



Short review

Effects of ginseng on stress-related depression, anxiety, and the hypothalamic–pituitary–adrenal axis



Seungyeop Lee, Dong-Kwon Rhee*

School of Pharmacy, Sungkyunkwan University, 2066 Seobu-ro, Jangan-gu, Su-Won 16419, Republic of Korea

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ABSTRACT

Ginseng effectively regulates the immune response and the hormonal changes due to stress, thus maintaining homeostasis. In addition to suppressing the occurrence of psychological diseases such as anxiety and depression, ginseng also prevents stress-associated physiological diseases. Recent findings have revealed that ginseng is involved in adjusting the hypothalamic–pituitary–adrenal axis and controlling hormones, thus producing beneficial effects on the heart and brain, and in cases of bone diseases, as well as alleviating erectile dysfunction. Recent studies have highlighted the potential use of ginseng in the prevention and treatment of chronic inflammatory diseases such as diabetes, rheumatoid arthritis, and allergic asthma. However, the mechanism underlying the effects of ginseng on these stress-related diseases has not been completely established. In this review, we focus on the disease pathways caused by stress in order to determine how ginseng acts to improve health. Central to our discussion is how this effective and stable therapeutic agent alleviates the anxiety and depression caused by stress and ameliorates inflammatory diseases.

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1. Introduction

In order to survive, all organisms must manage the physical and psychological effects of a variety of stressful situations. Stress represents a necessary response that maintains *in vivo* homeostasis upon exposure to environmental changes. When affected by a certain stressor, changes occur in the human body. This programmed response is known as a stress response. Stress can be divided into four types: chronic eustress (too little stress), acute stress (optimum stress), acute distress (too much stress), and chronic stress (burnout). When stress increases beyond a certain level, it leads to adverse health effects. Furthermore, chronic stress can cause depression and/or anxiety [1]. Thus, in this review, we will consider the beneficial effects of ginseng on the multidimensional symptoms and typical diseases caused by stress.

Ginseng is traditionally used as a medicinal herb in Korea, Japan, China, and the United States [2,3]. The reason for this long-established usage is that ginseng contains natural antioxidant compounds. These ginsenosides, which are extracted from the ginseng roots, leaves, stems, and fruit, have multiple pharmacological effects. They are subdivided into about 100 different categories [4]. In many studies, ginsenosides have been presented as an

effective treatment for organ damage and cell death, as well as for immunological and metabolic diseases [5–7]. In addition, these pharmacologically active constituents have been shown to support neurogenesis, synaptogenesis, neuronal growth, and neurotransmission, thus helping to protect the central nervous system from unexpected events; ginseng is also reported to be excellent for improving memory [8,9].

As a powerful natural antioxidant, ginseng effectively modulates apoptosis by reducing the excessive inflammatory response in acute or chronic inflammation [10]. Abnormal apoptosis can result in functional impairment of organs. The human body contains many different protein types, and their interactions maintain the balance of mechanisms related to proliferation, differentiation, and apoptosis. When this homeostasis is disturbed, it can damage the immune system and lead to several fatal diseases [11,12].

Many studies conducted over the past decade have revealed that ginseng has a range of positive effects on the human body, but a systematic perspective on the efficacy of ginseng in the treatment of stress *in vivo* is not available. Therefore, this review will consider whether ginseng modulates human stress-related changes and diseases, and evaluate how ginseng could potentially act as a therapeutic agent for stress-induced diseases.

* Corresponding author. School of Pharmacy, Sungkyunkwan University, 2066 Seobu-ro, Jangan-gu, Suwon 16419, Republic of Korea.

E-mail address: dkrhee@skku.edu (D.-K. Rhee).

2. Ginseng and stress

Ginseng has been used as an adaptogen to treat illness, both as a tonic and as a rejuvenator. In modern societies, we rarely depend on herbal remedies as the only treatment for critical and potentially fatal diseases. However, owing to an excessive amount of brain activity, overwork, and group living conditions, modern life involves constant exposure to stress. Moreover, the level of stress can be sustained over time because of the repetitive nature of some occupations; this can cause detrimental biological stress responses. When under certain kinds of stress, the human body secretes hormones and inflammatory cytokines, and chronic stress can promote the development of anxiety, depression, and even panic disorders, in severe cases. Therefore, adaptogens are often used to cope with day-to-day and/or workplace stress. Ginseng shows superior regulation of stress, as compared with that shown by other adaptogens [13]. This efficacy as an antistress agent has been demonstrated using various behavioral conditioned stress tests, such as swimming and immobilization tests. *In vivo* studies have also shown that ginseng has excellent antistress effects, as compared to appropriate controls [14,15].

This article considers the adaptogenic effects of ginseng and focuses on whether these can mitigate any diseases. To achieve this, we will explore the physical changes and symptoms associated with stress, and discuss whether ginseng ameliorates these phenomena.

3. Stress hormones

Hormones act as chemical messengers and are vital regulators of biorhythms such as physical growth, appetite, blood pressure, emotion, sexual function, body temperature, sleep, and hydration. When the human body undergoes changes, various organs secrete hormones into the bloodstream. Hormones then bind with specific receptors in the cells of the target organs to regulate particular biological mechanisms. When subjected to stress, the stress hormone, cortisol, is secreted to counteract stress and maintain homeostasis. However, prolonged cortisol secretion results in immunosuppression. Cortisol is produced and regulated by a major hormonal control center, the hypothalamic–pituitary–adrenal (HPA) axis, regulated by the sympathetic nervous system [16].

The HPA plays a pivotal role in regulating the majority of the endocrine hormones associated with the central nervous system. External stimuli can trigger secretion of the corticotrophin-releasing hormone (CRH) and arginine vasopressin from the hypothalamus, the starting point of the HPA. These hormones then act at the core of the HPA, the pituitary gland. CRH constitutes the primary pathway regulating the secretion of adrenocorticotropin. Arginine vasopressin then acts on the pituitary gland after the CRH receptors have been desensitized. Adrenocorticotropin hormone then stimulates the adrenal cortex, the last region of the HPA, triggering the release of cortisol (in humans) and corticosterone (in humans, rats, and mice) [16,17] (Fig. 1).

Cortisol interacts with the cytoplasmic glucocorticoid receptor. This hormone-receptor complex moves to the nucleus and regulates the expression of several genes [21].

In this manner, cortisol regulates the expression levels of a number of messenger RNAs and the expression of important cytokines in various organs and immune cells in order to counteract the effects of stress, or to regulate the action of T lymphocytes in a number of diseases.

4. Ginseng and the HPA

When a person faces a stressful environment, ginseng can improve their response by regulating the function of the HPA axis

[22]. Ginseng also has applications beyond everyday use in healthy people. It provides a potential treatment agent for patients with HPA axis disorders associated with hypersecretion of cortisol, including depression, asthma, hypertension, and posttraumatic stress disorder [23]. Identification of the mechanisms underlying these effects of ginseng could have the potential to provide approaches to the prevention of various diseases (Fig. 1). Therefore, further research is needed to investigate how ginseng modulates hormone secretion.

5. Ginseng in depression and anxiety

Depression is a severe mental illness without any apparent physical symptoms. However, physical problems can emerge as depression becomes more advanced. About 10–30% of patients with depression are unable to overcome the initial stages, and eventually succumb to extreme physical harm; this includes committing suicide, inflicting self-harm, and developing drug dependence, which affects their quality of life. Furthermore, the prevalence of depression is increasing and this represents a major clinical challenge [24].

Ginseng effectively suppresses stress, which is a major cause of depression. This activity has been demonstrated in depression tests using animal models. Ginseng demonstrated similar levels of efficacy as the commercially available antidepressant, fluoxetine [25]. In addition, depression can be associated with memory loss. This is because depression results in progressive damage to nerve cells [26]. This neuronal cell damage, coupled with a neuroinflammation-induced reduction in neurogenesis, can result in hippocampal cell death [27].

Ginseng is traditionally used to protect the nervous system. Ginseng is effective in memory improvement, and in the direct prevention of degenerative brain diseases such as Alzheimer's disease. The neuroprotective effect of ginseng may be useful in the prevention of depression. Indirectly, enhanced memory can ameliorate anxiety. In clinical studies, it was observed that memory loss was attenuated in elderly patients treated with anxiolytics. These clinical studies may indicate that ginseng has the potential to improve anxiety [28] (Fig. 1).

Research studies can employ self-testing using the depression, anxiety, and stress scale to measure anxiety, depression, and stress levels induced by the environment, including emotional and physical factors [29]. Stress is closely related to psychological disorders such as depression and anxiety. Thus, ginseng is potentially an effective candidate for easing stress and can therefore improve the symptoms of depression and anxiety.

6. Ginseng for disease treatment

Chronic stress can trigger such diseases because of abnormal immune responses and hormonal disorders. However, regular ingestion of ginseng has both preventive and therapeutic effects on several human diseases, including heart disease, stroke, diabetes mellitus (DM), rheumatoid arthritis (RA), osteoporosis, erectile dysfunction (ED), and allergic asthma. These diseases can be more prevalent in patients with depression and anxiety, in comparison to healthy individuals [30] (Fig. 1). This may reflect an increase in depression and anxiety in patients with a physical illness, because of their physical pain, or indicate that depression and anxiety predispose to secondary physical illnesses.

6.1. Vascular disease

Ginseng is an effective antioxidant, and also improves vasomotor function and prevents blood clots. These effects positively

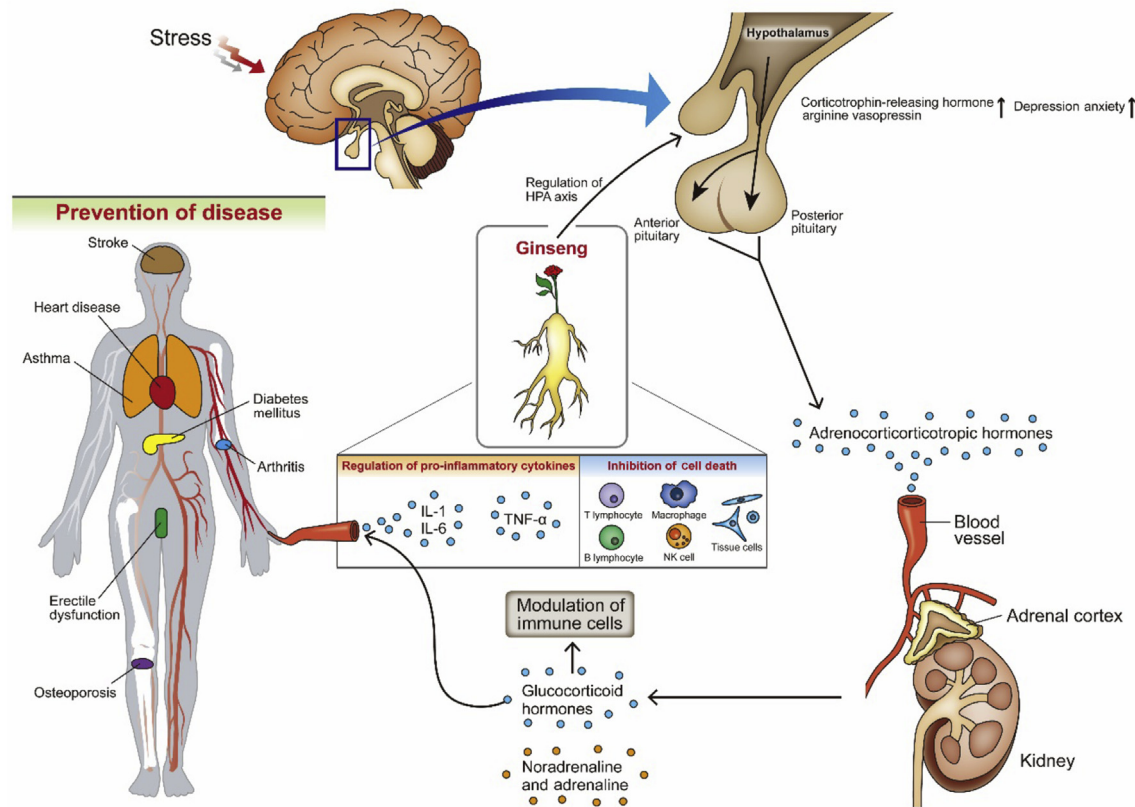


Fig. 1. The mechanism by which ginseng prevents disease via regulation of the endocrine and immune systems. Ginseng regulates the hypothalamic–pituitary–adrenal (HPA) axis. Ginseng thus prevents various diseases by ameliorating tissue injury and immune cell death, while modulating immune cells in order to limit inflammatory responses. The HPA axis is the major pathway regulating the immune response to stress; this is initiated by hypothalamic secretion of corticotrophin-releasing hormone (CRH) and secretion of arginine vasopressin (AVP) from the pituitary gland. CRH stimulates the pituitary gland to release adrenocorticotropic hormone (ACTH) into the bloodstream. ACTH in turn triggers the release of glucocorticoids, such as cortisol, from the adrenal cortex. In the event of severe stress-induced dysfunction of the HPA axis, endocrine homeostasis is disturbed; this can predispose the patient to a number of diseases. Patients with depression and anxiety exhibit increased production of HPA hormones, including CRH and AVP, as compared to healthy individuals [18]. Additionally, glucocorticoids and norepinephrine modulate proinflammatory cytokine production by immune cells. Consequently, chronic and severe stress causes immune dysfunction, which in turn can lead to various diseases [19]. It is well known that glucocorticoids suppress immune function during acute stress, thus increasing susceptibility to disease. However, should the stress become chronic, receptors become resistant to glucocorticoids and can no longer downregulate inflammatory processes [20]. IL, interleukin; TNF- α , tumor necrosis factor alpha.

improve cardiovascular health [31]. Cardiovascular diseases (CVDs) have a higher mortality rate than cancers worldwide, and in Western countries, CVDs account for more than half of the deaths. CVDs are also very closely related to stress. Research conducted over many decades has revealed that long working hours, noise, and poorer workplace environments proportionally increased the incidence of CVDs [32]. Ginseng alleviates such stress and could thus help to prevent CVD. In animal models, ginseng lowered the levels of reactive oxygen species in myocardial tissue and improved blood circulation, helping to maintain heart function [33].

Vascular abnormalities can also affect the nervous system, and stroke is the fifth deadliest disease in the United States. The resultant changes in the blood supply to the brain can cause necrosis of the brain tissue. Hypertension and atherosclerosis increase the risk for stroke [34]. Ginseng suppresses the oxidative stress induced by ischemia, a major driver of stroke-induced tissue damage. By regulating brain cell necrosis and the production of proinflammatory factors, it contributes to the prevention of deadly brain inflammation [35].

6.2. Osteoporosis

By regulating the HPA axis, ginseng influences the hormonal system. One of the hormones regulated in this manner is estrogen, a sex hormone that acts as an agonist in the brain, bones, and

heart. The effects of estrogen reduce the risk of developing CVD, stroke, and osteoporosis [33]. Ginseng has also been shown to upregulate the estrogen receptor in a range of cell types *in vitro*, indicating that it could increase the tissue effects of this hormone [36]. This phenomenon is observed in bone tissue. In postmenopausal women, where there is a sudden decline in estrogen levels, the probability of osteoporosis is proportionally increased. The bone tissue of patients with osteoporosis can fracture easily owing to a reduced bone density. This is related to the amount of estrogen supplied to osteoclasts. Estrogen inversely regulates the expression of interleukin (IL)-6, a proinflammatory cytokine. Chronic increases in the level of IL-6 result in osteoporosis and similar increases can also be observed in patients with depression or sleep disorders, or in those experiencing stress because of bad eating habits [37].

Ginseng promotes osteogenesis in the bone marrow stromal cell. In addition, by inhibiting receptor activator of nuclear factor kappa-B ligand, nuclear factor kappa-light-chain-enhancer of activated B cells, c-Jun N-terminal kinases, c-Fos, nuclear factor of activated T cells, cytoplasmic 1 (NFATc1), and the proinflammatory cytokines, tumor necrosis factor alpha (TNF- α) and IL-6, and by playing a role in osteoclast differentiation and bone resorption, it helps to prevent osteoporosis. However, further research is required to elucidate the exact mechanisms underlying these effects of ginseng [38].

6.3. Arthritis

Ginseng contributes to the prevention of the development of autoimmune diseases by suppressing the excessive secretion of proinflammatory cytokines induced by persistent stress. Therefore, ginseng is effective in preventing RA. TNF- α , a proinflammatory cytokine, can cause early joint inflammation or accelerate inflammatory cell infiltration in joints. Chronic destruction and disability of the joints may develop into RA. During this process, ginseng can help to prevent the autoimmune process underlying RA by inhibiting the major proinflammatory cytokine, TNF- α [39].

6.4. Erectile dysfunction

In addition to preventing disease by regulating estrogen in women, ginseng is also very effective in men. In modern societies, about 50% of the men aged between 40 and 70 yr experience ED because of aging, smoking, obesity, and a variety of other reasons; however, the primary cause of ED is anxiety [40].

Three methods of treatment exist for ED: oral drug administration, drug injections, and the use of a penile prosthesis. Most patients currently use oral drug treatment. Although treatment is available with sildenafil, the active ingredient of Viagra, periodic phytotherapies with herbal medicines may be preferred by some patients. Ginseng and other plants have shown excellent effects on sexual function. The effect of ginseng on ED has been verified by animal testing. Moreover, no side effects have been discovered in these studies; therefore, this approach may be appropriate for patients who prefer safer treatments [41,42].

6.5. Diabetes mellitus

Ginseng also affects metabolic disorders by modulating the HPA axis, the core of the hormonal regulation system. DM is one of the most prevalent metabolic diseases in modern societies. Stress can affect metabolism and cause chronic hyperglycemia. When an organism encounters an emergency, the autonomic nervous system reacts with the fight or flight response, which includes energy mobilization. Thus, the stress response involves the actions of a variety of hormones that raise the blood glucose concentration. Some patients with DM show increased insulin resistance and consequently have a reduced response to insulin. When stressful situations develop where energy is needed, the body cells of these

individuals cannot use the glucose present in the blood and instead metabolize fat as an energy source. Fat metabolism causes inflammation. Therefore, such stress reactions could eventually cause a fatal complication in patients with DM. This effect is only observed in patients with type 2 DM, which accounts for 95% of the total DM patient population. Regarding the correlation between type 1 DM and stress, the results published in the literature are more controversial [43]. Ginseng is more effective in patients with type 2 DM than in those with type 1 DM. This is because type 2 DM is associated with stress [44]. Furthermore, ginseng regulates glucose and lipid metabolism and supplies energy to the body to regulate fat cells. This helps to control certain health issues such as obesity, which can become an underlying cause of type 2 DM [45].

6.6. Allergic asthma

Ginseng is also effective in regulating the adaptive immune response because of its effects on lymphocytes. First, ginseng activates the MAP kinase pathway by activating various transcription factors, thus functioning as an anti-inflammatory agent. In addition to inhibiting the CD40 signaling that stimulates the interaction between antigen-presenting cells and T lymphocytes, ginseng can exert chronic anti-inflammatory and antiallergic effects [46]. As such, ginseng is effective for the treatment of allergic asthma caused by problems with the Th2-predominant T cell response. Asthma is an airway inflammation that can narrow the respiratory tract, causing shortness of breath and coughing. This can develop into a serious inflammatory condition that can be fatal [47]. The prevalence of asthma is increasing worldwide, and it is also closely associated with anxiety and depression, which are caused by stress [48].

7. Use of ginseng in the prevention of stress-induced diseases

Based on the association between ginseng and the various diseases caused by stress, several studies on cytokines and receptors involved in this activity are being conducted. The treatment of anxiety and depression caused by stress could reduce the prevalence of inflammatory diseases. Thus, the effects of ginseng on the anxiety and depression associated with the initial stage of chronic inflammation should also be studied.

Patients with anxiety and depression can develop a variety of diseases, as discussed above. This is because anxiety and depression

Table 1
Effects of ginsenosides in *in vivo* models of disease

Disease	Ginsenoside	Effective target	Experiment model	Ref.
Cardiovascular disease	Rb ₁	Myocardial infarction	Rat	[51]
	Re	Cardiomyocyte	Human, cat	[52]
	Rg ₁	Ventricular hypertrophy	Rat	[53]
	Rg ₃	Vascular smooth muscle	Rat and mice	[54]
Stroke	Rd	National Institutes of Health Stroke Scale	human	[55]
	Rg ₁	Formation of new synapses, cerebral cortex	Mice	[56]
		Hippocampus	Rat	[57]
Diabetes	Rb ₁	Antiobesity and antihyperglycemic effect	Rat	[58]
	Re	Antiobesity	Mice	[59]
	Rg ₃	Insulin signaling and glucose uptake	Rat	[60]
Rheumatoid arthritis	Rb ₁	Collagen	Mice	[39]
Osteoporosis	Rg ₁	Osteoblast	Rat	[61]
	Rb ₁	Osteoblast	Rat	[61]
	Rb ₂	Bone mass	Mice	[62]
	Rg ₃	Corpus cavernosum	Rat	[63]
Erectile dysfunction	Re	Corpus cavernosum	Rat	[64]
	Rg ₁	Testosterone level, corpus cavernosum	Mice	[65]
	Rb ₁	Bronchoalveolar lavage fluid	Mice	[66]
Asthma	Rh ₂	Bronchoalveolar lavage fluid, lung	Mice	[67]

can promote inflammatory responses. First, the proinflammatory cytokines such as IL-1, IL-6, interferon- γ , and TNF- α play a role. Second, oxidative or nitrosative stress can occur owing to the increased levels of reactive oxygen species and reactive nitrogen species. As a result, anxiety and depression can predispose patients to the development of cancers, neurodegenerative conditions, and inflammatory diseases [49].

In addition to defending against the increase in proinflammatory cytokines induced by anxiety and depression, ginseng can defend effectively against oxidative or nitrosative stress [50]. Although not yet fully clinically tested, ginseng effectively suppresses the chronic inflammation caused by stress-induced anxiety and depression and could therefore contribute to the prevention of secondary diseases. When ginsenosides are ingested, a number of biological effects occur. These include the prevention of tissue damage, as well as cellular regeneration and repair effects. Ginsenoside-mediated effects on target cells in various *in vivo* models used in recent studies are shown in Table 1.

8. Conclusion

Although existing drug treatments are often effective, continuous exposure to medicinal products can sometimes cause addiction or undesirable side effects. Moreover, population aging is increasing susceptibility to infectious diseases because of attenuated immune system function. Therefore, new treatment methods are required. Future studies should consider investigating alternatives to conventional drugs, such as medicinal plants. These have been used for more than a thousand years and generally carry a low risk of negative side effects. Ginseng provides a potential approach to regaining homeostasis after abnormal physiological changes caused by the stress of everyday life. The efficacy of this preparation has been demonstrated in various experiments conducted using human cells and animal models. A clearer understanding of the mechanisms underlying the effects of ginseng on human cytokine/metabolic systems and on stress-induced hormonal changes could facilitate the development of a wide range of treatments for patients with psychological and physical diseases.

Conflicts of interest

The authors declare no conflicts of interest.

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