COMMENTARY
Ginseng Pharmacology
MULTIPLE CONSTITUENTS AND MULTIPLE ACTIONS
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ABSTRACT. Ginseng is a highly valued herb in the Far East and has gained popularity in the West during the last decade. There is extensive literature on the beneficial effects of ginseng and its constituents. The major active components of ginseng are ginsenosides, a diverse group of steroidal saponins, which demonstrate the ability to target a myriad of tissues, producing an array of pharmacological responses. However, many mechanisms of ginsenoside activity still remain unknown. Since ginsenosides and other constituents of ginseng produce effects that are different from one another, and a single ginsenoside initiates multiple actions in the same tissue, the overall pharmacology of ginseng is complex. The ability of ginsenosides to independently target multireceptor systems at the plasma membrane, as well as to activate intracellular steroid receptors, may explain some pharmacological effects. This commentary aims to review selected effects of ginseng and ginsenosides and describe their possible modes of action. Structural variability of ginsenosides, structural and functional relationship to steroids, and potential targets of action are discussed.


KEY WORDS. Panax ginseng; Panax quinquefolius; ginsenosides; steroidal saponins; pharmacological effects; herbal medicine

The ginseng root has been used for over 2000 years, in the belief that it is a panacea and promotes longevity. As described in Chinese traditional medicine textbooks, its effectiveness reaches mythical proportions [1, 2]. The efficacy of ginseng was known in the West by the 18th century, and the study of ginseng has a long history [2]. Recently there has been a renewed interest in investigating ginseng pharmacology using biochemical and molecular biological techniques. Pharmacological effects of ginseng have been demonstrated in the CNS and in cardiovascular, endocrine, and immune systems. In addition, ginseng and its constituents have been ascribed antineoplastic, anti-stress, and antioxidant activity. It is an herb with many active components, and there is evidence from numerous studies that ginseng does have beneficial effects [1, 3].

Seven major species of ginseng are distributed in East Asia, Central Asia, and North America [2]. Most studies of ginseng, including those cited in this commentary, have utilized constituents from three common species: Panax ginseng (Asian ginseng), Panax quinquefolius (American ginseng), and Panax japonicus (Japanese ginseng).

Active constituents found in most ginseng species include ginsenosides, polysaccharides, peptides, polyacetylenic alcohols, and fatty acids [1]. There is a wide variation (2–20%) in the ginsenoside content of different species of ginseng [2]. Moreover, pharmacological differences within a single species cultivated in two different locations have been reported. For example, the potency of extracts from Panax quinquefolius, cultivated in the U.S.A., for modulating neuronal activity is significantly higher than for the same species cultivated in China [4].

PHARMACOLOGICAL EFFECTS
Most pharmacological actions of ginseng are attributed to ginsenosides [2]. More than twenty ginsenosides have been isolated [3], and novel structures continue to be reported, particularly from Panax quinquefolius and Panax japonicus [5]. Figure 1 illustrates the structures of some ginsenosides. Since cardiovascular effects of ginseng have been well documented [3, 6], they will not be discussed here.

Effects on the CNS
Ginseng has both stimulatory and inhibitory effects on the CNS [7], and may modulate neurotransmission. Ginsenosides Rb1 and Rg1 play a major role in these effects [8, 9].

MEMORY, LEARNING, AND NEUROPROTECTION. Results of several animal studies show that Rb1 [10], Rg1 [11], and Re [12] prevent scopolamine-induced memory deficits. Central
cholinergic systems have been implicated in mediating learning and memory processes [13]. Rb1 was shown to increase the uptake of choline in central cholinergic nerve endings [9], and to facilitate the release of acetylcholine from hippocampal slices [10]. Both Rb1 and Rg1 appear to partially reverse scopolamine-induced amnesia by increasing cholinergic activity. Results from these investigations suggest that ginsenosides may facilitate learning and memory and are able to enhance nerve growth [14, 15].

Ginsenosides may also possess the ability to protect neurons from ischemic damage. Rb1 was shown to rescue hippocampal neurons from lethal ischemic damage [16] and to delay neuronal death from transient forebrain ischemia [17] in vivo. In another study, Rg1 was shown to increase membrane fluidity of cortical cells from 27-month-old rats [18]. Rb1 increased the fluidity of synaptosomal membranes impaired by FeSO4-cysteine [19]. Both Rb1 and Rg1 significantly decreased the hippocampal [Ca^{2+}] level that was found to increase in aged rats [20].

**NEUROTRANSMITTER MODULATION.** Results of in vitro studies show that ginsenosides may modulate nerve transmission by decreasing the availability of neurotransmitters. Tsang et al. [8] demonstrated that ginseng extract concentration-dependently inhibits the uptake of GABA†, glutamate, dopamine, noradrenalin, and serotonin in rat brain synaptosomes. Ginsenosides compete with agonists for binding to GABAA and GABAB receptors [21]. Yuan et al. [22] demonstrated that Panax quinquefolius extracts interact with the ligand binding of GABAA receptors in brainstem neurons, which suggests that regulation of GABAergic neurotransmission may be an important action of ginseng.

**OTHER CNS EFFECTS.** An in vivo study that explored the effects of ginsenosides on drug-induced sleep showed that a mixture of Rb1, Rb2, and Rc prolonged hexobarbital sleeping time in mice, and decreased exploratory activity [23], suggesting a CNS-depressing effect. Other studies demonstrated that ginseng may ameliorate some adverse effects of morphine. Rats that were sensitized to morphine developed dopaminergic hyperfunction [24]. Kim et al. [25] showed that ginseng total saponin prevents the development of dopamine receptor supersensitivity induced by the chronic administration of morphine. Ginsenosides also may possess

![FIG. 1. Structures of ginsenosides discussed in the text. Based on chemical structure, there are two major groups: panaxadiols (A) and panaxatriols (B). Rb1, as shown in the lower part of (A), differs from other panaxadiols at the side chain. Ginsenoside Ro, a nonsteroidal saponin, is shown in (C).](image-url)
antinociceptive properties. Ginseng total extract and Rf were shown to inhibit Ca$^{2+}$ channels on primary sensory neurons to the same degree as opioids [26]. In addition, pretreatment of rats with ginsenosides inhibited substance P-induced pain behaviors [27].

Antineoplastic and Immunomodulatory Effects

Ginsenosides have been shown to exert anticarcinogenic effects in vitro through different mechanisms. Several ginsenosides show direct cytotoxic and growth inhibitory effects against tumor cells [28, 29]. Others have been shown to induce differentiation and inhibit metastasis [30, 31].

TUMOR CELL GROWTH INHIBITION AND APOPTOSIS. Ginsenoside Rh$_2$ inhibited growth and stimulated melanogenesis [28], and arrested cell cycle progression at the G$_1$ stage [32] in B16-BL6 melanoma cells. In association with G$_1$ arrest, there was a suppression of cyclin-dependent-kinase-2 activity. After oral administration, ginsenosides Rb$_1$, Rb$_2$, and Rc are metabolized by intestinal bacteria to a modified ginsenoside named M1 [33, 34]. Wakabayashi et al. [29] reported that M1 inhibited the proliferation of B16-BL6 mouse melanoma cells, and at a higher concentration induced cell death within 24 hr by regulating apoptosis-related proteins.

It has been reported that orally administered and subcutaneously injected Rh$_2$ inhibited growth of human ovarian cells transplanted into nude mice and significantly prolonged the survival times of the mice [35]. Intravenously or orally administered Rg$_3$ led to a decrease in lung metastasis of B16-BL6 melanoma cells [30]. Several studies that utilized medium-term and long-term anticarcinogenesis models in mice showed that ginseng extracts have a tumor inhibitory effect in mice exposed to chemical carcinogens [36, 37]. Results of a cohort study showed that ginseng consumers had a lower risk for gastric and lung cancer, suggesting that ginseng may have a non-organ-specific anticarcinogenic effect [38]. It seems that a large-scale, controlled clinical study is needed to validate this result.

ANTIMITOGENIC ACTIVITY. Sister chromatid exchange is regarded as a sensitive indicator of DNA damage [39] and significantly correlates with the mutagenic activities of many chemicals [40]. Rh$_2$ significantly suppressed both baseline and induced sister chromatid exchanges in human lymphocytes [41]. In addition, ginseng may enhance the proofreading activity of eukaryotic DNA polymerase. Cho et al. [42] showed that total ginseng extracts activated both polymerase and exonuclease activities of DNA polymerase $\delta$.

DIFFERENTIATION AND INHIBITION OF METASTASIS. In vitro studies demonstrated that Rh$_2$ and Rh$_3$ induced differentiation of promyelocytic leukemia HL-60 cells into granulocytes, possibly by modulating PKC isoforms [31]. Total ginseng extract was shown to induce differentiation of cultured Morris hepatoma cells [43]. In addition, Mochizuki et al. [30] showed that Rg$_3$ significantly inhibited the adhesion and invasion of B16-BL6 cells into reconstituted basement membranes, and inhibited pulmonary metastasis.

IMMUNOMODULATORY EFFECTS. In general, immunomodulatory and antitumorogenic activities of ginsenosides are discussed together. However, few investigations have viewed these two events as sequential steps. Yun et al. [44] followed the NK cell activity and the incidence of lung adenoma in mice treated with urethane or benzopyrenes. In mice administered ginseng, the NK activity was depressed for 4–24 weeks and then returned to control levels. Concurrently, in animals treated with ginseng, a lower incidence of lung adenoma was reported. Kim et al. [45] evaluated multiple immune system components in mice subchronically exposed to cyclophosphamide. This study also revealed that ginseng possesses some immunomodulatory properties, primarily associated with NK cell activity.

Ginsenoside Rg$_1$ was shown to increase both humoral and cell-mediated immune responses. Kenarova et al. [46] reported that spleen cells recovered from ginsenoside-treated mice injected with sheep red cells as an antigen showed significantly higher plaque-forming response and hemagglutinating antibody titers. In addition, Rg$_1$ increased the number of antigen-reactive T helper cells, T lymphocytes, and NK cells.

As described above, ginseng extracts and several ginsenosides have been shown to possess some anticarcinogenic and immunomodulatory effects. It will be interesting to see whether their efficacy can be observed in double-blind, randomized, placebo-controlled clinical studies.

WHY ARE THERE SO MANY DIVERSE EFFECTS?

Ginseng contains over twenty ginsenosides, and single ginsenosides have been shown to produce multiple effects in the same tissue [8, 47]. In addition, non-ginsenoside constituents of ginseng also exert pharmacological effects. Thus, it is not surprising that the overall activity of the herb is complex.

Ginsenosides and Steroids

Ginsenosides (except Ro) belong to a family of steroids named steroidal saponins [28, 31, 48]. They have been named ginsenoside saponins, triterpenoid saponins, or dammarane derivatives under previous classifications [49, 50]. Ginsenosides possess the four trans-ring rigid steroid skeleton, with a modified side chain at C-20 [51]. The classical steroid hormones have a truncated side chain (progesterone, cortisol, and aldosterone) or no side chain (estradiol and testosterone) [48, 52]. Many steroids have a $\beta$-OH group at C-3; ginsenosides (for example, Rb$_1$, Rb$_2$, Rc, and Rd) usually have a sugar residue attached to the same site [2, 51]. Sugar moieties are cleaved by acid hydrolysis during extraction, or by endogenous glycosidases to give the
Steroidal saponins, which share structural features with steroid hormones, have been used in the industrial synthesis of progesterone and pregnanolone [48]. Steroids possess numerous physiological activities, partly due to the nature of the steroid skeleton. The trans-ring junctions of the skeleton allow substituent groups, which interact with receptors, to be held in rigid stereochemically defined orientations [48]. In addition, the steroid skeleton endows the whole molecule with a favored structure to allow, for example, insertion into membranes [53]. Recent work showed that Rg1 is a functional ligand of the nuclear glucocorticoid receptor [54, 55].

**Structural Diversity of Ginsenosides**

As illustrated in Fig. 1, ginsenosides exhibit considerable structural variation. They differ from one another by the type of sugar moieties, their number, and their site of attachment. Some sugar moieties present are glucose, maltose, fructose, and saccharose. They are attached to C-3, C-6, or C-20. The binding site of the sugar has been shown to influence biological activity. Rg1 and Rh2 are structurally similar, except for the binding site of the β-d-glucopyranosyl group. In Rh1 the sugar is at C-6, and in Rh2, at C-3. Ginsenoside Rh2 decreased growth of B16-BL6 melanoma cells and stimulated melanogenesis and cell-to-cell adhesiveness. On the other hand, Rh1 had no effect on cell growth and cell-to-cell adhesiveness, but stimulated melanogenesis [47]. Significantly, only Rh2 was incorporated in the lipid fraction of the B16-BL6 melanoma cell membrane.

Ginsenosides also differ in their number and site of attachment of hydroxyl groups. Polar substituents interact with phospholipid head groups in the hydrophilic domain of the membrane. Consequently, the insertion of orientation of ginsenosides into membranes would be influenced by the number and site of polar OH groups. Differences in the number of OH groups were shown to influence pharmacological activity. Ginsenoside Rh2 and Rh3 differ only by the presence of an OH group at C-20 in Rh2. Although both Rh2 and Rh3 induced differentiation of promyelocytic leukemia HL-60 cells into morphological and functional granulocytes, the potency of Rh2 was higher [31].

**STEROISOMERISM**. Another factor that contributes to structural differences between ginsenosides is stereochemistry at C-20. Most ginsenosides that have been isolated are naturally present as enantiomeric mixtures [48, 56]. Since the modules with which they react in biological systems are also optically active, stereoisomers are considered to be functionally different chemical compounds [57]. Consequently, they often differ considerably in potency, pharmacological activity, and pharmacokinetic profile. Both 20(S) and 20(R) ginsenoside Rg2 inhibit acetylcholine-evoked secretion of catecholamines from cultured bovine adrenal chromaffin cells [58]. However, the 20(S) isomer showed a greater inhibitory effect.

Ganodermic acid S compounds are steroidal saponins that share structural features with ginsenosides [59]. Twelve compounds of ganodermic acid S are either paired stereo- or positional isomers and show differential activation of human phospholipase C and A2 by infiltrating into platelet membranes [60]. In this regard, the stereochemistry of the substituent was found to be the most important structural characteristic.

Structural alterations in the gut after oral administration also contribute to diversity. Certain ginsenosides, such as Rb1 and Rg1, are poorly absorbed after ingestion [61]. Rb1 was hydrolyzed to compound K by intestinal flora [34]; compound K was shown to increase the cytotoxicity of antineoplastic drugs [62] and to induce apoptosis in B16-BL6 melanoma cells [29].

**WHAT ARE THE UNDERLYING MECHANISMS OF ACTION?**

Ginsenosides are amphiphilic in nature [48], and have the ability to intercalate into the plasma membrane. This leads to changes in membrane fluidity, and thus affects membrane function, eliciting a cellular response. There is evidence to suggest that ginsenosides interact directly with specific membrane proteins. Moreover, like steroid hormones, they are lipid-soluble signaling molecules, which can traverse the plasma membrane and initiate genomic effects. Figure 2 illustrates possible sites of action of ginsenosides, which are discussed below.

**Ginsenosides and the Plasma Membrane**

Cellular membranes may exist under conditions of curvature stress, being close to the hexagonal phase transition [63]. Consequently, the physicochemical properties of these membranes are sensitive to changes in membrane components and lipophilic agents, which may modulate curvature stress [64].

It has become increasingly evident that the lipid environment of membrane proteins, including ion channels, transporters, and receptors, plays an important role in their function [53]. In artificial and biological membranes, cholesterol, a major membrane lipid, is organized into structural and kinetic domains or pools [65]. Membrane proteins are thought to be localized selectively in cholesterol-rich domains (ACh receptor) or in cholesterol-poor domains (the sarcoplasmic Ca2+-ATPase) [65]. Therefore, the biophysical properties of the different domains, rather than the bulk lipid, may selectively influence transmembrane protein function and mimic specificity at the effector level.

Ginsenosides may interact with the polar heads of membrane phospholipids and the β-OH of cholesterol through their OH groups. Moreover, their hydrophobic steroid backbone could intercalate into the hydrophobic interior of the bilayer. Both of these effects may contribute to altering the lipid environment around membrane proteins. Cholesterol is an intrinsic membrane lipid, which
shares the steroid backbone and amphipathic nature of ginsenosides. Cholesterol enrichment has an inhibitory effect on many membrane ATPases [53], and it may directly interact with the boundary lipids of ATPase and alter the intermolecular hydrogen bonds of the protein [66]. In contrast, ginsenoside Rb1 has been shown to increase Na\(^+\)-K\(^+\)-ATPase and Ca\(^{2+}\)-Mg\(^{2+}\)-ATPase activity in neurons [19]. It is possible that some ginsenosides interact with membrane cholesterol and displace it from the immediate environment of ATPases. Since removal of cholesterol will lead to an increase in membrane fluidity [67], conformational changes that ATPases undergo during their transport cycle [68] may be facilitated.

Only recently has non-genomic action by steroids been widely recognized. Evidence for these rapid effects is now available for steroids of all classes [69]. In many of these cases, the steroid effect occurs at the membrane level and is not associated with entry into the cell. Several mechanisms for these effects have been proposed, including changes in membrane fluidity and activity of steroid hormones on plasma membrane receptors [70]. Ginsenosides also may modify membrane protein structure by changing membrane dynamics and modulating activity of ion channels, membrane-bound receptors, and enzymes. Consequently, a single ginsenoside may be capable of interacting with multi-receptor systems.

**GINSENOSIDES AND MEMBRANE CHANNELS.** Ginsenoside effects on membrane channels show similarities to steroid hormones including progesterone, estrogen, and vitamin D metabolites, which modulate rapid Ca\(^{2+}\) influx in several tissues [70]. Several ginsenosides inhibit Ca\(^{2+}\) influx through voltage-gated Ca\(^{2+}\) channels in adrenal chromaffin cells [31]. Of the five ginsenosides that were tested (Rb1, Re, Rf, Rg1, and Rc), the inhibitory potency was highest for Rc. Tachikawa et al. [71] showed that in bovine adrenal chromaffin cells, Rg2 inhibited Na\(^+\) influx through nicotinic receptor-gated cation channels, possibly by binding to the receptor-operated Na\(^+\) channel. It is likely that the resulting decrease in catecholamine secretion may contribute to the anti-stress effects of Panax ginseng. Ginsenosides also can regulate Na\(^+\) channels on nerve cells. Using standard patch clamp techniques, our group recently observed that extracts of Panax quinquefolius caused partial inhibition of neuronal Na\(^+\) channels during activation and inactivation states (unpublished data).

Ginsenoside activity on membrane pumps is not limited to ion transporters. P-Glycoprotein is a membrane ATPase pump that actively exports cytotoxic compounds and contributes to anticancer multidrug resistance [72]. Several ginsenosides, including 20(S)Rh2, inhibit the transport function of P-glycoprotein and increase sensitivity to cancer chemotherapeutics in resistant cells [62].
GINSENOSIDES AND GABA RECEPTORS. Several ginsenosides (Rh1, Rh2, Rc, Re, Rf, and Rg3) [21] and total ginseng extracts [22] modulated the binding of the GABA$_A$ agonist muscimol. Ginseng extract and Rc decreased the affinity of binding of the GABA$_B$ agonist baclofen [21]. Like ginsenosides, steroidal compounds regulate GABAergic neurotransmission in the brain. Several endogenous steroids such as progesterone, androsterone, neurosteroids, and their metabolites stimulate GABA$_A$-mediated chloride ion flux [69].

GINSENOSIDES AND OTHER MEMBRANE PROTEINS. Agents that modify the physical properties of the phospholipid bilayer, such as its fluidity, can modulate the activity of membrane-bound G proteins in the absence of the receptors [73]. Some Ca$^{2+}$ channels in sensory neurons are linked to G protein-coupled receptors [26]. Ginsenoside Rf was shown to produce antinociception by inhibiting Ca$^{2+}$ channels on sensory neurons through a pertussis toxin-sensitive G protein [74]. However, whether Rf binds to the receptor or directly modulates G protein activity is not known.

One target molecule that may account for the anticancer effects of ginsenoside Rh$_2$ is Cdk2 [32], an intracellular cell cycle-regulating enzyme. It is not known whether Rh$_2$ directly inhibits Cdk2 activity. However, Cdk2 also can be suppressed indirectly via modulating signaling cascades originating at the cell membrane [75]. Rh$_2$ was shown to be incorporated in membranes to a level comparable to that of steroids [28]. That Rh$_2$ targets membrane components was also demonstrated by its ability to change membrane fluidity, adhesiveness, and cell surface sugar structures [28].

Some pharmacological effects of ginsenosides may be mediated by binding to steroid hormone receptors. Both neural and non-neural membrane steroid receptors have been reported, and in most cases steroids bind to the membrane receptors with specificity and modest affinity [70]. The differential effects of various ginsenosides on the lipid bilayer argue against a nonspecific activity. Rather, these effects suggest specific interaction between the ginsenoside and specific membrane proteins.

Membrane-associated enzymes that are sensitive to curvature strain such as PKC are highly responsive to perturbations of membrane structure [76]. Recent work has shown that the synergism exhibited by diacylglycerol and fatty acids in activating PKC is due to the synergistic effect of these molecules in inducing curvature strain in bilayers [64]. It was shown that ginsenosides Rh$_2$ and Rh$_3$ induced differentiation of human promyelocytic leukemia HL-60 cells into morphological and functional granulocytes by modulating PKC activity [31]. PKCs directly phosphorylate a number of intracellular proteins and regulate important cellular functions, including cell growth and cell differentiation [77]. Coincidentally, with the differentiation of HL-60 cells by ginsenoside Rh$_2$ there was an increase in PKC activity [31]. It is possible that ginsenoside Rh$_2$ and Rh$_3$ modulate PKC activity by altering curvature strain of the lipid bilayer. The ability of ginsenosides to independently target multiple plasma membrane-anchored proteins may account for the variety of responses that can be triggered.

Genomic Effects of Ginsenosides

As discussed earlier, ginsenosides belong to a family of steroids and share their structural characteristics [48]. Like steroids, they can traverse cell membranes freely. Moreover, their presence has been demonstrated within cells, particularly the nucleus [29]. According to the classical theory of steroid hormone action, steroids, which bind nuclear receptors, are thought to affect primarily the transcription of mRNA and subsequent protein synthesis [69]. Intracellular steroid binding proteins present possible attractive targets for ginsenosides.

A recent study showed the biological effects resulting from structural similarities between ginsenosides and steroids. Lee et al. [54] showed that Rg$_1$ is a functional ligand of the GR. In this regard, the binding of the synthetic glucocorticoid dexamethasone to the GR was competitively inhibited by Rg$_1$, although the affinity of Rg$_1$ for GR was lower than for dexamethasone. Ligand-occupied GR, when complexed with specific DNA sequences named GRE, regulated the transcription of target genes [78]. Subsequent to ligand binding, Rg$_1$ activated GRE containing reporter plasmids in a concentration-dependent manner. Moreover, the GR-mediated transactivation and growth inhibition of FTO2B cells by dexamethasone and Rh$_2$ were inhibited by the specific glucocorticoid antagonist RU486. Rg$_1$ exhibits many other features of a glucocorticoid, such as synergistic activation of gene transcription by cyclic AMP and the ability to down-regulate the GR content of cells [55].

After oral administration, ginsenosides Rh$_1$ and Rh$_2$ are metabolized by intestinal bacteria to compound K, also known as M1 [34], which induces apoptosis of tumor cells [29]. Compound K was shown to have a nucleosomal distribution [29]. This, together with the observation of up-regulation of the CDK inhibitor p27, and the down-regulation of c-Myc and cyclin D1, suggests that the modification of apoptosis-related proteins by compound K is induced by transcriptional regulation [29]. Another investigation showed the binding of Rh$_2$ to the transcription factor AP2 [79]. The subsequent genomic event was shown to be the induction of the SOD1 gene (Cu,Zn-superoxide dismutase), a key enzyme in the metabolism of oxygen free radicals.

SUMMARY AND FUTURE WORK

This commentary discusses ginsenoside effects that may be initiated at the cell membrane, as well as via intracellular protein binding. Consequently, ginsenosides may follow a dual model of action.

One pathway of ginsenoside activity involves binding to membrane receptors that trigger changes in electrolyte...
transport systems, and activation of signaling pathways. In this regard, differences in lipophilicity between the ginsenosides and the cholesterol content of membrane domains may be important. Future studies should be carried out to demonstrate the partitioning of ginsenosides in membranes, and determine whether they induce changes in the structure of membrane proteins. Another possible mechanism by which ginsenosides produce pharmacological effects is by binding to plasma membrane steroid receptors. Research in this area is still in its infancy, although there is a growing interest in non-genomic signaling by steroids.

The second pathway of ginsenoside activity involves binding to intracellular steroid receptors, where the ligand/receptor complex acts as a transcription factor in the nucleus. The demonstration of ginsenoside Rg1 as a functional ligand of the nuclear glucocorticoid receptor [54, 55] supports this view. More studies should be directed to showing that other ginsenosides may function as steroid receptor agonists, and to quantitating their binding. In this regard, computer-based imaging of functional groups on ginsenosides for the construction of pharmacophore models [80] would be useful. Future research also should focus on whether there is interaction between the two pathways of ginsenoside action, both of which may occur in the same cell. Therefore, the initial rapid response via membrane phenomena may be augmented by the delayed genomic response.

Two factors may contribute to the multiple pharmacological effects of ginseng. The first is the structural isomerism and stereoisomerism exhibited by ginsenosides, which increase their diversity. The second is the ability of ginsenosides to target membrane-anchored receptors and ion channels, as well as nuclear receptors. Certainly, the argument can be raised that evidence for most pharmacological effects of ginseng isomeric and stereoisomeric exhibited by ginsenosides, which supports this view. More studies should be directed to showing that other ginsenosides may function as steroid receptor agonists, and to quantitating their binding. In this regard, computer-based imaging of functional groups on ginsenosides for the construction of pharmacophore models [80] would be useful. Future research also should focus on whether there is interaction between the two pathways of ginsenoside action, both of which may occur in the same cell. Therefore, the initial rapid response via membrane phenomena may be augmented by the delayed genomic response.

Two factors may contribute to the multiple pharmacological effects of ginseng. The first is the structural isomerism and stereoisomerism exhibited by ginsenosides, which increase their diversity. The second is the ability of ginsenosides to target membrane-anchored receptors and ion channels, as well as nuclear receptors. Certainly, the argument can be raised that evidence for most pharmacological effects of ginseng has been obtained from in vitro studies, many of which have not been confirmed in vivo. Nevertheless, the view that ginsenosides may initiate effects at the plasma membrane by interacting with multireceptor systems, and that they also freely traverse the membrane and produce genomic effects, complements the intriguing pharmacology of ginseng.

This work was supported, in part, by the Tang Family Foundation, and the Clinical Practice Enhancement & Anesthesia Research Foundation.

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