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Safety Assessment of *Panax* spp Root-Derived Ingredients as Used in Cosmetics

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Abstract

The Cosmetic Ingredient Review Expert Panel (Panel) reviewed the safety of 13 *Panax* spp root-derived ingredients as used in cosmetics. *Panax* "spp" indicates that multiple species within the genus are used in cosmetics, but not all species within that genus. Four species are being considered in this safety assessment. These ingredients function mostly as skin-conditioning agents—miscellaneous, fragrance ingredients, skin-conditioning agents—humectant, skin-conditioning agents—emollient, and cosmetic astringents. The Panel reviewed available data related to these ingredients and addressed the issue of pulegone, a constituent of these ingredients and other ingredients, such as peppermint oil. The Panel concluded that these *Panax* spp root-derived ingredients are safe in the practices of use and concentration as given in this safety assessment.

Keywords

Panax spp, ginseng, safety, cosmetics

Introduction

Panax ginseng C. A. Meyer of the Araliaceae family is also called Chinese ginseng, Manchurian ginseng, or Korean ginseng.[1] It is a perennial herb indigenous to the mountainous forests of North China, Manchuria, and Korea. There are 4 other closely related plants of the Araliaceae family: *Panax quinquefolium* L. (American ginseng), *Panax japonicus* C. A. Meyer (chikusetsu ninjin or Japanese ginseng), and *Panax pseudoginseng* Wall (notoginseng, San-ch'i ginseng, and Himalayan ginseng). For the sake of brevity, *Panax* spp is used to designate the multiple species being considered. *Panax* "spp" indicates multiple species within the genus are used in cosmetics but not all species within that genus. Also, the convention for naming cosmetic ingredients is for the full genus and species name that is not italicized; therefore, when referring to an actual ingredient, this convention will be followed. when referring to the plants, the biological conventions of italicizing the plant name and abbreviating the genus name after the first mention will be followed.

Several ginseng-derived materials that are used in cosmetics involve root-derived ingredients, as distinct from ingredients derived from other plant parts. This safety assessment focuses on those ginseng ingredients that are derived from the root portion of the plant and does not address ginseng-derived ingredients that are prepared using other plant parts. The ingredients included in this report are:

- Panax ginseng root extract,
- hydrolyzed ginseng root,
- hydrolyzed ginseng root extract,
- hydrolyzed ginseng saponins,
- Panax ginseng root,
- Panax ginseng root powder,
- Panax ginseng root water,
- Panax ginseng root oil,
- Panax ginseng root protoplast,
- Panax japonicus root extract,
- Panax notoginseng root,
- Panax notoginseng root powder, and
- Panax quinquefolium root extract.

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Table 1. The Names, CAS Registry Nos Functions, and Definitions of the Ginseng Root-Derived Ingredients in This Safety Assessment.[5]

Ingredient	CAS No	Functions	Definition
Panax ginseng root extract	50647-08-0	Skin-conditioning agents—miscellaneous	The extract of the roots of *P ginseng*
Hydrolyzed ginseng root		Skin-conditioning agents—miscellaneous	The hydrolysate of *P ginseng* root derived by acid, enzyme, or other method of hydrolysis
Hydrolyzed ginseng root extract		Skin-conditioning agents—miscellaneous	The hydrolysate of *P ginseng* root extract derived by acid, enzyme, or other method of hydrolysis
Panax ginseng root	50647-08-0 (generic)	Skin-conditioning agents—miscellaneous	The roots of *P ginseng*
Panax ginseng root powder	50647-08-0 (generic)	Skin-conditioning agents—miscellaneous	The powder obtained from the dried, ground roots of *P ginseng*
Panax ginseng root water	50647-08-0 (generic)	Fragrance ingredients	An aqueous solution of the steam distillate obtained from the roots of *P ginseng*.
Panax ginseng root oil	50647-08-0 (generic)	Skin-conditioning agents—miscellaneous	The volatile oil obtained from the roots of *P ginseng*
Panax ginseng root protoplasts		Skin conditioning agent-humectant	The protoplasts derived from the roots of *P ginseng*
Panax japonicus root extract		Skin-conditioning agents—miscellaneous	The extract of the roots and rhizomes of *P japonicus*
Hydrolyzed ginseng saponins		Skin-conditioning agents—emollient	The saponins derived from ginseng that are hydrolyzed by acid, enzyme, or other method of hydrolysis.
Panax notoginseng root extract		Skin conditioning agent—humectant	The extract of the roots of *P notoginseng*
Panax notoginseng root powder		Skin-conditioning agents—miscellaneous	The powder obtained from the dried, ground roots of *P notoginseng*.
Panax quinquefolium root extract	90045-38-8	Cosmetic astringent	The extract of the roots of *P quinquefolium*.

The cosmetic functions of these ingredients include skin-conditioning agents—miscellaneous, fragrance ingredients, skin-conditioning agents—humectant, skin-conditioning agents—emollient, and cosmetic astringents.

There is some confusion as to whether or not *P ginseng*, *P quinquefolius*, *P japonicus*, and *P pseudoginseng* are used in cosmetics under their own names, all as *P ginseng*, or interchangeably under the generic name "ginseng." There is also speculation that there is no real difference among these plants in cosmetic application.[2] Because this is unresolved, each of these ingredients will be referred to specifically in this safety assessment.

To address the difficulty in assessing the properties and biological effects of ginseng, standardized extracts of both *P ginseng* C.A. Myer (G115) and *P quinquefolium* (CNT-2000) have been developed.[3] These extracts are standardized by the content of 6 saponins (Rb1, Re, Rc, Rd, Br2, and Rg1) and are used in several of the studies in this report. However, the composition of G115 and CNT-2000 is proprietary information and is not available.[4]

Chemistry

Definitions

The names, CAS Registry Nos., functions, and definitions of the ingredients in this safety assessment are listed in Table 1. CAS No. 50647-08-0 is generically used for several of the ginseng root ingredients, but several ingredients have no CAS Nos.

The *International Cosmetic Ingredient Dictionary and Handbook* (INCI) defines the terms extract, powder, oil, and water included in the names of these ingredients.[5]

Extract. Extracts are identified by the source of the material extracted. Many extracts are supplied with the extracting solvent and/or other diluents. Where evidence of isolation is presented, a botanical ingredient may be named as a chemical entity.

In most cases, the INCI names for plant extracts prepared by solvent extraction are assigned labeling names that identify the name of the plant and the solvent and thus represent the material it is extracted from. However, when the extraction solvent is carbon dioxide, carbon dioxide is not included in the INCI name since it evaporates. Additionally, solvents are not identified in the INCI name in cases where the solvent has been driven off and is not present in the final preparation.

Powder. The term "powder" is applied to the names for botanical materials that have been mechanically ground, irrespective of particle size.

Oil. The term may be used to name nontriglycerides when it applies to ingredients that are commonly recognized (eg, Panax ginseng root oil). Essential oils are prepared by a steam distillation process that yields 2 distinct fractions, a water-insoluble fraction and a water-soluble fraction. The water-insoluble fraction contains the term oil in the name, for example, Panax ginseng root oil.

Water. The term refers to the water-soluble fraction from the steam distilled plant material and is identified by the term "water" in the INCI name. The term water that refers to the instance wherein the water has come in contact with the named material does not apply here, as it is different from an ingredient that is prepared by adding water to a material prepared by solvent extraction, and the ingredient would then be called a mixture, for example, water (and) juniperus communis fruit extract.

Method of Manufacture

In general, ginseng or ginseng root refers to the dried root of the *P ginseng*, *P quinquefolius*, *P japonicus*, and *P pseudoginseng* plants. The plants may be from wild or cultivated sources.[6] If the root is raw or dried, then it is referred to as "white" ginseng. If it has been steamed and dried before extraction or pulverizing, it is referred to as "red" ginseng because of a change in coloring.[7] If it is steamed and dried 9 times, the coloring darkens more and the product is referred to as "black ginseng."[8,9]

Root extract. The extraction is performed by percolation with aqueous alcohol solution (60%) and then concentration under vacuum to dryness or percolation with propylene glycol followed by concentration under vacuum.[10]

The solvent for the root extract may be propylene glycol, propylene glycol + water, propylene glycol dicaprylate/dicaprate, butylene glycol, ethanol, ethanol + water, glycerin + water, caprylic/capric triglyceride, or helianthus annuus (sunflower) seed oil.[11] One supplier reports "aging" the *P ginseng* root in ethanol and butylene glycol (70% aqueous) for 6 weeks before filtering and evaporating the ethanol. This procedure results in a total of 4.61 ± 0.98 mg/g dry weight ginsenosides (2.75 ± 0.7 triol, 1.86 ± 0.3 diol, 0.73 ± 0.11 mg/g diol/triol).

One manufacturer reported that the extraction process consists of grinding the whole dried red ginseng and placing the ground ginseng root into an extraction solvent of ethanol (70%) for 12 hours at 20°C to 25°C.[12] The solvent is then filtered and evaporated to remove the ethanol to <1%. The product is then centrifuged, dried, and sterilized.

Saponins. Saponin glycosides are extractable from the ginseng roots with hot water or alcohols.[1] Saponins may be extracted from fresh raw *P quinquefolium* root using methanol (30%-100%) at room temperature, over heat, or under microwave conditions. Each of these processes gives a different ratio of saponins (ie, Re, Fb1, and mRb1) in the extract.[13] Variation in yield and type of yield also depends on sample size, extraction time, sample to solvent ratio, and solvent concentration.

One manufacturer reported the use of ultrahypothermia biotic extraction techniques to selectively yield ginsenosides.[14] However, there is no further explanation about this process. Temperature influences the extraction kinetics, solvent viscosities, extraction efficiencies, and overall recoveries in ultrahigh-pressure extraction.[15] Using 70% aqueous ethanol at 200 MPa, 60°C, was optimal for saponin yields. Other temperatures led to a decreased yield of saponin compounds.

Analytical Methods

Powdered ginseng may be verified by running it on thin-layer chromatography and comparing with a standard preparation under UV light.[8]

Impurities

Analysis of a Panax ginseng root extract concentrate showed lead, cadmium, and mercury were below the detection limits of 0.040, 0.051, and 0.010 mg/kg, respectively.[16] Aflatoxin B1 was measured at <0.3 μg/kg and B2, G1, and G2 at <0.3 μg/kg. Analysis of multiple pesticides showed that most of them were not detected except for Dichlorodiphenyldichloroethylene (DDE) (0.02 mg/kg), total dichlorodiphenyltrichloroethane (DDT) (0.03 mg/kg), total hexachlorocyclohexane (HCH) (0.030 mg/kg), Quintozen (0.020 mg/kg), and Pentachloranilin (0.020 mg/kg). Results of a microbiologic analysis, aerobic bacteria was found at 45 000 CFU/g, fungus at 20 CFU/g, and *Escherichia coli* at <10 CFU/g. A *P quinquefolium* root extract was reported to have 20 ppm of heavy metals and 2 pm of arsenic.[12]

Ginseng root extract product mixtures may contain low concentrations of preservatives such as 0.5% to 0.7% Bactiphen 2506 G (phenoxyethanol, methylparaben, ethylparaben, propylparaben, and butylparaben).[11] None of 35 fragrance allergens identified by the European Union were detected in Panax ginseng root extract.[14]

Physical and Chemical Properties

Physical and chemical properties of ginseng root-derived cosmetic ingredients are provided in Tables 2 and 3. Panax quinquefolium root extract is stable for 2 years in a sealed container.[12] This extract was stable at 1%, 2%, and 3% in ethanol at pH 2 to 10 (time not specified) and at 1%, 3%, and 5% at 40 to 80°C for up to 120 minutes. Saponins form colloidal solutions in water which foam upon shaking (frothing) and have a bitter taste.[1]

Constituents

According to the *Handbook of Phytochemical Constituents of GRAS Herbs and Other Economic Plants* and Dr Duke's Phytochemical and Ethnobotanical Databases, the constituents of ginseng roots include saponins and sapogenins, carbohydrates, organic acids (including amino acids), nonprotein nitrogenous substances, peptides, minerals, and enzymes.[2,17-20] Known constituents of *P ginseng, P quinquefolius*, *P japonicus*, and *P pseudoginseng* roots, and their concentration in the plant root are listed in Tables 4-7.

In Table 5, pulegone was reported as a constituent of *P quinquefolius*. Because of the toxicity of pulegone, in an earlier safety assessment of peppermint oil, the safety of the ingredient was assured only when the levels of pulegone were limited to ≤1% in the ingredient.[21]

Table 2. Physical and Chemical Properties of Ginseng Root Ingredients.

Property	Value	Reference
Panax ginseng root extract (red ginseng)		
Color	Pale yellow	12
Odor	Typical	12
pH (10% solution)	4.0-7.0	12
Specific gravity	0.980-1.100	12
Hydrolyzed ginseng root		
Odor	Characteristic	149
Hydrolyzed ginseng root extract		
None found		
Hydrolyzed ginseng saponins		
None found		
Panax ginseng root		
Physical form	Powder	149,150
Color	Yellowish white	149,150
Panax ginseng root powder		
Physical form	Powder	149
Color	Light yellowish white to light yellowish brown	149
Odor	Characteristic	149
Panax ginseng root water		
None found		
Panax ginseng root oil		
Physical form	Oil	44
Color	Pale white	44
Panax ginseng root protoplast		
None found		
Panax japonicus root extract		
None found		
Panax notoginseng root		
None found		
Panax notoginseng root powder		
None found		
Panax quinquefolium root extract		
	Liquid	12
Color	Pale yellow	12
Odor	Typical	12
Specific gravity	0.980-1.100	12
Solubility in water	Soluble	12
pH (10% aqueous)	4.0-7.0	12

Table 3. Physical and Chemical Properties of Saponins.

Property	Value	Reference
Ro		
Physical form	Needles	151
Color	Colorless	151
Melting point, °C	239-241	151
Rb1		
Physical form	Powder	151
Color	White	151
Melting point, °C	197-198	151
Rb2		
Physical form	Powder	151
Color	White	151
Melting point, °C	200-203	151
Rc		
Physical form	Powder	151
Color	White	151
Melting point, °C	199-201	151
Rd		
Physical form	Powder	151
Color	White	151
Melting point, °C	206-209	151
Re		
Physical form	Needles	152
Color	Colorless	152
Melting point, °C	201-203	152
Rf		
Physical form	Powder	152
Color	White	152
Melting point, °C	197-198	152
Rg1		
Physical form	Powder	152
Color	Colorless	152
Boiling point, °C	194-196	152
Rg2		
Physical form	Powder	152
Color	Colorless	152
Melting point, °C	187-189	152

Saponins (or ginsenosides), a sweet–bitter material, usually exist in plants in the form of glycosides known as "saponin glycosides."[1] Saponin glycosides are macromolecules and are composed of a "sugar" (glycone) and a "nonsugar" (aglycone). The aglycone is also called genin. The aglycones of ginseng are called sapogenins. The chemical structures of some of the prominent saponins in ginseng are shown in Figure 1.

More than 40 different saponins have been identified and isolated from the root of *P ginseng*.[22] Each saponin has at least 2 (carbon-3 and -20) or 3 (carbon-3, -6, and -20) hydroxyl groups, which are free or bound to monomeric, dimeric, or trimeric sugars. Saponins also exist as stereoisomers having either of 2 configurations for the position of hydroxyl group on carbon 20. Based on their chemical structures, saponins are generally divided into 2 groups: protopanaxadiols (PPD) and protopanaxatriols (PT). The sugar moieties in the PPD group attach to the 3-position of a dammarane-type triterpene as in Rb1, Rb2, Rc, Rd, Rg3, Rh2, and Rh3 (Figure 1A), whereas the sugar moieties in the PT group attach to 6-position of dammarane-type triterpene as in Re, Rf, Rg1, Rg2, and Rh1 (Figure 1B). The pseudoginsenoside F11 belongs to PT group, although the alkyl chain at the 20-position is replaced by a tetrahydrofuran ring (Figure 1D).

Analysis of commercially available *P ginseng* root preparations (both powder and liquid) show that these vary widely in the amount of saponins (Rb1, Rb2, Rc, Rd, Re, Rf, and Rg1).[23] Panax ginseng root extract is reported to have a ginsenoside content of 0.2% to 0.3%.[11] The saponins Rg1, Re, Rb1, Rc, Rb2, and Rd makeup >90% of the saponin content of *P ginseng* root.[24] Fresh roots have yielded higher amounts of panaxatriol (Re +Rf + Rg1 + Rg2 + Rh1; 2.8 mg/g DW) and panaxadiol (Rb1 + Rb2 + Rb3 +Rc +Rd + Rg3; 16 mg/g DW) saponins compared to dried roots and powdered roots.[25]

Table 4. Chemical Constituents of *Panax ginseng* Root.[17]

Constituent	Part	Lo, ppm	Hi, ppm
(−)-β-Panasinsene	Root essent oil		
1,8-Cineol	Root essent oil		
10-Acetyl-panaxytriol	Root		
1-o-α-Glucoside-propan-2-on-1-ol	Root		
20-(s)-Dihydroprotopanaxatrione	Root		
20(s)-Protopanaxadiol-3-o-β-d-glucopyranoside	Root		10
20-Glucosyl-ginsenoside	Root		50
20(r)-Ginsenoside-rh-1	Rhizome		
2-5-Dimethyl-tridecane	Root essent oil		
2-6-Diethyl-pyrazine	Root		
2-6-Ditert-butyl-4-methyl-phenol	Root essent oil		14 000
2-Ethyl-5-methyl-pyrazine	Root		
2-Ethyl-6-methyl-pyrazine	Root		
2-Glucoginsenoside-rf	Root		50
2-Iso-butyl-3-methoxy-pyrazine	Root		
2-Iso-propyl-3-methoxy-pyrazine	Root		
2-Iso-propyl-5-methyl-anisole	Root		
2-Methyl-hexanoic acid-ethyl-ester	Root		
2-Methyl-tetradecane	Root essent oil		29 000
2-Sec-butyl-3-methoxy-pyrazine	Root		
3-9-10-Triacetoxy-heptadeca-1-16-diene-4-6-diyne	Root		
3-Iso-propyl-2-methoxy-5-methyl-pyrazine	Root		
3-Sec-butyl-2-methoxy-5-methyl-pyrazine	Root		
4-Methyl-thiazole-5-ethanol	Root		
4-Oxy-oct-6-enoic acid-methyl-ester	Root		
5-Ethyl-2-3-dimethyl-pyrazine	Root		
9-10-Epoxy-heptadec-1-16-diene-4-6-diyn-3-one	Root		
9-10-Epoxy-heptadeca-1-16-diene-4-6-diyn	Root		
Acetyl-panaxydol	Root		2.1
Adenine	Root		
Adenosine	Root		90
Adenosine	Rhizome		
Adenyl-cyclase	Root		
Alanine	Root		
Allo-aromadendrene	Root essent oil		
α-Amylase	Root		
α-Fructose	Root		
α-γ-Dipalmitin	Root		
α-Glucose	Root		
α-Guaiene	Root		
α-Guaiene	Root essent oil		40 000
α-Humulene	Root essent oil		
α-Maltose	Root		
α-Maltosyl-β-d-fructofuranoside	Root		
α-Neoclovene	Root essent oil		
α-Panasinsene	Root		17.6
α-Panasinsene	Root essent oil		
α-Phellandrene	Root		
α-Phellandrene	Root essent oil		
α-Pinene	Root		
α-Pinene	Root essent oil		
α-Pyrrolidone	Root		
α-Santalene	Root essent oil		
α-Selinene	Root essent oil		
Aluminum	Root	5	22
Amino acids	Root		
Arachidic acid	Root		
Arginine	Root		

(continued)

Table 4. (continued)

Constituent	Part	Lo, ppm	Hi, ppm
Aromadendrene	Root essent oil		
Arsenic	Root		
Ascorbic acid	Root		0
Ash	Root	10 600	50 000
Aspartase	Root		
Aspartic acid	Root		
Behenic acid	Root		
Benzyl-β-primeveroside	Root		47
β-Amylase	Root		
β-Bisabolene	Root essent oil		
β-Carotene	Root		
β-Elemene	Root		
β-Elemene	Root essent oil		150 000
β-Eudesmol	Root essent oil		
β-Farnesene	Root		
β-Farnesene	Root essent oil		85 000
β-Fructose	Root		
β-Glucose	Root		
β-Guaiene	Root essent oil		
β-Gurjunene	Root essent oil	60 000	10 503
β-Humulene	Root essent oil		
β-Maaliene	Root		
β-Maltose	Root		
β-Neoclovene	Root essent oil		
β-Panasinsene	Root		10.2
β-Patchoulene	Root		
β-Patchoulene	Root essent oil		
β-Selinene	Root essent oil		80 000
β-Sitosterol	Root		
β-Sitosterol	Rhizome		
β-Sitosterol-3-o-β-d-glucoside	Root		
Bicyclogermacrene	Root		
Biotin	Root		0.9
Caffeic acid	Root		
Calcium	Root	611	4140
Campesterol	Root		
Campesterol-6′-linolenylglucoside	Root		
Campesterol-6′-linolylglucoside	Root		
Campesterol-6′-oleylglucoside	Root		
Campesterol-6′-palmitylglucoside	Root		
Campesterol-6′-stearylglucoside	Root		
Caproic acid-butyl-ester	Root		
Caproic acid-propyl-ester	Root		
Carbohydrates	Root	176 808	834 000
Carbon disulfide	Root		1500
Caryophyllene	Root essent oil		
Caryophyllene alcohol	Root essent oil		
Catalase	Root		
Cellulase	Root		
Cerebroside	Root		
Choline	Root	1000	2000
Chromium	Root	0.2	1.1
Chromium	Root		1.1
Cis-caryophyllene	Root essent oil		
Citral	Root		
Citral	Root essent oil		
Citric acid	Root		
Cobalt	Root	0.7	3.1

(continued)

Table 4. (continued)

Constituent	Part	Lo, ppm	Hi, ppm
Cobalt	Root		3.1
Copper	Root		17
Cysteine	Root		
Cystine	Root		
Daucosterine	Root		
Daucosterol	Root		
Daucosterol	Rhizome		
δ-Cadinene	Root		
Densichine	Root		
D-Fructose	Root		
D-Glucose	Root		
Diglycosyl diglyceride	Root		
Di-iso-propyl-sulfide	Root		
Disaccharides	Root		33 000
D-Sucrose	Root		
Elemene	Root		
Eo	Root	100	500
ε-Muurolene	Root essent oil		
Eremophilene	Root essent oil		23 000
Erucic acid	Root		
Estradiol	Root		
Estriol	Root		
Estrone	Root		
Eugenol	Root essent oil		
Falcarinol	Root	0.9	310
Falcarinol	Rhizome		
Fat	Root	3752	17 700
Ferulic acid	Root		
Fiber(crude)	Root		72 000
Fiber(dietary)	Root		301 000
Fluoride	Root		26.3
Folic acid	Root		
Fructose	Root	200	6000
Fumaric acid	Root		
Gadoleic acid	Root		
Galactose	Root		
Galanin	Root		
γ-Aminobutyric acid	Root		
γ-Elemene	Root essent oil	60 000	100 000
γ-Patchoulene	Root essent oil		
γ-Selinene	Root essent oil		
Ge	Root		
GENSENOSIDE RD [sic]	Root		
Gentisic acid	Root		
Germanium	Root	0.12	320
Ginsenan-pa	Root		235
Ginsenan-pb	Root		170
Ginsenan-s-i-a	Root		106.6
Ginsenan-s-ii-a	Root		90
Ginseng polypeptide	Root		
Ginseng polypeptide-gpp	Root		
Ginsenol	Root		9.6
Ginsenoside	Root		47 000
Ginsenoside-k	Root		
Ginsenoside-ng-r-2	Root		
Ginsenoside-ra	Root	100	300
Ginsenoside-ra-1	Root	100	300
Ginsenoside-ra-2	Root		300

(continued)

Table 4. (continued)

Constituent	Part	Lo, ppm	Hi, ppm
Ginsenoside-ra-3	Root		50
Ginsenoside-ra-o	Root		
Ginsenoside-rb	Root	11 300	40 000
Ginsenoside-rb	Rhizome		
Ginsenoside-rb-1	Root	1700	83 000
Ginsenoside-rb-1	Rhizome	8800	14 000
Ginsenoside-rb-1	Root bark		
Ginsenoside-rb-2	Root	100	23 000
Ginsenoside-rb-2	Root bark		
Ginsenoside-rb-2	Rhizome	4500	5700
Ginsenoside-rb-2-c	Root		
Ginsenoside-rb-3	Root		50
Ginsenoside-rb-c	Root		14 000
Ginsenoside-rb-c	Root bark		24 000
Ginsenoside-rb-group	Root		
Ginsenoside-rc	Root	500	25 000
Ginsenoside-rc	Root bark		
Ginsenoside-rc	Rhizome		4700
Ginsenoside-rc-2	Root		
Ginsenoside-rd	Root	380	21 200
Ginsenoside-rd	Root bark		
Ginsenoside-rd	Rhizome	700	1600
Ginsenoside-rd-2	Root		
Ginsenoside-re	Root	680	84 800
Ginsenoside-re	Rhizome	4700	5700
Ginsenoside-re-2	Root		
Ginsenoside-re-3	Root		
Ginsenoside-rf	Root	200	9200
Ginsenoside-rf	Rhizome		1500
Ginsenoside-rg	Root	4600	16 300
Ginsenoside-rg	Root bark		34 000
Ginsenoside-rg-1	Root	320	58 400
Ginsenoside-rg-1	Root bark		
Ginsenoside-rg-1	Rhizome	3800	4500
Ginsenoside-rg-2	Root	100	26 700
Ginsenoside-rg-2	Rhizome		
Ginsenoside-rg-3	Root	3	30
Ginsenoside-rh	Root		
Ginsenoside-rh1	Root		15
Ginsenoside-rh-2	Root		
Ginsenoside-r-o	Root	100	11 000
Ginsenoside-r-o	Rhizome	18 000	34 000
Ginsenosides	Root	10 720	30 000
Ginsenoside-z-r-1	Root		
Ginsenoyne-a	Root		12.8
Ginsenoyne-a-linoleate	Root		2.8
Ginsenoyne-b	Root		1.5
Ginsenoyne-c	Root		1.1
Ginsenoyne-d	Root		7.1
Ginsenoyne-e	Root		7.1
Ginsenoyne-f	Root		2.6
Ginsenoyne-g	Root		0.176
Ginsenoyne-h	Root		1.47
Ginsenoyne-i	Root		2.6
Ginsenoyne-j	Root		3.5
Ginsenoyne-k	Root		14.1
Ginsenoynes	Root		
Glucose	Root	100	9000

(continued)

Table 4. (continued)

Constituent	Part	Lo, ppm	Hi, ppm
Glutamic acid	Root		
Gly-arg-γ-glu-val-nh2	Root		
Glycine	Root		
Glycochenodeoxycholic acid	Root		
Glycocholic acid	Root		
Glycodeoxycholic acid	Root		
Gomsempsode-rb-2	Root		
Guanine	Root		
Gum	Root	27 560	130 000
Harman	Root		
Heneicosanoic acid	Root		
Heptadec-1-en-4,6-diyn-3,9,10-triol	Root		
Heptadec-1-en-4,6-diyne-3,9,10-triol	Root		
Heptadec-1-en-4,6-diyne-3,9-diol	Root		150
Heptadeca-1-4-diene-6-8-diyne-3-10-diol	Root		
Heptadeca-1-8-diene-4-6-diyn-3-10-diol	Root		
Heptadeca-1-8-diene-4-6-diyn-10-ol-3-one	Root		
Heptadeca-1-8-diene-4-6-diyn-3-10-dione	Root		
Heptadeca-1-8-diene-4-6-diyne-3-10-diol	Root		14.6
Heptadeca-1-9-diene-4-6-diyn-3-ol	Root		
Heptadeca-1-en-4,6-diyn-3,9-diol	Root		150
Heptadeca-1-ene-4-6-diyne-3-9-10-triol	Root		1.5
Heptadeca-1-trans-8-diene-4-6-diyne-3-10-diol	Root		5.2
Heptadecan-1-ol	Root essent oil		19 000
Heptadecan-2-one	Root essent oil		43 000
Heptadecanoic acid	Root		
Histidine	Root		20
Humulene	Root essent oil		24 000
Invertase	Root		
Iron	Root		180
Iso-butyl-propionate	Root		
Isoleucine	Root		
Iso-propyl-propionate	Root		
Karusan-a	Root		
Karusan-b	Root		
Karusan-c	Root		
Karusan-d	Root		
Karusan-e	Root		
Ketoglutaric acid	Root		
Kilocalories	Root		2740
Leucine	Root		
Lignoceric acid	Root		
Ligustrazine	Root		
Limonene	Root		
Limonene	Root essent oil		
Linalool	Root essent oil		
Linoleic acid	Root		140
Linolein	Root		
Linolenic acid	Root		
Lysine	Root		
Lysophosphatidylcholine	Root		
Lysophosphatidyl-inositol	Root		
Magnesium	Root	102	1950
Maleic acid	Root		
Malic acid	Root		
Malonyl-ginsenoside-rb-1	Root	2730	13 000
Malonyl-ginsenoside-rb-1	Rhizome	6900	13 000
Malonyl-ginsenoside-rb-2	Root	1370	11 000

(continued)

Table 4. (continued)

Constituent	Part	Lo, ppm	Hi, ppm
Malonyl-ginsenoside-rb-2	Rhizome	4000	4200
Malonyl-ginsenoside-rc	Root	1000	8400
Malonyl-ginsenoside-rc	Rhizome	3400	3500
Malonyl-ginsenoside-rd	Root	400	1200
Malonyl-ginsenoside-rd	Rhizome		
Maltol	Root		
Maltose	Root	5100	199 600
Manganese	Root	0.4	180
Mannitol	Root		
Mayurone	Root essent oil		
Methionine	Root		
Molybdenum	Root		
Monosaccharides	Root		15 000
Myristic acid	Root		
N-9-Formyl-harman	Root		0.1
Nervonic acid	Root		
N-Formyl-harman	Root		
Niacin	Root	17	80
Nicotinamide	Root		
Nicotinic acid	Root		
N-Nonacosane	Root		
N-Nonacosane	Rhizome		
Norharman	Root		
Notoginsenoside-r-1	Root		20
N-pentadecane	Root essent oil		18 000
O-α-d-glucopyranosyl . . . fructofuranoside	Root		
O-α-d-glucopyranosyl . . . glucopyranose	Root		
Oleanolic acid	Root	150	700
Oleic acid	Root		
Oxalic acid ethyl ester	Root		
Palmitic acid	Root essent oil		86 000
Palmitoleic acid	Root		
Panacene	Root		
Panasinsanol-a	Root		2.3
Panasinsanol-b	Root		12.5
Panaxacol	Root		
Panaxadiol	Root	700	6500
Panaxan-a	Root		
Panaxan-b	Root		
Panaxan-c	Root		
Panaxan-d	Root		
Panaxan-e	Root		
Panaxan-f	Root		
Panaxan-g	Root		
Panaxan-h	Root		
Panaxan-i	Root		
Panaxan-j	Root		
Panaxan-k	Root		
Panaxan-l	Root		
Panaxan-m	Root		
Panaxan-n	Root		
Panaxan-o	Root		
Panaxan-p	Root		
Panaxan-q	Root		
Panaxan-r	Root		
Panaxan-s	Root		
Panaxan-t	Root		
Panaxan-u	Root		

(continued)

Table 4. (continued)

Constituent	Part	Lo, ppm	Hi, ppm
Panaxatriol	Root	700	7700
Panaxatriol-glycoside	Root		
Panax-ginseng-20(s)-prosapogenin	Root		
Panax-ginseng-genin-f-1	Root		
Panax-ginseng-genin-f-2	Root		
Panax-ginseng-genin-f-4	Root		
Panax-ginseng-glycoprotein	Root		
Panax-ginseng-glycoside-p-1	Root		
Panax-ginseng-lipolytic-peptide	Root		
Panax-ginseng-polyacetylene-c	Root		
Panax-ginseng-polyacetylene-d	Root		
Panax-ginseng-polyacetylene-e	Root		
Panax-ginseng-polyacetylene-f	Root		
Panax-ginseng-polyacetylene-g	Root		
Panax-ginseng-protein	Root		
Panax glycoprotein	Root		
Panaxic acid	Root		
Panaxin	Root		
Panaxoside-a	Root		
Panaxoside-a-progenin-i	Root		
Panaxoside-b	Root		
Panaxoside-c	Root		
Panaxoside-d	Root		
Panaxoside-e	Root		
Panaxoside-f	Root		
Panax-polypeptide	Root		
Panax-polyphenolic-permethyl-ether	Root		
Panax-polysaccharide	Root	30 000	40 000
Panax-polysaccharide-gh-1	Root		
Panax-polysaccharide-gl-4	Root		
Panax-polysaccharide-gl-4-ii-b-1-ii	Root		
Panax-protein	Root		
Panax-saponin-a	Root		
Panax-saponin-c	Root		
Panaxydol	Root	357.1	440
Panaxydol-chlorohydrin	Root		13.5
Panaxydol-linoleate	Root		8.1
Panaxyne	Root		
Panaxyne-epoxide	Root	1.8	9
Panaxynol	Root		
Panaxynol-linoleate	Root		1.3
Panaxytriol	Root	14.2	250
Pantothenic acid	Root		6.6
Patchoulene	Root essent oil		20 000
P-Coumaric acid	Root		
Pectin	Root		
Pentadecanoic acid	Root		
Perlargonidin-3-o-β-d-glucoside	Root		
Perlolyrine	Root		1.6
Phenolase	Root		
Phenylalanine	Root		
Phosphatidic acid	Root		
Phosphatidyl choline	Root		
Phosphatidyl ethanolamine	Root		
Phosphatidyl glycerol	Root		
Phosphatidyl inositol	Root		
Phosphorus	Root	112	528
P-Hydroxycinnamic acid	Root		26

(continued)

Table 4. (continued)

Constituent	Part	Lo, ppm	Hi, ppm
Polyacetylenes	Root		
Polysaccharide	Root		
Polysaccharide	Rhizome		
Polysaccharide-sa	Root		
Polysaccharide-sb	Root		
Potassium	Root	515	10 700
Proline	Root		
Prorenin	Root		
Protein	Root	23 108	109 000
Protopanaxadiol	Root		
Protopanaxadiol-glycosides	Root		
Putrescine	Root		
Pyroglutamic acid	Root		
Pyruvic acid	Root		
Quinquenoside-r-1	Root		20
Rhamnose	Root		
Riboflavin	Root	0.4	1.8
Salicylic acid	Root		3.4
Saponin-ii	Root		
Saponin-iii	Root		
Saponin-iv	Root		
Saponins	Root		20 000
Saponin-v	Root		
Selenium	Root	0.5	2.5
Selina-4(14),7(11)-diene	Root essent oil		
Senecrassidiol	Root		
Serine	Root		
Sesquiterpenediol	Root		
Silicon	Root		
Sitosterol-6′-linolenylglucoside	Root		
Sitosterol-6′-linolylglucoside	Root		
Sitosterol-6′-oleylglucoside	Root		
Sitosterol-6′-palmitylglucoside	Root		
Sitosterol-6′-stearylglucoside	Root		
Sodium	Root	5	209
Spermidine	Root		
Spinacine	Root		33.3
Starch	Root	25 440	320 000
Starch	Rhizome		
Stearic acid	Root		
Stigmasterol	Root		
Stigmasterol-6′-linolenylglucoside	Root		
Stigmasterol-6′-linolylglucoside	Root		
Stigmasterol-6′-oleylglucoside	Root		
Stigmasterol-6′-palmitylglucoside	Root		
Stigmasterol-6′-stearylglucoside	Root		
Succinic acid	Root		
Sucrose	Root	1300	226 000
Sucrose	Rhizome		
Sugars	Root	19 080	90 000
Superoxide dismutase	Root		
Tartaric acid	Root		
Terpineol	Root		
Terpineol	Root essent oil		
Thiamine	Root	0.4	1.7
Threonine	Root		
Thuj-4(10)-ene	Root		
Tin	Root	3.4	16

(continued)

Table 4. (continued)

Constituent	Part	Lo, ppm	Hi, ppm
Trace elements	Root		
Trans-β-farnesene	Root essent oil		80 000
Trans-caryophyllene	Root essent oil		
Tricosanoic acid	Root		
Trimethyl pyrazine	Root		
Tripalmitin	Root		
Tyrosine	Root		
Uracil	Root		
Uridine	Root		
Valine	Root		
Vanillic acid	Root		55
Vitamin B_{12}	Root		
Water	Root		788 000
Xylose	Root		
Zinc	Root		27

Abbreviation: essent, essential.

Table 5. Chemical Constituents of *Panax quinquefolius* Root.[18]

Constituent	Plant part	Lo, ppm	Hi, ppm
1-2-9-10-Diepoxy-3-oxo-heptadeca-4-6-diyne	Root		1.7
1-Hydroxy-9-10-epoxy-c-oxo-heptadeca-4-6-diyne	Root		7.1
2-Phenyl-dodecane	Root essent oil		41 500
3-Phenyl-dodecane	Root essent oil		16 700
3-Phenyl-undecane	Root essent oil		16 700
4-Phenyl-dodecane	Root essent oil		15 600
6(r),7(s)-Epoxy-tetradeca-1,3-diyne	Root		
6-7-Epoxy-tetradeca-1-3-dien	Root		2.8
8-Acetoxy-9,10-epoxyheptadeca-4,6-diyn-1-en-3-ol	Root		2.2
Acetyl-panaxydol	Root		2.8
α-Caryophyllene-alcohol	Root essent oil	1457	23 135
α-Curcumene	Root essent oil	1626	8677
α-Elemene	Root essent oil	3352	19 550
α-Fructose	Root		
α-Glucose	Root		
α-Maltose	Root		
α-Muurolene	Root essent oil	2007	9855
Amino acids	Root		
β-Bisabolene	Root essent oil	6251	58 670
β-Cubebene	Root essent oil	997	13 216
β-Farnesene	Root essent oil		260 500
β-Fructose	Root		
β-Glucose	Root		
β-Gurjunene	Root essent oil	4908	78 900
β-Maaliene	Root essent oil	4938	6134
β-Maltose	Root		
β-n-Oxalo-l-α-β-diaminopropionic acid	Root		200
β-Sitosterol	Root		
Caproic acid	Root essent oil		28 600
Caryophyllene	Root essent oil		8670
Cis-β-farnesene	Root essent oil	4961	5279
Dibutyl-phthalate	Root essent oil	9860	29 274
D-Sucrose	Root		
Elemol	Root essent oil	2959	14 637
Eo	Root		

(continued)

Table 5. (continued)

Constituent	Plant part	Lo, ppm	Hi, ppm
Falcalinol	Root		558.3
Fructose	Root		3400
Galactose	Root		
Ginsenoside-a-1	Root		
Ginsenoside-f2	Root		180
Ginsenoside-frc	Root		
Ginsenoside-rb-1	Rhizome		
Ginsenoside-rb-1	Root	270	20 900
Ginsenoside-rb-2	Rhizome		
Ginsenoside-rb-2	Root	200	1000
Ginsenoside-rb-3	Root		300
Ginsenoside-rc	Rhizome		
Ginsenoside-rc	Root	630	3100
Ginsenoside-rd	Rhizome		
Ginsenoside-rd	Root	950	7700
Ginsenoside-rd-1	Root	3400	3700
Ginsenoside-re	Root	200	13 800
Ginsenoside-re-2	Root		
Ginsenoside-re-3	Root		
Ginsenoside-rf	Root		
Ginsenoside-rg	Root		
Ginsenoside-rg-1	Rhizome		
Ginsenoside-rg-1	Root	300	8600
Ginsenoside-rg-2	Root		80
Ginsenoside-rg-3	Root		
Ginsenoside-rh1	Rhizome		9800
Ginsenoside-rh1	Root		
Ginsenoside-rh-2	Rhizome		18 600
Ginsenoside-rh-2	Root		
Ginsenoside-r-o	Rhizome		
Ginsenoside-r-o	Root	700	1000
Ginsenosides	Root	24 400	38 800
Ginsenoyne-g	Root		5.7
Glucose	Root		3200
Guaiol	Root essent oil	4649	11 276
Gypenoside-f-11	Root		
Gypenoside-xvii	Root		300
Heptadeca-1-8-diene-4-6-diyne-3-10-diol	Root		15
Ledol	Root essent oil	6831	7680
Malonyl-ginsenoside-rb-1	Rhizome		
Malonyl-ginsenoside-rb-1	Root		
Malonyl-ginsenoside-rb-2	Rhizome		
Malonyl-ginsenoside-rb-2	Root		
Malonyl-ginsenoside-rc	Rhizome		
Malonyl-ginsenoside-rc	Root		
Malonyl-ginsenoside-rd	Rhizome		
Malonyl-ginsenoside-rd	Root		
Maltose	Root		3800
Myristic acid	Root		
N-hexadecane	Root essent oil		88 900
Nonadecadienoic acid-methyl-ester	Root essent oil	27 682	37 935
Octadecadienoic acid-methyl-ester	Root essent oil	13 701	56 439
Oleanolic acid	Root	600	980
Oleic acid	Root		
Palmitic acid	Root		
Palmitic acid	Root essent oil	6543	41 917
Palmitic acid-ethyl-ester	Root essent oil	35 913	73 504
Palmitic acid-methyl-ester	Root essent oil	16 744	63 486

(continued)

Table 5. (continued)

Constituent	Plant part	Lo, ppm	Hi, ppm
Panaquilin-e-1	Root		
Panaquilin-g-2	Root		
Panaxadiol	Root	3100	9600
Panaxan-a	Root		
Panaxan-b	Root		
Panaxan-c	Root		
Panaxan-d	Root		
Panaxan-e	Root		
Panaxatriol	Root	1500	12 540
Panax-polyacetylene-pq-1	Root		75.8
Panax-polyacetylene-pq-2	Root		6.6
Panax-polyacetylene-pq-3	Root		29.1
Panax-protein	Root		
Panaxydol	Root		950
Panaxytriol	Root		59.1
Protein	Root	80 600	102 500
Pseudo-ginsenoside-f-11	Root	70	400
Pulegone	Root essent oil		260 500
Quinquefolan-a	Root		
Quinquefolan-b	Root		
Quinquefolan-c	Root		
Quinquenoside-r-1	Root		100
Saponins	Root		
Stigmasterol	Root		
Sucrose	Root	39 000	158 600
Superoxide-dismutase	Root		
Trans-β-farnesene	Root essent oil	9768	63 517
Xylose	Root		

Abbreviation: essent, essential.

There are several chemical composition differences between *P ginseng* and *P quinquefolium* roots. Rf is present in *P ginseng* but not in *P quinquefolium*. The opposite is true for pseudoginsenoside F11.[26] Steaming the roots causes chemical degradation and conversion of original saponins to new compounds. Steaming is also associated with a decrease in the polar saponins Rg1, Re, Rb1, Rc, Rb2, Rb3, and Rd and an increase in the less polar Rg2, Rg3, Rg5, Rh2, Rk1, and Rs4.[27-29]

Table 8 shows the content of some of the saponins in both white (dried, unsteamed) and black (the steaming and drying process repeated 9 times) *P ginseng*. The polyphenol content is greater in black ginseng (approximately 35 mg/g) than in white ginseng (approximately 20 mg/g).[9] Table 9 shows a comparison of saponin content by extraction technique.[11,14]

Other Ginseng constituents. Carbohydrates were reported to be obtained in the aqueous extract of ginseng root in small amounts and were present as many different types of sugars or polysaccharides.[30-33] The most common monosaccharides from ginseng sources were glucose and fructose. Maltose and sucrose were the most common disaccharides. Trisaccharides, tetrasaccharides, and oligosaccharides are also found in ginseng root as well as ginseng pectin, a crude polysaccharide.

Nonamino organic acids are present in alcohol extracts of ginseng roots. The most common organic acids are citric, fumaric, ketoglutaric, maleic, malic, pyruvic, succinic, and tartaric acids and the fatty acids oleic, linoleic, and linolenic acids.[34,35]

The free amino acids found in ginseng are arginine, histidine, lysine, leucine, threonine, valine, phenylalanine, alanine, aspartic acid, glutamic acid, glycine, proline, tyrosine, and serine.[36] The amount of free amino acids in raw *P ginseng* roots decreases when the roots are steamed, more so at 120°C than 100°C.[37] Another nitrogenous substance in ginseng root is choline.[38]

Constituents reported for specific ingredients are as follows.

Panax ginseng root. To comply with the Japanese Pharmacopoeia, the dried material of both raw and steamed roots, Panax ginseng root must contain >0.10% ginsenoside Rg1 and >0.20% ginsenoside Rb1.[8]

Panax ginseng root powder. To comply with the Japanese Pharmacopoeia, the dried material of Panax ginseng root powder must contain >0.10% ginsenoside Rg1 and >0.20% ginsenoside Rb1.[8] The percentage of ginseng saponins from one sample of freeze-dried red ginseng extract powder was approximately 3.3%.[39] Ginseng saponins present were Rb1 (15.8%), Rb2 (7.8%), Rc (8.1%), Rd (7.6%), Re (3.2%), Rf (4.7%), Rg1 (1.9%), Rg2 (22.2%), Rg3 (24.2%), and Rh1 (4.7%) along with other minor saponins.

Table 6. Chemical Constituents of *Panax japonicus* Root (Rhizome).[20]

Constituent	Amount, ppm
Arabinose	
β-Sitosterol	
Calcium	7000
Campesterol	
Campesterol-6′-linolenylglucoside	
Campesterol-6′-linoylglucoside	
Campesterol-6′-oleylglucoside	
Campesterol-6′-palmitylglucoside	
Campesterol-6′-stearylglucoside	
Chikusetsusaponin-I-A	
Chikusetsusaponin-I-B	
Chikusetsusaponin-III	
Chikusetsusaponin-IV	
Chikusetsusaponin-IV-A	1900
Copper	6
Ginsenoside-R-O	
Ginsenoside-RD	6700
Ginsenoside-RG-2	
Glucose	
Glucuronic acid	
Iron	360
Magnesium	2400
Majonoside-R1	700
Majonoside-R2	1100
Manganese	43
Notoginsenoside-R2	300
Oleanolic acid	
Panatoxin	
Potassium	11 000
Saponins	70 000
Sitosetrol-6′-stearylglucoside	
Sitosetrol-6′-linolenylglucoside	
Sitosetrol-6′-linolylglucoside	
Sitosetrol-6′-oleylglucoside	
Sodium	499
Stigmasterol-6′-linolenylglucoside	
Stigmasterol-6′-linolylglucoside	
Stigmasterol-6′-oleylglucoside	
Stigmasterol-6′-palmitylglucoside	
Stigmasterol-6′-stearylglucoside	
Zinc	20

The concentration of saponins in ginseng root ingredients varies with the form. Ranges for food additives were found to be 4% to 8% saponins (calculated as Rg1). Actual root samples vary in their total saponin content from 0.5% to 3% (dry weight).[40,41]

Panax ginseng root oil. Ginseng oil contains volatile and nonvolatile fractions. The low boiling fraction (boils from 71°C to 110°C) contains the sesquiterpenes panacene and β-elemene (Figure 2). Panacene gives the characteristic fragrance of ginseng. The high boiling fraction (boils from 120°C-150°C) contains panaxynol.[42,43] *Panax japonicus* root oil yields were reported to be 0.451%, suggesting that one would need 15 pounds of root to produce 1 ounce of oil.[44]

Table 7. Chemical Constituents of *Panax pseudoginseng* (*notoginseng*) Root.[19]

Constituent	Amount, ppm
(20)-Protopanoxadiol	
(20)-Protopanaxatriol	
β-Sitosterol	
Daucosterol	
Ginsenoside RA	
Ginsenoside RA	
Ginsenoside RB	
Ginsenoside RB-1	
Ginsenoside RB-2	
Ginsenoside RE	
Ginsenoside RG-1	
Ginsenoside RG-2	
Ginsenosides	87 000
Notogenisnosides	
Panaxynal	
Quercetin	

Use

Cosmetic

Data on the usage of ingredient are provided by the manufacturers to the Food and Drug Administration's (FDA) Voluntary Cosmetic Registration Program, and a survey conducted by the Personal Care Products Council (Council) collected use concentrations for ingredients in this group (Table 10).[45,46]

The total number of uses of Panax ginseng root extract was 277 (196 leave-on products, 77 rinse-off products, and 4 diluted products) at maximum concentrations of 0.000002% to 0.5% (maximum of 0.5% in leave-on products, 0.3% in rinse-off products, and 0.0004% in diluted products). This included a maximum of 0.1% in eye, nail, and shaving products and lipsticks; 0.01% in face powders; and 0.3% in hair products. The Council further reported that white Panax ginseng root extract is used up to 0.04% in leave-on, 0.0003% in rinse-off, and 0.00009% in diluted products. Red Panax ginseng root extract was reported to be used up to 0.003% in both leave-on and rinse-off products.

Panax quinquefolium root extract was reported to be used in 430 cosmetic products (286 leave-on, 140 rinse-off, and 4 diluted for bath products) at maximum concentrations of 0.002% in rinse-off products (no concentrations of use were reported for leave-on and diluted products) including 30 eye products, 114 hair products, and 5 lipsticks. Panax quinquefolium root extract is used in 4 fragrance preparations and 5 hair sprays.

Panax ginseng root was reported to be used in 22 cosmetic products (16 leave-on and 6 rinse-off products, 2 underarm deodorants, and 17 dermal contact products), and there were no use concentrations reported for this ingredient. Panax notoginseng root was reported to be used at 0.0004% in dentifrices, and there were no uses reported to the FDA for this ingredient.

Panax ginseng root powder was reported to be used in 1 mud pack, and no concentration of use was reported. There were no

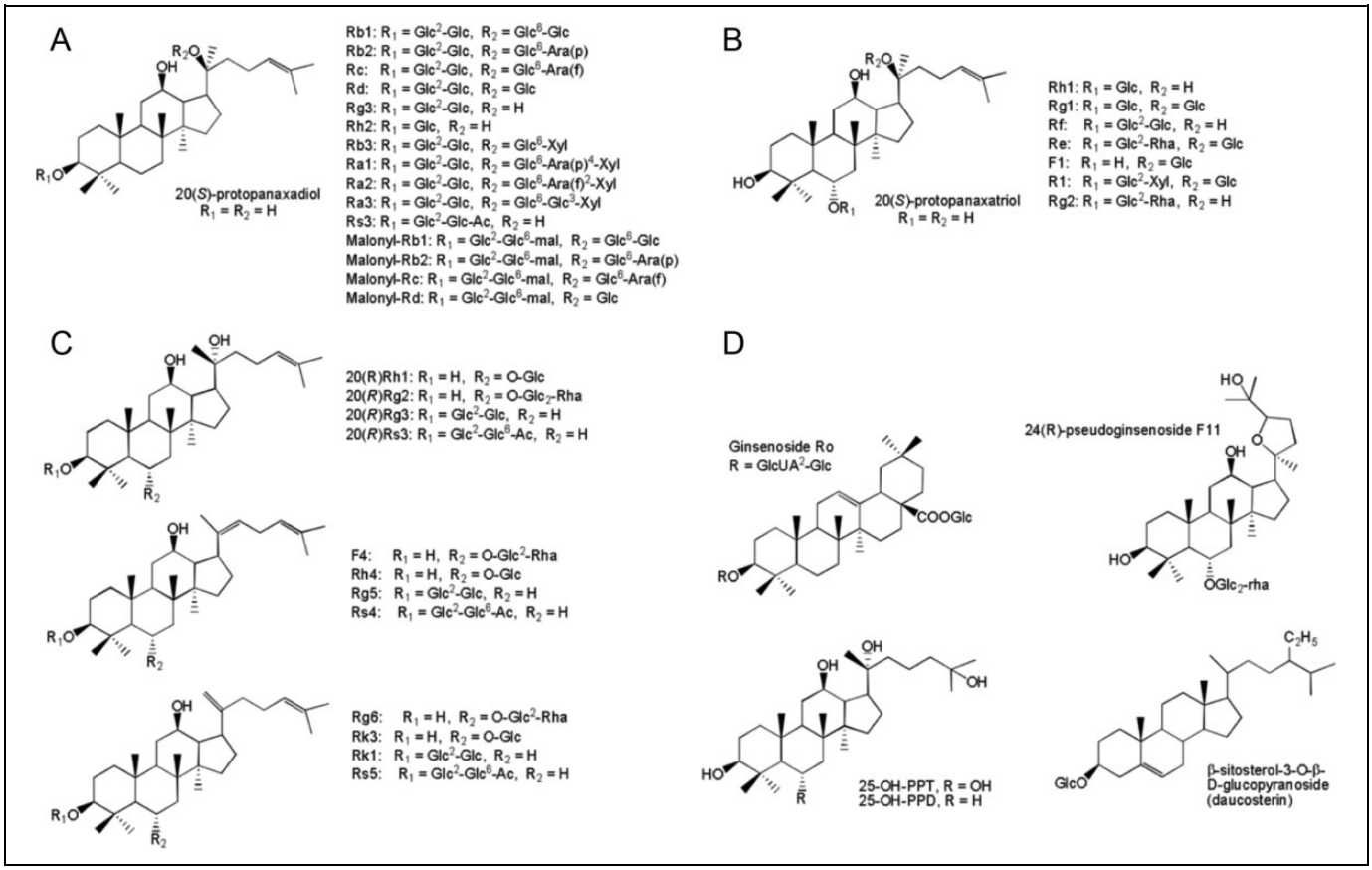

Figure. 1. Structure of selected saponins. A, protopanaxadiols (PPD), (B) protopanaxatriols (PT), (C) derivatives of PPD and PT, and (D) saponins. Glc, β-D-glucose; Rha, α-L-rhamnose; Ara(p), αL-arabinose(pyranose); Ara(f), α-L-arabinose(furanose); Xyl, β-D-xylose; GlcUA, β-D-glucuronic acid; mal, malonyl; Ac, acetyl.[22] Adapted from Lü JM, Yao Q, Chen C. Ginseng compounds: an update on their molecular mechanisms and medical applications. *CurrVasc Pharmacol*. 2009;7(3):293-302.

Table 8. Comparison of Saponin Content Between White (Dried, Unsteamed) and Black (Steamed and Dried 9 Times) Ginseng Extract (Extracted With 80% Ethanol).[9]

Saponin	White ginseng extract, mg/g	Black ginseng extract, mg/g
Rg1	7.81 ± 4.83	Not detected
Re	9.30 ± 0.88	Not detected
Rh1	0.74 ± 0.31	0.67 ± 0.15
Rb1	14.14 ± 1.35	2.96 ± 1.60
Rc	12.62 ± 3.02	1.61 ± 0.71
Rb2	6.97 ± 1.48	0.63 ± 0.21
Rd	2.88 ± 1.37	0.53 ± 0.44
Rg3(R)	Not detected	5.80 ± 1.42
Rg3(S)	Not detected	1.97 ± 0.53
Total	54.45 ± 5.08	14.17 ± 4.33

Table 9. Comparison of Saponin Content in Panax ginseng Root by Extraction Technique.[11,14]

	Content, %	
Saponin	3 batches of hydroglycolic extract	Ultrahypothermia biotic extract
Rg1	0.004-0.02	4.17
Re	Below 0.03[a]	18.99
Rf	NR	1.87
Rb1	0.05-0.06	34.49
Rg2	NR	2.30
Rh1	NR	13.31
Rc	Below 0.02[a]	-
Rb2	0.02-0.04	5.08
Rb3	NR	3.37
Rd	Below 0.02[a]	14.89
Rg3	NR	-
Rh2	NR	1.52

Abbreviation: NR, not reported.
[a]Detection limit.

uses reported for Panax ginseng root powder, hydrolyzed ginseng root, hydrolyzed ginseng root extract, hydrolyzed ginseng saponins, Panax ginseng water, Panax ginseng root oil, Panax ginseng root protoplasts, Panax japonicus root extract, or Panax notoginseng root powder.

Panax ginseng root extract, Panax ginseng root, and Panax quinquefolium root extract are used in fragrance preparation, hair sprays, and/or deodorants up to 0.1% and could possibly be inhaled. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm, with propellant sprays yielding a greater

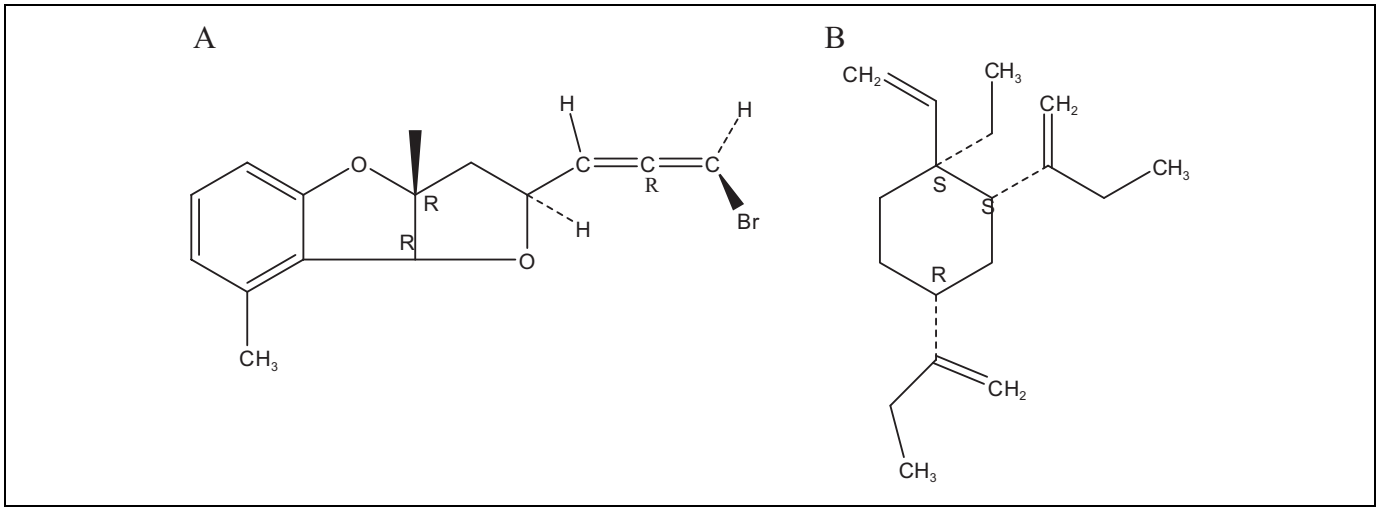

Figure 2. A, Panacene and (B) β-elemene.

fraction of droplets/particles below 10 μm compared with pump sprays.[47-50] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (ie, they would not enter the lungs) to any appreciable amount.[49,51] There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable.[52] However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays.

Noncosmetic

Ginseng root is widely used as an herbal medicine for its alleged tonic effect and possible curative and restorative effects.[53-65] Modern therapeutic claims suggest that ginseng has beneficial effects on cognitive function, physical and psychomotor performance, immune-modulation, diabetes mellitus, and herpes simplex type-II infections.[56,60,61,65-68] However, a systematic review of randomized controlled trials found that the efficacy of ginseng root extract could not be established for any of these effects.[69]

When used as a dietary supplement, unless otherwise prescribed, the recommended daily dose (taken in the morning) is dried root 0.5 to 2 g by decoction, and doses of other preparations would be calculated accordingly.[70] Ginseng is often an ingredient in energy drinks.

Toxicokinetics

Absorption, Distribution, Metabolism, and Excretion

In some studies of the effects of ginseng, the metabolite of the saponin Rb1, ''Compound K'' (20-*O*-B -D-glucopyranosyl-20(S)-protopanaxadiol), is used. Rb1 is poorly absorbed from the gut. Compound K is produced from Rb1 by a stepwise degradation of sugar moieties by intestinal microflora.[71-73]

Dermal/percutaneous/inhalation. No data on the dermal/percutaneous or inhalation absorption of ginseng root-derived ingredients were discovered, and no unpublished data were submitted.

Oral/intravenous/intraperitoneal

Panax ginseng root. Panax ginseng root (1 to 2 g in capsules; G115) was orally administered to subjects (n=2) on empty stomachs.[74] Blood and urine were sampled before and periodically for up to 24 hours after administration and were analyzed for saponins. In the plasma, at approximately 0.75 to 3.25 hours, Rh_1 was detected; approximately 3.75 to 5.25 hours, hydrated Rh_1; approximately 5.25 to 8.25 hours, Rb1; approximately 7.5 to 10.75 hours, compound K; approximately 8 to 11.75 hours, f_1/Rh_1 (not distinguished between the two); and approximately 8.75 to 10.25 hours, hydrated compound K. In the urine at 0 to 3 hours, Rg1, Rd, Re, Rb2, and Rc were detected. At 3 to 6 hours, Rh_1 was detected; 6 to 12 hours, Rb1 and compound k; and at 12 to 24 hours, f1/Rh1 and compound k were detected.

Ginseng saponins. The absolute bioavailability of Panax saponins were reported to range from 0.26% to 64.8% (Table 11). The low bioavailability of saponins may be attributable to their breakdown in the gastrointestinal tract, metabolism by intestinal microflora, and excretion in bile or urine.[75] It is also suggested that low membrane permeability may be an important factor in determining the extent of absorption.

The absolute bioavailability of the saponin 25-OH-PPD is 64.8% ± 14.3% (range 44.1%-75.9%) which is the highest among the reported ginseng compounds.[76] The author suggests that the higher absolute bioavailability found in the rats can be explained by the deglycosylated mother aglycone structure, lower molecular weight, and higher hydrophobility of 25-OH-PPD compared to saponin Rg3.

Table 10. Frequency and Concentration of Use of Panax spp Root-Derived Ingredients As Well As Use Concentration of White and Red *Panax ginseng* Root Extract According to Duration and Type of Exposure.[153,154,a]

Use type	Uses	Maximum concentration, %	Uses	Maximum concentration, %	Uses	Maximum concentration, %	Uses	Maximum concentration, %
	Panax ginseng root extract[b]		Panax ginseng root		Panax notoginseng root		Panax quinquefolium root extract	
Total/range	277	0.000002-0.5	22	NR	NR	0.0004	430	0.0005-0.002
Duration of use								
Leave-on	196	0.000002-0.5	16	NR	NR	NR	286	NR
Rinse-off	77	0.00000-0.3	6	NR	NR	0.0004	140	0.0005-0.002
Diluted for (bath) use	4	0.00004-0.0004	NR	NR	NR	NR	4	NR
Exposure type								
Eye area	30	0.00001-0.1	2	NR	NR	NR	30	NR
Incidental ingestion	4	0.0001-0.1	NR	NR	NR	0.0004	8	NR
Incidental Inhalation—sprays	10	0.00005-0.1[c]	2	NR	NR	NR	16	NR
Incidental inhalation—powders	6	0.0004-0.01	NR	NR	NR	NR	7	NR
Dermal contact	224	0.000003-0.5	17	NR	NR	NR	316	0.002
Deodorant (underarm)	NR	0.02	2	NR	NR	NR	2	NR
Hair—noncoloring	47	0.000002-0.3[d]	5	NR	NR	NR	97	0.0005
Hair—coloring	NR	0.0002-0.005	NR	NR	NR	NR	7	NR
Nail	NR	0.00001-0.1	NR	NR	NR	NR	1	NR
Mucous membrane	25	0.00004-0.1	1	NR	NR	0.0004	40	0.002
Baby	NR	NR	NR	NR	NR	NR	NR	NR
	Panax ginseng root powder		White Panax ginseng root extract		Red Panax ginseng root extract			
Total/range	1	NR	NS	0.00009-0.04	NS	0.00004-0.003		
Duration of use								
Leave-on	NR	NR	NS	0.0003-0.04	NS	0.00004-0.003		
Rinse-off	1	NR	NS	0.0003	NS	0.003		
Diluted for (bath) use	NR	NR	NS	0.00009	NS	NR		
Exposure type								
Eye area	NR	NR	NS	0.002	NS	NR		
Incidental ingestion	NR	NR	NS	NR	NS	NR		
Incidental Inhalation—sprays	NR	NR	NS	NR	NS	0.00004		
Incidental inhalation—powders	NR	NR	NS	0.0003	NS	NR		
Dermal contact	1	NR	NS	0.00009-0.04	NS	0.00004-0.003		
Deodorant (underarm)	NR	NR	NS	NR	NS	NR		
Hair—noncoloring	NR	NR	NS	0.0003	NS	0.003		
Hair—coloring	NR	NR	NS	NR	NS	NR		
Nail	NR	NR	NS	NR	NS	NR		
Mucous Membrane	NR	NR	NS	0.00009	NS	NR		
Baby	NR	NR	NS	NR	NS	NR		

Abbreviations: NR, none reported; NS, not surveyed.

[a]There were no reported uses for hydrolyzed ginseng root, hydrolyzed ginseng root extract, hydrolyzed ginseng saponins, Panax ginseng root, Panax ginseng root water, Panax ginseng root oil, Panax ginseng root protoplast, Panax japonicus root extract, and Panax notoginseng root powder.

[b]The VCRP listed Panax ginseng root extract and ginseng extract as separate ingredients. These were combined under Panax ginseng root extract.

[c]It is not known if this product is a spray.

[d]0.3% in a rinse-off noncoloring other hair preparation.

The National Toxicology Program (NTP) reported that the degradation and metabolism of saponins has been studied in animals and in vitro using acids, enzymes, and intestinal bacteria.[72,77-80] After oral administration, the protopanaxatriol saponins are hydrolyzed to saponin Rh1 and are hydrated under acidic conditions of gastric fluids. Protopanaxadiol saponins (Rb1) are metabolized to M1 [20-*O*-B-D-glucopyranosyl-20(S)-PPD] or compound-K in rats and humans by intestinal

Table 11. Pharmacokinetic Studies of Selected Saponins in Rats, Dogs, or Human Plasma (after Lu et al).[22]

Saponin	Species model, route	Dosage	Absolute bioavailability	Reference
25-OH-PPD	Rat, oral	10 mg/kg	64.8%	76
Rh2	Rat, oral	100 mg/kg	0.25%	155
Rh1, Rg1	Rat, iv, or ig	100 mg/kg	1.33%	156
R1, Rg1, Rd, Re, Rb1	Rat, oral	10 mg/kg	9.29%, 6.06%, 2.36%, 7.06%, and 1.18%	157,158
Rd	Dog, iv, oral	2 mg/kg (oral) 0.2 mg/kg (iv)	0.26%	159
Rg	Rat, oral	50 mg/kg	1.52%-6.60%	75
Rg3	Rat, oral	50 mg/kg	2.63	160,161
Multiple	Rat, oral	300 mg/kg	-	158
Rg1, Rb1	Rat, oral	50 mg/kg	18.4% (Rg1) 4.35% (Rb1)	162
Compound K	Rat, oral	20 mg/kg	35.0%	163

Abbreviations: iv, intravenous administration; ig, intragastric gavage; -, no data/not tested; PPD, protopanaxadiol.

Table 12. Pharmacokinetic Parameters of Saponins Administered to Rabbits.[85]

Saponin	Dose (exposure route)	$t_{1/2}$ (min)	$t_{1/2}$ abs (min)	f (%)
Semipurified A1	500 mg in 10% ethanol (iv)	68.8	-	39
Semipurified A1	500 mg in 10% ethanol (iv)	79.9	-	68
Semipurified A1	500 mg in 10% ethanol (iv)	136	-	79
A1	500 mg in propylene glycol/ethanol/NaCl (ip)	25.3	9.90	39
A1	500 mg in propylene glycol/ethanol/NaCl (iv)	59.9	-	-
A1	250 mg in 10% ethanol (iv)	20.2	-	44
A1	500 mg in 10% ethanol (ip)	104	11.3	68
Semipurified A2	500 mg in 10% ethanol (ip)	24.7	363	61
Semipurified A2	500 mg in 10% ethanol (iv)	69.5	-	61
B2	500 mg in 10% ethanol (iv)	49.8	-	17
B2	500 mg in 10% ethanol (ip)	69.9	324	18
C	250 mg in 10% ethanol (iv)	478	-	41
C	500 mg in 10% ethanol (ip)	412	318	41

Abbreviations: iv, intravenous administration; $t_{1/2}$, elimination half-life; $t_{1/2}$abs, absorption half-life; f, fraction excreted unchanged in the urine; ip, intraperitoneal administration.

anaerobes via stepwise cleavage of the sugar moieties.[78] Strains of the intestinal bacteria *Prevotella oris* hydrolyze Rb1.[81] Protopanaxadiol is formed from Rh2 as a result of deglycosylation by B16 melanoma cells in vitro.[82]

The absorption of Rb1 from the intestine of rats was low.[72] In mice, after an oral dose of Rb1 or M1 (2 mg/mouse), the M1 level in the serum gradually increased, peaked at 8 hours after oral administration of Rb1, and decreased with time, and intact Rb1 was not detected in the serum.[83] The level of M1 in the serum reached maximum at 8 hours (8.5 ± 0.4 μg/mL) after Rb1 administration and at 2 hours (10.3 ± 1.0 μg/mL) after M1 administration.

Rg1 was rapidly absorbed (30% after 1 hour) and metabolized by mice after oral administration. Mouse urine and feces contained little unchanged Rg1 but did contain high levels of metabolites including Rh1 and saponin Rg1 (protopanaxatriol). Rg1 showed an extremely short half-life of 27 minutes after intravenous administration to mini-pigs. In contrast, the PPD saponin Rb1 showed a half-life in the β-phase of 16 hours.[84]

In several studies using male New Zealand White rabbits, saponins (A1, Rg1, Rd, Re, and Rb2) were administered by oral, intraperitoneal (ip), and intravenous (iv) routes (Table 12).[85] In the oral study, no saponins were observed in the plasma, urine, or feces. The authors suggested that this is due to poor absorption in the gastrointestinal tract, binding within the gastrointestinal tract, microorganism metabolism, or an unreliable animal model. In humans, saponins are present in urine after oral ingestion.[86,87] about 1.2% of the dose (not provided) was recovered in 5 days. Generally, saponins are very poorly absorbed following oral administration in vivo.

Cytotoxicity

Panax ginseng root extract. In an in vitro assay, Panax ginseng root extract (0, 100, 250, 500, and 1000 μg/mL in ethanol) was not cytotoxic to human dermal fibroblast cells.[88]

Table 13. Acute Toxicity of Various Forms of Ginseng.[164]

Compound	Species	Exposure route	LD_{50}, mg/kg
Panax ginseng root	Rat	Oral	750
Panax ginseng root	Mouse	Oral	200
Panax ginseng root	Mouse	Ip	54
Ginseng root extract	Mouse	Ip	545
Saponin No. 3	Mouse	Ip	910
Ginseng, saponin extract	Mouse	Ip	637
Panabolide (TRIS-buffer extract of *P ginseng*)	Rat	Oral	> 12,000
Panabolide (TRIS-buffer extract of *P ginseng*)	Rat	Ip	550
Panabolide (TRIS-buffer extract of *P ginseng*)	Mouse	Oral	>2500
Panabolide (TRIS-buffer extract of *P ginseng*)	Mouse	Ip	>1050

Abbreviation: LD50, median lethal dose.

Toxicological Studies

Acute Toxicity

Nonhuman

Panax ginseng root extract. The Lethal Dose, 50% (LD_{50}) values using rodents for the root itself and for various forms and fractions of Panax ginseng root extract administered orally and ip are listed in Table 13.

Repeated Dose Toxicity

Dermal

Panax ginseng root extract. In a therapeutic efficacy test of red *P ginseng* root extract concentrate (0.2 mL) and Rg2 (1%; 0.2 mL), the test material was applied to the backs of 5-week-old female C57BL/6 mice after "shav[ing] with hair removal tape" for 14 days. No adverse effects were observed during treatment.[12]

Oral: Nonhuman

Panax ginseng root extract and Panax quinquefolius root extract. Male Wistar rats (n = 5) were orally administered *P ginseng* root water extract, heat-treated *P ginseng* root water extract, *P quinquefolius* root water extract, or heat-treated *P quinquefolius* root water extract (0, 100 mg/kg/d) by gavage for 15 days.[89] The extracts were heat treated by autoclave at 120°C for 3 hours then placed in an oven at 50°C for 3 days. Blood and urine were collected. No clinical signs or decreases in renal or hepatic function parameters of the treated rats were observed.

Panax ginseng root extract in the form of G115 (0, 1.5, 5, or 15 mg/kg/d) was administered in the feed of Beagle dogs (n=4/sex) for 90 days.[90] No consistent, dose–response relationship occurred, and all values (weight gain, hematology, urine chemistry) were within normal physiological ranges for Beagle dogs. Gross and microscopic examinations of major organs revealed no morphological or pathological effects. No evidence of toxicity was observed. The highest dose, 15 mg/kg, is approximately twice the recommended dose for humans.

LACA mice (n=90) were administered Panax ginseng root extract (aqueous extract; 8 mg/kg/d; 40 mg of whole root) in drinking water (1) from 8 weeks of age throughout life, (2) from 52 weeks throughout life, and (3) none.[91] There were no differences in mean weights or survival observed in the mice. Increased behavioral responses to mild stress were observed in the treatment groups.

It was reported in a review that rats (n and strain not provided) were orally administered Panax ginseng root extract (105-210 mg/kg/d) for 25 weeks.[92] No toxic effects were observed. No further details on this study were provided.

Panax ginseng root extract extracted with 80% aqueous ethanol was used in the next 4 studies.

F344/N rats (n=5/sex) were administered 0, 125, 250, 500, 1000, or 2000 mg/kg in 0.5% aqueous methylcellulose) by gavage 5 days/week for 16 days.[93] All rats survived to the end of the study. Mean body weight gain of 2000 mg/kg males was greater than that of the vehicle controls. There were no chemical-related gross or microscopic findings attributed to the administration of ginseng.

B6C3F1 mice (n=5/sex) were administered *P ginseng* root extract (0, 125, 250, 500, 1000, or 2000 mg/kg in 0.5% aqueous methylcellulose) by gavage 5 days/week for 17 days.[93] All mice survived to the end of the study. The final mean body weight of 1000 mg/kg males was significantly less than that of the vehicle controls, and all other groups were similar to controls. There were no statistically significant chemical-related gross or histopathologic changes in dosed mice.

F344/N rats (n=10/sex) were administered *P ginseng* root extract (0, 1000, 2000, 3000, 4000, or 5000 mg/kg) in sterile water by gavage 5 days/week for 14 weeks.[93] All rats survived to the end of the study. Mean body weights of all dosed groups were similar to those of the vehicle control groups. No lesions that were observed by gross or histopathologic examination were attributed to the administration of *P ginseng* root extract.

B6C3F1 mice (n=10/sex) mice were orally administered *P ginseng* root extract (0, 1000, 2000, 3000, 4000, or 5000 mg/kg) 5 days/week for 14 weeks.[93] All mice survived to the end of the study. Mean body weights of all dosed groups were similar to those of the vehicle control groups. Although sporadic incidences of lesions were observed in the vehicle control and 5000 mg/kg groups, there were no chemical-related gross or microscopic findings in dosed mice.

Inhalation: Nonhuman. No data were discovered on the repeated dose inhalation toxicity of ginseng root-derived ingredients. However, a material safety data sheet stated that Panax quinquefolium root extract may be irritating or toxic if inhaled.[12]

Table 14. Reproductive and Developmental Studies of *Panax ginseng* Root Extract (Extracted With Ethanol).

Species (n)	Dose	Details	Results	Reference
White Wistar rats (10)	20 mg/kg	Days 6-15 of gestation by gavage	No signs of toxicity or behavior changes. No differences between controls and treatment group for embryo and fetal abnormalities.	[165]
Sprague-Dawley Rats (15)	0, 1.5, 5, 15 mg/kg/d in corn oil mixed in feed	Mated after 3 weeks treatment; females continued treatment through gestation; at weaning, F1 started on treatment feed and mated at 13 weeks; F2 raised to 21 days. All rats killed and necropsied.	F1 males and females had no treatment-related effects (ie, body weight, feed consumption, hematology, clinical chemistry, ophthalmic, necropsy). Necropsy of F0 and F2 rats were unremarkable.	[166]

Reproductive and Developmental Toxicity

Panax ginseng *Root Extract*

No adverse effects were reported in 2 oral reproductive/developmental studies of Panax ginseng root extract up to 20 mg/kg using rats (Table 14). In addition, in the NTP 3-month study, rats dosed with up to 5000 mg/kg *P ginseng* root extract showed no treatment-related effects on reproductive organs, estrous cycling, or sperm parameters.[93]

Subcutaneous administration of a ginseng extract (extracted with ethanol; 0.5 mL/g) for 5 days enhanced the mating behavior of male rats.[94] The extract further stimulated spermatogenesis in rat and rabbit testes and increased the motility and survival of rabbit sperm outside the body.[95]

Saponins

In screening tests with whole immersion of embryos, the saponins Rb_1 (30-50 μg/mL) and Re (50 μg/mL) yielded changes in morphological scores in rat and mice embryos (Table 15). Rc (5, 50 μg/mL) had no effect on the morphological scores of rat embryos.

Saponins (6 mg/2 mL injection; composition not provided) injected into male rats (n=10; strain not provided) for 7 consecutive days did not increase testosterone levels in the plasma.[96]

Genotoxicity

Panax ginseng *Root Extract*

Panax ginseng root extract (0-1 mg/mL) produced inhibitory effects on DNA synthesis/mutagenesis, measured by thymidine incorporation into V79 Chinese hamster lung cells.[97] Panax ginseng root extract (0-3333 μg/plate) was not mutagenic to *Salmonella typhimurium* (strains TA97, TA98, TA100, TA102, TA104, and TA1535) with or without metabolic activation in an Ames test.[93] This test was repeated (up to 10 000 μg/plate) using *S typhimurium* (strains TA98 and TA100) and *E coli* (strain WP2 *uvrA*/pKM101) with the same result.

Ginseng Saponins

In an assay of the effects of saponins on mitosis, Rg1 stimulated mitosis in the bulb and seedling root tip cells of *Allium cepa*. It was most effective at 0.002 to 0.006 mg/mL. In contrast, saponin Rb1 (0-0.01 mg/mL) inhibited mitosis in the same cell line in a dose-dependent manner.[98] An aqueous and a 1-butanol extract containing saponins from *P quinquefolius* roots (up to 36 mg/mL) was not mutagenic in *S typhimurium* (TM677) with or without metabolic activation.[99]

Panax ginseng *Root Powder*

Dried *P ginseng* root powder dissolved in water (100 mg/mL) was negative in genotoxicity tests using *Bacillus subtilis* strains H17Rec+ and M45Rec- and in *S typhimurium* (TA98, TA100) with or without PCB-induced rat liver S9.[100]

Panax ginseng *Quinquefolius*

A water extract of *P quinquefolius* roots (up to 36 mg/mL) was not mutagenic in *S typhimurium* (TM677) with or without metabolic activation.[99] An Ames test of Panax quinquefolius root extract (extracted with water/butylene glycol; 30%-70%) using *S typhimurium* (strains TA98, TA100) did not demonstrate a potential for mutagenicity.[12]

Carcinogenicity

Panax ginseng *Root Extract*

Panax ginseng root extract (solvent not provided; 0, 50, and 75 ppm in feed for 5 weeks) did not increase the number of aberrant crypt foci in rat colons (n=10).[101]

F344/N rats (n=50/sex) were administered Panax ginseng root extract (0, 1250, 2500, or 5000 mg/kg) in sterile water by gavage for 5 days/week for 104 to 105 weeks.[93] Survival of 5000 mg/kg females was statistically significantly less than that of the vehicle controls; however, the deaths were not attributed to the administration of ginseng. Mean body weights of high-dose females were less than those of the vehicle controls after week 61 of the study, and mean body weights of other dosed groups of rats were similar to those of the vehicle controls

Table 15. In Vitro Developmental Studies of Saponins.

Species (n)	Concentration	Details	Results	Reference
Rb1				
Sprague-Dawley rats (27, 29, 25)	0, 5, 15, 30, 40, 50 μg/mL	9-day-old embryos were extracted from womb and cultured in equal volumes of rat serum and Dulbecco modified Eagle medium, penicillin, and streptomycin sulfate with Rb1. Embryos were examined after 48 hours. Mean yolk sac diameter and crown-rump length were measured. Embryonic morphologies were given a numerical score (of 0-5) to 17 morphological features depending on their stage of development. Only viable embryos were included.	There were no morphological changes at 5 and 15 μg/mL. There were morphological changes to the flexon, forelimb, and hindlimb in the 30 μg/mL group with a lower total morphological score compared to controls. There were additional morphological changes to the heart and eye in the 40 μg/mL group. There was additional morphological changes to the CRL and somite number. There were no effects to the yolk sac diameter. Authors concluded that saponin Rb1 had a teratogenic effect on rat embryos.	[167]
ICR mice (20-21)	0, 5, 15, 30, 40, 50 μg/mL	Same as above	There were no morphological changes at 5 and 15 μg/mL except for yolk sac diameter in the latter. There were morphological changes to the yolk sac diameter and circulation, midbrain, forebrain optic system, and total score in the 30 and 40 μg/mL groups with a lower total morphological score compared to controls. There were additional morphological changes to the CRL, head length, somite number, allantois, flexon, brachial arch, forelimb bud, and hindlimb bud in the 50 μg/mL group. There was additional morphological changes to the CRL and somite number. There were no effects to the yolk sac diameter. Authors concluded that saponin Rb1 had a teratogenic effect on rat embryos.	[168]
Rc				
Rats (23-25)	0, 5, 50 μg/mL	Same as above	There were no differences in yolk sac diameter, CRL, number of somites, and total morphological score among control and embryos exposed to 5.0 and 50.0 μg/mL Rc	[169]
Re				
Rats (23-25)	0, 5, 50 μg/mL	Same as above	Embryos exposed to 50.0 μg/mL Re had lower morphological scores for all parameters measured (see above) compared to controls. There was no difference between embryos exposed to Re and controls.	[169]

Abbreviation: CRL, crown-rump length.

throughout the study. No increases in the incidences of neoplasms or nonneoplastic lesions were attributed to the administration of ginseng. The incidence of mammary gland fibroadenoma was statistically significantly decreased in the high-dose females. There was no evidence of carcinogenicity under these conditions.

B6C3F1 mice (n=50/sex) mice were administered Panax ginseng root extract (0, 1250, 2500, or 5000 mg/kg) 5 days/week for 105 weeks.[93] Survival of dosed groups was similar to that of the vehicle control groups. Mean body weights of dosed mice were similar to those of the vehicle controls. No neoplasms or nonneoplastic lesions were attributed to the administration of ginseng. The incidence of mammary gland fibroadenoma was significantly decreased in the high-dose female group. There was no evidence of carcinogenicity under these conditions.

Cancer Prevention

Panax ginseng root. A number of in vitro and in vivo studies indicate that ginseng root and its extracts or its purified constituents have antitumor properties.[56,64,102-104] For example, the topical application of either the methanol extract of heat-processed *P ginseng* or the purified saponin Rg3 to the shaved backs of female ICR mice suppressed 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced skin tumor promotion.[102] *P ginseng* appears to inhibit tumor development, especially tumor promotion and progression, through anti-inflammatory, antioxidant, and apoptotic mechanisms involving changes in gene expression.[62,103,105-107] Other pertinent mechanisms under investigation involve the potential for ginseng and its constituents to influence immunosurveillance and neurotransmission.[103] However, the evidence for the antitumor effects of ginseng in humans is not conclusive, and no clinical trials have confirmed the efficacy of ginseng treatments in patients with cancer.

Irritation and Sensitization

Irritation

Dermal: Nonhuman

Ginseng saponins and other constituents. Saponin Rb1 (0.05%) or the metabolite compound K (0.2, 0.05%) was administered to the ears of ICR mice (n=not provided) after sensitization to oxazolone.[108] Then, a total of 20 μL of 1% oxazolone in a mixture of acetone and olive oil (4:1) was applied to both sides of the mouse ear every 3 days starting 7 days after sensitization. Ear thickness was measured. Seventy-two hours after each application of the oxazolone, Rb1 was topically applied in a total volume of 20 μL to both sides of the ear 30 minutes before and 3 hours after each application of oxazolone. There were no irritation effects reported for Rb1 or compound K.

The above-mentioned experiment was repeated with saponin Re (0.01% and 0.05%) and its metabolite Rh1 (0.01% and 0.05%) on 12-*O*-tetradecanoylphorbol- and oxazolone-induced dermatitis.[109] There were no irritation effects reported for either compound. Additionally, the study was repeated with saponin Rg5 (0.05%) and its metabolite Rh3 (0.02%, 0.05%) on oxazolone-induced dermatitis.[26] There were no irritation effects reported for either compound.

Inclusion of Panax ginseng root extract constituents Rh2 (0.1%) and Rh3 (0.1%) in a dermal test of 2-chloro-1,3,5-trinitrobenzene (TNCB) reduced the appearance of severe erythema/hemorrhage, edema, excoriation/erosion, and scaling/dryness compared to TCNB in vehicle alone using female NC/Nga mice (n = 7).[110]

In an ear thickness test, Panax ginseng root extract saponins Rg3 (0.02%, 0.05%), Rf (0.02%, 0.05%), and Rh2 (0.05%) applied to oxazolone-induced dermatitis on female ICR mice did not cause irritation and reduced the effects of the oxazolone.[111]

Dermal: Human

Panax ginseng root extract. In a human patch test (n=30) of Panax ginseng root extract (extracted with dichloromethane, then ethanol, dry residue added to water; 0, 1, 10, 20, and 100 mg/mL in petrolatum), the patch was left in place for 48 hours. There were no reactions observed at 1 hour and 24 hours after removal.[88] In another human patch test (n=30) of Panax ginseng root extract (concentration not provided), the patch was left in place for 48 hours. There were no reactions observed at 30 minutes and 24 and 48 hours after removal.[14]

In a human therapeutic efficacy test (n=15) of Panax ginseng root extract (extracted with butylene glycol; concentration not provided), there were no adverse effects reported at the time of treatment and at 4 and 8 weeks.[14]

Ginseng saponins and other constituents. Falcarinol (0.5 mg in ethanol) strongly aggravated histamine-induced edema, but did not induce edema by itself, in skin prick tests (n=4).[112] The test was repeated on 2 of the subjects 1 week later with the same results.

Sensitization

Panax ginseng root extract. A human repeated insult patch test (HRIPT; n=99) of a cuticle serum containing Panax ginseng root extract (0.1%; 0.2 g) resulted in no dermal irritation or allergic contact sensitization.[113] In an HRIPT (n=219) of a lipstick containing Panax ginseng root extract (1%; 0.2 g), there were no adverse effects or signs of sensitivity.[114] In an HRIPT (n=104) of a night cream product containing Panax ginseng root extract (0.1%; 0.2 g), there was no skin reactivity observed at any point in the study.[115]

Panax quinquefolium. In an HRIPT (n=10) of Panax quinquefolium root extract (10% aqueous), there were no signs of irritation or sensitization observed.[12]

Sensitization Reduction

Panax ginseng root extract. In a dermal test of TNCB using female NC/Nga mice (n = 7) that included Panax ginseng root extract (red; 0.1%), a reduced appearance of severe erythema/hemorrhage, edema, excoriation/erosion and scaling/dryness compared to TCNB in the vehicle alone was observed.[110]

In an ear thickness test, Panax ginseng root extract (water extract of red ginseng; 0.02%) administered to oxazolone-induced dermatitis on female ICR mice did not cause irritation and reduced the irritation effects of the oxazolone.[111]

Phototoxicity

Panax ginseng root extract. An ethanol extract of *P ginseng* (100%; 30 μL) was not phototoxic to *Candida albicans* exposed to 50 J/cm^2 UV-A radiation. Using the same treatment, hemolysis was observed in red blood cells.[116] The HaCaT cells were treated with ginseng root extract (0% or 1%) for 24 hours and then exposed to UV-B radiation (time not provided). At 24 hours after UV-B irradiation, survival was increased in the treatment group compared to controls.[14]

Panax ginseng root extract (100%; 10 pg/, 100 ng/mouse) or 3% vitamin C (1.5 mg/mouse) were administered topically to the dorsal region of each male albino hairless HOS: HR-1 mice (n=6) daily for 12 weeks.[117] The mice were exposed to 36 mJ/cm^2 UV-B radiation, which was subsequently increased to 54 mJ/cm^2 at weeks 1 to 4, 72 mJ/cm^2 at weeks 4 to 7, 108 mJ/cm^2 at weeks 7 to 10, and finally to 122 mJ/cm^2 at weeks 10 to 12. No phototoxic effects observed.

The backs of SKH-1 hairless mice (n=20) were exposed to UV lamps (80% UV-B and 20% UV-A).[39] The mice were exposed to 90 mJ/cm^2 3 times/week. The dose was increased by 10%/week until the dose reached 175 mJ/cm^2. Treatment stopped at 22 weeks. The experimental groups were (a) untreated control, (b) UV-irradiated control (ip with saline vehicle), (c) red ginseng root extract (25 mg/kg) ip in combination with UV irradiation, (d) UV-irradiated control (topical administration with cream base vehicle), and (e) red ginseng root extract topical (0.2%) administration in combination with UV-irradiation. The ip injections were administered 24 hours prior to each UV irradiation. Topical creams (0.2 mg/cm^2) were applied at least 15 minutes before UV irradiation. Topical and ip treatment with red ginseng root extract reduced the incidence of tumors, reduced tumor multiplicity, and delayed the time of first tumor appearance.

Panax ginseng root extract (extracted with ethanol; 0, 0.5%, 2.5%) was administered in the feed of male SKH-1 hairless mice.[118] The backs of the mice were exposed to UV radiation (approximately 30% UVA) 3 times a week for 12 weeks. The amount of irradiation was progressively increased from 100 mJ/cm^2 per exposure at week 1 (1 minimal erythematous dose = 100 mJ/cm^2) to 400 mJ/cm^2 at week 7. The authors reported a reduction in UV-induced wrinkle formation in both groups fed red ginseng extract compared with animals exposed to UV radiation without ginseng in their feed. No adverse effects were reported in the animals administered ginseng alone.

Saponins. Panax ginseng root extract saponin Rb1 (100 fg, 10 pg, and 1 ng/mouse) or 3% vitamin C (1.5 mg/mouse) were applied topically to the dorsal region of male albino hairless HOS: HR-1 mouse (n=6) every day for 12 weeks.[117] The mice were exposed to 36 mJ/cm^2 UVB, which was subsequently increased to 54 mJ/cm^2 at weeks 1 to 4, 72 mJ/cm^2 at weeks 4 to 7, 108 mJ/cm^2 at weeks 7 to 10, and finally to 122 mJ/cm^2 at weeks 10 to 12. There were no phototoxic effects were observed.

Clinical Use

Oral: Human. In multiple efficacy studies of orally administered Panax ginseng root extract for treatment or prevention of various maladies, the adverse effects attributable to the extract in placebo-controlled (150-11250 mg; Tables 16 and 17), comparative (200 mg; Table 18), and uncontrolled (105-4500 mg; Table 19) studies included flu/cold, headache, gastrointestinal complaints, nausea, diarrhea, and vomiting.[66]

Ginseng abuse syndrome. The characteristic signs and symptoms of overexposure to ginseng, "ginseng abuse syndrome," include morning diarrhea, skin eruptions, sleeplessness, nervousness, and hypertension.[119] In a study of ginseng abuse syndrome, subjects (n=133) using ginseng regularly for at least 1 month were surveyed.[120] It was not possible to differentiate those using *P ginseng* and subjects using Siberian ginseng (which is a different genus and species from *P ginseng*). Ginseng doses varied from 8 to 10 g 3 times a day for capsules; 0.5 to 3 g twice a day for roots; 1 to 2 g 3 times a day for ground powders; and 2.5 to 5 mL a day for extracts. Most subjects experienced central nervous system excitation and arousal. Fourteen subjects who ingested *P ginseng* roots experienced hypertension, nervousness, sleeplessness, skin eruptions, and morning diarrhea; 5 had edema; and 10 became euphoric, restless, agitated, and insomniac. Ten subjects taking high doses (15 g) felt depersonalization and confusion. The average daily dose of ginseng roots was 3 g for persons experiencing ginseng abuse syndrome. One user reported that abrupt withdrawal precipitated hypotension, weakness, and tremor. Ginseng abuse syndrome appeared periodically in the first 12 months of ginseng use but was rarely reported in follow-up examinations at 18 and 24 months. The author suggested that, taken together, these effects mimicked those of corticosteroid poisoning, strongly suggesting a steroidal mechanism of action.

Phytoestrogenic Activity

Summaries of case reports, in vivo, and in vitro studies on phytoestrogenic activity are provided in Table 20. Several anecdotal reports of ginseng-induced estrogenic activity were discovered. None of these reports identified the origin or source quality, or quantity of the ginseng in the products used by the subjects, or provided sufficient information to enable estimates of the total doses of ginseng to which the patients were exposed. Two of the products contained *P ginseng*, 1 contained Rumanian ginseng (*Eleutherococcus senticosus*; also known as Siberian ginseng), and the species of ginseng in the remaining products were not specified. Thus, it is not known whether the latter 3 products contained Rumanian/Siberian ginseng or other species. The distinction is important because *E. senticosus* does not contain ginsenosides. Other noteworthy unknowns from these reports include the diets, the use of other drugs, and the stress condition of the patients.[121-128]

The available in vivo animal evidence does not support the hypothesis that alcohol extracts of *P ginseng* or American ginseng have the potential to act as phytoestrogens. There were no signs of estrogenic activity in rats and mice orally administered up to 5000 mg/kg/d for 2 years.[129,130] In the NTP 3-month studies, estrous cycling was explicitly evaluated, and no differences were reported related to treatment with ginseng extract at any dose including the top dose of 5000 mg/kg of an ethanolic extract of *P ginseng*.[93]

Table 16. Reported Effects in Oral Studies Comparing Ginseng and Placebos (After Coon and Ernst 2002[66]).

Subject population	n treated	Preparation and daily dose	Duration	Reported effects: Ginseng	Reported effects: Placebo	Reference
Postmenopausal women	384	G115 200 mg	16 weeks	7 SAEs and 124 AEs Most frequent: flu/cold (36), headache (10), gastrointestinal (13)	9 SAEs and 133 AEs Most frequent: flu/cold (36), headache (10), gastrointestinal (13). Most frequent: flu/cold (35), headache (9), gastrointestinal (22)	170
Healthy men	36	G115 200 and 400 mg	8 weeks	Diarrhea (3)	None reported	171
Healthy volunteers	83	G115 200 mg	4 month	Nausea (1)	Nausea, dizziness, headache, stomach problems (5)	172
Healthy volunteers	227	G115 200 mg	12 weeks	Nausea, vomiting, anxiety, insomnia, epigastralgia (10)	Insomnia (1)	173
Healthy volunteers	28	G115 200 mg	3 weeks	Diarrhea (2)—no treatment group specified		174
Patients with psychoasthenic syndromes	60	G115 (dose not stated)	2 year	Itching, eye burning (2)	Urticaria, itching, stomach pain, giddy feelings (4)	175
Patients with hypertension	34	Red ginseng 4.5 g root (300 mg ginseng) ± other antihypertensive treatment	12 week	Upper abdominal discomfort (2). Also reported: diaphoresis, tiredness, constipation/dyspepsia (9)—no treatment group specified. Only 12 patients had ginseng alone	None reported	176
Healthy volunteers	22	Korean ginseng 1000 mg	30 days	Stimulation, improved motor efficiency, increased appetite, diarrhea, skin eruptions, sleeplessness, sleepiness (11)	Depression, improved motor efficiency, increased appetite, sleeplessness (7)	177
Elderly patients	49	Korean red ginseng 1.5g	10 days	Diarrhea (1)—no treatment group specified		178
Women with postmenopausal osteoporosis	45	Red ginseng 50 mg/kg/d	12 months	Digestion problem (3)	Digestion problem (1)	179
Patients with psychogenic impotence	35	Korean red ginseng 2700 mg	2 months	Digestive problem, diffuse itching (2)	None reported	180
Healthy volunteers	64	Red ginseng/white ginseng 11.25g	10 days	Hyper- or hypothermia, hot flushes, diarrhea, headache, insomnia, constipation, lip dryness, dizziness, loss of appetite—no treatment group specified		181
Healthy radio operators	32	Liquid ginseng root extract 2 mL	Single dose	Lighter hand and increased appetite (number of patients not reported)	None reported	182

Abbreviations: G115, standardized ginseng extract, 4% saponins (Ginsana, Pharmaton SA, Lugano, Switzerland); AE, adverse event; SAE, serious adverse event.

In vitro experiments using specific, purified ginsenosides, including Rg1, Rb1, and Rh1, showed that these ginsenosides can stimulate signal transduction pathways and produce estrogen receptor (ER)-mediated effects through direct or indirect interaction with ERα or ERβ in cells that express high levels of ERs. However, the crude extracts appear to be much less potent than some of the purified ginsenosides used in the in vitro studies. The potencies of the crude extracts may greatly depend on the extraction method (ie, methanol, water) used, and, in some cases, their effects may be attributable to naturally occurring, nonginsenoside components or impurities, such as mycotoxins, in the extracts.[129,131-144]

In an earlier CIR safety assessment of polyethylene glycol (PEG) soy sterols, the report stated that available data

Table 17. Placebo-Controlled Oral Trials of Ginseng in Which no Adverse Effects Were Reported (after Coon and Ernst 2002[66]).

Subject population	n treated	Daily dose	Duration	Comments	Reference
Healthy females	19	G115 200 mg	8 weeks	None	183
Healthy females	19	G115 200 mg	8 weeks	None	184
Healthy males	16	G115 200 mg	12 weeks	None	70
Patients with bronchitis	40	G115 200 mg	8 weeks	Adverse effects not specified	185
Healthy subjects	112	400 mg ginseng extract	8-9 weeks	Six patients discontinued the study due to illness	186
Healthy males	41	Standard ginseng extract 300 mg	8 weeks	None	187
Patients with unsettled complaints	30	Korean red ginseng powder 2.7g	6 weeks	None	188
Patients with erectile dysfunction	90	Korean red ginseng 1800 mg	3 months	None	189
Athletes	30	Chinese ginseng 1200 mg	6 weeks	None	190
Healthy nurses	12	Korean ginseng 1200 mg	3 days	None	191
Middle to old aged subjects	358	*Panax ginseng* 150 mg	2 months	No vomiting and/or long-term toxic effects observed	191
Patients with diabetes mellitus	36	Ginseng 100 or 200 mg	8 weeks	None	192

G115, standardized ginseng extract, 4% saponins (Ginsana®, Pharmaton SA, Lugano, Switzerland).

Table 18. Effects Reported in Comparative Oral Trials Comparing Ginseng to Another Treatment (after Coon & Ernst[66]).

				Effects reported (no. of patients)		
Subject population	n treated	Daily dose	Duration	Ginseng	Other treatment(s)	Reference
Patients with chronic bronchitis	75	G115 200 mg/antibacterial treatment	9 days	Not specified; Nine patients withdrew from the study spontaneously (no treatment group specified)	Not specified	193
Sportsmen	20	G115 200 mg/G115s	9 weeks	None reported	None reported	194
Patients with heart failure	45	Red ginseng (dose not stated)/ digoxin/both	15 pills	None reported	None reported	195
Regular users of ginseng	18	Self-regulated doses of *P ginseng* capsules (~518-1300 μg/d), teas (1-2 cups), extracts (2.5-5.0 mL), or root (0.5-3.0 g/d) with and without other stimulants	12 weeks	Ginseng—contact urticarial reaction (1), stimulation, feeling of wellbeing, nervousness	Ginseng and other stimulants—allergic reactions (2), ginseng abuse syndrome (1), stimulation, well-being	196

G115®, standardized ginseng extract, 4% saponins (Ginsana, Pharmaton SA, Lugano, Switzerland); G115s, standardized ginseng extract, 7% saponins (Pharmaton SA, Lugano, Switzerland); n, number of study participants.

on phytosterols are relevant independent of the plant source because of the similarity in structure across plant species.[145] Campesterol, stigmasterol, and β-sitosterol are the major phytosterol components, and among those, β-sitosterol predominates. In this safety assessment, data were available on phytosterol repeat-dose toxicity, estrogenic effects, reproductive toxicity, genotoxicity, and cell proliferation. The Panel noted that these phytosterols are poorly absorbed, have little estrogenic activity, and are not reproductive toxicants.

Case Reports

Panax ginseng root extract. A 39-year-old man developed hypertension, dizziness, and inability to concentrate during long-term ingestion of ginseng. He stopped taking ginseng, became normotensive within 5 days, and remained normotensive without treatment, and after 3 months his symptoms resolved.[146]

A 28-year-old woman developed a severe headache after ingesting a large quantity of ethanol-extracted ginseng. Cerebral angiograms showed a "beading" appearance in the anterior and posterior cerebral and superior cerebellar arteries, consistent with cerebral arteritis.[147]

Summary

Ginseng root-derived cosmetic ingredients include Panax ginseng root extract, hydrolyzed ginseng root, hydrolyzed ginseng root extract, hydrolyzed ginseng saponins, Panax ginseng root, Panax ginseng root powder, Panax ginseng root water, Panax ginseng root oil, Panax ginseng root protoplast, Panax japonicus root extract, Panax notoginseng root, Panax notoginseng

Table 19. Effects Reported in Uncontrolled Trials of Ginseng (after Coon and Ernst[66]).

Subject population	n	Daily dose	Duration	Adverse effects reported (no. of patients)	Reference
Patients with oligospermia	17	G115 400 mg	90 days	None reported	197
Patients with chronic respiratory disease	15	G115 400 mg	3 months	None reported	198
Postmenopausal women	49	G115 200 mg	3 months	None reported	199
Postmenopausal women with and without climacteric symptoms	20	Korean red ginseng 6 g	30 days	None reported	200
Male athletes	10	Pure ginseng extract 105 mg	2 days	None reported	201
Patients with essential hypertension	35	Ginseng extract 1000 mg	Up to 10 weeks	None reported	202
Healthy women	20	Epicutaneous extract of ginseng containing 14% ginsenosides	30 days	Patients withdrew after 12-15 days due to skin feeling "too tight" (3)	203
Patients with essential hypertension	19	Red ginseng powder 3 g	12 weeks	None reported	204
Patients with hypertension	17	Korean red ginseng 4.5 g	21-27 months	None reported	205
Patients with mild proteinemia and hypertension	24	Red ginseng 900 mg	2 months	Digestive problem (1)	206

root powder, and Panax quinquefolium root extract. The cosmetic functions of these ingredients include skin-conditioning agents—miscellaneous, fragrance ingredients, skin-conditioning agents—miscellaneous, skin-conditioning agent—humectant, skin-conditioning agents—emollient, and cosmetic astringent.

If the root is raw or dried, it is referred to as "white" ginseng. If it has been steamed and dried before extraction or pulverizing, it is referred to as "red" ginseng because of a change in coloring. If it is steamed and dried 9 times, the coloring darkens more and the product is referred to as "black ginseng." The constituents of ginseng roots include saponins and sapogenins, carbohydrates, organic acids (including amino acids), nonprotein nitrogenous substances, peptides, minerals, and enzymes.

The total number of uses of Panax ginseng root extract was 149 (102 leave-on products, 42 rinse-off products, and 5 diluted products) at maximum concentrations of 0.000002% to 0.5%. Panax ginseng root was reported to be used in 21 cosmetic products (15 leave-on and 6 rinse-off products). Panax notoginseng root was reported to be used at 0.0004% in rinse-off products. Panax quinquefolium root extract was reported to be used in 467 cosmetic products (317 leave-on, 146 rinse-off, and 4 diluted for bath products) at maximum concentrations of 0.002%. There were no uses reported for Panax ginseng root powder, hydrolyzed ginseng root, hydrolyzed ginseng root extract, hydrolyzed ginseng saponins, Panax ginseng root powder, Panax ginseng root water, Panax ginseng root oil, Panax ginseng root protoplasts, Panax japanicus root extract, or Panax notoginseng root powder.

There were no inhalation toxicokinetic data available. The saponins were poorly absorbed when orally administered as root extract or as individual components.

Panax ginseng root extract was not cytotoxic to human dermal fibroblasts up to 1000 μg/mL. The acute oral LD_{50} for rats was 750 mg/kg and 200 mg/kg for mice for Panax ginseng root. Ginseng root extract had an ip LD_{50} of 637 mg/kg. Oral administration of *P ginseng* root extract was nontoxic to rats up to 5000 mg/kg/d for up to 105 weeks, up to 5000 mg/kg for life for mice, and 15 mg/kg/d for 90 days for dogs.

There were no adverse effects reported in an oral reproductive study at 15 mg/kg/d or a developmental study up to 20 mg/kg/d Panax ginseng root extract using rats and no effects on reproductive organs, estrous cycle, or sperm parameters in 3-month studies. In embryo emersion studies using rats and mice, the total morphological scores of embryos exposed to 30 mg/mL of the saponin Rb1 were reduced. The total morphological scores of rat embryos exposed to 30 mg/mL of the saponin Re were reduced. There were no adverse effects to embryos exposed to Rc.

Panax ginseng root extract, up to 75 ppm in feed, did not increase the number of aberrant crypt foci in rat colons. Panax ginseng root extract was not carcinogenic to rats or mice up to 5000 mg/kg for 105 weeks. Panax ginseng root extract, Panax ginseng root powder, and Panax quinquefolius root extract were not mutagenic in Ames tests. Panax ginseng saponins were not mutagenic to *S typhimurium* up to 36 mg/mL.

P ginseng root extract suppressed TPA-induced skin tumor promotion in mice. Antitumor effects have not been established in humans. There were case reports of phytoestrogenic activity. In vivo tests did not find estrogenic activity in rats and mice up to 5000 mg/kg/d over 2 years. In vitro experiments showed that Rg1, Rb1, and Rh1 can stimulate signal transduction pathways and produce estrogen receptor-mediated effects through direct or indirect interaction with ERα or ERβ in cells that express high levels of ERs. Extracts were less potent.

Panax ginseng root extract was not irritating to mice up to 0.1% or humans up to 100 mg/mL. Falcarinol at 0.5 mg, Rb1 at 0.05%, Re at 0.05%, Rh1 at 0.05%, Rg5 at 0.05%, Rh3 at 0.05%, Rh2 at 0.1%, Rh3 at 0.1%, Rg3 at 0.05%, Rf at 0.05%, and compound K at 0.05% were not dermally irritating to mice. There was no sensitivity detected in HRIPTs of products containing Panax ginseng root extract up to 1%.

Table 20. Summaries of Reports/Studies on the Estrogenic Activity of Products Containing Ginseng and Ginseng Saponins, and Various Ginseng Extracts and Saponins.

Ginseng source/description	Report/study summary	Reference
Human—Anecdotal reports		
Fang Fang ginseng face cream (no information was found on the contents of the cream)	A 44-year-old woman who had undergone menopause at age 42 experienced 3 episodes of vaginal spotting after daily use of Fang Fang ginseng face cream for 1 month or more (Shanghai, China; formula unspecified). The bleeding episodes were associated with a decrease in follicle-stimulating hormone (FSH) levels and a disordered proliferative pattern on endometrial biopsy. The woman experienced no further bleeding after discontinuing use of the cream.	122
Panax ginseng; 200 mg/tablet (formula and duration not provided)	A 72-year-old woman experienced vaginal bleeding after ingesting 1 tablet daily of a Swiss-Austrian geriatric formula containing *P ginseng*	121
P ginseng powder (formula, dose, and exposure route not provided)	A 70-year-old woman developed mastalgia with diffuse nodularity after using a *P ginseng* powder for 3 weeks. The symptoms ceased after the use of the product was discontinued and reappeared with 2 additional rechallenges. Prolactin levels remained within normal limits.	124
"Rumanian" ginseng (form and amount not provided)	A 62-year old-woman who had undergone bilateral oophorectomy 14 years previously developed marked estrogenic effects, based on the microscopy of vaginal smears and gross appearance of the vaginal and cervical epithelium, after ingesting Rumanian ginseng 2 weeks per month for 1 year. Estrone, estradiol, and estriol levels were essentially unchanged over this time, but the effects on the vaginal smear coincided with the use of the product. The investigators found no estrogen in the product. However, a crude methanol extract of the product competed with estradiol for binding to estrogen and progesterone receptors in human myometrial cytosol.	126
Ginseng preparations (species, formula, amount, exposure route, and durations not provided)	5 Women aged 25-40 who had been taking ginseng preparations developed breast symptoms, including enlargement of the nipples.	123
Ginseng (species, formula, amount, and exposure route and duration not provided)	Male gynecomastia has also been reported after ginseng use.	125
Whole animal studies		
P ginseng (ethanol extracts; 2 weeks at 0, 125, 250, 500, 1000, or 2000 mg/kg 5 days/week; 3 months at 0, 1000, 2000, 3000, 4000, or 5000 mg/kg, 5 days per week)	Oral toxicity and carcinogenicity studies of ethanol extracts of *P ginseng* in Fischer 344 rats and B6C3F1mice studies, there were no significant differences in sperm parameters of male rats and mice or the estrous cyclicity of female rats and mice between the control and ginseng-treated groups. No evidence of hormonal effects in rats or mice was found in these studies, including the 2-year study (0, 1250, 2500, 5000 mg/kg 5 days per week).	130
P quinquefolium (purchased from a health-food vendor)	Alcohol extracts of *Panax quinquefolium* had no effect on uterine weight when administered by gavage (500 μL/d) to ovariectomized CD-1 mice for 4 days. In contrast, 100 μg/kg/d 17β-estradiol administered subcutaneously for 4 days increased the mean uterine weight 1.7-fold greater than the negative control group.	129
In vitro studies		
P quinquefolium "high" concentrations (ie, 1:500 dilution)	Alcohol extracts of *P quinquefolium* stimulated the growth of MCF-7 cells, which are estrogen receptor (ER)-positive human breast cancer cells. The proliferation rate of the treated cells was 2 times greater than that of untreated control cells, but the treatment did not transactivate (ie, did not increase the rate of gene expression of) either human ERα (hERα) or hERβ in transfected HeLa cells. The authors suggested that ginseng stimulates the growth of MCF-7 cells independent of estrogenic activity.	129
Panax quinquefolium (multisolvent extraction and a proprietary extract)	*P quinquefolium* extracts induced the expression of the estrogen-sensitive gene, pS2, and caused a dose-dependent decrease in the proliferation of MCF-7 cells.	134,135
P quinquefolium root (various extract solvents)	Extraction method of *P quinquefolium* root determined its ability to produce an estrogenic response in MCF-7 cells. A methanol extract, but not a water extract, increased MCF-7 cell proliferation in a concentration-dependent manner at low concentrations (5-100 μg/mL) when the cells were maintained under low-estrogen conditions. Higher concentrations of the methanol extract inhibited proliferation. The results of proliferation studies, ER binding assays, and pS2 and progesterone receptor (PgR) mRNA expression analyses all supported the conclusion that the water extract does not elicit estrogen-like activity. The authors proposed that the conflicting results of laboratory studies on the estrogenicity of ginseng may be attributable to differences in extraction methods.	138

(continued)

Table 20. (continued)

Ginseng source/description	Report/study summary	Reference
P ginseng and *P quinquefolius* root	Crude water or methanol extracts of *P ginseng* and *P quinquefolius* root can bind to purified ERα or ERβ (PanVera), but neither receptor type interacted with purified Rb1 or Rg1 (Indofine). However, the crude extracts contained zearalenone or zearalenone-like compounds that bind to ERα and ERβ, and 3 of the 4 root samples cultured positive for Fusarium fungus, which is the only known natural source of zearalenone. Zearalenone and its metabolites are well-known, potent estrogenic mycotoxins. The authors suggested that the findings could explain the sporadic reports of estrogen toxicity after ginseng use, as well as the conflicting results of in vitro studies of the estrogenic action of ginseng crude extracts and purified ginsenosides.	137
Rb1	50 μmol/L Rb1 obtained from the Korean Ginseng and Tobacco Research Institute (purity unspecified) activated the transcription of the estrogen-responsive luciferase reporter gene in MCF-7 cells. The effect was blocked by the specific ER antagonist ICI 182,780, indicating that the effect is ER dependent. The authors proposed that Rb1 acts as a weak phytoestrogen, presumably by binding and activating the estrogen receptor in these cells.	143
Rb1 from the Korean Ginseng and Tobacco Research Institute (purity unspecified)	Rb1 activated both ERα and ERβ, leading to the transactivation of estrogen-responsive luciferase genes in MCF-7 cells in a dose-dependent manner (up to 100 μmol/L). However, Rb1 did not displace the specific binding of [^{3}H]17β-estradiol from estrogen receptors in MCF-7 whole-cell ligand binding assays. Thus, Rb1 appears to activate both ERα and ERβ in these cells in the absence of ER binding.	133
Rb1 purchased from the National Institute for the Control of Pharmaceutical and Biological Products	Rb1 (>98% purity, 0 and 500 nmol/L for 24 hours) activated the antiangiogenic pigment epithelium-derived factor (PEDF) and suppressed endothelial cell tube formation, in human umbilical vein endothelial cells (HUVECs). These effects were mediated by ERβ, rather than ERα. In competitive ligand binding assays, Rb1 was able to displace a high-affinity fluorescent estrogen ligand from human recombinant ERβ, but not ERα.	144
Rc and Re	Rc and Re can stimulate MCF-7 cell growth and induce c-Fos expression independent of ER activation.	142
Re	Re did not enhance proliferation of MCF-7 cells.	136
Rg1 from the ethanol extracts of *P notoginseng*	Picomolar (pM) concentrations of 99% pure Rg1 from the ethanol extracts of *P notoginseng* can activate the ER in human breast cancer cells (MCF-7) and human endometrial cells (HeLa) without directly interacting with the ER.	131
Rg1	Rg1 stimulated MCF-7 cell proliferation and pS2 mRNA expression through activation of cross-talk between ERα-dependent and insulin growth factor 1 receptor (IGF-IR)-dependent pathways.	132
Rg1	Rg1 stimulates the transcription of the estrogen response element (ERE)-luciferase reporter gene through ERα and ERβ in human embryonic kidney cells (HEK293) transfected with either ERα or ERβ. However, Rg1 activated ERE-luciferase activity at lower concentrations (0.01 pM-1 μmol/L) through the ERα-mediated pathway, compared to the Rg1 concentration (1 μmol/L) required for activation through the ERβ-mediated pathway. Furthermore, 1 pM Rg1 rapidly induced the phosphorylation at the serine 118 residue of the AF-1 transcriptional activation domain of ERα within 5 minutes, suggesting that Rg1 activates ERα in a ligand-independent manner. The authors suggested that the results may help to explain the different effects of ginsenosides in different types of tissues.	140
Rg1	The estrogenic effects of Rg1 (>99% pure) in MCF-7 cells, including the ligand-independent activation of ERα, the induction of IGF-IR and estrogen-responsive pS2 expression, and the stimulation of cell proliferation, are mediated by the mitogen-activated protein kinase (MAPK) pathway.	141
Rh1	Rh1 (50 μmol/L) could activate ER in human breast cancer cells.	143
Rh2 (semi-synthesized; 10^{-7}-10^{-6} M)	Estrogenic potency of semi-synthesized ginsenoside-Rh_2 was examined with yeast 2-hybrid system, including expressed genes of human estrogen receptor, hERα, the coactivator TIF2, and lacZ as a reporter gene. Ginsenoside-Rh_2 exhibited moderate estrogenic activity at 10^{-7} to 10^{-6} mol/L. Its effect was approximately 30% of the activity of 17β-estradiol applied at half-effective concentration. The authors concluded that this indicated that Rh_2 is a weak phytoestrogen. Data obtained by yeast 2-hybrid assay reflect structure–activity relationship between tested compounds and 17β-estradiol. Rh_2 has some similarity in chemical structure with 17β-estradiol that might explain affinity of this glycoside to the hERα receptor.	139

Panax ginseng root extract was not phototoxic in *C. albicans* assays up to 100%. Panax ginseng root extract was not phototoxic to mice when administered dermally up to 0.2 mg/cm^2, ip at 25 mg/kg, or orally up to 2.25%. Dermally administered Rb1 was not phototoxic to mice up to 1 ng/mouse.

In multiple studies of orally administered Panax ginseng root extract ranging 105 to 11 250 mg to test for efficacy for treatment or prevention of various maladies, the adverse effects attributable to the extract in humans included flu/cold, headache, gastrointestinal complaints, nausea, diarrhea, and vomiting. The characteristic signs and symptoms of overexposure to ginseng, ''ginseng abuse syndrome,'' include morning diarrhea, skin eruptions, sleeplessness, nervousness, and hypertension.

Discussion

Although there are data gaps, the similarity in plant sources, constituents, functions, and concentrations in cosmetics allow grouping these ingredients together and interpolating the available dermal toxicological data to support the safety of the entire group.

The Panel expressed concern regarding pesticide residues and heavy metals that may be present in botanical ingredients. They stressed that the cosmetics industry should continue to use the necessary procedures to limit these impurities in the ingredient before blending into cosmetic formulation.

While aflatoxin has been detected in the roots of *P ginseng*, the Panel believes that aflatoxin should not be present in *P ginseng* root extract and botanical ingredients that are derived from *P ginseng*, *P quinquefolius*, *P japonicus*, and *P pseudoginseng*. The Panel expects that the cosmetics industry will use necessary procedures to ensure that $\leq$15 ppb of aflatoxin can be found in cosmetics as corresponding to ''negative'' aflatoxin content.

Pulegone is listed as a constituent of *P quinquefolius*. The Panel recalled that pulegone toxicity was a concern with peppermint oil that required adoption of a concentration limit of $\leq$1% of pulegone.[21] Since then, NTP has published a report on the toxicology and carcinogenicity of pulegone in rat and mice.[148] Because of the low use levels of ginseng-derived ingredients, including those derived from *P quinquefolius*, the Panel was confident that a toxic concentration of pulegone could not be reached in cosmetics. Recent data, for example, reported that *P quinquefolius* was used at a maximum of 0.002%. The Panel did, however, alert the cosmetics industry that should a ginseng root-derived ingredient be used in a cosmetic product with other botanical ingredients that may contain pulegone, specifically peppermint oil, the total amount of pulegone in the product should not exceed 0.03% for rinse-off products or 0.002% for leave-on products.

The Panel noted that not all of the constituents of *P japonicus*, *P notoginseng*, *P quinquefolium* roots were identified as they were for *P ginseng*. However, the Panel saw no need for concern due to the similar toxicity data, information on the saponins, and low concentrations of use.

The Panel was concerned about reports in the literature of phytoestrogenic effects of ginseng-related products. After further examination of these reports and other studies, the Panel concluded that attribution to *Panax* spp, root products for phytoestrogenic effects is unlikely. An extensive discussion of the potential estrogenic activity of plant phytosterols had been developed by the Panel for its safety assessment of PEGs soy sterol ingredients. Although no dermal absorption data were available, in the Panel's experience, plant phytosterols and phytosterol esters are not significantly absorbed. Extensive data show that these constituents are not estrogenic, are not reproductive toxicants, are not genotoxic, and are not carcinogenic.

The Panel discussed the issue of incidental inhalation exposure from deodorants, face powders, foot powders and sprays, and perfumes. There were no inhalation toxicity data available. However, the Panel noted that these ingredients are reportedly used at concentrations up to 0.1% in cosmetic products that may be aerosolized and up to 0.01% in other products that may become airborne, and that 95% to 99% of droplets/particles would not be respirable to any appreciable amount. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. The Panel considered other data available to characterize the potential for ginseng root-derived ingredients to cause systemic toxicity, irritation, sensitization, reproductive and developmental toxicity, genotoxicity, and phototoxicity. They noted the lack of systemic toxicity at high doses in acute and subchronic oral exposure studies and no irritation or sensitization in multiple tests of dermal exposure. There was no genotoxicity in in vitro and in vivo tests and no carcinogenicity in tests using rats and mice. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

Conclusion

The CIR Expert Panel concluded that the following ingredients are safe in the present practices of use and concentration described in this safety assessment:

- Panax ginseng root extract,
- hydrolyzed ginseng root*,
- hydrolyzed ginseng root extract*,
- hydrolyzed ginseng saponins*,
- Panax ginseng root*,
- Panax ginseng root powder,
- Panax ginseng root water*,
- Panax ginseng root oil*,
- Panax ginseng root protoplast*,
- Panax japonicus root extract*,
- Panax notoginseng root,
- Panax notoginseng root powder*, and
- Panax quinquefolium root extract.

*Not reported to be in use. Were ingredients in this group not to be in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.

Author Contribution

Becker, L. contributed to conception and design, contributed to acquisition, analysis, and interpretation, and drafted manuscript; Gill, L., Andersen, F. Alan, Bergfeld W., Belisto, D., Klaassen, C., Liebler, D., Marks, J. Shank, R., Slaga, T., and Snyder, P. contributed to conception and design, contributed to analysis and interpretation and critically revised manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Authors' Note

Unpublished sources cited in this report are available from the Director, Cosmetic Ingredient Review, 1620 L Street, NW, Suite 1200, Washington, DC 20036, USA.

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