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

Citation: Alnadari F, Abdin M, Ennab W, Mohedein A, Nasiru MM. 2020. Metabolism of Anthocyanins and Modulation of Gut Microbiome in Inflammatory Bowel Disease. J Food Chem Nanotechnol 6(4): 207-217.

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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 chemotactrant 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
As the researcher's recommendations, a variation in the gut microbiome can decrease [9] orpartake 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 methyleys, 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 phloroglucinol, protocatechuic acid [24], phloroglucinaldehyde, 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 microbiota 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 adolescens*, *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.

| Anthocyanin            | Compounds                        | MW (g/mol) | Dietary source          | Mechanism                                      | Reference                  |
|------------------------|----------------------------------|------------|-------------------------|------------------------------------------------|----------------------------|
| Cyanidin               | Cyanidin-3-O-glucoside           | 484.8      | Purple corn             | Gut microbiota metabolism                       | [115]                      |
|                        | Cyanidin 3-arabinoside           | 454.8      | Blueberry               | Glycogen synthesis                             | [24]                       |
|                        | Cyanidin 3-galactoside           | 449.4      | Lingonberry             | Metabolism                                     | [116, 117]                 |
|                        | Cyanidin 3-sophoroside           | 611.5      | Red raspberry           | Antioxidant capacity                            | [118, 119]                 |
|                        | Cyanidin-3-O-rutinoside          | 595.5      | Black mulberry          | Anti-inflammatory                              | [120]                      |
|                        | Cyanidin-3,5-O-diglucoside       | 611.5      | Pomegranate juice       | Inhibits NF-xB                                 | [121, 122]                 |
|                        | Cyanidin-3-O-sambubioside        | 581.5      | Hibiscus sabdariffa     | Reduce blood pressure                          | [123]                      |
|                        | Cyanidin 3-O-sophoroside         | 611.5      | Black peanut skins      | Tight junction protein                          | [14, 124]                  |
|                        | Cyanidin-3-sambubioside          | 581.5      | Black peanut skins      | Tight junction protein                          | [14, 124]                  |
| Peonidin               | Peonidin-3-O-rutinoside          | 609.6      | Blackcurrants           | Insulin-stimulated                             | [125, 126]                 |
|                        | Peonidin-3-O-galactoside         | 498.9      | Aronia                  | Antioxidant enzyme                             | [127]                      |
| Pelargonidin           | Pelargonidin-3-O-rutinoside      | 579.5      | Strawberries            | Inhibit α-glucosidase                          | [128]                      |
|                        | Pelargonidin 3-glucoside         | 433.4      | Strawberry              | Inhibits NF-xB                                 | [81]                       |
| Malvidin               | Malvidin-3-O-galactoside         | 528.9      | Chagalapoli             | Antioxidant activity                           | [129]                      |
|                        | Malvidin-3-O-glucoside           | 493.4      | Grape skin              | α-casein                                       | [130]                      |
| Delphinidin            | Delphinidin-3-O-rhamnoside       | 465.4      | Blackcurrant            | LPS stimulation                                 | [58]                       |
|                        | Delphinidin-3-O-galactoside      | 500.8      | Empetrum nigrum         | Antioxidant enzymes                            | [131, 132]                 |
|                        | Delphinidin-3-O-glucoside        | 500.83     | Blackcurrant juice      | Caspase-3 Activity                             | [61]                       |
|                        | Delphinidin-3-O-rutinoside       | 611.5      | Blackcurrant juice      | Caspase-3 Activity                             | [61]                       |
|                        | Delphinidin-3,5-O-diglucoside    | 627.5      | Maqui berry             | Tear                                           | [103]                      |
|                        | Delphinidin-3-sambubioside       | 597.5      | Hibiscus                | Inhibits NF-xB                                 | [82]                       |
|                        | Delphinidin-3-sambubioside-5-glucoside | 759.6 | Maqui berry            | Insulin-stimulated                             | [133]                      |
| Petunidin              | Petunidin-3-O-galactoside        | 516.9      | Chagalapoli             | Antioxidant activity                           | [129]                      |
|                        | Petunidin-3-O-glucoside          | 514.9      | Bilberries              | Activation of AMPK                             | [134]                      |
|                        | Petunidin-3-O-arabinoside        | 484.8      | Bilberries              | Activation of AMPK                             | [134]                      |

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). As such, 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 (zonulae occludens-, 1claudin-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 malvadin) 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 reported 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 in human gut HT-29 cells [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-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-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-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-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].

**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]. IκB kinase (IKK) and IκB 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 applying 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 lar-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 the extraction of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [78]; 3) Preservation of a strong intestinal junction boundary and function [45] or 4) Uptregulation 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-Trimethoxybenzene 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 MEK1/2/ERK1/2 transmission [83]. In that sense, Anthocyanin can hold back the NF-CNB pathway through a set of mechanisms: 1) Reduce IκB phosphorylation; 2) Inhibit the nuclear translocation of the NF-κB p65 subunit; 3) Suppress 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
exert 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 glycosphinoglipid 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 *Faciodibacterium, Odoribacter*, and *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 IκB 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**

Flavon-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], proteosome [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

Conceptualization: F. Alnadari, M. Abdin, W. Ennab, A. Mohedein, and M. M. Nasiru. Review of previous literature: F. Alnadari, M. Abdin, and W. Ennab. Writing of original draft: F. Alnadari, M. Abdin, W. Ennab, and A. Mohedein. Revising and editing of final draft: F. Alnadari and M. M. Nasiru.

Conflict of Interest

Authors declare no conflict of interest.

References

1. Fang J. 2014. Bioavailability of anthocyanins. Drug Metab Rev 46(4): 508–520. https://doi.org/10.3109/03602532.2014.978080
2. Hidalgo M, Oruna-Concha MJ, Kolida S, Walton GE, Kalliiratha S, et al. 2012. Metabolism of anthocyanins by human gut microflora and their influence on gut bacterial growth. J Agric and Food Chem 60(15): 3882-3890. https://doi.org/10.1021/jf3002153
3. Pojer E, Mattivi F, Johnson D, Stockley CS. 2013. The Case for anthocyanin consumption to promote human health: a review. Compr Rev Food Sci Food Saf 12(5): 483–508. https://doi.org/10.1111/1541-4337.12024
4. Sanchez-Patan F, Cueva C, Monagas M, Walton GE, Gibson GR, et al. 2012. In vitro fermentation of a red wine extract by human gut microbiota: changes in microbial groups and formation of phenolic metabolites. J Agric Food Chem 60(9): 2136–2147. https://doi.org/10.1021/jf2040115
5. Zhang X, Yang Y, Wu Z, Weng P. 2016. The modulatory effect of anthocyanins from purple sweet potato on human intestinal microbiota in vitro. J Agric Food Chem 64(12): 2582-2590. https://doi.org/10.1021/acs.jafc.6b00586
6. Roberfroid M, Gibson GR, Hoyles L, Mccartney AL, Rastall R, et al. 2010. Prebiotic effects: metabolic and health benefits. Br J Nutr 104 Suppl 2: S1–63. https://doi.org/10.1017/S0007114510003363
7. Rowland I, Gibson G, Heiniken A, Scott K, Swann J, et al. 2018. Gut microbiota functions: metabolism of nutrients and other food components. Eur J Nutr 57(1): 1–24. https://doi.org/10.1007/s00394-017-1445-8
8. Belkaid Y, Hand TW. 2014. Role of the microbiota in immunity and inflammation. Cell 157(1): 121–141. https://doi.org/10.1016/j.cell.2014.03.011
9. Morais CA, De Rosso VV, Estadella D, Pisani LP. 2016. Anthocyanins as inflammatory modulators and the role of the gut microbiota. J Nutr Biochem 33: 1–7. https://doi.org/10.1016/j.jnutbio.2015.11.008
10. Abraham C, Medzhitov R. 2011. Interactions between the host innate immune system and microbes in inflammatory bowel disease. Gastroenterology. 140(6): 1729–1737. https://doi.org/10.1053/j.gastro.2011.02.012
11. Pei R, Liu X, Belling B. 2020. Flavonoids and gut health. Curr Opin Biotechnol 61: 153–159. https://doi.org/10.1016/j.cjopbi.2019.12.018
12. Khoo HE, Azlan A, Tang ST, Lim SM. 2017. Anthocyanidins and anthocyanins: colored pigments as food, pharmaceutical ingredients, and the potential health benefits. Food Nutr Res 61(1): 1–21. https://doi.org/10.1080/16546628.2017.1361779
13. Abdin M, Hamed YS, Akhtar HMS, Chen D, Chen G, et al. 2020. Antioxidant and anti-inflammatory activities of target anthocyanins di-glucosides isolated from Syzygium cumini pulp by high speed counter-current chromatography. J Food Biochem 44(6): 1050–1062. https://doi.org/10.1111/jfbc.13209
14. Li S, Wu B, Fu W, Reddivari L. 2019. The anti-inflammatory effects of dietary anthocyanins against ulcerative colitis. Int J Mol Sci 20(10): 2588. https://doi.org/10.3390/ijms20102588
15. Martin J, Kuskoski EM, Navas MJ, Asuero AG. 2017. Antioxidant capacity of anthocyanin pigments. In: Justino G (ed) Flavonoids–from biosynthesis to human health, IntechOpen, pp 205–255.
16. Habtemariam S, 2019. Bilberries and blueberries as potential modulators of type 2 diabetes and associated diseases. In: Habtemariam S (ed) Medicinal foods as potential therapies for type-2 diabetes and associated diseases, Elsevier, pp 135–175. https://doi.org/10.1016/B978-0-08-102922-0.00007-9
17. Olivas-Aguire FJ, Rodrigo-Garcia J, Martinez-Ruiz ND, Cardenas-Robles AI, Mendoza-Diaz SO, et al. 2016. Cyanidin-3-O-glucoside: physical-chemistry, foodomics and health effects. Molecules 21(9): 1264. https://doi.org/10.3390/molecules21091264
18. Prior RL, Wu XL. 2006. Anthocyanins: structural characteristics that result in unique metabolic patterns and biological activities. Free Radic Res 40(10): 1014–1028. https://doi.org/10.1080/10715760600758522
19. Welch CR, Wu Q, Simon J. 2008. Recent advances in anthocyanin analysis and characterization. Curr Anal Chem. 4(2): 75–101. https://doi.org/10.2174/157341108784587795
20. Ma C, Yang L, Yang F, Wang W, Zhao C, et al. 2012. Content and color stability of anthocyanins isolated from Schisandra chinensis fruit. Int J Mol Sci 13(11): 1249-14310. https://doi.org/10.3390/ijms13111249
21. Kärland U, Moor U, Sandell M, Karjalainen RO. 2014. The impact of harvesting, storage and processing factors on health-promoting phytochemicals in berries and fruits. Process. 2(3): 596–624. https://doi.org/10.3390/pr2030596
22. Tian L, Tan Y, Chen G, Wang G, Sun J, et al. 2019. Metabolism of anthocyanins and consequent effects on the gut microbiota. Crit Rev Food Sci Nutr 59(6): 982-991. https://doi.org/10.1080/10408398.2018.1533517
23. He J, Giusti MM. 2010. Anthocyanins: natural colorants with health-promoting properties. Annu Rev Food Sci Technol 1: 163–187. https://doi.org/10.1146/annurev.food.080708.100754
24. Tian JI, Liao XJ, Wang YH, Si X, Shu C, et al. 2019. Identification of Cyanidin-3-arabinoside extracted from blueberry as a selective protein tyrosine phosphatase 1B inhibitor. J Agric Food Chem 67(49): 13624–13634. https://doi.org/10.1021/acs.jafc.9b06155
25. Nikolici NC, Savikin K, Bigovc D, Trifkovic K, Dordiev V, et al. 2019. Potential of encapsulated phytochemicals in hydrogel particles. In: Grumezescu AM (ed) Nanomaterials for drug delivery and therapy, Elsevier, pp 305-342.
Peng Y, Yan Y, Wan P, Dong W, Huang K, et al. 2020. Effects of long-term intake of anthocyanins from Lycium ruthenicum Murray on the gut microbiota modulation and anti-inflammatory properties of anthocyanins from the fruits of Lycium ruthenicum Murray in dextran sulfate-induced colitis in mice. *Free Radic Biol Med* 136: 96-108. https://doi.org/10.1016/j.freeradbiomed.2019.04.005

Peng Y, Yan Y, Wan P, Dong W, Huang K, et al. 2020. Effects of long-term intake of anthocyanins from *Lycium ruthenicum* Murray on the organism health and gut microbiota in vivo. *Food Res Int* 130: 108952. https://doi.org/10.1016/j.foodres.2019.108952

Fernandes I, De Freitas V, Mateus N. 2014. Anthocyanins and human health: how gastric absorption may influence acute human physiology. *Nutr Aging* 2(1): 1-14. https://doi.org/10.3233/NUA-130030

Kalt W. 2019. Anthocyanins and their C6-C3-C6 metabolites in humans and animals. *Molecules* 24(22): 4024. https://doi.org/10.3390/molecules24224024

Faria A, Pestana D, Azevedo J, Martel FT, Freitas VD, et al. 2010. Interplay of five peonidin-based anthocyanins extracted from purple sweet potato (*Ipomoea batatas*). *Molecules* 15(3): 1227-49. https://doi.org/10.3390/molecules15031227

Faria A, Pestana D, Azevedo J, Martel FT, Freitas VD, et al. 2014. Antioxidant and prebiotics activity of anthocyanins from black rice (*Oryza sativa*). *Food Chem* 146: 562-69. https://doi.org/10.1016/j.foodchem.2014.01.048

Zhou L, Xie MH, Yang F, Liu JK, 2020. Antioxidant activity of high purity blueberry anthocyanins and the effects on human intestinal microbiota. *LWT* 117: 108621. https://doi.org/10.1016/j.lwt.2019.108621

Yan YM, Peng YJ, Tang JL, Mi J, Lu L, et al. 2018. Effects of anthocyanins from the fruit of *Lycium ruthenicum* Murray on intestinal microbiota. *J Funct Foods* 48: 533-541. https://doi.org/10.1016/j.jff.2018.07.053

Wang H, Liu D, Ji Y, Liu Y, Xu L, et al. 2020. Dietary Supplementation of black rice anthocyanin extract regulates cholesterol metabolism and improves gut microbiota dysbiosis in C57BL/6J mice fed a high-fat and cholesterol diet. *Mol Nutr Food Res* 64(8): e1900876. https://doi.org/10.1002/mnfr.201900876

Sun H, Zhang P, Zhu Y, Lou Q, He S. 2018. Antioxidant and prebiotic activity of five peonidin-based anthocyanins extracted from purple sweet potato (*Ipomoea batatas* (L.) Lam.). *Sci Rep* 8(1): 5018. https://doi.org/10.1038/s41598-018-23397-0

Chen L, Jiang B, Zhong C, Guo J, Zhang L, et al. 2018. Chemoprevention of colorectal cancer by black raspberry anthocyanins involved the modulation of gut microbiota and SFRP2 demethylation. *Carcinogenesis* 39(3): 471-481. https://doi.org/10.1093/carcin/bgy009

Zhu Y, Sun H, He S, Lou Q, Yu M, et al. 2018. Metabolism and prebiotic activity of anthocyanins from black rice (*Oryza sativa* L.) *in vitro*. *PLoS One* 13(4): e0195754. https://doi.org/10.1371/journal.pone.0195754

Lee YM, Yoon Y, Yoon H, Park HM, Song S, et al. 2017. Dietary Anthocyanins against obesity and inflammation. *Nutrients* 9(10): 1089. https://doi.org/10.3390/nu9101089

Wu T, Gao Y, Guo X, Zhang M, Gong L. 2018. Blackberry and blueberry anthocyanin supplementation counteract high-fat-diet-induced obesity by alleviating oxidative stress and inflammation and accelerating energy expenditure. *Oxid Med Cell Longev* 2018: 4051322. https://doi.org/10.1155/2018/4051322

Cermonini E, Davari E, Mastaloudis A, Adamo AM, Mills DJ, et al. 2019. Anthocyanins protect the gastrointestinal tract from high fat diet-induced alterations in redox signaling, barrier integrity and dysbiosis. *Redox Biol* 26: 101269. https://doi.org/10.1016/j.redoxbiol.2019.101269

Su L., Shen L., Clayburgh DR, Nalle SC, Sullivan EA, et al. 2009. Targeted epithelial tight junction dysfunction causes immune activation and contributes to development of experimental colitis. *Gastroenterology* 136(2): 551-563. https://doi.org/10.1053/j.gastro.2008.10.081

Ullig HH, Powrie F. 2018. Translating immunity into therapeutic concepts for inflammatory bowel disease. *Annu Rev Immunol* 36: 755-781. https://doi.org/10.1146/annurev-immunol-042617-053055

Gersemann M, Becker S, Kubler I, Kosloski M, Wang G, et al. 2009. Differences in goblet cell differentiation between Crohn's disease and ulcerative colitis. *Differentiation* 77(1): 84-94. https://doi.org/10.1016/j.diff.2008.09.008

Chen T, Hu S, Zhang H, Guan Q, Yang Y, et al. 2017. Anti-inflammatory effects of Dioscorea alata L. anthocyanins in a TNBS-induced colitis model. *Food Funct* 8(2): 659-669. https://doi.org/10.1039/c6fo01273f

Dodda D, Chhajed R, Mishra J. 2014. Protective effect of quercetin against acetic acid induced inflammatory bowel disease (IBD) like symptoms in rats: possible morphological and biochemical alterations. *Pharmacol Rep* 66(1): 169-73. https://doi.org/10.1016/j.pharep.2013.08.013

Yao J, Wei C, Wang JY, Zhang R, Li YX, et al. 2015. Effect of resveratrol on Treg/T17 signaling and ulcerative colitis treatment in mice. *World J Gastroenterol* 21(21): 6572-6581. https://doi.org/10.3745/wjg.v21.i21.6572

Birzer ZT, Elias RJ, Vijay-Kumar M, Lambert J. 2016. (-)-Epigallocatechin-3-gallate decreases colonic inflammation and permeability in a mouse model of colitis, but reduces macronutrient digestion and exacerbates weight loss. *Mol Nutr Food Res* 60(10): 2267-2274. https://doi.org/10.1002/mnfr.201501042

Taylor RA, Leonard MC. 2011. Curcumin for inflammatory bowel disease: a review of human studies. *Altern Med Rev* 16(2): 152-156.

Zhao L, Zhang Y, Liu G, Hao S, Wang C, et al. 2018. Black rice anthocyanin-rich extract and rosmarinic acid, alone and in combination, protect against DSS-induced colitis in mice. *Food Funct* 9(5): 2796-2808. https://doi.org/10.1039/c7fo01490b

Kim YJ, Jo J, Song JL, Yang SG, Park KY. 2018. Anti-colitic effect of purple carrot on dextran sulfate sodium (DSS)-induced colitis in C57BL/6J mice. *Prev Nutr Food Sci* 23(1): 77-83. https://doi.org/10.3745/pnf.2018.23.1.77

Shi XM, Zhang GJ, Wu XL, Li YX, Ma Y, et al. 2011. Effect of low-temperature plasma on microorganism inactivation and quality of freshly squeezed orange juice. *IEEE Transactions on Plasma Science* 39(7): 1591-1597. https://doi.org/10.1109/tps.2011.2142012

Anderson K, Ryan N, Siddiqui A, Pero T, Volpedo G, et al. 2020. Black raspberries and protocatechuic acid mitigate db/db-induced contact hypersensitivity by down-regulating dendritic cell activation and inhibiting mediators of effector responses. *Nutrients* 12(6): 1701. https://doi.org/10.3390/nu12061701

Lee SG, Kim B, Yang Y, Pham TX, Park YK, et al. 2014. Berry anthocyanins suppress the expression and secretion of proinflammatory mediators in macrophages by inhibiting nuclear translocation of NF-kappaB independent of NFR2-mediated mechanism. *J Nutr Biochem* 25(4): 404-411. https://doi.org/10.1016/j.jnutbio.2013.12.001

Taverniti V, Fracassetti D, Del Bo C, Lanti C, Minuzzo M, et al. 2014. Immunomodulatory effect of a wild blueberry anthocyanin-rich extract
in human Caco-2 intestinal cells. J Agric Food Chem 62(33): 8346-8351. https://doi.org/10.1021/acs.jafc.2b00180

59. Yi W, Akoh CC, Fischer J, Krewer G. 2006. Absorption of anthocyanins from blueberry extracts by caco-2 human intestinal cell monolayers. J Agric Food Chem 54(15): 5651-5658. https://doi.org/10.1021/jf0531959

60. Leon-Gonzalez AJ, Sharif T, Kayali A, Abbas M, Dandache I, et al. 2015. Delphinidin-3-O-glucose and delphinidin-3-O-rutinoside mediate the redox-sensitive caspase 3-related pro-apoptotic effect of blackcurrant juice on leukemia Jurkat cells. Funct Food 17: 847-856. https://doi.org/10.1016/j.jff.2015.06.043

61. He L, He T, Farrar S, Ji L, Liu T, et al. 2017. Antioxidants maintain cellular redox homeostasis by elimination of reactive oxygen species. Cell Physiol Biochem 44(2): 532-553. https://doi.org/10.1159/000485089

62. Reddivari L, Vanamala J, Indukuri V, Xu B, Wang T, et al. 2020. Anthocyanin-containing purple potatoes ameliorate dss-induced colitis in mice. J Nutr Biochem 43(1): 26-36. https://doi.org/10.1016/j.jnutbio.2018.10.002

63. Le Phuong Nguyen T, Fenyvesi F, Remenyik J, Homoki JR, Gogolak P, et al. 2020. Reddivari L, Vanamala J, Indukuri V, Xu B, Wang T, et al. 2020. Anthocyanin-containing purple potatoes ameliorate dss-induced colitis in mice. J Nutr Biochem 43(1): 26-36. https://doi.org/10.1016/j.jnutbio.2018.10.002

65. Lee SG, Brownmiller CR, Lee SO, Kang HW. 2020. Anti-Inflammatory Action by Modulating Macrophage Phenotypes. Nutrients 12(4): 1089. https://doi.org/10.3390/nu12041089

66. Choe MR, Kang JH, Yoo H, Yang CH, Kim MO, et al. 2007. Cyanidin and cyanidin-3-O-β-D-glucoside suppress the inflammatory responses of obese adipose tissue by inhibiting the release of chemokines MCP-1 and MRP-2. Prev Nutr Food Sci 12(3): 148-153. https://doi.org/10.3746/pnfs.2007.12.3.148

67. Lee Y, Lee JY. 2019. Blackcurrant (Ribes nigrum) extract exerts an anti-inflammatory action by modulating macrophage phenotypes. Nutrients 11(5): 975. https://doi.org/10.3390/nu11050975

68. Lee Y, Pham TX, Bae M, Hu S, O'Neill E, et al. 2019. Blackcurrant (Ribes nigrum) prevents obesity-induced nonalcoholic steatohepatitis in mice. Obesity (Silver Spring) 27(1): 112-120. https://doi.org/10.1002/oby.22353

69. Pibberger H, Oehme A, Hofmann C, Dreiseitel A, Sand PG, et al. 2011. Bilberries and their anthocyanins ameliorate experimental colitis. Mol Nutr Food Res 55(11): 1724-1729. https://doi.org/10.1002/mnr.201100380

70. Boussenéa A, Cholé J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Za...
glucoside ameliorates lipopolysaccharide-induced acute lung injury by reducing TLR4 recruitment into lipid rafts. Biochemical Pharmacology 90(2): 126-134. https://doi.org/10.1016/j.bcp.2014.05.004

91. Speciale A, Cimino F, Saija A, Canali R, Virgili F. 2014. Bioavailability and molecular activities of anthocyanins as modulators of endothelial function. Genes Nutr 9(4): 404. https://doi.org/10.1007/s10549-014-0404-8

92. Xia M, Ling W, Zha H, Wang Q, Ma J, et al. 2007. Anthocyanin prevents CD40-activated proinflammatory signaling in endothelial cells by regulating cholesterol distribution. Arterioscler Thromb Vasc Biol 27(3): 519-524. https://doi.org/10.1161/ATV.A.0000524672.04573.2d

93. Moldogazieva NT, Lutensko SV, Terentiev AA. 2018. Reactive oxygen and nitrogen species-induced protein modifications: implication in carcinogenesis and anticancer therapy. Cancer Res 78(21): 6040-6047. https://doi.org/10.1158/0008-5472-can-18-0980

94. Krivets PR, Granger DN. 2012. Role of reactive oxygen and nitrogen species in the vascular responses to inflammation. Free Radic Biol Med 52(3): 556-592. https://doi.org/10.1016/j.freeradbiomed.2011.11.002

95. Xia Y, Zweier JL. 1997. Superoxide and peroxynitrite generation from inducible nitric oxide synthase in macrophages. Proc Natl Acad Sci USA 94(13): 6954-6958. https://doi.org/10.1073/pnas.94.13.6954

96. Dai LP, Dong XJ, Ma HH. 2012. Antioxidative and chelating properties of environmental studies. Cell Mol Biol (Noisy-le-grand) 58(4): 387-444. https://doi.org/10.3161/155620701205080760

97. Kamisoglu S, Capanoglu E, Grootaert C, Van Camp J. 2015. anthocyanin absorption and metabolism by human intestinal Caco-2 cells—a review. Int J Mol Sci 16(9): 21555-21574. https://doi.org/10.3390/ijms160921555

98. Dietrich C. 2016. Antioxidant functions of the aryl hydrocarbon receptor. Stem Cells Int 2016: 7943495. https://doi.org/10.1155/2016/7943495

99. Wang L, He X, Szklarz GD, Bi Y, Rojanasakul Y, et al. 2013. The aryl hydrocarbon receptor regulates PPARγ expression by regulating cholesterol distribution. J Biol Chem 288(38): 27324-27337. https://doi.org/10.1074/jbc.M113.498762

100. Bajpai VK, Alam MB, Quan KT, Kwon KR, Ju MK, et al. 2017. Antioxidant efficacy and the upregulation of Nr2-mediated HO-1 expression by (+)-lariciresinol, a lignan isolated from Rubia philippinensis, through the activation of p38. Sci Rep 7: 46035. https://doi.org/10.1038/srep46035

101. Lee S, Suh GY, Ryter SW, Choi AM. 2016. Regulation and function of the nucletide binding domain leucine-rich repeat-containing receptor, pyrin domain-containing-3 inflammasome in lung disease. Am J Respir Cell Mol Biol 54(2): 151-160. https://doi.org/10.1165/rcmb.2015-0231TR

102. Nakamura S, Tanaka J, Imada T, Shimoda H, Tsubota K. 2014. Delphinidin 3,5-O-diglucoside, a constituent of the maqui berry (Arctostaphylos chilensis) anthocyanin, restores tear secretion in a rat dry eye model. J Funct Foods 10: 346-354. https://doi.org/10.1016/j.jff.2014.06.027 https://doi.org/10.1016/j.jff.2014.06.027

103. Serra D, Paixao J, Nunes C, Diniz TC, Almeida LM. 2013. Cyanidin-3-glcose suppresses cytotoxic-induced inflammatory response in human intestinal cells: comparison with 5-aminosalicyclic acid. Planta 238(8): e73001. https://doi.org/10.1007/s00425-013-1749-0

104. Ferrari D, Cimino F, Fratantonio D, Molonia MS, Bashllari R, et al. 2017. Cyanidin-3-O-glucoside inhibits NF-kB signalling in intestinal epithelial cells exposed to TNF-alpha and exerts protective effects via Nrf2 pathway activation. Toxicol Lett 264: 51-58. https://doi.org/10.1016/j.toxlet.2016.10.014

105. Wang D, Xia M, Yan X, Li D, Wang L, et al. 2012. Gut microbiota metabolism of anthocyanin promotes reverse cholesterol transport in mice via repressing miRNA-10b. Circ Res 111(8): 967-981. https://doi.org/10.1161/CIRCRESAHA.112.266502

106. Adisakwattana S, Charoenlertrakul P, Yibschok-Anun S. 2009. Alpha-Glucosidase inhibitory activity of cyanidin-3-galactoside and synergistic effect with acarbose. J Enzyme Inhib Med Chem 24(1): 65-69. https://doi.org/10.1080/10623159.2008.998849

107. Lehtonen HM, Rantala M, Suomela JP, Viitanen M, Kallio H. 2009. Urinary excretion of the main anthocyanin in lingonberry (Vaccinium vitis-idaea), cyanidin 3-O-galactoside, and its metabolites. J Agric Food Chem 57(3): 4447-4451. https://doi.org/10.1021/jf900894k

108. Teng H, Fang T, Lin QY, Song HB, Liu B, et al. 2017. Red raspberry and its anthocyanins: Bioactivity beyond antioxidant capacity. Trends Food Sci Technol 66: 153-165. https://doi.org/10.1016/j.tifs.2017.05.015

109. Zhang Y, Wang F, Cui SX, and Qu XJ, 2018. Natural dietary compound in inflammation. Breast Cancer Res Treat 166(1): 345-354. https://doi.org/10.1007/s10549-018-45397-1

110. Chen H, Pu J, Liu D, Yu W, Shao Y, et al. 2016. Anti-inflammatory and antinoceptive properties of flavonoids from the fruits of black mulberry (Morus nigra L.). J Enzyme Inhib Med Chem 31(4): 701-708. https://doi.org/10.1111/jen.12384

111. Banerjee N, Talcott S, Safe S, Mertens-Talcott SU. 2012. Cytotoxicity of pomegranate polyphenolics in breast cancer cells in vitro and vivo: potential role of miRNA-21a and miRNA-155 in cell survival and inflammation. Breast Cancer Res Treat 136(1): 21-34. https://doi.org/10.1007/s10549-012-2224-0
121. Turfan O, Turkyilmaz M, Yemis O, Ozkan M. 2011. Anthocyanin and colour changes during processing of pomegranate (Punica granatum L., cv: Hicaznazar) juice from sacs and whole fruit. Food Chem 129(4): 1644-1651. https://doi.org/10.1016/j.foodchem.2011.06.024

122. Ojeda D, Jimenez-Ferrer E, Zamilpa A, Herrera-Arellano A, Tortoriello J, et al. 2010. Inhibition of angiotensin convertin enzyme (ACE) activity by the anthocyanins delphinidin- and cyanidin-3-O-sambubiosides from Hibiscus sabdariffa. J Ethnopharmacol 127(1): 7-10. https://doi.org/10.1016/j.jep.2009.09.059

123. Zhao Z, Wu M, Zhan Y, Zhan K, Chang X, et al. 2017. Characterization and purification of anthocyanins from black peanut (Arachis hypogaea L.) skin by combined column chromatography. J Chromatogr A 1519: 74-82. https://doi.org/10.1016/j.chroma.2017.08.078

124. Castro-Acosta ML, Smith L, Miller RJ, Mccarthy DI, Farrimond JA, et al., 2016. Drinks containing anthocyanin-rich blackcurrant extract decrease postprandial blood glucose, insulin and incretin concentrations. J Nutr Biochem 38: 154-161. https://doi.org/10.1016/j.jnutbio.2016.09.002

125. Xie LY, Vance T, Kim B, Lee SG, Caceres C, et al. 2017. Aronia berry polyphenolic compounds in blackcurrants. In: X International Rubus and Ribes Symposium, pp 436.

126. Xu Y, Xie L, Xie J, Liu Y, Chen W. 2019. Pelargonidin-3-O-rutinoside as a novel α-glucosidase inhibitor for improving postprandial hyperglycemia. Chem Commun 55(1): 39-42. https://doi.org/10.1039/C8CC07985D

127. Joaquin-Cruz E, Duenas M, Garcia-Cruz L, Salinas-Moreno Y, Santos-Buelga C, et al. 2015. Anthocyanin and phenolic characterization, chemical composition and antioxidant activity of chagualpoli (Ardisia compressa K.) fruit: A tropical source of natural pigments. Food Res Int 70: 151-157. https://doi.org/10.1016/j.foodres.2015.01.033

128. He Z, Xu M, Zeng M, Qin F, Chen J. 2016. Interactions of milk α-and β-casein with malvidin-3-O-glucoside and their effects on the stability of grape skin anthocyanin extracts. Food Chem 199: 314-322. https://doi.org/10.1016/j.foodchem.2015.12.035

129. Inoue H, Maeda-Yamamoto M, Neumi A, Murakami A. 2012. Delphinidin-3-O-galactoside protects mouse hepatocytes from (−)-epigallocatechin-3-gallate–induced cytotoxicity via up-regulation of heme oxygenase-1 and heat shock protein 70. Nutr Res 32(5): 357-364. https://doi.org/10.1016/j.nutres.2012.04.001

130. Koskela AK, Anttonen MJ, Soininne TH, Saviranta NM, Auriola S, et al. 2010. Variation in the anthocyanin concentration of wild populations of crowberries (Empetrum nigrum L subsp. hermaphroditum). J Agric Food Chem 58(23): 12286-12291. https://doi.org/10.1021/jf1037695

131. Rojo LE, Ribnicky D, Logendra S, Poulev A, Rojas-Silva P, et al. 2012. In vitro and in vivo anti-diabetic effects of anthocyanins from maqui berry (Aristotelia chilensis). Food Chem 131(2): 387-396. https://doi.org/10.1016/j.foodchem.2011.08.066

132. Muller D, Schantz M, Richling E. 2012. High performance liquid chromatography analysis of anthocyanins in bilberries (Vaccinium myrtillus L.), blueberries (Vaccinium corymbosum L.), and corresponding juices. J Food Sci 77(4): C340-C345. https://doi.org/10.1111/j.1750-3841.2011.02605.x

133. Takikawa M, Inoue S, Horio F, Tsuda T. 2010. Dietary anthocyanin-rich bilberry extract ameliorates hyperglycemia and insulin sensitivity via activation of AMP-activated protein kinase in diabetic mice. J Nutr 140(3): 527-533. https://doi.org/10.3945/jn.109.118216