Ginseng: A panacea linking East Asia and North America?

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According to ancient Chinese medical literature and Korean history, ginseng has been used since around 2000 BCE. It has been regarded as a very precious medicinal plant, on par with poppy, aloe, and garlic, the use of which goes back to the same period in other parts of the world. It is not surprising that the name *Panax*—meaning "all healing" in Greek—has been applied to this plant, because it has been used to treat various diseases from ancient times, and is also recognized, especially in Asian countries, as a health supplement that can increase energy and instill a sense of well-being. To date, fourteen species belonging to the *Panax* genus have been identified, and three species are widely circulated on the global market: *Panax ginseng* C.A. Meyer, cultivated mainly in Korea and northeastern China; *Panax quinquefolius* L. (American ginseng), grown mainly in the Canadian provinces of Ontario and British Columbia and the American state of Wisconsin; and *Panax notoginseng* Burkill, found in southern China (*1*).

History and use

P. ginseng is likely to have originated in Manchuria (now the northeast part of China) and in the ancient Three Kingdoms of Korea (*2*). The first description of ginseng in the history of traditional Chinese medicine appeared in the pre-Han era (BCE 33–48), over 2,000 years ago. In 1713, the Royal Society published a letter from Father Jartoux, a Jesuit missionary in China, containing a description of ginseng's botany, habitat, and medicinal uses (*3*). *P. quinquefolius* was discovered by American settlers in the mid-1700's in New England. This plant had long been used by the Native Americans, who valued the root for its curative powers and life-enhancing capabilities. Ginseng has purported use for the treatment of cancer, diabetes, and cardiovascular dysfunctions, as well as for cognitive enhancement with an apparently low rate of adverse effects. In combination with other materia medica, *P. ginseng* and *P. notoginseng* have been used in complex Chinese formulations for treating angina pectoris (*4, 5*).

Processing, chemistry, and metabolism

Most ginseng in today's market is cultivated in the field for 4 to 6 years. Ginseng is classified into three types, depending on how it is processed after harvest: fresh ginseng (can be consumed in its fresh state), white ginseng (dried after peeling), and red ginseng, which requires special preparation skills, such as steaming and drying under specific conditions. Technology for the long-term storage of red ginseng was developed by pioneers in ginseng manufacture, securing the foundation for this form of the root. The process of steaming stabilizes the ginseng with regard to metabolism, and transforms the secondary metabolites into less polar phytosteroids that are thought to be both more active in the body and safer.

The active ingredients in ginseng include ginsenosides and polysaccharides. Ginsenosides belong to the saponin family and are divided into 20(*S*)-panaxadiols and 20(*S*)-panaxatriols, depending on the dammarane skeleton and the number of hydroxyl groups that can be substituted with other groups (*1*). The biological activities of these phytosteroids have been studied intensively with regard to their structure-activity relationships. Asian ginseng typically contains six types of ginsenosides: panaxadiols (Rb_1, Rb_2, Rc, and Rd) and panaxtriols (Re and Rg_1). In contrast, American ginseng contains high levels of Rb_1, Rd, and Re (*6, 7*).

Ginsenosides are extensively metabolized in the gastrointestinal tract after oral administration (*8*), with sugar moieties being removed to generate the aglycones, 20(*S*)-protopanaxadiol (aPPD), and 20(*S*)-protopanaxatriol (aPPT), and the partially deglycosylated ginsenosides. Since most native ginsenosides are either poorly absorbed in the intestines or are quickly metabolized by deglycosylation, oxidation, and esterification in the intestine or the liver, they could be regarded as "pro-drugs." Thus, understanding the pharmacokinetics and pharmacodynamics of native ginsenosides and their metabolites is critical for their clinical application.

Standardization

Currently, there are many ginseng products on the market and the quality control of these commodities is of paramount importance. Quality control of ginseng extracts and finished products is usually based on the determination of specific bioactive ginsenosides. Although the international standard ISO 17217-1:2014 specifies minimum requirements and test methods for ginseng seeds and seedlings (*9*), ginseng extract should also be standardized such that each batch contains an acceptable concentration range of active ingredients to guarantee quality and efficacy from product to product. Distinguishing between *P. ginseng* and *P. quinquefolius*, which have similar chemical and physical properties but seemingly different pharmacological activities, is a challenge. Recently, all known ginsenosides were identified by metabolomics using high-performance chromatography/mass spectrometry analysis, and this large data set was statistically analyzed. In a targeted analysis, ginsenoside Rf was confirmed as a chemical marker present in processed *P. ginseng*, but not in processed *P. quinquefolius* (*10*).

Diverse pharmacological activities via multiple mechanisms

Given the structural similarity between ginsenosides and steroid hormones, we hypothesized that ginsenosides function as receptor agonists, partial agonists, or antagonists depending on the microenvironment. As shown in Figure 1, ginsenosides act by binding to steroid hormone receptors, such as androgen, estrogen, and glucocorticoid receptors, to modulate gene expression (*11–14*). We have previously reported that the dominance of Rg_1 leads to

angiogenesis, whereas Rb_1 exerts an opposing effect (*15*) through activation of glucocorticoid (*16*) and estrogen (*17*) receptors. In addition to their classic genomic effects, ginsenosides can also function through transcription-independent, nongenomic activation of signaling cascades, such as phosphoinositide 3-kinase/Akt, adenosine monophosphate-activated protein kinase, and calcium signaling that occurs outside the nucleus (*18–23*) (Figure 1). Ginsenosides are also implicated in ion channel regulation, including voltage-dependent and ligand-gated ion channels, for the control of cardiovascular function and hypertension (*24–26*). Recent developments have also revealed ginsenosides to be an important regulator of microRNAs (miRNAs) (*27–30*). Moreover, mRNA-like, noncoding RNAs were identified in ginseng, suggesting that it might exert a regulatory role through miRNAs and small interfering RNAs (siRNAs) (*31*). Whether these small RNAs could affect our body function awaits further investigation (*32*). A number of studies have demonstrated that ginsenosides, and especially their metabolites, interact with cytochrome P450 enzymes (CYPs) and adenosine triphosphate (ATP)-binding cassette transporters (ABC transporters, including breast cancer resistance protein, BCRP) (*33–36*). Given the fundamental roles of ABC transporters and CYPs in the absorption, transportation, and metabolism of nutrients, hormones, and environmental toxins, it is plausible that ginseng may exert its wide-ranging biological effects and health benefits by modulating the transportation and metabolism of vital substances in the human body (Figure 2). Intriguingly, aPPD and aPPT are BCRP inhibitors and therefore potential chemosensitizers (*37*). Ginseng root also contains acidic polysaccharides that appear to play important roles in immune modulation (*38*). In addition, ginseng polysaccharides have shown antifatigue (*39, 40*) and antidiabetic (*41*) effects. However, although numerous studies have been done in vitro and in vivo, very few clinical studies exist.

Challenges and opportunities

Despite playing an important role as a health supplement and medicine in East Asia for millennia, the clinical efficacy of ginseng remains to be established through stringent evidence-based validation. The synthesis of ginsenosides, including the backbone and its glycosylated derivatives, is extremely challenging. This bottleneck limits the development of

ginsenosides as drug candidates. Thus, developing novel techniques for enriching bioactive components in ginseng should be a top priority. For example, selective transformation of ginsenosides by specific intestinal microbes may provide a new opportunity for drug discovery. It is also an exciting prospect to obtain the full genome sequence of ginseng root as a precursor to manipulating the biosynthesis of specific ginsenosides and realizing a "ginsenoside factory" (*42–44*). A high-throughput, multidisciplinary approach should be developed to bring new insights into the molecular actions of ginsenosides and how the multiple, distinct signaling networks that it impacts are interconnected. Finally, more robust clinical trials should be designed and implemented. Only good clinical outcomes can instill faith in patients and the general public with regard to products derived from this time-honored treatment.

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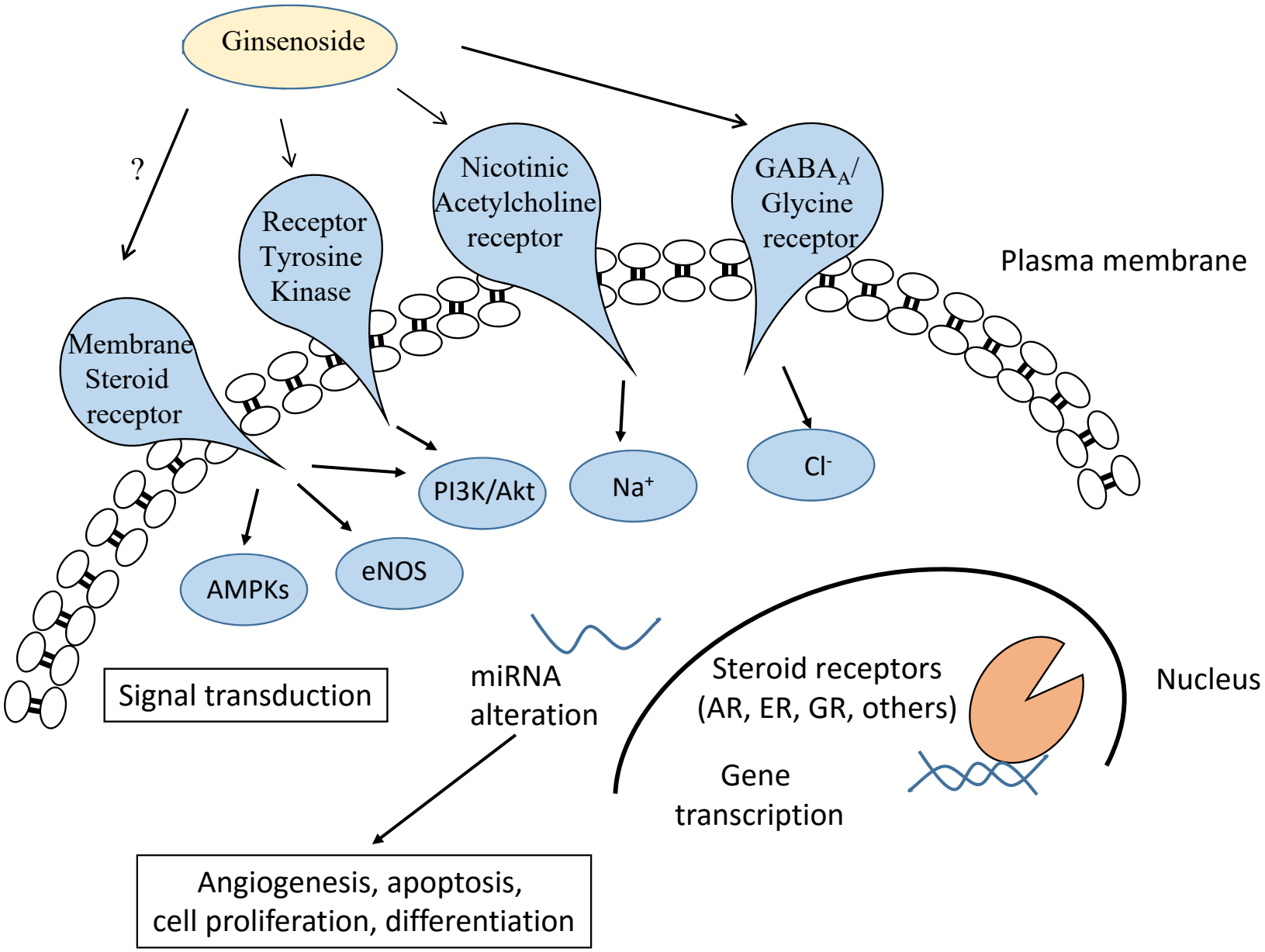
FIGURE LEGENDS

FIGURE 1. Schematic representation of genomic and nongenomic actions by ginsenosides. Ginsenosides can act through genomic effects by binding to steroid hormone receptors, such as androgen receptors (AR), estrogen receptors (ER), and glucocorticoid receptors (GR), to modulate gene expression. On the other hand, nongenomic activities, such as phosphoinositide 3-kinase/Akt (PI3K/Akt), adenosine monophosphate-activated protein kinases (AMPKs), and endothelial nitric oxide synthases (eNOS) that occur outside the

nucleus can also be involved in the mechanisms of action (MOAs) of ginsenosides. Ginsenosides are also implicated in ion channel regulation that includes the nicotinic acetylcholine receptor that results in sodium ion (Na^+) influx and the $GABA_A$/glycine receptor that conducts chloride (Cl^-) ions. In addition, ginsenosides can be a regulator of microRNAs (miRNAs) that modulate angiogenesis, apoptosis, cell proliferation, and differentiation.

FIGURE 2. Metabolism of ginseng. Ginsenosides can be converted into their metabolites that may contribute the majority of bioactivities by regulating the transportation and metabolism of crucial substances in the human body. Metabolism mainly occurs in the intestine and the liver by adenosine triphosphate (ATP)-binding cassette transporters (ABC transporters), cytochrome P450 enzymes (CYPs), and others.

Figure 1


Ginsenoside
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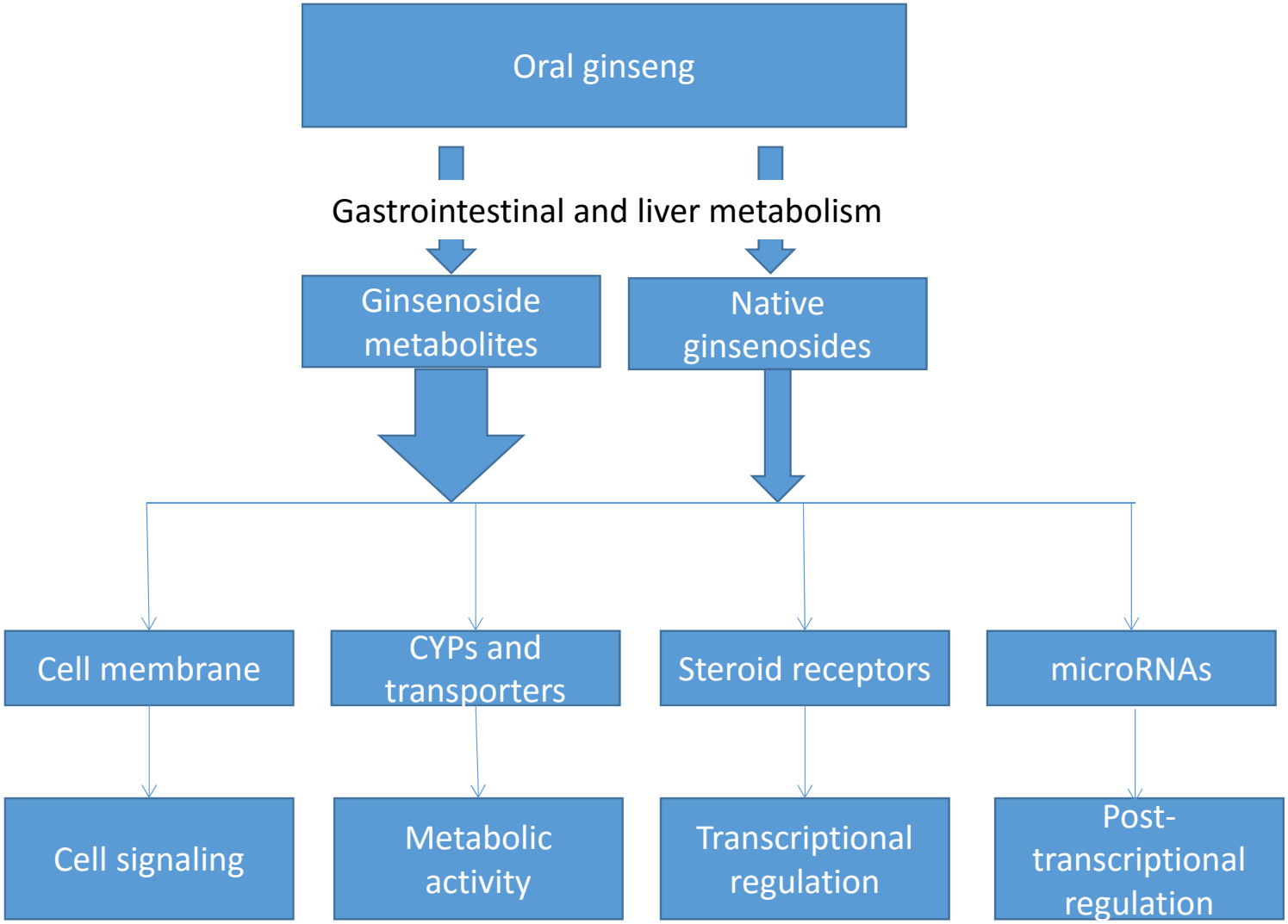
Receptor Tyrosine Kinase
Nicotinic Acetylcholine receptor
GABA$_A$/ Glycine receptor
Plasma membrane
Membrane Steroid receptor
PI3K/Akt
Na$^+$
Cl$^-$
AMPKs
eNOS
Signal transduction
miRNA alteration
Steroid receptors (AR, ER, GR, others)
Nucleus
Gene transcription
Angiogenesis, apoptosis, cell proliferation, differentiation

Figure 2


Oral ginseng
Gastrointestinal and liver metabolism
Ginsenoside metabolites
Native ginsenosides
Cell membrane
CYPs and transporters
Steroid receptors
microRNAs
Cell signaling
Metabolic activity
Transcriptional regulation
Post-transcriptional regulation