Anthocyanins and Chronic Diseases

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Anthocyanins constitute a subclass of flavonoids with more than 700 structurally different anthocyanin derivatives of 27 aglycons identified. Anthocyanins are glucosides of the anthocyanidins (precursors of anthocyanins), which are derivatives via the phenylpropanoid pathway. Due to their multiple phenyl groups, anthocyanins are rarely found as aglycons (anthocyanidins).

Keywords: anthocyanins ; inflammation ; oxidative stress

1. Introduction

Inflammation affects a wide variety of physiological and pathological processes. This condition is an essential component of immune surveillance and host defense. Although the pathological aspects of numerous mechanisms of inflammation are well recognized, their physiological functions are mostly unexplained.

Low-grade chronic inflammation (LGCI) is a pathological feature of a wide range of chronic conditions. LGCI is characterized by elevated concentrations of inflammatory markers in the absence of any overt symptoms. However, this condition has not yet been consistently defined or measured. Although there is likely a genetic predisposition, many other triggers can impact the inflammatory process. Some exogenous and endogenous factors such as smoking, air pollution, silica dust, recurrent episodes of acute inflammation, persistent infections, autoimmune disorders, and overweight or obesity have been identified. Several triggers including overproduction of reactive oxygen species (ROS) and advanced glycation end products (AGEs), mitochondrial dysfunction, renin–angiotensin system (RAS) deregulation, hormonal changes, uric acid (urate) crystals, oxidized lipoproteins, homocysteine, visceral adiposity, an imbalance in the gut microbiota, and accumulation of cell debris due to defective autophagy also play a significant role [1][2].

In recent years LGCI has been shown to contribute to most if not all chronic diseases typical of age-related decline of many functional systems in the older population. This phenomenon has been termed “inflamm-aging” [1][3]. LGI has also been given the name “metaflammation” (an inflammation of metabolic tissue), which originates from metabolic cells in response to excess nutrients [4]. There is a general lack of sensitive and specific biomarkers of low-grade chronic inflammation that can be used in human trials. In humans, the most well-accepted markers of systemic inflammation are a number of circulating pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and interleukin-8 (IL-8). To date, high-sensitivity C-reactive protein (hsCRP), fibrinogen, and such cellular biomarkers like the white blood cell and platelet counts have also been used to assess LGCI [5][6][7].

Current research provides links among the change in inflammatory profile and the risk of a number of chronic conditions, including metabolic syndrome (MetS), non-alcoholic fatty liver disease (NAFLD), type 2 diabetes mellitus (T2DM), cancer, cardiovascular, and neurodegenerative disease [4][8][9][10][11][12].

Inflammation and oxidative stress act as cooperative and synergistic partners in the pathogenesis of a wide variety of diseases, elevating adverse chronic diseases’ risk factors levels [13]. As an example, misdirected oxidative stress in various tissues potentiates inflammatory responses and inciting target organ damage [14]. Oxidative stress occurs when an organism accumulates more ROS than can be eliminated by antioxidant defense mechanisms. The accumulation of ROS and free radicals in a cell affects many important compounds, such as lipids, proteins, DNA, carbohydrates, and enzymes, and can result in cell damage [15]. In healthy humans, cells defend themselves against ROS-related damage through antioxidants that prevent or counterbalance oxidation even at low concentrations. The ROS and antioxidant protection against free radical tissue injury are in balance [16]. It has been reported that impaired oxidant—antioxidant status is involved in the etiopathogenesis of various complications [17][18][19].

Dietary factors are involved in regulating the inflammatory state and activating the endogenous antioxidant defenses. Protective dietary compounds such as polyphenols, which are consumed together with a human diet, may be beneficial in attenuating the potentially harmful risk factors of chronic diseases. Among them, anthocyanins are emerging potential

agents for counteracting the onset and progression of numerous non-communicable diseases such as neurodegenerative, cardiovascular, and metabolic diseases and cancer. They have been shown to stimulate immunomodulatory and antioxidant effects, thereby blunting the cooperative and synergistic deleterious effects of oxidative stress and pro-inflammatory cytokines and may, therefore, provide protection against chronic diseases [20][21]. Their anti-inflammatory activity has been widely investigated by many authors. In the query performed in the ClinicalTrials.gov database in May 2021, the keyword “anthocyanin” has identified 145 clinical studies in which anthocyanins were registered.

2. Anthocyanins and Their Antioxidant and Anti-Inflammatory Activity

Anthocyanins and their metabolites, which are found in food, possess many biochemical properties, but the best-investigated effect is their antioxidants [22][23][24]. These substances can be mediated by inhibition of both the activity and production of various pro-inflammatory important substances and enzymes, such as TNF-α, nitric oxide (NO), inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and lipoxygenase (LOX). They are also known for upregulating the production of glutamate-cysteine ligase (GCL) and of glutamate-cysteine ligase modifier subunit (GCLM), and consequently, the levels of reduced glutathione (GSH), in activated microglial cells [25][26]. Of natural substances, anthocyanins have been suggested to play an important role in the suppression of inflammation also by inhibition of nuclear factor-kappa B cells (NF-κB) activation, which, in turn, is responsible for the control of transcription of DNA, cytokine production, and cell survival [27][28]. For example, cyanidin-3-glucoside, major anthocyanin of black rice (Oryza sativa L.), inhibited nuclear translocation of NF-κB p50 and p65 signaling in a 5-Fluoruracil-induced oral mucositis rat model and in oral keratinocyte culture [29]. Another investigator showed that malvidin-3-glucoside, found in rabbiteye blueberry (Vaccinium ashei), also suppressed TNFα in human umbilical vein endothelial cells by inhibiting nuclear translocation of p65 of NF-κB [30]. Treatment with cyanidin-3- O -sophoroside and cyanidin-3- O -sambubioside from black peanut ameliorated UV-irradiated oxidative injury through the action of the nuclear factor erythroid 2-related factor 2 (Nrf2) by interaction with the NF-κB signaling pathway in human keratinocyte cells (HaCaT cells) and mice skin [31]. This finding suggested that anthocyanins from black peanut skin might regulate oxidative stress and the suppression of cell apoptosis and might be used as a potential protective agent against UV-B-induced skin damage.

These substances have the capacity to act as antioxidants, and they can mediate antioxidant effects mainly by free radical scavenging or by chelating metal ions. Mechanisms of antioxidant action include (1) their ability to reduce the release of ROS formation by inhibition of enzymes or by chelating trace elements involved in the free radical generation, (2) scavenging ROS, and (3) upregulation or protection of antioxidant defenses [32][33]. The chelation of metals seems to be crucial in the prevention of radical generation. Some of these flavonoids are capable of inhibiting the enzymes involved in ROS generation, for example, microsomal monooxygenase, glutathione S-transferase, mitochondrial succinoxidase, and dihydro-nicotinamide adenine dinucleotide (NADH) oxidase [34]. The antioxidant action of anthocyanins may also result from activation of not only antioxidant enzymes, such as catalase, glutathione peroxidase, and heme oxygenase-1 (HO-1), which have radical scavenging ability, but also by suppression of prostaglandin E2 (PGE2), which impairs T cell receptor signaling [35]. The anti-inflammatory activity of anthocyanins was evaluated by both in vitro and in vivo analysis (**Table 1**).

Table 1. In vivo and in vitro research update (studies published in 2020) on anthocyanins and their anti-inflammatory effects in pathological conditions.

Disorder/Substances	In Vitro or In Vivo Model	Mode of Action	References
Adipose Tissue Inflammation			
Delta-tocotrienol, (DT3), and tart cherry anthocyanins (TCA)	**3T3-L1 adipocytes**	**↓ IL-6 secretion and expression from adipocytes Down-regulation of Mip2, and COX-2 mediated via the NFkB**	**Harlan et al. [36]**
cyanidin-3-*O*-glucoside	**Murine 3T3-L1 hypertrophic adipocytes**	**Modulating the expression of the PPAR-ɣ, Inhibiting the inflammatory pathway modulated by NF-κB**	**Molonia et al. [37]**
Pulmonary Artery Hypertension			

Disorder/Substances	In Vitro or In Vivo Model		Mode of Action	References
Cyanidin-3-*O*-β-glucoside	Transforming growth factor-β1 (TGF-β1)-mediated human pulmonary arterial smooth muscle cells (SMCs), Pulmonary artery hypertension (PAH) rats	↓ ↑ ↓	IL-6, TNF-α and IL-10 SOD activity MAD Suppressive effect on PAH progression	Ouyang et al. [38]
Diabetes				
Padus racemose Anthocyanins	H2 O2 -induced rat insulinoma (INS-1) pancreatic cells damage		inhibiting the activation of p38 MAPK and NF-κB	Liu et al. [39]
Hypercholestrolemia and Hepatic Inflammation				
Black Raspberry (*Rubus occidentalis*)	Rats fed high-fat and high-choline diets	↓ ↓ ↓	cecal TMA and serum oxidized TMAO, TC, LDL mRNA expression of pro-inflammatory genes including NF-κB, IL-1β, IL-6, COX-2 protein expression of NF-κB and COX-2 in liver tissue	Lim et al. [40]
Cancer				
rice bran, cyanidin 3-glucoside	Human prostatic cancer (PC3) cells	↓ ↑	expression of Smad/Snail signaling molecules expression of cell surface protein, E-cadherin Inhibited matrix metalloproteinase-9 and NF-κB Mediating Snail/E-cadherin expression	Jongsomchai et al. [41]
Vitis coignetiae Pulliat (Meoru in Korea)	MCF-7 Human Breast Cancer Cells	↑	Inhibiting Akt and NF-κB activity Cisplatin (anti-cancer drug) sensitivity	Paramananthm et al. [42]
Dark Sweet Cherry (*Prunus avium)*	MDA-MB-453 breast cancer cells and athymic mice xenografted with MDA-MB-453 breast cancer cells	↑	Bax/Bcl-2 ratio Activation of MAPKs ERK1/2 and p38 Down-regulation of total oncogenic and stress-related Akt	Layosa et al. Noratto et al. [43][44]
Vitis coignetiae Pulliat (Meoru in Korea)	Hep3B Human Hepatocellular Carcinoma Cells		Inhibition of the activation NF-κB and suppressed the NF-κB-regulated proteins, Inhibition of proliferation, invasion, and angiogenesis	Kim et al. [45]
Gastric Ulcer				
Dried acai berries extract (*Euterpe oleracea*)	Ethanol-induced gastric ulcer in rats	↑ ↓	GSH content and GST and CAT activity MPO activity, TNF-a	Cury et al. [46]
Neuroinflammation				
Hibiscus sabdariffa L. (Malvaceae)	Streptozotocin-induced Alzheimer's disease in mice	↓ ↓	TNF-α, IL-6, and IL-1β Elevated MDA and MPO Reverse up-regulation in the amyloidogenic pathway	El-Shiekh et al. [47]
Delphinidin	Alzheimer's disease model in rats	↓ ↓	AChE, APP, and Aβ ROS overproduction in hippocampus	Heysieattalab et al. [48]
Portugal Blueberries (*Vaccinium corymbosum* L)	Mouse microglia N9 cell line	↓ ↓ ↓ ↑	Suppression of NF-kB and STAT1 NO, PGE2, COX-2 TNF-α Intracellular Production of ROS GSH	Serra et al. [25]
Cataract				

Disorder/Substances	In Vitro or In Vivo Model	Mode of Action	References
Cyanidin-3-*O*-glucoside	**High glucose-induced lens epithelial cell (SRA01/04)**	**Inhibition SRA01/04 cell apoptosis Regulation of the Bcl-2/Bax ratio Suppression of NF-κB activation and subsequent Cox-2 expression**	**Song et al. [28]**

↑—increase, ↓—decrease, Aβ—amyloid beta, AChE—acetylcholinesterase, Akt—protein kinase B, APP—amyloid precursor protein, Bax/Bcl—Bcl-2-associated X protein/B-cell lymphoma protein ratio, CAT—catalase, COX—cyclooxygenase, GSH—reduced glutathione GST—glutathione S—transferases, IL—interleukin, MAPK—mitogen-activated protein kinases, MAD—malondialdehyde, Mip2—macrophage inflammatory protein 2, MPO—metalloproteinase NFkB—nuclear-factor κB, PAH—pulmonary artery hypertension, PGE— prostaglandins, PPAR-ɣ—peroxisome proliferator-activated receptors gamma, ROS—reactive oxygen species, SOD—superoxide dismutase, STAT1—signal transducer and activator of transcription 1, TMA-trimethylamine, TMO—trimethylamine-*N*-oxide.

3. Summary

Low-grade chronic inflammation is a key factor in the pathogenesis of many chronic diseases. Therefore, identifying modifiable risk factors that could effectively lower LGCI would contribute to the prevention of chronic disease.

Growing numbers of pre-clinical studies suggest its modulatory effect on inflammation pathways. Nevertheless, quantifying the effect of anthocyanins on inflammation in randomized control trials is hard to assess. The evidence that supports the direct anti-inflammatory role of anthocyanins is relatively scarce or of low quality. However, it supports the anthocyanins' role in regulating inflammation. Over the past five years, at least 29 clinical studies have evaluated the relationship between anthocyanins supplementation and inflammation. However, inconsistencies between the result of RCTs and meta-analyses have been observed. The main limitations of the presented clinical data are the short length of observation, small samples, and a wide variety and dosages of anthocyanin supplements that were used. It must be underlined that anthocyanins interventions have been more widely investigated in the treatment of metabolic outcomes. Human studies have reported lower LDL-cholesterol and triglycerides and increased HDL-cholesterol. Thus, the data support an indirect and beneficial role of anthocyanins in improving LCGI.

Regarding anthocyanins' effects on inflammatory markers, there is a need for long-term clinical trials allowing for the long preclinical phase or quantifiable progression of inflammation. Future research and intervention should also take into account the validation of the reduction of inflammatory markers by these compounds as well as other potential regulatory effects such as gut microbiota activity, which anthocyanin bioactivity depends on. Furthermore, strategies for improving techniques to evaluate gut microbiota's impact on the bioavailability of anthocyanins are needed. Additionally, a better understanding of the role of anthocyanins in inflammation could not be fully established without knowledge of the effects of treatment of pure anthocyanins. The synthesis of pure anthocyanins for research purposes remains crucial. Further translational research is necessary to understand the pharmacological actions of anthocyanins in humans.

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