GINSENG: AN UPDATE

Saurabh Kumar Deo*, Rajesh Pandey¹, Jasbir Singh¹, Kuldip Singh Sodhi¹.
¹Professor, Department of Biochemistry, MMIMSR, Mullana, Ambala, Haryana, India.

Article INFO

Article history
Received 13/08/2014
Available online
31/08/2014

Keywords
Ginseng,
Alzheimer’s Disease,
Diabetes Mellitus,
Cirrhosis,
Cancer.

ABSTRACT

Ginseng (Panax ginseng, P. ginseng) is a dried root that has been widely used as a traditional medicine since ancient times because of its stimulative and tonic properties [1]. P. ginseng is known to exert a wide range of pharmacological effects both in vitro and in vivo [2]. Studies have investigated the favorable effects of ginseng on energy homeostasis, the cardiovascular system, nervous system, skeletal system etc. Clinically pertinent anti-aging, anti-fatigue, anti-stress, anti-atherosclerosis, anti-diabetic, hepatoprotective, anti-cancer, and anti-inflammatory activities have also been documented. Further investigations for its clinical implications including the supportive treatment of chronic diseases such as Alzheimer’s disease, diabetes mellitus, cirrhosis, cancer etc are strongly needed.

*Corresponding author
Saurabh Kumar Deo
Ph. D. Student,
Department of Biochemistry,
MMIMSR, Mullana, Ambala,
Haryana, India.
luvusaurabh2009@gmail.com
+91-7206594393, 8090972245

Present designation:
Demonstrator,
Department of Biochemistry,
Maharani Laxmi Bai Medical College,
Jhansi, U. P., India.


Copyright © 2014 This is an Open Access article distributed under the terms of the Indo American journal of Pharmaceutical Research, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

www.iajpr.com
INTRODUCTION

Ginseng (*Panax ginseng, P. ginseng*) is widely cultivated as a medicinal herb in northeast China. The ginseng dried roots have been widely used as a traditional medicine since ancient times because of its stimulative and tonic properties [1]. *P. ginseng* is known to exert a wide range of pharmacological effects both *in vitro* and *in vivo* [2].

History

Emperor Shen-Nung was the second of China's mythical emperors (3500-2600 BC). Widely considered the father of Chinese medicine, he catalogued over 365 species of medicinal plants which he personally tasted. Agricultural clan leader, Emperor Shen Nung, was said to have a ‘crystal-like belly’ to watch the reactions in his own stomach of the herbs he collected. Ginseng (Fig. 1) was one among Shen Nung’s contributions to herbal medicine. He experienced a warm and sexually pleasurable feeling after chewing the root. He advocated this as a treatment for erectile dysfunction and used it to stimulate sexual appetite. The reputation of ginseng as an aphrodisiac is based on the doctrine of signatures, since the adult root has a phallic shape. Shen-Nung believed that ginseng's resemblance to the human form is proof of its rejuvenative and aphrodisiac properties. It was believed that the closer the similarity to the human figure, the more potent the root. The use of ginseng for erectile dysfunction by Emperor Shen-Nung was unique for its time. It continues to hold parallels as a modern-day herbal aphrodisiac 5000 years on [3].

American ginseng (*Panax quinquefolius, L.*) is a perennial herb native to the deciduous forests of the eastern United States. Ginseng was one of the earliest marketable herbs to be harvested in this country. Wild ginseng was one of Minnesota’s first major exports. American ginseng is similar to Asian ginseng, *P. ginseng* which grows wild in Northern Manchuria and has been harvested there for thousands of years. Koreans have fed ginseng to race horses to enhance their performance on the track [4].

Functions

Ginseng was, and still remains a powerful symbol of divine harmony on earth. The old Chinese Canon of Medicine states that: “Ginseng strengthens the soul, brightens the eyes, opens the heart, expels evil, benefits understanding and if taken for prolonged periods of time will invigorate the body and prolongs one's life” [3]. Ginseng is reputed to affect human health in multiple positive ways [3, 4].

Energy homeostasis and anticancer activity

Obesity and the metabolic syndrome represent a major health problem in both Western and developing countries. Adenosine monophosphate (AMP)-activated protein kinase (AMPK) (Fig. 2) is a negative regulator of acetyl-coenzyme A (CoA) carboxylase (ACC) and 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGR) in the biosynthesis of fatty acids and cholesterol, respectively [5,6]. AMPK is a highly preserved sensor of cellular energy status, and appears to exist in essentially all eukaryotes as heterotrimeric complexes composed of a catalytic α subunit and regulatory β and γ subunits. The α subunit contains the kinase domain, with the conserved threonine residue that is the target for upstream kinases [liver kinase B1 (LKB1) and Ca²⁺-activated calmodulin-dependent kinase kinases (CaMKKs)] located within the activation loop. Phosphorylation at Thr172 is required for kinase activity and function in all species from yeast to man, and with the human kinase, causes >100-fold activation [7]. In mammals, all three subunits have multiple isoforms encoded by distinct genes (α1, α2; β1, β2; γ1, γ2, γ3), which assemble to form up to 12 heterotrimeric combinations [8].

Considering the role of AMPK in regulating energy balance at both the cellular and whole-body levels, this kinase occupies a pivotal position in studies regarding obesity, diabetes, and the metabolic syndrome [9]. By direct phosphorylation of metabolic enzymes and transcription factors, AMPK switches on catabolic pathways, such as the uptake of glucose and fatty acids, and their
metabolism by mitochondrial oxidation and glycolysis. In addition, AMPK switches off anabolic pathways, such as the synthesis of glucose, glycogen, and lipids in the liver. By promoting muscle glucose uptake and metabolism and by inhibiting hepatic gluconeogenesis, AMPK activation can explain the antidiabetic action of metformin. Type 2 diabetes is primarily caused by insulin resistance, which is strongly associated with excess triglyceride storage in liver and muscle. By switching off the synthesis of fatty acids and triglycerides and enhancing fat oxidation, AMPK activation might also explain the insulin-sensitizing action of metformin [10].

The uncontrolled proliferation of cancer cells is supported by a corresponding adjustment of energy metabolism. Nowadays, altered metabolism of tumor cells is widely recognized as an emerging hallmark and a potential drug target in cancer cells. Protein synthesis is the best-characterized process regulated by the mammalian target of rapamycin complex 1 (mTORC1). mTORC1 plays a key role in translational control by phosphorylating lots of translation regulators, including S6 kinase 1 (S6K1) [11]. The synthesis of fatty acids, triglycerides, cholesterol, RNA, and proteins are all upregulated in tumor cells. Notably, because protein synthesis requires a myriad of cellular energy, AMPK activation induced by metabolic stress significantly inhibits protein synthesis, resulting in AMPK–mTORC1 crosstalk: AMPK attenuates mTORC1 signaling through phosphorylation and activation of tuberous sclerosis 2, a negative regulator of mTORC1. AMPK also directly phosphorylates Raptor, which induces 14-3-3 binding to raptor and repression of mTORC1 activity. Other findings that AMPK caused the inhibition of progress through the cell cycle, and that the mechanism of AMPK activation required the presence of the tumor suppressor LKB1 also gave us the idea that AMPK activators might be beneficial in the prevention and/or treatment of cancer. AMPK activation switches off all of these pathways and would therefore be expected to exert an antitumor effect, reinforced by its ability to cause cell-cycle arrest. These effects of AMPK might explain the tumor suppressor effects of the upstream kinase LKB1, as well as findings that metformin usage reduces the risk of cancer in diabetics and that metformin and other AMPK activators (phenformin, A-769662) delay the onset of tumorigenesis [10].

Ginseng and ginsenosides (active components found in ginseng) are reported to activate AMPK in intact cells [10]. Some inhibit mitochondrial function, either inhibiting the respiratory chain (berberine and licochalcone A) or the adenosine triphosphate (ATP) synthase (EGCG and resveratrol), or acting as an uncoupler (curcumin). Respiratory chain and ATP synthase might have potential binding sites for xenobiotic compounds, and the production of mitochondrial poisons might be a suitable mechanism for plants to detect infection by pathogens [10]. CK and Rg3 induce apoptosis via the CaMKK–AMPK signaling pathway in HT-29 colon cancer cells, and these activities were confirmed using either compound C (a chemical inhibitor of AMPK) or small interfering RNA (siRNA) for AMPK or STO-609 (a chemical inhibitor of CaMKK) [10]. Kim et al also reported that CK inhibits cell growth, induces apoptosis via generation of reactive oxygen species, as well as decreasing cyclooxygenase-2 expression and prostaglandin E2 levels. These effects were induced via an AMPK-dependent pathway and were abrogated by a specific AMPK inhibitor, compound C [12]. More recently, Hwang et al reported that 20-O-β-D-glucopyranosyl-20(S)-protopanaxadiol (20-GPPD), a metabolite of ginseng saponin, causes apoptosis of colon cancer cells through the induction of cytoplasmic Ca^{2+}. 20-GPPD decreased cell viability, increased annexin V-positive early apoptosis, and induced sub-G1 accumulation and nuclear condensation of CT-26 murine colon cancer cells [13]. Although 20-GPPD-induced activation of AMPK played a key role in the apoptotic death of CT-26 cells, LKB1, a well-known upstream kinase of AMPK, was not involved in this activation [10,13].
Fig. 2: Acute and chronic metabolic effects of adenosine monophosphate (AMP)-activated protein kinase (AMPK) activation.

**Anti-inflammatory activity**

Water extract of KRG reduced the production of nitric oxide (NO), protected cells against NO-induced apoptosis, suppressed mRNA levels of inducible NO synthase (iNOS), cyclooxygenase (COX)-2, and interferon (IFN)-β, ameliorated EtOH/HCl-induced gastritis, and downregulated peritoneal exudate-derived NO production from lipopolysaccharide (LPS)-injected mice. The inhibition of these inflammatory responses by KRG was regulated through the suppression of p38, c-Jun N-terminal kinase (JNK), and TANK-binding kinase 1 (TBK1) and by subsequent inhibition of activating transcription factor (ATF)-2, cAMP response element-binding protein (CREB), and IRF-3 activation. Of the ginsenosides included in this extract, interestingly, G-Rc showed the highest inhibitory potency on IRF-3-mediated luciferase activity [14].

**Neuroprotective activity**

Alzheimer’s disease (AD) is an age-related progressive neurodegenerative disorder caused due to aggregation of misfolded proteins particularly fibrillary amyloid deposits in selective regions of central nervous system [15]. Amyloid-beta (Aβ) has a pivotal function in the pathogenesis of Alzheimer’s disease (AD). Aβ25-35 (20 μM) treatment for 24h caused apoptotic cell death, LDH release, phosphatidyserine externalization, mitochondrial membrane potential disruption, cytochrome c release, caspase-3 activation, PARP cleavage, and DNA fragmentation in PC12 cells. Aβ25-35 treatment led to autophagic cell death, by augmented GFP-LC3 puncta, conversion of LC3-I to LC3-II, and increased LC3-II/LC3-I ratio. Aβ25,35 treatment induced oxidative stress, as evidenced by intracellular ROS accumulation and increased production of mitochondrial superoxide, malondialdehyde, protein carbonyl, and 8-OHdG. Phytoestrogens have been proved to be protective against Aβ-induced neurotoxicity and regarded as relatively safe targets for AD drug development. Gypenoside XVII (GP-17) is a novel phytoestrogen isolated from Gynostemma pentaphyllum or Panax notoginseng. Pretreatment with GP-17 (10 μM) for 12h increased estrogen response element reporter activity, activated PI3K/Akt pathways, inhibited GSK-3β, induced Nrf2 nuclear translocation, augmented antioxidant responsive element enhancer activity, upregulated heme oxygenase 1 (HO-1) expression and activity, and provided protective effects against Aβ25,35-induced neurotoxicity, including oxidative stress, apoptosis, and autophagic cell death. In conclusion, GP-17 conferred protection against Aβ25,35-induced neurotoxicity through estrogen receptor-dependent activation of PI3K/Akt pathways, inactivation of GSK-3β and activation of Nrf2/ARE/HO-1 pathways [16].

Ginsenosides improve brain RNA content, promote brain protein synthesis, enhance dopamine function, regulate brain hormones, and improve microcirculation in central nervous system that might improve, repair and rehabilitation from stroke and brain injury. The ginsenoside saponins promote the proliferation of human embryonic neural stem cells (NSCs). When ginsenoside saponins were combined with EGF and bFGF, the effect of proliferation was two times more potent than the combination of just EGF or bFGF. Ginsenoside saponins promoted directed differentiation of NSCs into dopaminergic neurons [17]. When ginsenoside saponins were
combined with IL-1, the effect on proliferation was five times more potent than that induced by IL-1 alone. Tanshinone (20, 40, and 80 μmol/L) exhibited a protective effect on rat NSCs affected by hypoxia and oxidants in vitro [18]. Tanshinone had a greater protective effect on hypoxia damage than on oxidant damage at the same dose [19].

Anti-anxiety and anti-stress activity
At the level of brain or hypothalamic-pituitary-adrenal (HPA) axis, ginseng saponins appear to stimulate ACTH and subsequent cortisol production, suggesting that ginseng might help potentiate an acute stress response. The binding of corticosteroids to certain region of the brain was increased when given ginseng saponin, possibly indicating that ginseng acts to improve the negative feedback loop and sensitivity of the HPA axis to cortisol [20].

Bone homeostasis
Ginseng has antiosteoporotic potential on the growth and differentiation of murine MC3T3-E1 cells. Rg5:Rk1 is a mixture of protopanaxadiol-type ginsenosides, isolated from fresh P. ginseng root, via a repetitive steaming and drying process. Rg5:Rk1 treatment also increased the activities of proteins associated with osteoblast growth and differentiation in a dose-dependent manner. So, the Rg5:Rk1 mixture of ginsenosides improved the osteoblastic function of MC3T3-E1 cells by increasing their proliferative capacity. This improvement is due to the action of Rg5:Rk1 on BMP-2, which is mediated by Runx2-dependent pathways [2].

Reproduction
The root of P. ginseng improves testicular function both in humans and animals. However, the molecular mechanism by which ginseng exerts this effect has not been elucidated. Number of sperms, Sertoli cells and germ cells, and the Sertoli Cell Index decrease in the testis of aged rats (AR) relative to young control rats (YCR). However, those parameters were completely restored in GINST-treated AR (GINST-AR). Won et al identified 14 proteins that were differentially expressed between vehicle-treated AR (V-AR) and GINST-AR. Out of these, the expression of glutathione-S-transferase (GST) mu5 and phospholipid hydroperoxide (PH) glutathione peroxidase (GPx) was significantly up-regulated in GINST-AR compared to V-AR. The activity of GPx and GST, as well as the expression of glutathione, in the testis of GINST-AR was higher than that in V-AR. The levels of lipid peroxidation (LPO) increased in AR compared with YCR, but this change was reversed by GINST-AR. These results suggest that the administration of GINST enhances testicular function by elevating GPx and GST activity, thus resulting in increased glutathione, which prevents LPO in the testis [21].

Anti-infective effects
*Helicobacter pylori*-induced gastric inflammation includes induction of inflammatory mediators interleukin (IL)-8 and inducible nitric oxide synthase (iNOS), which are mediated by oxidant-sensitive transcription factor NF-kB. High levels of lipid peroxide (LPO) and increased activity of myeloperoxidase (MPO), a biomarker of neutrophil infiltration, are observed in *H. pylori*-infected gastric mucosa. KRG-extract (RGE) inhibits *H. pylori*-induced gastric inflammation. RGE suppressed *H. pylori*-induced mRNA and protein levels of KC (keratinocyte chemoattractant factor, a rodent IL-8 homolog), IL-1β, and iNOS in gastric mucosa. RGE also inhibited *H. pylori*-induced phosphorylation of IkBα and increases in LPO level and MPO activity of gastric mucosa. RGE did not affect viable *H. pylori* colonization in the stomach, but improved the histological grade of infiltration of polymorphonuclear neutrophils, intestinal metaplasia, and hyperplasia. In conclusion, RGE inhibits *H. pylori*-induced gastric inflammation by suppressing induction of inflammatory mediators (KC, IL-1β, iNOS), MPO activity, and LPO level in *H. pylori*-infected gastric mucosa [22].

Treatment of cardiovascular diseases
*P. ginseng* has been used traditionally for the treatment of cardiovascular diseases. Notoginsenoside F11 (F11) is a bioactive saponin from the leaves of *P. notoginseng*. F11 caused endothelium-dependent relaxations, which were abolished by 1-NAME (inhibitor of nitric oxide synthases) and ODQ (inhibitor of soluble guanylyl cyclase). F11 increased the cGMP level in mesenteric arteries. Glucocorticoid receptors (GR) and estrogen receptors beta (ERβ) were present in the endothelial layer and their antagonism by RU486 and PHTPP, respectively, inhibited F11-induced endothelium-dependent relaxations and phosphorylations of eNOS, Akt and ERK1/2. Inhibition of phosphoinositide-3-kinase (PI3K) by wortmannin and ERK1/2 by U0126 reduced F11-evoked relaxations and eNOS phosphorylation. Thus, F11 stimulates endothelial GRs and ERBs with subsequent activation of the PI3K/Akt and ERK1/2 pathways in mesenteric arteries. This phosphorylation of eNOS and the release of NO, which activates soluble guanylyl cyclase in the vascular smooth muscle cells, lead to relaxation [23].

Protective effect on alcoholic cirrhosis
Notoginseng showed significant reduction in liver ALT, AST, collagen fiber deposition, and TGF-beta1, Smad3 and CTGF mRNA expressions in liver tissues, with the increase in the expression quantity of Smad7 mRNA. Notoginseng can affect TGF-beta1/Smads signaling pathway and reduce the expression of CTGF [24].

Stimulation of insulin production
American ginseng root displays the ability to achieve glucose homeostasis both experimentally and clinically but the unknown mechanism used by ginseng to achieve its therapeutic effects on diabetes limits its application. Disruption in the insulin secretion of pancreatic beta cells is considered the major cause of diabetes. A mitochondrial protein, uncoupling protein-2 (UCP-2) has been found to play a critical role in insulin synthesis and beta cell survival. Ginseng suppresses UCP-2, down-regulates caspase-9
while increasing ATP and insulin production/secretion and up-regulates Bcl-2, reducing apoptosis. Stimulation of insulin production and prevention of beta cell loss by American ginseng extracts can occur via the inhibition of mitochondrial UCP-2, resulting in increase in the ATP level and the anti-apoptotic factor Bcl-2, while down-regulation of pro-apoptotic factor caspase-9 occurs, lowering the occurrence of apoptosis [25].

CONCLUSIONS

Ginseng is reputed to possess favorable metabolic, neuroprotective, skeletal, hepatoprotective, cardiovascular, reproductive, anti-infective and anticancer effects. The bottom line is that further characterization of ginsenosids and elucidation of their biochemical effects is likely to enable their use beyond traditional medicine.

Abbreviation

P. Ginseng= Panax ginseng
AMPK= Adenosine monophosphate- activated protein kinase
ACC= Acetyl- coenzyme A (CoA) carboxylase
HMGR= 3-hydroxy- methyl- glutaryl- CoA reductase
CaMKKs= Ca\(^{2+}\) activated calmodulin- dependent kinase kinases
mTORC1= Mammalian target of rapamycin complex 1
ATP= Adenosine triphosphate
siRNA= Small interfering RNA
20-GPPD= 20-O-β-D-glucopyranosyl-20(s)-protopanaxadiol
iNOS= Inducible NO synthase
COX= Cyclooxygenase
LPS= Lipopolysaccharide
ATF= Activating transcription factor
CREB= cAMP response element binding protein
AD= Alzheimer’s disease
YCR= Young control rates
PH= Phospholipid hydroperoxide
GPx= Glutathione peroxidase
LPO= Lipid peroxide
KC= Keratinocyte chemoattractant
GR= Glucocorticoid receptor

REFERENCES


