



The Impact of Antioxidant Diets, Nutraceuticals and Physical Activity Interventions in the Prevention of Cardiometabolic Diseases: An Overview

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Abstract

Hippocrates – Father of Medicine (ca 460-370 BC) – endorsed the curative effects of foods; he said: “Leave your drugs in the chemist’s pot if you can heal the patient with food”. This review focuses on the management of cardio-metabolic diseases (CMDs) with nutraceuticals and antioxidant diets such as *Allium sativum*, turmeric, soybean, peptides, phytosterols, resveratrol, polyphenolic substances etc. CMDs are a cluster of conditions linked to altered fat and carbohydrate metabolism as well as macro- and micro-vascular problems. CMDs cause severe pathophysiological and metabolic alterations in the body, resulting in the occurrence of chronic diseases like atherosclerosis, coronary heart disease and stroke, neurodegenerative ailments, fatty liver, kidney malfunction, hypercholesterolaemia, hyperlipidaemia, insulin resistance and some cancers, consequently imposing a very high economic burden on the healthcare costs. Currently used pharmacotherapies are not only expensive but also are associated with undesirable adverse events. Thus, there is an urgent need for affordable, cost-effective and alternative safe therapies for the prevention and management of CMDs. Holistic approaches targeted for health promotion and prevention of CMDs include the intake of antioxidant-rich diets, anti-inflammation wholesome foods and moderate physical activity (about 30 min/day). Such strategies will not only prevent obesity-related CMDs, type 2 diabetes mellitus (T2DM), coronary heart disease and stroke, but also will improve the quality of patient’s life and consequently reduce healthcare burdens. Nutraceuticals and probiotics exhibit anti-inflammation, anti-aging, anti-obesity and anti-diabetic effects, thereby reducing the adverse health risks associated with CMDs. Antioxidants protect cell membranes and DNA from excessive free radicals, which contribute to CMD related diseases. Physical exercise along with dietary interventions helps to mitigate oxidative stress, improve blood triglyceride levels, increase HDL-cholesterol and reduce LDL-cholesterol and reverse the biological markers associated with CMDs. Many studies have provided robust scientific evidence and demonstrated links between dietary interventions, nutraceuticals, probiotics, wholesome foods and physical activity for the prevention of CMDs. The major limitations in promoting nonpharmacological therapies for health and well-being benefits are a lack of public awareness and a paucity of clinical nutrition instruction for medical students on the merits of complementary methods for the prevention and management of CMDs. The goals of this review are to provide up-to-date knowledge about selected nutraceuticals, wholesome foods and physical activity in the prevention of CMDs and the underlying mechanisms associated with each intervention, which will ultimately improve patient’s quality of life and assist in reducing healthcare costs globally.

Key words: Cardiometabolic diseases; Cardiovascular diseases; Coronary heart disease; Hypertension; Antioxidant and anti-inflammation diets; Nutraceuticals; Physical activity.

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Introduction

The cardiometabolic diseases (CMDs) consist of a wide array of disorders characterised by abnormalities in glucose and fatty acid metabolism, which can lead to both systemic and localised vascular dysfunctions. CMD-induced pathophysiological changes cause hypertension, hyperlipidaemia, atherosclerosis, greater likelihood of developing coronary heart disease and stroke, non-alcoholic fatty liver, hyperglycaemia, insulin resistance, kidney dysfunction and some cancers.¹⁻⁴ The occurrence of non-communicable diseases (NCDs) like obesity, type 2 diabetes mellitus (T2DM), CMDs, neurological ailments, osteoarthritis and cancer are escalating all over the world. NCDs inflict a very high financial toll on the healthcare systems because prolonged hospital time is required for recovery, accompanied by high drug and physician expenses. It has been estimated that one in every three individuals suffers from CMDs worldwide⁵ and CMDs enhance the risk of cardiovascular diseases and neurological disorders such as dementia and cognition problems.⁶

Currently, CMDs are treated with pharmaceutical agents such as antihypertensives, antidiabetics and lipid-lowering drugs. However, these therapies are not only expensive but are also associated with undesirable adverse effects.⁷ Therefore, there exists an urgent need for cost-effective and alternative safe therapies for the management of CMD-related disorders. Some alternate strategies include dietary interventions (eg, lesser consumption of carbohydrates and saturated fat diet), weight reduction in obese patients through physical activity and lesser use of antihypertensive, antidiabetic and lipid-lowering drugs.⁷ Pharmaceutical therapies often target enzymatic pathways in patients. However, some drug therapies may produce undesirable side effects, thereby compelling the patients and the healthcare practitioners to make a risk-benefit analysis.⁸⁻¹² For example, switching over to angiotensin-converting enzyme (ACE) inhibitors and dose reduction of lipid-lowering statins for treating hypertension and reducing hypercholesterolaemia, respectively. The prolonged usage of ACE inhibitors is sometimes associated with adverse iatrogenic effects, including decreased kidney function, elevated potassium levels, hypotension, chronic cough, skin rashes, angioedema and foetal abnormalities due to oligohydramnios.¹³ The

most common side effects of cholesterol-lowering statins are drowsiness, insomnia, headache, muscle weakness muscle aches (myalgia) and flushing of the skin. Due to the occurrence of unwanted side effects of drugs, the usage of alternative remedies, eg, nutraceuticals and phytotherapies, antioxidant and anti-inflammation dietary interventions, functional foods, probiotics and physical activity have gained momentum for the management of CMDs.^{14,15}

It's now well recognised that wholesome foods, antioxidant and anti-inflammation diets can have a critical influence in the prevention of CMDs associated with T2DM and obesity. Lifestyle modifications such as smoking cessation, less alcohol consumption and moderate exercise (30 min/day) are significant contributors to the prevention of metabolic syndrome (MS), hypertension and some cancers. Obesity, T2DM and unhealthy dietary habits are considered the primary cause of CMDs and cardiovascular diseases (CVDs).¹⁶ The wide variety of risk factors associated with CMDs and CVDs are illustrated in Figure 1. The industrial revolution followed by the green revolution, agriculture mechanisation, urbanisation and technological advancements have profoundly altered the way we live and work, consume unhealthy processed foods and travel by car. Gadgets such as television, cell phones and tablets are frequently used for social and leisure activities. Less physical activity, night-time shift work, less sleep and less exposure to sunlight, intake Western-style diet and sugar-loaded drinks, saturated fat and fast-salty foods and unhealthy dietary habits contribute greatly to causing NCDs.¹⁷⁻¹⁹ Non-genetic factors involved in promoting obesity consist of overconsumption of carbohydrate-rich diets and lesser consumption of fibrous foods, as well as lesser expenditure of energy in the biochemical processes and the basal metabolic functions.²⁰ There is overwhelming evidence that wholesome foods and Mediterranean-type diet rich in fiber, nuts and seeds, omega-3 fatty acids, less red meat, low-fat dairy products and probiotics play a significant role in promoting healthy microbiota in the gastrointestinal tract and assist in the prevention of CMDs. Furthermore, nutraceuticals and antioxidant diets, consumption of fruits and vegetables also decrease insulin resistance and MS and consequently promote cardiovascular health.²⁰

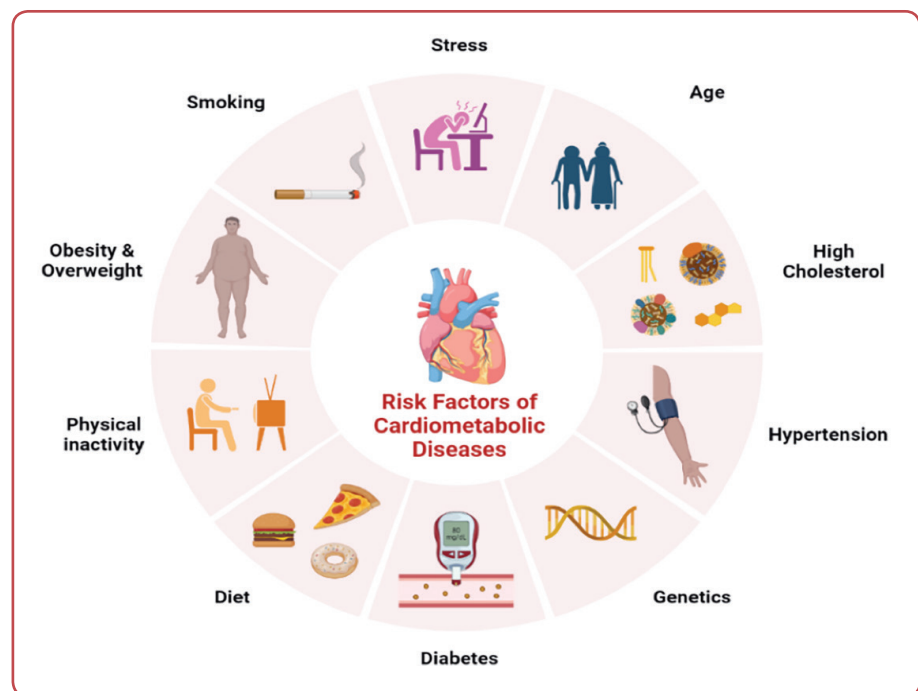


Figure 1: Risk factors associated with cardiometabolic and cardiovascular diseases

Many researches have shown that healthy eating habits and healthy dietary behaviour, as well as lifestyle modifications (eg, smoking cessation, low alcohol consumption, exercise) play a crucial role in the management and prevention of many nongenetic chronic illnesses. A number of studies have demonstrated a direct connection between the high incidence of CMDs and dietary habits, including high intake of ultra-processed foods, Western-style diets, foods and drinks spiked with sugar and high fat content and reduced consumption of fresh fruits and vegetables.²¹⁻²³ Antioxidant bioactive compounds present in wholesome foods have depicted a myriad of advantages, including anti-inflammation activity and protection against excessively produced free radicals which cause cell membrane injury and DNA damage.

The term “nutraceutical” refers to nutrient plus pharmaceutical that provides both therapeutic and health promotion advantages besides acting as food for energy.²⁴ Nutraceuticals are natural substances which are comprised of prebiotics, herbal remedies and plant-based substances with antioxidant and anti-inflammation properties, polyunsaturated fatty acids (PUFA) and culinary spices,²⁵⁻²⁷ thus offering an alternative means to confer therapeutic and health promotion activities and well-being objectives.²⁸ As a result, people are becoming more conscious about the consumption of high-quality wholesome foods, as well as doing physical exercise and smoking

cessation, which can collectively be beneficial in their quality of life, healthy aging and consequently prevention of non-communicable chronic diseases.²⁹⁻³¹

Nutraceuticals

As alluded to earlier, the term nutraceutical was coined by combining pharmaceutical and nutrient words. Nutraceuticals are referred to as substances/ingredients of natural origin that are found in foods or isolated from plants, chemically purified and concentrated for use in health and disease conditions, as well as for the prevention of chronic ailments.³² Therefore, the nutraceuticals exhibit both health protection and health promotion properties and can be used in the prevention and management of CMDs. They are generally recommended as part of the preventive strategy or treatment regimen for conditions such as hypertension, angina, arrhythmias, congestive heart failure (CHF) and hyperlipidaemias.³³ The subsequent sections of this review will discuss the mechanisms of action, efficacy and safety of delectated nutraceuticals that are efficacious in the prevention and management of CMDs. Table 1 summarises the results of clinical trials that have demonstrated the health advantages of nutraceuticals against the occurrence of CMDs. Additionally, Table 2 summarises the biological actions

Table 1: Questionnaire about knowledge and opinions about artificial intelligence

| N | Nutraceutical molecule | Description | Result | Reference |
|---|---|--|---|-----------|
| 1 | Omega-3 fatty acid | 11,324 participants were included in an open-label experiment and monitored for 3.5 years. | Fish oil consumption was connected to a 45 % decrease in sudden deaths and a 30 % and 20 % reduction in coronary and total mortality respectively. | [40] |
| 2 | Garlic | 13 placebo-controlled studies were conducted including 781 participants to understand the garlic supplementation effect on cholesterol levels. | A daily dose of standardised extract (600-900 mg) was shown to lower blood cholesterol levels by 0.41 mmol/L. | [41] |
| 3 | Garlic | Double-blinded, placebo-controlled study involving 51 subjects suffering from coronary heart disease. | 150 mg tablet twice a day for a year reduced CVD risk by 1.5 times in males and up to 1.3 times in females. The mode of action involved the reduction of LDL cholesterol levels. | [42] |
| 4 | Garlic | 30-month long; double-blinded, controlled, random study involving 90 subjects. | Supplementation of garlic leads to improvement in the cardiometabolic indices, intestine transit time and lipid accumulation product. | [43] |
| 5 | Garlic | Human pilot scale study involving 9 subjects. | Raw garlic juice was consumed by subjects for 7 days who were high trimethylamine N-oxide (TMAO) producers. The study showed a reduction in the formation of TMAO and an improvement in gut microbiota. | [44] |
| 6 | Dietary fibre | Ten prospective cohort studies including 245,186 women and 91,058 men followed up for 6 to 10 years were performed. | Every 10 g increment in overall dietary fibre content daily was correlated with a 27 % and 14 % decrement in the rate of coronary death and the risk of occurrence of all cardiac issues. | [45] |
| 7 | Soybean | A randomised controlled trial was conducted on 22 normolipidemic volunteers (5 males and 17 women). | HDL cholesterol and Apolipoprotein A-1 levels are increased by soy protein supplementation (56 mg). | [46] |
| 8 | Soybean | A study was conducted with 41 post-menopausal women and hyperlipidaemic men. | Soy foods minimize the chances of developing coronary artery disease (CAD) by reducing oxidised LDL cholesterol, blood lipids and blood pressure. | [47] |
| 9 | Probiotic and synbiotic supplementation | Controlled randomised trial involving 120 adults. | Both probiotic and symbiotic groups saw a decrease in hyperglycaemia. Further, hypertension and low HDL cholesterol were decreased in probiotic groups. | [48] |

CVD: cardiovascular disease; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; MS: metabolic syndrome; NO: nitric oxide;

and underlying mechanisms of different nutraceutical molecules.

a) Polyunsaturated fatty acids (PUFA)

PUFAs are present in eggs, fish meat and fish oil, which include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).³⁴ Multiple studies have been conducted to evaluate the preventive actions of PUFAs in CMDs. Omega-3 fatty acids have shown protection against cardiac arrhythmias by improving the electrical consistency of

myocardial cells and lengthening their relative refractory time.³⁵ They also have a protective potential against CMDs. In fact, scientific research has provided evidence that omega-3 fatty acids have a similar or better effect than statins in the prevention and treatment of hypercholesterolaemia.^{36, 37} Statins are known to substantially reduce the risk of stroke, myocardial infarction, coronary heart disease and overall cardiovascular risk, according to the results of a meta-analysis of 63 randomised controlled trials comparing

Table 2: Summary of biological actions and underlying mechanisms of nutraceuticals

| N | Nutraceutical | Action/Pathway | Mechanism | Reference |
|---|-----------------------------------|--|--|-----------|
| 1 | Omega-3 fatty acids (eg EPA, DHA) | Conversion to bioactive lipid mediators (eg, resolvins, protectins) via enzymatic pathways | Modulate inflammation, reduce oxidative stress, improve lipid profiles, lower blood pressure and reduce thrombosis, thereby preventing CVDs and MS. | [77–79] |
| 2 | Garlic | Cholesterol biosynthesis | Garlic compounds inhibit HMG-CoA reductase, a key enzyme in cholesterol biosynthesis, leading to reduced cholesterol synthesis and lower LDL cholesterol levels. | [80] |
| | | NO production | Allicin and S-allyl cysteine present in garlic enhances the production of NO in endothelial cells, which promotes vasodilation and helps maintain vascular health. | |
| | | Blood pressure regulation | By increasing NO production, lowering oxidative stress and blocking the activity of ACE, a crucial blood pressure regulator, allicin and S-allyl cysteine, two compounds found in garlic, lower blood pressure. | [81] |
| | | Antioxidant enzymes | Superoxide dismutase (SOD) and catalase, two antioxidant enzymes that guard against oxidative stress-related cardiovascular damage, are upregulated by allicin and allyl sulphides. | [82] |
| 3 | Dietary fibres | Anti-inflammatory effects | Fibers can have anti-inflammatory effects by modulating the production of inflammatory markers and cytokines, such as interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α), which are implicated in CVDs. | [83] |
| | | Modulation of gut microbiota | Fibers can modulate the composition and activity of gut microbiota, producing short-chain fatty acids (SCFAs), which have been associated with improved cardiovascular health through various mechanisms, including reduced inflammation and improved lipid metabolism. | [84] |
| | | Blood glucose | Fiber-rich diets, particularly those high in insoluble fibres, can slow down the digestion and absorption of carbohydrates, improving glycaemic control and reducing the risk of developing T2DM, a major risk factor for CVDs. | [85] |
| 4 | Soybean | Reduction of LDL-cholesterol | It has been demonstrated that soy protein, especially isoflavone-rich soy protein, lowers total and LDL cholesterol levels in both human and animal models. Soy decreases bile acid and cholesterol absorption from the gastrointestinal tract, raises bile acid excretion and improves liver LDL receptor activity and cholesterol production, leading to an increase in the elimination of cholesterol from the blood via the LDL receptor. | [86] |
| | | Antioxidant action | Since soy isoflavones function as antioxidants, they lessen the likelihood that LDL cholesterol may oxidise. This is crucial in lowering the risk of CVDs and atherosclerosis. As measured by indicators of lipid oxidation such as 8-epi prostaglandin F2 and thiobarbituric acid reactive compounds, it enhances the LDL's resistance to oxidation. Additionally, it increases the overall antioxidant capacity and, specifically, the alpha-tocopherol level in serum and liver, supporting the body's natural antioxidant defence. | [86] |
| | | Faecal excretion of bile acids | Soy protein has been shown to increase faecal excretion of bile acids, which may contribute to the cholesterol-lowering effects of soy. Higher faecal steroid excretion has been observed in isoflavone-rich soy protein compared to isoflavone-depleted soy protein. | [86] |
| 5 | Peptides | Competitive inhibitor of ACE enzyme | Inhibit ACE, a major target for developing antihypertensive agents, leading to decreased blood pressure. Up-regulate expression of ACE2, suppress inflammation, increase NO-mediated vasodilation and improve endothelial function, contributing to antihypertensive activity. | [87] |
| | | Regulation of blood pressure | Increase plasma levels of SOD and catalase, decrease total plasma level of peroxide and reduce blood pressure. | [87] |

| | | | | |
|---|------------|---|---|------|
| 6 | Prebiotics | Reduction of serum cholesterol | Prebiotics have been demonstrated in hypercholesterole animal models and human trials to lower total serum cholesterol levels. This is done through up-regulating the genes that make bile and produce cholesterol, as well as by increasing caeca digest, which may improve the body's ability to eliminate cholesterol. | [88] |
| | | Reduction of liver triacylglycerol accumulation | It has been shown to reduce triacylglycerol accumulation in the liver, which is often associated with obesity, a risk factor for CVDs. This suggests that prebiotics may have anti-obesogenic effects, potentially reducing the risk of CVDs in obese individuals. | [88] |
| | | Reduction of liver triacylglycerol accumulation | Prebiotics' potential for preventing and treating hypertension, a major CVD risk factor, is still being researched. However, prebiotics have been suggested to have potential blood pressure-lowering effects, which may contribute to the prevention of CVDs. | [88] |
| 7 | Prebiotics | Reduction of cholesterol levels | Probiotics, particularly <i>Bifidobacterium</i> species, reduce cholesterol levels <i>via</i> various processes. This includes bile acid amide bond hydrolysis, which results in the release of primary bile acids that are easily ejected from the gastrointestinal system, as well as cholesterol assimilation or precipitation in the gut, which reduces its absorption into the blood. In hypercholesterolemic adults, probiotic supplementation has been demonstrated to considerably decrease total and LDL cholesterol levels. | [88] |
| | | Improvement of vascular endothelial function | Some probiotics, such as <i>Lactobacillus plantarum</i> 299v, have been shown to improve vascular endothelial function, which is important for maintaining healthy blood vessels. This is performed by modulating the genes involved in intestinal cholesterol transport and liver cholesterol homeostasis. | [88] |
| | | Oxidative stress and inflammation reduction | Probiotics, such as <i>Lactobacillus</i> and <i>Bifidobacterium</i> species, have been found to suppress lipid peroxidation and the formation of reactive oxidative species (ROS), which may assist in alleviating oxidative stress and inflammation, both being prominent in CVDs. | [88] |

CVD: cardiovascular disease; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; MS: metabolic syndrome; NO: nitric oxide;

the action of statins and omega-3 supplements on cardiovascular events. On the other hand, as compared to the control group, only omega-3 supplementation significantly decreased the risk of myocardial infarction and coronary heart disease (CHD). Furthermore, when compared to omega-3 supplements, pravastatin and atorvastatin were found to be more effective in reducing the risk of CHD, myocardial infarction and overall CVDs. Therefore, omega-3 dietary supplements may not be as effective in preventing CVDs as pravastatin and atorvastatin.³⁸ There are three omega-3 fatty acid supplements currently marketed: namely, ethyl ester of omega-3 fatty acids, primarily EPA and DHA; ethyl eicosapentaenoic acid (IPE), the ethyl ester of EPA; and omega-3 carboxylic acids, a combination of long-chain omega-3 fatty acids in the form of free fatty acids: EPA and DHA make up the bulk of this mixture.³⁹

b) *Allium sativum*

Numerous biological properties like anti-hyperlipidaemic, anti-diabetic, anti-hypertensive and

immunomodulatory actions have been attributed to *Allium* species and highlighted by research studies.⁴⁹ To investigate the anti-hypertensive activity of garlic, a clinical trial was done in 56 CAD patients given garlic powder pills for three months. The placebo group experienced a significant increase in both systolic and diastolic blood pressure. On the other hand, the garlic supplementation group showed a significant decline in systolic blood pressure, especially in hypertensive patients. In view of these findings, garlic-based therapy can successfully reduce blood pressure in CAD patients, making it a safe adjunct therapeutic option for the high-blood pressure population.⁵⁰ Another randomised single-blinded and placebo-controlled trial demonstrated the anti-hyperlipidaemic action of garlic in 70 recruited patients with T2DM and dyslipidaemia. Garlic supplementation (300 mg tablets, twice a day) markedly improved the lipid profile. The experimental group subjects experienced considerable reductions in total and LDL cholesterol, as well as slightly high HDL cholesterol.⁵¹ A similar outcome

was found in a clinical trial involving 150 hyperlipidaemic patients. Results of the six-week trial pointed to a considerable drop in total and LDL cholesterol as well as an increase in HDL cholesterol.⁵² Both studies revealed marked beneficial impact of garlic products intervention in treating hypercholesterolemia. A very recent study also reported the beneficial actions of allicin in a preclinical model of metabolic syndrome. Weight increase, blood pressure, glucose intolerance and kidney damage markers were significantly reduced after allicin treatment. It was noted that the kidneys' inflammation and oxidative stress were also decreased. The authors concluded that these positive effects of allicin were mediated *via* the Nrf2 pathway.⁵³ Garlic produces antihyperlipidemic action by increasing the elimination of end products of cholesterol in the faces and decreasing endogenous cholesterol production. These actions markedly improve HDL : LDL ratio.⁵⁴ The phytochemical makeup of garlic could be a highly promising therapy for treating various cardiovascular conditions. Organosulfur-containing components are the main bioactive compounds present in allicin and alliin.⁵⁵ Thus, garlic's cholesterol-lowering ability has been linked to different organosulfur compounds as well as to a range of steroidal saponins. When the bioactive components of garlic: namely allicin and alliin are preserved from the biodegradation action of stomach acid, they can invoke additional beneficial effects to lower cholesterol levels.⁵⁶ Further research is needed to validate these findings and explore the pharmacological activities of *Allium* species bioactive compounds for the prevention or mitigation of CMDs and CVDs as well as determination of optimal therapeutic doses, efficacy, mechanisms and long-term safety.

c) Dietary fibres

Insoluble dietary fibres lower the risk of colon cancer and inflammatory pathology of the colon called diverticulitis, whereas soluble fibres considerably reduce serum cholesterol concentration, thereby lowering the risk of CVDs.^{57, 58} It has been reported that the insoluble flaxseed dietary fibre contains 6 % mucilage, which helps to reduce CHD risk.⁵⁹ Dietary fibres not only protect against CHD by reducing cholesterol levels, but also lower plasma triglyceride levels and high blood pressure, as well as help to stabilise postprandial blood glucose levels.⁶⁰ A number of studies have shown that dietary fibres adsorb bile acids and inhibit fat absorption from the gut and also promote healthy microflora in the gastrointestinal tract.^{61, 62}

d) Soybean

Soybeans have a wide variety of nutrients, while the two that have received the most focus include soy isoflavones and soy proteins.³³ Soybean isoflavones decrease LDL-cholesterol oxidation, prevent atherosclerosis and enhance vascular responsiveness.⁶³ According to Hermansen et al, high concentration of soy phospholipids, fibres and isoflavones not only lower LDL-cholesterol, improve LDL- : HDL-cholesterol ratio, triglycerides and total cholesterol levels by 15 %, 20 %, 6 % and 10 %, respectively; but also increase HDL-cholesterol by 5 %.⁶⁴

e) Peptides

Casein and whey proteins present in milk are rich in ACE inhibitor peptides and their intake is linked with the improvement of coronary heart disease.⁶⁵ Arginine is found in high concentrations in vegetable proteins. L-arginine serves as a precursor for nitric oxide synthase enzyme, enhances the production of nitric oxide (NO), which acts as a vasodilator and also contributes to the improvement of coronary vessels sympathetic responses. According to Palloshi et al, hypertensive and angina patients may benefit by taking L-arginine orally.⁶⁶

f) Prebiotics and probiotics

The consumption of prebiotics improves the composition of the intestinal microflora, leading to the predominance of certain gut bacteria that are beneficial for health and well-being. The beneficial bacteria include *Lactobacilli* and *Bifidobacterium* species. The prebiotics supplements enhance good gut microbes in the host, improve immune function and assist to prevent serious illnesses like cancer and CVDs.⁶⁷ Prebiotics containing nondigestible oligosaccharides promote healthy intestinal microbiota.^{68, 69} Probiotics when consumed in adequate amounts, have an advantageous influence on the host's health.⁷⁰ Probiotics from fermented dairy products cause decrease in blood cholesterol levels, whereas prebiotics with non-digestible fermentable carbohydrates can lower triacylglycerol levels. It has been reported that *Lactobacillus acidophilus*, *Lactobacillus bulgaricus* and *Bifidobacterium bifidum* significantly decrease cholesterol in the body.^{71, 72} Some investigators have suggested that the consumption of *Lactobacillus* and *Bifidobacterium* containing probiotics can help to reduce the incidence of CHD, stroke, hypertension and improve cholesterol and triglyceride levels.³³

g) Phytosterols

Since phytosterols have closely resembling chemical structures with cholesterol, phytosterols compete for the absorption of cholesterol in the small intestine and consequently retard the systemic bioavailability of cholesterol and its liver uptake, resulting in the lower levels of cholesterol in the bloodstream.⁷³ Consumption of plant

sterols were found to reduce LDL-cholesterol by 8-15 %.⁷⁴ Some studies found that dietary intake of 2-3 mg of plant sterols or stanols/per day can markedly decrease LDL-cholesterol levels by 9-20 %.⁷⁵ A number of investigators have suggested that phytosterol-ester from margarines could be used as statin replacement therapy and fibrate-based hypercholesterolemia.^{75, 76}

Antioxidant diets

Among other factors, oxidative stress and inflammation have been reported to be involved in the initiation and development of different chronic diseases, including cancer, atherosclerosis, diabetes, cardiovascular and neurodegenerative diseases. Antioxidants are polyphenolic substances

that include catechins, flavonoid glycosides, isoflavones and anthocyanins. Polyphenols are bioactive chemicals that have anti-inflammatory, anti-aging, anti-diabetes and anti-cancer properties.⁸⁹ The influence of flavonoids on arachidonic acid metabolism has been linked to their ability

Table 3: Clinical trials done with different antioxidant compounds

| N | Compound | Description | Result | Reference |
|---|--|---|---|-----------|
| 1 | Red wine (Resveratrol) | 15 CAD-suffering individuals were involved. | Purple grape juice or red wine consumption provided greater protection against oxidation of LDL-cholesterol as well as better endothelial function. | [106] |
| 2 | Mixture of turmeric (<i>Curcuma longa</i>) and <i>Spirulina maxima</i> | In a study involving patients with abdominal obesity was administered with 156.6/266 mg of Turmeric (<i>Curcuma longa</i>). <i>Spirulina maxima</i> for 12 weeks. | Patients who took Spirulina supplements had spiked serum levels of antioxidants than those who took a placebo. | [107] |
| 3 | α -Carotene and β -Carotene | A population-based trial including 392 tobacco users was conducted to assess the link between blood levels of antioxidants and atherosclerotic risk. | An inverse relationship was identified between α and β -carotene and atherosclerosis. | [108] |
| 4 | Ascorbic acid | A "Coronary Artery Risk Development in Young Adults" (CARDIA) study involving 2637 individuals. | Ascorbic acid levels in the blood were discovered to be inversely correlated with calcium in the blood arteries, a key sign of atherosclerosis. | [109] |
| 5 | Lycopene | A randomised trial involving 20 males and 4 females. | Supplementing lycopene decreased levels of total and LDL cholesterol. | [110] |
| 6 | Cocoa | A meta-analysis of data from 12 trials that explored the positive benefits of cocoa on cardiometabolic biomarkers in T2DM. | Cocoa-rich products lead to a reduction in LDL cholesterol, c-reactive protein, triglycerides and blood glucose in the long term. | [111] |
| 7 | <i>Camellia sinensis</i> capsules | The randomised, placebo-controlled and double-blind study which included 111 individuals. | <i>Camellia sinensis</i> capsules lowered blood pressure, LDL cholesterol, oxidative stress and a marker of chronic inflammation which are risk factors for CVD. | [112] |
| 8 | Coenzyme Q10 (CoQ10) | The meta-analysis study comprised 12 studies involving a total of 650 individuals suffering from diabetes complications and MS. | It has been demonstrated that CoQ10 reduces total and LDL cholesterol levels, which are significant CVD risk factors. Additionally, it has been hypothesised that CoQ10 may enhance vascular tone and endothelial function. | [113] |

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|----|-----------------------|---|--|-------|
| 9 | Amino acid L-arginine | The randomised, controlled, single-blind study involved 90 individuals who were obese. | L-arginine supplementation led to significant reductions in anthropometric variables (such as BMI, WC, TS and SS), blood pressure levels (SBP, DBP), FBS, HbA1c, LDL and MDA, as well as significant increases in HDL. Additionally, the intervention group's TG and TC levels were substantially reduced. | [114] |
| 10 | Quercetin | An evaluation of the impact of quercetin supplementation on lipid profiles and inflammatory markers in patients with MS and associated illnesses using data from 16 randomised clinical trials. | Total and LDL cholesterol and C-reactive protein were considerably lowered by quercetin administration. | [114] |

CVD: cardiovascular disease; CAD: coronary artery disease; BMI: body mass index, WC: waist circumflex; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBS: fasting blood sugar; MDA: malondialdehyde; TG: triglyceride; TC: total cholesterol; T2DM: type 2 diabetes mellitus;

to reduce the risk of CVDs.⁹⁰ Table 3 summarises the results of clinical trials and the beneficial effects of antioxidants against the occurrence of CMDs.

The free radicals play a vital part in the life of all organisms through their involvement in cell-cell communication and cell signal mechanisms. However, the unabated excessive production of reactive oxidative species (ROS) can lead to the oxidation of biomolecules (eg, nucleic acids, lipids and proteins) or the activation of proinflammatory signalling pathways, resulting in the activation of several transcription factors or the dysregulation of gene and protein expression followed by cell injury or cell death. Excessive ROS can be generated in the human body by mitochondrial damage, oxidative stress, dysregulation of basic metabolic functions, diabetes mellitus, obesity, as well as external factors such as cigarette smoking, X-rays, air pollution, ozone and industrial toxins.⁹¹ Increased production of ROS has been linked to the development of several chronic illnesses, including cancer, cardio-respiratory disorders, dementia and Alzheimer's disease, osteoarthritis and inflammatory bowel disease (IBD). Under normal physiological conditions, ROS are scavenged by endogenous antioxidants (eg, glutathione, dismutase enzyme, vitamins, minerals). Antioxidant deficiency combined with starvation makes people more susceptible to oxidative stress, thereby increasing the risks of CMDs, CVDs and some cancer types. The regulation of metabolic processes essential to the proper functioning of body organs is dependent on the presence of dietary antioxidants, amino acids, vitamins (A, C, D), trace metals (Zn, Cu, Se) and synthesis of glutathione. The multifaced advantages of antioxidant diets in health and disease have been reported by many clinical investigations because the dietary antioxidants mitigate the oxidative

stress and prevent the cellular damage caused by the highly reactive free radicals.⁹²

Antioxidant flavonoids are abundantly found in green and black teas, fresh fruits and vegetables and red wine.^{54, 93} Ignarro et al observed that lycopene present in tomatoes can decrease the oxidation of LDL-cholesterol in the blood stream.⁹⁴ Furthermore, lycopene consumption was found to be inversely related with the occurrence of CVDs.^{95, 96} Another study by Vita revealed that higher intake of polyphenols was associated with the decreased risk of CVDs.⁹⁷ Polyphenols were also reported to exert anti-tumour activities against prostate, larynx, lung, colon, tongue, gastric and breast cancers.^{98, 99} Foods rich in antioxidants, such as spirulina and turmeric play an important preventive role in the management of CMDs by curtailing the metabolic processes that trigger their onset.¹⁰⁰

To determine the effects of polyphenol supplementation in combination with calorie restriction and physical activity on body weight and fat deposition, body mass index (BMI) and waist circumference in overweight and obese persons, Llahá et al examined the findings of 15 randomised clinical studies. The results of these studies showed that consumption of isoflavone supplements helped non-Asian postmenopausal women to lose weight and more fat while exercising, thereby suggesting that intake of polyphenol supplements may have a positive health effect.¹⁰¹ An extensively researched flavonoid/flavonol for its anti-inflammatory properties is juglanin found in *Polygonum aviculare*. It was found that juglanin exerts its anti-inflammatory activity by blocking the TLR4/MAPK/NF- κ B pathway, which decreased the production of TNF-, IL-1 and IL-6.^{102, 103} Juglanin also reported to decrease the necrosis and excessive permeability of the blood-

brain barrier in the ischaemic condition of the brain by interfering with the vascular endothelial growth factor (VEGF) and VEGFR2 (VEGF-receptor 2) pathway.¹⁰⁴ Sun et al investigated the amelioratory effects of juglanin in myocardial injury and apoptosis of cardiomyocytes and found that it suppressed the inflammatory response after myocardial infarction by inactivating the MAPK pathway.¹⁰⁵

Physical activity

Physical activity refers to the general movement of the body in different situations and settings. Physical exercise provides multiple health advantages, including lower the risk of CVD related morbidity and mortality, prevent obesity and T2DM, improve cholesterol and lipid levels, reduce hypertension and coronary heart disease, decrease the risks of prostate, colon and breast cancer, reduce stress and enhance brain functions.^{116, 117} Beneficial neurological/psychological health outcomes have also been reported in several epidemiological and clinical investigations, that physical exercise can reduce stress and depression, enhance cognition, lower the risk of dementia and promote bone health.¹¹⁸ Physical exercise reduces the incidence of cardiometabolic illness.¹¹⁹ Regular physical exercise can lower diastolic and systolic blood pressure, with data supporting the advantages of both moderate-intensity (such as walking) and strenuous activity.¹²⁰ According to Carnethon et al, physical activity and aerobic exercise are inversely related to the development of hypertension and coronary heart disease risk. They found nearly 34 % reduction of hypertension in 4,618 men and women involved in the physical activity experiment.¹²¹ Excessive amount of systemic cholesterol as well as pathophysiology of atherosclerosis can also be reduced by physical activity.¹²² Intense physical exercise has been linked to the improvement of cholesterol levels by boosting the concentration of HDL-cholesterol while preserving and balancing elevations in triglycerides and lowering LDL-cholesterol.^{123, 124} Regular physical activity can reduce body weight and waist circumference in overweight and obese people and significantly reduce the incidence of cardiometabolic syndrome.¹²⁵ A comparative study involving 70 younger and 43 older (> 65 years) individuals was performed where the intricate relationship between physical activity and cardiometabolic

disease-causing risk factors was determined.¹²⁶ Another cohort study involved 24,960 respondents of at least 35 years suffering from diabetes, hypertension and/or heart disease. Out of these, 52 % of adults were victims of cardiometabolic diseases and were not physically active in their daily life and 34 % were residents of least activity-friendly areas, thus proving the importance of physical activity.¹²⁷ Similarly, another cohort study involving 341,331 participants suggested the importance of physical activity amongst other factors for the survival of both men and women suffering from cardiometabolic disorders.¹²⁸

Concluding remarks and future strategies

In this comprehensive review, efforts have been made to emphasise the significant roles of nutraceuticals, phytosterols, soybeans and polyphenolic diets containing high amounts of antioxidant and anti-inflammatory compounds as well as omega-3 PUFAs, which can help in preventing obesity, T2DM, CHD, CMD, CVD and other chronic non-communicable illnesses.

There is an upward trend of sedentary lifestyles among all age groups and genders, especially in the urban areas of India and other developing countries, along with the growing consumption of sodium chloride salt and sugar-loaded drinks, fatty food and unhealthy dietary habits.¹²⁹ The sedentary lifestyles have contributed to the high occurrence of obesity, T2DM and greater prevalence of CMDs, CVDs and NCDs. This review emphasises the impact of nutraceuticals, wholesome foods, probiotics and physical activity as cost-effective measures to counter the increased occurrence of cardiometabolic problems and associated disorders. Nutraceuticals are useful in risk management and prevention of CMDs like hypertension, CHF, hyperlipidaemias and coronary ailments. Antioxidant diets help to counter the oxidative stress and ROS-induced cellular damage by mopping ROS, as well as by interfering with various metabolic pathways and arresting the oxidative stress cycle, thus exhibiting properties like anti-inflammatory, anti-cancer, anti-obesity and anti-aging effects.¹³⁰ Physical exercise and wholesome diet interventions have an additive or synergistic actions in controlling conditions

like obesity, insulin resistance, stimulation of immune function, reduction of hyperglycaemia and hypercholesterolemia and consequently reducing the risk of CMDs.¹³¹

Evidence is now emerging that perturbation of gut microbiota can lead to an increased permeability of gut epithelium and leakage of microbial toxins into the systemic circulation, thus becoming a trigger for chronic NCDs ranging from IBD, CMD, CVD, T2DM, obesity and neurological illnesses. The consumption of fermented dairy products, including prebiotics and probiotics help to restore healthy microbiota in the host's gut and consequently reduce the risk of metabolic conditions, atherosclerosis and NCDs.

Nevertheless, the most important factor is to increase public and healthcare providers awareness regarding the pivotal role of nutraceuticals, dietary supplements, antioxidant-rich diets and physical activity in the prevention of CMDs, CVDs and NCDs. National policy guidelines can be developed which should include public health policies to promote educational settings to incorporate physical activity along with healthy dietary habits. In addition, national programs should be developed to enhance awareness among the physicians and general public regarding the important roles of physical activity and lifestyle modifications in the prevention of CMDs and CVDs at the primary healthcare levels. There is a large gap between scientific proof regarding these factors, the public health needs and implementation. The important task is to figure out how to translate the laboratory research findings into the successful public health and education programs. The public awareness and education strategies developed should comprise holistic approaches tailored towards the country's vegetarian and non-vegetarian populations. Hence, physical activity, dietary interventions and smoking cessation are needed to be prioritised as part of the CMD/CVD prevention agenda.¹³² In addition, medical students should be taught about the role of clinical nutrition and the merits of complementary methods for the prevention and management of NCDs, CMDs, CVDs etc.

Numerous epidemiological studies, meta-analysis, clinical trials and experimental findings have unequivocally shown the beneficial effects of dietary interventions, quitting cigarette smoking

and low alcohol consumption, healthy dietary habits and lifestyle modifications can improve overall health and well-being and reduce the risk of CMDs, CVDs, and NCDs. Also, lesser intake of sugar loaded drinks, carbohydrate containing deserts and processed foods, less red meat, low fat dairy products, and heart healthy diets can reduce the risk of CVDs by about 75 % to 80 %. Before some of the significant underlying causes of CVDs substantially affect an individual or a population at large, preventive interventions against CVDs must be directed at the primary health promotion level. Such preventive measures would not only assist in lowering hospital and medicine expenditures that burden the healthcare sectors of developed and developing nations, but will also reduce workforce absenteeism.¹³³

Recently Lee et al did meta-analysis of a large study sample comprised of 1,561 healthy men of middle ages (mean age 53-years) and reported that men with anxiety, intense worry and mood disorders are more prone to high incidence of cardiometabolic diseases such as CHD, stroke, hypertension and diabetes at earlier age and remain on a stable trajectory of heightened risk into older age. The authors suggested that assessment of cardiometabolic and psychological risk factors earlier in life would be helpful to reduce early morbidity and mortality caused by CHD and CVD.¹³⁴ The authors of this review propose that physical activity or exercise therapy and intake of wholesome foods, probiotics and omega-3-PUFA and avoidance from substances of abuse, would be impactful in treating neurotic and worrisome individuals with depression and anxiety disorders. Such approach will not only be cost-effective in treating mental disorders (depression, anxiety, mood swings), but also reduce the adverse reactions caused by antipsychotic and antidepressant drugs.

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Conflict of interest

None.

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