Molecular Aspects of Medicine 89 (2023) 101156

Contents lists available at ScienceDirect

Molecular Aspects of Medicine

journal homepage: www.elsevier.com/locate/mam

Review

Anthocyanin actions at the gastrointestinal tract: Relevance to their health benefits

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ARTICLE INFO

Keywords:
Flavonoid
Gastrointestinal tract
Inflammation
Endotoxemia
Microbiota
Polyphenols

ABSTRACT

Anthocyanins (AC) are flavonoids abundant in the human diet, which consumption has been associated to several health benefits, including the mitigation of cardiovascular disease, type 2 diabetes, non-alcoholic fatty liver disease, and neurological disorders. It is widely recognized that the gastrointestinal (GI) tract is not only central for food digestion but actively participates in the regulation of whole body physiology. Given that AC, and their metabolites reach high concentrations in the intestinal lumen after food consumption, their biological actions at the GI tract can in part explain their proposed local and systemic health benefits. In terms of mechanisms of action, AC have been found to: i) inhibit GI luminal enzymes that participate in the absorption of lipids and carbohydrates; ii) preserve intestinal barrier integrity and prevent endotoxemia, inflammation and oxidative stress; iii) sustain goblet cell number, immunological functions, and mucus production; iv) promote a healthy microbiota; v) be metabolized by the microbiota to AC metabolites which will be absorbed and have systemic effects; and vi) modulate the metabolism of GI-generated hormones. This review will summarize and discuss the latest information on AC actions at the GI tract and their relationship to overall health benefits.

1. Introduction

Understanding the role of the gastrointestinal (GI) tract on human health beyond its digestive functions has led to the generation of a substantial body of research and knowledge in the past couple of decades. Through the multiple actions of different cell types present at the GI lining as well as of the large microbiota population residing in the gut lumen, we now know that sustaining GI physiology is essential for maintaining health. These actions are not only relevant for GI pathologies, e.g. inflammatory bowel diseases (IBD) and celiac disease (Biasi et al., 2013; Fasano and Shea-Donohue, 2005), but also for systemic pathologies including cardiovascular disease (CVD), type 2 diabetes (T2D), non-alcoholic fatty liver disease (NAFLD), and neurological disorders (Bischoff et al., 2014; Brown, 2019; Damms-Machado et al., 2017; Odenwald and Turner, 2017).

The multiple biological processes occurring at the GI tract include: i) the absorption of dietary nutrients and bioactives; ii) the secretion of hormones and bioactive peptides that control, from local processes to whole body, lipid and carbohydrate metabolism (Ahlman and Nilsson, 2001; Rehfeld, 2017); iii) its function as the first physical barrier that prevents the entrance into the circulation of bacteria, food and bacterial toxins, and other unwanted materials into the circulation (Fasano and Shea-Donohue, 2005; Konig et al., 2016; Odenwald and Turner, 2017; Turner, 2009; Wells et al., 2017); iv) the regulation of the tolerance to food components and commensal bacteria, and the reaction towards pathogens through the largest body population of immune cells (Daneman and Rescigno, 2009; Hooper et al., 2012); and v) hosting the local microbiota which, in active cross-talk with the intestinal mucosa, provides multiple beneficial health actions locally and systemically (Blander et al., 2017; Hooper et al., 2012).

Dietary bioactives, including flavonoids, can regulate GI functions (Oteiza et al., 2018). Anthocyanins (AC) are flavonoids which, after dietary consumption, can reach high concentrations in the gut lumen either as parent compounds or the GI-generated metabolites (Czank et al., 2013b; Gonzalez-Barrio et al., 2010; He et al., 2005; Kahle et al.,

Abbreviations: NOX, NADPH oxidase.

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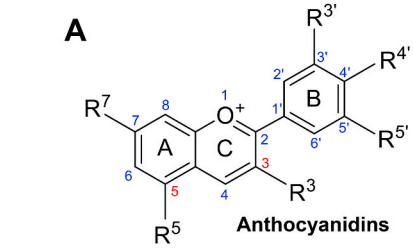
https://doi.org/10.1016/j.mam.2022.101156
Received 25 August 2022; Received in revised form 26 October 2022; Accepted 28 October 2022
Available online 12 November 2022

Abbreviations

AC	anthocyanin/s
C3G	cyanidin-3-glucoside
DSS	dextran sulfate sodium
CVD	cardiovascular disease
DPP-IV	dipeptidyl peptidase IV
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
GLP-2	glucagon-like peptide-2
GI	gastrointestinal
IBD	inflammatory bowel diseases
LPS	lipopolysaccharides
MLC	myosin light chain
MLCK	myosin light chain kinase
MLCP	MLC phosphatase
MUC2	mucin 2
NAFLD	nonalcoholic fatty liver disease
T2D	type 2 diabetes
TEER	transepithelial electrical resistance
TJ	tight junction
TNFα	tumor necrosis factor alpha
TG	triglycerides
Tff3	Trefoil factor 3
ZO-1	zonula occludens-1



AC	R_3'	R_4'	R_5'	R_3	R_5	R_7
Cyanidin	–OH	–OH	–H	–OH	–OH	–OH
Delphinidin	–OH	–OH	–OH	–OH	–OH	–OH
Peonidin	$–OCH_3$	–OH	–H	–OH	–OH	–OH
Malvidin	$–OCH_3$	–OH	$–OCH_3$	–OH	–OH	–OH
Pelargonidin	–H	–OH	–H	–OH	–OH	–OH
Petunidin	–OH	–OH	$–OCH_3$	–OH	–OH	–OH

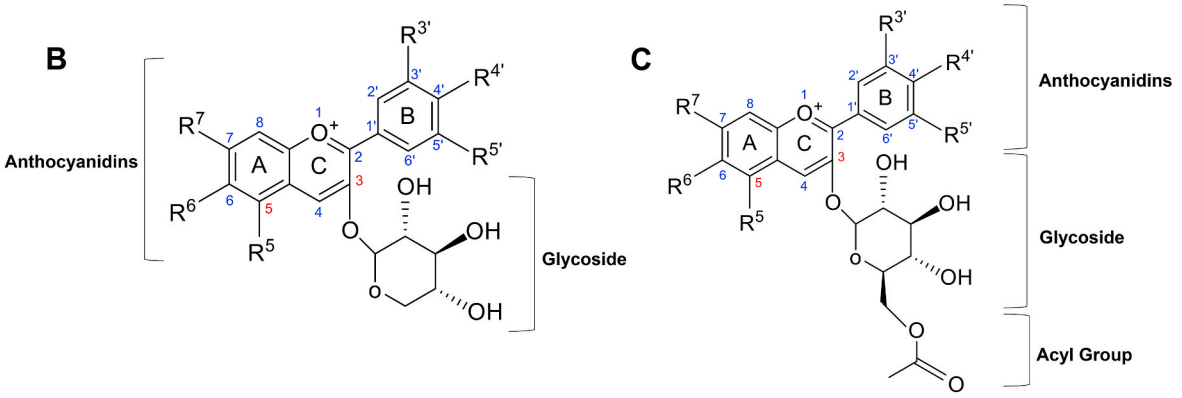


Fig. 1. Chemical structure of anthocyanidins and anthocyanins. A- Basic anthocyanidin chemical structure. Distribution of hydroxyl and methoxyl groups that defines the six most common anthocyanidins. B- Chemical structure of an anthocyanin: anthocyanidin glycosylated in positions 3. C- Chemical structure of an acylated anthocyanin.

2006; Kay et al., 2017; Overall et al., 2017; Vitaglione et al., 2007; Wu et al., 2006). This review will summarize current knowledge on the effects of AC on GI tract physiology, with emphasis on their potential mechanisms of action, and how these effects can help sustain human health.

2. Anthocyanidins and anthocyanins: chemistry and metabolism

Anthocyanidins have C6-C3-C6 flavonoid structure containing double bonds in the three rings and a positive charge in the heterocyclic benzopyran ring (Fig. 1 A). Different anthocyanidins are characterized by the position and number of hydroxy and methoxy groups, which defines the most common anthocyanidins present in plants, i.e. cyanidin, delphinidin, malvidin, peonidin, petunidin, and pelargonidin. *In planta*, anthocyanidins mostly exist as glycosides, which are referred to as anthocyanins (AC). Sugar moieties are linked to AC mostly as monomers, but also as dimers and trimers, at positions 3 or in some cases to position 5 (Fig. 1B). The main AC in plants are glucoside, galactoside, glucuronide, sophoroside, rutinoside, and arabinoside conjugates. Additionally, the glycosyl unit of AC can be acylated by one or more aromatic acids (Fig. 1C) (Crozier et al., 2006). When animals consume plants containing AC, the C6-C3-C6 structure can undergo substantial modifications in the GI tract, which ultimately can influence their biological effects (Overall et al., 2017).

Individual plant species have a unique genetically determined pattern of AC. This can vary from one major AC, such as black rice that contains only cyanidin-3-O-glucoside (C3G), to plants that contain multiple AC based on the several anthocyanidin structures illustrated in Fig. 1A. In addition, as observed for flavonoids in general, *in planta* AC concentrations depend on a number of factors including subspecies, i.e. different grape varieties and genotypes, and on the prevailing environmental conditions in which plants are grown (Boudet, 2007).

AC undergo different metabolic events throughout their passage along the GI tract (Kay et al., 2017; Williamson et al., 2018). Once ingested, most AC pass the stomach untransformed, being extensively metabolized in the intestine where the change from acidic to a higher pH can modify their structures (Prior 2012). In the small intestine, AC

monoglycosides undergo deglycosylation and are metabolized by phase II enzymes forming glucuronide-, sulfo-, and methyl-derivatives, which enter the systemic circulation (Czank et al., 2013). Di- and trisaccharide AC undergo limited deglycosylation in the upper GI tract (Dobani et al., 2021). In a study with ileostomy patients, it was observed that following consumption of red raspberries containing mainly cyanidin mono- and disaccharides, one fifth of AC intake was detected in ileal fluid. In subjects with a functioning colon, the AC in ileal fluid would pass to the lower bowel where they are subjected to microbial degradation, initially involving ring fission, generating low molecular weight catabolites, including phenylpropanoic, phenylacetic and benzoic acids, the latter undergoing hepatic conversion to hippuric acids (González-Barrio et al., 2011; Rodriguez-Mateos et al., 2013). The specificity of selected GI bacteria to metabolize AC will define the systemic presence of the different metabolites (Hanske et al., 2013; Bresciani et al., 2020). Results in human studies show that metabolites resulting from microbial catabolism account for most of the absorbed compounds after AC dietary consumption (Czank et al., 2013; Ludwig et al., 2015; Dobani et al., 2021). Overall, the resulting AC-derived metabolite(s) that actually interact with the biological target at the GI tract and systemically, will be the resultant of multiple factors: the consumed AC, environmental conditions, including diet, the characteristics of the host (e.g. genetics and disease states), and arguably most importantly, the resident microbiota which can vary from individual to individual.

3. Actions of anthocyanins at the gastrointestinal tract

3.1. Anthocyanins and lipid- and carbohydrate-metabolizing enzymes

Absorption of dietary lipids and complex carbohydrates requires their initial metabolism by enzymes present at the GI lumen and epithelium, including glycosidases and lipases. The possibility that ingested flavonoids could inhibit these enzymes is of particular interest because this would lead to decreased fat and carbohydrate absorption, either because of modifying the amount absorbed and/or the rate of absorption, counteracting subsequent hyperglycemia and dyslipidemia.

Carbohydrate digestion starts in the mouth through the action of salivary amylase, which cleaves starches into a disaccharide, maltose. Further degradation of starches and glycogen to maltose occurs in the small intestine through the action of pancreatic amylase. Finally, disaccharides are cleaved by α-glucosidases into monomers that can be subsequently absorbed. As recently reviewed, different plant extracts and individual bioactives present in fruits and vegetables, including those rich in AC, inhibit α-amylase and α-glucosidase at different extents (Papoutsis et al., 2021). For example, a study characterizing AC present in a *Morus australis* fruit extract showed that C3G and cyanidin-3-rutinoside inhibit maltase, sucrase, and isomaltase within a micromolar range of concentrations, partially inhibit glucoamylase, and do not inhibit α-amylase (Qiao et al., 2022). In support of a lack of effect of C3G on α-amylase, comparison of the effects of Haskap (*Lonicera caerulea* L.) berries collected at different harvesting dates, which determines major differences in C3G content, showed similar extent of inhibition of α-amylase and α-glucosidase (De Silva and Rupasinghe, 2020). On the other hand, AC and anthocyanidins, present in blackcurrant inhibited both α-glucosidase and amylase (Barik et al., 2020). The presence of a glycoside group in AC seems to be important in the capacity of these compounds to inhibit α-glucosidase. Thus, cyanidin, but not cyanidin-3-rutinoside and C3G, appear to inhibit α-glucosidase activity (Chen et al., 2020). In support of a stronger inhibitory capacity of anthocyanidins as compared with their glycosides, delphinidin had significantly higher capacity to inhibit the enzyme than, both its 3-*O* glucoside and galactoside (Promyos et al., 2020). When comparing the capacity of the anthocyanidins pelargonidin, cyanidin, peonidin, delphinidin, petunidin and malvidin to inhibit α-glucosidase, delphinidin resulted the most active (Promyos et al., 2020).

The capacity of AC and anthocyanidins to inhibit the different enzymes involved in carbohydrate digestion and absorption could be in part involved in the observed capacity of these compounds to improve the control of glucose homeostasis (Cremonini et al., 2022; Daveri et al., 2018; Guo et al., 2012; Prior et al., 2010; Sasaki et al., 2007). In healthy humans, consumption of a cyanidin- and delphinidin-rich extract with a high fat meal significantly mitigated the postprandial increase in plasma glucose and attenuated the spike of plasma insulin (Cremonini et al., 2022). Similarly, in patients with metabolic syndrome, AC-rich blueberries decreased postprandial hyperglycemia (Curtis et al., 2022). In agreement with these findings, several studies have reported a decrease in postprandial plasma glucose and insulin levels upon consumption of AC-rich berries and foods in healthy volunteers (Castro-Acosta et al., 2016, 2017; Törrönen et al., 2010, 2012) and by cyanidin-3-rutinoside in maltose- or sucrose-challenged rats (Adisakwattana et al., 2011). Overall, the above evidence supports the capacity of AC to decrease glucose absorption, in part through their capacity to inhibit GI luminal enzymes involved in carbohydrate absorption, particularly α-glucosidase. However, there is no direct evidence that such inhibition is operative and has a physiological relevance *in vivo*. Additionally, it should be considered that a direct effect of AC on intestinal epithelial cell glucose transporter expression could also contribute to AC capacity to mitigate hyperglycemia. However, this interesting hypothesis (Barik et al., 2020) has received limited experimental support.

In terms of lipid metabolism, triglycerides (TG) are cleaved by lingual, gastric and pancreatic lipases to monoacyl glycerol and free fatty acids, which are subsequently transported into enterocytes for TG re-synthesis, and then exported into nascent chylomicrons. Thus, inhibition of lipases in the gut lumen would result in decreased fatty acid absorption, and consequently, in TG synthesis and export. *In vitro,* numerous publications have provided evidence that AC-rich extracts from different fruits, vegetables, legumes, and cereals inhibit pancreatic lipase (Fabroni et al., 2016; You et al., 2011). Also *in vitro*, the pure compounds cyanidin, cyanidin-3,5-diglucoside and C3G were effective at inhibiting purified lipases (Fabroni et al., 2016), being cyanidin more effective than cyanidin-3,5-diglucoside (You et al., 2011). A thorough and elegant characterization of pancreatic lipase inhibition by several AC present in cranberries founds cyanidin-3-arabinoside, cyanidin-3-galactoside, peonidin-3-arabinoside and peonidin-3-galactoside as the most active (Xie et al., 2020a). Mechanistic studies showed that the B ring and glycosyl groups in AC are relevant in defining the capacity of these compounds to inhibit pancreatic lipase. Findings in animals and humans also support a potential *in vivo* effect of AC on pancreatic lipase, although they do not provide evidence of a direct molecular interaction and/or inhibition. Thus, AC mitigate hyperlipidemia and steatosis in rodent models of diet-induced obesity (Daveri et al., 2018; Prior et al., 2009). Recent evidence also showed that a cyanidin-and delphinidin-rich extract decreases the postprandial increase in plasma TG after consumption of a high fat meal by healthy humans (Cremonini et al., 2022). Overall, the inhibition of pancreatic lipase by specific anthocyanidins and AC emerges as one potential mechanism underlying their capacity to decrease plasma TG. However, as discussed before for AC's capacity to inhibit carbohydrate-metabolizing enzymes, further evidence is necessary to demonstrate the *in vivo* AC inhibitory action on GI lipases.

3.2. Anthocyanins and intestinal permeability

The immunoregulatory functions of the GI tract are sustained at multiple levels, including i) the intestinal barrier; ii) intestinal epithelial cells that sense microbes and regulate immune responses (Peterson and Artis, 2014); iii) a mucus layer that prevents the access of bacteria to the cell monolayer (Johansson and Hansson, 2016); iv) antimicrobial peptides released by Paneth cells (Lueschow and McElroy, 2020); and v) the resident immune system that controls the interactions of the epithelium with luminal bacteria to prevent inflammation (Hooper et al., 2012). While this section will address the effects of AC on barrier function,

sections 3.3. to 3.5. will address AC actions on other aspects of GI immunoregulatory functions.

The intestinal barrier is critical in sustaining human health (Martel et al., 2022; Odenwald and Turner, 2017) by preventing the transport to the circulation of bacterial toxins, as well as of toxins of dietary origin, which can initiate both local and systemic inflammation. Alterations in barrier function are associated to the development of several chronic diseases including not only GI pathologies, e.g. celiac disease and IBD, but also to those associated to obesity and unhealthy diets, e.g. CVD, T2D, NAFLD and neuroinflammation (Brown, 2019; Fasano and Shea-Donohue, 2005; Odenwald and Turner, 2017). The epithelial cell monolayer plays a central role in sustaining the barrier function by controlling the paracellular transport of substances through tight junctions (TJs) that link adjacent cells. TJs are constituted by a network of membrane proteins, i.e. occludin, claudins and junction adhesion molecule proteins; and cytosolic proteins, e.g. zonula occludens-1 (ZO-1), which interact with actomyosin peri-junctional filaments. Although different mechanisms can be involved in intestinal permeabilization, such as alterations in TJ protein turnover and cellular localization, the most relevant physiological regulation of TJ opening occurs via myosin light chain (MLC) phosphorylation (Al-Sadi et al., 2013; Buckley and Turner, 2018; Ye and Ma, 2008). MLC is phosphorylated by the serine/threonine protein kinase MLCK, which leads to the contraction of the actin-myosin ring causing TJ opening. In contrast, dephosphorylation by MLC phosphatase (MLCP) has the opposite effect (Al-Sadi et al., 2013; Buckley and Turner, 2018; Ye and Ma, 2008). These events are modulated by transcription factor NF-κB and by the mitogen activated kinase ERK1/2. In terms of mechanisms relating permeability and inflammation, both NF-κB and ERK1/2 promote MLCK transcription (Al-Sadi et al., 2013; Ma et al., 2004) while ERK1/2 phosphorylates and inhibits MLCP (Grassie et al., 2011; Ihara et al., 2015; Xiao et al., 2005), leading to TJ opening. In addition, given that both, NF-κB and ERK1/2 are redox-sensitive, activation of NADPH oxidases (NOX) or other cellular events that increase $O_2^{\cdot-}$ and H_2O_2 production, can contribute to barrier permeabilization.

AC protects the intestinal barrier from permeabilization in the context of inflammation and consumption of high fat diets. Thus, barrier permeabilization can be triggered by inflammation, cytokines, oxidants, an excessive production of bile acids, and LPS, the latter associated to dysbiosis (Capaldo and Nusrat, 2009; Murakami et al., 2016; Suzuki and Hara, 2010). A body of literature built on AC-rich foods and extracts support a beneficial action of AC on intestinal permeabilization both *in vitro* and *in vivo*. For example, using differentiated Caco-2 cell monolayers as a model of intestinal epithelium, AC extracts from bilberry, black kernel rice, blueberry, purple carrots, crowberry, red grape and sour cherry mitigated the loss of barrier integrity induced by proinflammatory stimuli (Cremonini et al., 2017; Ershad et al., 2021; Le Phuong Nguyen et al., 2018; Olejnik et al., 2016; Polewski et al., 2020). *In vivo*, supplementation with an AC-rich extract from *Lycium ruthenicum* (Tian et al., 2021) or with a cyanidin- and delphinidin-rich berry/rice extract (Cremonini et al., 2019; Iglesias et al., 2022) mitigated the loss of barrier integrity in mice fed a high fat diet. In a mouse model of ulcerative colitis, supplementation with a purple potatoes powder decreased dextran sulfate sodium (DSS)-induced intestinal permeabilization (Li et al., 2021). In support of a protection by AC of the GI barrier in humans, a cyanidin-and delphinidin-rich extract decreased the postprandial endotoxemia caused by consumption of a high fat meal in young healthy individuals (Cremonini et al., 2022).

The confirmation of the involvement of a specific AC and the characterization of their relative potency and mechanism(s) of action require the use of pure (or maximally purified) AC. The actions of purified AC on tumor necrosis factor alpha (TNFα)-induced barrier permeabilization showed that the 3-*O*-glucosides of cyanidin, delphinidin, malvidin, petunidin and peonidin have different effects (Cremonini et al., 2017). The capacity of these AC to inhibit monolayer permeabilization, evaluated as the monolayer transepithelial electrical resistance (TEER), was dependent on the anthocyanidin (cyanidin ~ delphinidin » petunidin > malvidin ~ peonidin). Supporting the particular benefits of cyanidin and delphinidin, the content of these anthocyanidins in seven different rice and berry extracts correlated with the extract's capacity to prevent TEER decrease, while no association was observed between TEER and the total anthocyanidin content (Cremonini et al., 2017). C3G, delphinidin-3-glucosides, and their microbiota metabolites protocatechuic acid and/or gallic acid prevented TNFα- and LPS-triggered permeabilization of Caco-2 cell monolayers by inhibiting oxidative stress, activation of NF-κB and ERK1/2 signaling pathway, and downstream, the phosphorylation of MLC (Cremonini et al., 2017, 2019; Iglesias et al., 2022). Both *in vivo* and *in vitro*, AC also act mitigating barrier permeabilization by preventing the decreased levels of TJ proteins, i.e. ZO-1, occludin and claudin-1, triggered by high fat diets and inflammatory stimuli (Cremonini et al., 2019; Iglesias et al., 2022).

Overall, and in the context of inflammation, high fat diets, and obesity, the mechanisms involved in the protection of barrier integrity by AC include the mitigation of the associated: i) decreased levels of the TJ proteins occludin, ZO-1 and claudin-1; ii) increased expression of NOX enzymes, i.e. NOX1 and NOX4; iii) upregulation of redox-sensitive pathways, i.e. NF-κB, ERK1/2; and iv) the downstream increased MLC phosphorylation and TJ opening. Protection of intestinal barrier integrity and prevention of endotoxemia can be a major mechanism in the capacity of AC to mitigate systemic inflammation and the associated diseases. While *in vitro* and *in vivo* (rodent) studies support the capacity of select anthocyanidins to protect intestinal barrier integrity, future clinical studies are needed to confirm these actions in humans.

3.3. Anthocyanins and goblet cells

Goblet cells are central components of the GI immune system not only for their relevance preserving barrier function, but as active participants of the innate immune response (Knoop and Newberry, 2018). Thus, goblet cells secret mucins that form a thick mucus layer that prevents the access of luminal bacteria to the epithelium, and produce microbicide peptides, cytokines and chemokines that activate resident immune cells. Goblet cells also synthesize Trefoil factor 3 (Tff3), a protein involved in the regulation of mucus density and mucosal healing (Taupin and Podolsky, 2003). Additionally, recent evidence shows the capacity of goblet cell to transport antigens from the GI lumen to be delivered to antigen-presenting immune cells in the lamina propria to initiate an adaptive immune response (Knoop and Newberry, 2018). Thus, conditions that affect goblet cell number and function can seriously compromise both, GI immune responses and barrier function.

The number and processes regulated by goblet cells are affected by different disease states and environmental factors, including IBD and unhealthy diets. AC and AC-containing extracts show protective actions in rodent models of ulcerative colitis and high fat diet-associated GI damage. In a rat model of DSS-induced colitis, supplementation with an AC-containing strawberry extract mitigated the associated structural alterations of the ileum and the colon, partially preventing a marked decrease in goblet cell number (Ghattamaneni et al., 2020). Dietary supplementation with a mulberry juice powder containing C3G and cyanidin-3-rutinoside also mitigated DSS-induced loss of body weight, colonic disease scores and decreased goblet cell number (Wang and Hatabu, 2019). In terms of the impact of Western style diets, high consumption of fat was associated with a decrease in the number and capacity of goblet cells to secrete mucins (Dinh et al., 2016; Tomas et al., 2016; Xie et al., 2020b). High fat diets impair mucin 2 (MUC2) secretion from ileal goblet cells through the transcriptional downregulation of meprin-β (Tomas et al., 2016), an enzyme that cleaves MUC2 at the N-terminal favoring mucus detachment and release (Schütte et al., 2014). Supplementation with a cyanidin- and delphinidin-rich extract to mice fed a high fat diet for 14 weeks prevented the decreased levels and increased retention of the mucin protein MUC2 in ileal goblet cells (Cremonini et al., 2019). A similar extract, supplemented for 4 weeks,

also reverted high fat diet-induced decrease in colonic goblet cell number and lower mRNA levels of Tff3 and Krüppel-like factor 4 (Klf4), a protein involved in goblet cell differentiation (Iglesias et al., 2022).

The protective effects of AC on goblet cells, barrier function, inflammation, oxidative stress and dysbiosis underscore the potential relevance of anthocyanidins in the modulation of GI immune responses.

3.4. Anthocyanins and the regulation of inflammation and the redox environment

GI inflammation has major adverse effects on intestinal function but can also extend systemically affecting other organs and tissues. GI inflammation can be triggered by food pathogens, dysbiosis, unhealthy diets (high fat/high sugar), and diseases of genetic origin, e.g. celiac disease and IBD. As previously discussed, a central contributor to intestinal and systemic inflammation is GI barrier permeabilization (Bashiardes et al., 2016; Cani et al., 2007a; Piya et al., 2013). Inflammation is associated with increased oxidant production, which activates redox-sensitive cascades that lead to the production of proinflammatory cytokines and chemokines, closing a self-feeding cycle.

Epidemiological studies link the consumption of AC-rich foods to a reduction of inflammation, including a decrease in serum C-reactive protein in U.S. adults (Chun et al., 2008) and in U.K. women (Jennings et al., 2014), and a decrease in an inflammation score (including 12 biomarkers of inflammation) in U.S. adults (Cassidy et al., 2015). The anti-inflammatory actions of AC have been largely studied in IBD (Li et al., 2019), and at a certain extent in diet-induced obesity. In terms of IBD, in mouse models of DSS-induced colitis, AC fractions isolated from red raspberries (Li et al., 2014), strawberries (Ghattamaneni et al., 2020) and purple sweet potatoes (Mu et al., 2021) attenuated colon altered structure and inflammation. In a model of trinitrobenzene sulfonic acid-induced colitis in mice, gavage with a blueberry AC-rich extract mitigated colon disease parameters and increased myeloperoxidase activity, nitric oxide, and cytokine levels (Wu et al., 2011). In humans with ulcerative colitis, consumption of an AC-rich bilberry extract for 6 weeks resulted in anti-inflammatory effects in the colon and improved disease activity (Biedermann et al., 2013; Roth et al., 2016). Thus, in colon biopsies, the AC-rich bilberry extract led to lower levels of NF-κB activation, and of the pro-inflammatory cytokines interferon gamma and TNFα.

In the context of high fat diets, the triggering of GI inflammation cannot be separated from oxidative stress. Select flavonoids have the capacity to regulate the cell redox environment (Fraga et al., 2018). AC and anthocyanidins have the chemical characteristics that afford the capacity to act as direct antioxidant, i.e. scavenging free radicals or chelating metals (Fraga, 2007). Such actions would be possible at the GI lumen and in cells of the intestinal mucosa, which are exposed to high AC concentrations. On the other hand, given the extensive gut metabolism and limited absorption of parent compounds, AC and anthocyanidin concentrations in blood and tissues is very low and does not allow a direct antioxidant action (Galleano et al., 2010). However, AC could also act through indirect antioxidant mechanisms by modulating the expression and/or activity of oxidant-generating enzymes, e.g. NOXs, and thus decreasing oxidant production, upregulating oxidant defenses through Nrf2-dependent and independent mechanisms, and preserving mitochondria function (Fraga, 2007).

NOXs constitute a family of widely distributed enzymes which modulation is essential to maintain cell redox homeostasis. While the production of small amounts of $O_2^{\cdot-}/H_2O_2$ is relevant in the regulation of signaling cascades, their excessive production is deleterious. It can cause oxidative damage to cell components and/or trigger the overactivation of signals that promote inflammation, TJ opening, and intestinal barrier permeabilization, affecting overall cell function and fate (Rokutan et al., 2008; Sies et al., 2017). NOX1 is present throughout the GI tract, being particularly expressed in the colon. NOX1 is largely the most abundant NOX isoform in intestinal epithelial cells, being involved in the modulation of membrane receptor-initiated signaling, e.g. epidermal growth factor receptor, in GI stem cell proliferation and differentiation, and in the regulation of intestinal barrier permeability (Cremonini et al., 2018; Truong and Carroll, 2012; van der Post et al., 2021). NOX1 overexpression and activation has been linked to pathologies, e.g. in an animal model of necrotic colitis (Kim et al., 2007), and also in humans with Crohn's disease and colorectal cancer (Cho et al., 2018; Szanto et al., 2005). Another NOX isoform, i.e. NOX4, is upregulated in mouse ileum upon high fat diet consumption, and in Caco-2 cells exposed to TNFα (Cremonini et al., 2019) or deoxycholic acid (Wang et al., 2020), a secondary bile acid that accumulates in the gut lumen upon high fat diet consumption. Flavonoids in general, have been shown to inhibit and/or decrease NOX1 and NOX4 expression, and/or the associated $O_2^{\cdot-}$ and H_2O_2 production triggered by fat (Cremonini et al., 2019), pro-inflammatory cytokines (Cremonini et al., 2017), growth factors and/or bile acids (Wang et al., 2020). In mice fed a high fat diet, both NOX1 and NOX 4, and the inducible nitric oxide synthase (iNOS or NOS2) were upregulated in the ileum (Cremonini et al., 2019). This upregulation was associated to oxidative stress, barrier permeabilization, and the overactivation of redox-sensitive signals, i.e. NF-κB and ERK1/2, promoting TJ opening and inflammation.

Supplementation with an extract rich in cyanidin and delphinidin prevented the upregulation of NOX1, NOX4 and NOS2 and the accumulation of adducts resulting from lipid and protein oxidative damage (4-hydroxynonenal (4-HNE)-protein adducts) (Cremonini et al., 2019). Supplementation with a cyanidin- and delphinidin-rich extract to high fat diet-fed mice also prevented NOX1 increased expression in the colon and prevented the associated NF-κB, JNK1/2 and ERK1/2 activation (Iglesias et al., 2022). *In vitro* (Caco-2 cell monolayers), the 3-O-glucosides of cyanidin and delphinidin, the cyanidin metabolite protocatechuic acid, and at a lesser extent peonidin 3-*O*-glucoside, inhibited TNFα-induced increase of NOX1 and NOX4 expression, prevented HNE-adducts accumulation, and ERK1/2 and NF-κB activation (Cremonini et al., 2019). On the other hand, exposure of Caco-2 cells to LPS, while increasing oxidant production and 4-HNE adducts levels, did not upregulate NOX1, suggesting the involvement of mechanisms independent of NOX1. Interestingly, products of AC metabolism, i.e. C3G, protocatechuic acid and gallic acid, also prevented LPS-mediated increase in 4-HNE levels (Iglesias et al., 2022), showing a protective antioxidant action.

In summary, the capacity of select AC to decrease oxidant production, mainly through NOX1 and/or NOX4 modulation, can be relevant for their beneficial effects at the GI tract. The prevention of the overactivation of redox-regulated signaling pathways, e.g. NF-κB, JNK1/2, and ERK1/2, appear essential to sustain intestinal barrier functions, and to prevent local and systemic inflammation.

3.5. Anthocyanins and the microbiota

The GI tract is populated by 10^{14} organisms, mostly bacteria, which keep a mutual beneficial relationship with the GI tract immune and endocrine systems (Maynard et al., 2012), help retrieve additional nutrients from ingested food, and have several metabolic capacities that impact health. The microbiota is involved in the synthesis of vitamins, bile acid metabolism, and production of short chain fatty acids that regulate body energy homeostasis (Kho and Lal, 2018). The GI microbiota composition is negatively affected, condition called dysbiosis, by unhealthy dietary habits (Moreira et al., 2012), obesity (Tilg and Kaser, 2011) and several disease states (Long et al., 2017; Mishra et al., 2016; Ohtani et al., 2014). On the other hand, diet and food components can also have beneficial effects in restoring/improving microbiota profiles, and/or changing the availability of carbohydrates and lipids to microbiota potentially modifying fermentation processes in the colonic region.

As mentioned before, the gut microbiota has a major relevance in the metabolism of AC, ultimately affecting the type and extent of metabolite

absorption and consequently potential local and systemic health benefits (Cassidy and Minihane, 2017). Person-to-person variations in microbiota profiles are considered as one important factor determining differences in inter-individual AC metabolism and bioavailability (Eker et al., 2019). Importantly, the impact of consuming foods rich in AC on the gut microbiota is highly relevant and has been reviewed elsewhere (Faria et al., 2014; Igwe et al., 2019). In brief, evidence from humans and rodent models support the capacity of dietary AC to modulate the microbiota composition. A systematic literature review including three *in vitro*, two animal studies plus one human trial, observed an increase in *Bifidobacterium* spp. in association with AC intake (Igwe et al., 2019). Increases in *Actinobacteria* and *Bacteroidetes* were also observed in several rodent models of AC supplementation (Eker et al., 2019). For example, supplementation of mice with cyanidin and delphinidin glycosides caused a shift in the overall clustering of cecum microbiota populations (Cremonini et al., 2019).

AC supplementation can also provide beneficial actions in the context of the adverse effects of unhealthy diets on the microbiota. Obesity and consumption of high fat and high carbohydrate diets are conditions characterized by dysbiosis in both, rodents and humans (Crovesy et al., 2020; Fan and Pedersen, 2021; Montrose et al., 2021; Moreira et al., 2012; Tilg and Kaser, 2011; Tomas et al., 2016; Turnbaugh et al., 2009). Among several alterations caused by excess fat consumption, consistent changes include a decreased relative abundance of *Bacteroidetes* and *Akkermansia* and an increased relative abundance of *Firmicutes* (Cani et al., 2007b; Cremonini et al., 2019; Crovesy et al., 2020; Tomas et al., 2016; Turnbaugh et al., 2009). The beneficial health effects of *Akkermansia muciniphila* and a link of its decreased abundance with disease has received consistent experimental support (Cani et al., 2022). Characterization of the effects of whole berry powders containing different AC on HFD-induced obesity in C57BL/6J mice showed the expansion of *Firmicutes,* and decreases of *Bacteroidetes* and *Actinobacteria* (Overall et al., 2017). Berry powders containing malvidin- and delphinidin-based AC were more effective than those derived from cyanidin; the type of glycosylation and acetylation was also important for these actions. In a C57BL/6J mouse model of HFD-induced obesity, supplementation with a cyanidin- and delphinidin-rich extract prevented HFD-induced increased *Firmicutes/Bacteroidetes* ratio, and decreased the relative abundance of *Akkermansia,* restoring the overall microbiota clustering to that observed in mice fed a low-fat diet (Cremonini et al., 2019). In a rat model of HFD and vitamin-induced atherosclerosis, an AC extract from *Lycium ruthenicum* mitigated the treatment-induced decrease in *Akkermansia*, *Bifidobacterium* and *Lactobacillus* (Luo et al., 2019).

While conclusive molecular associations between changes in particular microbiota components and beneficial health outcomes are limited, the mitigation of dysbiosis can in part explain some of AC health benefits. For example, as developed in the next section, AC-mediated changes in the microbiota could be involved in the regulation of glucagon-like peptide (GLP)-1 and GLP-2 production and secretion leading to improved glucose homeostasis and GI trophism (Cani et al., 2013; Cremonini et al., 2019; Daveri et al., 2018). The actions of AC on gut microbiota can also: i) benefit the GI barrier function, increasing bacteria populations that generate short chain fatty acids that contribute to the energy requirements of enterocytes (Luo et al., 2019); ii) contribute to preserve intestinal barrier integrity; and iii) regulate mucus secretion and release (Cremonini et al., 2019). Finally, changes in microbiota composition leading to an increase production of kynurenic acid, is proposed to mediate the capacity of AC to mitigate neuroinflammation (Marques et al., 2018), supporting the relevance of the called intestine-brain axis.

3.6. Anthocyanins and the gastrointestinal tract endocrine system

The GI tract is an important endocrine organ in the human body. Hormones are secreted from the enteroendocrine cells located along the GI tract, having local and systemic actions (Gribble and Reimann, 2019). Among the secreted hormones, ghrelin, gastrin, GLP-2 and the incretins GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) play a major role in the regulation of appetite and metabolic responses. Thus, the modulation of these hormones by bioactives emerge as a potential dietary strategy to mitigate, obesity and high fat/high carbohydrate diet-associated unhealthy conditions, particularly T2D.

Recent evidence suggest that GLP-1 and GLP-2 could be regulated by select AC. GLP-1 regulates satiety, insulin secretion from pancreatic β-cells, gut motility and lipid homeostasis. Stressing its importance in the regulation of glucose homeostasis, GLP-1 agonists, are currently used for the treatment of T2D (Agus et al., 2021). As an intestinotrophic hormone, GLP-2 mainly acts enhancing barrier function, increasing nutrient absorption and epithelial proliferation, and exerting protective and trophic actions in the small intestine (Markovic and Brubaker, 2019). In addition, GLP-2 regulates energy balance in part via the gut-brain axis (Baldassano et al., 2016; Ejarque et al., 2021). GLP-1 and GLP-2 are secreted in equimolar amounts by enteroendocrine L cells. They are both originated from the cleavage of proglucagon by the proteolytic enzyme proprotein convertase 1/3, and once released into the bloodstream are rapidly degraded by the enzyme dipeptidyl peptidase IV (DPP-IV). GLP-1 and GLP-2 bind to G protein-coupled receptors, which are located in different organs, such as pancreas, brain and GI tract.

In vivo and *in vitro* studies found that select flavonoids increase circulating levels of GLP-1 and GLP-2 by acting at different levels, including by promoting their release from L-cells, and/or by inhibiting DPP-IV activity (Cremonini et al., 2019, 2021; Kato et al., 2015). Increases of plasma GLP-1 has been observed in rodents after chronic dietary consumption of a cyanidin-and delphinidin-rich extract (Daveri et al., 2018), and acute gavage of grape seed and black currant extracts (Gonzalez-Abuin et al., 2014; Tani et al., 2017). Gavage of grape seed and black current extracts together with glucose administration caused a rapid increase in plasma GLP-1 which was proposed to be associated to an increased GLP-1 secretion (Gonzalez-Abuin et al., 2014; Tani et al., 2017). Long-term dietary consumption of a cyanidin- and delphinidin-rich extract by mice caused an increase in circulating GLP-1, which was associated to an increased expression of proglucagon and DPP-IV in the colon, without changes in plasma DPP-IV activity. Additionally, *in vitro* evidence using GLUTag cells as a model of enteroendocrine cells, showed that delphinidin 3-rutinoside, C3G, delphinidin-3-*O*-glucoside and their gut metabolites, protocatechuic acid and gallic acid, promote GLP-1 secretion through a protein kinase A-dependent mechanism and activation of Ca^{2+}/calmodulin-dependent kinase II (Cremonini et al., 2021; Kato et al., 2015; Tani et al., 2017). In differentiated Caco-2 cells, C3G was also highly effective inhibiting DPP-IV expression and activity (Gao et al., 2020). In terms of GLP-2, chronic consumption of a cyanidin- and delphinidin-rich extract increased GLP-2 in plasma (Cremonini et al., 2019). In a recent clinical trial, consumption of a high-fat meal together with a cyanidin- and delphinidin-rich extract improved postprandial hyperglycemia but did not change postprandial plasma levels of GLP-1 and GLP-2, showing a non-statistically significant decrease of plasma GIP compared to the placebo group (Cremonini et al., 2022). On the other hand, lower postprandial GIP plasma levels were observed after consumption of a high-carbohydrates meal together with an apple and blackcurrant drink (Castro-Acosta et al., 2017).

In summary, even when modulation of GLP-1, GLP-2 and GIP by AC can in part explain their beneficial actions, especially in the mitigation of T2D, further studies are needed to support such effects.

4. Relevance of anthocyanins actions at the gastrointestinal tract on overall health

Current human habits to consume diets high in fat and calories, and low in fruits and vegetables significantly contribute to the world burden

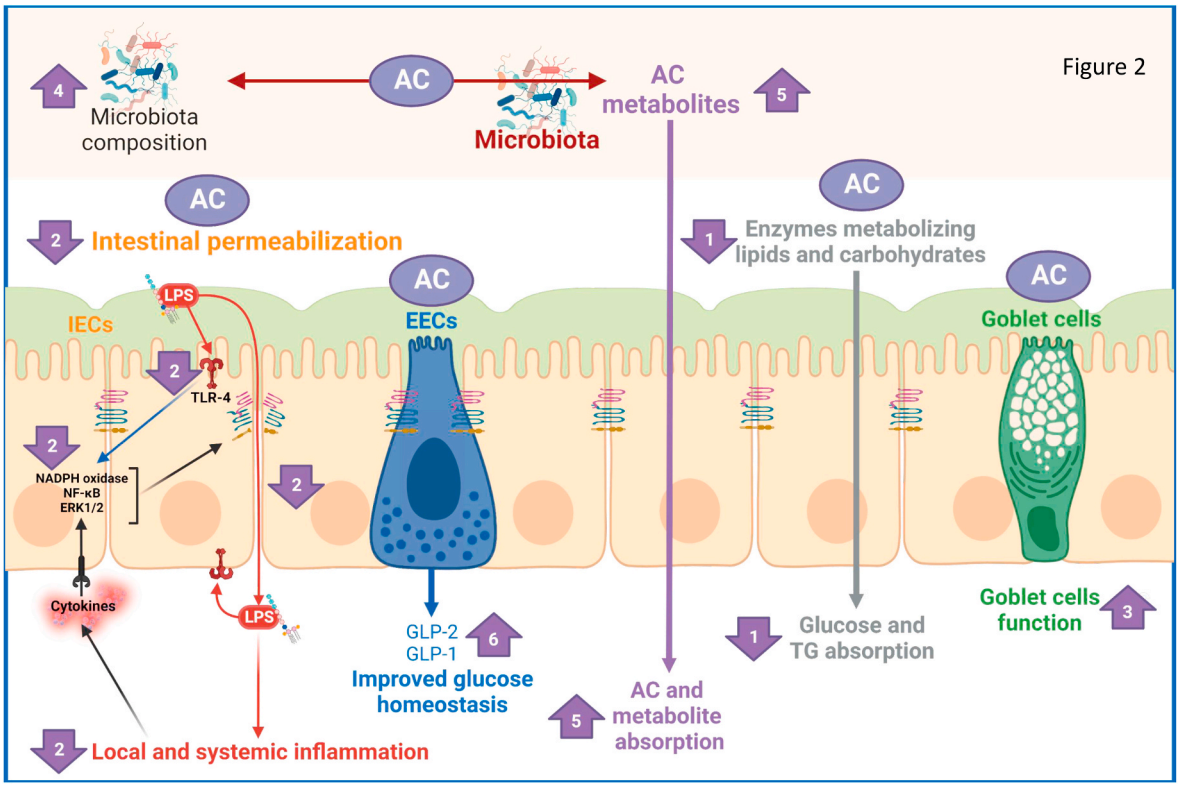


Fig. 2. Actions of anthocyanins at the GI tract. AC can act at different levels in the GI tract which can result in health benefits: 1- inhibiting GI glycosidases and lipases which can limit carbohydrate and lipid absorption; 2- preserving barrier integrity and preventing endotoxemia and the associated inflammation and oxidative stress; 3- sustaining goblet cell number, mucus production and immunological functions; 4- interacting with the microbiota and promoting a healthy microbiota profile; 5- being metabolized by the microbiota to AC metabolites which will be absorbed and have systemic effects; and 6- modulating the metabolism of GI-generated hormones, e.g. GLP-1, GIP and GLP-2, that regulate energy metabolism and GI trophism. Note: arrows indicate the effects of AC increasing or decreasing the outcome. IECs: intestinal epithelial cells; EECs: enteroendocrine cells.

of disease and mortality (Ezzati and Riboli, 2013). In terms of bioactives, AC intake was associated with decreased overall mortality (Ivey et al., 2017). The actions of AC at different levels at the GI tract can in part explain their proposed beneficial effects on human health. The modulation of lipid and glucose homeostasis as a consequence of AC actions inhibiting carbohydrate- and lipid-digesting intestinal enzymes, and consequently, lipid and glucose absorption, AC actions on GI-secreted hormones that regulate energy metabolism, i.e. GLP-1, GIP, and the mitigation of dysbiosis, could all contribute to AC capacity to improve cardiometabolic health (Yang et al., 2017). Accordingly, two meta-analysis studies indicated the association between berry consumption and improvements in parameters of CVD risk (García-Conesa et al., 2018; Luís et al., 2018). Several preclinical studies, already described in previous sections, support the action of AC decreasing hyperglycemia and hyperlipidemia, improving insulin sensitivity and mitigating steatosis. In humans, anthocyanin consumption decreases postprandial hyperglycemia and hyperlipidemia in healthy subjects (Cremonini et al., 2022). In individuals with metabolic syndrome, consumption of AC-rich blueberries improved postprandial increases of plasma glucose, insulin and total cholesterol and attenuated the decreased HDL-C related lipoproteins (Curtis et al., 2022). In support of the effects of AC on parameters of glucose metabolism, consumption of AC was found to be associated to a decreased diabetes risk (Bondonno et al., 2021).

A decrease in systemic inflammation due to the capacity of AC to sustain barrier function and control dysbiosis, can in part contribute to the association between AC consumption and a decreased risk for CVD (Cassidy, 2018; Cassidy et al., 2013; Wang et al., 2014). Additionally, the association between AC consumption and improved cognition has been linked to AC-mediated vascular effects and to a direct action of AC and their metabolites on the brain (Jennings et al., 2021). Considering that LPS reaches the brain, causing neuroinflammation, which can ultimately lead to neurological alterations, the capacity of AC to mitigate endotoxemia could also contribute to AC potential neuroprotective effects.

5. Conclusions

Available evidence strongly supports the beneficial effects of AC consumption in a number of pathologies, especially those having an inflammatory component. Several of these AC-mediated actions can be in part explained through their capacity to modulate different aspects of GI physiology that can result of systemic relevance. The evidence from studies in rodents fed with AC-rich foods and extracts is ample and is mechanistically supported by *in vitro* studies. Also results from clinical studies, although mostly involving a limited number of subjects, showed positive effects of AC-intake on human health. Future investigations are necessary that include: i) clinical trials involving long-term AC supplementation in a representative number of individuals; ii) the use of chemically well-characterized plant preparations, extracts or pure AC or anthocyanidins; and iii) the selection of strong outcomes which are recognized biomarkers of pathological or unhealthy conditions.

Acknowledgements

This work was supported by NIFA-USDA (CA-D*-XXX-7244-H) (PIO); and the Universidad de Buenos Aires (20020190100157BA) (CGF). PIO is correspondent researcher from CONICET, Argentina. Fig. 2 was created using BioRender.com.

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