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Molecular Mechanisms of Anthocyanins as A Potential Nutraceutical for Muscle Regeneration

Astrid Feinisa Khairani[1,3*], Christopher James Setiawan[2], Novi Shanty[1], Ronny Lesmana[1,4], Achadiyani Achadiyani[3], Nur Atik[1,3], Eko Fuji Ariyanto[5], Sunarjati Sudigdoadi[1,6]

[1]Graduate School of Master Program in Anti-Aging and Aesthetic Medicine, Faculty of Medicine, Universitas Padjadjaran, West Java, Indonesia.
[2]Undergraduate Program, Faculty of Medicine, Universitas Padjadjaran, West Java, Indonesia.
[3]Division of Cell Biology, Department of Biomedical Sciences, Faculty of Medicine, Universitas Padjadjaran, West Java, Indonesia.
[4]Division of Physiology, Department of Biomedical Sciences, Faculty of Medicine, Universitas Padjadjaran, West Java, Indonesia.
[5]Division of Biochemistry and Molecular Biology, Department of Biomedical Sciences, Faculty of Medicine, Universitas Padjadjaran, West Java, Indonesia.
[6]Division of Microbiology, Department of Biomedical Sciences, Faculty of Medicine, Universitas Padjadjaran, West Java, Indonesia.
*Corresponding Author:
Astrid Feinisa Khairani
Division of Cell Biology, Department of Biomedical Sciences, Faculty of Medicine, Universitas Padjadjaran
Address: Jalan Raya Bandung - Sumedang Km 21.6, Jatinangor, Sumedang, West Java, Indonesia, 45363
Email address: astrid.khairani@unpad.ac.id
Tel: +62-22-7795594

ABSTRACT

Anthocyanins, natural pigments belonging in the flavonoid group that can be found in different types of plants, are popular bioactive compounds with various beneficial properties. In the topic of skeletal muscle, overtraining, or pathological conditions can cause excessive ROS production and chronic inflammation, leading to degradation in function, mass, and regenerative capacity. There are two sides of ROS induced inflammation. Although inflammation is needed during skeletal muscle regeneration, chronic inflammation leads to detrimental effects. Thus, in the case of imbalance of ROS in chronic inflammation, further antioxidant supplementation might be required to counter the excessive ROS. Anthocyanins, as a nutraceutical, have the potential to improve muscle function and its regenerative capacity through its redox control, increasing protein synthesis, decreasing the breakdown of muscle protein, regulating mitochondria function, regulating autophagy, preventing apoptosis, improving gut dysbiosis, and inducing myogenesis. Here, we discussed and summarized the potential molecular mechanisms of anthocyanins as a nutraceutical to promote skeletal muscle regeneration and prevent muscle wasting.

Keywords: anthocyanins, muscle regeneration, nutraceutical, skeletal muscle

Corresponding Author: Astrid Feinisa Khairani
Division of Cell Biology, Department of Biomedical Sciences, Faculty of Medicine, Universitas Padjadjaran
Address: Jalan Raya Bandung - Sumedang Km 21.6, Jatinangor, Sumedang, West Java, Indonesia, 45363
Email address: astrid.khairani@unpad.ac.id
Tel: +62-22-7795594

INTRODUCTION

Skeletal muscle has significant contribution to health. Besides its basic functions in maintaining posture, breathing, and locomotion, skeletal muscle also plays important roles in nutrient store and metabolic regulator. Exercise is known to be an important factor that helps to maintain healthy skeletal muscle. Another important factor is food consumption. By having good exercise and healthy food consumption, muscle health will be maintained, thereby increasing life expectancy.[1,2] Even though exercise has the potential to improve health for the entire population, also note that exercise should be done within the adequate amount. Because condition related in exercise such as overtraining syndrome (OTS), which caused by imbalance exercise-induced fatigue and post-training rest may result in unfavorable effects including injury, burnout, and declined in physical performance.[3,4] Reactive oxygen species (ROS) formed by exercise can bring positive or negative impacts on health, depending on ROS concentration, duration of ROS exposure, and individual training status. Thus, excessive ROS, which is the result of excessive exercise, and individuals who do not understand the proper way of exercise can cause extreme oxidative damage, such as muscle weakness and fatigue, DNA mutations, lipid peroxidation, mitochondrial dysfunction, and apoptosis/necrosis that even cannot be compensated by the body's endogenous antioxidants. Therefore, antioxidant supplementation is required.[5] Skeletal muscle stress kinases and insulin protein signaling can be disrupted in the event of oxidative stress because of excessive exercise intensity.[6,7] Contrarily, physical inactivity or sedentary lifestyle can cause hyperinflammatory. This condition induces oxidative damage that harmful to health and increase the risk of chronic diseases.[8,9]

Beside exercise, it is important to take notice of daily food consumption to have healthy skeletal muscle. Consuming high-fat diets can lead to metabolic syndrome.[10] Obesity and metabolic disturbances are proven to be the cause of skeletal muscle mass impairment, such as changes in

fibers and satellite cells. Those changes can directly harm the regenerative potential mediated by satellite cells.[11,12] Another point of view of the food consumption importance is nutritional interventions can reduce and prevent the signs and symptoms of exercise-induced muscle damage (EIMD). EIMD is usually caused by doing intense and unaccustomed exercise, causing impairment to the muscle.[13,14] One of the nutritional interventions is by using bioactive compounds generated by plants. Bioactive compounds derived from plants can reduce inflammation by blocking oxidative damage and impacting the immune system. Polyphenols and phytochemicals present in the plant kingdom were recently suggested to provide regeneration and protection to muscle damage because of exercise and oxidative stress.[15]

Anthocyanin is arguably among the most popular bioactive compounds from plants that are presently being investigated. Aside from having the main function as an antioxidant and anti-inflammation, anthocyanin also acts as a cardioprotective, antidiabetic, cytoprotective, antimicrobial, antitumor, neuroprotective, and anti-obesity agent and even reduces mortality risk.[16,17] The provision of anti-inflammatory substance is known to increase the activation of satellite cells through Notch signaling in the initial phase of skeletal muscle regeneration. It then accelerates the repair of myofibers at a later stage of regeneration and mediates to a faster repair[18]. The provision of antioxidants also known to has beneficial effect in skeletal muscle by inhibiting the secondary inflammatory response, which then protects skeletal muscle against the impact of induced muscle damage.[19]

As one of the main beneficial effects of anthocyanin is its antioxidant activity, it can reduce the effects of ROS and inhibit leukocyte apoptosis. It is shown in the study involving mice and ethanol extract of purple sweet potato, which contains anthocyanin as its antioxidant components, the number of leukocyte count of treated groups were higher than the negative control group. With those results, this study can be used to support further the relation of increased leukocyte count and cytokine synthesis in skeletal muscle in the form of myokine, which substantially contributes to hypertrophy response.[20] One of the myokines that has a role in increasing muscle hypertrophy is Irisin. Irisin can activate muscle satellite cells and increase protein synthesis.[21] Irisin pathway in skeletal muscles can be activated by the administration of grape pomace extract (GPE), which contains anthocyanins as one of its abundant polyphenols compounds.[22] In addition, anthocyanin also has the ability to regulate proteasome activity.[23]

With the glimpse of anthocyanin functions mention before, it can be suggested that anthocyanin can improve regenerative capacity of skeletal muscle. Proper skeletal muscle regeneration process occurs through stimulation related to the process of protein synthesis, autophagy, satellite cells response capability that depends on mitochondria activity, apoptosis inhibition, and excellent redox control of ROS.[24,25]. Excessive chronic high inflammatory cytokines on intramuscular can disrupt regenerative capacity. They may interfere with the recovery by limiting the regeneration of damaged tissue.[26] Impaired mitochondrial function and or defective antioxidant defense accumulation of ROS can cause decreased proliferation and differentiation of muscle cells as a result of disruption in JAK-STAT signaling and autophagy that could inhibit myogenic differentiation.[27] The improvement of autophagy plays an important role in enhancing regenerative muscle function.[28] Therefore, when autophagy is attenuated, it could disrupt muscle regeneration by decreasing satellite cell differentiation.[29] This article aims to review anthocyanin effects and its molecular mechanisms involve in the particular pathway of skeletal muscle regeneration.

ANTHOCYANIN

Anthocyanin is a family of natural pigments common in the plant kingdom and is a group of flavonoids, a part of a larger group of compounds, namely, polyphenols. It is the pigment that responsible for colors, such as blue, purple, red, and orange in various plants and fruits. Although anthocyanin is a flavonoid, it has a positive charge on the oxygen atom in the C-ring of basic flavonoid structure. The aglycone form of anthocyanin, called anthocyanidin, is structurally based on flavylium or 2-phenylbenzopyrilium ions and hydroxyl and methoxy groups in various positions.[30,31] Anthocyanin can be found in some plants such as berries (bilberry, blueberry, blackberry, blackcurrant, chokeberry, strawberry, and elderberry). It also can be found in grapes, red/purple vegetables (such as purple sweet potato), 100% noncitric juice, and yogurt with a variable amount (as shown in Table 1). As a polyphenol compound, anthocyanin serves as a health supplementation and can be utilized for the prevention of chronic diseases.[32,33] The number and position of hydroxyl and methoxy groups, greater than 635 anthocyanins have been identified. Of these, 17 types of anthocyanidins are found in nature, with the six most frequently distributed being pelargonidin, cyanidin, peonidin, delphinidin, petunidin, and malvidin.[30,32,34] List of studies showing the advantages of anthocyanin in the musculoskeletal system can be seen in Table 2.

ANTHOCYANIN EFFECTS ON SKELETAL MUSCLE MASS REGULATION AND REGENERATION

The Effects Of Anthocyanin In Increasing Muscle Protein Synthesis

Protein synthesis and muscle cell regeneration can occur through the molecular mechanism involving the IGF1-PI3K-Akt/PKB-mTOR pathway. Mammalian target of rapamycin (mTOR) regulates protein synthesis in the skeletal muscle. It can be stimulated by the activation of PI3K/Akt. [35–37] Akt can synthesize muscle protein by activating mTOR, which leads to its interaction with various proteins to form complexes, one of them being mTORC1, which leads to Muscle protein synthesis (MPS) by phosphorylation of downstream proteins.[38,39] Insulin and IGF-1 serve as essential activators of mTOR.[40] IGF-1 induces muscle hypertrophy by activating the proliferation of satellite cells through the activation of Akt-mTOR as an initial response, which is important for muscle regeneration.[41,42]

There are several mechanisms showing the involvement of anthocyanin in protein synthesis. Firstly, anthocyanin directly involves the PI3K/Akt signaling pathway. It is supported by a study involving L6 myotube cells. It demonstrates that black soybean seed coat anthocyanin extract (BSSE) and cyanidin-3-O-glucoside substantially increased the protein levels of p-Akt/Akt and stimulated the phosphorylation of Akt.[43] Another study involving cardiac fibroblasts culture shows that anthocyanin can substantially increase the level of phosphorylation of Akt and or P-38.[44] Secondly, anthocyanin can directly increase the expression of IGF-1. It is shown in study

involving Prune extract-60% enriched polyphenol extract (PE60) Plum extract which contains anthocyanin and C2C12 cell line. The study shows that PE60 Plum extract cause a significant increase in protein synthesis.[45] Furthermore, several studies reported that anthocyanin also directly reduce the C-reactive protein (CRP) level.[46,47] It is also known that IGF-1 prevents an increase in CRP, which inhibit protein synthesis through mTOR inhibition.[39] Therefore, with the ability of anthocyanin to increase IGF-1 expression and reduce CRP level, it once again shows the role of anthocyanin in protein synthesis.

Another mechanism regarding the implication of anthocyanin in increasing protein synthesis is its role as a natural ACE inhibitor.[48] ACE inhibitor improves endothelial function and angiogenesis, reduces inflammation, improves mitochondrial function, enhances IGF-1 levels, promotes skeletal muscle glucose uptake, and suppresses proinflammatory cytokine levels including IL-6, which has important effects on the skeletal muscle.[49] Satellite cell (SC) proliferation, as well as skeletal muscle regeneration and expression of proliferation/differentiation markers of SC (MyoD, myogenin, and active-Notch), can be increased via inhibition of angiotensin II.[50]. In addition, anthocyanins also affect peripheral blood flow that improve muscle protein metabolism for increase to a maximum muscle protein synthesis[51,52]

Other mechanism related to protein synthesis is the involvement of insulin sensitivity or resistance. Amelioration of insulin resistance is known to prevent muscle wasting through the PI3K/Akt pathway.[53] Under good insulin sensitivity, insulin binding with its receptor causes the increase of PI3K activity, which then phosphorylates Akt. Akt then inhibits Forkhead box O (FoxO), resulting in a decrease of Atrogin-1, MuRF-1, and Muscle atrophy F-box (MAFbx) transcription and caspase-3. As a result, proteolytic activity is reduced. On the contrary, in the insulin resistance condition, the activity of P13K decreases, which causes the phosphorylation of Akt. Lower Akt level releases FoxO and caspase-3 inhibition, which ultimately increases proteolytic activity. Insulin resistance can be improved by anthocyanin through activating insulin signaling and increasing GLUT4 translocation.[54]

It is also worth mentioning that anthocyanin has an indirect involvement in muscle protein synthesis through improving gut microbiota diversity. High intakes of foods which have high anthocyanins component were proven to increase gut microbiota diversity, as shown in a community-based cohort study.[55] The numbers of probiotics especially increase following anthocyanin supplementation. Anthocyanin such as that in black rice components has shown a remarkable prebiotic potential. Consumption of anthocyanin by probiotics bacteria, including Bifidobacterium and Lactobacillus, has been reported to produce organic acids containing phenolic acids and short-chain fatty acids (SCFA). Specifically, anthocyanin in purple sweet potato can be utilized by the human intestinal microbiota to produce a substantial amount of SCFA, including formic acid, acetic acid, propionic acid, butyric acid, and lactic acid.[56,57] Gut microbiota can regulate circulating IGF-1. Most data available proposes that gut microbiota trigger host IGF-1 synthesis to influence growth. As one of the microbiota metabolites, SCFA are adequate to induce IGF-1 production. IGF family members are capable and function as an essential factor in regulating growth. Data from mice studies indicate that circulating IGF-1 levels are notably higher in mice with intact gut microbiota (conventional mice) instead of germ-free (GF) mice. This data suggests that manipulating gut microbiota composition, by anthocyanin supplementation, could be utilized to increase IGF-1 production and growth as a probability.[56–58] The imbalance of gut microbiota and the role of anthocyanins to restore it will be discussed later.

The Effects Of Anthocyanin In Preventing Muscle Protein Breakdown With Its Anti-Inflammatory And Antioxidant Properties

Anthocyanin has antioxidant effects and can reduce inflammation, which ultimately reduces oxidative stress (as seen in Figure 1).[59–61] Improvement of oxidative stress is known to reduce muscle protein breakdown.[62] Anthocyanin can inhibit LOX, COX-2, and arachidonic activity, thus showing an anti-inflammatory effect. Anthocyanin, from saskatoon, cherry, blueberry, cranberry, elderberry, and raspberry, is an effective COX-2 inhibitor. It is also known that anthocyanin from blueberry, cranberry juice, chokeberry concentrate, and pomegranate can inhibit LOX activity, effectively preventing leukotriene formation. Delphinidin, cyanidin, peonidin, and malvidin glycoside also serve as a competitive inhibitor of lipoxygenase.[63] The suppression of COX2 might decrease inflammation and muscle wasting, owing to PGE2 production inhibition.[64] PGE2 via the induction of intramuscular IL-6 and the proteolytic muscle ubiquitin ligase RING finger protein-1 (MuRF-1) led to increased protein degradation.[65] A study involving C2C12 myoblasts shows that delphinidin 27 intake may prevent disuse muscle atrophy by inducing the miR-23a expression and suppressing MuRF-1 expression.[66] Anthocyanin also has the ability to inhibit ROS generation and subsequent MAPK signaling, thus, once again, inhibiting inflammatory responses.[67] Reports regarding anthocyanin's effect as COX-2 inhibitor might contribute in preventing muscle protein breakdown is also supported by other research stated the consumption of COX inhibitors are reported to stimulate muscle cell growth.[68]

The antioxidant activity of anthocyanin is also shown by its ability to increase the total antioxidant capacity, total superoxide dismutase activity, and catalase activities and decrease malondialdehyde, lipid peroxidation marker.[69,70] Lipid peroxidation can prevent the disruption of the proliferation and differentiation of skeletal muscle myoblasts.[71] Anthocyanin also shows its antioxidant activity by its ability in capturing free radicals and or anions and inhibiting xanthine oxidase (XO). It also shows the suppression of the NO production and induction of Nrf2 transcription, triggering heme oxygenase-1 (HO-1) expression.[72] Increased ROS-induced cytokine signaling, proteolytic activity, and tissue degradation were all diminished by XO inhibition.[73] Anthocyanin is a potent α-glucosidase inhibitor with high radical scavenging properties, intense inhibitory activity toward 15-LO, and moderate inhibitory activity toward XO.[74] Another major antioxidant activity of anthocyanin is shown by its capability of regulating the Nrf2 pathway. Nuclear erythroid 2-related factor 2 (Nrf2) mediates the induction of antioxidant proteins. Nrf2 undergoes translocation from the cytosol to the nucleus, in which it binds to the antioxidant response element (ARE), leading to a cytoprotective response by upregulating antioxidant enzymes. Nrf2 safeguards the skeletal muscle via

antioxidant enzymes and tissue specificity mechanism.[75] A study of dimethylnitrosamine (DMN)-induced liver injury rats shows anthocyanin fraction (AF) from purple sweet potato effects on reducing this injury. AF increases transcription of antioxidant genes by triggering the Nrf2 translocation, thus inducing Nrf2-mediated antioxidant enzymes and reducing inflammatory mediators via NF-kB inhibition. As significant transcription factors, NF-kB and Nrf2 are involved in the regulation of proinflammatory and antioxidant genes, respectively.[76] Nrf2 functions as a redox-sensitive transcription factor, regulating the transcription of antioxidant enzymes, including HO-1, under the oxidative stress condition. Nrf2 mediates HO-1 to decrease ROS generation, resulting in oxidative stress-mediated apoptosis reduction. A study for anthocyanins from Hibiscus syriacus L. petals demonstrates its enhancing activity for Nrf2 expression translocation and expression of HO-1, leading to H2O2-induced apoptosis protection. Anthocyanin helps maintain a normal level of mitochondrial membrane potential and ROS generation in HaCaT keratinocytes by activating the Nrf2/HO-1 axis, exerting its cytoprotective effects against oxidative stress.[77]

Other molecular mechanism in preventing protein breakdown by anthocyanin supplementation is through secretory inhibition of proinflammatory cytokines and NF-κB activation.[78,79] Muscle protein degradation is regulated by a complex signaling pathway, which can be activated or suppressed by hormones and cytokines. Proinflammatory cytokines create an intricate network with modified hormone homeostasis, resulting in the inhibition of anabolic signals. In other words, proinflammatory cytokines harm muscle protein metabolism. The increased level of proinflammatory cytokines, including TNF-α, IL-1, IL-6, and IFN-γ is correlated with muscle mass loss and muscle wasting.[80] Those proinflammatory cytokines increase both ubiquitin expression and proteasome enzymatic activity. The effects of proinflammatory cytokines on muscle mass are mediated, at least partially, by NF-kB transcription factor activation.[81] The mechanism of anthocyanin in regulating NF-κB, TNF-α, and IL-6, will be further discussed next.

NF-κB is considered a central mediator of proinflammatory gene induction that plays a role in regulating and developing inflammation. NF-κB activation can activate the transcription of different genes and increase the production of inflammatory cytokines, chemokines, and adhesion molecules, regulating cell proliferation, apoptosis, morphogenesis, and differentiation.[82] Anthocyanin substantially inhibits LPS that induced several proinflammatory mediators by inhibiting the mitogen-activated protein kinase signaling pathway (MAPK pathway), leading to a decreased nuclear translocation of NF-κB and AP-1, two major transcription factors involved in the inflammation process. Anthocyanin also demonstrates potent anti-inflammatory activities by inhibiting TNF-α, IL-6, and NO in LPS-activated macrophage.[83]

TNF-α is produced by a variety of cells, such as macrophages, lymphocytes, and skeletal muscle cells. It is involved in both local and systemic inflammation by binding to its receptors, Tumor necrosis factor receptor (TNFR), TNFR1 and TNFR2. Among those two receptors, TNFR1 is believed to mediate muscle wasting. As a member of the TNF-α superfamily, Tumor necrosis factor alpha (TWEAK) has multiple biological functions, including apoptosis stimulation and inflammatory cytokine induction. TWEAK is believed to have adverse effects on muscle regeneration and induce muscle wasting by inhibiting myogenic differentiation through the activation of NF-κB and stimulating proteasome-dependent proteolysis.[81,84] TNF-α induces protein skeletal muscle degradation causing a substantial loss of muscle mass, which occurred via the decreasing rate of basal MPS, activating ubiquitin-proteasome pathway, and apoptosis of myonuclear of myotubes. TNF-α adversely affects regenerative muscle capacity by MyoD and MyoG destabilization. These specific muscle transcription factors are involved in the transition of satellite cells as well as their proliferation and differentiation.[85] Another study involving myotube cell cultures indicates that another effect of TNF-α on the skeletal muscle, specifically muscle atrophy, is its ability to trigger multiple cell responses, such as ceramide formation. Ceramide has been known to inhibit myogenic differentiation and protein synthesis in myotubes. It also enhances the NF-κB pathway and autophagy, resulting in enhancing proteolysis in myotubes. The accumulation of ceramide induced by TNF-α causing atrogin-1 upregulation harms protein synthesis and myotube size via eIF3f degradation.[86] Berry anthocyanins shows an effect on TNF-α. The study involving murine macrophage shows that berry anthocyanins substantially decrease TNF-α secretion. Result from this study showed possibility from anthocyanin as TNF-α inhibitor to counteract muscle regeneration that inhibit by ceramide.[87] Other studies involving high-fat diet (HFD) mice reported that purple sweet potato, which contains anthocyanin, decreased the expression of TNF-α. Those studies show purple sweet potato can effectively decreased the mRNA levels of TNF-α and the expression of TNF-α in the hippocampus of HFD mice.[88,89]

IL-6 might also have a role in skeletal muscle degradation but only in certain conditions, in which other circulating cytokines were present. A study involving rat muscles indicates that IL-6 alone does not have a substantial effect on protein breakdown.[90] The study shows the involvement of IL-6 in the stimulation of protein ubiquitination. IL-6 increases the ubiquitin ligase E3 α-II and thus is involved in cachexia development. Another study demonstrates IL-6 activation of the JAK/STAT signaling pathway, which results in inducing protein loss.[91] Chronically elevated circulating IL-6 levels were correlated with an impaired satellite cell response.[92] A clinical trial study shows the effect of anthocyanin supplementation on circulating IL-6. Anthocyanin supplementation indicates a substantial reduction of circulating IL-6 post-supplementation.[78] Antioxidant supplementation also shows a promising result as it decreases the immune cell-derived IL-6 response.[93] A trial done by involving trained cyclists and Montmorency cherry that has anthocyanin contents demonstrates a consequence of IL-6 reduction, proposing a dampening effect of an acute inflammatory stress response.[94] Another in vitro study shows that anthocyanin metabolites reduce VCAM-1 and IL-6 mRNAs. These findings further support the relation between anthocyanin and proinflammatory cytokine reduction, in this case, IL-6.[95]

The Effects Of Anthocyanin On Regulating JAK-STAT Signaling Pathway

Signal transducer and activator of transcription 3 (STAT3) signaling is known to play a role in muscle wastin

induced by the IL6/JAK/STAT3 signaling pathway. STAT3 damages skeletal muscle function and causes muscle disorders. A predominant STAT3 transcriptional signature tends to be responsible for skeletal muscle atrophy due to its correlation with the increased expression of skeletal muscle ubiquitin E3 ligases, Murf-1, and Atrogin-1. STAT 3 is also known to downregulate mTOR and p70S6K activity, which are the downstream effectors of the Akt signaling pathway involved in muscle differentiation but stay independent from Akt activation.[96] The inhibition of STAT3 using different STAT3 inhibitors shows a potential benefit to treating muscle disease. A study involving anthocyanin-containing bilberry extract (BE) indicates its ability to reduce IFN-γ-induced STAT1 and shows a substantial inhibitory activity of STAT3 and NF-kB activation.[97] Other studies involving yet another bilberry extract demonstrates suppression of STAT3 activation through suppression of proinflammatory cytokines, specifically IL6, and suppression of NF-kB through the NfkB-IL6 axis induced by ROS.[98] Involvement of anthocyanin in regulating STAT3 is further supported by a study involving Human umbilical vein endothelial cells (HUVECs) and aronia berry extract. Anthocyanin in aronia berry extract decreased STAT3 phosphorylation and the nuclear level of STAT3.[99]

The Effect Of Anthocyanin In Preventing Gut Microbiota Dysbiosis

Gut microbiota has an essential role in regulating muscle mass and function. As already reviewed above, anthocyanin has an indirect involvement in muscle protein synthesis through improving gut microbiota diversity. Therefore, imbalance gut microbial, known as gut microbiota dysbiosis, can cause muscle atrophy. Several mechanisms underlying muscle atrophy induced by dysbiosis were reported as follow: decreasing insulin sensitivity; decreasing gene transcription related to skeletal muscle growth and mitochondria function; decreasing amino acid, including glycine and alanine; decreasing colin serum, acetylcholine precursor, which acts as a key neurotransmitter in muscle and nerve signaling on neuromuscular junction; and decreasing gene expression which codes Rapsyn and Lrp4, two important proteins for neuromuscular junction function and assembly for skeletal muscle mass increase. On the contrary, improvement of gut microbiota diversity leads to decreased muscle atrophy markers, an increase of muscle oxidative metabolism capacity, and an increase of Rapsyn and Lrp4 expression.[100] Gut microbiota dysbiosis can activate NF- κB transcription factor, causing muscle atrophy and inflammation.[101]

Anthocyanin supplementation, as stated above, leading to a decreased nuclear translocation of NF-κB and AP-1, two major transcription factors involved in the inflammation process.[84] This information can be correlated with other reports that showing anthocyanin improve dysbiosis condition. Anthocyanin is proven to safeguard the gastrointestinal tract from high-fat diet-induced alterations in redox signaling, barrier integrity, and dysbiosis. Anthocyanin supplementation also showed to increase gut microbiota diversity through its body fat lowering effect.[55,102] Dietary supplementation of black rice anthocyanin extract (BRAE) improves gut microbiota dysbiosis as shown in a study involving C57BL/6J mice fed with a high-fat and high-cholesterol diet. BRAE is shown to significantly increased Bifidobacterium and Lactobacillus by qPCR analysis.[103] Anthocyanin supplementation reduced the activity of fecal bacterial enzymes and increase the content of fecal SCFA.[70] SCFAs, which are the gut microbiota's fermentation products, have an advantageous effect on gut health by enhancing barrier function, regulating lipid metabolism, and improving mucus secretion. SCFA also have beneficial contributions on muscle regeneration. Report said SCFA is able to enhance muscle regeneration by decreasing Atrogin-1 gene expression and increasing MyoD expression[100] When there is a dysbiosis condition in gut microbiota and the body's metabolic disorder that leads to hypercholesterolemia, changes to cholesterol synthesis happen, and SCFAs act as biomarkers in gut microbiota composition.[103] Other study involving cyanidin-3-O-glucoside (C3G) further support the involvement of anthocyanin in improving microbiota dysbiosis. C3G supplementation on wistar rats is indicated to regulates gut microbiota communities to be more beneficial by increasing *Lachnospiracea NK4A136 group* and Actinobacteria.[104] Although in this review it is suggested that anthocyanin is able to improve gut microbiota dysbiosis, there are limited information which discuss about anthocyanin metabolism in gastrointestinal tract and its involvement in directly affecting skeletal muscle regeneration. Therefore, more in-depth research is needed to be done.

The Effects Of Anthocyanin On Apoptosis By Regulating Caspase-3

Controlling of apoptosis-related factors, the release of cytochrome c, and the cleavage of caspase-9 and caspase-3 are important in the prevention of the early stages of apoptosis and consequently amelioration of disuse muscle atrophy because of protease activation and protein synthesis suppression induced by ROS, which contributes to muscle dysfunction that can cause muscle atrophy.[105] Caspase-3 can induce cleavage of Rpt2 and Rpt6 subunits in myotubes and increase proteasome activity.[106] Anthocyanins have the potency to inhibit caspase-3. It is shown in a study that cyanidin-3-O-glucoside, delphinidin-3-O-glucoside, pelargonidin-3-O-glucoside, and peonidin-3-O-glucoside have an anti-apoptosis activity via caspase-3 interaction in BIR2 region, which is an essential region to execute the apoptotic process in the cell. Thus, the proteolytic activity of muscle proteasomes could be inhibited and serve as an anti-apoptosis factor.[107] A study of purple sweet potato color (PSPC), a class of naturally occurring anthocyanins, further ensures the anti-apoptotic activity of anthocyanin by showing a notably reduced protein expression of cleaved-caspase-3 and Bax and caspase-3 activities in HFD-treated mouse livers.[108] Other studies also shows that the antioxidant activity of anthocyanin captures ROS and inhibits caspase-3 activation.[109,110] In addition, it is also known that improvement of oxidative stress can also improve gene expression correlated with apoptosis by the increased level of PGC-1α in the muscles, which also preserves mitochondrial biogenesis for the prevention of apoptosis because of Ca2+ deregulation.[111–113]

The Effects Of Anthocyanin On Regulating Mitochondria Activity

Proliferator-activated receptor coactivator (PGC-1α) controls necrosis, inflammatory response, and fibrotic tissue formation in impaired skeletal muscle.[114] It is the chief regulator from mitochondria, and oxidative metabolism can safeguard the skeletal muscle from atrophy. [101,115] Mitochondria are defense organelles

essential for muscle mass regulation and limitation of those prone to apoptosis, having a protective response to chronic exercise, disuse, aging, and disease.[116] Increased expression of PGC-1α plays a significant role in metabolism regulation, which is promoted by the AMPK pathway. The study of cyanidin-3-glucoside (Cy3G) shows its ability to increase the expression of PGC-1α by increasing intracellular Ca2+. The increase of intracellular Ca2+ caused the increased cAMP level and inhibited phosphodiesterase (PDE) activity by Cy3G. When the intracellular Ca2+ level is increased, it then phosphorylates AMPK, leading to CaMKK-AMPK pathway activation. Cy3G-induced PGC-1α upregulation through the CaMKK-AMPK pathway increases the mitochondrial content of the muscle cells.[117] In addition to mechanisms mentioned above, it is also important to note that anthocyanin increases mitochondrial biogenesis and metabolism by directly increased expression of sirtuin 1(SIRT1) level.[118] SIRT1 could increase protein synthesis via IGF-1–AKT signaling and reduce the breakdown via FoxO1 deactivation. SIRT1 directly prevents oxidative stress, reducing ubiquitin-proteasome system overactivation and thus emerges as a promising target in muscle wasting.[119]

The Effects Of Anthocyanin On Autophagy Regulation

Anthocyanin have been studied to induce autophagy by activating AMPK–mTOR signaling pathways. Study involving bilberry anthocyanins (BA) shows that BA consumption significantly increase the expression of p-AMPK and increases autophagy markers, such as Cathepsin B (CTSB) and ATPase H+ Transporting V0 Subunit C (ATP6 V0C).[70] Autophagy is needed to maintain the regenerative ability of muscle satellite cells.[120] Skeletal muscle fibers of collagen VI null (Col6a12/2) mice show signs of degeneration because of a block in autophagy, leading to the accumulation of damaged mitochondria and excessive apoptosis. Induction of autophagy in the skeletal muscles post-exercise can prevent the accumulation of damaged organelles and maintain cellular homeostasis.[121] Autophagy is also needed for basal myofiber homeostasis, and its deregulation can lead to myofiber degeneration. Defects of the autophagy-lysosome machinery have a role in the pathogenesis of various myopathies and muscular dystrophies, characterized by the presence of protein aggregates and the accumulation of abnormal mitochondria, and dilations of the sarcoplasmic reticulum.[122] Using autophagy as a process to remove aged, unnecessary, or damaged components, the young/healthy activate satellite cell recycling of those components into the building blocks, which are then later utilized for further proliferation process. The proliferated satellite cells will asymmetrically split, allowing the self-renewal of the activated stem cell into the quiescent state; likewise, it requires substantial cytoplasmic reorganization and remodeling. The satellite cell progeny will undergo subsequent differentiation into mature myogenic cells that can fuse with the damaged myofibers, leading to successful and complete regeneration[28].

The Effects Of Anthocyanin In Inducing Myogenic Differentiation

The administration of anthocyanin compounds shows a substantial increase of p-AMPK level expression.[123] AMPK has an essential role in regulating muscle mass and regeneration, and AMPKα1 has a significant role in stimulating anabolism and satellite cell dynamics during regeneration[124] Cyanidin is proven to promote shifting of muscle fiber oxidative metabolism that contains more abundant satellite cells and perfects mitochondria biogenesis, reduces the decrease of infiltrating macrophage, and eventually safeguards the muscle against dystrophy and maintains muscle function with its antioxidant and anti-inflammatory activity.[125]

The function of satellite muscle cells and its regenerative capacity can be impaired due to high-fat diet or metabolic syndrome. Increasing level of toxic lipid metabolites and proinflammatory cytokines from high-fat diet lead to the increase of intermyocellular fat, insulin and leptin resistance.[12] A study in high-fat diet mouse model supports the data regarding a protective effect of anthocyanins on skeletal muscle regeneration. The study showed anthocyanin supplementation decreased the proinflammatory cytokine profile through its antioxidant effect.[126] Meanwhile, others study showed relation between anthocyanin administration and brown adipogenesis. The specific expression of brown adipose tissue (BAT), and Uncoupling protein 1 (UCP1) could be enhanced by the administration of cyanidin 3-glucoside (C3G) and cyanidin 3-rutinoside (C3R), two anthocyanin compounds derived from mulberries.[127] In addition, a recent study shows that flavonoids are indicated to have an effect in inducing white adipose tissue (WAT) browning and activating BAT.[128] The induction of UCP1 which can increase the differentiation of fibro-/adipogenic progenitors (FAP to BAT) enhance muscle regeneration.[129]. BAT enhanced muscle regeneration through producing adipokines that participated in increasing muscle regeneration including IGF-1, basic fibroblast growth factor (bFGF), and Vascular endothelial growth factor (VEGF). Thus, it will activate proliferation and differentiation of satellite cell for a healthy skeletal muscle regeneration.[130]

Anthocyanin through increased PGC1α induces the release of FNDC5, which is then cleaved into irisin, as shown in study involving grape pomace extract consumption. FNDC5/Irisin pathway is activated which leads to AMPK phosphorylation and enhanced irisin plasma levels. Irisin can activate UCP1 to stimulate changes in the phenotype of white adipose tissue to brown adipose tissue that contain a much higher number of mitochondria and more capillaries for more tissue oxygen supply.[22] Muscle tissue oxygenation is also known to be improved by anthocyanin through increasing NO bioavailability, prevent NO from being converted to superoxide.[131] The O2 level could affect satellite cell activation during muscle regeneration. O2 levels on muscle tissue enhance muscle regeneration. The reduction of oxygen supply contributes to muscle damage as well as atrophy.[132,133] Another report of anthocyanin's effect is its ability to induced myokine's production and release. A study using anthocyanin-rich purple cauliflower treatment showed significantly increased brain-derived neurotrophic factor (BDNF) expression. The BDNF is known to be able to boost the response of satellite cells to promote signaling of the skeletal muscle regeneration.[134,135]

ANTHOCYANIN CAN IMPROVE MUSCLE PERFORMANCE BY ITS REGENERATIVE CAPABILITY

Exercise performance could not be optimal if there is a muscle injury marked by an increase in creatine kinase, resulting in muscle pain occurrence. Muscle pain following exercise can be reduced and prevented by administering antioxidants derived from polyphenols, one of which is an anthocyanin that can reduce creatine kinas

levels.[131,136–139] Blood flow, metabolic pathways, and peripheral muscle fatigue could affect exercise performance.[140] Anthocyanins promote fatty acid metabolism, mitochondrial biosynthesis via increased PGC-1α, and suppression of inflammatory cytokines, which can reduce the level of physical fatigue and improve exercise performance.[117,141,142] Anthocyanins can increase maximum oxygen consumption and antioxidant capacity and reduce inflammation and lipid peroxidation to aid the recovery muscle function.[143] Improved endothelial function and blood flow changes may be the mechanisms underlying an improved performance following anthocyanin supplementation. Future research is required to elucidate the potential effect of anthocyanin on oxidative stress. As an antioxidant for muscle performance, endurance, VO2max, and post-recovery muscle performance, it is still unclear and limited.[144]

CONCLUSION

The present review investigates molecular mechanisms of different food sources containing anthocyanin, which has a great potential to be developed into promising nutraceutical products for muscle regeneration. This bioactive compound involves various physiology effects for proper muscle regeneration, including acceleration in the myogenesis, muscle protein synthesis, protection from muscle protein degradation, protection on mitochondrial function, antiapoptotic effect, and autophagy regulation, antioxidant defense, and gut dysbiosis preventing effect. Therefore, these scientifically proven data recommend that anthocyanin has a high possibility of improving muscle regeneration. However, the efficacy of anthocyanin intake in skeletal muscle regeneration still gives rise to many unanswered questions that need further experimentation. We suggest more in-depth research that will discuss anthocyanin consumption with specific amounts and preparations and its effect on skeletal muscle regeneration is necessary. Hopefully, with those types of studies, the most effective amount and preparation of anthocyanin supplementation for skeletal muscle regeneration will be found. It is also worth noting that studies which discussed some specific markers in this review and their direct involvement in skeletal muscle regeneration are quite limited. Therefore, it is strongly suggested for future research that will address the effect on anthocyanin on specific markers involved in skeletal muscle regeneration pathways. As there is always a possibility of unwanted effects, we also suggest further studies that potentially discuss the side effects of anthocyanin consumption, especially on the topic of skeletal muscle regeneration. We hope that this essential information will provide ideas for the nutraceutical development of anthocyanin to improve the regeneration and maintenance of skeletal muscle health. Further research should aim at determining the dose and anthocyanin molecular interaction.

ETHICAL STATEMENTS

This review article doesn't include an animal or human experiment.

DECLARATION OF COMPETING INTEREST

The authors declare that there is no conflict of interest.

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FIGURES AND TABLES

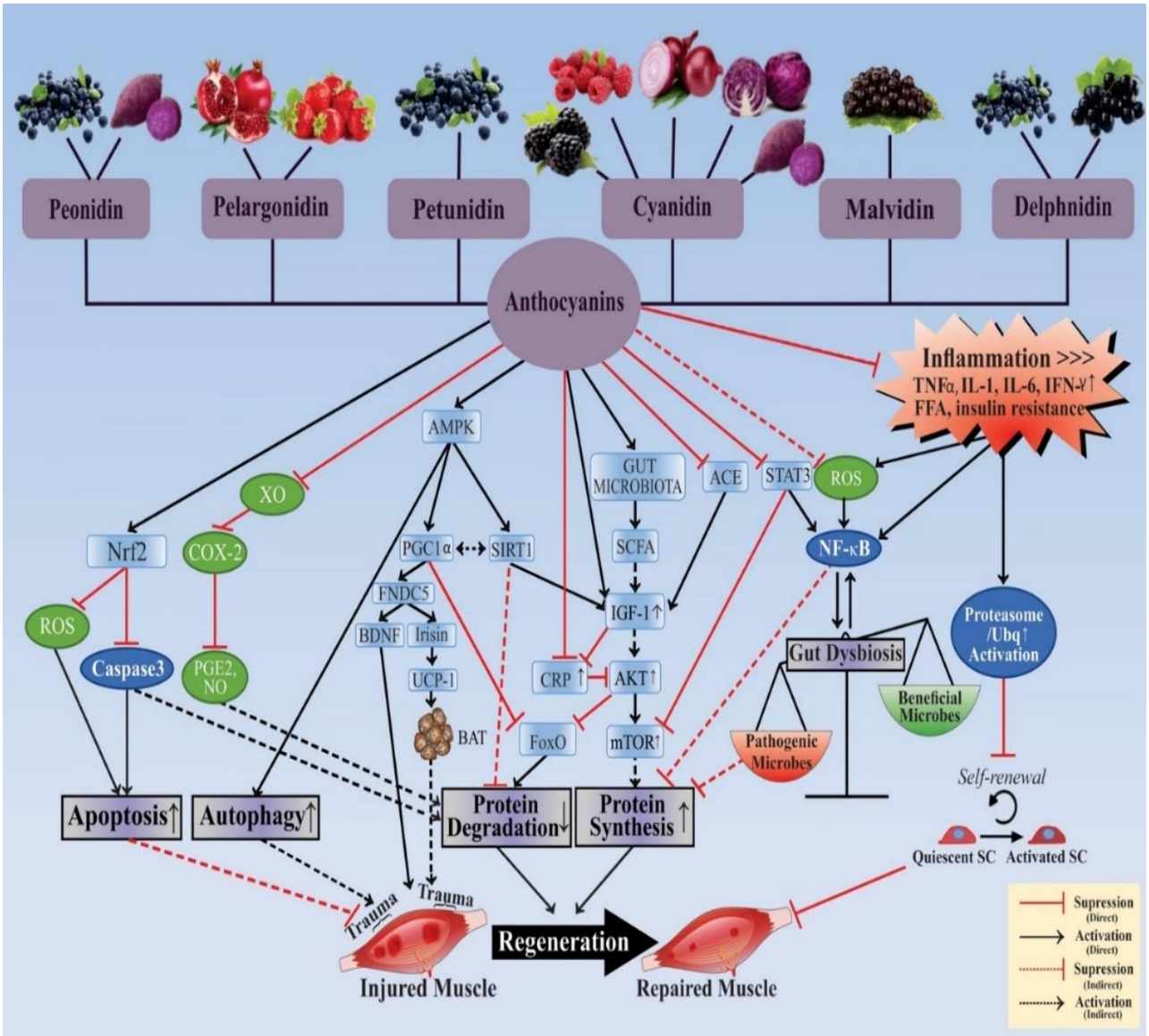

Figure 1. Molecular mechanisms of anthocyanin in skeletal muscle regeneration.

Anthocyanins increase the MPS rate through modulating IGF-1/PI3K/Akt/mTOR pathway, targeting SIRT1 factor, increasing mitochondrial biogenesis PGC-1α, regulating autophagy through the AMPK pathway and improving gut microbiota. Anthocyanins are diminishing the cascade inflammatory response crucial for muscle protein degradation by inhibiting activation of inflammatory signaling pathways and through its antioxidant action. Anthocyanin enhances antioxidant defense via Nrf2 for reducing ROS and preventing myonuclear apoptosis by inhibiting caspase-3. Anthocyanins might also exert muscle regeneration inducing UCP-1 for brown adipose tissue activation, indirectly inducing myokine secretion and activation, and reducing lipid peroxidation.

Table 1. Principal anthocyanins in human dietary source.[17,145–148]

Compound	Amount (mg/100 g FW)*	Source
Malvidin-3-glucoside	9.97	Red wine
	39.23	Black grapes
Cyanidin-3-glucoside	794.13	Black elderberries
	405.0	Bilberries
	138.72	Blackberries
	110–40	Apple
	25.07	Blackcurrants
	3.5	Blood orange
	2.88	Strawberry
	0.4	Red onion
	14.69 ± 2.03	Red raspberry
	26.72 ± 3.22	Cherry
	0.298 – 42.5	Purple cauliflower
Cyanidin-3-(6-malonylglucoside)	4.3	Blackberries
	1.5	Red onion
	1.76	Pure blood orange juice
	200 – 400	Red oak leaf and lollo lettuce
	8.289	Red chicory
Cyanidin-3-galactoside	557.67	Black chokeberries
	370.0	Bilberries
	48.69	Lingonberries
	5.9	Pistachio
Cyanidin-3-sambubioside	462.96	Black elderberries
Cyanidin-3-rutinoside	160.78	Blackcurrants
	143.27	Sweet cherries
	8.86	Blackberries
Cyanidin-3-arabinoside	252.76	Black chokeberries
	5.85	Lingonberries
Cyanidin 3,5-diglucoside	24 – 236	Pomegranate juice
	30.0	Red cabbage
Cyanidin 3-(sinapoyl)diglucoside-5-glucoside	31.0	Red cabbage
Cyanidin 3-(sinapoyl)(sinapoyl)-diglucoside-5-glucoside	28.0	Red cabbage
Cyanidin 3-(p-coumaroyl)-diglucoside-5-glucoside	25.0	Red cabbage
Cyanidin-3-caffeoyl-p-hydroxybenzoylsophoroside-5-glucoside	2.43	Purple sweet potato
Peonidin-3-glucoside	365.0	Blueberries
Peonidin-3-dicaffeoylsophoroside-5-glucoside	10.2	Purple Sweet Potato
Peonidin-3-caffeoyl-p-hydroxybenzoylsophoroside-5-glucoside	15.24	Purple Sweet Potato
Delphinidin-3-rutinoside	304.91	Blackcurrants
Delphinidin-3-glucoside	86.68	Blackcurrants
	5.0 – 104.0	Pomegranate juice
Delphinidin 3,5-diglucoside	37.0 – 530.0	Pomegranate juice
Delphinidin-3-O-(6″-p-coumaroyl-glucoside)	8.72	Eggplant
Pelargonidin-3-glucoside	47.2	Chokeberries
	47.14	Strawberry
Pelargonidin-3-rutinoside	2.48	Blackcurrant
	1.32	Strawberry
Pelargonidin 3,5-diglucoside	0.7 – 9.0	Pomegranate juice
Petunidin 3-O-glucoside	6.09 – 11.20	Blueberries
Petunidin 3-O-galactoside	9.05 – 12.73	Blueberries

Note: *milligrams of anthocyanin equivalent per 100 g Fresh Weight

Table 2. Advantages of anthocyanin in the musculoskeletal system

Markers by anthocyanin	Mechanism relates to the musculoskeletal system	Type of study	References
IGF-1	Induce muscle protein synthesis	In vitro	[45]
Akt	Induce muscle protein synthesis	In vivo (animal study)	[43,44]
CRP	Alternate the muscle protein synthesis	In vivo (animal, human study)	[46,47]
SCFA	Induce IGF-1 production	In vitro, In vivo (animal study)	[56,70]
ACE	Enhance IGF-1 levels	In vitro, In vivo (animal, human study)	[48]
	Suppress proinflammatory cytokine levels		
SCFA	Regulate muscle mass and function	In vitro, In vivo (animal, human study)	[55,56,102,103]
Caspase-3	Prevent muscle protein degradation and muscle protein synthesis suppression	In vitro, In vivo (animal, human study)	[107,109,110]
TNF-α, IL-1, IL-6, IFN-γ, NF-kb, FFA, insulin resistance (markers for oxidative stress)	Reduce muscle protein degradation	In vitro, In vivo (animal, human study/RCT)	[54,59–61] [67,78,79,83] [87–89,94,95] [123,126]
	Prevent decreasing rate of basal muscle protein synthesis		
	Prevent apoptosis of myotubes myonuclear		
	Prevent decreased proliferation and differentiation of muscle cells		
	Prevent inhibition of myogenic differentiation		
COX-2	Reduced muscle protein degradation	In vitro	[63]
XO	Reduce proteolytic activity and tissue degradation	In vitro, In vivo (animal, human study)	[72,74]
Nrf2	Reduce inflammatory mediators through NF-kB inhibition	In vitro, In vivo (animal, human study)	[72,76,77]
	Protect skeletal muscle		
	Maintain a normal function of mitochondrial		
	Induce apoptosis protection		
PGC-1α	Regulate necrosis, inflammatory response, and fibrotic tissue formation in injured skeletal muscle	In vivo (animal study)	[117]
	Protect skeletal muscle		
	Maintain a normal function of mitochondrial		
SIRT1	Induce muscle protein synthesis	In vitro	[118]
	Prevent muscle protein degradation		
AMPK	Regulating muscle mass and regeneration Induce autophagy to enhance the regenerative ability of the satellite cells	In vivo (animal study)	[123]
STAT3	Prevent protein synthesis suppression	In vitro, In vivo (animal study)	[97–99]
miR-23a	Regulate muscle protein degradation	In vitro, In vivo (animal study)	[66]
Tissue Oxygenation Index	Activate satellite cells	In vivo (human study)	[131]
Total Peripheral Resistance	Improve muscle protein metabolism	In vivo (RCT)	[51,52]
MDA, TBARS Value (Markers for lipid peroxidation)	Prevent the disruption of the proliferation and differentiation of myoblast	In vitro	[71]
UCP-1	Support brown fat regeneration	In vitro	[127]
Myokine	Activate satellite cells and increase muscle protein synthesis	In vivo (human study)	[22,134]