be effective in increasing access to healthy foods, but these efforts may not be seen as an economic priority to policy makers in the short-term (Downer et al., 2020 [R]; Marette & Réquillart, 2020 [R]).

Food as medicine is a concept that encourages healthy eating to improve health outcomes, especially for individuals with chronic or special health needs. Health providers are beginning to prescribe nutrient-rich foods to patients at risk for, or experiencing, chronic illnesses, obesity, and other non-communicable diseases (Downer et al., 2020 [R]). The prescription could be for therapeutic meals or for beans, fruit, and vegetables. Usually, the prescription is a voucher program subsidized by government or other agencies. The consumer is guided by a healthcare clinician towards an eating style that is focused on improving health outcomes. The benefits of these programs include reduced medical costs and fewer admissions to care facilities (Downer et al., 2020) [R].

A global focus on quality food as a requirement for healthy communities can provide incentives for the food industry interests to produce higher nutrient content at a lower cost. The policy in many countries is to supplement micronutrients, vitamins, and minerals in staple foods, such as, grain, dairy, and other products. This supplementation has reduced folic acid, iodine, iron, and vitamin deficiencies, and has been responsible for better-targeted health outcomes in specific populations. However, these policies have the potential to increase risks from overdoses in some vulnerable populations (Keats et al., 2019 [M]; Murphy & Westmark, 2020 [MC]; F.F. Zhang, et al., 2020 [R]).

The United Nations has a committee on world food security which is developing policies that will work to provide food security, impact human health, and sustain the environment. Food system activities, from production to waste disposal, are being addressed to increase sustainability for a growing human population (Drewnowski et al., 2020) [R]. The EAT-Lancet commission has developed a reference diet that should be affordable across countries and communities of varying economic status, while being health- and environmental-conscience. The reference diet is based on 2500kcal per day and uses the international comparison program of the World Bank to gauge costs. However, the diet was shown to exceed the daily per capita household income in the very low-income countries of south Asia and sub-Saharan Africa, so there is more work to be done to address this issue (Hirvonen et al., 2020) [S]. Limitations on many models proposed for sustainable healthy diets

include consumer behaviours and perceptions or market adjustments, such as during the current pandemic (Marette & Réquillart, 2020 [R]; Meunier, 2019 [r]).

## HERBAL PREVENTION AND TREATMENT OF CORONAVIRUS DISEASE 2019 (COVID-19)

Inquisitive minds from many countries propose and study the effects of agents to prevent, mitigate, and treat symptoms of a virus-mediated disease during a global pandemic. At the end of 2020, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected more than 83.5 million people, causing 1.825 million deaths in 192 countries or regions (John Hopkins Coronavirus Resource Center, 2020) [S]. The literature on the use of herbal, vitamin and mineral products used for similar previously studied viral infections was reviewed to indicate which products might be best to try against this new coronavirus (Boozari & Hosseinzadeh, 2021 [R]; P. Ho et al., 2021 [R]; Nugraha et al., 2020 [R]; Shahrajabian et al., 2020 [R]). Many herbal products have been seen to prevent viral attachment, penetration, or replication and/or to treat symptoms or complications of other coronavirus infections within in vitro and in vivo studies (Savant et al., 2021) [R].

In a computer-based (in silico) analysis (Luo et al., 2020) [R] of individual herbs for potential use for COVID-19, herbs used in traditional Chinese medicine (TCM) to treat respiratory and other known respiratory viruses revealed 10 frequently applied herbs and their most common uses as antipyretics, expectorants, cough suppressants and “dampness resolving” agents (see Table 1). From their analysis, eight core combinations of herbs from a review of 179 separate herbs were proposed that would be used in clusters depending on the individual patient and symptoms.

Glycyrrhiza glabra (Licorice) has traditionally been used for liver disorders and as an anti-inflammatory and anti-viral agent. Serum concentrations when used as a tea or in general consumption may not be as effective as an anti-viral agent in humans as much as the in vitro studies have shown (Bailly & Vergoten, 2020) [R]. One proposed mechanism of action in COVID-19 infection is to bind angiotensin converting enzyme 2 (ACE-2) blocking the virus from infecting nearby cells. Another is to disrupt cholesterol synthesis leading to a decrease in respiratory cell membrane permeability. Glycyrrhiza may induce pseudo-hyperaldosteronism and subsequent hypertension (Bailly & Vergoten, 2020 [R]; Boozari & Hosseinzadeh, 2021 [R]; Chrzanowski et al., 2021 [R]).

Curcuma longa (Turmeric) is used in food and medicine. Standardized extracts of turmeric have shown potential anti-inflammatory and anti-viral properties. Oral absorption has been increased with the addition of black pepper extract. Mechanisms proposed against coronaviruses, including COVID-19, involve reducing penetration and replication of the virus, as well as inhibition of ACE-2 receptors, reducing

TABLE. 1 Traditional Chinese medicine for viral respiratory ailments (Luo et al., 2020 [R]).

Herb	TCM name	Traditional attributes
<i>Glycyrrhiza radix</i>	Gan Cao	Adds herb synergy, nourishes Qi, alleviates pain, tonifies the spleen and stomach, eliminates phlegm, relieves cough
<i>Scutellariae radix</i>	Huang Qin	Purges fire, clears away heat, moistens aridity, detoxifies, shortens bleeding times
<i>Armeniaca semen Amarum</i>	Ku Xing Ren	Relieves cough and dyspnea, moistens intestines, relaxes bowels
<i>Lonicerae Japonica flos</i>	Jin Yin Hua	Clears away heat, detoxifies, expels wind/heat
<i>Forsythiae fructus</i>	Lian Qiao	Releases heat and detoxifies
<i>Ephedrae herba</i>	Ma Huang	Disperses lung Qi, relieves asthma, promotes diaphoresis, relieves exterior heat, detumescence and diuresis
<i>Poria</i>	Fu Ling	Promotes diuresis, dissolves dampness, strengthens the spleen, calms the mind
<i>Pogostemon cablin</i> (patchouli alcohol)	Guang Huo Xiang	Eliminates dampness, harmonizes spleen and stomach, stops vomiting, relieves exterior heat
<i>Citri reticulatae pericarpium</i>	Chen Pi	Regulates Qi, strengthens the spleen, expels dampness, dissolves phlegm
<i>Platycodonis radix</i>	Jie Geng	Promotes lung and pharynx function, eliminates phlegm, discharges pus

vascular coagulopathy. Turmeric doses of up to 6 g per day for over a month are not associated with serious AEs (Brendler et al., 2020) [R].

*Sambucus nigra* (Elderberry) has shown immunomodulatory effects in patients during influenza season, reducing severity and duration of symptoms. The results of several studies looking at its use with coronavirus are inconsistent and no evidence is yet available for COVID-19. Elderberry extract can cause increased insulin levels, decreased blood pressure, increased heart rate, gastrointestinal disturbances and dehydration. Inadequate preparation of elderberry can lead to cyanide toxicity (Adams et al., 2020 [R]; Brendler et al., 2020 [R]).

*Nigella sativa* may prevent lung inflammation in COVID-19 infections by inhibiting cyclo-oxygenase and 5-lipoxygenase pathways in arachidonic acid metabolism. *N. sativa* has been shown to modulate cellular and humoral immunity in human diseases. Appropriate dosing of *N. sativa* is unknown. *N. sativa* may change the absorption of amoxicillin (Kulyar et al., 2020) [H].

Vitamin D deficiency may lead to more severe outcomes of COVID-19 infection. In a review and meta-analysis of over 350 000 patients admitted to the hospital with the virus, there was no association with deficiency and viral acquisition. Once acquired, patients with vitamin D insufficiency (<50 nmol/L) were hospitalized more frequently and had higher mortality rates. Patients with normal serum concentration of Vitamin D had milder cases and were less likely to be hospitalized due to infection with the COVID-19 virus (Pereira et al., 2020) [M]. A decrease in the Intensive Care Unit (ICU) admission rate for elderly people taking vitamin D supplements was shown by Shah and colleagues (Shah et al., 2021) [M]. Vitamin D supplementation over 4000 IU per day for extended periods may be associated with hypercalcemia (Adams et al., 2020) [R].

Murai and associates (Murai et al., 2021) [MC] randomized 237 adult subjects admitted to the hospital for COVID-19 to

receive a single oral dose of 200 000 IU (5000 µg) vitamin D3 or placebo. No differences were seen between groups for length of stay, ICU admission or use of mechanical ventilation. Serum 25-hydroxyvitamin D level was elevated initially for those subjects in the active arm. AEs were limited to one patient who experienced vomiting after the vitamin D dose.

Ascorbic acid (Vitamin C) intravenous infusions are being studied in COVID-19 infections in several countries. There are anecdotal reports of symptom and outcome improvement with the use of high doses of vitamin C injection (Miranda-Massari et al., 2020) [H]. In one randomized controlled trial in the U.S., over 200 ambulatory patients diagnosed with SARS-CoV-2 were given oral zinc or vitamin C or both and no symptoms or outcomes differed compared with standard care. AEs from vitamin C reported included gastrointestinal complaints of nausea, diarrhea and stomach cramps (Miranda-Massari et al., 2020 [H]; Thomas et al., 2021 [MC]).

Chinese health authorities have published a guideline for the integrative use of TCM with Western practices for prevention and treatment of the COVID-19 viral illness. A comprehensive set of definitions of the disease, symptoms, and potential products from this guideline are provided (L.T.F. Ho et al., 2020 [H]; Wu et al., 2021 [M]). The Chinese patent medicine oral preparations, Lianhua Qingwen and Shufeng Jiedu, recommended by the Chinese guideline have early evidence of limiting respiratory and gastrointestinal symptoms in presumed or mild COVID-19 disease. The authors postulate the potential positive effects of various injected mixtures on the symptoms of more serious cases. They recommend that pharmacists document safety concerns as these products are utilized in studies and in the population (D. Zhang, et al., 2020) [S]. The evidence for complementary and alternative medicine practices and for supplements is limited and evolving. China has the most experience with herbal, vitamin, and mineral products but the

applications and mixture of agents is so varied that Randomized Controlled Trials (RCTs) are not always practical (Ang et al., 2020) [M]. The world is weighing the benefit of many agents in the prevention and treatment of COVID-19 infection, but global vaccination is the steady way forward (Alyami et al., 2020 [MC]; Brendler et al., 2020 [R]; Shankar et al., 2020 [r]).

## Review of herbal product AEs (2020)

### A. konjac (*Glucomannan*)

Dietary fibre has been used in promotion of weight loss. Glucomannan is a fibre derived from the *A. konjac* tuber and is contained in some weight loss supplements. Efficacy data is inconsistent across studies, with modest weight loss experienced by small numbers of subjects. No severe AEs from the use of products containing glucomannan are noted. Mild to moderate gastrointestinal tract disturbances, such as, diarrhoea or constipation are frequently experienced by subjects (Wharton et al., 2020) [R].

### *Camillia sinensis* (*tea*)

Green tea is prepared from the unoxidized leaves of the *Camillia sinensis* plant and contains caffeine and anti-oxidant catechins. Claims of weight loss properties of a beverage or extract from green tea are not conclusive and not always associated with caffeine content. Wharton and colleagues reviewed cases of severe AEs including acute liver failure leading to transplant and hospitalizations due to hypertension and elevated liver enzymes. Other study subjects were noted to have milder AEs, primarily gastrointestinal complaints, or diarrhoea (Wharton et al., 2020) [R]. Green tea extracts in high dose can cause headache, gastrointestinal disturbances, or tachycardia. The systematic review by Lin and associates of green tea used to reduce body weight gives no direct analysis of AEs (Lin et al., 2020) [M].

A recent review of experimental and non-experimental literature was conducted to assess green tea consumption in preventing cancer diagnoses or reducing mortality in adult subjects. Results are not conclusive due to the inconsistent phytosterol or caffeine content of brewed green tea beverages or dietary supplements, and the differences in the documentation of daily intake due to study protocol or non-experimental circumstances. Adverse events were described in more of the subjects receiving concentrated extracts than brewed tea, including elevations in liver enzymes, hypertension, insomnia, and gastrointestinal upset (Filippini et al., 2020) [M].

### *Citrus aurantium* (*bitter orange*)

Bitter orange extract from the peels of the fruit of *Citrus aurantium* is promoted to cause weight loss due to its p-synephrine content. While there were no studies

published between 2006 and 2016 to support this claim or show efficacy in obese individuals, a current review cites an older case of bitter orange extract associated with severe AEs including renal and respiratory failure and motor neuron impairment in lower extremities. A randomized controlled study of 67 subjects receiving 49 mg of bitter orange extract twice daily did not observe serious AEs or clinical changes (Wharton et al., 2020) [R] and a recent review of bitter orange extract and preparations containing this supplement claimed no direct correlation with serious AEs (Stohs & Ray, 2020) [R].

### *Curcuma longa* (*curcumin or turmeric*)

Lombardi (Lombardi et al., 2020) [A] reports seven cases from Italy of turmeric associated acute hepatotoxicity, diagnosed from over threefold transaminase increases with symptoms including jaundice, abdominal pain, itching, and changes in stool and urine colour, and provides a systematic review of available literature. Six of the cases were in middle-aged women (45–68 years of age) with doses of turmeric ranged from 250 to 1800 mg per day taken over 2 weeks to 8 months. In most cases, the patient took a combination product with curcumin or extract with other herbal ingredients, *Piper nigrum*, *Zingiber officinale* or B vitamins. In the seventh case, a 59-year-old man taking 280 mg turmeric daily, the adverse event was not assessed to be associated with turmeric. A positive response, lowering of transaminase serum concentrations, was attributed to de-challenge in most of the cases. Two cases required N-acetylcysteine treatment for resolution. Curcumin was causally associated with the liver injury in these cases. The literature review provides details of 23 cases of liver injury after the ingestion of curcumin products by individuals aged 25–78 years, using similar doses and duration. These cases were in patients that had underlying disease conditions and were on prescription medications, vitamins, or other herbals. The acute hepatitis or other liver injury for most patients resolved when the curcumin product was discontinued. In a 2009 study reviewed from Norway, two deaths occurred, but there was a concern with contamination of the product with nimesulide. The authors state that the mechanism of toxicity from curcumin was not clearly defined. The presence of piperine from *Piper nigrum* enhances turmeric absorption and may increase the risk in susceptible individuals. Also, synthetic curcumin use in some products may contribute to the risk of hepatotoxicity. Since 2019, the Italian Ministry of Health has required cautionary labelling regarding liver function alterations on curcumin containing dietary supplements (Lombardi et al., 2020) [A].

### *Garcinia cambogia*

A case of decreased vision and ocular pain in a 35-year-old woman taking *Garcinia cambogia* for weight loss associates this herb with the unexpected AE. She also

experienced headaches with nausea and vomiting. Her self-decided dose was twice the amount suggested on the packaging (4.5 g hydroxy citric acid (HCA)/day) for a week, and she used no other medications or supplements. Her ocular exam showed narrowing of the anterior chamber, swelling around the optic disc and macula in both eyes with retinal folds. After discontinuance of the *Garcinia cambogia* product and a short course of topical steroid eye drops, her ocular changes and symptoms resolved (Cho et al., 2020) [A].

A case of acute liver failure requiring transplantation in a middle-aged woman in Australia taking *Garcinia cambogia* for weight loss over a period of 2 months showed submassive necrosis of the liver on pathology sample. While *Garcinia cambogia* was found to have temporal correlation with the liver damage, there was no other acute or chronic liver diagnoses (McCarthy et al., 2020) [A].

*Garcinia cambogia* 1800 mg daily in combination with other plant-based ingredients over a period of 7 months caused acute hepatitis in a 26-year-old obese Canadian woman. She had intentionally lost 45 kg body weight over the time but stopped the supplement when she experienced nausea, fatigue, and jaundice. A liver biopsy showed lobular disarray with necrosis and reticulin collapse, along with acute inflammatory infiltration and cell damage consistent with acute hepatitis. No indications of steatosis, viral infection or chronic hepatic changes were seen. The patient's condition evolved negatively, and she exhibited encephalopathy and fulminant hepatitis leading to liver transplant. Although she had taken a product with other potential hepatotoxic agents, *Garcinia cambogia* was the probable associated agent with her acute hepatitis (Ferreira et al., 2020) [A].

A 22-year-old obese, body mass index (BMI)=41, woman from Florida, in the U.S., also took a combination weight-loss product with *Garcinia cambogia* 1800 mg and green tea components over a three-month period. She presented with fatigue, shortness of breath and cardiac symptoms, including chest pain and palpitations. Her laboratory analysis was consistent with leukocytosis and severe transaminitis [elevations of Alanine transaminase (ALT) 2399 u/L, Aspartate transaminase (AST) 4040 u/L]. All other causes of acute hepatitis were ruled out. The patient received *n*-acetylcysteine treatment and her transaminases declined. She was discharged to follow-up care with outpatient hepatology. The authors state the importance of public health alerts to minimize the use of over the counter (OTC) herbals for weight loss and other indications associated with high rates of serious AEs (Khetpal et al., 2020) [A].

The no-observed-adverse-effect-level (NOAEL) doses of the presumed active component of *Garcinia cambogia*, HCA, of 2800 mg per day are based on toxicologic studies in animals and humans. Most human studies using less

than this amount have shown minor side effects, such as, leg cramps, headache, gastrointestinal discomfort, among others. More serious AEs, including hepatitis and pancreatitis, have been associated with *Garcinia cambogia* products. Many implicated products include other herbal, vitamin, or mineral substances. Toxicity occurs in a low percentage of individuals in the studies reviewed, and when the products containing HCA are discontinued the symptoms resolve in most patients. There are four reports of necessitated liver transplants. Cases of mania and serotonin toxicity in six individuals taking *Garcinia* supplements with serotonin reuptake inhibitor (SSRI) anti-depressants or with bipolar diagnoses are consistent with HCA's SSRI activity (Andueza et al., 2021) [R].

### **Glycyrrhiza glabra (licorice)**

*Glycyrrhiza glabra* is effective and safe for most uses. It can cause pseudo-hyperaldosteronism in large or chronic doses, or in patients with renal or cardiac dysfunction. This can manifest as increases in blood pressure, hypokalemia, lower extremity edema, headaches, and other more serious side effects, such as cardiac arrest. *Glycyrrhiza glabra* may inhibit CYP450 enzyme 3A4. Patients taking digitalis, diuretics or antihypertensives should have blood pressure, heart rate, and body weights monitored closely if regularly taking *Glycyrrhiza glabra* products or teas. Patients on hypoglycemic agents or insulin should monitor blood glucose closely when using these products (El-Saber Batiha et al., 2020 [R]; Murray, 2020 [R]).

In a randomized, placebo-controlled study, 199 eczema patients were given oral compounded Glycyrrhizin (OCG) 75 mg capsules or placebo three times a day over a 4-week period. All patients also received topical corticosteroids daily and were monitored for skin clearance, physical and laboratory changes, and cardiac changes. The Eczema Area and Severity Index (EASI) was used to determine skin clearance and recurrence. Analysis was completed on 92 in the OCG arm and 97 in the placebo arm. EASI score mean absolute reduction ( $P < 0.001$  at 14 days and  $P = 0.002$  at 28 days) and itching ( $P < 0.001$  at 14 days and  $P = 0.016$  at 28 days) were reduced in the glycyrrhiza with corticosteroid group more than the placebo with corticosteroid group. Mild side effects were more prevalent in the OCG group (OCG 8.75% vs Placebo 5.7%,  $P > 0.05$ ), including lower limb edema, 3 subjects, and hypokalemia or high blood pressure, 1 subject each (Xu et al., 2020) [C].

### **Panax ginseng (Ginseng)**

AEs in the treatment arm of a study of a standardized *Panax ginseng* extract 3 g/day to treat liver toxicity with elevated transaminases were considered mild in 11 incidents among 26 subjects, and included gastrointestinal

complaints, chest pain, thigh numbness and elevation in creatine serum concentration. The placebo arm had 8 mild AEs during the study period among 25 subjects and 1 moderate AE of elevated liver enzymes. Most of the AEs were deemed not related to the study medication and there were no differences ( $P > 0.05$ ) in AE occurrences between groups. Clinical outcomes of the study were significant reductions in ALT ( $P = 0.009$ ) and GGT ( $P = 0.038$ ) in the treatment group (Shen et al., 2020) [c].

A review of dietary supplements used to reduce cardiovascular risks including safety concerns included *Panax ginseng*. Side effects with high dose, long term use of ginseng include diarrhoea, rash, nervousness, blood pressure changes, edema, and sleeplessness. Cases of more severe adverse events include hypertension and cardiac arrhythmias, including QT prolongation. Ginseng is considered safe for most patients, but more studies are needed (Shaito et al., 2020) [R].

Ginseng extracts may be injected in a procedure called pharmacopuncture, a Korean medicine technique. The technique uses injections of ginseng extracts at acupuncture sites or intravenously. Wild and cultivated ginseng and extracts of ginseng were reviewed. This technique is used in multiple disease states, including cancers, depression and musculoskeletal problems and has preliminary success in some cases and worsening of condition in others, with one death cited in a cancer patient. Side effects of the technique include headache, dry mouth, and tremor but similar side effects were seen in the placebo groups. More study of the technique is encouraged by the authors (Lee et al., 2020) [R].

### **Pausinystalia johimbe (Yohimbine)**

Yohimbine is discussed in a recent review of herbal sexual enhancers and potential AEs. Yohimbine is associated with moderate to severe cardiac AEs, including hypertension, sweating, tachycardia, chest pain and atrial fibrillation (Brunetti et al., 2020) [M]. A case of fatal toxicity of yohimbine taken for 2 months by a 27-year-old man prior to his collapse and death is presented. The man had sought medical advice about cardiac palpitations 3 weeks prior. Samples from the bodybuilder contained yohimbine at toxic levels in blood (8000 µg/L) and in his vitreous humour. No other substances were detected. The authors hope to discourage use due to lack of benefit to body builders and increased risk due to severe cardiac toxicity (Brunetti et al., 2020) [M]. Drevin presents a case of fatal toxicity of yohimbine taken for 2 months by a 27-year-old man prior to his collapse and death. The man had sought medical advice about cardiac palpitations 3 weeks prior. Samples from the bodybuilder contained yohimbine at toxic levels in blood (8000 µg/L) and in his vitreous humour. No other substances were detected (Drevin et al., 2020) [A].

Yohimbine toxicity occurred in four hospital workers in China from a product for male sexual enhancement bought from the internet, leading to death in one of the men. A powder was mixed in a liquid and ingested. Three of the middle-aged men exhibited vomiting, sweating, sinus tachycardia and headache on hospital evaluation at 10 h after ingestion. The fourth individual had similar but more severe symptoms and succumbed after the 10 h. On analysis, his blood concentrations of yohimbine were more than 5600 ng/mL, as compared to the others that survived whose blood concentrations were in the 250–470 ng/mL range. The deceased individual had significant toxicity, cardiac congestion, pulmonary edema, and pulmonary haemorrhage. The authors caution that absorption of yohimbine may vary among individuals and toxicity may not be predicted (Zhu et al., 2021) [A].

### **Piper methyslicum (kava)**

A phase-3 multi-site blinded RCT of Kava root extract was conducted on 171 Australian patients with generalized anxiety disorder (GAD). Kava from a high-grade cultivar underwent an aqueous extraction and standardized to 60 mg of kavalactones per tablet. Two tablets twice daily (equivalent to 240 mg per day, or placebo) were given to subjects for 16 weeks and all received placebo for an additional 2 weeks. Genetic, liver function and other safety analyses were performed at baseline and at several points during the 16 weeks. This kava product was not shown efficacious in treating GAD. No serious AEs were noted in the Kava group. At week 2 and week 16, seven subjects receiving Kava and two receiving the placebo had abnormal liver function tests (Sarris et al., 2020) [C].

Kava efficacy and safety as a plant-based therapy for anxiety was reviewed by Bian (Bian et al., 2020) [R] and included specific cultivar type and preparation techniques. Flavokavains A and B are associated with increased cytotoxicity and glutathione depletion in the liver. Hepatotoxic risk may be increased due to cultivar choice (non-noble), plant part used (stems), dose (over 120 mg/day alcoholic extract), method of preparation (alcohol extraction), adulteration, concurrent ethanol ingestion, herb-drug interactions (acetaminophen). The authors conclude that more human studies are needed but risk of hepatotoxicity is relatively low overall (Bian et al., 2020) [R] and included specific cultivar type and preparation techniques. Description of the use and safety of different plant parts, variations in cultivars, preparation and extraction methods, traditional use and commercial products allows the reader to grasp the complexity of kava use and the potential reasons for toxicity. The major kavalactones listed have differing pharmacologic actions on inflammatory markers and neurologic function. The flavokavain components are being investigated in certain cancers. Hepatotoxic risk may be increased due to



cultivar choice, plant part used, dose, method of preparation, adulteration, concurrent ethanol ingestion, herb-drug interactions. The authors conclude that more human studies are needed but risk of hepatotoxicity is relatively low overall (Bian et al., 2020) [R].

### **Valeriana officinalis L. (valerian)**

A systematic review of Valerian as used for cognitive disorders, including anxiety and sleep disruption, revealed no serious AEs in nearly 7000 subjects across 60 studies. No impairment of cognitive performance was discovered. Minor adverse events included stimulatory effects, vivid dreams, fatigue, dizziness, gastrointestinal symptoms, and depression, but were not clearly associated with the use of valerian products (Shinjyo et al., 2020) [M].

## V8

Severe hypoglycemia, serum blood glucose levels as low as 11 mg/dL, was reported by 17 patients following the ingestion of a male enhancement supplement tablet bought in southeastern U.S. convenience stores. The tablets were found to be adulterated with sildenafil 55–156 mg and glyburide 90–100 mg. This cluster of AE reports led to seizure of this product from retail outlets and a national public health alert through the FDA Med-Watch program. A warning that dietary supplements may contain prescription medications and can cause serious morbidity is reiterated (Ross et al., 2020) [S].

### **Withania somnifera (Ashwagandha)**

Ashwagandha is derived from the root of the *Withania somnifera* plant used in Ayurvedic medicine to treat stress, lack of energy, and anxiety. Liver injury in 5 patients was associated with ashwagandha use in a case series from the U.S. and Iceland. Presenting symptoms included jaundice, itching, and/or abdominal pain. Patients had either cholestatic or mixed liver injury. Liver function tests were elevated, ALT, AST, Total bilirubin and Alkaline phosphatase. All cases were considered moderate, and patients recovered after discontinuing the product (Björnsson et al., 2020) [A].

### **Homeopathy**

Stub and colleagues reviewed and analysed 41 observational homeopathy studies for adverse events and homeopathic aggravations. Reported adverse events from various homeopathy prescriptions included allergic responses, gastrointestinal tract disorders, headache, dizziness, and dermatitis. Fewer AEs were associated with homeopathic treatments as compared with controls

( $P < 0.0001$ ) or conventional medicine ( $P = 0.0004$ ). Homeopathy aggravations were associated with worsening of underlying conditions (Stub et al., 2020) [M].

## CONCLUSION

Complementary and alternative therapies are used worldwide to prevent and treat many ailments. The recent COVID-19 pandemic is no exception. Traditional Chinese medicine practices were considered and put into practice early in the prevention and treatment of this novel coronavirus before vaccines could be developed (Ho et al., 2020 [H]); Wu et al., 2021 [M]). Other herbal or vitamin products used to prevent or treat viral illnesses were utilized as an effort to control the spread and severity of the current illness (Savant et al., 2021) [R]. Inconsistent data and inherent toxicities of some herbals used, quinine, glycyrrhiza, turmeric and others, should cause the practitioner to be cautious (Nugraha et al., 2020) [R]. Pharmacovigilance of the use of dietary supplements continues in importance. If the generated information is correctly gathered, disseminated, and used, it will motivate best practices in manufacture and clinical expertise (van Wyk & Prinsloo, 2020) [R]. Sustainability and availability of food sources as described through nutrieconomics can promote better nutrition for people of many countries and communities, even those in lower economic strata (Drewnowski et al., 2020) [R]. Herbal and homeopathic therapies continue to cause minor and major side effects for consumers due to poor choice of product, mislabelling, misbranding, adulteration, or dosing (Crawford et al., 2020) [E].

Readers are advised to refer to articles published in SEDA-40, SEDA-41 and SEDA-42 for additional information and case reviews from prior years (Bellanger et al., 2018 [R]; Bellanger et al., 2019 [R]; Bellanger & Seeger, 2020 [R]).

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