Food and Chemical Toxicology 107 (2017) 362–372

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Review

Panax ginseng and *Panax quinquefolius*: From pharmacology to toxicology

Cesare Mancuso [a, *], Rosaria Santangelo [b]

[a] Institute of Pharmacology, Catholic University School of Medicine, Largo F. Vito, 1, 00168 Rome, Italy
[b] Institute of Microbiology, Catholic University School of Medicine, Largo F. Vito, 1, 00168 Rome, Italy

ARTICLE INFO

Article history:
Received 7 April 2017
Received in revised form
6 July 2017
Accepted 7 July 2017
Available online 8 July 2017

Keywords:
Compound K
Free radicals
Ginsenosides
Heme oxygenase
Herbal products
Medicinal plants

ABSTRACT

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.

Contents

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; C_{max}, 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-erythroid 2-related factor; PI3K, phosphoinositide 3-kinase; PPD, protopanaxadiol; PPT, protopanaxatriol; Ser, serine; $T_{1/2}$, half-life; T_{max}, time to reach the C_{max}.

* Corresponding author.
E-mail address: cesare.mancuso@unicatt.it (C. Mancuso).

http://dx.doi.org/10.1016/j.fct.2017.07.019
0278-6915/

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 ± 0.04 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, Rh4 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-glu-copyranosyl-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). Interesting 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 (C_{max}) 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, C_{max}, T_{max} (the time to reach C_{max}) and AUC_{0-24h} (an index of bioavailability) for *P. ginseng*-derived compound K, whereas fermentation reduces T_{max} and increases both C_{max} and AUC_{0-24h} (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