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Safety Review of Herbs and Supplements in Heart Disease, Diabetes, and COVID-19

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Abstract

Usage of supplements has increased dramatically this last decade. From herbs to vitamins and mineral, consumers are interested in improving health, self-treatment and preventing diseases. Often using information from the internet to self-prescribe, many consumers believe that natural products are safe, while many others avoid using these products because of the lack of an approval process by health officials in many countries. Herbs and other supplements including proteins, vitamins and minerals provide significant benefits to health. The lack of guidance from health professionals however can be problematic. When combined with drugs and disease, herbs can interact and cause side effects. Some of the steps to evaluate the safe use of supplements is to know their mechanism of action, clinical effect, and consumers' medical history. For example, an herb that induces liver enzymes will reduce the effect of a drug that is metabolized by these same enzymes. This can be life threating if the patient depends on this drug for normal function. Based on drug-herb interaction experience and literature review, this book chapter provides insights into safe use of echinacea, licorice, turmeric, and black seed in patients with heart disease, diabetes, and COVID-19.

Keywords: herbs, supplements, drug-herb interaction, safety, COVID-19, heart disease, diabetes

1. Introduction

Dietary supplements are defined in the United States as products that contain one or more dietary ingredient such as vitamins, minerals, herbs, botanicals, and amino acids and are intended to supplement the diet [1]. In other countries dietary supplements are named differently including natural health products, complementary medicines, food supplements, and others [2]. Nonetheless, "dietary supplements" is a general term for products that mostly contain herbs, botanicals, proteins, and/or vitamins and minerals that are used with the intention to promote health. Despite the legal framework, dietary ingredients are often used and recommended for treating or preventing diseases. In this chapter, "dietary supplements" will be used as a general term to encompass several dietary ingredients.

Usage of dietary supplements has increased this last two decades [2]. From herbs, proteins, to vitamins and minerals, consumers are interested in self-treatment and preventing diseases [3]. Often using information from the internet to self-prescribe, many consumers believe that natural products are safe, while

many others avoid using these products because of the lack of an approval process by health officials in many countries. Many dietary supplements provide significant benefits to health [4]. However, the lack of guidance from health professionals can be problematic.

Dietary supplements are likely safe when used as prescribed [4, 5]. But, when combined with drugs and disease, these products can interact and cause side effects [6, 7]. Some of the steps to evaluate the safe use of dietary ingredients is to know their mechanism of action, clinical effect, and consumers' medical history. For example, an ingredient that induces liver enzymes will reduce the effect of a drug that is metabolized by these same enzymes. This can be life threating if the patient depends on this drug for normal function.

Due to the benefits that several of these dietary ingredients provide, it is important to evaluate their safety for wide spread recommendation. Particularly due to times of pandemic such as the coronavirus disease 2019 (COVID-19) [8], ways to prevent disease severity and to be used as adjunct treatments are needed. Several dietary ingredients have been reported to be effective against COVID-19 in review articles. For this book chapter, 30 review articles and meta-analysis were evaluated for the selection of the dietary ingredients herein discussed. The selection criterium was based on the number of articles that cited the ingredients as being effective as well as the commonality and accessibility of the ingredients across the globe. Vitamins and minerals were excluded due to their safety being extensively researched. Because COVID-19 severity is worse among patients with diabetes and cardiovascular disease, the safety use of these ingredients in the context of these comorbidities are presented here.

2. Comorbidities and their drug treatments

2.1 COVID-19

COVID-19 is a respiratory infection caused by the virus named "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) [8]. COVID-19 is a novel disease officially declared as a pandemic on March 11th, 2020 [9, 10]. SARS-CoV-2 has infected 98.2 million people worldwide and caused 2.1 million deaths as of January 24th, 2021 [11]. COVID-19 is characterized by dry cough, fever, and fatigue symptoms in adults while in children rhinorrhea, abdominal pain, and diarrhea are also present [10]. SARS-CoV-2 binds directly to angiotensin converting enzyme 2 (ACE2) for subsequent entry into cells [10, 12]. Infected cells respond to the virus by generating pro-inflammatory cytokines and chemokines that sometimes lead to a cytokine storm which aggravates the disease [10, 12, 13]. Those with certain underlying health conditions such as respiratory disease, cardiovascular disease, and diabetes as well as older individuals seem to be at a higher risk for developing severe complications from the infection [14, 15]. Because SARS-CoV-2 has approximately 80% genomic homology with SARS-CoV-1, the virus that caused the 2002–2003 epidemic, many research studies have proposed the use of treatments that were effective against SARS-CoV-1 [9]. Current treatments for COVID-19 used in the clinics are ACE2 inhibitors, corticosteroids, chloroquine, anti-inflammatory tocilizumab, comostat, protease inhibitors (lopivavir and ritonavir), and RNA polymerase inhibitors (remdesivir, favipiravir) [16]. Some of the established protocols are: no treatment for mild cases besides acetaminophen for fever; hydroxychloroquine + azithromycin for moderate cases; tocilizumab or sarilumab for worsening respiratory function; and remdesivir, convalescent plasma, corticosteroids for respiratory failure. NSAIDs such as ibuprofen are not recommended

due to potential increase in ACE2 expression [17]. Lastly, it has been suggested that reduction in cholesterol decreases viral mRNA [18]. Thus, treatments that reduce cholesterol in addition to antivirals, anti-inflammatories, and respiratory support should be beneficial in managing COVID-19.

2.2 Heart disease and diabetes

As noted above, patients with heart disease and diabetes are more likely to develop severe COVID-19. Thus, many of these patients will be given medications for COVID-19 on top of the current heart/diabetes medications they take. For example, patients continue to take ACE inhibitors or angiotensin II receptor blockers (ARBs) during COVID-19 infection [17]. Furthermore, these are the patients more likely to benefit from dietary ingredients that assist in preventing or treating COVID-19. Due to multiple treatments at once, the likelihood of drug–drug and drug-herb

Drug categories	Liver metabolism	Renal excretion	References
ACE inhibitors: 1. Enalapril 2. Lisinopril	1. Metabolized to active metabolites 2. No liver metabolism	1. ~75% excretion in the urine 2. Excreted unchanged in urine	[21, 22]
ARBs: 1. Losartan 2. Irbesartan	1. CYP3A4 and CYP2C9 2. Glucuronide conjugation and CYP2C9 oxidation	1. Minimal renal excretion with oral administration 2. ~20% excretion in the urine	[22]
Hydroxychloroquine	Partially metabolized	Slowly excreted by the kidneys	[21]
Protease inhibitor, ritonavir	CYP3A4 and 2D6 inhibitor	Minimal renal excretion	[16, 23]
RNA polymerase inhibitor, remdesivir	CES1 to form active metabolite	~50% renal excretion	[22]
Corticosteroids and anti-inflammatories 1. Prednisone 2. Tocilizumab	1. Metabolized by CYP3A4 2. Metabolized by CYP3A4	1. Minimal renal excretion	[21, 24]
Antiplatelet, clopidogrel	CYP 2C19 forms active metabolite	~50% excreted in urine	[22]
Beta blocker, atenolol	Minimal metabolism	Major renal excretion	[21]
Cholesterol lowering: 1. Atorvastatin 2. Fluvastatin	1. Metabolized by CYP3A4 2. Metabolized by CYP2C9	1. Minimal renal excretion	[22, 25]
Diuretic, spironolactone	Extensive metabolized	Major renal excretion	[22]
Sulfonylureas 1. Glyburide 2. Glipizide	1. Extensive metabolized 2. Metabolized by CYP2C9	1. ~50% renal excretion 2. Minimal renal excretion	[21, 22, 25]
Meglitinides, repaglinide	Metabolized by CYP3A4	Minimal renal excretion	[21]
Metformin	Minimal metabolism	~90% renal excretion	[22]
Glitazones, pioglitazone	Metabolized by CYP2C8	~15–30% renal excretion	[21]

Table 1.
Metabolism and excretion of some common medications used in COVID-19, heart disease and diabetes.

interaction in these patients is high. Drug treatments for heart disease include several types: anticoagulants, antiplatelets, ACE inhibitors, ARBs, beta blockers, calcium channel blockers, cholesterol lowering, diuretics, and vasodilators [19]. For diabetes main medication classes include sulfonylureas, meglitinides, metformin, and glitazones [20]. The metabolism of some commonly prescribed of these medications are listed in **Table 1**. As noted, the most common cytochrome P450 enzyme involved in the metabolism of these drugs are CYP3A4, followed by CYP2C9, 2D6, and 2C8 [21–25]. Approximately half of them are primarily excreted via the kidneys.

3. *Echinacea* spp. (echinacea) – Antiviral and immune support

3.1 Echinacea in COVID-19

Echinacea has antiviral and immunomodulatory effects that seems to be promising against COVID-19 [13, 26]. Several studies have investigated the benefits of echinacea in treating and preventing respiratory tract infections such as the common cold, but not for other health purposes [27]. No studies have yet been completed on echinacea and COVID-19 [28]. A meta-analysis including 17 clinical trials found that echinacea is safe and effective in preventing or treating viral infections. In a separate analysis including 12 clinical trials, echinacea showed to decrease or not change pro-inflammatory cytokines associated with cytokine storm (IL-6, IL-1β, and TNF-α) and increase or not change anti-inflammatory or immune-stimulatory cytokines (IL-10, IL-2, IL-8, IL-3, and IFN-γ). These effects are beneficial during infections since immune stimulatory and anti-inflammatory effects are needed but pro-inflammatory cytokines can aggravate the disease. Adverse events were mild with the most common reported being insomnia, gastrointestinal, and anxiety. One case of serious erythema was reported. Most studies included healthy participants and echinacea dose and method of extraction were quite variable making it difficult to evaluate safety in patients with comorbidities [28].

3.2 Echinacea in diabetes

Not many studies have investigated the effects of echinacea in diabetes. In Wistar rats, 33 days of echinacea root extract showed hypoglycemic activity similar to glibenclamide. No safety parameters were investigated [29]. *Echinacea purpurea* flower extract and caffeic acid derivatives inhibited α-amylase, α-glucosidase, and ACE activities in a concentration-dependent manner [30].

3.3 Echinacea in heart disease

Almost no studies have evaluated the effects of echinacea on heart conditions such as hypertension and hypercholesterolemia. In one study with 374 elderly, 349 reported to use over-the-counter drugs and 43 reported to use herbal medicine. Echinacea was the most common herbal therapy used while aspirin, acetaminophen, laxatives, antiacids, and vitamins were the most common over-the-counter drugs [31]. This single study suggests the potential for interaction of echinacea with drugs.

3.4 Echinacea toxicity

In a review article, echinacea was considered to have a high or medium evidence for efficacy and safety [32]. Debatable concern of hepatotoxicity with echinacea when used for more than 8 weeks has been raised [6]. On the other hand, echinacea

has shown hepatic and renal protection against toxins in rats with no effect by itself on liver and kidney parameters including AST, ALT, ALP, blood urea nitrogen and creatinine [33]. No toxicity was found in rats and mice after oral or intravenous injection of *Echinacea purpurea* at high doses. No evidence of mutagenicity in vitro and in mice or carcinogenicity in hamster embryo cells [34]. Echinacea is contraindicated in patients with autoimmune disease. Little evidence to evaluate the effect of echinacea in renal impairment [35].

3.5 Echinacea pharmacokinetics

In vivo pharmacokinetics in 12 healthy men and women, *Echinacea purpurea* root inhibited CYP1A2 and induced CYP3A enzymes [36]. In another similar study with 13 healthy adults, *Echinacea purpurea* induced CYP3A enzymes but did not change the pharmacokinetics of ritonavir. Ritonavir is an inhibitor of CYP3A thus likely counteracted the induction caused by echinacea. No effect on p-glycoprotein was found [37]. In an in vitro study, *Echinacea purpurea* showed mixed effects on CYP3A4 and moderate inhibition of CYP2C9 [38]. A review article found echinacea to have high likelihood of drug-herb interaction [39].

3.6 Echinacea safety summary

Echinacea is likely safe when taken short-term, up to 8 weeks, in healthy adults. Unknown safety in patients with diabetes or heart disease. Caution should be taken when combining with medications metabolized by CYP3A, 1A2, and 2C9 enzymes.

4. *Glycyrrhiza sp.* root (licorice) – Antiviral and respiratory support

4.1 Licorice in COVID-19

Licorice root is used as a flavoring agent in food in many countries. In the United States, anise oil is often used for this purpose. Licorice is promoted as a dietary supplement for digestion, cough, infections, and others [40]. Frequently recommended by herbalists, licorice has recently shown to be the herb most frequently used for COVID-19 treatment [41, 42]. Several review articles have discussed the potential effectiveness of licorice in treating COVID-19 for its antiviral, anti-inflammatory, spasmolytic, and expectorant effects [9, 10, 12–14]. Some in vitro studies showed that the active component glycyrrhizin inhibits the replication of SARS-coronavirus (SARS-CoV) [43, 44]. Other in vitro studies showed that glycyrrhizin may prevent SARS-CoV-2 entry by binding to ACE2 receptors and other protein targets [45, 46]. Clinical trials of licorice use during COVID-19 are ongoing. Daily doses range from 250 mg 25% extract (62.5 mg glycyrrhizin) for 10 days to 2.28 g 3% extract (70 mg glycyrrhizin) for 7 days [47, 48].

4.2 Licorice in diabetes

Not many studies have investigated the effects of licorice in diabetes. In a clinical trial with 58 overweight and obese but otherwise healthy volunteers, 1.5 g licorice extract (<0.01% glycyrrhizin) for 8 weeks decreased insulin and HOMA-IR without side effects [49]. In cell cultures, de-glycyrrhizinated or regular licorice showed to be a potential therapeutic target in diabetic nephropathy [50]. In diabetic mice, licorice hydrophobic flavonoids demonstrated abdominal fat-lowering and hypoglycemic effects [51].

4.3 Licorice in heart disease

Cases of hypokalemia and hypertension have been reported after daily ingestion of licorice tea or after short-term high dose [52–54]. In one case patient was combining licorice with the glucocorticoid medication fludrocortisone [55]. The active components of licorice, glycyrrhizinates, inhibit the enzyme responsible for inactivating cortisol and bind to mineralocorticoid receptors resulting in reversible hyper-mineralocorticoid effects [56]. A meta-analysis with 18 clinical trials found that chronic daily intake of 100 mg glycyrrhizin increases systolic and diastolic blood pressure [57]. In another meta-analysis including 26 clinical trials and 985 subjects, mainly healthy and overweight but some with hypercholesterolemia, found licorice to reduce body weight and BMI but increase diastolic blood pressure. Licorice was given as licorice flavonoid oil with a dose range of 300 mg to 1.8 g/day for 2–16 weeks [58]. In a dose–response relationship investigation in healthy men and women, licorice root with 108 or 217 mg of glycyrrhizin per day for 4 weeks caused no adverse events. However, licorice with 380 and 814 mg glycyrrhizin caused headache, arterial hypertension, hyperkalemia, and peripheral edema. One individual had a family history of hypertension [59]. Lastly, a similar study compared adverse events in patients with hypertension versus normotensive individuals during 100 g licorice containing 150 mg glycyrrhetinic acid per day for 4 weeks. Systolic and diastolic blood pressure were slightly increased in normotensive (3.5 and 3.6 mmHg) but significantly greater increase in hypertensive patients (15.3 and 9.3 mmHg). Increase in urinary cortisol correlated with the rise in blood pressure [60]. These data suggest that glycyrrhizin at dose >200 mg/day short-term and > 100 mg/day long-term in patients or healthy individuals can cause reversible hyperkalemia and hypertension.

4.4 Licorice toxicity

Despite licorice being a substance generally recognized as safe (GRAS) in the United States [61] and regarded as having a high safety profile because it is consumed as food [32], licorice can cause hypertension and hypokalemia in a dose-dependent manner [57]. However, safe dose will vary depending on licorice's composition and the underlying medical conditions. Those with hypertension, heart or kidney disease are more sensitive to licorice toxicity [40]. In a study involving 360 subjects, no clinically significant change in renal function (potassium, blood urea nitrogen, and creatinine levels) were found in 98.3% of the subjects after ~19 days of ~8 g licorice per day taken as dietary supplements that contained other ingredients. The remaining 1.7% of subjects developed hyperkalemia [62]. In a safety and toxicity study with 39 healthy female and male volunteers aged 19–40 years old, glycyrrhizic acid was administered at 1, 2, and 4 mg/kg body weight daily for 8 weeks. A no-effect level of 2 mg/kg was found and applying a 100-safety factor, the acceptable daily intake of 0.2 mg/kg body weight was proposed. This is equivalent to 12 mg glycyrrhizic acid/day for a 60-kg person [63]. Similarly, based on review of in vivo and clinical evidence, an acceptable daily intake has been proposed to be 0.015–0.229 mg glycyrrhizin/kg body weight [64]. The acceptable daily intake without a safety factor is equivalent to 120 mg glycyrrhizic acid. This dose could be considered safe if used short-term in a situation of high benefit versus risk.

4.5 Licorice pharmacokinetics

Glycyrrhiza glabra has shown weak inhibition of CYP3A4 and moderate inhibition of CYP2B6, 2C8, 2C9, and 2C19. *Glycyrrhiza uralensis* showed strong inhibition

of CYP2B6, moderate inhibition of CYP2C8, 2C9, and 2C19, and no inhibition of CYP3A4 and 2D6. *Glycyrrhiza inflata* strongly inhibited CYP2C enzymes and moderately inhibited of CYP3A4, 1A2, 2B6, and 2D6. None of the three species inhibited CYP2E1 and 2A6. Glycyrrhizin content was highest in *G. uralensis* suggesting that glycyrrhizin is a weak inhibitor of the major enzymes CYP3A4 and 2D6 [65]. Weak inhibition of CYP3A4 and 2D6 by glycyrrhizin and *G. glabra* were also found in a different study [66].

4.6 Licorice safety summary

A safe daily dose for short-term use consists of licorice with less than 100 mg glycyrrhizin. For daily long-term use a dose of 12 mg glycyrrhizin has been proposed. COVID-19 studies are using short-term doses of <100 mg glycyrrhizin per day. Caution should be taken when combining licorice with medications. Licorice inhibits several cytochrome P450 enzymes including CYP1A2, 2B6, 2C8, 2C9, and 2C19. Only *G. inflata* inhibits CYP3A4 and 2D6.

5. *Curcuma longa* (turmeric) – Antiviral and anti-inflammatory

5.1 Turmeric in COVID-19

Turmeric has antiviral and anti-inflammatory effects that might benefit COVID-19 patients [10, 13]. It has also been hypothesized that the antioxidant effects of turmeric benefit diabetic patients during COVID-19 infection [67]. However, some has expressed concerns that curcumin, the main active component of turmeric, might increase the expression of ACE2 and worsen COVID-19 infection as well as increase pro-inflammatory cytokines and worsen COVID-19 in patients with cytokine storm [26]. In the contrary, curcumin binds to viral S protein and the viral attachment sites of the ACE2 receptor protein to inhibit the entry of SARS-CoV2 [18, 68]. In addition, curcumin has shown to reduce inflammatory cytokines in COVID-19 patients. In a clinical study with 40 COVID-19 patients, curcumin given as nano-curcumin at 160 mg/day for 14 days reduced the inflammatory cytokines IL-6 and IL-1β as well as clinical manifestations (fever, cough, dyspnea, headache, chest radiography, lymphocyte, white blood cells, and platelets count) in comparison to placebo-treated group. Both groups were taking atorvastatin, bromhexine, and betaferon concomitantly with 5–15% of them having diabetes, cardiovascular disease or renal disease. These results suggest the effectiveness and safety of curcumin in COVID-19 patients with underlying medical conditions [69].

5.2 Turmeric in diabetes

In clinical trials with type 2 diabetic patients, curcuminoids from 250 mg/day for 9 months to 1 g/day for 3 months improved glycemic control, β-cell function, insulin resistance, and reduced inflammatory cytokines with no major adverse effects. Minor side effects included diarrhea, constipation, vertigo, and itching. Some clinical and preclinical studies also showed that curcumin improve biomarkers of liver and kidney damage [70]. In a clinical trial on 46 patients with diabetic nephropathy, 1.5 g curcumin for 16 weeks improved 24-h urine analysis for albuminuria with no change in blood urea nitrogen, creatinine, fasting blood sugar, 2-h postprandial blood sugar, lipid profile, serum albumin, and hemoglobin A1C in comparison to placebo and baseline [71].

5.3 Turmeric in heart disease

A recent meta-analysis found that turmeric or curcumin have no effect on diastolic blood pressure and minor effect on systolic blood pressure when taken for longer than 12 weeks [72]. A meta-analysis that included 7 randomized, placebo-controlled clinical trials in patients with cardiovascular risk factors (i.e., non-alcoholic fatty liver disease, metabolic syndrome, type 2 diabetes, prehypertension, and dyslipidemia) found turmeric powder at 2–2.4 g/day for 1–2 months, turmeric extract with 0.6–1.9 g curcuminoids/day for 2–6 months, or curcumin at 70–80 mg/day for 2–3 months were effective in reducing serum LDL-cholesterol and triglycerides levels. Adverse events reported were abdominal pain, nausea, dyspepsia, constipation, and hot flushes. Hot flushes were also reported in the placebo group. In 3 of the trials patients were kept on their medications during the study; however, only one trial disclosed the name of the concomitant drug treatment (metformin) [73].

5.4 Turmeric toxicity

Turmeric has GRAS status in the United States [74]. Through a toxicological assessment, the European Food Safety Authority (EFSA) has recommended curcumin daily intake be ≤3 mg/kg body weight per day (180 mg/day in 60 kg individuals) [75]. In 2–year oral feed studies, turmeric oil at 79–85% curcumin showed no biological significantly differences in hematology, clinical chemistry (liver and kidney function markers), and urinalysis parameters, but showed to potentially cause carcinogenicity in mice and rats especially in females at doses ≥100 mg/kg body weight in rats and 300 mg/kg body weight in mice [76]. However, the EFSA concluded that curcumin is not carcinogenic and studies have demonstrated the benefits of curcumin as an adjunct treatment of cancer [77]. High daily dose of curcumin might cause hepatotoxicity. In rats, 25 and 100 mg/kg body weight for 90 days of curcumin induced liver injury through the generation of reactive oxygen species and pro-inflammatory cytokines as well as reduced antioxidant and detoxifying enzymes SOD and GST [78]. Similarly, 5% turmeric via diet for 90 days in female Wistar rats and 0.2% turmeric via diet in female Swiss mice was hepatotoxic. Human equivalent dose for these rodent studies ranged from 250 mg curcumin/day to 1 g–50 g turmeric/day [79, 80].

5.5 Turmeric pharmacokinetics

Turmeric constituents have shown to inhibit p-glycoprotein in vitro and in vivo models [81]. Inhibition of p-glycoprotein can lead to increased bioavailability of drugs [82]. Curcumin is primarily eliminated in the feces with little renal excretion in a rat study [76]. In a pharmacokinetics study with healthy adults, turmeric reduced the bioavailability of the beta-blocker talinolol [83]. Curcumin was safe and effective when combined with glyburide in patients with type 2 diabetes. Better cholesterol and glycemia control without hypoglycemic side effects were observed. Curcumin increased AUC but did not change C_{max} of glyburide [84]. In rats, curcumin increased the C_{max}, AUC_{0-t} and half-life of amlodipine – an antihypertensive drug [85]. Amlodipine is metabolized by CYP3A4 in humans [86]. Curcumin inhibits several hepatic CYP enzymes including 3A4, 1A2, 2B6 (competitive type of inhibition), 2D6 and 2C9 (non-competitive inhibition) in human recombinant cytochrome P450s [87]. However, it is been suggested that these effects are not clinically significant due to poor bioavailability of curcumin. In fact, in a pharmacokinetics study in healthy volunteers, 4 g curcuminoids +24 mg piperine to enhance bioavailability did not affect C_{max}, AUC, clearance, or half-life of drugs metabolized by CYP3A, CYP2C9, and UGT, SULT conjugation enzymes [88].

5.6 Turmeric safety summary

Turmeric is safe and effective at doses ≤250 mg curcumin/day. Higher doses are associated with hepatotoxicity and potentially carcinogenicity. Doses as low as 70–250 mg curcuminoids/day has shown to be effective in metabolic disorders and COVID-19. Although turmeric inhibits cytochrome P450 enzymes, these effects seem to be clinically negligible. Caution when taken with drugs that are substrates of p-glycoprotein in order to avoid drug overdose. Although turmeric has hypo-glycemic effects and might cause side effects such as fainting when combined with antidiabetic medications, this combination has shown to be safe in clinical trials.

6. *Nigella sativa* (black seed) – Anti-inflammatory and respiratory support

6.1 *Nigella sativa* in COVID-19

N. sativa is a plant native to South East Asia with several pharmacological effects including bronchodilation, antitussive, and anti-inflammatory and used as treatments of respiratory conditions, diabetes, cardiovascular diseases, among others [89, 90]. For example, in a clinical trial with 90 obese women, 3 g/day of *N. sativa* oil for 8 weeks reduced serum levels of TNFα and hsCRP in comparison to placebo with no adverse events reported [91]. In patients with asthma, 1 g *N. sativa* oil per day for 4 weeks reduced several inflammatory markers and improved pulmonary function [92]. Preclinical studies have shown that constituents in the methanolic extract of *N. sativa* seeds are responsible for the bronchodilator effect [93]. Recently, *N. sativa* has been regarded as a potential therapy for COVID-19 [13, 18, 94, 95]. For example, in a molecular docking-based study *N. sativa* inhibited SARS-CoV2 [94].

6.2 *Nigella sativa* in diabetes

Several clinical trials have been conducted to evaluate *N. sativa* in patients with type 2 diabetes [96]. For example, three controlled studies investigated the adjuvant use of 1–3 g/day *N. sativa* seeds powder or 2.5 ml/day *N. sativa* oil for 12 weeks in patients with type-2 diabetes. Significant and similar effects were observed with doses of 2 and 3 g/d on the reductions in fasting blood glucose, 2-hour postprandial glucose, HbA1C levels, and insulin resistance. Treatments were not associated with any adverse renal or hepatic functions throughout the study period. Patients were concomitantly taking oral hypoglycemic drugs (glibenclamide, metformin, rosiglitazone) but not insulin. Patients with coronary artery disease, valvular heart disease, heart failure, uncontrolled hypertension, renal failure and hepatic failure were excluded [97–99].

6.3 *Nigella sativa* in heart disease

In a meta-analysis including 11 randomized clinical trials with 860 hyperten-sive or normotensive individuals, *N. sativa* seeds versus placebo and one versus standard treatment significantly reduced systolic blood pressure by −3.60 mmHg and diastolic blood pressure by −2.80 mmHg. [100]. A similar meta-analysis including 17 randomized clinical trials with 1185 individuals with hyperlipidemia, obesity, hypertension, type 2 diabetes, or others, found that *N. sativa* seed powder or oil 1–3 g/day for up to 3 months reduces total cholesterol, LDL-cholesterol, and

triglycerides [101]. No adverse events were reported by the subjects [102, 103]. One study in elderly with hypertension reported mild adverse events including dyspepsia in 6 subjects (15.7%), nausea in 3 subjects (7.8%), and constipation in 2 subjects (5.2%). No electrolyte abnormalities, liver and renal toxicities, or orthostatic hypotension were observed [104].

6.4 *Nigella sativa* toxicity

N. sativa has GRAS status in the United States [74]. A randomized, placebo-controlled study with 40 healthy elderly investigated the safety profile after daily intake of 1 g *N. sativa* seed powder for 9 weeks. Results found no statistical changes in any of the biochemical markers of cardiac, liver, and kidney function [105]. In 70 patients with chronic renal disease, 2.5 ml/day *N. sativa* oil for 12 weeks was safe and effective in improving clinical and biochemical parameters of kidney function without adverse events [106]. In a clinical trial with obese women, *N. sativa* oil (which is present in whole seeds and polar seed extracts), reduced body weight, VLDL cholesterol and triglycerides [107]. Traditional toxicity studies in rodents have been performed. In mice, hepatotoxicity was observed after 14-days of oral dosing at 6–21 g/kg body weight of *N. sativa* seeds water extract. No signs of hepatotoxicity were observed with methanolic and chloroform extracts. Body weight reductions were seen in methanolic extracts [108]. Similar findings were observed with the water extract in rats with increases in serum gamma-glutamyl transferase and alanine aminotransferase, but no changes in alkaline phosphatase and degeneration of hepatocytes [109]. In another rat study, 1 g/day for 6 weeks of whole *N. sativa* seeds were protective against hyperlipidemia to a similar extent as simvastatin without adverse effects to liver markers [110]. Human equivalent doses are 30–100 g *N. sativa* extracts per day for the mice study, and 10 g whole seeds per day for the rat study [80].

6.5 *Nigella sativa* pharmacokinetics

One of the main active constituents in *N. sativa* seeds and oil is thymoquinone. Thymoquinone has shown to bind to human $\alpha(1)$-acid glycoprotein in the plasma [111] and inhibit CYP2C9 > 2D6 > 1A2 > 3A4 liver enzymes [112]. In hypertensive rats, *N. sativa* + alompidine showed greater reduction in blood pressure and heart rate than *N. sativa* alone, but no effect on alompidine pharmacokinetics (C_{max}, AUC_{0-t}, K_{el}, and terminal half-life) [113]. In another study in hypertensive rats, *N. sativa* + losartan showed greater reduction in blood pressure than *N. sativa* alone. *N. sativa* slightly reduced losartan C_{max} and AUC_{0-t} [114]. Alompidine is metabolized by CYP3A4 and losartan by CYP2C9 and 3A4 in humans. These data suggest that *N. sativa* has minimal effect on CYP3A4 but inhibits CYP2C9. In other words, *N. sativa* has antihypertensive effects on its own but potentiates the effect of drugs metabolized by CYP2C9 which can cause further drop in blood pressure and lead to side effects such as fainting.

6.6 *Nigella sativa* safety summary

N. sativa whole seeds, oil or polar extracts (i.e., non-aqueous) at human doses up to 3 g/day for 12 weeks beneficially affect inflammatory and metabolic markers without adverse effects on heart, liver, or kidneys in healthy adults as well as in patients with heart disease and diabetes. *N. sativa* reduces blood glucose and blood pressure. Thus, caution when combining with hypoglycemic and antihypertensive drugs to avoid side effects. *N. sativa* can increase the bioavailability of

drugs metabolized by CYP2C9 leading to higher risks of their side effects. Some diabetes and heart medications metabolized by CYP2C9 are losartan, fluvastatin, glipizide [25].

7. Interactions summary

The combination of several dietary ingredients might be desirable when their main mechanisms of action and clinical effects differ. For example, combination of an anti-inflammatory, antiviral, immunostimulant, and bronchodilator herbs might be recommended. Safety combination of black seed and turmeric has been demonstrated in a clinical study. *N. sativa* seed (1.5 g/d) and turmeric (2.4 g/d) in patients with metabolic syndrome for 4 weeks was safe and effective in reducing blood glucose, cholesterol, and blood pressure despite both ingredients having hypoglycemic and antihypertensive effects alone [115]. Any effect of echinacea on blood glucose and blood pressure is insufficient to evaluate. Licorice can increase blood pressure depending on the dose. Since turmeric and *N. sativa* have anti-hypertensive effects, the addition of licorice might be safe. All of the four dietary ingredients described here inhibit CYP2C9. All except *N. sativa* also inhibit CYP1A2. Turmeric and licorice also inhibit CYP2B6. Turmeric inhibits CYP3A4 and echinacea induces

Dietary ingredient	Level of evidence in COVID-19	Level of evidence in heart disease	Level of evidence in diabetes	Main interactions	References
Echinacea	None	None	Scarce: positive effect in 1 preclinical study	Induces CYP3A, inhibits CYP1A2, and CYP2C9	[27–29, 36, 38]
Licorice	Positive effects in vitro and 2 ongoing clinical trials	Negative effects in several clinical trials showing hypertension and hyperkalemia	Scarce: positive effects in 1 clinical, 1 preclinical, and 1 in vitro study	Safe dose <100 mg glycyrrhizin. Inhibits CYP1A2, 2B6, 2C8, 2C9, and 2C19. Only *G. inflata* inhibits CYP3A4 and 2D6	[45–61, 63–66]
Turmeric	Positive effects in vitro and 1 completed clinical trial	Positive effects in several clinical trials	Positive effects in several clinical trials	Safe dose ≤250 mg. Inhibits p-glycoprotein and not clinically significant inhibition of P450 enzymes	[68–77, 88]
Black seed	Positive effects in vitro	Positive effects in several clinical trials	Positive effects in several clinical trials	Inhibits CYP2C9	[94, 96–104, 111–114]

Table 2.
Summary of level of evidence for efficacy and safety of echinacea, licorice, turmeric, and black seed in COVID-19, heart disease, and diabetes.

it. Thus, caution should be taken when combining these dietary ingredients with drugs metabolized by CYP3A4, 2C9, 1A2 and 2B6. As presented in **Table 1**, many drugs used in COVID-19, diabetes, and heart disease are metabolized by CYP3A4 and 2C9. Caution should be taken with echinacea and turmeric because they induce or inhibit CYP3A4, respectively. Lastly, many drug examples presented in **Table 2** are excreted via urine. Turmeric and black seed are likely safe when combined with medications that are excreted by the kidneys. Caution when combining with licorice due to its potential to cause hyperkalemia. No sufficient evidence to evaluate echinacea's effect on kidney function.

8. Conclusions

All the four dietary ingredients discussed herein are safe for use short-term as in a setting of treating a disease. However, some might not be safe when taken long-term. For example, no safety data was found for echinacea in heart disease and diabetes. Long-term use of low dose or short-term use of high dose licorice can cause reversible hypertension. Hepatotoxicity might occur with long-term use of turmeric >250 mg/day. Lastly, all of these four dietary ingredients are metabolized by cytochrome P450 enzymes to some extent. Mostly they inhibit CYP2C9, 1A2 and 2B6. Caution with echinacea because it induces CYP3A4 and turmeric because it inhibits it.

Conflict of interest

The author declares no conflict of interest.

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