Involvement of Gut Microbiota, Microbial Metabolites and Interaction with Polyphenol in Host Immunometabolism

Andy W.C. Man, Yawen Zhou, Ning Xia and Huige Li *
Department of Pharmacology, Johannes Gutenberg University Medical Center, Langenbeckstr. 1, 55131 Mainz, Germany; wingcman@uni-mainz.de (A.W.C.M.); yawezhou@uni-mainz.de (Y.Z.); xianing@uni-mainz.de (N.X.)
* Correspondence: huigeli@uni-mainz.de

Received: 30 August 2020; Accepted: 1 October 2020; Published: 6 October 2020

Abstract: Immunological and metabolic processes are inextricably linked and important for maintaining tissue and organismal health. Manipulation of cellular metabolism could be beneficial to immunity and prevent metabolic and degenerative diseases including obesity, diabetes, and cancer. Maintenance of a normal metabolism depends on symbiotic consortium of gut microbes. Gut microbiota contributes to certain xenobiotic metabolisms and bioactive metabolites production. Gut microbiota-derived metabolites have been shown to be involved in inflammatory activation of macrophages and contribute to metabolic diseases. Recent studies have focused on how nutrients affect immunometabolism. Polyphenols, the secondary metabolites of plants, are presented in many foods and beverages. Several studies have demonstrated the antioxidant and anti-inflammatory properties of polyphenols. Many clinical trials and epidemiological studies have also shown that long-term consumption of polyphenol-rich diet protects against chronic metabolic diseases. It is known that polyphenols can modulate the composition of core gut microbiota and interact with the immunometabolism. In the present article, we review the mechanisms of gut microbiota and its metabolites on immunometabolism, summarize recent findings on how the interaction between microbiota and polyphenol modulates host immunometabolism, and discuss future research directions.

Keywords: inflammation; gut microbiota; polyphenol; metabolic diseases; metabolites

1. Introduction

The worldwide prevalence of obesity has emerged as a major cause of immunometabolism diseases including diabetes and cardiovascular diseases [1]. Immunometabolism has recently been described as the interface of the immune system and metabolism [2–4]. Indeed, chronic non-communicable diseases such as obesity, type 2 diabetes, and cardiovascular disease are recognized as the disruption of the interaction between the immune system and metabolism [5]. The increasing prevalence of immunometabolic diseases and the complicated connections between metabolic dysregulation and inflammation underline the need to reveal the metabolic programming of immune cells. The emerging field of immunometabolism has highlighted the significance of cellular metabolism in the regulation of immune cell activity. Under certain conditions, anabolic and catabolic metabolisms have become associated with pro- and anti-inflammatory immune responses, respectively [3]. Thus, modulation of specific metabolic pathways in immune cells may represent a novel strategy to inhibit inflammation and to promote the anti-inflammatory immune responses.

Gut microbiota is a complex ecosystem, which is composed by numerous species of microorganisms that highly interact with the host. The symbiotic interaction between the host and gut microbiota is
important for the host’s metabolism and health [6]. Therefore, gut microbiota has been considered as a virtual endocrine system with their metabolites modulating the host’s metabolic functions. Most of the gut microbiota identified consist of five phyla: Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria, and Verrucomicrobia. Their relative abundance and diversity of species are highly variable, and anaerobic Bacteroidetes and Firmicutes usually occupy more than 90% of the total gut microbiota population [7,8]. The composition of the gut microbiota can be affected by the host genome and environmental factors, such as usage of antibiotics and probiotics, lifestyle, hygiene status, and diet [8]. Due to the advancement of genome sequencing technologies, bioinformatics becomes an excellent research tool to identify and characterize the composition of microbiota [9]. It is widely accepted that gut microbiota dysbiosis is correlated with metabolic disorders and serious vascular complications [10]. Changes in dietary patterns promote a quick and reversible populational change of dominant gut microbiota [11]. Cardiometabolic diseases, such as obesity and diabetes, have been described as the result of an intricate crosstalk between individual genotypes, aging, environmental factors, dietary pattern, as well as the gut microbiota [12].

Polyphenols are water-soluble phenolic secondary metabolites of plants, and are categorized into several types including flavonoids, phenolic acids, and phenolic amides according to their chemical structures [13]. Polyphenols can be found largely in fruits and vegetables, while for humans, common sources of dietary polyphenol also include beverages and herbal products [14]. Polyphenols possess anti-oxidant and anti-inflammatory properties, while they are also important immunonutrients that have been extensively studied in the context of immune diseases [15–18]. However, polyphenols have relatively low bioavailability in our body, less than 10% of total polyphenol intake is absorbed in small intestines. The unabsorbed polyphenol may accumulate in large intestines and be metabolized by the gut microbiota into smaller, low molecular weight phenolic metabolites and absorbed into the body [19,20]. In addition, many studies support the theory that polyphenols with poor bioavailability possibly act primarily through the gut microbiota remodeling, which affects the microbial composition and function [21]. The majority of polyphenol researches have focused on their antimicrobial activity, but the newly emerging concept of polyphenols as potential prebiotics to shape the gut microbiota composition is concerned [22]. In this review, we will update different studies exploring the effect of gut microbiota and its metabolites on host immunometabolism. We will also describe why and how the interplay between polyphenol and gut microbiota helps to modulate immunometabolism and prevent immunometabolic complications.

2. Role of Gut Microbiota in Host Energy Metabolism and Immune Functions

Gut microbiota plays a central role in maintaining metabolic and immunological functions of host tissue and organs. In relation to the energy metabolism of the host, gut microbiota is involved in various metabolic functions, including enzymatic digestion, fermentation and absorption of complex dietary carbohydrates and proteins, and providing essential vitamins and amino acids for the host [23,24]. Increasing evidence from preclinical and clinical studies has highlighted that gut microbiota can modify immunometabolism by modulating epithelial and immune cells, which results in immune-inflammatory responses that favor the progression of diabetes and its complication [25].

Gut microbiota dysbiosis refers to the disruption of the dynamic interaction between the host and the microbial communities, as well as a bacterial imbalance between the ratio of aerobic and facultative anaerobic bacteria [26]. Many diseases, including inflammatory diseases, metabolic disorders, obesity, diabetes, and cardiovascular diseases, have been associated with specific bacterial dysbiosis [27]. Changes in the diversity and population of microbiota species, for example, the reduction of beneficial and anti-inflammatory species (including Faecalibacterium prausnitzii and Akkermansia muciniphila) or the colonization of proinflammatory bacteria (including Bacteroides and Ruminococcus gnavus) can facilitate the pathogenesis and chronicity of immunometabolic diseases [27,28]. Currently, Bacteroides, Lactobacillus, Eubacterium, and Roseburia are beneficial genera of bacteria identified to be involved in anti-inflammatory and antioxidant processes [29]. Moreover, Lactobacillus can use tryptophan as
an energy source and generate ligands of the aryl hydrocarbon receptor (AhR), which is involved in the organogenesis of intestinal lymphoid follicles (ILFs) and affect the secretion of anti-microbial peptides [30]. On the other hand, the Firmicutes to Bacteroidetes ratio is found significantly increased in obese mice [31]. Gut microbiota dysbiosis may also trigger the breakdown of gut barrier integrity which leads to local and systemic inflammation [26,32]. Rupture of the gut barrier integrity facilitates the translocation of bacteria fragments, including lipopolysaccharide (LPS) and peptidoglycan (PG), to the bloodstream. The translocation of bacterial components and other microbial-derived metabolites through the intestinal barrier to the systemic circulation can affect the inflammatory and oxidative state, as well as the cellular metabolism and immunity [11,33].

The concept that nutrients and gut microbiota have important roles in modulating insulin resistance and cellular metabolisms has been demonstrated systemically in animal models and in humans [2]. Indeed, gut microbiota transplantation from lean donors into subjects with metabolic disease can ameliorate insulin sensitivity, suggesting that microbiota and host metabolism are intrinsically linked [33]. By far, at least three major mechanisms have been identified as triggers of obesity-associated metabolic inflammation including endoplasmic reticulum (ER) stress, toll-like receptor 4 (TLR4) activation, and changes in gut microbiota [34]. Indeed, the innate immune component TLR4 has been identified as a receptor for saturated and polyunsaturated fatty acids [35], and TLRs signaling is involved in metabolic controls [36]. Moreover, TLR4 can also be activated in response to the LPS produced by Gram-negative bacteria [37]. The microbe-associated molecular pattern (MAMP) can provoke pro-inflammatory responses by activating TLR4, which in turn affect glucose metabolism and insulin signaling [38]. In addition, these pro-inflammatory responses can further stimulate the production of advanced glycation end products (AGEs) and other oxidative pathways, which are also involved in the immunometabolic impairment. Current researches support TLR4 as an important link among gut microbiota and immunometabolism.

Currently, gnotobiotic or germ-free mice are common animal models to study the effects of gut microbiota in host immunometabolism. Indeed, the significance of gut microbiota in modulating host metabolism is suggested when the reduced adiposity of germ-free mice can be reversed by colonization with a normal gut microbiota [39]. In addition, transplantation of microbiota from obese mice to either germ-free or antibiotics-treated mice induces greater weight gain than those receiving from lean mice [40,41]. Moreover, germ-free mice are more resistant to high-fat diet (HFD)-induced body weight gain compared to conventionally raised mice [42]. On the other hand, gnotobiotic mice show underdeveloped lymphoid tissues, impaired T and B cell functions, and decreased number of CD4+ T cells and antibody production [43]. Moreover, there is evidence showing that T helper 17 (Th17) and regulatory T cells are less efficient in germ-free mice compared to that of control during infection [44]. Colonization of germ-free mice with specific bacterial species can restore immunological functions [45,46]. However, the results from these germ-free mice studies may lack clinical relevance, as these mice are artificially maintained and lack early exposure to normal flora. The use of antibiotics treatment [47] or humanized animals (germ-free mice transplanted with human fecal microbiota) [48] may be a better model to investigate the interaction between microbiota and polyphenols in immunometabolic disease.

Furthermore, type 1 diabetes is long considered as an autoimmune disease, while it has been recently proposed that the crosstalk between gut microbiota and host immunometabolism may be a common molecular basis of both type 1 and type 2 diabetes [49]. In patients with type 1 diabetes, differences in intestinal microbiota composition are observed, suggesting the potential involvement of the gut microbiota in the etiology of type 1 diabetes [50–52]. In addition, a low gut microbe diversity has been linked to type 1 diabetes and β-cell autoimmunity [53]. During infancy, the presence of commensal intestinal microbiota is critical for various physiologic processes including stimulation of various arms of the innate and adaptive immune systems [54]. A randomized, double-blind, controlled intervention trial has also shown that highly hydrolyzed casein can reduce the risk of type 1 diabetes in genetically predisposed children and is associated with the change in gut microbiota composition influencing
the development of the immune system [55]. This suggests the significant role of gut microbiota in modulating the host metabolism and immunity, while the symbiosis between the host and gut microbiota is developed from birth and is critical for the host health. Therefore, shaping the gut microbiota can be a promising strategy to prevent the pathogenesis of immunometabolic diseases.

Indeed, the gut microbiota produces extremely diverse metabolites from the anaerobic fermentation of dietary components that reach the colon, as well as endogenous compounds that are generated by both the host and microorganisms [56]. Many of these metabolites are produced by the gut bacteria to inhibit the growth of their competitors, which are considered as a biological strategy for maintenance of diversity of commensal species, and elimination of pathogenic bacteria [57]. In addition, these gut microbiota metabolites are involved in various important physiological processes, including host energy metabolism and immunity. To date, thousands of microbial metabolites with known and unknown functions have been identified as components of the human metabolome [58,59]. Recent studies have been focused on uncovering the major role of bacterial metabolites in the regulation of host immunometabolism. Gut microbes and their metabolites are necessary for the host immune system to distinguish self and non-self at early life, as well as to activate the innate lymphoid cells, natural killer cells, cytotoxic, noncytotoxic, and helper lymphoid cells [60,61]. Here, we summarize the major findings on the effects of gut microbiota metabolites on the host immunometabolism. The growing understanding of the detailed mechanisms on how microbiota regulates host immunometabolism provides new opportunities to interfere with and protect against important pathogenesis.

2.1. Short-Chain Fatty Acids

SCFAs are a group of the most important of gut microbiota metabolites fermented from resistant starch or dietary fiber [62]. The predominant bacteria known to produce SCFAs are Akkermansia muciniphila, Prevotella spp., Ruminococcus spp., Faecalibacterium prausnitzii, Eubacterium rectale, and Roseburia spp. [63]. The major SCFAs include acetate, propionate, and butyrate. SCFAs are transported from the intestinal lumen into the blood circulation of the host and to the organs where they act as substrates or signal molecules. SCFAs are known to modulate multiple metabolism, inflammation, hormone production, lipogenesis, and gut homeostasis via binding to their receptors, which include G protein-coupled receptor 41 (GPR41), GPR43, GPR109A, and vascular olfactory receptor 78 (Olfr78) [64,65]. SCFAs are generally considered to have beneficial effects on host health.

Acetate and propionate are substrates to facilitate ATP production in muscles and liver [66]. Apart from that, SCFAs have been shown to increase the AMP-activated protein kinase (AMPK) activity in muscles and liver, while the activation of AMPK triggers the upregulation of peroxisome proliferator-activated receptor gamma coactivator (PGC-1α) [67]. PGC-1α is an important regulator of cholesterol, lipid, and glucose metabolism, partly by modulating the activity of peroxisome proliferator-activated receptor (PPARα, PPARδ, and PPARγ), liver X receptor (LXR), and farnesoid X receptor (FXR) [68,69]. Moreover, SCFAs have been shown to upregulate PGC-1α and uncoupling protein 1 (UCP1) in brown adipose tissues, and are associated with increased thermogenesis and fatty acid oxidation [67]. On the other hand, SCFAs can inhibit the de novo synthesis of fatty acids and lipolysis, which results in a total reduction of plasma level of free fatty acids [70] and a decrease in body weight [71,72]. In addition, SCFAs can trigger the local release of peptide tyrosine-tyrosine (PYY) and glucagon-like peptide-1 (GLP-1) from enteroendocrine L cells [73]. SCFA have been positively associated with elevated plasma levels of PYY and GLP-1 in both humans and mice studies [74,75]. These nutrient-sensing hormones are involved in the modulation of plasma glucose level, lipid metabolism, and fatty acids storage in the liver [76]. PYY is known as a satiety hormone that reduces appetite, while it can also enhance the insulin action on glucose disposal in skeletal muscles and adipose tissues [77,78]. GLP-1 is a key determinant of blood glucose homeostasis, which can promote the secretion of insulin and inhibit the secretion of glucagon by the pancreas [79]. Either administration of SCFAs or intake of dietary fibers increases GLP-1 and PYY plasma levels and glucose uptake by
Nutrients 2020, 12, 3054

In adipose tissue [80–82]. In addition, GLP-1 and PYY have receptors expressed in the brain that are involved in the regulation of host energy homeostasis, suggesting the significant contribution of SCFAs in intestine–brain crosstalk [83]. Therefore, high SCFAs levels are negatively correlated to the risk of obesity. Obesity has been associated with a reduced number of butyrate and propionate producing bacterial species in the gut microbiota [84]. Moreover, increased levels of propionate were detected in mice who had gastric bypass and in germ-free recipient mice receiving the gut microbiota from mice who had gastric bypass, whereas the germ-free recipient mice were also protected from diet-induced obesity [85]. In addition, both in vitro and in vivo experiments suggested that SCFAs increase the production of important adipokine, leptin, from adipose tissue [86,87].

SCFAs have been shown to be involved in immune responses and inflammatory conditions. A metagenomic study suggests that a consortium of lactate- and butyrate-producing gut bacteria can induce a sufficient amount of mucin synthesis to maintain gut integrity and prevent the development of autoimmune diseases including type 1 diabetes [53]. Mice deficient in one of the SCFA receptors, GPR43, show exacerbated inflammation in models of colitis and peripheral inflammation [88]. Moreover, SCFAs have been shown to elevate the number and function of induced regulatory T cells [89]. Propionate is associated with improved glucose homeostasis via improving pancreatic β-cell function [90,91]. Acetate and butyrate are involved in maintaining β-cell function by mediating B cells differentiation and function, enhancing the number and function of regulatory T cells and reducing the population of autoreactive T cells [92]. Butyrate has been shown to upregulate the regulatory T cells, which calm the mucosal immune response, suppress inflammation, and maintain mucosal integrity in the colon [60]. A recent study also suggests that butyrate is able to control the capacity of T cells by differentially regulating Th1 and Th17 cell differentiation and promoting IL-10 production in the induction of colitis [93]. Butyrate also inhibits histone deacetylase 3 (HDAC3) in monocytes during macrophage differentiation and induces metabolic changes that enhance the antimicrobial function of macrophage [94]. Butyrate is also beneficial against inflammation by inhibiting superoxide production and consequent Nod-like receptor pyrin domain 3 (NLRP3) inflammasome formation and activation [95]. On the other hand, butyrate has been shown to upregulate the expression of TLR4 and the phosphorylation of mitogen-activated protein kinases (MAPK) and nuclear factor kappa light chain enhancer of activated B cells (NF-κB) in colon cancer cell in vitro, which can further trigger pro-inflammatory response and initiate innate immunity against cancer cells. [96]. In vasculature, SCFAs can inhibit LPS or tumor necrosis factor alpha (TNF-α)-induced endothelial inflammatory responses and excessive vascular cell adhesion molecule 1 (VCAM-1) expression [64]. SCFAs can also induce leptin expression, which has been shown to contribute to both innate and adaptive immune response by stimulating the expression of CD25, CD39, CD69, CD71, and CD121a [97]; proinflammatory cytokines interleukin 6 (IL-6); and TNF-α from adipose tissues [98]. Together these data support that SCFAs are important bacterial messengers that modulate host immunometabolism.

2.2. Branched-Chain Amino Acids

BCAAs (including leucine, isoleucine, and valine) are essential amino acids that possess an aliphatic sidechain with a branch. BCAAs cannot be synthesized by humans and must therefore originate from ingested food or gut microbial synthesis. Gut microbiota is known to be involved partly in regulating the biosynthesis, transport, and metabolism of BCAAs [99,100]. Prevotella copri and Bacteroides vulgatus are known to be the main species that contribute to the increased circulating BCAA levels [101,102], while a potentially causal role of Bacteroides ovatus in mediating the biosynthesis of BCAAs in metabolic disorders has also been suggested recently [103].

Although BCAAs are now advertised as health supplements to build muscles and reduce exercise fatigue, high levels of BCAA, mainly derived from muscle protein and associated with specific gut microbiota compositions, have recently emerged as contributors of inflammation and may lead to the development of insulin resistance and diabetes [104]. Individuals with insulin resistance have been shown to possess altered microbiota composition and microbiota-derived metabolite profile with
Higher levels of circulating BCAA \[104,105\]. In mice, a challenge with \textit{Prevotella copri} led to increased circulating serum levels of BCAAs, insulin resistance, and an aggravation of glucose intolerance \[102\]. HFD-induced gut dysbiosis is associated with the increased circulating BCAA levels, while oral gavage with \textit{Bacteroides thetaiotaomicron} normalizes serum BCAA levels and alleviates diet-induced body weight gain and adiposity \[106\].

Mammalian target of rapamycin (mTOR) is a serine/threonine protein kinase present in two signaling complexes, mTORC1 and mTORC2 \[107\]. mTOR is particularly sensitive to BCAAs, while BCAAs are required for cell proliferation in mTORC1-dependent pathway \[108\]. High concentration of BCAAs promotes oxidative stress, inflammation and migration of human peripheral blood mononuclear cells via mTORC1 activation \[108\]. BCAAs trigger ROS formation in peripheral blood mononuclear cells through the activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 2 (NOX2) \[108\], which is particularly important in immune cells \[109\]. mTORC1 signaling is also a central regulator of cellular metabolism and T cell responses \[107\]. mTORC1 signaling is important for T cell development in the thymus; homeostasis in the periphery; and differentiation into CD4\(^+\) Th1, Th2, and Th17 cells, as well as cytotoxic CD8\(^+\) T cells \[110–112\]. mTORC2 is required for Th1 and Th2 cell differentiation \[113\]. In mice, BCAA-reduced diet decreases the numbers and proliferative capacity of Foxp3\(^+\) regulatory T cells \[114\].

Despite several lines of experimental evidence showing the positive association between gut dysbiosis, elevated BCAA levels, and insulin resistance, some observations are controversial. Inhibition of cytosolic branched-chain aminotransferase (BCAT1), the enzyme responsible for the reversible transamination of BCAA, reduces inflammation associated with decreased macrophage infiltration in animal models of collagen-induced arthritis or crescentic glomerulonephritis \[115\]. Deletion of mitochondrial branched-chain aminotransferase (BCAT2) increases energy expenditure and improved insulin sensitivity \[116\].

On the other hand, BCATs initiate bacterial branched-chain fatty acid (BCFA) synthesis by converting BCAAs into branched chain \(\alpha\)-keto acids \[117\]. BCFAs are rare in mammalian tissues, while they are essential membrane component of many bacterial species \[118\]. Dietary BCFAs have been shown to increase the expression of the anti-inflammatory cytokine, IL-10, as well as to reduce the incidence of necrotizing enterocolitis in infants \[119\]. BCFAs can also suppress LPS-induced IL-8 expression and reduce the expression of TLR4 in human intestinal epithelial cells \[120\]. All these data suggest the importance of controlling circulating BCAA levels in prevention of immunometabolic diseases. Further studies are needed to explore the role of other bacterial species in BCAA metabolism, while enhancing BCAA catabolism by modifying gut microbiota population could therefore be beneficial for host metabolism.

2.3. \textit{Trimethylamine-N-Oxide}

Gut microbiota can metabolize dietary L-carnitine, choline, and lecithin into trimethylamine (TMA), which is then converted to trimethylamine-N-oxide (TMAO) by flavin-monoxygenase 3 (FMO3) in the host liver \[121,122\]. Plasma TMAO concentrations are positively associated with \textit{Prevotella}, \textit{Peptococcaceae}, and \textit{Clostridiales}, while it is negatively correlated with \textit{Faecalibacterium prausnitzii} \[123,124\]. TMAO can induce vascular inflammation through MAPK and NF-\(\kappa\)B signaling in endothelial cells \[125\]. Circulating levels of TMAO are positively associated with the risk of atherosclerosis and other cardiovascular diseases \[126–128\]. Excessive TMAO is detected in type 2 diabetic patients with coronary artery disease \[129\]. Knocking down of host liver FMO3 in low density lipoprotein receptor (\textit{Ldlr})-deficient mice reduces the hepatic and plasma lipid levels, bile acid pool size, liver triglyceride secretion, ketone bodies, and glucose and insulin levels, resulting in the prevention of atherosclerosis \[130\]. Moreover, suppression of TMAO generation with a small molecule inhibitor of microbial TMA production can prevent atherosclerosis, suggesting the modification of the gut microbiota to suppress TMAO generation can be a potential target to prevent atherosclerosis and other diseases \[131\].
Elevated serum TMAO contributes to the pathogenesis of atherosclerosis by interfering with cholesterol metabolism, inducing inflammation, as well as altering the functions of endothelial cells, foam cells and macrophages [132,133]. TMAO increases TLR4 expression in endothelial cells. Inhibition of TLR4 expression protects endothelial cells from TMAO-associated tight junction protein disruption, as well as prevents metabolic inflammation [134]. TMAO impedes reverse cholesterol transport pathway by interrupting bile synthesis and metabolism [135]. Altered cholesterol metabolism is critical for the pro-inflammatory responses and pathogenesis of atherosclerosis, while accumulation of cholesterol accelerates pro-inflammatory responses [136]. TMAO can cause changes in the entire macrophage reverse cholesterol transport pathway [132], and mice fed with TMAO-containing diet show reduced rate of macrophage-specific reverse cholesterol transport [123]. TMAO can promote macrophage cholesterol accumulation in a microbiota-dependent manner by increasing cell surface expression of CD36 and scavenger receptor A (SR-A1) [137].

Plasma proteins associated with inflammation, cardiometabolic disease, and kidney disease also correlate with TMAO. Increased TMAO-producing bacteria are found in patients with rheumatoid arthritis, a chronic inflammatory disease which shares similar pathogenesis to atherosclerosis [133,138]. Elevated TMAO level is also detected in the animal model of arthritis [139]. TMAO enhances M1 macrophage polarization and activates Th1 and Th17 reactions via NLRP3 inflammasome activation [140], as well as promoting the activity of caspase-1, and the production of IL-1β and IL-18 [141,142]. TMAO modulates the activation of aortic macrophages and upregulates the gene expression of IL-1β in atherosclerotic plaque [143]. Recently, TMAO has also been associated with increased proinflammatory CD14++CD16+ monocytes in stroke patients [144]. In addition, TMAO can alter bile acid metabolism, partly by reducing bile acid synthesis and liver bile acid transporters to decrease the bile acid pool [123]. These suggest TMAO as an important microbial modulator of host immunometabolism.

2.4. Secondary Bile Acids

Bile acids are important digestive surfactants that facilitate digestion and absorption of lipids and fat-soluble vitamins. Primary bile acids are endogenously synthesized from cholesterol in liver, which are then further metabolized by the gut microbiota into secondary bile acids. These microbial-derived bile acids contribute to the host bile acid pool, while significant alterations of bile acid pool in germ-free mice compared to conventional mice are reported [145,146]. Moreover, bariatric surgery has been shown to associate with changes in the bile acids metabolism and in the microbiota population [147]. Moreover, fecal transplantation from patients that had Roux-en-Y gastric bypass to germ-free mice leads to less fat gain and increased postprandial bile acid compared to those receiving microbiota from obese people [148], suggesting the interrelationship between host energy metabolism and gut microbiota.

Secondary bile acids are important microbial metabolites that can activate important receptors [such as FXR and G-protein-coupled bile acid receptor 1 (GPBAR-1)] in the host tissues in order to regulate metabolic and immune processes [149]. Gut microbiota affects the bile acid pool not only by producing secondary bile acid but also inhibits host hepatic bile acid synthesis by inhibiting FXR [145]. It has been shown that bile acids have direct antimicrobial effects by destroying bacterial membranes due to their detergent properties, as well as indirect effects through activating FXR and inducing the expression of inducible nitric oxide synthase (iNOS) and IL-18 that modulate the gut microbiota via the immune system [149]. In addition, recent studies have demonstrated that the activation of intestinal FXR leads to hyperglycemia in obese state, suggesting that inhibition of FXR signaling might be efficient for preventing hyperglycemia [150,151]. Long-term oral treatment with FXR agonist results in exacerbated weight gain and glucose intolerance in obese mice [152]. Fxr-deficient mice on HFD feeding or cross-bred on a ob/ob background show protection against diet-induced obesity and improvement of glucose homeostasis compared to control mice [153]. Moreover, double Fxr and Ldlr-deficient mice on high-fat diet have improved lipid profile and ameliorated diet-induced obesity and atherosclerosis [154].
The receptor of secondary bile acids, GPBAR-1, has a role in energy homeostasis by promoting intracellular thyroid hormone activity as well as promoting thermogenesis in adipose tissues [155]. GPBAR-1-specific agonist INT-777, which is a derivative of chenodeoxycholic acid, ameliorates hepatic steatosis, adiposity, and improves insulin sensitivity in HFD-fed mice [156]. GPBAR-1 signaling controls glucose homeostasis by stimulating energy expenditure in brown adipose tissues and muscles and by promoting the release of GLP-1 in intestinal L cells [156]. Interestingly, a recent study has shown that FXR is also expressed in intestinal L cells and regulates GLP-1 synthesis [157].

Chronic exposure to high levels of bile acid can induce inflammation [158]. Since chronic hyperglycemia and oxidative stress are closely related to changes in monocyte and macrophage functions [159], modulation of GPBAR-1/FXR signaling by the gut microbiota may indirectly affect host immune functions. Moreover, Macrophages are major regulators of cytokine production in the gastrointestinal tract, while macrophages are activated by the binding of secondary bile acids with GPBAR-1 [160]. GPBAR-1 activation induces a partial transformation of macrophages from M1 to M2 phenotype, leading to an elevated IL-10 level which inhibits pro-inflammatory cytokines (TNF-α and IL-6) [161]. In this aspect, similar to TLR4, GPBAR-1 is also critical to recognize pathogen-associated molecular patterns and to activate immunity [162]. A recent study has shown that activation of GPBAR-1 significantly inhibits the TLR4/NF-κB pathway leading to the reduction of liver inflammation [163]. However, other studies have suggested that pharmacological activation of FXR ameliorates inflammation and preserves the intestinal barrier integrity in two murine colitis models [164], which is also mediated by the NF-κB signaling pathway [165]. This controversy of FXR effects on inflammatory response needs to be clarified in further studies.

2.5. Tryptophan Microbial Metabolites and Others

There is an array of bioactive microbial metabolites derived from the essential aromatic amino acid tryptophan. A few commensal bacteria are identified, including Peptostreptococcus russellii, Clostridium sporogenes, and Lactobacillus spp, to metabolized tryptophan into indole and its derivatives [166–168]. Many tryptophan derivatives, such as indole-3-acid-acetic (IAA), indole-3-aldehyde (IAld), indole-3-acetaldehyde (IAAld), indole-3-propionic acid (IPA), and indoleacrylic acid are ligands for aryl hydrocarbon receptor (AhR) [169,170], which is a transcription factor that plays an important role in immunological response and inhibits inflammation [171]. AHR signaling contributes to immune homeostasis by modulating T cell differentiation, Th17 development, and IL-22 production [172–174].

Recently, epidemiologic studies have shown the association between IPA and metabolic diseases. Serum IPA levels are negatively correlated with the risk of type 2 diabetes and low-grade inflammation [175,176]. In addition, administration of IPA represses hepatic inflammation and liver injury in rats, via inhibiting NF-κB signaling and reducing the levels of proinflammatory cytokines (TNFα, IL-1β, and IL-6) in response to endotoxin in macrophages [177]. Moreover, administration of IPA inhibits the expression of genes promoting fibrosis, and attenuates diet-induced anti-non-alcoholic steatohepatitis (NASH) phenotypes in HFD-fed rats [177]. Moreover, administration of IPA significantly ameliorates colitis and induces IL-10-mediated anti-inflammatory pathway in vitro [178].

Imidazole propionate has been shown to associate with glucose intolerance, deteriorated insulin signaling and diabetes [179]. Imidazole propionate impairs insulin signaling by activating MAPK, which then promotes p62 phosphorylation and mTORC1 activation [179]. Indoxylsulphate induces TNF-α production in macrophages in an AhR- and NF-κB-dependent manner [180].

Apart from those mentioned above, gut microbiota produce a broad spectrum of epigenetically active metabolites, such as folate and vitamins, that regulate the activity of host chromatin-modulating enzymes and genetic responses to environmental signals [181]. However, the function of these microbial metabolites in the host immunometabolism is still not elucidated. Nevertheless, the complicated regulation of the host immunometabolism by the gut microbiota and its metabolites warrant further investigations.
3. Metabolism of Polyphenols by Gut Microbiota

Dietary polyphenols are perceived as xenobiotics in humans, and their biological availability is reasonably poor comparing to other micro- and macro-nutrients. The structural complexity and polymerization of polyphenols also affects their absorption in small intestines [182]. Absorption of the consumed polyphenols in the small intestines is particularly low (less than 10%). The poor bioavailability is, therefore, a major concern for their development as therapeutic agents [183]. The unabsorbed polyphenols accumulate in the large intestines along with the bile conjugates in the lumen and are exposed to the gut microbial enzymatic activities [6].

In humans, the metabolism of dietary polyphenols is an important aspect that deserves detailed consideration and warrants further studies. Gut microbiota significantly contributes to the metabolism of dietary polyphenols leading to the generation of de novo and potentially bioactive compounds. As mentioned, more than 90% of the dietary polyphenols are not absorbed in the small intestines and reach the large intestines; thus gut microbiota is critically important in turning these polyphenols into bioavailable products [184]. In general, gut microbiota metabolizes glycosylated polyphenols into lower molecular weight phenolic compounds, such as small phenolic acids [185]. Indeed, these gut microbiota-derived polyphenolic metabolites are also important essential bioavailable polyphenolic acids. Polyphenols have been shown to undergo various enzymatic processes by gut microbiota, through which the polyphenol derivatives are in a form capable of being absorbed or even more bioactive [186,187]. Therefore, the protective effects of polyphenols also depend on how gut microbiota metabolize these compounds.

Currently, there are mainly in vitro studies and a few in vivo studies focusing on the effect of microbiota-derived polyphenolic metabolites in immunometabolism (Table 1). Gut microbiota are responsible for the metabolism of resveratrol to piceid [188], which shows a higher bioavailability and antioxidant activity than resveratrol [189]. One of the derivatives from proanthocyanidins, 3-Hydroxyphenylpyruvic acid (3-HPPA), has been shown to attenuate oxidized-LDL-induced cellular oxidative stress and inflammation via NF-κB pathways and inhibit the conversion of macrophage into foam cells via regulating cellular lipid metabolism in vitro [190]. On the other hand, 3-(3′-hydroxyphenyl) propionic acid (3-HPP) has been shown to regulate Akt and eNOS via insulin-stimulated signaling and promote NO production during high glucose conditions in endothelial cells in vitro [191]. Microbiota-derived metabolite of anthocyanins, protocatechuic acid (PCA), possesses anti-inflammatory effects by regulating NF-κB and MAPK activation in vitro [192] and attenuates oxidative stress and apoptosis by reducing expressions of TNF-α, IL-1β, and IL-6 in vivo [193]. Urolithins, a derivative of ellagitannins, has been shown to reduce TNFα-induced inflammation through inhibiting histone acetyltransferase (HAT) activity in monocytes in vitro [194]. A large portion of dietary anthocyanins are degraded by gut microbiota to free anthocyanidins, protocatechuic acid (PCA) and gallic acid (GA) [195], which confer protective effects against obesity and insulin resistance [196]. Moreover, GA has been shown to regulate mitochondrial function by activating AMPK and PGC1α, while SIRT1 knockdown significantly blunted such effect [197]. In HFD-fed mice, GA treatment protects diet-induced obesity, improves glucose and insulin homeostasis, and promotes thermogenesis by increasing uncoupling protein 1 (UCP1) expression in brown adipose tissue [197]. The main soy isoflavone, daidzein, can be metabolized by the gut microbiota to equol [198], which shows higher anti-oestrogenic activity, antioxidant capacity, and anti-cancer effects than daidzein [199]. Equol has been shown to reduce triglycerides, total cholesterol, and LDL-cholesterol and increase HDL-cholesterol in HFD-fed mice [200]. A study of the Japanese population suggests the potential role of equol in glycemic control, while overweight or obese group have more equol non-producers than the normal weight group [201]. These studies suggest that gut microbiota is particularly important in the metabolism of polyphenols into essential bioactive compounds. Nevertheless, the functions of these polyphenolic metabolites are not thoroughly studied. Further in vivo and clinical studies are warranted to investigate the function of these metabolites in modulating the host immunometabolism.
Table 1. Microbial-derived polyphenolic metabolites and their protective effects.

| Polyphenol Metabolizing Bacteria | Main Metabolite | Effects in Immunometabolism | Refs |
|---------------------------------|----------------|----------------------------|------|
| Proanthocyanidins | **Lactobacillus plantarum** | 3-Hydroxyphenylpyruvic acid (3-HPPA) | • ↓ macrophage foam cell formation | [190] |
| | **Enterococcus casseliflavus,** **Clostridium coccoides,** and **C. orbiscindens** | 3-(3′-hydroxyphenyl) propionic acid (3-HPP) | • ↑ NO production | [191,202,203] |
| | **Lactobacillus plantarum,** **Lactobacillus casei,** **Lactobacillus acidophilus,** and **Bifidobacterium lactis** | 3-hydroxybenzoic acid (3-HBA) | • ↓ inflammation | [186,204] |
| Anthocyanins | **Lactobacillus spp.** and **Bifidobacterium spp.** | Protocatechuic acid (PCA) | • ↓ obesity | [192,193,196] |
| | **Lactobacillus plantarum 299v** and **Bacillus subtilis** | Gallic acid (GA) | • ↓ thermogenesis | [197,205–207] |
| | **Bacteroides Ovatus spp.,** **Streptococcus intermedius spp.,** and **Ruminococcus productus spp.** | Equol | • ↓ atherosclerotic lesions | [198,200,208] |
| | **Bacillus cereus** | Piceid | • ↑ bioavailability than resveratrol | [189,204] |
| Ellagitannins | **Akkermansia muciniphila,** **Butyrivibrio spp.,** **Gordonibacter urthophilacis,** and **Gordonibacter pamelaeae** | Urolithins | • ↑ AMPK activity | [194,209–211] |
| | **Bacteroides distasonis,** **Bacteroides fragilis,** **Bacteroides ovatus,** **Clostridium coelatum,** and **Clostridium saccharogena** | Enterolactone | • ↓ oxidative stress | [205,206] |

IL, Interleukin; IFN, interferon; TNF, tumor necrosis factor; NK, natural killer; LPS, lipopolysaccharides; AMPK, 5′ adenosine monophosphate-activated protein kinase.

4. Effect of Polyphenols on the Composition of Gut Microbiota and Host Metabolism

Growing studies support the hypothesis that polyphenols with poor bioavailability possibly act primarily through the gut microbiota remodeling [21]. Unabsorbed polyphenols that reach the colon, as well as the metabolites generated, may interact with the gut microbiota, and may modulate microbial composition and function [207,208]. Previous polyphenol researches focused on their antimicrobial activity, while the concept of polyphenols as potential prebiotics to shape the gut microbiota composition is emerging [22]. In general, lowering the *Firmicutes/Bacteroidetes* ratio and colonization of specific beneficial bacterial species are considered to provide protection to the host against certain pathologies [20]. Gram-positive bacteria are more prompted to the action of polyphenols than Gram-negative bacteria, possibly due to the differences in their wall composition [6]. Polyphenols have been shown to increase the population of beneficial species such as *Bifidobacterium* and
Lactobacillus, which contribute to the gut barrier protection; Faecalibacterium prausnitzii, which possess anti-inflammatory effect by inhibiting the activation of NF-kB; and Roseburia sp., which produces butyrate [212,213]. Recent studies have suggested that the mucin-degrading bacterium Akkermansia muciniphila is an important player contributing to the anti-inflammatory and beneficial effects of dietary polyphenols in obesity [209–211]. Akkermansia muciniphila is presented in great abundance in healthy subjects, but it is reduced in patients with inflammatory and gastrointestinal diseases, obesity, and diabetes [210]. Moreover, ellagitannins have been shown to stimulate the growth of Akkermansia muciniphila in vivo [211]. Although the effect of polyphenols on gut microbiota modulation has gained much attention in recent years, the effects on specific gut bacteria and metabolites production are still not clear. Here, we summarize recent publications on the effect of polyphenols in modulation of gut microbiota and immunometabolism in animal models (Table 2).

Resveratrol treatment (0.4% in diet) has been shown to enhance the population of Akkermansia muciniphila, promote bile acid synthesis and reduce serum TMA and TMAO levels in both wild type mice and ApoE-/-mice [135]. However, another study has shown that resveratrol (15 mg/kg/day) normalizes serum insulin levels and insulin resistance without significant changes in Firmicutes/Bacteroidetes ratio in high-fat-and-sucrose-diet (HFD)-fed Wistar rats [214]. Camu camu extract (containing around 30% proanthocyanidins 30%) has been shown to prevent high-fat-high-sucrose-diet (HFHSD)-induced obesity, partly by increasing Akkermansia muciniphila population and the proportion of secondary and unconjugated bile acids in the plasma of mice [219]. Interestingly, instant caffeinated coffee has been shown to prevent HFD-induced obesity, partly by reducing Firmicutes/Bacteroidetes ratio and serum BCAA level, while increasing serum SCFA level in rat [228]. Moreover, purified citrus polymethoxyflavone-rich extract can attenuate HFD-induced obesity by reducing Firmicutes/Bacteroidetes ratio and downregulating mTOR signaling [103]. Two plant-derived polyphenols, carnosol and curcumin, have been shown to prevent the increase in glycolysis and spare respiratory capacity in response to LPS stimulation in human dendritic cells [18]. The regulation of metabolism by the two polyphenols is via activation of AMPK, which results in the inhibition of mTOR signaling [18]. Carnosol and curcumin also upregulate heme oxygenase-1 (HO-1), which is an important anti-inflammatory and antioxidant enzyme [232]. Recently, an untargeted metabolomics study has revealed the induction of anti-inflammatory prostaglandin pathway and modulation of gut microbiota by the consumption of curcumin-containing curcuma longa L. extract [233].
Table 2. Effect of polyphenols in different animal models of metabolic complications.

| Polyphenol         | Dose            | Animal Model               | Changes in Microbiota                                                                 | Metabolic or Functional Effects                              | Refs |
|-------------------|-----------------|----------------------------|--------------------------------------------------------------------------------------|-----------------------------------------------------------------|------|
|                   |                 |                            | ↑ Bacteroides, Lactobacillus, Bifidobacterium, and Akkermansia;                      | ↑ bile acid deconjugation; ↑ hepatic bile acid synthesis;         | [135]|
|                   |                 |                            | ↓ Prevotella, Ruminococcaceae, Anaerotruncus, Alstipes, Helicobacter, and Peptococcaceae; | ↓ plasma TMA and TMAO levels.                                  |      |
|                   | 0.4% in diet    | WT C57BL/6j mice           | ↑ Bacteroides (35.1% to 44.1%), ↓ Firmicutes (50.3% to 35.4%).                      |                                                                 |      |
| Resveratrol       | 0.4% in diet    | Choline-treated ApoE-/- mice | ↑ Bacteroides, Lactobacillus, Bifidobacterium, and Akkermansia;                      | ↑ bile acid deconjugation; ↑ hepatic bile acid synthesis; ↓ atherosclerosis; ↓ plasma TMA and TMAO levels. | [135]|
|                   |                 |                            | ↓ Prevotella, Ruminococcaceae and Biophila; ↑ Bacteroidetes (20.6% to 34.0%), ↓ Firmicutes (60.1% to 50.1%). |                                                                 |      |
|                   | 15 mg/kg/day    | HFSD-fed Wistar rats        | No change in Bacteroidetes and Firmicutes                                            | ↓ serum insulin levels and insulin resistance                   | [214]|
|                   | 200 mg/kg/day   | HFD-fed Kunming mice        | ↑ Lactobacillus and Bifidobacterium; ↓ Enterococcus faecalis; ↑ Bacteroidetes/Firmicutes ratio; | ↑ Fiaf expression in intestine; ↓ body and visceral fat weight; ↓ blood glucose and lipid levels. | [215]|
|                   | 1 mg/kg/day     | DSS-induced colitis Fischer F344 rats | ↑ Bifidobacterium, Lactobacilli; ↓ Enterobacteria                                  | ↑ colonic mucosa architecture; ↓ body weight loss; ↓ inflammation | [216]|
| Piceatannol       | 0.25% in diet   | HFD-fed C57BL/6 mice        | ↑ Lactobacillus, Firmicutes (45.8 to 74.5%); ↓ Bacteroidetes (52.0 to 21.4%).      | ↓ body weight and adiposity; ↓ blood glucose level; ↓ serum LDL-C, HDL-C and the LDL-C/HDL-C ratio. | [217]|
| (resveratrol analogue) | 45 mg/kg/day   | Obese Zucker rats           | Slight changes in Bacteroidetes and Firmicutes                                      | No profound effects                                             | [218]|
| Polyphenol                              | Dose                  | Animal Model   | Changes in Microbiota                                      | Metabolic or Functional Effects                                                                 | Refs     |
|----------------------------------------|-----------------------|----------------|-----------------------------------------------------------|-------------------------------------------------------------------------------------------------|----------|
| Camu camu extract (proanthocyanidins 30%) | 200 mg/kg/day         | HFHSD-fed C57BL/6j mice | ↑ Akkermansia muciniphila, Bifidobacterium and Barnesiella, ↓ Lactobacillus. | ↑ glucose tolerance and insulin sensitivity; ↑ energy expenditure; ↓ body weight gain and fat accumulation; ↓ adipose tissue inflammation and metabolic endotoxemia; ↓ hepatic steatosis; alter plasma bile acid pool size and composition. | [219]    |
| Pomegranate peel extract (containing 30% polyphenol, 8% punicalagin and 5% ellagic acid) | 0.2% in water (6 mg/day) | HFD-fed Balb/c mice | ↑ Bifidobacterium spp., Lactobacillus spp., Bacteroides-Prevotella spp. | ↓ serum cholesterol levels; ↓ inflammatory markers expression in visceral fat.                   | [220]    |
| Quercetin                              | 30 mg/kg/day          | HFSD-fed Wistar rats | ↓ Erysipelotrichaceae, Bacillus, Eubacterium cylindroides, ↓ Firmicutes/Bacteroidetes ratio | ↓ serum insulin levels and insulin resistance; ↓ microbiota dysbiosis.                           | [214]    |
| Quercetin and Resveratrol              | 30 mg/kg/day, 15 mg/kg/day, respectively | HFD-fed Wistar rats | ↑ Bacteroidales_S24-7_group, Christensenellaceae, Akkermansia, Ruminococcaceae, and its genera Ruminococcaceae, UCG-014, and Ruminococcaceae, UCG-005; ↓ Desulfovibrionaceae, Acidaminococcaceae, Coriobacteriaceae, Bilophila, Lachnoclostridium and its genus Lachnoclostridium; ↓ Firmicutes ↓ Firmicutes/Bacteroidetes ratio | ↑ adiponectin; ↓ body weight gain and visceral fat weight; ↓ serum lipids; ↓ serum inflammatory markers (TNF-α, IL-6, MCP-1); | [221]    |
| Daidzein                               | 20mg/kg/day           | B6C3F1 mice     | Not specified                                             | ↑ T cell population; ↓ B cell population; ↓ % of late apoptotic thymocytes.                    | [222]    |
|                                        | 0.1% in diet          | db/db mice       | Not specified                                             | ↑ AMPK phosphorylation; ↓ fasting blood glucose, serum total cholesterol levels.                 | [223]    |
| Polyphenol                                      | Dose                        | Animal Model                  | Changes in Microbiota                                                                 | Metabolic or Functional Effects                                                                 | Refs   |
|------------------------------------------------|-----------------------------|-------------------------------|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|--------|
| Polymeric procyanidins                         | 0.5% in diet                | HFHS-fed C57BL/6J mice        | ↑ Akkermansia; ↓ Clostridium, Lachnospiraceae, and Bifidobacterium; ↓ Firmicutes/Bacteroidetes ratio | ↑ lipid metabolism; ↓ weight gain; ↓ circulating LPS and gut permeability;                         | [224]  |
| Powered green tea leaves (Camellia sinensis)    | 4% in diet (in combination with Lactobacillus plantarum) | HFD-fed C57BL/6J mice        | ↑ Akkermansia; ↑ Lactobacillus.                                                      | ↓ body fat and hepatic triacylglycerol and cholesterol accumulation; ↓ inflammation.             | [225]  |
| Canarium album extract (containing around 465.35 mg/g polyphenol) | 20 mg/kg/day                | HFD-fed Kunming mice         | ↑ Firmicutes and Verrucomicrobia; ↑ Akkermansia; ↓ Bacteroidetes.                    | Not specified                                                                                     | [226]  |
| Concord grape polyphenols                       | 1% in diet                  | HFD-fed C57BL/6J mice        | ↑ Akkermansia muciniphila; ↓ Firmicutes/Bacteroidetes ratio                           | ↓ weight gain, adiposity and serum inflammatory markers; ↓ glucose intolerance.                  | [227]  |
| Coffee (instant caffeeinated coffee)           | 20 g/L in water             | HFD-fed SD rats              | ↑ Enterobacteria; ↓ Clostridium Cluster XI; ↓ Firmicutes/Bacteroidetes ratio          | ↑ serum SCFA level ↓ body weight, adiposity, liver triglycerides and energy intake; ↓ insulin resistance; ↓ serum BCAA level. | [228]  |
| Five types of arctic berries powdered extract bog blueberry, cloudberry, crowberry, alpine bearberry, lingonberry | 200 mg/kg/day               | HFDS-fed C57BL/6J mice       | ↑ Akkermansia muciniphila, Turicibacter, Oscillibacter.                                | ↓ fasting and postprandial hyperinsulinemia; ↓ liver triacylglycerol deposition; ↓ circulating endotoxins; ↓ hepatic and intestinal inflammation. | [229]  |
| Plum juice (containing around 1,270 mg gallic acid equivalents/mL) | drinking water              | Obese Zucker rats            | ↑ Lactobacillus and members of Ruminococca.                                         | ↓ body weight; ↓ fecal acetic and propionic acid level                                           | [230]  |
Table 2. Cont.

| Polyphenol | Dose | Animal Model | Changes in Microbiota | Metabolic or Functional Effects | Refs |
|------------|------|--------------|-----------------------|-------------------------------|------|
| Purified citrus polymethoxyflavone-rich extract (including 38.51% (w/w) nobiletin, 15.62% tangeretin, 3.43% sinensetin, and 3.29% 3,5,6,7,8,3′,4′-heptamethoxyflavone) | 120 mg/kg/day | HFD-fed C57BL/6J mice | ↑ *Bacteroides ovatus*; ↓ *Firmicutes/Bacteroidetes* ratio. | ↑ serum HDL-C; ↓ body weight gain, serum TC, TG and LDL-C; ↓ inflammation; ↓ gut dysbiosis; ↓ mTOR/P70S6K/SREBP pathway | [103] |
| Red raspberry polyphenols from whole fruit, seed, and pulp | whole fruit (0.4% in diet); seed (0.1% in diet); pulp (0.3% in diet) | HFD-fed C57BL/6 mice | Not specified | ↑ energy expenditure; ↓ body weight gain, dyslipidemia, and insulin resistance; ↓ inflammation, macrophage recruitment, ↓ adipocyte size in epididymal fat ↓ NLRP3 inflammasome activation | [231] |

WT, wild type; TMA, trimethylamine; TMAO, trimethylamine-N-oxide; apoE, Apolipoprotein E; HFSD, high-fat-and-sucrose-diet; HFD, high-fat diet; DSS, dextran sulfate sodium; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; HFHSD, high-fat-high-sucrose-diet; TNF, tumor necrosis factor; IL, Interleukin; MCP, monocyte chemoattractant protein; LPS, lipopolysaccharides; SCFA, short-chain fatty acids; BCAA, branched-chain amino acids; TC, total cholesterol; TG, triglyceride; mTOR, mammalian target of rapamycin; P70S6K, p70S6 kinase; SREBP, sterol regulatory element-binding protein; NLRP, NACHT, LRR and PYD domains-containing protein.
The discrepancies between the results of different studies could be due to the low bioavailability of polyphenols. Most studies are reported without considering or measuring the bioavailability and the chemistry of polyphenols in the animals. Moreover, another limitation is that the results obtained from in vitro studies (summarized in [234]) and in vitro animal studies about the role of polyphenol on gut microbiota cannot be directly extrapolated to physiological context, due to the very high doses polyphenols used. The wide variation in response to polyphenols could be due to the inter-individual differences in genome and microbiota on the studied models. Human intervention studies may further provide a better model for studying the effect of polyphenol on gut microbiota and immunometabolism modulation. To date, only a few human intervention studies have investigated the in vivo impact of polyphenols on the gut microbiota [235–238]. However, in vivo human studies also hold inevitable limitations including applied microbial techniques. Further in vivo researches are needed to understand the effect of polyphenols on gut microbiota and immunometabolism. Measuring the changes in microbial metabolome, together with the bacterial population, may act as a better study strategy.

5. Future Direction and Summary

Gut microbiota significantly contributes to the host immunometabolism. Gut microbiota is also an important factor that contributes to the bioavailability and effects of dietary polyphenols. Polyphenols are known as antioxidant and anti-inflammatory molecules. In addition, the induced changes of gut microbiota and the gut microbiota-derived polyphenolic metabolites also significantly contribute to the health effects of polyphenols in immunometabolism. The beneficial effects of polyphenols on immunometabolism are highly dependent on the gut microbiota. This review highlights the contribution of gut microbiota and its metabolites in host immunometabolism, as well as the effect of polyphenols in animal models of immunometabolic disease. However, the observed phenotypes in these animal studies are sometimes controversial and are not always conserved in human studies. The use of antibiotics treatment may provide inaccurate results as some resistant species may still be presented or selected [47]. It is important to note that 85% of the murine microbiome species are not yet detected in human microbiomes [239]. The use of humanized animal may be a good model to investigate the interaction between microbiota and polyphenols in immunometabolic diseases [48]. However, the humanization of mouse models may not adequately display the whole spectrum of relevant phenotype of human diseases [45,46]. Antibiotics-treated mice model can also be considered. These challenges in screening the accurate changes in the population of gut microbiota may be overcome by targeting the microbial metabolome. Currently, strong evidence on a causal relationship between the microbial metabolome and effect of polyphenols in modulating immunometabolism is still missing. To identify novel potential treatment targets, future study direction may focus on the microbial metabolomics and their effects on host immunometabolism.

Author Contributions: A.W.C.M. and Y.Z. wrote the initial draft of the manuscript. N.X. and H.L. critically reviewed and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: Original works from the authors’ laboratory contributing to this review were supported by grants LI-1042/1-1, LI-1042/3-1, LI-1042/5-1, and XI 139/2-1 from the Deutsche Forschungsgemeinschaft (DFG), Bonn, Germany. N.X. and H.L. were supported by research grants from the Boehringer Ingelheim Foundation for the collaborative research consortium "Novel and neglected cardiovascular risk factors: molecular mechanisms and therapeutic implications". Y.Z. was supported by a TransMed Research Fellowship from the University Medical Centre of Mainz.

Conflicts of Interest: The authors declare no conflict of interest.
References

1. Lee, Y.S.; Wollam, J.; Olefsky, J.M. An Integrated View of Immunometabolism. *Cell* 2018, 172, 22–40. [CrossRef] [PubMed]
2. Hotamisligil, G.S. Inflammation, metaflammation and immunometabolic disorders. *Nature* 2017, 542, 177–185. [CrossRef] [PubMed]
3. O’Neill, L.A.; Kishton, R.J.; Rathmell, J. A guide to immunometabolism for immunologists. *Nat. Rev. Immunol.* 2016, 16, 553–565. [CrossRef]
4. Palsson-McDermott, E.M.; O’Neill, L.A.J. Targeting immunometabolism as an anti-inflammatory strategy. *Cell Res.* 2020, 30, 300–314. [CrossRef] [PubMed]
5. Hotamisligil, G.S. Foundations of Immunometabolism and Implications for Metabolic Health and Disease. *Immunity* 2017, 47, 406–420. [CrossRef]
6. Cardona, F.; Andres-Lacueva, C.; Tulipani, S.; Tinahones, F.J.; Queipo-Ortuno, M.I. Benefits of polyphenols on gut microbiota and implications in human health. *J. Nutr. Biochem.* 2013, 24, 1415–1422. [CrossRef] [PubMed]
7. Castaner, O.; Goday, A.; Park, Y.-M.; Lee, S.-H.; Magkos, F.; Shioy, S.-A.T.E.; Schröder, H. The gut microbiome profile in obesity: A systematic review. *Int. J. Endocrinol.* 2018, 2018. [CrossRef] [PubMed]
8. Qin, J.; Li, R.; Raes, J.; Arumugam, M.; Burgdorf, K.S.; Manichanh, C.; Nielsen, T.; Pons, N.; Levenez, F.; Yamada, T.; et al. A human gut microbial gene catalogue established by metagenomic sequencing. *Nature* 2010, 464, 59–65. [CrossRef]
9. Collado, M.C.; Rautava, S.; Aakko, J.; Isolauri, E.; Salminen, S. Human gut colonisation may be initiated in utero by distinct microbial communities in the placenta and amniotic fluid. *Sci. Rep.* 2016, 6, 23129. [CrossRef]
10. Lazar, V.; Ditu, L.M.; Pircalabioru, G.G.; Picu, A.; Petcu, L.; Cucu, N.; Chifiriuc, M.C. Gut Microbiota, Host Organism, and Diet Triadlogue in Diabetes and Obesity. *Front. Nutr.* 2019, 6, 21. [CrossRef]
11. Walker, A.W.; Ince, J.; Duncan, S.H.; Webster, L.M.; Holtrop, G.; Ze, X.; Brown, D.; Stares, M.D.; Scott, P.; Bergerat, A.; et al. Dominant and diet-responsive groups of bacteria within the human colonic microbiota. *ISME J.* 2011, 5, 220–230. [CrossRef] [PubMed]
12. Franks, P.W.; McCarthy, M.I. Exposing the exposures responsible for type 2 diabetes and obesity. *Science* 2016, 354, 69–73. [CrossRef] [PubMed]
13. Tsao, R. Chemistry and biochemistry of dietary polyphenols. *Nutrients* 2010, 2, 1231–1246. [CrossRef] [PubMed]
14. Puupponen-Pimia, R.; Aura, A.M.; Oksman-Caldentey, K.M.; Myllarinen, P.; Saarela, M.; Mattila-Sandholm, T.; Poutanen, K. Development of functional ingredients for gut health. *Trends Food Sci. Technol.* 2002, 13, 3–11. [CrossRef]
15. Bruck, J.; Holstein, J.; Glocova, I.; Seidel, U.; Geisel, J.; Kanno, T.; Kumagai, J.; Mato, N.; Sudowe, S.; Widmaier, K.; et al. Nutritional control of IL-23/Th17-mediated autoimmune disease through HO-1/STAT3 activation. *Sci. Rep.* 2017, 7, 44482. [CrossRef]
16. Zhao, H.M.; Xu, R.; Huang, X.Y.; Cheng, S.M.; Huang, M.F.; Yue, H.Y.; Wang, X.; Zou, Y.; Lu, A.P.; Liu, D.Y. Curcumin Suppressed Activation of Dendritic Cells via JAK/STAT/SOCS Signal in Mice with Experimental Colitis. *Front. Pharmacol.* 2016, 7, 455. [CrossRef]
17. Magrone, T.; Russo, M.A.; Jirillo, E. Role of Immune Cells in the Course of Central Nervous System Injury: Modulation with Natural Products. *Curr. Pharm. Des.* 2016, 22, 701–708. [CrossRef]
18. Campbell, N.K.; Fitzgerald, H.K.; Fletcher, J.M.; Dunne, A. Plant-Derived Polyphenols Modulate Human Dendritic Cell Metabolism and Immune Function via AMPK-Dependent Induction of Heme Oxygenase-1. *Front. Immunol.* 2019, 10, 345. [CrossRef]
19. Pandey, K.B.; Rizvi, S.I. Plant polyphenols as dietary antioxidants in human health and disease. *Oxid. Med. Cell. Longevo.* 2009, 2, 270–278. [CrossRef]
20. Espin, J.C.; González-Sarrías, A.; Tomás-Barberán, F.A. The gut microbiota: A key factor in the therapeutic effects of (poly)phenols. *Biochem. Pharmacol.* 2017, 139, 82–93. [CrossRef]
21. Anhê, F.F.; Roy, D.; Pilon, G.; Dudonné, S.; Matamoros, S.; Varin, T.V.; Garofalo, C.; Moine, Q.; Desjardins, Y.; Levy, E. A polyphenol-rich cranberry extract protects from diet-induced obesity, insulin resistance and intestinal inflammation in association with increased *Akkermansia* spp. population in the gut microbiota of mice. *Gut* 2015, 64, 872–883. [CrossRef] [PubMed]

22. Etxeberria, U.; Fernandez-Quintela, A.; Milagro, F.I.; Aguirre, L.; Martinez, J.A.; Portillo, M.P. Impact of polyphenols and polyphenol-rich dietary sources on gut microbiota composition. *J. Agric. Food. Chem.* 2013, 61, 9517–9533. [CrossRef] [PubMed]

23. Vajro, P.; Paolella, G.; Fasano, A. Microbiota and gut-liver axis: Their influences on obesity and obesity-related liver disease. *J. Pediatr. Gastroenterol. Nutr.* 2013, 56, 461–468. [CrossRef] [PubMed]

24. Belizario, J.E.; Faintuch, J.; Garay-Malpartida, M. Gut Microbiome Dysbiosis and Immunometabolism: New Frontiers for Treatment of Metabolic Diseases. *Mediat. Inflamm.* 2018, 2018, 2037838. [CrossRef]

25. Fernandes, R.; Viana, S.D.; Nunes, S.; Reis, F. Diabetic gut microbiota dysbiosis as an inflammaging and immunosenescence condition that fosters progression of retinopathy and nephropathy. *Biochim. Biophys. Acta Mol. Basis Dis.* 2019, 1865, 1876–1897. [CrossRef]

26. Belizario, J.E.; Napolitano, M. Human microbiomes and their roles in dysbiosis, common diseases, and novel therapeutic approaches. *Front. Microbiol.* 2015, 6, 1050. [CrossRef]

27. Thaiss, C.A.; Zmora, N.; Levy, M.; Elinav, E. The microbiome and innate immunity. *Nature* 2016, 535, 65–74. [CrossRef]

28. Brown, E.M.; Sadarangani, M.; Finlay, B.B. The role of the immune system in governing host-microbe interactions in the intestine. *Nat. Immunol.* 2013, 14, 660–667. [CrossRef]

29. Karlsson, F.H.; Fak, F.; Nookaew, I.; Tremaroli, V.; Fagerberg, B.; Petranovic, D.; Backhed, F.; Nielsen, J. Endocannabinoids protect from diet-induced obesity in mice. *Gastroenterology* 2016, 150, 1437–1449.e7. [CrossRef] [PubMed]

30. Levy, M.; Thaiss, C.A.; Elinav, E. Metabolites: Messengers between the microbiota and the immune system. *Genes Dev.* 2016, 30, 1589–1597. [CrossRef]

31. Verdam, F.J.; Fuentes, S.; de Jonge, C.; Zoetendal, E.G.; Erbil, R.; Greve, J.W.; Buurman, W.A.; de Vos, W.M.; Rensen, S.S. Human intestinal microbiota composition is associated with local and systemic inflammation in obesity. *Obesity (Silver Spring)* 2013, 21, E607–E615. [CrossRef] [PubMed]

32. Reinoso Webb, C.; Koboziev, I.; Furr, K.L.; Grisham, M.B. Protective and pro-inflammatory roles of intestinal bacteria. *Pathophysiol. Int. Soc. Pathophysiol.* 2016, 23, 67–80. [CrossRef] [PubMed]

33. Vrieze, A.; Van Nood, E.; Holleman, F.; Salojarvi, J.; Kootte, R.S.; Bartelsman, J.F.; Dallinga-Thie, G.M.; Ackermans, M.T.; Serlie, M.J.; Oozeer, R.; et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. *Gastroenterology* 2012, 143, 913–916.e7. [CrossRef] [PubMed]

34. Velloso, L.A.; Folli, F.; Saad, M.J. TLR4 at the Crossroads of Nutrients, Gut Microbiota, and Metabolic Inflammation. *Endocr. Rev.* 2015, 36, 245–271. [CrossRef]

35. Huang, S.; Rutkowski, J.M.; Snodgrass, R.G.; Ono-Moore, K.D.; Schneider, D.A.; Newman, J.W.; Adams, S.H.; Hwang, D.H. Saturated fatty acids activate TLR-mediated proinflammatory signaling pathways. *J. Lipid Res.* 2012, 53, 2002–2013. [CrossRef]

36. Jin, C.; Henao-Mejia, J.; Flavell, R.A. Innate immune receptors: Key regulators of metabolic disease progression. *Cell Metab.* 2013, 17, 873–882. [CrossRef]

37. Takeuchi, O.; Hoshino, K.; Kawai, T.; Sanjo, H.; Takada, H.; Ogawa, T.; Takeda, K.; Akira, S. Differential roles of TLR2 and TLR4 in recognition of gram-negative and gram-positive bacterial cell wall components. *Immunity* 1999, 11, 443–451. [CrossRef]

38. Blandino, G.; Inturri, R.; Lazzara, F.; Di Rosa, M.; Malaguarnera, L. Impact of gut microbiota on diabetes mellitus. *Diabetes Metab.* 2016, 42, 303–315. [CrossRef]

39. Backhed, F.; Ding, H.; Wang, T.; Hooper, L.V.; Koh, G.Y.; Nagy, A.; Semenkovich, C.F.; Gordon, J.I. The gut microbiota as an environmental factor that regulates fat storage. *Proc. Natl. Acad. Sci. USA* 2004, 101, 15718–15723. [CrossRef]

40. Ellekilde, M.; Selfjord, E.; Larsen, C.S.; Jakesevic, M.; Rune, I.; Tranberg, B.; Vogensen, F.K.; Nielsen, D.S.; Bahl, M.I.; Licht, T.R.; et al. Transfer of gut microbiota from lean and obese mice to antibiotic-treated mice. *Sci. Rep.* 2014, 4, 5922. [CrossRef]
41. Ridaura, V.K.; Faith, J.J.; Rey, F.E.; Cheng, J.; Duncan, A.E.; Kau, A.L.; Griffin, N.W.; Lombard, V.; Henrissat, B.; Bain, J.R.; et al. Gut microbiota from twins discordant for obesity modulate metabolism in mice. *Science* **2013**, *341*, 1241214. [CrossRef] [PubMed]

42. Ding, S.; Chi, M.M.; Scull, B.P.; Rigby, R.; Schwerbrock, N.M.; Magness, S.; Jobin, C.; Lund, P.K. High-fat diet: Bacteria interactions promote intestinal inflammation which precedes and correlates with obesity and insulin resistance in mouse. *PLoS ONE* **2010**, *5*, e12191. [CrossRef] [PubMed]

43. Round, J.L.; Mazmanian, S.K. The gut microbiota shapes intestinal immune responses during health and disease. *Nat. Rev. Immunol.* **2009**, *9*, 313–323. [CrossRef] [PubMed]

44. Pandiyan, P.; Bhaskaran, N.; Zou, M.; Schneider, E.; Jayaraman, S.; Huehn, J. Microbiome Dependent Regulation of Tregs and Th17 Cells in Mucoса. *Front. Immunol.* **2019**, *10*, 426. [CrossRef] [PubMed]

45. Laukens, D.; Brinkman, B.M.; Raes, J.; De Vos, M.; Vandenberghe, P. Heterogeneity of the gut microbiome in mice: Guidelines for optimizing experimental design. *FEMS Microbiol. Rev.* **2016**, *40*, 117–132. [CrossRef]

46. Fritz, J.V.; Desai, M.S.; Shah, P.; Schneider, J.G.; Wilmes, P. From meta-omics to causality: Experimental models for human microbiome research. *Microbiome* **2013**, *1*, 14. [CrossRef] [PubMed]

47. Kennedy, E.A.; King, K.Y.; Baldridge, M.T. Mouse Microbiota Models: Comparing Germ-Free Mice and Antibiotics Treatment as Tools for Modifying Gut Bacteria. *Front. Physiol.* **2018**, *9*, 1534. [CrossRef]

48. Bowey, E.; Adlercreutz, H.; Rowland, I. Metabolism of isoflavones and lignans by the gut microflora: A study in germ-free and human flora associated rats. *Food. Chem. Toxicol. Int. J. Publ. Br. Ind. Biol. Res. Assoc.* **2003**, *41*, 631–636. [CrossRef]

49. Nielsen, D.S.; Krych, L.; Buschard, K.; Hansen, C.H.; Hansen, A.K. Beyond genetics. Influence of dietary factors and gut microbiota on type 1 diabetes. *FEBS Lett.* **2014**, *588*, 4234–4243. [CrossRef]

50. Reyes, A.; Wu, M.; McNulty, N.P.; Rohwer, F.L.; Gordon, J.I. Gnotobiotic mouse model of phage-bacterial host dynamics in the human gut. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 20236–20241. [CrossRef]

51. Mejia-Leon, M.E.; Petrosino, J.F.; Ajami, N.J.; Dominguez-Bello, M.G.; de la Barca, A.M. Fecal microbiota imbalance in Mexican children with type 1 diabetes. *Sci. Rep.* **2014**, *4*, 3814. [CrossRef] [PubMed]

52. Murri, M.; Leiva, I.; Gomez-Zumaquero, J.M.; Tinañones, F.J.; Cardona, F.; Sorigué, F.; Queipo-Ortuno, M.I. Gut microbiota in children with type 1 diabetes differs from that in healthy children: A case-control study. *BMC Med.* **2013**, *11*, 46. [CrossRef] [PubMed]

53. Brown, C.T.; Davis-Richardson, A.G.; Giongo, A.; Gano, K.A.; Crabb, D.B.; Mukherjee, N.; Casella, G.; Drew, J.C.; Ilonen, J.; Knip, M.; et al. Gut microbiome metagenomics analysis suggests a functional model for the development of autoimmunity for type 1 diabetes. *PLoS ONE* **2011**, *6*, e25792. [CrossRef] [PubMed]

54. Vaarala, O.; Atkinson, M.A.; Neu, J. The “perfect storm” for type 1 diabetes: The complex interplay between intestinal microbiota, gut permeability, and mucosal immunity. *Diabetes* **2008**, *57*, 2555–2562. [CrossRef] [PubMed]

55. Knip, M.; Virtanen, S.M.; Becker, D.; Dupre, J.; Krischer, J.P.; Akerblom, H.K.; Group, T.S. Early feeding and risk of type 1 diabetes: Experiences from the Trial to Reduce Insulin-dependent diabetes mellitus in the Genetically at Risk (TRIGR). *Am. J. Clin. Nutr.* **2011**, *94*, 1814S–1820S. [CrossRef]

56. Rooks, M.G.; Garrett, W.S. Gut microbiota, metabolites and host immunity. *Nat. Rev. Immunol.* **2016**, *16*, 341–352. [CrossRef]

57. Ostaff, M.J.; Stange, E.F.; Wehkamp, J. Antimicrobial peptides and gut microbiota in homeostasis and pathology. *EMBO Mol. Med.* **2013**, *5*, 1465–1483. [CrossRef]

58. Abubucker, S.; Segata, N.; Goll, J.; Schubert, A.M.; Izard, J.; Cantarel, B.L.; Rodriguez-Mueller, B.; Zucker, J.; Thiagarajan, M.; Henrissat, B.; et al. Metabolic reconstruction for metagenomic data and its application to the human microbiome. *PLoS Comput. Biol.* **2012**, *8*, e1002358. [CrossRef]

59. Pornputtapong, N.; Nookaew, I.; Nielsen, J. Human metabolic atlas: An online resource for human metabolism. *Database J. Biol. Databases Curation* **2015**, *2015*, bav068. [CrossRef]

60. Honda, K.; Littman, D.R. The microbiota in adaptive immune homeostasis and disease. *Nature* **2016**, *535*, 75–84. [CrossRef] [PubMed]

61. McDermott, A.J.; Huffnagle, G.B. The microbiome and regulation of mucosal immunity. *Immunology* **2014**, *142*, 24–31. [CrossRef] [PubMed]

62. Kau, A.L.; Ahern, P.P.; Griffin, N.W.; Goodman, A.L.; Gordon, J.I. Human nutrition, the gut microbiome and the immune system. *Nature* **2011**, *474*, 327–336. [CrossRef] [PubMed]
63. Ohira, H.; Tsutsui, W.; Fujioka, Y. Are Short Chain Fatty Acids in Gut Microbiota Defensive Players for Inflammation and Atherosclerosis? J. Atheroscler. Thromb. 2017, 24, 660–672. [CrossRef] [PubMed]
64. Li, M.; van Esch, B.C.; Henricks, P.A.; Folkerts, G.; Garssen, J. The anti-inflammatory effects of short chain fatty acids on lipopolysaccharide-or tumor necrosis factor α-stimulated endothelial cells via activation of GPR41/43 and inhibition of HDACs. Front. Pharmacol. 2018, 9, 533. [CrossRef]
65. Wang, L.L.; Guo, H.H.; Huang, S.; Feng, C.L.; Han, Y.X.; Jiang, J.D. Comprehensive evaluation of SCFA production in the intestinal bacteria regulated by berberine using gas-chromatography combined with polymerase chain reaction. J. Chromatogr. B Anal. Technol. Biomed. Life Sci. 2017, 1057, 70–80. [CrossRef]
66. Hernandez, M.A.G.; Canfora, E.E.; Jocken, J.W.E.; Blaak, E.E. The Short-Chain Fatty Acid Acetate in Body Weight Control and Insulin Sensitivity. Nutrients 2019, 11, 1943. [CrossRef]
67. Gao, Z.; Yin, J.; Zhang, J.; Ward, R.E.; Martin, R.J.; Lefevre, M.; Cefalu, W.T.; Ye, J. Butyrate improves insulin sensitivity and increases energy expenditure in mice. Diabetes 2009, 58, 1509–1517. [CrossRef]
68. Jager, S.; Handschin, C.; St-Pierre, J.; Spiegelman, B.M. AMP-activated protein kinase (AMPK) action in skeletal muscle via direct phosphorylation of PGC-1α. Proc. Natl. Acad. Sci. USA 2007, 104, 12017–12022. [CrossRef]
69. Lin, J.; Yin, J.; Zhang, J.; Ward, R.E.; Martin, R.J.; Lefevre, M.; Cefalu, W.T.; Ye, J. Butyrate improves insulin sensitivity and increases energy expenditure in mice. Diabetes 2009, 58, 1509–1517. [CrossRef]
70. Ge, H.; Li, X.; Weiszmann, J.; Wang, P.; Baribault, H.; Chen, J.L.; Tian, H.; Li, Y. Activation of G protein-coupled receptor 43 in adipocytes leads to inhibition of lipolysis and suppression of plasma free fatty acids. Endocrinology 2008, 149, 4519–4526. [CrossRef]
71. Lin, H.V.; Frassetto, A.; Kowalik, E.J., Jr.; Nawrocki, A.R.; Lu, M.M.; Kosinski, J.R.; Hubert, J.A.; Szeto, G.; Yao, X.; Forrest, G.; et al. Butyrate and propionate protect against diet-induced obesity and regulate gut hormones via free fatty acid receptor 3-independent mechanisms. PLoS ONE 2012, 7, e35240. [CrossRef] [PubMed]
72. Kondo, T.; Kishi, M.; Fushimi, T.; Kaga, T. Acetic acid upregulates the expression of genes for fatty acid oxidation enzymes in liver to suppress body fat accumulation. J. Agric. Food Chem. 2009, 57, 5982–5986. [CrossRef] [PubMed]
73. Larraufie, P.; Martin-Gallausiaux, C.; Lapaque, N.; Dore, J.; Gribble, F.M.; Reimann, F.; Blottiere, H.M. SCFAs strongly stimulate PYY production in human enteroendocrine cells. Sci. Rep. 2018, 8, 74. [CrossRef] [PubMed]
74. Delzenne, N.M.; Cani, P.D.; Daubioul, C.; Neyrinck, A.M. Impact of inulin and oligofructose on gastrointestinal peptides. Br. J. Nutr. 2005, 93 (Suppl. 1), S157–S161. [CrossRef] [PubMed]
75. Samuel, B.S.; Shaito, A.; Motoike, T.; Rey, F.E.; Backhed, F.; Manchester, J.K.; Hammer, R.E.; Williams, S.C.; Crowley, J.; Yanagisawa, M.; et al. Effects of the gut microbiota on host adiposity are modulated by the short-chain fatty-acid binding G protein-coupled receptor, Gpr41. Proc. Natl. Acad. Sci. USA 2008, 105, 16767–16772. [CrossRef] [PubMed]
76. Steinert, R.E.; Feinle-Bisset, C.; Asarian, L.; Horowitz, M.; Beglinger, C.; Geary, N.; Ghrelin, C.C.K. GLP-1, GIP, peptide YY, ghrelin, adiponectin and tumour necrosis factor-α. Br. J. Nutr. 2010, 103, 460–466. [CrossRef] [PubMed]
82. Christiansen, C.B.; Gabe, M.B.N.; Svendsen, B.; Dragsted, L.O.; Rosenkilde, M.M.; Holst, J.J. The impact of short-chain fatty acids on GLP-1 and PYY secretion from the isolated perfused rat colon. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2018**, *315*, G53–G65. [CrossRef] [PubMed]

83. Heiss, C.N.; Olofsson, L.E. Gut Microbiota-Dependent Modulation of Energy Metabolism. *J. Innate Immun.* **2018**, *10*, 163–171. [CrossRef] [PubMed]

84. Le Chatelier, E.; Nielsen, T.; Qin, J.; Pritfi, E.; Hildebrand, F.; Falony, G.; Almeida, M.; Arumugam, M.; Bato, J.M.; Kennedy, S.; et al. Richness of human gut microbiome correlates with metabolic markers. *Nature* **2013**, *500*, 541–546. [CrossRef]

85. Liou, A.P.; Paziuk, M.; Luevano, J.M., Jr.; Machineni, S.; Turnbaugh, P.J.; Kaplan, L.M. Conserved shifts in the gut microbiota due to gastric bypass reduce host weight and adiposity. *Sci. Transl. Med.* **2013**, *5*, 178ra141. [CrossRef]

86. Hong, Y.H.; Nishimura, Y.; Hishikawa, D.; Tsuzuki, H.; Gotoh, C.; Choi, K.C.; Feng, D.D.; Chen, C.; Lee, H.G.; et al. Acetate and propionate short chain fatty acids stimulate adipogenesis via GPCR43. *Endocrinology* **2005**, *146*, 5092–5099. [CrossRef]

87. Zaibi, M.S.; Stocker, C.J.; O’Dowd, J.; Davies, A.; Bellahcene, M.; Cawthorne, M.A.; Brown, A.J.; Smith, D.M.; Arch, J.R. Roles of GPR41 and GPR43 in leptin secretory responses of murine adipocytes to short chain fatty acids. *FEBS Lett.* **2010**, *584*, 2381–2386. [CrossRef]

88. Maslowski, K.M.; Vieira, A.T.; Ng, A.; Kranich, J.; Sierro, F.; Yu, D.; Schilter, H.C.; Rolph, M.S.; Mackay, F.; Artis, D.; et al. Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43. *Nature* **2009**, *461*, 1282–1286. [CrossRef]

89. Arpaia, N.; Campbell, C.; Fan, X.; Dikiy, S.; van der Weeken, J.; deRoos, P.; Liu, H.; Cross, J.R.; Pfeffer, K.; Coffer, P.; et al. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. *Nature* **2013**, *504*, 451–455. [CrossRef]

90. Pingitore, A.; Chambers, E.S.; Hill, T.; Maldonado, I.R.; Liu, B.; Bewick, G.; Morrison, D.J.; Preston, T.; Wallis, G.A.; Tedford, C.; et al. The diet-derived short chain fatty acid propionate improves beta-cell function in humans and stimulates insulin secretion from human islets in vitro. *Diabetes Obes. Metab.* **2017**, *19*, 257–265. [CrossRef]

91. Chambers, E.S.; Viardot, A.; Psichas, A.; Morrison, D.J.; Murphy, K.G.; Zac-Varghese, S.E.; MacDougall, K.; Preston, T.; Tedford, C.; Finlayson, G.S.; et al. Effects of targeted delivery of propionate to the human colon on appetite regulation, body weight maintenance and adiposity in overweight adults. *Gut* **2015**, *64*, 1744–1754. [CrossRef] [PubMed]

92. Marino, E.; Richards, J.L.; McLeod, K.H.; Stanley, D.; Yap, Y.A.; Knight, J.; McKenzie, C.; Kranich, J.; Oliveira, A.C.; Rossello, F.; et al. Gut microbial metabolites limit the frequency of autoimmune T cells and protect against type 1 diabetes. *Nat. Immunol.* **2017**, *18*, 552–562. [CrossRef] [PubMed]

93. Chen, L.; Sun, M.; Wu, W.; Yang, W.; Huang, X.; Xiao, Y.; Ma, C.; Xu, L.; Yao, S.; Liu, Z.; et al. Microbiota Metabolite Butyrate Differentially Regulates Th1 and Th17 Cells’ Differentiation and Function in Induction of Colitis. *Inflamm. Bowel Dis.* **2019**, *25*, 1450–1461. [CrossRef] [PubMed]

94. Schulthess, J.; Pandey, S.; Capitani, M.; Rue-Albrecht, K.C.; Arnold, I.; Franchini, F.; Chomka, A.; Iltot, N.E.; Johnston, D.G.W.; Pires, E.; et al. The Short Chain Fatty Acid Butyrate Imprints an Antimicrobial Program in Macrophages. *Immunity* **2019**, *50*, 432–445.e7. [CrossRef]

95. Yuan, X.; Wang, L.; Bhat, O.M.; Lohner, H.; Li, P.L. Differential effects of short chain fatty acids on endothelial Nlrp3 inflammasome activation and neointima formation: Antioxidant action of butyrate. *Redox. Biol.* **2018**, *16*, 21–31. [CrossRef]

96. Xiao, T.; Wu, S.; Yan, C.; Zhao, C.; Jin, H.; Yan, N.; Xu, J.; Wu, Y.; Li, C.; Shao, Q.; et al. Butyrate upregulates the TLR4 expression and the phosphorylation of MAPks and Nk-kappaB in colon cancer cell in vitro. *Oncol. Lett.* **2018**, *16*, 4439–4447. [CrossRef]

97. Gabay, C.; Dreyer, M.; Pellegrinelli, N.; Chicheportiche, R.; Meier, C.A. Leptin directly induces the secretion of interleukin 1 receptor antagonist in human monocytes. *J. Clin. Endocrinol. Metab.* **2001**, *86*, 783–791. [CrossRef]

98. Santos-Alvarez, J.; Gobena, R.; Sanchez-Margalet, V. Human leptin stimulates proliferation and activation of human circulating monocytes. *Cell. Immunol.* **1999**, *194*, 6–11. [CrossRef]

99. Yoon, M.S. The Emerging Role of Branched-Chain Amino Acids in Insulin Resistance and Metabolism. *Nutrients* **2016**, *8*, 405. [CrossRef]
100. Amorim Franco, T.M.; Blanchard, J.S. Bacterial Branched-Chain Amino Acid Biosynthesis: Structures, Mechanisms, and Drugability. Biochemistry 2017, 56, 5849–5865. [CrossRef]

101. Zhao, X.; Han, Q.; Liu, Y.; Sun, C.; Gang, X.; Wang, G. The Relationship between Branched-Chain Amino Acid Related Metabolomic Signature and Insulin Resistance: A Systematic Review. J. Diabetes Res. 2016, 2016, 2794591. [CrossRef] [PubMed]

102. Pedersen, H.K.; Gudmundsdottir, V.; Nielsen, H.B.; Hytölylainen, T.; Nielsen, T.; Jensen, B.A.; Forslund, K.; Hildebrand, F.; Prifiti, E.; Falony, G.; et al. Human gut microbes impact host serum metabolome and insulin sensitivity. Nature 2016, 533, 376–381. [CrossRef] [PubMed]

103. Zeng, S.L.; Li, S.Z.; Xiao, P.T.; Cai, Y.Y.; Chu, C.; Chen, B.Z.; Li, P.; Li, J.; Liu, E.H. Citrus polymethoxyflavones attenuate metabolic syndrome by regulating gut microbiome and amino acid metabolism. Sci. Adv. 2020, 6, eaax6208. [CrossRef] [PubMed]

104. Arany, Z.; Neinast, M. Branched Chain Amino Acids in Metabolic Disease. Curr. Diabetes Rep. 2018, 18, 76. [CrossRef]

105. Allin, K.H.; Tremaroli, V.; Caesar, R.; Jensen, B.A.H.; Damgaard, M.T.F.; Bahl, M.I.; Licht, T.R.; Hansen, T.H.; Nielsen, T.; Dantøft, T.M.; et al. Aberrant intestinal microbiota in individuals with prediabetes. Diabetologia 2018, 61, 810–820. [CrossRef]

106. Liu, R.; Hong, J.; Xu, X.; Feng, Q.; Zhang, D.; Gu, Y.; Shi, J.; Zhao, S.; Liu, W.; Wang, X.; et al. Gut microbiome and serum metabolome alterations in obesity and after weight-loss intervention. Nat. Med. 2017, 23, 859–868. [CrossRef]

107. Saravia, J.; Raynor, J.L.; Chapman, N.M.; Lim, S.A.; Chi, H. Signaling networks in immunometabolism. Cell Res. 2020, 30, 328–342. [CrossRef]

108. Zhenyukh, O.; Civantos, E.; Ruiz-Ortega, M.; Sanchez, M.S.; Vazquez, C.; Peiro, C.; Egidio, J.; Mas, S. High concentration of branched-chain amino acids promotes oxidative stress, inflammation and migration of human peripheral blood mononuclear cells via mTORC1 activation. Free. Radic. Biol. Med. 2017, 104, 165–177. [CrossRef]

109. Drummond, G.R.; Selemidis, S.; Griendling, K.K.; Sobey, C.G. Combating oxidative stress in vascular disease: NADPH oxidases as therapeutic targets. Nat. Rev. Drug Discov. 2011, 10, 453–471. [CrossRef]

110. Yang, K.; Blanco, D.B.; Chen, X.; Dash, P.; Neale, G.; Rosencrance, C.; Easton, J.; Chen, W.; Cheng, C.; Dhungana, Y.; et al. Metabolic signaling directs the reciprocal lineage decisions of alphabeta and gammadelta T cells. Sci. Immunol. 2018, 3, [CrossRef]

111. Chornoguz, O.; Hagan, R.S.; Haile, A.; Arwood, M.L.; Gamper, C.J.; Banerjee, A.; Powell, J.D. mTORC1 Promotes T-bet Phosphorylation to Regulate Th1 Differentiation. J. Immunol. 2017, 198, 3939–3948. [CrossRef] [PubMed]

112. Liang, Z.; Zhang, L.; Su, H.; Luan, R.; Na, N.; Sun, L.; Zhao, Y.; Zhang, X.; Zhang, Q.; Li, J.; et al. MTOR signaling is essential for the development of thyMIC epithelial cells and the induction of central immune tolerance. Autophagy 2018, 14, 505–517. [CrossRef] [PubMed]

113. Delgoffe, G.M.; Pollizzii, K.N.; Waickman, A.T.; Heikamp, E.; Meyers, D.J.; Horton, M.R.; Xiao, B.; Worley, P.F.; Powell, J.D. The kinase mTOR regulates the differentiation of helper T cells through the selective activation of signaling by mTORC1 and mTORC2. Nat. Immunol. 2011, 12, 295–303. [CrossRef] [PubMed]

114. Ikeda, K.; Kinoshita, M.; Kayama, H.; Nagamori, S.; Konypracha, P.; Unemoto, E.; Okumura, R.; Kurakawa, T.; Murakami, M.; Mikami, N.; et al. Slc3a2 Mediates Branched-Chain Amino-Acid-Dependent Maintenance of Regulatory T Cells. Cell Rep. 2017, 21, 1824–1838. [CrossRef]

115. Papathanassiu, A.E.; Ko, J.H.; Imprialou, M.; Bagnati, M.; Srivastava, P.K.; Vu, H.A.; Cucchi, D.; McAdoo, S.P.; Ananieva, E.A.; Mauro, C.; et al. BCA1 controls metabolic reprogramming in activated human macrophages and is associated with inflammatory diseases. Nat. Commun. 2017, 8, 16040. [CrossRef]

116. She, P.; Reid, T.M.; Bronson, S.K.; Vary, T.C.; Hajnal, A.; Lynch, C.J.; Hutson, S.M. Disruption of BCATm in mice leads to increased energy expenditure associated with the activation of a futile protein turnover cycle. Cell Metab. 2007, 6, 181–194. [CrossRef]

117. Passalacqua, K.D.; Zhou, T.; Washington, T.A.; Abouaita, B.H.; Sonenshein, A.L.; O’Riordan, M. The branched chain aminotransferase IlvE promotes growth, stress resistance, and pathogenesis of Listeria monocytogenes. bioRxiv 2020. [CrossRef]

118. Kaneda, T. Iso- and anteiso-fatty acids in bacteria: Biosynthesis, function, and taxonomic significance. Microbiol. Rev. 1991, 55, 288–302. [CrossRef]
119. Ran-Ressler, R.R.; Khailova, L.; Arganbright, K.M.; Adkins-Rieck, C.K.; Jouni, Z.E.; Koren, O.; Ley, R.E.; Brenna, J.T.; Dvorak, B. Branched chain fatty acids reduce the incidence of necrotizing enterocolitis and alter gastrointestinal microbial ecology in a neonatal rat model. *PloS ONE* **2011**, *6*, e29032. [CrossRef]

120. Yan, Y.; Wang, Z.; Greenwald, J.; Kothapalli, K.S.; Park, H.G.; Liu, R.; Mendralla, E.; Lawrence, P.; Wang, X.; Brenna, J.T. BCFA suppresses LPS induced IL-8 mRNA expression in human intestinal epithelial cells. *Prostaglandins Leukot. Essent. Fatty Acids* **2017**, *116*, 27–31. [CrossRef]

121. Rath, S.; Heidrich, B.; Pieper, D.H.; Vital, M. Uncovering the trimethylamine-producing bacteria of the human gut microbiota. *Microbiome* **2017**, *5*, 54. [CrossRef] [PubMed]

122. Koeth, R.A.; Wang, Z.; Levison, B.S.; Bu, J.A.; Org, E.; Sheehy, B.T.; Britt, E.B.; Fu, X.; Wu, Y.; Li, J.; et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nat. Med.* **2013**, *19*, 576–585. [CrossRef] [PubMed]

123. De Bruyne, T.; Steenput, B.; Roth, L.; De Meyer, G.R.Y.; Santos, C.N.D.; Valentova, K.; Dambrova, M.; Hermans, N. Dietary Polyphenols Targeting Arterial Stiffness: Interplay of Contributing Mechanisms and Gut Microbiome-Related Metabolism. *Nutrients* **2019**, *11*, 578. [CrossRef] [PubMed]

124. Wang, Z.; Roberts, A.B.; Bu, J.A.; Org, E.; Gu, X.; Che, N.; Charugundla, S.; Qi, H.; Wu, Y.; et al. Flavin containing monooxygenase 3 exerts broad effects on glucose and lipid metabolism and atherosclerosis. *Int. J. Mol. Sci.* **2019**, *20*, 3228. [CrossRef] [PubMed]

125. Roncal, C.; Martinez-Aguilar, E.; Orbe, J.; Ravassa, S.; Fernandez-Montero, A.; Saenz-Pipaon, G.; Ugarte, A.; Estella-Hermoso de Mendoza, A.; Rodriguez, J.A.; Fernandez-Alonso, S.; et al. Trimethylamine-N-Oxide (TMAO) Predicts CardiacArrhythmic Mortality in Peripheral Artery Disease. *Sci. Rep.* **2019**, *9*, 15580. [CrossRef] [PubMed]

126. Liu, X.; Xie, Z.; Sun, M.; Wang, X.; Li, J.; Cui, J.; Zhang, F.; Yin, L.; Huang, D.; Hou, J.; et al. Plasma trimethylamine N-oxide is associated with vulnerable plaque characteristics in CAD patients as assessed by optical coherence tomography. *Int. J. Cardiol.* **2018**, *265*, 18–23. [CrossRef]

127. De Bruyne, T.; Steenput, B.; Roth, L.; De Meyer, G.R.Y.; Santos, C.N.D.; Valentova, K.; Dambrova, M.; Hermans, N. Dietary Polyphenols Targeting Arterial Stiffness: Interplay of Contributing Mechanisms and Gut Microbiome-Related Metabolism. *Nutrients* **2019**, *11*, 578. [CrossRef] [PubMed]

128. Chen, M.L.; Yi, L.; Zhang, Y.; Zhou, X.; Ran, L.; Yang, J.; Zhu, J.D.; Zhang, Q.Y.; Mi, M.T. Resveratrol Attenuates Trimethylamine-N-Oxide (TMAO)-Induced Atherosclerosis by Regulating TMAO Synthesis and Bile Acid Metabolism via Remodeling of the Gut Microbiota. *mBio* **2016**, *7*, e02210–e02215. [CrossRef]

129. Roncal, C.; Martinez-Aguilar, E.; Orbe, J.; Ravassa, S.; Fernandez-Montero, A.; Saenz-Pipaon, G.; Ugarte, A.; Estella-Hermoso de Mendoza, A.; Rodriguez, J.A.; Fernandez-Alonso, S.; et al. Trimethylamine-N-Oxide (TMAO) Predicts CardiacArrhythmic Mortality in Peripheral Artery Disease. *Sci. Rep.* **2019**, *9*, 15580. [CrossRef] [PubMed]

130. Wang, Z.; Roberts, A.B.; Bu, J.A.; Org, E.; Charugundla, S.; Qi, H.; Wu, Y.; et al. Flavin containing monooxygenase 3 exerts broad effects on glucose and lipid metabolism and atherosclerosis. *Int. J. Mol. Sci.* **2019**, *20*, 3228. [CrossRef] [PubMed]

131. Canyelles, M.; Tondo, M.; Cedo, L.; Farras, M.; Escola-Gil, J.C.; Blanco-Vaca, F. Trimethylamine N-Oxide: The Good, the Bad and the Unknown. *Toxins (Basel)* **2016**, *8*, 326. [CrossRef] [PubMed]

132. Koeth, R.A.; Wang, Z.; Levison, B.S.; Buffa, J.A.; Org, E.; Sheehy, B.T.; Britt, E.B.; Fu, X.; Wu, Y.; Li, J.; et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nat. Med.* **2013**, *19*, 576–585. [CrossRef] [PubMed]

133. Velasquez, M.T.; Ramezani, A.; Manal, A.; Raj, D.S. Trimethylamine N-Oxide: The Good, the Bad and the Unknown. *Toxins (Basel)* **2016**, *8*, 326. [CrossRef] [PubMed]

134. Singh, G.B.; Zhang, Y.; Boini, K.M.; Koka, S. High Mobility Group Box 1 Mediates TMAO-Induced Endothelial Dysfunction. *Int. J. Mol. Sci.* **2019**, *20*, 3570. [CrossRef] [PubMed]

135. Chen, M.L.; Yi, L.; Zhang, Y.; Zhou, X.; Ran, L.; Yang, J.; Zhu, J.D.; Zhang, Q.Y.; Mi, M.T. Resveratrol Attenuates Trimethylamine-N-Oxide (TMAO)-Induced Atherosclerosis by Regulating TMAO Synthesis and Bile Acid Metabolism via Remodeling of the Gut Microbiota. *mBio* **2016**, *7*, e02210–e02215. [CrossRef]
138. Vaahtovuo, J.; Munukka, E.; Korkeamaki, M.; Luukkainen, R.; Toivanen, P. Fecal microbiota in early rheumatoid arthritis. *J. Rheumatol.* 2008, 35, 1500–1505. [CrossRef]

139. Weljie, A.M.; Dowlatabadi, R.; Miller, B.J.; Vogel, H.J.; Jirik, F.R. An inflammatory arthritis-associated metabolite biomarker pattern revealed by 1H NMR spectroscopy. *J. Proteome Res.* 2007, 6, 3456–3464. [CrossRef]

140. Wu, K.; Yuan, Y.; Yu, H.; Dai, X.; Wang, S.; Sun, Z.; Wang, F.; Fei, H.; Lin, Q.; Jiang, H.; et al. The gut microbial metabolite trimethylamine N-oxide aggravates GVHD by inducing M1 macrophage polarization in mice. *Blood* 2020, 136, 501–515. [CrossRef]

141. Chen, M.L.; Zhu, X.H.; Ran, L.; Lang, H.D.; Yi, L.; Mi, M.T. Trimethylamine-N-Oxide Induces Vascular Inflammation by Activating the NLRP3 Inflammosome Through the SIRT3-SOD2-mtROS Signaling Pathway. *J. Am. Heart Assoc.* 2017, 6. [CrossRef] [PubMed]

142. Ke, Y.; Li, D.; Zhao, M.; Liu, C.; Liu, J.; Zeng, A.; Shi, X.; Cheng, S.; Pan, B.; Zheng, L.; et al. Gut flora-dependent metabolite Trimethylamine-N-oxide accelerates endothelial cell senescence and vascular aging through oxidative stress. *Free Radic. Biol. Med.* 2018, 116, 88–100. [CrossRef] [PubMed]

143. Fatkhullina, A.R.; Peshkova, I.O.; Dzutsev, A.; Aghayev, T.; McCulloch, J.A.; Thovarai, V.; Badger, J.H.; Vats, R.; Sundd, P.; Tang, H.Y.; et al. An Interleukin-23-Interleukin-22 Axis Regulates Intestinal Microbial Homeostasis to Protect from Diet-Induced Atherosclerosis. *Immunity* 2018, 49, 943–957.e9. [CrossRef] [PubMed]

144. Haghihia, A.; Li, X.S.; Liman, T.G.; Bledau, N.; Schmidt, D.; Zimmermann, F.; Krankel, N.; Widera, C.; Sonnenschein, K.; Haghihia, A.; et al. Gut Microbiota-Dependent Trimethylamine N-Oxide Predicts Risk of Cardiovascular Events in Patients With Stroke and Is Related to Proinflammatory Monocytes. *Arterioscler. Thromb. Vasc. Biol.* 2018, 38, 2225–2235. [CrossRef]

145. Sayin, S.I.; Wahlström, A.; Felin, J.; Jantti, S.; Marschall, H.U.; Ram, K.; Angelin, B.; Hyotylainen, T.; Oresic, M.; Backhed, F. Gut microbiota regulates bile acid metabolism by reducing the levels of tauro-beta-muricholic acid, a naturally occurring FXR antagonist. *Cell Metab.* 2013, 17, 225–235. [CrossRef]

146. Swann, J.R.; Want, E.J.; Geier, F.M.; Spagou, K.; Wilson, I.D.; Sidaway, J.E.; Nicholson, J.K.; Holmes, E. Systemic gut microbial modulation of bile acid metabolism in host tissue compartments. *Proc. Natl. Acad. Sci. USA* 2011, 108 (Suppl. 1), 4523–4530. [CrossRef]

147. Wang, W.; Cheng, Z.; Wang, Y.; Dai, Y.; Zhang, X.; Hu, S. Role of Bile Acids in Bariatric Surgery. *Front. Physiol.* 2019, 10, 374. [CrossRef]

148. Jansen, P.L.; van Werven, J.; Aarts, E.; Berends, F.; Janssen, I.; Stoker, J.; Schaap, F.G. Alterations of hormonally active fibroblast growth factors after Roux-en-Y gastric bypass surgery. *Dig. Dis.* 2011, 29, 48–51. [CrossRef]

149. Wahlström, A.; Sayin, S.I.; Marschall, H.U.; Backhed, F. Intestinal Crosstalk between Bile Acids and Microbiota and Its Impact on Host Metabolism. *Cell Metab.* 2016, 24, 41–50. [CrossRef]

150. Jiang, C.; Xie, C.; Lv, Y.; Li, J.; Krausz, K.W.; Shi, J.; Brocker, C.N.; Desai, D.; Amin, S.G.; Bisson, W.H.; et al. Intestine-selective farnesoid X receptor inhibition improves obesity-related metabolic dysfunction. *Nat. Commun.* 2015, 6, 10166. [CrossRef]

151. Li, T.; Owsley, E.; Matozef, M.; Hsu, P.; Novak, C.M.; Chiang, J.Y. Transgenic expression of cholesterol 7alpha-hydroxylase in the liver prevents high-fat-diet-induced obesity and insulin resistance in mice. *Hepatology* 2010, 52, 678–690. [CrossRef]

152. Watanabe, M.; Horai, Y.; Houten, S.M.; Morimoto, K.; Sugizaki, T.; Arita, E.; Matakì, C.; Sato, H.; Tanigawara, Y.; Schoonjans, K.; et al. Lowering bile acid pool size with a synthetic farnesoid X receptor (FXR) agonist induces obesity and diabetes through reduced energy expenditure. *J. Biol. Chem.* 2011, 286, 26913–26920. [CrossRef]

153. Parseus, A.; Sommer, N.; Sommer, F.; Caeser, R.; Molinero, A.; Stahlman, M.; Greiner, T.U.; Perkins, R.; Backhed, F. Microbiota-induced obesity requires farnesoid X receptor. *Gut* 2017, 66, 429–437. [CrossRef] [PubMed]

154. Zhang, Y.; Wang, X.; Vales, C.; Lee, F.Y.; Lee, H.; Lusis, A.J.; Edwards, P.A. FXR deficiency causes reduced atherosclerosis in Ldlr-/- mice. *Arterioscler. Thromb. Vasc. Biol.* 2006, 26, 2316–2321. [CrossRef] [PubMed]

155. Watanabe, M.; Houten, S.M.; Matakì, C.; Christoflofite, M.A.; Kim, B.W.; Sato, H.; Messaddeq, N.; Harney, J.W.; Ezaki, O.; Kodama, T.; et al. Bile acids induce energy expenditure by promoting intracellular thyroid hormone activation. *Nature* 2006, 439, 484–489. [CrossRef] [PubMed]
156. Thomas, C.; Gioiello, A.; Noriega, L.; Strehle, A.; Oury, J.; Rizzo, G.; Macchiarulo, A.; Yamamoto, H.; Matakı, C.; Pruzanski, M.; et al. TGR5-mediated bile acid sensing controls glucose homeostasis. Cell Metab. 2009, 10, 167–177. [CrossRef]

157. Trabelsi, M.S.; Daoudi, M.; Pravitt, J.; Ducastel, S.; Touche, V.; Sayin, S.I.; Perino, A.; Brighton, C.A.; Sebti, Y.; Klusa, J.; et al. Farnesoid X receptor inhibits glucagon-like peptide-1 production by enteroendocrine L cells. Nat. Commun. 2015, 6, 7629. [CrossRef] [PubMed]

158. Vaughn, B.P.; Kaiser, T.; Staley, C.; Hamilton, M.J.; Reich, J.; Graiziger, C.; Singroy, S.; Kabage, A.J.; Sadowsky, M.J.; Khoruts, A. A pilot study of fecal bile acid and microbiota profiles in inflammatory bowel disease and primary sclerosing cholangitis. Clin. Exp. Gastroenterol. 2019, 12, 9–19. [CrossRef]

159. Poznyak, A.; Grechko, A.V.; Poggio, P.; Myasoedova, V.A.; Alfieri, V.; Orekhov, A.N. The Diabetes Mellitus-Atherosclerosis Connection: The Role of Lipid and Glucose Metabolism and Chronic Inflammation. Int. J. Mol. Sci. 2020, 21, 1835. [CrossRef]

160. Cao, W.; Tian, W.; Hong, J.; Li, D.; Tavares, R.; Noble, L.; Moss, S.F.; Resnick, M.B. Expression of bile acid receptors in gastric adenocarcinoma. Am. J. Physiol. Gastrointest. Liver Physiol. 2013, 304, G322–G327. [CrossRef]

161. Jia, W.; Xie, G.; Jia, W. Bile acid-microbiota crosstalk in gastrointestinal inflammation and carcinogenesis. Nat. Rev. Gastroenterol. Hepatol. 2018, 15, 111–128. [CrossRef] [PubMed]

162. West, A.C.; Jenkins, B.J. Inflammatory and non-inflammatory roles for Toll-like receptors in gastrointestinal cancer. Curr. Pharm. Des. 2015, 21, 2968–2977. [CrossRef] [PubMed]

163. Yang, H.; Zhou, H.; Zhuang, L.; Auwerx, J.; Schoonjans, K.; Wang, X.; Feng, C.; Lu, L. Plasma membrane-bound G protein-coupled bile acid receptor attenuates liver ischemia/reperfusion injury via the inhibition of toll-like receptor 4 signaling in mice. Liver Transpl. 2017, 23, 63–74. [CrossRef]

164. Gadaleta, R.M.; van Erpecum, K.J.; Oldenburg, B.; Willemse, E.C.; Renooij, W.; Murzilli, S.; Klomp, L.W.; Siersma, P.D.; Schipper, M.E.; Danese, S.; et al. Farnesoid X receptor activation inhibits inflammation and preserves the intestinal barrier in inflammatory bowel disease. Gut 2011, 60, 463–472. [CrossRef] [PubMed]

165. Gadaleta, R.M.; Oldenburg, B.; Willemse, E.C.; Spitz, M.; Murzilli, S.; Salvatore, L.; Klomp, L.W.; Siersma, P.D.; van Erpecum, K.J.; van Mil, S.W. Activation of bile salt nuclear receptor FXR is repressed by pro-inflammatory cytokines activating NF-kappaB signaling in the intestine. Biochim. Biophys. Acta 2014, 1846, 495–503. [CrossRef] [PubMed]

166. Williams, B.B.; Van Benschoten, A.H.; Cinemarcip, P.; Donia, M.S.; Zimmermann, M.; Taketani, M.; Ishihara, A.; Kashyap, P.C.; Fraser, J.S.; Fischbach, M.A. Discovery and characterization of gut microbiota decarboxylases that can produce the neurotransmitter tryptamine. Cell Host Microbe 2014, 16, 495–503. [CrossRef] [PubMed]

167. Lamas, B.; Richard, M.L.; Leducq, V.; Pham, H.P.; Michel, M.L.; Da Costa, G.; Briendeau, C.; Jegou, S.; Hoffmann, T.W.; Natividad, J.M.; et al. CARD9 impacts colitis by altering gut microbiota metabolism of tryptophan into aryl hydrocarbon receptor ligands. Nat. Med. 2016, 22, 598–605. [CrossRef] [PubMed]

168. Wlodarska, M.; Luo, C.; Kolde, R.; d’Hennezel, E.; Annand, J.W.; Diep, C.E.; Krastel, P.; Schmitt, E.K.; Siersma, P.D.; van Erpecum, K.J.; Cassat, S.; et al. CARD9 impacts colitis by altering gut microbiota metabolism of tryptophan into aryl hydrocarbon receptor ligands. Proc. Natl. Acad. Sci. USA 2019, 106, 3698–3703. [CrossRef]

169. Wikoff, W.R.; Anfora, A.T.; Liu, J.; Schultz, P.G.; Lesley, S.A.; Peters, E.C.; Siuzdak, G. Metabolomics analysis reveals large effects of gut microflora on mammalian blood metabolites. Proc. Natl. Acad. Sci. USA 2009, 106, 5169–5174. [CrossRef] [PubMed]

170. Hubbard, T.D.; Murray, I.A.; Bisson, W.H.; Lahoti, T.S.; Gowda, K.; Amin, S.G.; Patterson, A.D.; Perdew, G.H. Adaptation of the human aryl hydrocarbon receptor to sense microbiota-derived indoles. Sci. Rep. 2015, 5, 12689. [CrossRef] [PubMed]

171. Mascañfroni, I.D.; Takenaka, M.C.; Yeste, A.; Patel, B.; Wu, Y.; Kenison, J.E.; Siddiqui, S.; Basso, A.S.; Otterbein, L.E.; Pardoll, D.M.; et al. Metabolic control of type 1 regulatory T cell differentiation by AHR and HIF1-alpha. Nat. Med. 2015, 21, 638–646. [CrossRef] [PubMed]
173. Kimura, A.; Naka, T.; Nohara, K.; Fujii-Kuriyama, Y.; Kishimoto, T. Aryl hydrocarbon receptor regulates Stat1 activation and participates in the development of Th17 cells. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 9721–9726. [CrossRef] [PubMed]

174. Monteleone, I.; Rizzo, A.; Sarra, M.; Sica, G.; Sileri, P.; Biancone, L.; MacDonald, T.T.; Pallone, F.; Monteleone, G. Aryl hydrocarbon receptor-induced signals up-regulate IL-22 production and inhibit inflammation in the gastrointestinal tract. *Gastroenterology* **2011**, *141*, 237–248, e1. [CrossRef] [PubMed]

175. Tuomainen, M.; Lindstrom, J.; Lehtonen, M.; Auriola, S.; Pihlajamaki, J.; Peltonen, M.; Tuomilehto, J.; Uusitupa, M.; de Mello, V.D.; Hanhineva, K. Associations of serum indolepropionic acid, a gut microbiota metabolite, with type 2 diabetes and low-grade inflammation in high-risk individuals. *Nutr. Diabetes* **2018**, *8*, 35. [CrossRef]

176. De Mello, V.D.; Paananen, J.; Lindstrom, J.; Lankinen, M.A.; Shi, L.; Kuusisto, J.; Pihlajamaki, J.; Auriola, S.; Lehtonen, M.; Rolandsson, O.; et al. Indolepropionic acid and novel lipid metabolites are associated with a lower risk of type 2 diabetes in the Finnish Diabetes Prevention Study. *Sci. Rep.* **2017**, *7*, 46337. [CrossRef]

177. Zhao, Z.H.; Xin, F.Z.; Xue, Y.; Hu, Z.; Han, Y.; Ma, F.; Zhou, D.; Liu, X.L.; Cui, A.; Liu, Z.; et al. Indole-3-propionic acid inhibits gut dysbiosis and endotoxin leakage to attenuate steatohepatitis in rats. *Exp. Mol. Med.* **2019**, *51*, 1–14. [CrossRef]

178. Alexeev, E.E.; Lanis, J.M.; Kao, D.J.; Campbell, E.L.; Kelly, C.J.; Battista, K.D.; Gerich, M.E.; Jenkins, B.R.; Walk, S.T.; Kominsky, D.J.; et al. Microbiota-Derived Indole Metabolites Promote Human and Murine Intestinal Homeostasis through Regulation of Interleukin-10 Receptor. *Am. J. Pathol.* **2018**, *188*, 1183–1194. [CrossRef]

179. Koh, A.; Molinaro, A.; Stahlman, M.; Khan, M.T.; Schmidt, C.; Manneras-Holm, L.; Wu, H.; Carreras, A.; Jeong, H.; Olofsson, L.E.; et al. Microbially Produced Imidazole Propionate Impairs Insulin Signaling through mTORC1. *Cell* **2018**, *175*, 947–961.e17. [CrossRef]

180. Qin, Y.; Wade, P.A. Crosstalk between the microbiome and epigenome: Messages from bugs. *J. Biochem.* **2018**, *163*, 105–112. [CrossRef] [PubMed]

181. Appeldoorn, M.M.; Vincken, J.P.; Gruppen, H.; Hollman, P.C. Procyanidin dimers A1, A2, and B2 are absorbed without conjugation or methylation from the small intestine of rats. *J. Nutr.* **2009**, *139*, 1469–1473. [CrossRef] [PubMed]

182. Subramanian, L.; Youssef, S.; Bhattacharya, S.; Kenealey, J.; Polans, A.S.; van Ginkel, P.R. Resveratrol: Challenges in Translation to the Clinic—A Critical Discussion. *Clin. Cancer Res.* **2010**, *16*, 5942–5948. [CrossRef] [PubMed]

183. Manach, C.; Williamson, G.; Morand, C.; Scalbert, A.; Remesy, C. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. *Am. J. Clin. Nutr.* **2005**, *81*, S230–S242. [CrossRef] [PubMed]

184. Marin, L.; Miguélez, E.M.; Villar, C.J.; Lombó, F. Bioavailability of dietary polyphenols and gut microbiota metabolism: Antimicrobial properties. *BioMed Res. Int.* **2015**, *2015*. [CrossRef]

185. Fabris, S.; Momo, F.; Ravagnan, G.; Stevanato, R. Antioxidant properties of resveratrol and piceid on lipid peroxidation in micelles and monolamellar liposomes. *Biophys. Chem.* **2008**, *135*, 76–83. [CrossRef]

186. Zhang, Y.-Y.; Li, X.-L.; Li, T.-Y.; Li, M.-Y.; Huang, R.-M.; Li, W.; Yang, R.-L. 3-(4-Hydroxyphenyl) propionic acid, a major microbial metabolite of procyanidin A2, shows similar suppression of macrophage foam cell formation as its parent molecule. *RSC Adv.* **2018**, *8*, 6242–6250. [CrossRef]
Qian, Y.; Babu, P.V.A.; Symons, J.D.; Jalili, T. Metabolites of flavonoid compounds preserve indices of endothelial cell nitric oxide bioavailability under glucotoxic conditions. *Nutr. Diabetes* 2017, 7, e286. [CrossRef] [PubMed]

Wang, Y.; Zhou, J.; Fu, S.; Wang, C.; Zhou, B. Preventive Effects of Protocatechuic Acid on LPS-Induced Inflammatory Response in Human Gingival Fibroblasts via Activating PPAR-gamma. *Inflammation* 2015, 38, 1080–1084. [CrossRef] [PubMed]

Xi, Z.; Hu, X.; Chen, X.; Yang, Y.; Ren, J.; Wang, B.; Zhong, Z.; Sun, Y.; Yang, G.Y.; Sun, Q.; et al. Protocatechuic acid exerts protective effects via suppression of the P38/JNK- NF-kappaB signalling pathway in an experimental mouse model of intracerebral haemorrhage. *Eur. J. Pharmacol.* 2019, 854, 128–138. [CrossRef] [PubMed]

Kiss, A.K.; Granica, S.; Stolarczyk, M.; Melzig, M.F. Epigenetic modulation of mechanisms involved in inflammation: Influence of selected polyphenolic substances on histone acetylation state. *Food Chem.* 2012, 131, 1015–1020. [CrossRef]

Aura, A.M.; Martin-Lopez, P.; O’Leary, K.A.; Williamson, G.; Oksman-Caldentey, K.M.; Poutanen, K.; Santos-Buelga, C. In vitro metabolism of anthocyanins by human gut microflora. *Eur. J. Nutr.* 2005, 44, 133–142. [CrossRef]

Arques, J.L.; Rodriguez, E.; Langa, S.; Landete, J.M.; Medina, M. Antimicrobial activity of lactic acid bacteria in dairy products and gut: Effect on pathogens. *Biomed. Res. Int.* 2015, 2015, 584183. [CrossRef]

Zhang, T.; Hu, Q.; Shi, L.; Qin, L.; Zhang, Q.; Mi, M. Equol attenuates atherosclerosis in apolipoprotein E-Deficient Mice by Inhibiting Endoplasmic Reticulum Stress via Activation of Nrf2 in Endothelial Cells. *Endocrinology* 2015, 156, 157–168. [CrossRef]

Yuan, J.P.; Wang, J.H.; Liu, X. Metabolism of dietary soy isoflavones to equol by human intestinal microflora—Implications for health. *Mol. Nutr. Food. Res.* 2007, 51, 765–781. [CrossRef]

Usui, T.; Tochiya, M.; Sasaki, Y.; Muranaka, K.; Yamakage, H.; Himeno, A.; Shimatsu, A.; Inaguma, A.; Ueno, T.; Uchiyama, S.; et al. Effects of natural S-equol supplements on overweight or obesity and metabolic syndrome in the Japanese, based on sex and equol status. *Clin. Endocrinol. (Oxf.)* 2013, 78, 365–372. [CrossRef] [PubMed]

Najmanova, I.; Pourova, J.; Voprsalova, M.; Pilarova, V.; Semecky, V.; Novakova, L.; Mladenka, P. Flavonoid metabolite 3-(3-hydroxyphenyl)propionic acid formed by human microflora decreases arterial blood pressure in rats. *Mol. Nutr. Food Res.* 2016, 60, 981–991. [CrossRef] [PubMed]

Wang, J.; Bi, W.; Cheng, A.; Freire, D.; Vempati, P.; Zhao, W.; Gong, B.; Janle, E.M.; Chen, T.Y.; Ferruzzi, M.G.; et al. Targeting multiple pathogenic mechanisms with polyphenols for the treatment of Alzheimer’s disease-experimental approach and therapeutic implications. *Front. Aging Neurosci.* 2014, 6, 42. [CrossRef]

Wu, J.; Deng, Z.; Sun, M.; Zhang, W.; Yang, Y.; Zeng, Z.; Wu, J.; Zhang, Q.; Liu, Y.; Chen, Z.; et al. Polydatin protects against lipopolysaccharide-induced endothelial barrier disruption via SIRT3 activation. *Lab. Invest.* 2020, 100, 643–656. [CrossRef] [PubMed]

Rowland, I.; Gibson, G.; Heinken, A.; Scott, K.; Swann, J.; Thiele, I.; Tuohy, K. Gut microbiota functions: Metabolism of nutrients and other food components. *Eur. J. Nutr.* 2018, 57, 1–24. [CrossRef]

Mali, A.V.; Joshi, A.A.; Hegde, M.V.; Kadam, S.S. Enterolactone modulates the ERK/NF-kappaB/Snail signaling pathway in triple-negative breast cancer cell line MDA-MB-231 to revert the TGF-beta-induced epithelial-mesenchymal transition. *Cancer Biol. Med.* 2018, 15, 137–156. [CrossRef]

Tzounis, X.; Rodriguez-Mateos, A.; Vulevic, J.; Gibson, G.R.; Kwik-Uribe, C.; Spencer, J.P. Prebiotic evaluation of cocoa-derived flavanols in healthy humans by using a randomized, controlled, double-blind, crossover intervention study. *Am. J. Clin. Nutr.* 2011, 93, 62–72. [CrossRef]

Kawabata, K.; Yoshioka, Y.; Terao, J. Role of Intestinal Microbiota in the Bioavailability and Physiological Functions of Dietary Polyphenols. *Molecules* 2019, 24, 370. [CrossRef]
209. Moreno-Indias, I.; Sanchez-Alcoholado, L.; Perez-Martinez, P.; Andres-Lacueva, C.; Cardona, F.; Tinahones, F.; Queipo-Ortuno, M.I. Red wine polyphenols modulate fecal microbiota and reduce markers of the metabolic syndrome in obese patients. *Food Funct.* 2016, 7, 1775–1787. [CrossRef]

210. Correa, T.A.F.; Rogero, M.M.; Hassimotto, N.M.A.; Lajolo, F.M. The Two-Way Polyphenols-Microbiota Interactions and Their Effects on Obesity and Related Metabolic Diseases. *Front. Nutr.* 2019, 6, 188. [CrossRef]

211. Plovier, H.; Everard, A.; Druart, C.; Depommier, C.; Van Hul, M.; Geurts, L.; Chilloux, J.; Ottman, N.; Duparc, T.; Lichtenstein, L.; et al. A purified membrane protein from Akkermansia muciniphila or the pasteurized bacterium improves metabolism in obese and diabetic mice. *Nat. Med.* 2017, 23, 107–113. [CrossRef] [PubMed]

212. Everard, A.; Belzer, C.; Geurts, L.; Ouwerverkerk, J.P.; Druart, C.; Bindels, L.B.; Guiot, Y.; Derrien, M.; Muccioli, G.G.; Delzenne, N.M.; et al. Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obesity. *Proc. Natl. Acad. Sci. USA* 2013, 110, 9066–9071. [CrossRef] [PubMed]

213. Henning, S.M.; Summanen, P.H.; Lee, R.P.; Yang, J.; Finegold, S.M.; Heber, D.; Li, Z. Pomegranate ellagitannins stimulate the growth of Akkermansia muciniphila in vivo. *Anaerobe* 2017, 43, 56–60. [CrossRef]

214. Etxeberria, U.; Arias, N.; Boque, N.; Macarrulla, M.T.; Portillo, M.P.; Martinez, J.A.; Milagro, F.I. Reshaping faecal gut microbiota composition by the intake of trans-resveratrol and quercetin in high-fat sucrose diet-fed rats. *J. Nutr. Biochem.* 2015, 26, 561–566. [CrossRef] [PubMed]

215. Qiao, Y.; Sun, J.; Xia, S.; Tang, X.; Shi, Y.; Le, G. Effects of resveratrol on gut microbiota and fat storage in a mouse model with high-fat-induced obesity. *Food Funct.* 2014, 5, 1241–1249. [CrossRef]

216. Larrosa, M.; Yanez-Gascon, M.J.; Selma, M.V.; Gonzalez-Sarrias, A.; Toti, S.; Ceron, J.J.; Tomas-Barberan, F.; Dolaro, P.; Espin, J.C. Effect of a low dose of dietary resveratrol on colon microbiota, inflammation and tissue damage in a DSS-induced colitis rat model. *J. Agric. Food. Chem.* 2009, 57, 2211–2220. [CrossRef]

217. Tung, Y.C.; Lin, Y.H.; Chen, H.J.; Chou, S.C.; Cheng, A.C.; Kalyanam, N.; Ho, C.T.; Pan, M.H. Piceatannol Exerts Anti-Obesity Effects in C57BL/6 Mice through Modulating Adipogenic Proteins and Gut Microbiota. *Molecules* 2016, 21, 1419. [CrossRef] [PubMed]

218. Hijona, E.; Aguirre, L.; Perez-Matute, P.; Villanueva-Millan, M.J.; Mosqueda-Solis, A.; Hasnaoui, M.; Nepveu, F.; Senard, J.M.; Bujanda, L.; Aldamiz-Echevarria, L.; et al. Limited beneficial effects of piceatannol supplementation on obesity complications in the obese Zucker rat: Gut microbiota, metabolic, endocrine, and cardiac aspects. *J. Physiol. Biochem.* 2016, 72, 567–582. [CrossRef] [PubMed]

219. Anhé, F.F.; Nachbar, R.T.; Varin, T.V.; Trottier, J.; Dudonné, S.; Le Barz, M.; Feutry, P.; Pilon, G.; Barbier, O.; Desjardins, Y. Treatment with camu camu (*Myrciaria dubia*) prevents obesity by altering the gut microbiota and increasing energy expenditure in diet-induced obese mice. *Gut* 2019, 68, 453–464. [CrossRef]

220. Neyrinck, A.M.; Van Hee, V.F.; Bindels, L.B.; De Backer, F.; Cani, P.D.; Delzenne, N.M. Polyphenol-rich extract of pomegranate peel alleviates tissue inflammation and hypercholesterolaemia in high-fat diet-induced obese mice: Potential implication of the gut microbiota. *Br. J. Nutr.* 2013, 109, 802–809. [CrossRef]

221. Zhao, L.; Zhang, Q.; Ma, W.; Tian, F.; Shen, H.; Zhou, M. A combination of quercetin and resveratrol reduces obesity in high-fat diet-fed rats by modulation of gut microbiota. *Food Funct.* 2017, 8, 4644–4656. [CrossRef] [PubMed]

222. Huang, G.; Xu, J.; Guo, T.L. Isoflavone daidzein regulates immune responses in the B6C3F1 and non-obese diabetic (NOD) mice. *Int. Immunopharmacol.* 2019, 71, 277–284. [CrossRef] [PubMed]

223. Cheong, S.H.; Furuhashi, K.; Ito, K.; Nagaoka, M.; Yonezawa, T.; Miura, Y.; Yagasaki, K. Daidzein promotes glucose uptake through glucose transporter 4 translocation to plasma membrane in L6 myocytes and increasing energy expenditure in diet-induced obese (NOD) mice. *Front. Nutr.* 2020, 7, 153. [CrossRef] [PubMed]

224. Masumoto, S.; Terao, A.; Yamamoto, Y.; Mukai, T.; Miura, T.; Shoji, T. Non-absorbable apple procyanidins prevent obesity associated with gut microbial and metabolic changes. *Sci. Rep.* 2016, 6, 31208. [CrossRef]

225. Axling, U.; Olsson, C.; Xu, J.; Fernandez, C.; Larsson, S.; Strom, K.; Ahrens, S.; Holm, C.; Molin, G.; Berger, K. Green tea powder and Lactobacillus plantarum affect gut microbiota, lipid metabolism and inflammation in high-fat fed C57BL/6 mice. *Nutr. Metab.* 2012, 9, 105. [CrossRef]

226. Zhang, N.N.; Guo, W.H.; Hu, H.; Zhou, A.R.; Liu, Q.P.; Zheng, B.D.; Zeng, S.X. Effect of A Polyphenol-Rich Canarium album Extract on the Composition of the Gut Microbiota of Mice Fed a High-Fat Diet. *Molecules* 2018, 23, 2188. [CrossRef]
227. Roopchand, D.E.; Carmody, R.N.; Kuhn, P.; Moskal, K.; Rojas-Silva, P.; Turnbaugh, P.J.; Raskin, I. Dietary Polyphenols Promote Growth of the Gut Bacterium Akkermansia muciniphila and Attenuate High-Fat Diet-Induced Metabolic Syndrome. *Diabetes* 2015, 64, 2847–2858. [CrossRef]

228. Cowan, T.E.; Palmnas, M.S.; Yang, J.; Bomhof, M.R.; Ardell, K.L.; Reimer, R.A.; Vogel, H.J.; Shearer, J. Chronic coffee consumption in the diet-induced obese rat: Impact on gut microbiota and serum metabolomics. *J. Nutr. Biochem.* 2014, 25, 489–495. [CrossRef]

229. Anhe, F.F.; Varin, T.V.; Le Barz, M.; Pilon, G.; Dudonne, S.; Trottier, J.; St-Pierre, P.; Harris, C.S.; Lucas, M.; Lemire, M.; et al. Arctic berry extracts target the gut-liver axis to alleviate metabolic endotoxaemia, insulin resistance and hepatic steatosis in diet-induced obese mice. *Diabetologia* 2018, 61, 919–931. [CrossRef]

230. Noratto, G.D.; Garcia-Mazcorro, J.F.; Markel, M.; Martino, H.S.; Minamoto, Y.; Steiner, J.M.; Byrne, D.; Suchodolski, J.S.; Mertens-Talcott, S.U. Carbohydrate-Free Peach (*Prunus persica*) and Plum (*Prunus salicina*) Juice Affects Fecal Microbial Ecology in an Obese Animal Model. *PLoS ONE* 2014, 9, e101723. [CrossRef]

231. Fan, R.; You, M.; Toney, A.M.; Kim, J.; Giraud, D.; Xian, Y.; Ye, F.; Gu, L.; Ramer-Tait, A.E.; Chung, S. Red Raspberry Polyphenols Attenuate High-Fat Diet-Driven Activation of NLRP3 Inflammasome and its Paracrine Suppression of Adipogenesis via Histone Modifications. *Mol. Nutr. Food. Res.* 2020, 64, e1900995. [CrossRef] [PubMed]

232. Campbell, N.K.; Fitzgerald, H.K.; Malara, A.; Hambly, R.; Sweeney, C.M.; Kirby, B.; Fletcher, J.M.; Dunne, A. Naturally derived Heme-Oxygenase 1 inducers attenuate inflammatory responses in human dendritic cells and T cells: Relevance for psoriasis treatment. *Sci. Rep.* 2018, 8, 10287. [CrossRef] [PubMed]

233. Peron, G.; Sut, S.; Dal Ben, S.; Voinovich, D.; Dall’Acqua, S. Untargeted UPLC-MS metabolomics reveals multiple changes of urine composition in healthy adult volunteers after consumption of curcuma longa L. extract. *Food. Res. Int.* 2020, 127, 108730. [CrossRef] [PubMed]

234. Ozdal, T.; Sela, D.A.; Xiao, J.; Boyacioglu, D.; Chen, F.; Capanoglu, E. The Reciprocal Interactions between Polyphenols and Gut Microbiota and Effects on Bioaccessibility. *Nutrients* 2016, 8, 78. [CrossRef]

235. Clavel, T.; Fallani, M.; Lepage, P.; Levenez, F.; Mathey, J.; Rochet, V.; Serezat, M.; Sutren, M.; Henderson, G.; Bennefa-Pelissero, C.; et al. Isoflavones and functional foods alter the dominant intestinal microbiota in postmenopausal women. *J. Nutr.* 2005, 135, 2786–2792. [CrossRef]

236. Li, Z.; Henning, S.M.; Lee, R.P.; Lu, Q.Y.; Summanen, P.H.; Thames, G.; Corbett, K.; Downes, J.; Tseng, C.H.; Finegold, S.M.; et al. Pomegranate extract induces ellagitannin metabolite formation and changes stool microbiota in healthy volunteers. *Food Funct.* 2015, 6, 2487–2495. [CrossRef]

237. Moorthy, M.; Chayakunapruk, N.; Jacob, S.A.; Palanisamy, U.D. Prebiotic potential of polyphenols, its effect on gut microbiota and anthropometric/clinical markers: A systematic review of randomised controlled trials. *Trends Food Sci. Technol.* 2020, 99, 634–649. [CrossRef]

238. Dueñas, M.; Muñoz-González, I.; Cueva, C.; Jiménez-Girón, A.; Sánchez-Patán, F.; Santos-Buelga, C.; Moreno-Arribas, M.; Bartolomé, B. A survey of modulation of gut microbiota by dietary polyphenols. *BioMed Res. Int.* 2015, 2015. [CrossRef]

239. Ley, R.E.; Turnbaugh, P.J.; Klein, S.; Gordon, J.I. Microbial ecology: Human gut microbes associated with obesity. *Nature* 2006, 444, 1022–1023. [CrossRef]