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Review

The role of anthocyanin in obesity

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Abstract

Obesity has become a serious global problem that has affected around 13% of the world's population. This disease is closely related to promoting lipogenesis and decreases lipolysis, accumulating adipose tissue, thus interfering with its regulation. Adipose tissue has been considered the main endocrine and secretory organ, which also becomes the energy reservoir in the form of triglyceride and secretes many mediators called adipokines, including hormones and inflammatory mediators that play a role in the pathogenesis of obesity. The adipose tissue accumulation induces hyperleptinemia, which stimulates leptin resistance and mild systemic inflammation, resulting in systemic organ disruptions. At the same time, anthocyanin is a glycoside that has the potential as an antiobesity agent through several pathways, including lipogenesis inhibition, lipolysis promotion, inhibition of lipid absorption, increasing fat oxidation, regulation of obesity-related hormones, and oxidative stress reduction. This compound has the potential to modulate the *de novo lipogenesis* pathway through the inhibition of transcription factors and enzymes involved. Moreover, activating epinephrine receptors on the adipose cell surface promotes the epinephrine-induced lipolysis pathway and enhances lipid oxidation and energy utilization. By regulating metabolism and maintaining the adipose tissue's homeostasis, anthocyanin can potentially ameliorate obesity.

Keywords: anthocyanin, lipid metabolism, lipogenesis, lipolysis, obesity.

Introduction

Excessive fat accumulation on the body as the characteristic of obesity has become an epidemic in the United States and a serious global problem, with the cases rising every year. The prevalence of obesity worldwide has tripled in the period from 1980 to 2018. In 2016, it is estimated that more than 13% of the world's population is obese. WHO also estimates that 39% of the world's population is overweight [1]. Based on data in Indonesia, the prevalence of obesity in adults reaches 23.1%, which is more experienced by women [2]. Obesity is chronic inflammation and becomes a risk factor for several diseases with high mortality and morbidity, including fatty liver disease, NAFLD, cardiovascular disease, and type 2 diabetes mellitus. Obese patients have a higher risk of developing type 2 diabetes mellitus, a 2.85 times higher risk of developing NAFLD [3], and a 3.5 times higher risk of developing hypertension [4].

Excessive high-calorie intake, a sedentary lifestyle with a lack of physical activity, and genetic predisposition are the risk factors for obesity development. Reduced physical activity and high-calorie foods are increasing in the era of globalization, especially for the urban population [5]. The development of the risk factor contributes to the disturbance in the body's balance of fat metabolism in adipose tissue. Increasing calorie intake promotes adipose tissue formation and accumulation through adipogenesis or lipogenesis. Leptin is the hormone for satisfaction and is found resistant in most cases of obesity, which leads to excessive food intake. Leptin receptor (Leprb2) and Jak/STAT signaling pathway have been investigated regarding leptin abnormality response. Meanwhile, inappropriate energy expenditure with a sedentary lifestyle causes the inhibition of adipose tissue catabolism and energy consumption through lipolysis reduction [6]. The reduction of epinephrine-induced lipolysis is also found in obese patients and promotes extensive fat accumulation in the body [7].

Currently, some natural ingredients have been developed as an alternative treatment for obesity. A previous meta-analysis by Maunder *et al.* (2020) showed the effectiveness of some natural sources in ameliorating obesity, including *Sphaeranthus indicus*, *I. gabonensis*, and *C. quadrangularis* [8]. Anthocyanin, a water-soluble flavonoid compound, is extensively investigated. A Meta-Analysis by Park *et al.* (2021) showed a significant reduction in body mass index (BMI) in obese patients who are treated with anthocyanin supplementation (MD=−0.36, 95% CI=−0.58 to −0.13). Anthocyanins can regulate lipolysis through epinephrine-induced lipolysis and can inhibit the process of adipose tissue formation (lipogenesis) through suppression of the transcription factor of lipogenesis, including Sterol Response Element Binding Proteins (SREBPs) [9]. This compound can also ameliorate lipid profile, thus maintaining lipid metabolism. Moreover, the high antioxidant activity of anthocyanin also contributes to reducing systemic chronic inflammation in obese patients, thus reducing the risk for other disease-related obesity, which is less investigated [10]. Therefore, the authors aimed further to compile a review on the antiobesity effects of anthocyanins.

Obesity

Obesity is a group of metabolic diseases characterized by excessive fat accumulation in the body. The major pathology process of obesity is closely related to excessive food intake and appropriate energy expenditure, resulting in fat deposition. Obesity can be diagnosed using the Body Mass Index (BMI) calculation. This system also interprets the risk of comorbidities based on BMI score. A BMI of more than 30 is considered obesity [11].

Adipose tissue regulation

As the largest endocrine component in the human body, on the molecular basis of adipose tissue, excessive cellular reactions and metabolism occur and are involved in various physiological and homeostatic regulations of the body. The function of adipose tissue varies greatly depending on its ability to synthesize and release cytokines, hormones, growth factors, and extracellular matrix proteins. These things are collectively referred to as adipokines and affect various physiological and pathological processes of the body [12]. Uniquely, in the lean population, macrophages found in adipose tissue actively secrete anti-inflammatory cytokines, including interleukin-1 (IL-1), IL-10, IL-3, and Transforming Growth Factor-Beta (TGF- β). Meanwhile, under conditions of excessive adipose tissue accumulation in obese individuals, adipose tissue will produce several pro-inflammatory cytokines, including TNF-α, IL-6, and angiotensin II, as the response to abnormal fat accumulation in the body. The hormones secreted by adipose, such as leptin which inhibits appetite, adiponectin which plays a role in fat and glucose regulation, and resistin which is involved in increasing pro-inflammatory cytokines [13, 14].

Under normal conditions, adipose tissue will undergo metabolism and maintain homeostasis. Food from the diet that enters the body will be used to produce energy and carry out physiological functions, and some will be converted into energy reserves. The largest form of the body's energy reserves is adipose tissue. As stated above, adipose tissue mostly comprises fat cells (adipocytes) with a triglyceride fat component. Triglycerides are a combination of free fatty acid molecules obtained from food absorption through a process called lipogenesis. If the body needs more energy, the body will be given a signal that will break down (hydrolyze) triglycerides into free fatty acids again through a process called lipolysis. These fatty acids will then undergo oxidation to produce energy [15, 16].

Lipogenesis pathway

Lipogenesis is the synthesis of triglycerides/TGs (also called triacylglycerols/TAGs) from dietary sources of fatty acids. This process is tightly regulated in adipose tissue as well as other organs, including the liver, pancreas, and heart, to maintain body homeostasis. The synthesis of TG through fatty acid esterification involves the activation of FFA (free fatty acids into acyl-CoA through the formation of diacylglycerol (DAG) and monoacylglycerol (MAG), which react with glycerol-3-phosphate (G3P). The sources of glycerol-3-phosphate and Acyl-CoA are free fatty acid and plasma glycerol. G3P can be sourced from the glycolysis of glucose, which is influenced by the activity of the glycerol kinase (GK) enzyme, which converts glycerol into G3P. In addition, in the glycolysis pathway, dihydroxyacetone-3P (DHAP) can also be converted to G3P

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by glycerol phosphate dehydrogenase. The formation of G3P can also occur with non-carbohydrate materials through a process called glyceroneogenesis. These materials must be capable of being metabolized into pyruvate, which will then be converted by the enzyme phosphoenolpyruvate carboxylase (PEPCK) (Figure 1) [15, 17].

Moreover, the substrates can also be synthesized through glycogenesis and *de novo*, which play a significant role in synthesizing TG in the liver. *De novo lipogenesis* (DNL) is a fairly complex process that involves converting circulating carbohydrates or proteins into fatty acids, which are then used to synthesize triglycerides. DNL mostly occurs in the liver when some carbohydrates are stored as glycogen in the liver, and the excess will be converted into fatty acids and TG [18]. In this process, ATP-citrate lyase (ACL) will convert citric acid to acetyl-CoA and then to malonyl-CoA by acetyl-CoA carboxylase (ACC). Melony-CoA is then converted to FFA by the multi-enzymatic complex Fatty Acid Synthase or FAS and then converted to FA-CoA by the enzyme acetyl-CoA synthetase (ACSS). FA-CoA and G3P will be converted through the acylation process by glycerol-3-phosphate acyltransferase (GPAT) and acyl-CoA acylglycerol-3-phosphate acyltransferase (AGPAT) into phosphatidic acid (PA). This compound is then dephosphorylated by phosphohydrolase (PAP2) to form diacylglycerol (DAG). DAG will then be converted into TAG with a diacylglycerol acyltransferase (DGAT) catalyst. The increase in DNL was activated by transcription factors of the Sterol Response Element Binding Protein (SREBPs) class that regulates ACC, ACL, ACSS, and FAS. In addition, these enzymes are also regulated by other transcription factors such as Liver X Receptor (LXRα) and ChREBP or Carbohydrate Response Element Binding Protein [17].

Lipolysis pathway

Increased energy requirements cause hydrolysis of adipose tissue to become free fatty acids that can be oxidized to ATP by the body. The process of hydrolysis of TAG into FFA into the circulation is called lipolysis. The first step is hydrolyzing TAG into DAG by adipose triglyceride lipase (ATGL), which can release one fatty acid. Then, DAG is converted to MAG by monoacylglycerol lipase (MGL) and releases one fatty acid. Another possible pathway is the complete hydrolysis of DAG molecules by hormone-sensitive lipase (HSL), which can release two FFA molecules and one glycerol molecule into circulation [17].

Lipid esters, including TG, DAG, MAG, and other water and fat-soluble substrates, can be hydrolyzed by intracellular lipase capable of HSL. However, its main function is to hydrolyze DAG to MAG or hydrolyze DAG

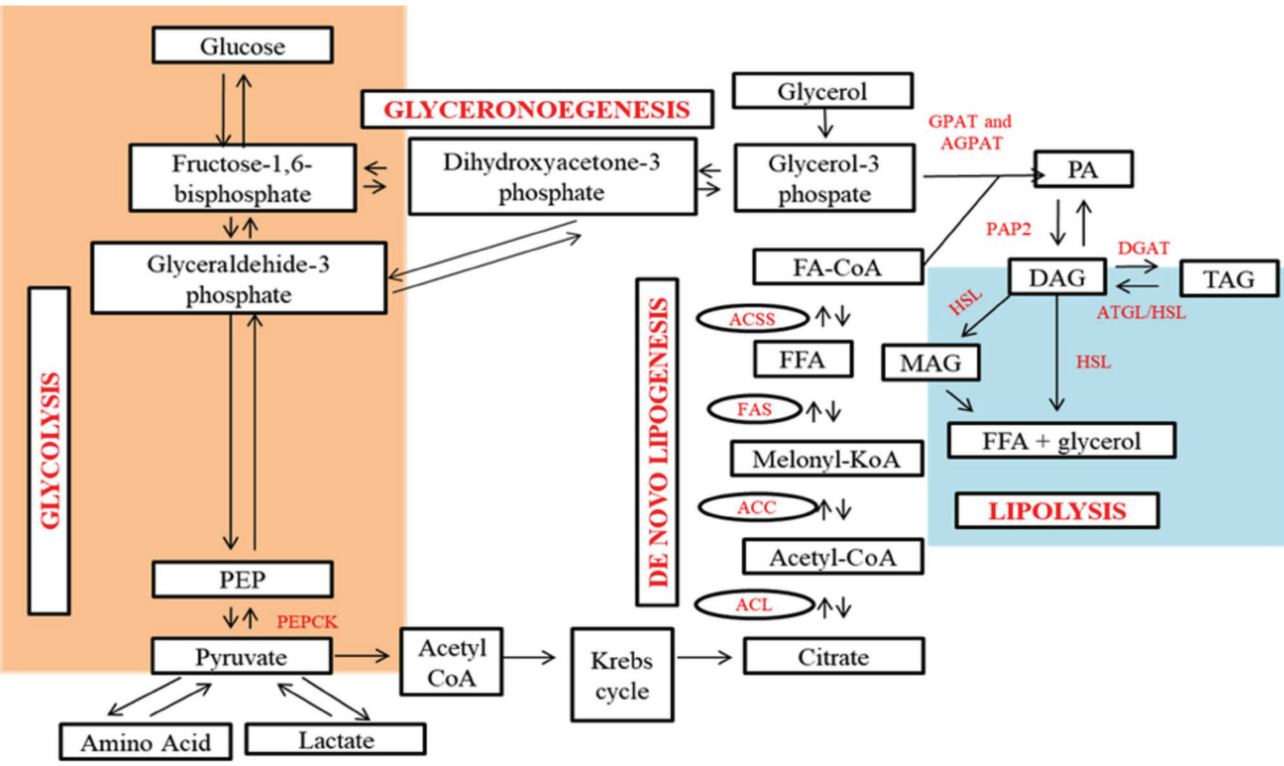

Figure 1: Schematic pathway of lipogenesis and lipolysis. The orange background indicates the glycolysis pathway. The blue background indicates the lipolysis pathway.

directly to release FFA. HSL is activated by several hormonal processes, one of which is through the epinephrine signaling pathway [17]. Adipose tissue has 3 types of epinephrine receptors (adrenergic receptors), namely 1, 2, and 3. A previous study by Lim *et al.* (2019) reported that type 3 epinephrine receptors were found to affect lipolysis [19]. The epinephrine receptor's phosphorylation causes adenylate kinase stimulation, which converts ATP to cAMP and activates cAMP-dependent protein kinase (PKA). PKA will then phosphorylate and activate HSL, which can hydrolyze TAG into DAG, convert DAG into MAG to release 1 FFA molecule, or completely hydrolyze DAG into glycerol and FFA [20].

Anthocyanins-related pathway in obesity

Anthocyanins are water-soluble glycosides. This compound is derived from 2-phenylbenzopyrylium or flavylium salts. Anthocyanins are heterogeneous molecules containing anthocyanidins (aglycones) derived from flavylium (phenyl benzo pyridium). Anthocyanins are considered one of the flavonoids even though they have a positive charge on the C-ring oxygen atom in the basic structure of flavonoids. In nature, most anthocyanins are derived from six glycol molecules: cyanidin, delphinidin, pelargonidin, peonidin, malvidin, and petunidin. Currently, more than 500 anthocyanin derivatives are available in plants; one of the most well-known anthocyanins is cyanidin-3-glucoside [9].

Anthocyanins are blue, red, or purple pigments commonly found in plants, especially in fruits, bulbs, and flowers. Anthocyanin stability depends on pH, light, temperature, and structure. Under acidic conditions, anthocyanins will be expressed as red pigments and blue in alkaline conditions. Anthocyanins can be found in plants such as blueberries (Vaccinium Ashei, Vaccinium corymbosum), cranberry (Vaccinium oxycoccos), mulberry (Morus australis P.), sweet potato sweet purple (Ipomoea batatas), carrot black bean (Daucus carota L.), red radish (Raphanus raphanistrum subsp. Sativus), black soybean (Glycine max), and others. Anthocyanins have been studied and become candidates for the therapy of various diseases. These compounds can act as anti-diabetic, anti-microbial, anti-cancer, antiobesity, and anti-inflammatory, preventing vascular heart disease. In anthocyanins, there are conjugated double bonds between chalcones and quinoidal bases with keto groups, which are efficient antioxidants as free radical scavengers. In addition, the glycosylated B-ring of anthocyanins also contributes to antioxidant activity, and ortho-hydroxylation and methylation can increase antioxidant activity (Table 1) [21–28].

Lipogenesis inhibition

Several compounds are required for adipose tissue synthesis, including glycerol and FFA. The major production of glycerol and FFA is in the liver through *de novo lipogenesis*. Some enzymes, including ACC, ACL, ACSS, and FAS, are required to convert carbohydrate metabolism derivatives into fatty acids. The expression of these enzymes is closely regulated by Sterol Response Element Binding Proteins (SREBPs).[17] Several anthocyanin compounds have been investigated to affect this pathway. A previous study by Park (2015) showed the potency of anthocyanin-rich black carrots fermented extract with Aspergillus oryzae (Black Carrot extracts fermented with Aspergillus oryzae/BCAO) were able to significantly reduce hepatic triglycerides by decreasing the expression of the SREBP-1 and FAS genes [29]. The cyaniding 3-glucoside compound in purple corn (purple corn color/PCC) can also suppress triacylglycerol synthesis by reducing SREBP-1. Blueberries also

Table 1: The study's characterization investigated the molecular effect of anthocyanin from several sources in ameliorating obesity and obesity-related conditions.

Source	Composition	Subject	Molecular Mechanism of Action	Ref.
Purple corn color/PCC (*Zea mays* L.)	Cyaniding 3-glucoside	Isolated rat adipocytes	Downregulation of SREBP-1	[22]
Black Soybean (*Glycine max*)	Cyanidin-3-O-glucoside, delfinidin-3-O -glucoside, and petunidin-3-O-glucoside	3T3-L1 cells	Epinephrine receptor phosphorylation and HSL activation	[23]

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Table 1: Continued.

Source	Composition	Subject	Molecular Mechanism of Action	Ref.
Blueberry anthocyanin/BA (*Vaccinium corymbosum*)	Pentuidine 3-arabinoside, delfinidine 3-glucoside and cyaniding 3-galactoside	Male C57BL/6 mice	Downregulation of FAS, PPAR-γ, TNF-α, and IL-6	[24]
Purified blueberry anthocyanins (*Vaccinium corymbosum*)	3-O-β-glucosides of pelargonidin, cyanidin, peonidin, delphinidin, petunidin, and malvidin	C57BL/6J mice	Reduce PPAR-γ and FAS gene, Reduce TNF-α and IL-6, reduction of serum leptin	[25]
Litchi flower–water extract (LFWE) (*Litchi chinensis Sonn.*)	Phenolic acids, flavonoids, condensed tannins, anthocyanins	Male Wistar rats and *in vitro* lipase activity assay	Reduce *in vitro* lipase activity	[26]
Bilberries (*Vaccinium myrtillus*) and Blackcurrant (*Ribes nigrum*)	3-O-β-glucosides of cyanidin and delphinidin constituted	Clinical trials ACTRN: 12615000293561	Reduce pro-inflammatory cytokines secretions (TNF-α, IL-6, and CCL2) and reduce BMI	[27]
Anthocyanin (Metox) capsule	Unspecified	Randomized, placebo-controlled trial	Reduce pro-inflammatory cytokines (TNF-α and IL-6)	[28]

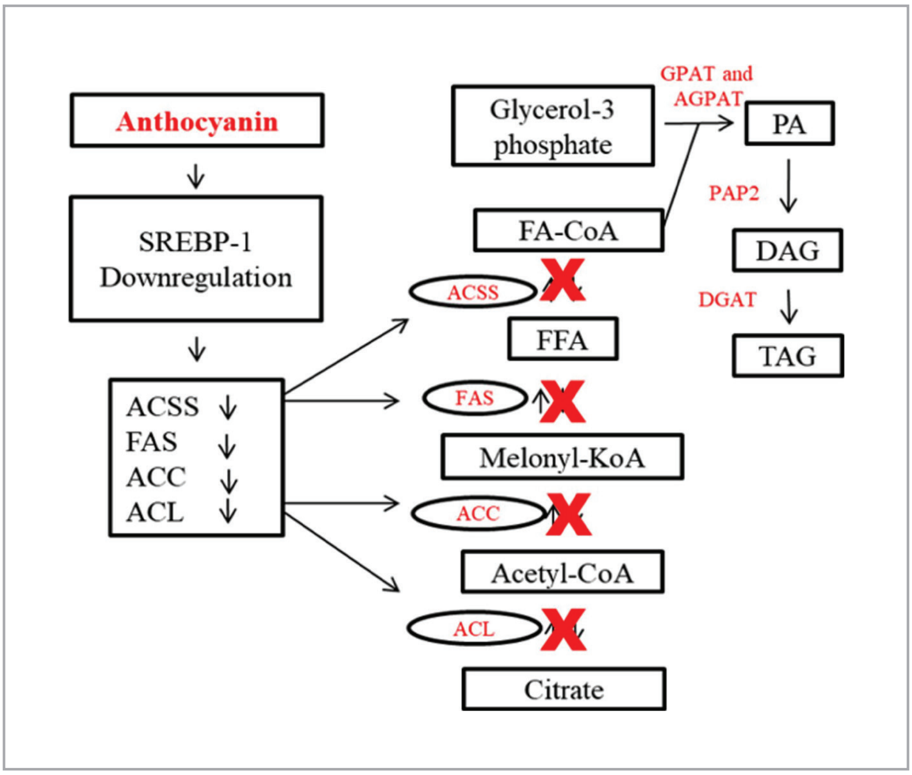

Figure 2: Mechanism of action of anthocyanin in inhibiting lipogenesis by downregulated gene-encoded enzyme-related lipogenesis.

contain anthocyanin compounds (Blueberry anthocyanins/BA) which consist of several different structures, namely pentuidine 3-arabinoside, cyanidin 3-galactoside, and delphinidin 3-glucoside which can downregulate the gene encoding FAS (Figure 2) [24].

Lipolysis promotion

An increase in energy requirement will induce energy reserves hydrolyzation in TG into free fatty acids through lipolysis, which will then be oxidized to become ATP. Under physiological conditions (such as the response to fight or flight), the body will secrete the hormone adrenaline or epinephrine. This hormone will increase the body's metabolism, thus stimulating the hydrolysis of TG into free fatty acids through the process called the epinephrine-induced lipolysis mechanism [17,30]. Anthocyanins are compounds that can affect this pathway. In previous studies by Kim *et al.* (2012), it has been found that anthocyanins in black soybeans (which mostly contain anthocyanin compounds, such as delphinidin-3-O-glucoside, petunidin-3-O-glucoside/P3OG, and cyanidin-3-O-glucoside) can phosphorylate receptors epinephrine in adipose tissue. This pathway then activates HSL, which converts TAG into free fatty acids that can be oxidized in the liver or muscle. This process can significantly reduce body weight in obese patients (Figure 3) [20, 23].

Lipid absorption inhibition

This mechanism focuses on the activity of the gastrointestinal system in reducing energy absorption. Lipid molecules derived from food can be absorbed or can cross the epithelium in the intestinal villi after being converted by lipase into FFA. Therefore, a mechanism that can inhibit the pancreatic lipase enzyme is needed to reduce the absorption of lipids into the human circulatory system. Several studies found that the anthocyanin compound cyanidin 3-glucoside had a significant ability to suppress pancreatic lipase enzymes and reduce the absorption of up to 58% of cholesterol [26].

Increase fat oxidation

The increase in energy use referred to in this mechanism is the role of anthocyanins in stimulating fatty acid oxidation in mitochondria. The enzyme that is activated is the activated protein kinase enzyme (AMPK), an enzyme that is responsible for regulating energy production signals. AMPK causes increased expression of the gene PPARgcla, which encodes a regulator of lipid

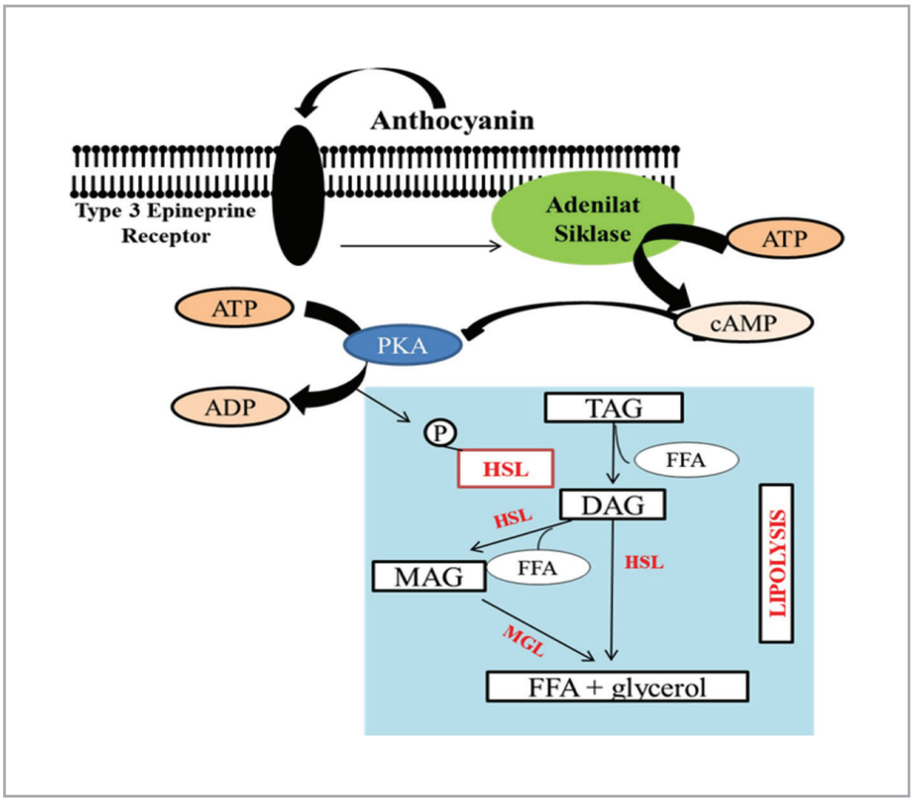

Figure 3: Mechanism of action of anthocyanin in inducing lipolysis through activation of epinephrine receptor and promoting of epinephrine-induce lipolysis pathway.

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oxidation in mitochondria. Therefore, when this enzyme is activated, it causes a decrease in circulating triglycerides. In this mechanism, the anthocyanin fraction can cause an increase in AMPK phosphorylation, thereby increasing fatty acid oxidation [26].

Regulate obesity-related hormones

The decrease in adipose tissue caused by anthocyanins results in a decrease in the amount of leptin and systemic circulating inflammatory mediators. One of the signals related to obesity is leptin resistance caused by negative feedback from hyperleptinemia. The decrease in serum leptin to close to physiological conditions in the administration of anthocyanins causes negative feedback as compensation for hyperleptinemia can be reduced and increases leptin sensitivity. Reduced inflammatory mediators such as IL-6 and TNF-α will reduce inflammation that can damage insulin receptors. This will also prevent and reduce insulin resistance. In addition, it was also found that anthocyanins can reduce the expression of SOCS3, a protein that is involved in negative feedback on leptin signaling and is involved in the mechanism of insulin receptor damage. The reduced expression of this protein also indicates an increase in insulin sensitivity in the body, while its central effect on leptin signaling is not widely known [31].

Reduce oxidative stress

Obesity is also characterized by chronic inflammation and oxidative stress in the body. This is the result of overactivity of adipose tissue that actively secretes inflammatory mediators, including TNF-α and IL-6, and also induces reactive oxygen production, thus increasing oxidative stress. The oxidative stress of obesity is related to many complications of the disease, including insulin resistance and diabetes mellitus, leptin receptor disruption and leptin resistance, cardiovascular disease, and cancer. Anthocyanin has antioxidant activity that can be the potential pathway in reducing chronic oxidative stress on obesity, thus preventing systemic organ disruption. A previous study by Bae *et al.* (2015) reported the antioxidant activity based on the DPPH assay of crowberry (200 ug/mL) that inhibits 65% of radical scavenging.[32] This study was also strengthened by a clinical trial by Vugic *et al.* (2020), which showed the potency of anthocyanin in reducing cytokines that cause inflammation, including IL-6 and CCL2, and TNF-α in obese patients significantly [27].

Conclusion

Increased food intake and lack of energy consumption exacerbated by leptin resistance are the major mechanisms leading to excessive fat accumulation and obesity—disturbance of lipid homeostasis and metabolism in obesity results in the promotion of lipogenesis and lipolysis reduction. Anthocyanin, a water-soluble glycoside with high metabolites and antioxidant activity, has the potential to regulate and maintain homeostasis of adipose tissue, thus ameliorating obesity through several pathways, including lipogenesis inhibition, lipolysis promotion, inhibition of lipid absorption, increasing fat oxidation, obesity-related hormone regulation, and oxidative stress reduction. Lipogenesis is inhibited by downregulating enzyme-related lipogenesis, including SREBP-1 and FAS while promoting lipolysis through epinephrine receptor phosphorylation and HSL activation.

Conflict of interest

The authors declare no conflict of interest.

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