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CLINICAL REVIEW
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Importance of functional food compounds in cardioprotection through action on the epigenome

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Food constituents can either promote cardiovascular health or serve in its demise. In view of the lack of more effective pharmacological interventions in cardiovascular disease (CVDs), attention has focused on the potential protective effects of diet. Food components and their metabolites are emerging as major regulators of the human epigenome, which is being linked to CVDs. In this review, we summarize data from studies that suggest an important role for bioactive food compounds in cardioprotection and the potential for harnessing the epigenome as a nutrient sensor target in CVDs. While clinical data strongly support a role for effective diet intervention in CVDs protection, studies linking changes to human epigenome are now warranted for mechanistic insight and development of personalized care.

Keywords Functional foods • Heart failure • Epigenetics • Nutrigenomics • Metabolism

Introduction

Ischaemic heart disease is the leading cause of cardiovascular diseases (CVDs), health complications, and cost worldwide.[1] However, beyond the management of traditional cardiovascular risk factors[2] (i.e. smoking, sedentariness, obesity, hypertension, diabetes mellitus, dyslipidaemia, and psychosocial stress), there has been limited success to translate novel cardiovascular drugs to the clinic.[3] A major leap forward was the discovery that enhancing endogenous adaptive responses to injury without changing the DNA sequence could halt onset and/or progression of CVDs.[4] The regulatory mechanisms recapitulated by the term 'epigenetics' are emerging as promising avenues to impact cell fate and function into the human heart.[4] The influence of the 'edible' environment (foods) on the human epigenome has become a significant research focus partly because of its potential to prevent CVDs without caloric restriction (CR).[4] Although prolonged CR protects hearts of obese[5] and non-obese[6] adults, relatively few individuals can adhere to so challenging a lifestyle. Alternatively, intake of epigenetically active compounds[4] through daily consumption of foods with scientifically proven health benefits (functional foods) or long-term adherence to a well-characterized diet like the Mediterranean diet can reduce risk of mortality[7] and prevent heart failure (HF).[8]

Functional foods are foods taken as part of the usual diet and contain bioactive compounds exerting more beneficial preventive than curative effects, beyond adequate nutritional actions. They fall into three general categories: (i) conventional foods, (ii) modified foods through enrichment or fortification, and (iii) synthetic food ingredients.[9]

Here, we review how bioactive compounds contained in organic and conventional foods impact CV health and disease through epigenetic mechanisms. Further, we critically discuss challenges and opportunities for dietary intervention in cardioprotection.

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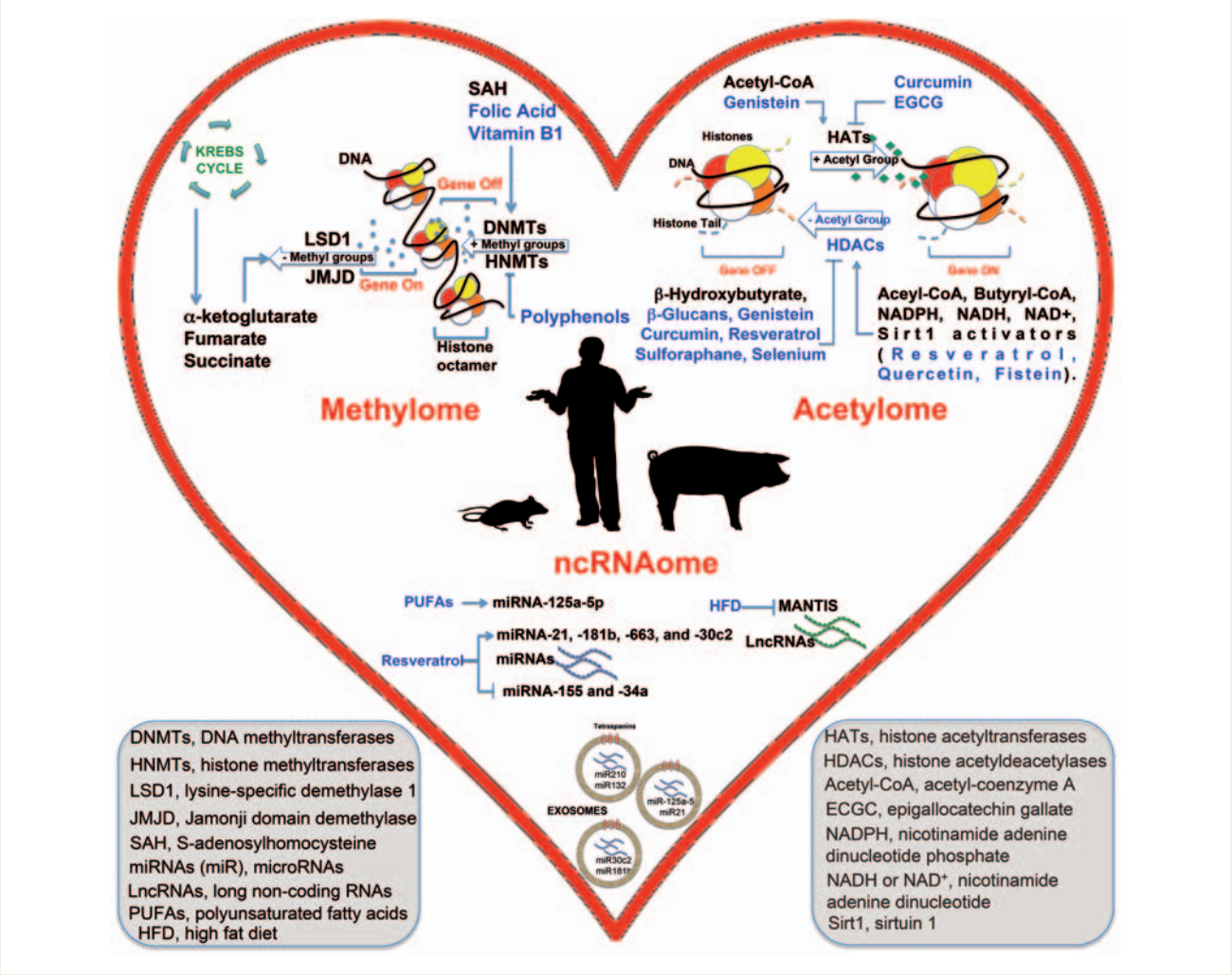

Figure 1 The scheme recapitulates main epigenetic mechanisms (methylome, acetylome, and ncRNAome) modulated by dietary bioactive compounds enriching functional foods dedicated to cardioprotection in animal models and humans.

The epigenome

The epigenome is a code critical for guiding expression of genes through chemical changes of DNA, histones, and non-coding RNAs [microRNAs (miRNAs): <22 nucleotides; long non-coding RNAs (lncRNAs): >200 nucleotides]. The epigenome is highly conserved across species. Thus, understanding of cardiac epigenetic machinery in animal models of CVDs is clinically relevant.[4] Recent evidences imply that both intrinsic and extrinsic cues simultaneously impact epigenomic read-out and phenotypic outcomes[4] (*Figure 1*).

The main epigenetic mechanisms include modification of cytosine on DNA by methylation and of histone tails by acetylation and methylation. Chromatin organization is modulated by these modifications to either conform chromatin permissive for gene activation (euchromatin) or gene repression (heterochromatin). The reversible nature, tissue, and temporal specificity of methylation reactions (methylome), acetylation (acetylome), and non-coding RNAs (ncRNAome) appear to be modulated by dietary constituents and metabolism across species[4] (summarized in *Figure 1*).

Bioactive food compounds and the cardiovascular epigenome

Feeding the methylome

Methylations of CpG regions by DNA methyltransferases (DNMTs) generally repress gene activity, while demethylation results in gene activation.[4] Deregulated DNMTs activity has been correlated with HF in animal models and humans.[10] DNA methyltransferases inhibitors attenuate specific patterning of genes involved in cardiac remodelling in rats.[10] Similarly, the 30–40% CR decreases age-related DNA methylation pattern in mice, rhesus monkeys, and humans.[11]

Histone type 3 (H3) methylation by histone methyl transferases (HNMTs) at lysine (K) 4, 36, and 79 is associated with euchromatin, while that at K9 and 27 and at histone type 4 (H4)K20 underlies heterochromatin.[10] In mice, a 30% increase in overall methylation status was reported during a hypertrophic response, while trimethylation of H3K4 or K9 was also notable in HF.[10] Changes in DNA methylation have also been detected in human atherosclerosis and coronary artery diseases (CADs).[12]

Both DNMTs and HNMTs utilize mitochondrial S-adenosyl-L-methionine (SAM) derived from methionine with production of S-adenosylhomocysteine (SAH), which is converted to homocysteine (hyc). S-adenosyl-L-methionine serves as an effective methyl donor while SAH is a potent modulator of DNMTs and HNMTs activity.[4] Dietary folic acid (200 μg/day) and vitamin B1 (0.8–1 mg/day) are essential for conversion of hyc to methionine.[12] Peas, liver, and fortified breakfast cereals contain both folic acid and vitamin B1, and may regulate chromatin methylation. Low levels of folic acid and high levels of serum hyc have been related to CADs and vascular dysfunction through hypermethylation in patients.[12]

Nuclear methylation is also controlled by demethylase enzymes such as lysine-specific demethylase (LSD) and Jamonji domain demethylase (JMJD), which are 2-oxoglutarate-dependent dioxygenases.[12] Lysine-specific demethylase 1 is sensitive to flavin adenine dinucleotide (FAD), a redox cofactor, and can demethylate H3K4 to repress key metabolic genes and activity. Of note is the regulation of demethylases by α-ketoglutarate (αKG), succinate and fumarate generated from acetyl coenzyme A (acetyl-CoA) during the Krebs Cycle (KC) which further links food metabolism to cardiac epigenome.[4] Indeed, reduced intracellular synthesis of αKG due to uncontrolled hyperglycaemia hampers the demethylation cycle and leads to higher levels of methylated DNA in human cardiac cells isolated from diabetic donors and in diabetic mice fed a high-fat diet.[13] Polyphenols, secondary metabolites enriching plant foods, are potent inhibitors of DNMTs and regulate genes encoding important enzymes including sirtuin-type deacetylases and transcription factors in *in vitro* and *in vivo* models.[14]

Feeding the acetylome

Histone tails acetylation mediated by histone acetyltransferases (HATs) leads to euchromatin, whereas histone deacetylation by deacetylases (HDACs) leads to heterochromatin with reduced DNA accessibility.[4] Histone acetyltransferases catalyze transfer of an acetyl group from acetyl-CoA to lysine residues of histones, which are sensitive to its concentration as determined by glycolysis or KC fuelled by food.[4] The onset of HF is associated with reversion from free fatty acids (FFAs) to glucose metabolism. This switch lowers acetyl-CoA levels due to pyruvate dehydrogenase kinase-4 overactivation, which inactivates conversion of pyruvate to acetyl-CoA. Both acetyl-CoA and β-hydroxybutyrate are derived from pyruvate and impact the epigenome.[4] While acetyl-CoA is known to activate HATs,[4] β-hydroxybutyrate inhibits HDAC1 and increases histone acetylation that induces antioxidant genes.[15] Blood levels of β-hydroxybutyrate are increased during fasting or CR,[15] when the liver switches to FFAs oxidation, but also in human HF, alcoholic, and diabetic ketoacidosis.[15] Similarly, dietary compounds may regulate HATs (i.e. curcumin, catechin, genistein, diallyl disulfide) and HDACs (i.e. β-glucan, sulforaphane, curcumin, butyrate, resveratrol, quercetin) activity.[4] Fibre fermentation by gut microbiota increases butyrate levels[16] while barley β-glucan (BBG), a viscous fibre, inhibits Class I HDACs and increases mitochondrial antioxidant status in cultured human endothelial cells.[17] *In vivo*, the regular intake of pasta containing 3% BBG protected ischaemic-reperfused murine heart through activation of proangiogenic mechanisms and mitophagy.[18]

Nicotinamide adenine dinucleotide (NAD+), a coenzyme produced during cellular redox reactions, regulates Class III HDACs, also termed sirtuins (Sirts).[4] The sirtuins that rely on NAD+ activity are generally cardioprotective in both animal models and humans.[4] Strategies to increase cellular NAD+ levels or to activate sirtuins enhanced cardioprotection through transcriptional regulators (c-jun and NF-kB), while loss of NAD+ generating capacity occurred in hypertrophy, ischaemic, and oxidative stress.[10] Although polyphenols stimulate Sirts activity in cells and rodents,[19] nicotinamide riboside, a NAD+ precursor abundant in cow milk, stimulates Sirt1 preventing cardiac injury in septic mice,[20] and arterial stiffness in older humans.[21]

Feeding the ncRNAome

In excess of 60% of human genes are regulated by miRNAs and a single miRNA can target multiple pathways.[4] The miRNAs are also becoming reliable biomarkers for various physiopathological conditions,[4] as their levels are easily detectable in body fluids.[10] MicroRNAs are released into exosomes, small nanovesicles mediating cell-to-cell communication.[22] Exosomes secreted from cardiac progenitor cells are highly cardioprotective in animal models of myocardial infarction (MI),[22] because they can deliver higher levels of anti-apoptotic and proangiogenic miRNAs.[22]

Dietary components can modulate the expression of certain miRNAs. In type-2 diabetic and hypertensive patients with CADs, consumption of grape extract containing over 8 mg of resveratrol for 1 year attenuated pro-inflammatory responses through up-regulation of miRNA-21, -181 b, -663, and -30c2 and down-regulation of miRNA-155 and -34a.[23] In healthy subjects fed almonds and nuts rich in polyunsaturated fatty acids (PUFAs) (30 g/day), elevated plasma levels of miRNA-125a-5p were related to high levels of adiponectin, a cardioprotective adipose tissue-derived hormone.[23]

Finally, Lnc RNAs, which recruit chromatin modifiers like the polycomb group at gene loci,[4] influence DNMTs and HNMTs activity.[4] Lnc RNAs can modulate translation, splicing and miRNA formation[5] and can influence angiogenic function through diet in primates.[24]

Clinical evidence for a cardioprotective role of bioactive compounds in conventional foods

Epidemiological and randomized clinical trials suggest that consumption of conventional whole foods is cardioprotective and food biocompounds act irrespective of age,[25] sex,[25] ethnicity,[25] country of residence,[25] and level of education[25] of individuals. They may be beneficial in various CVDs including hypertension,[25] peripheral artery diseases (PADs),[26] CADs,[25] stroke,[25] and HF.[7,8,10]

The impact of conventional foods on CVDs has implications beyond health. In the USA, increasing consumption of fruits and vegetables could save over $1500/person/year in CVDs treatment and has been proposed as a viable means to reduce medical expenditures.[27] Emphasis on fish and plant-based diets is becoming popular with the belief that this would curtail the prevalent obesity and metabolic disorders related to the Western diet, which is strongly associated with CVDs. A brief summary of the biological and epigenetic effects detected in main clinical CV trials of some conventional foods is described below (*Table 1*).

Table 1 Biological and epigenetic effects of functional foods in humans

Food group	Sub-category	Bioactive compounds	Biological effects	Epigenetic effects
Nuts	Peanuts	Protein, fibre, phytosterols, phenolics	↓Total and LDL cholesterol levels, plasma atherogenic index, arterial pressure; ↑ HDL levels and serum total antioxidant capacity[28]	↑ Methylation *cg01081346 CPT1B/CHKB-CPT1B*[29]
	Walnuts	ALA, LA, phenolics, β-tocopherols, carotenoids	↓ LDL levels; improves endothelial function [Ref. 28; 41 of 28]	
	Pistachios	Monounsaturated fatty acids, carotenoids, phytosterols, phenolics, β-tocopherols	↑ HDL cholesterol levels; ↓LDL oxidation by increasing serum paroaxonase 1 and arylesterase activities; ↓activity of stearoyl-CoA desaturase [Ref. 27 of 28]	
	Almonds	Monounsaturated fatty acids, α-tocopherols, fibre, protein	↓LDL levels and peripheral insulin resistance[28]	
	Hazelnuts	Monounsaturated fatty acids, α-tocopherols, carotenoids	↓triglycerides and apo-B concentrations[28]	
Whole grains	Barley, oats, rye	β-glucan, α-tocotrienols, phenolics, folate, phytic acid, fibre, protein	↓Total and LDL cholesterol levels; ↑satiety and intestinal transit time; ↑Bacteroidetes; improves insulin sensitivity and endothelial function; antioxidant and anti-inflammatory activity [Ref. 159 of 32; 33–34]	↑ SCFA, inhibitor of Class I HDACs [Ref. 33; 25 of 34]
	Whole wheat	Phenolics, β-tocotrienols, phytic acid, ferulic acid, B-vitamins, iron, magnesium, zinc, selenium, fibre, protein	Antioxidant and anti-inflammatory activity; ↑satiety and intestinal transit time; ↓ cholesterol levels[30]	
	Flaxseed	ALA, SDG, fibres, protein	Antiatherogenic effect; anti-inflammatory activity; improves vascular function and blood pressure; ↓cholesterol levels; antiarrhythmic action[31]	
Fish	Fatty fish	EPA, DHA, vitamin D and B12	Antiarrhythmic action; ↓Triglycerides levels and platelet aggregation; Improves HDL cholesterol levels and endothelial function; anti-inflammatory [Refs. 5 and 7 of 35; 36]	↓Methylation: *cg00011856 (IGFBP5) cg24455383 (AKT3)* ↑ Methylation: *cg05655647 (ATF1) cg15656521 (HDAC4)*[36]
Fruits, vegetables, and EVOO	Fruits and green leafy vegetables	Polyphenols, vitamin C, carotenoids, flavonoids, folate, fibre, minerals	Inhibits platelet aggregation; ↓Vascular tone; prevents LDL oxidation; hypoglycaemic; anticoagulant; anti-inflammatory [Ref. 11 of 26; 30]	↓ Methylation *cg17071192 GNAS/GNAS-AS*[29]
	EVOO	Monounsaturated fatty acids, phenolics (oleuropein, tyrosol, 3,4-dihydroxyphenylethanol)	↓Blood pressure, triglycerides, total and LDL cholesterol levels; ↑ HDL levels; ↓lipid oxidation; inhibits platelet aggregation, improves insulin resistance and endothelial function; anti-inflammatory; antioxidant activity [Ref. 37; 3 of 37]	↓ *miRNA-146b-5p, -19a-3p, -181b-5p,-107,-769-5p,-192-5p* ↑ *miRNA -23b-3p,-519b-3p*[37]
Polyphenol rich beverages and cocoa	Wine, beer	Polyphenols (anthocyanins, quercetin, resveratrol, flavonoids)	Improves lipid profile; ↓Inflammation; vasodilation; inhibits platelet aggregation; increases insulin sensitivity[38]	↓ DNA methylation by DNMTs down-regulation[42]
	Chocolates, cocoa drinks	Flavanols (epicatechin, catechin, procyanidins), flavonols (quercetin)	Induces coronary vasodilation; ↓blood pressures; improves insulin resistance and glucose	

Continued

Table 1 *Continued*

Food group	Sub-category	Bioactive compounds	Biological effects	Epigenetic effects
			tolerance; inhibits platelet aggregation; anti-oxidant activity[39–41]	
Coffee		Caffeic acid, chlorogenic acids, diterpenes, quinides, lignans	Antioxidant; anti-inflammatory; antiplatelet activity [Ref. 43; 4 of 43]	↓ DNA methylation by DNMTs inhibition[44]

↑, Significant increase; ↓, significant decrease; ALA, alpha-linolenic acid; ATF, activating transcription factor; CHKB, choline kinase beta; CPT, carnitine palmitoyltransferase; DHA, docosahexaenoic acid; DNMTs, DNA methyltransferases; EPA, eicosatetraenoic acid; EVOO, extra virgin olive oil; HATs, histone acetyltransferases; HDACs, histone deacetylases; HDL, high-density lipoprotein; IGFBP, insulin-like growth factor binding protein; LA, linoleic acid; LDL, low-density lipoprotein; miRNA, microRNA; SCFA, short chain fatty acids; SDG, secoisolariciresinol diglucoside.

Nuts

Most nuts contain proteins, α-linolenic acid (ALA), fibres, plant sterols, monounsaturated fats, vitamin E, selenium, and L-arginine. Nuts consumption has been associated with a decreased risk of CV mortality, more in women than in men at high-CV risk.[45] Regular intake of nuts improves endothelial function,[28] circulating lipid profiles,[28] and inflammatory markers[28] through changes in DNA methylation levels[29] and butyrate production by gut microbiota.[46]

Whole grain

An inverse relationship between whole grain intake, CVDs risk, and all-cause mortality is implicit from meta-analyses of prospective cohort studies.[30] Ischaemic stroke,[25] CADs,[25] hypertension,[31] HF,[10] and PADs[26,30] are beneficially impacted by whole grain intake although not all grains may be effective. The FLAX-PAD Trial,[31] a randomized, double-blinded, placebo-controlled, year-long trial reported that ground flaxseed led to a significant reduction of blood pressure (BP) and circulating cholesterol levels, attenuated inflammation, and improved vasodilation.[31]

Similarly, daily intake of 3–5 g of plant β-glucan in humans lowered low-density lipoprotein (LDL)-cholesterol and postprandial glycaemic response.[32] The CV benefits may depend on the molecular weight (MW) of β-glucan fibres affecting gut microbiota composition. The intake of 3 g/day of β-glucan with higher MW (1349 kDa) had more cholesterol-lowering effects by increasing bacteroidetes, able to produce propionate (HDACs inhibitor), and reducing Firmicutes population,[33] linked to type-2 diabetes, and obesity.[33] A 2-month dietary consumption of pasta containing BBG (3 g/100 g of pasta) improved endothelial function by increasing saccharolytic metabolism of gut microbiota,[34] which increases plasma levels of butyrate. Pasta enriched in flaxseed or β-glucan was more effective in counteracting metabolic CV risk,[47] but different individual responses of gut microbiota to similar intakes of dietary fibres due to genetic or epigenetic factors should be investigated.

Fish

High fish (not dried) consumption (40–60 g/day or 2–4 times/week) reduced CV risk in a healthy Mediterranean population.[35] An increase in high-density lipoprotein (HDL)-cholesterol levels is involved in the protective action of dietary fish,[48] which is the main source of omega (Ω)-3 FFAs-[docosahexaenoic acid (DHA); eicosapentaenoic acid (EPA)]. Indeed, marine Ω-3 FFAs (≥500 mg/day) reduced mortality in a Mediterranean population at high-CV risk.[48] Although clinical studies for epigenetic effects of marine PUFAs are in their infancy, mechanisms underlying cardioprotection imply the regulation of DNA methylation.[36]

Fruits, vegetables, and extra virgin olive oil

A meta-analysis of 22 randomized clinical trials estimated the effects of consumption of berries on cardiovascular risk factors in 1251 subjects.[49] A significant reduction of systolic BP was related to lower risk of CV morbidity.[49] Wild berries and some wild green vegetables (i.e. purslane, molokia, and stamnagathi) are rich sources of ALA, also readily available in walnuts, canola, and extra virgin olive oil (EVOO). Elevated intake of ALA is cardioprotective in persons who do not eat fish yet are less effective than marine PUFAs.[48] Although daily consumption of >3 servings of fruits and vegetables decreases prevalence of PADs,[26] excessive intake of fructose, a monosaccharide abundant in fruits, is associated with increased risk of developing gout, an independent CV risk factor, and postprandial hypertriglyceridaemia.[50] Long-term EVOO supplementation of Mediterranean diet favourably decreased major CV events in high-CV-risk population,[29,45] and a single dose of EVOO rich in polyphenols (i.e. oleuropein, tyrosol, 3,4-dihydroxyphenylethanol) was associated with hypoglycaemia in healthy subjects through epigenetics as opposed to refined oils low in polyphenols.[37]

Polyphenols-rich beverages and cocoa

The polyphenols of red wine (i.e. resveratrol, anthocyanins, procyanidin, myricetin, quercetin, and tannins) and beer (i.e. phenolic acids, prenylated chalcones, flavonoids, catechins, and pro-anthocyanidins) may cardioprotect by improving lipid profiles, endothelial function, and BP.[38] Cocoa is another dietary source of flavanols [i.e. (+)-catechin, (-)-epicatechin, procyanidins] and flavonols (i.e. quercetin, isoquercitrin), which are epigenetically active. A meta-analysis of 32 randomized clinical trials revealed that the intake of flavanol-rich cocoa products (1.4–105 g/day) exerts a BP-lowering effect[39] by increasing NO synthesis.[40] Moreover, regular intake of dark chocolate (70% cocoa) induces an immediate coronary vasodilation,[41] linked with lower risk of MI and ischaemic cardiopathy.[51] However, since chocolate has high calorie content and can induce complications such as increases in body weight and diabetic risk, intake should

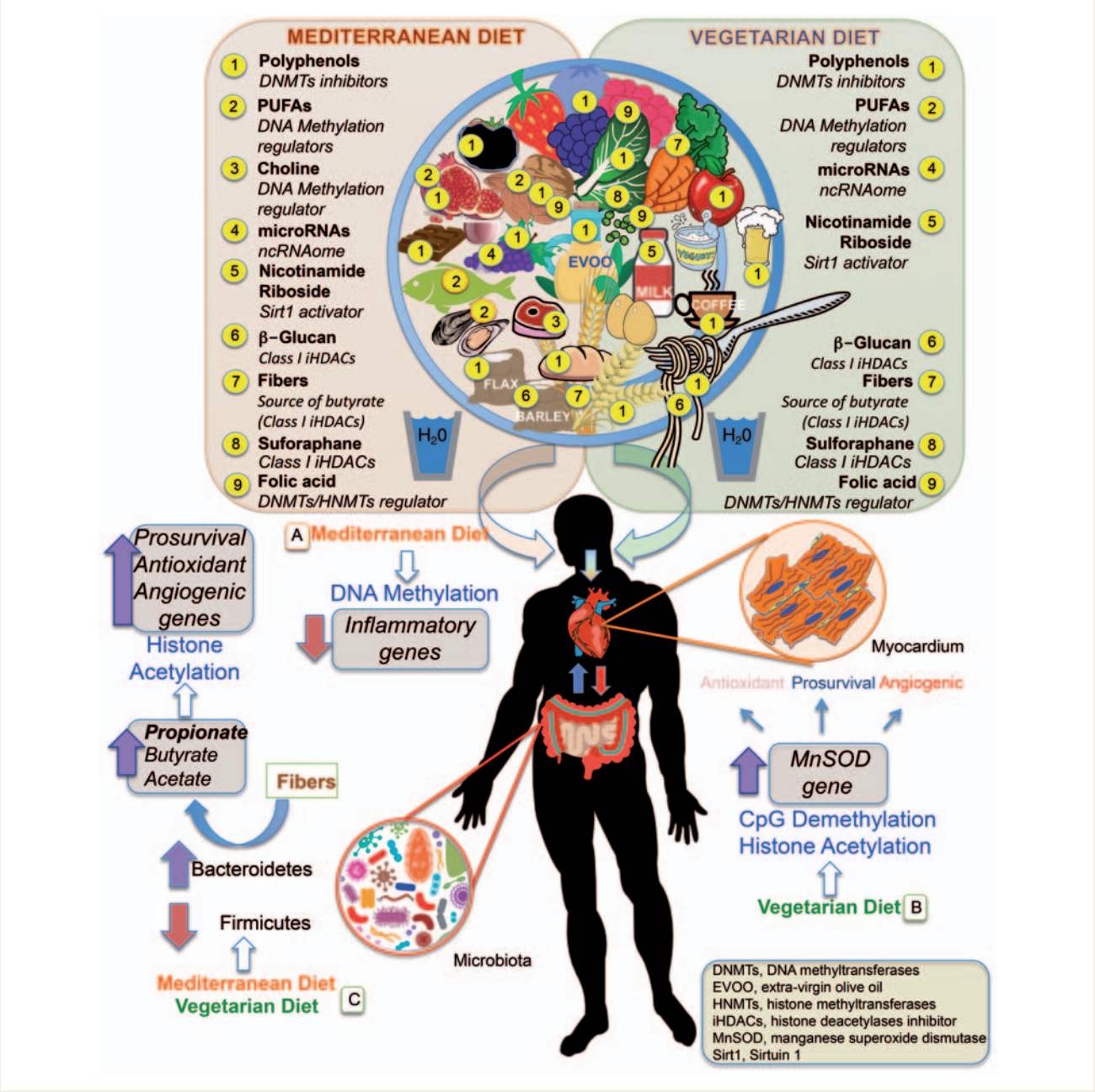

Figure 2 Dietary patterns feeding the epigenome for cardioprotection. Food constituents and their conversion by gut microbiota further generate bioactive compounds modulating gene activity via regulation of the epigenome to enhance cardioprotection. H_20, water.

be monitored in CV patients. Cocoa polyphenols attenuate DNMTs and global methylation in humans with favourable impact on CVDs risk.[42] In fact, they enhance vascular function in humans and also impact epigenetic markers in human monocytes thus reducing inflammation.[42]

Coffee

Moderate consumption of coffee (3 cups/day) is associated with lower CV risk. Extensive intake did not induce arrhythmias in HF patients or increase CV risk.[43] Despite the rise of LDL cholesterol levels induced by diterpens, CV mortality was reduced by 19% after daily intake of 3–4 cups of caffeinated or decaffeinated coffee.[43] Cardioprotection may be due to the improvement in glucose metabolism by chlorogenic acid and to the anti-inflammatory role of quinides, lignans, and trigonelline.[44] The habitual addition of sugar to coffee counteracts its effects on glucose metabolism.[44] The coffee polyphenols (caffeic and chlorogenic acids) are potent inhibitors of DNMTs in humans.[44]

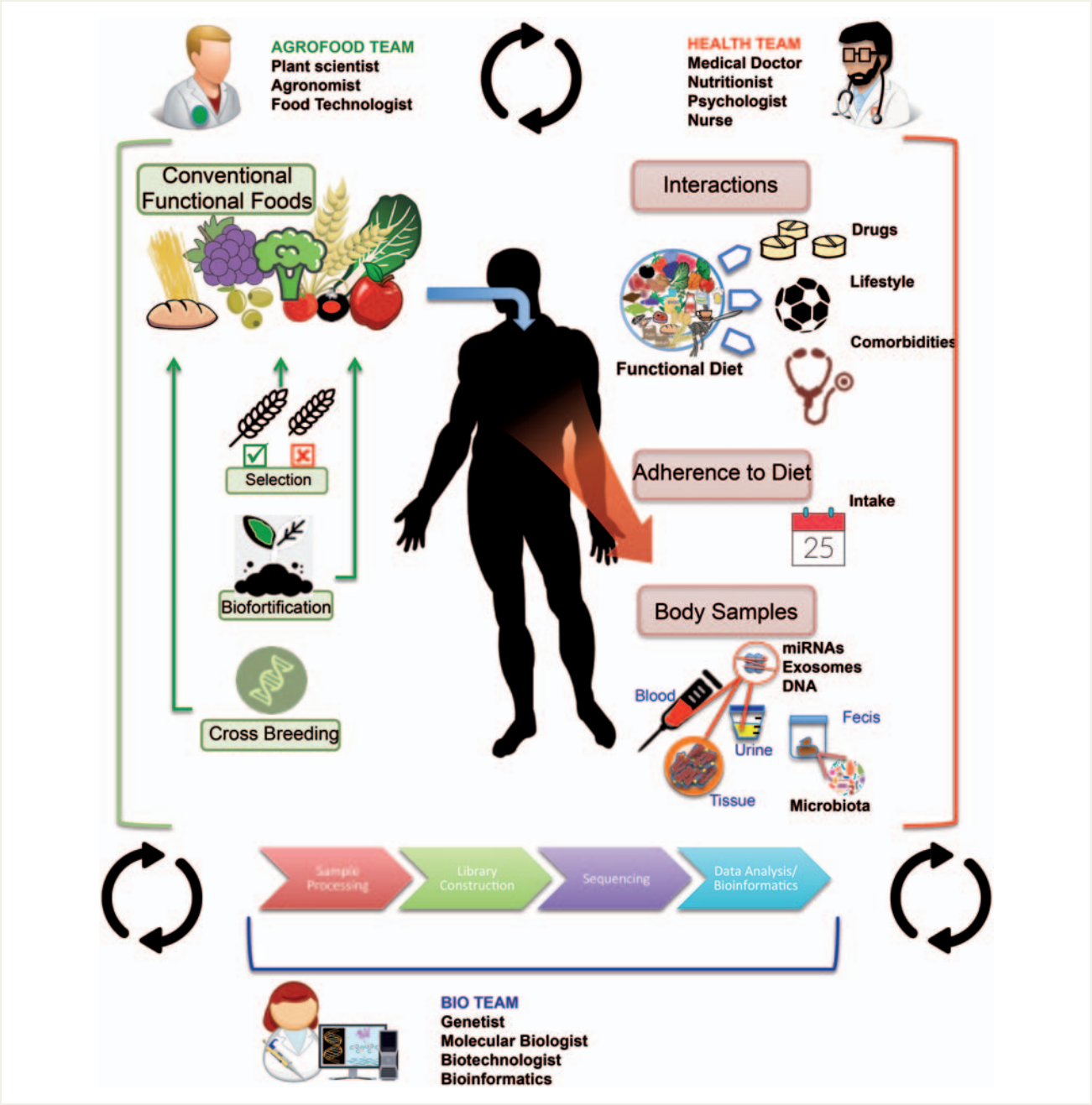

Figure 3 Team-based approach from discovery to clinical practice of cardioprotective functional diet. An interactome comprising an Agrofood, Health, and Bio teams is essential to connect food science to health delivery.

Conclusions and future perspectives

Experimental and clinical data have shown that bioactive food compounds modulate effectors of cardioprotective gene expression (*Figure 1*). The challenges posed now are to further define the adaptive regulatory mechanisms of the cardiac epigenome under various dietary patterns (Mediterranean[8,29,45,48], and vegetarian[7,26] diets) in a complete meal (*Figure 2*).

Clinical trials assessing conventional food consumption are different than those involving drugs (Supplementary material online, *Table S1*). Principal Investigators should be cognizant of the unique confounding variables including adherence to diet, lifestyle, nutrient–nutrient, or drug–nutrient, or comorbidity–nutrient interactions. The challenge in terms of food constituents, concentrations, processing, water/lipid solubility and stability, bioconversion, metabolites, interactions, and time of intake with a focus on variety of epigenetic players needs careful evaluation in the context of CV health (*Figure 3*).

However, these challenges should not dissuade researchers from initiating trials using functional foods as an intervention of choice in both healthy subjects at risk of CVDs and patients prone to chronic HF in combination with conventional drugs. In order to assess the impact of different whole food combination on CVDs and define priorities for intervention and prevention, it is critical to determine the cause/effect relationships and connections with the epigenome. Therefore, the future of precision nutrition tailored for CVDs will not be solely based on how rare genetic variations affect response to nutrients (*nutrigenetics*), but more importantly on the effects of nutrients on CV epigenome in the presence of different risk factors or stressors (*nutrigenomics*). Circulating epigenetic markers may not always reflect dietary epigenetic effects at a tissue/cell level in both healthy individuals and patients at different stages of disease. Large-scale efforts to decipher global epigenetic regions using refined tools (i.e. next generation sequencing, bioinformatics, pathway analysis, and large-scale datasets) and their regulation across the human genome together with targeted development of model systems will aid in defining cause/effect relationships and optimal composition and intake of ingredients (*Figure 3*). Despite a paucity of beneficial clinical trial results, a team-based approach may be helpful in understanding inter-individual response to a cardioprotective diet in the presence of common genetic variants and a similar microenvironment, and how this response intersects with the epigenome to personalize outcomes.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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