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Flavonoids, Dairy Foods, and Cardiovascular and Metabolic Health: A Review of Emerging Biologic Pathways

Dariush Mozaffarian, MD, DrPH, FACC[*] and **Jason HY Wu, PhD, FAHA**[*]

Friedman School of Nutrition Science & Policy (DM), Tufts University, Boston, MA; and the George Institute for Global Health (JW), Faculty of Medicine, University of New South Wales, Sydney, Australia

Abstract

A growing body of nutritional science highlights the complex mechanisms and pleiotropic pathways of cardiometabolic effects of different foods. Among these, some of the most exciting advances are occurring in the area of flavonoids, bioactive phytochemicals found in plant foods; and in the area of dairy, including milk, yogurt, and cheese. Many of the relevant ingredients and mechanistic pathways are now being clarified, shedding new light on both the ingredients and the pathways for how diet influences health and well-being. Flavonoids, for example, have effects on skeletal muscle, adipocytes, liver and pancreas, and myocardial, renal, and immune cells, for instance related to AMPK phosphorylation, eNOS activation, and suppression of NF-κB and TLR4. Effects of dairy are similarly complex and may be mediated by specific amino acids, medium-chain and odd-chain saturated fats, unsaturated fats, branched-chain fats, natural *trans* fats, probiotics, vitamin K1/K2, and calcium, as well as by processing such as fermentation and homogenization. These characteristics of dairy foods influence diverse pathways including related to mammalian target of rapamycin, silent information regulator transcript-1, angiotensin-converting enzyme, peroxisome proliferator-activated receptors, osteocalcin, matrix glutamate protein, hepatic de novo lipogenesis, hepatic and adipose fatty acid oxidation and inflammation, and gut microbiome interactions such as intestinal integrity and endotoxemia. The complexity of these emerging pathways and corresponding biologic responses highlights the rapid advances in nutritional science and the continued need to generate robust empiric evidence on the mechanistic and clinical effects of specific foods.

Keywords

nutrition; flavonoids; dairy; cardiovascular disease; diabetes

Address for correspondence: D. Mozaffarian, 150 Harrison Ave, Boston MA 02111, dariush.mozaffarian@tufts.edu.

[*]These authors contributed equally to this work.

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Introduction

Dietary habits are a major determinant of cardiometabolic diseases including heart disease, stroke, and type 2 diabetes.[1] In the US, for example, poor diet contributes to nearly half of all cardiometabolic deaths, causing an estimated 1,000 deaths each *day*.[2] The resulting global health and economic burdens are staggering.[3]

In recent years, nutritional science has been transformed by an explosion of evidence, shedding new light on key compounds and pathways for how diet influences health and well-being. Among these, some of the most exciting advances are occurring in the areas of flavonoids, bioactive phytochemicals found in a range of plant foods; and dairy foods, including milk, yogurt, and cheese.

For these factors, the emerging evidence on the relevant ingredients and biologic mechanisms highlights the importance of investigating the pleiotropic pathways of effects of foods. We performed a narrative review of the emerging science and innovative discoveries in the understanding of how flavonoids and dairy foods influence cardiometabolic health, with a focus on experimental studies and molecular mechanisms, as well as supportive clinical evidence.

Flavonoids

Flavonoids are polyphenolic phytochemicals that include flavonols (in onions, broccoli, tea, and various fruits), flavones (in parsley, celery, and chamomile tea), flavanones (in citrus fruits), flavanols (flavan-3-ols) such as catechins and procyanidins (in cocoa, apples, grapes, red wine, and tea), anthocyanidins (in colored berries and red wine), and isoflavones (in soy) (Table 1).[4–7]

The structural diversity of flavonoids contribute to differences in their ability to modulate specific molecular pathways. Differences in absorption, distribution, metabolism, and elimination following consumption further modify their bioavailability, site of action, and formation of bioactive metabolites.[8] Whereas some flavonoids are well absorbed and distributed to multiple tissues, others have limited absorption – although such flavonoids could still have systemic effects via interaction with the microbiota.[9] Isoflavones and catechins have in particular been extensively studied (and covered by recent reviews) with regards to their cardiometabolic effects.[10–14] As reviewed below, compelling experimental evidence suggests that flavonoids influence multiple physiologic pathways related to cardiometabolic diseases (Figure 1).

Microbial-Generated Flavonoid Metabolites

Colonic microbiota can enzymatically convert flavonoids into small phenolic acids and aromatic metabolites.[15, 16] Feeding studies that trace metabolic conversion suggest that such flavonoid catabolites are readily absorbed in the colon and often possess longer half-lives and reach substantially higher systemic concentrations than parent compounds.[17–19] Such observations have increased interest in these microbiota-generated metabolites, including whether they mediate cardiometabolic effects of dietary flavonoids. *In vitro* studies provide

preliminary concordant evidence. At physiologically relevant doses, several microbiome-derived phenolic metabolites suppressed production of pro-inflammatory cytokines and vascular adhesion molecules, compared with their parent flavonoids.[20–22] Several microbial-derived flavonoid metabolites also protected against pancreatic beta-cell dysfunction and death.[23]

Dietary flavonoids may also alter gut microbial composition, for example due to probiotic-like properties and stimulation of growth of specific bacteria.[24, 25] In animal models of obesity, feeding of flavonoids altered gut microbial community structure, including increased levels of Akkermansia muciniphila[26–28] which appear to confer metabolic benefits.[29, 30] Flavonoids may also influence the gut microbiota production of short-chain fatty acids (SCFA, up to 6 carbons in length).[31] SCFA, predominantly acetic (2:0), propionic (3:0), and butyric (4:0) acids, are produced by large intestinal bacteria mainly from fermentation of non-digestible or poorly digestible carbohydrates (e.g., dietary fiber).[32] In addition to being an energy source, experimental studies suggest that microbial-produced SCFA act as signaling molecules and can influence host energy metabolism, glucose-insulin homeostasis, production of endocrine hormones (e.g. GLP-1), and inflammatory pathways. In some studies in mice and rats, dietary SCFA protected against weight gain, improved glucose tolerance, and increased insulin sensitivity.[33–36] However, conflicting results have also been observed: in mice fed a high-fat/calorie diet, oral or intravenous acetate reduced food intake and weight gain,[36, 37] while intra-gastric infusion in rats fed a high-fat/calorie diet had the opposite effect.[38] The reasons for these differences remain unclear, highlighting the need for further mechanistic studies including in humans. Experimental evidence suggests that physiologic effects of SCFA are partly mediated by specific G-protein coupled receptors (GPR) present in multiple cells and tissue types including colon, adipose, and the sympathetic nervous system.[39] Specific SCFA may also act via different pathways: for example, in rats, metabolic benefits of dietary propionic acid required GPR activation whereas butyrate did not.[34] GPR signaling[40] or other mechanisms such as epigenetic modification[41] may account for anti-hypertensive and anti-inflammatory effects of SCFA in some cellular and animal studies.[42, 43] It remains unclear how much the variability of gut-produced SCFAs depends on flavonoids, and the clinical relevance of microbiota-generated SCFA in humans is being elucidated.[44] Yet, the overall emerging evidence supports bi-directional interactions between flavonoid consumption and gut microbiota composition and function that alter physiologic pathways relevant to cardiometabolic health.

Glucose-insulin homeostasis

A large number of animal-experimental studies have tested the effects of purified flavonoid compounds or flavonoid-rich plant extracts on insulin-glucose homeostasis, with a substantial number suggesting possible benefits. Flavonoids may influence glucose metabolism in the small intestine, muscle, adipose, liver, and pancreas via a number of molecular mechanisms. In vitro studies suggest a variety of flavonoids inhibit key enzymes involved in the digestion and absorption of dietary carbohydrates including α-amylase, α-glucosidase, and sodium-dependent glucose transporter, which may contribute to reduced post-prandial glycaemia.[45] Flavonoids could also improve glucose-insulin homeostasis via multiple signaling pathways. Cell culture and animal studies have identified adenosine 5′-

adenosine monophosphate-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor-γ (PPAR-γ) as two of the key pathways via which some flavonoids enhance muscle glucose uptake and improve adipocyte function.[46–50]. Flavonoid treatment in animal models also led to reduced liver fat accumulation and improved hepatic insulin sensitivity, which were related to reductions in de novo lipogenesis and increase in fatty acid β-oxidation.[51–54] Finally, cellular and animal studies suggest several types of flavonoids protected pancreatic β-cells against glucotoxicity and inflammation, and enhanced insulin secretion.[55–57] Activation of AMPK has again been implicated in mediating the effects of flavonoids on insulin secretion, but other mechanisms including modulation of intra-cellular calcium through activation of membrane ion channels have also been identified for specific flavonoids.[58, 59]

Nitric oxide bioavailability, redox status, and vasoregulation

In animal experiments, administration of flavonoids exerted vasorelaxation effects and lowered blood pressure.[60] There is strong evidence that a key pathway via which flavonoids regulate vascular health is through altered nitric oxide (NO) metabolism. Influence of flavonoids on NO could be further divided into direct and indirect mechanisms.[7] Several flavonoids can directly increase endothelial nitric oxide synthase (eNOS) expression and activity (the main source of NO in the vasculature), leading to enhanced production of NO.[61–63] Effects on eNOS level could be mediated through activation of AMPK.[64] Flavonoids could also indirectly enhance NO bioavailability through lowering the production or enhance removal of reactive oxygen species that are known to breakdown NO. Treatment with different subgroups of flavonoids increased the activity of endogenous anti-oxidant enzymes including sodium oxide dismutase and catalase, reduced superoxide radical generation by NADPH oxidase, and lowered protein and lipid biomarkers of oxidative stress.[65–67] In addition to regulating vascular function through NO, other NO independent mechanisms have also been observed in *in vitro* studies for flavonoids such as direct stimulation or inhibition of vascular calcium ion channels.[68]

Weight maintenance

Supplementation with flavonoids prevented diet-induced weight gain in several animal models of obesity. In these investigations, flavonoids did not appear to influence energy intake,[69–72] suggesting they may contribute to weight regulation by increasing energy expenditure. For example, luteolin (a flavonoid abundant in pepper, apple skins, and carrots) up-regulated AMPK and PPAR-γ coactivator 1-α (PGC-1α) signaling cascades, leading to elevated thermogenic gene expression in brown and subcutaneous adipose tissues, and enhanced energy expenditure in C57BL/6 mice fed low or high fat diets.[72] Other flavonoids have also demonstrated an ability to induce brown fat-specific genes and proteins in cultured adipocytes.[73] Additional mechanisms via which flavonoids could increase energy expenditure have been observed in animal feeding studies, including stimulation of the sympathetic nerve system,[74] and increased skeletal muscle mitochondrial biogenesis and function.[71, 75] Several types of flavonoids may also prevent fat accumulation via reduced lipogenesis, and increased β-oxidation of fatty acids as demonstrated in cultured adipocytes and mice.[76–78]

Anti-inflammatory effects

Some flavonoids have demonstrated anti-inflammatory properties in adipose and myocardial tissues in animal studies following varied inflammatory stimuli including ischemia-reperfusion, diabetes, medication use, and high-fat diet.[79–85] In these models, oral supplementation with flavonoids led to reduced inflammatory cell infiltration, lowered levels of pro-inflammatory cytokines and tissue fibrosis, and improved cell survival and function. A central pathway that appeared to mediate the anti-inflammatory effect of several flavonoids was inhibition of signaling via nuclear factor-κB (NF-κB).[82–84] However, other mechanisms are likely involved and have been identified for specific flavonoids – for example, hexameric procyanidins (present in high concentrations in cocoa, tea, and apples) inhibited the binding of tumor necrosis factor-α to its receptor and subsequent pro-inflammatory activation in cultured cells.[86]

Clinical effects

A growing body of laboratory studies and randomized trials support cardiometabolic benefits of flavonoid-rich foods such as cocoa, tea, and berries. Flavonoid-rich cocoa produces small but measurable benefits on blood pressure (BP), endothelial function, insulin resistance, and blood lipids.[87–89] In a systematic review and meta-analysis of 42 RCTs,[88] chocolate, cocoa, and flavan-3-ol significantly reduced mean arterial pressure (−1.64mm Hg, 95% CI: −3.27, −0.01 mm Hg), improved flow-mediated dilatation (1.34%; 95% CI: 1%, 1.68%), lowered HOMA-IR (−0.67, 95% CI, −0.98, −0.36), and marginally improved LDL-C and HDL-C (−0.07 and +0.03mmol/L, respectively). BP-lowering has been seen with as little as 6.3 g/day of dark chocolate (~30 kcal/day, i.e. about 1.5% of total daily energy added to habitual diets without recommendations for other dietary calories).[90] These benefits appear related to improved endothelial production of nitric oxide,[90] a fundamental pathway for vascular and metabolic health that suggests the potential for benefits beyond lowering of BP alone. Accumulating data suggest green or black tea can also modestly reduce BP in pre-hypertensive and hypertensive individuals – a meta-analysis of 10 trials suggests reduction of SBP and DBP by 2.36 and 1.77 mm Hg, respectively – although risk of bias in most of these trials could not be fully evaluated due to insufficient reported information.[91] A systematic review and meta-analysis of 22 RCTs of berries found moderate improvements in SBP (−2.72mm Hg; 95% CI, −5.32, −0.12), as well as small improvements in glycemic control (HbA1C, −0.20%), body mass index (−0.36kg/m^2), LDL-C (−0.21mmol/L), and inflammatory biomarkers (tumor necrosis factor-α, −1pg/mL).[92] Yet, most of these RCTs were small and of limited duration (<6 months).

Complementary to interventional evidence, observational studies evaluating dietary flavonoids or flavonoid-rich foods have observed lower risk of cardiometabolic events.[93–99] For example, among >90,000 middle-aged nurses followed for 18 years, those with in the highest vs. lowest quintile of estimated dietary anthocyanin intake had 32% lower risk of incident myocardial infarction (95% CI, 4%, 51%, P=0.03); however, other major subclasses of flavonoids (flavanones, flavan-3-ol, flavonols, flavones, and flavonoid polymers) and total flavonoids were not associated with myocardial infarction.[94] Sub-class specific associations were also observed in other population-based cohort studies, including for flavanones and ischemic stroke,[95, 96] and flavonols and type 2 diabetes.[93] These findings suggest potential

heterogeneous effects of different types of flavonoids in relation to specific cardiometabolic outcomes. Estimation of dietary flavonoid intake has important limitations including errors in self-recall and inaccuracies in food composition databases.[100] Assessment of urine or blood flavonoid biomarkers is therefore a complementary approach to examining exposure, but has only been utilized in a handful of long-term studies. These have predominantly focused on isoflavones and type 2 diabetes, and suggest moderate inverse associations for daidzein and genistein, major isoflavones in soy foods.[101] Data for other flavonoid biomarkers and risk of cardiometabolic diseases are scarce and inconsistent.[102–105] Additional studies with larger sample sizes across population groups with diverse demographic and dietary habits are needed.

There is also evidence for cardiometabolic benefits of nuts and extra-virgin olive oil, rich in other types of phenolic compounds (e.g. phenolic acids and lignans). In the PREvencion con DIeta MEDiterranea (PREDIMED) trial, participants at high risk of cardiovascular disease were randomized to a Mediterranean dietary pattern and provided with daily extra-virgin olive oil or mixed nuts (walnuts, hazelnuts, and almonds). Compared to the control diet (advice to reduce dietary fat), the intervention diets significantly improved cardiovascular disease (CVD) risk factor profiles including LDL-cholesterol, blood pressure, and inflammatory biomarkers;[106–108] and resulted in ~30% lower risk of death, myocardial infarction, or stroke.[109] Participants in the intervention groups also demonstrated less gain in central adiposity and decreases in body weight after ~5 years of follow-up.[110] Meta-analysis of prospective cohort studies provide further support of cardiometabolic benefits of higher nuts consumption: for each 1 oz (28 g) per day, about 30% lower risk of coronary heart disease (CHD) (n=11 studies, RR=0.71, 95% CI, 0.63, 0.80) and 39% lower risk of diabetes (n=4 studies, RR=0.61, 95% CI, 0.43, 0.88).[111]

Overall, growing evidence supports meaningful cardiometabolic benefits of foods rich in flavonoids and other phenolics. These findings support recommendations to increase dietary consumption of these foods and provide clear impetus for additional mechanistic trials, prospective cohorts, and clinical trials to better characterize the specific compounds of interest and their dose-response effects.

Dairy Foods

Dairy products contribute about 10% of all calories in the US diet.[112] Yet, for such a major share of the food supply, relatively little research has evaluated the direct health impact of consuming dairy foods. Traditional dietary recommendations on dairy derive mostly from theoretical considerations about isolated nutrients (e.g., eat three daily servings to obtain calcium or vitamin D for bone health; eat low-fat products to reduce calories for weight gain and saturated fat for heart disease),[113] rather than empiric evidence on actual mechanistic and clinical effects of milk, cheese, yogurt, butter, or other dairy foods. Growing evidence suggests that different dairy foods have complex cardiometabolic effects based on potential interrelated influences of a range of nutrients and other characteristics such as probiotics, fermentation, and possibly homogenization (Figure 2). We do not discuss the potential role of vitamin D here, which has been extensively reviewed elsewhere.[114, 115]

Calcium

Cell culture and animal experiments have assessed calcium and cardiometabolic risk, alone or in conjunction with other dairy components. In several animal models of obesity, calcium supplementation inhibited weight gain, attenuated hepatic steatosis, and reduced hyperglycemia and insulin resistance.[116–119] These effects were potentially mediated by correction of leptin and glucagon-like peptide 1 (GLP-1) signaling,[118, 120] reduced levels of calcitriol (1,25-dihydroxyvitamin D3), suppression of hepatic and adipose lipogenesis, [121, 122] and alterations in gut microbiota composition.[123, 124] However, other animal models have not demonstrated such benefits.[125–127] For example, in a mouse model of diet-induced obesity, calcium supplementation caused weight gain relative to control.[127] In a meta-analysis of 20 trials including 2711 participants, calcium supplementation did not significantly lower body weight (−0.17 kg, 95%CI: −0.70, 0.37) or body fat (−0.19 kg, 95%CI: −0.51, 0.13).[128] In comparison, dairy foods increase lean mass and reduce body fat, compared to control, in the presence of energy restriction for weight loss (see Clinical Effects, below); suggesting that other components beyond calcium may be relevant.

In short-term trials in humans, calcium supplements modestly lower BP, with mean difference (95% CI) for SBP, −1.43 mmHg (−2.15, −0.72 mmHg, I^2=0%); and for DBP, −0.98mmHg (−1.46, −0.50 mmHg, I^2=49%).[129] In some animal models of hypertension, reduction in BP following calcium supplementation were linked to improvement in both endothelial dependent and independent arterial relaxation, enhanced hyperpolarization of vascular smooth muscle, increased sodium excretion, and downregulation of renal angiotensin-converting enzyme.[130–133] However, whether calcium intake has similar effects on these pathways in humans is not clear. Meta-analysis of long-term randomized trials found that calcium supplementation resulted in trends towards moderately elevated risk of myocardial infarction.[134, 135] For example, in the study by Mao et al, the odds ratio (95% CI) for the calcium supplemented compared to the placebo group was 1.28 (0.97−1.68, P=0.08, I^2=0%).[135] Genetic variants related to higher serum calcium level also relates to elevated risk of myocardial infarction and coronary artery disease in Mendelian randomization studies.[136] The potential for increased risk has been hypothesized to relate to postprandial hypercalcemia that occurs with supplements, in comparison to intake from foods, that may contribute to vascular calcification. Overall, calcium is not a convincing driver of cardiometabolic benefits of dairy foods, although effects could also depend on supplement vs. dietary sources.

Dairy protein

Bovine milk contains around 32–34g/l protein, largely casein (used to make curds during milk processing; ~80% of dairy protein) and also whey protein (~20%).[137] Both casein and whey protein include several smaller protein fractions and differ in amino acid composition. [137] In some animal studies, enriching diets with casein, whey protein, or complete milk protein improved glucose-insulin and cardiometabolic risk factors.[138–140] Such benefits might relate to specific dairy amino acids. For example, whey protein is rich in the branched-chain amino acids (BCAA) leucine, isoleucine, and valine, that activates important signaling pathways including mammalian target of rapamycin (mTOR), and silent information regulator transcript 1;[141, 142] which could contribute to enhanced thermogenesis

and insulin secretion.[143] However, BCAA supplementation in animal studies has shown mixed results related to metabolic outcomes.[144–147] Relatively few controlled trials of intact milk protein isolates have been performed in humans.[148] Several focused on casein-derived lactotripeptides, which significantly lowered systolic (men difference, −2.95mmHg, 95% CI, −4.17, −1.73mmHg) and diastolic BP (men difference, −1.51mmHg, 95% CI, −2.21, −0.8mmHg) based on pooled results across studies; although these findings should be interpreted cautiously due to substantial heterogeneity and potential for publication bias.[149] Other short-term clinical studies (up to 12 weeks) evaluated effects of milk protein on glucose-insulin homeostasis: overall favorable effects were observed, but long-term studies remain limited.[137]

Bioactive peptides derived from dairy protein may also contribute, generated during fermentation (e.g. in the production of cheese or kefir, sour milk) via action of bacterial proteolytic enzymes, or during gastrointestinal (including microbiota-related) digestion.[150] Several short peptides (3–4 amino acids in length) from casein and whey protein demonstrated inhibitory activity towards angiotensin-converting enzyme in vitro.[151] Other dairy derived peptides have also been shown to moderately inhibit dipeptidyl peptidase-4,[152, 153] which may contribute to increased half-live of incretin hormones (gastric inhibitory peptide and glucagon-like peptide-1) and improved glycemic control.[143] On the other hand, the relevance of such dairy-derived bioactive peptides has been challenged based on their low bioavailability, which produces circulating levels in the pM to nM range.[154]

Overall, experimental and short-term human metabolic studies support potential cardiometabolic benefits of dairy protein, but the relative efficacy of casein vs. whey protein, effects of individual amino acids vs. peptide metabolites, and corresponding molecular mechanisms and relevant pathways remain understudied.

Dairy fats

Dietary guidelines generally recommend low/non-fat dairy based on LDL-raising effects of myristic (14:0) and stearic (16:0) saturated fatty acids, underemphasizing positive effects of these fatty acids on VLDL, chylomicron remnants, and HDL-cholesterol[155] and paying even less attention to potential health effects of the many other fatty acids which comprise the majority of dairy fat (e.g. 14:0 plus 16:0 comprise ≤40% of total fatty acids in cow, sheep and goat's milk).[156] These include medium-chain saturated fats (MCSFA) (between 6 to 12 carbons, i.e. 6:0 to 12:0), odd-chain saturated fats (OCSFA) (15:0, 17:0), monounsaturated and polyunsaturated fatty acids (18:1n-9, 18:2n-6 and 18:3n-3), branched-chain saturated fats, and trace amounts of natural (ruminant) *trans* fats (e.g., trans-palmitoleic acid, trans-16:1n-7).[156–158] Dairy fat is also a source of phospholipids (milk fat globule membrane) and fat-soluble vitamins including D, K, and K2 (produced during fermentation; see below).

MCSFA, representing ~6-17% of dairy milk fatty acids, have different molecular and metabolic activities than longer chain fatty acids. For example, whereas longer chain SFA (16:0 and 18:0) activated NF-κB and decreased insulin sensitivity in cultured skeletal muscle cells, the MCSFA 8:0 and 12:0 did not.[159] MCSFA also enhanced mitochondrial oxidative capacity and reduced lipid accumulation in cultured muscle cells relative to

16:0.[160] These effects may account for observed reductions in body fat accumulation and insulin resistance in animals fed high MCSFA vs. longer chain SFA.[160, 161] On the other hand, relative to a low-fat control diet, high fat feeding with MCSFA enhanced hepatic de novo lipogenesis and triglyceride accumulation, and reduced hepatic insulin sensitivity, in animal models.[161, 162] Induction of hepatic lipogenesis could be due to MCSFA activation and signaling via liver X Receptor-α.[163] Notably, many of the prior animal experiments examining MCSFA were obesity models and also focused on fruit (coconut) sources, and thus the metabolic effects of dairy-derived MCSFA under eucaloric conditions (e.g., substituting for other types of dietary fatty acids) remain unclear.

The biologic effects of trans-16:1n-7, branched-chain saturated fats, and OCSFA have received relatively little attention. It has been hypothesized[164] that dietary trans-16:1n-7 could exert similar effects as dietary cis-16:1n-7, which when consumed in the diet or produced outside the liver appears to act in a negative feedback loop to inhibit hepatic de novo lipogenesis, improve insulin sensitivity, and reduce inflammation;[165–169] with corresponding risk factor improvements in one human trial.[170] In cultured INS-1 β cells, treatment with trans-16:1n-7 activated PPAR-γ and the transcription factor pancreatic duodenal homeobox (PDX)-1.[171] Yet, relevance of such effects on glucose-insulin homeostasis and other molecular effects of trans-16:1n-7 remain unknown. Potential mechanisms of branched chain saturated fats also remain little explored. A branched chain FA (15-methyl-hexadecanoic acid) exhibited similar effects on PPAR-γ and PDX-1 as trans-16:1n-7 in cultured INS-1 β cells under basal conditions, and additionally countered high glucose mediated suppression of PDX-1.[171] Intake of branched-chain saturated fats is not insubstantial – with estimated average at ~500mg/day in the US (primarily from dairy and beef products),[158] compared to between 125-160mg/day for seafood derived long-chain n-3 polyunsaturated fats.[172] These findings highlight the potential quantitative importance of dietary intake of branched-chain saturated fats and the need to further assess their biologic functions. OCSFA from dairy fat are incorporated into a range of tissues including blood, liver, and adipose.[173, 174] In addition to serving as an energy source via β-oxidation, other metabolic functions have been proposed such as enabling replenishment of the citric acid cycle and improving mitochondrial function,[174] but such hypotheses remain to be tested in rigorous experimental investigations.

Milk fat globule membrane

Milk fat is naturally bound by milk fat globule membranes (MFGM), a tri-layered membrane rich in polar lipids (phospholipids and sphingolipids) and proteins, enclosing a triglyceride core (globule) of fatty acids.[175] These polar lipids and proteins in MFGM appears to be bioactive. In mice, supplementation with sphingolipids and bovine milk phospholipids reduced serum cholesterol and hepatic lipid accumulation, attributed to reduced intestinal cholesterol uptake and changes in hepatic gene expression.[176–178] Possible anti-inflammatory properties have also been reported – mice fed a MFGM-enriched diet exhibited decreased inflammatory responses to a systemic lipopolysaccharide (LPS) challenge, possibly due to reduced gut permeability.[179] Processing of dairy products can change the content and structure of MFGM – for instance, homogenization may destroy MFGM.[180] A recent randomized trial among 57 overweight adults compared the effects on

blood lipids and genetic expression of consuming ~15% of calories from whipping cream (intact MFGM) vs. butter (little MFGM due to homogenization), otherwise equivalent in contents of dairy fat and saturated fat. After 8 weeks, those consuming butter had predictable increases in LDL-C and apolipoprotein B:A-I ratio, while those consuming whipping cream showed no changes in their lipid profile.[180] The whipped cream group demonstrated significantly lower expression of 19 genes in peripheral blood mononuclear cells, including *USP45*, *MDM2*, *SNRPN*, and *CAPZA1*, supporting effects of MFGM on genetic expression. Similar blunted effects on total and LDL-C have been seen in cross-over trials comparing cheese to butter or non-dairy saturated fat (see Clinical Effects, below)[181, 182]. These findings suggest that MFGM and corresponding processing methods that preserve or destroy it may have important implications for cardiometabolic effects of dairy fat.

Probiotics

A growing body of evidence supports health effects of probiotics in foods, live microorganisms which can alter foods' characteristics as well as host responses following consumption.[183] Both yogurt and kefir (a fermented milk drink) often contain live bacteria (kefir can also contain yeasts). In several animal models of obesity and diabetes, dairy products with probiotics demonstrated cardiometabolic benefits compared to those without probiotics. For example, in C57BL/6 mice fed high-calorie/fat diets, animals given kefir had reduced weight gain, hepatic steatosis, LDL-C, and IL-6 levels compared to mice given unfermented milk.[184] Such changes were accompanied by altered expression of hepatic and adipose tissues genes related to fatty acid oxidation (*AOX, PPAR-α*) and inflammation (*MCP-1*). Other studies suggest that efficacy is probiotic specific: e.g., compared to unfermented milk, milk fermented with different strains of *Lactobacillus rhamnosus* improved glucose tolerance and fasting glucose to varying extents in a diabetic rat model.[185] The molecular mechanisms for probiotics' health effects appear to involve changes in both composition and function of host gut microbiota.[186] For instance, microbiota composition in animals was altered by probiotic dairy products such as yoghurt and kefir.[184, 187, 188] Such compositional changes may enhance intestinal epithelial integrity and reduce low grade inflammation due to endotoxemia (leakage of gut-microbiota derived LPS into systemic circulation), a putative contributor to obesity-related diseases.[189] Probiotics also appear to influence host microbiota function, e.g. altering production of functional mediators such as SCFA that may exert local and systemic effects on host metabolism.[190, 191] In sum, animal-experimental studies and human trials support a role for probiotics and probiotic-microbiome interactions in protective effects of yogurt for weight gain, obesity, and related metabolic conditions such as gestational diabetes.[192–203]

Cheese, fermentation, and vitamin K

There are two major forms of vitamin K: K1 (phylloquinone, rich in green-leafy vegetables and certain vegetable oils) and K2 (menaquinone, MK, differentiated by the number of isoprene residues, MKn). Several vitamin K2-producing bacteria species are commonly used in industrial dairy fermentation, and cheese is a major source of vitamin K2 (especially MK7, -8, and -9) in Europe and North America.[204, 205]

All forms of vitamin K act as cofactors for post-translational carboxylation of protein glutamate residues into gamma-carboxy glutamate, required for vitamin K-dependent proteins (VKDP) to become active. While coagulation factors such as factors VII, IX, and X are well known VKDP, growing evidence suggests that additional VKDP influence cardiometabolic health.[204] This includes osteocalcin (made in bone cells) and matrix glutamate protein (MGP, primarily made in vascular smooth muscle cells and cartilage). Animal studies support a role of osteocalcin in improving beta-cell proliferation, insulin expression, and upregulation of adiponectin in adipocytes.[206] In several metabolic studies, vitamin K supplementation increased carboxylated osteocalcin concentrations and reduced insulin resistance.[207, 208] However, results were not always consistent in human studies,[209] and opposing directions of associations between carboxylated/undercarboxylated forms of osteocalcin with insulin sensitivity have been observed in mice vs. human, suggesting possible species differences.[210] Levels of dietary vitamin K and proportions of osteocalcin that must be γ-carboxylated to improve glucose-insulin homeostasis also remain unclear.[211] Similarly, while it has been hypothesized that vitamin K may reduce CVD risk by augmenting MGP, an inhibitor of vascular calcification, this has not yet been convincingly established. In several rats and mice studies, supplementation with vitamin K reduced arterial calcification, but whether such effects were mediated by MGP carboxylation or other mechanisms remains unclear.[212–214]

Human metabolic studies demonstrate that specific types of vitamin K2 have longer half-lives and reach higher circulating levels than vitamin K1. For instance, compared to a half-life of 1-2 hours for vitamin K1, MK-7 and MK-9 have estimated half-lives of 2–3 days,.[215, 216] These differences in bioavailability may have functional consequences – in one study among healthy adults, supplementation with MK-7 induced more complete carboxylation of osteocalcin.[216] Such findings suggest that vitamin K2 moieties (representing ~15–20% of total dietary vitamin K in Western diets, with the rest as vitamin K1), may disproportionally contribute to vitamin K activity in vivo.[205] Furthermore, recent cohort studies suggest that K2, but not K1, is linked to lower CVD risk.[217–219] For example, in a prospective cohort study among 16,057 women aged 49–70 years, the hazard ratio for the risk of CHD per 10μg/day (equivalent to ~1SD) of K2 intake was 0.91 (95% CI, 0.81, 1.00, P=0.04), but K1 intake was not related to CHD risk.[219] Given these findings as well as the specific links of cheese and fermented milk to clinical outcomes (see below), the potential role of fermentation and vitamin K2 in cardiometabolic risk represents a new area of promise for further research.

Clinical Effects

In short-term randomized trials, consumption of milk or overall dairy products increases lean mass and reduces body fat, especially in the setting of energy-restricted weight loss diets.[128, 220, 221] Long-term effects are less clear and may vary by type of dairy. Observationally, several studies suggest that children who drink more low-fat milk gain more weight over time, while those who drink more whole-fat milk gain less weight.[222–226] Few long-term trials have been performed in children, other than multi-component dietary interventions that preclude inference on dairy per se.[227, 228]

In longitudinal studies among adults, relationships between dairy intake and weight, CVD, and diabetes endpoints vary more by food type (e.g., cheese, yogurt, milk, butter) than fat content.[229–235] For example, neither low-fat nor whole milk are appreciably related to long-term weight gain,[196, 236, 237] perhaps related to subtle caloric compensation: when people eat more low-fat dairy, they on average increase their consumption of carbohydrates, while people who eat more full-fat dairy on average decrease their carbohydrate intake.[237] Cheese consumption similarly appears relatively neutral for long-term weight gain; although this might be modified by carbohydrate intake: weight gain is seen when cheese is accompanied by refined carbohydrates, and relative weight loss is seen when cheese replaces refined carbohydrates.[237] Yogurt appears consistently protective against long-term weight gain, [196, 236, 237] even if sugar-sweetened (although in this case, only about half the benefit is seen, compared with unsweetened yogurt[237]).

While increased intake of saturated fat from dairy products would be expected to increase LDL-C,[238] recent randomized controlled trials support heterogeneity in such effects depending on the type of dairy foods consumed. For instance, in a randomized cross-over trial among 49 men and women, consuming equivalent amounts of fat and saturated fat from cheese, as compared to butter, lowered total, LDL, and HDL cholesterol concentrations.[181] Similar blunted effects on total and LDL-C were seen in a randomized controlled cross-over trial comparing saturated fat from milk or cheese with saturated fat from non-dairy sources; [182] as well as comparing whipping cream to butter.[180] Such heterogeneous responses may be explained by other components in dairy (e.g. calcium) or by specific processing methods (e.g., presence or absence of MFGM, see above).[239] Such counterbalancing effects, as well as beneficial effects of saturated fat on levels of triglyceride-rich VLDL-C,[238] could explain why meta-analyses of long-term cohort studies demonstrate no significant associations of total dairy consumption with CHD events and actually lower risk of stroke, without consistent differences comparing reduced vs. regular fat products.[240]

Associations of dairy foods with risk of type 2 diabetes also vary by food type: yogurt, but not milk, is consistently associated with lower risk; while consumption of cheese, which has highest calorie, fat, and saturated fat content, also associates with lower risk in several although not all studies.[232, 234, 235, 241, 242] These differences may be partly elucidated by the divergent associations of total milk (generally unassociated with diabetes) vs. fermented milk (linked to lower risk),[234, 241, 243] suggesting a potential role for metabolic benefits of fermented products such as cheese (see above).

Interestingly, dairy fat itself may promote cardiometabolic health. In cohorts utilizing objective biomarkers, higher blood levels of dairy fatty acids consistently associate with lower incidence of diabetes[244–248] and perhaps CHD,[249–251] with mixed findings for stroke. [252] As described above, mechanistic explanations for these observations remain unclear, which could include metabolic effects of fermented foods (especially cheese, a major source of dairy fat), links of such biomarkers to MFGM, specific fatty acids (e.g., branched-chain fatty acids, MCSFA, specific ruminant trans fats), other lipid-soluble factors, or unknown endogenous (non-dietary) determinants of these blood biomarkers.[253]

Future Directions and Conclusions

Modern nutritional science is elucidating the diversity of ingredients and mechanisms by which foods influence health. Numerous *in vitro* and animal studies support pleiotropic effects of flavonoids on multiple risk factors and pathways relevant to cardiometabolic diseases. While molecular mechanisms continue to be clarified, identified signaling pathways include AMPK, PPAR-γ, PGC-1α, and NF-κB. Existing experimental studies also have methodologic limitations and the potential for publication bias, and the relevance of their findings to humans remain unclear. In addition, with more than 5,000 naturally occurring flavonoids identified to date,[254] observed effects on molecular pathways for some flavonoids are unlikely to be generalizable to others. Many *mechanistic* studies to-date have focused on parent aglycone forms of flavonoids, and frequently at supra-physiological concentrations (e.g., 25 to 100μM, whereas systemic circulating concentrations *in vivo* are unlikely to reach ≥ 10μM).[21, 255] While findings based on supra-physiologic doses may be relevant for the development of flavonoids as pharmacologic agents, they are less generalizable to cardiometabolic effects of flavonoids at usual dietary levels of intake. Further, prior experimental studies have generally not accounted for complexities in flavonoid bioavailability and metabolism. For instance, most dietary flavonoids (except for flavan-3-ol) are found as glycosides, bound to one or more sugar moieties,[7] which generally require hydrolysis prior to intestinal absorption.[8] Following absorption, flavonoids undergo phase-I and phase-II metabolism and are transformed into diverse glucuronidated, sulphated, and methylated metabolites.[64] Unabsorbed flavonoids are also catabolized by colonic bacteria into a number of phenolic acids. Compared with their parent compounds, many flavonoid metabolites have longer half-lives and achieve much higher concentrations in circulation.[22] Cardiometabolic effects of flavonoids observed in animal studies may therefore be largely attributable to their metabolites, rather than the pre-metabolized flavonoids. Yet, relatively few investigations have evaluated potential biologic effects of flavonoid metabolites, partly limited by lack of available synthetic standards.[20, 22] Based on the promise of these compounds for physiologic health, future mechanistic, experimental, and clinical studies are needed that take into account the diversity of types, bioavailability, and metabolism of flavonoids and their metabolites to better understand the most appropriate form and pathways for clinical benefits.

Similarly, for dairy foods, a variety of ingredients and processing methods appear to influence cardiometabolic health. Potentially relevant ingredients include specific amino acids, medium-chain and odd-chain saturated fats, unsaturated fats, branched-chain fats, natural *trans* fats, probiotics, vitamin K1/K2, and calcium, as well as by processing techniques such as fermentation and homogenization. Corresponding pathways of effects include those related to mTOR, silent information regulator transcript-1, angiotensin-converting enzyme, peroxisome proliferator-activated receptors, osteocalcin, matrix glutamate protein, hepatic de novo lipogenesis, hepatic and adipose fatty acid oxidation and inflammation, and gut microbiome interactions such as intestinal integrity and endotoxemia.

For both flavonoids and dairy foods, the complexity of the emerging mechanistic pathways and responses is remarkable. This new evidence highlights the tremendous growth in knowledge, as well as the extent of what remains to be learned, on how different dietary

factors influence health. Given the prime importance of nutrition for cardiovascular and metabolic health, these results support the need for vigorous further investigation on the relevant components, biologic pathways, and clinical effects of these and other foods.

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Abbreviations

AMPK	5’-monophosphate-activated protein kinase
BCAA	branched-chain amino acids
BCSFA	branched-chain saturated fats
BP	blood pressure
CHD	coronary heart disease
CVD	cardiovascular disease
DBP	diastolic blood pressure
eNOS	endothelial nitric oxide synthase
ERK1/2	extracellular signal-regulated kinases 1 and 2
GLP-1	glucagon-like peptide 1
GPR	G-protein coupled receptors
GLUT4	glucose transporter type 4
IRS2	insulin receptor substrate-2
LPS	lipopolysaccharide
MAPK	mitogen-activated protein kinase
MCSFA	medium-chain saturated fatty acids
MFGM	milk-fat globule membranes
MGP	matrix glutamate protein
MK	menaquinone
mTOR	mammalian target of rapamycin
NF-κB	nuclear factor-κB
NO	nitric oxide
OCSFA	odd chain saturated fatty acids

PDX	pancreatic duodenal homeobox
PGC-1α	peroxisome proliferator-activated receptor-gamma coactivator-1α
PKA	protein kinase-A
PPAR	peroxisome proliferator-activated receptors
PREDIMED	PREvencion con DIeta MEDiterranea trial
RCT	randomized controlled trial
SBP	systolic blood pressure
SCFA	short chain fatty acids
SREBP-1c	sterol regulatory element binding protein-1c
TG	triglycerides
TLR4	toll-like receptor 4
VKDP	vitamin K-dependent proteins

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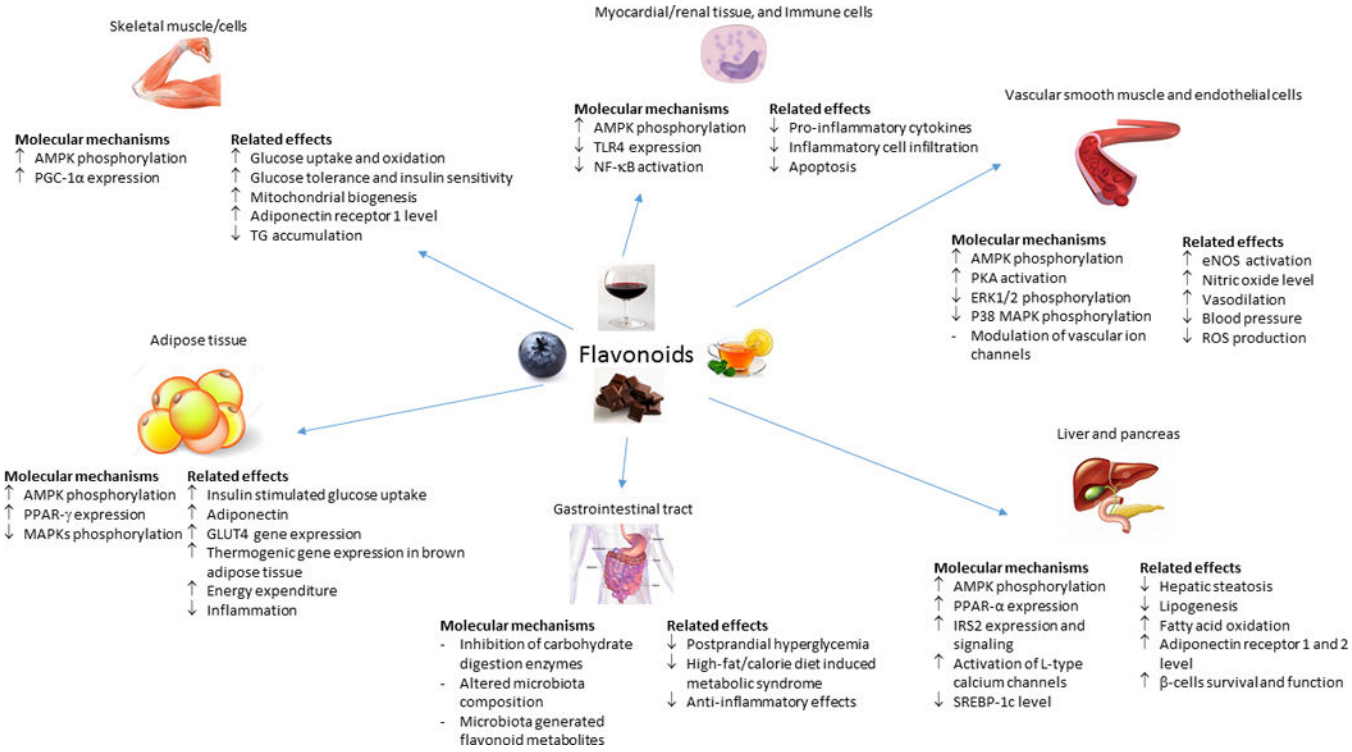

Figure 1. Selected cardiometabolic benefits of flavonoids and potential underlying molecular mechanisms

In vitro and animal studies support bioactivity of purified flavonoids or flavonoids-rich plant extracts across multiple tissues. Relevant molecular pathways appear to include: 1) Modulation of gene expression and signaling pathways. Enhancement of AMPK phosphorylation and activation appears to be a common mechanism affected by several types of flavonoids. Modulation of other signaling pathways have also been observed including increased expression of PPAR-γ and inhibition of NF- κB activation; 2) Interaction with gut-microbiota. Dietary flavonoids may alter gut-microbial composition due to probiotic-like properties and stimulate growth of specific bacteria (e.g. Akkermansia muciniphila) that may confer metabolic benefits. Conversely, metabolism of dietary flavonoids by gut bacteria generates downstream metabolites (e.g. phenolic acids) that may possess unique properties and/or reach higher circulating and tissue concentrations compared to parent flavonoids, thus enhance biologic activity of flavonoids; 3) Direct flavonoid-protein interactions. Growing evidence suggest flavonoids may stimulate and inhibit protein function, including ion channels in the vasculature and liver, and carbohydrate digestive enzymes (α-amylase and α-glucosidase) in the gastrointestinal tract. Such effects may partly contribute to regulation of vascular tone and glucose metabolism. Abbreviations: AMPK, 5'-monophosphate-activated protein kinase; ERK1/2, extracellular signal-regulated kinases 1 and 2; GLUT4, glucose transporter type 4; IRS2, insulin receptor substrate-2; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; PGC-1α, peroxisome proliferator-activated receptor-gamma coactivator-1α; PKA; protein kinase-A; PPAR, peroxisome proliferator-activated receptors; SREBP-1c, sterol regulatory element binding protein-1c; TG, triglycerides; TLR4, toll-like receptor 4,

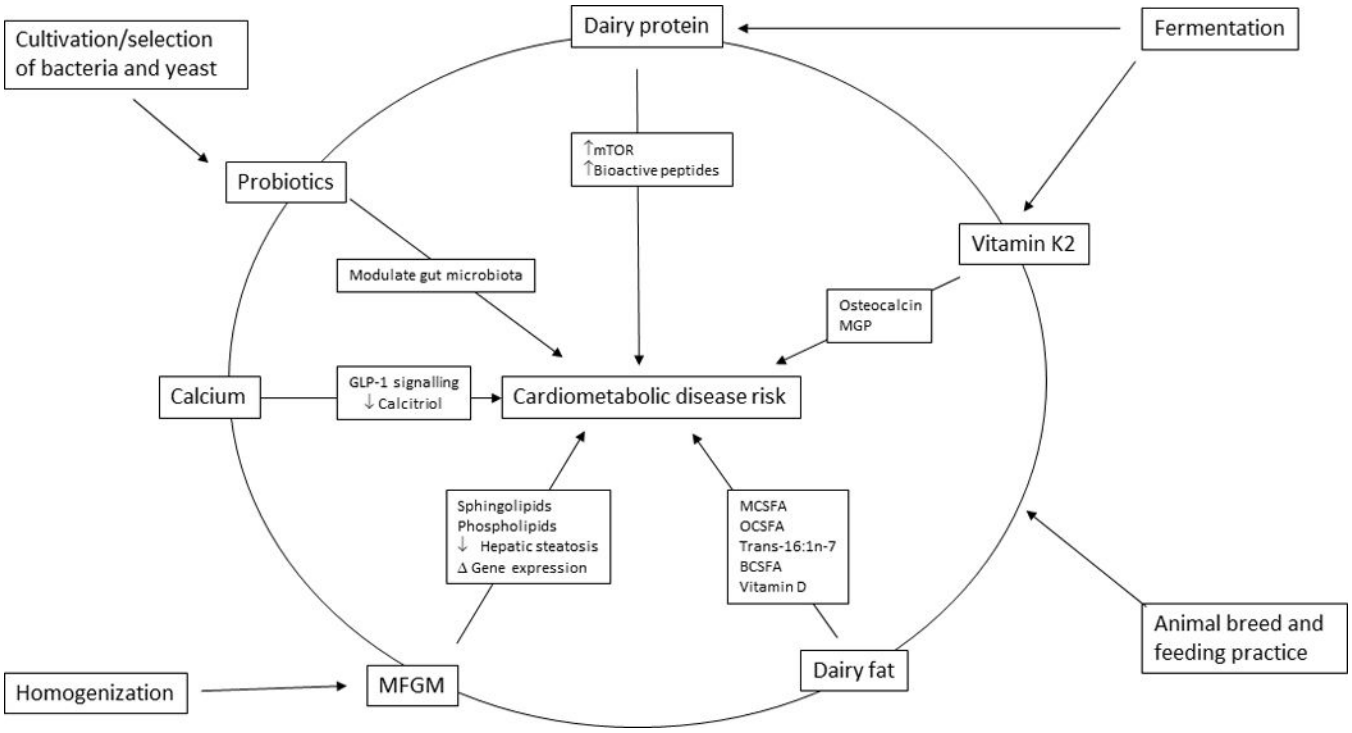

Figure 2. Relevant characteristics of dairy foods and selected molecular pathways potentially linked to cardiometabolic disease risk

Dairy foods are characterized by a complex mixture of nutrients and processing methods that may influence cardiovascular and metabolic pathways. Relevant constituents include specific fatty acids, calcium, and probiotics. Relevant processing methods may include animal breeding and feeding, fermentation, selection and cultivation of bacterial and yeast strains (e.g., as fermentation starters), and homogenization. Such modifications can alter the food's composition (e.g., fermentation leads to production of vitamin K2 from vitamin K1) as well as its lipid structures (e.g., homogenization damages MFGM), each of which can affect downstream molecular and signaling pathways.

Abbreviations: BCSFA, branched-chain saturated fats; GLP-1, glucagon-like peptide 1; MCSFA, medium-chain saturated fats; MFGM, milk-fat globule membranes; MGP, matrix glutamate protein; mTOR, mammalian target of rapamycin; OCSFA, odd chain saturated fats.

Table 1

Subtypes of flavonoids and their typical food sources[1,2]

Flavonoids													
Anthocyanidins		**Flavanols (flavan-3-ols)**		**Flavanones**		**Flavones**		**Flavonols**		**Proanthocyanidins**		**Isoflavones**	
Major flavonoids	**Food sources**	**Major flavonoids**	**Food sources**	**Major flavonoids**	**Food sources**	**Major flavonoids**	**Food sources**	**Major flavonoids**	**Food sources**	**Major flavonoids**	**Food sources**	**Major flavonoids**	**Food sources**
Cyanidin Delphinidin Malvidin Pelargonidin Peonidin Petunidin	Berries, red wine	Catechins epicatachins	Apricots, cocoa, chocolates, red grapes, red wine, tea	Eriodictyol Hesperetin naringenin	Citrus fruit, mint, tomatoes	Apigenin Luteolin	Celery, parsley	Isohamnetin Kaempferol Myricetin Quercetin	Apples, blueberries, broccoli, curly kale, leeks, onions, red wine, tea	Theaflavins Thearubigins	Apples, chocolates, grapes	Daidzein Genistein Glycitein	Soybeans, soy foods

[1] Major flavonoids include the 6 major subclasses consumed in the United States (anthocyanidins, flavanols, flavanones, flavones, flavonols, and proanthocyanidins),[4] as well as isoflavones, which are regularly consumed by populations with a high intake of soy and legumes.[5]

[2] Typical food sources according to Gu et al. for proanthocyanidins,[6] and Bondonno et al. for all other subtypes of flavonoids.[7]