

Letter to the editor:

ARE BERRIES USELESS BY-PRODUCTS OF GINSENG? RECENT RESEARCH ON THE POTENTIAL HEALTH BENEFITS OF GINSENG BERRY

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Dear Editor,

Since the ginseng root (*Panax ginseng* C. A. Meyer) has long been used as a valuable medicinal plant in traditional oriental medicine, current pharmaceutical studies have sought to reveal its other potential applications. These include a wide array of ameliorative effects that encompass those for anti-oxidation, anti-inflammatory, antihistamines, anti-obesity, anti-diabetic, anti-tumor, enhancing immune system function, adjusting blood pressure, sexual potentiation and so on (Li and Gong, 2015; Kim et al., 2016b; Patel and Rauf, 2017; Zhang et al., 2017).

When culturing ginseng, cultivators are required to choose between harvesting the seed for further plantings or removing the inflorescences to increase root development (Fiebig et al., 2005), which suggests that the ginseng berry (fruit) may be considered a useless by-product of ginseng. However, phytochemical analyses determined that ginseng berries contained higher amounts of total ginsenosides than the root (Kim et al., 2009). In addition, ginsenoside Re, a major constituent of the ginseng berry, exhibited multiple pharmacological activities including anti-diabetic, anti-inflammatory, anti-oxidation, neuroprotective, anti-arrhythmic and anti-ischemic effects, as well as supporting osteoblast differentiation and cardiovascular health (Chen et al., 2008; Lee et al., 2012; Peng et al., 2012; Kim et al., 2017c; Huang et al., 2016; Kim et al., 2017a). These findings indicate the potential of ginseng berries as beneficial biomaterials for the food and medical industries; however, ginseng berries have long been underappreciated.

To introduce the ginseng berry as a potential source of herbal medicine, we summarized key findings that demonstrate the pharmacological properties of ginseng berries (Table 1). This

report also emphasizes the potential of ginseng berries to be employed in new herbal medicine, and we hope that this report will stimulate future research on the ginseng berry for its applications in the pharmaceutical industry.

Table 1: Recent studies on the biological and pharmacological activities of ginseng berries

Effect	Summary	Reference
Anti-obesity and anti-diabetic effects	Ginseng berry (fully ripe berry) extracts exhibited anti-adipogenesis effects in 3T3-L1 murine adipocytes by inhibiting lipid accumulation.	Yang et al., 2014
	Steam-dried ginseng berry fermented with <i>Lactobacillus plantarum</i> improved the pathologic indices of type 2 diabetes mellitus by improving insulin and glucose tolerance in <i>db/db</i> mice.	Kim et al., 2012b
	Red (ripe) and green (unripe) berry extracts (70 % EtOH) improved glycemic control (reduced blood glucose levels and improved glucose tolerance) in streptozotocin-induced diabetic mice, as well as increased glucose-stimulated insulin secretion. In addition, both extracts increased the proliferation of INS-1 rat beta cells.	Park et al., 2012
	Ginseng berry extracts (70 % EtOH) improved age-related decline of insulin signaling in mice via inhibition of decreasing expression of forkhead box protein O1 (FOXO1) and peroxisome proliferator-activated receptor gamma and increasing phosphorylation of insulin receptor substrate (IRS1) and protein kinase B (PKB).	Seo et al., 2015
	Ginseng berry extracts (70 % EtOH) improved the fasting and postprandial glucose levels in those with fasting glucose levels of 110 mg/dL or higher, suggesting that ginseng berry extracts may be beneficial in diabetic patients to improve glycemic control.	Choi et al., 2017
Effect on erectile dysfunction	Ginseng berry extracts (70 % EtOH) displayed a relaxant effect on isolated rabbit corpus cavernosum smooth muscles in a dose-dependent manner (10 mg/ml to 150 mg ml ⁻¹). In addition, ginseng berry extracts increased the intracavernosal pressure in an <i>in vivo</i> rat model in both a dose (20, 40, 100 and 150 mg kg ⁻¹ day ⁻¹)- and duration (1, 2, 3 and 4 weeks)-dependent manner. The authors have concluded that these effects of ginseng berry extracts may be mediated by nitric oxide production.	Cho et al., 2013
	Oral administration of the Korean ginseng berry tablet (350 mg ginseng berry extract per tablet) improved male sexual function indices, including the international index of erectile function and the premature ejaculation diagnostic tool.	Choi et al., 2013
Anti-inflammation and immune-modulation activities	Ginseng berry extracts (70 % EtOH; oral administration) inhibited the activation of colon-infiltrating T cells, neutrophils, intestinal CD103 ⁺ CD11c ⁺ dendritic cells and macrophages in dextran sodium sulfate treated C57BL/6 mice. In addition, ginseng berry extracts inhibited the shortening of colon length induced by dextran sodium sulfate treatment. These indicate that ginseng berry extracts have immune-suppressing effects that protect against experimentally-induced colitis.	Zhang et al., 2016

Effect	Summary	Reference
	Ginseng berry extracts (70 % EtOH) increased the expression of phase II genes [heme oxygenase-1 (HO1) and glutamine-cysteine ligase], and suppressed the production of reactive oxygen species (ROS), nuclear factor-κB (NF-κB) activation and expression of inflammatory genes [tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, inducible nitric oxide synthase and cyclooxygenase-2] in lipopolysaccharide-stimulated RAW264.7 cells.	Kim et al., 2012a
Anti-myocardial infarction and antidepressant effects	Ginseng berry extracts up-regulated serotonin (5-hydroxytryptamine; 5-HT) levels and down-regulated 5-HT _{2A} receptor and serotonin transporter levels in Sprague-Dawley rats complicated with myocardial infarction, depression and myocardial infarction. The authors have concluded that ginseng berry extracts may regulate the re-uptake of 5-HT from serum to platelets by modulating the level of 5-HT _{2A} receptor in platelets, as well as those of serotonin transporters in both serum and platelets.	He et al., 2016
Anti-tumor activity	Crude ginseng berry saccharides (composed of galactose, glucose, rhamnose and arabinose in the molar ratio of 6.1:2.0:1.1:3.2) inhibited Lewis lung carcinoma (LLC) tumor growth and lung metastasis in C57BL/6 mice by activating immune functions such as the enhancement of natural killer cell-mediated cytotoxicity, increase of IL-2 and interferon-γ concentrations in the serum and increasing the ratio of CD4 ⁺ /CD8 ⁺ in LLC-bearing mice.	Wang et al., 2015
	Ginseng berry extracts (70 % EtOH) promoted the up-regulation of co-stimulatory molecules [CD86, major histocompatibility complex (MHC) class I and MHC class II] and the production of pro-inflammatory cytokines (IL-6, IL-12 and TNF-α) in mouse splenic dendritic cells. In addition, <i>in vivo</i> administration of ginseng berry extracts induced Th1 and Tc1 immune responses (promoting the generation of Th1 and Tc1 cells) and Ag-specific T cell proliferation that inhibit tumor cell growth. These suggest that the anti-tumor activity of ginseng berry extracts can be mediated by enhancing antitumor immune responses.	Zhang et al., 2015
	Ultrasonicated ginseng berry extracts induced apoptosis in HepG2 cells (liver hepatocellular cells) through the induction of the following proteins: caspase-3, Bcl-2 and Box, as well as enhanced the production of intracellular ROS, which are involved in the intrinsic apoptotic pathway.	Jung et al., 2016
Anti-pigmentation and anti-aging effects	Ginseng berry extracts (70 % EtOH) exhibited anti-melanogenic effects (inhibition of melanin accumulation and tyrosinase activity) on human melanoma cells, anti-aging effects (life span extension and reduction of lipofuscin accumulation) on the aging model organism <i>Caenorhabditis elegans</i> , and inhibited the accumulation of the age-related lipofuscin pigments in human dermal fibroblasts. The authors have concluded that these effects may be due to the activation of anti-oxidation-FoxO3a signaling.	Kim et al., 2016a
Anti-atherogenic effects and the improvement of blood flow	Administration of ginseng berry extracts (70 % EtOH) reduced atherosclerotic lesions without lowering serum lipid levels in ApoE ^{-/-} mice fed with high-fat-diet for 16 weeks. In addition, ginseng berry extracts inhibited the NF-κB-mediated expression of atherogenic inflammatory genes via induction of Nrf2-mediated phase II gene (HO1 and glutamine-cysteine ligase) expression.	Kim et al., 2012a

Effect	Summary	Reference
	In mice fed with a high-fat-diet, administration of a ginseng berry hot water extract resulted in an improved blood flow by decreasing intima-media thickness through the regulation of blood coagulation factors (PT, aPTT, Col/EPI and Col/ADP) related to lipid metabolites.	Kim et al., 2017b
Effect on diabetes induced cognitive impairment	The ethyl acetate fraction of ginseng berry extracts (80 % EtOH) improved cognitive behavior of high-fat-diet induced diabetic mice. In addition, the ethyl acetate fraction also inhibited the acetylcholinesterase activity and malondialdehyde levels of diabetic mice brain tissues.	Park et al., 2015
Anti-hangover property	Ginsenoside-free molecules from steam-dried ginseng berries significantly reduced the level of blood ethanol and serum acetaldehyde in BALB/c mice by modulating the expression of cytochrome P450 (CYP2E1), catalase and aldehyde dehydrogenase.	Lee et al., 2014

Conflict of interest

The authors declare no conflict of interest.

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