Abstract

Excessive exercise causes the loss of inherent physiological function of the muscles through skeletal muscle lesioning. This damage can induce various complications such as nerve injury, vascular lesions, and osteocytes damage. At the molecular level, reactive oxygen species (ROS) play an important role in the development of muscle damage. Although the excess production of ROS induces oxidative stress, these molecules are inevitably produced during the respiratory process of the human body. Therefore, ROS are important molecules in both physiological phenomena and as etiological factors. In the present review, we will address the role of antioxidants in skeletal muscle damage. Specifically, we will review studies suggesting that the intake of ginseng (the root of Panax ginseng C.A. Meyer) could be a strategy for treating skeletal muscle disorders. Ginseng is the most commonly consumed herbal medicine for increasing stamina in athletes. However, numerous athletes consume ginseng without understanding its pharmacological effects on the body. Hence, we will discuss the role of compound K in the biological and pharmacological effects of ginseng. In particular, we suggest that compound K is potentially useful against muscle damage.

[Keywords] Antioxidant, Exercise, Skeletal Muscle Damage, Panax Ginseng C.A. Meyer, Compound K

1. Introduction

The World Anti-Doping Agency (WADA), which was established by the International Olympic Committee (IOC), regulates sport-related doping. However, numerous athletes attending several international competitions still make the frequent mistakes of causing damage to their health or even death through medication abuse and misuse. Therefore, it is necessary to develop a reliable treatment to protect athletes. Natural compounds are rich in antioxidants that are essential to improve disease risk factors associated with reactive oxygen species (ROS) generation in the human body[1][2].

Especially, a recent influential medical report documented that ginseng has a central medical role in maintaining physical activity and psychological stability[3]. Compound K is an intestinal bacterial metabolite of ginsenoside. It has been reported to possess various pharmacological activities such as anticancer, antidiabetic, antiviral, anti-inflammation, antivascular disorders, and anti-osteoarthritis[4]. However, its protective effect on skeletal muscle damage remains unclear. In this study, we aimed to discuss the potential efficacy of compound K against skeletal muscle lesions. This review will demonstrate that compound K may be a potent muscle recovery agent that acts by regulating ROS-induced muscle damage.

2. Excessive Exercise-Induced Oxidative Stress in Skeletal Muscle

The Therapeutic Potential of Compound K, an Intestinal Metabolite Ginsenoside in SKELETAL MUSCLE DAMAGE

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Regular exercise activates the antioxidant enzymes in the human body, which are involved in several beneficial responses such as the reduction of lipid peroxidation, protection against tissue damage, and the improvement of endogenous ROS scavenging abilities. However, prolonged intense physical activity has been reported to lead to adverse effects in the muscle such as hyperfunctioning, temporary immunosuppression, and muscle cell damage[5][6][7]. Especially, repeated muscle contraction through high-intensity exercise is implicated in the accumulation of ROS, and the consequent myocyte death can lead to fatal injuries in athletes[8]. While muscle injury induces lesions and trauma, the membranes around the muscle tissue are also gradually damaged, leading to the loss of inherent physiological functions. Therefore, the regulation of ROS generation during exercise is critical and relevant to ensure recovery from muscle damage and improvement of performance[9][10][11].

3. Compound K

Ginseng, the root of Panax ginseng C.A. Meyer, is the most widely consumed herbal medicine worldwide. The major active component of ginseng is a saponin or ginsenoside, which has been identified in over 80 kinds of ginseng glycosides from various species. Ginsenosides are classified as protopanaxadiol, protopanaxatriol, oleanolic ginsenosides, and ginsenoside metabolites. <Figure 1> shows the chemical structure of a ginseng metabolite saponin, compound K, which is synthesized by the intestinal bacteria after the intake of ginseng.

Figure 1. Chemical structure of compound K.

(20 – O – β – (D-glucopyranosyl)-20(S) – protopanaxadiol)

4. Pharmacological Effects of Compound K

Recently, various studies have reported that ginsenosides exhibit a diverse range of pharmacological effects against cancer and degenerative diseases. Moreover, compound K, an intestinal metabolite ginsenoside, has various pharmacological activities in vivo and in vitro.

4.1. Anti-vascular disorder effect of compound K

Endothelial dysfunction and the activation of vascular smooth muscle cells such as their migration and proliferation are key mechanisms in the development of vascular lesions. These signaling pathways are involved in responses to intracellular oxidative stress and mitogen-activated protein kinase (MAPK) signals[12][13]. MAPKs consist of three kinases, extracellular signal-regulated kinase (ERK) 1/2, p38 MAPK (p38) and c-Jun N-terminal kinase (JNK).

As shown in <Figure 2>, compound K controls the major cellular mechanisms in the pathology of vascular disorders. Compound K induces the defense mechanisms that enhance the expression of endothelial nitric oxide synthase (eNOS), MAPKs, and protein kinase B (PKB, AKT) in endothelial cells. Furthermore, compound K diminished the migration and proliferation of smooth muscle cell through the regulation of phosphorylated (p)ERK[14].

Some studies and our present claim suggest that compound K suppresses the generation of ROS and MAPKs. Therefore, compound K is a potential therapeutic agent as well as a regulator of MAPKs.

Figure 2. Effect of compound K on vascular disorder.

Note: SMC: the smooth muscle cell, EC endothelial cells, eNOS: endothelial nitric oxide synthase, pERK1/2: phosphorylated extracellular signal-regulated kinase
4.2. Anticancer effects of compound K

In Western countries, cancer is the second leading cause of death. Hence, the development of effective chemopreventive agents from natural products is one of the important strategies for combating cancer. Furthermore, diverse studies have reported the anticancer effects of compound K against numerous types of cancer cells such as colon, gastric, bladder, and breast cancers, as well as hepatocarcinoma and leukemia[15-32]. As shown in Figure 3, the anticancer effect of compound K induces cell cycle arrest and apoptosis. The major pharmacological mechanism of compound K involves the activation of caspases or membrane potential-related apoptosis. The major pharmacological effect of compound K underlying its anticancer effect is apoptosis through the regulation of MAPKs.

4.3. Antidiabetic effects of compound K

The western dietary behavior and sedentary lifestyle may influence the development of diabetes. The number of individuals with diabetes worldwide is estimated to be at 380 million in the year 2025. Type 2 diabetes(TD2) is characterized by glucose metabolism disorders through insulin resistance and pancreatic dysfunction.

Interestingly, compound K, an intestinal metabolite ginsenoside, has shown pharmacological activity in a TD2 model. As shown in Figure 4, Compound K induced hypoglycemia by enhancing the secretion of insulin. The mediating signaling pathway involves the regulation of glucose transporter 2(GLUT2), and co-treatment with metformin and compound K showed a synergic effect on the underlying secretion of insulin. Furthermore, TD2 is a complex disorder, which involves immunosuppressive responses and, consequently, the activation of T-cells induced the death of pancreatic β-cell. Compound K inhibits T-cell activation by promoting the regulatory T-cell(Treg)[33][34].

4.4. Effects of compound K in osteoarthritis

Rheumatoid arthritis is caused by a chronic inflammation and autoimmune responses in the joint. Although the immune system of the body regulates homeostasis, chronic inflammation induces irreversible damage to the cartilage, tendons, and bones. Especially, the production of cytokines is implicated in T-cell
activation. The pathogenic mechanism involves the increased secretion of cytokines, which is recognized as a crucial damaging event. As shown in Figure 5, the major effect of compound K in arthritis is likely the regulation of immune responses against inflammation. Compound K significantly induced Treg, consequently suppressing the T-cell proliferation and related cytokine production. MAPKs are also involved in the phenomena underlying Treg-cell development[35][36][37].

Figure 5. Molecular mechanism of compound K in diabetes.

Figure 6. Possible mechanism of action of compound K in reactive oxygen species(ROS)-induced skeletal muscle damage.

Note: MAPK pathway, namely RAS-Raf-MEJ-ERK signaling, is the extracellular mitogen-bound signal pathways. MEK: mitogen-activated protein kinase kinase, ROS: reactive oxygen species.

Compound K, an intestinal bacterial metabolite of ginsenoside, is one of the therapeutic agents used against muscle damage by athletes during exercise. However, the data on the practical pharmacological and health implications of its use need to be further elucidated, especially for athletes.

In addition, further studies are required to establish the mechanisms underlying the antioxidant actions of compound K and determine its suitability for treatment. Ginseng has been used as a Korean traditional medicine for the enhancement of stamina. However, it is difficult for the body to effectively absorb the phytonutrients in ginseng because absorption capacity differs between individuals and involves the intestinal bacteria flora. The human intestine contains different types of intestinal bacteria, which help the digestion and absorption of nutrients. Therefore, we emphasize that there is an urgent need to improve the knowledge of suitable regimens and formulations for the rational intake of ginseng.
6. References

6.1. Journal articles


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