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Review

Panax ginseng and Panax quinquefolius: From pharmacology to toxicology

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A B S T R A C T

The use of Panax ginseng and Panax quinquefolius in traditional Chinese medicine dates back to about 5000 years ago thanks to its several beneficial and healing properties. Over the past few years, extensive preclinical and clinical evidence in the scientific literature worldwide has supported the beneficial effects of P. ginseng and P. quinquefolius in significant central nervous system, metabolic, infectious and neoplastic diseases. There has been growing research on ginseng because of its favorable pharmacokinetics, including the intestinal biotransformation which is responsible for the processing of ginsenosides - contained in the roots or extracts of ginseng - into metabolites with high pharmacological activity and how such principles act on numerous cell targets. The aim of this review is to provide a simple and extensive overview of the pharmacokinetics and pharmacodynamics of P. ginseng and P. quinquefolius, focusing on the clinical evidence which has shown particular effectiveness in specific diseases, such as dementia, diabetes mellitus, respiratory infections, and cancer. Furthermore, the review will also provide data on toxicological factors to support the favorable safety profile of these medicinal plants.

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Abbreviations: AD, Alzheimer’s disease; ADAS-Cog, Alzheimer’s disease assessment scale-cognitive subscale; ARI, acute respiratory illness; AUC, area under the curve; BID, BH3 interacting-domain death agonist; CBS, cystathionine-β-synthase; CGL, cystathionine-γ-lyase; ChAT, choline acetyl transferase; Cmax, peak plasma concentration; COX-2, cyclooxygenase-2; DA, dopamine; ENOS, endothelial nitric oxide synthase; GLUT, glucose transporter; h, hour(s); HO, heme oxygenase; HUVEC, human umbilical vein endothelial cells; IL, interleukin; iNOS, inducible nitric oxide synthase; I/R, ischemia/reperfusion; LD, lethal dose; MMSE, mini-mental status examination; NO, nitric oxide; Nrf2, nuclear factor-e, roxidized 2-related factor; PI3K, phosphoinositide 3-kinase; PPD, protopanaxadiol; PPT, protopanaxatriol; Ser, serine; T1/2, half-life; Tmax, time to reach the Cmax.

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0278-6915/© 2017 Elsevier Ltd. All rights reserved.
1. Introduction

The reason why we decided to write such an article is to provide the reader with an exhaustive overview about ginseng, one of the most appreciated medicinal plants with beneficial effects on several types of diseases. The use of ginseng in traditional Chinese medicine dates back to about 5000 years ago, by the legendary Emperor Shennong who, as reported in literature, was the first to classify hundreds of medicinal and poisonous herbs, giving rise to the bedrock of the oldest Pharmacopoeia in the world (Yun, 2001). The term ginseng, from the Chinese jen-shen, means “plant-man”, possibly due to the anthropomorphic shape of its root (Yun, 2001). It is also believed that, according to Oriental medicine, ginseng roots contain the three main human essences, i.e. the body, mind and spirit and, therefore, it is considered “The Lord of herbs” (Yun, 2001).

Botanical preparations of ginseng may result from several species of Panax (from the Greek: pan akheia, meaning “cure of all diseases”) (Yun, 2001). Thirteen species of ginseng have been identified, but the most common used are the Panax ginseng (or Korean ginseng) grown in China and Korea and Panax quinquefolius (or American ginseng) grown in the United States (Virginia and Wisconsin) and Canada (Ontario, Quebec) (Baeg and So, 2013). Indeed, the world’s largest producer of ginseng is China (44.749 tons), followed by South Korea (27.480 tons), Canada (6486 tons) and the United States (1054 tons) (Baeg and So, 2013). Data collected in 2009 confirm that Hong Kong is the biggest importer of ginseng root, whereas Canada is the biggest exporter in the world (Baeg and So, 2013). As far as the market distribution is concerned, South Korea is the largest in the world; however, in this Country the domestic consumption of ginseng is larger than the amount exported (Baeg and So, 2013). Ginseng is also used as an ingredient to season foods, such as chewing gums, candies and beverages. Remarkably successful is ginseng coffee which can be drunk in many coffee bars, but also prepared at home.

Other herbal products are commonly sold under the name of ginseng, but they are not derived from the Panax species. These products include Siberian ginseng (Eleutherococcus senticosus) and Brazilian ginseng (Pfaffia paniculata). Siberian ginseng contains eleutherosides, but not ginsenosides. This review will evaluate the pharmacological and toxicological properties of P. ginseng and P. quinquefolius, the two most studied varieties, focusing on pharmacokinetics, pharmacodynamics and clinical evidence on the efficacy of these medicinal plants for the treatment of important pathologies. Data on the toxicology of P. ginseng and P. quinquefolius will also be provided.

2. Pharmacokinetics of ginseng

The bioactive compounds in ginseng are about thirty triterpene glycosides, called ginsenosides. From a chemical viewpoint, these glycosides are divided into either the 20(S)-protopanaxadiol group (PPD), which includes ginsenosides Rb1, Rb2, Rg3, Rc and Rd or 20(S)-protopanaxatriol (PPT), which comprises ginsenosides Re, Rg1, Rg2 and Rh1, depending on their aglycone moieties (Kim et al., 2013a) (Table 1). In fresh ginseng, ginsenosides Rb1, Rb2, Rc, Re and Rg1 are the main ones (70–80% of total ginsenosides) (Koh et al., 2015). P. ginseng roots often undergo specific processes to promote their preservation and effectiveness, including steaming (red ginseng), air-drying and fermentation (fermented red ginseng) (Koh et al., 2015). Both steaming and air-drying reduce the amount of ginsenosides compared to those contained in the fresh root by approximately 50%; nevertheless, the total amount of remaining ginsenosides, after steaming and air-drying, varies between 14 ± 0.45 mg/g and 18 ± 4.5 mg/g (Koh et al., 2015). These conservation procedures also alter the quality of ginsenosides, e.g. steaming results in the formation of novel compounds, such as, Rb4 and Rf2, whereas steaming and air-drying significantly increase the amount of Rb1 with respect to fresh ginseng, suggesting that other ginsenosides are transformed into Rb1 during the process (Koh et al., 2015).

Ginseng is given orally and, once administered, it is metabolized by intestinal microflora through phase I reactions, such as deglycosylation, oxygenation and hydration (Wang et al., 2011). Deglycosylation is the reaction responsible for transforming the ginsenosides Rb1, Rb2, Rb3, Rc and Rd into 20-O-β-D-glucopyranosyl-20(S)-PPD, also known as compound K, which is the main metabolite with pharmacological effects (Lee et al., 2009; Wang et al., 2011); in addition, through deglycosylation, the ginsenosides Rg1 and Re are transformed into Rh1 and F1 (Wang et al., 2011). In the gut, these reactions are sustained by bacteria belonging to the genera Bacteroides, Bifidobacterium, Eubacterium, Clostridium, Lactobacillus, Peptostreptococcus, Fusobacterium and Prevotella (Xu et al., 2017).

Pharmacokinetic studies in humans reported that, after ingestion of P. ginseng powder (12 g per os in 100 ml of water), the mean compound K transforming activity for ginsenoside Rb1 is 1381.1 ± 427.8 μmol/(h·g) (Lee et al., 2009). Blood absorption of compound K starts 4 h after the administration of P. ginseng powder and reaches the maximum 9–14 h after the administration (Lee et al., 2009). Interestingly data by Wang et al. (2011) on P. quinquefolius (10 g per os with a cup of water), showed that ginsenoside Rb1 peak plasma concentration (Cmax) occurred 4 h after the administration, whereas, at this time point, compound K was not detected, in agreement with Lee et al. (2009). Table 2 reports the main pharmacokinetic parameters for both Rb1 and compound K in subjects receiving supplements of several P. ginseng or P. quinquefolius preparations. It is also worth underlining how the previously described methods affect the pharmacokinetics of compound K (Table 2). Steaming reduces, Cmax, Tmax (the time to reach Cmax) and AUC0–24h (an index of bioavailability) for P. ginseng-derived compound K, whereas fermentation reduces Tmax and increases both Cmax and AUC0–24h (Table 2). The latter data support the fact that fermented red ginseng produces active compound K faster and in a greater amount.

Interestingly, Wan et al. (2017) reported the influence of Asian or Western diets on compound K and ginsenoside Rb1 formation and absorption in six healthy male volunteers, supplemented with P. quinquefolius powder (2 g/day per os for 7 days). Individuals eating a Western diet showed a marked decrease in ginsenoside
Table 1
Chemical names and selected pharmacological actions of ginsenosides. For details about ginsenosides Rb1 and compound K, see text.

| Ginsenoside | Chemical Name | Selected Pharmacological Actions | Reference(s) |
|------------|---------------|----------------------------------|--------------|
| Rb2 | (25S,4S,5S,6R)-2-[(2S,3R,4S,5S,6R)-4,5-dihydroxy-6-(hydroxymethyl)-2-yloxy]-6-(hydroxymethyl)oxane-3,4,5-triol | Inhibition of inflammation or apoptosis in mouse macrophage RAW264.7 and bone marrow-derived mesenchymal stem cells, respectively, by the up-regulation of GP120; inhibition of UBV-induced production of ROS in human dermal fibroblasts and keratinoocytes; prevention of lethal infection by HIV in mice; lowering of cholesterol and triglycerol levels in 3T3-L1 adipocytes; enhancement of fibrinolytic activity in bovine aortic endothelial cells. | Huang et al., 2017; Gao et al., 2015; Oh et al., 2015a, 2015b; Yoo et al., 2013; Kim et al., 2009; Liu et al., 2003 |
| Rg3 | (2S,3R,4R,5R,6S)-2-[(2S,3R,4S,5S,6R)-4,5-dihydroxy-6-(hydroxymethyl)oxan-3-yl]oxy-6-(hydroxymethyl)oxane-3,4,5-triol | Improvement of proliferation and inhibition of apoptosis in NMDA-treated HT22 murine hippocampal neurons; induction of apoptosis and inhibition of proliferation, metastasis and angiogenesis in cancer experimental models; inhibition of HCV propagation by reducing p21; potentiation of paclitaxel cytotoxicity through the inhibition of NFkB signaling in human triple-negative breast cancer lines. | Zhang et al., 2017; Sun et al., 2017; Kim et al., 2017a; Yuan et al., 2017 |
| Rc | 2-[(2S,3R,4S,5S,6R)-4,5-dihydroxy-6-(hydroxymethyl)oxan-3-yl]oxy-6-(hydroxymethyl)oxan-3,4,5-triol | Inhibition of inflammation in activated RAW264.7 macrophages, human synovial cells, and HEK293 cells by inhibiting TLR4/MyD88 and TRIF pathways, and ERK, JNK, and p38/ATF-2 signaling; inhibition of lipogenesis in 3T3-L1 adipocytes; enhancement of fibrinolytic activity in bovine aortic endothelial cells. | Yu et al., 2017; Yang and Kim, 2015; Kim et al., 2000 |
| Rd | 2-[(2S,3R,4S,5S,6R)-4,5-dihydroxy-6-(hydroxymethyl)oxan-3-yl]oxy-6-(hydroxymethyl)oxan-3,4,5-triol | Prevention of TMT-induced damage in mouse primary hippocampal neuron culture by decreasing cell apoptosis via regulation of Bcl-2, bcl-2-like protein 4 and caspase-3; reduction in Aβ formation and cognitive function in ovariectomized rats by the estrogen-like activity; attenuation of breast cancer metastasis formation by decreasing caspase-3 expression in breast cancer lines. | Hou et al., 2017; Yan et al., 2017; Wang et al., 2016; Xie et al., 2016 |
| Re | (25S,4R,5R,6S)-2-[(2S,3R,4S,5S,6R)-4,5-dihydroxy-6-(hydroxymethyl)oxan-3-yl]oxy-6-(hydroxymethyl)oxan-3,4,5-triol | Improvement of cognitive dysfunction in diabetic mice by reducing AChE activity and increasing ACh content in the brain; inhibition of Aβ production via PPARγ-related inhibition of RAC1 expression and activity in N2a/APP695 cells; inhibition of neuroinflammation in a hSOD1G93A transgenic mouse by inhibiting the TLR4 pathway; promotion of bone health by inhibiting osteoclast differentiation and stimulating osteoblast differentiation in mouse mammary carcinoma 4T1 cells and in 4T1 cell-inoculated mice; protection from IR damage by inhibiting the hyperphosphorylation of Nrf2 subunit and decreasing its expression levels in cell membrane, respectively. | Kim et al., 2017b; Cao et al., 2016; Cai and Yang, 2016; Kim et al., 2016a; Huang et al., 2016 |
| Rg1 | (25S,4R,5R,6S)-2-[(2S,3R,4S,5S,6R)-4,5-dihydroxy-6-(hydroxymethyl)oxan-3-yl]oxy-6-(hydroxymethyl)oxan-3,4,5-triol | Hepatoprotection through the modulation of the Keap1-Nrf2ARE pathway in preclinical models; amelioration of cigarette smoke-induced lung fibrosis by the down-regulation of TGF-β1/Smad pathway in pulmonary fibroblasts and COPD rats; induction of nuclear differentiation of ADSC through the microRNA-124 signaling; improvement of d-gal-induced POF by increasing both antioxidant pathways and FSH receptor protein expression. | Gao et al., 2017; Guan et al., 2017; Dong et al., 2017; He et al., 2017 |
| Rg2 | (2S,3R,4R,5R,6S)-2-[(2S,3R,4S,5S,6R)-4,5-dihydroxy-6-(hydroxymethyl)oxan-3-yl]oxy-6-(hydroxymethyl)oxan-3,4,5-triol | Cardioprotection against hydrogen peroxide-mediated injury in H9c2 cells through the up-regulation of SOD and GSH-PX activities and down-regulation of caspase-3 and caspase-9 expression; protection from inflammatory damage in HUVEC by reducing VCAM-1 and ICAM-1 expression; inhibition of hepatic glucose production via AMPK-induced GSK3β phosphorylation and induction of SHP gene expression. | Fu et al., 2015; Choi et al., 2013; Yuan et al., 2012 |
| Rh1 | (2S,3R,4R,5R,6S)-2-[(2S,3R,4S,5S,6R)-4,5-dihydroxy-6-(hydroxymethyl)oxan-3-yl]oxy-6-(hydroxymethyl)oxan-3,4,5-triol | Prevention of sleep deprivation-induced cognitive impairment in mice by reducing oxidative stress in cortex and hippocampus; reduction of oxidative stress-induced damage in rat primary astrocytes through the up-regulation of MAPK and Nrf2/ARE signaling; osteoblast differentiation, osteogenic stimulation and antioxidant effect in mouse proteoblastic MC3T3-E1 cells via the BMP-2/RUNX2 signaling pathways. | Lu et al., 2017; Jung et al., 2016; Siddiqi et al., 2014 |
The main pharmacokinetic parameters of compound K and ginsenoside Rb1.

Table 2

| Sources               | \( C_{\text{max}} \) (ng/ml) | \( T_{\text{max}} \) (h) | \( \text{AUC}_{0-24} \) (ng h/ml) | \( T_{1/2} \) (h) | References                |
|-----------------------|-------------------------------|--------------------------|-----------------------------------|-----------------|---------------------------|
| **Compound K**        |                               |                          |                                   |                 |                           |
| P. ginseng            | 27.9 ± 24^a                   | 11 ± 2                   | 222 ± 221                         | NC              | Lee et al., 2009         |
| Red P. ginseng        | 3.2 ± 1.7^b                   | 9 ± 1                    | 12.7 ± 8                          | NC              | Choi et al., 2010        |
| Fermented red         | 254 ± 51^c                    | 2.5 ± 1                  | 1467 ± 296                        | NC              | Choi et al., 2010        |
| P. ginseng            | 68 ± 40^d                     | 1.9 ± 0.5                | NC                                | 10 ± 6          | Kim et al., 2013a        |
| P. quinquefolius      | 7.3 ± 1.3^e                   | 12                       | NC                                | NC              | Wang et al., 2011        |

| Ginsenoside Rb1       |                               |                          |                                   |                 |                           |
| P. quinquefolius      | 19.9 ± 5.4^d                  | 4                       | NC                                | NC              | Wang et al., 2011        |

N.C., not calculated; \( T_{1/2} \), half-life.

^a Data from 34 healthy Korean male subjects treated with 12 g ginseng with 100 ml of water.

^b Data from 24 healthy Korean male subjects treated with 3 g ginseng with 240 ml of water.

^c Data from 10 healthy Korean male subjects treated with 5 g ginseng with 100 ml of water.

^d Data from 6 healthy American subjects (5 males and 1 female) treated with 10 g ginseng with a cup of water.

Rb1 plasma levels vis-à-vis with a significant increase in compound K plasma levels compared to those eating an Asian diet (Wan et al., 2017). On the other hand, ginsenoside Rb1 and compound K fecal levels resulted much higher in individuals consuming a Western diet than an Asian diet. These findings suggest both an increased conversion of ginsenoside Rb1 into compound K in Western-diet subjects with a longer duration of ginseng-microbiota interaction in the colon without compound absorption (Wan et al., 2017). As the Asian diet is based on various vegetables and rice, whereas the Western diet is rich in fats and animal proteins, it is likely that these differences are responsible for the alteration of enteric microbiota population affecting ginseng metabolism and absorption (Genton et al., 2015; Janssen and Kersten, 2015; Moco et al., 2012; Simpson and Campbell, 2015; Wan et al., 2017). Indeed, Wu et al. (2011a) have shown that an increase in Bacteroides enterotype, with its above mentioned role in the ginseng intestinal microbiota transformation, was positively associated with animal proteins and high intake of fats.

Ginsenosides are metabolized in the liver by oxygenation through the 3A4 isof orm of cytochrome P-450 and undergo enterohepatic recirculation (Qi et al., 2011). Excretion mainly occurs through the feces (see above) and only 0.2%–1.2% of ginsenosides are excreted intact by the urine (Cui et al., 1997; Qi et al., 2011).

3. Pharmacodynamics of ginseng

This section outlines the main mechanisms through which ginseng exerts its pleiotropic effects; among ginsenosides, attention has particularly been focused on Rb1 (the most abundant in steamed/air dried P. ginseng and extracts of P. quinquefolius) and compound K (the main active principle formed through the intestinal phase I metabolism of ginsenosides) (Koh et al., 2015; Wang et al., 1999). However, other ginsenosides, although less abundant, have relevant pharmacological effects as summarized in Table 1.

3.1. Immune system

The modulation of the immune response is one of the most beneficial effects of ginseng. In vivo and in vitro studies reported that both P. ginseng (2 g/kg per os) and P. quinquefolius (5–500 μg/ml) stimulated B-lymphocyte proliferation and increased interleukin(II)-2, IL-10 and interferon-γ production in mouse spleen cells (Liou et al., 2006; Wang et al., 2001, 2004). P. quinquefolius increased the natural killer cell number in mouse spleen and bone marrow (Miller et al., 2012) (Fig. 1). Interestingly, compound K (40 mg/kg and 160 mg/kg per os) exerted an anti-inflammatory activity by suppressing memory B cell subsets, CD40L expression on T cells and CD40 expression on B cells in a rat model of adjuvant induced arthritis (Chen et al., 2016a).

3.2. Nervous system

A dry native extract of P. quinquefolius standardized to 10–12% total ginsenosides, Cerebro™, at doses 30, 100 or 300 mg/kg/day per os for 16 days, increased acetylcholine production by up-regulating choline-acetyltransferase in the brain of mice challenged with β-amyloid1-42 (Aβ1-42); consequently, learning and memory functions significantly improved in these animals (Shin et al., 2016) (Fig. 1). Interestingly, red ginseng-derived compound K (1.5–10 mg/kg/day per os for 2 weeks) reverted scopolamine-induced memory impairment in C57BL/6 mice by favoring the nuclear translation of the transcription factor nuclear factor erythroid 2-related factor (Nrf2) and further enhancement of the cell stress response (see below) (Seo et al., 2016). Korean red ginseng (20–60 mg/kg/day per os for 3 days) inhibited anxiety-like behavior in rats undergoing ethanol-withdrawal by increasing dopamine (DA) brain levels (Zhao et al., 2014). In mice exposed to chronic unpredictable stress, the administration of an aqueous extract of P. quinquefolius (100–200 mg/kg per os prior to the stress) reverted both corticosterone plasma levels and the stress-induced depletion of noradrenaline (NA), DA and serotonin (5-HT) in the hippocampus and cortex by restoring the regulation of the stress axis and decreasing interleukin production (Rasheed et al., 2008) (Fig. 1).

Both red ginseng and fermented red ginseng had an important antinociceptive activity (fermented red ginseng > red ginseng) in a
mouse model of acetic-acid induced abdominal constriction response, perhaps mediated by a significant suppression of nitric oxide (NO) production (Jung et al., 2012). Ramarao and Bhargava (1990) described that a *P. ginseng* extract (200 mg/kg *per os*) produced analgesia in male Sprague Dawley rats through an opiate-independent mechanism. In the same experimental model, the ginseng extract (25–50 mg/kg *per os*) antagonized the morphine analgesic response, whereas, at the dose of 25 mg/kg *per os*, ginseng counteracted the morphine-induced cataleptic effect (Ramarao and Bhargava, 1990).

### 3.3. Cardiovascular system

An aqueous extract of Korean red ginseng rapidly up-regulated endothelial NO synthase (eNOS) via the phosphoinositide 3-kinase (PI3K)/Akt-pathway in human umbilical vein endothelial cells (HUVEC) (Kim et al., 2007) (Fig. 1). Ginsenoside Rb1 (0.001–10 μM) acutely upregulated eNOS by phosphorylating Ser1177 and increased NO production in human aortic endothelial cells (Yu et al., 2007). Ginsenoside Rb1 (0.1–10 μg/ml) also preserved both endothelial NO production in HUVEC from the toxic effects of oxidized low-density-lipoproteins and endothelium-dependent relaxation of porcine coronary arteries exposed to homocysteine (He et al., 2007; Zhou et al., 2005).

A standardized *P. ginseng* extract (80 mg/kg/day *per os* for 90 days) reduced infarct size, improved cardiac performance, induced survival signals and suppressed cardiomyocyte apoptosis in 18 month-old rats with ischemia/reperfusion (I/R) injury. Such events occurred through the up-regulation of pro-survival pathways, such as Akt and eNOS, together with the down-regulation of members of the apoptotic cascade, including caspase-3/7 (Luo et al., 2015). Red ginseng extract (250–500 mg/kg/day *per os* for 7–9 days) improved ventricular hemodynamic function parameters, reduced ST segment and QRS complex intervals and increased antioxidant myocardial levels in both pigs and rats with isoproterenol-induced cardiac injury (Lim et al., 2013a, 2014). Similarly, Korean red ginseng (250–500 mg/kg/day *per os* for 14 days) suppressed both lactate dehydrogenase and creatine kinase-MB fraction and cardiac troponin I and reduced oxidative stress-induced damage in guinea pigs with I/R injury; as a consequence, aortic flow, coronary flow, cardiac output and left ventricular systolic pressure increased (Lim et al., 2013b). A *P. quinquefolius* extract (50 mg/kg/day *per os* for 7 days) decreased infarct size and myocardial apoptosis in mice with I/R damage via activation of eNOS (Wu et al., 2011b). Intriguingly, both compound K (10 mg/kg *per os*) and ginsenoside Rb1 (40 mg/kg *per os*) reproduced the cardioprotective effects discussed above, in particular they reduced infarct size, cardiomyocyte apoptosis and mitochondrial swelling in rodent models of I/R injury (Tsutsumi et al., 2011; Wu et al., 2011c).

Unfortunately, these preclinical findings, suggesting a protective role for ginseng in cardiovascular diseases, did not entail any further clinical development. A possible explanation is that, when designing clinical trials with the purpose of evaluating the effect of drugs on subjects with myocardial infarction or other severe heart diseases, hard endpoints are typically employed (e.g. cardiovascular morbidity or mortality, all-cause death, etc.) in order to highlight the most clinically important effects able to change the history and clinical course of the disease. Therefore, it is worth considering the difficulty, in clinical trials, in using medicinal herbs, such as ginseng, rather than a well-defined drug, for therapeutic purposes, in people at risk of death for cardiovascular diseases. On the other hand, the use of soft endpoints, more suitable for clinical studies on herbal products, provides results which are not always easily applicable to the treatment of severe cardiovascular diseases, such as myocardial infarction.

Extracts of *P. ginseng* and *P. quinquefolius* (0.05 mg/ml) exhibited both anticoagulant and antiplatelet effects in a reconstituted system of human plasma (Lau et al., 2009; Li et al., 2013). A Korean red ginseng extract (200–500 mg/kg/day *per os* for 1 or 8 weeks) inhibited collagen- and thrombin-induced platelet aggregation in rats and rabbits (Hwang et al., 2008; Jin et al., 2007). Both the antiplatelet and anticoagulant effects reported in these studies, have raised concerns on the risk of severe bleedings in subjects on anti-coagulant and anti-thrombotic therapies and supplemented with ginseng (see Section 6).
3.4. Metabolism

It has been shown that ginseng exerts beneficial effects on both lipid and glucose metabolism. Fermented red ginseng (150 mg/kg/day per os for 8 weeks) decreased fasting blood glucose level and increased serum insulin and glucose tolerance in streptozotocin-induced diabetic mice (Jang et al., 2017). In a rat model of high-fructose diet-induced metabolic disorder, fermented red ginseng (250 mg/kg/day per os for 8 weeks) reduced hyperlipidemia and hypertension together with an up-regulation of insulin receptor substrate 1 and glucose transporter (GLUT) type 4 in the muscle (Kho et al., 2016) (Fig. 1). In a well-known preclinical model of obesity (ob/ob mice), fermented red ginseng (0.5–1% in drinking water for 16 weeks) decreased body weight and blood glucose levels compared with control ob/ob animals; both GLUT-1 and GLUT-4 mRNA were increased in the ginseng group (Cheon et al., 2015). Korean red ginseng (400 mg/kg/day for 7 days) increased glucose-induced insulin release from Balb/c mouse islets and decreased apoptosis thus enhancing the metabolic function (Kim et al., 2016b). It is worth pointing out that compound K and ginsenoside Rb1 are responsible for the same effects on glucose metabolism ascribed to ginseng preparations (Chen et al., 2016b; Shen et al., 2015).

3.5. Cancer

Many preclinical studies have shown that P. ginseng counteracts cancer growth through several mechanisms, including the inhibition of angiogenesis and stimulation of apoptotic cell death (Sagar et al., 2006a, 2006b). In addition, Choi et al. (2012) reported that Korean red ginseng (50–100 μg/ml) decreased the expression of both cystathionine-β-synthase and cystathionine-γ-lyase - the enzymes responsible for hydrogen sulfide synthesis - in HUVEC. In this study, the Authors showed, in the same cell line, a ginseng-related decrease in the expression of pro-inflammatory molecules and enzymes, such as IL-6 and IL-8, cyclooxygenase-2 and inducible NOS (iNOS) (Choi et al., 2012) (Fig. 1). Furthermore, Korean red ginseng effectively abrogated hydrogen sulfide-induced angiogenesis (Choi et al., 2012). Compound K (2.5–10 μg/ml) inhibited angiogenesis in HUVEC by suppressing sphingosine-1-phosphate-induced cell migration via modulation of sphingosine kinase-1 (Shin et al., 2014). Likewise, compound K inhibited basic fibroblast growth factor-induced angiogenesis in HUVEC through the reduced phosphorylation of p38 mitogen-activated protein kinase and Akt (Jeong et al., 2010). Lastly, compound K was shown to inhibit the viability of HL-60 human leukemia cells through the (i) activation of caspase-3, caspase 8 and caspase-9, (ii) loss of mitochondrial membrane potential, (iii) release of cytochrome c, (iv) mitochondrial translocation of Bid and Bax and (v) down-regulation of Bcl-2 and Bcl-xL (Cho et al., 2009).

3.6. Cell stress response

Ginseng exhibited a remarkable antioxidant effect through the enhancement of the cell stress response, mainly by up-regulating heme oxygenase-1 (HO-1), a member of the heat shock protein family (Dattilo et al., 2015; Mancuso and Barone, 2009) (Fig. 1). Heme oxygenase-1, exerts its pleiotropic effects by reducing heme concentrations, toxic under conditions of redox imbalance, producing the gaseous neuromodulator carbon monoxide and, ultimately, generating biliverdin, the precursor of the strong endogenous antioxidant bilirubin (Barone et al., 2009; Mancuso et al., 1997, 2008, 2012; Navarra et al., 2000). The upregulation of HO-1 is currently considered a conserved mechanism by which herbal products exert beneficial effects in many organs and tissues (Catino et al., 2016; Feton et al., 2015; Mhilla et al., 2017). A water extract of Korean red ginseng (0.25–2 mg/ml) induced HO-1 expression through the activation and nuclear translocation of Nrf2 in both HUVEC and neuron-like PC12 cells (Park et al., 2010; Yang et al., 2011). Furthermore, the cytoprotective effect of Korean red ginseng against free radical-induced damage was abolished either by specific silencing of the Nrf2 gene or administration of the HO inhibitor zinc-protoporphyrin-IX, thus suggesting the main role of HO-1 in ginseng-induced cytoprotection (Park et al., 2010; Yang et al., 2011). Compound K (25–50 μM) suppressed the cytotoxic activation of BV2 microglial cells challenged with bacterial endotoxin through the up-regulation of HO-1 (Park et al., 2012). Ginsenoside Rb1 (10–100 μg/ml) inhibited 6-OH-DA-induced oxidative injury in SH-SYSY neuroblastoma cell line through the Nrf2-related HO-1 overexpression (Hwang and Jeong, 2010).

4. Clinical studies

Ginseng is considered both a substance that can improve physical and mental skills and a reinvigorating product which is able to help the body regain the physiological functions after exposure to stressful or painful stimuli. Unfortunately, clinical trials carried out to investigate this effect have given rise to rather contrasting results. A randomized, double-blind, placebo-controlled clinical study included 90 subjects (21 men and 69 women) experiencing chronic fatigue for more than 6 months; the randomization lead to the formation of three groups, 30 subjects each receiving, daily and for 4 weeks, either placebo or 250 mg soft capsules with an ethanol extract of P. ginseng (Kim et al., 2013b). The individuals treated with P. ginseng did not have any significant effects on fatigue severity with respect to the placebo group (Kim et al., 2013b). However, the mental fatigue symptoms, but not physical symptoms, significantly improved by both 1 g and 2 g P. ginseng compared with the placebo groups (Kim et al., 2013b). Interestingly, in these subjects, P. ginseng, at both the doses, reduced reactive oxygen species and lipid peroxidation and increased reduced glutathione compared to the placebo group (Kim et al., 2013b).

Regarding the effect of P. ginseng on cognition, Geng et al. (2010) published an extensive systematic review which included nine randomized, double-blind, placebo-controlled studies (eight of which enrolled healthy participants) and concluded there was no convincing evidence to support the cognitive enhancing effect of ginseng. Following this report, additional clinical studies in literature described the beneficial effects of Cereboost (100–400 mg per os) on the short-term working memory performance in both 52 middle-aged healthy adults (Ossoukhova et al., 2015) and 32 healthy young adults (Scholey et al., 2010). Although these Authors did not provide any direct evidence about the mechanism(s) underlying the nootropic effect of Cereboost™, they speculated a possible role for the activation of both cholinergic and dopaminergic brain systems and modulation of NO production. With regard to dementia, Heo et al. (2011, 2012) reported the beneficial effects of Korean red ginseng, in doses ranging from 1.5 to ~4.5 g/day to 4.5–9.0 g/day per os for 24 weeks, on the cognitive performance of subjects with probable Alzheimer’s disease (AD) (N = 30) or moderately severe AD (N = 30). In these groups, ginseng significantly improved both ADAS-Cog test (which evaluates memory, language, praxis, attention and other cognitive abilities) and MMSE test (which evaluates orientation, attention, calculation, language and basic motor skills). The same Authors, confirmed the beneficial effects of Korean red ginseng up to 96 weeks of treatment on subjects with probable AD (Heo et al., 2011). Similarly, positive results on cognitive skills and memory function were described by Lee et al. (2008) who treated 58 patients with AD with P. ginseng...
powder (4.5 g/day per os for 12 weeks). The reduction of both Aβ1-42 and tau protein neurotoxicity together with the potentiation of cholinergic pathways and the enhancement of long-term potential are among the determinants of this ginseng-induced neurocognitive improvement in AD subjects (Heo et al., 2011). Intriguingly, ginseng showed beneficial effects as an adjuvant treatment in subjects suffering from mood disorders and psychosis. Jeong et al. (2015) showed how Korean red ginseng (3 g/day per os for 8 weeks) improved residual symptoms in 35 female individuals who remitted from major depression and hypothesized multiple mechanisms, including the NO-mediated modulation of the stress axis and the increased production of NA, DA and 5-HT. Regarding mood disorders and their adverse effects, Chen and Hui (2012) reported the beneficial effects of HT1001™ (200 mg/day per os for 4 weeks), an extract of *P. quinquefolius* consisting of a mixture of ginsenosides Rb1, Rg1 and other bioactive phytochemicals, on extrapyramidal symptoms in 64 subjects with schizophrenia and claimed, as a possible mechanism, the ACh-mediated regulation of DA transmission.

Positive results were obtained with *P. quinquefolius* and *P. ginseng* in the metabolic regulation of glucose in subjects with or without diabetes mellitus. This was the aim of a systematic review that evaluated 165 clinical studies, of which recruited 339 subjects with type 1 and type 2 diabetes mellitus and 7 enrolled 431 subjects without diabetes mellitus (Shishtar et al., 2014). Among these 16 clinical trials, 11 used parallel and 5 used crossover designs, and thirteen had placebo as comparator (Shishtar et al., 2014). The main result in this review deals with the ability of ginseng to significantly reduce fasting blood glucose compared to controls; neither fasting plasma insulin nor glycaated hemoglobin resulted modified in the group of patients receiving ginseng (Shishtar et al., 2014).

More recent clinical studies reported beneficial effects of *P. ginseng* and *P. quinquefolius* in preventing infections of the upper respiratory tract. In a randomized, double-blind, placebo-controlled trial involving 100 healthy volunteers, Lee et al. (2012) reported that Korean red ginseng (3 g/day per os for 12 weeks) significantly reduced the episodes of acute respiratory illness (ARI), mainly due to rhinovirus and coronavirus infections, in the 50 subjects randomized in the treatment arm with respect to the 50 individuals in the control group. A patented poly-furanosyl-pyranosyl-saccharide-rich extract of *P. quinquefolius*, COLD-FX, showed a beneficial effect on common cold. As described by Predy et al. (2005), who conducted a randomized, double-blind, placebo-controlled trial enrolling 323 healthy volunteers who had contracted at least two colds in the past year, COLD-FX (200 mg twice a day per os for 4 months) significantly reduced the proportion of subjects with two or more Jackson-verified colds compared to the placebo group. The *P. quinquefolius* extract significantly reduced also the total symptom score and the total number of days of cold symptoms in the ginseng-treated group (Predy et al., 2005). In a similar clinical trial carried out on 43 community-dwelling adults aged 65 or older, the 22 subjects in the COLD-FX group (200 mg twice a day per os for 4 months) reported a significant reduction of ARI and ARI-related symptoms during the last 2 months of treatment (McElhaney et al., 2006). The anti-infective effect of ginseng can be ascribed to both the strengthening of immune functions (see also Section 3.1) and the direct inhibition of virus replication (Lee et al., 2012). Scaglione et al. (1996) designed a randomized, double-blind, placebo-controlled trial involving 227 volunteers to study the effect of a standardized *P. ginseng* extract, Ginsana G115 (100 mg/day per os for 12 weeks), on both common cold and influenza. These Authors showed a significant decrease in the incidence of common cold or influenza illness in the G115 group between weeks 4 and 12 (Scaglione et al., 1996). Interestingly, subjects treated with the ginseng extract had an increase in anti-influenza antibody titers and natural killer cell activity (Scaglione et al., 1996). However, due to their heterogeneity, these clinical studies are unsatisfactory to guarantee a therapeutic effect of ginseng in such pathologies.

Limited results, although quite interesting, have been reported on the preventive role of ginseng in patients at risk of or affected by cancer. Yun et al. (2010) conducted a randomized, double-blind, placebo controlled clinical trial on 643 subjects with chronic atrophic gastritis who received Korean red ginseng extract powder 1 g/week per os for 3 years and followed for 8 years. Among these 643 patients, 24 developed cancers during the 11 years, in particular lung and stomach cancers (14 out for 24). The Authors reported a significant reduction of relative non-organ-specific cancer risk in male subjects treated with Korean red ginseng compared to the placebo group (Yun et al., 2010). Further studies focused on the role of ginseng in contrast to cancer-related fatigue. In an open label study, Yennurajalingam et al. (2015) evaluated the effect of *P. ginseng* (800 mg/day per os for 29 days) in 30 patients affected by cancer-related fatigue. In these subjects, *P. ginseng* reduced fatigue and improved both quality of life and appetite and sleep at night (Yennurajalingam et al., 2015). Similar results had been shown by Barton et al. (2013), who included 364 cancer survivors in a multicenter, double-blind, randomized, placebo-controlled phase III clinical trial; these subjects received 2 g/day *P. quinquefolius* per os for 8 weeks and the fatigue evaluated. A significant improvement of cancer-related fatigue was detected at 8 weeks, and the greatest benefit was reported in patients still receiving an active cancer treatment (Barton et al., 2013). Among the possible mechanisms through which ginseng could affect cancerogenesis, worth mentioning are the inhibition of angiogenesis and the down-regulation of cellular pathways, such as iNOS or COX-2 (see also Section 3.5). Concerning the beneficial effects of ginseng in preventing cancer-related fatigue, these seem to be linked to the reduction of inflammatory processes and modulation of cortisol release through the stress axis.

The previously reported clinical trials were not been able to determine which of the ginsenosides originally present in the roots of *P. ginseng* or *P. quinquefolius* or those resulting from metabolism by the intestinal microbial flora can be considered responsible for the described therapeutic effects. Nevertheless, the parallelism between the pharmacological effects described for ginsenoside Rb1 and the compound K with those found in clinical studies using raw formulations or extracts of *P. ginseng* or *P. quinquefolius*, allow to conclude how these two ginsenosides can be considered active ingredients responsible, for the majority of the therapeutic effects, attributed to ginseng.

### 5. Adverse effects

In most cases, no significant side effects have been observed in the supplementation with *P. ginseng* and *P. quinquefolius*. However, vaginal bleeding and mastalgias have been reported by some patients due to the estrogenic effect of ginseng (Greenspan, 1983; Kabalak et al., 2004; Oh et al., 2010; Palmer et al., 1978). In patients taking high doses of *P. ginseng* (more than 2.5 g/day) central nervous system (CNS) effects have been reported, such as insomnia (Coon and Ernst, 2002; Scaglione et al., 1996), tachyarrhythmias (Kabalak et al., 2004), hypertension (Siegel, 1980) and nervousness (Coon and Ernst, 2002; Siegel, 1979). Other reported adverse effects of *P. ginseng* are headaches and gastrointestinal disorders (Coon and Ernst, 2002).

### 6. Interactions and precautions

Psychiatric patients taking *P. ginseng* with other drugs, such as...
phenelzine or other monoaminooxidase inhibitors, have reported headaches, tremulousness and manic episodes (Coon and Ernst, 2002; Jones and Runikis, 1987; Shader and Greenblatt, 1985). Due to its well-known estrogen-like effect, ginseng should be used with extreme caution in women taking progestogens for the possible worsening of side effects of the latter (Greenspan, 1983; Punnonen and Lukola, 1980). Subjects treated with warfarin or other anticoagulants or antiplatelet drugs, should avoid taking ginseng-based supplements due to the high risk of bleedings (Chen and Hui, 2012; Coon and Ernst, 2002; Janetzky and Moreale, 1997). Subjects receiving digoxin or corticosteroids should also be cautious when taking ginseng (Chen and Hui, 2012; Dasgupta and Reyes, 2005; Miller, 1998). Owing to the immunomodulatory effects described above, immunocompromised subjects, treated with immune-stimulating therapies or with autoimmune disorders, should also take ginseng with caution.

7. Panax ginseng and Panax quinquefolius toxicology

7.1. Toxicity

According to the National Toxicology Program (2011), P. ginseng, given per os, shows LD50 values of 750 mg/kg and 200 mg/kg in rats and mice, respectively. Quite different are the results by Francantonio Berté who studied the toxicological profile of Ginsana G115 and found LD50 values greater than 5000 mg/kg per os and 1000 mg/kg intraperitoneal for rats and mice (Carabin et al., 2000). The same extract was given to rats at doses of 4000 mg/kg per os for 20 days and both hematological and histological biomarkers were found normal at the end of the study (Carabin et al., 2000). Ginsana G115 administered to beagle dogs in doses up to 15 mg/kg for 90 days did not cause any sub-chronic toxicity (Hess et al., 1983). Chronic studies in male and female F344/N rats and B6C3F1 mice treated with P. ginseng at doses up to 5000 mg/kg for 2 years did not show any toxic effect; furthermore, no increases in the incidence of cancer or non-neoplastic lesions were detected (National Toxicology Program, 2011).

7.2. Reproductive and developmental toxicology

On the basis of the studies by Chan et al. (2004) and Liu et al. (2005, 2006), ginsenosides Rb1, Rg1 and Re were responsible for embryotoxic and teratogenic effects in rodent whole embryo cultures. For this reason, P. ginseng should be considered with caution during the first trimester of gestation (Chan et al., 2004; Liu et al., 2005, 2006; Seely et al., 2008). Hess et al. (1982) studied the safety of Ginsana G115 on growth, reproduction, lactation and maturation of male and female Sprague-Dawley rats. At doses ranging from 1.5 to 15 mg/kg per os, Ginsana G115 did not show adverse effects on the reproductive parameters evaluated or treatment related effects on animal behavior, physical appearance or food consumption (Carabin et al., 2000; Hess et al., 1982). Dietary mixtures of purified P. ginseng at doses of 1% and 5% for 60 days did not cause any significant change in the weight of the testis, epididymis or seminal vesicles; interestingly, rats in the 5% group exhibited a marked increase in testosterone plasma levels (Carabin et al., 2000; Fahim et al., 1982). A systematic review by Seely et al. (2008) suggested that breast-feeding women should not be supplemented with P. ginseng.

7.3. Carcinogenicity

No chronic carcinogenetic studies of ginseng in experimental animals have been found in literature.

7.4. Genetic toxicology

A P. quinquefolius water extract was used to study the mutagenicity in Salmonella typhimurium strain TM677. At concentrations up to 36 mg ginseng extract/ml of culture media, no mutagenic response was detected (Carabin et al., 2000; Chang et al., 1986). Interestingly, in cultured Chinese hamster V79 cells, P. ginseng (0–1 mg/ml) induced DNA synthesis, but increased the rate of DNA excision repair processes upon treatment with ultraviolet radiation or methyl methanesulfonate (National Toxicology Program, 2011; Rhee et al., 1991). Furthermore, ginsenosides Rb1 and Rg1 exhibited anti-mutagenic activity in S. typhimurium strain TA100 (Ohhsuka et al., 1995; National Toxicology Program, 2011).

8. Conclusions

Unlike other herbal products, clinically limited by unfavorable pharmacokinetics, ginseng has been extensively studied in humans and the pharmacological actions - which have proven effective in many diseases - have been well characterized. Moreover, ginseng has had nearly no toxic effects in case of controlled intake. However, Siegel (1979) described a “ginseng abuse syndrome” characterized by previously described symptoms of CNS hyperactivity, skin eruptions and morning diarrhea, although it became evident in the case of high dose intake of ginseng (up to 15 g/day). Thus, considering the consumption of ginseng in the Western and in the Eastern world, its intake merely at toxic doses, should be considered scarcely frequent although it cannot be completely ruled out. It is worth focusing on the intake of ginseng products by subjects receiving cardiac, antidepressants and anti-hemorrhagic medications for possible side effects.

In conclusion, among the herbal supplements on the market, ginseng is the most widely studied also by appropriate clinical trials highlighting the beneficial effects compared to a low number of potential toxic effects.

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