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The gut microbiota and cardiovascular health benefits: A focus on wholegrain oats

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Abstract

Existing scientific data suggest that a high intake of wholegrain foods contributes to improved gut health and a reduced risk of cardiovascular disease. Wholegrain oats are rich in dietary fibre and an important source of many bioactive components, including minerals, vitamins and phenolic compounds. The oat β-glucans have been reported to lower low-density lipoprotein cholesterol through their ability to increase the viscosity of intestinal chime, change the gut microbiota composition and increase the production of short-chain fatty acids, which may contribute to the inhibition of hepatic cholesterol synthesis. Oats are also a rich source of phenolic acids, which are predominantly bound to cell wall polysaccharides through ester bonds. This bound state within oats means that phenolic acid bioavailability will largely be determined by interactions with the colonic microbiota in the large intestine. However, results from *in vitro*, animal and human studies have been inconsistent in relation to the impact of oats on the gut microbiota, possibly due to differences in experimental techniques and because compounds in oats, other than β-glucans, have not been considered. This review focuses on the interaction of oat β-glucans and phenolic acids with gut microbiota, and the subsequent link to cardiovascular health.

Keywords: cardiovascular disease, gut health, gut microbiota, oat, phenolic acids, β-glucans

Introduction

A high intake of wholegrains is related to improved gut health (Cooper *et al.* 2015) and reduced risk of cardiovascular disease (CVD) (Thies *et al.* 2014b; Aune *et al.* 2016). The health benefits of wholegrains might be due to effects on inflammation (Nilsson *et al.* 2008a; Singh *et al.* 2013), fasting blood glucose (Pick *et al.* 1996; Jensen *et al.* 2006) and markers of lipid metabolism (Pins *et al.* 2002; Behall *et al.* 2004; Jonnalagadda *et al.* 2011; Johansson-Persson *et al.* 2014; Tang *et al.* 2015;

Aune *et al.* 2016). A recent meta-analysis of observational studies indicates that diets rich in wholegrains are associated with a 21% reduction [relative risk (RR) = 0.79 (95% CI: 0.74, 0.85)] in CVD risk (Ye *et al.* 2012). However, the median daily wholegrain intake in the UK, estimated from secondary analysis of data from the *National Diet and Nutrition Survey* Rolling Programme 2008/2009–2010/2011, is 20 g/day for adults and 13 g/day for children, which is higher than in 2000/2001 but remains low and well below the US wholegrain recommendation of 48 g/day (no UK wholegrain dietary reference value exist) (Mann *et al.* 2015).

It has been suggested that the cardiovascular protective effects of wholegrain oats are mainly due to their

dietary fibre content, in particular, soluble oat β-glucans, with established blood cholesterol- and glucose-lowering properties (Tappy *et al.* 1996; Tosh 2013; Whitehead *et al.* 2014; Tosh & Chu 2015). However, oats are also a rich dietary source of phenolic acids and avenanthramides (a class unique to oats) and several randomised, controlled, crossover studies have suggested that a range of phenolic compounds may be responsible for some of oat's health effects (Lamport *et al.* 2017; Lockyer *et al.* 2017; Mills *et al.* 2017). However, the phenolic acids in oats are linked to cell wall polysaccharides by ester linkages and this means their absorption will be limited until they reach the large intestine where they may undergo extensive bioconversion by colonic microbiota to yield various bioactive metabolites that express local intestinal effects in the gut, and also systemic effects following absorption (Vitaglione *et al.* 2008; Williamson & Clifford 2017). Previous data have suggested that, in addition to fibre and non-digestible carbohydrates, phenolics may beneficially modulate the gut microbiota composition and activity (Connolly *et al.* 2012b, 2016), which may play role in the prevention of chronic diseases (He & Shi 2017). For example, the secreting metabolites, such as secondary bile acids (BAs), short-chain fatty acids (SCFAs) and trimethylamine-N-oxide (TMAO), act as hormone-like factors and are sensed by dedicated receptor systems in the human host to play a role in the pathogenesis of CVD (Brown & Hazen 2015). In this review, we provide a concise introduction into human gut health and the contribution that the microbiota play in influencing markers of CVD pathophysiology, before outlining the cardiovascular benefits of oat intake and how these are mediated, in part, by the gut microbiome.

Gut health and the host gut microbiota

The human gastrointestinal tract is a diverse and dynamic microbial ecosystem, comprising approximately 10^{14} bacterial cells and up to 1000 different species (Thursby & Juge 2017). Firmicutes and Bacteroidetes are the two dominant phyla, representing more than 90% of all the phylotypes, followed by lower relative abundances of Actinobacteria, Proteobacteria, Fusobacteria and Verrucomicrobia (Robles Alonso & Guarner 2013; Power *et al.* 2014; Zhang *et al.* 2015). Commonly considered as the most beneficial bacterial genera are bifidobacteria, lactobacilli and butyrate producers, such as *Eubacterium rectale*, *Roseburia* species (Robles Alonso & Guarner 2013). An appropriate balance between harmful and health-promoting gut microbiota can support human health by: (1) maintaining host immune homeostasis; (2) increasing the efficiency of energy production in the gut through fermentation of non-digestible dietary compounds; (3) synthesising vitamins, such as B_{12} and K; (4) controlling intestinal epithelial cell proliferation (Clarke *et al.* 2014); (5) stimulating immunological defence; (6) creating a protective barrier; and (7) inhibiting the growth of potential pathogens (Gibson & Roberfroid 1995; Gibson 1998; Gong & Yang 2012; Ahmed Nasef *et al.* 2014; D'Argenio & Salvatore 2015; Okumura & Takeda 2017).

Conversely, an unfavourable gut microbiota composition and function (*i.e.* dysbiosis) can trigger the development of diseases through intestinal-derived endogenous endotoxins, such as lipopolysaccharides, indoxyl sulphate and L-carnitine (Prakash *et al.* 2011). These metabolites may potentiate the development of acute diseases, such as diarrhoea and chronic diseases, including obesity, metabolic diseases, cancer and CVD (Tang & Hazen 2014; Tuohy *et al.* 2014; Dao *et al.* 2015). There has been a long understanding of the interaction between environmental factors and gut microbiota, including that of pH, peristalsis, redox potential and nutrient availability (Nicholson *et al.* 2012). Dietary changes are thought to be responsible for around 57% of the variation in the gut microbiota, compared with only 12% for genetics (Brown *et al.* 2012). For example, a study showed that the microbiota of mice fed a low-fat, polysaccharide-rich diet markedly increased in populations of Firmicutes, and decreased in levels of *Clostridium*, *Eubacterium*, *Enterococcus* and *Bacteroides* spp when the mice were switched to a high-sugar/high-fat diet (Turnbaugh *et al.* 2009; Nguyen *et al.* 2015). On the other hand, a high-fibre diet can limit the growth of potentially pathogenic *E. coli.* (Zimmer *et al.* 2012), which has been observed in humans within 24 hours following a change from a high-fat/low-fibre diet to one which is low-fat/high-fibre (Wu *et al.* 2011).

The role of the gut microbiota in the pathophysiology of cardiovascular disease

Prebiotic effects

Shifts in the gut microbiota composition have been associated with a wide variety of diseases, including CVD (Garcia-Mantrana *et al.* 2018). The promotion of the growth of specific beneficial gut microbiota is believed to have preventative effects on CVD due to the influence of these bacteria on human physiology/metabolism, including the ability to reduce total serum

cholesterol, low-density lipoprotein (LDL) cholesterol and inflammation (Sun & Buys 2015; Ejtahed *et al.* 2011). Dietary substrates which induce changes in the growth of favourable bacteria are referred to as 'prebiotics', which pass largely unmetabolised in the upper gastrointestinal tract and are selectively utilised by host microorganisms conferring a health benefit (Gibson *et al.* 2017). Established prebiotics are carbohydrate-based but other substances, such as polyphenols (Tzounis *et al.* 2011; Queipo-Ortuño *et al.* 2012) and polyunsaturated fatty acids (Kankaanpaa *et al.* 2001; Peluso *et al.* 2014), might also fit the updated definition as they can affect the gut microbiome, although more studies are needed to show subsequent health effects. Prebiotics may reduce risk factors of CVD through the stimulation of growth of *Bifidobacterium* and *Lactobacillus*, and the subsequent production of SCFAs (LeBlanc *et al.* 2017), or possibly through the reduction in plasma cholesterol (Hooper *et al.* 2002) and/or fasting plasma glucose and insulin (Ooi & Liong 2010; Saini *et al.* 2010; Ruan *et al.* 2015). Furthermore, consumption of prebiotics has been linked to improved intestinal function, such as reduced gastrointestinal inflammation (Laparra & Sanz 2010; Vieira *et al.* 2013) and mineral absorption, and modulation of energy metabolism, satiety and immune function (Gibson & Roberfroid 1995; Gibson 1998; Pereira & Gibson 2002; Nicholson *et al.* 2012).

Structural effects

The large gut's enormous surface area helps to absorb nutrients, water and electrolytes from food but at the same time, it needs to provide a tight barrier against harmful substances and pathogens. One way in which the gut microbiota may confer health effects is via their potential to maintain large gut integrity (Konig *et al.* 2016). Gut hyperpermeability (leaky gut) results from structural changes induced by Gram-negative bacteria, which allows bacterial cell wall products, such as lipopolysaccharide and peptidoglycans, to enter into the bloodstream and activate macrophages. Also, gut microbiota-derived lipopolysaccharide can induce foam cell formation, and this can reduce reverse cholesterol transport and increase insulin resistance, hyperlipidaemia, vascular inflammation (Aki *et al.* 2008) and thus increase CVD risk.

Bile acid synthesis/clearance/metabolism

BAs have indirect (through cholesterol metabolic pathways) and direct effects (through interaction with myocytes) on blood cholesterol levels, atherosclerotic plaque formation and myocardial function and thus are hypothesised to reduce CVD risk (Khurana *et al.* 2011). Figure 1 illustrates the pathways of BA synthesis and cholesterol biotransformation in the liver (Ridlon *et al.* 2006). Primary BAs are further metabolised via conjugation to glycine or taurine in the liver, synthesised to bile salts and transported to the gallbladder. Following a meal and the release of cholecystokinin from the duodenum, the gallbladder contracts resulting in bile salts flowing into the duodenum, which in turn promotes the absorption of dietary lipids (Wahlstrom *et al.* 2016). The bacteria in the lower intestine are capable of converting primary BAs, by deconjugation and hydroxyl group oxidation at C-3, C-7, and C-12, and 7a/b-dehydroxylation, to secondary BAs, which predominate in human faeces (Sagar *et al.* 2015; Wahlstrom *et al.* 2016). Even though some are lost in faeces, most BAs are absorbed in the ileum and return to the liver where they are deconjugated and released into the small intestine (Ridlon *et al.* 2006). The genera of the gut microbiota involved in BA metabolism are *Bacteroides, Bifidobacterium, Clostridium, Lactobacillus* and *Eubacterium* (Gérard 2014). BA metabolites resulting from microbial transformation may act as signalling molecules and regulate cardiovascular function through the TGR5 (G-coupled protein receptor) and FXR (farnesoid x receptor), thus potentially inhibiting inflammation and maintaining epithelial cell integrity (Miyazaki-Anzai *et al.* 2014), and modifying vascular tone (Nie *et al.* 2015; Wahlstrom *et al.* 2016). Furthermore, *Bacteroides fragilis*, *B. vulgatus*, *Clostridium perfringens*, *Listeria monocytogenes* and several species of *Lactobacillus* and *Bifidobacterium* interfere with cholesterol absorption from the gut by deconjugating bile salts, via bile salt hydrolases (Jones *et al.* 2008), which means cholesterol is less easily absorbed and more likely to be excreted in faeces, resulting in lowered blood cholesterol (Hofmann 1999; Ridlon *et al.* 2006; Nicholson *et al.* 2012; Tuohy *et al.* 2014).

Short-chain fatty acids

SCFAs are the major end product of both carbohydrate and amino acid bacterial fermentation in the human large intestine (Morrison & Preston 2016). The main SCFAs are acetate, propionate and butyrate; less common are formate, valerate, caproate and branched-chain fatty acids (Macfarlane & Macfarlane 2003; Nicholson *et al.* 2012). Butyrate can be metabolised by colonocytes or absorbed and metabolised further in the liver, where they are metabolised
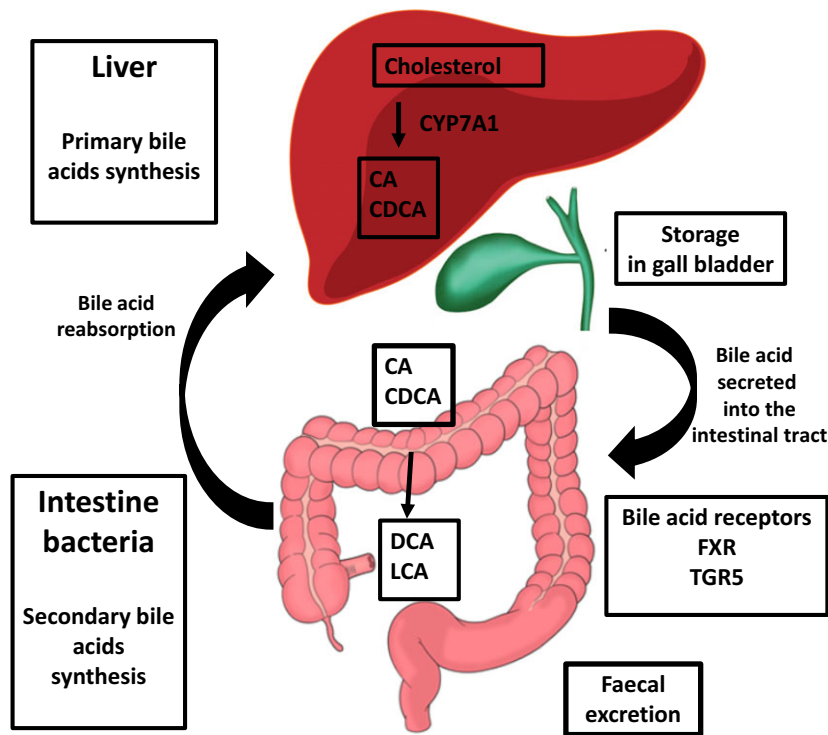
Figure 1 Bile acid biosynthesis. Primary bile acid synthesis in the liver: cholesterol is synthesised to cholic acid (CA) and chenodeoxycholic acid (CDCA) by the cholesterol 7 alpha-hydroxylase (CYP7A1) enzyme. In the intestinum, the bacterial 7 alpha-dehydroxylase converts the CA and CDCA to deoxycholic acid (CDA) and lithocholic acid (LCA), respectively. The bile acid receptors FXR farnesoid x receptor (FXR) and G protein-coupled bile acid receptor (TGR5) regulate bile acid synthesis, glucose homeostasis and lipid metabolism. [Colour figure can be viewed at wileyonlinelibrary.com]

(Ríos-Covián *et al.* 2016). SCFAs can act as an energy source for gut epithelial cells, improve intestinal defence against pathogens, modulate inflammation and possibly influence satiety (Russell *et al.* 2013). Butyrate may play a key role in regulating gene expression, inflammation and maintaining homeostasis of colonic mucosa through stimulating the production and release of the gut hormone glucagon-like peptide-2 (GLP-2) in enteroendocrine L cells (Tappenden *et al.* 2003; Hamer *et al.* 2008; Louis & Flint 2009). In addition, SCFAs decrease systemic levels of blood lipids by inhibiting hepatic cholesterol synthesis and/or redistributing cholesterol from plasma to the liver (Pereira & Gibson 2002). SCFAs are also thought to bind to specific G protein-coupled receptors, leading to the favourable regulation of lipid and glucose metabolism in the context of CVD (den Besten *et al.* 2013; Canfora *et al.* 2015; Kasubuchi *et al.* 2015). Another gut microbiota metabolism-dependent effect is the microbial conversion of choline and L-carnitine to trimethylamine (TMA) to TMAO. TMAO is thought to increase atherosclerotic CVD by altering cholesterol transport, potentially increasing macrophage activation (Randrianarisoa *et al.* 2016).

Oat components

Oats (*Avena sativa*) are unique among cereals due to their multifunctional characteristics and nutritional profile (Table 1). They supply protein, carbohydrate (primarily starch), crude fat, dietary fibre, unique antioxidants and vitamins and minerals (Welch 1994; Sadiq Butt *et al.* 2008; Menon *et al.* 2016). Oats have been grown for thousands of years, mainly as an animal feed crop, but during the 19th century, oats gained recognition as a 'healthy' food (Menon *et al.* 2016). Numerous reviews suggest that diets rich in oats may reduce inflammatory bowel disease and coeliac disease (Haboubi *et al.* 2006; Thies *et al.* 2014), attenuate CVD progression (Ruxton & Derbyshire 2008; Thies *et al.* 2014), and regulate glucose control in type 2 diabetes (Connolly *et al.* 2012b; Hou *et al.* 2015).

The nutrient profile and quality of oats depend on several factors, such as growth environment, genotype and the interaction between environment and genotype (Peterson *et al.* 2005). The main constituent (60%) of oat grains is starch (rapidly digestible, slowly digestible and resistant), located in the

Table 1 Nutritional composition of raw oat bran. Data from the US Department of Agriculture National Nutrient Database (USDA 2015)

Nutrient	Value per 100 g
Energy (kcal)	246
Protein (g)	17.30
Total fat (g)	7.03
Fatty acids, total saturated (g)	1.6
Fatty acids, total monounsaturated (g)	2.38
Fatty acids, total polyunsaturated (g)	2.77
Total carbohydrate (g)	66.22
Sugar (g)	1.45
β-glucans (g)*	4.5–5.6
Arabinoxylans (g)*	3.83–13.20
Non-starch polysaccharide (g)	7.1
Calcium (mg)	58
Iron (mg)	5.41
Potassium (mg)	566
Sodium (mg)*	4
Magnesium (mg)	235
Zinc (mg)	3.11
Thiamine (mg)	1.17
Riboflavin (mg)	0.22
Niacin (mg)	0.93
Vitamin B (mg)	0.16
Folate (μg)	52
Vitamin E (mg)	1.01
Vitamin K (μg)	3.2
Total phenolic (mg)*	35.1–87.4

*Data from Shewry *et al.* (2008).

endosperm. Resistant starch is recognised as a fermentable fibre source for gut microbiota, which results in the production of SCFAs in the colon (Ovando-Martínez *et al.* 2013; Gangopadhyay *et al.* 2015; Rasane *et al.* 2015). Moreover, oats are a source of high-quality protein, lipids (especially unsaturated fatty acid such as oleic, linoleic and palmitic acid), traces of minerals (mainly calcium and iron), B and E vitamins and phenolic compounds (Gangopadhyay *et al.* 2015; Rasane *et al.* 2015; Menon *et al.* 2016).

Oat phytochemicals

Dietary phenolics, such as hydroxycinnamic, hydroxybenzoic acids and avenanthramides, are natural phenolic components in oats (Shewry *et al.* 2008). They are found in three different forms within the oat food matrix: as soluble free acids; as soluble conjugates esterified to low molecular weight components such as sugars; and as insoluble bound acids esterified to high molecular weight components, including lignin, cell wall polysaccharides such as arabinoxylan (Stevenson *et al.* 2012) and storage proteins in the aleurone layer and the pericarp (Shewry *et al.* 2008). The main hydroxycinnamic acids present in oats include ferulic acid, caffeic, p-coumaric (Fig. 2), o-coumaric and sinapic acids. Hydroxybenzoic acid derivatives are protocatechuic, syringic, vanillic, *p*-hydroxybenzoic and gallic acids (Kern *et al.* 2003; El-Seedi *et al.* 2012; Kumar & Pruthi 2014; Yang *et al.* 2014).

Hydroxycinnamic acids all have a C_6C_3 carbon skeleton with a double bond in the side chain that may have a cis or trans configuration. By far the most abundant hydroxycinnamic in oats is the trans-ferulic acid, with contents ranging from 95 to 386 μg/g (Shewry *et al.* 2008). Analytical data indicate that, on average, 19% of these phenolic acids (range: 50–110 μg/g) are present in the soluble state, 34% as conjugates (range: 111–314 μg/g) and 47% bound (range: 131–640 μg/g) (Shewry *et al.* 2008). Another phenolic group specific to oats are the avenanthramides (AVA) (Fig. 3), consisting of an amide conjugate of anthranilic acid and hydroxycinnamic acids. The three major subgroups are avenanthramide-A (AVA-A), avenanthramide-B (AVA-B) and avenanthramide-C (AVA-C), which occur in the bran or outer layers of the kernel (Manach *et al.* 2004). Total contents of avenanthramides in oats range from 42 to 91 μg/g (Emmons & Peterson 1999; Liu *et al.* 2004; Manach *et al.* 2004; Chen *et al.* 2007).

Fibre

Wholegrain oats are typically 10%–12% fibre, of which roughly 40% is soluble and 60% insoluble (cellulose) (Menon *et al.* 2016). Mixed-linkage (1-3)(1-4)-β-D-glucans (β-glucans) (82% water-soluble fraction) together with arabinoxylans are important sources of soluble as well as insoluble dietary fibre (Shewry *et al.* 2008; El Khoury *et al.* 2012). The soluble β-glucans located throughout the subaleurone cell walls are one of the most commonly studied components of oats (Kim *et al.* 2006; Cloetens *et al.* 2012; Rebello *et al.* 2014; Zhang *et al.* 2016). A 100 g of oats contains 3–6 g β-glucans (Shewry *et al.* 2008).

Bioavailability of phytochemicals and physiological effects of β-glucans

It has been estimated that only 5%–10% of dietary polyphenols are absorbed in the small intestine, with the remaining fraction reaching the large intestine where they are metabolised by the gut microbial community (Manach *et al.* 2005; Cardona *et al.* 2013).
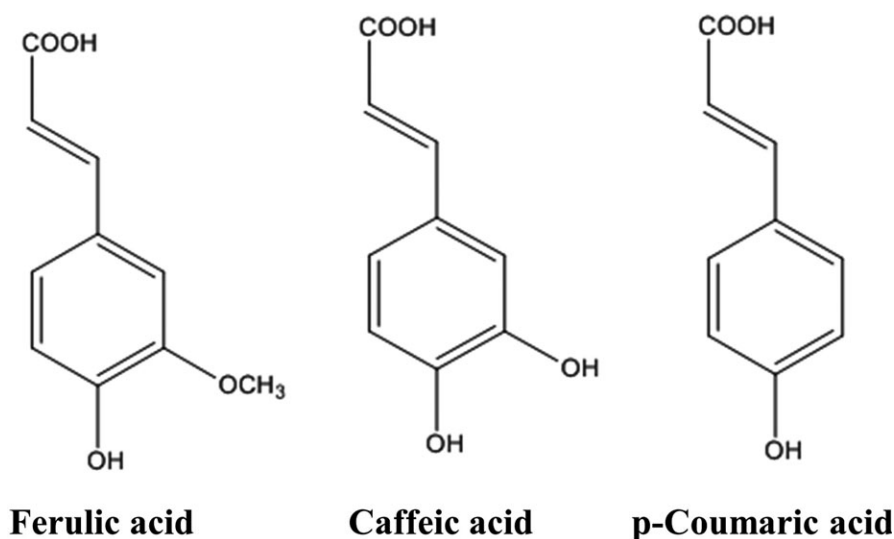
Figure 2 Chemical structure of the main hydroxycinnamates in oats.

The absorption and metabolism of ferulic acid can be affected by the form of food matrix ingested (Kern *et al*. 2003; Rein *et al*. 2013). Counterintuitively, fibre-bound ferulic acid in wheat bran has been observed to be more bioavailable than free ferulic acid (Rondini *et al*. 2004). The differences observed in their absorption may relate to the rapid cleavage of the fibre–phenolic ester bond by the intestinal microbiota, which generates a higher amount of free phenolic acids in the large gut, increases their time in the plasma and decreases the level of urinary excretion (Chesson *et al*. 1999; Rondini *et al*. 2004). Our group reported intake of 60 g oat bran (2.5 mg avenanthramides, 28.6 mg phenolic acids) resulted in elevated urinary excretion of 30 phenolic acids metabolites, amounting to total recovery of 22.9% ± 5.0%, mainly between 0–2 and 4–8 hours (Schar *et al*. 2017). The predominant metabolites included vanillic acid, 4- and 3-hydroxyhippuric acids and sulphate conjugates of benzoic and ferulic acid (accounting for two-thirds of total phenolic excretion). The results suggest that bound phenolic acids present in oats are rapidly released by the microbiota. Similarly, another human study (Zhang *et al*. 2017) showed peak plasma concentrations of avenanthramides between 2 and 3 hours after high (229.6 mg/kg) AVA intake and 1 and 2 hours for low AVA intake (32.7 mg kg). AVA-B demonstrated a longer half-life and a slower elimination rate than AVA-A and AVA-C. The bioactive properties of polyphenols are greatly dependent on their bioavailability (Chen *et al*. 2004; Kroon *et al*. 2004; Manach *et al*. 2004; Chen *et al*. 2007). These polyphenols have been observed to inhibit vascular smooth muscle cell proliferation and enhance nitric oxide production (Nie *et al*. 2006).

The physiological activity of β-glucans is in part related to their effects on bile reabsorption and through their ability to increase intestinal chyme viscosity, effects that are dependent on both the concentration and molecular weight of the β-glucans consumed (Shewry *et al*. 2008; Menon *et al*. 2016). The molecular weight of β-glucans varies between 100 000 and 1 200 000 g/mol, and those of a small molecular size (370 000 g/mol) have been reported to be less effective at reducing cholesterol levels (Kim *et al*. 2006) compared with those of high molecular weight

Avenanthramides

AVA-A – R_1 = OH, R_2 = H

AVA-B – $R_1 = R_3$ = OH, R_2 = OCH$_3$
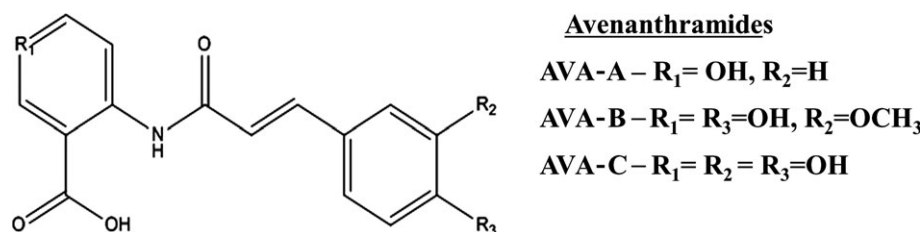
AVA-C – $R_1 = R_2 = R_3$ = OH

Figure 3 Chemical structure of the avenanthramide in oats. Avenanthramide-A (AVA), avenanthramide-B (AVB) and avenanthramide-C (AVC).

(Braaten *et al.* 1994). The solubility of β-glucans is another important factor influencing their physiological activity (El Khoury *et al.* 2012). Their ability to form highly viscous small intestinal chyme likely contributes to the health benefits of β-glucans, as it has been reported that there is an inverse linear relationship between measures of postprandial blood glucose and insulin responses (to an oral glucose load) and the viscosity of the chyme (Wood *et al.* 2000; Chen & Raymond 2008; Wolever *et al.* 2018).

Cardiovascular benefits of the oat intake

Atherosclerosis is one of the main underlying pathophysiological processes in CVD development (Stamler *et al.* 1986; Shepherd *et al.* 1995), with several different actions, such as oxidation of LDL cholesterol, adhesion of monocytes across the endothelial surface, development of monocytes to macrophages and the formation foam cells (Andersson & Hellstrand 2012). The potential modulation of atherogenic pathways following oat intake has been suggested and may involve anti-inflammatory activity, the maintenance of endothelial function and the reduction in plasma cholesterol (Fig. 4) (Ryan *et al.* 2007, 2011;

Jonnalagadda *et al.* 2011; Thies *et al.* 2014; Whitehead *et al.* 2014; Shen *et al.* 2016). Additionally, oat fibre and phenolics are capable of interacting directly with the gut microbiota, leading to a shift in their profile and composition, secondary changes in cholesterol and bile metabolism, and the production of key metabolites such as SCFAs and phenolic acids metabolites (Fig. 4).

Effects of oat intake on microbiome composition – *in vitro* and animal data

Several *in vitro* fermentation (Table 2) and animal studies (Table 3) suggest that increased oat intake leads to gut microbiota alterations. *In vitro* fermentation of oat grains has been shown to increase *Bifidobacterium* and *Lactobacillus* populations (Connolly *et al.* 2010) and *Bacteroides* and *Prevotella* groups (Chappell *et al.* 2015), whilst decreasing clostridia levels (Kedia *et al.* 2009). However, although oat-derived β-glucans extracts increased *Lactobacillus–Enterococcus* after 5 hours and *Bacteroides* after 24 hours in one *in vitro* study, they were found to not influence bifidobacterial growth (Hughes *et al.* 2008). In another *in vitro* study, it has been reported that the
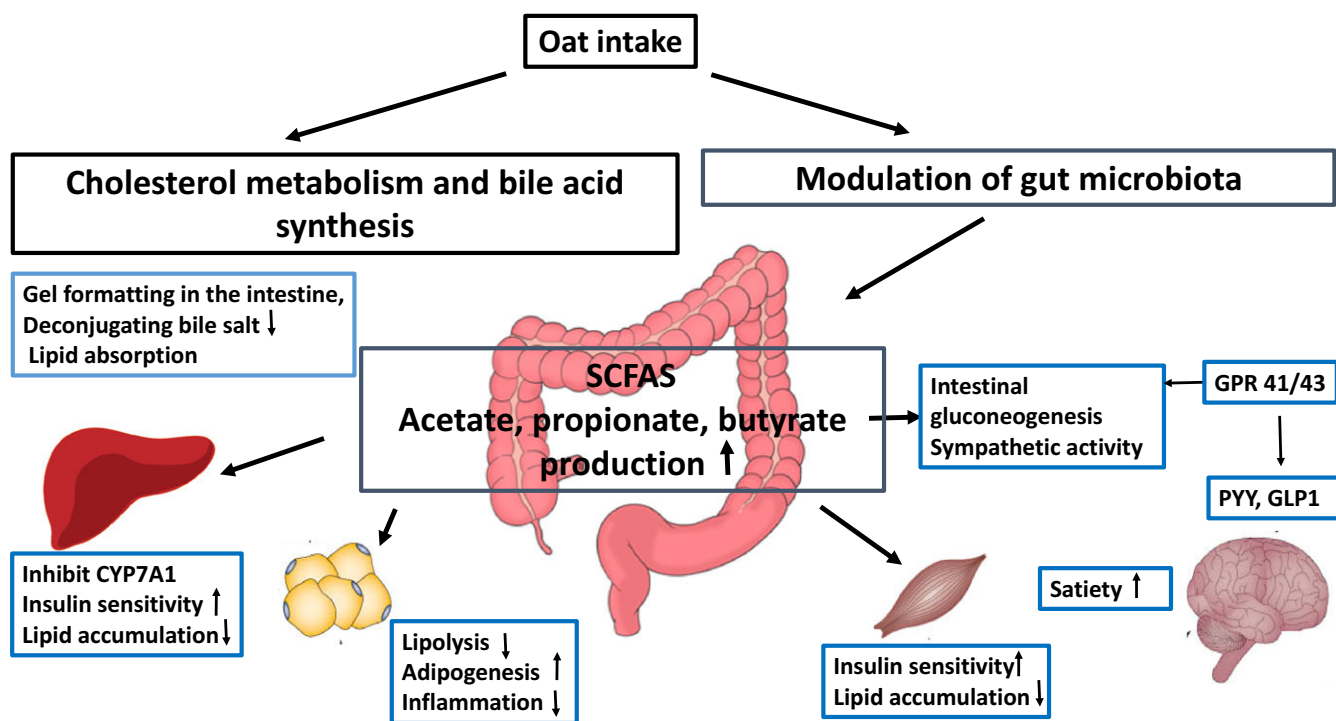
Figure 4 Potential mechanisms in the digestion system of the cardiovascular benefits of oats. Oats may interact directly with the gut microbiota leading to a shift in their profile and composition, changes in cholesterol and bile metabolism, and the production of key metabolites such as short-chain fatty acids. Abbreviations: SCFAs (short-chain fatty acids), GPR41 and GPR43 (G protein-coupled receptor), PYY (peptide YY), GLP1 (glucagon-like peptide 1) and CYP7A1 (cholesterol 7 alpha-hydroxylase). [Colour figure can be viewed at wileyonlinelibrary.com]

Table 2 The impact of oats on the gut microbiota and short-chain fatty acid (SCFA) production based on data from *in vitro* studies at 24 hours

Reference	Intervention	Effects on bacterial composition	Effects on SCFA production

Hughes *et al.* (2008)	Oat-derived β-glucans
	Low molecular
	  weight (LMW) 150 kDa
	High molecular
	  weight (HMW) 230kDa
		Atopobium ↑ - LMW and HMV
		Bacteroides – Prevotella ↑ - LMV
		Lactobacillus/Enterococcus ↓ - LMV and HMV
		Clostridium histolyticum ↑ - LMV and HMV
			Acetate ↑ -
			LMV, HMV
			Propionate ↑ -
			LMV, HMV

Kedia *et al.* (2009)	Oat bran fraction (OB) Whole oat flour (WOF)	*Bifidobacterium* ↑ - OB and WFO *Lactobacillus/Enterococcus* ↑ - OB *Clostridium* ↓ - 24 hours, OB *Clostridium* ↑ - 24 hours, WOF	Acetate, butyrate, propionate ↑ - OB, WOF

Kim and White (2009)	Oat-derived β-glucans
	Low β-glucans
	  (LB) – 5.31% β-glucans
	High β-glucans
	  (HB) – 7.70% β-glucans
		No data	Acetate, butyrate, propionate ↑ -
			  LB, HB
			No significant
			  differences between LB vs. HB

Connolly *et al.* (2010)	Oat grain flakes 0.53–0.63 mm (size 23) 0.85–1.0 mm (size 25–26)	*Bifidobacterium* genus ↑ - size 25–26 *Eubacterium* ↑ - sizes 23 and 25–26	Acetate ↑ - size 23 Acetate, propionate, butyrate ↑ - size 25–26
Connolly *et al.* (2012b)	Wholegrain oat-based cereals • Jumbo porridge oat (JPO) • 100% wholegrain aggregate (WGA) • Granola (G) • 70% wholegrain loops (WGL) • Instant porridge (IP)	JPO, IP, G, WGA *Bifidobacterium* ↑ JPO, G – *Atopobium* ↑ G, WGA, IP, WGL - *Bacteroides, Prevotella* ↑ G, WGA, WGL - *Lactobacillus/Enterococcus* ↑ P, WGA – *Clostridium* ↓	Acetate, propionate ↑ - JPO, IP, WGA, WGL, IP Butyrate ↑ - IP, WGA
Connolly *et al.* (2012a)	Toasted (T), partially toasted (PT) and raw (R) wholegrain wheat flakes	*Bifidobacterium* genus ↑ - T, PT and R *C. hystolyticum* subgroup, *Lactobacillus* ↑ - R	Acetate, propionate ↑ - T, PT R
Chappell *et al.* (2015)	Belinda oats	*Bacteroides* ↑ *Firmicutes* ↓	Acetate, propionate, butyrate ↑

β-glucans are fermented by *Bacteroides* spp but not by *Lactobacillus* and *Bifidobacterium* (Crittenden *et al.* 2002). The fermentation of oats in anaerobic, pH-controlled, faecal batch cultures has been shown to increase SCFA production, with significant increases in acetate, propionate and butyrate levels (Hughes *et al.* 2008; Kedia *et al.* 2009; Kim & White 2009; Connolly *et al.* 2010, 2012b).

Consumption of oats by rodents has been reported to result in many specific changes in their microbiota, such as increases in the growth of *Prevotellaceae*, *Lactobacillaceae* and *Alcaligenaceae* families 175.5% ($P = 0.03$), 184.5% ($P = 0.01$) and 150.0% ($P = 0.004$). However, these results are not consistent with the findings from other animal studies that indicate oat bran intake increases only *Bifidobacterium* and *Lactobacillus* growth (Drzikova *et al.* 2005;

Berger *et al.* 2014). The range of oat products used in these studies, including oat flour and bran (Drzikova *et al.* 2005), or insoluble fibre and soluble fibre combinations (Zhou *et al.* 2015), might explain the reported variability in microbiota growth in rodents. Hence, further well-designed *in vitro* and human studies are required to examine which oat components may result in beneficial changes to the microbiota.

Overall, these studies indicate inconsistent findings regarding the influence of oats on the growth of the microbiota and their diversity, which might be partly explained by the various different study and experimental designs. It is also important to note that these studies considered only the influence of the β-glucans fraction within oats and not other oat bioactives, such as polyphenols, which have also been observed to

Table 3 Animal studies examining the effects of oat intake on growth of gut microbiota and short-chain fatty acid (SCFA) production

Reference	Intervention (*duration*)	Oat effects on bacterial composition and/or SCFA production compared to control	Animals
Drzikova *et al.* (2005)	Oat flour (F); oat bran (B); oat flour (F) (autoclaved) (*6 weeks*)	*Bifidobacterium* genus ↑ - F, B *Bacteroides* ↑ - F	Rats
Immerstrand *et al.* (2010)	Oat bran (OB; β-glucans – 1800 kDa or 2348 kDa) Processed oat bran (POB; β-glucans – 1311 kDa, 241 kDa, 56 kDa, 21 kDa, 10 kDa) (*4 weeks*)	Acetate, propionate, butyrate ↑ - OB, POB	Mice
Berger *et al.* (2014)	High fat diet – barley husks, rye bran, fibre residue from oat milk (*4 weeks*)	*Lactobacillus* ↑ propionate, butyrate ↑	Mice
Zhou *et al.* (2015)	Wholegrain oat flour (WGO), Low bran oat flour (LBO) (*8 weeks*)	Prevotellaceae, Lactobacillaceae, and *Alcaligenaceae* families relative abundance – ↑ - WBO Clostridiaceae, Lachnospiraceae families – ↑ - LBO	Mice

interact with the gut microbiota (van Duynhoven *et al.* 2011; Cardona *et al.* 2013; Kay 2015).

Effects of oat intake on microbiome composition – human trials

Whilst *in vitro* (Kedia *et al.* 2009; Connolly *et al.* 2010, 2012a) and animal studies (Immerstrand *et al.* 2010; Berger *et al.* 2014) indicate that oat intake increases the production of SCFAs, these effects are difficult to quantify in humans as SFCAs are rapidly absorbed or utilised in the large intestine. For example, butyrate is almost entirely used by the colonocytes as their preferred energy substrate (Cummings *et al.* 1987), propionate is primarily absorbed and removed by the liver (Hong *et al.* 2005), whilst acetate passes into the peripheral circulation (Roediger 1980). The use of *in vitro* tools can help to investigate whether various substrates lead to increased SCFA generation, as faecal SCFA measurements are an uncertain estimate of colonic SCFA production (Valeur *et al.* 2016).

Findings from human trials on the effects of oats on the microbiota vary, possibly due to differences in study design (*i.e.* intervention dose, study duration, study population, the method of microbial enumeration) and because these studies assessed the effects of fibre but not the polyphenols in oats (Table 4). Two randomised controlled trials provide evidence that wholegrain wheat may exert effects on gut microbiota (Costabile *et al.* 2008; Vitaglione *et al.* 2015). A daily intake of 48 g of wholegrain wheat significantly increased the growth of *Bifidobacterium* (0.8 $\log_{10}$ cells per g faeces) and *Lactobacillus* (0.6 $\log_{10}$ cells per g faeces) and increased plasma ferulic acid levels

(Costabile *et al.* 2008). In contrast, intake of 70 g per day of wholegrain wheat was found not to increase levels of *Bifidobacterium*, although faecal ferulic acid levels were found to be associated with an increase in *Bacteroides*, Firmicutes and a reduction in *Clostridium* (Vitaglione *et al.* 2015). To date, no human trials have studied the direct effects of extracted or purified oat phenolic acids on the growth of the microbiota, or whether they contribute to the prebiotic effects of wholegrain intake, although data do exist on the impact of flavanols, which have been found to promote the growth of specific beneficial bacteria (Tzounis *et al.* 2011). These data suggest that phenolic acids present in wholegrain cereals may potentiate gut microbiota diversity; however, further research is required to distinguish between the effects of fibre and polyphenols on gut health.

Impact of oat intake on cholesterol metabolism and bile acid synthesis

Oat β-glucans have been suggested to lower cholesterol by causing an increased viscosity of the intestinal chime (Ryan *et al.* 2007). The gel formed is thought to act as a physical barrier to lipid (triglycerides) absorption in the small intestine, in particular that of cholesterol reabsorption (Bae *et al.* 2010; Andersson & Hellstrand 2012; Bao *et al.* 2014). β-glucans have also been shown to bind to luminal BAs, which increases the excretion of bile in the faeces and triggers an increase in hepatic conversion of cholesterol into BAs, thereby decreasing blood cholesterol levels (Lia *et al.* 1995; Bae *et al.* 2010; Grundy *et al.* 2017). It has been reported that the intake of 75 g of

Table 4 The relationship between oats, the growth of gut microbiota and short-chain fatty acid (SCFA) production based on data from human intervention trials

Reference	Intervention (duration)	Oat effects on bacterial composition and/or SCFA production compared to control
Bridges *et al.* (1992)	20 (38–73 years) hypercholesterolaemic men Oat bran – 34 g/day total fibre and 13.4 g/day soluble fibre Control – 14 g/day total fibre and 3 g/day soluble fibre (*3 weeks*)	SCFA in peripheral serum Serum acetic acid ↑
Mårtensson *et al.* (2005)	56 adults (20–70 years, 24 men/32 women) with moderately increased plasma cholesterol levels Fermented oat-based products (FO) (3–3.5 g/day – β-glucans) Fermented ropy, oat products (FRO) Fermented dairy-based product (control) (*Control – 3 weeks, treatment – 5 weeks*)	Total bacteria count ↑ *Bifidobacterium* ↑ - FO, FRO
Nilsson *et al.* (2008b)	25 healthy adults (20–47 years, 10 men/15 women) 40 g β-glucans enriched oat bran (40 g oat bran, 20 g dietary fibre, 10 g glucan in four slices of bread) Control – baseline samples, week 0 (*12 weeks*)	SCFAs in faeces Acetic, propionic, butyric, isobutyric, isovaleric - ↑
Valeur *et al.* (2016)	10 healthy adults (22–49 years, 2 men/8 women) 60 g oatmeal porridge (8.5 g fibre, 4.7 g glucans) Control – baseline samples, day 1 (*1 week*)	Intestinal gas production SCFAs and no changes – faeces β-galactosidase and urease - ↓ Rectal level of PGE$_2$ – no significant difference
Connolly *et al.* (2016)	32 mild or hypercholesterolaemia adults (23–64 years, 12 men/20 women) Wholegrain oat granola (WGO) - 45 g granola breakfast cereals (6.3 g fibre, 2.9 g glucans) Non-wholegrain (NWG) – 45 g non-wholegrain breakfast cereals (control) (3 g fibre, no glucans) (*6 weeks*)	SCFAs no significance differences Total bacteria count ↑ *Bifidobacterium* ↑ *Lactobacilli* ↑

extruded oat bran (11 g β-glucans) resulted in a near doubling of serum 7 alpha-hydroxy-4-cholesten-3-one concentration within 8 hours, which lead to increased BA synthesis (Andersson *et al.* 2002). BA excretion is well known to stimulate cholesterol uptake from the circulation, resulting in a decreased serum cholesterol concentration (Grundy *et al.* 2017).

Oat intake and short-chain fatty acid production

SCFA production is highly dependent on the donor and availability of substrates (Cook & Sellin 1998). The ability of oats (and isolated β-glucans) to increase SCFA production is well established (Connolly *et al.* 2010, 2012a; Berger *et al.* 2014). After 12 hours of *in vitro* fermentation, oat bran (containing 22% oat

β-glucan) induced significantly higher concentrations of propionate compared to other prebiotic dietary fibres, such as inulin and xylooligosaccharide (Carlson *et al.* 2017). The production of SCFAs in the large intestine following oat consumption has been reported and postulated to contribute to reductions in serum lipids and other CVD risk markers (Andersson & Hellstrand 2012). As such, SCFAs may act as mediators of the beneficial effects of wholegrain oat intake of human CVD. These effects might be dependent on SCFAs' ability to: (1) affect liver and muscle cellular metabolism via their potential to increase insulin sensitivity and decrease lipid accumulation in liver (Oda *et al.* 1994; Ulmius *et al.* 2011; Zhang *et al.* 2012; Chang *et al.* 2013; McNabney & Henagan 2017); (2) suppress cholesterol synthesis, increase fatty acid

oxidation and decrease *de novo* fatty acid synthesis in the liver (Andersson *et al.* 2002, 2017; Cloetens *et al.* 2012; Han *et al.* 2015); (3) increase adipogenesis and decrease lipolysis (Gao *et al.* 2015; Heimann *et al.* 2016); (4) modulate satiety through their potential to bind to G protein-coupled receptors (GPR41, GPR43), leading to the increased production of the gut hormones glucagon-like peptide-1 and peptide YY (Hooda *et al.* 2010; Koh *et al.* 2016; Rebello *et al.* 2016) and regulate satiety centrally (Bridges *et al.* 1992; Canfora *et al.* 2015; Canfora & Blaak 2017); and 5) improve colon and liver glucose homeostasis via their induction of intestinal gluconeogenesis (den Besten *et al.* 2013; Bourassa *et al.* 2016; Cheng *et al.* 2017; Jayachandran *et al.* 2018) (Fig. 4). In addition, butyric acid has been reported to increase phenolic acid absorption in the colon (Ziegler *et al.* 2016), which subsequently may induce endothelium-dependent vasodilation (Suzuki *et al.* 2002, 2007; Choi *et al.* 2012). Recent studies have also indicated that the ratio of acetate and propionate may be important for defining the precise effects of SCFAs on various physiological systems. For example, a high serum acetate:propionate ratio has been associated with reductions in total serum cholesterol in men (Weitkunat *et al.* 2017; Boets *et al.* 2017; Wolever *et al.* 1996).

Conclusions

Evidence suggests that wholegrain oats may reduce CVD risk due to their influence on lipid metabolism and plasma cholesterol levels. Oat β-glucans are likely to be partly responsible for any effects as they can change the gut microbiota composition, increase cholesterol excretion in the gut and increase the levels of SCFAs, which may inhibit hepatic cholesterol synthesis and affect glucose homeostasis in adipose tissues and muscle cells. However, inconsistent findings from *in vitro*, animal and human studies have been reported regarding the influence of oat intake on these outcomes, possibly due to differences in experimental techniques and the focus on β-glucan rather than other compounds present in oats, such as phenolic acids and avenanthramides, which may also contribute to beneficial changes in the gut microbiota and lipid/cholesterol metabolism. Clinical, observational and experimental studies to date have not explored the extent to which cardiovascular benefits are dependent on oat fibre or phenolic acid levels. Hence, further randomised, controlled trials are required to examine the relative effects of oat phenolics on microbial pathways and cardiovascular risk markers.

Conflict of interest

The authors declare no conflict of interests.

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