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AHA SCIENTIFIC STATEMENT

Complementary and Alternative Medicines in the Management of Heart Failure: A Scientific Statement From the American Heart Association

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ABSTRACT: Complementary and alternative medicines (CAM) are commonly used across the world by diverse populations and ethnicities but remain largely unregulated. Although many CAM agents are purported to be efficacious and safe by the public, clinical evidence supporting the use of CAM in heart failure remains limited and controversial. Furthermore, health care professionals rarely inquire or document use of CAM as part of the medical record, and patients infrequently disclose their use without further prompting. The goal of this scientific statement is to summarize published efficacy and safety data for CAM and adjunctive interventional wellness approaches in heart failure. Furthermore, other important considerations such as adverse effects and drug interactions that could influence the safety of patients with heart failure are reviewed and discussed.

Key Words: AHA Scientific Statements ■ coenzyme Q10 ■ complementary therapies ■ dietary supplements ■ heart failure ■ tai chi ■ yoga

Complementary and alternative medicine (CAM) has been traditionally used to define medical practices, products, or systems that do not conform to the standard beliefs of conventional medicine. Approaches to implementing these unconventional strategies may differ. Complementary therapy is a nonmainstream approach used in combination with conventional medicine, whereas an alternative approach replaces conventional therapy altogether.[1] There is a lack of federal guidance and regulation of CAM products sold in the United States, and these agents are readily accessible to consumers with increasing popularity. It is estimated that >30% of patients with heart failure (HF) use CAM, and 1 of 5 patients have used herbal therapy annually.[1–3] Misconceptions regarding their purported efficacy have largely driven the popularity of these products, whereas adverse effects have been underemphasized and underreported. Furthermore, patients who purchase over-the-counter CAM products often receive prescription medications, concomitant use of which could lead to serious drug interactions when taken together.

Because public consumers have unregulated access to CAM, educating the public and clinicians about these products remains a priority. This scientific statement is intended for patients, the general public, all health care professionals directly or indirectly managing patients with HF, and those who use alternative therapeutic approaches and nontraditional medicine in practice. A comprehensive literature search was performed using the Natural Medicines Database, PubMed, clinicaltrials.gov, and Cochrane Library to retrieve and review data from primary literature, review articles, consensus documents, and abstracts of landmark studies published before November 2021. This scientific

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statement includes 2 primary areas of focus: (1) review of evidence for efficacy of CAM therapy in patients with HF, and (2) review of safety of CAM therapy in patients with HF including CAM interactions with HF treatment and adverse effects of CAM therapy on HF progression.

The writing group was composed of cardiologists, scientists, pharmacists, and a nurse practitioner with expertise and knowledge in clinical practice and research of CAM in the setting of acute and chronic HF, and federal regulation of nutraceuticals. This scientific statement included representatives from the American Heart Association Council on Clinical Cardiology, Council on Cardiovascular and Stroke Nursing, Council on Epidemiology and Prevention, and was developed through the American Heart Association Clinical Pharmacology Committee in collaboration with the Heart Failure and Transplantation Committee.

GLOBAL UTILIZATION AND SOCIAL DETERMINANTS OF HEALTH

CAM is broadly used across the world. The estimated international prevalence varies considerably, ranging from 10% to 76%.[4] A 2020 systematic review of 231 studies representing 51 countries and 6 continents demonstrated continental similarities and differences in reasons for using CAM.[4] CAM has been supported in parts of the world for perceived benefits and safety profiles and for dissatisfaction with conventional medications, particularly in the Americas. Although certain populations may support CAM for affordability and accessibility, others may support CAM to exert greater control over individual health as part of holistic care. In certain countries, social networks are a major supporting factor for CAM and may be incorporated under physicians' recommendations. CAM use may also be influenced by traditions and beliefs.[4]

In the United States, CAM use has been higher among White than Black individuals,[5,6] and higher among patients who perceived their health care quality as poor compared with those with higher health care quality.[5] College graduates have also been more likely to use CAM than those with less education.[5,6] Although these trends are noteworthy, the most important finding may be that patients do not share their ongoing CAM use with their health care professionals approximately half of the time.[5]

There are limited data on CAM use among US patients with HF. One study included older patients with HF from 8 medical centers in Ohio.[7] In this study, White patients were more likely to use nonprescriptive over-the-counter medications, including vitamins, compared with other races and ethnicities, but not herbal therapies.[7] No significant differences in CAM use were observed for other demographics.[7] However, receipt of care by a cardiologist was associated with significantly higher use of both over-the-counter medications and herbal therapies.[7] Likewise, a single-center study in Michigan identified no significant difference in utilization of CAM across patient sex, race, or ethnicity.[3] It is unclear whether results from other regions with greater cultural diversity and immigration would demonstrate higher frequency of CAM use.

To improve the quality of care of patients with HF and to prevent potential adverse effects, it is prudent to inquire about CAM use at every patient encounter. Although there are international and national trends for CAM use, each individual may have different reasons for and against using CAM. Health care professionals are responsible for providing education about the risks and benefits of use in tandem with guideline-directed medical therapy for HF.[8] Shared decision-making between patients and clinicians may highlight patient goals and identify ways to safely integrate CAM into the care plan when desired.

Considerations for Clinical Practice

1. Health care professionals are strongly encouraged to inquire about CAM use with their patients at every clinical visit.
2. Health care professionals should consider discussing the interactions, benefits, and adverse-effect profile of CAM and guideline-directed medical therapy using a shared decision-making model with patients.

OVERSIGHT AND REGULATION OF CAM

Guidance for industry regarding the regulation of CAM products by the US Food and Drug Administration (FDA) was published in 2006[9] in response to the growing use of CAMs in the United States and perceived confusion about whether components used in CAMs were subject to regulation by federal agencies under the Federal Food, Drug, and Cosmetic Act or Public Health Service Act. These acts established that, depending on the CAM therapy or practice, a product used in a CAM therapy or practice may be subject to regulation as a biological product, cosmetic, drug, device, or food (including food additives and dietary supplements) and neither act exempts CAM products from regulation.

CAM therapies are divided into 4 domains: biologically based practices, energy therapies, manipulative and body-based methods, and mind-body medicine. Alternative medical systems, once considered a fifth domain, are now considered as a separate category because they use components contained in the aforementioned domains.

Biological-based products include (but are not limited to) botanicals, animal-derived extracts, vitamins, minerals, fatty acids, amino acids, proteins, prebiotics* and probiotics,† whole diets, and "functional foods." The

*Defined as nondigestible food ingredients that beneficially affect the host by selectively stimulating the growth, activity, or both of one or a limited number of bacteria in the colon.

†Defined as live microbial food supplements that beneficially affect the host animal by improving its intestinal microbial balance.

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intended use of a product plays a central role in how it is regulated, and many biologically based products within this domain are subject to statutory and regulatory requirements under the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act. For instance, a botanical intended to treat a disease would be regulated, in general, as a drug, one taken orally to affect the structure of the body would be regulated as a dietary supplement, whereas one used to flavor food would be regulated as a food or food additive. Likewise, probiotics may be regulated as dietary supplements, foods, or drugs depending on the intended use of the products. In the official Homeopathic Pharmacopeia of the United States (official National Formulary), a biological product is defined as a drug when it is intended to be used in the diagnosis, cure, mitigation, treatment, or prevention of disease, and to affect the structure or function of the body. A new drug is defined as one that is not generally recognized as safe and effective for uses outlined in its label. All biological products require an effective license for production; their package is plainly marked with the product's name, the producer's name and address, and the product's expiration date.

Articles for food or drink are considered as foods unless there are claims that make the product subject to the drug definition. The Dietary Supplement Health and Education Act passed by Congress in 1994[10] established the term "dietary supplement" and stipulated that these products would be regulated like foods, a distinction that exempted manufacturers from conducting premarketing safety and efficacy testing and eliminated FDA premarketing regulatory authority (Supplemental Table 1). A product is considered a drug if it is used to treat a specific condition, whereas it is regulated as a dietary supplement if it is given to maintain health in some manner. All dietary supplements require labeling that includes the following: (1) the statement of identity (name of the dietary supplement), (2) the net quantity of contents statement (amount of the dietary supplement), (3) the nutrition labeling, (4) the ingredient list, and (5) the name and place of business of the manufacturer, packer, or distributor.[11] In addition, according to Dietary Supplement Health and Education Act guidelines, manufacturers are prohibited from marketing products that are misbranded or adulterated.[12] Manufacturers are responsible for the purity and safety of their products; however, as previously mentioned, the FDA is not authorized to review dietary supplement products for safety and effectiveness before they are marketed.[13] Because the manufacturing process is not overseen by the FDA, health care professionals and patients should use caution and diligence to assure content safety. A relevant example of a dietary supplement that has potential to cause harm and that may be purchased today is red yeast rice supplement. In 1998, the FDA determined that red yeast rice supplement contained significant amounts of monacolin K (ie, lovastatin) and determined that this product was an unapproved drug and legal action was taken.[14] RYR supplements may be sold if they only have trace amounts of monacolin K. However, in a recent study evaluating the amount of monacolin K in 28 brands of RYR supplements, it was found that 21% had amounts that would be considered in the range of an unapproved drug.[15] Some products had levels similar to 10 mg of lovastatin. In addition, RYR products may contain a contaminant (citrinin) that can lead to kidney damage. Before recommending or purchasing any dietary supplement, reviewing consumer websites that determine actual supplement content from specific manufacturers is advised.[16,17]

The US Pharmacopeia has established standards for drugs and also botanical and dietary supplements in the United States that ensures compliance with standards for quality, quantity, purity, strength, packaging, and labeling. Many dietary supplements have not achieved US Pharmacopeia designation, but select supplements and manufacturers have qualified and can be found on their verification website.[18]

Mind-body medicine is also considered under the CAM domain. Mind-body medicine "typically focuses on intervention strategies that are thought to promote health, such as relaxation, hypnosis, visual imagery, meditation, yoga, biofeedback, tai chi, qi gong, reiki, cognitive-behavioral therapies, group support, autogenic training, and spirituality."[9] This domain is not typically regulated under Dietary Supplement Health and Education Act or Public Health Service Act, although, if specific types of equipment such as biofeedback machines are used, these may fall under FDA jurisprudence.[10]

Cannabis or marijuana and traditional Chinese medicine are other plant-based products which have also been used in HF[19,20] but will not be discussed in this scientific statement given the differences in their FDA regulation compared with other CAM agents. The medical use of marijuana is partially regulated by the FDA along with individual states[21] and, therefore, legal use of this product can vary depending on geography. However, a recent American Heart Association scientific statement has been published on the use of medical marijuana and recreational cannabis on cardiovascular health and addresses regulation and discusses current literature in depth.[19] traditional Chinese medicine has also been more recently explored for its potential benefits as adjunctive therapy in HF.[20] However, such therapy is provided as a formulation that may contain dozens of active ingredients with complex individualized doses, which adds uncertainty when attempting to determining efficacy and safety.[22] At present, the FDA does not provide any guidance on CAM as a formulation or traditional Chinese medicine specifically.[9]

Further data and clarity would be needed before any substantive assessment could be made on this topic.

Considerations for Clinical Practice and Public Health Initiatives:

1. Because the manufacturing process is not overseen by the FDA, health care professionals and patients should be aware of the current lack of federal oversight and regulation if considering CAM.

SAFETY AND POTENTIAL FOR TOXICITY

Dietary supplements are not regulated with the same rigorous requirements as pharmaceutical agents, which undergo strict testing in phase 1 to 3 clinical trials to ensure both efficacy and safety. In the United States, the FDA MedWatch program[23] can receive safety reports associated with prescription and over-the-counter medicines from patients and health care professionals and publishes safety alerts when necessary. Maintaining a database of serious adverse events can help identify and manage important safety concerns.

CAM agents can cause toxicity either through direct organ toxicity, or through drug-drug interactions. For example, kava is made from *Piper methysticum*, a plant native to the western Pacific islands. In the South Pacific, kava is consumed as a beverage socially in ceremonies to promote relaxation, similar to how alcohol is consumed in Western societies. Kava is thought to reduce stress, anxiety, and insomnia, and can be taken in tea, capsule, powder, or liquid form. However, there have been many reports of liver toxicity, leading to a warning from the FDA, and banned or restricted use in many countries, including Germany, Switzerland, France, Canada, and the United Kingdom. A list of commonly used dietary supplements and associated toxicities can be found in Supplemental Table 2.

St. John's wort is a CAM agent that is also a potent inducer of the cytochrome P450 system (CYP isoenzyme 3A), and thus can reduce the plasma concentrations of many common drugs including warfarin, simvastatin, methadone, calcineurin inhibitors, and many others.[24]

CLINICAL EFFICACY IN HF

The use of several CAM agents has been examined in observational studies and clinical trials of patients with HF. In some reports, the use of specific CAM agents has been associated with improvement in HF symptoms, functional capacity, quality of life, and major adverse cardiac events outcomes. Although CAM agents should not supplant or replace standard guideline-directed medical therapy, HF clinicians should be familiar with the clinical effects of CAM agents in patients with HF (Supplemental Figure 1), because these agents may be used in the treatment of HF and non-HF conditions, and patients may prefer to take these agents independent of health care professional advice. In this section and in Table 1, the evidence for clinical efficacy of commonly used CAM agents is reviewed.

Alcohol

The effect of alcohol consumption on HF has not been studied in large-scale randomized trials. Observational data suggest that, in low-to-moderate amounts, alcohol may be associated with a reduced risk of developing HF[25,29,30,32] with differential risk reduction by sex.[31] The US Dietary Guidelines for Americans 2020–2025 defines moderate alcohol intake as ≤2 drinks in 1 day for men and ≤1 drink in a day for women.[135] The definitions of low-to-moderate alcohol intake across these observational studies have been variable, which complicates designating any threshold consumption level to be associated with benefit. In a substudy of the GISSI trial (Gruppo Italiano per lo Studio della Sopravvivenza nell Insufficienza Cardiaca-HF), those who consumed at least 3 glasses of wine per day had the lowest depression scores and the best health status perception compared with those who drank lesser daily amounts and less frequently.[27] On the other hand, habitual consumption or abuse of alcohol is known to be a cause of cardiomyopathy and HF as a result of cardiotoxicity even at lower doses if consumed habitually or excessively (see Alcohol in the next section).

Coenzyme Q10/Ubiquinone/Ubiquinol

Coenzyme Q10 (CoQ10) naturally occurs in small amounts in organ meats and oily fish and is a cofactor in many biological pathways including oxidative phosphorylation. Because HF results in an ATP-depleted state, exogenous administration of CoQ10 has been hypothesized to result in metabolic benefit.[136] Researchers found modest benefit with CoQ10 supplementation by improving LV ejection fraction[37] and quality of life[46] in small-scale studies. In the largest randomized trial of CoQ10 in 420 patients with HF, Q-SYMBIO (Coenzyme Q10 as Adjunctive Treatment of Chronic Heart Failure With Focus on Symptoms, Biomarker Status [Brain-Natriuretic Peptide], and Long-Term Outcome [Hospitalizations/Mortality]), CoQ10 treatment was not associated with any significant changes in 6-minute walk distance, or N-terminal pro-B type natriuretic peptide levels compared with placebo, but was associated with a significant improvement of New York Heart Association functional class and reduction in major adverse cardiovascular events at 2 years (hazard ratio [HR], 0.50 [95% CI, 0.32–0.80]; *P*=0.003).[43] Furthermore, in a more recent literature analysis, CoQ10 treatment was associated with a reduction in all-cause mortality.[137] However, larger-scale randomized-controlled trials are needed before any definitive conclusion can be reached. Therefore, CoQ10 supplementation remains of uncertain value in HF at this time.[36–39,90]

Table 1. Clinical Efficacy Studies of Complementary and Alternative Medicines on Heart Failure

Complementary and alternative medicines agent	Mechanism of action	Major evidence	HF outcomes: benefit	HF outcomes: harm	HF outcomes: negative or unknown	Interaction with HF therapies	Adverse effects	Pregnancy, lactation, or both	Sources
Alcohol (Also listed in Table 2: Adverse effects and Interactions)	Moderate doses may have multiple effects on biological markers and processes including beneficial effects on high-density lipoprotein, low-density lipoprotein cholesterol oxidation, platelet aggregation and adhesion, fibrinolysis, and inflammation. Alcohol products that contain polyphenols (eg, wine) may have additional cardioprotective effects including improving endothelial function, decreasing oxidative stress, and decreasing platelet aggregation. In contrast, high-dose levels may lead to increased oxidative stress, triglycerides, and certain adhesion molecules.	Meta-analysis: Padilla et al, 2010[25] Subanalysis of RCT: Aguilar et al, 2004[26] Observational: Cosmi et al, 2015[27] Djousse et al, 2008[28] Djousse et al, 2007[29] Bryson et al, 2006[30] Walsh et al, 2002[31] Abramson et al, 2001[32] Cooper et al, 2000[33]	Association of reduced risk for developing HF, lowest in men who consumed 8–14 drinks/wk and in women who consumed 3–7 drinks/wk[319] Association of reduced incident HF with consumption of 5–7 drinks/wk although benefit may be restricted to individuals with coronary artery disease[29] Association of reduced incident HF in hypertensive male physicians with light-to-moderate alcohol consumption[28] Infrequent and light-to-moderate drinking associated with a 10%–23% lower risk of HF[25] Low-to-moderate alcohol consumption associated with lower risk of HF among community-dwelling adults aged ≥65 y[32] Light-to-moderate alcohol consumption independently associated with reduced risk of all-cause mortality in patients with ischemic LV dysfunction[33] Light-to-moderate consumption at baseline or after MI did not alter risk of development of HF requiring hospitalization in patients with LV dysfunction after MI[26] Moderate wine consumption associated with better perception of health status, less frequent depressive symptoms, lower plasma biomarkers of vascular inflammation[27]			May decrease efficacy of diuretics or vasodilators	Flushing, confusion, emotional lability, perceptual and sensational disturbances, blackouts, lack of coordination and trouble walking, central nervous system depression, drowsiness, respiratory depression, hypothermia, hypoglycemia, nausea, vomiting, diarrhea, abdominal pain[17] Chronic heavy ingestion can lead to dependence, malnutrition, amnesia, dementia, somnolence, cardiac myopathy, hepatotoxicity, and cirrhosis, pancreatitis, hypomagnesemia, skeletal myopathies, Wernicke encephalopathy, Korsakoff psychosis, chronic cerebellar syndrome, mouth cancer, esophageal cancer, pharyngeal cancer, laryngeal cancer, and liver cancer[17] Chronic intake associated with increased risk of all-cause mortality, ischemic stroke, and hypertension[17]	Teratogenic Associated with significant risk of spontaneous abortion, fetal alcohol syndrome, neurological and psychological dysfunction in infants and children exposed to alcohol in utero[17] Alcohol is secreted in breast milk. Can cause abnormal psychomotor development, infant's sleep-wake disruption, reduction in mother's milk production[17]	Not applicable
Coenzyme Q10 CoQ10 Ubiquinone (oxidized form) Ubiquinol (reduced form)	Antioxidant Cellular membrane stabilizer Cofactor in many metabolic pathways, including oxidative phosphorylation	Meta-analysis: Khan et al, 2021[35] Lei and Liu, 2017[36] Madmani et al, 2014[37] Fotino et al, 2013[38] Sander et al, 2006[39] Systematic review: Jafari et al, 2018[40] Rosenfeldt et al, 2003[41] RCT: Zhao et al, 2015[42] Mortensen et al, (Q-SYMBIO) 2014[43] Khatta et al, 2000[44] Watson et al, 1999[45] Hofman-Bang et al, 1995[46] Morisco et al, 1993[47] Observational: Molyneux et al, 2008[48]	Plasma concentration an independent predictor of mortality[48] Decrease in mortality with supplementation compared with placebo[35] Reduction in time to unplanned hospital stay resulting from worsening HF, cardiovascular death, mechanical assist implantation, or urgent cardiac transplantation[43] Significant improvement in NYHA class at 2 y[43] Improvement in exercise capacity compared with placebo[36,46] Improvement in quality of life[46] Subgroup RCT data demonstrate improvement in LVEF in patients with HF[37] Reduction in hospitalization for worsening HF in patients on conventional HF therapy[47] Reduction in atrial fibrillation episodes[42]	No major harms	No clear effect on LVEF or exercise capacity[37,44] No improvement in LV systolic function or quality of life in patients with chronic LV dysfunction after 3-mo trial of oral CoQ10 administration compared with placebo[45]	May have additive effects of lowering blood pressure with vasodilators May decrease anticoagulant effects of warfarin Statin therapy may theoretically lower CoQ10 levels	Generally well tolerated Most common adverse effects are gastrointestinal (<1%)	Evidence for safety in pregnancy at 100 mg twice daily dose with potential to decrease risk of preeclampsia[49] Insufficient information regarding risk of use in lactation	Occurs in small amounts in organ meats, oily fish, soybean oil

(*Continued*)

Table 1. Continued

Complementary and alternative medicines agent	Mechanism of action	Major evidence	HF outcomes: benefit	HF outcomes: harm	HF outcomes: negative or unknown	Interaction with HF therapies	Adverse effects	Pregnancy, lactation, or both	Sources
D-Ribose	Enhances regeneration of ATP	RCT: Omran et al, 2003[50] Observational: Bayram et al, 2015[51] MacCarter et al, 2009[52]	Improvement in self-perceived quality of life[50] Improved diastolic functional parameters on echocardiography[50] Improvement in ventilatory efficiency, peak oxygen consumption, oxygen uptake efficiency on cardiopulmonary exercise testing[51] Improvement in echocardiographic tissue Doppler velocity[51]	No major harms		No major interactions	Generally well tolerated Reported adverse effects include gastrointestinal, headache, hypoglycemia	Insufficient information available regarding use in pregnancy and lactation	Naturally occurring in many foods including red meat, poultry, fish, nuts, dairy
Omega-3 fatty acids Fish oil Eicosapentaenoic acid/docosahexaenoic acid (EPA/DHA) Polyunsaturated fatty acids (PUFA)	Potential mechanisms include acyl-coenzyme A inhibition, increased hepatic mitochondrial and peroxisomal β-oxidation, decreased hepatic lipogenesis, increased plasma lipoprotein lipase activity EPA/DHA inhibit esterification of other fatty acids	Meta-analysis: Xin et al, 2012[53] Xin et al, 2012[54] Djousse et al, 2012[55] RCT: Djousse et al, (VITAL-HF) 2020[56] Oikonomou et al, 2019[57] Moertl et al, 2011[58] Nodari et al, 2009[59] Tavazzi et al, 2008[60] Mehra et al, 2006[61] Subanalysis of RCT: Ghio et al, 2010[62]	Significant risk reduction in time to death and composite end point of time to death or cardiac hospitalization in the n-3 PUFA group[60] Significant increase in LVEF[57,60,62]; also improvement in global longitudinal strain[57] Dose-dependent increase in LVEF and decrease in LV dimensions[58] Decrease in inflammation indices (high sensitivity C-reactive protein, ST2),[58] ST2,[57] tumor necrosis factor-α,[61] IL-6[54] Lower risk of incident HF with intake[55] Decreased nonsustained ventricular tachycardia in idiopathic dilated cardiomyopathy[59] Exploratory analysis finding in VITAL-HF of significant reduction in recurrent HF hospitalization with supplementation versus placebo[56]	No major harms	No significant reduction in first HF hospitalization rate[56]	May have additive effects of lowering blood pressure with vasodilators	Generally well tolerated in moderation but may increase incidence of atrial fibrillation at higher doses (≥4 g) Most common adverse effects include abdominal pain, nausea, diarrhea, halitosis, dyspepsia	Likely safe for use in pregnancy and lactation when consumed at or below the daily recommended level of 1.4 g daily for pregnant women and 1.3 g daily for breastfeeding women	Naturally occurring in fish
Hawthorn *Crataegus* spp. (Also listed in Table 2: Adverse effects and Interactions)	Concentration-dependent increase of myocardial contractility through possible mediation by cAMP-independent inhibition of Na^+/K^+-ATPase Prolongs action potential and refractory period Vasorelaxation by an endothelium-dependent and NO-mediated mechanism Antioxidant through generation of free radical oxygen species	Meta-analysis: Pittler et al, 2008[63] Daniele et al, 2006[64] Pittler et al, 2003[65] RCT: Zick et al, (HERB-CHF) 2009[66] Holubarsch et al, (SPICE) 2008[67] Degenring et al, 2003[68] Tauchert, 2002[69] Zapfe, 2001[70] Weikl et al, 1996[71] Schmidt et al, 1994[72] Leuchtgens et al, 1993[73] Observational: Schroder et al, 2003[74] Taucher et al, 1999[75] Prospective cohort: Habs[76] Subanalysis of RCT: Zick et al, 2008[77]	Significant improvement in maximal workload using bicycle ergometry[69,70] Increase in exercise tolerance[68,70] Reduction of the pressure×heart rate product (systolic blood pressure in mm Hg times heart rate per min and divided by 100)[70,71,73,78] Improvement in HF symptoms (eg, dyspnea, fatigue, palpitations)[69,73,75,76]	Potential for progression of HF risk at baseline in adults >18 y with HF with NYHA class II or III and LVEF ≤40% and especially in those with LVEF ≤35%, over 6 mo[77]	Effects of hawthorn in patients on guideline-directed medical therapy for HFrEF are limited because most studies with hawthorn were done in individuals on minimal background HFrEF therapy Insufficient evidence regarding safety past 16 wk of use RCT in >5000 patients with Crataegus extract WS 1442 did not meet primary end point of reduced cardiac events including death attributable to HF or HF hospitalizations. Adverse effects were similar between WS 1442 and placebo[67]	Theoretical potentiation of coronary and peripheral vasodilators[79] Conflicting evidence on interaction with digoxin[79,80] Appears to be safe when used in combination with angiotensin-converting enzyme inhibitors, β-blockers[67,79]	Generally well tolerated with mild-to-moderate side effects[64] Cardiac (eg, palpitations, chest pain)[71,72] Gastrointestinal concerns[69,71,72] Neurological (eg, dizziness, migraine, headache)[69,71] Influenza-like symptoms[67,69] Potential increased risk of orthostatic hypotension[79] Potential increased risk of arrhythmia[79]	Insufficient information available regarding use in pregnancy and lactation	Naturally occurring in hawthorn leaves, flowers, and berries

(*Continued*)

Table 1. Continued

Complementary and alternative medicines agent	Mechanism of action	Major evidence	HF outcomes: benefit	HF outcomes: harm	HF outcomes: negative or unknown	Interaction with HF therapies	Adverse effects	Pregnancy, lactation, or both	Sources
L-Arginine (Also listed in Table 2: Adverse effects and Interactions)	Substrate for NO synthesis, thereby improving endothelial function	RCT: Salmani et al, 2021[81] Fontanive et al, 2009[82] Watanabe et al, 2000[83] Hambrecht et al, 2000[84]	Significant improvement in 24-h urinary GMP excretion and creatinine clearance; significantly higher urine sodium and glomerular filtration rate after saline load[83] Significant improvement in endothelium-dependent vasodilation after 4 wk[84] Significant improvement in LV structure and function, quality of life after 10 wk[81] Significant improvement in NYHA class[82]	No major harms		Potential risk of hypotension with concomitant vasodilator, nitrates, phosphodiesterase type 5 inhibitor use	Generally well tolerated Can cause gastrointestinal adverse effects	Evidence for safety when used at ≤12 g daily or lower dose for 2 d to 8 wk Insufficient information available regarding use in lactation	Naturally occurring in many foods including red meat, poultry, fish, dairy
L-Carnitine	Involved in fatty acid transport from cytosol to mitochondria, fatty acid oxidation, and lipid metabolism Reduces oxidative stress	Meta-analysis: Song et al, 2017[85] RCT: Serati et al, 2010[86] Iliceto et al, 1995[87] Rizos, 2000[88] Anand et al, 1999[89] Anand et al, 1998[90]	Significant improvement in mortality rate[88] Significant improvements in NYHA class, LVEF, LV dimensions, stroke volume, cardiac output, echocardiographic parameters of diastolic filling, serum B type natriuretic peptide and N-terminal pro-B type natriuretic peptide levels[85] Significant improvement in echocardiographic indices in diastolic function[86] Attenuation of LV remodeling through 1 y after MI[87] Increase in peak Vo_2, exercise time; reduction in LV dimensions[90]	No major harms	Conflicting mortality data (benefit vs no effect)	None reported	Generally well tolerated Infrequent side effects include gastrointestinal	Insufficient information available regarding use in pregnancy Supplemental doses reportedly safe in breast milk and formula Secreted in breast milk	Naturally occurring in foods, highest concentrations in red meat
Thiamine Vitamin B_1 (Also listed in Table 2: Adverse effects and Interactions)	Coenzyme required for cellular energy production and function of portions of Krebs cycle, thereby essential for ATP metabolism	Meta-analysis: Jain et al, 2015[91] Systematic review: DiNicolantonio et al, 2013[92] RCT: Smithline et al, 2019[93] Keith et al, 2019[94] Schoenenberger et al, 2012[95] Smithline et al, 2007[96] Shimon et al, 1995[97]	Improvement in LVEF after 7 d of IV thiamine compared with baseline but not compared with placebo with long-term furosemide therapy[97] Significant improvement in LVEF in symptomatic chronic HFrEF[43]	No major harm	Conflicting data on improvement in LVEF; no improvement in quality of life or exercise capacity[94] No significant differences in HF hospitalization rate, hospital length of stay, dyspnea score in acutely decompensated patients[95] No improvement in dyspnea[93]	Possible reduction in thiamine in patients on high-dose loop diuretic therapy[97]	Generally well tolerated Rarely causes dermatitis or other hypersensitivity reactions	Insufficient information available regarding use in pregnancy and lactation	Naturally occurring in many foods including beef, pork, yeast, legumes, nuts, grains (oats, rice, seeds, wheat, whole-grain cereals), fruit, dairy
Vitamin C Ascorbic acid	Reduces free oxygen radicals, thereby protecting against oxidative stress Reduces inflammatory markers and plays role in maintaining normal immune function	Observational: Wannamethee et al, 2013[98]	Associated with a significantly lower risk of incident HF in men with and without previous MI[98]	No major harms	No direct investigation of the impact of dietary vitamin C supplementation on HF incidence or prognosis have been performed	No major interactions	Generally well tolerated Infrequent adverse effects include gastrointestinal	Likely safe in pregnant and breastfeeding women at daily recommended doses (not exceeding UL 2000 mg daily over age 19 y)	Naturally occurring in fruits and vegetables, particularly citrus fruits

(*Continued*)

Table 1. Continued

Complementary and alternative medicines agent	Mechanism of action	Major evidence	HF outcomes: benefit	HF outcomes: harm	HF outcomes: negative or unknown	Interaction with HF therapies	Adverse effects	Pregnancy, lactation, or both	Sources
Vitamin D Ergocalciferol (vitamin D_2) Calcifediol (23-hydroxyvitamin D) Cholecalciferol (vitamin D_3) Calcitriol (1,25-dihydroxycholecalciferol)	Regulator of gene transcription and protein synthesis	Meta-analysis: Wang et al, 2019[99] Jiang et al, 2016[100] RCT: Djousse et al, (VITAL-HF) 2020[56]	Significant increase in 25(OH)D and interleukin-10 levels; significant decrease in tumor necrosis factor-α[100,108] Low levels of 25(OH)D and 1,25-dihydroxyvitamin D associated with worse NYHA class, worse LV function, deaths attributable to HF, sudden cardiac death[113]	No major harms with routine supplementation	No improvement in functional capacity or quality of life in older adults ≥70 y with 25-hydroxyvitamin D levels <50 nmol/L (20 ng/mL) at baseline[107]	Increased risk for digoxin toxicity and reduced nondihydropyridine calcium channel blocker effectiveness attributable to potential for hypercalcemia with high doses of vitamin D	Generally well tolerated	Safe in pregnant and breastfeeding women at daily recommended doses (not exceeding UL 4000 IU daily)	Naturally occurring in fish, eggs, and fortified dairy
		Zittermann et al, 2019[101] Zittermann et al, 2017[102] Witte et al, 2016[103] Boxer et al, 2014[104] Dalbeni et al, 2014[105] Boxer et al, 2013[106] Witham et al, 2010[107] Schleithoff et al, 2006[108] Observational: Amin et al, 2013[109] Gotsman et al, 2012[110] Ameri et al, 2010[111] Boxer et al, 2010[112] Pilz et al, 2008[113] Zittermann et al, 2008[114] Boxer et al, 2008[115]	Low calcitriol levels associated with higher heart transplant listing status and higher rate of death or cardiac transplantation.[114] Larger LV dimensions and lower fractional shortening in individuals with 25(OH)D<25 nmol/L[111] Lower 25(OH)D levels correlated with markers of increased frailty[115] and with lower peak oxygen consumption[112] Supplementation independently associated with reduced mortality[110] Decrease in serum aldosterone with supplementation[104] Improvement in echocardiographic LV function and dimensions[103] Significant improvement in LVEF with supplementation in elderly patients with deficiency[105] Restoration of 25(OH)D level associated with improvement in NYHA class and 6MW distance[109]		No improvement in peak Vo_2 or secondary outcomes of physical performance with vitamin D_3 supplementation[103,106] No mortality reduction[102] No significant reduction in first HF hospitalization rate[56]	Increased risk for hypercalcemia with concomitant use of thiazide diuretics			
Acupuncture	Thought to impact neural impulses, release endorphins, opioids, or both and result in sympatholysis, stimulate neurotransmitters	Systematic review: Lee et al, 2016[116] RCT: Kristen et al, 2010[117] Middlekauff et al, 2002[118]	Significant improvement in 6MW distance, quality of life and reduced heart rate variability[117] Eliminated surges in sympathetic activation during mental stress[118]	No major harms	No significant improvements in LVEF or peak Vo_2[117,118]	None known	Generally well tolerated Potential adverse effects include bruising, pain, and swelling	Possibly safe during pregnancy when performed with sterile procedures Insufficient information available regarding use in lactation	Not applicable

(*Continued*)

Table 1. Continued

Complementary and alternative medicines agent	Mechanism of action	Major evidence	HF outcomes: benefit	HF outcomes: harm	HF outcomes: negative or unknown	Interaction with HF therapies	Adverse effects	Pregnancy, lactation, or both	Sources
Yoga Tai chi	Effects on cardiovascular system postulated to be attributable to increased parasympathetic and decreased sympathetic activity	Meta-analysis: Huang et al, 2021[119] Chen et al, 2020[120] Taylor-Pilae and Finley, 2020,[121] Ren et al, 2017[122] Gomes-Neto et al, 2014[123] RCT/nonrandomized clinical trial: Krishna et al, 2014[124] Krishna et al, 2014[125] Yeh et al, 2013[126] Redwine et al, 2012[127] Yeh et al, 2011[128] Caminiti et al, 2011[129] Pullen et al, 2010[130] Pullen et al, 2008[131] Barrow et al, 2007[132] Yeh et al, 2004[133] Observational: Howie-Esquivel et al, 2010[134]	Improvement in graded exercise test, peak Vo_2, quality of life; significant reductions in inflammatory markers (IL-6 and high sensitivity C-reactive protein) with yoga[131] Positive impact on peak Vo_2 and health-related quality of life with yoga[123] Improvements in flexibility, treadmill time, peak Vo_2, quality-of-life scores, and decrease in inflammatory biomarkers (IL-6, C-reactive protein, extracellular superoxide dismutase) with yoga in African American patients with HF[130] Significant decrease in heart rate, blood pressure with yoga[125] Improvements in endurance, strength, balance with yoga[134] Improved quality of life, increased 6MW distance, decreased B type natriuretic peptide with tai chi[133] Improved quality of life, exercise self-efficacy, mood with tai chi[133] Higher increase in 6MW distance after tai chi training in HF with preserved ejection fraction[126] Reduction in systolic blood pressure and N-terminalpro-B type natriuretic peptide[129] and somatic depression scores[127] with tai chi	No major harms	No significant difference in 6MW distance, peak Vo_2[128]	None known	Generally well tolerated	Yoga: possibly safe during pregnancy and lactation without adverse effect on birth outcomes with the exception of aggressive yoga exercises Tai chi: insufficient information available regarding use in pregnancy and lactation	Not applicable

HERB CHF indicates Hawthorn Extract Randomized Blinded Chronic Heart Failure; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; 6MW, 6-minute walk; NYHA, New York Heart Association; Q-SYMBIO, Coenzyme Q10 as Adjunctive Treatment of Chronic Heart Failure Focusing on changes in Symptoms, Biomarker Status, and long-term Outcome; RCT, randomized clinical trial; SPICE, Survival and Prognosis: Investigation of Crataegus Extract WS 1442 in CHF; and VITAL-HF, Vitamin D and Omega-23 Trial-HF.

Table 2. Clinical Studies of Complementary and Alternative Medicines That Interact With Heart Failure Therapy or Worsen Heart Failure

Complementary and alternative medicines agent	Mechanism of action	Major evidence	HF outcomes: benefit	HF outcomes: harm	HF outcomes: negative or unknown	Interaction with HF therapies	Adverse effects	Pregnancy, lactation, or both	Sources
Alcohol (Also listed in Table 1 for efficacy)	Increases adrenergic activity Myocardium toxicity Increases urinary excretion of Na^+ and K^+	Subanalysis of an RCT: Ariansen et al, 2012[142] 9193 patients with hypertension Prospective cohort study: Nicolas et al, 2002[143] 55 men with alcoholism with cardiomyopathy Systematic review: Alwis et al, 2020[144] Observational: Cosmi et al, 2015[27] Djousse et al, 2008[28] Djousse et al, 2007[29] Bryson et al, 2006[30] Walsh et al, 2002[29] Abramson et al, 2001[32] Cooper et al, 2000[33]		New-onset atrial fibrillation in patients consuming >10 drinks/wk and living with hypertension and LV hypertrophy (HR, 1.60 [0.94–2.72]) Cardiomyopathy could develop in patient consuming 6–7 drinks/d	Negative effects and outcomes are dose related.	May potentiate the effect of diuretics or vasodilators	Flushing, confusion, emotional lability, perceptual and sensational disturbances, blackouts, lack of coordination and trouble walking, central nervous system depression, drowsiness, respiratory depression, hypothermia, hypoglycemia, nausea, vomiting, diarrhea, abdominal pain[17] Chronic heavy ingestion can lead to dependence, malnutrition, amnesia, dementia, somnolence, cardiac myopathy, hepatotoxicity, and cirrhosis, pancreatitis, hypomagnesemia, skeletal myopathies, Wernicke encephalopathy, Korsakoff psychosis, chronic cerebellar syndrome, mouth cancer, esophageal cancer, pharyngeal cancer, laryngeal cancer, and liver cancer[17] Chronic intake associated with increased risk of all-cause mortality, ischemic stroke, and hypertension[17]	Teratogenic Associated with significant risk of spontaneous abortion, fetal alcohol syndrome, neurological and psychological dysfunction in infants and children exposed to alcohol in utero[17] Alcohol is secreted in breast milk. Can cause abnormal psychomotor development, infant's sleep-wake disruption, reduction in mother's milk production[17]	Variable
Aloe vera	Stimulant laxative	Systematic review: Tachjian et al, 2010[145]				Cardiac glycosides: could reduce potassium levels, therefore increasing the risk of digoxin toxicity		Possibly unsafe	
Bitter orange	Sympathomimetic Inhibits cytochrome P450 3A4 metabolism	RCT: Bui et al, 2006 15 healthy subjects[146] RCT: Malhotra et al, 2001 10 healthy subjects[147]				Increase blood pressure and heart rate up to 5 h after ingestion[146]	May counteract the effect of antihypertensive drugs taken by patients with HF and exacerbate the effect of stimulants Inhibits cytochrome P450 3A4 metabolism of drugs like felodipine[147]	Likely safe in amount found in food Possibly unsafe if used for medicinal purposes (supplements)	
Blue cohosh	Probably acts through multiple tissue-dependent mechanisms, including estrogenic (or antiestrogenic), serotonergic, antioxidative, and inflammatory or anti-inflammatory	Case report: Fetrow and Avila, 1999[148]		May cause tachycardia, hypertension May cause angina through coronary vasoconstriction May increase glycemia		Theoretically decrease the effect of antihypertensive and antidiabetic drugs		Likely unsafe because it can induce labor	

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Table 2. Continued

Complementary and alternative medicines agent	Mechanism of action	Major evidence	HF outcomes: benefit	HF outcomes: harm	HF outcomes: negative or unknown	Interaction with HF therapies	Adverse effects	Pregnancy, lactation, or both	Sources
Caffeine	Stimulant Antagonist of adenosine Increases urinary excretion of Na^+ and K^+	RCT: Zuchinali et al, 2016[149] 51 patients with HF RCT: Bailey et al, 2016[150] 13 normotensive subjects Systematic review: Van Dijk et al, 2018[151] Systematic review: Alwis et al, 2020[144]		Consumption before a cardiac perfusion measurement may lead to false positives in both healthy patients and patients with coronary artery disease	Consumption of 500 mg within 5 h did not lead to greater risk of arrythmias compared to placebo.	Caffeine increased systolic and diastolic blood pressure, and a double dose of felodipine was needed to eliminate the pressor effect induced by caffeine[150] May potentiate the effect of diuretics	Anxiety Diarrhea Diuresis Gastric irritation Headache Insomnia Muscular tremor Nausea Restlessness Chronic use: dependence	Possibly safe with moderate consumption	
Devil's claw	Inhibit cytochrome P450 3A4 and 2C9	Case report: Cuspidi et al, 2015[152] Case report: Shaw et al, 1997[153]		May increase blood pressure		May increase international normalized ratio when used with warfarin[152,153]		Possibly unsafe	
Ginkgo biloba	Ginkolide B component inhibits platelet-activating factor with decreased arachidonate-independent platelet aggregation; CYP450 2C9 inhibitor; does not affect hepatic CYP3A4, but unknown if it affects intestinal CYP3A4.	Meta-analysis: Pittler et al, 2000[154] Systematic review: Nicolai et al, 2009[155] Zeng et al, 2005[156]	Possible improvement in intermittent claudication[154]	May increase risk of bleeding in patients on anticoagulation	Unknown	Unknown if ginkgo interacts with guideline-directed medical therapy for HF. Interacts with warfarin because it inhibits CYP450 2C9 so can increase INR.	Headaches, dizziness, palpitations, gastrointestinal disturbances, bleeding disorders, and skin hypersensitivity reactions	Possibly unsafe in pregnancy. There is weak evidence from animal and in vitro studies that ginkgo biloba has antiplatelet activity and therefore its use during labor could possibly prolong bleeding time.[157] There are no data on safety during breastfeeding.	Naturally occurring in ginkgo tree leaves
Gossypol	Polyphenolic compound that has shown a number of valuable biological properties such as antifertility, antioxidation, and antitumor activities	Prospective cohort: Wu et al, 1989[158] Kovacic, 2003[159]		At doses >40 mg, it has been reported to cause circulatory problems and HF	Negative	May increase risk of cardiac glycoside toxicity attributable to K^+-depleting effects. Increased risk of hypokalemia in patients on K^+-depleting diuretics	Generally well tolerated when used at doses <20 mg daily. Most common side effects are nausea, vomiting, diarrhea, and hypokalemia. If used ≥20 mg daily for >1 y, it has been associated with multiple side effects, including circulatory problems.	Likely unsafe in pregnancy. Seems to have abortifacient and uterine stimulant effects. Possibly unsafe in lactation, so avoid use.	Stem, seeds, and roots of the cotton plants where it acts as a natural defensive agent by causing infertility in insects
Grapefruit juice	Inhibition of the intestinal cytochrome P-450 3A4 system responsible for first-pass metabolism of many medications. Thus, it increases the bioavailability of drugs by decreasing their presystemic metabolism.	Prospective cohort: Libersa et al, 2000[160] Zitron et al, 2005[161] Piccirillo, 2008[162]		At doses >1000 mL it can cause worsening arrhythmias in patients with cardiomyopathy	Negative	Grapefruit juice inhibits metabolism and increases absorption of amiodarone. It inhibits metabolism and increases absorption and plasma concentrations of statins. It increases bioavailability of a single dose of carvedilol by 16%. It might reduce effectiveness of losartan but needs further study. It impairs the antiplatelet effects of clopidogrel and ticagrelor by inducing inhibition of CYP2C19. It can also increase effects of warfarin. It inhibits CYP450 3A4 so can have additive effects with QT prolonging drugs like amiodarone, dofetilide, disopyramide, procainamide, sotalol.	Generally, well tolerated. Large amounts can cause QT prolongation and worsening arrhythmia in patients with cardiomyopathy. It can also cause mineralocorticoid excess.	Inconclusive. Some data suggest insufficient information about safety of using medicinal amounts and others say that it is safe as long as mother is not on a medication that is affected by the CYP-450 3A4 system or on QT prolonging drugs.	Juice from grapefruits

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Table 2. Continued

Complementary and alternative medicines agent	Mechanism of action	Major evidence	HF outcomes: benefit	HF outcomes: harm	HF outcomes: negative or unknown	Interaction with HF therapies	Adverse effects	Pregnancy, lactation, or both	Sources
Guar gum	Water-soluble, gel-forming fiber that normalizes the moisture content of the stool, absorbing excess liquid in diarrhea, and softening the stool in constipation. May help decrease the amount of cholesterol and glucose that is absorbed in the stomach and intestines.	Superko et al, 1988[163] Knopp et al, 1999[164] Tuomilehto et al, 1983[165] Salenius et al, 1995[166] Simons et al, 1982[167] Observational: Lembcke et al, 1982[168]	Guar gum 7–10 g per meal seems to reduce systolic blood pressure and diastolic blood pressure. Also can attenuate hypotension after intraduodenal and oral glucose load possibly by slowing gastric emptying and glucose absorption. Possible reduction in cholesterol absorption.	No clear harm other than potential poor absorption of medications	Unknown	Can slow digoxin absorption	Generally well tolerated. Possible gastrointestinal effects like abdominal cramping, pain, bloating, diarrhea, flatulence, heartburn, loose stools.	Possibly safe	Naturally occurring in seed of the guar plant
Hawthorn (Also listed in Table 1 for efficacy)	Concentration-dependent increase of myocardial contractility through possible mediation by cAMP-independent inhibition of Na^+/K^+-ATPase Prolongs action potential and refractory period Vasorelaxation by and endothelium-dependent and NO-mediated mechanism	Meta-analysis: Pittler et al, 2008[63] Daniele et al, 2006[64] Pittler et al, 2003[65] RCT: Zick et al, (HERB-CHF) 2009[66] Holubarsch et al, (SPICE) 2008[67] Degenring et al, 2003[68] Tauchert, 2002[69] Zapfe, 2001[70] Weikl et al, 1996[71] Schmidt et al, 1994[72] Leuchtgens et al, 1993[73] Observational: Schroder et al, 2003[74] Taucher et al, 1999[75] Prospective cohort: Habs, 2004[76] Subanalysis of RCT: Zick et al, 2008[77]	Significant improvement in maximal workload using bicycle ergometry[69,70] Increase in exercise tolerance[68,70] Reduction of the pressure×heart rate product (systolic blood pressure in mm Hg times heart rate per minute and divided by 100)[70,71,73,78] Improvement in HF symptoms (eg, dyspnea, fatigue, palpitations)[69,73,75,76]	Potential for progression of HF risk at baseline in adults >18 y with HF with NYHA class II or III and LVEF ≤40% and especially in those with LVEF ≤35%, over 6 mo[77]	Effects of hawthorn in patients on guideline-directed medical therapy for HFrEF as most studies with hawthorn were done in individuals on minimal background HFrEF therapy Insufficient evidence regarding safety past 16 wk of use RCT in >5000 patients with Crataegus extract WS 1442 did not meet primary end point of reduced cardiac events including death attributable to HF or HF hospitalizations. Adverse effects were similar between WS 1442 and placebo[67]	Theoretical potentiation of coronary and peripheral vasodilators[79] Conflicting evidence on interaction with digoxin[79,80] Appears to be safe when used in combination with angiotensin-converting enzyme inhibitors, β-blockers[67,79]	Generally well tolerated with mild-to-moderate side effects[64] Cardiac (eg, palpitations, chest pain)[71,72] Gastrointestinal complaints[69,71,72] Neurological (eg, dizziness, migraine, headache)[69,71] Influenza-like symptoms[67,69] Potential increased risk of orthostatic hypotension[79] Potential increased risk of arrhythmia[79]	Insufficient information available regarding use in pregnancy and lactation	Naturally occurring in hawthorn leaves, flowers, and berries
Khella	The constituents of khella (visnadin, visnagin, and khellin) seem to have calcium channel blocking activity	Observational: Rauwald et al[169] Duarte et al[170] Duarte et al[171] Prospective cohort: Harvengt and Desager, 1983[172]	Visnadin is the most active constituent of khella. It can inhibit vascular smooth muscle contraction and seems to dilate peripheral and coronary vessels and increase coronary circulation.[170,171] The khellin constituent also acts as a vasodilator. There is some preliminary evidence that khellin might also increase high-density lipoprotein cholesterol levels without affecting total cholesterol or triglyceride concentrations[172]	Visnagin, one of the constituents of khella, has some negative chronotropic and inotropic effects.	Negative	Khella might decrease the effectiveness of cardiac glycosides like digoxin The khella constituent visnadin has negative inotropic effects that might counter the effects of cardiac glycosides[17]	Nausea, dizziness, constipation, lack of appetite, headache, itching, and insomnia, elevated liver function tests, photosensitivity	The active constituent, khellin, has uterine stimulant activity	Naturally occurring in dried, ripe fruit of the khella plant

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Table 2. Continued

Complementary and alternative medicines agent	Mechanism of action	Major evidence	HF outcomes: benefit	HF outcomes: harm	HF outcomes: negative or unknown	Interaction with HF therapies	Adverse effects	Pregnancy, lactation, or both	Sources
L-Arginine (Also listed in Table 1 for efficacy)	Substrate for NO synthesis, thereby improving endothelial function	RCT: Salmani et al, 2021[81] Fontanive et al, 2009[82] Schulman et al, 2006[173] Watanabe et al, 2000[83] Hambrecht et al, 2000[84]	Significant improvement in 24-hour urinary cGMP excretion and creatinine clearance; significantly higher urine sodium and glomerular filtration rate after saline load[83] Significant improvement in endothelium-dependent vasodilation after 4 wk[84] Significant improvement in LV structure and function, quality of life after 10 wk[81] Significant improvement in NYHA class[82]	Does not improve vascular stiffness measurements or EF and may be associated with higher postinfarction mortality so should not be used after MI[173]	Negative	Potential risk of hypotension with concomitant vasodilator, nitrates, phosphodiesterase type 5 inhibitor use	Generally well tolerated Can cause gastrointestinal adverse effects, increased blood urea nitrogen/serum creatinine, decreased platelet count	Evidence for safety when used at ≤12 daily or lower dose for 2 d to 8 wk Insufficient information available regarding use in lactation	Naturally occurring in many foods including red meat, poultry, fish, dairy
Licorice	Glycyrrhetinic acid,[174] one of the active metabolites in licorice, can lead to a syndrome of apparent mineralocorticoid excess through direct and indirect effects. It inhibits the enzyme 11-β-hydroxysteroid dehydrogenase enzyme type 2, with a subsequent increase in the activity of cortisol. Licorice binds directly to the mineralocorticoid receptor, as does cortisol, producing the potential to cause elevated sodium and reduced potassium levels. Finally, glycyrrhetinic acid can inhibit hepatic metabolism of aldosterone through suppression of 5-β reductase activity	Observational: Komagamine et al[175] Penninkilampi et al, 2017[176]		Sodium retention, hypertension, hypokalemia, cardiac arrest		Renin-angiotensin-aldosterone system inhibitors, anticoagulants	Sodium retention, hypertension, hypokalemia, rhabdomyolysis, hypertensive encephalopathy, arrhythmias, cardiac arrest	Avoid	Can be found in black licorice, licorice-flavored diet gum, cough mixtures and licorice tea. The FDA advises against consuming >40–50 g/d for >2 wk
Lily of the Valley (*Convallaria majalis*)	Contains cardiac glycosides, that are potent inhibitors of cellular Na^+/K^+-ATPase. The increase in intracellular Na^+ leads to an accumulation of intracellular calcium through the Na^+-Ca^{2+} exchanger, leading to increased inotropy	Review: Yarnell and Abascal[177]	Has a long history of use for patients with mild HF because it contains active cardiac glycosides, but is not as potent as digoxin			Effects potentiated in the setting of hypokalemia or in combination with digoxin	Arrhythmias, confusion, lethargy, anorexia, nausea, vomiting, diarrhea, blurred vision, changes in color perception		All parts of the plant are considered toxic, with the greatest concentration of glycosides being in the roots. The attractive red berries are the most common source of poisoning in children

(*Continued*)

Table 2. Continued

Complementary and alternative medicines agent	Mechanism of action	Major evidence	HF outcomes: benefit	HF outcomes: harm	HF outcomes: negative or unknown	Interaction with HF therapies	Adverse effects	Pregnancy, lactation, or both	Sources
Oleander	Contains cardiac glycosides that are potent inhibitors of cellular Na^+/K^+-ATPase. The increase in intracellular Na^+ leads to an accumulation of intracellular calcium via the Na^+-Ca^{2+} exchanger, leading to increased inotropy	Experimental: Botelho et al, 2020[178]	Has a long history of use for patients with mild HF, particularly in Eastern medicine, as it contains active cardiac glycosides, but is not as potent as digoxin	Botelho et al[178] demonstrated administration of digoxin, ouabain, and oleandrin at 50 µg/kg every 24 h for 21 d to Wistar rats demonstrated that only oleandrin promoted moderate focal necrosis of cardiomyocytes, and elevation of B type natriuretic peptide in the groups that received oleandrin and ouabain relative to the digoxin group		Effects potentiated in the setting of hypokalemia	Arrhythmias, confusion, lethargy, anorexia, nausea, vomiting, diarrhea, blurred vision, changes in color perception		Yellow oleander (*Thevetia peruviana*) and common oleander (*Nerium oleander*) which is an evergreen shrub. All parts of the plant are considered toxic, including the leaves, flowers, twigs, and stems.
Strophanthus	Contains cardiac glycosides, which are potent inhibitors of cellular Na^+/K^+-ATPase. The increase in intracellular Na^+ leads to an accumulation of intracellular calcium through the Na^+-Ca^{2+} exchanger, leading to increased inotropy	Experimental: Botelho et al, 2020[178]	Ouabain, also known as g-strophanthin, and the related K-strophanthin were widely used in the late 19th century and early to mid-20th century to treat HF as both oral and intravenous formulations	Botelho et al, 2022,[178] demonstrated administration of digoxin, ouabain, and oleandrin at 50 µg/kg every 24 h for 21 d to Wistar rats demonstrated that only oleandrin promoted moderate focal necrosis of cardiomyocytes, and elevation of B type natriuretic peptide in the groups that received oleandrin and ouabain relative to the digoxin group		Effects potentiated in the setting of hypokalemia	Arrhythmias, confusion, lethargy, anorexia, nausea, vomiting, diarrhea, blurred vision, changes in color perception Ouabain, also known as g-strophanthin, was traditionally used as an arrow poison in eastern Africa for both hunting and warfare		*Strophanthus gratus* and *Strophanthus kombe*. The seeds have the highest concentration of cardiac glycosides, whereas the leaves, fruit, and milk from the plants contain lower concentrations. Ouabain is also an endogenous factor that is secreted by the adrenal glands in humans and other mammals and is present in blood at nanomolar concentrations.[180]
Policosanol	Precise mechanism is uncertain. Suggested mechanisms include (1) inhibition of hepatic cholesterol synthesis, (2) enhancement of low-density lipoprotein binding, uptake, and degradation, (3) intraintestinal lipid-lowering effect	Meta analysis: Askarpour et al, 2019[180] RCT: Mercurio et al, 2020[181]	Mercurio et al[202] demonstrated 24 wk of treatment with a nutraceutical combination of policosanol, berberine, and red yeast rice extract reduced LV mass in patients with metabolic syndrome and LV hypertrophy Meta-analysis by Askarpour et al, 2019,[180] demonstrated reduction of systolic blood pressure and diastolic blood pressure in a total of 19 studies						Policosanols are long-chain aliphatic alcohols that are found in natural sources, including beeswax, wheat germ, rice bran, and sugarcane

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Table 2. Continued

Complementary and alternative medicines agent	Mechanism of action	Major evidence	HF outcomes: benefit	HF outcomes: harm	HF outcomes: negative or unknown	Interaction with HF therapies	Adverse effects	Pregnancy, lactation, or both	Sources
Thiamine (Also listed in Table 1 for efficacy)	Thiamine deficiency impairs production of ATP, leading to accumulation of adenosine. The ensuing reduction in systemic vascular resistance leads to a compensatory high-output HF state	Meta-analysis: DiNoccolantonio et al, 2013[182] RCT: Shimon et al, 1995[97]	Shimon et al, 1995,[97] performed an RCT where 30 participants were randomly assigned to thiamine 200 mg/d IV or placebo, followed by oral thiamine 200 mg/d as outpatients for 6 wk. LVEF rose by 22% (0.27±0.10 to 0.33±0.11; $P<0.01$). A recent meta-analysis of randomized, double-blind, placebo-controlled trials indicated that thiamine supplementation results in a significant net improvement in LVEF (3.28% [95% CI, 0.64%–5.93%]) in patients with systolic HF.[92]			Loop diuretics may lead to thiamine deficiency	Severe thiamine deficiency can cause cognitive impairment (Wernicke encephalopathy), peripheral neuropathy (dry beriberi), or HF (cardiac, or wet beriberi)		
Vitamin E	α-Tocopherol, the most active form of vitamin E, acts as an antioxidant. α-Tocopherol has been shown to reduce atherosclerotic lesions, platelet adherence and aggregation, and improve endothelial function	RCT: The HOPE and HOPE-TOO Trial Investigators[183] Marchioli et al, 2006[184] Chae et al, 2012[185]	In the Women's Health Study,[185] women aged >45 y randomly assigned to vitamin E 600 IU every other day was not associated with increased risk for systolic HF. A prespecific subgroup analysis showed a 40% reduction in the risk of HF with preserved ejection fraction.	Vitamin E ≥400 IU/d may increase the risk of developing new-onset HF. In patients without HF, the HOPE study[183] showed a 13% increased risk for incident HF and a 21% increased risk for hospitalization for HF in patients randomly assigned to vitamin E 400 IU/d compared with placebo. In the GISSI-Prevenzione trial,[184] patients with baseline LV dysfunction (EF <50%) randomly assigned to vitamin E had a 50% increased risk for symptomatic HF compared with placebo		Anticoagulant and antiplatelet medications	Hemorrhage, inhibition of platelet aggregation	Recommended dietary allowances based on age. Adequate intake of vitamin E for ages ≥14 y is 15 mg.[186]	Naturally occurring in plant-based oils, nuts, seeds, fruits, and vegetables

ATP indicates, adenosine triphosphate; EF, ejection fraction; FDA, US Food and Drug Administration; GISSI, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico; HERB CHF, Hawthorn Extract Randomized Blinded Chronic Heart Failure; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; INR, international normalized ratio; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; Q-SYMBIO, Coenzyme Q10 as Adjunctive Treatment of Chronic Heart Failure With Focus on Symptoms, Biomarker Status; RCT, randomized clinical trial; SPICE, Survival and Prognosis: Investigation of Crataegus Extract WS 1442 in CHF; and VITAL-HF, Vitamin D and Omega-3 Trial-HF.

Omega-3 Polyunsaturated Fatty Acids/Fish Oil/Eicosapentaenoic Acid/Docosahexaenoic Acid

Omega-3 polyunsaturated fatty acids (PUFAs) are found in fish, soybean oil, and organ meats and are generally safe and well tolerated with gastrointestinal symptoms being the most common adverse effects. In GISSI-HF, there were modest reductions in hospital admission for cardiovascular causes (adjusted HR, 0.92 [99% CI, 0.849–0.999], *P*=0.009) and death (adjusted HR, 0.91 [95.5% CI, 0.833–0.998], *P*=0.041) in patients with chronic New York Heart Association II to IV HF who consumed 1 g of omega-3 PUFA daily (850–882 mg eicosapentaenoic acid/docosahexaenoic acid) daily versus placebo.[60] In the VITAL-HF study (Vitamin D and Omega-23 Trial-HF), participants who consumed 1 g of omega-3 PUFA (460 mg eicosapentaenoic acid/380 mg docosahexaenoic acid) did not have a significant reduction in first HF hospitalization rate, compared with placebo, over a median follow-up of 5.3 years (HR, 0.96 [95% CI, 0.80–1.14]; *P*=0.61). However, a secondary analysis demonstrated a significant reduction in recurrent HF hospitalization among adults taking omega-3 PUFA supplementation versus placebo (HR, 0.86 [95% CI, 0.74–0.998]; *P*=0.048). In other smaller randomized placebo-controlled trials in HF, omega-3 PUFA supplementation has led to improvement in left ventricular (LV) systolic function.[57,58,62] Although omega-3 PUFA supplementation does not seem to cause harm in HF, investigators demonstrated a higher incidence of atrial fibrillation with high-dose omega-3 PUFA administration in 2 large clinical trials.[138,139] This risk appears to be dose-related and increased when exceeding 2 g/d of fish oil.[140] In the 2022 American College of Cardiology/American Heart Association/Heart Failure Society of America HF guidelines, omega-3 PUFA supplementation is recommended (Class of Recommendation: 2b, Level of Evidence: B-R) in patients with New York Heart Association II to IV symptoms as adjunctive therapy to reduce mortality and cardiovascular hospitalizations.[141] Supplementation should not occur at the expense of other guideline-directed medical therapies and may provide benefit when used at a <4 g total daily dose.

Thiamine/Vitamin B_1

Thiamine is a water-soluble B complex vitamin and coenzyme required for oxidative phosphorylation and myocardial energy generation. It is not endogenously synthesized by humans and naturally occurs in dietary sources such as whole grains, legumes, and yeast. Severe thiamine deficiency is a well-known cause of HF (ie, wet beriberi), thought to arise from the depletion of ATP from cardiac myocytes. However, many patients with HF have a relative thiamine deficiency from micronutrient depletion associated with chronic diuretic use, dietary factors, advancing age, and other comorbid conditions.[92] Therefore, the hypothesis that thiamine supplementation in patients with HF may be beneficial has been explored.[91] However, in a double-blind, placebo-controlled randomized trial of daily oral thiamine supplementation in ambulatory patients with HF with reduced ejection fraction, no differences in quality-of-life scores, 6-minute walk distance, N-terminal pro-B type natriuretic peptide levels, or LV ejection fraction after 6 months were observed.[94] Data from small randomized studies suggest that thiamine supplementation in patients with chronic HF may be associated with small, net improvement in LV ejection fraction.[92,97] Thiamine supplementation in patients with HF and without clinically significant thiamine deficiency may not be efficacious and should be avoided.

Vitamin D/Ergocalciferol (Vitamin D_2)/Calcifediol (23-hydroxyvitamin D)/Cholecalciferol (Vitamin D_3)/Calcitriol (1,25-Dihydroxycholecalciferol)

Vitamin D is naturally occurring in fish, eggs, and fortified dairy. Supplementation for HF has been variably associated with decreased serum inflammatory markers[99,100,108] and improved LV function in some age groups,[101,103,105] but without improvement in mortality[102] or functional capacity,[106,107] and with conflicting impact on quality of life.[99,107] The recent VITAL-HF trial examined the efficacy of vitamin D_3 (2000 IU/d) supplementation for the prevention of incident HF over a median follow-up of 5.3 years and did not demonstrate a significant reduction in hospitalization for first HF event compared with placebo (HR, 0.93 [95% CI, 0.78–1.11]; *P*=0.4).[56] Overall evidence regarding its use in patients with HF remains inconclusive.

Yoga, Tai Chi

Yoga and tai chi are safe and well-tolerated adjunctive therapies for patients with HF. Their salutary effects on the cardiovascular system are proposed to be attributable to increased parasympathetic and decreased sympathetic activity. In randomized trials of yoga in combination with standard medical therapy for HF, improvements in exercise tolerance and quality of life and reduction in serum inflammatory markers were found.[123,130,131] Excellent adherence to practice among subjects, higher 6-minute walk distance, and lower depression scores compared with aerobic exercise was demonstrated in a small, randomized trial of tai chi in patients with HF with preserved ejection fraction. In a cohort of ambulatory patients with HF with reduced ejection fraction, a 12-week group-based tai chi program resulted in improvements in quality of life, mood, and exercise self-efficacy.[128] Although dedicated trials of yoga and tai chi in HF have had low enrollments compared with trials other complementary and alternative HF therapies, both have shown promise as beneficial forms of exercise and cardiac rehabilitation.

Considerations for Clinical Practice

1. Omega-3 PUFAs (fish oil) have the strongest evidence among CAM agents for clinical benefit in patients with HF and can safely be used in moderation.
2. Clinical data do not support routine thiamine supplementation in the absence of deficiency in patients with HF.
3. Yoga and tai chi can be used as adjunctive wellness approaches to guideline-directed medical therapy to improve exercise tolerance and quality of life.

CAM AGENTS THAT INTERACT WITH HF THERAPY OR WORSEN HF

Many commonly used agents may interact with current medical therapy or worsen outcomes in patients with HF. CAM agents with evidence of harm with respect to HF and HF management are listed in the next sections. We recognize that there is a growing list of CAM products. Rather than creating an exhaustive list, we included the commonly used agents with potential or known interactions with cardiac medications or with direct cardiovascular effects (Table 2).

When an adverse reaction is suspected to be associated with CAM, causality can be assessed using a standardized tool[187,188] and reported to the local health authority using Center for Food Safety and Applied Nutrition,[189] FDA adverse event reporting system,[23] and Health Canada MedEffect reporting systems.[190]

Alcohol

Excessive amounts of alcohol can cause deleterious cardiovascular effects.[2] Intake of >10 drinks per week is associated with increased new-onset atrial fibrillation in patients with hypertension and LV hypertrophy.[191] With even higher consumption (6–7 drinks/d), cardiomyopathy can develop but can be reversible with abstention from alcohol and medical treatment if alcohol abuse is not of long duration.[143,192]

Caffeine

Data suggest that coffee consumption of 500 mg within 5 hours is not associated with greater risk of arrythmias compared with placebo in regular coffee drinkers.[149] The consumption of caffeine before a cardiac perfusion measurement may lead to false positives in both healthy patients and patients with coronary artery disease.[151] Although one study found reduced risk of future HF in association with coffee intake,[193] other data suggested neutral effects from coffee consumption.[194] Association of the effect of coffee consumption and HF is confounded by other variables and awaits further confirmation by large-scale studies. Moderate caffeine consumption (<300–400 mg/d), is usually considered safe, and is not associated with adverse health or cardiovascular effects in the general population. However, there is wide interpatient variability with respect to caffeine sensitivity and rate of metabolism which may confer risk in individuals with a tendency toward tachyarrhythmias, especially if consumed in excessive amounts.

Gossypol

Gossypol is a polyphenolic compound found in the stem, seeds, and roots of cotton plants where it acts as a natural defense agent for the plant. It has been used as a male oral contraceptive and has some antimalarial properties. Gossypol depletes serum potassium,[195,196] and can lead to significant hypokalemia in patients on potassium-depleting diuretics which can increase risk of cardiac glycoside toxicity.[197] Chronic use at doses >20 mg daily for >1 year has been associated with multiple side effects, including circulatory problems.[159] Acute toxic effects have been observed with cottonseed in livestock and laboratory animals that include cardiac irregularities, circulatory failure, and pulmonary edema with subchronic exposure.[198]

Grapefruit Juice

Grapefruit juice inhibits intestinal CYP-450 3A4 responsible for first-pass metabolism and, thus, increases the bioavailability of drugs by decreasing their presystemic metabolism. Grapefruit juice increases absorption of and inhibits metabolism of amiodarone,[198] can increase bioavailability of carvedilol by 16%, and may reduce effectiveness of losartan.[199] Furthermore, coadministrations with amiodarone, dofetilide, and sotalol can potentially increase the risk of QT prolongation so should be used with caution in patients with HF and comorbid atrial fibrillation.[161,200,201] Although a single modest exposure to grapefruit juice may not produce any clinically significant interactions, higher risk was observed in older patients >70 years of age, and the consumption of ≥200 mL juice or whole grapefruit ingested within 4 hours of other medications of concern can potentially produce significant pharmacokinetic adverse effects. Moreover, repeated ingestion of grapefruit juice may produce cumulative effects and exacerbate the magnitude of interaction. Although a 10-hour interval between grapefruit juice and drug administration has been shown to reduce the impact of potential interactions,[202] consumption should be avoided given the potential interaction and unpredictability that can arise with other concomitant drugs.

Hawthorn

Naturally occurring in hawthorn leaves, flowers, and berries, hawthorn leads to a concentration-dependent increase in myocardial contractility, prolongs action potentials and refractory periods, and leads to vasorelaxation by an endothelium-dependent and NO-mediated mechanism. There is likely a pharmacodynamic interaction between hawthorn and digoxin, but not a pharmacokinetic interaction; as such,

this combination should be avoided.[79,80] However, most data suggest that it is safe in combination with angiotensin-converting enzyme inhibitors and β-blockers.[79,203]

L-Arginine

The amino acid L-arginine is a substrate for NO synthesis and is naturally occurring in red meat, poultry, fish, and dairy. However, in randomized controlled trial data, initiation of L-arginine after infarction was associated with increased risk of death in older patients. Therefore, administration of L-arginine should be avoided after acute myocardial infarction.[173]

Licorice

Glycyrrhetinic acid, one of the active metabolites in black licorice (glycyrrhizin), can lead to a syndrome of apparent mineralocorticoid excess through direct and indirect effects.[174] The clinical manifestations include sodium retention, hypertension, hypokalemia, and even cardiac arrest.[176] This potential risk may be potentiated in patients receiving mineralocorticoid receptor antagonists. Because of these potential adverse effects, licorice and its derivatives are currently regulated under the Code of Federal Regulations[204] and provide maximum levels of allowable glycyrrhizin in food. Although black licorice can produce serious side effects, red licorice is flavored through means other than licorice plant extract and would therefore not produce additional risk.

Lily of the Valley, Oleander, Strophanthus, Ouabain

The digitalis glycosides (digoxin) are the best known of the cardiac glycosides and represent the only drug in this class commonly used in clinical settings. However, many additional cardiac glycosides have been identified in at least 12 different families of plant species, including lily of the valley, yellow oleander, and common oleander, *Strophanthus*, and ouabain.[205] These plants have a long history of therapeutic use for patients with mild HF and atrial fibrillation, particularly in Eastern medicine. Because of the narrow therapeutic index associated with cardiac glycosides, acute accidental poisoning is common, and symptoms of nausea, palpitations, or visual disturbances could indicate toxicity. The effects can be potentiated in the setting of hypokalemia, so these agents should not be combined with potassium-wasting drugs, such as loop diuretics and corticosteroids, without careful monitoring of potassium levels.

Vitamin E

Sources of naturally occurring vitamin E have been found in plant-based oils, nuts, seeds, fruits, and vegetables. However, only moderate consumption should be encouraged given that doses in excess of 400 IU/d may increase the risk of incident HF. Results from the HOPE study (Heart Outcomes Prevention Evaluation) showed an increased risk of incident HF and risk for HF hospitalization in patients without HF at baseline who were randomly assigned to vitamin E 400 IU/d compared with placebo.[206] This risk appears to be consistent in a more recent analysis[137] and thus should be used with caution at high doses.

Considerations for Clinical Practice

A multidisciplinary team with pharmacist involvement can improve drug therapy management and safety in patients with HF who use CAM.

1. Health care professionals may perform causality assessment of potentially CAM-related adverse reactions and interactions to determine likelihood of CAM-induced harm.
2. Reporting of CAM-related adverse reactions to health authorities is encouraged although causality assessment remains unclear.
3. Routine evaluation of CAM in HF management is important to improve patient safety, and continued use is strongly discouraged if adverse effects, drug interactions, or both are known to cause harm.

MULTIDISCIPLINARY APPROACH TO IMPROVE PUBLIC AWARENESS AND SAFETY

A collaborative, multidisciplinary discussion of CAM therapies can improve care delivery for patients with HF who aim to use these approaches as additional tools for healing. Discussing the use of CAM and other mind/body-altering substances is just as important as prescribed medications. Unfortunately, because many CAM treatments are not evidence-based, health care professionals may not know how to integrate this information into traditional clinical practice. Patients may fear criticism from health care professionals and may not disclose their use. In previous research, <15% of cardiac patients discussed CAM with their clinician.[207] Many patients may not recognize these therapies as potentially problematic because CAM therapies are thought to be more natural compared with traditional FDA-approved medications.[207] Thus, health care professionals caring for patients with HF should be prepared to openly discuss CAM use without offering critique or judgment so they can obtain a full understanding of the range of treatments being used and potential interactions.

Pharmacists in the community have access to prescribed medications and are in a unique position to counsel and assess patients who select CAM.[207] Although this critical intervention is not routinely done because of time constraints, it should still be encouraged. In the hospital setting, pharmacists are more likely to inquire and document CAM use.[207] A multidisciplinary team approach involving cardiologists, nurses, advanced practice clinicians, and pharmacists can improve documentation of CAM and also reduce adverse drug reactions or drug-CAM interactions.[208] A

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team-based approach would optimize care by encouraging patient disclosure of CAM during medication reconciliation by nurses and pharmacists, harnessing the expertise of pharmacists with interactions and drug therapy management while offloading cardiologists and advanced practice clinicians managing other areas of diagnosis and medical care. Collaboration with practitioners of whole medical systems, chiropractors, and osteopathic medicine is still needed and should be encouraged to create open dialogue and transparency about adjunctive self-therapies to better harmonize overall wellness for the patient with HF.

Considerations for Clinical Practice and Public Health Initiatives

1. Health care professionals are strongly encouraged to initiate an open dialogue with patients without judgment about their current CAM therapies, when applicable.
2. Multidisciplinary collaboration with practitioners of traditional and nontraditional medical systems are encouraged to improve transparency, safety, and wellness in patients with HF who use CAM as adjunctive treatment to guideline-directed medical therapy.

GAPS IN RESEARCH AND FUTURE DIRECTION

There is substantial interest in and wide use of CAM in patients with HF. However, these interventions are being used with limited to no high-quality evidence of efficacy. The use of CAM including dietary supplements for the prevention and treatment of disease is a multibillion dollar market. The use of CAM by patients with HF is commonplace despite the lack of high-quality evidence to support their use.[2] In general, there is little quality evidence for an important treatment effect from these therapies. When tested in randomized clinical trials in HF, many specific CAM therapies have failed to improve cardiovascular outcomes in well-designed clinical trials. As in other cardiovascular disease states, there are no definitive data to support the role of CAM in patients with HF. However, there are a number of CAM therapies in which there is a significant body of evidence from preclinical and clinical research suggesting that some of these therapies may have clinically important beneficial effects in HF.

Although there is substantial promise for some of these CAM interventions, there are likely many agents being used providing no benefit or even resulting in unintended harm. There is an urgent need for additional mechanistic and translational studies, and well-designed, sufficiently powered randomized clinical trials, as well, to evaluate CAM in patients with HF. It is only through these randomized clinical trials that the high-quality evidence base, sufficient to provide guideline recommendations, will be generated. Engagement of patients with HF in helping to shape the research questions, prioritizing the outcomes to be studied, designing and conducting the trials, and playing an important role in dissemination is vital. It is also essential that equity, diversity, and inclusion be prioritized in all aspects of trial design, conduction, dissemination, and implementation.

There are a variety of potential funding sources for randomized clinical trials. The National Center for Complementary and Integrative Health provides funding for mind and body interventions and natural product studies, targeting support for all phases of clinical intervention development. The National Center for Complementary and Integrative Health has published a series of clinical trial–specific funding opportunity announcements for investigators[209] and resources to support the development of clinical research.[210] The funding opportunity announcements encourage applications for multicenter clinical trials evaluating the effects of mind and body interventions in the National Center for Complementary and Integrative Health designated areas of high research priority. These areas of research may include efficacy, effectiveness, and pragmatic randomized clinical trials. The National Center for Complementary and Integrative Health funding opportunities are designed to help address the gaps in current research and build a stronger evidence base for these interventions.

Considerations for Research Initiatives

1. There is an urgent need for additional mechanistic studies, and well-designed, sufficiently powered randomized clinical trials, as well, to evaluate the safety and efficacy of CAM in patients with HF.
2. Pragmatic randomized clinical trials may help to better inform patients, clinicians, and policy makers regarding the benefits and potential risks of CAM.
3. Engagement of patients with HF to help shape the research questions, prioritize the outcomes to be studied, design and conduct the trials, and play an important role in dissemination along with ensuring equity, diversity, and inclusion being prioritized in CAM research are essential.

SUMMARY/CONCLUSION

The increasing trend in utilization of complementary and alternative therapies in the United States spans across diverse populations and ethnicities. These agents are frequently purchased without consultation from a health care professional and are rarely reported during office visits by patients. Limited published reports suggest that select alternative therapies might have some clinical benefit, whereas others could worsen HF or interact with medications commonly used by adults with HF (Figure). More research and well-powered randomized controlled trials are warranted to further evaluate CAM efficacy and adverse effects in this population. Education, communication, and collaboration between patients, multidisciplinary health care professionals, and nontraditional

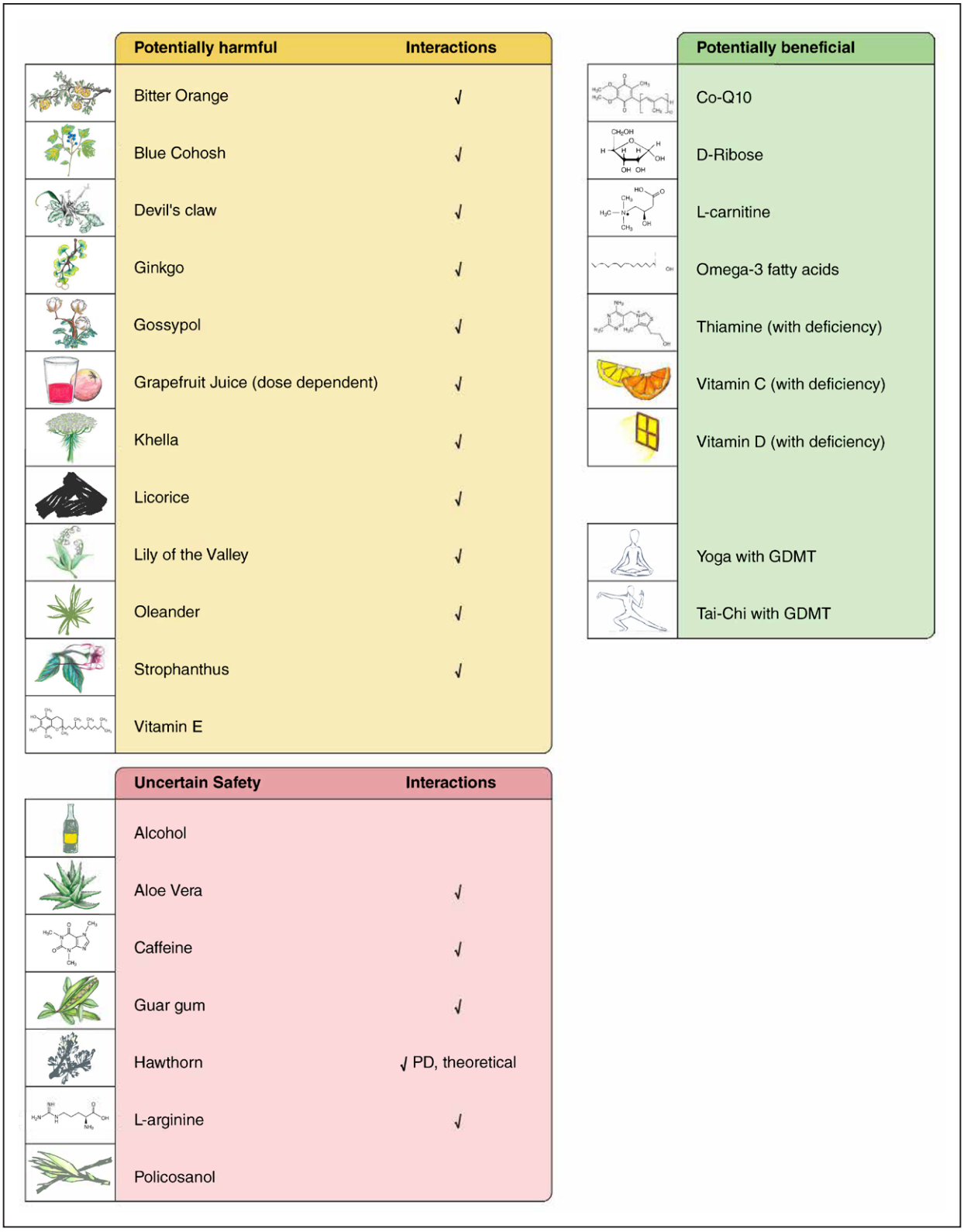

Figure. Complementary and alternative medicines that are potentially harmful (listed in yellow section), agents that are potentially beneficial (listed in green section), and agents with bidirectional effects that can be beneficial in certain individuals at certain doses but can be harmful in others and usually at increased doses (listed in pink section), in patients with heart failure.
Potential interactions with cardiac medications are noted by check marks under interactions title. Co-Q10 indicates coenzyme Q10; GDMT, guideline-directed medical therapy; and PD, pharmacodynamic. Drawings and artwork of CAM products with permission of artist Elise Dilci. Copyright 2022. Graphite and pencil on paper. Self-collection.

practitioners are encouraged in patients with HF to promote transparency and improve outcomes.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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*Modest.

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*Modest.

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