

INTEGRATIVE MEDICINE FOR PREVENTION AND TREATMENT OF CARDIOVASCULAR AND METABOLIC DISEASE

A therapeutic outline

This therapeutic outline provides an introduction to a variety of integrative medicine therapies that have been used and researched in the management of cardiovascular and metabolic diseases. This includes treatments with either nutraceuticals¹ or herbal medicine monotherapies² or where these are used adjunctively with conventional medical treatments. Mind-body, manual, lifestyle, and other traditional therapies are also reviewed.

The outline has been drafted by experts in the field. However, it is not meant to be an exhaustive review of scientific evidence, such as a systematic review or meta-analysis, which is not its purpose. This outline provides a description of the therapy and a brief narrative review of the emerging evidence considered by the researchers at NICM Health Research Institute to be important science being undertaken in the area of integrative medicine for prevention and treatment of cardiovascular and metabolic diseases.

Why people use integrative medicine for cardiovascular and metabolic diseases

The term 'cardiovascular disease (CVD)' refers to a group of conditions that affect the heart and blood vessels including diseases such as hypertension, atherosclerosis, stroke, coronary and peripheral artery disease, and vascular diseases.(1) CVD accounts for 31.5% of yearly deaths worldwide.(2) There are multiple environmental and genetic risk factors which increase the risk for CVD including calorie dense and nutritionally poor diets, physical inactivity, excessive smoking or alcohol consumption and obesity.(3)

The term 'metabolic syndrome' refers to a group of risk factors or conditions that often occur together and increase a person's risk of developing cardiovascular and metabolic diseases such as non-alcoholic fatty liver disease and type 2 diabetes.(4) These risk factors or conditions include hypertension, insulin resistance, central obesity, and abnormal circulatory lipid levels.(5) Approximately one in three adults in Australia suffer from metabolic syndrome,(6) however the prevalence has been shown to vary between countries.(7-9) While lifestyle therapies including diet modulation and increased physical activity remain cornerstone therapies for achieving weight loss and the management of obesity-related disease,(10-14) many people with CVD use complementary medicine (CM) to help manage their conditions.(15)

¹ Nutraceuticals are nutrient-based natural products which are produced via pharmaceutical good manufacturing practice, standardised and optimised.

² A monotherapy describes a treatment that has only a single active ingredient. The single active ingredient could be a medicine or a vitamin or a single herbal ingredient.

An Australian study investigating the use of CM therapies and products amongst people with type 2 diabetes or CVD found that 43% of respondents had used CM in the previous year and 12% of respondents had done so specifically to address these conditions.(16)

Effectiveness of integrative medicine for cardiovascular and metabolic diseases

The following evidence summary provides an overview of potential clinical areas of benefit from the use of integrative medicine in cardiovascular and metabolic disease. An overview of reviews was undertaken, including a systematic search of PubMed/Medline and Cochrane Collaboration publications to September 2021 limited to English language papers. We provide a brief narrative review only of the emerging evidence in key clinical areas as understood by expert researchers in the field.

There is an extensive and growing clinical research literature assessing the effectiveness of foods, nutraceuticals and herbal medicines for cardiovascular and metabolic health, ranging from diets that are protective of cardiovascular health, to ingredients that positively effect metabolic parameters that feed into cardiovascular disease and metabolic disease risk, as well as the growing clinical research literature on foods and nutrients with anti-inflammatory properties.

Foods, nutraceuticals, and herbal medicines for cardiovascular and metabolic health

Certain foods contain high levels of nutrients which offer unique cardioprotective benefits.

Foods and nutrients found to promote cardiovascular health

- [*Diets high in fish protective of cardiovascular health*](#) – Regular fish intake is considered an integral component of a cardio-protective diet.(17, 18) Higher fish intake is associated with a lower incidence of heart failure, lower sudden cardiac death, stroke and myocardial infarction.(19) Various governing bodies recommend the consumption of fish one to three times per week.(20)
- [*Omega-3 fatty acid³ supplements for heart disease*](#) - Recent systematic reviews and meta-analyses on the effects of marine omega-3 fatty acids have interpreted clinical trial data in slightly differing ways. One 2020 meta-analysis, reviewing 16 randomised controlled trials (RCTs) with 81,073 participants, found supplementation with omega-3 fatty acids was associated with a significant reduction of cardiac mortality. Higher benefits were achieved by patients in secondary cardiovascular prevention, using more than 1gm/day dosage and taking

³ Omega-3 fatty acids - found in high amounts in oily fish and seafood and to a lesser extent in grass fed meat, pastured eggs and from a variety of plant-based food stuffs such as walnuts and fresh green vegetables and some nut oils.

EPA alone.(21) In contrast however, another 2020 meta-analysis (reviewing 86 trials with 162,796 participants) concluded there was only low to moderate certainty evidence that increasing omega-3 fatty acids supplementation reduces the risk of coronary heart disease mortality and events.(22) A previous meta-analysis in 2019 (involving 127,477 participants) had also found that marine omega-3 polyunsaturated fatty acids supplementation significantly reduced the risk of myocardial infarction, coronary heart disease death, total coronary heart disease, cardiovascular disease death, and total cardiovascular disease and that risk reduction was linearly associated with dose, however no benefits were found for stroke.(23) While further randomised controlled studies are required to elucidate the dose-response, it appears that supplementing 2g/day of omega-3 long chain polyunsaturated fatty acids will likely contribute to reduced cardiovascular risk and mortality. It should be noted these latest reviews contradict some earlier reviews that claimed no benefit from omega-3 supplementation; however, the benefits of omega-3 fatty acids appears to be dose-dependent and many of the earlier studies did not include dosages sufficient to elicit detectable benefits.(24-26) Omega-3 long chain polyunsaturated fatty acid supplements also appear to reduce high triglycerides (19, 27-29) and confer a modest positive benefit in heart failure.(19) There is evidence that omega-3 long chain polyunsaturated fatty acid supplements also play a role in improving the lipoprotein profile by decreasing the fraction of atherogenic small, dense LDL.(27)

- [*Omega-6 fatty acid⁴ supplements for cardiovascular disease*](#) – The evidence of the effect of omega-6 on CVD remains controversial with evidence that omega-6 fatty acids are inversely associated with cardiovascular death and CHD risk.(30, 31) Human dietary trials have shown that increased omega-6 fatty acid has adverse effects on platelet aggregation and endothelial function (32) or high sensitivity-CRP levels.(33) A recent Cochrane systematic review (2015) found no statistically significant effects of either increased or decreased omega-6 intake on CVD risk factors.(34)
- [*Flaxseed to improve blood lipid profile*](#) - The consumption of flaxseed, which is a plant food source of omega-3 fatty acids, specifically alpha-linolenic acid, has been shown to reduce total cholesterol and LDL cholesterol.(35) Early studies involving healthy human participants showed that the regular consumption of flaxseed reduced total cholesterol by 6-11% and LDL cholesterol by 9-18%.(36-38) Further randomised controlled studies in hypercholesterolemic patients showed that the consumption of flaxseed reduced total cholesterol by 5-17% and LDL cholesterol by 4-10%.(39-41) In addition to this, there is evidence from a meta-analysis published in 2021 (six RCTs) that flaxseed supplementation reduces plasma lipoprotein(a) levels. Lipoprotein(a) is a type of LDL-C and elevated levels put a person at risk of heart disease.(42)
- [*Phytosterols \(or plant sterols\)⁵ to improve cholesterol*](#) – A significant body of research has established that the supplementation of regular diets with plant sterols at doses of 1.5-3 g per day results in LDL-cholesterol reductions of 7.5-12%,(43) and that plant sterols are both

⁴ Omega-6 fatty acids are found in high amounts in seed oils such as canola oil and manufactured foodstuffs that contain these oils and to a lesser extent in nuts, grains and grain fed meats.

⁵ Phytosterols are substances in plants that fall into two broad groups (sterols and stanols) and which play a structural role in plant membranes similar to that of cholesterol in animal membranes.

effective and safe cholesterol-lowering agents.(44) Furthermore, a recent systematic review and meta-analysis concluded that phytosterol supplementation lowers atherogenic apo-lipoproteins⁶ and increases anti-atherogenic apo-lipoproteins in the blood of adults.(45) Plant sterol supplementation can be used as an adjunct to a healthy diet, to treat common hypercholesterolemia (either as a monotherapy in less serious cases or in combination therapy with statins and other lipid-lowering drugs in more serious cases), and to treat of metabolic syndrome and diabetes.(44)

- [*Phytosterols \(or plant sterols\) to improve blood pressure*](#) – A systematic review and meta-analysis published in 2020 including 19 RCTs found that supplementation with phytosterols can decrease by SBP and DBP.(46)
- [*Soy to improve cholesterol*](#) – Soy protein high in isoflavones⁷ has been shown to lower serum LDL cholesterol,(47-49) with administration of S-equol to non-equol⁸ producers also proving beneficial.(50) Furthermore, there is evidence that prebiotics⁹ in the diet can increase colonic fermentation and the hypocholesterolemic effects of soy.(51)
- [*Cocoa to improve blood pressure*](#) – Cocoa, which is high in flavanols, appears to have a blood pressure lowering effect, specifically on diastolic blood pressure, with a greater effect seen with high-flavanol cocoa rather than low-flavanol cocoa;(52-54) this is consistent with research that shows flavanol-rich cocoa and foods containing it, such as dark chocolate, improve endothelial function thus have a positive effect on blood pressure.(55, 56)
- [*Ginger to improve blood pressure*](#) – Ginger lowers both SBP and DBP according to a recent systematic review and meta-analysis including six RCTs (n=345 participants).(57) When studies were categorised based on participants' mean age, ginger dosage and duration of intervention, SBP and DBP were significantly decreased only in the subset of studies with mean age including participants 50 years of age or younger, with a follow-up duration of 8-weeks or less and ginger doses of 3g/day or more.
- [*Cinnamon improves blood pressure*](#) – Recent systematic reviews and meta-analyses have shown that cinnamon supplementation significantly decreases both SBP and DBP in health adults (58) and in those with type 2 diabetes.(59)
- [*Berries for cardiovascular risk and health*](#) – Many berries such as blackcurrants, blueberries, raspberries, cherries, and blackberries have been shown to be high in anthocyanins.(60) There is strong epidemiological evidence reporting a strong association between anthocyanin intake and reduced risk for cardiovascular disease and coronary heart disease.(61) Recent systematic reviews have reported that berries, or anthocyanin consumption more specifically, significantly reduces systolic blood pressure.(60, 62) These reports are corroborated by a

⁶ Apo-lipoproteins are proteins that bind lipids to form lipoproteins; they transport lipids in blood, cerebrospinal fluid and lymph.

⁷ Isoflavones are substituted derivatives of isoflavone, a type of naturally occurring isoflavonoids, which are often referred to as phytoestrogens. Isoflavones are produced almost exclusively by the members of the Fabaceae or Leguminosae family, which is commonly known as the legume, pea or bean family.

⁸ Equol is a key metabolite of digestion of soy diadzin (a soy protein) and non-equol equol producers are people who cannot convert daidzin into S-equol through their intestinal bacterial flora.

⁹ Prebiotics are specialized plant fibres that beneficially nourishes the good bacteria already in the large bowel or colon and are found in a variety of foods including garlic, onion, and leek.

recent study, which found that consuming 11g wild blueberry powder (equivalent to 100g of fresh wild blueberries) twice daily for one month improved flow-mediated dilation and 24-hour blood pressure compared to a placebo control (powdered drink) and that this result was mediated by the anthocyanin content of the berries.(63) These findings are consistent with those of a systematic review published in 2021 which found that supplementation with berry anthocyanins positively impacts memory, markers of vascular function and blood pressure.(64)

- [Berries to improve blood lipid profile](#) - Strawberries improve serum lipids - lowering total cholesterol, LDL cholesterol and triglycerides.(65, 66) Others berries, such as blueberries do not show this effect.(67) A recent systematic review involving 22 RCTs and more than 1251 participants reported that consumption of berries significantly reduced LDL cholesterol.(62)
- [Garlic supplementation to improve blood pressure](#) - S-allylcysteine, the main active compound in aged garlic extract, has been reported to effectively reduce blood pressure in individuals with hypertension.(68) There is no apparent hypotensive effect of garlic consumption on individuals with normal blood pressure.(69-71)
- [Garlic to improve blood lipids](#) - Research suggests that garlic supplementation reduces total cholesterol levels. A 2018 meta-analysis of 14 trials which assessed the effects garlic supplementation on blood lipids found that garlic supplementation led to a statistically significant reduction in total cholesterol.(72) This finding is supported by previous reviews.(73, 74) The evidence on the effect of garlic supplementation on other blood lipid measures, such as LDL cholesterol, HDL cholesterol and triglycerides is not consistent.(72-74)
- [Bergamot juice to improve blood lipids and reduce cardio-metabolic risk](#) - A 6-month prospective study involving 80 participants with moderate hypercholesterolemia found Bergamot derived flavonoids - from a Bergamot-derived extract Bergavit¹⁰ - significantly reduced plasma lipids (total cholesterol, triglycerides and LDL cholesterol) and improved lipoprotein profile (by decreasing atherogenic small, dense LDL particles) in this cohort. Furthermore, the study found that Bergavit significantly reduced carotid artery thickening after 6-months of supplementation.(75)
- [Dairy products to improve blood pressure](#) - Dairy products, such as milk, cheese, and sour milk products, contain significant amounts of antihypertensive peptides¹¹. Interventional studies have shown that milk products, which contain casein protein, have been shown to have a beneficial effect on blood pressure in participants with hypertension.(76, 77) A systematic review and meta-analysis of RCTs concluded that milk-derived tripeptides have a hypotensive effect in hypertensive adults.(78)
- [Vitamin C to reduce blood pressure](#) - A 2012 review assessed the effect of vitamin C supplementation on systolic and diastolic blood pressure and included 29 RCTs (n=1407 participants). The researchers concluded that vitamin C supplementation modestly reduced

¹⁰ Bergavit is a bergamot juice derived flavonoid extract containing a variety of flavonoids including naringin, neoeriocitrin, and neohesperidin.

¹¹ A peptide is a compound consisting of two or more amino acids linked in a chain.

systolic and diastolic blood pressure: the pooled changes in SBP and DBP were -3.84 mm Hg (95% CI: -5.29, -2.38 mm Hg; $P < 0.01$) and -1.48 mm Hg (95% CI: -2.86, -0.10 mm Hg; $P = 0.04$). Trials included in the meta-analysis were small and there was significant heterogeneity of effects across studies, and the median dose was 550mg/day and for 8-weeks. The blood pressure lowering effect was greater when analysis was restricted to trials with hypertensive patients: corresponding reductions in SBP and DBP were -4.85 mm Hg ($P < 0.01$) and -1.67 mm Hg ($P = 0.17$). Greater BP reductions were seen when trials showing elevated baseline ascorbic acid concentrations were excluded, indicating that individuals with low pre-existing vitamin C intakes would be more likely to benefit from vitamin C supplementation than those with high pre-existing vitamin C intakes.(79)

- [Green tea to improve blood lipid profile](#) - While the evidence is mixed that drinking green tea or taking green tea supplements improves a person's blood lipid profile - specifically reducing LDL-cholesterol and/or triglycerides due to the high catechin¹² polyphenols content - the evidence overall seems in favour.(80, 81)
- [Green tea to improve blood pressure](#) - A recent meta-analysis including 24 RCTs (n=1697 participants) found that green tea significantly reduced both SBP and DBP over the short-term with more trials needed to determine if there is a longer term effect or not.(82)
- [Oats to reduce total and LDL cholesterol](#) - There is now significant scientific agreement that consumption of oats, due to the high soluble beta-glucan¹³ content, can reduce total and low density LDL cholesterol, thereby reducing the risk of coronary heart disease.(83, 84)
- [Zinc supplementation for blood lipids](#) - A 2020 systematic review and meta-analysis assessing the effect of zinc supplementation on cardiometabolic risk factors found that zinc supplementation significantly decreased plasma triglyceride levels, very-low-density lipoprotein levels, and total cholesterol levels.(85)
- [Zinc supplementation for blood lipids](#) - Zinc supplementation has also been shown to improve SBP but has no effect on DBP.(86)
- [Chromium to improve blood pressure](#) - A meta-analysis published in 2021 found that supplementation with chromium significantly decreased by SBP and DBP.(87) Supplementation with chromium yeast and brewer's yeast had the greatest impact on SBP.
- [Melatonin to improve blood pressure in people with metabolic disorders](#) - A meta-analysis published in 2019 including eight RCTs demonstrated that melatonin supplementation significantly decreased blood pressure - both SBP and DBP - in people with metabolic disorders.(88)

¹² Catechins are a type of phenolic compounds very abundant in tea, cocoa, and berries to which are ascribed a potent antioxidant activity, especially to epigallocatechin-3-gallate (EGCG).

¹³ Beta glucans are sugars that are found in the cell walls of bacteria, fungi, yeasts, algae, lichens, and plants, such as oats and barley.

- [Melatonin to improve blood pressure in people with metabolic disorders](#) - There is evidence from a recent systematic review and meta-analysis that melatonin supplementation significantly improves blood lipid profile by decreasing LDL-C and TGs.(89)
- [Psyllium to improve blood pressure in people with hypertension](#) - A recent meta-analysis that analysed the effect of psyllium supplementation on blood pressure of hypertensive people found that psyllium supplementation saw a significant reduction in SBP in this cohort, with the hypotensive effect of psyllium stronger in subjects with higher baseline blood pressure.(90)
- [Probiotics to improve blood pressure](#) - A large number of meta-analyses have been completed recently assessing the effectiveness of probiotic supplementation in lowering blood pressure. These reviews concur that using a probiotic supplement results in a statistically significant decrease in both SBP and DBP in people with hypertension. While the clinical significance of the decrease is uncertain, the lack of side effects suggests use of probiotics is a useful treatment for hypertension - either as an adjunct to standard medical therapeutics or as a monotherapy where blood pressure is only slightly elevated.(91-94)
- [Probiotics to improve blood lipids](#) - Probiotic supplementation has been shown to decrease TC and LDL-C in individuals with hypercholesterolaemia in a meta-analysis including 19 RCTs (n=967 participants) published in 2019.(95)
- [Curcumin to improve glucose metabolism](#) - A meta-analysis of RCTs (n= 1277 participants) assessing the efficacy and safety of curcumin for improving glucose metabolism in people with cardiovascular risk factors found that supplementation with curcumin or combined curcuminoids improves glucose metabolism in this cohort.(96)
- [Quercetin to improve blood lipids](#) - Quercetin supplementation significantly reduces TC and LDL-cholesterol levels in patients with MetS and related disorders according to a systematic review and meta-analysis published in 2020 (n=16 RCTs included in the meta-analysis).(97)
- [Quercetin to improve systolic blood pressure](#) - A meta-analysis of eight RCTs published in 2019 to determine the effect of quercetin supplementation on blood pressure and endothelial function in patients with MetS and related disorders found a significant reduction in SBP (WMD: -1.69; 95% CI: -3.22, -0.17) following the intake of quercetin supplements but not DBP (WMD: -3.14; 95% CI: -8.24, 1.95).(98)
- [L-carnitine to improve blood lipids](#) - L-carnitine has a positive effect on lipid profile in adults with cardiovascular risk factors. A systematic review and meta-analysis published in 2020 including 24 RCTs (n=1569 participants) found supplementation with L-carnitine saw a significant reduction in TC (WMD: -13.73 [95% CI: -22.28, -5.17] mg/dL; P < 0.001) and LDL-C (WMD = - 7.70 [95% CI: - 11.80, -3.61]mg/dL; p < 0.001) and saw a significant increase in HDL-C (WMD = 0.82 [95% CI: 0.44, 1.21] mg/dL; P > 0.001). While there was no effect on TGs, there was also a positive effect on Lp(a) levels (WMD = - 7.13 [95% CI: -9.82,- 4.43]mg/dL; P < 0.001).(99) Interestingly, another meta-analysis published the same year including nine RCTs in the meta-analysis found that L-carnitine supplementation had a positive effect on TGs and HDL-C when supplemented at a dose of more than 1g/day.(100)

- [L-carnitine and effect on blood pressure](#) - The evidence on the effect of L-carnitine supplementation on blood suggests a positive effect on blood pressure. A systematic review and meta-analysis of RCTs published in 2019 (n=10 RCTs) concluded that L-carnitine supplementation significantly reduced DBP (-1.162 mmHg, 95% CI: -2.020, -0.303, p=0.008) without changing SBP levels significantly (-0.085 mmHg, 95% CI: -1.455, 1.285, p=0.903).(101) A meta-analysis of nine RCTs published a year later concluded that L-carnitine supplementation significantly reduced SBP.(100)
- [Capsicum annuum for blood lipids](#) - A meta-analysis of 11 RCTs (n= 609 participants) showed that supplementation with Capsicum annuum (in capsules, pills or freshly chopped chilli) resulted in a significant reduction in LDL-C in a cohort of individuals with MetS but there was no effect on other blood lipids studied (TC or HLD-C).(102)

Foods, nutrients, and vitamins for metabolic health

- [Marine source omega-3 fatty acid supplements improve insulin signalling and glucose metabolism in people with metabolic syndrome¹⁴](#) - There is evidence that individuals with metabolic syndrome benefit from supplementation with omega-3 fatty acids from marine sources through improved insulin signalling and the prevention of alterations in glucose homeostasis which are commonly seen in individuals with metabolic syndrome. Such supplementation appears to contribute to reducing insulin resistance in muscle and diminishes the risk of developing type 2 diabetes.(27) A recent animal study showed that omega-3 fatty acid supplementation improves key metabolic outcomes such as improved insulin sensitivity and a reduces build-up of ceramides and diacylglycerols in ectopic fat depots (103). A study assessing the effects of 8-week omega-3 fatty acid supplementation showed that when compared to a placebo, fatty acid supplementation significantly reduced low-density lipoprotein cholesterol and total cholesterol.(104)
- [Unfermented tea or green tea for obesity around the midline](#) - Central obesity is one of the defining features of metabolic syndrome and there is good evidence from clinical studies of significant but modest beneficial effects of unfermented tea or green tea (in extract form or tea form) on body mass index (BMI)(105-113) and waist circumference(105, 108-112) due to the high polyphenol content; black tea, which is fermented, has an effect but not as pronounced as green tea.(113)
- [Resveratrol¹⁵ for risk factors for metabolic and cardiovascular disease](#) - Resveratrol has been shown to positively affect cardiovascular and metabolic risk factors with evidence showing

¹⁴ Metabolic syndrome classically refers to the combination of three or more different components: 1) abdominal obesity; 2) a high concentration of serum triacylglycerols; 3) a low concentration of HDL cholesterol or current treatment for reduced HDL cholesterol; 4) elevated blood pressure or current antihypertensive treatment; and 5) high fasting concentrations of plasma glucose or current treatment for elevated glucose.

¹⁵ Resveratrol is a phenol, an aromatic organic compound with the molecular formula C₆H₅OH, found in the skin of grapes, blueberries, raspberries, and mulberries.

that the regular consumption leads to decreases in body weight, BMI, fat mass and waist circumference (114). There is disagreement about its positive effects in type 2 diabetes patients and on endothelial function/blood pressure, inflammation, and cardiovascular markers.(115-120) However, recent systematic reviews suggest a positive effect of resveratrol supplementation on markers of glycaemic control and blood glucose metabolism in T2Ds.(120, 121)

- [*Capsaicin for increased use of energy*](#) - Capsaicin, a compound in red chilies and capsicum, has been shown to enhance thermogenesis¹⁶ in humans which can reduce fat mass and/or help with maintenance of weight.(122-124)
- [*High flavanol cocoa to reduce glycaemia and improve insulin sensitivity*](#) - Cocoa products, in particular high-flavanol cocoa, benefits glycaemia, with reports of decreased insulin resistance with high-flavanol cocoa supplementation and enhanced insulin sensitivity with dark chocolate consumption.(52, 125)
- [*Cinnamon lowers fasting blood glucose levels*](#) - Cinnamon contains plant chemicals shown to have a beneficial effect on blood glucose levels in individuals with insulin resistance or type 2 diabetes.(126-130) Cinnamon appears to be particularly beneficial for those individuals who are at high risk for or suffer from metabolic disease due to its insulin mimetic effects. (131)
- [*Fenugreek to improve glucose metabolism and blood lipids*](#) - A 2016 systematic review of 10 trials assessing the overall effects of fenugreek on blood glucose levels and blood lipid levels in both diabetics and people with prediabetes found that fenugreek supplementation had significant effects on a number of blood glucose related measures as follows: decreased levels of fasting blood glucose - mean difference = -0.84mmol/L, 95% CI -1.38 to -0.31, p=0.002; blood glucose measured two hours after lunch or dinner - mean difference = MD -1.30mmol/L, 95% CI -1.78 to -0.83, p<0.0001; and HbA1c levels - mean difference = -1.16, 95% CI -1.23 to -1.09, p<0.00001). Furthermore, total cholesterol was reduced (mean difference = -0.30mmol/L, 95% CI-0.56 to -0.03, p=0.03), and there were non-significant trends in reductions in triglycerides and LDL cholesterol levels and increases in HDL cholesterol levels.(132)
- [*Curcumin for glycaemic control and improvements in lipid profiles*](#) - A review published in 2019 (a systematic review and meta-analysis) assessed the effect of curcumin/turmeric on metabolic factors in people with MetS and found that supplementation with curcumin/turmeric resulted in significant improvements in fasting blood glucose, TGs, HDL-C, and DBP.(133) Furthermore, there is evidence from a RCT involving 240 people diagnosed with prediabetes, that supplementation with a curcumin extract slowed down the progression from prediabetes to type 2 diabetes (T2D).(134)
- [*Vitamin D supplementation in people with cardiovascular disease*](#) - Trials assessing the effect of vitamin D supplementation on blood pressure, insulin sensitivity/glucose metabolism, and lipid parameters in people with cardiovascular disease have shown conflicting results.(135)

¹⁶ Thermogenesis is a process in which heat is produced in the biological system and the fuel for heat production comes from lipids and fat.

However, a meta-analysis published in 2019 assessing the effectiveness of vitamin D supplementation on glycaemic control, lipid profiles and C-reactive protein (CRP) levels in people with coronary artery disease demonstrated the beneficial effects of vitamin D supplementation on improving glycaemic control, HDL-C and CRP levels.(136) Furthermore, a meta-analysis published the following year which examined the effect of vitamin D supplementation on cardiac outcomes in patients with coronary artery disease found supplementation with vitamin D had significant favourable effects on DBP and parathyroid hormone.(137)

- [Vitamin E supplementation](#) - A 2011 review evaluated the effect of vitamin E supplementation on glycaemic control in type 2 diabetes. The review included nine RCTS (n = 418 participants) and concluded that there was no beneficial effect of vitamin E supplementation in improving glycaemic control in unselected patients with type 2 diabetes, but that HbA1c may decrease with vitamin E supplementation in patients with inadequate glycaemic control or low serum levels of vitamin E.(138)
- [Zinc supplementation](#) - A 2020 systematic review and meta-analysis assessing the effect of zinc supplementation on cardiometabolic risk factors found that zinc supplementation significantly decreased fasting blood glucose levels.(85)
- [Whey protein for metabolic health](#) - A systematic review and meta-analysis assessing the effects of whey protein on glycaemic control and blood lipids in people with MetS (and related disorders) found that supplementation with whey protein had a beneficial effect on glycaemic control - specifically significantly reducing HbA1c and insulin and improving insulin resistance - and blood lipids - specifically reducing TC, LDL-C and TGs.(139)
- [Probiotics to support metabolic health](#) - Recent meta-analyses show that supplementation with probiotics has a positive effect on blood pressure in people with hypertension, significantly reducing both SBP and DBP, but that the effect is more significant in individuals with T2D and hypertension.(91, 92, 94, 140) The meta-analysis by Liang and colleagues (2021) revealed further that supplementation with probiotics in type 2 diabetics also significantly improved markers of glycaemic control and blood lipid.(140) Furthermore, there is evidence that intake of probiotics for patients with MetS may offer a discrete improvement in some of the clinical characteristics of the MetS and a decrease in inflammatory biomarkers.(141)
- [Quercetin for glycaemic control](#) - A recent systematic review and meta-analysis including nine RCTs concluded that supplementation with quercetin had a significant effect on fasting blood glucose, a marker of glycaemic control, where the dosage was at least 500mg/day and the duration of treatment was 8-weeks or more.(142)
- [Capsicum annum supplement to improve body weight](#) - A systematic review and meta-analysis assessing the effects of capsicum annum¹⁷ supplementation on components of metabolic syndrome concluded there was a marginally significant effect on body weight. However, the authors pointed out a number of limitations of the review including that only a

¹⁷ The species *Capsicum annum* encompasses a wide variety of shapes and sizes of peppers, both mild and hot, such as bell peppers, jalapeños, New Mexico chile, and cayenne peppers.

small number of trials were included (many with significant ROB) and that larger well-designed clinical trials were needed to investigate the efficacy and safety of this dietary supplement in the treatment of MetS.

- [*L-carnitine supplementation to improve markers of glycaemic control*](#) - A 2020 systematic review and meta-analysis assessing the effect of zinc supplementation on cardiometabolic risk factors found that zinc supplementation significantly decreased fasting blood glucose levels.(85)

Foods and nutrients with anti-inflammatory properties

- [*Diets high in polyphenols, such as the Mediterranean diet, lower inflammation*](#) - A diet high in polyphenols¹⁸, such as a Mediterranean diet, is currently recommended as having a beneficial impact on inflammation.(143, 144) Studies assessing the effect of a Mediterranean diet on markers on inflammation have shown that individuals on a Mediterranean diet display significantly lower C-reactive protein (CRP) compared to those not on the Mediterranean diet, and when a Mediterranean diet is combined with weight loss other markers of inflammation are also reduced IL-6, IL-8 and TNF-alpha.(145, 146) However, emerging evidence has suggested that pre-existing inflammation may play a role in the responsiveness to polyphenols. For instance, those with metabolic syndrome and dyslipidaemia have a higher inflammatory load than those with metabolic syndrome but no dyslipidaemia, leaving individuals with metabolic syndrome and dyslipidaemia less responsive to polyphenols, which may be the result of a greater inflammatory burden.(147, 148)
- [*Polyphenol supplementation for inflammation*](#) - Results from clinical trials conducted on patients with metabolic syndrome report conflicting results with regard to the most common inflammation biomarkers following polyphenol supplementation (highly sensitive C-reactive protein, tumour-necrosis factor, interleukin-6, and monocyte chemoattractant protein 1.(65, 67, 115, 117, 147, 149-155) However, a systematic review and meta-analysis published in 2012 showed that both acute and chronic fruit-derived polyphenol supplementation led to improved vascular outcomes such as flow mediated dilation testing for vascular endothelia function.(156)
- [*Grapefruit to lower inflammation*](#) - Grapefruit, which is rich in polyphenols, has demonstrated anti-inflammatory effects specifically in individuals with baseline CRP elevation.(157) Grapefruit juice has also been shown to inhibit genotoxicity of cells exposed to hydrogen peroxide further highlighting its anti-oxidant and anti-inflammatory properties.(158)

¹⁸ Polyphenols, which are bioactive plant compounds found in many fruit and vegetables found in particular abundance in tea, berries, apples, citrus fruits, and chocolate, are associated with health benefits in diseases characterised by inflammation and oxidative stress, particularly CVD and malignancy (Merone L, McDermott R. Nutritional anti-inflammatories in the treatment and prevention of type 2 diabetes mellitus and the metabolic syndrome. *Diabetes Res Clin Pract* 2017; 127: 283-253).

- [Curcumin for inflammation](#) - The primary curcuminoids in turmeric, and curcumin more specifically, have been consistently shown to decrease inflammatory markers in patients with metabolic syndrome and type 2 diabetes, including CRP.(159)
- [Polyphenols in ginger](#) - The polyphenols in ginger are known to decrease inflammatory markers with studies showing that ginger, when compared to a placebo, significantly decreases inflammatory markers such as TNFa, IL-6 and CRP.(160-162)
- [Quercetin for inflammation](#) - A systematic review and meta-analysis published in 2020 including 16 RCTs concluded that quercetin supplementation significantly reduced CRP levels in patients with MetS and related disorders, which is a marker of inflammation in the body.(97)

Mind-body therapies for cardiovascular and metabolic health

- [Yoga](#) - Five reviews and several meta-analyses of studies of yoga-based interventions for cardiovascular disease and hypertension have reported moderate to clinically important effects.(163-167) Cramer and colleagues(167) reviewed and meta-analysed 44 RCTs with a total of 3,168 participants and reported that relative to usual care or no intervention, yoga-based interventions improved numerous factors associated with cardiovascular disease. Specifically, yoga-based interventions were associated with clinically and statistically significant improvements ($p < 0.01$, overall effect across combinations of healthy, non-diabetic high-risk, or Type 2 diabetic samples) in both systolic (MD = -5.85 mm Hg) and diastolic blood pressure (MD = -4.12 mm Hg), waist circumference (MD = -1.95 cm), waist/hip ratio (MD = -0.02), total cholesterol (MD = -13.09 mg/dl), VLDL (MD = -5.70 mg/dl), triglycerides (MD = -20.97 mg/dl), and insulin resistance (HOMA-IR; MD = -0.19). Relative to exercise, yoga-based interventions also showed clinically and statistically significant improvements in blood levels of HDL (MD = 4.24 mg/dl). Effects of yoga-based interventions were comparable or superior to that of guideline-endorsed interventions for managing cardiovascular disease risk such as exercise or psychological interventions.(168, 169)
- [Tai chi](#) - There is a growing body of research related to the effect of tai chi on cardiovascular disease and risk factors to determine its effectiveness as either a stand-alone or adjunctive treatment. Research to date has focused on cardiovascular function, specifically blood pressure (170-174), and psychological wellbeing and quality of life of people with or at risk of cardiovascular disease,(175-177) and physical capacity of people having suffered stroke.(178-182)
 - [Tai chi for high blood pressure](#) - While there is encouraging evidence that tai chi may be beneficial in high blood pressure, the methodological quality of current studies is weak. A 2008 systematic review concluded tai chi may have beneficial effects on blood pressure.(172) The eight studies included in the review reported a statistically significant within-group reduction in mean blood pressure after tai chi exercise, however these studies were of low quality. A more recent review published in 2013 assessed the effectiveness of tai chi for essential hypertension.(174) This review found

tai chi compared to routine care improved systolic blood pressure (SBP) (WMD: -12.43 [-12.62,-12.24]; $P < 0.00001$; 10 trials) and diastolic blood pressure (DSP) (WMD: -6.03 [-6.16, -5.90]; $P < 0.00001$; 10 trials). Tai chi was effective in reducing SBP and DBP in one RCT when compared to antihypertensive drugs, but adjunctive treatment of antihypertensive medication¹⁹ with tai chi exercise saw no difference in blood pressure when compared to antihypertensive medication treatment alone. However, the poor methodology of these studies was also noted. A third systematic review of four clinical trials assessing the effectiveness of tai chi in reducing resting blood pressure in the elderly concluded the evidence for tai chi in reducing BP was limited.(173) Finally, a 2014 Cochrane review assessing the effectiveness of tai chi for primary prevention of CVD found that while there was some evidence of beneficial effect of tai chi on CVD risk factors such as high blood pressure, this effect was not consistent across all studies and the included studies were small and of short duration.(183)

- [Tai chi for chronic heart failure](#) - A meta-analysis of 13 RCTs published in 2017 examined the effectiveness of tai chi in improving physical performance in people with chronic heart failure. The primary outcomes of interest specified were 6-minute mean walking distance (6MWD) and QOL. The 10 trials included in the meta-analysis showed that tai chi could significantly improve 6MWD (random-effects model: WMD, 51.01 m; 95% CI, 30.49-71.53; $P < 0.00001$). The eight studies that reported on QOL showed that tai chi practise resulted in improved QOL as measured by the Minnesota Living with Heart Failure Questionnaire (MLHFQ): those practicing tai chi showed significantly lower MLHFQ scores than those not practising tai chi (random-effects model: WMD, -10.37 points; 95% CI, -14.43 to -6.32; $P < 0.00001$). (184)
- [Meditation for cardiovascular health](#) - The American Heart Association reviewed the evidence on potential benefits of meditation on cardiovascular risks and published a statement in 2017. Despite the generally poor methodological quality of studies, the American Heart Association concluded that studies suggest a possible benefit of meditation on cardiovascular disease risk reduction.(185)

Manipulative and body-based therapies for cardiovascular and metabolic health

- [Massage therapy for essential hypertension](#) - A 2015 review examined the effectiveness of massage therapy for the treatment of essential hypertension. The review demonstrated that massage combined with antihypertensive drugs is more effective than antihypertensive drugs alone in lowering both systolic blood pressure (SBP - mean difference: - 6.92 (- 10.05, - 3.80); $P < 0.0001$) and diastolic blood pressure (DPB - mean difference: - 3.63 (- 6.18, - 1.09); $P = 0.005$). Furthermore, massage appears beneficial for reducing SBP (MD: - 3.47 (- 5.39, - 1.56); $P = 0.0004$) for hypertensive patients as compared with antihypertensive drugs.(186)

¹⁹ The antihypertensive drugs were reserpine or compound rutin tablets.

However, the majority of studies included in the review are of poor methodological quality and further research is warranted.

- [Spinal manipulation for hypertension](#) – A systematic qualitative review published in 2012 concluded that there is a lack of low bias evidence to support the use of spinal manipulation for the treatment of hypertension.(187)

Dietary management of obesity-related disease

- [Exercise for people with major depressive disorder \(MDD\)](#) – Dietary behaviours play a key role in the pathogenesis of many cardiometabolic diseases including hypertension, arterial disease and type 2 diabetes, also known as obesity-related diseases.(3) While these behaviours can increase the risk of disease, dietary adjustments can also be used to treat and prevent the onset of cardiometabolic disease.(188) Importantly, it is well accepted that as little as ~5% of body weight loss can lead to significant improvements in many cardiometabolic risk factors and in some instances, the remission of type 2 diabetes.(189, 190)

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