Circulating bile acids as a link between the gut microbiota and cardiovascular health: impact of prebiotics, probiotics and polyphenol-rich foods

Article

Published Version

Creative Commons: Attribution 4.0 (CC-BY)

Open Access

Pushpass, Rose-Anna G., Alzoufairi, Shouq, Jackson, Kim G. ORCID logoORCID: https://orcid.org/0000-0002-0070-3203 and Lovegrove, Julie A. (2022) Circulating bile acids as a link between the gut microbiota and cardiovascular health: impact of prebiotics, probiotics and polyphenol-rich foods. Nutrition Research Reviews, 35 (2). pp. 161-180. ISSN 0954-4224 doi: https://doi.org/10.1017/S0954422421000081 Available at https://centaur.reading.ac.uk/100078/

It is advisable to refer to the publisher's version if you intend to cite from the work. See Guidance on citing.

To link to this article DOI: http://dx.doi.org/10.1017/S0954422421000081

Publisher: Cambridge University Press

All outputs in CentAUR are protected by Intellectual Property Rights law, including copyright law. Copyright and IPR is retained by the creators or other copyright holders. Terms and conditions for use of this material are defined in the End User Agreement.
CentAUR
Central Archive at the University of Reading
Reading’s research outputs online
Circulating bile acids as a link between the gut microbiota and cardiovascular health: impact of prebiotics, probiotics and polyphenol-rich foods

Rose-Anna G. Pushpass, Shouq Alzoufairi, Kim G. Jackson and Julie A. Lovegrove*
Hugh Sinclair Unit of Human Nutrition, Department of Food and Nutritional Sciences, and Institute for Cardiovascular and Metabolic Research, University of Reading, Harry Nursten Building, Whiteknights, Pepper Lane, Reading, RG6 6DZ, UK

Abstract
Beneficial effects of probiotic, prebiotic and polyphenol-rich interventions on fasting lipid profiles have been reported, with changes in the gut microbiota composition believed to play an important role in lipid regulation. Primary bile acids, which are involved in the digestion of fats and cholesterol metabolism, can be converted by the gut microbiota to secondary bile acids, some species of which are less well reabsorbed and consequently may be excreted in the stool. This can lead to increased hepatic bile acid neo-synthesis, resulting in a net loss of circulating low-density lipoprotein. Bile acids may therefore provide a link between the gut microbiota and cardiovascular health. This narrative review presents an overview of bile acid metabolism and the role of prebiotics, probiotics and polyphenol-rich foods in modulating circulating cardiovascular disease (CVD) risk markers and bile acids. Although findings from human studies are inconsistent, there is growing evidence for associations between these dietary components and improved lipid CVD risk markers, attributed to modulation of the gut microbiota and bile acid metabolism. These include increased bile acid neo-synthesis, due to bile sequestering action, bile salt metabolising activity and effects of short-chain fatty acids generated through bacterial fermentation of fibres. Animal studies have demonstrated effects on the FXR/FGF-15 axis and hepatic genes involved in bile acid synthesis (CYP7A1) and cholesterol synthesis (SREBP and HMGCR). Further human studies are needed to determine the relationship between diet and bile acid metabolism and whether circulating bile acids can be utilised as a potential CVD risk biomarker.

Key words: Bile acids: Prebiotics: Probiotics: Polyphenols: Cardiovascular disease: Gut microbiota

(Received 3 June 2020; revised 24 March 2021; accepted 5 April 2021)

Introduction
Cardiovascular diseases (CVD) are a major cause of mortality and disability in the UK (1). Since diet and low-density lipoprotein (LDL)-cholesterol (LDL-C) are both important modifiable CVD risk markers, there is considerable interest in dietary strategies which can reduce LDL-C levels for disease prevention (2). Probiotic, prebiotic and polyphenol-rich interventions have reported beneficial effects on the fasting lipid profile, with changes in the gut microbiota composition thought to play an important role in lipid regulation. Emerging evidence suggests that bile acids may act as a link between changes in the gut microbiota and cardiovascular health, via effects on circulating lipids, inflammation and glycaemia, with the profile and concentration of circulating bile acids considered to be a potential novel biomarker of disease risk (3).

Bile acids are synthesised in the liver from cholesterol and form the major component of bile (4). They are stored in the gall-bladder before being released into the gut in response to food intake, where they emulsify dietary fats to facilitate adsorption of lipids and lipid-soluble vitamins (4). Bile acids are significantly modified in the gut by bacterial enzymes (5). Bile salt hydrolase (BSH), bile acid inducible (BAI) and bile acid dehydratase enzymes, expressed by certain species of gut bacteria can modify bile acids to generate unconjugated and secondary bile acids (6). These converted bile acids may be less well absorbed in the intestine, and as such, the proportion of bile acids being excreted may be affected by the microbial population in the gut (7). The vast majority (95 %) of bile acids are recycled back to the liver via the hepatic portal circulation in what is known as the enterohepatic cycle (8). However, a small percentage will escape recycling and are excreted in the faeces. Bile acid neo-synthesis is an effective system for cholesterol regulation in the body, taking cholesterol out of the circulation to be used for synthesis of new bile acids, replacing those lost in the faeces. Certain foods including probiotics, prebiotics and those rich in polyphenols have been shown to alter the gut microbiome, enhancing growth of probiotic bacteria with bile acid metabolising activity. Since high circulating LDL-C levels are a significant risk factor for CVD (9), the ability of probiotic bacteria to reduce cholesterol via bile acid modification in the gut could be key for dietary interventions in reducing disease risk and improving population health. This narrative review will provide an overview of bile acid metabolism and determine the role of probiotics, prebiotics and polyphenol-rich foods in modulating circulating bile acids and lipid risk markers for CVD.

* Corresponding author: Julie A Lovegrove, email: j.a.lovegrove@reading.ac.uk
Bile acids and modulation of CVD risk markers

Bile acids are synthesised through two distinct pathways, the classical and alternative pathways (see Fig. 1 for an overview). For an in-depth discussion on the synthesis of bile acids, the reader is directed to an excellent review by Li and Chiang (10). Within the liver, classic bile acid synthesis is initiated in the hepatocytes via cholesterol hydroxylation, catalysed by the cholesterol 7α-hydroxylase (CYP7A1) enzyme, part of the cytochrome P450 enzyme family (11). This is the rate-limiting step in bile acid synthesis and leads to conversion of cholesterol to 7α-hydroxycholesterol. CYP7A1 expression is regulated by farnesoid X receptor (FXR), via a feedback mechanism, by an increase in bile acids following food intake. FXR can be directly activated in hepatocytes or by bile acids in the gastro-intestinal (GI) tract. In the intestine, FXR activation leads to expression of fibroblast growth factor (FGF) 19, which travels to the liver to activate FGF receptor 4 (FGFR4) and ultimately suppresses expression of CYP7A1, inhibiting bile acid synthesis (10). The alternative bile acid pathway occurs in the mitochondria and produces mainly chenodeoxycholic acid, and can therefore theoretically occur in all cell/tissue types. Evidence of alternative bile acid synthesis has been shown to occur in the brain, macrophages and liver (12-14). In this pathway, hydroxylation of cholesterol leads to its conversion to oxysterols catalysed by sterol 27-hydroxylase. 7α-hydroxylated oxysterols are eventually converted to primary bile acids in enzymatic pathways common to both the classic and alternate bile acid pathways (Fig. 1) (15). In the final step of bile acid synthesis, bile acids are conjugated to an amino acid, either glycine or taurine, via formation of a thioester intermediate, which is catalysed by the bile acid choly-CoA synthetase and bile acid CoAminoo acid N-acyltransferse enzymes (16,17). Conjugated bile acids, known as bile salts, have greater water solubility and are secreted into bile which is stored in the gallbladder. The hormone cholecystokinin is the main regulator of gallbladder contraction and sphincter of Oddi relaxation which facilitates the release of bile through the bile duct and duodenal papilla to the duodenum during the post-prandial phase (18,19). Following food intake, nutrients, including fatty acids and some amino acids, are sensed in the small intestine (the duodenum), resulting in secretion of cholecystokinin by enteroendocrine cells and promoting absorption in the intestine (20).

Sterol regulatory element-binding proteins (SREBP) belong to a family of basic helix-loop-helix leucine-zipper transcription factors which are regulated by intracellular levels of cholesterol/oxysterols and are vital in the regulation of fatty acid and cholesterol synthesis (21). SREBP-1c (produced from the SREBP-1 gene) is mainly involved in fatty acid synthesis, while SREBP-2 (encoded by the SREBP-2 gene) is implicated in the synthesis of cholesterol (10,22). SREBP-1c expression is induced by insulin as well as activation of liver X receptor (LXR)-α by oxysterols (23) required to generate fatty acids for the synthesis of cholesterol esters (24). Transcription factors for SREBP2 are preserved as an inactive precursor in the endoplasmic reticulum membranes when oxysterol levels are high, for example during synthesis of bile acids. However, conversion of intracellular oxysterols to primary bile acids leads to transportation of the SREBP2 precursor to the Golgi apparatus where it is cleaved by proteases to release the amino-terminal portion of the protein from its membrane-bound precursor. This protein then migrates to the nucleus where it can activate the transcription of the LDL-receptor gene, increasing the expression of receptors on the surface of the hepatocytes and leading to an increase in intracellular cholesterol levels (22). Interestingly, studies in mice have shown that overexpression of CYP7A1 leads to increased hepatic expression of SREBP2, suggesting a link between bile acid synthesis and hepatic cholesterol regulation (25).

Enterohepatic circulation allows for recycling of bile acids and other substances that are absorbed from the intestine, packaged as lipid micelles, and transported back to the liver via portal blood circulation (see Fig. 2 for an overview) (9). In addition, some free hydrophobic bile acids are reabsorbed by passive diffusion in the GI tract. Once in the liver they are secreted into the bile and subsequently re-enter the intestine. A large proportion (95%) of bile acids are recycled in this way, with the remaining 5% being excreted in faeces (26). Enterohepatic recycling is important to preserve the bile acid pool which is vital for many functions of the liver and GI tract such as bile flow, solubilisation and excretion of cholesterol as well as intestinal absorption of lipophilic compounds (27). In addition, this process conserves cholesterol and bile acids for re-use and avoids the loss of these valuable sterols which would otherwise need to be endogenously synthesised or obtained from the diet.

The microbiota residing in the GI tract can influence the proportions of primary and secondary bile acids (27). This is because several species of gut bacteria, including Clostridium, Enterococcus, Bifidobacterium, Lactobacillus and members of the genus Bacteroides, are capable of converting primary bile acids into secondary bile acids, such as lathocholic acid (LCA) and deoxycholic acid (DCA), via 7α-dehydroxylase (RAI encoded) enzymes and further conversion into unconjugated forms, in the distal ileum by SH enzymes (Table 1) (28). In the large intestine, bile acids undergo bacterial bio-transformations including de-conjugation followed by further metabolism such as oxidation of hydroxyl groups and dihydroxylation (29). Secondary bile acids, especially the more hydrophobic ones, are less well absorbed in the enterohepatic cycle, and therefore a greater amount may be excreted in the faeces, leading to a net loss of cholesterol (30). This is because bacterial de-conjugation results in more hydrophobic bile acids which are poorly absorbed via passive diffusion. Table 1 presents the relative hydrophobicity of the main bile acids. LCA is commonly cited as the most hydrophobic bile acid (30); however, the hydrophobicity index for un-conjugated LCA could not be found in the literature. Meanwhile, conjugated bile acids can be more easily taken up by ileal bile acid transporters/apical bile acid transporters (IBAT/ABAT) transporters (17). The secondary bile acids constitute up to 35% of the circulating bile acids and have important regulatory functions in metabolic processes including weight maintenance and glucose/lipid tolerance (31). As such, the gut microbiota plays an important role in the enterohepatic circulation and cholesterol regulation.

A mechanistic link between gut microbiota composition and host physiology is thought to occur via the microbiologically produced secondary bile acids. These act as key regulators in several metabolic processes since they are considered to be stronger
Fig. 1. Metabolism of bile acids: bile acid synthesis occurring in the liver from cholesterol via host cytochrome P450 enzymes, through the classic and alternative bile acid synthetic pathways. Conjugation of bile acids occurs in the liver, with further modification of BA moieties by microbes in the GI tract which can de-conjugate using bile salt hydrolases (BSH). This results in free primary bile acids which can be further modified by microbes for example dehydroxylation via bile acid-inducible (BAI) enzymes to yield a variety of secondary bile acids (such as deoxycholic and lithocholic acid). Reprinted from Molecular Aspects of Medicine, 56, Sarah L. Long, Cormac G.M. Gahan, Susan A. Joyce, Interactions between gut bacteria and bile in health and disease, Pages No. 54–65, Copyright (2017), with permission from Elsevier.
agonists for several receptors involved in host metabolism compared with primary bile acids. Bile acids activate specific nuclear receptors including FXR, vitamin D receptor (VDR), pregnane X receptor (PXR) and the G-protein-coupled receptor TGR5 which are implicated in cell signalling pathways in both the liver and the GI tract (see Table 1 for signalling potential of common bile acids). FXR activation has been linked to the maintenance of normal triglyceride (TAG) and cholesterol levels, as well as regulating factors in the liver and intestine which influence CVD risk such as lipid and glucose homeostasis, endothelial function and atherosclerosis. Meanwhile, the secondary bile acids LCA and DCA act as powerful ligands for TGR5. This influences several important metabolic pathways, such as thermogenesis, energy metabolism and glucose homeostasis. Activation of TGR5 leads to increased intestinal production of the gut hormone glucagon-like peptide (GLP)-1 promoting insulin secretion and regulation of appetite, and increased energy expenditure via conversion of thyroid hormone T4 into the active form, T3.

The profile of secondary bile acids, both in the GI tract and systemically, may differ in conjunction with improved and diminished host health. For instance, in animal models, increased circulating levels of taurocholate have been associated with greater proliferation of the gut bacteria Bilophila wadsworthia, which are related to inflammatory bowel disease. Higher serum concentrations of DCA, a secondary bile acid produced via colonic microbial transformation of cholic acid, have been found in obese mice, likely due to dysbiosis of the gut microbiota such as a proliferation of clostridium species. Meanwhile levels of other secondary bile acids may be linked with beneficial effects on host health. For example, increased levels of ursodeoxycholic acid (UDCA) and its glycine and taurine conjugates in bariatric surgery patients have been demonstrated alongside increased insulin sensitivity. Furthermore, a study in rats by Basso et al. found higher levels of UDCA after partial gastrectomy which occurred in conjunction to enhanced insulin sensitivity and fat distribution, independent of weight loss. Increased levels of circulating bile acids are also found in Roux-en-Y gastric bypass patients because, when the duodenum and proximal jejunum are bypassed, bile acids do not mix with food until they reach the mutual portion of the jejunum. This means that greater concentrations of bile acids are delivered to the jejunum, and their uptake by IBAT/ABAT transporters is increased in the ileum. As a consequence, higher concentrations of bile acids occur in the portal vein, and more bile acids are released into the systemic circulation. Furthermore, alterations of the gut microbiota are known to occur following bariatric surgery, with a tendency toward reduced Firmicutes-to-Bacteroides ratio and an increase in Proteobacter, which can alter the proportions of secondary bile acids in the intestinal bile acid pool through increased BSH activity.

Systemic effects of secondary bile acids on host health have also been demonstrated by direct consumption or intrajejunal administering of specific secondary bile acids. For example, intake of UDCA given as granules, in healthy human subjects has been linked with improved postprandial blood glucose levels and raised GLP-1 secretion. This gut hormone controls glucose-induced insulin excretion and gastric emptying. Furthermore, consumption of UDCA in rats has been shown to reduce fructose-induced metabolic syndrome, demonstrated by the addition of 150 mg/kg UDCA to drinking-water. Moreover, in humans, intrajejunal taurocholic acid has been reported to decrease blood glucose and activate release of satiety hormones such as GLP-1 and peptide YY.

Bile acids are thought to regulate various receptors influencing the regulation of metabolism and lipid profiles. Various secondary bile acids act as strong or weak agonists of FXR and TGR5, while some can suppress their activity, for example tauro-β-muricholic acid, an FXR antagonist. Therefore, the profile of circulating bile acid (BA) in contact with these receptors in different tissues may determine their level of regulation. Activation of such nuclear receptors may provide the key to linking the microbiota composition and activity with cardiovascular health via the bile acid converting activity of certain strains of gut bacteria. In light of this, circulating bile acids may represent useful biomarkers of cardiovascular health in humans.

Fig. 2. Enterohepatic circulation of cholesterol and bile acids: between 0.2 and 0.6 g bile acid is synthesised per day in the liver to maintain the human bile acid pool which is made up of approximately 3 g of bile acids. Absorption of nutrients following food intake results in stimulation of the gallbladder, which releases bile acids into the small intestine. In the ileum, conjugated bile acids can be easily reabsorbed by active transport, while a small amount of unconjugated bile acids are reabsorbed by passive diffusion in the small and large intestines. Bile acids are then extracted from the portal blood by the liver. Small amounts of bile acids are excreted in the faeces (approximately 5 %) and must be replaced by neo-synthesis in the liver.
Table 1. Circulating bile acids and their signalling potential

| Bile acid                   | Mean fasting plasma concentration μM (± SD) n=80 | Hydrophobicity index (HI) (167) | Nuclear receptors agonist/antagonist |
|-----------------------------|-------------------------------------------------|---------------------------------|-------------------------------------|
| **Primary bile acids**      |                                                 |                                 |                                     |
| Taurocholic acid            | 0.26 (0.45)                                     | 0.00                            |                                     |
| Glycocholic acid            | 0.51 (0.52)                                     | +0.07                           |                                     |
| Taurochenodeoxycholic acid  | 0.22 (0.22)                                     | +0.46                           |                                     |
| Glycochenodeoxycholic acid  | 0.49 (0.35)                                     | +0.51                           |                                     |
| Chenodeoxycholic acid       | 0.89 (1.05)                                     | +0.59                           | Mild TGR5 agonist (158), potent FXR agonist (159), PXR agonist (60) |
| Cholic acid                 | 1.02 (1.83)                                     | +0.13                           | FXR agonist (159), TGR5 agonist (131) |
| **Secondary bile acids**    |                                                 |                                 |                                     |
| Ursodeoxycholic acid        | 0.02 (0.03)                                     | –0.31                           | Potent TGR5 agonist (158), VDR agonist (160), PXR agonist (161), FXR agonist (158) |
| Lithocholic acid            | 0.02 (0.01)                                     | –                                | Potent TGRS agonist (158), FXR agonist (158), PXR agonist (160), Potent TGRS agonist (162) |
| Deoxycholic acid            | 0.94 (0.66)                                     | +0.72                           |                                     |
| Taurolithocholic acid       | 0.00 (0.00)                                     | +1.00                           |                                     |
| Hyocholic acid              | 0.01 (0.01)                                     | –                                |                                     |
| Glycohyocholic acid         | 0.29 (0.30)                                     | –0.26                           | LXRα agonist (143) |
| Tauro-ursodeoxycholic acid  | 0.02 (0.02)                                     | –0.47                           |                                     |
| Hyodeoxycholic acid         | 0.86 (0.60)                                     | –                                | LXRα agonist (143) |
| Taurodeoxycholic acid       | 0.21 (0.26)                                     | +0.59                           | TGRS agonist (164) |
| Glycosodeoxycholic acid     | 0.07 (0.06)                                     | –0.43                           |                                     |
| Glycolithocholic acid       | 0.54 (0.68)                                     | +1.05                           | VDR agonist (160) |
| Glycodeoxycholic acid       | 0.23 (0.22)                                     | +0.65                           |                                     |
| Tauro-α muricholic acid     | 0.05 (0.04)                                     | –0.84                           | FXR antagonist (131) |
| Taurohyocholic acid         | 0.02 (0.01)                                     | –0.39                           |                                     |
| Taurohydroxycholic acid     | 0.02 (0.02)                                     | –0.31                           | Potent LXRα agonist (163) |
| Glycohyocholic acid         | 0.05 (0.04)                                     | –0.40                           |                                     |
| Tauro-β-muricholic acid     | 0.00484 (0.00043) (165)                         | –0.78                           | FXR antagonist (166) |

Abbreviations: FXR, farnesoid X receptor; LXRα, liver X receptor α; PXR, pregnane X receptor; TGR5, G-protein-coupled bile acid receptor 1; VDR, vitamin D receptor.

Adapted from circulating bile acid concentrations measured in fasting plasma using LC-MS/MS in healthy adults between the ages of 18 and 45 years (165). Hydrophobicity index (HI) quantitatively defines the merged hydrophilic or small intestine. Indeed, increased expression of BSH in these mice led to reduced weight gain and lower levels of plasma cholesterol and liver triglycerides (5). Therefore, any dietary component which has the ability to influence the proliferation of bacteria with BSH activity in the gut may also modulate bile acid homeostasis and the ability to impact on host cardiovascular health.

Fibres such as β-glucans, found in oats, and pectin, found in apples, and polyphenols such as proanthocyanidins, catechins or tannins, have been reported to possess bile acid sequestering activity (52,53). This can cause the bile acids to travel unabsorbed into the colon where they are excreted or transformed again into secondary bile acids by the colonic bacteria. Studies have shown that pharmaceutical sequestering agents may decrease circulating LDL-C, reduce obesity, improve insulin sensitivity and induce thermogenesis (54). Therefore, bile acid sequestering agents have potential for treatment of metabolic disease.

Table 1. Circulating bile acids and their signalling potential

| Bile acid                   | Mean fasting plasma concentration μM (± SD) n=80 | Hydrophobicity index (HI) (167) | Nuclear receptors agonist/antagonist |
|-----------------------------|-------------------------------------------------|---------------------------------|-------------------------------------|
| **Primary bile acids**      |                                                 |                                 |                                     |
| Taurocholic acid            | 0.26 (0.45)                                     | 0.00                            |                                     |
| Glycocholic acid            | 0.51 (0.52)                                     | +0.07                           |                                     |
| Taurochenodeoxycholic acid  | 0.22 (0.22)                                     | +0.46                           |                                     |
| Glycochenodeoxycholic acid  | 0.49 (0.35)                                     | +0.51                           |                                     |
| Chenodeoxycholic acid       | 0.89 (1.05)                                     | +0.59                           | Mild TGR5 agonist (158), potent FXR agonist (159), PXR agonist (60) |
| Cholic acid                 | 1.02 (1.83)                                     | +0.13                           | FXR agonist (159), TGR5 agonist (131) |
| **Secondary bile acids**    |                                                 |                                 |                                     |
| Ursodeoxycholic acid        | 0.02 (0.03)                                     | –0.31                           | Potent TGR5 agonist (158), VDR agonist (160), PXR agonist (161), FXR agonist (158) |
| Lithocholic acid            | 0.02 (0.01)                                     | –                                | Potent TGRS agonist (158), FXR agonist (158), PXR agonist (160), Potent TGRS agonist (162) |
| Deoxycholic acid            | 0.94 (0.66)                                     | +0.72                           |                                     |
| Taurolithocholic acid       | 0.00 (0.00)                                     | +1.00                           |                                     |
| Hyocholic acid              | 0.01 (0.01)                                     | –                                |                                     |
| Glycohyocholic acid         | 0.29 (0.30)                                     | –0.26                           | LXRα agonist (143) |
| Tauro-ursodeoxycholic acid  | 0.02 (0.02)                                     | –0.47                           |                                     |
| Hyodeoxycholic acid         | 0.86 (0.60)                                     | –                                | LXRα agonist (143) |
| Taurodeoxycholic acid       | 0.21 (0.26)                                     | +0.59                           | TGRS agonist (164) |
| Glycosodeoxycholic acid     | 0.07 (0.06)                                     | –0.43                           |                                     |
| Glycolithocholic acid       | 0.54 (0.68)                                     | +1.05                           | VDR agonist (160) |
| Glycodeoxycholic acid       | 0.23 (0.22)                                     | +0.65                           |                                     |
| Tauro-α muricholic acid     | 0.05 (0.04)                                     | –0.84                           | FXR antagonist (131) |
| Taurohyocholic acid         | 0.02 (0.01)                                     | –0.39                           |                                     |
| Taurohydroxycholic acid     | 0.02 (0.02)                                     | –0.31                           | Potent LXRα agonist (163) |
| Glycohyocholic acid         | 0.05 (0.04)                                     | –0.40                           |                                     |
| Tauro-β-muricholic acid     | 0.00484 (0.00043) (165)                         | –0.78                           | FXR antagonist (166) |

Abbreviations: FXR, farnesoid X receptor; LXRα, liver X receptor α; PXR, pregnane X receptor; TGR5, G-protein-coupled bile acid receptor 1; VDR, vitamin D receptor.

Adapted from circulating bile acid concentrations measured in fasting plasma using LC-MS/MS in healthy adults between the ages of 18 and 45 years (165). Hydrophobicity index (HI) quantitatively defines the merged hydrophilic–hydrophobic balance of bile salts, based on bile salt capacity factor logarithms calculated using reversed-phase high-performance liquid chromatography (HPLC) and standardised arbitrarily to the indices of taurocholate (HI 0) and taurolithocholate (HI 1) (167).
Gut dysbiosis
A deviation from the natural balance in the gut microbiota (dysbiosis) is associated with obesity and conditions such as inflammatory bowel disease (55). Reduced diversity and decreased levels of certain bacteria in the gut can lead to activation of the mucosal immune system, resulting in damage to the GI tract, which is particularly evident in inflammatory bowel disease (56). Dysbiosis may also result in alterations in bile acid metabolism which can further disrupt gut homeostasis via effects on bacterial deconjugation, transformation and desulphation of bile acids (57). This interruption of normal bile acid metabolism may result in increased intestinal epithelial inflammation and gut permeability, allowing translocation of bacterial lipopolysaccharides across the gut-blood barrier, which in turn results in systemic inflammation. A high-fat diet has been frequently associated with dysbiosis and bile acid dysregulation (58). This reflects the importance of bile acids as postprandial signalling molecules that can affect gut mucosal defences via both antibacterial and anti-inflammatory actions reducing the synthesis of pro-inflammatory cytokines (TNF-α, monocytes and macrophages) (59). In addition, decreased synthesis of secondary bile acids leads to reduced activation of nuclear receptors such as FXR, PXR, TGR5 and VDR. This can cause changes in bile acid synthesis and have a negative impact on lipid homeostasis (60). Dysbiosis and the resulting interruption to the intestinal epithelial barrier is therefore linked with several diseases, including non-alcoholic fatty liver disease and cardiometabolic diseases (61). Consumption of probiotics, prebiotics and polyphenol-rich foods may restore the balance of gut microbiota, regulating bile acid metabolism and restoring nuclear receptor activation.

Probiotics
Probiotics are beneficial strains of bacteria with positive effects on host health. Both Bifidobacterium and Lactobacillus species have been identified as probiotics with BSH activity, with the highest BSH activity identified in Bifidobacterium breve and Lactobacillus plantarum LA3 strains (62). BSH enzymes catalyse the first step in the conversion of conjugated primary bile acids into unconjugated species, allowing further transformation into secondary bile acid species, and may therefore lead to reduced reabsorption of bile acids in the enterohepatic cycle since secondary bile acids may be less easily absorbed. Certain secondary bile acids may be more readily excreted from the body, and bile acid neo-synthesis and LDL clearance may be enhanced (63,64). LCA, for example, as the most hydrophobic bile acid, is reabsorbed poorly into the enterohepatic circulation, and thus, greater levels of LCA are excreted in the faeces (65).

Effects on lipid metabolism
Several studies using animal models have demonstrated reduced circulating LDL-C levels following probiotic supplementation (65-71). Such results have also been replicated in human studies with the findings of a meta-analysis including 13 trials reporting a combined mean net change in total cholesterol (total participants n = 485) of −1.66 mM LDL-C as −1.27 mM and TAG as −0.45 mM (72) in those individuals treated with probiotics versus controls. Jones et al. (73) found that the consumption of Lactobacillus reuteri for 6 weeks reduced total and LDL-C by 8.9 % and 4.8 %, respectively, in healthy hypercholesterolaemic men and women. The treatment group (n = 56) consumed 115 g of natural yoghurt and 10 g of microcapsules containing BSH-active L. reuteri (equivalent to 1.4 × 109 CFU), twice per day, compared with a placebo group (n = 58) given 125 g of natural yoghurt (73). Similarly, Costabile et al. (65) observed a significant decrease in LDL-C (by 13.9 %) and a non-significant tendency for a reduction in total cholesterol (by 2 %) in healthy adults following 12 weeks of supplementation with Lactobacillus plantarum (2 × 109 CFU (0.1 g) twice daily) compared with a placebo (twice daily in the same capsular format) (65). Meanwhile, Martoni et al. (74) found reduced serum LDL-C in hypercholesterolaemic adults (n = 10), compared with baseline concentrations, after 4 weeks of consuming a delayed-release probiotic capsule (Lactobacillus reuteri NCIMB 30242, 3–9 × 1010 CFU twice daily) (74).

Effects on bile acids
Studies have been performed in animals and, to a lesser extent, in humans to provide further insights into the link between bile acid metabolism and lipid regulation in response to probiotic intake. A summary of studies which have investigated the effect of probiotic supplementation on bile acids in humans (n = 4) and animal models (n = 16) is presented in Table 2 and Supplementary Table 1, respectively. Several studies in animal models have found increased excretion of bile acids in stools following intervention with various probiotic bacteria strains (66,68,71,75-78). However, in the limited number of human trials measuring faecal bile acid levels following chronic probiotic use, an effect on bile acid excretion has not been demonstrated (74,79). Additionally, a study by Oshiro et al. (80) on premature infants born between 24 and 31 weeks of gestation, found that supplementing parenteral nutrition with Bifidobacterium breve resulted in reduced faecal total bile acids compared with a placebo. (80). These discrepancies highlight the need for further human studies examining the tentative link between probiotic bacteria and bile acid/absorption/excretion.

Prebiotics
A dietary prebiotic is defined as ‘a substrate that is selectively utilized by host microorganisms conferring a health benefit’ (81). The most common prebiotics are carbohydrate substrates, and the majority of studies associated with prebiotics and bile acid profiles or cholesterol homeostasis have been performed using β-glucans, fructans, fructose polysaccharide inulin oligosaccharides or galacto-oligosaccharides (62). Dietary prebiotics can alter the microbiota profile in the gut in a dose-dependent manner, and recent evidence, from a limited number of studies, suggests this may impact upon CVD risk markers. For example, a recent review of 16S r-RNA studies on prebiotics and the microbiome found that, generally, consumption of inulin-type fructans (n = 17 studies) in human studies resulted in increased...
abundance of *Bifidobacterium* but had little effect on other gut microbes (85). Meanwhile, supplementation with glucose-based fibres, such as types of resistant starch, had wider effects on the microbial community, especially abundance of *Ruminococcus* species. Galacto-oligosaccharides, xylo-oligosaccharides and arabinoxylan-oligosaccharides (*n* = 8 studies) generally led to increases in *Bifidobacteria* and only slight increases in relative abundance of other gut microbes (85).

**Effects on lipid metabolism**

Prebiotic consumption is thought to improve cardiovascular health via favourable effects on the blood lipid profile. A reduction in total cholesterol levels was demonstrated by Wang *et al.* (86) following chronic intake of barley β-glucan in *n* = 30 mildly hypercholesterolaemic adults (mean serum total cholesterol 5.49 mM). In this study, participants consumed breakfast with 3 g high-molecular-weight, 5 g low-molecular-weight or 3 g low-molecular-weight barley β-glucan (given as breakfast foods in the format of crepes, tortillas, porridge and chips formulated from barley to contain β-glucan varying in molecular weight) or a control diet (breakfast foods formulated from wheat and rice to substitute barley) for 5 weeks. They found that, while serum total cholesterol was reduced significantly by 2.18%, after intake of 3 g high-molecular-weight barley β-glucans, cholesterol absorption and synthesis (both assessed using stable isotope methods) were unaffected (84). Increased serum 7α-hydroxy-4-cholesten-3-one concentrations, representing synthesis of bile acids, was noted in participants following consumption of the high-molecular-weight β-glucan. These results indicate that the cholesterol-lowering action of β-glucans may be related to enhanced bile acid synthesis, utilising circulating cholesterol, as opposed to inhibition of cholesterol synthesis or absorption. Another study by Nicolucci (2017) demonstrated a reduction in serum TAG in healthy, overweight children (*n* = 22) following supplementation with 8 g/d of oligofructose-enriched inulin for 16 weeks, compared with an isonenergetic dose of 3.3 g/d of maltodextrin placebo. The improvement in serum lipids coincided with increased faecal *Bifidobacterium* proliferation, many strains of which have strong BSH activity (85). In a study by Cronin *et al.* (86), daily calcium supplements (800 mg/d) consumed with short-chain fructo-oligosaccharides (3 g/d) for 24 months led to a time-by-treatment effect on the reduction in total and LDL-C levels in postmenopausal women (*n* = 300) compared with daily calcium (800 mg) alone (86). The authors speculated that the reduced cholesterol absorption in the gut could be due to increased binding with the fructo-oligosaccharides, and potentially the bile acids, promoting their excretion in the stool.

**Effects on bile acids**

As with probiotics, several studies (*n* = 16) have found a link between consumption of prebiotic foods and altered bile acid profiles or metabolism (Table 2 and Supplementary Table 1). For example, a number of studies in animal models have shown increased excretion of total bile acids in the faeces after chronic supplementation (between 4 and 17 weeks duration) with a prebiotic compared with a control intervention (87–90). This has also been demonstrated in two human studies (95,91). In some cases, the enhanced excretion of bile acids could be related to increased proliferation of probiotic bacteria, including *Lactobacillus* and *Bifidobacterium* in the gut, possibly due to the BSH activity of such strains of bacteria. For example, Drzíkova *et al.* (92) found, in addition to increased faecal total bile acids and reduced serum total cholesterol, an increase in gut proliferation of *Bifidobacterium* following consumption of 500 g oat-based extrudates, in the form of oat flour or oat bran, for 6 weeks in rats (*n* = 10) (92). Similarly, Meneses *et al.* (87) found increased gut *Lactobacillus* proliferation, as well as increased bile acid excretion, in mice (*n* = 8) after ingestion of *Ganoderma lucidum*, an oriental fungus with prebiotic properties, with a high-cholesterol diet (67). This was also related to improved lipid profiles, with reduced serum total cholesterol (by 19.2–27.1 %), LDL-C (by 4.5–35.1 %) and TAG (by 16.3–46.6 %) concentrations in the mice. A study by Gunnness *et al.* (90) also found that a diet rich in oat β-glucans for 28 d reduced blood total bile acids, total and LDL-C compared with a control diet (no addition of β-glucan) in pigs (*n* = 6) (90). These findings were associated with increased faecal UDCA, changes in faecal HDCA and LCA (non-significant) and an overall reduction in faecal fatty acids, suggesting that β-glucans can alter bile acid metabolism. These results could provide, in part, the mechanism for the cholesterol-lowering effect of such foods since consumption of prebiotics can enhance proliferation of bacteria with bile acid metabolising activity in the gut.

In contrast, in a study by Wu *et al.* (106), faecal secondary bile acids were reduced, while primary bile acids were increased in healthy adults (*n* = 15) after consumption of konjac (4.5 g/d), a high-molecular-weight, non-ionic, linear glucomannan consisting of β-1,4-linkages which resist digestion in the upper GI tract and is thus a rich source of soluble fibre. This was despite gut *Bifidobacterium* and *Lactobacillus* growth being increased, indicating a prebiotic effect, with enhanced proliferation of BSH bacteria strains. Although the effect on lipid profiles was not measured in this study, it may be that different mechanisms are involved in the cholesterol-lowering effect of some prebiotic foods, other than bile acid metabolising activity and subsequent reduced adsorption/increased neo-synthesis of bile acids. For example, it is known that konjac consumption can increase SCFA production in the gut and thus can modulate both BA profiles and SCFA concentrations (93).

Some studies have also found addition of prebiotics to the diet to modulate circulating bile acid levels. For example, Hijoja *et al.* (94) found reduced serum bile acids after a high-fat diet supplemented with 2 % oligofructose-enriched inulin with extracts of horse chestnut (1 %) and/or flaxseed (2 %) in rats (*n* = 12), compared with a high-fat diet alone. For rats treated with inulin alone, this was also linked with reduced total cholesterol and TAG concentrations, as well as increased *Lactobacilli* in the stools (94). However, a study by Lærke *et al.* (95) found no effect of rye wholemeal and rye bran on circulating bile acids in hypercholesteraemic pigs (*n* = 8) despite reduced plasma total-to-LDL-C ratio (95). Although faecal bile acid excretion was not measured, it is also possible that the effect observed is dependent on both the type of prebiotic consumed and the animal species used. For example, pig models have a closer similarity to human lipid metabolism compared with rat models. In
| Author                          | Number (n) – study duration/design | Diet/daily dose                                                                 | Results                                                                 |
|--------------------------------|-----------------------------------|--------------------------------------------------------------------------------|-------------------------------------------------------------------------|
| **Probiotics**                 |                                   |                                                                                |                                                                         |
| (80)                           | n = 18 (Group I), n = 17 (Group II) Infants born between 24 and 31 weeks of gestation, BW < 1 500 g DB, RCT 8 weeks | Group I: parenteral nutrition (PN), with glucose (8 %; glucose infusion rate: 3–4 mg/kg/d), amino acids (1.0–1.5 g/kg/d), and fatty acids (Intralipos; high content of n-6: ~0.5–1.0 g/kg/d) + mother’s colostrum as a trophic feeding + mother’s breast milk fortified with HMS-1 (Morinaga, Tokyo, Japan) and medium-chain TAG oil with placebo supplementation once daily  | Group II: ↓total faecal BAs  |
|                                |                                   | Group I: usual diet, no intervention Group II: MS patients following usual diet, no intervention | Group I versus Group II: ↑stool total bile acids, proportions of primary, secondary, taurine- or glycine-conjugated bile acids  | Group I: faecal bacterial counts, including *Bifidobacterium*, ↑total faecal organic acids; ↑total faecal SCFAs and plasma n-3 fatty acids  |
|                                |                                   | Group III: MS patients following usual diet with (3 bottles a day, 65 ml, containing *Lactobacillus casei* Shirota at a concentration of 10⁸/ml) Group II versus Group III: ↔ proportions of primary, secondary, taurine- or glycine-conjugated bile acids  | N/A  | Group I versus Group II: ↓Bacteroidetes-to-Firmicutes ratio, no change in *Bacteroides* and *Prevotella*  |
| (79)                           | n = 16 (Group I), healthy n = 15 (Group II), adults with MS (identified from outpatient clinic) n = 13 (Group III), adults with MS RCI 12 weeks | Group I: usual diet with standard-release probiotic capsule (*Lactobacillus reuteri* NCIMB 30242). During week 1, subjects received 3.0 × 10⁶ CFU L. *reuteri* once daily; during weeks 2, 3 and 4, subjects received 3.0 × 10⁶ CFU, 6.0 × 10⁵ CFU and 9.0 × 10⁵ CFU respectively, twice daily with lunch and dinner | Group II versus baseline: ↔ plasma mean total BA, conjugated and unconjugated BA  | Group I: ↑LDL-C (ns) and total plant sterol  |
|                                |                                   | Group II: ↑plasma mean total BA, conjugated and unconjugated BA post 1 week Group III: ↑plasma total BA, conjugated and unconjugated BA  | Group I versus baseline: ↑LDL-C, ↑total plant sterols  | Group II: ↑LDL-C, ↑total plant sterols  |
|                                |                                   | Group II: ↑plasma total BA, conjugated and unconjugated BA  | Group II: no change in total plant sterols  | Group II: no change in total plant sterols  |
| (74)                           | n = 5 (Group I), HyperChol n = 5 (Group II), HyperChol n = 4 (Group III), healthy RCI 4 weeks followed by 2-week post-intervention period | Group I: usual diet with delayed-release probiotic capsule (*Lactobacillus reuteri* NCIMB 30242) (6.0 × 10⁶ CFU) twice daily with lunch and dinner | Group I: ↑LDL-C (ns) and total plant sterol  | Group I: no change in faecal microbiome  |
|                                |                                   | Group II: ↑plasma mean total BA, conjugated and unconjugated BA  | Group II: no change in faecal microbiome  | Group II: no change in faecal microbiome  |
|                                |                                   | Group III: ↑plasma total BA, conjugated and unconjugated BA  |                                                                         |                                                                         |
| Author | Number (n) – study duration/design | Diet/daily dose | Results |
|--------|----------------------------------|----------------|---------|
| **Prebiotics** | | | **Bile acids** | **Lipid profiles** | **Gut microbiota** |
| (85) | | | **Group I:** usual diet with 8 g/d (55.2KJ AU/d) of oligofructose-enriched inulin | **Group I:** ↓ primary BAs | **Group I:** ↑ in faecal Bifidobacterium, ↓ in faecal Bacteroides vulgatus |
| | | | **Group I:** ↔ BAs from baseline | | |
| | n = 22 (Group I) n = 20 (Group II) Healthy children, 7–12 years old, OW or O (>85th percentile of BMI) DB, PCT 16 weeks | **Group I:** 7-d cycle menus of a typical low-fibre Taiwanese diet (diet provided energy and typical nutrient pattern of the adult population in Taiwan) supplemented with konjac (4.5 g/d) | **Group II:** ↑ primary BAs | | |
| | | | **Group I:** ↓ serum triglycerides | | |
| | | | **Group II:** ↑ faecal Bifidobacterium, ↓ faecal Bacteroides vulgatus | | |
| | n = 15 per group (2 groups) Healthy DB, PCT 4 weeks | | | **N/A** | |
| (167) | | | | | |
| | n = 16 Healthy 12 weeks (2-week pre-treatment phase, 8-week treatment phase and 2-week post-treatment phase) Adults with history of proctocolectomy for ulcerative colitis (n = 7) or Crohn’s disease (n = 2) Short-term interventional CO 3 d treatment, 4 d washout, 3 d treatment | Free choice of diet and during the 8-week treatment phase with 3.5 g of ispaghula husk (in the form of one sachet of Fybogel Orange) mixed in 150 ml of cold water, twice a day after breakfast and after the evening meal | **Treatment I:** ↑ faecal lithocholic and isolithocholic acids, ↓ ratio of lithocholic acids to deoxycholic acid, bile acid parameters returned to initial values subsequent to treatment | **N/A** | **Group I:** ↑ faecal Bifidobacteria and Lactobacilli levels |
| | | | **Treatment I versus Treatment II:** ↑ median excretion of BAs | | |
| | | | **Treatment II:** TC excretion remained unchanged, ↓ TC absorption, ↓ serum lathosterol concentration (reflecting cholesterol synthesis) | | |
| (91) | | | **Treatment I:** basal menu composed of common food items with 75 g of breakfast cereals based on extruded oat bran concentrate with native β-glucans | | |
| | | | **Treatment I versus Treatment II:** ↓ serum TC, LDL-C and TAG | | |
| | | | **Treatment II:** basal menu composed of common food items with 75 g of breakfast cereals based on extruded oat bran concentrate with hydrolysed β-glucans | | |
| | n = 9 Adults with history of proctocolectomy for ulcerative colitis (n = 7) or Crohn’s disease (n = 2) Short-term interventional CO 3 d treatment, 4 d washout, 3 d treatment | **Treatment I:** 2 apples per day (Renetta Canada, rich in PAs) **Treatment II:** sugar- and energy-matched apple control beverage **Treatment III:** VOO naturally containing 80 mg phenolic compounds (PC)/kg **Treatment II:** PC-enriched VOO containing 500 mg PC/kg, from olive oil | **Treatment I versus Treatment II:** ↓ relative proportion of isolithocholic acid (referred to the total of faecal BAs) versus pre-treatment | **N/A** | | |
| | | | **Treatment II:** similar changes in BAs but exploratory analysis confirmed link between TC and circulating LCA and GUDCA, ↑LCA associated with ↓ TC and TC↓ as GUDCA↑ in females only | | |
| | | | **Treatment III:** ↓ serum ox-LDL concentrations | | |
| | | | **Treatment I versus Treatment III:** numbers of Bifidobacterium versus Treatment I | | |
| Author | Number (n) – study duration/design | Diet/daily dose                                                                 | Results                                                                 |
|--------|-----------------------------------|---------------------------------------------------------------------------------|-------------------------------------------------------------------------|
|        |                                   | **Bile acids**                                                                  | **Lipid profiles**                                                      | **Gut microbiota**                                                      |
|        |                                   | Treatment III: PC-enriched VOO containing a mixture of 500 mg PC/kg from olive oil and thyme, 1:1 | N/A                                                                     | N/A                                                                     |
|        | (133) n = 16 (6 M/10 F) Healthy CO trial, 6-week (3 cycles of 2 weeks each) | Treatment I: 84 g/d of sun-dried raisins (SDR)                                  | ↓ in faecal BAs from baseline, remained low with Treatments II/III      | Treatment III: no effect on bacterial profile                            |
|        |                                   | Treatment II: 126 g/d of SDR                                                    | Major ↓ in faecal lithocholic, deoxycholic, chenodeoxycholic and cholic acids, concentrations remained low with Treatments II/III |
|        |                                   | Treatment III: 168 g/d of SDR                                                  | N/A                                                                     | N/A                                                                     |
|        |                                   | **Treatment I**: NCEP Step 1 diet with black tea prepared as powder              | ↔ on levels and proportions of faecal BAs                               | **Group I**: ↓ TC and LDL-C, ↓ TAG levels                                |
|        | (135) n = 13 Healthy RCT, DB, CO 21 d treatment, 4-week washout               | Treatment II: National Cholesterol Education Program Step I type diet with placebo prepared as powder | N/A                                                                     | N/A                                                                     |
|        |                                   | **Group I**: black tea extract (BTE) tablets (250 mg) containing 166.5 mg BTE (66.6 %) | Group II: ↔ in key Bas                                                  | **Group I**: ↓ TC and LDL-C, ↓ TAG levels                                |
|        | (114) n = 47 Borderline HyperChol RGC, DB 3 months                            | **Group II**: placebo tablets containing dextrin (66.6 %)                       | Group II: ↔ in key Bas                                                  | N/A                                                                     |
|        |                                   | Usual diet maintained throughout                                               | Group II: ↔ in key Bas                                                  | N/A                                                                     |

**Abbreviations:** BA, bile acid; BSH, bile salt hydrolysing; BW, body weight; CO, crossover; DB, double blind; HDL-C, high-density lipoprotein cholesterol; HyperChol, hypercholesteraemic; LDL-C, low-density lipoprotein cholesterol; MS, metabolic syndrome; O, obese; OW, overweight; PCT, placebo control trial; RCPI, randomised controlled prospective intervention; RCT, randomised control trial; RGC, randomised group comparison; SCFA, short-chain fatty acid; TC, total cholesterol; TAG, triacylglycerol; VOO, virgin olive oil.
addition, certain prebiotics, especially inulin-type fructans, may have a positive effect on endothelial function via effects on the gut microbiota, bile acid profiles and activation of the nitric oxide (NO) synthase/NO pathway responsible for NO-dependent endothelium relaxation. Inulin-type fructans promote proliferation of *Bifidobacterium*, which contribute to NO generation by reducing pH and acidic non-enzymatic reduction of nitrite (96). Cattray *et al.* (97) demonstrated a positive effect of inulin-type fructans on endothelial dysfunction, an important marker of CVD, in mice (97). Apoe<sup>−/−</sup> mice were fed an n-3 polysaturated fatty acid (PUFA)-depleted diet (12 weeks) with or without inulin-type fructans supplementation (for last 15 d of the study). Endothelial dysfunction was completely reversed in the mesenteric and carotid arteries, through activation of the NO synthase/NO pathway. In addition, inulin-type fructan supplementation led to increased proliferation of NO-producing bacteria and *Akkermansia*, with reduced abundance in bacteria which are implicated in synthesis of secondary bile acids. The observed changes in bile acid composition, along with increased L-cell density and enhanced GLP-1 production, were proposed as being responsible for activation of the NO synthase/NO pathway and ultimately for preservation of endothelial function.

Although some potential mechanisms for beneficial effects of prebiotics on CVD risk have been derived from the animal studies presented above, the lack of studies conducted in humans which have included measures of gut microbiota composition and markers of bile acid metabolism warrants further study, as the links between bile acid and lipid regulation remain inconclusive.

**Polyphenol-rich foods**

Diets high in phenolic compounds such as fruits and vegetables are considered to have beneficial effects on gut health. In addition to fibre, polyphenols have also been reported to reach the gut intact where they are fermented by the resident bacteria leading to generation of smaller phenolic compounds which can be absorbed in the colon (99). For example, procyanidins are metabolised by the gut bacteria into several metabolites such as phenyl valerolactone and phenylacetic and phenylpropionic acids which are more easily absorbed and capable of producing systemic effects including anti-inflammatory and vasodilatory effects (99,100).

The prebiotic effect of apples, specifically the high-polyphenol-containing Renetta Canada variety, was highlighted by a study conducted by Koutsos *et al.* (101). Using a batch culture colonic model inoculated with faeces from healthy human donors (n = 3), the apples induced substantial changes in the composition and metabolic activity of the gut microbiota in vitro, with a reduction in abundance of *Bacteroides*, and enhanced proliferation of *Proteobacteria, Bifidobacteria* and *Faecalibacterium prausnitzii*, found relative to inulin and cellulose control models (101). Sembries *et al.* (102) also showed increased faecal Lactobacilli and *Bifidobacterium* following addition of apple pomace (the dried solid by-product of apple product manufacturing) to the diet of rats (n = 12) for 4 weeks (102). However, apples and apple pomace contain other active components which could have affected the gut microbiota such as fibre in the form of pectin. Prebiotic effects have also been shown for red wine, known to be high in polyphenols, in humans (n = 20) (103). Consumption of red wine (272 ml/d) enhanced the growth of *Blautia coccoideae–Eubacterium rectale* groups, *Bifidobacterium, Eggerthella lenta* and *Bacteroides uniformis*, while growth of *Clostridium and Clostridium histolyticum* was inhibited after 20 d compared with consumption of an alcohol control (100 ml/d gin). However, such beneficial effects on composition of the gut microbiota were not found in a recent study by Wallace *et al.* (104). Indeed, ingestion of a high-polyphenol boysenberry beverage (750 mg polyphenols) did not give rise to any significant changes in faecal bacteria, including total Lactobacilli, *Bifidobacterium* and *Bacteroides* or *Clostridium perfringens* in healthy human volunteers (n = 25) (104). The discrepancies between different studies may be due to different polyphenol doses, the selected comparator intervention, types of food given and the polyphenolic compounds they contain, with an effect in particular of the food matrix.

**Effects on lipid metabolism**

Polyphenols, particularly complex polyphenols, such as proanthocyanidins, have been found to influence the enterohepatic circulation via sequestering of bile acids within the colon and/or increasing the proliferation of gut microbiota involved in the de-conjugation and hydrolysis of primary to secondary bile acids (105–108). For example, supplementation with green tea polyphenols (3.2 g epigallocatechin gallate (EGCG) per kg of high-fat chow) was found to increase faecal bile acid concentrations by 1.5-fold in mice (n = 20), from approximately 0.4 μmol/d to 1.1 μmol/d (109). This likely occurs owing to inhibition of bile acid micelles because of hydrophobic interactions with polyphenolic compounds such as EGCG. This phenomenon has been demonstrated in *in vitro* studies to lead to the elimination of phosphatidylcholine and cholesterol from the micellar structure, which results in reduced bile acid solubility (110). Bile acid binding assays have revealed that, in *in vitro* mixtures, 30 % of taurocholic acid, 70 % of glycocholic acid and 25 % of taurodeoxycholic acid could be bound by grape seed extract (containing 50.8 g total flavanols per 100 g of extract) and similarly by the polyphenols gallic acid, catechin and epicatechin (111,112). Further studies, particularly in humans, would be valuable to fully understand the impact of increased polyphenol intakes on bile acid sequestering action.

Indeed, consumption of polyphenols has been shown to improve dyslipidaemia in several human studies. Koutsos *et al.* (113) found a beneficial effect of consuming two high-polyphenol Renata Canada apples daily (total polyphenols, 239 mg/d) for 8 weeks on lipid profiles, with reduced serum total and LDL-C and TAG concentrations in slightly hypercholesteraemic subjects (n = 40) (113). The changes in serum lipids were also associated with small but significant improvements in endothelium-dependent microvascular vasodilation, a marker of endothelial function and another indicator of cardiovascular health. No significant changes in circulating bile acids were found, but further exploratory analysis demonstrated links between circulating LCA and glycodeoxycholic acid (GUDCA) and the total cholesterol response in women. Fujita
and Yamagami (2008) found a similar response to black tea polyphenols, with improved circulating total and LDL-C and TAG levels following 3 months of supplementation with 166.5 mg black tea extract (taken in tablet form) \((n = 47)\) \((114)\). Furthermore, Tzounis et al. \((170)\) also demonstrated significant reductions in plasma TAG concentrations in healthy human volunteers \((n = 22)\), following ingestion of a high-cocoa-flavanol drink (494 mg cocoa flavanols/d) for a 4-week period, compared with a low-cocoa-flavanol drink (23 mg cocoa flavanols/day). This occurred concurrently with significantly increased *Bifidobacterium* and Lactobacilli populations, as well as significantly reduced Clostridia counts in the gut, demonstrating the potential link between polyphenol-induced alterations in gut microbiota and improved CVD risk markers.

Beneficial effects of polyphenols on CVD risk are not limited to improved lipid profiles. In rat models of CVD, the polyphenol resveratrol (0-4 % administered in a standard chow diet) was shown to lower production of trimethylamine-N-oxide. This amine oxide is generated from choline, betaine and carnitine by gut microbial metabolism of red meat and fat \((48)\) and is linked with an increased risk for significant adverse cardiovascular events \((115)\). Trimethylamine-N-oxide encourages development of atherosclerosis (narrowing of arteries caused by fatty plaques, leading to CVD), and plays a role in cholesterol uptake and BA synthesis, reducing reverse cholesterol transport and downregulating hepatic CYP7A1 activity \((116,117)\). Indeed, in the same rat model, a reduction in vascular disease was observed \((48)\). The findings observed were shown to correlate with the increased production of new bile acids due to changes in the enterohepatic bile acid pool with reduced FXR antagonists (such as TβMCA) and increased proportion of secondary bile acids such as chenodeoxycholic acid, DCA and UDCA as well as reduced FXR-FGF15 pathway after modulation of the gut microbiota. Resveratrol was found to significantly increase expression of CYP7A1, leading to increased BA synthesis in the liver while also enhancing the growth of *Lactobacillus* and *Bifidobacterium* in the gut \((48)\). It was suggested, therefore, that consumption of this polyphenol can limit the effects of trimethylamine-N-oxide on CVD development by promoting greater uptake of circulating cholesterol by the liver to make new bile acids.

**Effects on bile acids**

Evidence from the animal studies may provide an explanation for the potential mechanisms of action behind polyphenol-induced improvements in lipid risk markers, since these beneficial effects are linked to changes in circulating and excreted bile acids. A summary of studies conducted in humans and animals is presented in Table 1 and Supplementary Table 1 (see supplementary material), respectively. Aprikan et al. \((118)\) found that the daily consumption of apples decreased plasma total and LDL-C (by 22 % and 70 %, respectively) concentrations in rats, which were associated with increased faecal excretion of total bile acids (+56 % in lean and +30 % in obese rats) \((118)\). A recent study by Ravn-Haren et al. \((119)\) also demonstrated a beneficial effect of apple pomace on total cholesterol levels in mice \((n = 40)\), with an associated increase in excreted total and primary bile acids after 4 weeks of consumption \((119)\). In another study, similar results were shown following supplementation with the green tea polyphenol, EGCG, with reduced serum cholesterol concentrations and severity of fatty liver disease and increased faecal excretion of cholesterol and total lipids in mice \((n = 50)\). Reduced intestinal and increased faecal excretion of total bile acids was also found, indicating an effect on bile acid reabsorption and neo-synthesis as a potential mechanism for the observed reduction in cholesterol levels \((109)\).

A pattern of increased faecal bile acids, with reduced serum total and LDL-C and TAG concentrations, has been shown in multiple studies in animal models, using a range of polyphenols (EGCG, kaempferol, anthocyanins, flavonoid extracts, quercetin and resveratrol) and high-polyphenol-containing foods (pu-erh tea, cassini herbal tea and red yeast rice) \((120-129)\). Conversely, one study by Zhang et al. \((120)\) found no change in TAG or total cholesterol levels, but increased LDL-C, despite increased faecal total bile acid excretion and up-regulation of hepatic CYP7A1 following administration of quercetin (0-4 %) in rats \((n = 20)\) \((129)\). These reported inconsistencies may be due to other studies investigating the effect of quercetin on hypercholesterolemic animals or those fed a high-cholesterol diet, while Zhang et al. used healthy rodents with a standard diet formulation (AIN-93G diet) \((121,129,130)\).

A study by Guo et al. \((131)\) found that treatment with phenolic blueberry extract (5 g per litre of drinking-water daily, 14 weeks) led to improved markers of metabolic disease in mice \((n = 9)\), in conjunction with enhanced brown adipose tissue energy expenditure and improved hepatic lipid metabolism through TGR5 and FXR activation \((131)\). Notably, the phenolic extract led to increased proliferation of *Akkermansia*, *Bifidobacterium*, *Lactobacillus* and *Desulfoviridus* in the gut, which correlated with increased plasma secondary bile acids such as chenodeoxycholic acid, DCA and LCA and reduced circulating tauro-(α)-muricholic acid (TαMCA) and tauro-(β)-muricholic acid (TβMCA), both of which are potent FXR inhibitors \((131)\). Similarly, a study by Anhe et al. \((132)\) showed treatment of mice \((n = 12)\) with polyphenol-rich extract of camu camu (an Amazonian fruit, daily oral doses (200 mg/kg) of re-suspended crude extract for 8 weeks), led to improved metabolic health with improved glucose tolerance, reduced weight gain and adiposity and blunted metabolic inflammation and endotoxaemia \((132)\). This was linked to enhanced brown adipose tissue energy expenditure and strongly correlated with increased expression of TGR5 in brown adipocytes \((132)\). In addition, the extract led to altered plasma bile acid profiles, with reduced circulating TαMCA and TβMCA and increased proportion of β-muricholic acid, ω-muricholic acid, chenodeoxycholic acid, DCA and UDCA as well as decreased circulating bile acids and increased proportion of secondary and of unconjugated bile acids. This was coupled with a significant increase in gut *Akkermansia muciniphila* and a reduction in *Lactobacillus*. These results indicate that activation of nuclear receptors, TGR5 and FXR play a key role in reduced metabolic disease risk from consumption of phenolic compounds and related to microbial metabolism of bile acids, resulting in alterations in the bile acid pool with reduced FXR antagonists (such as TαMCA and TβMCA) and increased FXR/TGR5 agonists (such as cholic acid).

However, most of the above studies only quantified total bile acids and did not measure bile acid profiles and were conducted in animal models. Thus, further mechanistic studies investigating polyphenol consumption, microbiota modulation and changes in circulating bile acid profiles in humans are warranted.
The effect of phenolic compounds on bile acids may be specific to the type of polyphenol and the matrix in which it is given. In humans, consumption of sun-dried raisins for 6 weeks resulted in reduced faecal bile acids compared with baseline levels, especially for lithocholic, deoxycholic, chenodeoxycholic and cholic acids (133,135). It is worth noting that, while raisins are high in phenolic compounds (total phenolic content approximately 9–12 mg of gallic acid equivalents per gram), they also contain high levels of fibre, which could play a role in altering bile acid profiles either physically by binding of bile acids and inhibiting their resorption or via effects on the gut microbiota (134). Furthermore, black tea polyphenols, given as a powder or in tablet form, have been shown to have no effect on excreted bile acids in humans, despite their beneficial effect on lipid profiles (114,135). Future studies could be useful to further investigate links between changes in bile acids and improvements in CVD risk markers following polyphenol consumption.

Potential mechanisms of action

The studies highlighted above indicate that a number of potential mechanisms may exist by which dietary components that promote beneficial changes on gut microbiota composition impact on lipid regulation (Fig. 3).

BSH activity

In addition to effects on absorption of bile acids, via bile acid metabolising action initiated by BSH activity, the ability of pre/probiotics and polyphenol-rich foods to either stimulate or inhibit FXR may also affect their ability to impact upon host metabolism. In a study by Degirolamo et al. (78), the probiotic mixture VSL#3 (containing BSH active probiotic strains) had a significant effect on bile acid profiles in mice after oral gavage with 50 × 10⁷ CFU/d for 21 d, compared with daily oral gavage with saline for the same duration (78). The high levels of BSH activity inhibited the enterohepatic FXR response and led to increased excretion of total bile acids in the faeces with no effect on the faecal CA/CA ratio but a reduced ratio of faecal conjugated:unconjugated bile acids. In addition, a reduction in gut FGFR4 expression and increased bile acid synthesis in the liver was shown; however, serum lipids were not measured. FGFR4 is the mouse homologue of FGFR9 (released upon activation of FXR) which migrates to the liver to activate the cellular receptor FGFR4, inhibiting CYP7A1 expression (130). Conversely, Choi et al. (171) found increased FXR expression in mice following a high-fat diet supplemented with L. curvatus and L. plantarum (n = 10) for 6 weeks. This was coupled with changes in metabolic markers such as reduced plasma TAG. Similarly, in humans, FGFR9 expression may be increased in response to gut proliferation with probiotic bacteria. For example, in addition to effects on LDL-C concentrations, Martoni et al. (70) found that Lactobacillus reuteri supplementation led to stimulation of the FXR axis as well as increased levels of circulating bile acids. As such, in addition to further in vitro studies on probiotics and bile acid excretion, studies on the effect of probiotics and food components, which lead to increased proliferation of probiotic bacteria in the gut, on FXR activity would also be of interest.

Bile acid sequestrants

Another mechanism to explain the increased excretion of bile acids following consumption of prebiotics and polyphenol-rich foods could be due to the bile sequestering capacity of these dietary components (Fig. 3). Dietary fibre such as β-glucans and polyphenol compounds can bind to bile acids in the intestine to drive the bile acids down to the colon, which modifies their absorption and excretion (157). This leads to a reduction in hepatic bile acid concentration and, in turn, activates CYP7A1, the enzyme responsible for conversion of cholesterol to bile acids (138). A number of studies have noted increased hepatic CYP7A1 expression, indicating bile acid neo-synthesis following consumption of polyphenolic compounds in animals (139,140). In rodents, increased CYP7A1 expression has been shown in conjunction with reduced serum total cholesterol and TAG following administration of grape seed polyphenolics (134,142). In line with these findings, Downing et al. (142) showed elevated faecal bile acids and reduced serum bile acids following administration of grape seed polyphenols in rats (n = 8) (143). In addition, the grape seed polyphenols resulted in reduced serum TAG levels and increased faecal excretion of cholesterol and total lipids. However, serum total cholesterol was not affected in this study. Quifer et al. (144) also found increased faecal excretion of cholesterol, as well as increased excretion of secondary bile acids deoxycholic and lithocholic acid, following grape seed extract (GSE) consumption in pigs (n = 6) (144).

Evidence for increased CYP7A1 expression in the liver has also been demonstrated in animal models with consumption of prebiotics. Mandimika et al. (99) found increased hepatic CYP7A1 expression and improved circulating lipid profiles after consumption of broccoli fibre (75 g/kg daily) in rats (n = 16) fed a high-corn-oil diet for 17 weeks. However, Lërke et al. (95) found that consumption of rye wholemeal and rye bran led to inhibition of CYP7A1 expression in hypercholesteraemic pigs (n = 8) along with reduced plasma TC/LDL-C; therefore, the effect may be specific to type of prebiotic given and animal model used (95).

Chronic supplementation with prebiotics may also lead to increased hepatic CYP7A1. For example, a study by Jeun et al. (71) found a greater CYP7A1 expression, coupled with increased bile acid excretion and improved lipid profiles, following supplementation with L. plantarum (10⁹ CFU) in mice (n = 7) for 4 weeks (71). Similarly, Michael et al. (76) showed the same effects on CYP7A1 expression, bile acid excretion and improved blood lipids, following 14 d of consumption of L. plantarum (10⁸ CFU/d) in mice (n = 12) (76). The effect on CYP7A1 expression and lipid profiles was revealed by Wang et al. (116), while Zhai et al. (75) also found a similar effect on bile acid excretion but did not include measurement of lipid parameters (75,149). These results demonstrate a beneficial effect of L. plantarum on CVD risk markers, which may be in part mediated by increased bile acid neo-synthesis.

Expression of lipid synthesis genes

In addition, fermentation of soluble fibres by the gut bacteria results in the production of SCFAs which are easily absorbed into the portal vein and can then be metabolised in the liver. There is some evidence that SCFA, particularly propionic acid, are
involved in suppression of 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGR), the rate-limiting enzyme for cholesterol synthesis in the liver, leading to up-regulation of LDL receptors (Fig. 3) \(^{(146)}\). For example, Meneses et al. \(^{(87)}\) showed that a high-cholesterol diet supplemented with extract of Ganoderma lucidum (0·5–1·0 %) for 43 d in C57BL/6 mice \((n = 8)\) led to reduced expression of HMGR coupled with an increase in LDL-receptor gene expression in the liver \(^{(97)}\). These changes in gene expression coincided with reduced serum total and LDL-C, TAG levels, and hepatic total cholesterol and TAG content. Supplementation with probiotic bacteria, Enterococcus faecium (5·0 \(\times\) \(10^9\) CFU/ml in PBS, 1 ml/d) for 35 d has also been shown to inhibit expression of hepatic HMGR, while increasing LDL-receptor and CYP7A1 expression in mice \((n = 5)\), with resulting improvements in serum lipid profiles \(^{(97)}\). Similar effects have been demonstrated for polyphenol extracts with reduced HMGR expression after consumption of a flavonoid- and saponin-rich extract \((0·25–0·5 \%)\) with a high-cholesterol diet for 35 d in mice \((n = 8)\) \(^{(120)}\). These changes were in parallel to the increased faecal bile acid secretion and bile acid neo-synthesis \((increased\ CYP7A1\ in\ the\ liver)\) observed, as well as beneficial effects on circulating lipid profiles. Conversely, several studies have shown that consumption of prebiotics, probiotics or polyphenol-rich foods may result in up-regulation of hepatic HMGR expression. For example, Damodharan et al. \(^{(77)}\) found increased HMGR expression in mice \((n = 8)\), following ingestion of L. acidophilus \((3 \times 10^8\ CFU/ml)\) with a high-cholesterol diet for 32 d \(^{(77)}\). This was despite an increase in hepatic LDL-receptor expression and reduced serum LDL-C. A study by Parnell et al. \(^{(150)}\) also showed increased hepatic HMGR as a result of oligofructose and inulin supplementation \((10–20 \%)\) for 10 weeks in rats \((n = 8)\). Indeed, Mandimika et al. \(^{(99)}\) demonstrated increased hepatic HMGR expression in rats \((n = 16)\) when fed broccoli fibre \((75 g/kg\ daily)\) as part of a high-corn-oil diet for 17 weeks \(^{(89)}\). This was despite improvements in circulating lipid profiles and increased excretion of bile acids. In addition, Mueller et al. \(^{(147)}\) found an association between increased serum propionate and raised LDL-C in humans \((n = 16\)) using linear regression models to examine the relationship between changes in SCFAs with cardio-metabolic parameters following introduction of different diets \((carbohydrate-rich, protein-rich and unsaturated-fat-rich)\) for 6 weeks \(^{(147)}\). These contrasting findings could reflect the differences in lipid metabolism pathways which exist between rats and humans. Further studies are needed to fully elucidate the role of SCFAs in regulating cholesterol synthesis in humans.

There is limited evidence that the different SCFA have differential effects of lipid metabolism, although this has mainly been demonstrated in rodent models. The major SCFA in the colon is acetate, which has been shown to up-regulate hepatic lipid synthesis \(^{(140)}\). Meanwhile, propionate has been reported to reduce cholesterol synthesis via inhibition of HMGR, in animal models \(^{(149)}\). Therefore, it is possible that dietary components which reduce the acetate-to-propionate ratio may inhibit de novo lipid synthesis to reduce serum lipids \(^{(150)}\). Different strains of bacteria produce different amounts of each type of SCFA, which may explain the differences observed in studies investigating the effects of gut-microbe-altering foods on HMGR expression. For example, Bifidobacteria and Lactobacilli do not produce butyrate \(^{(151)}\). Lactobacillus rhamnosus is capable of producing significant amounts of propionate but not either butyrate or acetate. Meanwhile, strains of Bifidobacterium B. longum and B. bifidum both produce acetate, with the latter also capable of propionate production \(^{(152)}\). The majority of butyrate-producing bacteria belong to the Firmicutes phylum, including the families...
**Bile acids, gut microbiota and cardiovascular health**

**Ruminococcaceae and Lachnospiraceae**\(^{(155)}\). However, the situation is likely to be more complicated since SCFA profiles remain similar between individuals despite significant inter-individual differences in gut microbiota composition, likely due to the vast overall numbers of SCFA-producing bacteria in the gut\(^{(154)}\).

The evidence for an effect of foods which may increase production of SCFAs on expression of hepatic HMGR is conflicting, and reductions in plasma cholesterol may not occur solely via inhibition of cholesterol synthesis in the liver. Indeed, it has been shown that SCFAs can up-regulate expression of hepatic SREBP2 mRNA, resulting in activation of LDL-receptor gene expression and, therefore, improved circulating lipoprotein profiles via enhanced clearance of circulating LDL particles\(^{(155)}\). Increased expression of SREBP2 mRNA in the liver has been shown in a limited number of studies in animal models following both probiotic\(^{(77)}\) and prebiotic supplementation\(^{(156)}\).

Studies investigating the mechanisms underlying the relationship between circulating bile acids and lipid CVD risk markers in response to probiotics, prebiotics and polyphenol-rich foods have been predominately conducted in animals. However, these findings are not always transferable between species. Some animals, including rats, do not have a gall bladder and thus may display differences in bile acid flow in response to food intake. This unfortunately presents a limitation of using animal models for looking at bile acid metabolism and highlights the need for more studies to be performed in humans which incorporate measures of bile acid metabolism and CVD risk.

**Conclusion**

There is a growing body of evidence for a link between the consumption of probiotics, prebiotics and polyphenol-rich foods and the gut microbiota, which may be due to effects on bile acid metabolism. It has been shown that these dietary components can encourage bile acid excretion and neo-synthesis, providing a mechanism for the beneficial effects of these compounds on circulating lipid profiles. Animal model studies have demonstrated an effect of probiotics, prebiotics and polyphenol-rich foods/extracts on the FXR/FGF-15 axis as well as generally increasing expression of hepatic CYP7A1 (the rate-limiting enzyme for bile acid synthesis) and potential effects on endogenous cholesterol synthesis via SREBP and HMGR genes leading to the enhanced clearance of circulating LDL. It is evident that further research in humans is needed to fully define the relationship between diet and bile acid metabolism to determine the mechanisms behind the beneficial effects of these dietary components on host health and CVD risk. Further research could establish if circulating bile acids can be utilised as a biomarker to identify potential inflammatory and metabolic health in humans as well as which dietary components can potentially influence this relationship.

**Financial Support**

R.G.P. was supported by the BBSRC (grant number BB/P028290/1) as part of the project HDHL-Biomarkers: CirculAting Bile Acids as biomarkers of metabolic health - Linking microbiota, Diet and Health (CABALA_DIET&HEALTH), and S.A. was supported by a Kuwait Government studentship award.

**Conflict of Interest**

None.

**Authorship**

R.G.P. conducted the literature searches and wrote the main body of text. S.A. assisted with literature searches and compiling of tables. J.A.L. and K.G.J. participated in the concept and planning of the review as well as revision of the manuscript, and J.A.L. was responsible for the final content of the manuscript.

**Supplementary material**

To view supplementary material for this article, please visit https://doi.org/10.1017/S0954422421000081

**References**

1. Bhatnagar P, Wickramasinghe K, Williams J et al. (2015) The epidemiology of cardiovascular disease in the UK 2014. Heart 101, 1182–1189.
2. Lewington S, Whitlock G, Clarke R et al. (2008) Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55000 vascular deaths (vol 370, pg 1829), 2007. Lancet 372.
3. Long SL, Gahan CG, Joyce SA (2017) Interactions between gut bacteria and bile in health and disease. Mol Asp Med 56, 54–65.
4. Bauer E, Jakob S, Mosenthin R (2005) Principles of physiology of lipid digestion. Asian-Australas J Anim Sci 18, 282–295.
5. Joyce SA, Gahan CG (2016) Bile acid modifications at the microbe-host interface: potential for nutraceutical and pharmaceutical interventions in host health. Annu Rev Food Sci Technol 7, 313–333.
6. Joyce SA, MacSharry J, Casey PG et al. (2014) Regulation of host weight gain and lipid metabolism by bacterial bile acid modification in the gut. Proc Natl Acad Sci 111, 7421–7426.
7. Begley M, Hill C, Gahan CGM (2006) Bile salt hydrolase activity in probiotics. Appl Environ Microbiol 72, 1729–1738.
8. Chiang JY (2013) Bile acid metabolism and signaling. Compr Physiol 3, 1191–1212.
9. Grover SA, Dorais M, Coupal L (2005) Improving the prediction of cardiovascular risk: interaction between LDL and HDL cholesterol. Epidemiology 14, 315–320.
10. Li T, Chiang JY (2014) Bile acid signaling in metabolic disease and drug therapy. Pharmacol Rev 66, 948–983.
11. Staels B, Fonseca VA (2009) Bile acids and metabolic regulation: mechanisms and clinical responses to bile acid sequestration. Diabetes Care 32, S237–S245.
12. Ogundare M, Theofilopoulos S, Lockhart A et al. (2010) Cerebrospinal fluid stereoidomics: are bioactive bile acids present in brain? J Biol Chem 285, 4666–4679.
13. Zheng X, Chen T, Zhao A et al. (2016) The brain metabolome of male rats across the lifespan. Sci Rep 6, 24125.
14. Chiang JY (2009) Bile acids: regulation of synthesis. J Lipid Res 50, 1955–1966.
15. Li T, Chiang JY (2012) Bile acid signaling in liver metabolism and diseases. *J Lipids* **2012**, 1–9.

16. Falany CN, Johnson MR, Barnes S et al. (1994) Glycine and taurine conjugation of bile acids by a single enzyme. Molecular cloning and expression of human liver bile acid CoA: amino acid N-acetyltransferase. *J Biol Chem* **269**, 19375–19379.

17. Pircher PC, Kitto JL, Petrowski ML et al. (2003) Farnesoid X receptor regulates bile acid-amino acid conjugation. *J Biol Chem* **278**, 27703–27711.

18. Portincasa P, Di Ciaula A, Wang HH et al. (2008) Coordinate regulation of gallbladder motor function in the gut-liver axis. *Hepatology* **47**, 2112–2126.

19. Russell DW (2009) Fifty years of advances in bile acid synthesis and metabolism. *J Lipid Res* **50**, S120–S125.

20. Costarelli V, Sanders T (2001) Acute effects of dietary fat composition on postprandial plasma bile acid and cholecystokinin concentrations in healthy premenopausal women. *Br J Nutr* **86**, 471–477.

21. Sato R (2010) Sterol metabolism and SREBP activation. *Arch Biochem Biophys* **501**, 177–181.

22. Janowski BA, Shan B, Russell DW (2001) The hypocholesterolemic agent LY295147 reverses suppression of sterol regulatory element binding protein processing mediated by oxysterols. *J Biol Chem* **276**, 45408–45416.

23. Eberle D, Hegarty B, Bossard P et al. (2004) SREBP transcription factors: master regulators of lipid homeostasis. *Biochimie* **86**, 839–848.

24. Tontonoz P, Mangelsdorf DJ (2003) Liver X receptor signaling pathways in cardiovascular disease. *Mol Endocorinic* **17**, 985–993.

25. Miyake JH, Doung X-DT, Strauss W et al. (2001) Increased production of apolipoprotein B-containing lipoproteins in the absence of hyperlipidemia in transgenic mice expressing cholesterol 7a-hydroxylase. *J Biol Chem* **276**, 23304–23311.

26. Mertens KL, Kalsbeek A, Soeters MR et al. (2017) Bile acid signaling pathways from the enterohepatic circulation to the central nervous system. *Front Neurosci* **11**, 617.

27. Staley C, Weingarden AR, Khoruts A et al. (2017) Interaction of gut microbiota with bile acid metabolism and its influence on disease states. *Appl Microbiol Biotechnol* **101**, 47–64.

28. Ridlon JM, Harris SC, Bhowmik S et al. (2016) Consequences of bile salt biotransformations by intestinal bacteria. *Gut Microbes* **7**, 22–39.

29. Lefebvre P, Cariou B, Lien F et al. (2004) Bile acid signaling and perspective on the signal of ursodeoxycholic acid, the most hydrophilic bile acid, in the heart. *Biomolecules* **8**, 159.

30. Wahlstrom A, Sayin SI, Felin J et al. (2015) Gut microbiota regulates bile acid metabolism by reducing the levels of tauro-beta-muricholic acid, a naturally occurring FXR antagonist. *Cell Metab* **17**, 225–235.

31. Joyce SA, Gahan CGM (2014) The gut microbiota and the metabolic health of the host. *Curr Opin Gastroenterol* **30**, 120–127.

32. Chen M-L, Yi L, Zhang Y et al. (2016) Resveratrol attenuates trimethylamine-N-oxide (TMAO)-induced atherosclerosis by regulating TMAO synthesis and bile acid metabolism via remodeling of the gut microbiota. *MBio* **7**, e02210–e02215.

33. Koutsos A, Tuohy K, Lovegrove J (2015) Apples and cardiovascular health—is the gut microbiota a core consideration? *Nutrients* **7**, 3959–3998.

34. Arora T, Singh S, Sharma RK (2013) Probiotics: interaction with gut microbiome and antiobesity potential. *Nutrition* **29**, 591–596.

35. Jones BV, Begley M, Hill C et al. (2008) Functional and comparative metagenomic analysis of bile salt hydrolase activity in the human gut microbiome. *Proc Natl Acad Sci* **105**, 15380–15385.

36. Ikeda I, Imasato Y, Sasaki E et al. (2010) Black-tea polyphenols decrease micellar solubility and intestinal absorption of cholesterol in rats. *Biochim Biophys Acta Lipids Lipid Metab* **17**, 141–146.

37. Ikeda I, Yamahira T, Kato M et al. (2010) Black-tea polyphenols decrease micellar solubility of cholesterol in vitro and intestinal absorption of cholesterol in rats. *J Agric Food Chem* **58**, 8591–8595.

38. Watanabe M, Morimoto K, Houten SM et al. (2012) Bile acid binding resin improves metabolic control through the induction of energy expenditure. *PLOS One* **7**, e38286.

39. Matsuoka K, Kanai T (2015) The gut microbiota and inflammatory bowel disease. *Semin Immunopathol* **37**, 47–55.
bile salts. Gut Microbe 6, 57–65.
75. Zhao Q, Liu Y, Wang C et al. (2019) Lactobacillus plantarum CCFM8661 modulates bile acid enterohepatic circulation and increases lead excretion in mice. Food Funct 10, 1455–1464.
76. Michael D, Davies T, Moss J et al. (2017) The anti-cholesterol-
77. et al. (2020) Expert consensus document: the International Scientific Association for Prebiotics and Probiotics (ISAPP) consensus statement on the definition and scope of prebiotics. Nat Rev Gastroenterol Hepatol 14, 491.
78. Figueroa-González I, Quijano G, Ramirez G et al. (2011) Probiotics and prebiotics—perspectives and challenges. J Sci Food Agric 91, 1341–1348.
79. Swanson K, de Vos W, Martens E et al. (2016) Effects of supplementation with a calcium-rich marine-derived multi-mineral supplement and short-chain fructo-oligosaccharides on serum lipids in postmenopausal women. Br J Nutr 115, 658–665.
80. Meneses ME, Martinez-Carrera D, Torres N et al. (2016) Hypcholesterolemic properties and prebiotic effects of Mexican Ganoderma lucidum in C57BL/6 mice. PLoS One 11, e0159631.
81. Santos J, Espardaler J, Mancebo R et al. (2012) Selective in vivo effect of chitosan on fatty acid, neutral sterol and bile acid excretion: a longitudinal study. Food Chem 134, 940–947.
82. Mandimika T, Paturi G, De Guzman CE et al. (2016) Effects of dietary broccoli fibre and corn oil on serum lipids, faecal bile acid excretion and hepatic gene expression in rats. Int J Mol Sci 17, 1278–1291.
83. Cronin BE, Allsopp PJ, Slevin MM et al. (2015) Influence of consumption of probiotics on the human gut microbiome assessed by 16S rRNA-based approaches: a review. Benef Microbes 11, 101–129.
84. Wang Y, Harding SV, Thandapilly SJ et al. (2017) Barley β-glucan reduces blood cholesterol levels via interrupting bile acid metabolism. Br J Nutr 118, 822–829.
85. Nicolucci AC, Hume MP, Martinez I et al. (2017) Prebiotics reduce body fat and alter intestinal microbiota in children who are overweight or with obesity. Gastroenterology 153, 711–722.
86. Cronin BE, Alloppj PJ, Slevin MM et al. (2016) Effects of supplementation with a calcium-rich marine-derived multi-mineral supplement and short-chain fructo-oligosaccharides on serum lipids in postmenopausal women. Br J Nutr 115, 658–665.
87. Meneses ME, Martinez-Carrera D, Torres N et al. (2016) Hypcholesterolemic properties and prebiotic effects of Mexican Ganoderma lucidum in C57BL/6 mice. PLoS One 11, e0159631.
88. Santos J, Espardaler J, Mancebo R et al. (2012) Selective in vivo effect of chitosan on fatty acid, neutral sterol and bile acid excretion: a longitudinal study. Food Chem 134, 940–947.
89. Mandimika T, Paturi G, De Guzman CE et al. (2016) Effects of dietary broccoli fibre and corn oil on serum lipids, faecal bile acid excretion and hepatic gene expression in rats. Food Chem 134, 1272–1278.
90. Guinness P, Michiels J, Vanhaecke L et al. (2016) Reduction in circulating bile acid and restricted diffusion across the intestinal epithelium are associated with a decrease in blood cholesterol in the presence of oat β-glucan. FASEB J 30, 4227–4238.

66. Ma C, Zhang S, Lu J et al. (2017) Bile acid is a significant host factor shaping the gut microbiome of diet-induced obese mice. BMIC Biol 15, 1–15.
67. Sannasidippana TH, Lumd PA, Clarke SR (2017) In vitro antibacterial activity of unconjugated and conjugated bile salts on Staphylococcus aureus. Front Microbiol 8, 1581.
68. Carding S, Verheke B, Vipond DT et al. (2015) Dysbiosis of the gut microbiota in disease. Microb Ecol Health Dis 26, 26191.
69. Oner O, Aslim B, Aydaä SB (2014) Mechanisms of cholesterol-
70. et al. (2020) Reduction in circulating bile acid and restricted diffusion across the intestinal epithelium are associated with a decrease in blood cholesterol in the presence of oat β-glucan. FASEB J 30, 4227–4238.
91. Ellegård I, Andersson H (2007) Oat bran rapidly increases bile acid excretion and bile acid synthesis: an ileostomy study. *Euro J Clin Nutr* 61, 938–945.

92. Drzíková B, Dongowski G, Gebhardt E (2005) Dietary fibre-rich oat-based products affect serum lipids, microbiota, formation of short-chain fatty acids and steroids in rats. *Br J Nutr* 94, 1012–1025.

93. Chen H-L, Cheng H-C, Wu W-T et al. (2008) Supplementation of konjac glucomannan into a low-fiber Chinese diet promoted bowel movement and improved colonic health in constipated adults: a placebo-controlled, diet-controlled trial. *J Am Coll Nutr* 27, 102–108.

94. Hjiova E, Bomba A, Bertková I et al. (2012) Prebiotics and bioactive natural substances induce changes of composition and metabolic activities of the colonic microflora in cancerous rats. *Acta Biochim Pol* 59.

95. Lærke HN, Pedersen C, Mortensen MA et al. (2008) Rye bread reduces plasma cholesterol levels in hypercholesterolaemic pigs when compared to wheat at similar dietary fibre level. *J Sci Food Agric* 88, 1385–1393.

96. Sobko T, Reinders C, Jansson E et al. (2011) Gastrointestinal bacteria generate nitric oxide from nitrate and nitrite. *Nitric Oxide* 13, 272–278.

97. Carty E, Bindels LB, Tailleux A et al. (2018) Targeting the gut microbiota with inulin-type fructans: preclinical demonstration of a novel approach in the management of endothelial dysfunction. *Gut* 67, 271–283.

98. Hervert-Hernández D, Goñi I (2011) Dietary polyphenols and human gut microbiota: a review. *Food Rev Int* 27, 154–169.

99. Holt RR, Heiss C, Kelm M et al. (2012) The potential of flavanol and procyanidin intake to influence age-related vascular disease. *J Nutr Gerontol Geriatr* 31, 290–323.

100. Zhang L, Wang Y, Li D et al. (2016) The absorption, distribution, metabolism and excretion of procyanidins. *Food Funct* 7, 1273–1281.

101. Koutsos A, Lima M, Conterno L et al. (2017) Effects of commercial apple varieties on human gut microbiota composition and metabolic output using an in vitro colonic model. *Nutrients* 9, 533.

102. Sembrès S, Dongowski G, Mehrlander K et al. (2006) Physiological effects of extraction juices from apple, grape, and red beet pomaces in rats. *J Agric Food Chem* 54, 10269–10280.

103. Queipo-Ortuño MI, Boto-Ordoñez M, Murri M et al. (2012) Influence of red wine polyphenols and ethanol on the gut microbiota ecology and biochemical biomarkers. *Am J Clin Nutr* 95, 1321–1334.

104. Wallace AJ, Eady SL, Hunter DC et al. (2015) No difference in fecal levels of bacteria or short chain fatty acids in humans, when consuming fruit juice beverages containing fruit fiber, fruit polyphenols, and their combination. *Nutr Res* 35, 23–34.

105. Scalbert A, Williamson G (2000) Dietary intake and bioavailability of polyphenols. *J Nutr* 130, 2075S–2085S.

106. Kemppainen RA, Bolca S, Roger LC et al. (2010) Novel approaches for analysing gut microbes and dietary polyphenols: challenges and opportunities. *Microbiology* 156, 3224–3231.

107. Patti AM, Toth PP, Giglio VR et al. (2017) Nutraceuticals as an important part of combination therapy in dyslipidaemia. *Curr Pharm Des* 23, 2496–2503.

108. Naumann S, Haller D, Eisner P et al. (2020) Mechanisms of interactions between bile acids and plant compounds—a review. *Int J Mol Sci* 21, 6495.

109. Huang J, Feng S, Liu A et al. (2018) Green tea polyphenol EGCG alleviates metabolic abnormality and fatty liver by decreasing bile acid and lipid absorption in mice. *Mol Nutr Food Res* 62, 1700696.

110. Ogawa K, Hirose S, Nagaoka S et al. (2016) Interaction between tea polyphenols and bile acid inhibits micellar cholesterol solubility. *J Agric Food Chem* 64, 204–209.

111. Adisakwattana S, Moonrat J, Sirichaith S et al. (2010) Lipid-lowering mechanisms of grape seed extract (Vitis vinifera L) and its antihypercholesteremic activity. *J Med Plant Res* 4, 2113–2120.

112. Ngamukote S, Mäkynen K, Thilawech T et al. (2011) Cholesterol-lowering activity of the major polyphenols in grape seed. *Molecules* 16, 5054–5061.

113. Koutsos A, Riccadonna S, Ulaszewska MM et al. (2020) Two apples a day lower serum cholesterol and improve cardiometabolic biomarkers in mildly hypercholesterolemic adults: a randomized, controlled, crossover trial. *Am J Clin Nutr* 111, 307–318.

114. Fujita H, Yamagami T (2008) Antihypercholesterolemic effect of Chinese black tea extract in human subjects with borderline hypercholesterolemia. *Nutr Res* 28, 450–456.

115. Velasquez M, Ramezani A, Manal A et al. (2016) Trimethylamine N-oxide: the good, the bad and the unknown. *Toxins* 8, 326.

116. Senthong V, Li X-S, Hudec T et al. (2016) Plasma trimethylamine N-oxide, a gut microbe–generated phosphatidylcholine metabolite, is associated with atheroclerotic burden. *J Am Coll Cardiol* 67, 2620–2628.

117. Koeth RA, Wang Z, Levison BS et al. (2012) Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nat Med* 19, 576.

118. Aprikian O, Busserolles Jrm, Manach C et al. (2002) Lyophilized apple counteracts the development of hypercholesterolemia, oxidative stress, and renal dysfunction in obese Zucker rats. *J Nutr* 132, 1969–1976.

119. Ravn-Hansen G, Krath BN, Markowski J et al. (2018) Apple pomace improves gut health in Fisher rats independent of seed content. *Food Funct* 9, 2931–2941.

120. Chavez-Santoscoy RA, Gutierrez-Urbe JA, Granados O et al. (2014) Flavonoids and saponins extracted from black bean (Phaseolus vulgaris L) seed coats modulate lipid metabolism and biliary cholesterol secretion in C57BL/6 mice. *Br J Nutr* 112, 886–899.

121. Mathew B, Youseph B, Dessalle T et al. (2012) Hypolipidaemic effect of leucodophilinidin derivative from Ficus bengalensis Linn on cholesterol fed rats. *Res J Chem Sci* 6, 606X.

122. Feng D, Sun J-g, Sun R-b et al. (2015) Isoflavones and pheynols contained in Xuezhikang capsules modulate cholesterol homeostasis in high-fat diet mice. *Acta Pharmacol Sin* 36, 1462–1472.

123. Lee Y-N, Hsu G-SW, Lin W-T et al. (2016) Hypolipidemic and antioxidative effects of Glossogyne tenuifolia in hamsters fed an atherogenic diet. *J Med Food* 19, 513–517.

124. Gong J, Peng C, Chen T et al. (2010) Effects of theabrownin from Pu-erh tea on the metabolism of serum lipids in rats: mechanism of action. *J Food Sci* 75, H182–H189.

125. Miura D, Miura Y, Yagasaki K (2005) Hypolipidemic action of dietary resveratrol, a phytoalexin in grapes and red wine, in hepatoma-bearing mice. *J Med Food* 7, 1393–1400.

126. Wang D, Xiao M, Gao S et al. (2012) Cyanidin-3-O-β-glucoside upregulates hepatic cholesterol 7α-hydroxylase expression and reduces hypercholesterolemia in mice. *Mol Nutr Food Res* 56, 610–621.

127. Ushiroda C, Naito Y, Takagi T et al. (2019) Green tea polyphenol (epigallocatechin-3-galllate) improves gut dysbiosis and serum bile acids dysregulation in high-fat diet-fed mice. *J Clin Biochem Nutr* 18, 116–118.
Bile acids, gut microbiota and cardiovascular health

128. Hoang M-H, Jia Y, Mok B et al. (2015) Kaempferol ameliorates symptoms of metabolic syndrome by regulating activities of liver X receptor-β. J Nutr Biochem 26, 868–875.

129. Zhang M, Xie Z, Gao W et al. (2016) Quercetin regulates hepatic cholesterol metabolism by promoting cholesterol-tobile acid conversion and cholesterol efflux in rats. Nutr Res 36, 271–279.

130. Daniel RS, Devi K, Augusti K et al. (2003) Mechanism of action of antithromogenic and related effects of Ficus bengalensis Linn. flavonoids in experimental animals.

131. Guo J, Han X, Tan H et al. (2019) Blueberry extract improves obesity through regulation of the gut microbiota and bile acids via pathways involving FXR and TGR5. Science 19, 676–690.

132. Anhê FF, Nachbar RT, Varin TV et al. (2019) Treatment with camu camu (Myrciaria dubia) prevents obesity by altering the gut microbiota and increasing energy expenditure in diet-induced obese mice. Gut 68, 453–464.

133. Spiller GA, Story JA, Lodics TA et al. (2004) Effects of a controlled diet and black tea drinking on the fecal microflora composition and the fecal bile acid profile of human volunteers in a double-blinded randomized feeding study. J Nutr 134, 473–478.

134. Inagaki T, Choi M, Moschetta A et al. (2005) Fibrolast growth factor 15 functions as an enterohepatic signal to regulate bile acid homeostasis. Cell Metab 2, 217–225.

135. Chen J, Huang X-F (2009) The effects of diets enriched in beta-glucans on blood lipoprotein concentrations. J Clin Lipidol 3, 154–158.

136. Theuwissen E, Mensink RP (2007) Simultaneous intake of sun-dried raisins on bile acid excretion, intestinal transit time, and fecal weight: a dose–response study. J Med Food 6, 87–91.

137. Williamson G, Carugh A (2010) Polyphenol content and health benefits of raisins. Nutr Res 30, 511–519.

138. Mai V, Karkl A, Harrensen H et al. (2004a) Effects of a controlled diet and black tea drinking on the fecal microflora composition and the fecal bile acid profile of human volunteers in a double-blinded randomized feeding study. J Nutr 134, 473–478.

139. Wright RS, Anderson JW, Bridges SR (2000) Propionate inhibits hepatocyte lipid synthesis. Proc Soc Exp Biol Med 195, 26–29.

140. Downing LE, Heidker RM, Caiozzi GC et al. (2016) Dietary procyanidins selectively modulate intestinal farnesoid X receptor by 6α-hydroxy bile acids and cholesterol excretion and inhibition of hepatic lipogenesis. PLoS One 10, e0140267.

141. Quifer-Rada P, Choy YY, Calvert CC et al. (2016) Use of metabolomics and lipidomics to evaluate the hypocholesterolemic effect of proanthocyanidins from grape seed in a pig model. Mol Nutr Food Res 60, 2219–2227.

142. Wang G, Huang W, Xia Y et al. (2019) Cholesterol-lowering potentials of Lactobacillus strain overexpression of bile salt hydrolase on high cholesterol diet-induced hypercholesterolemic mice. Food Funct 10, 1684–1695.

143. Hara H, Haga S, Aoyama Y et al. (1999) Short-chain fatty acids suppress cholesterol synthesis in rat liver and intestine. J Nutr 129, 942–948.

144. Mueller NT, Zhang M, Juraschek SP et al. (2020) Effects of high-fiber diets enriched with carbohydrate, protein, or unsaturated fat on circulating short chain fatty acids: results from the OmniHeart randomized trial. Am J Clin Nutr 111, 545–554.

145. Sunagawa K, Suraga K, Oshima Y et al. (2006) Dietary acetic acid reduces serum cholesterol and triacylglycerols in rats fed a cholesterol-rich diet. Br J Nutr 95, 916–924.

146. Wright RS, Anderson JW, Bridges SR (1990) Propionate inhibits hepatocyte lipid synthesis. Proc Soc Exp Biol Med 195, 26–29.

147. Jiao R, Zhang Z, Yu H (2018) Specific substrate-driven changes in human faecal microbiota composition contrast with functional redundancy in short-chain fatty acid production. BMJ J 12, 610–622.

148. Zhao Y, Liu J, Hao W et al. (2017) Butyrate-producing bacteria supplemented in vitro to Crohn’s disease patient microbiota increased butyrate production and enhanced intestinal epithelial barrier integrity. Sci Rep 7, 1–14.

149. Reichardt N, Vollmer M, Holtop G et al. (2018) Specific substrate-driven changes in human faecal microbiota composition contrast with functional redundancy in short-chain fatty acid production. BMJ J 12, 610–622.
165. Han J, Liu Y, Wang R et al. (2015) Metabolic profiling of bile acids in human and mouse blood by LC–MS/MS in combination with phospholipid-depletion solid-phase extraction. Anal Chem 87, 1127–1136.

166. Ginos BN, Navarro SL, Schwarz Y et al. (2018) Circulating bile acids in healthy adults respond differently to a dietary pattern characterized by whole grains, legumes and fruits and vegetables compared to a diet high in refined grains and added sugars: a randomized, controlled, crossover feeding study. Metabolism 83, 197–204.

167. Wu W-T, Cheng H-C, Chen H-L (2011) Ameliorative effects of konjac glucomannan on human faecal β-glucuronidase activity, secondary bile acid levels and faecal water toxicity towards Caco-2 cells. Br J Nutr 105, 593–600.

168. Chaplin M, Chaudhury S, Dettmar P et al. (2000) Effect of ispaghula husk on the faecal output of bile acids in healthy volunteers. J Steroid Biochem Mol Biol 72, 283–292.

169. Martín-Peláez S, Mosele JI, Pizarro N et al. (2017) Effect of virgin olive oil and thyme phenolic compounds on blood lipid profile: implications of human gut microbiota. Euro J Nutr 56, 119–131.

170. Tzounis X, Rodriguez-Mateos A, Vulevic J et al. (2011) Prebiotic evaluation of cocoa-derived flavanols in healthy humans by using a randomized, controlled, double-blind, crossover intervention study. The American journal of clinical nutrition 93, 62–72.

171. Choi I-D, Kim S-H, Jeong J-W et al. (2016) Triglyceride-lowering effects of two probiotics, Lactobacillus plantarum KY1032 and Lactobacillus curvatus HY7601, in a rat model characterized by whole grains, legumes and fruits and vegetables compared to a diet high in refined grains and added sugars: a randomized, controlled, crossover feeding study. Metabolism 83, 197–204.

172. Zhou J, Tang L, Shen C-L et al. (2018) Green tea polyphenols modify gut-microbiota dependent metabolisms of energy, bile constituents and micronutrients in female Sprague–Dawley rats. J Nutr Biochem 61, 68–81.

173. Xie M, Chen G, Wan P et al. (2018) Effects of dicaffeoylquinic acids from Ilex kudingcha on lipid metabolism and intestinal microbiota in high-fat-diet-fed mice. J Agric Food Chem 67, 171–183.

174. del Bas JM, Crescenti A, Arola-Arnal A et al. (2015) Intake of grape procyanidins during gestation and lactation impairs reverse cholesterol transport and increases atherogenic risk indexes in adult offspring. J Nutr Biochem 26, 1670–1677.

175. Sheng L, Jena PK, Liu H-X et al. (2018) Obesity treatment by epigallocatechin-3-gallate–regulated bile acid signaling and its enriched Akkermansia muciniphila. FASEB J 32, 6371–6384.

176. Salazar N, Neyrinck AM, Bindels LB et al. (2019) Functional effects of EPS-producing Bifidobacterium administration on energy metabolic alterations of diet-induced obese mice. Front Microbiol 10, 1809.

177. Natividad JM, Lamas B, Pham HP et al. (2018) Bilophila wadsworthia aggravates high fat diet induced metabolic dysfunctions in mice. Nat Commun 9, 1–15.

178. Kuo S-M, Merhige PM, Hagey LR (2013) The effect of dietary prebiotics and probiotics on body weight, large intestine indices, and fecal bile acid profile in wild type and IL10−/− mice. PLoS One 8.

179. Liu Y, Chen K, Li F et al. (2020) Probiotic LGG prevents liver fibrosis through inhibiting hepatic bile acid synthesis and enhancing bile acid excretion in mice. Hepatology 2050.

180. de Almeida Jackix E, Monteiro EB, Raposo HF et al. (2013) Taioba (Xanthosoma sagittifolium) leaves: nutrient composition and physiological effects on healthy rats. J Food Sci 78, H1929–H1934.

181. Dongowski G, Jacobasch G, Schmiedl D (2005) Structural stabilities of Bile acid glucuronidase activ-. J Agric Food Chem 53, 9257–9267.

182. Villanueva-Suárez M-J, Pérez-Cózar M-L, Mateos-Aparicio I et al. (2016) Potential fat-lowering and prebiotic effects of enzymatically treated okara in high-cholesterol-fed Wistar rats. Int J Food Sci Nutr 67, 828–833.

183. Guinnes P, Williams BA, Gerrits WJ et al. (2016) Circulating triglycerides and bile acids are reduced by a soluble wheat arabinoxylan via modulation of bile concentration and lipid digestion rates in a pig model. Mol Nutr Food Res 60, 642–651.