Journal of Food Chemistry & Nanotechnology

https://doi.org/10.17756/jfcn.2020-103

Research Article

Open Access

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

Fawze Alnadari[1, 2], Mohamed Abdin[1, 3], Wael Ennab[5], Amani Mohedein[2] and Mustapha Muhammad Nasiru[1, 4*]

[1]*College of Food Science and Technology, Nanjing Agricultural University, Nanjing, Jiangsu, China*
[2]*Department of Food Science and Technology, Faculty of Agriculture, Sana'a University, Sana'a, Yemen*
[3]*Agriculture Research Center, Food Technology Research Institute, Giza, Egypt*
[4]*Department of Food Science and Technology, Federal University, Dutsin-Ma, Katsina State, Nigeria*
[5]*Department of Animal Science and Technology, Nanjing Agricultural University, Nanjing, China*

***Correspondence to:**
Mustapha Muhammad Nasiru
Department of Food Science and Technology
Faculty of Agriculture and Agricultural Technology, Federal University
Dutsin-Ma, Katsina State, Nigeria
Tel: +2349030515070
E-mail: mustaphamnasiru@gmail.com

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.

Published by United Scientific Group

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.

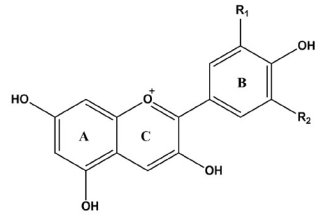
Types of Anthocyanin and its Content in Foods

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 phloroglucinol, protocatechuic acid [24], phloroglucinaldehyde, phenylacetic, phenylpropionic acids [25], and 2,4,6-trihydroxybenzaldehyde [26] with varying degrees of hydroxylation.

A



B

Anthocyanidin	R1	R2	R3
Pelargonidin	H	OH	H
Aurantinidin	H	OH	H
Cyanidin	OH	OH	H
Delphinidin	OH	OH	OH
Pulchellidin	OH	OH	OH
Peonidin	OCH3	OH	H
Rosinidin	OCH3	OH	H
Petunidin	OCH3	OH	OH
Europinidin	OCH3	OH	OH
Malvidin	OCH3	OH	OCH3
Hirsutidin	OCH3	OH	OCH3
Capensinidin	OCH3	OH	OCH3

Figure 1: (A) Chemical structures of anthocyanins **(B)** Anthocyanidin structure.

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 heterocycle 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

Table 1: Distribution of anthocyanins commonly occurring in plants.

Anthocyanin	Compounds	MW (g/mol)	Dietary source	Mechanism		Reference
				Promotes	Repressing	
Cyanidin	Cyanidin-3-O-glucoside	484.8	Purple corn	Gut microbiota metabolism	miRNA-10b	[115]
	Cyanidin 3-arabinoside	454.8	Blueberry	Glycogen synthesis	PTP1B	[24]
	Cyanidin 3-galactoside	449.4	Lingonberry	Metabolism	α-Glucosidase	[116, 117]
	Cyanidin 3-sophoroside	611.5	Red raspberry	Antioxidant capacity	Oxidative-stress related diseases	[118, 119]
	Cyanidin-3-O-rutinoside	595.5	Black mulberry	Anti-inflammatory	Cytokines	[120]
	Cyanidin-3,5-O-diglucoside	611.5	pomegranate juice	Inhibits NF-κB	Breast cancer cells	[121, 122]
	Cyanidin-3-O-sambubioside	581.5	Hibiscus sabdariffa	Reduce blood pressure	ACE	[123]
	Cyanidin 3-O-sophoroside	611.5	Black peanut skins	Tight junction protein	Oxidative stress	[14, 124]
	Cyanidin 3-sambubioside	581.5	Black peanut skins	Tight junction protein	Oxidative stress	[14, 124]
Peonidin	Peonidin-3-O-rutinoside	609.6	Blackcurrants	Insulin-stimulated	Postprandial glycemia	[125, 126]
	Peonidin-3-O-galactoside	498.9	Aronia berry	Antioxidant enzyme	Cholesterol	[127]
Pelargonidin	Pelargonidin-3-O-rutinoside	579.5	Strawberries	Inhibit α-glucosidase	Blood glucose levels	[128]
	Pelargonidin 3-glucoside	433.4	Strawberry	Inhibits NF-κB	JNKMAPK phosphorylation	[81]
Malvidin	Malvidin-3-O-galactoside	528.9	Chagalapoli	Antioxidant activity	-	[129]
	Malvidin-3-O-glucoside	493.43	Grape skin	α-casein	β-casein	[130]
Delphinidin	Delphinidin-3-O-rhamnoside	465.4	Blackcurrant	LPS stimulation	IL-1β mRNA levels	[58]
	Delphinidin-3-O-galactoside	500.8	Empetrum nigrum	Antioxidant enzymes	EGCG-induced cytotoxicity	[131, 132]
	Delphinidin-3-O-glucoside	500.83	Blackcurrant juice	Caspase-3 Activity	p-Akt, p-Bad, and Bcl-2	[61]
	Delphinidin-3-O-rutinoside	611.5	Blackcurrant juice	Caspase-3 Activity	p-Akt, p-Bad, and Bcl-2	[61]
	Delphinidin-3,5-O-diglucoside	627.5	Maqui berry	Tear	Reactive oxygen	[103]
	Delphinidin-3-sambubioside	597.5	Hibiscus	Inhibits NF-κB	Cytokines	[82]
	Delphinidin 3-sambubioside-5-glucoside	759.6	Maqui berry	Insulin-stimulated	Glucose production	[133]
Petunidin	Petunidin-3-O-galactoside	516.9	Chagalapoli	Antioxidant activity	-	[129]
	Petunidin-3-O-glucoside	514.9	Bilberries	Activation of AMPK	Acetyl-CoA carboxylase	[134]
	Petunidin-3-O-arabinoside	484.8	Bilberries	Activation of AMPK	Acetyl-CoA carboxylase	[134]

Protein tyrosine phosphatase 1B (PTP1B), Dietary Supplement (DS), angiotensin-converting enzyme (ACE), Epigallocatechin-3-gallate (EGCG)

microbiota may be modulated by anthocyanins found in food matrices, which are often taken along with proteins, polysaccha1rides, 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]. *In vivo* simulation study, [31] proven Pelargonidine-3-O-glucoside from the fruit of Lycium ruthenicum Murray demonstrated a greater control capability than anthocyanins in the phase of cyclooxygenase-2, tumor necrosis factor α (TNF-α), interferon γ (IFN-γ), and free fatty acid receptor 2 in mice. Particularly, for the novel desirable microbes, *Faecalibacterium prausnitzii,* and *Akkermansia muciniphila* are very abundant human intestinal microbes that are seen in healthy people,

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].

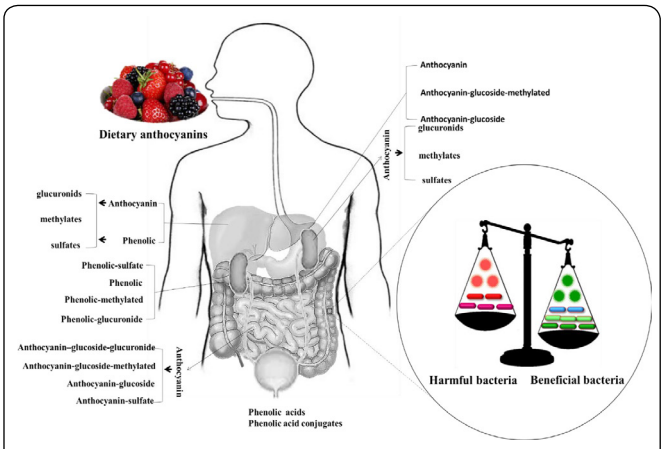


Figure 2: Dietary anthocyanins inhibit the metabolic disease related to obesity by regulating the intestinal microflora ecology, for example, increasing beneficial bacteria ratios such as *Akkermansia muciniphila*, *Faecalibacterium prausnitzii*, *Bifidobacterium*, and *Allisonella*.

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*).

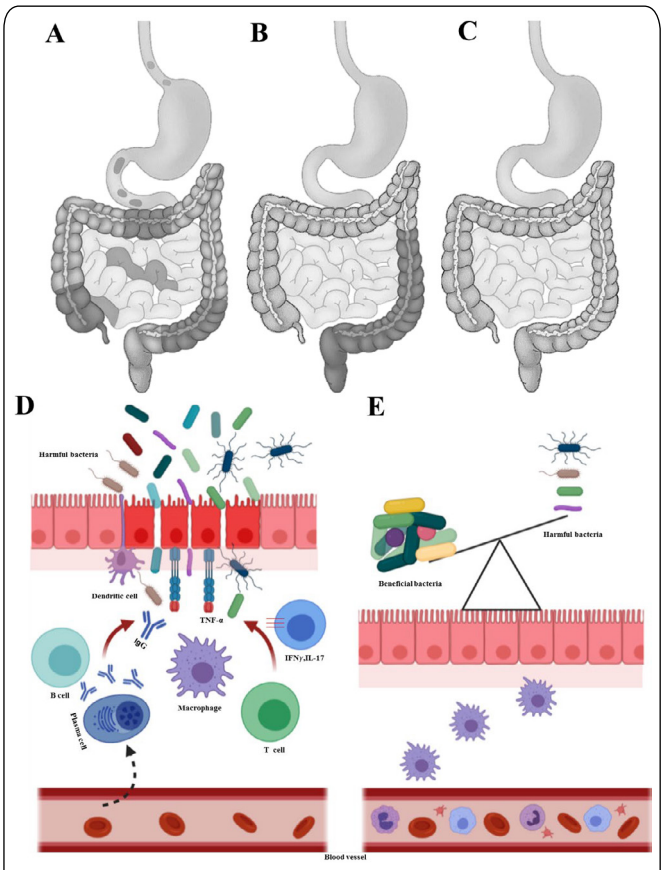


Figure 3: Features of inflammatory bowel diseases **(A)** Crohn's disease **(B)** Ulcerative colitis **(C)** normal **(D)** Disruption of the intestinal epithelial barrier **(E)** Reduced inflammation due to gut metabolite.

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 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-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 intracell 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 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 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-a 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) 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 a-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 *Faecalibacterium*, *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 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

Flavanol-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

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 and M. M. Nasiru. Extraction and preparation of tables and figures: M. Abdin, W. Ennab, and A. Mohedein. Revision 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, Kallithraka 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, Heinken 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, Bolling B. 2020. Flavonoids and gut health. *Curr Opin Biotechnol* 61: 153-159. https://doi.org/10.1016/j.copbio.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. Martín 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/org/10.1016/B978-0-08-102922-0.00007-9
17. Olivas-Aguirre 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 JE. 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): 14294-14310. https://doi.org/10.3390/ijms131114294
21. Kårlund A, Moor U, Sandell M, Karjalainen RO. 2014. The impact of harvesting, storage and processing factors on health-promoting phytochemicals in berries and fruits. *Processes*. 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 JL, 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. Nikolić NĆ, Šavikin K, Bigović D, Trifković K, Đorđević 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.

26. Faria A, Fernandes I, Norberto S, Mateus N, Calhau C. 2014. Interplay between anthocyanins and gut microbiota. *J Agric Food Chem* 62(29): 6898-6902. https://doi.org/10.1021/jf501808a
27. Eker ME, Aaby K, Budic-Leto I, Brncic SR, El SN, et al. 2019. A review of factors affecting anthocyanin bioavailability: possible implications for the inter-individual variability. *Foods* 9(1): 2. https://doi.org/10.3390/foods9010002
28. Lila MA. 2004. Anthocyanins and human health: an *in vitro* investigative approach. *J Biomed Biotechnol* 2004(5): 306-313. https://doi.org/10.1155/S111072430440401X
29. Tong Y, Deng H, Kong Y, Tan C, Chen J, et al. 2020. Stability and structural characteristics of amylopectin nanoparticle-binding anthocyanins in *Aronia melanocarpa*. *Food Chem* 311: 125687. https://doi.org/10.1016/j.foodchem.2019.125687
30. Cassidy A, Minihane AM. 2017. The role of metabolism (and the microbiome) in defining the clinical efficacy of dietary flavonoids. *Am J Clin Nutr* 105(1): 10-22. https://doi.org/10.3945/ajcn.116.136051
31. Peng Y, Yan Y, Wan P, Chen D, Ding Y, et al. 2019. Gut microbiota modulation and anti-inflammatory properties of anthocyanins from the fruits of *Lycium ruthenicum* Murray in dextran sodium sulfate-induced colitis in mice. *Free Radic Biol Med* 136: 96-108. https://doi.org/10.1016/j.freeradbiomed.2019.04.005
32. 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
33. 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
34. Kalt W. 2019. Anthocyanins and their C6-C3-C6 metabolites in humans and animals. *Molecules* 24(22): 4024. https://doi.org/10.3390/molecules24224024
35. Faria A, Pestana D, Azevedo J, Martel FT, Freitas VD, et al. 2010. Absorption of anthocyanins through intestinal epithelial cells - putative involvement of GLUT2. *Mol Nutr Food Res* 53(11): 1430-1437. https://doi.org/10.1002/mnfr.200900007
36. 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
37. 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
38. 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
39. 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
40. 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
41. Zhu Y, Sun H, He S, Lou Q, Yu M, et al. 2018. Metabolism and prebiotics activity of anthocyanins from black rice (*Oryza sativa* L.) *invitro*. *PLoS One* 13(4): e0195754. https://doi.org/10.1371/journal.pone.0195754
42. 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
43. 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: 4051232. https://doi.org/10.1155/2018/4051232
44. Cremonini E, Daveri E, Mastaloudis A, Adamo AM, Mills D, 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.redox.2019.101269
45. 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
46. Uhlig HH, Powrie F. 2018. Translating immunology into therapeutic concepts for inflammatory bowel disease. *Annu Rev Immunol* 36: 755-781. https://doi.org/10.1146/annurev-immunol-042617-053055
47. Gersemann M, Becker S, Kubler I, Koslowski 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
48. 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
49. 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
50. Yao J, Wei C, Wang JY, Zhang R, Li YX, et al. 2015. Effect of resveratrol on Treg/Th17 signaling and ulcerative colitis treatment in mice. *World J Gastroenterol* 21(21): 6572-6581. https://doi.org/10.3748/wjg.v21.i21.6572
51. Bitzer 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
52. Taylor RA, Leonard MC. 2011. Curcumin for inflammatory bowel disease: a review of human studies. *Altern Med Rev* 16(2): 152-156.
53. 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
54. Kim YJ, Ju 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/10.3746/pnf.2018.23.1.77
55. 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
56. Anderson K, Ryan N, Siddiqui A, Pero T, Volpedo G, et al. 2020. Black raspberries and protocatechuic acid mitigate dnfb-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
57. 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 NRF2-mediated mechanism. *J Nutr Biochem* 25(4): 404-411. https://doi.org/10.1016/j.jnutbio.2013.12.001
58. 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/jf502180j

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-glucoside and delphinidin-3-O-rutinoside mediate the redox-sensitive caspase 3-related pro-apoptotic effect of blackcurrant juice on leukaemia 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. *Curr Dev Nutr* 4(Supplement_2): 426-426. https://doi.org/10.1093/cdn/nzaa045_059
63. Le Phuong Nguyen T, Fenyvesi F, Remenyik J, Homoki JR, Gogolak P, et al., 2018. Protective effect of pure sour cherry anthocyanin extract on cytokine-induced inflammatory Caco-2 monolayers. *Nutrients* 10(7): 861. https://doi.org/10.3390/nu10070861
64. Desjardins J, Tanabe S, Bergeron C, Gafner S, Grenier D. 2012. Anthocyanin-rich black currant extract and cyanidin-3-O-glucoside have cytoprotective and anti-inflammatory properties. *J Med Food* 15(12): 1045-1050. https://doi.org/10.1089/jmf.2011.0316
65. Lee SG, Brownmiller CR, Lee SO, Kang HW. 2020. Anti-Inflammatory and antioxidant effects of anthocyanins of *Trifolium pratense* (Red Clover) in lipopolysaccharide-stimulated RAW-267.4 macrophages. *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/jfn.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. Piberger 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/mnfr.201100380
70. Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Fraisse D, et al. 2016. Polyphenol-rich grape pomace extracts protect against dextran sulfate sodium-induced colitis in rats. *J Sci Food Agric* 96(4): 1260-1268. https://doi.org/10.1002/jsfa.7214
71. Fukui H. 2016. Increased intestinal permeability and decreased barrier function: does it really influence the risk of inflammation? *Inflamm Intest Dis* 1(3): 135-145. https://doi.org/10.1159/000447252
72. Zhang Q, Luna-Vital D, De Mejia EG. 2019. Anthocyanins from colored maize ameliorated the inflammatory paracrine interplay between macrophages and adipocytes through regulation of NF-κB and JNK-dependent MAPK pathways. *J Funct Foods* 54: 175-186. https://doi.org/10.1016/j.jff.2019.01.016
73. Israel A. 2010. The IKK complex, a central regulator of NF-kappaB activation. *Cold Spring Harb Perspect Biol* 2(3): a000158. https://doi.org/10.1101/cshperspect.a000158
74. Liu T, Zhang L, Joo D, Sun SC. 2017. NF-kappaB signaling in inflammation. *Signal Transduct Target Ther* 2: 17023. https://doi.org/10.1038/sigtrans.2017.23
75. Oeckinghaus A, Ghosh S. 2009. The NF-kappaB family of transcription factors and its regulation. Cold Spring Harb Perspect Biol *Cold Spring Harb Perspect Biol* 1(4): a000034. https://doi.org/10.1101/cshperspect.a000034
76. Basuroy S, Seth A, Elias B, Naren AP, Rao R. 2006. MAPK interacts with occludin and mediates EGF-induced prevention of tight junction disruption by hydrogen peroxide. *Biochem J* 393(Pt 1): 69-77. https://doi.org/10.1042/bj20050959
77. Huang W, Yan Z, Li D, Ma Y, Zhou J, et al. 2018. Antioxidant and anti-inflammatory effects of blueberry anthocyanins on high glucose-induced human retinal capillary endothelial cells. Oxid Med Cell Longev 2018: 1862462. https://doi.org/10.1155/2018/1862462
78. Wakabayashi N, Slocum SL, Skoko JJ, Shin S, Kensler TW. 2010. When NRF2 talks, who's listening? *Antioxid Redox Signal* 13(11): 1649-1663. https://doi.org/10.1089/ars.2010.3216
79. Pereira SR, Pereira R, Figueiredo I, Freitas V, Dinis TC, et al. 2017. Comparison of anti-inflammatory activities of an anthocyanin-rich fraction from Portuguese blueberries (*Vaccinium corymbosum* L.) and 5-aminosalicylic acid in a TNBS-induced colitis rat model. *PLoS One* 12(3): e0174116. https://doi.org/10.1371/journal.pone.0174116
80. Fossen T, Rayyan S, Andersen OM. 2004. Dimeric anthocyanins from strawberry (*Fragaria ananassa*) consisting of pelargonidin 3-glucoside covalently linked to four flavan-3-ols. *Phytochemistry* 65(10): 1421-1428. https://doi.org/10.1016/j.phytochem.2004.05.003
81. Sogo T, Terahara N, Hisanaga A, Kumamoto T, Yamashiro T, et al. 2015. Anti-inflammatory activity and molecular mechanism of delphinidin 3-sambubioside, a Hibiscus anthocyanin. *Biofactors* 41(1): 58-65. https://doi.org/10.1002/biof.1201
82. Giridharan S, Srinivasan M. 2018. Mechanisms of NF-κB p65 and strategies for therapeutic manipulation. *J Inflamm Res* 11: 407-419. https://doi.org/10.2147/jir.s140188
83. Kalita D, Holm DG, Labarbera DV, Petrash JM, Jayanty SS. 2018. Inhibition of alpha-glucosidase, alpha-amylase, and aldose reductase by potato polyphenolic compounds. *PLoS One* 13(1): e0191025. https://doi.org/10.1371/journal.pone.0191025
84. Chen JG, Wu SF, Zhang QF, Yin ZP, Zhang L. 2020. Alpha-Glucosidase inhibitory effect of anthocyanins from Cinnamomum camphora fruit: Inhibition kinetics and mechanistic insights through in vitro and in silico studies. *Int J Biol Macromol* 143: 696-703. https://doi.org/10.1016/j.ijbiomac.2019.09.091
85. Bieberich E. 2018. Sphingolipids and lipid rafts: Novel concepts and methods of analysis. *Chem Phys Lipids* 216: 114-131. https://doi.org/10.1016/j.chemphyslip.2018.08.003
86. Meng G, Liu Y, Lou C, Yang H. 2010. Emodin suppresses lipopolysaccharide-induced pro-inflammatory responses and NF-kappaB activation by disrupting lipid rafts in CD14-negative endothelial cells. *Br J Pharmacol* 161(7): 1628-1644. https://doi.org/10.1111/j.1476-5381.2010.00993.x
87. Płóciennikowska A, Hromada-Judycka A, Borzęcka K, Kwiatkowska K. 2015. Co-operation of TLR4 and raft proteins in LPS-induced pro-inflammatory signaling. *Cell Mol Life Sci* 72(3): 557-581. https://doi.org/10.1007/s00018-014-1762-5
88. González-Sarrías A, Romo-Vaquero M, García-Villalba R, Cortés-Martín A, Selma MV, et al. 2018. The endotoxemia marker lipopolysaccharide-binding protein is reduced in overweight-obese subjects consuming pomegranate extract by modulating the gut microbiota: A randomized clinical trial. *Mol Nutr Food Res* 62(11): e1800160. https://doi.org/10.1002/mnfr.201800160
89. Fu Y, Wei Z, Zhou E, Zhang N, Yang Z. 2014. Cyanidin-3-O-beta-glucoside inhibits lipopolysaccharide-induced inflammatory response in mouse mastitis model. *J Lipid Res* 55(6): 1111-1119. https://doi.org/10.1194/jlr.m047340
90. Fu Y, Zhou E, Wei Z, Wang W, Wang T, et al. 2014. Cyanidin-3-O-β-

glucoside ameliorates lipopolysaccharide-induced acute lung injury by reducing TLR4 recruitment into lipid rafts. B*iochemical 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/s12263-014-0404-8

92. Xia M, Ling W, Zhu 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/10.1161/01.ATV.0000254672.04573.2d

93. Moldogazieva NT, Lutsenko 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. Kvietys 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 U S A* 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 anthocyanins in azolla imbricata induced by cadmium. *Polish Journal of Environmental Studies* 21(4): 837-844.

97. Kamiloglu 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 interacts with nuclear factor erythroid 2-related factor 2 to mediate induction of NAD(P)H:quinoneoxidoreductase 1 by 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Arch Biochem Biophys* 537(1): 31-38. https://doi.org/10.1016/j.abb.2013.06.001

100. Bajpai VK, Alam MB, Quan KT, Kwon KR, Ju MK, et al. 2017. Antioxidant efficacy and the upregulation of Nrf2-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 nucleotide 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 (*Aristotelia 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, Dinis TC, Almeida LM. 2013. Cyanidin-3-glucoside suppresses cytokine-induced inflammatory response in human intestinal cells: comparison with 5-aminosalicylic acid. *PLoS One* 8(9): e73001. https://doi.org/10.1371/journal.pone.0073001

104. Ferrari D, Cimino F, Fratantonio D, Molonia MS, Bashllari R, et al. 2017. Cyanidin-3-O-glucoside modulates the *in vitro* inflammatory crosstalk between intestinal epithelial and endothelial cells. Me*diators Inflamm* 2017: 3454023. https://doi.org/10.1155/2017/3454023

105. Lin CY, Wang WH, Chen SH, Chang YW, Hung LC, et al. 2017. lipopolysaccharide-induced nitric oxide, prostaglandin E2, and cytokine production of mouse and human macrophages are suppressed by pheophytin-b. *Int J Mol Sci* 18(12): 2637. https://doi.org/10.3390/ijms18122637

106. Sozański T, Kucharska AZ, Dzimira S, Magdalan J, Szumny D, et al. 2018. Loganic acid and anthocyanins from cornelian cherry (*Cornus mas* L.) fruits modulate diet-induced atherosclerosis and redox status in rabbits. *Adv Clin Exp Med* 27(11): 1505-1513. https://doi.org/10.17219/acem/74638

107. Poustka F, Irani NG, Feller A, Lu Y, Pourcel L, et al. 2007. A trafficking pathway for anthocyanins overlaps with the endoplasmic reticulum-to-vacuole protein-sorting route in Arabidopsis and contributes to the formation of vacuolar inclusions. *Plant Physiol* 145(4): 1323-1335. https://doi.org/10.1104/pp.107.105064

108. Dreiseitel A, Schreier P, Oehme A, Locher S, Rogler G, et al. 2008. Inhibition of proteasome activity by anthocyanins and anthocyanidins. *Biochem Biophys Res Commun* 372(1): 57-61. https://doi.org/10.1016/j.bbrc.2008.04.140

109. Parrado-Fernandez C, Sandebring-Matton A, Rodriguez-Rodriguez P, Aarsland D, Cedazo-Minguez A. 2016. Anthocyanins protect from complex I inhibition and APPswe mutation through modulation of the mitochondrial fission/fusion pathways. *Biochim Biophys Acta -Molecular Basis of Disease* 1862(11): 2110-2118. https://doi.org/10.1016/j.bbadis.2016.08.002

110. Zhang Y, Liao XJ, Chen F, Wu JH, Hu XS. 2008. Isolation, identification, and color characterization of cyanidin-3-glucoside and cyanidin-3-sophoroside from red raspberry. *Eur Food Res Technol* 226: 395-403. https://doi.org/10.1007/s00217-006-0550-3

111. Wang F, Song ZY, Qu XJ, Li F, Zhang L, et al. 2018. M10, a novel derivative of Myricetin, prevents ulcerative colitis and colorectal tumor through attenuating robust endoplasmic reticulum stress. *Carcinogenesis* 39(7): 889-899. https://doi.org/10.1093/carcin/bgy057

112. Zikri NN, Riedl KM, Wang LS, Lechner J, Schwartz SJ, et al. 2009. Black raspberry components inhibit proliferation, induce apoptosis, and modulate gene expression in rat esophageal epithelial cells. *Nutr Cancer* 61(6): 816-826. https://doi.org/10.1080/01635580903285148

113. Ferrari D, Speciale A, Cristani M, Fratantonio D, Molonia MS, et al. 2016. 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

114. 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

115. Adisakwattana S, Charoenlertkul P, Yibchok-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/10.1080/14756360801906947

116. 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(10): 4447-4451. https://doi.org/10.1021/jf900894k

117. 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

118. Zhang YS, Wang F, Cui SX, and Qu XJ, 2018. Natural dietary compound naringin prevents azoxymethane/dextran sodium sulfate-induced chronic colorectal inflammation and carcinogenesis in mice. *Cancer Biol Ther* 19(8): 735-744. https://doi.org/10.1080/15384047.2018.1453971

119. Chen H, Pu J, Liu D, Yu W, Shao Y, et al. 2016. Anti-inflammatory and antinociceptive properties of flavonoids from the fruits of black mulberry (*Morus nigra* L.). *PLoS One* 11(4): e0153080. https://doi.org/10.1080/15384047.2018.1453971

120. 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-27a 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. Hicaznar) 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. Rumpunen K, Vagiri M, Ekholm A. 2011. Polyphenolic compounds in blackcurrants. In: X International Rubus and Ribes Symposium, pp 436.

126. Xie LY, Vance T, Kim B, Lee SG, Caceres C, et al. 2017. Aronia berry polyphenol consumption reduces plasma total and low-density lipoprotein cholesterol in former smokers without lowering biomarkers of inflammation and oxidative stress: a randomized controlled trial. *Nutr Res* 37: 67-77. https://doi.org/10.1016/j.nutres.2016.12.007

127. 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

128. 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 chagalapoli (*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

129. 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

130. Inoue H, Maeda-Yamamoto M, Nesumi 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

131. Koskela AK, Anttonen MJ, Soininen 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

132. 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

133. 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

134. 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