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Review

# Recent advances in understanding the anti-obesity activity of anthocyanins and their biosynthesis in microorganisms

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A R T I C L E I N F O

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A B S T R A C T

*Background:* Obesity is a serious health problem and the cause for social and economic burdens. Currently, there is still no cure for obesity, while the investment of time and money for one is huge. Recent years, the possibility of developing natural products from fruits and vegetables with bioactivities into anti-disease agents has become a hot spot in research. Thus, anthocyanins are increasingly causing more attention, as they have been proved to show anti-obesity effects. Furthermore, recent advances in biosynthesis of anthocyanins in microorganisms have illustrated a promising way in producing these valuable compounds in large scales.
*Scope and approach:* Anthocyanins have great importance in developing a cure for obesity and biosynthesis in microorganisms has high potential in their massive production. This review therefore highlights the recent advances in the anti-obesity effects of anthocyanins and their biosynthesis in microorganisms. We have comprehensively discussed the molecular mechanisms involved in the anti-obesity effects of anthocyanins, the physicochemical and physiological properties of anthocyanins, the suitability of anthocyanins in anti-obesity therapies as well as the possibility of biosynthesis in microorganisms in future application.
*Key findings and conclusions:* Anthocyanins have shown anti-obesity effects through multiple mechanisms, and biosynthesis of anthocyanins in microorganisms could have extensive applications. Inhibiting lipid absorption, regulating lipid metabolism, increasing energy expenditure, suppressing food intake and regulating gut microbiota are major mechanisms involved. Moreover, anthocyanins are promising candidates in developing anti-obesity therapies. Further studies are required to explore therapeutic uses of anthocyanins in treating obesity and application of biosynthesis of anthocyanins in microorganisms in industries.

## 1. Introduction

Obesity has become a serious problem that is causing a heavy burden to the economy and negative effects on people's longevity and life quality worldwide. Obesity is defined as a body mass index (BMI) equal to or more than 30 by World Health Organization (WHO), while overweight is defined as a BMI equal to or more than 25. BMI is calculated through the weight in kilograms divided by the square of the height in meters. According to a report from WHO, in 2014, about 39% of adults aged 18 years and over were overweight (38% of men and 40% of women), more than 1.9 billion, and 13% of the world's adult population (11% of men and 15% of women) were obese. This number has more than doubled between 1980 and 2014. In 2013, 42 million children under the age of 5 were overweight or obese. Obesity is driving global increases in type 2 diabetes, cardiovascular diseases, and several types of cancer, according to a Lancet commission on obesity (Swinburn, Dietz, & Kleinert, 2015). Obesity is also a prerequisite for metabolic syndrome, which is defined as a clustering of risk factors including central obesity, insulin resistance, dyslipidemia and hypertension (Carr & Brunzell, 2004; Nguyen, Magno, Lane, Hinojosa, & Lane, 2008). It is a physiological status as a result of an imbalance between energy consumption and energy expenditure. Thus, regulating the energy imbalance either through decreasing energy intake or increasing energy use is a promising strategy for the prevention and treatment of obesity.

Anthocyanins are anthocyanidins with sugar groups. Anthocyanidin is a subgroup of flavonoids that shows high bioactivities such as antioxidant effects. Basic structure of flavonoids is called C6-C3-C6, which is a skeleton of diphenylpropane formed by two benzene rings (ring A and B) with the linkage of a three-carbon chain that forms a closed

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pyran ring (C ring) with A ring. Flavonoids can be subdivided into different subgroups depending on the carbon of C ring to which B ring is attached, as well as the degree of unsaturation and oxidation of C ring. General subgroups are flavones, flavanones, isoflavones, flavonols, flavanonols, flavan-3-ols and anthocyanidins (Manach, Scalbert, Morand, Rémésy, & Jiménez, 2004). Anthocyanidins are characterized by having an oxonium, namely 2-phenylbenzopyrylium (Hendry & Houghton, 1996). There are more than 20 different anthocyanidins in total, while 6 of them are reported most frequently to be bioactive: cyanidin, delphinidin, pelargonidin, malvidin, peonidin and petunidin. The most widespread anthocyanins in nature are the glycosides of cyanidin, delphinidin and pelargonidin. (Kong, Chia, Goh, Chia, & Brouillard, 2003). Our group has recently reported that extracts of anthocyanins-rich raspberry, blackberry, mulberry and bayberry show antioxidant activity (Bao et al., 2016; Chen et al., 2016c; Xu, Hu, Bao, Xie, & Chen, 2017), protective effects such as protection against acrylamide-induced oxidative stress (Chen, Su, Xu, & Jin, 2017a; Chen, Su, Xu, Bao, & Zheng, 2016a; Li, Bao, & Chen, 2018), and ethyl carbamate-induced cytotoxicity (Chen, Xu, Zhang, Su, & Zheng, 2016b; Chen, Li, Bao, & Gowd, 2017b; Zhang et al., 2017; Bao et al., 2018). During the past decade, the anti-obesity effects of anthocyanins have gained increasing attention. Various anthocyanins extracts and purified anthocyanins are reported to have anti-obesity effects, such as preventing body weight gain and inhibiting lipid accumulation in adipose tissue.

This review summarizes recent advances on the anti-obesity effects of anthocyanins and the mechanisms involved. We first discussed characteristics of anthocyanins, such as physicochemical properties, metabolism and bioavailability, as well as their therapeutic use. We also summarized the effects of anthocyanins on obesity associated oxidative stress and inflammation. Anthocyanins are generally extracted from natural sources. This method is troubled with problems including high expenses, low efficiency and complex processes. In contrast, biosynthesis in microorganisms is a promising way to achieve massive production of anthocyanins. In this review, the recent advances in the biosynthesis of anthocyanins in microorganisms are also addressed at length to provide future perspectives on the production and application of anthocyanins.

## 2. Anthocyanins with anti-obesity effects and the major mechanisms involved

Anthocyanins widely exist in nature, such as fruits, seeds and flowers, giving them attractive colors. Extraction of anthocyanins from natural sources has been conducted by research groups all over the world. Many anthocyanins extracts and purified anthocyanins are reported to have anti-obesity effects in *in vitro* experiments, animal studies and clinical trials. Anthocyanins may exert beneficial effects in obesity by 1.) inhibiting lipid absorption, 2.) increasing energy expenditure, 3.) regulating lipid metabolism, 4.) suppressing food intake, and 5.) regulating gut microbiota (as shown in Table 1 and Fig. 1).

### 2.1. Inhibit lipid absorption

Inhibiting digestion and absorption of nutrients is a strategy focused on gastrointestinal mechanism to reduce energy intake. Excessive dietary fat intake, especially of saturated fat often results in hyperlipidemia and increased weight of adipose tissue. As dietary fat could not be directly absorbed without the action of pancreatic lipase, developing pancreatic lipase inhibitors is a rather appealing way to attenuate the status of obesity (Birari & Bhutani, 2007).

Litchi flower-water extracts (LFWEs) that contain some anthocyanins showed a suppressive effect on *in vitro* lipase activity (Wu et al., 2013a). Inhibitory effects on pancreatic lipase of extracts from samples commonly used in Mediterranean diet were reported along with their anthocyanins contents. Samples include fruits (blackberry, mulberry, sumac drupe, blood orange and pomegranate), vegetables (red cabbage and violet cauliflower), cereals (black rice); citrus vegetative tissues (young lemon shoots), legume seeds (black bean); citrus by-products (blood orange peel) and cereal processing by-products (black rice hull). The results showed a wide variation of anthocyanins contents in the extracts. Blood orange and pomegranate juice had the highest anthocyanins contents and showed the highest effect in inhibiting pancreatic lipase activity (Fabroni, Ballistreri, Amenta, Romeo, & Rapisarda, 2016).

### 2.2. Increase energy expenditure

Energy expenditure is closely related to mitochondrial function. The AMP-activated protein kinase (AMPK) is a key mediator of signals in energy balance (Steinberg & Kemp, 2009). AMPK increases expression of the gene *Ppargc1α*, which encodes the regulator of mitochondrial biogenesis peroxisome-proliferator-activated receptor γ coactivator 1 α (PGC1α) (Luo, Saha, Xiang, & Ruderman, 2005; Wu, Puigserver, Andersson, Zhang, Adelmant, Mootha, et al., 1999). AMPK inhibits cellular lipid metabolism upon activation of stimuli such as metabolic stress and cytokines derived from adipocyte such as leptin and adiponectin. AMPK also inhibits triglyceride synthesis and stimulate fatty acid oxidation and mitochondrial biogenesis. Thus the activation of AMPK will potentially reduce hypertriglyceridemia and elevate triglycerides storage in muscle and liver (Hardie, 2008). Also, in adipose tissues, a group of mitochondrial proteins called uncoupling proteins mediate thermogenesis (Cannon & Nedergaard, 2004; Spiegelman & Flier, 2001).

Consumption of chokeberry extracts (CBE) that contain at least 10% anthocyanins up-regulated *peroxisome-proliferator-activated receptor γ* (*Pparγ*) mRNA level (Qin & Anderson, 2012). Ovariectomized female rats were fed four different high fat diets with 2% dextrin (OVX control), 2% BC (black carrot extracts), 2% BCLP (BC fermented with *Lactobacillus plantarum*) or 2% BCAO (BC fermented with *Aspergillus oryzae*) for 12 weeks, with 10 rats in each group. Another 10 rats were given sham operation and fed a high fat diet with 2% dextrin and served as control. BC, BCLP and BCAO all decreased fat mass and weight gain as well as prevented increase in total serum and LDL cholesterol and triglycerides compared with OVX control, with the effects in ascending orders. BCAO had lower cyanidin 3-rutinoside, malvidin 3, 5-diglycoside and delphinidin 3-glucoside contents as well as much higher cyanidin and malvidin contents compared with BC. The mechanism was suggested to be through phosphorylated AMPK (pAMPK) to phosphorylated Acetyl CoA carboxylase (pACC) (Park et al., 2015). Black soybean seed coat extract (BE) containing 9.2% cyanidin 3-glucoside, 6.2% epicatechin and 39.8% procyanidins were fed to mice for 14 weeks. BE suppressed fat accumulation in the mesenteric adipose tissue by up-regulating uncoupling proteins (UCPs). The gene and protein expression levels of UCP-1 in brown adipose tissue and UCP-2 in white adipose tissue were up-regulated (Kanamoto et al., 2011). Anthocyanins fraction (AF) from purple sweet potato was supplemented at 200 mg/kg per day to mice and reduced weight gain. AF also improved serum lipid parameters and inhibited hepatic triglyceride accumulation. AF increased AMPK phosphorylation and down-regulated the expression level of SREBP-1, thus reducing ACC and FAS expression (Hwang et al., 2011).

### 2.3. Regulate lipid metabolism

Dyslipidemia is a common feature of obesity. Decreasing lipogenesis and increasing lipolysis are two aspects to regulate lipid metabolism. The strategy is stimulating triglyceride hydrolysis to reduce fat storage, which requires oxidation of newly released fatty acids. Regulators of fatty acid acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS) are target in this process (Luo et al., 2005). Sterol regulatory element-binding proteins (SREBPs) family are transcription factors associated with fatty acid synthesis. SREBP-1a, SREBP-1c and SREBP-2 are