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The potential role of phenolic compounds on modulating gut microbiota in obesity

REVIEW ARTICLE

The potential role of phenolic compounds on modulating gut microbiota in obesity

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Abstract

Obesity is a rising public health issue and challenge which is tightly correlated with socio-economic development paralleled with increased energy intake and sedentary behavior that subsequently cause adipose tissue accumulation. Physiological and metabolic status changes during obesity development have been suggested with low grade inflammation of gastrointestinal tract. The gut microbiota plays an essential role in regulating whole body energy metabolism and also lipid accumulation, and immunity of host. However, the detail mechanism of which the gut microbiota composition influence obesity development in humans still need deeper investigation owing to the complex pathophysiology of such disease. Recently, the consumption of phenols-rich food has been showed to have physiological function that attribute to improve gut microbiota and benefit body weight management. Here, we review the current knowledge regarding phenolic compounds that regulate the development of obesity and the importance of the axis that link dietary-induced gut microbiota change and metabolic health of host. We also discuss dietary intervention reshaping gut bacterial community to modulate obesity.

Keywords: Obesity, Gut microbiota, Phenolic compounds

Contents

1. Introduction

Obesity is a multifactorial chronic disorder, with a global prevalence over 600 million people, and it has also demonstrated a drastically increased over the past decades. According to the World Health Organization (WHO), people who have a body mass index (BMI) > 30 are defined as obesity [1]. The common pathway to develop obesity is via excessive calories consumption compared with calories burned; in modern lifestyle, increased intake of fats and sugars, and

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insufficient physical activity which could eventually lead to obesity. Obesity stimulated the secretion of pro-inflammatory cytokines, which increase the risk of developing insulin resistance and type 2 diabetes mellitus (T2DM) [2–4]. Indeed, obese adipose tissue expansion is correlated with adipocyte hypertrophy and accompanied by altering population of immune cells and elevated adipokines production [5–7]. Recent studies pay much attention on host and environmental factors which might influence energy homeostasis [4,8–10].

It is well known that dietary habits greatly influence the composition and diversity of gut microbiota which play a pivotal role in inflammation and obesity [11,12]. Although genetic variants were indeed associated with determination of body weight, the explanation of raising incidence of obesity is fairly modest. Since the evidence of lean mice received transplants from human intestinal microbiota suggested that the obese phenotype can be transfer form donor [13], the manipulation of dietary pattern to microbiota bio-function has sparked considerable interest. Bacteroidetes are able to degrade dietary polysaccharides, metabolizes dietary toxins, against enteric bacterial and particularly specialized to target resistant dietary polymers which are structural components of plants [14,15]. Therefore, diet change in intestine interact with gut microbiota could prevent against obesity and its related complications even liver disease [16–18].

Polyphenols are abundant phytochemicals ubiquitously present in plants such as fruits and vegetables, and exhibit a wild spectrum of pharmacological or nutritional properties and are known to prevent against oxidative stress and disease-related complications [18,19]. Based on the difference in chemical structure, polyphenols can be further classified in series main classes, includes phenolic acids, flavonoids, stiblins, curcuminoids, and lignans [20,21]. The bioavailable portion of nature compounds which might exert the action as a potential prebiotics for the maintenance of gut microbiota balance. The potential use of phenolic compounds help preventing obesity via increasing calorie expenditure, decrease adipogenesis, inhibit adipocyte differentiation, and regulate lipid metabolism were systemically documented [22–24]. This review offer a systemic literature related to the role of phenolic compounds in the pharmacological strategies for *in vivo*, *in vitro*, and even clinical investigation to assess the anti-obesity effect through modulation of microbiota.

2. Obesity

Fundamentally, obesity is a result of excessive fat accumulation which contributed by several factors, including long-term energy consumption, physical inactivity, metabolism, genetic makeup, medication and other environmental factors [25]. Recent studies demonstrate that excessive consumption of high-fat food represents a major environmental factor which is greatly associated with obesity related insulin resistance, glucose intolerance, and cholesterol

Fig. 1. Schematic representation of obesity and its related complication. The progression of obesity involves multiple physiological changes that may contribute to obesity related co-morbidities.

metabolism [26–28], which can contributed to the pathogenesis of obesity co-morbidities (Fig. 1). Among environmental factors, gastrointestinal microbiota diversity is believed to affect energy metabolism of host and food intake is described to shape the microbiota composition [29]. As mentioned earlier, germ-free mice with humanized gut microbiome from obese people showed an increased in body weight [30,31]; high-fat diet altered gut community, resulting in a changes of microbiome gene expression [32,33]. The adipose tissue was characterized as a passive reservoir for energy storage but also known to play a pivotal role in both autocrine and endocrine level [34–37], glucose homeostasis [38,39], dyslipidemia [40], and inflammation [41]. Obesity increased lipid production and subsequently leaded to free fatty acids released, which cause lipid peroxidation and related lipotoxicity [42]. The intrahepatic lipid accumulation was associated with upregulation of genes involved in lipid catabolism and pro-inflammatory cytokines, such as peroxisome proliferator-activated receptor gamma (PPARγ) [43] and tumor necrosis factor alpha (TNF-α). Notably, some studies suggested that inflammatory factors including TNF-α, interleukin 1α (IL-1α), interleukin 6 (IL-6), and C-reactive protein (CRP) are linked to impaired insulin resistance and low-grade chronic inflammation of gastrointestinal tract [44,45]. Studies on the gene expression of inflammatory factors have revealed that a higher inflammatory status was observed in high-fat diet feeding mice [46]. In addition, adipose tissue excess also increased reactive oxygen species (ROS) formation and free fatty acids release, and subsequently leads to the development of oxidative stress. Oxidative stress is critical to induce DNA methyltransferase 1 (DNMT1) expression and is associated with aberrant DNA methylation [46]. Dietary interventions such as calorie restriction, probiotic supplementation are emerged to modulated gut microbiota and provide valuable impact in therapeutic measurement of metabolic disorders. Recently, nature products, polyphenols have proposed to improve glucose metabolism [47], which also as potent epigenetic active antioxidants and ameliorating oxidative stress. Thus, the used of phenol-rich foods have demonstrated to reduce gut microbiota dysbiosis, improve systemic inflammatory status, and insulin signaling of diet-induced obese mice model, which shows promise as a potential strategy to alleviate obesity-associated diseases.

3. Obesity and microbiota

In this part, we will pay our attention on the role of gut microbiota in the pathogenic mechanisms of obesity. Recently, gut microbiota represent a metabolic gateway, through the interaction with host nutritional environment, particularly involved in modulation of chronic condition such as inflammation, energy imbalance and body weight increase [48,49]. Human gut microbiota is a complex ecosystem and recent evidence suggested a role of microbiota in fat metabolism.

Diet represents an instrumental factor in alternating the symbiotic relationship of mammalian gut microbiota, which deeply involved in the functions of metabolic diseases. It was suggested that the ratio of Firmicutes/Bacteroidetes represent the imbalance status of gastrointestinal tract, and served as an indicator of health condition [50]. High-sugar or high-fat diet consumption, particularly abundant in saturated fatty acids, result in increasing the relative abundance of Firmicutes species at intestinal level in mice models [13]. Data obtained in mice and humans indicated that short-term diet intervention caused a reduction in the abundance of Bacteroidetes within a single day, and these changes may result from the modulation of microbiota gene expression, altered metabolic pathway [51,52]. Similar effect was found in controlled-feeding study that high-fat/low-fiber or low-fat/high-fiber diet intervention rapidly changed gut microbiota composition within 24 h, although the enterotype change required long-term dietary alteration [53]. Moreover, a high-fat and high-sugar dietary modification did not induce obesity and obesity-associated metabolic complication in germ-free mice model [54]; other evidence from microbiota transplantation suggested that an intestinal dysbiosis significantly increase body fat accumulation and particularly insulin resistance [54,55]. These evidences reveal that the obese phenotype is transferrable via the intestinal microbiota in mice.

The direct or indirect effect of high-fat diary consumption cause increase microbiota–produced lipopolysaccharide (LPS), which is regarding as a potential mechanism that triggers the development of inflammation through toll-like receptor 4 (TLR4) dependent pathway. Studies in mice showed that 2–4 weeks consumption of high-fat diet was associated with high LPS level in plasma, which was named metabolic endotoxemia [56]. Furthermore, elevated LPS concentration is linking to reduce intestinal tight junction protein expression, subsequently lead to the lost of intestinal barrier integrity [57,58]. Although the interactions between gut microbiota and changes in intestinal epithelium integrity have been documented, the convincing evidence and prominent mechanism that coordinate these observations still needed to be further investigate.

Table 1. Summary of studies investigating the impact of obesity and associated gut microbiota dysbiosis.

Subjects	Main Finding	References
Overweight and normal-weight pregnant women	↑Bacteroides ↑Staphylococcus	[59]
Obese people assigned to FAT-R Obese people or CARB-R low calorie diet	↓Bacteroidetes ↑Firmicutes	[60]
Obese and lean twins	↑Actinobacteria ↓Bacteroidetes	[61]
ob/ob and lean ob/+ mice	↓Bacteroidetes ↑Firmicutes	[13]
C57BL6J (WT) and Fiaf −/− mice	↑Firmicutes/Bacteroidetes	[62]
Morbidly obese individuals vs. normal weight individuals	↑Prevotellaceae	[63]
Twin-pairs from UK population	↓Christensenellaceae families ↓Rikenellaceae families ↓Mollicutes class ↓Dehalobacterium genus	[64]
LifeLines-DEEP participants	↓Akkermansia genus ↓Christensenellaceae family ↓Tenericutes phylum	[65]
ob/ob mice and HF-fed male C57BL/6 mice	↓Akkermansia muciniphila	[66]

Accumulated evidences revealed that obesity is greatly correlated with the richness of gut microbiota, which may lead to the reduction the diversity and composition. Comparison of the differences in microbial composition across the human subjects, diet-induced obese mice and genetic modified animal model clearly showed the dysbiosis in the richness and diversity of gut microbiota (Table 1) [13,59–66]. Except for the evidences of dietary effects on gut microbiota that we mentioned previously, gut microbiota aberrancies appear to mediate the risk of specific disease development. Emerging studies strengthened the interplay between gut microbiota dysbiosis and obesity-related complication and identified several texa that significantly correlated with the development and pathophysiological consequences of diseases both in human subjects and animal models (Table 2) [65,67–70].

4. Phenolic compounds and microbiota

High-fat diet-fed mice as a model for the dysbiosis of gut microbiota have been well documented. Recently, the anti-obesity effect of certain phytochemicals has been explored to reverse high-fat diet-induced change on microbiota composition and intestinal physiology [71]. For instance, the imbalance between Firmicutes to Bacteriodetes is largely linked to obesity development and insulin resistance. Concerning plant secondary metabolites, polyphenols may protect against obesity-associated metabolic complications and even weight loss [72,73]. In a similar way, feeding C57BL/6J mice with high-fat diet supplemented with green tea, oolong tea, and black tea infusion for 13 weeks that increased diversity and change the community of gut microbiota, and decrease high-fat diet-induced accumulation of lipids in adipose tissue and increase in body weight [74]. Among these three types of tea, several phenolic compounds including phenolic acids, flavonols and alkaloids, which may modulated the composition of gut microbiota such as Alistipes, Rikenella, Akkermansia etc. Anthocyanins-rich fruits such as grapes and berries show promise as potential inhibitor for reducing inflammatory cytokines through nuclear factor kappa light

Table 2. Summary of studies investigating the relationship of obesity-related complication and gut microbiota profiles.

Obesity-relative complication	Subjects	Main Finding	References
Dyslipidemia	Human/LifeLines-DEEP cohort	↓Bacteroidetes phylum	[65]
Gastrointestinal abnormalities	CD and UC patients	↓Firmicutes phylum ↑Bacteroidetes phylum	[67]
Hypertension	HFD/Female SD rat	↑Firmicutes/Bacteroidetes ↓Lactobacillus genus ↑Verrucomicrobia phylum	[68]
Pulmonary abnormalities	OSAHS patients/China	↓Ruminococcaceae	[69]
Type 2 diabetes	Human/Iran	↑Lactobacillales ↓Bacteroides spp	[70]

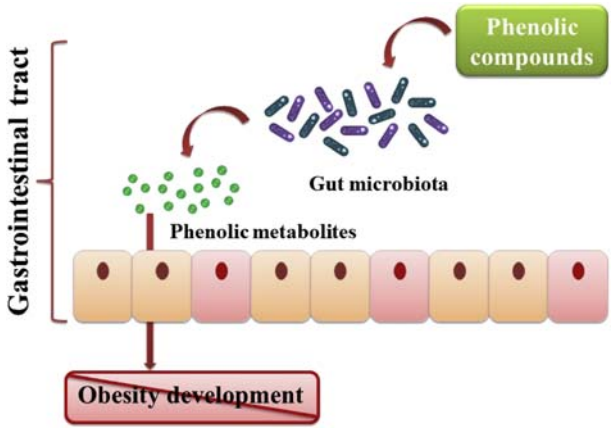


Fig. 2. Crosstalk between the obesity, gut microbiota, and phenolic compounds. The gut microbiota was emerging as a key environmental factor, producing certain secondary metabolites through digestion of phenolic compounds with the consequence of influencing obesity development.

chain enhancer of activated B cells (NF-κB) signal transduction and increase PPAR level [75]. Moreover, results of experiments in which diets-based supplement infusion given to moderate fat diet feeding mice reduced fatty acid profiles, inflammatory markers, and deleterious sulfidogenic bacteria; increase the abundance of *Akkermansia mucinophila* resides in the mucus layer of proximal colon [76]. A combination of quercetin and resveratrol dramatically prevent the development of obesity induced by high-fat diet as well as restore gut microbiota dysbiosis in rats [77]. Other lipid improving effect of betacyanins extract from red pitaya has also shown a negative regulation of Firmicutes; increase the relative abundance of Akkermansia [78].

It was reported that most of dietary polyphenols reached the large intestine, where they are extensively digested by colon microbiota (e.g Bifidobacterium) into simple phenolic compounds, such as phenolic acid. As such, they are absorbed into

Table 3. Summary of the impact of phenolic acid on anti-obesity effects.

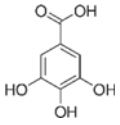
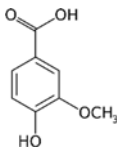
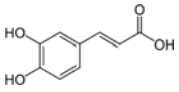
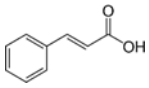
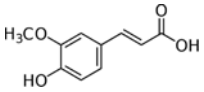
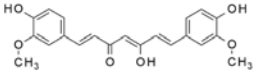
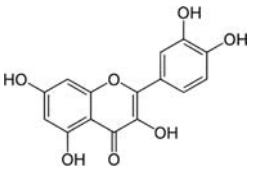
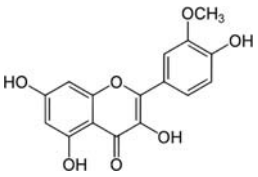
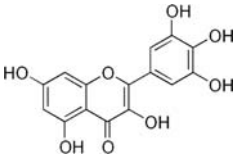
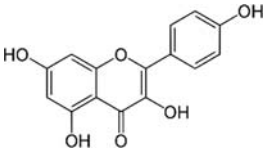
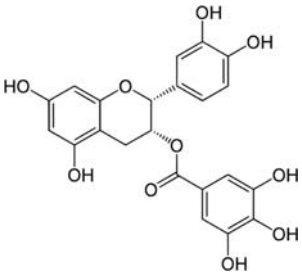
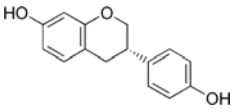
Phenolic acids	Structures	Subjects	Main Finding	References
Gallic acid		male C57BL/6 mice (HFD)	↓final body weight	[96]
Vanillic acid		male C57BL/6 mice (HFD)	↓final body weight, WAT weight, liver weight ↓liver tissue lipid size, WAT tissue lipid size ↑BAT weight ↓serum LDL/TG/cholesterol/FFA	[97]
		male *db*/*db* mice	↓final body weight, eWAT weight, iWAT weight	
		3T3-L1 cells	↑BAT weight ↓serum LDL/cholesterol ↓MDI-Induced adipogenesis	
Caffeic acid		male C57BL/6 mice (HFD)	↓final body weight ↓serum TG/cholesterol/FFA/FAS activity ↓liver TG/cholesterol	[98]
Cinnamic acid		male Rat (HFD)	↓final body weight ↓serum TG/cholesterol/LDL-C/leptin/lipase activity ↑serum HDL-C	[99]
Ferulic acid		male Swiss mice (HFD)	↓final body weight, abdominal fat weight ↓serum TG/cholesterol/leptin/amylase activity/lipase activity/insulin ↓EAT lipid size	[100]
Curcumin		3T3-L1 cells	↑p-AMPK, p-ACC ↑fatty acid oxidation	[101]
		male C57BL/6 mice (HFD)	↓final body weight, body fat weight, liver weight	

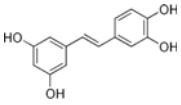
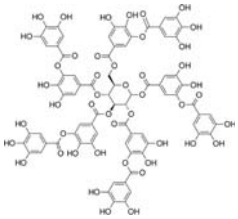
Table 4. Summary of the impact of flavonoids on anti-obesity effects.

Flavonoids	Structures	Subjects	Main Finding	References
Quercetin		male C57BL/6 mice (HFD)	↓final body weight, EAT weight, SAT weight ↓EAT adipocyte size ↓serum leptin ↑EAT p-AMPK, SIRT1 ↑BAT *Ucp1*	[102]
Isorhamnetin		3T3-L1 cells	↓3T3-L1 adipocyte differentiation ↓*PPAR-γ, C/EBP-α, Krox 20, PGC-1, Adiponetin*	[109]
Myricetin		male C57BL/6 mice (HFD)	↓final body weight, EAT weight, SAT weight, PAT weight ↓EAT adipocyte size ↓serum TG/leptin/TNF-α/insulin/MDA ↑serum adiponectin/GPX/T-AOC ↓EAT *PPARγ, C/EBPα, SREBP-1c*	[103]
Kaempferol		male C57BL/6 mice (HFD)	↓final body weight, EAT weight, VAT weight, PAT weight ↓serum TG/insulin/leptin ↓liver TG ↑liver FAS activity ↓liver PPARγ	[104]
Epicatechin		male C57BL/6 mice (HFD)	↓final body weight ↓serum TG/FFA/insulin/leptin ↓liver p-IKKα, p-JNK, PTP1B ↓EAT p-IKKα, p-JNK, PTP1B	[105]
Daidzein		male ICR mice (HFD)	↓final body weight, EAT weight, MAT weight, PAT weight, SAT weight ↓plasma cholesterol/LDL-C/FFA ↑plasma HDL-C ↓liver cholesterol/FFA	[106]

blood circulation by the portal vein that may have effect on peripheral tissue and contributed to local and systemic health [14,79]. Taken into account the phenol-derived microbial metabolites obtained from parents compounds such as epigallocatechin gallate (EGCG), chlorogenic acid, anthocyanins, and procyanidins which were reported to determine specific gut microbiota species that generates catalytic abilities to processing phenolic structure and consequently provided an antibacterial properties [80]. For example, degradation of polymers into oligomers and the gallate esters of EGCG convert into pyrogallol by decarboxylation, which is further enhancing the growth of Bifidobacterium and clostridium. From anthocyanins, gallic acid, and syringic acid are produced by Lactobacteria and Bifidobacteria that may responsible for increasing the population of Bifidobacterium species [81,82]. In summary, theses evidences revealed that the changes of microbiota upon phenolic compounds supplementation which may correlate with its biometabolites advantages.

Collectively, several features of dietary phytochemicals have been previously investigated in the

Table 5. Summary of the impact of other phenolic compounds on anti-obesity effects.

Other phenolic compounds	Structures	Subjects	Main Finding	References
Piceatannol		male C57BL/6 mice (HFD)	↓final body weight, PAT weight, RAT weight ↓PAT adipocyte size ↓serum cholesterol ↑serum HDL-C ↑liver pAMPKα, pACC ↓liver PPARγ, C/EBPα, FAS	[107]
Tannic acid		3T3-L1 cells	↓adipogenesis ↓ PPARγ, FAS	[108]

literature, including the modulation of brown and beige adipose tissue recruitment and metabolism. Hence, the phenolic compounds that are digested/absorbed by gut microbiota showed the potential effects on healthy status due to their bioactivities. Intriguingly, the bioavailable proportion is a triangular relationship between dietary ingredients, human healthy, and gut microbial ecosystem (Fig. 2). However, the precise mechanisms responsible for the metabolic improvement of bioactive compounds have not yet been clearly elucidated, and are needed further investigation.

5. Phenolic compounds and obesity

According to structure properties, phenols are further divided into phenolic acids, flavonoids, stilbenes and lignans, which are distributed in fruits and vegetables of plant sources. Biological activities of phenolic substances have been studied extensively in recent years. Numerous epidemiological studies suggest that the consumption of phenolic-rich foods may reduce the incidence of chronic diseases, including obesity and obesity-related complications such as insulin resistance, gastrointestinal abnormalities, and dyslipidaemia [83,84]. Evidence from cellular study demonstrated that certain dietary polyphenols (catechins, EGCG, resveratrol, and curcumin) reduced adipocytes viability, proliferation, and differentiation, and shows further antioxidant effect and increased lipolysis [85–87]. Moreover, tea polyphenols was demonstrated to dose dependently retard body weight gain and fat accumulation in high-fat diet induced animal model. There is also evidence of population-based cohort studies by which polyphenols contained food protect against the incident of obesity that may associated with nutrient-dense source of polyphenol intake rather than energy-dense, which eventually lead to a reduction of calorie intake. Compelling evidence elucidated a significant correlation of flavonoids between obesity and weight management [88].

Green tea catechin, such as EGCG shows strong anti-oxidant and anti-obesity effects by increasing lipolysis, promoting energy expenditure and inhibit appetite, though weight management have been proposed to be a coefficient with caffeine intake by conducting meta-analysis of cohort study [89]. Among the compounds of plants, including gingernone A, quercetin, piceatannol, and cinnamon polyphenol extract has been described as suppressor to adipogenesis, inhibited adipose tissue inflammation through modulation of signaling pathway in high-fat diet-induced obese animal model [90–93]. Recently, microRNA (miRNAs) are found to closely correlate with obesity related inflammatory response through the regulation of miR-221, miR-222, and miR-155 and subsequently increased IL-6 and TNF-α expression [94]. Similar effects appear to be present for proanthocyanidins extracts also demonstrated to have inhibitory effects on lipogenesis by suppressing the hepatic lipid regulatory miR-122 in obese rat [95].

Although the anti-inflammatory and antioxidant activities of intervention studies suggest prevention effect related to obesity in phenols compounds consumption, they must be complete understanding in the maintenance of health status and beneficial level of intake. Excepted for these evidences mentioned before, Tables 3–5 categorizing studies based on phenolic acid, flavonoids, and other

phenolics that showed an anti-obesity effect and involved several signal transductions and elicit cellular responses, subsequently lead to body weight loss [96–109]. Although such phenol-base studies have wildly investigated, the dose variation and treatment frequency in-vivo and in-vitro still needed to be further confirmed.

6. Conclusion

This narrative review showed a comprehensive view of the preventive role of phenolic compounds in the obesity development through modulating gut microbiota. Dietary habit and modest lifestyle play a crucial role for the prevention and management of obesity. Growing evidences suggested the role of dietary change and secondary lifestyle in obesity prevention. Although the energy restriction is the most common way to manage obesity, bioactive compounds in native plants, such as phenols, shows its antiobesity properties. There is substantial evidence to support the effects of gut microbiota composition for the catabolism and absorption of bio-metabolites derived from dietary phenols. Moreover, the overall composition of microbiota at baseline might modulate gut microbiota diversity after dietary intervention. Studies *in vitro* and *in vivo* have used to reveal the benefit effects of phenolic compound amount dietary patterns as well as regulated gut microbiota ecology. Concerning the multitude of phenolic compounds, with its structure complexity, resident of absorption and catalytic roles in gut microbiota that make it need deeper insight into detail mechanism, and further human clinical trial are needed to elucidate the safety and health-promoting implications.

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Conflict of interest

The authors declare that no conflicts of interest exist.

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