Yin and Yang of ginseng pharmacology: ginsenosides vs gintonin

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Ginseng, the root of Panax ginseng, has been used in traditional Chinese medicine as a tonic herb that provides many beneficial effects. Pharmacologic studies in the last decades have shown that ginsenosides (ginseng saponins) are primarily responsible for the actions of ginseng. However, the effects of ginseng are not fully explained by ginsenosides. Recently, another class of active ingredients called gintonin was identified. Gintonin is a complex of glycosylated ginseng proteins containing lysophosphatidic acids (LPAs) that are the intracellular lipid mitogenic mediator. Gintonin specifically and potently activates the G protein-coupled receptors (GPCRs) for LPA. Thus, the actions of ginseng are now also linked to LPA and its GPCRs. This linkage opens new dimensions for ginseng pharmacology and LPA therapeutics. In the present review, we evaluate the pharmacology of ginseng with the traditional viewpoint of Yin and Yang components. Furthermore, we will compare ginsenoside and gintonin based on the modern view of molecular pharmacology in terms of ion channels and GPCRs.

Keywords: ginseng; ginsenoside; gintonin; lysophosphatidic acid; ion channels; G protein-coupled receptors; Ca²⁺; traditional Chinese medicine

Introduction

Since ginsenosides (ginseng saponins) were first identified as active ingredients in ginseng, many studies have shown that ginsenosides negatively regulate ion channels[1]. For example, ginsenoside Rg₅ inhibits not only voltage-gated Ca²⁺ and Na⁺ channels but also ligand-gated ion channels such as 5-HT₃ receptors[2–4]. Furthermore, ginsenosides stimulate anion-gated GABAₐ and glycine receptors[5, 6]. Therefore, ginsenosides decrease the excitability of excitable cells by inhibition of cation influx and stimulation of anion influx across the plasma membrane.

Crude ginseng saponin fractions elevate the intracellular Ca²⁺ levels in mammalian cells and activate Ca²⁺-activated Cl⁻ channels in Xenopus oocytes[7]. However, this effect was not explained by ginsenosides. Recently, the active ingredients responsible for the Ca²⁺ rise were elucidated as novel glycolipoproteins and named gintonins[8]. Gintonin is a complex of glycosylated ginseng proteins containing lysophosphatidic acids (LPAs). LPA is a representative mitogenic lipid mediator[9]. Gintonin activates G protein-coupled receptors (GPCRs) for LPA[8]. Unexpectedly, the action of ginseng is now linked to LPA and its GPCRs and vice versa. This linkage opens new dimensions for ginseng pharmacology and LPA therapeutics.

Ginsenosides tend to attenuate cell excitations by blocking cation Ca²⁺ and Na⁺ influxes or by enhancing anion Cl⁻ influx. However, gintonin induces transient Ca²⁺ elevation and activation of MAPK, PI3K, PKC, and Rho kinase via LPA receptors to evoke stimulatory cellular responses[4, 8, 10, 11]. Thus, ginsenoside acts as a negative regulator (Yin), and gintonin acts as a positive regulator (Yang) for ginseng pharmacology. The pharmacological actions of ginseng are now explainable and complementary with the opposing actions of gintonin and ginsenoside. Therapeutic application of LPA might be expanded by traditional usages of ginseng and vice versa. In this article, both traditional and modern ginseng pharmacology will be discussed from the viewpoint of Yin and Yang.

Ginseng and ginsenosides

Ginseng, the root of Panax ginseng CA Meyer, has been used for thousands of years in Asian countries such as Korea, China, and Japan. Panax means ‘all heal’ in Greek, and the
Chinese characters of ginseng originated from the human-like shape of the ginseng root\textsuperscript{[12]}. The traditional beneficial effects of ginseng are replenishment of vital energy, mood elevation, and longevity. Therefore, in ancient times, ginseng was considered as a panacea that provided eternal youth\textsuperscript{[1, 12]}. In addition, modern pharmacological studies have revealed ginseng’s adaptogenic activities against stress, fatigue, cardiovascular dysfunction, and various diseases, including cancer and neurodegenerative disorders. Its active components also have been intensively studied over the past decades.

The representative active ingredients of ginseng are ginsenosides (ginseng saponin), which are derivatives of the triterpenoid dammarane\textsuperscript{[31]}. More than 100 different types of ginsenosides have been isolated and identified from the roots of Korean and American ginseng\textsuperscript{[13]}. Each ginsenoside is composed of three parts, including a hydrophilic four-ring backbone structure, an attached carbohydrate portion, and an aliphatic side chain (Figure 1).

**Ginsenosides and the modulation of ion channels**

Because ginsenosides were first identified as the active ingredients in ginseng, many studies have demonstrated negative regulation of ion channels by ginsenosides\textsuperscript{[11]}. Their actions are stereoselective, but they lack the specificity and selectivity of other channel inhibitors. The EC\textsubscript{50} values of ginsenosides are in the µmol/L range, and many ion channels are affected. For example, the EC\textsubscript{50} values for the ginsenoside Rg\textsubscript{3} are approximately 0.41–97.3 µmol/L\textsuperscript{[4, 14–20]}. The ginsenoside Rg\textsubscript{3} not only inhibits voltage-gated Ca\textsuperscript{2+}, K\textsuperscript{+}, and Na\textsuperscript{+} channels, ligand-gated 5-HT\textsubscript{3} \(\alpha7\) nicotinic acetylcholine, and NMDA receptors but also activates K\textsuperscript{+} channels such as KCNQ K\textsuperscript{+}, BK\textsubscript{ca}, and hERG K\textsuperscript{+}\textsuperscript{[4, 14–21]}. Other ginsenosides enhance the activation of anion GABA\textsubscript{A} and glycine receptors\textsuperscript{[22, 23]} (Table 1). Therefore, ginsenosides decrease the cellular excitability of excitable cells by inhibiting cation influx and by stimulating anion influx across plasma membranes.

Site-directed mutagenesis experiments have identified ginsenoside interaction site(s), and homology docking modeling has provided three-dimensional configurations for ginsenosides and channel proteins\textsuperscript{[15, 16, 18, 24]} (Figure 1). For example, the hydroxyl groups on the second carbohydrate in ginsenoside Rg\textsubscript{3} form stable hydrogen bonds with the core amino acids of channel proteins (Figure 1). The 1st or 2nd amino acids after the K\textsuperscript{+} channel ‘signature sequence’ (TXGYGD) at the pore entrances have been shown to interact with ginsenoside Rg\textsubscript{3}. That is, K318 in the KCNQ K\textsuperscript{+} channel, S631 in the hERG K\textsuperscript{+} channel, Y360 in the BK\textsubscript{ca} K\textsuperscript{+} channel, K531 in the K\textsuperscript{+}v1.4 channel, and K859 in the neuronal Na\textsuperscript{+} channel. Similarly, the amino acids I417, N418, and L421 in the Na\textsuperscript{+}v1.2 channel, I433, N434, and L437 in the Na\textsuperscript{+}v1.4 channel, L417, N428, and L431 in the L-type Ca\textsuperscript{2+} channel, V291, F292, and I295 in the 5-HT\textsubscript{3} channel, and L247 in the \(\alpha7\) nicotinic acetylcholine receptor were found to interact with ginsenosides\textsuperscript{[14, 18, 20]} (Table 1 and Figure 1). Therefore, ginsenosides have regulatory effects in a broad range of ion channels with low affinities, but their common factor is that they stabilize membrane potentials and attenuate cellular activities.

**Ginsenosides in ginseng pharmacology**

Ginsenosides decrease the excitability of neuronal cells by inhibiting cation influx and/or by stimulating anion influx. These pharmacologic actions of ginsenosides are linked to reductions in the excitabilities of neurons, smooth muscle cells, and cardiomyocytes. Furthermore, the ginsenoside-induced modulation of Ca\textsuperscript{2+} and K\textsuperscript{+} channels results in the dilation of blood vessels via relaxation of smooth muscles\textsuperscript{[25–29]}. In bradycardia, it induces relaxation of the cardiomyocytes, which explains its anti-hypertensive and cardioprotective effects\textsuperscript{[30–35]}. In addition, ginsenoside-induced inhibition of the cation-gated NMDA receptor and neuronal Na\textsuperscript{+} channels and

**Table 1. Summary of the EC\textsubscript{50} and IC\textsubscript{50} values of ginsenoside-induced inhibitions or stimulations of the activities of various voltage-gated ion or ligand-gated ion channels.**

| Voltage-gated ion channels | Ginsenoside | EC\textsubscript{50} or IC\textsubscript{50} (µmol/L) | Interacting amino acids |
|----------------------------|------------|---------------------------------|------------------------|
| Ca\textsuperscript{2+}     | L          | Rg\textsubscript{3}, Rb\textsubscript{1} | 39.9±9.5\textsuperscript{[1, 2]} | L417, N428, L431 |
|                           | N          | Rg\textsubscript{3}              | 64.4±13.6\textsuperscript{[3]} |                          |
|                           | P/Q        | Rg\textsubscript{3}              | 29.6±11.3\textsuperscript{[3]} |                          |
|                           | R          | Rg\textsubscript{3}              | 57.5±12.2\textsuperscript{[3]} |                          |
|                           | T          | Rg\textsubscript{3}              | 97.3±12.4\textsuperscript{[3]} |                          |
| K\textsuperscript{+}      | Kv1.4      | Rg\textsubscript{3}              | 32.6±2.2\textsuperscript{[1]} | K531 |
|                           | BK\textsubscript{ca} | Rg\textsubscript{3} | 15.3±3.1\textsuperscript{[3]} | Y360 |
|                           | hERG       | Rg\textsubscript{3}              | 0.41±0.05\textsuperscript{[3]} | S631 |
|                           | KCNQ       | Rg\textsubscript{3}              | 15.2±8.7\textsuperscript{[4]} | K318 |
| Na\textsuperscript{+}     | Nav1.2     | Rg\textsubscript{3}              | 32.0±6.0\textsuperscript{[5]} | I417, N418, L421 |
|                           | Nav1.4     | Rg\textsubscript{3}              | 58.5±6.3\textsuperscript{[6]} | I433, N434, L437 |
|                           | Nav1.5     | Rg\textsubscript{3}              | 16.1±2.8\textsuperscript{[7]} |                          |
| Ligand-gated ion channels | Ginsenoside | EC\textsubscript{50} or IC\textsubscript{50} (µmol/L) |                          |
|                           | GABA\textsubscript{A} | Rc                          | 53.0±12.3\textsuperscript{[8]} |                          |
|                           | Glycine    | Rc                              | 49.8±9.8\textsuperscript{[9]} |                          |
|                           | 5-HT\textsubscript{3} | Rg\textsubscript{3} | 27.6±4.3\textsuperscript{[10]} | V291, F292, I295 |
|                           | Nicotinic acetylcholine | \(\alpha3\beta4\) | 60±14\textsuperscript{[11]} |                          |
|                           | \(\alpha1\beta1\delta\epsilon\) | Rg\textsubscript{3} | 16±9\textsuperscript{[12]} |                          |
|                           | \(\alpha7\) (L247A mutant) Rg\textsubscript{3} | 33±1±1.3\textsuperscript{[12]} | L247 |
|                           | NMDA       | Protopanaxatriol | 48±16\textsuperscript{[13]} |                          |

EC\textsubscript{50} values are shown for BK\textsubscript{ca}, hERG, and KCNQ K\textsuperscript{+} channels and GABA\textsubscript{A} and glycine receptors and IC\textsubscript{50} values are shown for the remainder and were determined in oocytes expressing these ion channels or receptors.
its stimulation of anion-gated GABA<sub>A</sub> receptors and glycine receptors explain the neuroprotective and anxiolytic effects of ginseng<sup>[10,36]</sup>. It is also possible that ginseng attenuation of cisplatin-induced nausea and vomiting is due its inhibition of 5-HT<sub>3</sub> ion channels<sup>[37]</sup>.

**Discovery of gintonin**

The crude ginseng total saponin (cGTS) fraction contains approximately 50% ginsenosides by weight. Furthermore, the cGTS fraction increases intracellular Ca<sup>2+</sup> in mammalian cells and activates endogenous Ca<sup>2+</sup>-activated Cl<sup>-</sup> channels in *Xenopus* oocytes, whereas ginsenosides do not. These data imply that some unidentified ginseng component(s) is responsible for the Ca<sup>2+</sup> increase<sup>[7]</sup>. In addition, the cGTS fraction-induced Ca<sup>2+</sup> increases are both reversible and transient. Precise and continuing studies over the past twenty years have elucidated a signaling pathway downstream of cGTS in oocytes, namely the unknown membrane target protein-G<sub>q/11</sub>-PLC<sub>β3</sub>-IP<sub>3</sub>-Ca<sup>2+</sup> release<sup>[38]</sup>. Later, homologous desensitization by cGTS was shown to be mediated through GRK2 and β-arrestin I in oocytes, strongly implying GPCR involvement (Figure 2)<sup>[39]</sup>.

In 2011, the active ingredient in cGTS was finally separated by anion exchange chromatography after ginseng butanol extraction<sup>[40]</sup>. The novel non-saponin ingredient was designated as gintonin, where *gin* was derived from ginseng, *ton* from the tonic effects of ginseng, and *in* from internal Ca<sup>2+</sup> stores through IP<sub>3</sub> receptors. The increased Ca<sup>2+</sup> levels activate many kinases.

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**Figure 1.** Virtual docking model of ginsenoside Rg<sub>3</sub> to chick α7 nicotinic acetylcholine receptor (nACHr mutant L247T) and hydrogen bonds. Virtual dockings of ginsenoside Rg<sub>3</sub> to chick α7 nicotinic acetylcholine receptor (AChR, L247T mutant) channel homology models. (A) Top view of the highest-ranked docking model of ginsenoside Rg<sub>3</sub> to chick α7 nicotinic acetylcholine receptor (nACHr mutant, L247T) channel. The channel is shown as a cartoon diagram, and ginsenoside Rg<sub>3</sub> is represented by a ball and chain model. Subunits are shown in different colors. (B) Side view of the docking model of ginsenoside Rg<sub>3</sub> to nACHR receptor. One of the subunits is omitted in side view for clarity. (C) Poseview analysis of protein-ligand interactions. Hydrogen bonds are denoted by dotted lines. Spline sections indicate hydrophobic contacts, highlight the hydrophobic regions of ginsenoside Rg<sub>3</sub>, and provide the identities of contacting amino acids. The roman numerals in parenthesis indicate subunits of the pentamer. Adapted from Lee et al<sup>[38]</sup>.

**Figure 2.** Schematic diagram of gintonin-mediated signal transduction pathways. For the desensitization, gintonin activates LPA GPCRs, which leads to activation of GRK2. The activated GRK2 phosphorylates the LPA GPCRs and then β-arrestin I is recruited. The recruited β-arrestin I inhibits GPCR-G protein coupling. For cellular responses, gintonin activates LPA GPCRs, which leads to activation of phospholipase C (PLC). The activated PLC produces IP<sub>3</sub> and diacylglycerol (DAG). DAG activates protein kinase C (PKC), which phosphorylates Ca<sup>2+</sup> channels. IP<sub>3</sub> mobilizes Ca<sup>2+</sup> from internal Ca<sup>2+</sup> stores through IP<sub>3</sub> receptors. The increased Ca<sup>2+</sup> levels activate many kinases.
protein. Six different gintonin have been identified, and all six induce intracellular Ca\(^{2+}\) increases in mammalian cells and Xenopus oocytes, confirming that gintonin is responsible for cGTS-induced Ca\(^{2+}\) mobilization. Gintonin is composed of carbohydrates, lipids, and proteins, such as, ginseng major latex-like protein and ginseng ribonuclease-like storage proteins. Thus, gintonin is part of a novel class of glycolipoproteins in ginseng that induces intracellular Ca\(^{2+}\) increases in mammalian cells. Ginseng contains 0.2% gintonin by weight (Table 2).

**Table 2. A brief comparison of ginseng components, gintonin, and ginsenosides.**

|                      | Gintonin | Ginsenosides |
|----------------------|----------|--------------|
| Molecular weight (M\(_w\)) | Native M\(_w\): 67 kDa | 0.6–1.3 kDa |
|                      | Apparent M\(_w\): 13 kDa |              |
| Composition          | Glycolipoprotein: carbohydrates (Glucose), lipids (LPA C\(_{18:2}\)), and ginseng proteins (GLP and GSP) | Dammarane glycosides |
| Content in ginseng   | 0.2% | 3%–4% (Sum of individual ginsenosides) |
| Target protein on cell membrane and signal cascades | LPA receptors, transient \([\text{Ca}^{2+}]\) elevation via PTX-sensitive and -insensitive G proteins coupled PLC pathway | Non-selective interactions with ion channels and receptors, do not have signal transduction pathway |
| Desensitization after repeated treatment on cells | Induction of rapid desensitization | No desensitization |

**Gintonin activation of GPCRs for LPA**

During additional studies with the gintonin, it was shown that phospholipase A\(_1\) had attenuating effects on gintonin. This finding highlighted the importance of position 1 esterification on the fatty acid component, which suggests that gintonin contains phospholipids. Previously, Tigiyi and Miledi demonstrated that LPA bound to serum albumin could sufficiently activate Ca\(^{2+}\)-activated Cl\(^-\) channels in Xenopus oocytes, and digestion with PLA\(_1\) prevented this activation. Furthermore, using methanol extraction, they demonstrated LPA dissociation from serum albumin. Building upon this reference, researchers examined whether gintonin contained LPAs by liquid chromatography-electrospray ionization/multi-stage mass spectrometry (LC-ESI-MS/MS) analysis. LC-ESI-MS/MS analysis showed that 9.5% of gintonin is composed of lysophosphatidic acids (LPAs), such as LPA C\(_{18:2}\), LPA C\(_{16:0}\) and LPA C\(_{18:1}\), indicating that the bioactive component(s) of gintonin (with respect to the Ca\(^{2+}\) response) is a LPA.

LPA is an intercellular lipid mediator that functions as a mitogen with hormone- and growth-factor-like activities in most cell types. Currently, three EDG family GPCRs (LPA\(_{1–3}\)) and three purinergic GPCRs (LPA\(_{4–6}\)) have been reported to act as LPA receptors. Hwang et al demonstrated that gintonin activates LPA receptors in GPCR-expressing B103 mammalian cells and in *Xenopus* oocytes. Gintonin only activates LPA receptors specifically, not other GPCRs, such as S1P, fatty acids, 5-HT\(_{1C}\) and muscarinic acetylcholine receptor subtypes (m1, m3, and m5). Furthermore, the LPA GPCRs have different affinities for gintonin, which follow a decreasing order of LPA\(_2\) > LPA\(_3\) > LPA\(_1\) > LPA\(_4\) > LPA\(_5\) > LPA\(_6\). Furthermore, gintonin has 3- to 130-fold greater affinity for LPA GPCRs than free LPA. This might be due to ginseng proteins in gintonin because the protein components of gintonin may function as efficient LPA carriers to effectively carry LPA to LPA receptors and protect LPA from hydrolyzing enzymes. Based on the average molecular weight of gintonin (20 kDa), four LPA molecules could most likely bind to one molecule of ginseng protein. The LPA content in ginseng is 80 to 240-fold higher than in other plants, which in part explains its unique pharmacologic properties. Somewhat unexpectedly, the action of ginseng is now linked to LPA and its GPCRs and vice versa, and this linkage opens new dimensions for ginseng pharmacology and LPA therapeutics (Table 2).

**Gintonin in ginseng pharmacology**

Gintonin induces transient Ca\(^{2+}\) elevation and activates MAPK, PI3K, PKC, and Rho kinase via LPA receptors to evoke stimulatory cellular responses (Figure 2). Gintonin evokes cell proliferation and migration and morphological changes in human umbilical vein endothelial cells and PC12 neuronal cells. These effects of gintonin are consistent with those caused by LPAs via GPCRs and diverse G proteins, such as Ga\(_{12/13}\), Ga\(_{i1}\), and Ga\(_{12/13}\). Gintonin hinders the amyloidogenic pathway and induces non-amyloidogenic pathways that produce beneficial soluble A\(_{PPa}\) (sAPP\(_{a}\)) in neurons by activating LPA receptors. Gintonin also reduces the release of A\(_{\beta_1-42}\) and attenuates A\(_{\beta_1-40}\)-induced cytotoxicity. In addition, gintonin has been shown to rescue A\(_{\beta_1-40}\)-induced cognitive dysfunction in mice. Furthermore, in a transgenic murine Alzheimer’s disease model, long-term oral administration of gintonin effectively attenuated both amyloid plaque deposition and short- and long-term memory impairment. Thus, gintonin may contribute to the memory-improving effects of ginseng, which have been proven in human trials.

Autotaxin was found as an autocrine factor released by tumors, which stimulates tumor growth and migration. Later, autotaxin was identified as lysophospholipase D, which produces LPA from lysophosphatidylcholine. Autotaxin and LPA function as mitogenic and motility signals in various cancers, including neuroblastoma, hepatoma, lung cancer, ovarian cancer, metastatic breast cancer, and melanoma. A recent report showed that LPA C\(_{18:2}\), which is highly abundant in gintonin, inhibits autotaxin activity. Furthermore, Hwang et al showed that gintonin inhibits autotaxin activity in vitro and metastasis of B16/F10 melanoma cells in vivo. Vessel formation in tumors was also reduced in gintonin-treated mice. These effects may contribute to the anti-cancer effects of
Yin and Yang of ginseng pharmacology

In Chinese medicine, Yin and Yang are opposite and complementary forces that combine to form a whole. Ginseng pharmacology is interesting because the two active components have opposite effects and complement the entire effect of ginseng. For example, ginsenosides stabilize membrane potentials via the dual modulation of ion channels, but gintonin and LPA activate many cellular responses via GPCR activation. Ginsenosides inhibit Ca\(^{2+}\) influx, but gintonin induces a transient Ca\(^{2+}\) rise, and ginsenosides have low affinity for calcium but are relatively abundant in ginseng, whereas gintonin has a higher affinity for calcium but is only present at low levels (Table 2). Thus, it is highly likely that ginsenosides act as a Yin component to gintonin’s Yang component to produce the effects of ginseng. Therefore, it appears that the healing effects of *Panax* are the result of a harmonious balance between the positive and negative actions of ginsenosides and gintonins, reminiscent of the Yin and Yang forces in Chinese medicine.

Concluding remark and perspective

Our understanding of ginseng pharmacology has advanced tremendously during the last few decades. Ginsenosides were considered to be the active ingredients of ginseng for 5 decades. However, many researchers used ginseng extract (the butanol fraction) for pharmacologic studies because individual ginsenosides were scarce and difficult to purify. As a result, other components were included in these pharmacology experiments. Gintonin is now considered as a part of the ginseng fraction, and the LPAs in this fraction are considered responsible for a variety of the biological effects of ginseng, which are mediated through GPCRs. Furthermore, it appears that the pharmacological actions of ginseng can now be explained by the complementary opposing actions of gintonin and ginsenoside. One example might be the anticancer effects of the ginseng extract. Many ginsenosides have shown clear anticancer activity in different cancer cell lines by regulation of cell proliferation\[^{[39]}\]. Gintonin exhibited autotoxin inhibition *in vitro* and inhibition of metastasis of B16/F10 melanoma cells *in vitro*\[^{[40]}\]. Therefore, both components in ginseng may act synergistically and complementarily for the anti-tumor efficacy of ginseng.

How ginsenosides and gintonin work together in the body or whether ginsenosides affect the actions of gintonin or *vice versa* remains to be established. Future studies are required to elucidate the pharmacological effects of the different actions of ginsenosides and gintonin with respect to their individual contributions and the effects of whole ginseng in biological systems. Future research will undoubtedly expand our knowledge of ginseng pharmacology and the applications of LPA. In addition, the therapeutic application of LPA might be facilitated by knowledge of the traditional usages of ginseng. Although new drug developments based on targeting LPA receptors are in the pipeline, gintonin might provide alternative therapies for pathologic conditions related to LPA and LPA receptor-related diseases.

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References

1. Nah SY, Kim DH, Rhim H. Ginsenosides: are any of them candidates for drugs acting on the central nervous system? CNS Drug Rev 2007; 13: 381–404.
2. Lee JH, Choi SH, Lee BH, Yoon IS, Shin TJ, Pyo MK, et al. Modifications of the aliphatic side chain of 20(S)-ginsenoside Rg3 cause an enhancement or loss of brain Na\(^{+}\) channel current inhibitions. Biol Pharm Bull 2008; 31: 480–6.
3. Choi SH, Lee JH, Pyo MK, Lee BH, Shin TJ, Hwang SH, et al. Mutations Leu427, Asn428, and Leu431 residues within transmembrane domain-I-segment 6 attenuate ginsenoside-mediated L-type Ca\(^{2+}\) current channel inhibitions. Biol Pharm Bull 2009; 32: 1224–30.
4. Lee BH, Lee JH, Lee SM, Jeong SM, Yoon IS, Choi SH, et al. Identification of ginsenoside interaction sites in 5-HT\(_{1}\) receptors. Neuropharmacology 2007; 52: 1139–50.
5. Jang S, Ryu JH, Kim DH, Oh S. Changes of [3H]MK-801, [3H] muscimol and [\(^{3}H\)]flunitrazepam binding in rat brain by the prolonged ventricular infusion of transformed ginsenosides. Neurochem Res 2004; 29: 2257–66.
6. Kim S, Kim T, Ahn K, Park WK, Nah SY, Rhim H. Ginsenoside Rg\(_{1}\) antagonizes NMDA receptors through a glycine modulatory site in rat cultured hippocampal neurons. Biochem Biophys Res Commun 2004; 323: 416–24.
7. Choi S, Rho SH, Jung SY, Kim SC, Park CS, Nah SY. A novel activation of Ca\(^{2+}\)-activated Cl\(^{-}\) channel in *Xenopus* oocytes by Ginseng saponins: evidence for the involvement of phospholipase C and intracellular Ca\(^{2+}\) mobilization. Br J Pharmacol 2001; 132: 641–8.
8. Hwang SH, Shin TJ, Choi SH, Cho HJ, Lee BH, Pyo MK, et al. Gintonin, newly identified compounds from ginseng, is novel lysophosphatidic acids-protein complexes and activates G protein-coupled lysophosphatidic acid receptors with high affinity. Mol Cells 2012; 33: 151–62.
9. Choi JW, Chun J. Lysophospholipids and their receptors in the central nervous system. Biochim Biophys Acta 2013; 1831: 20–32.
10. Kim JH, Cho SY, Lee JH, Jeong SM, Yoon IS, Lee BH, et al. Neuropeptotective effects of ginsenoside Rg3 against homocysteine-induced excitotoxicity in rat hippocampus. Brain Res 2007; 1136: 190–9.
11. Shin TJ, Kim HJ, Kwon BJ, Choi SH, Kim HB, Hwang SH, et al. Gintonin, a ginseng-derived novel ingredient, evokes long-term potentiation through N-methyl-D-aspartic acid receptor activation: Involvement of LPA receptors. Mol Cells 2012; 34: 563–72.
12. Choi KT. Botanical characteristics, pharmacological effects and medicinal components of Korean *Panax* ginseng C A Meyer. Acta Pharmacol Sin 2008; 29: 1109–18.
Nag SA, Qin JJ, Wang W, Wang MH, Wang H, Zhang R. Ginsenosides as anticancer agents: in vitro and in vivo activities, structure-activity relationships, and molecular mechanisms of action. Front Pharmacol 2012; 3: 25.

Lee JH, Jeong SM, Kim JH, Lee BH, Yoon IS, Choi SH, et al. Effects of ginsenosides and their metabolites on voltage-dependent Ca2+ channel subtypes. Mol Cells 2006; 21: 52–62.

Choi SH, Shin TJ, Hwang SH, Lee BH, Kang J, Kim HJ, et al. Ginsengside Rg3 (3) decreases hERG K+ channel deactivation through Ser631 residue interaction. Eur J Pharmacol 2011; 663: 59–67.

Choi SH, Shin TJ, Lee BH, Chu DH, Choe H, Pyo MK, et al. Ginsenoside Rg3 activates human KCNQ1 K+ channel currents through interacting with the K318 and V319 residues: a role of KCNE1 subunit. Eur J Pharmacol 2010; 637: 138–47.

Lee JH, Jeong SM, Kim JH, Lee BH, Yoon IS, Choi SH, et al. Characteristics of ginsenoside Rg3-mediated brain Na+ current inhibition. Mol Pharmacol 2005; 68: 1114–26.

Lee JH, Lee BH, Choi SH, Yoon IS, Pyo MK, Shin TJ, et al. Ginsenoside Rg3 inhibits human Kv1.4 channel currents by interacting with the Lys531 residue. Mol Pharmacol 2008; 73: 619–26.

Kang D, Lee JY, Yang JY, Jeong SM, Lee JH, Nah SY, et al. Evidence that the tertiary structure of 20(S)-ginsenoside Rg3(3) with tight hydrophobic packing near the chiral center is important for Na+ channel regulation. Biochem Biophys Res Commun 2005; 333: 1194–201.

Lee BH, Choi SH, Pyo MK, Shin TJ, Hwang SH, Kim BR, et al. A role for Leu247 residue within transmembrane domain 2 in ginsenoside-mediated alpha7 nicotinic acetylcholine receptor regulation. Mol Cells 2009; 27: 591–9.

Kim CS, Son SJ, Kim HS, Kim YD, Lee KS, Jeon BH, et al. Modulating effect of ginseng saponins on heterologously expressed HERG currents in Xenopus oocytes. Acta Pharmacol Sin 2005; 26: 551–8.

Choi SE, Choi S, Lee JH, Whiting PJ, Lee SM, Nah SY. Effects of ginsenosides on GABA_A receptor channels expressed in Xenopus oocytes. Arch Pharm Res 2003; 26: 28–33.

Noh JH, Choi S, Lee JH, Betz H, Kim JI, Park CS, et al. Effects of ginsenosides on glycine receptor alpha1 channels expressed in Xenopus oocytes. Mol Cells 2003; 15: 34–9.

Choi SH, Shin TJ, Lee BH, Hwang SH, Lee SM, Lee BC, et al. Ginsenoside Rg3 enhances large conductance Ca2+-activated potassium channel currents: a role of Tyr360 residue. Mol Cells 2011; 31: 133–40.

Kwan CY, Kwan TK. Effects of Panax notoginseng saponins on vascular endothelial cells in vitro. Acta Pharmacol Sin 2000; 21: 1101–5.

Li Z, Chen X, Niwa Y, Sakamoto S, Nakaya Y. Involvement of Ca2+-activated K+ channels in ginsenosides-induced aortic relaxation in rats. J Cardiovasc Pharmacol 2001; 37: 41–7.

Kim ND, Kang SY, Park JH, Schini-Kerth VB. Ginsenoside Rg3 mediates endothelium-dependent relaxation in response to ginsenosides in rat aorta: role of K+ channels. Eur J Pharmacol 1999; 367: 41–9.

Chung I, Kim ND. Ginseng saponins enhance maxi Ca2+-activated K+ currents of the rabbit coronary artery smooth muscle cells. J Ginseng Res 1999; 23: 230–4.

Chung I, Lee JH. Ginsenoside Rg3 increases the ATP-sensitive K+ channel activity in the smooth muscle of the rabbit coronary artery. J Ginseng Res 1999; 23: 235–8.

Jeon BH, Kim CS, Kim HS, Park JB, Nam KY, Chang SJ. Effect of Korean red ginseng on blood pressure and nitric oxide production. Acta Pharmacol Sin 2000; 21: 1095–100.

He H, Xu J, Xu Y, Zhang C, Wang H, He Y, et al. Cardioprotective effects of saponins from Panax japonicus on acute myocardial ischemia against oxidative stress-triggered damage and cardiac cell death in rats. J Ethnopharmacol 2012; 140: 73–82.

Li HX, Han SY, Ma X, Zhang K, Wang L, Ma ZZ, et al. The saponin of red ginseng protects the cardiac myocytes against ischemic injury in vitro and in vivo. Phytomedicine 2012; 19: 477–83.

Bai CX, Takahashi K, Masumiyah H, Sawanobori T, Furukawa T. Nitric oxide-dependent modulation of the delayed rectifier K+ current and the L-type Ca2+ current by ginsenoside Re, an ingredient of Panax ginseng. in guinea-pig cardiomyocytes. Br J Pharmacol 2004; 142: 567–75.

Furukawa T, Bai CX, Kajihara A, Ozaki E, Kawano T, Nakaya Y, et al. Ginsenoside Re, a main phytosterol of Panax ginseng, activates cardiac potassium channels via a nongenomic pathway of sex hormones. Mol Pharmacol 2006; 70: 1916–24.

Attele AS, Wu JA, Yuan CS. Ginseng pharmacology: multiple constituents and multiple actions. Biochem Pharmacol 1999; 58: 1685–93.

Kim TW, Choi HJ, Kim NJ, Kim DH. Anxiolytic-like effects of ginsenosides Rg3 and Rh2 from red ginseng in the elevated plus-maze model. Planta Med 2009; 75: 836–9.

Kim JH, Yoon IS, Lee BH, Choi SH, Lee JH, Jeong SM, et al. Effects of Korean red ginseng extract on cisplatin-induced nausea and vomiting. Arch Pharm Res 2005; 28: 680–4.

Choi S, Kim HJ, Ko YS, Jeong SW, Kim YI, Simonds WF, et al. G α11 coupled to mammalian phospholipase C beta 3-like enzyme mediates the ginsenoside effect on Ca2+-activated Cl− current in the Xenopus oocyte. J Biol Chem 2001; 276: 48797–802.

Lee JH, Jeong SM, Lee BH, Nah HS, Kim BK, Kim JI, et al. Prevention of ginsenoside-induced desensitization of Ca2+-activated Cl− current by microinjection of inositol hexakisphosphate in Xenopus laevis oocytes: involvement of GRK2 and beta-arrestin I. J Biol Chem 2004; 279: 9112–21.

Pyo MK, Shin TJ, Choi SH, Lee BH, Pyo MK, Lee JH, et al. Novel glycophospholipids from ginseng. J Ginseng Res 2011; 35: 92–103.

Hwang SH, Shin EJ, Shin TJ, Lee BH, Choi SH, Kang J, et al. Gintonin, a ginseng-derived lysophosphatic acid receptor ligand, attenuates Alzheimer’s disease-related neuropathies: involvement of non-amyloidogenic processing. J Alzheimers Dis 2012; 31: 207–23.

Tigyi G, Miledi R. Lysophosphatidic acid induces actin cytoskeleton reorganization and neurite retracing in PC12 pheochromocytoma cells. J Biol Chem 1992; 267: 21360–7.

Yoon HR, Kim H, Cho SH. Quantitative analysis of acyl-lysophosphatic acid in plasma using negative ionization tandem mass spectrometry. J Chromatogr A Analyt Technol Biomed Life Sci 2003; 788: 85–92.

Houben AJ, Moelaena WH. Autotaxin and LPA receptor signaling in cancer. Cancer Metastasis Rev 2011; 30: 557–65.

Hwang SH, Lee BH, Kim HJ, Cho HJ, Shin HC, Im KS, et al. Suppression of metastasis of intravenously-inoculated B16/F10 melanoma cells by the novel ginseng-derived ingredient, gintonin: Involvement of autotaxin inhibition. Int J Oncol 2013; 42: 317–26.

Tokumura A, Majima E, Kariya Y, Tominaga K, Kogure K, Yasuda K, et al. Identification of human plasma lysophospholipase D, a lysophosphatic acid-producing enzyme, as autotaxin, a multifunctional phos-
phodiesterase. J Biol Chem 2002; 277: 39436–42.

47 Umezu-Goto M, Kishi Y, Taira A, Hama K, Dohmae N, Takio K, et al. Autotaxin has lysophospholipase D activity leading to tumor cell growth and motility by lysophosphatidic acid production. J Cell Biol 2002; 158: 227–33.

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