Molecular targets of exercise mimetics and their natural activators

Young Jin Jang¹ & Sanguine Byun²,*
¹Major of Food Science & Technology, Seoul Women’s University, Seoul 01797, ²Department of Biotechnology, College of Life Science and Biotechnology, Yonsei University, Seoul 03722, Korea

Physical exercise can be effective in preventing or ameliorating various diseases, including diabetes, cardiovascular diseases, neurodegenerative diseases, and cancer. However, not everyone may be able to participate in exercise due to illnesses, age-related frailty, or difficulty in long-term behavior change. An alternative option is to utilize pharmacological interventions that mimic the positive effects of exercise training. Recent studies have identified signaling pathways associated with the benefits of physical activity and discovered exercise mimetics that can partially simulate the systemic impact of exercise. This review describes the molecular targets for exercise mimetics and their effect on skeletal muscle and other tissues. We will also discuss the potential advantages of using natural products as a multi-targeting agent for mimicking the health-promoting effects of exercise. [BMB Reports 2021; 54(12): 581-591]

INTRODUCTION

The health benefits of exercise have been well-established. Exercise is closely related to health conditions of bone, immune system, brain, and reproductive system as well as skeletal and cardiovascular systems (1). Physical exercise has been shown to have a positive impact on a wide range of diseases including obesity, metabolic diseases, cardiovascular disease, cancer, neurodegenerative disease, and osteoporosis (2, 3). Exercise also has anti-depressant effects and improves immune function, and therefore may contribute as a defense strategy against infectious diseases such as COVID-19 (4, 5). Nevertheless, exercising on a regular basis may be an option for everyone. Therefore, exercise mimetics, pharmacologic therapeutics that mimic the health benefit effects of exercise, have been proposed as an alternative option (1). Exercise mimetics may, to some extent, generate health benefits without performing actual exercise.

Recent studies have identified pathways that are activated during physical exercise and found critical signaling molecules that contribute to the health-promoting effects of exercise. In this review, we will discuss the potential targets of exercise mimetics and the need for developing exercise mimetics from natural sources.

SKELETAL MUSCLE ADAPTATION AND HEALTH BENEFITS OF EXERCISE

Exercise promotes skeletal muscle adaptation and these adaptive changes are the basis for the health benefits of exercise (6). Endurance exercise and resistance exercise induce different adaptive changes to the skeletal muscle (7). The major adaptive changes of endurance exercise include increase in mitochondrial density, oxidative function, and capillarization (7). It is also well-known that endurance exercise promotes transformation of glycolytic muscle fibers to oxidative muscle fibers (2). Oxidative muscle fibers are rich in mitochondria compared with glycolytic muscle fibers, have higher myoglobin content, and are more densely vascularized (2). They also perform increased fatty acid oxidation due to the increased levels of lipid-metabolizing enzymes, which provide extra energy for performance and reduce the dependence on glucose (8). This results in increased lactate tolerance and endurance capacity (8). On the other hand, resistance exercise leads to increased muscle strength and power as a result of neuromuscular adaptation (9). Resistance exercise promotes development of glycolytic muscle fibers and directly increases the size of muscle fibers (9). The enlargement of muscle fibers is attributed to upregulation of protein synthesis and selective hypertrophy of fast twitch fibers (10). Although endurance exercise and resistance exercise both provide health benefits, there can be some differences in the particular effect each type produces. For instance, endurance exercise is known to be more effective in reducing cardiovascular risks, while resistance training can be more effective in maintaining muscle mass and physical function. Combination of endurance exercise and resistance exercise have been reported to be more potent in reducing insulin resistance and functional limitation in abdominally obese adults, compared to either modality alone (7).

Exercise has a positive effect not only on skeletal muscles, but also on various organs and tissues including the heart, brain, adipose tissue, liver, blood vessels, and bones (11). There-
fore, the effect of exercise goes beyond improving muscle function and strength, leading to other health-promoting effects on cardiovascular function, memory, immunity, metabolism, and aging (12-14). While the impact of physical training or exercise mimetics on multiple organs are well-documented, the underlying molecular mechanism is still unraveling (15). In this regard, myokines have been suggested as an important factor to explain the multiple benefits of exercise (16). Myokines are peptides synthesized and released by myocytes in response to muscular contraction (16). Myokines are implicated in the autocrine regulation of muscle function as well as in paracrine and endocrine regulation of other tissues and organs including adipose tissue, liver, and brain (16). Secretome profiling of primary human skeletal muscle cells revealed 305 myokines (17). While the role of each myokine is still under investigation, certain myokines appear to have a physiological effect on other parts of the body leading to favorable health outcomes, and thus represent a promising target for exercise mimetics. In addition, studies have found specific genes expressed in multiple tissues that mimic the diverse effects of exercise when activated. Thus, modulating the activity or expression of these genes could potentially simulate certain aspects of physical training. Next, we will describe some of the potential targets of exercise mimetics.

**MOLECULAR TARGETS OF EXERCISE MIMETICS**

**Irisin**

Irisin is a hormone-like myokine induced by exercise, and is also expressed in small amounts in bone, brain, and other tissues (18, 19). The peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) is a critical regulator of exercise-induced skeletal muscle adaptation (20). And exercise-driven upregulation of PGC-1α in muscle promotes the synthesis of fibronectin domain-containing protein 5 (FNDC5), which is subsequently cleaved to generate irisin (18, 21). The level of irisin positively correlates with muscle mass and muscle strength (19) and injection of irisin rescues denervation-induced loss of skeletal muscle mass by enhancing satellite cell activation and reducing protein degradation (22). Also, upregulation of the PGC-1α/FNDC5/irisin pathway has been suggested to be responsible for the exercise-mediated accelerated recovery of myopathy through increasing mitochondrial fission and mitophagy (23).

Irisin acts as a link between muscle and other tissue and organs, and has positive effects on obesity, insulin resistance, type 2 diabetes, brain, and bone health (24). Irisin attenuated LPS-induced inflammation in mature adipocytes (25). Exercise has been known to have major impacts on adipose tissue browning and fat metabolism (26). The conversion of white to brown adipose tissue mediated by exercise has been reported to be through inducing irisin which stimulates the expression of UCP-1, the master regulator of brown adipose tissue (27). The benefit of physical exercise on bone mineral density is widely accepted, and irisin has been reported to play an active role between skeletal muscles and bones (19). Irisin promotes cortical bone mass and strength as well as osteoblast differentiation through regulating expression of bone-specific genes and upstream signaling pathways (24). In addition, exercise increases the hippocampal expression of FNDC5, the precursor of irisin, in mice, in a PGC-1α-dependent manner (28). Irisin stimulates neurogenesis, synaptic plasticity, and cognitive function by up-regulating the expression of brain-derived neurotrophic factor (BDNF), demonstrating that irisin may act as a link between exercise and brain function (29).

**Brain-derived neurotrophic factor (BDNF)**

BDNF is a polypeptide belonging to the neurotrophin family. It regulates neuronal proliferation, differentiation, maturation, and plasticity in neurogenesis (30). Varying intensity of exercise has been reported to increase BDNF mRNA expression in the hippocampus of mice (31, 32). BDNF has been known to play a crucial role in exercise-induced neurogenesis, synaptic plasticity, and improved cognition. Interestingly, plasma concentration of BDNF is also increased by exercise (33). Notably, BDNF is increased in human skeletal muscle after exercise as well as in electrically stimulated muscle cells (34). Induction of BDNF through exercise and its multifaceted effect on the various organs suggests BDNF as a myokine. Running induces upregulation of BDNF in skeletal muscle and is involved in exercise-induced skeletal muscle regeneration (35). BDNF decreases the atrophy of skeletal muscle following exercise and is mediated via AMPK phosphorylation (36). BDNF acts in an autocrine or paracrine fashion with strong effects on peripheral metabolism, including fat oxidation, and subsequent effects on the size of adipose tissue (37). BDNF is also effective against insulin intolerance and has been shown to play an important role in angiogenesis, cardiovascular development, and cardioprotection (38). Furthermore, circulating BDNF levels are decreased in patients with obesity, type 2 diabetes, cardiovascular disease, depression, and Alzheimer’s disease (34).

**Interleukin-6 (IL-6)**

IL-6 was originally identified as a proinflammatory cytokine, synthesized by the liver and expressed in monocytes and macrophages, contributing to immune responses (1). However, IL-6 is also produced and released by skeletal muscle after prolonged exercise and may function as a myokine, independent from controlling inflammatory responses (39). It is well known that the level of circulating plasma IL-6 as well as expression of IL-6 receptor in skeletal muscle are upregulated after exercise (40, 41). By contrast, the plasma TNF-α level was not increased by exercise and only slightly increased in extremely strenuous exercise conditions such as marathons (40). IL-6 production in muscle is independent of nuclear factor-κB activation, and thus differs from the mechanism observed in immune cells (42). IL-6 has beneficial effects on muscle formation and growth (39). IL-6 knockout mice showed impaired hypertrophic muscle growth, which is attributed to blunted accretion of myonuclei.
Moreover, several studies suggest that IL-6 acts as a myokine in other organs. Exercise decreases visceral adipose tissues and this effect of exercise is abrogated by IL-6 blockade (43). IL-6 contributes to hepatic glucose production during exercise (44). IL-6 also enhances fat oxidation in skeletal muscle via AMPK activation and increases lipolysis in skeletal muscle with little effect on adipose tissue (39). Additionally, glucose uptake and fatty acid oxidation by IL-6 in skeletal myotube were abolished by an AMPK-dominant negative construct, further suggesting a connection between exercise, AMPK, IL-6, and metabolism (45). Adult IL-6 knockout mice show impaired neurogenesis suggesting that lack of IL-6 might be detrimental to neurogenesis in the adult brain (46). Collectively, induction of IL-6 appears to contribute to the metabolic and neurogenic effects generated by physical exercise.

**AMP-activated protein kinase (AMPK)**

AMPK is the master regulator of metabolism sensing energy supplies (47). AMPK is activated in skeletal muscle during exercise in response to increased binding of AMP and decreased binding of ATP (48). Transgenic mice carrying inactive muscle-specific AMPK showed reduced exercise capacity and impaired glucose tolerance and insulin response (49). AMPK activation is required for exercise-induced mitochondrial biogenesis via PGC-1α (47). Many studies showed that the AMPK activator, 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) mimics the effects of exercise. AICAR consumption alone enhanced running endurance by 44% and metabolic genes in sedentary mice (50). AICAR increases the levels of glucose transporter type 4 (GLUT4) and mitochondrial enzyme in skeletal muscle (51). AICAR also increases angiogenesis and vascularization by inducing VEGF-A expression, which in turn facilitates stable supply of oxygen and nutrients similar to exercise (52). AICAR was used as a "next-generation" performance-enhancing drug in the Olympic Spanish Cycling Team, and a sports doctor was arrested for doping (2).

AICAR also has a positive effect on other organs. AICAR reduces circulating levels of triglyceride and blood pressure and promotes hepatic fat consumption (53). Further, AICAR inhibits inflammatory response and cytokine levels. AICAR inhibits NF-κB DNA binding and cytokine expression in human macrophages (54). Notably, AICAR treatment improved spatial memory and neurogenesis in spite of the poor permeability through the blood-brain barrier, suggesting that the positive effect of AICAR in the brain is probably due to the indirect effect of AMPK activation in other organs (52, 55). AICAR improved cognition and motor function in mice, but it was abolished in mice carrying mutant muscle-specific AMPKα2 (56). These results suggest the importance of muscle AMPK activation on the effects of AICAR in brain. Although it was a transient effect, AICAR also enhanced hippocampus cell number and BDNF protein levels in mice (57).

**Peroxisome proliferator-activated receptor δ (PPARδ)**

PPARs are a family of nuclear hormone receptors that sense metabolic status and are involved in lipid metabolism (58). There are three isoforms, PPARα, β/δ, and γ, and PPARδ is the predominant form in skeletal muscle (59). Selective PPARδ agonist GW501516 increased the number of oxidative myofibers and the level of running endurance in adult mice (50). Exercise-induced performance improvement was attenuated in PPARδ-deficient mice (8). These effects are attributed to PPARδ-induced suppression of glucose catabolism; glucose sparing delays hypoglycemia and extends running time (8). PPARδ overexpression increases AMPK activity, and PPARδ activity is also stimulated by AMPK (60). PPARδ also plays a critical role in metabolic diseases. Constitutive PPARδ activation in mouse adipocytes resulted in reduced fat composition and prevented high-fat diet-induced obesity (61). GW501516 also induces fatty acid oxidation and ameliorates obesity and insulin resistance in mice (62). In obese monkeys, GW501516 attenuated dyslipidemia, lowering triglyceride and LDL-c levels while increasing HDL-c (63). Cardiomyocyte-restricted PPARδ knockout decreased the rate of fatty acid oxidation, resulting in lipid accumulation in the heart (64).

GW501516 has a positive effect on the brain, although it hardly crosses the blood-brain barrier. Administration of GW501516 improves hippocampal neurogenesis and spatial memory (55). These results suggest that the positive effect of GW501516 on the brain is likely due to the indirect exercise mimetic effects (52). GW501516 was developed because of its possible beneficial effects on metabolic diseases and cardiovascular diseases, but its carcinogenic properties were identified in animal studies (52). The discovery of safer small molecules that can increase PPAR activity can be a strategy to develop exercise mimetics.

**Estrogen-related receptor γ (ERRγ)**

ERRγ is a member belonging to the nuclear receptor super-family and plays a key role in regulating skeletal muscle adaptation to exercise through regulating mitochondria biogenesis, angiogenesis, and oxidative muscle remodeling (65-67). Transgenic mice expressing ERRγ in skeletal muscle exhibit red muscles, larger mitochondria, and improved oxidative capacity and vascularization (68, 69). ERRγ is highly expressed in oxidative and vascularized muscle and is induced by endurance exercise (65). While ERRγ-induced oxidative muscle transformation and vascularization is independent of PGC-1α (68), exercise and ERRγ individually and cooperatively attenuate muscle damage in PGC-1α knockout mice (67). ERRγ is recognized as a promising target of exercise mimetics because of its role in direct regulation of oxidative muscle remodeling (2). Further, overexpression of ERRγ attenuates the symptoms of Duchenne muscular dystrophy and muscle damage (70). These results suggested that genetic activation of ERRγ led to exercise-like phenotype in...
skeletal muscle with positive effects towards muscular disease (47). However, only a few studies reported the effects of ERRγ agonist on skeletal muscle or muscular disease. ERRγ agonist GSK4716 increases genes involved in mitochondrial biogenesis, fatty acid oxidation, and TCA cycle in mouse myotubes (69).

However, studies on activating ERRγ in other organs have not always met with positive results. ERRγ was reported to block hepatic insulin signaling via transcriptionally regulating LIPI1 expression (71). Inverse agonist of ERRγ also ameliorates chronic alcohol-induced liver injury in mice (72). Also, treatment with an inverse agonist of ERRγ resulted in antimicrobial effect and improved host survival (73). However, the systemic effect of ERRγ activation in various organs or diseases requires further examination.

THE NEED FOR DEVELOPING EXERCISE MIMETICS FROM NATURAL PRODUCTS

Exercise mimetics should have physiological effects in various tissues or organs in order to mimic the pleiotropic effects of physical exercise. Modulating the activity or expression of a single gene may not be sufficient to generate the multiple effects observed in exercise. Also, as physical exercise induces broad-ranging effects on various types of cells, tissues, and organs, it is highly unlikely that a single pharmacological agent can mimic the complex and wide-ranging effects. However, the combination of compounds affecting two different exercise-mediated targets has been shown to elicit synergistic effects in terms of mimicking the response to exercise (50). Hence, multi-targeting pharmacological agents have a greater potential to simulate the effect of exercise rather than single-targeting compounds. In this regard, exercise mimetics may be more effective if designed as a polypill, for polypills could target multiple pathways to closely simulate the complexity of the exercise response. Some natural bioactive compounds have been shown to display multi-targeting effects (74, 75). While compounds with less selectivity are generally not favored in the conventional drug discovery concept, certain compounds with the right combination of multi-targets may be useful in the case of exercise mimetics. In this context, natural extracts containing various compounds or multi-targeting compounds could have benefits for a potential exercise mimic.

Further, the constant activation of metabolic pathways by exercise mimetics can induce a chronic catabolic state, with potentially deleterious outcomes (15). It is likely that exercise mimetics would be applied for a long period for the purpose of maintaining health and preventing diseases, and since natural products are safer, they may more suitable than drugs for long-term consumption. Considering the side effects induced by the use of single-targeting drugs, natural products may be preferred as exercise mimetics. Several natural products have been identified to increase skeletal muscle mass, strength, and function. However, the effects on various organs and the relationship between skeletal muscle and other organs should be investigated to develop exercise mimetics. Table 1 lists natural compounds used as exercise mimetics base on in vivo studies. The exercise mimetic effects observed in muscle (e.g. increased skeletal muscle mass, strength, and exercise capacity) and in other tissues/organisms are separately described.

CANDIDATES FOR NATURAL EXERCISE MIMETICS

Resveratrol, a stilbene-structured compound naturally occurring in plants, increased oxidative muscle fibers by regulating the AMPK-PGC-1α pathway, and enhanced grip strength, and exercise capacity in high-fat diet-induced obese mouse model (52, 76). Notably, resveratrol increased serum BDNF concentration, a myokine increased by exercise, and it is possible that the positive effects on muscle are mediated by activating AMPK as BDNF contributes to anti-atrophic effect of exercise via the AMPK-PGC-1α pathway (36, 77). Ursolic acid, a natural triterpene compound found in various fruits and vegetables, induced exercise mimetic effects in various animal models (Table 1) (78). It also increased serum irisin levels and maximal muscle strength in a clinical study, suggesting that ursolic acid may exert other health beneficial effects in humans (79). Apigenin, a natural flavone abundant in various plants such as parsley and celery, increases serum irisin and FNDC5 mRNA expression in skeletal muscle (80). Apigenin also restored isoflavone-induced BDNF suppression in aged rat hippocampus and high-fat diet-induced downregulation of AMPK phosphorylation in skeletal muscle (81, 82). These may explain some of the health benefits of apigenin including improved cognitive function, insulin resistance, and the suppression of inflammation. Daidzein, a natural isoflavone found in soybean, suppresses ciplatin-induced muscle atrophy by regulating the Glut4/AMPK/FoxO pathway (83). Since it is unknown whether daidzein regulates AMPK in other tissues, it is not clear whether the health effects on other tissues are mediated via AMPK activation of skeletal muscle although soy isoflavone increased AMPK activity in visceral fat and 3T3-L1 cells (84). Quercetin is a natural flavonoid occurring in vegetables, fruits, tea, and wine (85). The target of quercetin has not been identified in relation with exercise mimetic effects, but quercetin increases BDNF level in the rat brain, which partially recapitulates exercise effects (32, 86). Tomatidine is abundant in green tomatoes but is typically reduced by 99% following ripening to red tomato (87). The exercise target of tomatidine is unknown, but it stimulates protein synthesis by increasing mTORC1 activity in mouse skeletal muscle and improves skeletal muscle function (87). Tomatidine also attenuates inflammation and nonalcoholic fatty liver disease and extends health span (88-90). Seaweeds Codium fragile and Undaria pinnatifida extracts improve running endurance and skeletal muscle mass by upregulating PPARY and ERRγ, AMPK and ERRγ, respectively (6, 91). γ-Oryzanol, containing a mixture of triterpene alcohols and sterol ferulates found in rice bran oil, is a well-known antioxidant used by body builders and athletes to boost strength and increase muscle gain (92). It improves...
| Name         | Model                              | Feeding period          | Effect on muscle                        | Target                | Other physiological effects | Ref       |
|--------------|------------------------------------|-------------------------|-----------------------------------------|-----------------------|----------------------------|-----------|
| Resveratrol  | Male KM mice 21 days               | 400 mg/kg for 12 weeks  | • Oxidative muscle fiber ↑              | AMPK                  | • Spatial memory ↑         | (52, 76, 77, 94) |
|              | High-fat diet-induced obesity model| 4 g/kg of food (400 mpk) | • Grip strength ↑                       |                       | • Serum BDNF ↑             |           |
|              |                                    | for 16 weeks            | • Rotarod activity ↑                    |                       | • Blood glucose, body weight↓ |           |
|              |                                    |                         |                                         |                       | • Immune system ↑          |           |
| Ursolic acid | High-fat diet-induced obesity model| 0.14% ursolic acid      | • Grip strength ↑                       |                       | • Tumors ↓                 | (78, 79, 95) |
|              | Fasting (24 hr) induced muscle atrophy model | 25 mg/ml ursolic acid twice injection for 24 hr | • Skeletal muscle mass ↑                |                       | • Fasting glucose ↓        |           |
|              | 10 months old male C57BL/6         | 200 mg/kg, twice a day for 7 days | • Type2a, slow-twitch fiber, myoglobin ↑ | AMPK                  | • Anti-obesity              |           |
|              | 22 months old male C57BL/6         | 0.27% ursolic acid for 2 months | • Grip strength ↑                       |                       | • Bone formation ↑         |           |
|              | Korean healthy men                 | 450 mg/d for 8 weeks    | • Maximal muscle strength ↑             | Irisin                | • Memory impairment ↓      |           |
| Apigenin     | High-fat diet-induced obesity model (9 weeks) | 0.1% apigenin diet for 8 weeks | • Muscle atrophy ↓                      | AMPK                  | • Inflammation ↓           |           |
|              | 6 weeks old male C57BL/6           | 0.2, 0.4% apigenin diet for 7 weeks | • Running endurance in treadmill ↑     |                       |                           |           |
|              | Sciatic nerve denervation-induced muscle loss model | 1% apigenin diet for 2 weeks | • Running endurance in treadmill ↑     | Irisin                |                           |           |
|              | 16 months old male C57BL/6         | 25, 50, 100 mg/kg/day for 9 months | • Skeletal muscle mass ↑                |                       |                           |           |
|              |                                    |                         | • Frailty index ↑                       |                       |                           |           |
| Daidzein     | Cisplatin induced muscle atrophy model | 20, 80 mg/kg daidzein for 12 days | • Frailty index ↑                       | AMPK                  | • Inflammation ↓           | (83, 99-103) |
|              | 8 week old female mice             | 0.1% daidzein for 1 week | • Frailty index ↑                       |                       | • Breast cancer ↓          |           |
|              |                                    |                         | • Grip strength ↑                       |                       | • Plasma lipid profile ↑   |           |
|              |                                    |                         | • Running endurance in treadmill ↑     |                       | • Fasting blood glucose ↓  |           |
|              |                                    |                         | • Spatial learning, memory ↑           |                       | • Obesity ↓                |           |
|              |                                    |                         | • BDNF level ↑                          |                       |                           |           |
Table 1. Continued

| Name | Model | Feeding period | Effect on muscle | Target | Other physiological effects | Ref |
|------|-------|----------------|------------------|--------|-----------------------------|-----|
| 5 Quercetin | High-fat diet-induced obesity model | 0.05%, 0.1% quercetin for 9 weeks | • Skeletal muscle mass ↑ | • Inflammation ↓ | (85, 86, 104-112) |
| | Dexemethasone induced muscle atrophy model | 0.15, 0.45% quercetin glycoside in drinking water for 7 days | • Skeletal muscle mass ↑ | • Insulin sensitivity ↑ | |
| | 24 week old male C57BL/6 mice | 1.5, 3.0 g/L quercetin glycoside in drinking water for 24 weeks | • Grip strength ↑ | • Cognitive function ↑ | |
| | 8 week old male ICR mice | 12.5, 24 mg/kg for 7 days | • Running endurance in treadmill ↑ | • BDNF expression ↑ | |
| | 26 male badminton players | 1000 mg per day for 2 months | • Voluntary wheel running ↑ | • Healthspan ↑ | |
| 6 Tomatidine | 7 week old male C57BL/6 | 0.05% tomatidine for 5 weeks | • Skeletal muscle mass ↑ | • Obesity ↓ | (87-90) |
| | Fasting-induced muscle atrophy model | 25 mg/kg tomatidine at the beginning of the fast and 12 h later | • Specific force ↑ | • Nonalcoholic fatty liver disease ↓ | |
| | Limb immobilization induced muscle atrophy model | 25 mg/kg tomatidine every 12 h for 8 days | • Specific force ↑ | • Lifespan, healthspan ↑ | |
| 7 Codium fragile extract | 19 week old male C57BL/6 mice | 0.1% Codium fragile extract diet for 10 weeks | • Running endurance in treadmill ↑ | PPARδ, ERα, AMPK, ERRγ | (91, 113-117) |
| | | | • Skeletal muscle mass ↑ | • Arterial thrombosis ↓ | |
| | | | | • Inflammatory cytokine ↓ | |
| | | | | • Anti-obesity | |
| 8 Undaria pinnatifida extract | 12 week old male C57BL/6 | 0.25% U pinnatifida extracts for 8 weeks | • Running endurance in treadmill ↑ | AMPK, ERRγ | (6, 118-122) |
| | | | • Skeletal muscle mass ↑ | • Growth and metastasis of cancer | |
| | | | | • Anti-obesity | |
| | | | | • Presynaptic Plasticity ↑ | |
| | | | | • Recover immunity | |
| | | | | • Insulin resistance ↓ | |
| | | | | • Anti-obesity | |
| | | | | • Inflammatory cytokine ↓ | |
| 9 γ-Oryzanol | 74 week old male C57BL/6 | 0.02% γ-Oryzanol diet for 13 weeks | • Running endurance in treadmill ↑ | PPARδ, ERRγ | (92, 123-128) |
| | | | • Grip strength ↑ | • Improve cognitive function | |
| | | | | • Antidepressant-like effect | |
| | | | | • Insulin resistance ↓ | |
| | | | | • Anti-obesity | |
| | | | | • Immune response ↑ | |
| | 32 health young men (18-32 yr) | 600 mg/day γ-Oryzanol and resistance training for 9 weeks | • Skeletal muscle strength ↑ | | |
| 10 Hydrangea serrata tea | 12 weeks old male C57BL/6 | 0.25%, 0.5% H. serrata extract for 6 weeks | • Running endurance in treadmill ↑ | PPARδ | (93, 129, 130) |
| | | | • Skeletal muscle mass ↑ | | |

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muscle function by upregulating PPARδ and ERRγ activity in skeletal muscle (92). *Hydrangea serrata* tea has an approximately 1000-fold higher sweetness than sugar and therefore has been used as a sugar substitute by diabetic patients. It also increases exercise endurance and muscle mass by enhancing PPARδ expression in the skeletal muscle (93). All of these exercise mimetics have been reported to exhibit health benefits beyond improving muscle function, suggesting the potential for development as a natural exercise mimic. A more comprehensive investigation is further needed to fully understand the health-promoting effect in connection with exercise.

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CONFLICTS OF INTEREST

The authors have no conflicting interests.

REFERENCES

1. Gubert C and Hannan AJ (2021) Exercise mimetics: harnessing the therapeutic effects of physical activity. Nat Rev Drug Discov 20, 862-879
2. Fan W and Evans RM (2017) Exercise mimetics: impact on health and performance. Cell Metab 25, 242-247
3. O’Gorman DJ, Karlsson HK, McQuaid S et al (2006) Exercise training increases insulin-stimulated glucose disposal and GLUT4 (SLC2A4) protein content in patients with type 2 diabetes. Diabetologia 49, 2983-2992
4. Ernst C, Olson AK, Pinel JP, Lam RW and Christie BR (2006) Antidepressant effects of exercise: evidence for an adult-neurogenesis hypothesis? J Psychiatry Neurosci 31, 84-92
5. Wang M, Baker JS, Quan W, Shen S, Fekete G and Gu Y (2020) A preventive role of exercise across the SARS-CoV-2 pandemic. Front Physiol 11, 572718
6. Ahn J, Ha TY, Ahn J et al (2020) Undaria pinnatifida extract feeding increases exercise endurance and skeletal muscle mass by promoting oxidative muscle remodeling in mice. FASEB J 34, 8068-8081
7. Egan B and Zierath JR (2013) Exercise metabolism and the molecular regulation of skeletal muscle adaptation. Cell Metab 17, 162-184
8. Fan W, Waizenegger W, Lin CS et al (2017) PPARdelta promotes running endurance by preserving glucose. Cell Metab 25, 1186-1193 e1184
9. Hughes DC, Ellesøen S and Baar K (2018) Adaptations to endurance and strength training. Cold Spring Harb Perspect Med 8, a029769
10. Bandy WD, Lovelace-Chandler V and McKitrick-Bandy B (1990) Adaptation of skeletal muscle to resistance training. J Orthop Sports Phys Ther 12, 248-255
11. Warburton DE, Nicol CW and Bredin SS (2006) Health benefits of physical activity: the evidence. CMAJ 174, 801-809
12. Mercken EM, Carboneau BA, Kryszk-Walker SM and de Cabo R (2012) Of mice and men: the benefits of caloric restriction, exercise, and mimetics. Ageing Res Rev 11, 390-398
13. Li S and Laher I (2017) Exercise mimetics: running without a road map. Clin Pharmacol Ther 101, 188-190
14. Carey AL and Kingwell BA (2009) Novel pharmacological approaches to combat obesity and insulin resistance: targeting skeletal muscle with ‘exercise mimetics’. Diabetologia 52, 2015-2026
15. Hawley JA, Joyner MJ and Green DJ (2021) Mimicking exercise: what matters most and where to next? J Physiol 599, 791-802
16. Lee JH and Jun HS (2019) Role of myokines in regulating skeletal muscle mass and function. Front Physiol 10, 42
17. Hartwig S, Raschke S, Knebel B et al (2014) Secretome profiling of primary human skeletal muscle cells. Biochim Biophys Acta 1844, 1011-1017
18. Chen N, Li Q, Liu J and Jia S (2016) Irisin, an exercise-induced myokine as a metabolic regulator: an updated narrative review. Diabetes Metab Res Rev 32, 51-59
19. Liu L, Guo J, Chen X, Tong X, Xu J and Zou J (2021) The role of irisin in exercise-mediated bone health. Front Cell Dev Biol 9, 668759
20. Lira VA, Benton CR, Yan Z and Bonen A (2010) PGC-1alpha regulation by exercise training and its influences on muscle function and insulin sensitivity. Am J Physiol Endocrinol Metab 299, E145-E161
21. Bostrom P, Wu J, Jedrychowski MP et al (2012) A PGC1-alpha-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature 481, 463-468
22. Reza MM, Subramaniam N, Sim CM et al (2017) Irisin is a pro-myogenic factor that induces skeletal muscle hypertrophy and rescues denervation-induced atrophy. Nat Commun 8, 1104
23. He W, Wang P, Chen Q and Li C (2020) Exercise enhances mitochondrial fission and mitophagy to improve myopathy following critical limb ischemia in elderly mice via the PGC1α/FNDC5/irisin pathway. Skelet Muscle 10, 25
24. Korta P, Pochec E and Mazur-Bialy A (2019) Irisin as a multifunctional protein: implications for health and certain diseases, Medicina (Kaunas) 55, 485
25. Mazur-Bialy A1, Bilski J, Pochec E and Brzozowski T (2017) New insight into the direct anti-inflammatory activity of a myokine irisin against proinflammatory activation of adipocytes. Implication for exercise in obesity. J Physiol Pharmacol 68, 243-251
26. Otero-Diaz B, Rodriguez-Flores M, Sanchez-Munoz V et al (2018) Exercise induces white adipose tissue browning across the weight spectrum in humans. Front Cell Dev Biol 9, 668759
27. Castillo-Quan JI (2012) From white to brown fat through virus 2 (SARS-CoV-2) pandemic. Front Physiol 9, 572718
28. Wrann CD, White JP, Salogiannnis J et al (2013) Exer-
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29. Islam MR, Varalis S, Young MF et al (2021) Exercise hormone irisin is a critical regulator of cognitive function. Nat Metab 3, 1058-1070

30. Liu PZ and Nusslock R (2018) Exercise-mediated neurogenesis in the Hippocampus via BDNF. Front Neurosci 12, 52

31. Gomez-Pinilla F, Ying Z, Roy RR, Molteni R and Edgerton VR (2002) Voluntary exercise induces a BDNF-mediated mechanism that promotes neuroplasticity. J Neurophysiol 88, 2187-2195

32. Soya H, Nakamura T, Deocaris CC et al (2007) BDNF induction with mild exercise in the rat hippocampus. Biochem Biophys Res Commun 358, 961-967

33. Nilsson J, Ekblom O, Ekblom M et al (2020) Acute increases in brain-derived neurotrophic factor in plasma following physical exercise relates to subsequent learning in older adults. Sci Rep 10, 4395

34. Bishop-Bailey D (2013) Mechanisms governing the health and performance benefits of exercise. Br J Pharmacol 170, 1153-1166

35. Yu T, Chang Y, Gao XL, Li H and Zhao P (2017) Dynamic expression and the role of BDNF in exercise-induced skeletal muscle regeneration. Int J Sports Med 38, 959-966

36. Zhang Z, Wang B and Fei A (2019) BDNF contributes to the skeletal muscle anti-atrophic effect of exercise training through AMPK-PGC1alpha signaling in heart failure mice. Arch Med Sci 15, 214-222

37. So B, Kim HJ, Kim J and Song W (2014) Exercise-induced myokines in health and metabolic diseases. Integr Med Res 3, 172-179

38. Motamedi S, Karimi I and Jafari F (2017) The interrelationship of metabolic syndrome and neurodegenerative diseases with focus on brain-derived neurotrophic factor (BDNF): kill two birds with one stone. Metab Brain Dis 32, 651-665

39. Munoz-Canoves P, Scheele C, Pedersen BK and Serrano AL (2013) Interleukin-6 myokine signaling in skeletal muscle: a double-edged sword? FEBS J 280, 4131-4148

40. Pedersen BK, Steensberg A, Fischer C et al (2003) Searching for the exercise factor: is IL-6 a candidate? J Muscle Res Cell Motil 24, 113-119

41. Pedersen BK and Fischer CP (2007) Beneficial health effects of exercise—the role of IL-6 as a myokine. Trends Pharmacol Sci 28, 152-156

42. Pedersen BK and Febbraio MA (2008) Muscle as an endocrine organ: focus on muscle-derived interleukin-6. Physiol Rev 88, 1379-1406

43. Weddell-Neegaard AS, Lang Lehrsok L, Christensen RH et al (2019) Exercise-induced changes in visceral adipose tissue mass are regulated by IL-6 signaling: a randomized controlled trial. Cell Metab 29, 844-855 e843

44. Febbraio MA, Hiscock N, Sacchetti M, Fischer CP and Pedersen BK (2004) Interleukin-6 is a novel factor mediating glucose homeostasis during skeletal muscle contraction. Diabetes 53, 1643-1648

45. Carey AL, Steinberg GR, Macaulay SL et al (2006) Interleukin-6 increases insulin-stimulated glucose disposal in humans and glucose uptake and fatty acid oxidation in vitro via AMP-activated protein kinase. Diabetes 55, 2688-2697

46. Bowen KK, Dempsey R and Vemuganti R (2011) Adult interleukin-6 knockout mice show compromised neurogenesis. Neureport 22, 126-130

47. Fan W, Atkins AR, Yu RT, Downes M and Evans RM (2013) Road to exercise mimetics: targeting nuclear receptors in skeletal muscle. J Mol Endocrinol 51, T87-T100

48. Richter EA and Ruderman NB (2009) AMPK and the biochemistry of exercise: implications for human health and disease. Biochem J 418, 261-275

49. Fuji N, Seifert MM, Kane EM et al (2007) Role of AMP-activated protein kinase in exercise capacity, whole body glucose homeostasis, and glucose transport in skeletal muscle -insight from analysis of a transgenic mouse model. Diabetes Res Clin Pract 77 Suppl 1, S92-S98

50. Narkar VA, Downes M, Yu RT et al (2008) AMPK and PPARdelta agonists are exercise mimetics. Cell 134, 405-415

51. Winder WW, Holmes BF, Rubink DS, Jensen EB, Chen M and Holloszy JO (2000) Activation of AMP-activated protein kinase increases mitochondrial enzymes in skeletal muscle. J Appl Physiol (1985) 88, 2219-2226

52. Guerrieri D, Moon HY and van Praag H (2017) Exercise in a pill: the latest on exercise-mimetics. Brain Plast 2, 153-169

53. Buhl ES, Jesten N, Pold R et al (2002) Long-term AICAR administration reduces metabolic disturbances and lowers blood pressure in rats displaying features of the insulin resistance syndrome. Diabetes 51, 2199-2206

54. Kirchner J, Brune B and Namgaladze DZ (2018) AICAR inhibits NFKappaB DNA binding independently of AMPK to attenuate LPS-triggered inflammatory responses in human macrophages. Sci Rep 8, 7801

55. Kobilo T, Yuan C and van Praag H (2011) Endurance factors improve hippocampal neurogenesis and spatial memory in mice. Learn Mem 18, 103-107

56. Kobilo T, Guerrieri D, Zhang Y, Collica SC, Becker KG and van Praag H (2014) AMPK agonist AICAR improves cognition and motor coordination in young and aged mice. Learn Mem 21, 119-126

57. Guerrieri D and van Praag H (2013) Exercise-mimetic AICAR transiently benefits brain function. Oncotarget 6, 18293-18313

58. Zizola C, Kennel PJ, Akashi H et al (2015) Activation of PPARdelta signaling improves skeletal muscle oxidative metabolism and endurance function in an animal model of ischemic left ventricular dysfunction. Am J Physiol Heart Circ Physiol 308, H1078-H1085

59. Braissant O, Foufelle F, Scotto C, Dauca M and Wahli W (1996) Differential expression of peroxisome proliferator-activated receptors (PPARs): tissue distribution of PPAR-alpha, -beta, and -gamma in the adult rat. Endocrinology 137, 354-366

60. Greene NP, Fluckey JD, Lambert BS, Greene ES, Riechneman SE and Crouse SF (2012) Regulators of blood lipids and lipoproteins? PPARdelta and AMPK, induced by exercise, are correlated with lipids and lipoproteins in overweight/
obese men and women. Am J Physiol Endocrinol Metab 303, E1212-E1221
61. Reilly SM and Lee CH (2008) PPAR delta as a therapeu-
tic target in metabolic disease. FEBS Lett 582, 26-31
62. Tanaka T, Yamamoto J, Iwasaki S et al (2003) Activation
of peroxisome proliferator-activated receptor delta induces
fatty acid beta-oxidation in skeletal muscle and attenuates
metabolic syndrome. Proc Natl Acad Sci U S A 100,
15924-15929
63. Oliver WR Jr, Shenk JL, Snaith MR et al (2001) A
selective peroxisome proliferator-activated receptor delta
agonist promotes reverse cholesterol transport. Proc Natl
Acad Sci U S A 98, 5306-5311
64. Cheng L, Ding G, Qin Q et al (2004) Cardiomyocyte-
65. Badin PM, Vila IK, Sopariwala DH et al (2016) Exercise-
like effects by Estrogen-related receptor-gamma in muscle
do not prevent insulin resistance in db/db mice. Sci Rep
6, 26442
66. Matsakas A, Macharia R, Otto A et al (2012) Exercise
training attenuates the hypermuscular phenotype and
restores skeletal muscle function in the myostatin null
mouse. Exp Physiol 97, 125-140
67. Fan W, He N, Lin CS et al (2018) ERRgamma promotes
angiogenesis, mitochondrial biogenesis, and oxidative
remodeling in PGC1alpha/beta-deficient muscle. Cell Rep
22, 2521-2529
68. Narkar VA, Fan W, Downes M et al (2011) Exercise and
PGC1alpha-independent synchronization of type I muscle
metabolism and vasculature by ERRgamma. Cell Metab
13, 283-293
69. Rangwala SM, Wang X, Calvo JA et al (2010) Estrogen-
related receptor gamma is a key regulator of muscle mito-
chondrial activity and oxidative capacity. J Biol Chem
285, 22619-22629
70. Matsakas A, Yadav V, Lorca S and Narkar V (2013) Muscle
ERRgamma mitigates Duchenne muscular dystrophy via
metabolic and angiogenic reprogramming. FASEB J 27,
4004-4016
71. Kim DK, Kim JR, Koh M et al (2011) Estrogen-related
receptor gamma (ERRgamma) is a novel transcriptional
regulator of phosphatidic acid phosphatase, LIPIN1, and
inhibits hepatic insulin signaling. J Biol Chem 286,
38035-38042
72. Kim DK, Kim YH, Jang HH et al (2013) Estrogen-related
receptor gamma controls hepatic CB1 receptor-mediated
CYP2E1 expression and oxidative liver injury by alcohol.
Gut 62, 1044-1054
73. Kim DK, Jeong IH, Lee JM et al (2014) Inverse agonist of
estrogen-related receptor gamma controls Salmonella typhi-
murium infection by modulating host iron homeostasis.
Nat Med 20, 419-424
74. Byun S, Lim S, Mun JY et al (2015) Identification of a
dual inhibitor of janus kinase 2 (JAK2) and p70 ribo-
somal S6 kinase1 (S6K1) pathways. J Biol Chem 290, 23553-
23562
75. Shin EJ, Lee JS, Hong S, Lim TG and Byun S (2019)
Quercetin directly targets JAK2 and PKCdelta and pre-
vents UV-induced photoaging in human skin. Int J Mol
Sci 20, 5262
76. Jiang Q, Cheng X, Cui Y et al (2019) Resveratrol
regulates skeletal muscle fibers switching through the
Adipor1-AMPK/PGC-1alpha pathway. Food Funct 10,
3334-3343
77. Wicinski M, Malinowski B, Weclawicz MM, Grzesk E
and Grzesk G (2017) Resveratrol increases serum DBNF
congenations and reduces vascular smooth muscle cells
contractility via a NOS-3-independent mechanism.
Biomed Res Int 2017, 9209254
78. Seo DY, Lee SR, Heo JW et al (2018) Ursolic acid in
health and disease. Korean J Physiol Pharmacol 22,
235-248
79. Bang HS, Seo DY, Chung YM et al (2014) Ursolic
Acid-induced elevation of serum irisin augments muscle
strength during resistance training in men. Korean J Physiol
Pharmacol 18, 441-446
80. Jang YJ, Son HJ, Choi YM, Ahn J, Jung CH and Ha TY
(2017) Apigenin enhances skeletal muscle hypertrophy
and myoblast differentiation by regulating Pmmt7. Oncotarget
8, 78300-78311
81. Shen L, Xie W, Xie W, Zhuang W, Jiang C and Liu N
(2017) Apigenin attenuates isoflurane-induced cognitive
dysfunction via epigenetic regulation and neuroinflamma-
tion in aged rats. Arch Gerontol Geriatr 73, 29-36
82. Choi WH, Son HJ, Jang YJ, Ahn J, Jung CH and Ha TY
(2017) Apigenin ameliorates the obesity-induced skeletal
muscle atrophy by attenuating mitochondrial dysfunction
in the muscle of obese mice. Mol Nutr Food Res 61,
1700218
83. Zhang H, Chi M, Chen L et al (2021) Daidzein alleviates
cisplatin-induced muscle atrophy by regulating Glut4/AMPK/
FoxO pathway. Phytheres Res 35, 4363-4376
84. Tan J, Huang C, Luo Q et al (2019) Soy isoflavones
ameliorate fatty acid metabolism of visceral adipose
tissue by increasing the AMPK activity in male rats with
diet-induced obesity (DIO). Molecules 24, 2809
85. Zhao Y, Chen B, Shen J et al (2017) The beneficial effects
of quercetin, curcumin, and resveratrol in obesity. Oxid
Med Cell Longev 2017, 1459497
86. Rahvar M, Ovij AA and Mashayekhi FJ (2018) Effect of
quercetin on the brain-derived neurotrophic factor gene
expression in the rat brain. Bratisl Lek Listy 119, 28-31
87. Dyle MC, Ebet SM, Cook DP et al (2014) Systems-based
discovery of tomatidine as a natural small molecule in-
hibitor of skeletal muscle atrophy. J Biol Chem 289,
14913-14924
88. Kuo CY, Huang WC, Liou CJ, Chen LC, Shen JJ and Kuo
ML (2017) Tomatidine attenuates airway hyperrespon-
siveness and inflammation by suppressing Th2 cytokines
in a mouse model of asthma. Mediators Inflamm 2017,
5261803
89. Wu SJ, Huang WC, Yu MC et al (2021) Tomatidine
ameliorates obesity-induced nonalcoholic fatty liver disease
in mice. J Nutr Biochem 91, 108602
90. Fang EF, Waltz TB, Kassahun H et al (2017) Tomatidine
attenuates the hypermuscular phenotype and myoblast
differentiation in PGC1alpha/beta-deficient muscle. Cell Rep
8, 78300-78311
91. Matsakas A, Macharia R, Otto A et al (2012) Exercise
training attenuates the hypermuscular phenotype and
restores skeletal muscle function in the myostatin null
mouse. Exp Physiol 97, 125-140
92. Fan W, He N, Lin CS et al (2018) ERRgamma promotes
angiogenesis, mitochondrial biogenesis, and oxidative
remodeling in PGC1alpha/beta-deficient muscle. Cell Rep
22, 2521-2529
93. Narkar VA, Fan W, Downes M et al (2011) Exercise and
PGC1alpha-independent synchronization of type I muscle
metabolism and vasculature by ERRgamma. Cell Metab
13, 283-293
94. Rangwala SM, Wang X, Calvo JA et al (2010) Estrogen-
related receptor gamma is a key regulator of muscle mito-
chondrial activity and oxidative capacity. J Biol Chem
285, 22619-22629
95. Matsakas A, Yadav V, Lorca S and Narkar V (2013) Muscle
ERRgamma mitigates Duchenne muscular dystrophy via
metabolic and angiogenic reprogramming. FASEB J 27,
4004-4016
96. Kim DK, Kim JR, Koh M et al (2011) Estrogen-related
receptor gamma (ERRgamma) is a novel transcriptional
regulator of phosphatidic acid phosphatase, LIPIN1, and
inhibits hepatic insulin signaling. J Biol Chem 286,
38035-38042
97. Kim DK, Kim YH, Jang HH et al (2013) Estrogen-related
receptor gamma controls hepatic CB1 receptor-mediated
CYP2E1 expression and oxidative liver injury by alcohol.
Gut 62, 1044-1054
98. Kim DK, Jeong IH, Lee JM et al (2014) Inverse agonist of
estrogen-related receptor gamma controls Salmonella typhi-
murium infection by modulating host iron homeostasis.
Nat Med 20, 419-424
99. Byun S, Lim S, Mun JY et al (2015) Identification of a
dual inhibitor of janus kinase 2 (JAK2) and p70 ribo-
somal S6 kinase1 (S6K1) pathways. J Biol Chem 290, 23553-
23562
100. Shin EJ, Lee JS, Hong S, Lim TG and Byun S (2019)
Quercetin directly targets JAK2 and PKCdelta and pre-
vents UV-induced photoaging in human skin. Int J Mol
Sci 20, 5262
91. Ahn J, Kim MJ, Yoo A et al (2021) Identifying Codium fragile extract components and their effects on muscle weight and exercise endurance. Food Chem 353, 129463
92. Ahn J, Son HJ, Seo HD et al (2021) Gamma-oryzanol improves exercise endurance and muscle strength by up-regulating PPARdelta and ERRgamma activity in aged mice. Mol Nutr Food Res 65, e2000652
93. Jang YJ, Ahn J, Son HJ, Jung CH, Ahn J and Ha TY (2019) Hydrangea serrata tea enhances running endurance and skeletal muscle mass. Mol Nutr Food Res 63, e1801149
94. Malaguarnera L (2019) Influence of resveratrol on the immune response. Nutrients 11, 946
95. Kunkel SD, Suneja M, Ebert SM et al (2011) mRNA expression signatures of human skeletal muscle atrophy: identify a natural compound that increases muscle mass. Cell Metab 13, 627-639
96. Choi WH, Jang YJ, Son HJ, Ahn J, Jung CH and Ha TY (2018) Apigenin inhibits sciatric nerve denervation-induced muscle atrophy. Muscle Nerve 58, 314-318
97. Wang D, Yang Y, Zou X, Zhang J, Zheng Z and Wang Z (2020) Antioxidant apigenin relieves age-related muscle atrophy by inhibiting oxidative stress and hyperactive mitophagy and apoptosis in skeletal muscle of mice. J Gerontol A Biol Sci Med Sci 75, 2081-2088
98. Salehi B, Venditti A, Sharifi-Rad M et al (2019) The emerging impact of quercetin in the treatment of prostate cancer. Biomed Pharmacother 138, 111548
99. Davis JM, Murphy EA, Carmichael MD and Davis B (2009) Quercetin increases brain and muscle mitochondrial biogenesis and exercise tolerance. Am J Physiol Regul Integr Comp Physiol 296, R1071-R1077
100. Ogawa M, Kitano T, Kawata N et al (2017) Daidzein regulates proinflammatory adipokines and insulin action in skeletal muscle of ob/ob mice. J Nutr Food Sci 9, 760
101. Davis JM, Murphy EA, Carmichael MD and Davis B (2009) Quercetin increases brain and muscle mitochondrial biogenesis and exercise tolerance. Am J Physiol Regul Integr Comp Physiol 296, R1071-R1077
102. Liu X, Suzuki N, Santosh Laxmi YR, Okamoto Y and Sakamoto Y, Naka A, Ohara N, Kondo K and Iida K (2018) Daidzein regulating proinflammatory adipokines thereby improving obesity-related adipokines and obesity-associated type 2 diabetes. Biofactors 44, 407-417
103. Das D, Sarkar S, Bordoloi J, Wann SB, Kalita J and Manna P (2018) Daidzein, its effects on impaired glucose and lipid metabolism and vascular inflammation associated with type 2 diabetes. Biofactors 44, 407-417
104. Le NH, Kim CS, Park T et al (2014) Quercetin protects against obesity-induced skeletal muscle inflammation and atrophy. Mediators Inflamm 2014, 834294
105. Anhe GF, Okamoto MM, Kinote A et al (2012) Quercetin decreases inflammatory response and increases insulin action in skeletal muscle of db/db mice and in L6 myotubes. Eur J Pharmacol 689, 285-293
106. Otsuka Y, Egawa K, Kanzaki N, Izumo T, Rogi T and Shibata H (2019) Quercetin glycosides prevent temperature-induced muscle atrophy in mice. Biochem Biophys Rep 18, 100618
107. Ghafoori-Fard S, Shabestari FA, Vaezi S et al (2021) Emerging impact of quercetin in the treatment of prostate cancer. Biomed Pharmacother 138, 111548
108. Geng L, Liu Z, Wang S et al (2019) Low-dose quercetin positively regulates mouse healthspan. Protein Cell 10, 770-775
109. Kanzaki N, Takemoto D, Ono Y et al (2019) Quercetin glycosides improve motor performance and muscle weight in adult mice. J Nutr Food Sci 9, 760
110. Davis JM, Murphy EA, Carmichael MD and Davis B (2009) Quercetin increases brain and muscle mitochondrial biogenesis and exercise tolerance. Am J Physiol Regul Integr Comp Physiol 296, R1071-R1077
111. Daneshwar P, Hariri M, Ghiassvand R et al (2013) Effect of eight weeks of quercetin supplementation on exercise performance, muscle damage and body muscle in male badminton players. Int J Prev Med 4, 553-557
112. Dajas F, Abin-Carrizy QA, Arendondo F et al (2015) Quercetin in brain diseases: Potential and limits. Neurochem Int 89, 140-148
113. Kim TI, Kim YJ and Kim K (2021) Extract of seaweed Codium fragile inhibits integrin alphabeta3-induced outside-in signaling and arterial thrombosis. Front Pharmacol 12, 685948
114. Yang Y, Lim J, Li C, Lee S and Hong S (2021) Effects of sulfated polysaccharides isolated from Codium fragile on inflammatory cytokine gene expression and Edwardsiella tarda infection in rockfish, Sebastes schlegeli. Fish Shellfish Immunol 112, 125-134
115. Park HB, Hwang J, Zhang W et al (2020) Polysaccharide from Codium fragile induces anti-cancer immunity by activating natural killer cells. Mar Drugs 18, 626
116. Monnai C, Rod-In W, Jang AY et al (2020) Immune-enhancing effects of anionic macromolecules extracted from Codium fragile coupled with arachidonic acid in RAW264.7 cells. PLoS One 15, e0239422
117. Kolisi RBA, Jardak N, Hajkacem F et al (2017) Anti-obesity effect and protection of liver-kidney functions by Codium fragile sulphated polysaccharide on high fat diet induced obese rats. Int J Biol Macromol 102, 119-129
118. Eltman SM, Mehanna RA, Bary AA, Elnaggar YSR and Abdallah OY (2021) Undaria pinnatifida fucoidan-rich extract recovers immunity of immunosuppressed mice. J Microbiol Biotechnol 30, 439-529
119. Maqueshudul Haque Bhuiyan M, Mohibbullah M, Hannan MA et al (2015) Undaria pinnatifida fucoidan nanoparticles loaded with quinacrine attenuate growth and metastasis of pancreatic cancer. Int J Biol Macromol 170, 284-297
120. Li L, Wang Y, Yuan J, Liu Z, Ye C and Qin S (2020) Undaria pinnatifida improves obesity-related outcomes in association with gut microbiota and metabolomics modulation in high-fat diet fed mice. Appl Microbiol Biotechnol 104, 10217-10231
121. Marqueshudul Haque Bhuiyan M, Mohibbullah M, Hannan MA et al (2015) Undaria pinnatifida fucoidan nanoparticles loaded with quinacrine attenuate growth and metastasis of pancreatic cancer. Int J Biol Macromol 170, 284-297
122. Lee HH, Cho Y, Kim GH and Cho H (2020) Undaria pinnatifida fucoidan-rich extract recovering immunity of immunosuppressed mice. J Microbiol Biotechnol 30, 439-447
123. Oh JH, Kim J and Lee Y (2016) Anti-inflammatory and anti-diabetic effects of brown seaweeds in high-fat diet-induced obese mice. Nutr Res Pract 10, 42-48
124. Rungratanawanich W, Cenini G, Mastinu A et al (2019) Gamma-oryzanol improves cognitive function and modu-
lates hippocampal proteome in mice. Nutrients 11, 753
124. Araujo SM, Bortolotto VC, Poetini MR et al (2021) Gamma-oryzanol produces an antidepressant-like effect in a chronic unpredictable mild stress model of depression in Drosophila melanogaster. Stress 24, 282-293
125. De Mattei L, Francisqueti-Ferron FV, Garcia JL et al (2021) Antioxidant and anti-inflammatory properties of gamma-oryzanol attenuates insulin resistance by increasing GLUT-4 expression in skeletal muscle of obese animals. Mol Cell Endocrinol 537, 111423
126. Wang L, Lin Q, Yang T et al (2017) Oryzanol modifies high fat diet-induced obesity, liver gene expression profile, and inflammation response in mice. J Agric Food Chem 65, 8374-8385
127. Shin SY, Kim HW, Jang HH et al (2017) Gamma-oryzanol-rich black rice bran extract enhances the innate immune response. J Med Food 20, 855-863
128. Eslami S, Esa NM, Marandi SM, Ghasemi G and Eslami S (2014) Effects of gamma oryzanol supplementation on anthropometric measurements & muscular strength in healthy males following chronic resistance training. Indian J Med Res 139, 857-863
129. Han HS, Lee HH, Gil HS et al (2021) Standardized hot water extract from the leaves of Hydrangea serrata (Thunb.) Ser. alleviates obesity via the AMPK pathway and modulation of the gut microbiota composition in high fat diet-induced obese mice. Food Funct 12, 2672-2685
130. Myung DB, Han HS, Shin JS et al (2019) Hydrangenol isolated from the leaves of hydrangea serrata attenuates wrinkle formation and repairs skin moisture in uvb-irradiated hairless mice. Nutrients 11, 2354