Proceedings of the Nutrition Society (2019), **78**, 340–350 doi:10.1017/S0029665119000545
 First published online 10 April 2019

The Nutrition Society Summer Meeting was held at the University of Leeds, UK on 10–12 July 2018

Conference on 'Getting energy balance right'
Symposium 3: Dietary factors in energy metabolism

The role of bioactives in energy metabolism and metabolic syndrome

A. Bordoni[1]*, C. Boesch[2], C. Malpuech-Brugère[3], C. Orfila[2] and L. Tomás-Cobos[4]
[1]*Department of Agri-Food Sciences and Technologies, University of Bologna, Cesena (FC), Italy*
[2]*School of Food Science and Nutrition, University of Leeds, Leeds, UK*
[3]*Université Clermont Auvergne, INRA, UNH, Unité de Nutrition Humaine, CRNH Auvergne, France*
[4]*AINIA, Valencia, Spain*

Some food bioactives potentially exert anti-obesity effects. Anthocyanins (ACN), catechins, β-glucan (BG) and *n*-3 long chain PUFA (LCPUFA) are among the most promising candidates and have been considered as a strategy for the development of functional foods counteracting body weight gain. At present, clinical trials, reviews and meta-analyses addressing anti-obesity effects of various bioactives or bioactive-rich foods show contradictory results. Abdominal obesity is an important criterion for metabolic syndrome (MetS) diagnosis along with glucose intolerance, dyslipidaemia and hypertension. Food bioactives are supposed to exert beneficial effects on these parameters, therefore representing alternative therapy approaches for the treatment of MetS. This review summarises outcomes on MetS biomarkers in recent clinical trials supplementing ACN, catechins, BG and *n*-3 LCPUFA, focusing mainly on anti-obesity effects. Overall, it is clear that the level of evidence for the effectiveness varies not only among the different bioactives but also among the different putative health benefits suggested for the same bioactive. Limited evidence may be due to the low number of controlled intervention trials or to inconsistencies in trial design, i.e. duration, dose and/or the method of bioactive supplementation (extracts, supplements, rich or enriched food). At present, the question 'Are bioactives effective in weight management and prevention of metabolic syndrome?' remains inconclusive. Thus, a common effort to harmonise the study design of intervention trials focusing on the most promising bioactive molecules is urgently needed to strengthen the evidence of their potential in the treatment of obesity, MetS and related diseases.

Anthocyanins: β-glucan: Catechins: *n*-3 long chain PUFA: Metabolic syndrome

A fundamental principle of nutrition and metabolism is that body weight (BW) change is associated with an imbalance between the energy intake and energy expenditure. On this basis, it is commonly and simplistically theorised that some people become overweight simply because they eat too much and exercise too little. Although this is theoretically true, different contributors to energy balance must be considered and need a better understanding. For example, diet composition, nutrient bioavailability and bioactives could have a role in energy balance.

The different thermic effects of macronutrients could result in different energy expenditure. For example, higher protein diets have been shown to be more conducive to weight loss than lower protein diets[(1)]. The Preventing Overweight Using Novel Dietary Strategies (POUNDS LOST) trial examined the role of macronutrients on overall energy expenditure and its components under well-controlled conditions[(2)]. This randomised trial involving 811 overweight adults evidenced that low-energy, isoenergetic diets with different macronutrient ratio (fats:

Abbreviations: ACN, anthocyanins; BG, β-glucan; BP, blood pressure; BW, body weight; C, catechins; ECG, epicatechin; EGCG, epigallocatechin gallate; FO, fish oil; GTC, green tea catechin; HOMA, Homeostatic model assessment; IR, insulin resistance; LCPUFA, long chain PUFA; MD, mean difference; MetS, metabolic syndrome; OO, olive oil; RCT, randomised controlled trial; T2D, type 2 diabetes; WC, waist circumference.

***Corresponding author:** A. Bordoni, email alessandra.bordoni@unibo.it

proteins:carbohydrates = 20:15:65; 20:25:55; 40:15:45 or 40:25:35) were equally successful in promoting weight loss and the maintenance of weight loss over a 2-year period.

Low glycaemic load diets have been reported to improve weight-loss maintenance[3]. This could be ascribed at least in part to a reduced nutrient availability due to the high fibre content of low glycaemic load diets.

Some bioactives have been shown to exert anti-obesity effects through suppression of appetite, inhibition of carbohydrate and lipid digestive enzymes[4], regulation of lipid metabolism, and increase in energy expenditure[5]; and they have been considered as a new strategy for the development of anti-obesity functional foods.

Anthocyanins (ACN), catechins, β-glucan (BG) and *n*-3 long chain PUFA (*n*-3 LCPUFA) are among the most promising candidates, although clinical trials using the pure bioactives or bioactive-rich foods demonstrate inconsistent findings. This review examines the main recent findings coming from clinical intervention studies using the earlier cited bioactives. Few trials specifically address the effect of bioactives on BW or BMI, but evidence regarding these parameters can come from trials focused on metabolic syndrome (MetS). Abdominal obesity is an important criterion for MetS diagnosis along with glucose intolerance, dyslipidaemia and hypertension[6], and the selected bioactives have been used in several trials aimed to improve MetS.

Summarised outcomes on MetS biomarkers in clinical trials supplementing ACN, catechins, BG and *n*-3 LCPUFA are outlined later, focusing on anti-obesity effects.

Anthocyanins

ACN comprise a subgroup of flavonoids abundant in many fruit and vegetables, in particular, berries and grapes and their products such as juice and wine. Particularly rich in ACN are berries such as blackberries, black currants, black elderberries and blueberries with some varieties producing about 400–500 mg ACN/100 g[7,8]. ACN are water-soluble glycosylated pigments produced through plant secondary metabolism and responsible for the red, purple or blue colours. Most predominant ACN compounds are derived from pelargonidin, cyanidin, delphinidin, petunidin, peonidin and malvidin base structures, differing with regard to position and number of hydroxyl groups, degree of methylation, type and number of sugar moieties, ultimately leading to a large diversity of ACN and their composition in different plants. The major ACN found in most plants is cyanidin-3-glucoside.

Reduction of weight gain following ACN supplementation in rodents has been associated with modulation of hepatic lipid metabolism, such as reduction of sterol regulatory element-binding protein-1 mRNA levels, inhibition of enzymes involved in fatty acid and TAG synthesis and up-regulation of lipolytic enzymes[9]. Furthermore, energy expenditure has been found accelerated in high-fat diets-induced obese mice following blackberry and blueberry ACN supplementation[10]. Similarly, Solverson *et al.*[11] reported an increase in fat oxidation in a recent randomised controlled trial (RCT) in twenty-seven overweight or obese males given blackberries (1500 mg/d) with high-fat diets for 7 d.

Daneshzad *et al.*[12] conducted a systematic review and meta-analysis of nineteen RCT evaluating effects of ACN supplementation on cardio-metabolic biomarkers including BW, BMI, waist circumference (WC), blood pressure (BP), lipid profile and glycaemic status. Duration of supplementation ranged from 1 to 96 weeks with ACN doses ranging from 31·5 to 1050 mg daily. While there was no significant effect of ACN supplementation on BW, WC, BMI, BP (systolic and diastolic), a sub-group analysis revealed that ACN intake for more than 12 weeks led to a 2·42 kg reduction in BW (mean difference (MD) −2·42 kg; 95 % CI −4·46, −0·38; $P = 0·020$) and a 0·75 kg/m^2 decrease in BMI (MD −0·75 kg/m^2; 95 % CI −1·38, −0·23; $P = 0·005$). Given the overall lack of effect on anthropometric markers and BP, duration as well as ACN dose may be the most likely sources for heterogeneity observed among different trials. This is in line with Amiot *et al.*[13] who included six ACN supplementation studies in their systematic review on the effects of dietary polyphenols on MetS markers and reported highly variable results on BMI, WC, BP, lipid profile and glucose metabolism which are likely to relate to the different amounts of ACN provided through different berry food products (berry type, juice or powder product, extract) given over a supplementation periods of 6–8 weeks. Most effective was a mixture of berries (bilberry, blueberry, sea buckthorn) taken daily over 8 weeks to reduce BMI and WC[14]; aronia extract (300 mg daily over 2 months) was able to significantly reduce BMI[15]. Conversely, a 6-week daily supplementation with freeze-dried strawberry powder (equivalent to 500 g fresh strawberries) caused no changes in anthropometric indices and serum glucose[16].

ACN may exert hypoglycaemic effects through a combination of mechanisms including inhibition of carbohydrate digestion through inhibition of salivary and pancreatic α-amylase and α-glucosidase, inhibition of intestinal glucose absorption[17], stimulation of insulin secretion[18] and increased glucose uptake in peripheral tissues through up-regulated GLUT4 and its utilisation[19,20]. Furthermore, cyanidin-3-glucoside has been shown to lead to increased differentiation of pre-adipocytes into smaller and insulin-sensitive adipocytes[21] and exerts insulin-like effects in human adipocytes by up-regulating PPARγ activity[22]. Other mechanisms related to decreased insulin resistance (IR) involve activation of AMPK and insulin receptor substrate 1 and reduced inflammation[9]. In addition, ACN may act in the gut to modulate postprandial blood glucose, insulin and incretin response[23].

High intake of ACN has been associated with significantly lower peripheral IR and high-sensitivity C-reactive protein levels[24]. Soltani *et al.*[25] have shown that the daily consumption of ACN-rich cornelian berry (*Cornus mas L.*) improved glycaemic control significantly by increasing insulin and reducing HbA1 levels in patients with type 2 diatetes (T2D), and a 12-week RCT in 138 Chinese adults with prediabetes or early untreated diabetes revealed that purified ACN favourably affects glycaemic control and lipid profile, in particular in patients with

https://doi.org/10.1017/S0029665119000545 Published online by Cambridge University Press

elevated metabolic markers[26]. As well, a recent systematic review and meta-analysis involving thirty-two RCT with a minimum duration of 2 weeks demonstrated a consistently improved glycaemic control (reduced fasting glucose, 2 h postprandial glucose and glycated Hb) in both healthy and metabolically diseased populations, although in particular in subjects with existing hyperglycaemia[27]. This review also indicated significant reductions in total cholesterol and LDL-cholesterol levels across the thirty-two RCT.

Daneshzad *et al.*[12] could not confirm effects on HbA1c, serum insulin and blood lipid profile in their systematic review/meta-analysis when all nineteen studies were included. Sub-grouping for interventions over 300 mg ACN/d and duration over 12 weeks significantly lowered Homeostasis model assessment (HOMA)-IR (−21 %). ACN supplementation periods over 12 weeks significantly increased HDL-cholesterol and reduced LDL-cholesterol levels, and ACN supplementation >300 mg significantly reduced total cholesterol by 6·69 mg/dl and LDL-cholesterol levels by 8·60 mg/dl. Hassellund *et al.*[28], investigating the impact of ACN on cardiovascular risk factors and inflammation in pre-hypertensive men, emphasise the importance of ACN supplementation period over the dose in intervention studies, which is confirmed by Zhu *et al.*[29] demonstrating significantly reduced LDL-cholesterol and increased HDL-cholesterol levels after 24 weeks of ACN supplementation. Further, Alvarado *et al.*[30] confirmed that LDL-cholesterol only decreased significantly after 12 weeks and not after 4 and 8 weeks of ACN supplementation.

Also, in the systematic review/meta-analysis by Daneshzad *et al.*[12] significant reductions for total cholesterol, TAG and LDL-cholesterol, and significant increase for HDL-cholesterol were observed among patients with hypercholesterolaemia, indicating that ACN supplementation may provide a higher benefit to these patients in comparison to healthy individuals. Similar conclusions were drawn from a previous systematic review of Wallace *et al.*[31] evaluating effects of purified ACN and ACN-rich extracts on markers of CVD (total cholesterol, TAG, LDL-cholesterol, HDL-cholesterol, BP) in healthy and diseased subjects in supplementation trials ranging from 3 to 24 weeks and ACN doses from 7·4 to 640 mg/d stating that largest reductions (particularly LDL-cholesterol) could be achieved in subjects with elevated levels.

To summarise, ACN and ACN-rich foods are generally accepted to benefit (maintaining) healthy BW, improvement of glucose and lipid metabolism which has been demonstrated at least partially in a number of intervention studies. Variations seen in outcomes of individual studies may be due to varying ACN dose and duration of intervention trials with a duration of 12 weeks and amounts about 300 mg ACN being considered beneficial. However, the source of ACN *per se* might have a strong impact on its effectivity. Highly methylated ACN such as malvidin and petunidin have demonstrated to be more effective at reducing negative metabolic consequences (body composition, energy expenditure, mitochondrial dysfunction) in high-fat diet fed C57BL/6 mice[32]. At present, to classify ACN and/or ACN sources based on their effectiveness is not possible. Future studies need to consider the ACN concentration and profile, the possible synergism between different ACN and other bioactives within the same source, as well as factors such as processing and intake patterns.

Catechins

Catechins are a group of polyphenols, flavan-3-ols, belonging to one of most common group of polyphenolics in the human diet, the flavonoids. The name catechin is derived from Cutch tree (*Acacia catechu L.f.*). Catechins are present in abundant concentrations in a variety of fruit, vegetables and plant-based beverages such as apple, berries, cacao beans, black soya bean, hops, tea, beer, wine and fruit juice[33]. The consumption of food rich in catechins is associated with potential health benefits partly based on the antioxidant properties of polyphenols[34]. The chemical structure of catechin consists of two benzene rings (A- and B-rings) and a dihydropyran heterocycle (the C-ring) with a hydroxyl group on C_3. There are two chiral centres on the molecule on C_2 and C_3. Catechin stereoisomers in *cis* ((−)-epicatechin) or *trans* ((+)-catechin) configuration, with respect to C_2 and C_3, are flavan-3-ol compounds. Through esterification with gallate groups, flavanols can form gallic acid conjugates epicatechin (ECG), epigallocatechin and epigallocatechin gallate (EGCG). Condensed catechins are obtained via polymerisation. The most common oligomers derived from ECG are A-type and B-type procyanidins[35].

This review of the clinical trials performed to evaluate the potential health effects of catechins on reducing the risk factors of MetS is focused on the results of human trials performed with food or food supplement or extracts rich in catechins. Studies have mainly been performed with cocoa and green tea, which are considered the richest dietary sources of catechins. Particularly, cocoa contains catechin, ECG and oligomers, and green tea is rich in EGCG, which is considered to be the most potent catechin and responsible for its health properties[36,37].

Hibi *et al.*[38] studied the effects of continual intake of green tea catechins (GTC) in MetS. In particular, the authors led a *post hoc* pooled analysis of data obtained from published reports (six human trials) to assess the effects of continual intake of GTC-containing beverages (540–588 mg/d) on abdominal fat area reduction and improvements in MetS (total 921 subjects). The studies were run in healthy Japanese adults (BW: 71·8 (SD10) kg; WC: 88·9 (SD7·3) cm; BMI: 26·8 (SD2·3) kg/m^2) that consumed GTC for 12 weeks. Volunteers were categorised as pre-MetS and MetS at the initiation of the trial. Results show that BW and BMI were significantly lower in the group receiving the high GTC dose, mean 564 (SD19) mg GTC/d (BW: −1·69 kg, 95 % CI −1·84, −1·53; BMI: −0·65 kg/m^2, 95 % CI −0·70, −0·59 from baseline). WC and abdominal fat area (total fat area, visceral fat area and subcutaneous fat area) decreased significantly from baseline in the high GTC group, and the decrease was significantly greater than that in the low GTC group (35 (SD50) mg/d; $P < 0·001$). Moreover, the

https://doi.org/10.1017/S0029665119000545 Published online by Cambridge University Press

analysis of the subclass exposed that in both groups, low and high catechins, an improvement was observed in the proportion of subjects who improved from pre-MetS to healthy, and from MetS to healthy or pre-MetS, in 30·2 % of subjects in the low-catechin group and 41·5 % of subjects in the high-catechin group. However, the rate was significantly higher in the high-catechin group than in the low-catechin group ($P = 0·024$, χ^2 test).

In contrast, a randomised, doubled-blind, placebo-controlled study by Mielgo-Ayuso *et al.*[34] reported no effect after the consumption of EGCG (300 mg/d) for 12 weeks in eighty-three premenopausal women (BMI 30·0–39·9 kg/m^2). It did neither improve BW nor metabolic risk factors such as blood lipids.

A review carried out by Keske *et al.*[39] showed the heterogenicity of the results in trials aimed to link consumption of EGCG/green tea with glucose tolerance and insulin sensitivity. In patients with T2D, green tea extract (EGCG 860 mg/d) for 16 weeks significantly reduced HOMA-IR, glycosylated haemoglobin (HbA1c) and fasting insulin levels[40], and consumption of more than three cups of tea daily was associated with a 17–35 % lower risk of T2D[41]. Shimada *et al.*[42] revealed that oolong tea consumption for 4 weeks (EGCG 45 mg/d) significantly increases plasma adiponectin levels by 9·9 % and lowers HbA1c levels by 3·3 % in patients with various coronary risk factors. Additionally, there was a slight, but NS, decrease in the fasting plasma glucose levels. Hosoda *et al.*[43] used a higher dose of oolong tea treatment (EGCG 390 mg/d) for 4 weeks and reported lower fasting plasma glucose levels in people with T2D. In contrast, green tea consumption (540 mg/d polyphenols, EGCG content unknown) for 2 months had no apparent effect on metabolic markers such as fasting serum glucose and insulin, HbA1c and HOMA-IR[44]. The proportion of flavanols (ratio of catechins is different in oolong tea than in green tea) and the study duration are critical aspects to modulate glucose metabolism positively.

The results of intervention studies indicate that consumption of flavan-3-ols is associated with an improvement of lipid homeostasis parameters such as HDL-cholesterol and LDL-cholesterol. Tokede *et al.*[37] analysed ten RCT of interventions (total 320 participants) administering dark chocolate/cocoa products for 2–12 weeks. Eight of the studies were comparing flavanol-rich cocoa or dark chocolate with either flavanol-poor white chocolate or a matching placebo. One study compared milk chocolate with cocoa butter and one compared a supplemented diet with dark chocolate and cocoa podwer with an unsupplemented diet. Therefore, the intake of catechins was heterogenous, from 963 to 88 mg/d compared with control intake from 0 to 75 mg catechins. The differences in catechin intake between cocoa/chocolate group and control ranged from 8·74 % to more than 100 %. The authors reported a significant reduction in serum LDL-cholesterol and total cholesterol levels (−5·90 and −6·23 mg/dl, respectively; data as MD of the results of the ten studies). No statistically significant effects were observed for HDL-cholesterol and TAG. Hooper *et al.*[45] described the marginally significant effects of cocoa products on LDL-cholesterol (−0·07 mM; 95 % CI −0·13, 0·00 mM), HDL-cholesterol (0·03 mM; 95 % CI 0·00, 0·06 mM) and cholesterol (data referred as MD of the differences in each study between cocoa group and control).

Hartley *et al.*[46] carried out an analysis of RCT lasting al least 3 months which investigated the effects of black or green tea or tea extracts involving healthy adults or those at high risk of CVD. The global analysis of the consumption of black tea (1 g extract/d, 1·29 g black tea polyphenols/d; three serving of black tea (200 ml/serving) and 318 mg black tea catechin/d) was found to produce statistically significant reductions in LDL-cholesterol (MD −0·43 mM, 95 % CI −0·56, −0·31). Green tea (58·91 mg catechin in green tea, 500 mg green tea polyphenols/d, 375 mg green tea extract/d, 200 mg theanine and 400 mg decaffeinated catechin green tea extract/d) was also found to produce statistically significant reductions in total cholesterol (MD −0·62 mm, 95 % CI −0·77, −0·46) and LDL-cholesterol (MD −0·64 mM, 95 % CI −0·77, −0·52). When both tea types were analysed together they showed favourable effects on LDL-cholesterol (MD –0·48 mM, 95 % CI −0·61, −0·35).

The meta-analysis of Desch *et al.*[47] and Hooper *et al.*[45] confirmed the BP-lowering capacity of flavanol-rich cocoa products. Desch *et al.*[47] analysed 297 participants including six cross-over and four parallel-group designs. Although the studies displayed a diverse spectrum of treatment regimens (duration 2–8 weeks and intake 6·8–902 mg/d flavanol), results revealed that the mean BP reduction was −4·5 mmHg (95 % CI −5·9, −3·2; $I^2 = 89$ %) for systolic BP and −2·5 mmHg (95 % CI −3·9, −1·2; $I^2 = 90$ %) for diastolic BP. Hooper *et al.*[45] reviewed the effects of chocolate, cocoa and flavan-3-ols including forty-two acute or short-term chronic (≤18 weeks) RCT that comprised 1297 participants. They observed reductions in diastolic BP (−1·60 mm Hg; 95 % CI −2·77, −0·43 mm Hg) and mean arterial pressure (−1·64 mm Hg; 95 % CI −3·27, 0·01 mm Hg). Although some studies did not identify dose-dependent effects of ECG, subgrouping by ECG dose suggested greater effects for systolic and diastolic BP at doses >50 mg/d. In the earlier reported meta-analyses by Hibi *et al.*[38] a significant decrease of systolic BP compared with baseline was observed only in the high catechin group (−11 mmHg, 95 % CI −2·1, −0·1; $P < 0·01$). The eleven RCT analysed by Hartley *et al.*[46] evidenced that black tea consumption significantly reduced systolic BP (MD −1·85 mmHg, 95 % CI −3·21, −0·48), and green tea consumption significantly decreased both systolic and diastolic BP (MD −3·18 mmHg, 95 % CI −5·25, −1·11 and MD −3·42, 95 % CI −4·54, −2·30, respectively).

Most of the studies in the literature have been performed using catechins from tea or cocoa, and have evidenced that the dose exerting positive effects strongly depends on the physiological parameters that are being studied. Overall, catechins from tea seem to be effective in most of the MetS risk factors at a daily intake above 390 mg. The effect of cocoa's C is evident on BP with an intake from 6·5 mg/d.

Overall, several *in vitro* and *in vivo* animal studies are elucidating the potential mechanisms of action of

https://doi.org/10.1017/S0029665119000545 Published online by Cambridge University Press

catechins and they are on the way to demonstrate that flavan-3-ols can modulate metabolic pathways of the glucose and lipid metabolism and BP. It has been reported that EGCG up-regulates LDL receptor mRNA, reduces ApoB levels and inhibits pancreatic lipase, thereby reducing the absorption of dietary lipids[48]. Therefore, the modulation of molecules in lipid and glucose metabolism and the reduction on the delivery of proinflammatory cytokines as IL-6[49] by catechins could contribute to reducing cholesterolaemia (LDL-cholesterol and total cholesterol) and BW. *In vitro* studies in several cell types (myocytes, adipocytes and hepatocytes) have reported that green tea or EGCG have insulin-mimetic metabolic actions. EGCG stimulates the uptake of glucose by stimulation of GLUT4 translocation[39]. Analysis in endothelial cells show the enhancement of nitric oxide production by EGCG[48,50]. Apart from the metabolic regulation, recent studies are focusing on assessing the epigenetic modulation of candidate genes of MetS by flavan-3-ols[48].

Although these mechanisms could justify positive effects of catechins in human subjects, results of clinical intervention studies are still controversial. This is probably due to discrepancies among studies, including varying experimental designs, type and doses of catechin. Further research is needed to draw robust conclusions.

β-Glucan

BG is a NSP found in the cell walls of endosperm and aleurone cells of grains. BG consists of short β-(1,4)-D-glycans (cellotriosyl and cellotetraosyl units) linked to each other by β-(1,3) linkages leading to polymers of high molecular weight ranging from 8 to 200 kDa[51]. This specific chemical structure is responsible for its physical properties, such as high solubility and viscosity which may contribute to the health benefits attributed to BG[52], in particular those attributed to improvements of cardiometabolic health. Oat and barley are rich in BG, and most of the studies have been performed using BG from oat or barley.

Elevated WC is one of the criteria for MetS. However, clinical studies on BG have not focused on this anthropological parameter. A 4 % decrease of the WC was observed following adoption of a healthy diet that included 'viscous fibres' amongst other dietary improvements[53], which also saw improvement in a number of metabolic markers including fasting glucose, total and HDL-cholestrol. Beck *et al.*[54] observed a significant effect of oat BG consumption (5–9 g/d) at breakfast on BW and WC, together with improvements in metabolic markers and alterations in levels of satiety hormones including leptin, and peptide YY. The study, however, showed that an energy-restricted diet had similar effects compared with oat BG consumption, which did not enhance the effectiveness of energy restriction. It is worth noting that the EFSA panel did not find sufficient evidence to substantiate a link between BG consumption and a reduction in appetite or BW (maintenance or achievement of normal BW)[55], although the panel did not consider evidence related to WC.

Conversely, EFSA supported a health claim stating that regular consumption of BG contributes to the maintenance of normal blood cholesterol concentrations for foods that provide 'at least 3 g/d BG from oats, oat bran, barley, barley bran, or from mixtures of non-processed or minimally processed BG in one or more servings'[55]. The US Food and Drugs Administration provided a similar recommendation[56].

A meta-analysis of epidemiological studies reported beneficial effects on blood lipids associated with consumption of soluble fibre from both oats and barley, but reported high levels of heterogeneity and called for well-controlled intervention studies[57]. A meta-analysis of RCT showed that oat BG at doses higher than 3 g/d reduced LDL-cholesterol and total cholesterol significantly compared with control, with little or no effect on HDL-cholesterol and TAG irrespective of dose or study duration[58]. The authors specified that the effectiveness of oat BG is linked to its high molecular weight and associated physicochemical properties, however called for more dose–response and longer studies to evaluate impacts of chronic consumption of oat BG in healthy and MetS populations.

Ibrugger *et al.*[59] compared the effects of BG from oats and barley and showed that neither affected blood lipids significantly compared with the control. However, the consumption of 3·3 g/d oat BG led to the largest observed decrease in total cholesterol and LDL-cholesterol, as well as significantly reducing TAG. The authors identified a lack of systematic studies, with great differences amongst studies in terms of study foods, dose and study duration. Few of the intervention studies investigated the dose–effect relationship between oat BG and blood cholesterol. Biorklund *et al.*[60] reported that consuming a drink containing 5 g/d oat BG resulted in a 6·7 % decrease in LDL-cholesterol, while consumption of the drink containing 10 g/d oat BG reduced LDL-cholesterol by only 3·7 %, compared with control drink. Kerckhoffs *et al.*[61] highlighted that processing of oats could have an adverse effect on the cholesterol lowering effect. Charlton *et al.*[62] showed that 1·5 g/d provided as cereal flakes was just as effective as 3 g/d provided as porridge in lowering blood cholesterol. Wolever *et al.*[63] showed the importance of molecular weight for the effectiveness of oat BG towards cholesterol markers[63]. The impact of processing on oat BG properties has been recently reviewed by Grundy *et al.*[64]. In healthy people, BG consumption does not appear to affect lipid homeostasis[65].

Epidemiological studies have supported the association between whole-grain intake and improved metabolic risk factors for T2D and MetS[66,67]. The fasting glucose concentrations decreased across increasing quartile categories of whole-grain intake. However, few clinical trials have focused on the impact of the consumption of BG on glucose metabolism. Many studies investigating BG and lipid homeostasis have also investigated impacts on glucose homeostasis. The EFSA panel supported a claim that consuming 4 g BG from oats or barley for each 30 g available carbohydrate decreased post-prandial glycaemic response without disproportionally increasing insulin response. The effect was observed

https://doi.org/10.1017/S0029665119000545 Published online by Cambridge University Press

when BG was incorporated into carbohydrate-rich food (e.g. bread or pasta) and when combined into a meal[55]. Consuming at least 4 g BG per meal, from either oats or barley, and where the BG is soluble and has a molecular weight >250 000g/mol is sufficient to significantly reduce post-prandial area under curve by 27 (SD3) mmol min/l for meals with about 30–80 g available carbohydrates[68]. He *et al.*[69] carried out a meta-analysis of controlled intervention trials, and showed that consumption of either whole-grain oats or BG extracted from oats was associated with strong significant reducing effects on fasting glucose and fasting insulin in T2D patients, but no effect on hyperlipidaemic subjects. A moderate effect was observed for obese subjects without hyperlipidaemia. A long-term (6 months) substitution of regular white bread with a functional bread enriched with fibre (7·62 g/100 g of bread, mostly BG) in the everyday diet of subjects with T2D induced no statistical difference on the fasting glucose level, but a significant decrease was observed for the post-prandial plasma glucose ($P = 0{\cdot}001$) and mean plasma glucose ($P = 0{\cdot}02$) with the 'functional bread' compared with the control bread[70]. In this study, other metabolic markers such as blood lipids and BP were not affected.

Few clinical trials have specifically studied the effects of the consumption of BG on BP. The results of the different studies show discrepancies. Past results obtained with healthy volunteers generally did not demonstrate an effect of the consumption of fibres on BP compared with low-fibre grain supplementation[71]. However, a recent meta-analysis concluded that systolic and diastolic BP could be reduced by 2·9 mmHg (95 % CI 0·9, 4·9) and 1·5 mmHg (95 % CI 0·2, 2·7), respectively, by diets rich in BG, for a median difference in BG of 4 g in healthy volunteers[72]. The consumption of BG should thus help to manage BP of non-healthy people, especially people at risk of MetS. In 2006, Behall *et al.*[73] demonstrated the effects of consuming controlled portions of whole-grain rice and barley BG on BP in twenty-five overweight/obese mildly hypercholesterolaemic women. Both whole-grain rice and barley BG interventions led to significant decreases in diastolic BP and the mean arterial pressure, especially in post-menopausal women. In a randomised cross-over design, the consumption of a diet enriched in legumes and barley by overweight women for 4 weeks induced a significant reduction (−3 %, $P < 0{\cdot}05$) of the diastolic BP but no effect was observed on systolic BP compared with the equivalent diet without legumes and barley[74]. A similar observation was made in healthy and obese men and women consuming multifunctional diets that included BG amongst other health-enhancing constituents[53]. However, it is difficult to dissociate the effect of BG from other constituents in the diet.

Summarising, there is strong and consistent evidence that consumption of BG impacts on lipid metabolism, with strong caveats relating to the dose and molecular size required for effects. There are multiple mechanisms associated with the effects of BG on lipid metabolism which may be acting in concert to excerpt positive effects. Proposed mechanisms include increased gut permeability[75], reduced lipid digestion and absorption[52], decreased bile reabsorption through physical barrier and bile colonic metabolism[76], increased bile acid production and SCFA metabolism[77] which impact on cholesterol homeostasis. There is also strong evidence supporting a role for BG in control of post-prandial glucose, but its effect may be attributed to fibre in general, rather than specifically to BG.

The evidence for other markers of MetS including BW, fasting glucose and BP are less well established. It is clear that further research is needed, also focusing on BG-matrix interactions and implications of food processing.

n-3 Long chain PUFA

n-3 LCPUFA, namely EPA and DHA have been suggested as potential anti-obesity bioactives[5], and growing evidence is emerging about the role of white adipose tissue in mediating the beneficial effects of marine *n*-3 PUFA in obesity-associated metabolic disorders. EPA and DHA have been shown to reduce BW and fat deposition in human clinical studies[78]. Their mechanism of action is supposed to be multiple. After consumption, these fatty acids are incorporated into cell membranes where they modulate membrane protein function, cellular signalling and gene expression[79]. Incorporation of EPA and DHA into tissues may modify inflammatory and immune reactions, mainly by inhibiting pro-inflammatory interleukins, therefore counteracting low-grade chronic inflammation caused by obesity. It has been suggested that MetS is the consequence of adipose tissue abnormalities. Therefore, *n*-3 LCPUFA could target adipose tissue inflammation and improve systemic metabolism[80]. In addition, several trials indicate that *n*-3 LCPUFA reduce hypertension, total cholesterol and TAG levels in the body, being a perfect candidate to develop nutritional strategies to counteract MetS.

In 2012 and 2013, the effects of EPA and DHA have been in the focus of two reviews emphasising several limitations, including varying experimental designs, type and doses of *n*-3 PUFA, making it impossible to draw robust conclusions[81,82]. Other trials have been performed in the following years using supplements, fish oil (FO) or enriched foods.

In the single-blind, parallel trial described by Oh *et al.*[83] a placebo or *n*-3 PUFA as supplement (1, 2 or 4 Omacor® capsules each containing 460 mg EPA ethyl ester and 380 mg DHA ethyl ester) were randomly administered to 176 patients with primary hypertriglyceridaemia (>150 mg/dl) once daily for 2 months. *n*-3 PUFA treatment dose-dependently and significantly decreased TAG and TAG/HDL-cholesterol and improved flow-mediated dilation but caused no significant modification in BMI compared with placebo.

Likewise, no modification in fat-free mass, upper-body subcutaneous fat mass and visceral fat mass across the intervention or between groups was observed in the prospective, randomised, placebo-controlled, double-blind study by Hames *et al.*[84] involving insulin-resistant, overweight or obese adults aged 18–65 years. Participants

https://doi.org/10.1017/S0029665119000545 Published online by Cambridge University Press

were randomly assigned to placebo (4·2 g oleic acid/d) or received a supplement containing 3·9 g EPA + DHA/d. Although EPA and DHA concentration in plasma and adipose tissue significantly increased in the *n*-3 group, there was no improvement in adipose tissue markers of inflammation. BMI (+0·7; $P = 0·03$), percentage of body fat (0·9 %; $P = 0·009$) and leg fat mass (0·5 kg; $P = 0·02$) increased for participants in both groups at the end of the intervention, and the changes were not different between groups.

Supplementation with *n*-3 LCPUFA did not improve the effect of a hypoenergetic diet in the RCT by Tardivo *et al.*[85]. The trial included eighty-seven postmenopausal Brazilian women with MetS, who were randomised to diet alone or diet plus *n*-3 supplementation, 900 mg/d. After 6 months, despite significant reductions in BMI and WC observed in both groups, there were no changes in body fat or muscle mass. Intervention with *n*-3 LCPUFA was associated with significant reduction in systolic (<12·2 %) and diastolic (<8·2 %) BP, serum TAG concentration (<21·4 %) and IR (<13·1 %; $P < 0·05$), as well as a reduction in serum IL-6 concentration (<28·5 %; $P = 0·034$).

In contrast, a significant effect on body fat upon *n*-3 LCPUFA supplementation was observed by Barbosa *et al.*[86]. In this double-blind, placebo-controlled, randomised clinical trial, a supplement containing *n*-3 LCPUFA (3 g/d; 37 % EPA and 23 % DHA) or placebo (3 g/d sunflower oil) were administered for 2 months. Study participants were eighty men and women, aged 30–74 years, with some classic CVD risk factors (overweight, hypertension, dyslipidaemia, diabetes, smoking) with or without treatment and without previous cardiovascular event. The *n*-3 group showed a significant reduction of body fat compared with the placebo group, without any significant modification in BW, BMI and WC. In the treated group, an increase in serum adiponectin was detected. Adiponectin synthesis is inversely proportional to the amount of adipose tissue[86]; in animals, increased *n*-3 LCPUFA consumption is associated with increased adiponectin levels, however the results are controversial in human subjects[87]. Results of this trial confirm that *n*-3 LCPUFA consumption reduces body fat, leading to increased concentration of adiponectin and this, in turn, could further influence the reduction of fat mass.

Overall, although *n*-3 LCPUFA as supplements modify some MetS and CVD-related parameters they seem to have no effect on BW and BMI. On the contrary, a significant reduction of body fat could be related to the administration of supplements containing 3 g/d EPA + DHA.

The effect of an increased dietary intake of *n*-3 LCPUFA could be different. The RCT of the LIPGENE study[88] involved volunteers aged 35–70 years with BMI 20–40 kg/m^2, characterised by at least three of the following five criteria: high WC, high fasting glycaemia, high TAG, high BP, low HDL-cholesterol. Each subject was randomly stratified to one of four dietary interventions for 12 weeks: high SFA; high MUFA; *n*-3 diet including 1·24 g/d *n*-3 LCPUFA with a ratio of 1·4 EPA:DHA; control diet, including control high-oleic acid sunflower seed oil capsules. Volunteers were stratified according to their IR. MetS subjects without IR (lower HOMA-IR) showed improvement in metabolic risk factors related to MetS, such as obesity, BP and lipid markers, after consumption of the *n*-3 LCPUFA diet. In addition, in subjects without IR, WC was reduced after consumption of the control and *n*-3 LCPUFA diets compared with the high SFA and high MUFA diets (all $P < 0·05$).

Based on the evidence of the health benefits related to the consumption of oily fish[89], some trials administered *n*-3 LCPUFA as FO, enriched oils or enriched food. The intervention study by Venturini *et al.*[90] included 102 patients (eighty-one women and twenty-one men) with MetS (mean age 51·45 (SD 8·27) years) aimed to compare extra virgin olive oil (OO) and FO effects, also investigating their possible synergism. Patients in the control group were instructed to maintain their usual diet; FO group received 3 g/d FO (ten capsules, each one containing 180 mg EPA and 120 mg DHA); OO group received 10 ml/d OO; and the fourth group (FOO) received 3 g/d FO and 10 ml/d OO. After 90 d intervention, no intragroup changes in anthropometric parameters were observed compared with baseline. In the FOO group, after treatment a significant decrease in LDL-cholesterol, and total cholesterol/HDL-cholesterol and LDL-cholesterol/HDL-cholesterol indexes was observed compared with baseline.

Fifty-nine subjects with early-stage T2D or MetS participated in an 8-week, randomised, single-blind, parallel intervention study[91]. Individuals received either corn oil, a botanical oil combination (borage (*Borago officinalis* L.)/echium oil (*Echium plantagineum* L.)) or FO (EPA 3·58 g/d and DHA 2·44 g/d). FO supplementation induced a marked increase in serum levels of *n*-3 LCPUFA, HDL-cholesterol and insulin, and a decrease in serum TAG. No indication of the effect on anthropometric data was reported by the researchers.

A randomised, cross-over, five diet period, controlled feeding study was conducted by Liu *et al.*[92] on 130 participants with BMI 22–40 kg/m^2 with central obesity plus at least one other MetS criteria. Five treatment oils: rapeseed oil, CanolaOleic (high-oleic acid rapeseed oil), CanolaDHA (high-oleic acid rapeseed oil with DHA), maize/saff (maize/safflower oil) and flax/saff (flax/safflower oil) were incorporated into smoothies that participants consumed twice daily. The quantity of oil was calculated based on participant energy needs, and it provided 18 % of total energy. The impact of each test diet on BW and body composition was low, and mainly on android fat mass that significantly decreased from baseline on the rapeseed and CanolaOleic oil diets only. The reduction in android fat mass was positively correlated with decreases in cardiometabolic risk factors including TAG, systolic and diastolic BP after all diets except the maize/saff lower oil group.

In a double-blind randomised trial, thirty-six patients with MetS received 500 ml/d semi-skimmed milk (placebo) or 500 ml/d skimmed milk enriched with 275 mg EPA + DHA and 7·5 g oleate and underwent 24 weeks of high-intensity interval training[93]. Treatment did not increase *n*-3 LCPUFA plasma concentration, and a similar decrease in BW, WC, body fat mass, trunk fat mass and BP were observed in placebo and treated group. However, insulin sensitivity, serum concentration of C-reactive protein and HDL-cholesterol improved only in the treated group.

https://doi.org/10.1017/S0029665119000545 Published online by Cambridge University Press

As for supplements, the increase of *n*-3 LCPUFA intake by FO or enriched-food significantly improves different physiological parameters without clear effect on BW, BMI and other anthropometric parameters.

The effect of *n*-3 LCPUFA was also investigated in combination with other bioactives. Eventy-eight individuals (thirty-three men and forty-five women), aged 35–70 years, with a large BMI (27–35 kg/m^2) and WC (men >102 cm, women >88 cm) and at least one more component of the MetS were recruited in the trial reported by Bondia-Pons *et al.*[94]. Participants were randomly assigned to one of four different nutritional interventions for the duration of 8 weeks. Diets only differed for the content of *n*-3 LCPUFA and polyphenols. Dependency network analysis showed a different pattern of associations between lipidomics, dietary and clinical variables after the dietary interventions, but no modification in BMI or WC were observed in any group.

Foods with a combination of high-oleic acid rapeseed oil-DHA and barley BG have been used in the CONFIDENCE trial, a randomised, single-blind cross-over trial with four treatment phases of 28 d each[95]. The possible synergism between DHA and other bioactives was also in the focus of the EU project PATHWAY-27 (Pivotal assessment of the effects of bioactives on health and wellbeing. From human genoma to food industry)[96] that investigated the role and mechanisms of action of DHA, oat BG and ACN, alone and in combination, in the counteraction of MetS considering them not as stand-alone molecules but as ingredients of food. In PATHWAY-27, three monocentric, parallel-arm, randomised, double-blind pilot trials and a multicentre, randomised, placebo-controlled, parallel-arm dietary intervention study were performed on subjects at risk of MetS. At present, neither CONFIDENCE nor PATHWAY-27 results are available in the literature to report on the outcomes of potential combined effects in interventions involving DHA, BG (and ACN).

Based on available results, the increased intake of *n*-3 LCPUFA seem to have an effect on BW and BMI only if it is associated to modification of the whole diet so we can argue that it is not simply due to LCPUFA themselves. The effectiveness of *n*-3 LCPUFA on other parameters has been evidenced in trials using both supplements and enriched food with differences related to the daily dose, the duration of the intervention and the EPA:DHA ratio.

Conclusion

Bioactives are a promising field of study for alternative strategies to reduce the onset and progression of MetS and its related pathologies including obesity. Some bioactives, such as ACN, catechins, BG and *n*-3-LCPUFA, are considered good candidates since they have demonstrated positive effects in reducing MetS risk acting through different mechanisms. There are therefore opportunities to investigate synergistic effects. However, there are still gaps in the evidence for some bioactives due to the low number of controlled intervention trials available or to inconsistent results among different trials likely caused by differences between dose and treatment time as well as the characteristics of the enrolled population. The inconsistencies could be also related to the source of the bioactive (extracts, supplements, enriched food, diet) that could impact on the bioavailability of the bioactive compounds. Bioavailability is seldom considered in intervention trials, neither its possible modification due to food processing. In addition, lifestyle factors, including dietary habits, play a fundamental role in intervention studies using bioactives.

Since bioactives are food components, their intake can be increased in different ways, i.e. modifying the dietary pattern, including enriched foods in the diet (with or without modification of the dietary pattern) or administering supplements. Although the differences among these possible treatments are huge and evident, thus far no studies have been performed to compare the efficacy of diet *v.* enriched-foods *v.* supplements as bioactive vehicle. Anyway, conclusions from such trials could be difficult to interpret since bioactive consumption by dietary modification impacts on the dietary pattern. As an example, an increased *n*-3 LCPUFA consumption can only be achieved by including additional servings of oily fish, which is hard to achieve without reducing consumption of other food, while an increased catechin intake could be effected more simply through additional consumption of tea, with no or limited effect on the consumption of other food items. Also limiting the comparison to a specific bioactive, it is hard to extrapolate from different trials whether diet, enriched foods or supplements have acted more efficiently in exerting the claimed health effects mainly because the results of different studies are strongly dependent on the dosage, period of intervention, characteristics of the population and the condition studied.

Dietary intervention trials aimed to verify the effectiveness of bioactive are more intriguing than drug trials. The effect of food bioactives is generally weaker than drugs, so it can be more easily masked by interfering factors. Apart from supplements, increased bioactive intake modifies the usual diet making it difficult to discriminate the contribution of the dietary modification to the final effect. In summary, the demonstration of bioactive effectiveness is an uphill struggle. Nevertheless, it is worth tackling since bioactives are generally well accepted by consumers, generally safe and may be an alternative or additional therapeutic resource with considerable potential in the treatment of MetS. Therefore, increased effort should be made within the scientific community to design high-quality clinical intervention trials with clearly defined and comparable supplementations and cohorts to increase the evidence for bioactive supplementation for the field to move forward towards evidence-based recommendations for prevention and targeted intervention strategies. Harmonisation of study design for bioactive effectiveness would be a positive step towards gathering robust evidence. The PATHWAY-27 consortium published scientific guidelines to guide the scientific community to design trials for bioactive effectiveness[97].

Acknowledgements

The authors thank all participants of the PATHWAY-27 EU project.

Financial Support

None.

Conflict of Interest

None.

Authorship

The authors had joint responsibility for the overall preparation of this paper. Specifically, L. T. C. took care of the catechins section, C. B. of the ACN section, C. M. B. and C. O. of the BG and A. B. of the *n*-3 LCPUFA section.

References

1. Eisenstein J, Roberts SB, Dallal G *et al.* (2002) High-protein weight-loss diets: are they safe and do they work? A review of the experimental and epidemiologic data. *Nutr Rev* **60**, 189–200.
2. Sacks FM, Bray GA, Carey VJ *et al.* (2009) Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. *N Engl J Med* **360**, 859–873.
3. Bosy-Westphal A & Muller MJ (2015) Assessment of fat and lean mass by quantitative magnetic resonance: a future technology of body composition research? *Curr Opin Clin Nutr Metab Care* **18**, 446–451.
4. Sakulnarmrat K, Srzednicki G & Konczak I (2014) Composition and inhibitory activities towards digestive enzymes of polyphenolic-rich fractions of Davidson's plum and quandong. *LWT – Food Sci Technol* **57**, 366–375.
5. Torres-Fuentes C, Schellekens H, Dinan TG *et al.* (2015) A natural solution for obesity: bioactives for the prevention and treatment of weight gain. A review. *Nutr Neurosci* **18**, 49–65.
6. Eckel RH, Alberti KG, Grundy SM *et al.* (2010) The metabolic syndrome. *Lancet* **375**, 181–183.
7. Khoo HE, Azlan A, Tang ST *et al.* (2017) Anthocyanidins and anthocyanins: colored pigments as food, pharmaceutical ingredients, and the potential health benefits. *Food Nutr Res* **61**, 1–21.
8. Vendrame S, Del Bo C, Ciappellano S *et al.* (2016) Berry fruit consumption and metabolic syndrome. *Antioxidants* (*Basel*) **5**, e34.
9. Belwal T, Nabavi SF, Nabavi SM *et al.* (2017) Dietary anthocyanins and insulin resistance: when food becomes a medicine. *Nutrients* **9**, 1111.
10. Wu T, Gao Y, Guo X *et al.* (2018) Blackberry and blueberry anthocyanin supplementation counteract high-fat-diet-induced obesity by alleviating oxidative stress and inflammation and accelerating energy expenditure. *Oxid Med Cell Longev* [Epublication 2018].
11. Solverson PM, Rumpler WV, Leger JL *et al.* (2018) Blackberry feeding increases fat oxidation and improves insulin sensitivity in overweight and obese males. *Nutrients* **10** [Epublication August 2018].
12. Daneshzad E, Shab-Bidar S, Mohammadpour Z *et al.* (2018) Effect of anthocyanin supplementation on cardio-metabolic biomarkers: a systematic review and meta-analysis of randomized controlled trials. *Clin Nutr* [Epublication ahead of print version].
13. Amiot MJ, Riva C & Vinet A (2016) Effects of dietary polyphenols on metabolic syndrome features in humans: a systematic review. *Obes Rev* **17**, 573–586.
14. Broncel M, Kozirog M, Duchnowicz P *et al.* (2010) *Aronia melanocarpa* extract reduces blood pressure, serum endothelin, lipid, and oxidative stress marker levels in patients with metabolic syndrome. *Med Sci Monit* **16**, CR28–CR34.
15. Lehtonen HM, Suomela JP, Tahvonen R *et al.* (2011) Different berries and berry fractions have various but slightly positive effects on the associated variables of metabolic diseases on overweight and obese women. *Eur J Clin Nutr* **65**, 394–401.
16. Moazen S, Amani R, Rad AH *et al.* (2013) Effects of freeze-dried strawberry supplementation on metabolic biomarkers of atherosclerosis in subjects with type 2 diabetes: a randomized double-blind controlled trial. *Ann Nutr Metab* **63**, 256–264.
17. Castro-Acosta ML, Lenihan-Geels GN, Corpe CP *et al.* (2016) Berries and anthocyanins: promising functional food ingredients with postprandial glycaemia-lowering effects. *Proc Nutr Soc* **75**, 342–355.
18. Johnson MH & de Mejia EG (2016) Phenolic compounds from fermented berry beverages modulated gene and protein expression to increase insulin secretion from pancreatic beta-cells *in vitro*. *J Agric Food Chem* **64**, 2569–2581.
19. Luna-Vital DA & Gonzalez de Mejia E (2018) Anthocyanins from purple corn activate free fatty acid-receptor 1 and glucokinase enhancing *in vitro* insulin secretion and hepatic glucose uptake. *PLoS ONE* **13**, e0200449.
20. Rozanska D & Regulska-Ilow B (2018) The significance of anthocyanins in the prevention and treatment of type 2 diabetes. *Adv Clin Exp Med* **27**, 135–142.
21. Matsukawa T, Inaguma T, Han J *et al.* (2015) Cyanidin-3-glucoside derived from black soybeans ameliorate type 2 diabetes through the induction of differentiation of preadipocytes into smaller and insulin-sensitive adipocytes. *J Nutr Biochem* **26**, 860–867.
22. Scazzocchio B, Vari R, Filesi C *et al.* (2011) Cyanidin-3-O-beta-glucoside and protocatechuic acid exert insulin-like effects by upregulating PPARgamma activity in human omental adipocytes. *Diabetes* **60**, 2234–2244.
23. Castro-Acosta ML, Smith L, Miller RJ *et al.* (2016) Drinks containing anthocyanin-rich blackcurrant extract decrease postprandial blood glucose, insulin and incretin concentrations. *J Nutr Biochem* **38**, 154–161.
24. Jennings A, Welch AA, Spector T *et al.* (2014) Intakes of anthocyanins and flavones are associated with biomarkers of insulin resistance and inflammation in women. *J Nutr*, **144**, 202–208.
25. Soltani R, Gorji A, Asgary S *et al.* (2015) Evaluation of the effects of *Cornus mas* L. Fruit extract on glycemic control and insulin level in type 2 diabetic adult patients: a randomized double-blind placebo-controlled clinical trial. *Evid Based Complement Alternat Med* [Epublication October 2015].
26. Yang L, Ling W, Yang Y *et al.* (2017) Role of purified anthocyanins in improving cardiometabolic risk factors in Chinese men and women with prediabetes or early untreated diabetes-a randomized controlled trial. *Nutrients* **9** [Epublication October 2017].
27. Yang L, Ling W, Du Z *et al.* (2017) Effects of anthocyanins on cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials. *Adv Nutr* **8**, 684–693.
28. Hassellund SS, Flaa A, Kjeldsen SE *et al.* (2013) Effects of anthocyanins on cardiovascular risk factors and inflammation in pre-hypertensive men: a double-blind randomized placebo-controlled crossover study. *J Hum Hypertens* **27**, 100–106.

https://doi.org/10.1017/S0029665119000545 Published online by Cambridge University Press

29. Zhu Y, Huang X, Zhang Y *et al.* (2014) Anthocyanin supplementation improves HDL-associated paraoxonase 1 activity and enhances cholesterol efflux capacity in subjects with hypercholesterolemia. *J Clin Endocrinol Metab* **99**, 561–569.
30. Alvarado J, Schoenlau F, Leschot A *et al.* (2016) Delphinol (R) standardized maqui berry extract significantly lowers blood glucose and improves blood lipid profile in prediabetic individuals in three-month clinical trial. *Panminerva Med* **58**, Suppl. 1, 1–6.
31. Wallace TC, Slavin M & Frankenfeld CL (2016) Systematic review of anthocyanins and markers of cardiovascular disease. *Nutrients* **8** [Epublication January 2016].
32. Skates E, Overall J, DeZego K *et al.* (2018) Berries containing anthocyanins with enhanced methylation profiles are more effective at ameliorating high fat diet-induced metabolic damage. *Food Chem Toxicol* **111**, 445–453.
33. Braicu C, Ladomery MR, Chedea VS *et al.* (2013) The relationship between the structure and biological actions of green tea catechins. *Food Chem* **141**, 3282–3289.
34. Mielgo-Ayuso J, Barrenechea L, Alcorta P *et al.* (2014) Effects of dietary supplementation with epigallocatechin-3-gallate on weight loss, energy homeostasis, cardiometabolic risk factors and liver function in obese women: randomised, double-blind, placebo-controlled clinical trial. *Br J Nutr* **111**, 1263–1271.
35. Bernatoniene J & Kopustinskiene DM (2018) The role of catechins in cellular responses to oxidative stress. *Molecules* **23**, 965.
36. Suzuki T, Pervin M, Goto S. *et al.* (2016) Beneficial effects of tea and the green tea catechin epigallocatechin-3-gallate on obesity. *Molecules* **21** [Epublication September 2016].
37. Tokede OA, Gaziano JM & Djousse L (2011) Effects of cocoa products/dark chocolate on serum lipids: a meta-analysis. *Eur J Clin Nutr* **65**, 879–886.
38. Hibi M, Takase H, Iwasaki M *et al.* (2018) Efficacy of tea catechin-rich beverages to reduce abdominal adiposity and metabolic syndrome risks in obese and overweight subjects: a pooled analysis of 6 human trials. *Nutr Res* **55**, 1–10.
39. Keske MA, Ng HL, Premilovac D *et al.* (2015) Vascular and metabolic actions of the green tea polyphenol epigallocatechin gallate. *Curr Med Chem* **22**, 59–69.
40. Hsu CH, Liao YL, Lin SC *et al.* (2011) Does supplementation with green tea extract improve insulin resistance in obese type 2 diabetics? A randomized, double-blind, and placebo-controlled clinical trial. *Altern Med Rev* **16**, 157–163.
41. Jing Y, Han G, Hu Y *et al.* (2009) Tea consumption and risk of type 2 diabetes: a meta-analysis of cohort studies. *J Gen Intern Med* **24**, 557–562.
42. Shimada K, Kawarabayashi T, Tanaka A *et al.* (2004) Oolong tea increases plasma adiponectin levels and low-density lipoprotein particle size in patients with coronary artery disease. *Diabetes Res Clin Pract* **65**, 227–234.
43. Hosoda K, Wang MF, Liao ML *et al.* (2003) Antihyperglycemic effect of oolong tea in type 2 diabetes. *Diabetes Care* **26**, 1714–1718.
44. Fukino Y, Shimbo M, Aoki N *et al.* (2005) Randomized controlled trial for an effect of green tea consumption on insulin resistance and inflammation markers. *J Nutr Sci Vitaminol* **51**, 335–342.
45. Hooper L, Kay C, Abdelhamid A *et al.* (2012) Effects of chocolate, cocoa, and flavan-3-ols on cardiovascular health: a systematic review and meta-analysis of randomized trials. *Am J Clin Nutr* **95**, 740–751.
46. Hartley L, Flowers N, Holmes J *et al.* (2013) Green and black tea for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev*, CD009934.
47. Desch S, Schmidt J, Kobler D *et al.* (2010) Effect of cocoa products on blood pressure: systematic review and meta-analysis. *Am J Hypertens* **23**, 97–103.
48. Legeay S, Rodier M, Fillon L *et al.* (2015) Epigallocatechin gallate: a review of its beneficial properties to prevent metabolic syndrome. *Nutrients* **7**, 5443–5468.
49. Nieto JA, Jaime L, Arranz E *et al.* (2017) Winemaking by-products as anti-inflammatory food ingredients. *Food Agric Immunol* **28**, 1507–1518.
50. Osakabe N (2013) Flavan 3-ols improve metabolic syndrome risk factors: evidence and mechanisms. *J Clin Biochem Nutr* **52**, 186–192.
51. Roubroeks JP, Mastromauro DI, Andersson R *et al.* (2000) Molecular weight, structure, and shape of oat (1-->3), (1-->4)-beta-D-glucan fractions obtained by enzymatic degradation with lichenase. *Biomacromolecules* **1**, 584–591.
52. Wang Q & Ellis PR (2014) Oat beta-glucan: physico-chemical characteristics in relation to its blood-glucose and cholesterol-lowering properties. *Br J Nutr* **112**, Suppl. 2, S4–S13.
53. Tovar J, Johansson M & Bjorck I (2016) A multifunctional diet improves cardiometabolic-related biomarkers independently of weight changes: an 8-week randomized controlled intervention in healthy overweight and obese subjects. *Eur J Nutr* **55**, 2295–2306.
54. Beck EJ, Tapsell LC, Batterham MJ *et al.* (2010) Oat beta-glucan supplementation does not enhance the effectiveness of an energy-restricted diet in overweight women. *Br J Nutr* **103**, 1212–1222.
55. EFSA Panel on Dietetic Products, N.a.A. (2011) Scientific Opinion on the substantiation of health claims related to beta-glucans from oats and barley and maintenance of normal blood LDL-cholesterol concentrations (ID 1236, 1299), increase in satiety leading to a reduction in energy intake (ID 851, 852), reduction of post-prandial glycaemic responses (ID 821, 824), and "digestive function" (ID 850) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. *EFSA J* **9**, 2207.
56. USDA (2018) USDA Code of Federal Regulations – Title 21 Food and Drugs 'Chapter 1- Food and Drugs Administration, sub-chapter B – Food for human consumption'. [Online]. https://www.ecfr.gov/cgi-bin/text-idx?SID=2d2aeedc9a8718efaefd92a31fecba16&mc=true&tpl=/ecfrbrowse/Title21/21CIsubchapB.tpl (accessed August 2018).
57. Tiwari U & Cummins E (2011) Meta-analysis of the effect of beta-glucan intake on blood cholesterol and glucose levels. *Nutrition* **27**, 1008–1016.
58. Whitehead A, Beck EJ, Tosh S *et al.* (2014) Cholesterol-lowering effects of oat beta-glucan: a meta-analysis of randomized controlled trials. *Am J Clin Nutr* **100**, 1413–1421.
59. Ibrugger S, Kristensen M, Poulsen MW *et al.* (2013) Extracted oat and barley beta-glucans do not affect cholesterol metabolism in young healthy adults. *J Nutr* **143**, 1579–1585.
60. Biorklund M, van Rees A, Mensink RP *et al.* (2005) Changes in serum lipids and postprandial glucose and insulin concentrations after consumption of beverages with beta-glucans from oats or barley: a randomised dose-controlled trial. *Eur J Clin Nutr* **59**, 1272–1281.
61. Kerckhoffs DA, Hornstra G & Mensink RP (2003) Cholesterol-lowering effect of beta-glucan from oat bran in mildly hypercholesterolemic subjects may decrease when beta-glucan is incorporated into bread and cookies. *Am J Clin Nutr* **78**, 221–227.
62. Charlton KE, Tapsell LC, Batterham MJ *et al.* (2012) Effect of 6 weeks' consumption of beta-glucan-rich oat products on cholesterol levels in mildly hypercholesterolaemic overweight adults. *Br J Nutr* **107**, 1037–1047.
63. Wolever TMS, Tosh SM, Gibbs AL *et al.* (2010) Physicochemical properties of oat *β*-glucan influence its

https://doi.org/10.1017/S0029665119000545 Published online by Cambridge University Press

ability to reduce serum ldl cholesterol in humans: a randomized clinical trial. *Am J Clin Nutr* **92**, 723–732.
64. Grundy MM & Fardet A (2018) Processing of oat: the impact on oat's cholesterol lowering effect. *Food Funct* **9**, 1328–1343.
65. Lovegrove JA, Clohessy A, Milon H *et al.* (2000) Modest doses of beta-glucan do not reduce concentrations of potentially atherogenic lipoproteins. *Am J Clin Nutr* **72**, 49–55.
66. McKeown NM, Meigs JB, Liu S *et al.* (2002) Whole-grain intake is favorably associated with metabolic risk factors for type 2 diabetes and cardiovascular disease in the Framingham Offspring Study. *Am J Clin Nutr* **76**, 390–398.
67. Sahyoun NR, Jacques PF, Zhang XL *et al.* (2006) Whole-grain intake is inversely associated with the metabolic syndrome and mortality in older adults. *Am J Clin Nutr* **83**, 124–131.
68. Tosh SM (2013) Review of human studies investigating the post-prandial blood-glucose lowering ability of oat and barley food products. *Eur J Clin Nutr* **67**, 310–317.
69. He LX, Zhao J, Huang YS *et al.* (2016) The difference between oats and beta-glucan extract intake in the management of hba1c, fasting glucose and insulin sensitivity: a meta-analysis of randomized controlled trials. *Food Funct* **7**, 1413–1428.
70. Tessari P & Lante A (2017) A multifunctional bread rich in beta glucans and low in starch improves metabolic control in type 2 diabetes: a controlled trial. *Nutrients* **9**, 297.
71. Margetts BM, Beilin LJ, Vandongen R *et al.* (1987) A randomized controlled trial of the effect of dietary fibre on blood pressure. *Clin Sci* **72**, 343–350.
72. Evans CE, Greenwood DC, Threapleton DE *et al.* (2015) Effects of dietary fibre type on blood pressure: a systematic review and meta-analysis of randomized controlled trials of healthy individuals. *J Hypertens* **33**, 897–911.
73. Behall KM, Scholfield DJ & Hallfrisch J (2006) Whole-grain diets reduce blood pressure in mildly hypercholesterolemic men and women. *J Am Diet Assoc* **106**, 1445–1449.
74. Tovar J, Nilsson A, Johansson M *et al.* (2014) Combining functional features of whole-grain barley and legumes for dietary reduction of cardiometabolic risk: a randomised cross-over intervention in mature women. *Br J Nutr* **111**, 706–714.
75. Mackie A, Rigby N, Harvey P *et al.* (2016) Increasing dietary oat fibre decreases the permeability of intestinal mucus. *J Funct Foods* **26**, 418–427.
76. Gunness P, Michiels J, Vanhaecke L *et al.* (2016) Reduction in circulating bile acid and restricted diffusion across the intestinal epithelium are associated with a decrease in blood cholesterol in the presence of oat beta-glucan. *FASEB J* **30**, 4227–4238.
77. Thandapilly SJ, Ndou SP, Wang Y *et al.* (2018) Barley beta-glucan increases fecal bile acid excretion and short chain fatty acid levels in mildly hypercholesterolemic individuals. *Food Funct* **9**, 3092–3096.
78. Parra D, Ramel A, Bandarra N *et al.* (2008) A diet rich in long chain omega-3 fatty acids modulates satiety in overweight and obese volunteers during weight loss. *Appetite* **51**, 676–680.
79. Bordoni A, Di Nunzio M, Danesi F *et al.* (2006) Polyunsaturated fatty acids: from diet to binding to ppars and other nuclear receptors. *Genes Nutr* **1**, 95–106.
80. Kalupahana NS, Claycombe KJ & Moustaid-Moussa N (2011) (*n*-3) fatty acids alleviate adipose tissue inflammation and insulin resistance: mechanistic insights. *Adv Nutr* **2**, 304–316.
81. Lorente-Cebrian S, Costa AG, Navas-Carretero S *et al.* (2013) Role of omega-3 fatty acids in obesity, metabolic syndrome, and cardiovascular diseases: a review of the evidence. *J Physiol Biochem* **69**, 633–651.
82. Martinez-Victoria E & Yago MD (2012) Omega 3 polyunsaturated fatty acids and body weight. *Br J Nutr* **107**, Suppl. 2, S107-S116.
83. Oh PC, Koh KK, Sakuma I *et al.* (2014) Omega-3 fatty acid therapy dose-dependently and significantly decreased triglycerides and improved flow-mediated dilation, however, did not significantly improve insulin sensitivity in patients with hypertriglyceridemia. *Int J Cardiol* **176**, 696–702.
84. Hames KC, Morgan-Bathke M, Harteneck DA *et al.* (2017) Very-long-chain omega-3 fatty acid supplements and adipose tissue functions: a randomized controlled trial. *Am J Clin Nutr* **105**, 1552–1558.
85. Tardivo AP, Nahas-Neto J, Orsatti CL *et al.* (2015) Effects of omega-3 on metabolic markers in postmenopausal women with metabolic syndrome. *Climacteric* **18**, 290–298.
86. Barbosa MM, Melo AL & Damasceno NR (2017) The benefits of omega-3 supplementation depend on adiponectin basal level and adiponectin increase after the supplementation: a randomized clinical trial. *Nutrition* **34**, 7–13.
87. Lopez-Huertas E (2012) The effect of epa and dha on metabolic syndrome patients: a systematic review of randomised controlled trials. *Br J Nutr* **107**, Suppl. 2, S185–A194.
88. Yubero-Serrano EM, Delgado-Lista J, Tierney AC *et al.* (2015) Insulin resistance determines a differential response to changes in dietary fat modification on metabolic syndrome risk factors: the LIPGENE study. *Am J Clin Nutr* **102**, 1509–1517.
89. Lavie CJ, Milani RV, Mehra MR *et al.* (2009) Omega-3 polyunsaturated fatty acids and cardiovascular diseases. *J Am Coll Cardiol* **54**, 585–594.
90. Venturini D, Simao AN, Urbano MR *et al.* (2015) Effects of extra virgin olive oil and fish oil on lipid profile and oxidative stress in patients with metabolic syndrome. *Nutrition* **31**, 834–840.
91. Lee TC, Ivester P, Hester AG *et al.* (2014) The impact of polyunsaturated fatty acid-based dietary supplements on disease biomarkers in a metabolic syndrome/diabetes population. *Lipids Health Dis* **13**, 196.
92. Liu X, Kris-Etherton PM, West SG *et al.* (2016) Effects of canola and high-oleic-acid canola oils on abdominal fat mass in individuals with central obesity. *Obesity* (*Silver Spring*) **24**, 2261–2268.
93. Ortega JF, Morales-Palomo F, Fernandez-Elias V *et al.* (2016) Dietary supplementation with omega-3 fatty acids and oleate enhances exercise training effects in patients with metabolic syndrome. *Obesity* (*Silver Spring*) **24**, 1704–1711.
94. Bondia-Pons I, Poho P, Bozzetto L *et al.* (2014) Isoenergetic diets differing in their *n*-3 fatty acid and polyphenol content reflect different plasma and HDL-fraction lipidomic profiles in subjects at high cardiovascular risk. *Mol Nutr Food Res* **58**, 1873–1882.
95. Ramprasath VR, Thandapilly SJ, Yang S *et al.* (2015) Effect of consuming novel foods consisting high oleic canola oil, barley beta-glucan, and dha on cardiovascular disease risk in humans: the confidence (canola oil and fibre with dha enhanced) study – protocol for a randomized controlled trial. *Trials* **16**, 489.
96. PATHWAY-27 Consortium (2013) PATHWAY-27 Website. [Online]. http://www.pathway27.eu/ (accessed August 2018).
97. PATHWAY-27 Consortium. Scientific guidelines for the substantiation of health benefits from a (bioactive-enriched) food. http://www.pathway27.eu/

https://doi.org/10.1017/S0029665119000545 Published online by Cambridge University Press