Pharmacology of Ginsenosides

115

Kar Wah Leung

Contents

Abstract

Ginseng is also known as "The King of All Herbs." It not only possesses superior status in the field of traditional Chinese medicine and being extensively used in Chinese communities for thousands of years, it is one of the most popular herbs in the world and accounts for over 800 million US dollar of international market. Many scientific approaches (e.g., bioassays and omics studies) have been used to

K.W. Leung
The Division of Life Science, Hong Kong University of Science and Technology, Hong Kong, SAR, China
e-mail: kwl_melody@yahoo.co.uk

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unlock the mechanisms behind the biological effects of ginseng. Frequently, ginsenosides are being said to be the most pharmacologically active constituents in ginseng. In this chapter, we will cover the basic biochemistry and pharmacology of ginsenosides, as well highlight how ginsenosides work in human body with respect to various pathological conditions, including cancer and age-related disorders. Lastly, we will discuss the possibilities of developing ginsenosides into targeted therapeutic agents to benefit the human society.

Keywords
Ginseng • ginsenosides • steroidal hormone receptors

Abbreviations
ER Estrogen receptor
GR Glucocorticoid receptor

1 Introduction

The word "ginseng" is translated from the pronunciation of the Chinese words "人蔘" (Renshen) that means "essence of men," and is conventionally referring to the Asian ginseng (*Panax ginseng*). The botanical name *Panax* means "all-healing" in Greek, which is first coined by the Russian botanist Carl A. Meyer in 1843 (Image 115.1). The *Panax* family consists of at least nine species, and are mostly named by their geographic origins, although they could be cultivated and processed elsewhere. For example, American ginseng (*Panax quinquefolium*) was discovered by a Jesuit priest Father Joseph Francois Lafitau near Montreal/Ottawa, Canada, in 1716. Later, he started to export wild American ginseng to China and experiment on ginseng cultivation technique. As time goes by, China now becomes the second largest producer and exporter of the American ginseng. Other members of the family include *Panax notoginseng* (Sanqi 三七/ Tian-qi 田七), *Panax japonicus* (Japanese ginseng), *Panax vietnamensis* (Vietnamese ginseng), and *Panax trifolius* (Dwarf ginseng).

Siberian ginseng (*Eleutherococcus senticosus*) is also frequently found in the market. However, Siberian ginseng is only distantly related to the Panax family and can be considered as an entirely different plant. It contains a different set of active components that leads to distinct biological activities. Therefore, Siberian ginseng is now more commonly known as Eleuthero to avoid confusion.

Ginseng is a slow-growing perennial herbaceous plant that grows to about a half meter tall. Wild ginseng could be found in cold (optimal growing temperature is 8–15 °C) and well-shaded areas of moist hardwood forests. It takes the plant approximately 10 years to grow into maturity (has 4–5 long leaves with red berries) (Image 115.2). Because of the increasing popularity of this powerful herb, wild ginseng is almost being ripe off. Both wild Asian and American ginsengs are now protected under the Convention on International Trade in Endangered Species of

Image 115.1 The drawing depicts American ginseng adopted from the book of American Medical Botany: (1817) [1]

Image 115.2 A mature ginseng plant. (The image is adopted from http://www.herbs.org/)

Wild Fauna and Flora (CITES), an international trade agreement that is signed by 135 nations in 1973 and went into effect in 1975 (Image 115.3).

To meet demand of trade needs from the whole world, many countries start growing ginseng using systematic farm cultivation and wood grown wild-simulation approaches. Farm cultivated ginsengs usually grow faster (4–6 years to maturity) and

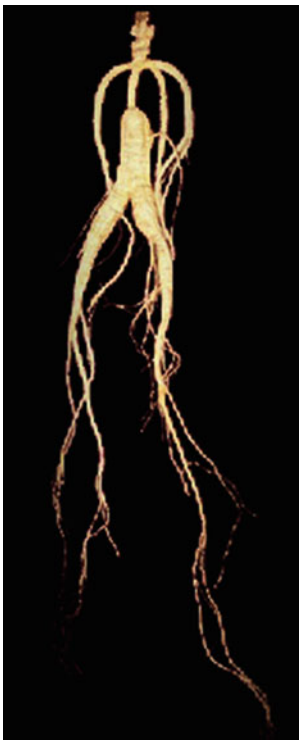


Image 115.3 The image shows a typical ginseng root. The shape of the root resembles a "little human" with a head, a body and four limbs. A wild Panax ginseng roots grown in a desirable shape can worth tens of thousands of dollars

lost the "man-like" appearance compared to the wild-simulated ginsengs (8–10 years to maturity). China is the main producer (50 %) of the cultivated ginseng, followed by South Korea (32 %), the United States (7.5 %), Japan (2.3 %), Canada (2.2 %), North Korea (1.2 %), and all others (4.6 %). Annual world production of cultivated ginseng is over 5,000 t [2], and accounts for over half a billion US dollar of international market value. Hong Kong SAR, China, acts as the world's clearing-house for ginseng, which imports 3,895 t in 1990 [2]. Apart from a substantial consumption within Hong Kong, significant amount of ginseng is redistributed to China, Taiwan, Japan, Malaysia, Singapore, North America, and Europe.

The ginseng species share more or less the same set of active components, although each has a unique composition prolife to give its unique biological properties. The constituent composition of a ginseng species can also be affected by a range of factors, such as age and part of the plant, cultivation method, harvesting season, and preservation method [3, 4]. The ginseng roots air-dried after harvested appear to be white, while the darker-colored red roots are produced by steaming at 98–100 °C for 2–3 h before drying [5]. The steaming process transforms the major medicinal constituents of ginseng into novel compounds that adds unique therapeutic values to these red roots [6–10]. In 2001, some roots are steamed at an even higher temperature (120 °C for 4 h) to enhance the antitumor properties of the ginseng, and this new type

of ginseng is known as Sun ginseng [11–16]. The Sun ginseng is also found to possess enhanced anxiolytic effects compared to white and red ginsengs [17].

2 Chemical Constituents of Ginseng

Ginseng has been widely used in Chinese community for thousands of years. It is generally believed that consuming ginseng or ginseng extracts can support overall health and boost the immune system. It is accepted by the European countries and the United States to be used in complementary and alternative therapies [18, 19]. However, the mechanisms of ginseng's biological actions are still not fully understood. Identifying and characterizing the pharmacological active components of ginseng is a key area in ginseng researches. To date, majority of the effects of ginseng points to three categories of constituents, they are polysaccharides, phenolics, and flavonoids, and saponins.

2.1 Polysaccharides

The polysaccharides of the ginseng comprised 40 % (by weight) of the root. This class of compound was first isolated and documented in 1966 [20]. Most biologically active carbohydrates in ginseng are acidic polysaccharides, known as ginsan, which have the typical structure of pectin [21, 22].

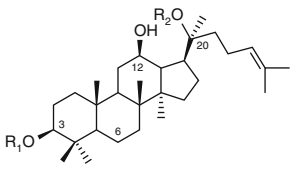
Ginseng polysaccharides have both stimulating and suppressive actions on the immune system. It was found that ginseng polysaccharides increases serum IgG levels, activates the reticuloendothelial system (RES), and anti-complementary and alkaline-phosphatase-inducing activities [21]. At the same time, ginseng polysaccharides are reported to calm down enteric immune responses by activating Peyer's patch lymphocyte [23]. Ginseng polysaccharides also possess anticancer, antimutagenic, and radioprotective effects [22, 24, 25].

2.2 Phenolics and Flavonoids

Phenolics and flavonoids are powerful plant-derived antioxidants. These compounds demonstrate radical-scavenging and ferrous ion–chelating activities. Ginseng's phenolics and flavonoids comprised 2–7 % (by weight) of the root [26], in which quercetin and kaempferol are the most abundant ones [27]. Quercetin and kaempferol can also be found in *Ginkgo biloba* and St. John's wort, and ginseng-specific phenolics and flavonoids have not been identified.

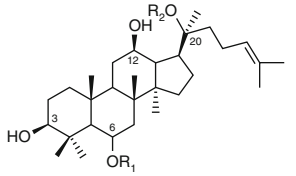
2.3 Saponins

Ginseng triterpene saponins are also known as Ginsenosides. This class of compounds accounts for most of the ginseng's biological activities. Ginsenosides



Protopanaxadiols

	R_1	R_2	Formula	T_{melt} (°C)
Rb_1	*-glc^2-glc*	*-glc^6-glc*	$C_{54}H_{92}O_{23}$	*198–200.5*
Rb_2	*-glc^2-glc*	*-glc^6-ara(p)*	$C_{53}H_{90}O_{22}$	*200–202*
Rc	*-glc^2-glc*	*-glc^6-ara(f)*	$C_{53}H_{90}O_{22}$	*198–201*
Rd	*-glc^2-glc*	*-glc*	$C_{48}H_{82}O_{18}$	*206–209*
Rg_3	*-glc^2-glc*	-H	$C_{42}H_{72}O_{13}$	*298–303*
Rh_2	*-glc*	-H	$C_{36}H_{62}O_8$	*218–220*



Protopanaxatriols

	R_1	R_2	Formula	T_{melt} (°C)
Re	*-glc^2-rha*	*-glc*	$C_{48}H_{82}O_{18}$	*199–201*
Rf	*-glc^2-glc*	-H	$C_{42}H_{72}O_{14}$	*197–198*
Rg_1	*-glc*	*-glc*	$C_{42}H_{72}O_{14}$	*194–195*
Rg_2	*-glc^2-rha*	-H	$C_{42}H_{72}O_{13}$	*183–184*
Rh_1	*-glc*	-H	$C_{36}H_{62}O_9$	*248–252*

Fig. 115.1 Images depicted the structures of protopanaxadiol (*PPD*) and protopanaxatriol (*PPT*) (Figure adopted from Leung et al. [82]. *glc* glucosyl, *ara*(*p*) pyranosyl arabinosyl, *ara*(*f*) furanosyl arabinosyl, *rha* rhamnose

can be found in all parts of the plants – the roots, stems, leaves, as well as flowers. Each part of the plant contains distinct ginsenoside profiles [28]. Being the most concentrated region, the root contains 3–6 % (by weight) of ginsenosides, and the overall saponin content is directly proportional to the age. On average, the root saponin content reaches peak levels at around 6 years of age for cultivated ginseng, and at least 10 years for the wild ones [29, 30].

To date, more than a 100 naturally occurring ginsenosides have been isolated from roots, leaves, stems, fruits, and flower heads of ginseng [31]. The triterpenoid core of ginsenosides is a four-ring structure with various sugar moieties (e.g., glucose, rhamnose, xylose, and arabinose) attached to the C-3, C-6, and C-20 positions. Ginsenosides are named according to the chromatographic polarity in alphabetical order with a prefix "R" that stands for the root [32]. Therefore, Ra is the least polar ginsenoside and Rg3 is more polar than Rg1. The presence or absence of the C-6 carboxyl group categorize ginsenosides into two groups – the 20(S)-protopanaxatriol (PPT) (Re, Rf, Rg1, Rg2, Rh1) and the 20(S)-protopanaxadiol (PPD) (Rb1, Rb2, Rb3, Rc, Rd, Rg3, Rh2, Rs1), respectively [33] (Fig. 115.1).

Besides the common ginsenosides (Rb1, Re, Rg1, Rg3), ginsenoside composite varies among ginseng species. For example, ginsenoside Rf is unique to Asian ginseng and F11 is found exclusively in American ginseng. Thus, the Rf/F11 ratio is used as a phytochemical marker to distinguish American ginseng from Asian ginseng [34, 35]. Such differences can generally correlate with the physiological properties of the ginseng – American ginseng is described to be cooling and soothing to body conditions, while Asian varieties are thought to be "hot" and stimulating – although detailed ginsenoside property identification is still under investigation. The heat-processed red ginseng contains multiple unique ginsenosides, including Rg3, Rg5, Rk1, Rk2, Rk3, Rs4, Rs5, Rs6, and Rs7 [36]. It is these unique ginsenosides to produce the signature effects of the red ginseng.

3 Ginsenosides Are Part of the Defense Mechanisms in Ginseng

Over evolution, plants eliminate most of the non-necessary biological pathways and reserve those benefit to its own survival. Thus, we ask what is the purpose for ginseng to make the saponins called ginsenosides?

Plants produce antibiotic substances to defense themselves from insect and microbial attack, such as nicotine from tobacco leaves [37], rotenone from derris tree roots [38], pyrethroids from chrysanthemum flowers [39], and triterpenoids from neem tress [40]. Evidence indicated that ginsenosides are one of the phytoanticipins to protect the ginseng plant.

Ginsenosides are constantly synthesized by the ginseng plant prior to pathogenic invasion, and defensive stress signals, such as methyl jasmonate and salicylic acid, can enhance ginsenoside production and accumulation by 3–4 times, as illustrated in ginseng root cells' in vitro culture [41–44]. Ginsenosides are found to possess antimicrobial and fungitoxic properties [45–47], and the bitter taste keeps insects and animals from feeding on them [48]. Ginsenosides share high degree of molecular structure similarity with the insect molting and metamorphosis hormone ecdysteroids, suggesting ginsenosides may be an agonist to the ecdysteroid receptor. Thus, ginsenosides may protect the plant by interfering with the life cycle of herbivorous insects [49] (Fig. 115.2). These lines also verify the folk belief that wild ginsengs grown in a more challenged environment contain larger amount of ginsenosides and have greater biological effects compared to the cultured ginseng, thus are sold at a much high price range. To reproduce the quality of wild ginseng, ginseng growers developed the "wild simulating cultivation" approach to provide a more natural environment for the plants.

4 The "Yin and Yang" Actions of Ginseng

Ginsengs are described as an "adaptogens." The concept of "adaptogen" was first proposed by a Soviet pharmacologist and toxicologist, Dr Nikolai Vasilievich Lazarev (1895–1974). At that time, adaptogen is a substance that can be administrated to individuals of any health condition to increase nonspecific resistance to various kinds of biological stresses. However, adaptogenicity can hardly be proved by scientific evidence. Here I reframe it and elaborate this property of ginseng in the yin and yang concept.

The "yin and yang" concept in Chinese is the coexistence and balance of opposing forces, such as light and dark, good and evil, calm and irritation. Unlike most of the other herbs, ginseng is commonly taken by its own. This would be explained by the coexistence of ginsenosides of various properties, and consumption of ginseng alone can lead to a combination of effects, which resemble "Fufang" (複方) in Chinese medicinal concept, or the cocktail therapy in the Western approach. Taking angiomodulation effects as an example, angiogenic properties of ginseng are related to the compositional ratio between ginsenosides Rg1 and Rb1. Asian ginseng with

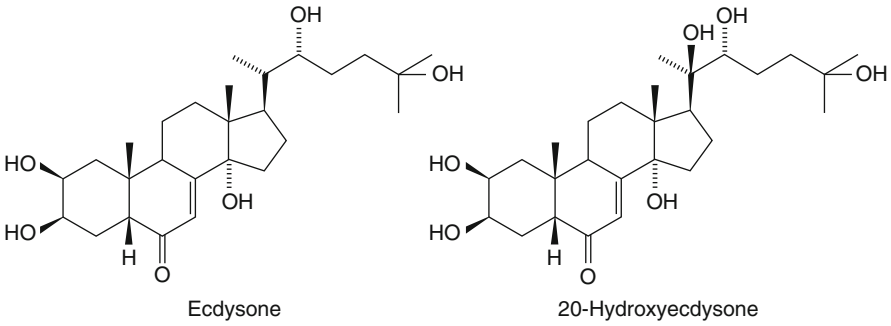


Fig. 115.2 Molecular structures of the insect molding hormones ecdysone and 20-Hydroxyecdyson. Structural similarities between ginsenosides and the ecdysone suggest ginsenosides maybe analogs to ecdysone receptors

higher Rg1 levels is found to promote growth of blood vessels and consumption of Asian ginseng can reduce hypertension. In contrary, American ginseng that contains more Rb1 is found to suppress angiogenesis, and is used in cancer treatment. The coexisting Rg1 and Rb1 interact with different receptors and give ginseng the ability to balance the dynamic equilibrium of human physiological processes. We will discuss the ginsenoside-receptor interactions later in this chapter.

5 Standardized Ginseng Extracts

Because of complex composition of the ginseng and some of the ingredients are having contrasting actions, variations in composition will lead to inconsistent experimental results. For this reason, standardized extracts are made and are commercially available to minimize variability among preparations. Two commonly used standardized extracts are G115 from *P. ginseng* (total ginsenoside adjusted to 4 %) (Pharmaton SA, Switzerland) and NAGE from *P. quinquefolius* (total ginsenoside content adjusted to 10 %) (Canadian Phytopharmaceuticals Corporation, Canada). Studies on these two ginseng extracts using high-performance liquid chromatography (HPLC) found ginsenosides Rb1, Rb2, Rc, Rd, Re, and Rg1 in both G115 and NAGE, and ginsenoside Rg2 in G115 only. Comparing G115 and NAGE: G115 has higher Rg1, but NAGE has higher in Rb1 and Re [50–52].

Moreover, the butanol-soluble fraction of Sun ginseng is formulated into KG-135 which contains Rk3 Rs3, Rs4, Rs5, Rs6, and Rs7 in addition to the major antitumor ginsenosides [16, 53].

6 Biotransformation of Ginsenosides

As a group of defensive phyto-compounds, ginsenosides may require certain degree of transformation to gain its full activity in mammalian system. In fact, major

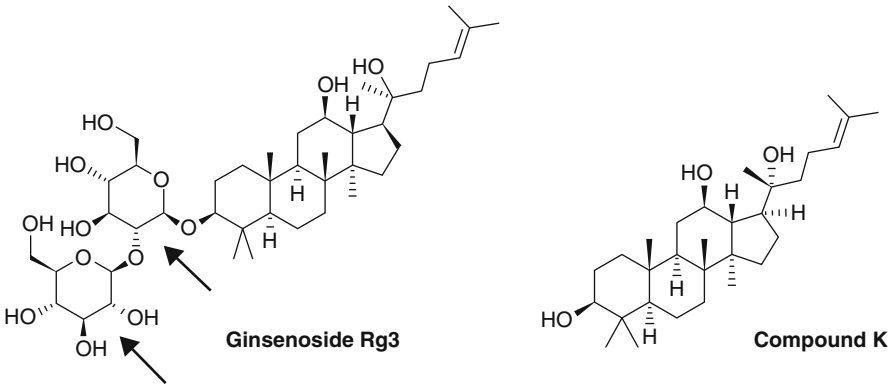


Fig. 115.3 Molecular structures of ginsenoside Rg3 and its metabolite Compound K. *Arrows* indicate the C3 glucoses to be deglycosylated by the microflora

ginsenosides, such as Rg1, Rg3, Rb1, Re, and Rc, are bulky molecules that are poorly membrane permeable. Moreover, these ginsenosides are antigenic in the circulatory system. Antibodies against these ginsenosides can be purified from immunized animals and are commercially available [54–57].

Ginsenosides in orally consumed ginseng preparations are subjected to acid hydrolysis, glycosyl elimination, and intestinal microflora-driven sugar moiety cleavage [58–60]. Following biodegradation, PPDs are converted to compound K (also known as M1 or IH901) and panaxadiol, while ginsenoside F1 and panaxatriol are the major metabolites of PPTs. Several bacterial strains are identified and selected transforming enzymes are overexpressed using recombinant DNA technique for in vitro ginsenoside modification [61].

Studies have shown that ginsenoside metabolites indeed have greater biological effects compared to the naturally occurring ginsenosides [62–64]. Ginsenoside Rh2, compound K, and panaxadiol, the metabolites of Rg3, are found to have greater antitumor activities than ginsenoside Rg3 itself [62, 65]. Similarly, compound K, panaxatriol, and panaxadiol possess the human liver enzyme cytochrome P450 inhibitory effects that are not found in the bulk ginsenosides Rb1, Rb2, Rg1, and Re [64] (Fig. 115.3).

7 Bioavailability of Ginsenosides

Multiple systematic actions of ginsenosides are reported and intensively investigated, but how ginsenosides are absorbed from the digestive system and reach the systemic organs remains largely unknown.

Although ginsenosides have the basic structure of a steroid, the sugar side chains increase the hydrogen bond count and polar surface area that hurdle effective permeability of these compounds across the membranes. The side chains are prone to degradation via hydrolytic cleavages and deglycosylations. Thus, availability of

intact ginsenosides from the intestine is extremely low [58, 66, 67]. To detect the ginsenosides in the blood samples after consumption using high-performance liquid chromatography, only 3.29–18.4 % Rg1 and 0.64–4.35 % Rb1 are detected in rat serum after oral administration of the ginsenosides [67–71].

Ginsenosides are shown to be transported across the intestinal mucosa in an energy-dependent and non-saturable manner [68, 69, 72]. The sodium-dependent glucose co-transporter-1 may be involved in this process [73]. Several approaches has been tested to increase the bioavailability of ginsenosides, including coadministration of ginsenosides with adrenaline [74], emulsification of ginsenosides into lipid-based formulation [75, 76], micronization of the ginsenoside particle and consequently increase the dissolution rate [77], and suppression of p-glycoprotein efflux system [78]. However, not a single approach is proved to enhance the bioavailability of all ginsenoside.

After absorption, ginsenosides continue to be biologically modified, such as oxidation and small degree of deglucosylation at the tissue levels [79]. As well, circulating ginsenosides and their deglycosylated products were subject to rapid and extensive biliary excretion through active transport, resulting in short biological half-lives and low systemic exposure levels [79].

8 Physiological Effects of Ginseng

Being crowned as the King of Herbs, ginseng has diverse activities on multiple organ systems in human regardless of the low bioavailability. In this chapter, biological effects on cardiovascular system, cancer, diabetes, immune system, and neurological system will be reviewed.

8.1 Pro- and Anti-angiogenesis

Ginsenosides are found to be able to modulate angiogenesis in both directions via altering genes involved in cell architectural dynamics, adhesion, and migration. For example, ginsenoside Rg1 interacts with glucocorticoid receptor (GR) and stimulates angiogenesis through augmenting the production of nitric oxide (NO) and vascular endothelial growth factor (VEGF) in endothelial cells [80, 81]. Angiogenesis promotion can accelerate wound healing and support stroke recovery. At the same time, ginsenoside Rb1 interacts with estrogen receptor-beta (ER-β) and enhances the production of anti-angiogenic pigment epithelium-derived factor (PEDF) from the endothelial cells [82]. Since tumor mass attracts blood vessels, suppressing angiogenesis ginsenosides is then exploited as part of the anticancer treatment.

8.2 Anticancer

American ginseng has been shown to have powerful anticancer properties, and heat-processed red ginseng has more potent inhibition on tumor growth compared

to the untreated white ginseng. Patients with stage-3 gastric cancer taking red ginseng were observed to have a higher 5-year disease-free survival rate and better restoration of immune functions during adjuvant chemotherapy compared to control patients [83]. Regular consumption of ginseng also demonstrates a dose-dependent decrease in risk of cancer in Korea [84, 85]. Besides the anti-angiogenic properties of certain class of ginsenosides that have been exploited as an anticancer modality, ginsenosides Rg3 and Rh2 are shown to inhibit growth of several cancer cell lines [86, 87] and capable in reversing the multidrug resistance properties of cancer cells by inhibiting the efflux transporter P-glycoprotein (P-gp) [88–90]. Inhibition of P-gp leads to the improvement of bioavailability of several orally administrated anticancer drugs and could be taken to assist cancer chemotherapy [91, 92]. "Anticancer capsules" of Rg3 alone or in combination with ginsenoside Rh2 are available in Mainland China as over-the-counter drugs.

8.3 Combat Diabetes

In genetically obese diabetic KK-CA model, intraperitoneal injection of ginseng root extract can significantly lower blood glucose levels [93, 94]. As well, total ginseng berry extract reduces body weight and improves glucose homeostasis in type-2 diabetic ob/ob mice [95]. Particularly, treatment with ginsenoside Re lowers the elevated fasting blood glucose to normal levels and enhances glucose tolerance capacity in diabetic mice, but has no effects in the nondiabetic littermates [95]. Yet the mechanism of such effects is unclear. In human studies, consumption of 3 g of American ginseng root 40 min before the test meal significantly lowered blood glucose level in both nondiabetic subjects and diabetic patients [96].

8.4 Immune System Enhancement

Ginseng is shown to be an immunostimulant. It activates macrophages of healthy and fungal-infected mice [97, 98], as well as in mice exposed to the cold-water swim stress [99]. Ginseng also assists recovery of natural killer (NK) cells function in immunosuppressed mice [100, 101]. In a randomized, placebo-controlled double-blind trial, volunteers were treated with an influenza vaccine plus either placebo or a standard ginseng extract G115 over a 3-month period [102]. The frequency of upper respiratory infections (i.e., colds and flus) was significantly reduced by three times in the ginseng group compared to the placebo. In addition, antibody titers and NK activities were significantly higher in the ginseng group [102]. In a study, hot-water wild ginseng extracts resulted in increased lymphocyte proliferation both in vitro and in mouse model, while extracts from cultured ginseng had no effect [103]. This finding paralleled to the folk belief that wild ginseng has stronger immunomodulating effects compared to the cultured or domesticated ones.

Besides the cancer-combating potential, ginseng is often taken by patients in advance stage tumor for its immune stimulation properties. Cancer patients are

inherently immunosuppressive due to tumor-derived factors and the standard treatments, such as chemotherapy [104, 105]. Thus, many patients choose ginseng preparations to complement their standard cancer treatments.

9 Cellular Signal Transduction Pathways

Given the steroidal structure of ginsenosides, it has been shown to interact with the ligand binding sites of various steroid hormone receptors – ginsenosides Rg1 [82, 106] and Re [107] are functional ligands of the glucocorticoid receptor (GR), whereas ginsenosides Rh1 [108] and Rb1 [82] are functional ligands of the estrogen receptor (ER). However, the effects elicited by the ginsenoside-receptor complex are not as prominent as the native agonist of the steroidal receptors, i.e., the glucocorticoid and estrogen for the GR and ER, the ginsenosides may therefore function as partial agonists, which ginsenoside compensate for the insufficient steroidal activities when the intrinsic ligand is absent or inadequate in the system, while reversibly occupying the steroidal receptor with low affinity to modulate the steroidal effects when large amount of intrinsic ligand is present. This hypothesis also explained the adaptogenic properties of ginseng to bring extreme physiological conditions back to balance.

Moreover, each ginsenoside is able to bind to multiple steroid hormone receptors with different affinity. In addition to GR, ginsenosides Rg1 acts through ER and elicits cross-talking with insulin-like growth factor-1 receptor (IGF-IR) in neuronal cells [109]. Effects of ginsenoside Re on cardiac myocytes are related to ER alpha isoform, androgen receptor, and progesterone receptor [110]. The end metabolites PD and PT bind and activate both GR and ER in endothelial cells [111]. The multi-target properties of ginsenosides may explain why ginseng has a wide range of beneficial effects.

On the other hand, taking ginseng preparation enhances the mood and health-related quality of life in menopausal women with no change in female hormone–related physiological parameters, e.g., follicle-stimulating hormone (FSH) and estradiol levels, endometrial thickness, maturity index, and vaginal pH were not affected by the treatment [112], indicating some of the beneficial effects of ginseng are not mediated via steroidal hormone receptors. Other studies showed that ginsenosides can modulate expressions and functions of receptors, such as receptor tyrosine kinases (RTK) [113], serotonin receptors (5-HT) [114], NMDA receptors [115], and nicotinic acetylcholine receptors (AChR) [116]. Thus, ginsenosides are involved in a very complicated network of actions and more research is required to acquire thorough understanding.

10 Conclusion

Although ginsengs come in many different varieties and different molecular composition, the active effective compound is ginsenosides. The structural analyses, binding studies, and functional investigations demonstrated the steroidal hormone receptor partial agonist properties of ginsenosides and explained the multiple therapeutic

effects of this group of molecules. At the same time, ginsenosides modulate the activities of other cellular signaling pathways that awaits further investigations. This allelopathic property of ginseng attracts growing attention since many diseases, such as cancer, neurodegenerative disorders, and metabolic syndromes, are not isolated conditions of a single organ, and promising cure are currently unavailable. Therefore, unraveling the action mechanisms of the natural occurring systemic modulatory compounds, like ginsenosides, would be beneficial to the overall community welfare.

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