Review Article

Contribution of anthocyanin-rich foods in obesity control through gut microbiota interactions

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Abstract

Obesity is characterized by low-grade inflammation and a number of metabolic disorders. Distal gut microbes' content (microbiota) is not yet fully understood but evidence shows that it is influenced by internal and external factors that modulate its composition and function. The evidence that gut microbiota composition can differ between healthy and obese individuals, as well as for those who maintain specific dietary habits, has led to the study of this environmental factor as a key link between the pathophysiology of obesity and gut microbiota. Data obtained about the role of anthocyanins (ACNs) in microbiota may lead to different strategies to manipulate bacterial populations and promote health. Anthocyanins have been identified as modulators of gut microbiota that contribute to obesity control and these bioactive compounds should be considered to have a prebiotic action. This review addresses the relevance of knowledge about the influence of anthocyanins-rich food consumption on microbiota, and their health-promoting potential in the pathophysiology of obesity.

Keywords: *obesity; microbiota; anthocyanins; nutrition; diet*

1. Introduction

Obesity is recognized as an inflammatory disease, and hypertrophy of the adipose tissue leads to metabolic and hemodynamic dysfunction through the production of adipokines [1]. Changes in lifestyle and diet in the post-industrialized/westernized era have been argued to contribute to the increasing global incidence of obesity by altering the genetic composition and metabolic activity of intestinal bacteria, thereby leading to significant consequences in local and systemic health [2]. In this context, there is increasing interest in understanding the role of gut microbiota as an intermediary factor between environmental and food behavior and its impact on the central nervous system [3]. Microorganisms in the large intestine play an important physiological role in vital processes such as digestion, vitamin synthesis, and metabolism [4]. The complex interaction between diet and gut microbiota may contribute to an individual's overall health and the incidence of chronic disorders such as obesity [5]. Dietary composition, for example, fatty acids, consumption of artificial sweeteners, and dietary emulsifiers alters microbiota composition and can contribute to inflammatory processes, weight gain, adiposity, and metabolic disorders [6].

On the other hand, fruit and vegetable-based diets with antioxidant, anti-inflammatory, anticarcinogenic, anti-adipogenic, and antidiabetic activity, particularly anthocyanin (ACNs)-rich diets, have been recommended to reduce the potential development of chronic diseases. ACNs are flavonoids in fruits and vegetables that render them vivid red to blue in color and they are abundant in the human diet. With more than 700 ACNs already identified in nature, they are the primary polyphenols in berries, such as blackcurrants, black elderberries, blackberries, bilberries, whortleberries, blueberries, açai berries, and juçara berries [7–10]. ACN derivatives have differing aglycone (anthocyanidin, *i.e.*, cyanidin, delphinidin, malvidin, peonidin, pelargonidin, and

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petunidin) and glycone moieties (attaches to sugar residues, such as glucose, xylose, galactose, arabinose, and rhamnose) [11]. There are also differences in the position and number of hydroxyl groups, degree of methylation, and type and number of aliphatic or aromatic acids (*p*-coumaric, caffeic, and ferulic acid) [12], with cyanidin-3-glucoside (Cy-3-glu) being the most abundant ACN in plants [11].

Because of their healthy biological effects, it has been demonstrated that ACNs and their metabolites have preventive properties against body fat accumulation [13] and are potent modulators of inflammatory processes that seem to attenuate the lipopolysaccharides (LPS)-induced nuclear factor-kappa B (NF-κB) translocation to the nucleus cellular and mediate inflammatory responses [14–16]. ACNs are associated with beneficial changes in the gut microbiota as they might promote intestinal colonization by specific groups of bacteria, particularly *Bifidobacterium* spp., *Lactobacillus* spp., and *Akkermansia muciniphila* [10,17–20]. These bacteria contribute to the overall health of an individual as they participate in the activation and absorption of provitamins and phenolic compounds, enhance gut barrier function, increase mucus secretion, and modulate lipid metabolism and intestinal immune response through cytokine stimulus [21,22]. These evidences confer a prebiotic action to ACNs [10,23].

This review summarizes the current knowledge concerning health benefits and obesity control characteristics associated with the consumption of ACNs and microbiota interactions.

2. Anthocyanins and Gut Microbiota Modulation

Different polyphenols have been suggested to affect the viability of colonic bacterial groups, implying that dietary modulation with polyphenols may play a role in reshaping the gut microbial community and enhance host/microbe interaction to provide beneficial effects such as weight loss [10]. There is broad agreement that dietary polyphenols, in particular ACNs, have the ability to modulate colonic bacteria growth [24], which may play a role in the control of several parameters involved in the development of metabolic diseases associated with obesity [25].

Several studies have shown evidence of a wide range of health-promoting characteristics of ACN-rich foods, including protection against weight gain and metabolic disorders observed with a high-fat diet [15,23,26,27]; reduction in the risk of several chronic diseases, such as type 2 diabetes and cardiovascular diseases [15]; improvement in lipid profiles, inflammatory markers, and immunoregulatory cytokines; and reduction in the membrane component of gram-negative bacteria, such as lipopolysaccharides (LPS) which induce NF-κB transactivation in humans and animals [28–32].

To achieve these health benefits, ACN–gut microbiota interactions should be considered to understand their biological functions. The dichotomy between the biotransformation of ACNs into a potentially more bioactive, low molecular weight metabolite [33], and modulation of the gut microbiota composition by ACNs contributes to positive health outcomes [34].

ACNs have a low bioavailability, and it is estimated that only 5%–10% of the total polyphenol intake is absorbed in the small intestine [22]. The food matrix can also influence phenolic compound bioavailability during digestion [35]. Moreover, most dietary ACNs arrive intact at the colon and may interact with the microbiota to be biotransformed and metabolized before being absorbed across the intestinal mucosa [10]. This interaction can involve hydrolysis, demethylation, reduction, decarboxylation, dehydroxylation, or isomerization of these compounds into simpler components that modulate absorption and biological activity [33]. The first step in ACN bacterial hydrolysis involves cleavage of the sugar moiety leading to the formation of ACN aglycon, and the second phase includes degradation into simple phenolic acids by the activities of two bacterial enzymes, in particular α-L-rhamnosidase and β-D-glucosidase, in the small intestine [36,37].

The degradation of phenolic acids by enteric bacterial or chemical conversions may produce other metabolites, including protocatechuic acid, syringic acid, vanillic acid, phloroglucinol aldehyde, phloroglucinol acid, and gallic acid [31,37]. These acidic metabolites are probably absorbed through monocarboxylic acids transported by epithelial cells [10]. The low level of oxygen in the small and particularly, the large intestine should also be considered because low oxygen may protect the ACN structure. The concentration of bacteria in the small intestine can be expected to increase distally, thus increasing the susceptibility of microbial-mediated catabolism of ACNs [38].

It is considered that gut microbiota can increase the bioavailability of the phenolic content of food and quadruple its antioxidant activity [22,39]. ACNs and metabolites concurrently formed in the intestine have the ability to promote and inhibit the growth of bacterial groups [18]. ACNs can exert an antimicrobial activity with inhibitory effects on the growth of a wide range of human pathogenic bacteria, both gram-negative (*Citrobacter freundii*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Salmonella enterica* ser. *typhimurium*) and gram-positive (*Listeria monocytogenes*, *Staphylococcus aureus*, *Bacillus subtilis*, and *Enterococcus faecalis*). Mechanisms underlying ACN activity include both membrane and intracellular interactions of these compounds [40], such as inducing the release of LPS molecules from the outer membrane of gram-negative bacteria [10].

ACNs are generally active by different microbes; however, gram-positive bacteria are usually more susceptible to the action of ACNs than gram-negative bacteria [41]. Nonetheless, only a few bacterial genera (*e.g.*, *Bifidobacterium*, *Lactobacillus*, *Akkermansia*, *Bacteroides*, and *Eubacterium*), which catalyze the metabolism of phenolics, have been described as contributing to the health benefits of the host [20,41].

An increase in *Bifidobacterium* is favored in the presence of carbohydrates, non-digestible carbohydrates, and ACNs

[42], and it is recognized as one of the most important bacterial groups associated with human health [19]. Among its benefits, studies have reported anti-obesity effects [43] and cholesterol regulation [44]. An increase in the expression of zonula occludens-1 (ZO-1) has also been reported [45]; ZO-1 is a peripheral membrane protein involved in the regulation of paracellular permeability that is associated with a complex of proteins localized at the apical side of epithelial cell membranes–claudin and occludin–that form a tight junction barrier in the lumen against microorganisms and food antigens [46].

Studies have already shown a role of ACNs in the bifidogenic effect by a reduction in inflammatory markers and beneficial changes in gut microbiota by competition for a growth substrate *in vitro* [47], in humans [48], and in animals [49].

Previous data by our research group using a metabolic programming model revealed that supplementing the diet of pregnant rats with juçara berries (262.4 mg ACN/100 g fresh matter) reduced metabolic and inflammatory markers and increased *Lactobacillus* and *Bifidobacterium* spp. expression of genomic DNA and ZO-1 gene in their offspring, demonstrating that phenolic compounds present in this fruit contribute to the control of inflammation and prevention of the development of chronic diseases through the intestinal pathway up until adulthood [50,51].

Recently, Guergoletto et al. [52] reported the potential prebiotic effect of juçara berries by modulating the colonic microbiome *in vitro*. They found that it promoted bifidogenic effects, including the antimicrobial effect on pathogenic microorganisms by increasing the production of short-chain fatty acids (SCFAs), acetate, and propionate.

The dietary administration of dealcoholized red wine extract for 16 weeks to rats changed their intestinal microbiota populations from a predominance of *Bacteroides*, *Clostridium*, and *Propionibacterium* spp. to a predominance of *Lactobacillus*, *Bifidobacterium* spp., and *Bacteroides*, showing that the role of ACNs in intestinal modulation favors an increase in beneficial bacteria [42].

Supplementing diet-induced obese mice with cranberry and grape extracts resulted in lower intestinal and systemic inflammation, improved metabolic features, and increased the abundance of *A. muciniphila* in their gut microbiota with a prebiotic effect [20,53]. *A. muciniphila* inhabits the mucus layer and is one of the most abundant members of the human gut microbiota, comprising between 1% and 5% of our intestinal microbes [20]. It is associated with increased mucus layer thickness, improved glucose homeostasis, alleviated metabolic endotoxemia, and improved cardiometabolic parameters in obese individuals undergoing caloric restriction [20,54]. Currently, *A. muciniphila* has been considered as a therapeutic option to target human obesity and associated disorders [54].

Recently, several studies have considered ACN benefits after degradation by colonic microbiota. These metabolites may contribute to the bioavailability of ACNs [37] and may be responsible for antioxidant [55] and protective effects as nitric oxide production increases [56]; they inhibit angiotensin-converting enzymes to improve blood pressure [47]; minimize weight gain and improve glucose metabolism [31]; improve the plasma lipid profile and inflammation [57]; positively modulate the intestinal bacterial population by enhancing the growth of *Bifidobacterium* spp., *Lactobacillus* spp., and *Enterococcus* spp.; and reduce *Clostridium histolyticum*, a potentially harmful bacterium [47].

Therefore, there is a broad consensus that ACNs have prebiotic effects similar to the modulation of gut microbiota composition [18,24]. This benefits bacteria that are linked to reducing LPS levels [57] and selective antimicrobial activities against pathogenic gut bacteria [22] (Fig. 1), contributing to chronic disease control even though the mechanisms have not yet been elucidated [57].

3. Anthocyanins in Obesity and Interplay with Gut Microbiota

The Western diet has altered the genetic composition and metabolic activity of our resident microorganisms (the human gut microbiome). Such diet-induced changes in gut-associated microbial communities are now suspected of contributing to growing epidemics of chronic disease, including obesity, in the developed world [58].

Normal weight and obese individuals have a different microbiota composition. Emerging data have suggested that obese individuals have a higher ratio *Firmicutes/Bacteroidetes* than normal weight controls. Moreover, when they lose weight, *Firmicutes* abundance decreases and becomes more similar to that in lean subjects [59], reinforcing the hypothesis that specific bacteria genera and species participate in the regulation of energy homeostasis, modulation of energy balance, expansion of the adipose tissue, and glucose metabolism, leading to a chronic inflammatory state [60–64] (Fig. 2).

Although different therapies have been suggested to attenuate obesity including appetite or food control, chemically manufactured medicines, different herbal drugs, and physical exercise, obesity management remains a critical issue because of its drastic outcomes. ACNs are valuable compounds that play an important role in maintaining human health as they can be used prophylactically and therapeutically owing to several properties [11,13,65]. Besides that, ACNs can normalize the ratio between beneficial and pathogenic bacteria and plasma endotoxemia and reduce the impact of a high-fat diet on the host's metabolism [66]. Early reports suggested that antioxidant properties alone are responsible for ACNs health-promoting effects; however, it is now appreciated that ACNs act beyond their antioxidant properties and likely influence an array of cell signaling, anti-inflammatory, and gene expression pathways [39].

ACNs have been shown to exert different degrees of antioxidant and anti-inflammatory activities, depending on their chemical structure [12]; therefore, the effects of diverse ACN-rich berries have been tested. Recently, a study on three

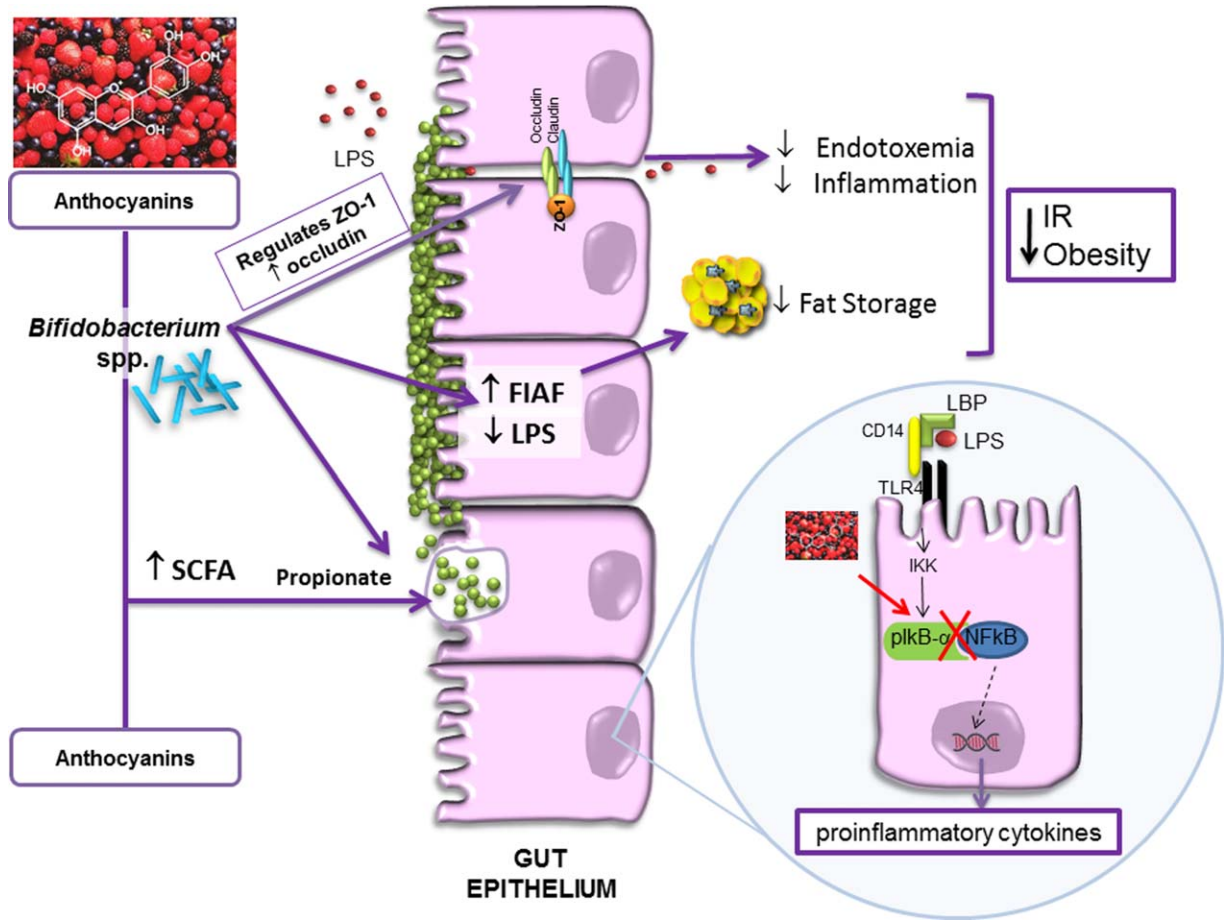

FIG 1

The potential prebiotic effect of anthocyanins on gut microbiota and obesity. SCFA: short-chain fatty acids; FIAF: fasting-induced adipose factor; LPS: lipopolysaccharide; ZO-1: zonula occludens-1; IR: insulin resistance. Anthocyanins and metabolites formed in the intestine change the composition of the gut microbiota. This is associated with restored tight-junction protein (ZO-1 and Occludin) distribution and localization. Hence, the gut permeability is decreased and plasma lipopolysaccharide (LPS) levels (metabolic endotoxemia) are lowered, improving low-grade inflammation and obesity-related comorbidities. Anthocyanins decrease the activity of transcription factor NF-κB in the cell nucleus by decreasing gene expression of inflammatory cytokines; exerting its anti-inflammatory action. Anthocyanins have the ability to promote the growth of Bifidobacterium *spp., which increases the intestinal production of FIAF that inhibits fat storage in the host.* Bifidobacterium *spp. degrades SCFA; propionate stimulates mucus secretion and contributes to thickening of the mucus layer. While reduced mucus layer thickness favors microbiota encroachment.*

prospective human cohorts demonstrated that a higher intake of flavonoid-rich foods, mainly ACNs, may contribute to weight maintenance in adulthood and may help in refining dietary recommendations for the prevention of obesity and its potential consequences [67].

Basu et al. [68] found that ingestion of 742 mg of blueberry ACNs for 8 weeks significantly improved blood pressure and oxidized low-density lipoprotein (LDL)-cholesterol levels, whereas blood glucose levels, body weight, and waist circumference were not improved in obese individuals. Similarly, other researchers have not shown alterations in body weight gain and white adipose tissue weight in mice fed a high-fat diet after the ingestion of blueberry juice (1887 μg/mL ACN) in place of drinking water over a period of 72 days [65]. However, consumption of high doses (200 mg/kg) of blueberry ACNs by high-fat diet induced obese male mice over 8 weeks reduced their body weight by 19.4%; decreased serum glucose levels; attenuated epididymal tissue; improved lipid profiles; and significantly down-regulated tumor necrosis factor alfa (TNFα), interleukin 6, peroxisome proliferator-activated receptors (PPARγ), and fatty acid synthesis (FAS) gene expression levels [69].

These studies highlight the potential of ACNs in weight control and/or metabolic disorders related to overweight. However, the results depend of the dose and species of fruit or compound administered. Nonetheless, how microbial pathways influence weight gain and how ACNs affect obesity remains uncertain. Next, we summarize the mechanisms involved in the relationship between gut microbiota and obesity and ACNs role in these processes.

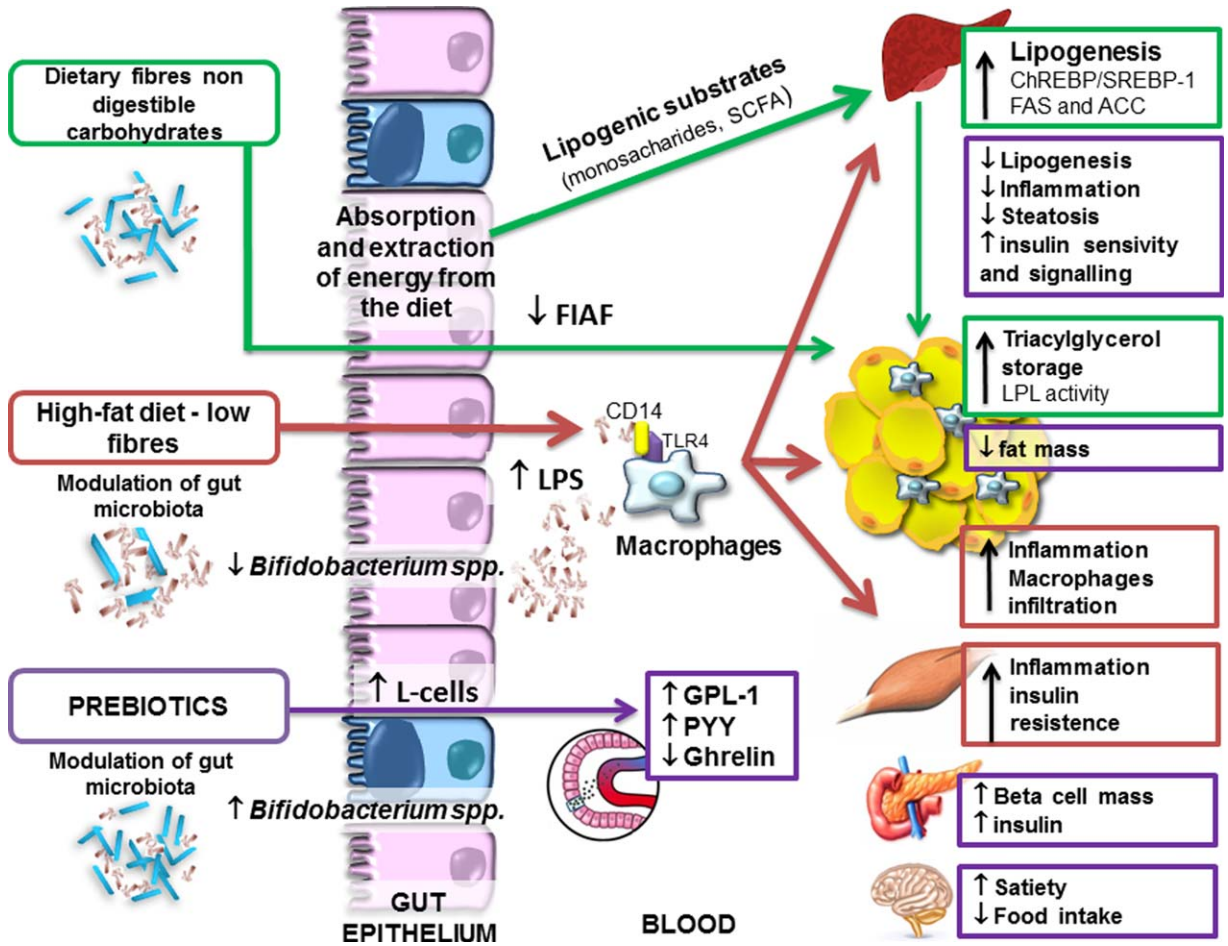

FIG 2

Dietary contribution in changes in gut microbiota, fat storage, and development of metabolic disorders via LPS-induced. SCFA: short-chain fatty acids; ACC: acetyl-CoA carboxylase; FAS: fatty acid synthase (FAS); ChREBP: Carbohydrate responsive element-binding protein; SREBP-1: Sterol responsive element-binding protein; FIAF: fasting-induced adipose factor; LPL: lipoprotein lipase; LPS: lipopolysaccharide; TLR-4: toll like receptor 4; GLP-1: glucagon-like peptide-1; PYY: peptide YY. Gut microbiota might be involved in energy storage. Environmental factor such as gut microbiota may regulate energy storage by providing lipogenic substrates (SCFA, monosaccharides) to the liver, increasing hepatic lipogenesis and/or by suppressing the FIAF in the gut, which increase LPL. It contributes to the release of fatty acids and triacylglycerol from circulating lipoproteins in adipose tissue. Consumption of the Western diet (high in saturated/trans fat and simple sugars and low in fibers) is one of the leading causes of obesity worldwide. Obesity-linked dysbiosis is associated with disrupted intestinal barrier. Western diet causes changes in gut microbiota by specifically decreases Bifidobacterium *spp. It is associated with a higher gut permeability leading to higher plasma LPS levels (metabolic endotoxemia) that promotes low-grade inflammation-induced metabolic disorders (insulin resistance, diabetes, obesity, steatosis, adipose tissue macrophages infiltration). Prebiotics increase* Bifidobacterium *spp., decrease plasma LPS levels and normalized low-grade inflammation (decreased endotoxemia and proinflammatory cytokines). This modulation is associated with changes in the plasma gut peptides levels (enhanced GLP-1 and PYY, and reduced ghrelin). These effects are associated with satiety, weight loss, increase in insulin sensitivity, reduction in fat mass, and low-grade inflammation characterizing obesity.*

3.1. Lipogenesis

The mechanisms of the apparent weight gain implied an increase in the intestinal glucose absorption, energy extraction from non-digestible food component, and concomitant higher glycemia and insulinemia, two key metabolic factors regulating lipogenesis [70]. Moreover, glucose and insulin are also known to promote hepatic *de novo* lipogenesis by the expression of several key enzymes, such as acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS), which are controlled by carbohydrate-responsive element-binding protein (ChREBP) and sterol-responsive element-binding protein (SREBP-1) [71]. Germ-free mice exhibited decreased hepatic ChREBP and SREBP-1 mRNA levels by modulation of lipogenesis by energy extraction from SCFAs [72]. These data provide evidence that the digestion of polysaccharides by microbial enzymes and increase in saccharide delivery to the liver participate in higher lipogenesis.

ACNs can reduce the expression of PPARγ, FAS, and ChREBP [69,73], and differentiation of preadipocytes from the

subcutaneous and visceral adipose tissue, suggesting inhibitory effects on adipogenesis in the white adipose tissue. Recently, You et al. [74] demonstrated that Cy-3-glu may act in brown adipogenesis increasing the number of mitochondria.

Açai seed extract reduces lipogenesis and glucose levels because of reduced expressions of SREBP-1c and the enzyme HMG-CoA reductase and increased expressions of AMP-activated protein kinase (AMPK) in mice that were fed a high-fat diet [8]. AMPK plays an important role in the regulation of fatty acids and glucose metabolism, favoring weight control as well as appetite regulation. The activity of this enzyme is anabolic when inhibited, blocking catabolic processes. The diversity of the microorganisms in the gut can suppress fatty acid oxidation in the muscle via mechanisms involving inhibition of AMPK and favor adiposity and insulin resistance [71,75].

The activation of AMPK and fasting-induced adipose factor (FIAF) lead to an inhibition of lipoprotein lipase (LPL), an enzyme that regulates triacylglycerol metabolism and that can be modulated by the microbiota [72]. FIAF participation in lipid metabolism was reinforced when it was shown that germ-free $FIAF^{-/-}$ mice were not protected from diet-induced obesity and they demonstrated increased weight gain, intra-abdominal adiposity, and higher leptin and insulin levels, despite similar food intake, comparing with $FIAF^{+/+}$ mice [75]. This set of experiments demonstrated, for the first time, that an environmental factor, such as gut microbiota, may regulate energy storage [71].

A new insight demonstrated that gut microbiota plays an unexpectedly important role in post-dieting weight regain, and it could have been avoided or treated by altering microbiome function or composition. In addition, flavonoid-based "post-biotic" intervention ameliorates excessive secondary weight gain. The possible mechanism for this action is that flavonoids impact energy expenditure by induction of the major thermogenic factor uncoupling protein-1 in the brown adipose tissue [76].

These evidences indicate a beneficial role of dietary ACNs in preventing weight gain. The underlying mechanisms have been hypothesized to involve factors including, but not restricted to, suppression of fat absorption from the gut, adipocyte differentiation, fatty oxidation, and sympathetic activation of thermogenesis [77].

3.2. Energy Homeostasis Mechanism

The energy balance is regulated via neuronal and hormonal signals. There is equilibrium between orexigenic and anorexigenic neuropeptides in the hypothalamus and brain stem to regulate food intake, body weight, and energy homeostasis. In obesity, there is a complex disorder involving an imbalance in orexigenic and anorexigenic circuits and stimulation of the intracellular neuropeptide Y (NPY), which further effects food intake and lipid accumulation [78]. Neurons of the arcuate nucleus that produce NPY exhibit enhanced expression of gamma-aminobutyric acid (GABA), a G-protein coupled receptor (GPR) and main inhibitory neurotransmitter in the central nervous system. Thus, GABA can inhibit a tonic restraint to elicit a feeding response directly or in conjunction with NPY and other orexigenic signals [79].

Recently, Badshah et al. [78] demonstrated an efficient anti-obesity capacity of black soybean ACNs via regulating the expression of NPY and GABA in the hypothalamus. The exact mechanism underlying these modifications by this ACNs treatment is unclear. However, GABA may be an intermediate influence on the microbiota in the gut–brain axis. It is located throughout the gastrointestinal tract and is found in enteric nerves as well as in endocrine-like cells, implicating GABA as both a neurotransmitter and an endocrine mediator influencing gastrointestinal function. Experimental fecal extraction studies revealed that GABA was increased following Roux-en-Y gastric bypass surgery and that it could have been derived from the microbial processing of putrescine [80,81]. Increased expression of fecal GABA is consistent with the well-defined increase of glucagon-like peptide 1 (GLP-1), an anorexigenic gut hormone. Furthermore, ACNs may induce GLP-1 secretion and contribute to energy homeostasis [82].

The activation of GLP-1 receptors, mainly GPR43 and 41 (also called free fatty acid receptors 2 and 3, respectively), induce the secretion of peptide YY (PYY) and leptin, hormones that influence intestinal function and appetite regulation by inhibiting orexigenic neurons of the arcuate nucleus [43–45]. PYY favors the reduction of gut motility and increased energy harvest from the diet, in particular SCFAs, which are substrates for hepatic lipogenesis. Therefore, gut microbiota may interfere with the central nervous system based on the presence or absence GPR41, thereby influencing the central regulation of appetite and satiety [45] through the modulation of PYY and SCFA absorption [43,44].

Access to the central nervous system is tightly controlled by the blood–brain barrier (BBB); it is likely that a small and specific set of bacterial metabolites modulate brain morphology. The gut microbiota is also crucially involved in modulating BBB [83] as germ-free mice have a more permeable BBB than conventional mice [84]. ACN gut microbiota metabolites can cross BBB and be allocated to various brain regions, suggesting that these compounds may deliver their antioxidants and centrally signal and modify capabilities [85,86], although the mechanisms remain unclear. However, it is worth highlighting that ACNs have a prebiotic effect that contributes to the modulation of gut peptides, inducing effects on satiety and food intake [87].

3.3 Obesity Inflammation Pathway

Obesity is characterized by the massive expansion of adipose tissues and is associated with inflammatory complications. LPS was identified as a trigger factor for the early development of inflammation and metabolic diseases. High LPS levels form a complex containing LPS-binding proteins and the CD14 co-receptor that is recognized by Toll-like receptor 4, a transmembrane receptors, triggering an inflammatory response through the complex signaling pathways

with NF-κB activation and the subsequent expression of pro-inflammatory cytokines [60].

The activated NF-κB pathway may also impair insulin signaling, which can lead to insulin resistance. LPS has been found at a significantly higher level in the serum of obese than lean individuals, and it is associated with a high-fat diet, particularly containing saturated fatty acids [6,88,89]. It creates a metabolic endotoxemia that causes alterations in bacterial diversity and microbiota balance (dysbiosis), damage to the mucosal integrity, and dramatically increases intestinal permeability, reducing the expression of epithelial tight junction proteins [60,88,90]. It is even questionable as to whether LPS induces weight gain or only enhances subclinical inflammation and contributes to metabolic changes, such as insulin resistance, regardless of adiposity induction [88].

Changes in the number and size of adipocytes affect the microenvironment of expanded fat tissues and are accompanied by alterations in adipokine secretion, adipocyte death, local hypoxia, and fatty acid fluxes. Chronic over-nutrition triggers uncontrolled inflammatory responses, leading to systemic low-grade inflammation and metabolic disorders, such as insulin resistance [91].

ACNs act on the adipose tissue, inducing changes in adipokine expression levels, as adiponectin, which enhances insulin sensitivity, in rat [92] and human adipocytes [93]. Adiponectin also lowers muscle triglyceride levels by increasing the influx and combustion of free fatty acids resulting in decreased hepatic level of triglycerides [65]. It has recently been reported that a diet supplemented with wild blueberry powder significantly increased blood adiponectin levels and decreased inflammatory marker levels in the white adipose tissue [94], including those related to cardiovascular risk (C-reactive protein (CRP), interleukins, TNFα, and Vascular cell adhesion protein 1 (VCAM-1)) [95]; decreased NF-κB activity [96] and serum LPS levels [97]; and ameliorated dyslipidemia [98], showing the anti-inflammatory effects of the different ACNs present in the fruit [31].

4. Concluding Remarks and Future Perspectives

ACNs seem to have an anti-obesity effect with properties that prevent body fat accumulation, insulin resistance, dyslipidemia, and inflammation while contributing to energy homeostasis and satiety. The exact molecular mechanism of their anti-obesity effects should be clarified; their benefits may be linked to ACN microbiota modulation.

There is an insufficient understanding about the difference in ACN metabolism and biotransformation in the gastrointestinal tract of normal weight versus obese individuals as well as the role of intact versus disrupted gut microbiomes in these processes.

The literature shows that a wide variety of results and techniques were employed in the studies, such as different ACN sources and the biotransformation of ACNs in either a food matrix or isolated. This makes it difficult to understand the exact mechanism of each individual compound. Nevertheless, there is broad agreement that ACNs have health-promoting effects, have the ability to modulate colonic bacterial growth, improve chronic low-grade inflammation, and may indeed exert a prebiotic activity. It is crucial to emphasize the benefits for bioavailability and/or bioactivity from ACN metabolites that are synthesized by colonic microbiota.

Thus, microbiota modulation through dietary interventions with ACN-rich foods may offer new directions for the prevention and/or treatment of obesity. Future studies are still required to understand these mechanisms and to be able to specifically understand the interaction between the type of bacteria and different metabolites derived from the degradation of ACNs.

Conflicts of Interest

There is no conflict interest.

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