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Invited Mini Review

Molecular targets of exercise mimetics and their natural activators

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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 not 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.

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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-

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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 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 upregulating 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

(39). 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 appears to interact with AMPK and synergistically regulates exercise endurance genes (50). In line with this, GW501516 has been listed as an illegal drug by the World Anti-Doping Agency similar to AICAR (52).

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 LIPIN1 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 mimetic.

Further, the constant activation of metabolic pathways of 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 for 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/organs 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 isoflurane-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 cisplatin-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 PPARδ 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

Table 1. Candidates of exercise mimetics from natural sources

	Name	Model	Feeding period	Effect on muscle	Target	Other physiological effects	Ref
1	Resveratrol	Male KM mice 21 days	400 mg/kg for 12 weeks	・Oxidative muscle fiber ↑	AMPK	・Spatial memory ↑ ・Neurogenesis ↑ ・Serum BDNF ↑ ・Blood glucose, body weight ↓ ・Immune system ↑	(52, 76, 77, 94)
		High-fat diet-induced obesity model	4 g/kg of food (400 mpk) for 16 weeks	・Grip strength ↑ ・Rotarod activity ↑			
2	Ursolic acid	High-fat diet-induced obesity model	0.14% ursolic acid for 6 weeks	・Grip strength ↑ ・Skeletal muscle mass ↑ ・Running endurance in treadmill ↑		・Tumors ↓ ・Fasting glucose ↓ ・Anti-obesity ・Bone formation ↑ ・Memory impairment ↓ ・Inflammation ↓	(78, 79, 95)
		Fasting (24 hr) induced muscle atrophy model	25 mg/ml ursolic acid twice injection for 24 hr	・Skeletal muscle mass ↑			
		10 months old male C57BL/6	200 mg/kg, twice a day for 7 days	・Type2a, slow-twitch fiber, myoglobin ↑	AMPK		
		22 months old male C57BL/6	0.27% ursolic acid for 2 months	・Grip strength ↑ ・Skeletal muscle mass ↑ ・Specific force ↑			
		Korean healthy men	450 mg/day for 8 weeks	・Maximal muscle strength	Irisin		
3	Apigenin	High-fat diet-induced obesity model (9 weeks)	0.1% apigenin diet for 8 weeks	・Muscle atrophy ↓ ・Running endurance in treadmill ↑	AMPK	・Cognitive function by regulating BDNF signaling ↑ ・Reverse depression by upregulating BDNF ・Blood glucose, serum lipid, insulin resistance index ↓ ・Tumor growth ↓ ・Inflammation ↓	(80-82, 96-99)
		6 weeks old male C57BL/6	0.2, 0.4% apigenin diet for 7 weeks	・Running endurance in treadmill ↑ ・Skeletal muscle mass ↑	Irisin		
		Sciatic nerve denervation-induced muscle loss model	1% apigenin diet for 2 weeks	・Muscle atrophy ↓			
		16 months old male C57BL/6	25, 50, 100 mg/kg/day for 9 months	・Frailty index ↑ ・Grip strength ↑ ・Running endurance in treadmill ↑ ・Muscle atrophy ↓			
4	Daidzein	Cisplatin induced muscle atrophy model	20, 80 mg/kg daidzein for 12 days	・Skeletal muscle mass ↑ ・Grip strength ↑	AMPK	・Inflammation ↓ ・Breast cancer ↓ ・Plasma lipid profile ↑ ・Fasting blood glucose ↓ ・Insulin resistance ↑ ・Obesity ↓ ・Spatial learning, memory ↑ ・BDNF level ↑	(83, 99-103)
		8 week old female mice	0.1% daidzein for 1 week	・Skeletal muscle mass ↑			

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 ↓ • Insulin sensitivity ↑ • Cognitive function ↑ • BDNF expression ↑ • Healthspan ↑ • Obesity ↓	(85, 86, 104-112)
		Dexamethasone induced muscle atrophy model	0.15, 0.45% quercetin glycoside in drinking water for 7 days	• Skeletal muscle mass ↑			
		24 week old male C57BL/6 mice	1.5, 3.0 g/L quercetin glucoside in drinking water for 24 weeks	• Grip strength ↑ • Rotarod time ↑ • Skeletal muscle mass ↑			
		8 week old male ICR mice	12.5, 24 mg/kg for 7 days	• Running endurance in treadmill ↑ • Voluntary wheel running ↑			
		26 male badminton players	1000 mg per day for 2 months	• Endurance exercise performance ↑			
6	Tomatidine	7 week old male C57BL/6	0.05% tomatidine for 5 weeks	• Skeletal muscle mass ↑ • Specific force ↑ • Grip strength ↑		• Inflammation ↓ • Nonalcoholic fatty liver disease ↓ • Lifespan, healthspan ↑	(87-90)
		Fasting-induced muscle atrophy model	25 mg/kg tomatidine at the beginning of the fast and 12 h later	• Skeletal muscle mass ↑ • Specific force ↑			
		Limb immobilization induced muscle atrophy model	25 mg/kg tomatidine every 12 h for 8 days	• Skeletal muscle mass ↑			
7	*Codium fragile* extract	19 week old male C57BL/6 mice	0.1% Codium fragile extract diet for 10 weeks	• Running endurance in treadmill ↑ • Skeletal muscle mass ↑	PPARδ ERRγ	• Arterial thrombosis ↓ • Inflammatory cytokine ↓ • Anti-cancer immunity • Immune enhancing • Anti-obesity	(91, 113-117)
8	*Undaria pinnatifida* extract	12 week old male C57BL/6	0.25% U pinnatifida extracts for 8 weeks	• Running endurance in treadmill ↑ • Skeletal muscle mass ↑	AMPK ERRγ	• Growth and metastasis of cancer • Anti-obesity • Presynaptic Plasticity ↑ • Recover immunity • Insulin resistance ↓ • Inflammatory cytokine ↓	(6, 118-122)
9	γ-Oryzanol	74 week old male C57BL/6	0.02% γ-Oryzanol diet for 13 weeks	• Running endurance in treadmill ↑ • Grip strength ↑	PPARδ ERRγ	• Improve cognitive function • Antidepressant-like effect • Insulin resistance ↓ • Inflammation ↓ • Anti-obesity • Immune response ↑	(92, 123-128)
		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 8 weeks	• Running endurance in treadmill ↑ • Skeletal muscle mass ↑	PPARδ	• Anti-obesity • Inflammation ↓ • Total cholesterol and low-density lipoprotein, insulin ↓	(93, 129, 130)

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 mimetic. 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.

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