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Apigenin as a promising myocyte protectant against damage and degradation

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Abstract: Myocytes power the movement of all organs in the body. Damage to and degradation of myocytes causes hypokinesia and muscle-related degenerative diseases. Apigenin, a kind of flavone, is being used to treat many disorders. It exerts a host of different pharmacological activities, such as anti-inflammatory, anti-mutagenic, cardioprotective, and antioxidant effects. Accordingly, apigenin is considered a promising candidate for myocyte protection. In this review, we introduced the characteristics of apigenin. The means of apigenin protection of myocytes as well as the mechanism were summarized and discussed. The protective effects can be classified into proliferation-promoting, anti-inflammatory, atrophy-preventing, metabolism-increasing, and antioxidative effects. Additionally, we provided some outlook on the valuable applications of apigenin in sports medicine, which eagerly require further fundamental research.

Introduction

Myocytes can contract and relax, allowing them to a crucial role in body movement. Thus, they are the power source for movement. However, improper exercise causes exercise fatigue originally resulting from energy burn-out and myocyte hypoxia, producing numerous free radicals (Verhavert *et al.*, 2020; Zhou and jiang, 2019). Oxidative imbalance leads to some serious consequences, including decreased pH, inflammatory responses, and hypoimmunity (Jayakumar *et al.*, 2020; Li *et al.*, 2020; Baldelli *et al.*, 2019; Mulkey *et al.*, 2003). This imbalance can accelerate necrosis and the apoptosis of myocytes, reducing exercise performance (Narasimhan and Rajasekaran, 2016). In addition, aging and obesity can also induce myocyte atrophy (Yatsenko *et al.*, 2020; Lee *et al.*, 2016). Therefore, protecting myocytes against damage and degradation becomes very important for preventing hypokinesia and muscle-related degenerative diseases.

It is widely believed that nutrient supplementation is an effective way to keep muscles healthy (Ganapathy and Nieves, 2020). Among the various sports supplements, herbs and their extracts have attracted more attention due to their high efficiency and low toxicity (Zhang *et al.*, 2014). Polyphenols can reduce oxidative damage and promote myocyte survival (Carresi *et al.*, 2016). *Astragalus* polysaccharide can inhibit the autophagy and apoptosis of C2C12 myoblasts by regulating apoptosis-related protein (B-cell lymphoma-2 (Bcl-2), cytochrome C (cyto-C), and cysteine protease 3 (caspase-3)) (Yin *et al.*, 2015). *Astragalus* polysaccharide also prevents muscle cell atrophy by activating the ubiquitin-proteasome pathway (Geng *et al.*, 2017). *Gentianella acuta* can inhibit the nuclear factor κB/cyclooxygenase-2 (NF-κB/COX-2) signaling pathway to down-regulate inflammatory factors, preventing myocardial ischemia/reperfusion injury (Ding, 2016). Recently, apigenin (API) has been recognized as a bioactive compound that possesses a host of different pharmacological activities, such as anti-inflammatory, anti-mutagenic, cardioprotective, and antioxidant effects (Kashyap *et al.*, 2018). API was reported to relieve muscle atrophy by inhibiting oxidative stress apoptosis in the skeletal muscle of mice (Wang *et al.*, 2020). API can also reduce eye fatigue by relaxing ciliary muscles

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(Kim *et al.*, 2018). Accordingly, API is considered a promising candidate for myocytes protection. Several research teams and our group have focused on this issue. Herein, we summarized the protective effects and mechanism of API on myocytes. The information in this review can provide a theoretical basis for API as a promising myocyte protectant against damage and degradation.

Characteristics of API

API is a kind of flavonoid and exists in a wide variety of vegetables, fruits, beans, and teas. The API content is relatively high in celery (2154 mg/kg dry weight), guava (579 mg/kg dry weight), wolfberry leaves (547 mg/kg dry weight), bilimbi fruit (458 mg/kg dry weight), pepper (272 mg/kg dry weight), kumquat (219 mg/kg dry weight), garlic (217 mg/kg dry weight), Chinese cabbage (187 mg/kg dry weight), bell French peas (176 mg/kg dry weight), snake gourd (42 mg/kg dry weight), daun turi (39 mg/kg dry weight), and kadok (34 mg/kg dry weight) (Nabavi *et al.*, 2018; Yang *et al.*, 2008; Miean and Mohamed, 2001). API is chemically known as 4',5,7-trihydroxyflavone with the molecular formula $C_{15}H_{10}O_5$ and a molecular weight of 270.24. The basic carbon skeleton of API has a flavan nucleus. Its structure consists of 15 carbons arranged in two aromatic rings connected by a 3-carbon bridge, forming a diphenyl propane structure. Three hydroxyl groups are present at positions 5 and 7 on the chromone and 4', respectively. It also has an oxo group on the chromone at position 4 (Fig. 1) (Hassanpour *et al.*, 2020; Ali *et al.*, 2017).

API has acquired importance over the past few years as a salutary and health-promoting agent because of its low intrinsic toxicity. According to *in vitro*, *in vivo*, and clinical trial studies, API has been used to treat autoimmune diseases because of its anti-inflammatory effect (Kairi *et al.*, 2018), nervous system diseases by virtue of its antioxidant function (Ginwala *et al.*, 2016), cancer, from its ability to regulate the cell cycle (Kashyap *et al.*, 2018), and other diseases due to its pharmacological properties (Ali *et al.*, 2017).

Protective effect of API on myocytes

Promoting proliferation

The phosphatidylinositol 3-kinase/serine-threonine protein kinase/mammalian target of the rapamycin (PI3K/AKT/mTOR) signaling pathway plays an important role in regulating the cell cycle. AKT is the downstream target protein of PI3K. When AKT is activated, cells can escape from apoptosis, and proliferation is promoted (Rychahuo *et al.*, 2005). In C2C12 cells, AKT can be activated by API, and the expression of phosphorylated AKT (pAKTSer473) increases. Then, pAKTSer473 phosphorylates glycogen synthase kinase-3β (GSK3β), which mediates the degradation of cyclinD1 protein to promote cell proliferation. And the cellular viability of C2C12 increased about 10% compared to the control group. (Kulabas *et al.*, 2018). Besides, AKT can phosphorylate cell cycle inhibitors ($p21^{WAF1}$ and $p27^{Kip1}$) to inhibit cyclinD1/cyclin-dependent kinases 4 (CDK4), promoting cell cycling from the G1 phase to the S phase (Cheung and Testa, 2013; Hua *et al.*, 2008).

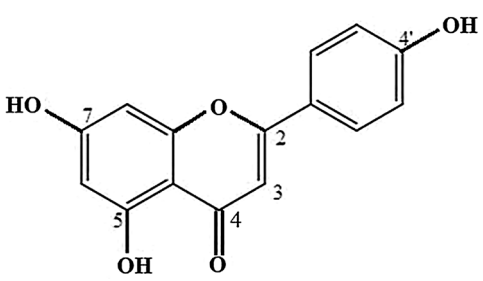

FIGURE 1. Chemical structure of API.

Mitochondria are organelles in cells that supply energy for cell proliferation. The mitochondrial biogenesis and mitochondrial function of skeletal muscle cells were shown to increase after API treatment. Increased mitochondrial size and the mtDNA (peroxisome proliferator-activated receptor-γ coactivator-1α (PGC1α), mitochondrial transcription factor (mt-TFAM). and cytochrome c (CyCs)) contents have been observed in API-treated mouse skeletal muscle cells. Therefore, skeletal muscle fiber size was significantly increased, and there was a tendency toward an increase in the skeletal muscle mass (Choi *et al.*, 2017). These results suggest that API can ameliorate mitochondrial function and promote myocyte proliferation.

Anti-inflammatory effects

It is well known that many flavonoids selectively or non-selectively inhibit cyclooxygenase (COX), lipoxygenase (LOX), phospholipase (PLA), and nitric oxide synthase (NOS), which are the major contributors to inflammation. API has been found to suppress lipopolysaccharide (LPS)-induced nitric oxide (NO) production and COX-2 expression (Gutierrez-Venegas and Gonzalez-Rosas, 2017). In an acute lung injury mouse model, API lowered the production of some inflammatory cytokines (interleukin-6 (IL-6), interleukin-1β (IL-1β) and tumor necrosis factor α (TNF-α)) via inhibiting the COX-2 and NF-κB activation pathways (Wang *et al.*, 2014). Further, studies also reported that API exerted anti-chronic inflammatory effects. API was capable of normalizing the expression of many colonic inflammatory markers in a bowel disease model (Mascaraque *et al.*, 2015). These studies demonstrate the anti-acute and chronic inflammatory effects of API.

Choi *et al.* (2017) investigated the effects of API on inflammatory cytokines such as monocyte chemoattractant protein 1 (MCP-1), IL-1β, TNF-α, and IL-6 in the skeletal muscle of obese mice. After API treatment, the mRNA expression of those inflammatory cytokines decreased significantly. TNF-α and IL-6 levels were also lower in the serum of the API-treated mice. API probably inhibited the NF-κB activation pathways in the myocytes of the obese mice. In view of the anti-acute and chronic inflammatory effects of API, it can be inferred that both acute inflammation induced by exhaustive exercise and chronic inflammation induced by chronic diseases can be normalized by API. In this way, myocytes can be protected from inflammatory injury.

Preventing atrophy

The pathological characteristics of muscle atrophy show the progressive loss of muscle mass and strength. It is a complex process, and its exact causes have not been identified. Some studies reported that skeletal muscle was

atrophied as a result of inflammatory conditions such as sepsis (Liu *et al.*, 2019). Recent research has suggested that skeletal muscle atrophy is potentially induced by some atrophic stimuli (Rosa-Caldwell and Greene, 2019; Rienzo *et al.*, 2019; Li *et al.*, 2017), which disturb the balance between the synthesis and breakdown of myofibrillar proteins. Acting on specific targets can regulate signal transduction pathways to promote the synthesis or degradation of muscle proteins to control muscle hypertrophy or atrophy (Pipis *et al.*, 2019).

The results of studies by Shiota *et al.* (2015) showed that API could significantly inhibit LPS-induced c-Jun N-terminal kinase (JNK) phosphorylation in C2C12 myotubes. In this manner, LPS-mediated muscle atrophy can be prevented by API via the downregulation of muscle atrophy F-box (MAFbx/atrogin-1) expression. API also regulated the expression of other atrophic genes, such as myosin heavy chain (MyHC) IIa and muscle-specific ring finger protein 1 (MuRF1), to prevent muscle atrophy. Moreover, API can increase the nuclei ratio of C2C12 cell nucleus compared to the palmitic acid-treated cells, which is a similar environment to the obese state, by downregulating the expression of MuRF1 (Choi *et al.*, 2017). Therefore, API has great potential use for preventing muscle atrophy.

Increasing metabolism

Skeletal muscle is the most important peripheral tissue contributing to the uptake of glucose into cells, a process underlying insulin control. The glucose uptake of myocytes, as well as glucose utilization, is reduced in people with insulin resistance. Consequently, myocytes suffer from functional degeneration, and type 2 diabetes mellitus is more likely to develop (Meng *et al.*, 2020). Insulin-induced glucose uptake initially takes place through translocation of glucose transport-4 (GLUT4) on the cell membrane. And in insulin resistance, GLUT-4 is down-regulated, resulting in decreased insulin-stimulated glucose uptake and metabolism. API, as the effective constituent, significantly increased GLUT4 expression in muscle cells both *in vitro* and *in vivo* (Kulabas *et al.*, 2018; Li *et al.*, 2007). This is because API activated the upstream protein AKT (Tan *et al.*, 2020).

Additionally, API also increased enzyme lipoprotein lipase (LPL) and peroxisome proliferator-activated receptor γ (PPARγ) levels in an insulin-resistant C2C12 cell model (Kulabas *et al.*, 2018). LPL is a key enzyme in lipid metabolism. Low LPL activity may induce abnormal lipid metabolism (Hao *et al.*, 2016). And PPARγ plays an important role in lipid-mediated insulin resistance in muscle and hepatic cells (Kim *et al.*, 2020). Those results indicated that API could participate in normalizing lipid metabolism. Another metabolism-related key protein, adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK), was also activated in obese mice by API (Choi *et al.*, 2017). AMPK is effective in balancing glucose metabolism (Trinchese *et al.*, 2020) and enhancing mitochondrial function (Sun *et al.*, 2020).

Antioxidant function

The three hydroxyl groups at positions 5, 7, and 4', and the C-C double bond between Positions 2 and 3 in the chemical structure of API can react with free radicals. The two hydroxyl groups at positions 5 and 7 can chelate metal ions to inhibit the production of free radicals. Those characteristics confer API with antioxidant activity. API not only scavenges free radicals directly but also enhances the antioxidant ability of cells by regulating heme oxygenase (HO-1), glutamate-cysteine ligase, catalytic subunit (GCLC) and glutamate-cysteine ligase, modifier subunit (GCLM) gene transcription via the extracellular regulated protein kinases 2 (ERK2)/nuclear factor E2-related factor 2 (Nrf2)/antioxidant response element (ARE) signaling pathways (Hassanpour and Niknam, 2020; Huang *et al.*, 2013). Many studies have found that API helps in preventing oxidative stress injury by increasing the expression of antioxidant enzymes both at the mRNA and protein levels in several cells (Ogura *et al.*, 2020; Zhang *et al.*, 2019; Xu *et al.*, 2016). However, to the best of our knowledge, there is no published study focusing on the direct antioxidant effects of API on myocytes. Our group found that API significantly increased the viability of skeletal muscle cells under oxidative stress induced by tert-butyl hydroperoxide. It is probable that API activates the Nrf2 and mitogen-activated protein kinase (MAPK) signaling pathways (data not published). Therefore, it can be inferred that API has effective antioxidant effects, protecting myocytes against oxidative stress injury.

Conclusion and outlook

Myocytes are the power source for the movement of all organs of the body. Myocyte damage and degradation cause hypokinesia and muscle-related degenerative diseases. API, a kind of flavone, has been used as a salutary and health-promoting agent because of its low intrinsic toxicity. The evidence gathered in this review indicates that API possesses hopeful pharmacological activity as an agent protecting myocytes against damage and degradation. API protects myocytes by promoting proliferation, exerting anti-inflammatory and antioxidant effects, preventing atrophy, increasing metabolism, and activating the respective signaling pathways (Fig. 2).

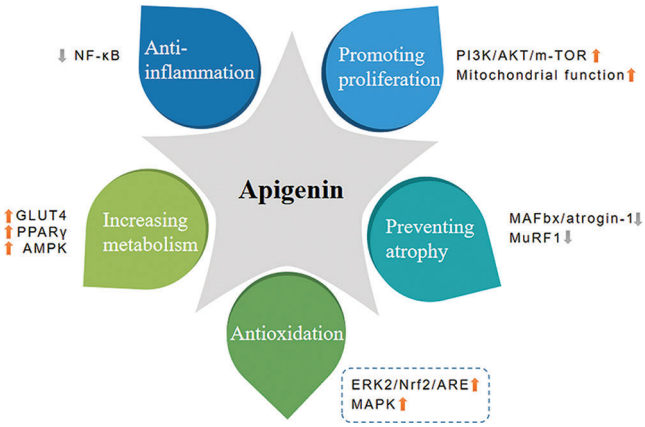

FIGURE 2. Protective effect on myocytes and its mechanism (promoting proliferation: up-regulate PI3K/AKT/mTOR pathway (Kulabas *et al.*, 2018) and enhance mitochondrial function (Choi *et al.*, 2017); anti-inflammation: down-regulate NF-κB pathway (Choi *et al.*, 2017); preventing atrophy: down-regulate MAFbx/atrogin-1 (Shitota *et al.*, 2015) and MuRF1 (Choi *et al.*, 2017) expression; increasing metabolism: increase GLUT4 express (Tan *et al.*, 2020; Kulabas *et al.*, 2018; Li *et al.*, 2007), PPARγ level (Kulabas *et al.*, 2018) and activate AMPK (Trinchese *et al.*, 2020; Sun *et al.*, 2020) and antioxidation: probably up-regulate ERK2/Nrf2/ARE and MAPK pathways) of API.

However, studies on the protective effect of API on myocytes are still scarce. And all of the research has focused on the obesity model. In fact, API also performs effectively in acute conditions. Therefore, its protective effect on myocytes in exercise models needs to be investigated. The results of such studies would make valuable contributions to sports medicine.

The remarkable effect of API on cardioprotection also needs to be noted (Zhang *et al*., 2015). API can reduce myocardial ischemia/reperfusion injury and attenuate anoxia/reoxygenation-induced myocardium injury (Quan *et al*., 2020; Feng *et al*., 2018; Chen *et al*., 2016; Hu *et al*., 2015; Yang *et al*., 2015). API can depress contractions in arterial smooth muscle cells induced by various vasoconstrictors (Jing *et al*., 2019). These vascular pharmacological activities of API would play an equally important role in whole-body exercise in the field of sports medicine.

Overall, API holds great potential in protecting myocytes against damage and degradation to prevent hypokinesia and muscle-related degenerative diseases. Therefore, fundamental research into API is warranted.

Availability of Data and Materials: Not Applicable.

Author Contribution: The authors confirm contribution to the paper as follows: project conception: Xiao Huang and Zhuying Wang; paper preparation: Xiao Huang and Zhihai Yu; references collection and analysis: Lijuan Ning, Yu Lei, and Xuefei Zhang. All authors reviewed and approved the final version of the manuscript.

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Conflicts of Interest: The authors declare that they have no conflicts of interest to report regarding the present study.

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