Metabolism of Anthocyanins and Modulation of Gut Microbiome in Inflammatory Bowel Disease

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Received: October 20, 2020
Accepted: December 29, 2020
Published: December 31, 2020


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Abstract

Anthocyanins are pigments extracted from different plant parts with a great ability to scavenge anti-inflammatory activity and free radicals. The anthocyanin ingestion promotes the synthesis of gut microbiome and host cells. The anthocyanin metabolism shows large variability between individuals. Inter-individual disparities in the metabolites of anthocyanin could modify the development of particular intestinal bacteria. Pre-clinical trials have ascertained that there was a great correlation between anthocyanin consumption and modification of intestinal immune function. This paper sums up the literature on the useful roles of anthocyanin-rich nutrients in the medication and prevention of inflammatory bowel diseases. This takes into account the modification of the gut microbiome and microorganisms produced. Thus, this review would pave the way for natural remedies for human chronic and intestinal diseases during understanding the uses and mechanisms of anthocyanins.

Keywords

Anthocyanin, Metabolism, Intestinal health, Inflammation, Microbiota

Abbreviations

IBD: Inflammatory bowel diseases; DSS: Dextran sodium sulfate; MPO: Myeloperoxidase; NOS: Nitric oxide synthase; MAPK: Mitogen-activated protein kinases; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; ROS: Reactive oxygen species; RNS: Reactive nitrogen species; MCP-1: Monocyte chemoattractant protein-1; MRP-2: Macrophage inflammatory protein-related protein-2; ERK: Lar-regulated kinase; AhR: Aryl hydrocarbon receptor; Nrf2: Nuclear factor erythroid 2-related factor 2; IL-6: Interleukin 6; JNK: c-Jun N-terminal kinases; LPS: Lipopolysaccharide; NADPH: Nicotinamide adenine dinucleotide phosphate; HFD: High-fat diet; IFN-γ: Interferon γ

Introduction

Latest research has highlighted some functional aspects of the human intestinal microbial relationship [1-5]. Gut microbiota operates a broad array of physiological roles and possesses enzymatic and metabolic functions that influence the diet and host’s health [6, 7]. Thus, its efficacy, integrity, and modification of diverse microbiota may have significant consequences for systemic and local
health [8, 9]. As the researcher’s recommendations, a variation in the gut microbiome can decrease [9] or partake in disease susceptibilities such as gastrointestinal inflammation [10]. Gastrointestinal inflammation promotes several lingering inflammatory conditions including cardiovascular disease, Alzheimer’s disease, diabetes, colon cancer, and inflammatory bowel disease [11]. Anthocyanins are a type of flavonoid, a form of polyphenol phytochemicals that suppress inflammation in chronic disease in animal genres [12]. Numerous reports mentioned the power of anthocyanins in inhibiting inflammation. Anthocyanins engage in biological functions like reducing oxidative stress, constraining inflammatory symptoms, and arrangement of cellular signaling transductions [13]. Consequently, anthocyanins have been reported to enhance the protection against intestinal inflammation and reduce chronic diseases [14]. The objective of the present review is to explore the usage of anthocyanin for intestinal protection. It will identify the distribution of anthocyanin in food, synthesis of anthocyanin and bioavailability, and suggest pathways that can clarify the anti-inflammatory role of anthocyanins in the gut.

Types of Anthocyanin and its Content in Foods

Anthocyanins occur naturally as pigments in the flavonoid family [15], which are responsible for red, blue, and yellow coloring in fruits and vegetables [12]. Anthocyanins are glycosidic forms of the 15-carbon skeleton [16], comprising of two (2) benzyl rings (A and B) and a heterocyclic ring (C) structures (Figure 1A). On this basis, the sugar levels differ but are generally a mono as cyanidin-3-O-glucoside [17] or disaccharide unit, frequently glucose, galactose, arabinose, or rhamnose [18]. A lot of anthocyanins are found in fruits as glycosylated at 3-OH (3-O-monoglycosides) and, to a smaller degree, at both 3-OH and 5-OH (3,5-O-diglycosides) [19]. The most commonly known anthocyanins are dependent on twelve anthocyanidins: pelargonidin, aurantinidin, cyanidin, delphinidin, pulchellidin, peonidin, rosinidin, petunidin, europinidin, malvidin, hirsutidin, and capensinidin (Figure 1B). Nonetheless, about 700 anthocyanins were isolated from plants [20]. The anthocyanins content in edible plant (Table 1) parts depends on before and after harvesting treatments like storage conditions, food processing technique, plant genotype, and other environmental factors [21].

Metabolism and bioavailability

Anthocyanins are thoroughly absorbed through metabolizing enzymes or colonic microflora to methylates, sulfates, and glucuronides in the bowel altered in the kidneys and liver (Figure 2) [22]. Nevertheless, transfer to circulation, absorption of tissue, and urine excretion are fairly limited [23]. Additionally, anthocyanin metabolism of microbiota produces common aldehyde and phenolic intermediates consisting of chlorogluconic, protocatechic acid [24], chlorogluconaldehyde, phenylacetic, phenylpropionic acids [25], and 2,4,6-trihydroxybenzaldehyde [26] with varying degrees of hydroxylation.

Dietary anthocyanins catabolism exhibits significant inter-individual variability [27]. It is interesting to state that several individuals can absorb anthocyanins better than others [28, 29], due to polymorphisms of these intestinal enzymes and carriers [30]. Present in vivo research on intestinal microflora breakdown of anthocyanins has suggested that bacterial metabolism includes the separation of glycosidic bonds and the mortification of heterocyclic anthocyanidin [31, 32]. Specific enzymes are involved when anthocyanins are easily digested by different pathways through the stomach and small intestine [33, 34]. Several investigations have ascertained that anthocyanins in the food component can be ingested into the digestive tract and ultimately processed into the intestinal epithelium [35]. Although some of the anthocyanins consumed in the presence of glycosides, esters, and polymers are not taken into the gastrointestinal tract, travel directly to the intestinal tract and are changed by intestinal enzymes [22] or to the colonic microflora [26].

Mechanism of anthocyanin anti-inflammatory activity

There is vast interest in anthocyanin-rich plant products in favor of their anti-inflammatory effects, which are utilized by alteration of cell redox condition, modification of intestinal immune response, and suppress inflammation through overt and indirect pathways, as summarized below:

Gut microbiota

Many reports have supported that an anthocyanin-rich diet has favorable dominance on the deterrence of metabolic illness (Table 1). Anthocyanin metabolites can re-organize gut microflora by obstructing the progress of pathogens and enhancing beneficial genera namely Bifidobacterium spp. [36], Lactobacillus spp. [31], Akkermansia muciniphila, Faecalibacterium prausnitzii [31], Allisonella [37], or Actinobacteria (Figure 2) [31]. The consumption of anthocyanins could upgrade health by decreasing the supply of endotoxins inside the human body and raising the conversion factor of major to minor bile acids [38]. Where intestinal
Microbiota may be modulated by anthocyanins found in food matrices, which are often taken along with proteins, polysaccharides, and other components [39]. In vivo (human) anthocyanins could enhance the creation of favorable bacteria, for example, *Bifidobacterium* spp. and *Lactobacillus−Enterococcus* spp. [2]. In vitro microbial cultivations have revealed that peonidin-based elements in purple sweet potato anthocyanins are very susceptible to cause a spread of *Bifidobacterium adolescentis*, *Lactobacillus acidophilus*, *Bifidobacterium infantis*, and *Bifidobacterium bifidum* and they prevented the manifestation of *Salmonella typhimurium* and *Staphylococcus aureus* [40]. Similarly, black raspberry anthocyanin substitute could boost comparative richness of *Faecalibacterium prausnitzii*, *Eubacterium rectale*, and *Lactobacillus*, and lower the comparative richness of *Desulfovibrio* spp. and *Enterococcus* spp. [41]. Black rice and cyanidin-3-O-glucoside anthocyanin have been established to stimulate substantial growth in the amount of *Bifidobacteria* and *Lactobacilli* [42].

### Table 1: Distribution of anthocyanins commonly occurring in plants.

<table>
<thead>
<tr>
<th>Anthocyanin</th>
<th>Compounds</th>
<th>MW (g/mol)</th>
<th>Dietary source</th>
<th>Mechanism</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyanidin</td>
<td>Cyanidin-3-O-glucoside</td>
<td>484.8</td>
<td>Purple corn</td>
<td>Gut microbiota metabolism miRNA-10b</td>
<td>[115]</td>
</tr>
<tr>
<td></td>
<td>Cyanidin 3-arabinoside</td>
<td>454.8</td>
<td>Blueberry</td>
<td>Glycogen synthesis PTP1B</td>
<td>[24]</td>
</tr>
<tr>
<td></td>
<td>Cyanidin 3-galactoside</td>
<td>449.4</td>
<td>Lingonberry</td>
<td>Metabolism α-Glucosidase</td>
<td>[116, 117]</td>
</tr>
<tr>
<td></td>
<td>Cyanidin 3-sophoroside</td>
<td>611.5</td>
<td>Red raspberry</td>
<td>Antioxidant capacity Oxidative-stress related diseases</td>
<td>[118, 119]</td>
</tr>
<tr>
<td></td>
<td>Cyanidin-3-O-rutinoside</td>
<td>595.5</td>
<td>Black mulberry</td>
<td>Anti-inflammatory Cytokines</td>
<td>[120]</td>
</tr>
<tr>
<td></td>
<td>Cyanidin-3,5-O-diglucoside</td>
<td>611.5</td>
<td>pomegranate juice</td>
<td>Inhibits NF-κB Breast cancer cells</td>
<td>[121, 122]</td>
</tr>
<tr>
<td></td>
<td>Cyanidin-3-O-sambubioside</td>
<td>581.5</td>
<td>Hibiscus sabdariffa</td>
<td>Reduce blood pressure ACE</td>
<td>[123]</td>
</tr>
<tr>
<td></td>
<td>Cyanidin 3-O-sophoroside</td>
<td>611.5</td>
<td>Black peanut skins</td>
<td>Tight junction protein Oxidative stress</td>
<td>[14, 124]</td>
</tr>
<tr>
<td></td>
<td>Cyanidin 3-sambubioside</td>
<td>581.5</td>
<td>Black peanut skins</td>
<td>Tight junction protein Oxidative stress</td>
<td>[14, 124]</td>
</tr>
<tr>
<td>Peonidin</td>
<td>Peonidin-3-O-rutinoside</td>
<td>609.6</td>
<td>Blackcurrants</td>
<td>Insulin-stimulated Glucose production</td>
<td>[125, 126]</td>
</tr>
<tr>
<td></td>
<td>Peonidin-3-O-galactoside</td>
<td>498.9</td>
<td>Aronia</td>
<td>Antioxidant enzyme Cholesterol</td>
<td>[127]</td>
</tr>
<tr>
<td>Pelargonidin</td>
<td>Pelargonidin-3-O-rutinoside</td>
<td>579.5</td>
<td>Strawberries</td>
<td>Inhibit α-glucosidase Blood glucose levels</td>
<td>[128]</td>
</tr>
<tr>
<td></td>
<td>Pelargonidin 3-glucoside</td>
<td>433.4</td>
<td>Strawberry</td>
<td>Inhibits NF-κB</td>
<td>[81]</td>
</tr>
<tr>
<td>Malvidin</td>
<td>Malvidin-3-O-galactoside</td>
<td>528.9</td>
<td>Chagalapoli</td>
<td>Antioxidant activity</td>
<td>[129]</td>
</tr>
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<td></td>
<td>Malvidin-3-O-glucoside</td>
<td>493.43</td>
<td>Grape skin</td>
<td>α-casein</td>
<td>[130]</td>
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<tr>
<td>Delphinidin</td>
<td>Delphinidin-3-O-rhamnoside</td>
<td>465.4</td>
<td>Blackcurrant</td>
<td>LPS stimulation IL-1β mRNA levels</td>
<td>[58]</td>
</tr>
<tr>
<td></td>
<td>Delphinidin-3-O-galactoside</td>
<td>500.8</td>
<td>Empetrum nigrum</td>
<td>Antioxidant enzymes EGCG-induced cytotoxicity</td>
<td>[131, 132]</td>
</tr>
<tr>
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<td>Delphinidin-3-O-gluicoside</td>
<td>500.83</td>
<td>Blackcurrant juice</td>
<td>Caspase-3 Activity</td>
<td>[61]</td>
</tr>
<tr>
<td></td>
<td>Delphinidin-3-O-rutinoside</td>
<td>611.5</td>
<td>Blackcurrant juice</td>
<td>Caspase-3 Activity</td>
<td>[61]</td>
</tr>
<tr>
<td></td>
<td>Delphinidin-3,5-O-diglucoside</td>
<td>627.5</td>
<td>Maqui berry</td>
<td>Tear</td>
<td>[103]</td>
</tr>
<tr>
<td></td>
<td>Delphinidin-3-sambubioside</td>
<td>597.5</td>
<td>Hibiscus</td>
<td>Inhibits NF-κB</td>
<td>[82]</td>
</tr>
<tr>
<td></td>
<td>Delphinidin 3-sambubioside-5-glucoside</td>
<td>759.6</td>
<td>Maqui berry</td>
<td>Insulin-stimulated Glucose production</td>
<td>[133]</td>
</tr>
<tr>
<td>Petunidin</td>
<td>Petunidin-3-O-galactoside</td>
<td>516.9</td>
<td>Chagalapoli</td>
<td>Antioxidant activity</td>
<td>[129]</td>
</tr>
<tr>
<td></td>
<td>Petunidin-3-O-glucoside</td>
<td>514.9</td>
<td>Bilberries</td>
<td>Activation of AMPK Acetyl-CoA carboxylase</td>
<td>[134]</td>
</tr>
<tr>
<td></td>
<td>Petunidin-3-O-arabinoside</td>
<td>484.8</td>
<td>Bilberries</td>
<td>Activation of AMPK Acetyl-CoA carboxylase</td>
<td>[134]</td>
</tr>
</tbody>
</table>

Protein tyrosine phosphatase 1B (PTP1B), Dietary Supplement (DS), angiotensin-converting enzyme (ACE), Epigallocatechin-3-gallate (EGCG)
they also decreased the rates that are linked with inflammation and alteration of the physiological pathways implicated in the rise of obesity [9]. Additionally, anthocyanins may have anti-obesity effects through their anti-inflammatory activity [43]. As ascertained by [44], anthocyanin-rich blackberry and blueberry extract intake prevents food-induced obese inflammation in mice by inhibition of high-fat food (HFD)-induced liver adipogenesis and epididymal adipose cells in obese mice [44]. This anti-obesity can inhibit HFD-induced intestinal barrier dysfunction [45].

**Alleviation effect on inflammatory bowel diseases (IBD)**

Crohn’s disease (it is a type of IBD that may affect the entire intestinal system from mouth to anus) (Figure 3A) and ulcerative colitis (it mostly affects colon and rectum) (Figure 3B) reflect two key types of IBD that have since been among the major gastroenterological issues in the world during the past couple of decades. A lot of the IBD signs is the damage of the gut epithelial membrane that could run to inflammation [46], further inducing bacterial translocation, and the spread of other antigens (Figure 3D). Intestinal epithelial cells, such as goblet cells that contain trefoil factors and mucins, and Paneth cells that manufacture antimicrobial peptides in epithelial crypts [47], bring the defensive mucous surface together and be the cornerstone to the work of the gut barrier. IBD has been related to defect-producing mucus and a loss of the number of goblet tissues [48]. Consequently, preserving the tightness and consistency of the gut membrane is also an important aim in the curing of IBD. The most popular medications for IBD therapy, such as flavonoids, are currently available [49], quercetin [50], resveratrol [51], epigallocatechin-3-gallate [52] and curcumin [53] are among the most prominent polyphenolic compounds whose therapeutic consequences on IBD have been tested in animal models (Figure 3C and E). Such as, there is rising pressure for therapeutic substitutes extracted from natural and functional foods for IBD treatment, namely polyphenols, terpenoids, and alkaloids. Anthocyanins from black rice [54], black raspberry [41], purple carrot [55] and blueberry [56] have been identified to have a strong alleviation outcome on the mouse model of IBD. More specifically, black raspberry anthocyanins will counteract the disparity in the intestinal microbiota caused by dextran sodium sulfate (DSS), which is to say the rise in the relative abundance of Desulfovibrio sp. And the decline in relative abundances of Lactobacillus, Faecalibacterium prausnitzii, and Eubacterium rectale [41]. Likewise, the latest research established that anthocyanins from *Lycium ruthenicum* Murray had protective benefits in IBD across multiple pathways, including blocking pro-inflammatory cytokines (TNF-α, interleukin 6 (IL-6), interleukin 1β, IFN-γ, monocyte chemoattractant protein-1 (MCP-1), lipopolysaccharide (LPS), prostaglandin E2 and its associated mRNA), the close junction proteins (zonaulaire occludens-, Claudin-1 and occludin, and their relevant mRNA) and modulating the microbiome of the intestine [31]. The primary IBD-related bacteria were distinguished by the correlation analysis (Lachnospiraceae, Parabacteroides, Oscillibacter, Helicobacter, Parasutterella, and Porphyromonadaceae).

**Immunomodulation**

Much research on the immunomodulatory function of anthocyanins focuses on their anti-inflammatory ability. Several elements involved in intestinal immunity have been strongly involved in colitis pathogenesis, including dendritic cells [57], macrophages [58], B-cells, T-cells, eosinophils, neutrophils, and their secreted chemokines and cytokines [14]. There has been mounting proof from animal research and human clinical tests that diets abundant in anthocyanins could guard against inflammation and escalate intestinal permeability, along with
the promotion of colon health through their capacity to modify bacterial progression and the microbial atmosphere in the intestines [14]. In recent research by Taverniti et al. [59], the ingestion of anthocyanin-rich blueberry modifies the differentiation of Caco-2 cells and the resulting activation and penetration of pro-inflammatory immunocytes in the colon [59, 60]. Additionally, the intake of delphinidin-3-O-glucoside and delphinidin-3-rutinoside-rich blackcurrant extract modulated the transcription of genes linked to cell cycle guidelines and apoptosis that are deregulated in colon cancer [61]. The p-Coumaroyl anthocyanin concentrate (containing peonanin, petanin, pelanin, and malvanin) extracted from the deep purple potato cultivar Jayoung demonstrated an inhibitory impact on transcription and translocation of the kappa-light-chain nuclear factor activated B cells (NF-κB) in RAW264.7 macrophages [62]. Furthermore, the application of deep purple potatoes full of petunidin and malvidin demonstrated to increase the production of pro-inflammatory cytokines, thus attenuating dextran sodium sulfate (DSS)-induced colitis in mice [63]. A different in vitro research recorded that a natural sour cherry anthocyanin extract, applied to human Caco-2 cells, reverted the p65 subunit from the cytosol to the nucleus [64]. Anthocyanin-rich black currant isolate and cyanidin-3-O-glucoside application significantly inhibited the lipopolysaccharide-induced exudation of interleukin-6 by human macrophages [65]. Cyanidin-3-O-glucoside can decrease the formation of COX-2 prostaglandin E2 (PGE2)-induced colitis in mice [66]. Cyanidin and cyanidin-3-O-glucoside had a distinct protective action on macrophage migration, macrophage inflammatory protein-related protein-2 (MRP-2), and pro-inflammatory chemokines monocyte MCP-1 and in vitro [67]. Black currant supplementation in the obese-associated chronic inflammation mice model showed increased acetate production and decreased manifestation levels of IL-1β and IL-6 mRNA against the control rats [68]. In the same study, Lee et al. [69] confirmed that the intake of black currant weakens hepatic inflammation and splenocyte-stimulated lipopolysaccharide inflammatory reactions in obese mice [69]. The preventive role of anthocyanin separated from bilberries has been described in the trinitrobenzene sulphonic acid-induced model of colitis mice, where researchers observed that anthocyanin therapy is not only preserved IL-10 secretion but also decreased serum rates TNF-α, IL-1, IL-6, and IFN-γ [70]. More studies found that mice complemented with 100 mg/kg black rice extract through oral gavage found a drop in DSS-induced colonic IL-6, IL-1β, and TNF-α expression rates and Myeloperoxidase (MPO) rates that are linearly linked to neutrophil infiltration [54]. Different results are recorded in research using grapes where anthocyanin-rich grape pomace extracts have been established to deter a DSS-induced rise in IL-6, MPO, and nitric oxide synthase (NOS) produced by bacterial products and pro-inflammatory cytokines [71].

**Intestinal barrier function and inhibitory mechanism**

Acute inflammation destabilizes the integrity of the gastrointestinal tract and enhances susceptibility to endotoxin, which aggravates the inflammation [72]. Anthocyanins reduce inflammation by various intracellular signaling pathways such as NF-κB and mitogen-activated protein kinases (MAPK) [73]. IkB kinase (IKK) and IkB phosphorylates would be triggered resulting from the disintegration of NF-κB, this will occur due to stimuli reaction, such as bacterial antigens, cytokines, and oxidative stress [74]. NF-κB is then translocated into the nucleus, connects to the stimulus element, and switches on the transcription of numerous pro-inflammatory genes [75]. NF-κB is broadly expressed and correlates to the ‘quick-acting’ key transcription component, thereby performing a key and prompt role in reacting to dangerous cellular stimuli [76]. Anthocyanins can enhance the performance of the intestinal membrane through the following mechanisms: 1) Decrease epithelial permeability via interaction with tight junction proteins and the actin cytoskeleton by a lute-regulated kinase (ERK) 1/2 ERK 1/2 and inhibit oxidative stress-induced barrier dysfunction in vitro [77]; 2) Reduction of oxidative stress by triggering of the extraction of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [78]; 3) Preservation of a strong intestinal junction boundary and function [45] or 4) Upregulation of nuclear factor erythroid 2-related factor 2 (Nrf2) lessened NF-κB initiation and obstruct cytokine induction of inducible nitric oxide synthetase, cyclooxygenase-2 and IL-8 in HT-29 cells [79]. Anthocyanin-rich fraction consumption from Portuguese blueberries (Vaccinium corymbosum L.) reduced 2, 4, 6-Trinitrobenzene sulfonic acid-induced risk to the gut epithelium membrane and significantly reduced inflammatory cytokine production owing to repression of ERK and c-Jun N-terminal kinases (JNK) phosphorylation [80]. In the animal model and cell model, Delphinidin 3-sambubioside and Delphinidin decreased the creation of IL-6, MCP-1, and TNF-α and tapered mouse paw edema caused by LPS and down-regulated NF-κB trail and MEK1/2-ERK1/2 transmission [81]. Cellular transmission research showed that Delphinidin 3-sambubioside and Delphinidin down-regulated NF-κB trail and MEK1/2-ERK1/2 transmission [82]. Pelargonidin 3-glucoside-rich strawberry extract inhibited high-fat/high-sucrose diet-influenced gut infection by suppressing the NF-κB trail and minimizing cyclooxygenase-2 and TNF-α protein transcription. In that sense, Anthocyanin can hold back the NF-CNB pathway through a set of mechanisms: 1) Reduce IkB phosphorylation; 2) Inhibit the nuclear translocation of the NF-κB p65 subunit; 3) Supress TLR4 signaling [83].

Conversely, the preliminary conclusion of the existing research showed that potato polyphenolic mixtures significantly hindered both α-amylase and α-glucosidase activity, with equivalent and far higher efficacy than acarbose, respectively [84]. Although Cinnamomum Camphora fruit extract and individual cyanidin have been determined to have significant preventive action on α-glucosidase, cyanidin 3-rutinoside and cyanidin-3-O-glucoside have not been proved to have an inhibitory action on α-glucosidase [85]. Additionally, anthocyanins have been expressed to have additional efficiency in hindering α-glucosidase and then acarbose. Two types of binding methods between anthocyanins and enzymes have been perceived as (i) cyanidin exerted promptly connect to amino acid deposits in the functioning positions of enzymes and prevent the attachment of the substrate; (ii) cyanidin
exerted interact with amino acid deposits near the functioning spot and close the channel to the active center.

**Lipid rafts**

Lipid carriers are complex plasma membrane structures distinguished by excessive cholesterol and glycosphingolipid content and cell transmitting proteins [86]. It serves a significant function in the communicating direction of TLR4. Reports suggest that lipid matrix destruction may suppress LPS-induced immune response [87, 88]; therefore, it is essential for LPS/TLR4 signaling. Petunidin rich in *Lycium ruthenicum* in hale and hearty adults decreased fecal endotoxin and improved fecal short-chain fatty acids [32]. Ingestion of anthocyanin supplements for four weeks could have decreased serum lipopolysaccharide-binding protein, a precursor of metabolic endotoxemia, in obese persons [89]. This change has been connected with the alteration of *Facellibacterium, Odoribacterium, Parvimonas*. Anthocyanins such as cyanidin-3-O-β-glucoside interrupt the lipid raft association and restrain the inflammatory signaling of NF-κB and MAPK downstream [90], Fu et al. [90] also proved that cyanidin-3-O-β-glucoside lowered the creation of LPS-induced cytokines by blocking NF-κB and Irf3 activation in the lung of acute lung damaged mice [91]. Anthocyanins happen to interrupt lipid rafts by either preventing oxidation of cholesterol or depleting cholesterol, which would then enable downstream pro-inflammatory signaling and lipid rafting [92, 93].

**Reactive oxygen and nitrogen species**

Flavonoid-anthocyanin compounds can inhibit inflammation in the guts by direct or indirect processes that mitigate oxidative stress. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) were created in abundance during systemic inflammation, disrupting redox homeostasis [62]. ROS and RNS perform important functions in cancer commencement and development [94]. Thus, the purpose of deregulation of reactive oxygen and nitrogen species is closely linked to intestinal inflammation [95]. Intestinal inflammation enhances the penetration of immunocytes namely macrophages and neutrophils; effective NADPH oxidase and MPO release huge quantities of ROS and lessen endogenous antioxidant enzymes, resulting in strong cytotoxicity in the intestinal tissue [11]. Also, bacterial compounds and pro-inflammatory cytokines cause enhanced development of inducible NOS in infected macrophages; the overproduction of nitric oxide integrates with superoxide anions and generates peroxynitrites that cause oxidation and nitration [96]. Anthocyanins display good antioxidant function in *vitro* through scavenging free radicals and chelating metals [97]. Nevertheless, as a result of the reduced stability and low bioavailability in *vivo* [98], the plasma level of anthocyanins is usually too small to have significant antioxidant benefits [15]. The antioxidant action of anthocyanins is therefore likely to be mediated by the cytosolic aryl hydrocarbon receptor (AhR) and the Nrf2 pathway [99]. This AhR-dependent activation of Nrf2 by 2,3,7, 8-Tetrachlorodibenzo-p-dioxin is linked with Nrf2 hindered initiation and DNA binding kinetics relative to AhR activation kinetics [100]. Certain peonidin, petunidin, cyanidin, malvidin, delphinidin, pelargonidin bind to AhR and then induce the dissociation of the Kelch-like ECH-associated protein 1 (Keap1)/Nrf2 complex by physical associations with Nrf2 and Keap1, thereby enhancing the translocation of Nrf2 to the nucleus and the following expression of standard antioxidant enzymes [101] such as glutathione peroxidase, superoxide dismutase, peroxiredoxin, heme oxygenase-1, and catalase. By lowering oxidative stress, anthocyanin can marginally withhold the nucleotide-binding oligomerization domain [15], the leucine-rich repeat-containing family of genes, and the pyrin-containing 3 inflammatory groups [102]. In contemporary research in humans, Nakamura et al. [103] proved that the berry extract and its precursor delphinidin 3,5-O-diglucoside inhibited the creation of ROS from the lacrimal gland [103]. *In vitro* experiments also indicate that cyanidin-3-O-β-glucoside inhibits NOS protein and mRNA expression and hence reduces nitric oxide overproduction [104]. *In vitro* studies also demonstrate that cyanidin-3-O-β-glucoside inhibits NOS [105], lipopolysaccharide-induced, and COX-2 expression and hence reduces nitric oxide overproduction [106]. Anthocyanin-containing cornelian cherry helps avoid fed-induced atherosclerosis, and the ingestion of fruit containing in these mixtures can have beneficial implications on the cardiovascular system [107].

**Endoplasmic reticulum**

Increasing data indicate that anthocyanins can impact performance on the endoplasmic reticulum (ER) [108], proteasome [109], and mitochondria machinery, and many ancillary elements, such as peroxisomes, to activate transmission pathways as inflammation [110]. In the DSS-influenced colitis pattern, delphinidin reduced ER stress-induced autophagy in colorectal mucosal cells, thereby attenuating the frequency of colitis [111]. Myricetin derivative avoided ulcerative colitis and colorectal tumor by attenuating vigorous ER tension in irritated colonic mucosal tissues in the murine azoxymethane/ DSS hybrid [112]. Black raspberry concentrate ingestion modulated the gene transcription of epidermal development signal receptor, thymidylate synthase, cyclin-dependent kinase inhibitor 1A in malignant colonic tissues, whereas the cluster of distinction 44 and beat-catenin is modulated in malignant and regular tissues [113]. Cyanidin-3-O-glucoside reduced ER stress and inflammation via phosphatidylinositol 3-kinase/protein kinase B activation and c-Jun N-terminal kinase, activating transcription factor 6, and especially NF-κB suppression [114].

**Experimental simulation results, conclusion, and future perspectives**

Human intervention studies revealed that anthocyanin compounds can be utilized as remedies for inflammatory bowel diseases. Additionally, it has been ascertained that anthocyanin-rich foods could be produced to treat colitis and colon cancer in rodent models [14]. Correspondingly, there are less validating proofs from human interaction trials. Preliminary experiments of pigments in vegetables and fruit for the obstructing of ulcerative colitis have been promising. Anthocyanin-rich foods modulate biomarkers related to
gut inflammation in stable individuals, but there is minimal clinical evidence of modulating gut immune function. Cell-centered experiments on the anti-inflammatory potency of anthocyanins and immune function should be planned and interpreted with caution, considering the significance of bioaccessibility and anthocyanin metabolism [98]. The abundance of information indicates that anthocyanins and their metabolites affect multiple inflammation-related mechanisms in the intestine. However, the advantage of these pathways for healing and preventive action in humans remains unclear. Advancement in this field would take a deeper comprehension of how the dietary matrix and inter-individual variations in anthocyanin metabolism affect the well-being of the intestines. The promising findings of these trials support the ongoing production of anthocyanin-rich foods for clinical use in inflammatory bowel disease, and some advancement has been accomplished in mechanisms studies, but the designs and approach of these studies need to be complemented in the future.

Author's Contribution

Conflict of Interest
Authors declare no conflict of interest.

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Metabolism of Anthocyanins and Modulation of Gut Microbiome in Inflammatory Bowel Disease

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