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Review Article

Role of Essential Nutrients for Cardiovascular Health: Risk and Management of Drug Interaction

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ABSTRACT

Background: Chronic diseases account for about 59% of the 56.5 million deaths reported worldwide and 46% of the global burden of the disease. Nearly half of deaths from chronic disease are attributed to cardiovascular disease, obesity, and diabetes. The present review will give an outline about the role of essential nutrients on cardiovascular health, chemistry, dose, drug metabolism and pharmacokinetics, mechanism of action, risk, and discuss the evidence-based risk and management of drug interaction.

The information was collected from books, and electronic search (PubMed, Science Direct, Lilca and Scielo) and PRISMA.

Discussion: Nutrient in the form of pharmaceuticals available can be used for the prevention and treatment of cardiac diseases. Adverse drug reactions, nutrients-drug interactions, and iatrogenic diseases have been identified as significant factors responsible for patient morbidity and mortality. A better understanding of these mechanisms and recent developments in laboratory technology can help assess possible drug interactions when drugs are prescribed at the same time. Increased knowledge of inter-individual variation in drug decomposition capacity and recent results related to nutrient and nutraceutical influence can be used to reduce adverse drug reactions and disease iatrogenic.

Conclusion: There is a need to enhance and foster interdisciplinary communication between medical herbalists, physicians, and dieticians. According to dieticians food may interact with conventional drugs and that drugs may affect nutritional status, in order to provide the patient with proper dietary suggestions, and to allow the maximum effectiveness and safety of drug therapy, while preserving/correcting the nutritional status.

Keywords: Food, Supplements, Cardiovascular drugs, Interactions, Risk management

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INTRODUCTION

Diet and nutrition are important factors in the promotion and maintenance of good health throughout life and also play as a risk factor for chronic diseases (Matsudo V, *et al*., 2002). As per calculations, in 2001, chronic diseases contributed approximately 60% of the 56.5 million total reported deaths in the world contributed by chronic diseases and approximately 46% of the global burden of disease (WHO, 2002). The share of the NCD burden is expected to reach 57% by 2020. Nearly half of deaths from chronic diseases are caused by cardiovascular disease. The 2016 Heart Disease and Stroke Statistics update of the AHA reported that the overall death rate from CHD was 102.6 per 100,000 (Mozaffarian D, *et al*., 2016). There is a strong relationship between SCD and CHD (Montagnana M, *et al*., 2008). Clinical and post-mortem studies as well as data from death certificates revealed that 62%-85% of patients who suffer out-of-hospital SCD have evidence of prior CHD, 10% have other structural cardiac abnormalities, and 5% have no structural cardiac abnormality (Kannel WB and Thomas Jr HE, 1982; Zheng ZJ, *et al*., 2001). A surveillance study of SCD from Ireland concluded that the majority of cases occurred at home and that successful resuscitation of SCD was especially associated with ventricular fibrillation as presenting rhythm (Byrne R, *et al*., 2008). IHD was also the greatest single cause of death in 2000, accounting for an estimated 6.0 million deaths. Individual populations face different challenges and each population has unique health burdens, however, CVD remains one of the greatest health challenges both nationally and worldwide (McAloon CJ, *et al*., 2016). Obesity is associated with some of the major risk factors for CVD, such as hypertension and low concentrations of High-Density Lipoprotein-cholesterol (HDL-cholesterol) (WHO, 2002). Arterial blood pressure and Hypercholesterolemia are key factors in the development of CVD.

LITERATURE REVIEW

Extensive study has been done in order to derive the solution to the question at hand. The majority of the study conducted revolves around the usage of e-books, most of which focused exclusively on essential nutrients. Additionally, government websites provided more information regarding what types of medications are used on cardiovascular diseases, as well as the short-term and long-term effects of their use. Furthermore, a couple of case studies detailed some students in India, and how their health improved with a conversion to a essential nutrients. The sources that are being used are several academic, peer-reviewed research papers, books, journals, and case studies. The mode of methodology that will be used to carry out the research is mixed between data analysis and experiments given in the case studies.

There has been a boom in their sales as patients rush to self-medicate, either in the hope that these products will be effective in treating diseases unsatisfactorily treated with pharmaceuticals, or that the adverse effects of some pharmaceuticals may be avoided. On whole, 'Nutraceuticals' has led to the new era of medicine and health, in which the food industry has become a research-oriented sector and that is used for the improvement of health, by preventing or treating disease (Das L, *et al*., 2012). The relation between nutraceuticals and other health products for various diseases are presented in *Figure 1*.

Nutraceuticals in the form of macronutrients, micronutrients algae, and herbs are recommended together with physical exercise for prevention and treatment of CVD (Muredzi ED, 2023). *Table 1* presents some of the more recognizable nutraceuticals substances grouped according to food-source providers (Wildman RE, 2016).

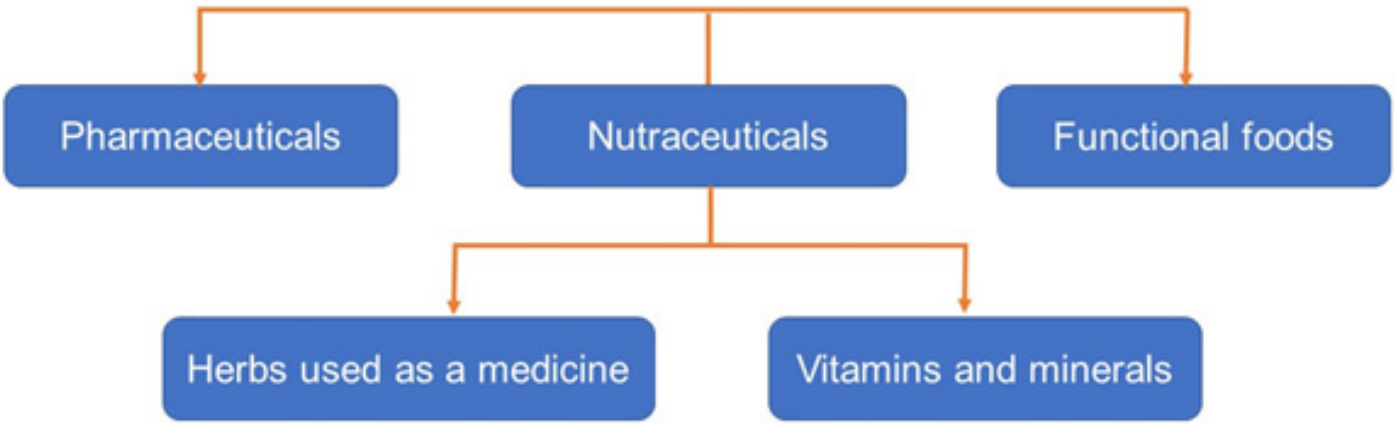

Figure 1: The relationship between nutraceuticals and other health products

Table 1: Examples of nutraceutical substances grouped by food source

Plants		Animals	Microbials
Ascorbic acid	Potassium	Eicosapentaenoic Acid (EPA)	*Bifidobacterium bifidum*
β-glucan	Glutathione	Conjugated Linoleic Acid (CLA)	*Saccharomyces boulardii* (yeast)
Cellulose	Lycopene	Lecithin	*L. acidophilus* (NCFB 1748)
Daidzein	β-carotene	Minerals	
Gallic acid	Lignin	Coenzyme Q10	
Indole-3-carbinol	Geraniol	Zinc	
Luteolin	Genistein	Choline	*Lactobacillus acidophilus* (LC1)
Lutein	Hemicellulose	Calcium	*Streptococcus salvarius (S. thermophilus)*
Perillyl alcohol	Capsaicin	Selenium	
Pectin	α-Tocopherol	Creatine	
Quercetin	δ-Limonene	Spingolipids	*B. infantis*
Selenium	Nordihydrocapsaicin		*B. longum*
γ-Tocotrienol	Allicin	DocosaHexenoic Acid (DHA)	

DISCUSSION

Risk of cardiovascular disease

Cardiovascular disease is the leading cause of premature morbidity and mortality in industrialized countries. Serum cholesterol correlates with the risk of coronary artery disease, myocardial infarction, and coronary death (Anderson KM, *et al*., 1987). Several studies have addressed the relation between the intake of Polyunsaturated Fatty Acids (PUFAs) and cardiovascular disease and the effect of increased PUFA intake on cardiovascular events. The low mortality from cardiovascular disease among traditionally living Eskimos and Alaskan Natives has been attributed to less atherosclerosis in the coronary arteries (Middaugh JP, 1990). The factors affecting the risk of heart disease are summarized in *Figure 2* (Dominguez H, 2013).

Nutraceutical diet for better cardiovascular health

Several nutraceutical substances are found in higher concentrations in specific foods or food families. These include capsaicinoids, which are found primarily in pepper fruit, and allyl sulfur (organo sulfur) compounds, which are particularly concentrated in onions and garlic. The table provides a listing of certain nutraceuticals that are considered unique to certain foods or food families (Wildman RE, 2016). Major Dietary factors are known to influence cardiovascular risk (*Table 2*) (Dominguez H, 2013).

Essential nutrition required to maintain the heart health is depicted in *Figure 3*. Minerals exert various effects on CVD. Diets with high zinc/copper ratios are hypercholesterolemia (Bastida S, *et al*., 2000). Some minerals play a central role in blood pressure regulation; however, apart from sodium or potassium, little is known about the effects of minerals on CVD. Increased intakes of magnesium and calcium decrease blood pressure and the risk of being hypertensive (Rodenas S, *et al*., 2011).

Sodium: A modest reduction (9-12 to 5-6 g/day) in salt intake for four or more weeks causes significant falls in blood pressure in both hypertensive and normotensive individuals. Reduction in salt intake of 3 g/day would result in the reduction of incidence CHD (5.9%-9.6%), stroke (5.0%-7.8%) (Bibbins-Domingo K, *et al*., 2010).

Figure 2: Major dietary factors affecting Coronary Heart Disease (CHD) risk

Table 2: Major dietary factors affecting Coronary Heart Disease (CHD) risk

Factors	TC	LDLc	HDLc	TG	BP	Aggregation	ED	Oxidation	Others
Energy	↑↑	-	↑	↓	-	-	↓	-	↑ Bodyweight
Fat	↑↑	↑	↑	-	-	-	↓	-	↑ Factor VII
Saturated fatty acids (C_{12}-C_{16})	↑↑↑	↑↑↑	↑	-	↑	↑	↑	↓↓	↑ Insulin resistance
Monounsaturated fatty acids	↓↓	↓↓	↑	-	↓	-	↓	↓?	↓ Fibrinolysis; ↓ PAI
n-6 polyunsaturated fatty acids	↓↓↓	↓↓↓	↓↓	-	-	-	-	-	↑
n-3 polyunsaturated fatty acids	↓?		↑	↓↓	↓↓	↓	↓	↓?	-
Trans fatty acids	↑	↑	↓	↑	↑	↑?	-	-	↑ Lp(a); ↑ Insulin resistance
Cholesterol	↑	↑	↑[W]	-	-	-	-	-	-
Alcohol*	↓	↓	↑	↓	↓	↓	↓	↓↓	Various effects
Digestible carbohydrates			↓	↑↑**	-	-	↓	↓↓	**Insulin resistance
Vegetable/fish protein	↓		↑	↓	-	-	↓	-	↑ (NO)
Animal protein	↑	↑	-	-		-	↓	-	-
Fiber	↓	↓	-	-	↓	-	↓	-	-
Phytosterols	↓↓	↓↓	-	-	-	-	↓	↓?	↓ Antioxidants
Folate/vitamin	-	-	-	-	-	↓?	↓	-	↑ Homocysteine
B12/vitamin B6									
Vitamin E	↓?	-	-	-	-	↓	↓	↓	-
Ca	↓	-	-	-	↓	-	-	-	-
Zn/Cu ratio	↑	↑	-	-	-	-	-	-	-
Polyphenols*	↓	↓	↑	↓	↓	↓	↓	↓↓	Most information *in vitro*
Coffee	↑↑ ***	↑↑ ***	-	↑↑ ***	-	-	-	↓↓	-

Note: TC: Total Cholesterol; LDLc: Low-Density Lipoprotein Cholesterol; HDLc: High-Density Lipoprotein Cholesterol; TG: Triglycerides; BP: Blood Pressure

↑: Increase; ↑↑: Abnormal increase; ↓: Reduce; ↓↓: Abnormal reduction; ↓? and ↑?: Limited scientific evidence; *: High consumption; [W]: Effects in women; **Fructose; ***Cafestol and Kawheol (coffee diterpene)

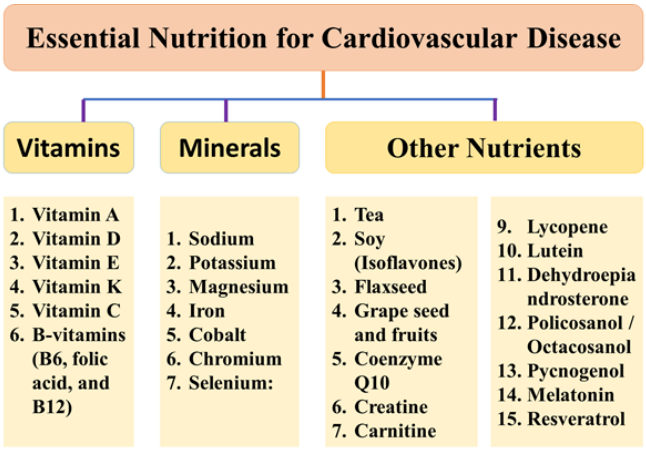

Figure 3: Essential nutrients for cardiovascular disease

Potassium: The risk of stroke varies greatly with potassium intake: The relative risk of stroke in the highest quintile of potassium intake (average of 110 mmol/day) is almost 40% lower (He FJ and MacGregor GA, 2001).

Vitamin A: It is a liposoluble compound derived from animal tissues. Retinal, retinoic acid and β-carotene have potential activity against atherosclerosis and inflammatory diseases also have antioxidant activity (Walden R and Tomlinson B, 2012). Consumption of carotenoid-rich vegetables has been linked to a reduced risk of coronary artery disease. An oxygenated carotenoid (Lycopene) whose antioxidant activity is two times higher than that of β-carotene. Tomatoes are the best source of lycopene (Sesso HD, *et al*., 2012).

Vitamin C: The population with vitamin C deficiency, found at high risk for coronary heart disease (Simon JA, 1992). Antioxidant properties of Vitamin C may synergistically act with vitamin E, this leads to a reduction in peroxyl radicals' formation and lipid peroxidation blocking (Mikirova NA, *et al*., 2008). Citrus extract plus ascorbate strongly inhibited atherosclerosis (Vinson JA, *et al*., 1998). Plant flavonoids are powerful antioxidants for heart disease (Vinson JA, *et al*., 1995). Studies have shown a reverse relationship between plasma renin activity levels and vitamin D, coronary artery calcification, and hypertension, (Resnick LM, *et al*., 1986).

Vitamin E: Vitamin E antioxidant and anticoagulant properties stabilized plaque, platelet aggregation, reduced inflammation, enhancing vasodilation, expression of adhesion molecules on the arterial wall are the potential mechanisms of cardio-protection (MI and thrombotic stroke) with vitamin E (Meagher EA, *et al*., 2001). High fiber consumption reduces postprandial glucose responses after carbohydrate-rich meals and lowers total and LDL cholesterol levels (Weickert MO and Pfeiffer AF, 2008). The polyphenolic contentis used for CVD prevention (Ullah MF and Khan MW, 2008). Red wine (polyphenolic) taken before food increases serum antioxidant activity which activates the platelet NO synthase and inhibits the platelet activation and production of reactive oxygen species, for at least 4 hours (Maxwell S, *et al*., 1994). Sudden death and heart attack incidences decreased by consumption of flavonoids (luteolin, kaempferol, apigenin, myricetin, and quercetin) intake assessed by dietary history. Flavonoid rich apples, black tea and onions were considered the most suitable foods. Moderate consumption of wine was found beneficial on ischemic CVD (Gresele P, *et al*., 2008). Resveratrol, induces the expression of several longevity genes, and prevents aging-related decline in cardiovascular function (Das DK, *et al*., 2011).

Flavanol-rich cocoa: They are suggested to have anti-inflammatory properties, antioxidant properties, antihypertensive effects, and anti-platelet aggregation. Platelet reactivity reduces and coronary vasomotion improved by Dark chocolate. It was found a significant decrease in the risk of the combined outcome of first MI or stroke in people in the top quartile compared to those in the bottom quartile of chocolate consumption (Buijsse B, *et al*., 2010). It seemed to be partly due to a drop in blood pressure in people who consume more chocolate. Vitamin K deficiency in the diet has been linked to an increased risk of atherosclerosis and soft-tissue calcification (Erkkilä AT and Booth SL, 2008). High level of potassium, magnesium, and calcium can lead to lower blood pressure and lower CDA and stroke (Houston MC and Harper KJ, 2008). The multiple cardio-protective and physiological activities of magnesium include calcium channel-blocking effects, antiarrhythmic effects, inhibition of blood coagulation, and improvement in NO release from coronary endothelium (Shechter M, *et al*., 1999). However, potassium and magnesium need to be avoided in the event of kidney failure. The health significance of iron is well known, with increasing attention being paid to the identification and treatment of iron deficiency in heart failure. Anemic patients (Hb ≤ 12 g/dL) with stable CHF, intravenous injections of iron sucrose only for 12 days decreased symptoms, improved exercise capacity, and increased hemoglobin (Anker SD, *et al*., 2009).

Trace minerals

Chromium: Chromium is an essential mineral that appears to have a beneficial role in the regulation of insulin action, metabolic syndrome, and cardiovascular disease (Hummel M, *et al*., 2007). Chromium is important for the metabolism of glucose and lipids and can contribute to the regression of cholesterol-induced atherosclerosis. The deficiency of chromium may influence glucose and lipid metabolism and affect atherosclerosis (Schroeder HA, 1967). Insulin resistance can be an important factor in disrupting lipid metabolism, the favorable effect of chromium on glucose or insulin metabolism can be a key factor in improving lipid profile (Balk EM, *et al*., 2007). Insufficient selenium in the soil can cause cardiac arrhythmias, CHF, multifocal myocardial necrosis, with cardiomyopathy. Primary prevention trials and most secondary prevention studies suggest that supplementation does not significantly reduce ischemic CVD events (Hercberg S, *et al*., 2004). L-carnitine was used as a supplemental treatment for Percutaneous Coronary Intervention (PCI) for Non-ST Elevation Acute Coronary Syndrome (NSTEMI).

DHA and EPA can improve many CVD risk factors, including lowering of plasma triglycerides, blood pressure, platelet aggregation, and inflammation, and improvement of vascular reactivity at the dose of >3 g/day (Breslow JL, 2006). A link has been established between fish oil supplementation and a significant reduction in deaths due to heart causes (León H, *et al*., 2008). Coenzyme Q10 (ubiquinone) has been used in oral forms to treat various cardiovascular disorders including angina pectoris, hypertension, and CHF (Greenberg ER, *et al*., 1996).

Algae and cardiovascular health

The importance of algae as components of functional foods with special application to cardiovascular diseases, due to their high dietary fiber, mineral, vitamins, and phytochemical contents, and their polyunsaturated fatty acid. Effects of seaweeds and alga compounds on cholesterol metabolism, lipoprotein levels, and thrombosis/blood coagulation have presented in *Table 3*.

There has been a combined effort among scientists to explore and utilize varying food sources to develop functional foods to cater to the ever-increasing demand from the consumers, who seek health-promoting roles of dietary compounds (Mendis E and Kim SK, 2011). Marine organisms are considered safer alternatives to some existing synthetic drugs as they exhibit significant biological properties. Marine bioactive include peptides, fatty acids, carbohydrates especially Sulfated Polysaccharides (SPs). Time is useful in food industries and performs the healing junctions like anti-hyperlipidemic, antioxidant, anti-diabetic, and these all functions contribute towards cardiac protection (Tufail T, *et al*., 2018). Nutrient used to prevent the risk of heart diseases are summarized in *Table 4*. Interaction between essential nutrient and conventional cardiovascular drugs are briefly summarized in *Table 5* and graphically presented in *Figure 4*.

Table 3: Effect of seaweeds and alga compounds on cholesterol metabolism, lipoprotein levels, and thrombosis/blood coagulation

Seaweeds and alga compounds	Source and content	Bioactivity	References
Whole algae orlipids extracts (unicellular alga *Nannochloropsis* sp.)	DHA-enriched oils from algae	Reduce the plasma and liver cholesterol levels in male rats	Werman MJ, *et al*., 2003
Polysaccharides and alginates	*Sargassum horneri*, Different red and brown seaweeds	• Potent anticoagulant • Decreases LDL-cholesterol in rats • Useful in the prevention of hyperlipidemia and thrombosis	Athukorala Y, *et al*., 2009
Amino sugar-containing fucansulfate	*Ecklonia kurome, Fucus* sp.	Anticoagulant and antithrombin activities	Nishino T, *et al*., 1994
Brown seaweed fucans	*Ascophyllum nodosum*	Anticoagulant	Chevolot L, *et al*., 1999
Marine algae	*Undaria pinnatifida* (Wakame)	Anti-arteriosclerotic Decreases the concentration of serum and liver triacylglycerol	Murata M and Nakazoe JI, 2001
Heparinoid-active sulphated polysaccharides	*Laminaria hyperborea*	Anticoagulant (sulfate-ester form)	Shanmugam M and Mody KH, 2009
Porphyran	Nori (The dried alga contains protein, ash, vitamins, and carbohydrate+Zn, Cu, Mn, and Se)	Regulates blood-cholesterol levels Decreases blood pressure	Noda H, 1993
Dipeptides	*Undaria pinnatifida*	Antihypertensive	Sato M, *et al*., 2002

Table 4: Nutritional summary for prevention of heart disease risk

Nutrients and their source	Chemistry and dose	Metabolism and pharmacokinetics	Therapeutic areas and use	References
1. Tea Source-*Camellia sinensis* (top two leaves and the bud)	• Polyphenols act as catechins • Dose: 5-100 mg/day of tea polyphenols	Tea polyphenols have low bioavailability due to their high molecular weights and a high number of hydroxyl substituents. The hydroxyl groups may hinder the absorption of the compounds across the gut lumen.	Cardiovascular, bone, skin and oral health, cancer prevention and weight management (antioxidant)	Mukhtar H and Ahmad N, 2000
2. Soy (Isoflavones) Source-Whole soybeans, soy sauce, tofu (soybean curd)	• Genistein (1-150 mg/100 g) • Daidzein (0.5-91 mg/100 g) • Glycitein, isoflavones (0.4 to 2.4 mg/g), Oestradiol (estrogens in humans)	In healthy individuals, an extract of soy did not induce the cytochrome P450 isoenzyme CYP3A49. *In vitro*, soybean products and an extract of hydrolyzed soybean, as well as soybean isoflavones genistein and daidzein, inhibited CYP2C9, and CYP3A49	Cardiovascular, mental, bone, women's and skin health, cancer prevention (antioxidant and estrogenic)	Dewell A, *et al*., 2006
3. Flaxseed Source-*Linum usitatissimum* L. (Linaceae)	• Seeds contain linolenic acid • Linoleic seeds also contain the lignans secoisolariciresinol and its diglucoside.	Administration of 10 g flaxseed to humans resulted in large increases in fecal lignan excretion, from 727 to 12,871 nmol/day.	Cardiovascular health, cancer prevention, women's health. (antioxidant and weakly oestrogenic)	Rowland I, *et al*., 2003

4. Coenzyme Q10 Source-(Fatty fish, cereals, poultry, and vegetables,	• It is an endogenously synthesized lipid-soluble antioxidant • Dose: 100-360 mg/day	In the gastrointestinal tract, the uptake of coenzyme Q10 is relatively slow and is dependent on postprandial. It is present in human plasma at a level of 1 mg/L.11	Cardiovascular health, cancer prevention, respiratory, skin and animal health (antioxidant)	Weber C, *et al*., 1997
5. Creatine Source-Synthesized in the kidney, liver, and pancreas	• It is also named as creatine monohydrate. • Red meat and fish contain 4-10 g/kg of creatine phosphate.	Plasma level of creatine is maximum within 2 hrs after ingestion of dose under 10 g but it takes 3 hrs or more when ingested more than 10 g. Clearance depends on both skeletal muscle and renal function.	Heart and neuromotor disorder, muscular dystrophy, Parkinson's disease, and Huntington's disease	Persky AM and Brazeau GA, 2001
6. Carnitine Source-Synthesized from lysine and methionine in the liver and kidney	Two isomeric forms, the D- and L-forms Dose: 2-4 g/day	Bioavailability: 54%-87%, depending on a food level, and the bioavailability from supplements (0.5-0.6 g) has been estimated to be 14%-18% of the dose.	Sports enhancement, cardiovascular and bone health, weight optimization, veterinary health	Kletzmayr J, *et al*., 1999
7. Lycopene Source-A natural red pigment found in plants, fruits, and vegetables like tomatoes	• It is closely related to beta-carotene and is thought to reduce the risks of coronary heart disease • Dose: 10-40 mg/day	Plasma concentrations ranging from 0.22 to1.06 μmol/L. After administration of tomato juice which contains high level of lycopene, peak plasma concentrations were reported from 24 to 48 hours, and elimination half-life was estimated to be 48-72 hours.	Cardiovascular disease and cancer prevention, especially prostate cancer.	Diwadkar-Navsariwala V, *et al*., 2003
8. Lutein source-Present in green vegetables, particularly spinach)	• Lutein (and zeaxanthin) • Dose: 10-40 mg/day	The bioavailability depends upon the chemical and physical nature of the food source, and co-consumed material, particularly the fat content.	Cardiovascular, eye, and skin health (antioxidant)	Alves-Rodrigues A and Shao A, 2004
9. Dehydroepiandrosterone Source-outer layer of the adrenal glands	• DHEA is converted to DHEAS, and further to androstenedione, and androstenediol, and testosterone. • Dose: 5-25 mg/day	It is an endogenous hormone synthesized and excreted mainly in the adrenal gland. The elimination half-life of DHEA is 15-38 minutes, and for DHEAS it is 7-22 hours. Oral absorption is excellent.	Cardiovascular and mental health, veterinary health	Pepping J, 2000
10. Policosanol/Octacosanol Source-Superficial fruit, leaves, and whole grains	• It is made up of a mixture of alcohols whose principal component is octacosanol. Triacontanol, as well as hexacosanol, are also present. • Dose: 100 mg/day	Absorption of octacosanol has been 'assumed' to range between 10% and 35%, and bioavailability ranges between 5% and 12%. It is unlikely that policosanol will metabolize or inhibit other drugs that are substrates of liver enzymes.	Cardiovascular disorders and also used in Parkinson's disease, and for enhancing athletic performance.	Lin Y, *et al*., 2004
11. Pycnogenol Source-Bark of *Pinus pinaster*	• Standardized water extract-flavonoid polyphenols and procyanidins, catechin, epicatechin. • Dose: 25-200 mg/day	Metabolites of procyanidins were identified after oral intake by humans, and maximum excretion was seen after between 8 and 15 hours, indicating slow absorption and metabolism.	Cardiovascular, eye, respiratory, and oral health (antioxidant)	Düweler KG and Rohdewald P, 2000
12. Melatonin Source-Bananas, tomatoes, cucumbers, and beetroots	• Melatonin (N-[2-(5-Methoxyindol-3-yl)ethyl] acetamide) is the primary hormone biosynthesized from the amino acid tryptophan • Dose: 0.3-25 mg/day	Oral doses of melatonin have a short half-life and are quickly cleared, and even very high nightly doses of 50 mg are cleared by the following morning However, after two weeks of high daily dosing, lipid storage occurs.	Cardiovascular health, cancer prevention, sports enhancement, sleep improvement, and bone health (antioxidant)	-
The legal classification of melatonin: In the UK, the Medicines and Healthcare Products Regulatory Agency (MHRA) has restricted to prescribe melatonin, available on a named patient basis only. There are no licensed products in the UK, so it is unlawful to promote melatonin. However, in the USA it may be sold as a food supplement, under the Dietary Supplement Health and Education Act of 1994. British residents can legally bring melatonin purchased in the USA home, for personal use.				

13. Resveratrol Source-Leaves, skins and petals of *Vitis vinifera*, and also in wines and grape juice	• It is a polyphenol found in grapes and the majority of the vine and wine products • Dose: 15-200 mg/day	After oral administration of 25 mg resveratrol to humans, the highest plasma concentrations were detected after 30 minutes, which returned to baseline after 2 hours. In other studies, the effect of resveratrol on *CYP1A2* was very small.	Anti-aging effects, antioxidant, oestrogenic, antiplatelet effects, cardiovascular diseases, including atherosclerosis.	Wolter F, and Stein J, 2002
14. Grape seed pro-anthocyanidin Source-Extract of *Vitis vinifera* L. (Vitaceae)	• Dimeric procyanidins have been classified as procyanidins B1, B2, B3, and B4 depending on the configuration of catechin and epicatechin subunits. • Dose: 1500 mg/day	The pro-anthocyanidins are poorly absorbed in the small intestine, and it is thought that ingestion results in metabolism by colonic bacteria. 3-Hydroxy-phenylpropionic acid has been identified as the major metabolite.	Promotes general cardiovascular health and skin health (antioxidant)	Ward NC, *et al*., 2004

Table 5: Descriptive interaction between essential nutrients and cardiovascular drugs

Nutrients+drug	Dose	Evidence-based drug interaction	References
Tea+alprazolam	Alprazolam 2 mg dose before and after decaffeinated supergreen tea extract.	• Alprazolam pharmacokinetics is not affected by green tea extract. • MOA-Catechins, at similar, doses, ↔ the metabolism of drugs	Donovan JL, *et al*., 2004
Tea+antiplatelets	Tea along with aspirin of 325 mg daily	No significant effect on platelet aggregation	Hodgson JM, *et al*., 2002
Tea+buspirone	4 capsules of green tea catechin (tea flavonoids) extract daily for 28 days	21% AUC reduced with a single dose of 10 mg buspirone	Chow HS, *et al*., 2006
Tea+cyclosporin or tacrolimus	-	• Cyclosporin levels are not significantly affected by Epigallocatechin gallate (green tea catechin). • It also seems to protect from renal damage induced by cyclosporin	Zhong Z, *et al*., 2006
Tea+flurbiprofen	-	• Infused black tea (Lipton Brisk tea) did not interfere with the elimination of the flurbiprofen half-life. • MOA-(Flurbiprofen (probe drug for CYP2C9 activity))-The pharmacokinetic interactions resulting from this mechanism of black tea and other CYP2C9 substrates is improbable.	Greenblatt DJ, *et al*., 2006; Dai YH, *et al*., 2003
Tea+piperine	Tea+piperine (500 micromoles/L)	• Piperine slightly increased the bioavailability of green tea Epigallocatechin-3-Gallate (EGCG) by inhibiting glucuronidation and gastrointestinal transit, • 30% increase in the AUC1-5.	Lambert JD, *et al*., 2004
Tea+irinotecan	-	• Pharmacological action of green tea catechin is inhibited due to the formation of active irinotecan metabolites. • There was no metabolism induction for CYP3A4 and the glucuronidation induction (UGT1A1) was small and variable.	Mirkov S, *et al*., 2007
Black tea	Black tea-150 ml, 10 women with (anaemia) and (without anaemia)	↓ in the absorption of radiolabelled iron by 59% in anaemic women) and by 49% in without anaemic women	
Green tea	37 mg catechins as green tea extract	Reduce iron absorption by 26%	
Tea+losartan	Subjects: 42 , 4 capsules for 4 weeks daily of green tea extract+25-mg losartanas	There is no expectation of interaction between decaf green tea extract and losartan.	Zijp IM, *et al*., 2000
Tea+warfarin	Tea (2 to 4 liters daily for one week)	↓ INR of warfarin from a range of 3.2 to 3.79 and 1.37	Parker DL, *et al*., 2009
Isoflavones+cardiovascular	-	In patients with angina pectoris, minimize activation of platelet surface. This indicates that kudzu may increase the risk of haemorrhage when used with antiplatelets or blood thinners. Caution is warranted for concurrent use.	Shaikh AS, *et al*., 2020

Isoflavones+digoxin	Biochanin A (100 mg/kg) of a 20 mg/kg dose of digoxin taken orally	↑ the AUC and maximum serum levels (75%). ↔ a terminal half-life and ↔ in mean residence time of digoxin	Peng SX, *et al*., 2006
Isoflavones+fexofenadine	Biochanin A (100 mg/kg)	Around 30 % and 57 % of oral bioavailability increased and peak plasma concentration of fexofenadine 20 mg/kg.	Peng SX, *et al*., 2006
Isoflavones+nicotine	Subjects: 7 healthy Japanese (non-smokers) Isoflavone tablet six times daily	There is around 24% ↓ in nicotine metabolism MOA: the metabolism of nicotine is slightly ↓ by Soya isoflavones due to CYP2A6 inhibition.	Nakajima M, *et al*., 2006
With paclitaxel	Genistein 10 mg/kg (orally)	Paclitaxel AUC is modest ↑.	Li X and Choi JS, 2007
Isoflavones+tamoxifen	Subjects: 17 women with confirmed breast cancer. Daily 200 mg isoflavone	No ↑ in the tumor over 2 to 6 weeks before the surgery	Messina MJ and Loprinzi CL, 2001
Isoflavones+theophylline	Subjects: 20 healthy non-smoking subjects, pre-treatment. 200 mg daidzein twice daily for 10 days+100 mg single dose	↑ AUC and half-Life of the disposal from approximately 9 hours to approximately 12 hours. The cytochrome P450 isoenzyme CYP1A2 of theophyllines appears mild to isoflavones.	Monostory K and Vereczkey L, 1996
Flaxseed+anticoagulant	Flaxseed oil-rich diet α-linolenic acid 20.5 g daily for 56 days	↔ significant effect on prothrombin times, bleeding times, or partial prothrombin times	Prasad K, 2009
Flaxseed+antidiabetics	68 patients+supplement containing 360 mg of flaxseed lignin	↔ Effect on blood-lipid profile, 0.1% ↓ of (HbA1c).	Lemay A, *et al*., 2002
Coenzyme Q10+piperine	Subject: 12 healthy subjects, piperine 5mg (Bioperine) with coenzyme Q10 90 mg.	↔ in the pharmacokinetics of coenzyme Q10 (AUC and maximum level or time to the maximum level)	(Itagaki S, *et al*., 2009; Badmaev V, *et al*., 2000)
Coenzyme Q10+warfarin	Coenzyme Q10 100 mg per day 4 weeks in 21 Warfarin stabilized patients	↔ In the INR or the required dose of warfarin.	Landbo C and Almdal TP, 1998
With aldosterone	Single-dose of coenzyme Q10	↑ the sodium reabsorption stimulated	Igarashi T, *et al*., 1975
Creatine+caffeine	500 mg/kg creatine supplement and 5 mg/kg caffeine capsules for 3 days daily	Lack benefits of creatine in exercises for the extension of the knee on 4th day. One subject experienced some GIT discomfort during use.	Zhou Q, Chowbay B, 2002; Vandenberghe K, *et al*., 1996; Steenge GR, *et al*., 2000
Lycopene+food	13 healthy+lycopene for 14 days as 300 g tomato soup and 60 g tomato paste.	↔ in the serum levels of lycopene between a high-fat monounsaturated-fat-enriched diet, and a high-carbohydrate low-fat diet.	Ahuja KD, *et al*., 2003
Lycopene+beta-carotene	A single dose of beta-carotene of 60 mg with lycopene (10 healthy subjects)	In comparison to lycopene administered alone, to significantly improve lycopene AUC by about 4-fold.	Johnson EJ, *et al*., 1997
With probucol	Lycopene + 500 mg probucol two times	Serum lycopene levels were further reduced by 30%.	Elinder LS, *et al*., 1995
Lycopene+sucrose polyesters	194 healthy subjects, the+Olestra 18 g daily	↓ serum levels of dietary lycopene up to about 30%. It decreases the synthesis of fat-soluble vitamins.	Koonsvitsky BP, *et al*., 1997
Policosanol+anticoagulants	Policosanol 200 mg/kg+warfarin 200 mg/kg for 3 days in rats.	• If policosanol did not increase the extension • Policosanol has caused bleeding time from warfarin	Carbajal D, *et al*., 1998
Policosanol+beta blockers	60 to 80 years age group taking beta-blockers+5 mg policosanol tablets daily	Decrease blood pressure after 1 year from about 141/83 mmHg to 131/81 mmHg, after 3 years decrease to 126/79 mmHg.	Castano G, *et al*., 2004
With Phenazone	Phenazone 10 mg/kg 25 mg/kg per day.	↔ Pharmacokinetics	Pérez-Souto N, *et al*., 1991

Policosanol+nitroprusside	Sodium nitroprusside+200-mg/kg policosanol (pre-treated)as single oral dose	↑ antiplatelet and hypotensive effect of sodium nitroprusside	Arruzazabala ML, *et al.*, 2001
Melatonin+benzodiazepines	16 healthy (55 years old), prolonged-release melatonin 2 mg with zolpidem (10 mg)	↑ impairment of cognitive function. Melatonin alone did not affect cognitive function. ↔ pharmacokinetic	(Otmani S, *et al.*, 2008; Golombek DA, *et al.*, 1992)
Melatonin+caffeine	Caffeine significantly ↑the levels of single doses of supplementary melatonin and reduces melatonin synthesis by contesting cytochrome P450 CYP1A2 isoenzyme metabolism.		Obochi GO, *et al.*, 2010
Melatonin+carbamazepine	Children with epilepsy undergoing carbamazepine monotherapy administered	↔ Serum levels of carbamazepine and its metabolite.	Gupta M, *et al.*, 2004
Melatonin+nifedipine	Melatonin immediate-release capsules 5 mg per night were given to 47 people with mild.	Systemic and diastolic blood pressure rose moderately (6.5 mmHg and 4.9 mmHg respectively), and the cardiac rhythm increased (3.9 bpm).	Lusardi P, *et al.*, 2000
Melatonin+oestrogens	In subjects who took a dual oral contraceptive, AUC and a maximum amount of a daily 6 mg dose of melatonin was about 4 times higher		Hilli J, *et al.*, 2008
Melatonin+propofol	IV propofol+3- or 5-mg+melatonin orally, 100 minutes preoperatively,	• Loss of eyelash reflex, was ↓ 15%. • Very small ↓ in the required dose of propofol	Turkistani A, *et al.*, 2007
Melatonin+psoralens	-	Methoxsalen and psoralenic 5-methoxy block melatonin metabolism and increase levels. Increased levels of 5-methoxy psoralen were demonstrated. Psoralens are effective cytochrome P450 CYP1A2 inhibitors.	Souêtre E, *et al.*, 1989
Melatonin+SSRIs	7 healthy subjects Dose: 40 mg citalopram	No effect on or excretion from the body of endogenous melatonin.	Foster BC, *et al.*, 2015
Melatonin+tobacco	8 tobacco smokers Dose: 25-mg dose melatonin	• AUC of melatonin was almost 3-fold higher. • Tobacco smoking ↓ melatonin levels.	Ursing C, *et al.*, 2005
With warfarin	-	Melatonin may ↑ or ↓ the INR in response to warfarin	Herxheimer A, *et al.*, 1996
Resveratrol+aspirin	Resveratrol+50 high-risk cardiac patients taking aspirin	Resveratrol significantly ↓ platelet aggregation	Stef G, *et al.*, 2006
Resveratrol+diclofenac	-	Reveratrol can be addictive with NSAIDs such as diclofenac sodium in some antiplatelet effects.	Yu C, *et al.*, 2003
Resveratrol+mephenytoin	-	• Resveratrol will affect the metabolism of mephenytoin. • It is used as a probe substrate for cytochrome P450 isoenzyme CYP2C19 activity.	Yu C, *et al.*, 2003
With paclitaxel	-	Resveratrol mildly impaired paclitaxel in rats and human liver microsomes.	Václavíková R, *et al.*, 2003
Grapeseed+vit C	Vitamin C alone	↓ Systolic blood pressure (1.8 mmHg)	Ward NC, *et al.*, 2005
With midazolam	Grapeseed extract+midazolam	No major impacts on midazolam pharmacokinetics.	Nishikawa M, *et al.*, 2004
Grapefruit+fexofenadine	-	For note, the AUC of Fexofenadine is mildly decorated by grapefruit juice and, to a lesser degree, by naringenin, a flavonoid of grapefruit.	Bailey DG, *et al.*, 2007
With calcium-channel blockers	12 healthy+ homogenised grapefruit extract from the segment free parts+felodipine	The AUC of felodipine ↑ by 3.2-fold (homogenised grapefruit) and 3.6-fold (extract)	Sica DA, 2006
Grapefruit+warfarin	A couple, well stabilized on warfarin, took a few drops of a grapefruit extract.	Hematoma was formed after another 3 days, and its INR was determined to be 7.9 and 5.1 INR (Standard deviation) with no sign of bleeding.	Peynaud D, *et al.*, 2007; Brandin H, *et al.*, 2007

Note: ↑: Increase; ↓: Decrease; ↔: No significant change; INR: International Normalised Ratio

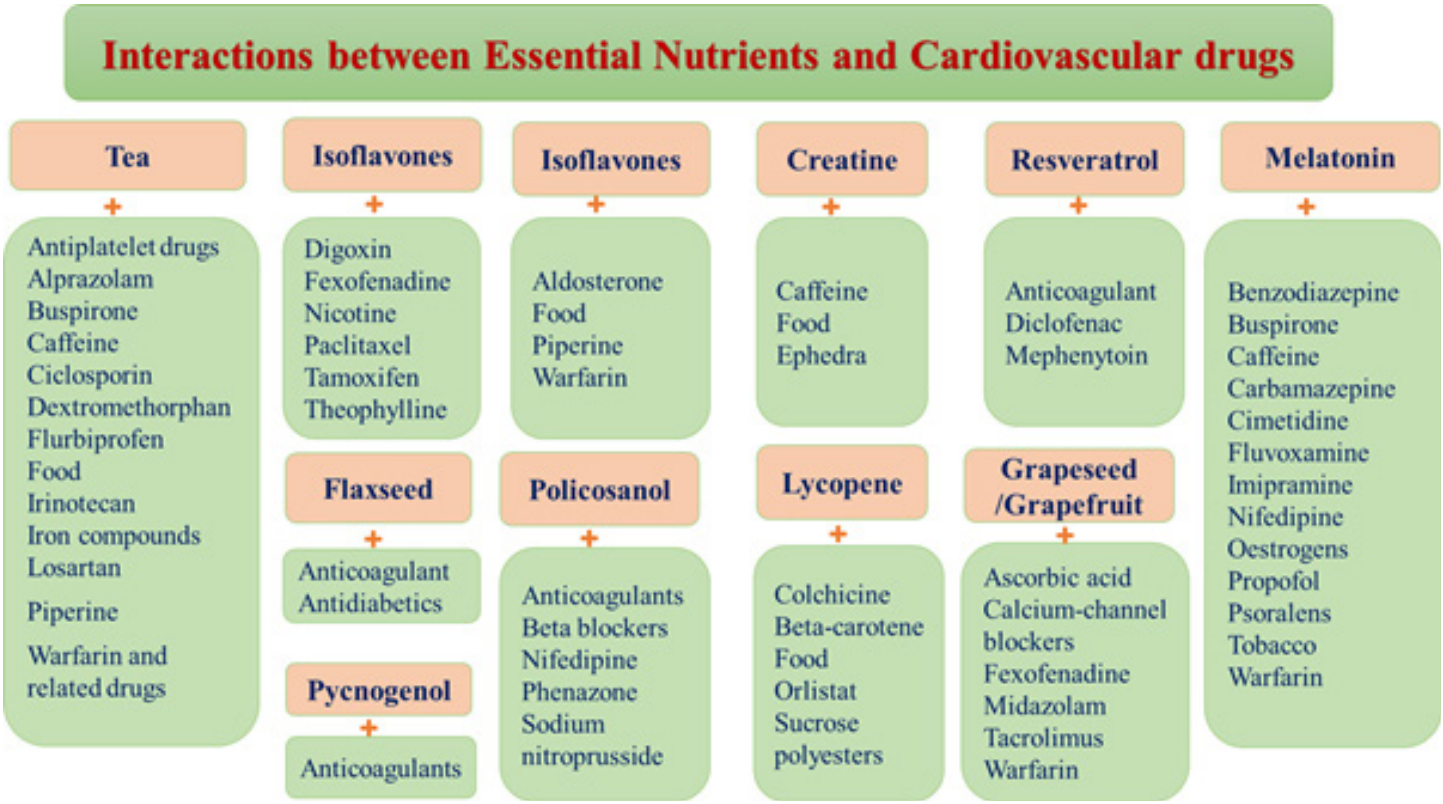

Figure: 4 Graphical representations of interaction between food, supplements and cardiovascular drugs

CONCLUSION

The findings of major clinical trials usually do not support the cardiovascular advantages of antioxidant vitamin or other EMN supplements, and recommendations typically prescribe improved ingestion of foods abundant in these ingredients, not particular additional supplements. Omega-3 PUFAs may be an exception and niacin has an effect on plasma lipids at pharmacological doses. In most cases, scientific test data is not adequate to support conclusive guidelines for nutrients used in CVD prevention or treatment. Concomitant use of nutrients, herbs, and conventional drugs may present with untoward events. The evidence available in the literature indicates various mechanisms through which this can occur. By interacting with conventional medication, nutrients may precipitate manifestations of toxicity or in the other extreme, therapeutic failure. Good knowledge of the potential of commonly consumed nutrients to interact with prescription medicines, irrespective of the nature of the evidence available, will equip health professionals in their practice. Apart from those demonstrated insignificant number of human subjects, not all reported interactions are clinically significant. As such, more clinically relevant research in this area is necessary. This review provides information on commonly used nutrients for cardiac health and their potentials for interactions within the levels of evidence currently available.

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