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Review Article

Clinical uses of Ginseng

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Abstract

As a powerful natural antioxidant, ginseng effectively modulates apoptosis by reducing the excessive inflammatory response in acute or chronic inflammation. When this homeostasis is disturbed, it can damage the immune system and lead to several fatal diseases. Ginseng has excellent anti stress effects, as compared to appropriate controls. Prolonged cortisol secretion results in immunosuppression. Cortisol is produced and regulated by a major hormonal control center, the hypothalamicepituitaryeadren al (HPA) axis, regulated by the sympathetic nervous system. Adrenocorticotropic 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). Cortisol interacts with the cytoplasmic glucocorticoid receptor. This hormone-receptor complex moves to the nucleus and regulates the expression of several genes. Ginseng has the potential to improve anxiety. 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 mmellitus (DM), rheumatoid arthritis (RA), osteoporosis, erectile dysfunction (ED), and allergic asthma. When a person faces a stressful environment, ginseng can improve their response by regulating the function of the HPA axis. 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. Ginseng is an effective antioxidant, and also improves vasomotor function and prevents blood clots. These effects positively improve cardiovascular health. Ginseng alleviates such stress and could thus help to prevent CVD. By regulating brain cell necrosis and the production of pro inflammatory factors; it contributes to the prevention of deadly brain inflammation.

Ginseng has been used for the treatment or prevention of diseases for thousands of years in eastern countries, and over the last three decades, it has gained popularity in the Americas, Canada, and Europe. Ginseng occupies a prominent position on the list of best-selling natural products in the world (FM, 2009). It is included in the pharmacopoeias of China, Japan, Germany, France, Austria, and the United Kingdom. Asian ginseng (Panax ginseng Meyer) and American ginseng (Panax quinquefolius L.) are the two most recognized ginseng botanicals in the world. 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. Ginsenosides have effective treatment for organ damage and cell death, as well as for immunological and metabolic diseases. 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.

Kew Words: diabetes mmellitus; rheumatoid arthritis, osteoporosis; erectile dysfunction

Introduction

Recent in vitro studies using a standardized North American ginseng extract (CNT-2000 from Panax quinquefolium) reported direct free radical scavenging of stable radicals as well as the prevention of both site specific and non-site specific hydroxyl radical mediated deoxyribose and DNA degradation (Kitts *et al*., 2000).

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 (Kim, 2012). 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 (Nah *et al*., 2007; Helms, 2004 and Nguyen *et al*., 2015). 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 (Liao *et al*., 2002 and Lee *et al*., 2007).

As a powerful natural antioxidant, ginseng effectively modulates apoptosis by reducing the excessive inflammatory response in acute or chronic inflammation (Thatte *et al*., 2000). When this homeostasis is disturbed, it can damage the immune system and lead to several fatal diseases (Hasegawa, 2004 and Leung *et al*., 2007). In vivo studies have also shown that ginseng has excellent anti stress effects, as compared to appropriate controls (Kim *et al*., 2013 and Dang *et al*., 2009).

Prolonged cortisol secretion results in immunosuppression. Cortisol is produced and regulated by a major hormonal control center, the hypothalamicepituitaryeadrenal (HPA) axis, regulated by the sympathetic nervous system (Guilliams and Edwards, 2010). Adrenocorticotropic 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) (Tomas *et al*., 2013). Cortisol interacts with the cytoplasmic glucocorticoid receptor. This hormone-receptor complex moves to the nucleus and regulates the expression of several genes (Medzhitov and Horng, 2009).

When a person faces a stressful environment, ginseng can improve their response by regulating the function of the HPA axis (Park *et al*., 2005). 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 (Choi *et al*., 2011). Furthermore, the prevalence of depression is increasing and this represents a major clinical challenge (Al-Harbi, 2012). 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 (Xu *et al*., 2010).In addition, depression can be associated with memory loss. This is because depression results in progressive damage to nerve cells (Dong *et al*., 2016). This neuronal cell damage, coupled with a neuroinflammation-induced reduction in neurogenesis, can result in hippocampal cell death (Van Kampen *et al*., 2014).

These clinical studies may indicate that ginseng has the potential to improve anxiety (Churchill *et al*., 2002). 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 mmellitus (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 (Clarke and Currie, 2009).

Ginseng is an effective antioxidant, and also improves vasomotor function and prevents blood clots. These effects positively improve cardiovascular health (Kim, 2012). 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 (Backe *et al*., 2012). 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 (Lee and Kim, 2014). By regulating brain cell necrosis and the production of pro inflammatory factors; it contributes to the prevention of deadly brain inflammation (Rastogi *et al*., 2014). Ginseng has also been shown to up regulate the estrogen receptor in a range of cell types in vitro, indicating that it could increase the tissue effects of this hormone (Nguyen *et al*., 2015).

However, further research is required to elucidate the exact mechanisms underlying these effects of ginseng (Siddiqi *et al*., 2013). 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 pro inflammatory cytokine, TNF-a (Kim *et al*., 2007). 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 (Hedon, 2003).

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 (Kim *et al*., 2009 and de Andrade *et al*., 2007). 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 (Hong *et al*., 2013). 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 (Yuan *et al*., 2012).

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 anti-allergic effects (Song *et al*., 2012). This can develop into a serious inflammatory condition that can be fatal (Chung and Marwick, 2010). The prevalence of asthma is increasing worldwide, and it is also closely associated with anxiety and depression, which are caused by stress (Kullowatz *et al*., 2007).

Anxiety and depression can predispose patients to the development of cancers, neurodegenerative conditions, and inflammatory diseases (Maes *et al*., 2012). In addition to defending against the increase in pro inflammatory cytokines induced by anxiety and depression, ginseng can defend effectively against oxidative or nitrosative stress (Hong and Lyu, 2011).

Korean ginseng (the root of Panax ginseng Meyer) is one of the most popular medicinal plants used in traditional medicine in East Asian countries including Korea (Kiefer and Pantuso, 2003). Ginseng contains various pharmacologically active substances such as ginsenosides, poly-saccharides, polyacetylenes, phytosterols, and essential oils, and among those, ginsenosides are considered the major bioactive compounds (Park *et al*., 2005). Korean Red Ginseng (KRG) is a heat-processed ginseng which is prepared by the repeated process of steaming and air-drying fresh ginseng (Jang *et al*., 2008). KRG has been shown to possess enhanced pharmacological activities and stability compared with fresh ginseng because of changes in its chemical constituents such as ginsenosides Rg2, Rg3Rh1, andRh2, which occur during the steaming process (Kim et al., 2000). Currently, numerous studies have reported the beneficial effects of KRG on diverse diseases such as cancer, immune system disorder, neuronal disease, and cardiovascular disease (Kim and Park, 2010; Helms, 2004; Kim *et al*., 2014 and Vuksan *et al*., 2010). In addition, KRG and its purified components have also been shown to possess protective activities against microbial infections (Lim *et al*., 2002).

The root of Panax ginseng Meyer has been used medicinally for thousands of years in China, Korea, and Japan for prophylactic and curative properties in cases of decreased physical and mental capacities such as tiredness, exhaustion, and weakness and during convalescence (Sandberg and Corrigan, 2020; European Scientific Cooperative on Phytotherapy, 2003; European Medicines Agency, 2013 and Park *et al*., 2012).

In the early Middle Ages, ginseng was introduced into Europe by Arabian merchants; however, owing to ignorance about the “root with the human shape,” its use was banned, and it was referred to as ‘Moorish devil’s “business (Baeg and So, 2013). Currently, ginseng is available on the market

worldwide in a variety of forms such as fresh ginseng, dried ginseng, boiled and dried ginseng, and red ginseng or as various products based on ginseng extracts. These are sold either as food, dietary, or health supplements or as herbal medicinal products (HMPs) (Blumenthal, 2003 and Bilia, 2014). The quality and composition of the active components can vary according to several factors including plant species, the method of cultivation, age, and part of the plant used (Leung and Wong, 2010). Owing to this complexity, work is still ongoing to understand the pharmacology of the ginsenosides. Pharmacokinetic and toxicology profiles support the observed efficacy of ginsenosides in clinical studies (Xu *et al*., 2017). When ginseng is administered orally, a significant fraction of ginsenosides is metabolized by intestinal microflora into compound K, which is now considered to be the main constituent with pharmacological effects (Wang *et al*., 2011 and Lee *et al*., 2009). Ginseno-sides are primarily metabolized in the liver and enter into the enterohepatic recirculation resulting in excretion largely through feces (Qi et al., 2011). Many pharmacological effects have been investigated through in vivo and in vitro studies for different ginseng preparations. The results have provided evidence in the antioxidant effects of ginseng in various experimental models through the enhancement of the cell stress response (Park *et al*., 2010), in inhibition of apoptosis in cultured neuronal cells (Kim *et al*., 2014 and Lin *et al*., 2009), and in the neuroprotective activity in animal models of ischemic stroke (Kim *et al*., 2009), and Parkinson (Van Kampen *et al*., 2014 and 2003) and Alzheimer diseases (Choi *et al*., 2017). Various in vivo studies have reported that the activity of ginseng on the central nervous system including learning/memory enhancement Dong et al. (2017), improvement of cognitive deficits (Tan *et al*., 2015), reduction of addiction behavior, and opioid-induced hyperalgesia (Yayeh *et al*., 2016). Ginseng can inhibit proliferation and motility of cancer cell lines in vitro (Kim et al., 2017; Seo and Kim, 2011 and Ho *et al*., 2012), and it possesses anti-carcinogenic activity in animal models (Wong *et al*., 2010; Lee *et al*., 2010 and Bespalov *et al*., 2014).

The anticarcino-genic effects of ginseng may be partly due to its ability to inhibit angiogenesis (Sagar *et al*., 2006). Notably, modulation of the immune response has been extensively characterized as pharmacological effects of ginseng, proving that it is able to modulate multiple immune cell types, in terms of proliferation, phagocytic activity (Kang *et al*., 2008), cytokine expression (Jang and Shin, 2010 and Larsen *et al*., 2004), and production of antibodies (Park *et al*., 2015). Studies performed in animals have demonstrated that ginseng induces a strong immune response, protecting from both viral and bacterial infections (Zhuo *et al*., 2017; Silvestrini *et al*., 2017 and Lee *et al*., 2015) and enhancing the protection conferred by vaccination (Xu *et al*., 2012). Pharmacological effects on the cardiovascular system have also been reported, where ginseng was able to influence nitric oxide production in vascular endothelial cells (Kim *et al*., 2007 and Yu *et al*., 2007) and to improve cardiac performance exerting cardio protective effects in rat models (Luo *et al*., 2015 and Lim *et al*., 2013). It has also been shown that ginseng has positive effects on both lipid and glucose metabolism in vivo [Shin and Yoon, 2017 and Liu *et al*., 2014). Chronic studies in rats and mice treated with ginseng at doses up to 5000 mg/kg for 2 years did not show any toxic effects; furthermore, no increases in the incidence of cancer or nonneoplastic lesions were detected (National Toxicology Program, 2011).

More recently, a series of systematic reviews have analyzed the clinical trials that have been conducted with ginseng and the effectiveness of ginseng on cognitive function (Geng *et al*., 2010 and Lee *et al*., 2009), metabolism (Shishtar *et al*., 2014), erectile dysfunction (Jang *et al*., 2000), cardiovascular function (Xiang et al., 2008), vitality (Lee and Son, 2011), and improvement of the immune system (Seida *et al*., 2011 and An *et al*., 2015). Measures of quality assurance such as good agricultural and collection practices and good manufacturing practices are mandatory requirements to obtain constant efficacy and safety profiles of such products (Bilia, 2015 and Van Breemen *et al*., 2007).

According to the World Health Organization "standardization is the process of pre-scribing a set of standards or inherent characteristics, constant parameters, definitive qualitative and quantitative values that carry an assurance of quality, efficacy, safety, and reproducibility" (European Medicines Agency, 2011). Only products fulfilling the basic requirements of quality have reproducible safety and efficacy profiles (World Health Organization, 2000). According to the European pharmacopoeia (Council of Europe, 2013).

G115 is obtained by ethanol extraction (40%V/V) of the dried roots of P. Ginseng Meyer and standardized on the total content (4 %) of major ginsenosides. In this context, the standardized ginseng extract G115 is regarded as different from other ginseng extracts owing to its unique manufacturing process and represents an excellent example of a standardized extract capable of providing constant safety and efficacy profiles. Quality of G115 is in compliance with the US and European pharmacopoeias (United States Pharmacopoeial Convention, 2012 and Council of Europe, 2013).

In 2005, a review by Scaglione et al. (2005) highlighted the effectiveness of G115 in increasing endurance and vitality in a number of non-good clinical practice (GCP) studies, despite several clinical studies with ginseng not having shown any significant effect on the enhancement of physical performance. G115 effect sizes (Cohen's d) were 0.86, confirming that neurocognitive enhancement from well-characterized extracts can pro-duce cognition-enhancing effects of similar magnitude to those from pharmaceutical interventions (0.77 for modafinil) (Neale *et al*., 2012).

In addition, G115 was able to counteract the inhibition of gene expression of 50AMP-activated protein kinase and proliferator-activated receptor gamma coactivator-1ainduced by prolonged exercise (Pannacci *et al*., 2016). G115 is also effective in reducing lipid peroxidation, inflammation, and release of myocellular proteins (Cabral de Oliveira *et al*., 2002). Further analyses revealed that G115 was effective in preserving mitochondrial membrane integrity and reducing nitrate concentration and carbonyl contents in vastus and rectus muscles (de Oliveira *et al*., 2005), and it was able to protect the muscle from exercise-induced oxidative stress irrespective of the fiber type (Voces *et al*., 2004). A significant reduction in low-density lipoprotein, total cholesterol, low-density lipoprotein/high-density lipoprotein, and cholesterol/high-density lipoprotein ratios, higher alpha lipoic acid, was found (El-Farok *et al*., 2013).

A series of studies by Reay et. al. (2005 and 2006) investigated the effects of G115 on blood glucose levels. Two studies reported significant decreases in fasting blood glucose levels, measured one hour after a single dose of G115 (200 or 400 mg/day) in healthy volunteers, but no effect on postprandial glucose (after a 25-g glucose drink) response. The benefits to glucose regulation associated with long-term ginseng use may only be present in populations with compromised glucose control (Reay *et al*., 2009). A more recent study has proposed that G115 modulates the immune response by reducing the peak of cytokine release after a few weeks of stress and stimulates the innate immune response, gradually facilitating host defense and potentiating the response against bacterial or pathogenic challenge (Pannacci *et al*., 2006).

Moreover, G115 (200 mg/day) was more effective in reducing the bacterial clearance than in the participants receiving only antibiotics. Statistically significant differences between treatment groups were observed on Days 4, 5, 6, and 7 (p ¼0.0049, p¼0.0104, p¼0.0175, and p¼0.0182, respectively), whereas a borderline trend was seen on Day 8 (p¼0.0554) (Scaglione *et al*., 2001).

Finally, Engels et al proved that intake of G115 (400 mg/day) did not affect mucosal immunity, physical performance, and heart rate recovery. Before and after the intervention, each participant performed three consecutive 30-s Wingate tests interspersed with 3-min recovery periods under controlled laboratory conditions. The secretory immunoglobulin A secretion rate, secretory immunoglobulin A: protein ratio, and saliva flow rate were lower after exercise at baseline ($P<0.05$) in the G115 group (Engels *et al.*, 2003).

Two studies by Gross et al. (2002) demonstrated that G115 (200 mg/day) improved pulmonary function tests and respiratory endurance in patients with COPD. In the first study [103], forced vital capacity (FVC) changed from 32.1% to 67.3% ($p<0.05$) and to 72.8% ($p<0.01$) after 1.5 and 3 months, respectively, whereas forced expiration volume in one second (FEV1) improved from 34.75% to 44.5% ($p<0.05$) and to 47.3% ($p<0.05$) for the same period. These findings were validated in a second study where it was observed that for G115-treated patients, all respiratory function parameters significantly increased above baseline compared with the placebo control (Xue *et al.*, 2011). The observed increases were as follows: FVC, 32.5%; FEV1, 0-27.0%; peak expiration flow, 27.5%; forced expiratoryflow50, 45.4%; forced expiratory flow75, 56.9%; maximum ventilation volume, 40.4%; MIP, 47.0%; and maximal oxygen consumption, 37.5% (Xue *et al.*, 2011). An optimized protocol study based on previous randomized controlled trials (RCTs) and systematic reviews on Quality of Life (QoL) improvements using ginseng for COPD was developed (Wu *et al.*, 2014). G115 administration fully prevented the development of locomotor deficits (Van Kampen *et al.*, 2014). Sünram-Lea et al. (2005), Kennedy et al. (2004), Kennedy et al. (2002), Scholey and Kennedy (2002), and Kennedy et al. (2001) assessed that G115 enhances cognition effects comparable with those from modafinil therapy. After chronic dosing, the results revealed both improvement and decrement in aspects of cognition and mood (Reay et al., 2008). In a further study, the same research group investigated the effects of treatment with G115 on subjective mood and aspects of working memory processes after a dose of 200 or 400 mg of G115 (Reay *et al.*, 2010). In this study, dose-related treatment effects ($p <0.05$) were found. Kennedy et al. (2003) investigated the electroencephalograph effects of G115 (200 mg/day) or a ginkgo extract (EGb761, 360 mg/ day).

At doses ranging from 1.5 to 15 mg/kg/day, G115 did not show adverse effects on the reproductive parameters evaluated or treatment-related effects on animal behavior, physical appearance, or food consumption. No chronic carcinogenetic studies of ginseng on experimental animals have been found in the literature (Mancuso and Santangelo, 2017). However, drug interactions can occur, in particular, in anticoagulants such as warfarin (Cheng, 2005). G115 has also been used and marketed as a medical product worldwide for decades, but no serious adverse events have been reported. Ginseng has been used for the treatment or prevention of diseases for thousands of years in eastern countries, and over the last three decades, it has gained popularity in the Americas, Canada, and Europe. Ginseng occupies a prominent position on the list of best-selling natural products in the world (FM, 2009). It is included in the pharmacopoeias of China, Japan, Germany, France, Austria, and the United Kingdom. Asian ginseng (Panax ginseng Meyer) and American ginseng (Panax quinquefolius L.) are the two most recognized ginseng botanicals in the world (Ang-Lee *et al.*, 2001). Although ginseng has long been broadly used in clinical settings worldwide, few clinical trials on ginseng have been conducted (Firenzuoli and Gori, 2007 and Chen *et al.*, 2014).

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