



Review Article

Dietary polyphenols in lipid metabolism: A role of gut microbiome

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ABSTRACT

Polyphenols are a class of non-essential phytonutrients, which are abundant in fruits and vegetables. Dietary polyphenols or foods rich in polyphenols are widely recommended for metabolic health. Indeed, polyphenols (i.e., catechins, resveratrol, and curcumin) are increasingly recognized as a regulator of lipid metabolism in host. The mechanisms, at least in part, may be highly associated with gut microbiome. This review mainly discussed the beneficial effects of dietary polyphenols on lipid metabolism. The potential mechanisms of gut microbiome are focused on the effect of dietary polyphenols on gut microbiota compositions and how gut microbiota affect polyphenol metabolism. Together, dietary polyphenols may be a useful nutritional strategy for manipulation of lipid metabolism or obesity care.

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1. Introduction

With the development of society and economy, obesity has become an epidemic health problem worldwide (Morgen and Sørensen, 2014; Duan et al., 2019). Obesity is a result of imbalanced energy intake, energy expenditure, and host lipid metabolism (Adriouch et al., 2017). Various factors could alter lipid metabolism, such as eating habits, exercise, and gut microbiota (Amiot et al., 2016; Yin et al., 2018, 2020; Cao et al., 2019; Song et al., 2019; Li et al., 2020). The direct evidence between gut microbiota and lipid metabolism was demonstrated in germ-free mice, which kept lean even when fed with a high-fat diet (Lewis et al., 2020). Fecal microbial transplantation further confirms the

role of gut microbiota in obesity development evidenced by that the colonization of germ-free mice with an ‘obese microbiota’ accumulated more body fat than the colonization with a ‘lean microbiota’ (Zhang et al., 2019b). Accordingly, the manipulation of gut microbiota (dietary polyphenols, probiotics, fiber-rich diet, and other active compounds) may be a potential novel target to influence host lipid metabolism or treat obesity (Azad et al., 2018; Guan et al., 2019; Wang et al., 2019; Guo et al., 2020).

Polyphenols are a large family of bioactive substances from tea, fruits, vegetables, roots, seeds, cocoa, and wine. According to the non-absorbing characteristic in the small intestine, 90% to 95% dietary polyphenols reach the colon and then transform into bioactive products by gut microbiota (Ozdamar et al., 2016; Ding et al., 2019). Accumulating evidence suggested that dietary polyphenols and the microbiota-generated metabolites show positive effects on human health, including lipid metabolism (Das et al., 2016; Joseph et al., 2016). Firstly, polyphenols influence gut microbiota compositions in obese subjects, which further affect the host lipid metabolism (Anhe et al., 2019). In turn, gut microbiota metabolize polyphenols into bioactive molecules to improve the lipid regulatory bioavailability (Fig. 1). In this review, we will clarify the relationship between dietary polyphenols and lipid metabolism and discuss the potential role of gut microbiota.

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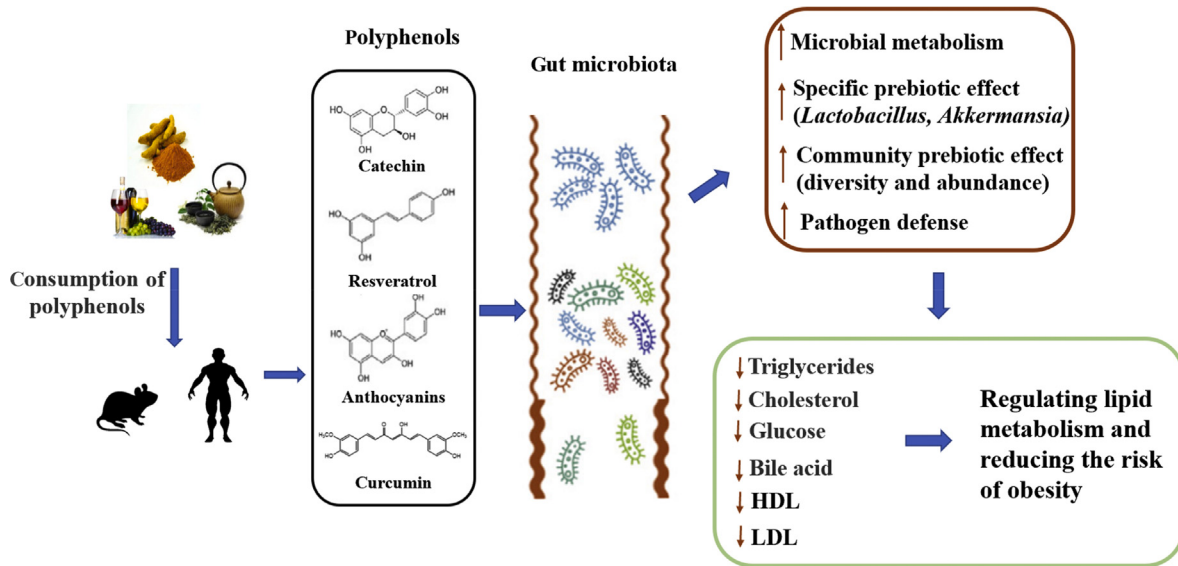


Fig. 1. Gut microbiota mediates the lipid metabolic benefits of dietary polyphenol. Dietary polyphenols are metabolized by microorganisms to produce small active molecules, which further influence gut microbes to regulate host lipid metabolism. HDL = high-density lipoprotein; LDL = low-density lipoprotein.

2. Polyphenols and lipid metabolism

Polyphenols were first discovered by Nobel Prize laureate Dr. Albert Szent-Györgyi in 1937 and named vitamin P later by other researchers (Grzybowski and Pietrzak, 2013). Vitamin P is a non-essential phytonutrient (mostly flavanones) and these compounds are now classified as polyphenols, including flavonoids, stilbenes, phenolic acids, and lignans. Flavonoids contains various bioactive substances, i.e., anthocyanins (ACN), flavanols, flavones, flavanols, flavanones, and isoflavone. Stilbenes, phenolic acids, and lignans are collectively considered as non-flavonoids polyphenols (Rasines-Perea and Teissedre, 2017; Fraga et al., 2019).

Dietary polyphenols are generally recommended for clinical benefits (Macready et al., 2014), such as metabolic disorders. Growing evidence indicated that polyphenols are involved in lipid metabolism and may prevent obesity development (Adriouch et al., 2017). For example, administration with polyphenol-rich plant extract improved plasma lipid levels and endotoxaemia, macrophage recruitment infiltration to adipose tissues, and adipose accumulation of cholesterol and cholesterol oxides in obese animals (Aires et al., 2019). In clinic trails, significant inverse correlations were observed between dietary polyphenols and body weight, body mass index, waist circumference, and waist-to-height ratio by a 5-year follow-up (Guo et al., 2017). In another randomized, double-blind, placebo-controlled clinical trial, dietary polyphenols might reduce cardiovascular disease risk and atherosclerosis via lowering triglyceride levels (Ishida et al., 2018). To conclude, a polyphenol-rich intake may lead to a healthy life through regulating lipid metabolism and reducing obesity risk.

2.1. Flavonoids and lipid metabolism

Flavonoids are a class of more than 6,000 phenolic compounds widely found in fruits, vegetables, nuts, tea, grains, cocoa, and other plants. Recently, numerous animal and human clinical trials have confirmed the lipid regulatory role of flavonoids and their preventive effects in metabolic diseases (Mulvihill et al., 2016; Rupasinghe et al., 2016; Casanova et al., 2019; Zhang et al., 2019a). In the mice model, dietary baicalin, a major flavonoid in *Scutellaria baicalensis*, accelerated lipid oxidation and prevented diet-induced

obesity (Dai et al., 2018). The intraperitoneal injection of licochalcone A also showed an improvement of lipid metabolism (triglycerides, low-density lipoprotein, and free fatty acids) in high-fat diet-induced obesity and the mechanism might be associated with NAD-dependent deacetylase sirtuin-1 (SIRT1)/5' AMP-activated protein kinase (AMPK) pathway in obese mice (Liou et al., 2018, 2019). Oxidative stress and inflammation have been widely identified in obese subjects, and antioxidant or anti-inflammatory therapeutic strategies of flavonoids are suggested to treat obesity. For example, dietary flavonoids increased the activity of serum antioxidant enzymes and downregulated pro-inflammatory indexes, which might further improve host lipid metabolism (Wu et al., 2018).

2.2. Stilbenes and lipid metabolism

Resveratrol (RSV) is a major kind of stilbene and has been extensively studied for its anti-obesity, metabolic, and glucose homeostasis effects (León et al., 2017; Ardid-Ruiz et al., 2018; Sun et al., 2018; Andrade et al., 2019; Gimeno-Mallench et al., 2019; Mohammadi and Shafiq, 2019; Springer and Moco, 2019; Yue et al., 2019). Furthermore, the interaction between gut microbiota and resveratrol has recently attracted much interest in the research community because of its potential role in preventing obesity (Chaplin et al., 2018; Zhou et al., 2019a). Dietary resveratrol modified gut microbiota compositions (resveratrol-microorganisms) and reversed the abundances of *Lactococcus*, *Clostridium XI*, *Oscillibacter*, and *Hydrogenoanaerobacterium* in obese mice (Jung et al., 2016). In addition, resveratrol reduced the level of gut microbiota-derived metabolite trimethylamine-N-oxide (TMAO, an early biomarker of adipose dysfunction) by remodeling the intestinal microbiota (Chen et al., 2016; Barrea et al., 2018). Accordingly, the transplantation of resveratrol-microorganisms into high-fat diet-fed mice promoted the development of beige adipocytes in white adipose tissue and improved lipid metabolism (Wang et al., 2020).

2.3. Phenolic acids and lipid metabolism

Phenolic acids, mainly found in grains, wine, some berries, and nuts, also play a beneficial role in regulating lipid metabolism (Tajik

et al., 2017; Naveed et al., 2018). Oral phenolic acid reversed the increase in body weight and improved lipid metabolism (i.e., triglycerides, cholesterol, high density lipoprotein, low density lipoprotein, and very low-density lipoprotein) in mice fed a high-fructose diet and the mechanism might be associated with hormones (i.e., insulin, leptin, and adiponectin) (Ibitoye and Ajiboye, 2018). Previous studies have shown that danshenolic acid regulated obesity and related metabolic diseases by reducing the expression of liver genes (i.e., sterol regulatory element binding protein 1 (*SREBP1*), fatty acid synthase (*FAS*), stearyl coenzyme A desaturase 1 (*SCD1*). Additionally, ferulic acid also improved the glucose and lipid homeostasis in high-fat diet-induced obese mice by inhibiting the protein expression of liver gluconeogenesis, such as phosphoenolpyruvate carboxylase (*PEPCK*) and glucose-6-phosphatase (*G6Pase*) (Naowaboot et al., 2016).

2.4. Lignans and lipid metabolism

Lignans mainly include secoisolariciresinol, lariciresinol, matairesinol, pinoresinol, medioresinol, and syringaresinol, and with the clarification of the new lignan structure, the property spectrum has also been broadened (Durazzo et al., 2018). The regulatory role of lignans in lipid metabolism and obesity has been widely reported (Zhang et al., 2015; Scharinger et al., 2016; Jahagirdar et al., 2018). For example, 7-hydroxymatairesinol (7-HMR), a plant-based lignan, limited the weight and fat gain and lowered serum lipids, cholesterol, and triglycerides of mice induced by a high-fructose diet (Biasiotta et al., 2018). The mechanism might be related to increasing the level of peroxisome proliferator-activated receptor α (*PPAR α) and carnitine palmitoyl transferases 1c and 2 (*Cpt1c* and *Cpt2*) (key genes involved in fatty acid oxidation) (Chan et al., 2018). More importantly, further research confirmed that the anti-hyperlipidemic effect of lignan is achieved by down-regulating the liver X receptor α (*LXR α)/*SREBP1c*/*FAS*/acetyl-CoA carboxylase (*ACC*) and *SREBP2*/3-hydroxy-3-methylglutaryl-coenzyme A reductase (*HMGCR*) signaling pathways (Sun et al., 2017).**

3. Host–microbe interplay in the lipid metabolic benefits of dietary polyphenols

Although abundant studies reported that polyphenols have antioxidant (Das et al., 2016), anti-inflammatory (Joseph et al., 2016), anti-obesity (Xu et al., 2015), antibacterial (Lu et al., 2018), and anti-cancer (Gorlach et al., 2015) benefits, because of the low bioavailability of polyphenols, a novel view points out that polyphenols interact with intestinal microbes to affect host lipid metabolism (Anhê et al., 2019). On the one hand, polyphenols affect the structure of gut microbiota, such as Firmicutes, Bacteroidetes, and Actinobacteria (Chambers et al., 2019); on the other hand, gut microbiota further improves the bioavailability of polyphenols and promotes the production of polyphenol metabolites including bile acids and short-chain fatty acids (Fernandes et al., 2014), which regulate lipid homeostasis (Fig. 1) (Castro-Barquero et al., 2018).

3.1. Impact of dietary polyphenols on microbial ecology in obese subject

The role of polyphenols in anti-obesity has been widely reviewed and the main mechanisms include causing satiety, promoting energy expenditure by stimulating brown fat-producing heat, regulating fat cells, and inhibiting lipid breakdown (Meydani and Hasan, 2010; Wang et al., 2014; Rupasinghe et al., 2016). However, recent studies also confirm the key role of polyphenols in host lipid metabolism and obesity development through regulating gut microbiota. For example, grape seed extract affected the compositions of microbiota

by increasing the relative abundances of Lachnospiraceae, unclassified Clostridiales, *Lactobacillus*, and Ruminococcaceae (Rasines-Perea and Teissedre, 2017). Resveratrol modified intestinal microbes in obese mice by reducing the relative abundances of Turicibacteraceae, *Moryella*, Lachnospiraceae, and *Akkermansia* and by increasing the relative abundances of *Bacteroides* and *Parabacteroides* (Sung et al., 2017). Meanwhile, in vitro experiments have also shown that polyphenols act as prebiotics by promoting the growth of beneficial bacteria such as *Lactobacillus* spp. and *Bifidobacterium* spp., and plum polyphenols have been reported to reduce body weight in obese rats by altering gut microbial structure by increasing *Faecalibacterium* spp., *Lactobacillus* spp., and *Bacteroides* spp. (Noratto et al., 2014). Together, dietary polyphenol intervention can regulate gut microbial ecology, making it more conducive to health by increasing the abundances of probiotics (Marchesi et al., 2016).

3.2. Microbial metabolites of dietary polyphenols

Recent studies have demonstrated the role of dietary polyphenols in the prevention of obesity and obesity-related diseases (Wang et al., 2014). However, most polyphenolic compounds escape the digestion and absorption of the small intestine, and are metabolized by microorganisms in the colon (Ozdal et al., 2016). Polyphenols are mainly hydrolyzed by the microbial enzymes, responsible for the hydrolysis release of o-glucosides and the cleavage of carbon-carbons, resulting in smaller molecules that are more active than natural compounds. Therefore, gut microbiota is highly linked to the bioavailability of polyphenols. In this review, catechins, resveratrol, curcumin, and anthocyanins will be fully introduced.

3.2.1. Catechins

Catechins are the major polyphenolic compounds in green tea, including epigallocatechin-3-gallate (EGCG), epigallocatechin (EGC), epicatechin-3-gallate, epicatechin, gallo catechins, and gallo catechin gallate (Khan and Mukhtar, 2018). EGCG is hydrolyzed to EGC and gallic acid in the first stage of metabolism and then EGC is converted to 1-(3',4',5'-trihydroxyphenyl)-3-(2'',4'',6''-trihydroxyphenyl) propan-2-ol, which is further transformed to 1-(3'-dihydroxyphenyl)-3-(2'',4'',6''-trihydroxyphenyl) propan-2-ol. In addition, a part of 1-(3'-dihydroxyphenyl)-3-(2'',4'',6''-trihydroxyphenyl) propan-2-ol is converted to 5-(3',5'-dihydroxyphenyl)-pentanoic acid and a small portion is converted to 3,5-dihydroxyphenylpropionic acid (3,5-DHPPA) (Mitchell et al., 2019). Furthermore, metabolomics analysis also revealed that EGC produces 5-(3',4',5'-trihydroxyphenyl)- γ -valerolactone and then forms 5-(3',5'-trihydroxyphenyl)- γ -valerolactone in tea polyphenols, and epicatechin is biotransformed into 5-(3',4'-dihydroxyphenyl)- γ -valerolactone. The γ -valerolactone ring of 5-(3',5'-trihydroxyphenyl)- γ -valerolactone and 5-(3',4'-dihydroxyphenyl)- γ -valerolactone could be opened through hydrolysis, yielding 4-hydroxy-5-(dihydroxyphenyl)-valeric acid. Microbial dehydroxylation reactions could further convert 4-hydroxy-5-(dihydroxyphenyl)-valeric acid to 5-(dihydroxyphenyl)-valeric acid and then to 3-hydroxyphenyl-valeric acid (Zhou et al., 2019b). Some microorganisms have been shown to participate in EGCG biotransformation, including *Enterobacter aerogenes*, *Raoultella planticola*, *Klebsiella pneumoniae* susp., *Pneumoniae*, *Bifidobacterium longum* subsp. *infantis*, *Clostridium orbiscindens*, and *Eubacterium ramulus* (Takagaki and Nanjo, 2010; Kutschera et al., 2011).

3.2.2. Resveratrol

Resveratrol is metabolized by the gut microbes in the large intestine to generate dihydroresveratrol, lunularin, and 3,4'-

dihydroxy-trans-stibene (Muhammadi and Shafiq, 2019). The analysis of 16S rRNA sequences indicated that lunularin is positively associated with higher abundances of Bacteroidetes, Actinobacteria, Verrucomicrobia, Cyanobacteria, and a lower abundance of Firmicutes (Bode et al., 2013). Importantly, new bacterial strains *Slackia equolifaciens* and *Adlercreutzia equolifaciens* are found to convert resveratrol to dihydroresveratrol (Bode et al., 2013). Resveratrol and its metabolites have widely been reported to involve in lipid metabolism and the mechanisms include: (1) inhibiting adipocyte growth by modulating a panoply of protein targets such as nuclear hormone receptor-type, nuclear factor kappa-B (NF- κ B), enolases, and sirtuins; (2) increasing thermogenesis by regulating central energy pathway signaling and protein targets (AMPK, mammalian target of rapamycin [mTOR], and protein kinase B [PKB, also known as Akt]); (3) reducing inflammation by inhibiting cyclooxygenases (COX) and quinone reductase 2 (QR2) enzymes, and activating SIRT1 (Leixuri et al., 2014; Muhammadi and Shafiq, 2019).

3.2.3. Curcumin

Due to its low bioavailability, curcumin is generally metabolized by microbiota in the colon (Di Meo et al., 2019). The curcumin metabolic pathway includes reduction, methylation, demethoxylation, hydroxylation, and acetylation by gut microorganisms, and the main products contain tetrahydrocurcumin (THC), dihydroferulic acid (DFA), and 1-(4-hydroxy-3-methoxyphenyl)-2-propanol (Tsuda, 2018; Zam, 2018). In addition, curcumin can be metabolized by *Pichia pastoris* into 4 major metabolites, such as 5-hydroxy-7-(4-hydroxy-3-methoxyphenyl)-1-(4-hydroxyphenyl) heptan-3-one, 5-hydroxy-1,7-bis (4-hydroxy-3-methoxyphenyl) heptan-3-one, 5-hydroxy-1,7-bis (4-hydroxyphenyl) heptane-3-one, and 1,7-bis (4-hydroxy-3-methoxyphenyl) heptan-3,5-diol (Zam, 2018). Several microbiota such as *Escherichia coli*, *Blautia* sp. (*mrg-pmf1*), *Bifidobacterium*, *Lactobacillus*, *Pichia anomala*, and *Bacillus megaterium dcmb-002* have often been found to be involved in the biotransformation of curcumin (Shen and Ji, 2019). Curcumin and its metabolites involve in lipid metabolism mainly by targeting the following pathways: (1) inhibiting the formation and differentiation of adipocytes by down-regulating proliferator-activated receptor γ (PPAR γ), CCAAT/enhancer-binding protein α (C/EBP α), extracellular-signal-regulated kinase (ERK), c-Jun N-terminal kinases (JNK), and p38 and activating wnt/ β -catenin and SIRT1; (2) reducing inflammation via inhibiting monocyte chemoattractant protein-1 from 3T3-L1 adipocytes and down-regulating the inflammatory transcription factors NF- κ B and activator protein-1 (AP-1); (3) promoting antioxidants by activating NFE2-related factor 2 (Nrf2) (Bradford, 2013; Zhao et al., 2017).

3.2.4. Anthocyanins

Most of anthocyanins can reach the colon and undergo various enzymatic process by microbiota such as the cleavage of the sugar moiety and the formation of anthocyanin aglycon (Khan et al., 2020), and anthocyanin aglycon can be biotransformed into simple phenolic acids by 2 bacterial enzymes (α -L-rhamnosidase and β -D-glucosidase) (Esposito et al., 2015). Then phenolic acids are further degraded into protocatechuic acid, syringic acid, vanillic acid, phloroglucinol aldehyde, phloroglucinol acid, and gallic acid (Pojer et al., 2013). The metabolic processes of anthocyanin include the cleavage of glycoside bond, the decomposition of anthocyanin heterocyclic ring, and the demethylation, which is associated with *E. ramulus* and *Clostridium saccharogumia* (Tian et al., 2019). Anthocyanins and metabolites improve obesity primarily by inhibiting lipogenesis (Jamar et al., 2017), reducing inflammation (Lee et al., 2017; Peng et al., 2019), promoting energy homeostasis (Elena et al., 2017), and improving insulin resistance (Tarun et al., 2017).

4. Conclusions

During the past decades, remarkable progress has been made in our understanding of dietary polyphenols and host lipid metabolism. In this review, we summarized the basis for the understanding of lipid metabolic benefits of dietary polyphenols and discussed the interaction between dietary polyphenols and gut microbiota, which further regulates the lipid metabolism. Despite the progress made in the understanding of dietary polyphenols, gut microbiota, and lipid metabolism over the past few years, there are still a number of prominent research avenues to be explored. For example, how dietary polyphenols shape gut microbiota and how microbiota further targets host lipid metabolism? Different polyphenols have different roles in gut microbiota, and the specific mechanisms targeting host lipid metabolism should be investigated. In addition, the effects of polyphenols in the clinic should be fully studied and the dietary guidelines of polyphenols to control the development of obesity will become more prominent. In the future, polyphenol recipe will promote a series of effective methods to guide us in maintaining healthy habits and controlling obesity.

Author contributions

Jie Ma: writing—original draft preparation, revision and investigation. Yongmin Zheng: revision. Wenjie Tang: conceptualization. Wenxin Yan and Houfu Nie: investigation. Jun Fang: supervision. Gang Liu: validation.

Conflict of interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the content of this paper.

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