



Mini Review

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# The Biomedical Functions and Related Mechanisms of Anthocyanin-Rich Extracts from Different Plant-Based Food

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## Abstract

Anthocyanins are a group of natural edible functional pigments, which not only provide the attractive color for plant, but also generate biomedical functions on various chronic diseases. Dietary interventions of anthocyanins are being investigated extensively which are associated with the prevention of chronic disorders and diseases. This review has summarized the latest research on the biomedical functions (including cholesterol control, asthma inflammation inhibition, retinal cells and liver fibrosis protection) of anthocyanin extracts from various food-based plants. The mechanisms of anthocyanin biomedical activity were attributed by the antioxidative, anti-inflammatory, and anti-proliferative properties, as well as the ability to regulate gene expression and metabolic pathways.

## Introduction

Anthocyanins, a class of water-soluble pigments widely found in plants [1]. They have the typical structure of flavonoids and are derivatives of 2-phenylbenzocchidic cations with C6-C3-C6 as the basic backbone. Anthocyanins are glycoside derivatives of anthocyanidins. There are more than 300 different anthocyanins in nature. They were found in a variety of fruits and vegetables such as purple sweet potato, cranberry, blueberry, grape, elderberry, black currant, purple carrot and red cabbage, ranging in color from red to blue [1]. The types of anthocyanins mainly include delchindin, cyanidin, petunidin and peonidin.

Anthocyanin has been already reported about its antioxidant ability and its effect on some chronic diseases. Epidemiological studies have found that long-term intake of plant foods rich in flavonoids can reduce the incidence of chronic cardiovascular diseases (CVD) and generate anti-mutation and anti-tumor activities [2]. For example, red wine anthocyanin extracts had strong inhibitory activity against the growth of colon cancer cells HCT-15 and gastric cancer cells AGS [3]. Also, anthocyanin-rich extracts have exhibited great performance on attenuating low

density lipoproteins oxidation, lipid peroxidation, dyslipidemia and reduced levels of CVD molecular biomarkers as well as improved total plasma antioxidant capacity [4]. Since the exploration of anthocyanin bioactivity continuously progresses, more biomedical functions of anthocyanin have been discovered. Therefore, in this review, the latest research on the biomedical functions of anthocyanin extracts such as the protective effect on asthma, hyperlipidemia, retinal damage etc. and the related mechanisms were introduced and discussed. It will provide essential information for develop functional food or dietary supplements using anthocyanin extracts.

## Latest Biomedical Functions and Related Mechanisms of Anthocyanin Extracts

### Anti-glycation function

Advanced glycation end product (AGE) is a complex group of compounds that formed through Maillard reaction, a non-enzymatic reaction between free amino groups of protein and the carbonyl group of reducing sugar [5]. It is one of the important factors that induce diabetes and other chronic diseases. In the study



of Wu et al (2009), mulberry anthocyanins were extracted and used in a BSA/glucose model system in order to investigate inhibitory effect of Mulberry anthocyanins on AGEs formation [6]. The results indicated that AGEs decreased significantly ( $P < 0.05$ ) with the increase of mulberry anthocyanin concentrations. The SDS-PAGE electrophoretogram also showed that mulberry anthocyanin extract could inhibit the formation of protein crosslinking caused by glycosylation reaction. Meanwhile, the protein carbonyl and thiol groups content were significantly reduced with the treatment of mulberry anthocyanins [7]. It indicated that the mulberry anthocyanin extracts inhibited AGEs formation induced by hydroxyl radicals (-OH) by protecting thiol and capturing reactive carbonyl intermediates.

### Cholesterol regulation

The physiological activity of cholesterol metabolism of *Lonicera caerulea* berry extracts (LCBE) has been evidenced in both *in vitro* and *in vivo* models. The effects of LCBE on cholesterol absorption and transport, as well as on the expression of genes controlling cholesterol synthesis, efflux, and absorption, were investigated in a Caco-2 cell monolayer model. The results showed that 40 and 80  $\mu\text{g/ml}$  of LCBE significantly reduced cholesterol absorption and transport, which further inhibited the cholesterol accumulation in a Caco-2 cell monolayer model [8]. Also, gene and protein expression of synthetic critical of cholesterol (SREBP2) and absorption (NPC1L1 and ACAT2) were significantly inhibited by LCBE ( $p < 0.01$ ). Furthermore, LCBE showed a potential function promoting cholesterol efflux through upregulation of mRNA and/or protein levels of ABCA1 and ABCG5/G8 ( $p < 0.01$ ). It was therefore concluded that LCBE exhibited hypocholesterolemic performance via multiple mechanisms, including modulation of cholesterol biosynthesis, absorption, and efflux-related gene expression.

In the *in vivo* model, the hypolipidemic effect of LCBE was confirmed using high cholesterol diet (HCD)-induced hypercholesterolemia rats. The result demonstrated that LCBE treatment decreased body and organ weights significantly ( $p < 0.01$ ) [8]. In addition, it normalized abnormal plasma lipoprotein levels and decreased liver cholesterol levels in hypercholesterolemic rats ( $p < 0.01$ ). LCBE also improved histopathological features of the hepatic and heart aortas in rats fed an HCD. Compared to the HCD control group, LCBE treatment significantly decreased levels of total cholesterol, total glyceride, low-density lipoprotein cholesterol, increased high-density lipoprotein cholesterol. LCBE treatment promoted greater neutral and acidic sterol excretion ( $p < 0.01$ ), and improved the antioxidant capacity of colon tissue, colon contents, and blood. Moreover, trimethylamine N-oxide (TMAO) levels also decreased in plasma ( $p < 0.01$  vs HCD group). On the molecular level, dietary LCBE treatment promoted the metabolism of cholesterol

to bile acids and their efflux by activating PPAR $\gamma$ -LXR $\alpha$ -ABCA1/CYP7A1 pathways and downregulating the mRNA and protein expression of cholesterol biosynthesis gene SREBP2 [9]. Moreover, NPC1L1, ACAT2, and MTP mRNA and protein expression were reduced, while ABCG5/8 expression increased ( $p < 0.01$ ) after LCBE treatment [8]. These results indicated that the therapeutic effect of LCBE is associated with efflux metabolism and reduced absorption of dietary cholesterol and biosynthesis through regulating the related genes.

### Asthma inflammation inhibition

In recent years, inhibition of Th2 cell activation in the treatment of asthma has become a research concern. Anthocyanins are glycosides formed by the combination of anthocyanins and various sugars by sugar bonds. Generally, Th2 cells, mast cells, monocytes, lymphocytes, eosinophils and neutrophils are the main inflammatory cells, which release cytokines and play important roles in asthma [10]. These cytokines could also induce the release of histamine and leukotriene resulting in airway hyperresponsiveness. Specially, Th2 cytokines, such as IL-4 and IL-5, regulate the body's immune response, inducing IgE production and chemotactic eosinophils [11]. Thus, the pathogenesis of asthma is related to the imbalance of Th1/Th2 cells. In the study of Arora et al (2016), the total number of cells in bronchitis alveolar lavage fluid and lymphocytes, eosinophils and neutrophils significantly decreased after anthocyanin extracts treatment in asthma mice [12]. In addition, asthma Th2 cytokines IL-4 and IL-5 levels in lung tissue of mice were significantly reduced. As a result, the anthocyanin extract inhibited the hyperresponsiveness of airways in mice and pulmonary inflammatory cell infiltration by inhibiting the Th2 cytokines IL-4 and IL-5.

### Retinal cells protection

Bulberry anthocyanin extract protected retinal pigment epithelium (RPE) cells from damage induced by H<sub>2</sub>O<sub>2</sub>, as indicated by morphological observation [13]. Also, anthocyanins from blueberries are capable of reducing A<sub>2</sub>E-epoxidation by quenching singlet oxygen and protecting RPE cells from A<sub>2</sub>E cytotoxicity [14]. Apoptosis in the RPE cells treated by anthocyanin extracts decreased approximately three times compared with control group. Thus, the anthocyanin extracts could inhibit oxidative damage induced by H<sub>2</sub>O<sub>2</sub> in RPE cells and change the expression of apoptotic factors through antioxidant activity.

### Liver fibrosis inhibition

**Effect of anthocyanin extracts on liver fibrosis in TGF- $\beta$ -induced HSC-T6 cells:** Anthocyanins can effectively inhibit aspartate aminotransferase (AST), alanine aminotransferase (ALT) and other liver function indicators [15]. Also, it reduces the mRNA

level of inflammatory factors such as interleukin-1 (IL-1) and interleukin-6 (IL-6) and inhibit the expression of alpha smooth muscle motor protein ( $\alpha$ -SMA) and other proteins [16].

**Effect of anthocyanin extracts on liver fibrosis in mice:** Anthocyanin extracts have a regulatory effect on the body weight of mice and has a significant inhibitory effect on the abnormal increase of liver coefficient in liver fibrosis mice [17]. It showed a significant protective effect on liver function indexes in the blood and liver tissue of liver fibrosis mice. Enhanced levels of antioxidant related enzymes (SOD, GSH-PX) also indicated that anthocyanin extracts can alleviate the symptoms of liver fibrosis in a dose-dependent manner [18]. Meanwhile, the expression of inflammatory factors (IL-1, IL-6, TNF- $\alpha$ , COX-2) in liver tissue were inhibited. The inhibition of the expression of TGF- $\beta$ 1 and P-Smad2 protein in the TGF- $\beta$ / Smad signaling pathway were observed with the treatment of anthocyanin extract during liver fibrosis [19,20]. The above results suggested that inhibition of liver fibrosis by anthocyanin extracts may be achieved through the TGF- $\beta$ / Smad signaling pathway and reduce the accumulation of inflammation factors in liver tissue, thereby achieving the effect of delaying liver fibrosis.

## Conclusion

It has been widely studied that anthocyanin extracts are associated with multiple bioactivities including scavenging free radical damage/oxidative stress, protecting cells, tissues and vital organs. This review has reported the latest biomedical functions of anthocyanin rich extracts such as antiglycation effect, cholesterol regulation, retinal cells protection and positive effect on asthma inflammation and liver fibrosis. It would provide essential information for consumers, healthcare providers, and the food and health industry to understand the relationship between anthocyanins and health. It is highly recommended that daily intake can mitigate the risk of diseases.

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## Conflict of Interest

The authors have no conflicts of interest to declare.

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