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GINSENOSIDES FROM *PANAX* SPECIES: RECENT TRENDS AND INSIGHTS ON GINSENG PRODUCTS AS HERBAL MEDICINE

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ABSTRACT

Ginseng species are widely gaining popularity in treatment of multiple diseases, being used in traditional systems of medicine for thousands of years. The bioactive components comprise a class of triterpenoid saponins, known as ginsenosides and demonstrate key pharmacological activities including anticancer, neuroprotective and antioxidant, among others. Across the globe, ginseng has been a component of various commercial products and formulations, highlighting its prospects as "drug-like" candidates in drug discovery studies. Although, studies have suggested that it is overall a safe product but interactions with other drugs may be a cause of concern. In addition, the product adulteration during developmental stage and substitution with inferior varieties may also lead to indiscriminate applications in the global ginseng market. The review aims to provide insights on the recent ginseng products, formulation development and its potential to act like herbal medicine, in the present context and how development of biomarkers and authentication methods would benefit the metabolite pharmacological validation of ginseng products.

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INTRODUCTION

The traditional medicines and formulations from *Panax* species continue to gain popularity as herbal medicines, marketed globally for pharmacological attributes. Known as the 'King of Herbs', ginseng has been extensively explored in traditional medicine for the treatment of multiple diseases and shows prospects in the present era as well. Different species of Panax namely *Panax notoginseng, P. ginseng and P. quinquefolius* (Family: Araliaceae) constitute the main source of the bioactive compounds, ginsenosides. Among the 13 recognized ginseng species, *P. ginseng, P. notoginseng, P. quinquefolius, P. japonicas, P. vietnamensis* are some of the commonly used species in herbal formulations. In addition to its pharmacological attributes, ginseng is used in health supplements, and agriculture, among others (Ahmed Ratan *et al.*, 2020) (Figure 1).

Figure 1. *Panax ginseng*

Ginsenosides are triterpene saponins classified as oleanane and dammarene saponins on the basis of their aglycone moiety (Christensen, 2009). Till date, more than 180 ginsenoside analogues have been reported; while Rb2, Re, Rg1, Rb1 and Rc are regarded as major ginsenosides (Kim *et al.*, 2017; Kim *et al.*, 2018). The different ginsenoside analogues demonstrate multiple pharmacological activities and project an economic worth of US$ 2.1 billion, according to global medicinal plant trade (Manzanilla *et al.*, 2018). Among the plant parts, ginseng roots are the key constituents of ginsenosides and price of the plant varies with growth conditions, age, cultivars impacting quality of medicinal traits of ginseng (Kim *et al.*, 2012). The bioactive ginsenosides show antimicrobial, antiviral, antiinflammatory, neuroprotective activities with several targets identified for ginseng metabolites (Kim *et al.*, 2018; Kim *et al.*, 2018; Wahid *et al.*, 2010). The steroidal moiety of ginsenosides confers diverse pharmacological properties to the bioactive constituents, showing interaction with cell membranes, receptors (intracellular and extracellular), membrane ion channels leading to transcriptional changes (Han *et al.*, 2018; Mohanan *et al.*, 2018). Ginseng formulations and ginsenosides are being extensively studied worldwide for their pharmacological functions and emerging as promising novel therapeutic agents (He *et al.*, 2018), as represented in Table 1.

Furthermore, ginsenosides analogues have been documented to show therapeutic effects in neurological disorders namely Parkinson disease, Huntington disease and Alzheimer's disease in clinical research. The plant species show potential to be further studied and used as herbal medicine, however, authentic validation methods including biomarkers need to be developed for product validation and metabolic profiling of ginsenosides. Discussing the recent and upcoming trends in ginseng research (particularly ginseng formulations and commercial products) and their pharmacological relevance, the mini-review aims to draw attention to the commercial prospects and marketing of ginseng products, need to address the existing bottlenecks and how an extensive research on ginsenoside profiling and validation would improve its commercial development.

Table 1. Some commercially available ginsenoside products and their validation methods

Ginseng herbal product	Bioactive constituents	Validation method	Reference
P. ginseng	Root component (0.1% Rb1 ginsenoside, 0.2% Rg1 ginsenoside)	DNA barcoding	Palhares *et al.*, 2015
P. notoginseng (Shuxiong tablets)	*P. notoginseng* rhizome	QTOF/UPLC	Yao *et al.*, 2016
P. ginseng	Root mixture	NIR barcoding	Dong *et al.*, 2020
P. ginseng	Rhizome and dried roots	DNA barcoding	Zhang *et al.*, 2019
P. ginseng, P. quinquefolius (capsules, tablets)	Dried plant extract	HPLC, RFLP markers	Del Serrone *et al.*, 2006
Functional food (ginseng pills)	Herbal plant mixture	HPLC	Wang *et al.*, 2019
Food supplement for diabetes	Composition of ginseng gels, ginseng roots and bitter melon	UPLC/MS	Xie *et al.*, 2019
P. ginseng, P. quinquefolius	Fresh and dried ginseng roots	HPLC, PCR	Mihalov *et al.*, 2000
Weight loss supplements	Ginseng extract and capsule	UHPLC–DAD	Ahmad *et al.*, 2020

BIOACTIVITY AND PHARMACOKINETICS OF GINSENOSIDES ANALOGUES

Panax species (Family: Araliaceae) is cultivated worldwide, primarily in 35 countries for its pharmacological properties. The components of ginseng vary with its geographical habitat, climate, plant part and extraction methods (Ahmed Ratan *et al.*, 2020). In *P. quinquefolius* and *P. notoginseng*, main ginsenoside analogues are pseudoginsenoside F11 and notoginsenoside R1 while ginsenoside Rf is present in different geographic *Panax* species (Qi *et al.*, 2011a). The ginsenosides are sub-categorized into protopanaxadiol, protopanaxatriol and miscellaneous types, showing variation among species (Yang *et al.*, 2014). Significant literature reviews on chemical composition and diversity of ginsenosides are available discussing the - structural diversity and properties of ginsenoside analogues (Ahmed *et al.*, 2020; Yang *et al.*, 2014). Clinical studies have demonstrated the therapeutic prospects of ginsenoside analogues: ginsenoside Rf (with taurine) show synergistic action for enhanced expression of brain-derived neurotrophic factor (BDNF) in SH-SY5Y human neuroblastoma cells, showing neuroprotective activity (Lee *et al.*, 2020). Another significant study by Dhuna *et al.* (2019) showed that ginsenosides act as positive modulators of P2X4 receptors in HEK-293 cells, suggesting a positive role in hypertensive disorders (Dhuna *et al.*, 2019). However, some pharmaco-kinetic properties of ginsenosides do not comply with drug-likeness and have limitations; studies have shown low absorption of triterpenoids on oral administration, low permeability of membranes and very high molecular weight, raising the subject of further improvement. Some examples indicate better bioavailability of ginsenosides

Rg1, Re, and Rh1 and R1 compared with ginsenoside Rd, Rg3, Rh2 and Rb1, respectively (Kim *et al.*, 2018; Qi *et al.*, 2011b). Few studies have shown ginsenoside analogues show interaction with drugs like phenelzine and warfarin, respectively. In this direction, chemi-informatics approaches need to be adopted for synthesis of new ginsenoside analogues, with improved pharmaco-kinetic properties. In addition, more analogues need to be scientifically validated *in vitro* to establish their pharmacological roles and toxicity profiles for development as prospective therapeutic agents. Studies into ginseng toxicity assessment showed that indiscriminate misuse of ginseng results in uterus bleeding, manics, atrial fibrillation, gynecomastia, hepatitis among others. Moreover, ethanol plant extract may cause cerebral arteritis (Paik and Lee, 2015) and Stevens-Johnson syndrome (Ryu and Chien, 1995). A thorough understanding and toxicity assessment is essential for determination of safety of ginseng products before approval for commercial purposes.

GINSENG FORMULATIONS AND GLOBAL MARKET

The herb has been extensively studied and used in the traditional system of medicine and as food supplements, presently in the global market for herbal medicine. Studies have shown the details of 507 herbal products of ginseng marketed globally (Ichim and Boer, 2021). The commercial products are extensively sold in countries like Australia, South Korea, South American countries and Asia, among others. Although a number of commercial products including ginseng extracts and formulations are available, very few have been scientifically validated for their potential pharmacological attributes. However, considering the rising demand of global supply of ginseng, adulteration with low yielding varieties and low grade materials adversely influence the ginseng supply/market (Huang *et al.*, 2017), calling for illegal trade in some cases. In addition, factors like low-grade substances and waste processing further contribute to deceptive trade of the product (Huang *et al.*, 2017). According to international guidelines, herbal medicine and supplements should not have adulteration and should be of pure grade (Simmler *et al.*, 2018) and on purpose adulteration consists of substitution of products and contamination (Shanmughanandhan *et al.*, 2016). In addition, major concerns regarding adulteration of products differentially influence the ginseng market, a substantial difference between their medicinal attributes and economic returns (Zhao *et al.*, 2020). The improper use due to product adulteration affects the supply chain, severely hampering the global market. Therefore, the use of biomarkers for validation of ginseng varieties and secondary metabolite profiling, becomes essential. An interesting study by Ichim and Boer (2021) aimed to investigate the authentication of food supplements and ginseng products, available (sold) in the global market. The study suggested variation in commercial ginseng products and adulteration between different continents, highest in South America and negligible in Africa, respectively. Furthermore, product substitution with different *Panax* species as well as different plant parts, was also reported (Ichim and Boer, 2021). Although ginseng formulations and products hold key significance with pharmacological attributes, the commercial market for ginseng products remains disorganized and poorly regulated. Authentication and validation studies on ginseng extract formulations being relatively few, product adulteration accounts for major challenges and needs to be addressed. Scientific validation employing sophisticated techniques consisting of NMR, HPLC and TLC forms the platform for quality control of the product and formulation, with development of biomarkers would further benefit the metabolite quanti-

fication, and pharmacological validation of ginseng products. Addressing these gaps and bottlenecks, would define the basis of development of authentic ginseng products and a proper global market supply.

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