Therapeutic Actions of Anthocyanins in Chronic Diseases

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Anthocyanins are secondary metabolites and distributed in flowers, fruits and vegetables. They provide various colours such as red, pink, blue and purple. To date, more than 700 anthocyanins have been identified in nature. These anthocyanins have been associated with many health benefits through different mechanisms. Some of the therapeutic potentials of anthocyanins and their mechanisms of action are highlighted.

anthocyanins oxidative stress gut microbiota inflammation

1. Mechanisms of Action of Anthocyanins in Disease

Functional foods containing anthocyanins have been studied for health benefits but most of these studies have been in cells or animal models of human disease, rather than in human clinical trials. In this section, the recent literature has been reviewed to summarise the potential mechanisms of anthocyanins in chronic diseases such as changes in the gut microbiota, decreased oxidative stress, decreased inflammation and increasing insulin-like growth factor 1 (IGF-1) (**Figure 1**). The multiple changes in chronic disease states and the interactions between these mechanisms indicate that it is unlikely that any one mechanism is responsible for therapeutic responses in any particular disease state. However, an improved understanding of these mechanisms may allow more logical therapeutic choices to be made.

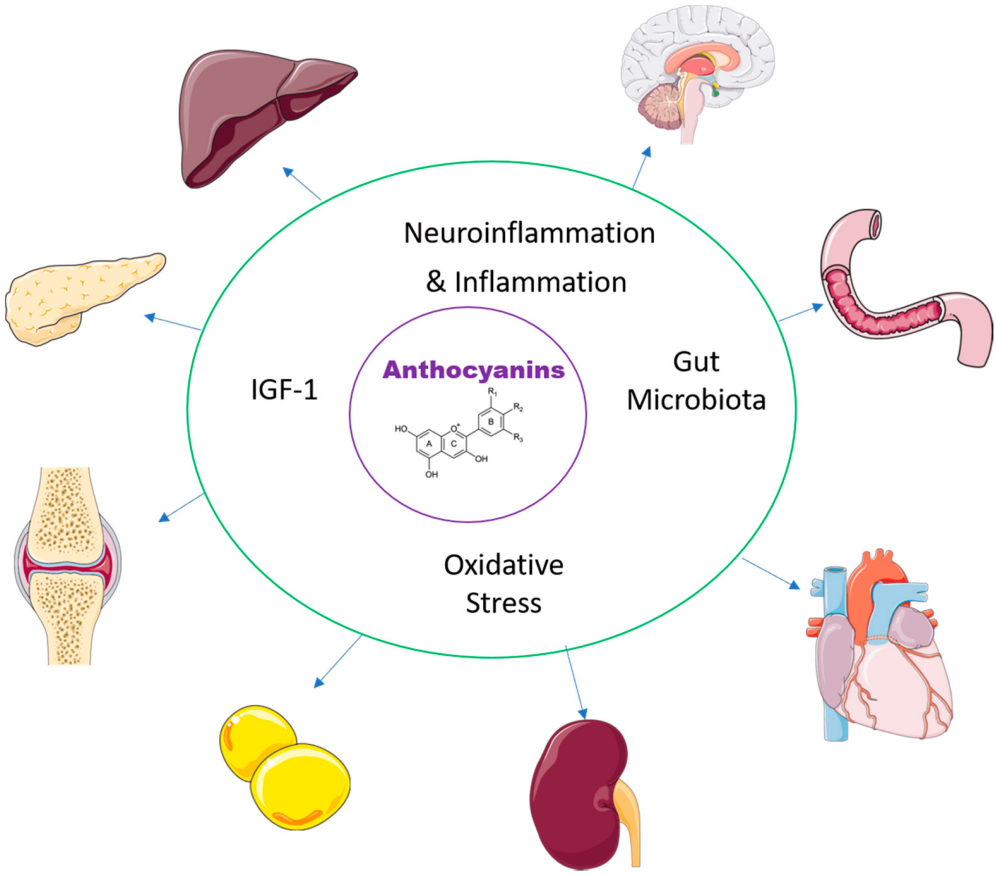

Figure 1. Effects of anthocyanins in the major organs.

1.1. Gut Microbiota

After ingestion, functional foods first interact with the microorganisms in the gastrointestinal tract, collectively known as the gut microbiota. This complex micro-ecosystem is essential for many functions including digestion, regulation of the immune system and stabilising the intestinal barrier. Nutrients change the microbiota and intestinal barrier function, for example by the synthesis of folate to increase methylation and so change gastrointestinal function by epigenetic modifications [1]. Further, the gut microbiota may metabolise the functional foods. These microbial metabolites may produce physiological responses in the intestine and after absorption and distribution in the body. However, the metabolites may also lead to the development of chronic low-grade inflammation both in the intestine and throughout the body [2]. The bacterial metabolites that influence the immune signalling pathways include short-chain fatty acids, indole and indole acid derivatives, choline, bile acids, N-acyl amides, vitamins and polyamines [3]. Under physiological conditions when the inflammatory processes have achieved their aims, the resolution of inflammation is mediated by pro-resolving lipid mediators produced in damaged tissues, giving a further potential intervention to reduce inflammation through activating these pro-resolving pathways [4]. Changes in the gut microbiota have been suggested as being responsible for a wide range of diseases such as gastrointestinal diseases including inflammatory bowel disease [5], neurological disorders [6] including schizophrenia [7] and Parkinson's disease [8], metabolic syndrome [9], cardiovascular disease [10], chronic kidney disease [11] and type 2 diabetes [12], providing a potential target for the management of these diseases.

Anthocyanins can be absorbed in the stomach by specific transporters such as sodium-dependent glucose co-transporter 1, metabolised by the gut microbiota in the colon and modified by phase I and II metabolic enzymes in liver cells followed by enterohepatic circulation before distribution of anthocyanins and derivatives and accumulation in tissues [13]. These metabolites could independently alter organ structure and function in chronic disease states; for example, a major metabolite of anthocyanins, protocatechuic acid, has demonstrated antioxidant, anti-inflammatory and neuroprotective properties [14]. Concentrations in studies with isolated cells were usually around 10–100 μM while daily doses in rodents were around 10–100 mg/kg. Pharmacokinetic studies in humans after an oral dose of 500 mg cyanidin 3-glucoside show that serum concentrations of protocatechuic acid and its metabolites peaked at around 0.1 μM but were present in the circulation for longer and at higher concentrations than the parent anthocyanin [15]. In addition, protocatechuic acid may decrease cognitive and behavioural impairment, neuroinflammation and excessive production of reactive oxygen species [16].

Anthocyanins also act as prebiotics to modify the microbiota, in particular enhancing *Lactobacillus* spp. and *Bifidobacterium* spp. [17]. Both effects potentially lead to cardioprotective and neuroprotective responses and decreased bone loss in the ageing population [18]. Regulation of the gut microbiota by polyphenols, including anthocyanins, may reduce kidney injury to treat pre-existing chronic kidney disease [19]. Anthocyanins such as cyanidin 3-glucoside may be potential prebiotics, as purified cyanidin 3-glucoside (7.2 mg/kg/day) and anthocyanin-containing Saskatoon berry (8.0 mg/kg/day) administration for 11 weeks reduced high-fat high-sucrose diet-induced changes in the gut microbiota in mice [20].

1.2. Oxidative Stress

Low concentrations of reactive oxygen and nitrogen species (ROS/RNS) such as hydrogen peroxide, superoxide anions, hydroxyl radicals, nitric oxide and peroxynitrate are important in the defence against pathogenic microorganisms. Higher concentrations cause cellular damage leading to cell death by actions on DNA, proteins and lipids, a condition known as oxidative/nitrative stress. Oxidative stress is a key activator of disease onset and progression, overlapping with inflammation, providing the rationale for the effectiveness of anthocyanins in obesity, cardiovascular and neurological diseases [21].

Mitochondria are the major source of intracellular ROS as leakage of electrons through the respiratory chain. Accumulation of ROS in mitochondria disrupts normal function leading to depolarisation of the mitochondrial membrane. In high-energy-consuming cells such as cardiomyocytes, impaired mitochondrial activity will interfere with glucose and fatty acid metabolism leading to cardiomyopathy. Anthocyanins and their metabolite, protocatechuic acid, could decrease mitochondrial ROS concentrations and so reduce damage [22]. Further, some anthocyanins including cyanidin 3-glucoside may form an additional transport chain in damaged mitochondria as electron acceptors at Complex I to reduce cytochrome C and increase ATP production [23].

An additional target to reduce oxidative stress is DNA methylation as it is important in the long-term regulation of gene expression. Plant-derived antioxidants such as anthocyanins may be involved in epigenetic mechanisms to reverse aberrant methylation and oxidative stress without changing the underlying gene sequences [24]. These

diseases occur through the regulation of epigenetic enzymes and chromatin remodelling complexes. Potential therapeutic targets include diseases that are increased in patients with metabolic syndrome, including atherosclerosis, diabetes, cancer and Alzheimer's disease [24].

Further, mitochondrial DNA may be displaced from cells by cell-death-triggering stressors into extracellular compartments. This defective mitochondrial quality control may increase low-grade chronic inflammation by NLRP3 and other pathways [25]. This could provide pathways for compounds such as anthocyanins to improve mitochondrial function and decrease inflammation.

1.3. Inflammation

Low-grade chronic inflammation underlies many chronic systemic diseases, especially age-related decline and metabolic disorders [26][27][28][29][30][31]. In obesity, it is characterised by the secretion of a complex range of pro- and anti-inflammatory cytokines from expanding adipocytes in visceral adipose tissue known as adipokines that initiate and sustain the inflammation [32]. These adipokines impact remote organ function to produce the complications of cardiometabolic disease [33].

The bacteria in the gut microbiota regulate the permeability of the intestines with some species promoting a "leaky gut". This allows microbial metabolites and components of the bacteria, such as lipopolysaccharides, to enter the circulation and start an inflammatory reaction by the release of cytokines. Further, gut microbiota allow the conversion of complex carbohydrates, not digested by the host, to short-chain fatty acids such as butyrate which are absorbed and may be anti-inflammatory [34]. As increased inflammation is associated with many diseases such as cardiovascular disease, diabetes, obesity, inflammatory bowel disease and cancer, understanding the role of the gut microbiota in these diseases is important.

In obesity, increased inflammatory responses occur with pro-inflammatory macrophages accumulating in adipose tissue, possibly with hypoxia as the initiating event leading to greater expression of hypoxia-inducible factor 1-α and increased inflammatory responses in the liver, pancreatic islets and gastrointestinal tract [35]. Adipose tissue inflammation decreases remote organ function, considered causative for the complications of obesity [33]. The role of the hypothalamus in the regulation of energy homeostasis is well-known. The inflammatory activation of glial cells in the hypothalamus leads to changes in feeding habits, thermogenesis and adipokine signalling, leading to metabolic disorders [36]. Further, maternal obesity and inflammation may lead to metabolic reprogramming in the foetus, which could influence both childhood and adult body weight and composition, thus increasing the risk of transgenerational transmission of obesity [37].

The anti-inflammatory responses to anthocyanins have been shown in many in vivo and in vitro systems; further, anthocyanins regulate pro-inflammatory markers in both healthy and chronic disease states [38]. There are many mechanisms for the anti-inflammatory effects of anthocyanins that could be applicable in chronic inflammatory diseases, including inhibiting the release of pro-inflammatory factors, reducing TLR4 expression, inhibition of the NF-κB and MAPK signalling pathways, and reducing the production of NO, ROS and prostaglandin E_2 [39].

Reducing inflammation in the brain may play a role in anthocyanin-induced changes in chronic disease. Prolonged neuroinflammation damages brain function, possibly causing and accelerating long-term neurodegenerative diseases including dementia [40]. The gut-microbiota-brain axis allowing bidirectional communication is important in maintaining the homeostasis of the central nervous system as well as the gastrointestinal tract. Thus, much recent research has focused on the relationships between gut microbiota and neurological disorders such as schizophrenia and autism spectrum disorder and neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease and ischaemic stroke, which involve the death of vulnerable populations of neurons [41]. Dysbiosis of the gut microbiota has been associated with the progression of both systemic inflammation and neuroinflammation [42]. Mediators of neuroinflammation include microglia, astrocytes and oligodendrocytes as well as damaged and dysfunctional mitochondria [43].

Anthocyanins and their metabolites produce neuroprotective activities by decreasing neuroinflammation, preventing excitotoxicity, preventing aggregation of proteins, activating pro-survival pathways while inhibiting pro-apoptotic pathways and improving axonal health [44][45]. The wide range of potential mechanisms to overcome neurotoxicity with anthocyanins such as cyanidin glucoside includes suppression of c-Jun N-terminal kinase activation, amelioration of cellular degeneration, activation of the brain-derived neurotrophic factor signalling and restoration of Ca^{2+} and Zn^{2+} homeostasis [46]. Blueberry extract (150 mg/kg/day) containing anthocyanins promoted neuronal autophagy to decrease neuronal damage in transgenic APP/PS1 mice with mutations associated with early-onset Alzheimer's disease. Further, protocatechuic acid may be the major metabolite producing neuroprotection [47]. Possible changes in amino acid metabolism have been suggested as the mechanism of improved attention, feelings of alertness and mental fatigue after 3 months' treatment with tart cherries containing anthocyanins and other polyphenols in middle-aged adults [48]. These changes could be beneficial if they can be translated to patients with neurological or neurodegenerative diseases.

However, most studies have been performed in cell culture or in pre-clinical animal models. Thus, the roles of anthocyanins and their metabolites in existing neurodegenerative diseases in humans where significant neuronal loss has already occurred are uncertain but possible. Targeting neuroinflammation with anthocyanins is therefore a promising strategy in the treatment of neurological disease [45] although the translation of results from animal models to patients with neurological disease requires further research. Further, direct pharmacological actions in the brain of orally administered anthocyanins require that anthocyanins pass through the blood–brain barrier, yet the permeability of anthocyanins has been shown to be low [49]. This suggests that the major reason for decreased neurotoxicity with anthocyanins could be that changes in gut microbiota lead to decreased neuroinflammation.

1.4. IGF-1

The neuropeptide IGF-1 has important roles in the development and maturation of the brain [50]. Cyclic glycine-proline (cGP), a neuropeptide formed from the N-terminal tripeptide fragment of IGF-1, activates and normalises IGF-1 essential for body growth, neurological function and lifespan [51][52]. However, IGF-1 may play opposing roles in the ageing brain, where chronic neurodegenerative, cardiovascular and metabolic diseases are more likely to

have a pathological effect [53]. The study of the interactions of IGF-1 and anthocyanins is relatively recent but it is providing a potential mechanism for their therapeutic benefits.

The interaction of cGP with bound/free IGF-1 may mediate the therapeutic benefits of anthocyanins in reducing blood pressure and improving cognitive health [54]. cGP has a higher binding affinity to the IGF binding protein-3 (IGFBP-3) than IGF-1 itself, thereby increasing the free concentrations of active IGF-1 in the plasma. IGF-1 reduced hypertension in pre-clinical models of hypertension [55]. This could account for the normalisation of blood pressure in obese adults with mild hypertension [56].

Decreased peripheral and cerebrospinal fluid IGF-1 concentrations could be a potential marker for the cognitive decline and progression of Alzheimer's disease. In the brain of Alzheimer's disease patients, bioavailable IGF-1 deficiency was shown with increases in bound IGFBP-3 and bound cGP [57]. As IGF-1 is involved in synaptogenesis, increased bioavailable IGF-1/cGP could improve brain function in Alzheimer's disease. Consumption of blackcurrant supplement containing 35% anthocyanins at a dose of ~600 mg daily increased cGP concentrations in both the plasma and cerebrospinal fluid in humans, showing that the lipophilic nature of cGP enabled rapid transfer across the blood–brain barrier [58]. This could support the hypothesis that anthocyanins are effective both in reducing blood pressure and improving brain function by increasing IGF-1 and cGP in the brain. The mechanisms through which dietary anthocyanins increase cGP in plasma and cerebrospinal fluid are currently under investigation. One study showed that blackcurrant juice contained both anthocyanins and cGP [58].

2. Therapeutic Actions of Anthocyanins in Chronic Diseases

2.1. Delaying Cognitive Decline

Cognitive decline is a characteristic of ageing including three major features of immunosenescence as inflamm-ageing, vascular ageing and brain ageing [59]. As inflammation is the common underlying mechanism, anti-inflammatory flavonoids may have a role in preventing cognitive decline. Higher flavonoid intakes were associated with a decreased subjective cognitive decline in US men and women with the strongest associations for flavones, flavanones and anthocyanins [60]. Supplementation with fish oil, blueberries or a combination for 24 weeks was given to 76 patients aged 62–80 years with self-perceived cognitive decline. Both individual interventions produced fewer cognitive symptoms and the combination improved memory discrimination [61]. Further, older adults with mild cognitive impairment at risk of dementia improved working memory after a 16 week intervention with blueberries with a daily dose of 269 mg cyanidin 3-glucoside equivalents [62]. In 49 patients over 70 years old with mild to moderate dementia, 12 week intervention with cherry juice containing anthocyanins improved verbal fluency, short-term memory and long-term memory, together with lowered systolic blood pressure [63]. These results suggest a role for the anti-neuroinflammatory responses of anthocyanins in moderating cognitive decline in older adults. Human intervention studies suggest that daily strawberry or blueberry intakes may improve cardiovascular and metabolic parameters and possibly improve cognitive function [64]. Further, modifications in the gut microbiota were partially linked to the neuroprotective properties of a blackberry anthocyanin-rich extract in Wistar rats fed a high-fat diet [65].

2.2. Modulating Neurodegenerative and Neurological Diseases

Neurodegenerative disorders such as Parkinson's disease, Alzheimer's disease and amyotrophic lateral sclerosis are characterised by the death of neurons and loss of signalling networks leading to impairment of both cognitive and motor function. Neuroinflammation is an important aspect of neurological and neurodegenerative diseases and the role of anthocyanins to reduce neuroinflammation has been outlined in **Section 1.3**. Further, the effects on gut microbiota, oxidative stress and inflammation suggest that anthocyanins could be neuroprotective, as shown in animal models of neurological and neurodegenerative diseases, and in studies using cell cultures [46].

Parkinson's disease is a slowly developing neurodegenerative disorder with accumulating disability and no current therapy to slow down disease progression [66]. Observational studies have suggested that dietary antioxidants in humans may decrease the risk of Parkinson's disease but only two of these studies involved anthocyanins to give a pooled relative risk of 0.76 [67]. Potential mechanisms include reduction of antioxidant stress, reducing excitotoxic insults, reducing neuroinflammation, preventing protein aggregation and endoplasmic reticulum stress and reducing apoptosis [44]. However, these studies have mostly been performed in animal models or cell cultures rather than in patients with Parkinson's disease. The development of Parkinson's disease has been associated with IGF-1, especially increased concentrations at the onset of the disease [68]. Cerebrospinal fluid concentrations of IGF-1 and cGP in Parkinsonian patients were increased after supplementation with blackcurrant anthocyanins, suggesting that anthocyanins may modulate IGF-1 function and thereby improve disease state [58].

The role of neuroinflammation, especially microglial activation, in the trajectory of Alzheimer's disease suggests possible therapeutic options for anthocyanins [69]. Disturbances of the gut microbiota may worsen signs of Alzheimer's disease by activating signalling pathways such as the TLR4/NF-κB, ROS/JNK and NF-κB/BACE1 pathways; inhibiting these pathways with anthocyanins was suggested to decrease neuroinflammation and Alzheimer's pathology [70]. In a mouse model of Alzheimer's disease, altered gut microbiota were associated with an increased NLRP3 inflammasome, enhanced astrogliosis and microglial activation [71]. Transplantation of the gut microbiota from Alzheimer's disease patients into APP/PS1 double transgenic mice as a model of the disease increased expression of NLRP3 and led to more severe cognitive impairment [72]. Further, in mouse models of Alzheimer's disease, remodelling of the gut microbiome with sodium oligomannate suppressed neuroinflammation to decrease disease progression [73]. A clinical trial in 818 mild-to-moderate Alzheimer's disease patients with sodium oligomannate for 36 weeks showed sustained improved in cognition [74], demonstrating the potential of this intervention. As anthocyanins may reduce neuroinflammation [44][45][46], they could be useful options for Alzheimer's disease by remodelling the gut microbiome. However, improvements in patients with Alzheimer's disease given anthocyanins have not been reported. In contrast, dietary consumption of strawberries has been associated with a decreased risk of Alzheimer's dementia [75].

Amyotrophic lateral sclerosis is characterised by neuron apoptosis followed by skeletal muscle atrophy [76] with proposed mechanisms including oxidative stress, neuroinflammation and mitochondrial dysfunction. While no reports on the treatment of human amyotrophic lateral sclerosis with anthocyanins have been found, the

anthocyanin metabolite, protocatechuic acid, sustained neuromuscular function with improved motor function and decreased gliosis in the hSOD1^{G93A} mouse model of this disease [77].

Few studies have investigated the roles of anthocyanins to treat neurological disease in humans. Human studies using anthocyanins in insomnia, anxiety or depression suggest potential therapeutic benefits but reported studies are few and the patient numbers were low [78]. In eight patients aged over 50 years, tart cherry juice improved both sleep duration and efficiency with procyanidin B2 proposed as the major bioactive compound [79]. Further, patients with Parkinson's disease scored lower on anxiety and depression scores after administration of blackcurrant concentrate (300 mg twice daily for 4 weeks) increased cGP concentrations in cerebrospinal fluid [58]. Clearly, further studies in humans with anthocyanins or their metabolites in these prevalent neurodegenerative and neurological diseases are necessary.

2.3. Protecting the Liver

The liver is an important organ for lipid metabolism as it plays vital roles in fatty acid synthesis and lipid circulation through lipoprotein metabolism [80]. Anthocyanins have shown beneficial effects on these lipid metabolic pathways in the liver. Mulberry anthocyanin extract in human hepatoma cells HepG2 reduced fatty acid synthesis and increased fatty acid oxidation in response to lipid accumulation by oleic acid. Anthocyanins from mulberry extract also inhibited acetyl coenzyme A carboxylase through AMP-activated protein kinase [81]. These responses were associated with reduced expression of sterol regulatory element-binding protein-1 (SREBP-1), fatty acid synthase, glycerol 3-phosphate acyltransferase, 3-hydroxy-3-methyl-glutaryl CoA reductase, adipocyte-specific fatty acid binding protein and SREBP-2 along with increased expression of peroxisome proliferator activated receptor α and carnitine palmitoyl-transferase-1 [81]. Similar results were obtained with delphinidin 3-sambubioside (100 or 200 μg/mL) from *Hibiscus sabdariffa* L. in HepG2 cells induced with oleic acid [82].

Non-alcoholic fatty liver disease (NAFLD) is a multifactorial disease defined as the accumulation of triglycerides in hepatocytes in the absence of ethanol consumption. It has a global prevalence of 25% yet no approved drug therapy [83]. Anthocyanins may decrease NAFLD by changing the gut microbiota, providing antioxidant and anti-inflammatory responses and improving lipid and glucose metabolism to reduce risk factors [84]. As an example, delphinidin 3-sambubioside (15 or 30 mg/day) in high-fat-diet-fed rats reduced body weight gain, visceral fat, abdominal fat and hepatic lipid deposition [82]. In patients with NAFLD, intervention for 12 weeks with a bilberry and blackcurrant mixture containing 320 mg anthocyanins improved insulin resistance, indicators of liver injury and clinical evolution [85]. However, meta-analysis of 12 randomised clinical trials in patients with metabolic disorders did not show significant effects of anthocyanin supplementation on the liver enzymes, ALT and AST [86].

2.4. Protecting the Heart and Blood Vessels

Hypertension remains the leading cause of cardiovascular disease and premature death, with an increased incidence in low- and middle-income countries [87]. As such, reducing cardiovascular disease using nutraceuticals has an obvious appeal. Anthocyanins reduced the risk of coronary heart disease and cardiovascular disease

mortality but had no effect on myocardial infarctions, stroke or total cardiovascular disease [88]. A further analysis confirmed the decreased risk of cardiovascular disease with evidence that the protection could involve improved lipid profiles and decreased circulating pro-inflammatory cytokines [89]. An umbrella review showed a reduced risk of hypertension and improved markers of cardiometabolic disease but no effect on systolic or diastolic blood pressures [90]. However, a small observational study reported decreased blood pressures in mildly hypertensive patients given Queen Garnet plum juice containing 255 mg cyanidin 3-glucoside equivalents for 12 weeks [56].

The major sites of cardiovascular action of anthocyanins appear to be the vasculature rather than myocardial tissue. In rats with left anterior descending artery occlusion and reperfusion, cyanidin 3-glucoside at doses of 10 and 20 mg/kg/day protected heart tissue from ischaemia-reperfusion injury by attenuating oxidative stress and ferroptosis-related protein expression [91].

Atherosclerosis is an inflammatory vascular disease [92]. Oxidative stress and inflammatory signalling in cells in the atherosclerotic plaque such as macrophages and endothelial cells can be reduced by direct antioxidant actions, by inducing intracellular Nrf2 activation and antioxidant gene expression and by anti-inflammatory responses such as increased antioxidant capacity of HDL and decreasing lipid/protein oxidation [93]. Physiologically relevant concentrations of cyanidin 3-glucoside and its metabolites decreased expression of the inflammatory mediators, IL6 and VCAM-1, in human vascular endothelial cells in culture [94]. In hydrogen peroxide and LPS-stimulated diabetic human aortic endothelial cells, berry anthocyanins at 50 µL/mL reduced oxidative stress and inflammation by inhibition of the NF-κB signalling pathway [95].

A preliminary event in the development of atherosclerosis is the increased apoptosis of endothelial cells [96]. Cyanidin 3-glucoside decreased inflammation, suppressed apoptosis, lowered blood lipid concentrations and improved artery wall structure and function in rabbits fed a high-fat diet [97]. Berry anthocyanins may protect the vasculature in cardiometabolic disease by inducing NO production and decreasing inflammation and oxidative stress [98] as well as changes in the gut microbiota [99]. Further, Queen Garnet plum juice containing approximately 250 mg cyanidin 3-glucoside reduced the postprandial effects of a high-fat high-energy meal on vascular endothelial function and inflammatory responses in older humans [100]. Platelet aggregation is more likely following endothelial damage in humans. Platelet aggregation *in vitro* was decreased in healthy subjects following 21 day supplementation with Queen Garnet plum juice containing approximately 200 mg cyanidin 3-glucoside [101].

2.5. Maintaining Glucose Homeostasis

Type 2 diabetes is a chronic disease defined by hyperglycaemia leading to microvascular and macrovascular damage. The prevalence of diabetes has been increasing globally since 1990, attributed to living environments and lifestyle leading to poorer nutrition and increased sedentary behaviour [102]. Diabetes is more prevalent in people aged 65 years and older including 122 million of this population of 652 million, or around 19%; further, prediabetes affects 48% of the 26 million older adults in the USA. The risk to these patients is increased by multiple comorbidities, increased incidence of hypoglycaemia, increased dependence on care and worsening frailty [103]. A marked decrease in all-cause mortality rates of 30–35% in diabetics in the USA and England has been related to

decreases in mortality from cardiovascular disease. Cancer rates have remained unchanged in diabetes patients but this is now an increased percentage of deaths while mortality rates from dementia and liver disease have increased [104]. Treatment of diabetes now includes glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors, with potential clinical use of adiponectin and fibroblast growth factor 21, so that these compounds will allow personalised approaches to lower blood glucose concentrations [105].

Large prospective cohort trials in the USA have shown an inverse relationship between a healthy plant-based diet and the risk of developing diabetes [106]. Further, diets containing polyphenols such as anthocyanins may reduce the risk of developing diabetes [107]. In clinical trials in diabetes, anthocyanins reduced blood glucose and HbA1c concentrations and improved insulin secretion and resistance [107][108]. Various studies have identified beneficial impacts of dietary polyphenolic compounds including anthocyanins on glucose homeostasis. These impacts were observed through many potential mechanisms in organs such as intestine, liver, muscle, adipocytes and pancreatic β-cells, along with their effects on gut microbiota [109][110]. Studies on animal models of diabetes have shown that anthocyanins can improve the diabetic phenotype by a range of mechanisms including preventing pancreatic β-cell inflammation, modifying enzymes in glucose metabolism and changing adipocyte function [111]. Anthocyanins decrease hyperglycaemia and insulin resistance by mechanisms including inhibition of carbohydrate metabolising enzymes such as α-amylase and α-glucosidase, increased glucose-stimulated insulin secretion by pancreatic β-cells and regulation of liver function to improve insulin resistance and changes in the gut microbiota [112]. Anthocyanins may also decrease hyperuricaemia, which is tightly linked to hyperglycaemia [112]. In insulin-resistant HepG2 cells, mulberry anthocyanin extract increased glucose consumption, glucose uptake and glycogen content [113]. Mulberry anthocyanin extract at 50 and 125 mg/kg/day doses also decreased fasting blood glucose, serum insulin, leptin, triglyceride and cholesterol concentrations and increased adiponectin levels in db/db mice [113]. These effects of anthocyanins were further improved in the presence of metformin. In mice, a combination of anthocyanins (100 mg/kg/day) and metformin (50 mg/kg/day) improved blood glucose concentrations, insulin resistance and organ damage as well as increasing beneficial bacteria in the gut microbiome and short-chain fatty acid content [114].

Reversal of changes in the gut microbiota in diabetes is a possible mechanism for improved metabolic health. Obese mice fed a high-fat high-sucrose diet and blueberry anthocyanins with faecal transplantation lost body weight and improved insulin resistance [115]. Diabetic patients have a decreased abundance of short-chain-fatty-acid-producing bacteria and tryptophan-metabolite-producing bacteria and an increased abundance of branched-chain amino-acid-synthesising bacteria and sulphate-metabolising bacteria. The unbalanced gut microbiota and microbial metabolites may be altered by interventions such as faecal transplantation, metformin or acarbose treatment, or probiotic supplementation [116].

The IGF axis has been suggested as a potential target for the treatment of diabetes and insulin resistance. Treatment with anthocyanins (320 mg/day for 12 weeks) in 56 patients with untreated fasting hyperglycaemia decreased blood glucose and C-peptide concentrations and increased blood IGFBP-4 fragments, suggesting that anthocyanins can improve glucose homeostasis by activating the IGF system [117].

Intestinal absorption of anthocyanins is through both sGLT1 and GLUT2 transporters. In addition, in animal models and isolated cell studies rather than in human clinical trials, anthocyanin treatment increased GLUT4 protein levels and translocation in peripheral tissues, which may alleviate obesity- and diabetes-induced metabolic dysfunction [118]. Further, anthocyanins and protocatechuic acid modulated intestinal glucose homeostasis in mice by increasing GLP-1 secretion and decreasing ileum expression of dipeptidyl peptidase IV [119]; these findings need to be reproduced in diabetic humans.

2.6. Protecting the Kidneys

Chronic kidney disease is a major public health problem with an estimated global prevalence of 13.4%, including around 5 to 7 million people needing renal replacement therapy [120]. The disease has high morbidity and mortality and no cure. Kidney function decrease can be slowed by dietary and lifestyle adjustments, especially in people with hypertension or diabetes, as well as managing cardiovascular risk, reducing the risk of infection and preventing acute kidney injury [121]. Gut dysbiosis has been suggested as a cause of chronic kidney disease [11], thus specific age-related changes in the gut microbiota may amplify the development of kidney damage [122]. Changes in the gut microbiota are associated with changes in intestinal permeability and the development of a leaky gut. Nutritional interventions such as dietary fibre may be protective in the development of a leaky gut by the production of short-chain fatty acids, while dietary fats may worsen gut function by production of lipopolysaccharides [123]. The altered gut microbiota in chronic kidney disease produces increased amounts of kidney toxins such as indoxyl sulfate, p-cresyl glucuronide, p-cresyl sulfate and indole-3-acetic acid, which then undergo increased systemic translocation to produce oxidative stress injury to the kidney [124].

Many nutritional constituents, including anthocyanins, slow down the inflammatory process in chronic kidney disease to potentially delay progression of the disease [125]. A range of polyphenols, including anthocyanins, increase gut microbiota such as *Bifidobacteria* spp. and *Lactobacillus-Enterococcus* spp., leading to protection of the intestinal barrier and decreased colonic inflammation in kidney disease. In addition, the high antioxidant responses to anthocyanins should further decrease intestinal damage [19]. These results from animal studies on kidney function have not been translated to humans, although plant-dominant low-protein diets are recommended to improve patient outcomes in chronic kidney disease [11].

2.7. Decreasing Obesity

The increase in the prevalence of obesity over the last 50 years has been described as a pandemic that increases the risk of many diseases including cardiovascular disease, diabetes, fatty liver, dementia and osteoarthritis [126]. For anthocyanins to be effective in chronic diseases such as obesity, they must act on relevant target cells. There is good evidence that anthocyanins interact with adipocytes, endothelial cells, inflammatory cells, hepatocytes, intestinal cells and gut microbiota, but they do not act on platelets, skeletal muscle cells, hepatic stellate cells or pancreatic β-cells [127].

A systematic review with meta-analysis of randomised clinical trials concluded that anthocyanin supplementation of 300 mg/day or less for 4 weeks was sufficient to lower body mass index and body weight, with the greatest decrease in people from the Middle East [128]. An extract from black rice mainly containing cyanidin 3-glucoside given to 47 obese postmenopausal Korean women for 12 weeks decreased lower trunk fat and total body fat percentage, possibly by reducing body fat accumulation and increasing lipolysis [129].

The anti-obesity responses to anthocyanins are likely to be a combination of different mechanisms including reduction of oxidative stress, inflammation and lipogenesis to increase lipolysis and thermogenesis and regulate satiety [130] and reversing changes in the gut microbiota. Actions of ROS that lead to obesity include regulation of adipocyte differentiation, mitochondrial dysfunction, increased endoplasmic reticulum stress, decreased lipolysis and lipogenesis, inflammation, altered adipokine production and over-activation of the sympathetic nervous system. Thus, natural products including anthocyanins that scavenge ROS could act on multiple mechanisms to prevent or reverse obesity [131]. As changes in the gut microbiota may initiate and maintain obesity-associated inflammation, suppression of the microbiota changes by anthocyanins may be relevant in reducing body fat accumulation [132]. Further, gut metabolites such as short-chain fatty acids from dietary sources may prevent obesity while metabolites from protein in the distal colon such as ammonia, phenols and branched-chain amino acids might worsen metabolic health [133].

The interplay between inflammation and obesity and its regulation by anthocyanins suggests that natural products containing anthocyanins are a strategy to reduce obesity-related chronic conditions [134]. As an example, the anthocyanins in Queen Garnet plums at a dose of approximately 200 mg/day for 4 weeks decreased body weight by 0.6 kg in healthy individuals together with increased blood adiponectin and decreased blood leptin concentrations [135].

2.8. Increasing Bone Repair

Continual bone remodelling requires formation of new bone by osteoblasts and removal of old bone by osteoclasts. Chronic debilitating disorders of bone function and repair include osteoarthritis [136], most notable for degradation of the articular cartilage and synovial membrane inflammation causing pain and loss of function, and osteoporosis including decreased bone density and quality increasing the risk of fracture [137].

Anthocyanin-containing fruits have shown promise in reducing the symptoms of arthritis in animal models and in human cells in culture [138]. In mice made osteoarthritic by destabilisation of the medial meniscus, cyanidin (50 mg/kg/day for 8 weeks) was protective by regulating the Sirt6/NF-κB signalling axis [139]. Further, cyanidin suppressed interleukin-1β-induced inflammatory changes in human chondrocytes. Anthocyanins from purple corn showed anti-inflammatory effects on AGE-induced human articular chondrocytes by inactivation of the NF-κB and MAPK signalling pathways [140]. Davidson's plum containing cyanidin 3-glucoside (8 mg/kg/day) reduced obesity-induced degeneration of knee cartilage in rats with diet-induced metabolic syndrome [141]. In osteoporosis, bone regeneration may be stimulated by anthocyanins by stimulating bone formation and inhibiting bone resorption [142]; examples include peonidin 3-glucoside and cyanidin [143]. Anthocyanins may also alter bone remodelling in

osteoporosis by epigenetic regulation of osteoblast differentiation and apoptosis, and bone mineralisation [144]. Further, purple corn anthocyanins and protocatechuic acid produced anti-inflammatory effects on advanced glycation end-products in human articular chondrocytes by inactivation of the NF-κb and MAPK signalling pathways [140].

The hypothesis of a “gut–joint axis” has been proposed to connect the changes in the gut microbiota and osteoarthritis factors such as age, gender, metabolism, central nervous system and joint injury [143][145]. Decreasing serum lipopolysaccharides and inflammatory responses by chronic ampicillin and neomycin treatment of osteoarthritic mice changed the microbiota and improved the signs of osteoarthritis [146]. The gut microbiota may alter bone metabolism and absorption and so changes in the microbiota may be a potential intervention to improve osteoporosis [147].

Treatment options for osteoarthritis and osteoporosis may then include altering bone formation and removal, decreasing inflammation and reversing gut microbiota changes with anthocyanins. Further studies are needed to determine whether increased dietary intake of anthocyanins in humans is associated with a decreased risk of developing osteoarthritis or osteoporosis.

2.9. Protecting and Repairing the Gastrointestinal Tract

Inflammatory bowel disease (IBD) as a chronic relapsing-remitting gastrointestinal disease has been used as a case study of the evolution of modern diseases by a description of the changing epidemiological patterns from the Industrial Revolution and projected to 2050 [148]. The gut microbiota in IBD patients shows decreases in beneficial bacteria and increases in pathogenic bacteria including changes that may precipitate relapse [149]. Restoring dysbiosis by increasing the production of short-chain fatty acids from dietary fibre by the microbiota may be useful to support therapy of IBD [150]. Dietary anthocyanins may alter the bacterial metabolism within the intestines and so reduce inflammation, for example in ulcerative colitis [151]. In addition, anthocyanins such as cyanidin 3-glucoside and their phenolic metabolites may improve the structure and function of the intestinal barrier and reduce oxidative stress to reduce IBD [152].

Helicobacter pylori is a major cause of human gastric disease around the world, especially gastric ulcers. Berry extracts containing anthocyanins produced antimicrobial activity against *H. pylori* in a high-throughput bacterial assay [153]. Black rice extract containing cyanidin 3-glucoside inhibited the biogenesis of virulence proteins in *H. pylori* and decreased apoptosis of *H. pylori*-infected cells [154]. Further, reduction of oxidative stress and inflammation may play a role in the reduction of peptic ulcers caused by ethanol and non-steroidal anti-inflammatory drugs and increased healing of acetic-acid-induced ulcers by malvidin [155]. In DSS-induced IBD in rats, cyanidin 3-glucoside and extracts of Queen Garnet plums at 8 mg/kg/day effectively reversed gastrointestinal symptoms [156] to a similar extent as sulphasalazine (~350 mg/kg/day) [157].

2.10. Moderating Physiological Changes in Exercise

Increased oxidative stress, inflammation, muscle damage, fatigue and fat oxidation may decrease exercise performance, for example in cycling [158]. Fruit-derived anthocyanins at doses of 8–3600 mg/day for up to 8 weeks reduced these responses to exercise and increased NO production to improve vascular function and muscle oxygenation. In addition, functional and subjective recovery after exercise was improved by anthocyanins probably due to their antioxidant and anti-inflammatory effects [159].

2.11. Protection against Cancer

Anthocyanins can exert effects in colorectal and breast cancer in animal studies whereas these results have not been replicated in human studies [160][161]. Anthocyanins can help in preventing DNA damage from oxidative stress in the initial stage of tumour formation. Other effects of anthocyanins may be through the inhibition of proliferation of cancer cells and migration of metastatic cells [162]. Anthocyanins interfered with cell signalling pathways related to cell growth and differentiation, apoptosis, oxidative stress and inflammatory responses in cell culture studies [163] [164]. Three important signalling pathways have been identified in these chemopreventive effects of anthocyanins—AMP-activated protein kinase, PI3K/AKT/mTOR and JAK-STAT pathways [160]. Lack of suitable responses in human studies in preventing or reversing various cancers may suggest the need for further human studies in cancer patients with appropriate doses and duration of treatment.

2.12. Moderating Ageing

Ageing is associated with changes in physiological systems. Older adults are prone to developing chronic diseases, including cardiovascular disease, cancer, neurodegenerative disorders and osteoporosis [18]; anthocyanins can help in preventing these complications. Thus, it can be hypothesised that anthocyanins will be helpful in preventing these ageing-associated changes. Vision and eye health are also impacted during the ageing process and anthocyanins have shown beneficial effects on glaucoma when administered at 50 mg/day for up to 2 years [165]. Anthocyanins from pomegranate have shown anti-ageing effects on the skin with improved skin permeation in aged humans [166].

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