American Ginseng Root
Panax quinquefolius L.

Standards of Analysis, Quality Control, and Therapeutics

Editor
Roy Upton RH DAyu

Associate Editor and Monograph Coordinator
Pavel Axentiev MS

Research Associate
Diana Swisher MA
This monograph is dedicated to the memory of noted Chinese pharmacologist the late Professor Yingjie Chen, who began the development of this monograph, and Yuzhen Yan, a natural products chemist and gifted botanical photographer. Their passing is a great loss to the scientific research of traditional Chinese medicine.

Authors

History and Traditional Indications
David Winston RH (AHG) Herbal Therapies Research Library Broadway, NJ

American Herbal Pharmacopoeia®
Scotts Valley, CA

Botanical Identification
Alison Graff PhD
American Herbal Pharmacopoeia®
Scotts Valley, CA

Macroscopic Identification
Roy Upton RH D'Ayu
American Herbal Pharmacopoeia®
Scotts Valley, CA

Microscopic Identification
Prof Dr Reinhard Langer
AGES Pharm Med
Vienna, Austria

Commercial Sources and Handling
Robert Beyfuss PhD
Cornell University
Ithaca, NY

Roy Upton RH D'Ayu
American Herbal Pharmacopoeia®
Scotts Valley, CA

Constituents
Yuan-Chun Ma PhD
Canadian Phytopharmaceuticals Corp.
Richmond, BC, Canada

Analytical
High Performance Thin Layer Chromatography (HPTLC)
Eike Reich PhD
Anne Schibli Ms Pharm
CAMAG-Laboratory
Muttenz, Switzerland

High Performance Liquid Chromatography (HPLC)
Paula Brown MS
Michael Chan
British Columbia Institute of Technology
Burnaby, Canada

Therapeutics
Pharmacokinetics
Richard Ko PhD
Herbal Synergy
Oakland, CA

Clinical Efficacy and Pharmacodynamics
Yingjie Chen PhD
Song Liyan
Shenyang Pharmaceutical University
Shenyang, People's Republic of China

Pavel Aventiev MS
American Herbal Pharmacopoeia®
Scotts Valley, CA

Safety Profile
Zoe Gardner PhD
Traditional Medicinals
Sebastopol, CA

International Status
Josef Brinckmann
Traditional Medicinals
Sebastopol, CA

Traditional Chinese Medicine Supplement
Thomas Avery Garran MTOM LAc
Institute of Clinical Acupuncture and Oriental Medicine
Honolulu, HI

Reviewers
Dan Bensky DO
Seattle, WA

Eric Brand
Paradigm Publications
San Diego, CA

Francis Brinker ND
Eclectic Institute, Inc.
University of Arizona
Tucson, AZ

Michael Chung
Superior Trading Co.
San Francisco, CA

Jeanine Davis PhD
North Carolina State University
Mills River, NC

Dou De-Qiang
Liaoning University of Traditional Chinese Medicine
Dalian, People's Republic of China

Robert Eidus
North Carolina Ginseng & Goldenseal Company
Marshall, NC

Doug Elliott
Union Mills, NC

Michael Flannery MA MLS
Lister Hill Library of the Health Sciences
Birmingham, AL

Sandra Carol Miller PhD
McGill University
Montreal, Canada

Daniel E. Moerman PhD
University of Michigan-Dearborn
Dearborn, MI

Al Oliver BSA
Chase, BC, Canada

W Scott Persons
Tuckasegee Valley Ginseng
Tuckasegee, NC

Chen Pei PhD
United States Department of Agriculture
Beltsville, MD

Xie Peishan
Macau University of Science and Technology
Macau, People's Republic of China

Art Presser PharmD
Huntington College of Health Sciences
Knoxville, TN

Chris Rundell BA
Threshold Enterprises
Scotts Valley, CA

James Snow RH (AHG)
Tai Sophia Institute
Laurel, MD

Amal Soumyanath PhD
Oregon Health & Science University
Portland, OR

Vladimir Vukos PhD
University of Toronto
Toronto, ON, Canada

Dave Wang
Queens Library
Laurelton, NY

Anthony Windust PhD
Institute for National Measurement Standards
National Research Council Canada
Ottawa, ON, Canada

Zhang Yifang MS
Association for the Development of MCM He Medical School
Shanghai, People's Republic of China

Chun-Su Yuan MD PhD
University of Chicago
Chicago, Illinois

Jeffrey C Yuen
Swedish Institute Inc.
New York, NY

Final Reviewers

Dennis VC Awang PhD FCIC
MediPlant Natural Products Consulting Service
Surrey, BC, Canada

Joseph M Betz PhD
Office of Dietary Supplements
National Institutes of Health
Bethesda, MD

Doug Bradley
Ontario Ginseng Growers Association
Simcoe, ON, Canada

Paula Brown
British Columbia Institute of Technology
Burnaby, BC, Canada

Michael McGuflin
American Herbal Products Association
Silver Spring, MD

Aivia Romm MD CPH
Tufts University School of Medicine
Boston, MA

Butch Weege
Ginseng Board of Wisconsin
Waunau, WI

Medical Disclaimer
The information contained in this monograph represents a synthesis of the authoritative scientific and traditional data. All efforts have been made to ensure the accuracy of the information and findings presented. Those seeking to utilize botanicals as part of a health care program should do so under the guidance of a qualified health care professional.

Statement of Nonendorsement
Reporting on the use of proprietary products reflects studies conducted with these and is not meant to be a product endorsement.

Design & Composition
Beau Barnett
Santa Cruz, CA

Cover Photograph
American ginseng
© 2012 Steven Foster

American Herbal Pharmacopoeia®
American Ginseng Root
2012
**Nomencature**

**Botanical Nomenclature**
*Panax quinquefolius* L.

**Botanical Family**
Araliaceae

**Pharmaceutical Nomenclature**
*Radix Panacis quinquefolii*

**Pharmacopoeial Definition**
American ginseng root consists of the dried roots of *Panax quinquefolius* L. containing not less than 4.0% total ginsenosides calculated on a dried weight basis.

**Common Names**

- **English:** American ginseng, North American ginseng.
- **French:** Ginseng d’Amérique, ginseng d’Amérique du Nord.
- **Chinese:** 西洋參, xī yáng shèn (pinyin).
- **German:** Amerikanischer ginseng.

**History**

**Nomenclatural History**
The genus name *Panax* is derived from the Greek *pan*-, all and *akés*, a cure. Thus, *Panax* shares the same linguistic roots with *panacea* (Stearn 1996). The species name *quinquefolius*, originally spelled *quinquefolium* by Linnaeus, refers to the plant’s five-fingered leaves. *Quinquefolium* arose from Linnaeus’ treatment of *Panax* as neuter and continues to be frequently cited. According to the International Code of Botanical Nomenclature, however, *Panax* is treated as a masculine noun (McNeill et al. 2006). Hence, the species name should be spelled *quinquefolius*.

The common name “ginseng” was attributed to American ginseng due to its botanical relationship with Asian ginseng (*Panax ginseng*), with which it also shares similar medicinal properties. “Ginseng” is a corruption of the Chinese *ren shen* (人参), which literally means man-root. The Cherokee similarly referred to the herb as *yuwi usdi* or little man due to the often human-like shape of the root (Winston and Maimes 2007). The Huron-Iroquois name *garantogen* (gar-ent-oguen) also describes the “man-like” features of the root (Higby 2002; Rafinesque 1828).

**Native American Use**
American ginseng is a native North American medicinal plant. According to Moerman (1998), American ginseng was not among the most widely used of medicinal plants by Native Peoples, ranking low in the 2582 herbs cited. Indigenous use of American ginseng historically included the Penobschts, who reportedly used a tea of the root to increase a woman’s fertility (Speck 1917). The Cherokee gathered the root and used the decoction for headaches, as an expectorant, for cramps and “weakness of the womb” (Hamel and Chiltoskey 1975; Mooney 1891). The Creeks in northern Georgia believed American ginseng to be “a highly esteemed remedy” and drank an infusion of the root for shortness of breath, croup in children, coughing, and fevers (Swanton 1928). The Houma of Louisiana boiled the root as an antiemetic and mixed it with alcohol to treat rheumatism (Speck 1941). The Meskwi people used American ginseng as a panacea, believing that it gave other medicines greater power, considered it a “universal remedy” for children and adults, and also used it as a “love medicine” (Smith 1928). The Iroquois historically used the root for a long list of ailments, including vomiting, asthma, “bad blood,” poor appetite, as a wash for sore eyes and skin problems, and as a general tonic (Herrick 1995; Moerman 1998).

Undoubtedly, a number of the uses ascribed to Native peoples (e.g., palsy, thrush, etc.), especially to the Iroquois, have been adopted from the Chinese and, subsequently, European settlers, whereas the use of the plant as a love charm is more consistent with Native American tradition. When the plant was first found in the New World by French Jesuits, it was noted that the Iroquois did not particularly prize the herb. Subsequent to learning of the high regard placed on it by the Chinese, the Iroquois adopted its use as a panacea. Many native peoples gathered the roots to barter with white traders. It is unclear how much of the popularity of this root was based on traditional native usage, and how much was due to its high economic value to Asians (Millspaugh 1887; Vogel 1970). Benjamin Smith Barton, in his acclaimed *Medical Botany* (1810), noted that the Indians made tea from the leaves and the roots of American ginseng, but it did not appear that they “so highly esteem the Ginseng as their Tartar brethren in Asia do.” However, the Iroquois used American ginseng extensively and, like the Cherokee, often added it to strengthen the effects of other...
herbs (Herrick 1995), a practice that still persists (Winston 2010, personal communication to AHP, unreferenced).

American Ginseng and the Economic Development of America
American ginseng roots featured prominently in the early colonial development of America, as it was the first major export to the Orient. European colonists reportedly first became aware of American ginseng in 1715, after a Jesuit, Father Joseph François Lafitau (1681-1746), found it growing near Montreal, Canada (Pelchat 2003). Lafitau had read of “Chinese” ginseng in 1711 in what was the first written account of the plant by a Westerner, authored by a fellow Jesuit in China, Father Pierre Petrus Jartoux. Lafitau asked local Iroquois people if they knew the plant, but none responded favorably. After 3 months of intense searching, Lafitau happened upon the plant, with its full red berries, while walking from a house he was having built. His Iroquois housekeeper noted that it was “all over in the deep woods nearby” (Higby 2002).

Jartoux had learned of the importance of the root while surveying the area of the Changbai Shan mountain range in Northeastern China. Jartoux wrote a description of the plant in 1711. In 1718 he writes a description of the plant, noting its high value and suggesting that it may be found in other similar climates, most notably, in Canada.

Table 1 Historical timeline of the use of American ginseng root

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1709-1711</td>
<td>French Jesuit missionary Father Petrus Jartoux learns of the use of Asian ginseng in 1709 while in Manchuria. In 1711 he writes a description of the plant, noting its high value and suggesting that it may be found in other similar climates, most notably, in Canada.</td>
</tr>
<tr>
<td>1716</td>
<td>Another Jesuit, Father Lafitau, in Canada, reads the writings of Jartoux and after 3 months of searching finds American ginseng near Montreal, Canada.</td>
</tr>
<tr>
<td>1718</td>
<td>American ginseng trade begins in Montreal.</td>
</tr>
<tr>
<td>1738</td>
<td>Benjamin Franklin announces that “ginseng” has been found in the former British Colonies.</td>
</tr>
<tr>
<td>1753</td>
<td>Linnaeus names the American species of ginseng Panax quinquifolium.</td>
</tr>
<tr>
<td>1765</td>
<td>First entry of American ginseng into a Chinese materia medica, the Thoroughly Revised Materia Medica.</td>
</tr>
<tr>
<td>1784</td>
<td>George Washington reports in his diary meeting pack-horses carrying ginseng in Virginia. Thirty tons of American ginseng roots are shipped in the cargo ship, the Empress of China, from the American colonies to Guangzhou, China.</td>
</tr>
<tr>
<td>1801</td>
<td>American ginseng is included in the first American Herbal of Samuel Stearns, who reported that it was “beneficial in coughs, consumptions and spasmodic disorders.”</td>
</tr>
<tr>
<td>1842-1882</td>
<td>American ginseng root is included in the supplementary list of drug ingredients in the United States Pharmacopoeia (USP), then removed.</td>
</tr>
<tr>
<td>1890s</td>
<td>Concerns are raised for diminishing supply of the root. First state legislation restricts collection. American ginseng cultivation begins, as wild supplies continue to dwindle.</td>
</tr>
<tr>
<td>1905</td>
<td>King’s American Dispensatory, the standard text of Eclectic medical practitioners, reports on the use of the root “as a mild tonic and stimulant most effective over extended periods of time for nervous dyspepsia, mental exhaustion from overwork, nervous prostration, and cerebral anemia.”</td>
</tr>
<tr>
<td>2000</td>
<td>American ginseng is included in the Pharmacopoeia of the People’s Republic of China.</td>
</tr>
<tr>
<td>2005</td>
<td>American ginseng is included in the Dietary Supplements section of the United States Pharmacopoeia-National Formulary.</td>
</tr>
</tbody>
</table>

A description of ginseng was written in a publication of the French Jesuits and was subsequently translated into English and published in the Philosophical Transactions of the Royal Society of London in 1713. The same communication was republished in its entirety almost 100 years later in the 1809 edition of the Philosophical Transactions of the Royal Society of England. In his account Jartoux stated:

[It is in general between the 39th and 47th deg. of north latitude and between the 10th and 20th deg. of east longitude from the meridian of Pekin [Beijing]. There is a long tract of mountains, which the thick forests, that cover and encompass them, render almost impassable. On the declivities of these mountains, in thick forests, on the banks of torrents, or about the roots of trees, and amidst a thousand different sorts of plants, the ginseng is found. It is not to be met with in plains, valleys, marshes, the bottoms of rivulets, or in places too much exposed and open. If the forest take fire and be consumed, this plant does not appear till 2 or 3 years after; it also lies hid from the sun as much as possible; which shows us that heat is an enemy to it. All which makes me believe, that it is to be found in any other country in the world, it may be particular in Canada, where the forest and mountains, according to the relation of those that have lived there, very much resemble these here.

2 American Herbal Pharmacopoeia® • American Ginseng Root • 2012
Jartoux also provided detailed information of the medicinal virtues ascribed to the plant by the Chinese. After reading Jartoux’s description and months of searching, Lafitau found the North American species of Panax believing it to be the same plant as in China and “proof” of the land-bridge believed at that time to one connect North America and Asia. Lafitau sent a letter to the Duke of Orleans, noting his discovery, had the plant identified by a local botanist, who apparently believed it to be the same plant as that described by Jartoux, sent samples to Jartoux, who subsequently arranged for the import of American ginseng from Canada to China, and the North American ginseng trade began. Lafitau prepared an elaborate memoir on his discovery, Mémoire présenté à Son Altesse royale Monseigneur le duc d’Orléans . . . concernant la précieuse plante du gin-seng de Tartarie, découverte en Canada . . . . (Memoir submitted to His Royal Highness the Duke of Orleans . . . . regarding the precious Tartarian ginseng plant, discovered in Canada) (1718). Two hundred years later, the noted pharmaceutical historian Edward Kremers described Lafitau’s memoir on American ginseng as “the first printed contribution to American materia medica” (Higby 2002).

American ginseng was subsequently recognized and referred to by some of the most prominent leaders of early US history. It was none other than Benjamin Franklin who announced the availability of ginseng as occurring in the “British Colonies” (Franklin 1738). In 1784, on a trip west to his lands on the Kanawha River in what is now West Virginia, George Washington wrote in his diary: “I meet with many mules and packs laden with ginseng going east over the Forbes-Braddock Road.”

After the split from England, the American Colonists had few trading partners and still had to pay their debt to France for France’s support of the American Revolutionary War. Upon learning of the value of ginseng to the Chinese, a cargo ship, the Empress of China, partially owned by Robert Morris, a signer of the Declaration of Independence, was commissioned by merchants of New York and Philadelphia in 1784, stocked with 30 tons of ginseng roots, and shipped to Guangzhou, China. The ship’s surgeon, Dr. Robert Johnston, had the dubious task of collecting the roots. Part of the success of the American ginseng trade was that in 1699 the Manchu Emperor enacted strict decrees to forbid private harvesting of Chinese ginseng roots, which placed government control over the Chinese ginseng trade. During the rule of the Kangxi Qing dynasty (1662-1722) tens of thousands of people were sent east of Shanhaiguan to look for the root. This led to a significant decline in supplies in China, paving the way for American supplies to fill the void, sometimes being declared as authentic Chinese ginseng. Eventually, the value in American ginseng grew into its own, fueling the developing American economy from the streets of New York and Philadelphia to the backwoods of Virginia and Kentucky. As today, China was the primary source of exportation where it continues to be highly valued, at one time being referred to as “green gold.” Based on government data, it is estimated that between 1790 and 1890 more than 31,000,000 pounds were exported (Higby 2002), almost driv-
ed through Guangzhou, a seaport near Hong Kong known for its subtropical climate. This might have led to the belief by folk doctors that American ginseng is more yīn, since it was assumed to come from the south.

American ginseng was official in the **United States Pharmacopeia** (USP) from 1842 to 1882 but always occupied a place on the secondary list of remedies. It was also included in the **United States Dispensatory** (USD) from the 1st edition in 1833 to the 24th edition in 1947, though the USD reported: “The extraordinary medicinal virtues formerly ascribed to ginseng had no other existence than in the imagination of the Chinese. It is little more than a demulcent, and in this country is rarely employed as a medicine.” Further, however, the USD reports on experiments demonstrating both sedative and stimulating effects (Wood and Lawall 1937). American ginseng is currently included in the USP (USP34 2010a) and in the **Pharmacopoeia of the People’s Republic of China** (PPRC 2005) but is absent from the **European Pharmacopoeia, Korean Pharmacopoeia, Japanese Pharmacopoeia**, and most other international pharmacopoeias.

---

### Identification

**Botanical Identification**

*Panax quinquefolius* L. Herbaceous perennial from branched taproot; aromatic due to the presence of volatile oils. **Stem**: Erect, simple (rarely branched), 1-6 dm tall. **Leaves**: One whorl of 3-5 leaves, each palmately-compound, petiolate; leaflets (3-)5(-7), petiolulate, blade oblong to obovate, 6-15 cm long, (2-)2.5-8 cm wide, central leaflets larger than the lateral; margin serrate or dentate; apex abruptly or boldly acuminate. **Inflorescence**: Umbel, terminal, solitary; peduncle 1-25 cm long; 6-20-flowered. **Flowers**: Perfect, radially symmetric, with a nectariferous disc on top of the ovary; sepals 0-5, 0.2 mm long, triangular, persistent; petals 5, white or greenish, 0.5-1 mm long, valvate, erect, apices acute and inflexed, caducous; stamens 5, inserted onto disc alternate with petals, spreading; ovary 2-carpellate, inferior, styles (1-)2(-3), 1-2 mm long. **Fruit**: Drupe, approximately 10 mm in diameter, bright red; seeds 1-3, creamy-white, hemispherical, 5-6 mm long, 4-5 mm wide. **Chromosome number**: 2n = 44, 48.

**Distribution**: Rich woods in well-drained soil. Plants emerge in late April to early May, flower from June to July, and fruit from mid-August to September. From the northeastern United States and adjacent Canada, west to South Dakota, and south to Oklahoma and Georgia. This species is considered threatened or endangered in many states (see Species Conservation) (Gleason and Cronquist 1991; Hu et al. 1980; Linnaeus 1753 [original citation]; McGregor et al. 1986; Proctor and Bailey 1987; Xiang and Lowry 2008; Schlessman 1985; Thompson 1987; Zomlefer 1994).

---

![Figure 2 American ginseng’s life cycle](image-url)
Figure 3  Botanical characteristics of American ginseng (*Panax quinquefolius* L.)

3a. One-year-old (single-pronged) American ginseng plant in its natural habitat.
3b. A group of young American ginseng plants in natural habitat.
3c. Two-pronged stage of American ginseng.
3d. Three-pronged stage of American ginseng.
3e. A mature flowering American ginseng plant.
Figure 3 (continued) Botanical characteristics of American ginseng (*Panax quinquefolius* L.)

3f. Flower spike of American ginseng beginning to blossom in early summer.

3g. Mature, ready-to-harvest, American ginseng plant with ripe fruit.

3h. Close-up of American ginseng fruit.

3i. Roots of 1, 2, and 3-year-old (from left to right, in pairs) woods-cultivated American ginseng plants.

3j. Distribution range of wild American ginseng.

Photographs courtesy of: (3a, b, e, g, h) © 2012 Steven Foster; (3c, d, f) James W. Wallace, Jr.; (3i) Kim Fadiman; (3j) USDA Plants Database. Photos (3c, d, g, i) from *Growing & Marketing Ginseng, Goldenseal & Other Woodland Medicinals* (Persons and Davis 2005), © 2005 Bright Mountain Books, Fairview, NC, used with permission.
Macroscopic Identification

Field-cultivated American ginseng roots: Field-cultivated roots occur in dried form, with lateral roots removed, or as the rootlets (“fiber”) traded alone. The roots vary considerably in appearance, depending on the age of the plant at the time of harvesting, the drying temperature, and the cultivation process. Cultivated American ginseng roots are graded by the guidelines established by the United States Department of Agriculture (USDA) (size, percentage of defects) or by those established by the National Standard of the People’s Republic of China (see Qualitative Differentiation and Tables and Figure therein).

Whole field-cultivated roots are 3-20(-24) cm long and 0.5-2.2(-3.4) cm in diameter. The average weight of an individual root is 10-12 g. Between the annual aerial stem and the root occasionally present is a slender vertical rhizome bearing scars from past stems. The number of scars and the length of the rhizome correspond with the age of the root. Where the rhizome attaches to the root, the root widens abruptly and becomes ovoid, cylindrical, or spindle-shaped. At the base, it is often divided into 2-3 equal branches. Some cultivated roots, called “spider” or “octopus” roots, have multiple branches without the main body; such roots are presumably formed after the main root is destroyed by pathogenic Rhizoctonia spp. and are of considerably lower value.

The roots are yellowish-brown to dark brown on the outside, often with vertical creases and annular wrinkles of various depths that are densest towards the root crown. The fracture is short and starchy. In cross section, the bark is thin with reddish-brown secretory cavities, and the cortex and stele are a pale yellowish-white with darker annular markings and reddish-brown secretory cavities. The wood is arranged radially, with wide medullary rays. It is light, hard, and sticky to the touch.

American ginseng roots are also occasionally traded in their fresh form. The macroscopic characteristics of fresh roots are similar to those of the dried, except that fresh roots are smoother, lighter in color, and higher in weight due to retained moisture.

Woods-grown American ginseng roots: These are generally larger, longer, and thinner than field-cultivated American ginseng, more wrinkled, and with a higher number of branches and rootlets. A typical woods-grown root weighs 6-8 g. Woods-grown roots are almost exclusively sold intact.

Wild-simulated American ginseng roots: Cultivated American ginseng roots are usually smoother, lighter in color, larger, and denser compared to wild roots of the same age. Cultivated roots are typically sweeter in taste, while wild roots are more bitter. When cooked, wild roots often retain enough flavor to be boiled for a 2nd time, while cultivated roots can be boiled only once (Chung 2011, personal communication to AHP, unreferenced).

Macroscopic and Organoleptic Differences between Wild and Cultivated American Ginseng Roots

Wild-simulated American ginseng roots of varying morphology, depending on the intensity of the cultivation practices used. The roots range in their characteristics from being reminiscent of woods-cultivated roots to those that are indistinguishable from true wild roots. Wild-simulated roots are almost exclusively sold intact.

Wild American ginseng roots: Wild roots are generally the smallest of the American ginseng roots on the market. First year roots are 25-50 mm in diameter and can double or triple in size in the first few years of growth until the plant begins to seed, at which time growth slows to about 20% per year. Plants can live for more than 100 years (see Figure 25). The oldest root ever recorded was 182 years old. Each year, the base of the aerial stem detaches from the rhizome just below the ground level. This leaves the characteristic root scars that form the “neck” (rhizome), which can be used to determine the age of the root (USFWS 2011a). The roots are yellowish-white to beige, short, squat, fleshy, and fusiform (spindle-shaped), 5-12 cm long, 1-2.5 cm in diameter. The roots are often transversely wrinkled and have irregular bumps throughout. Younger roots are round, often with thinner rootlets emerging, while older roots are often branched, demonstrating the human-like shape. The cross section of the root shows a hard central portion surrounded by a thick, soft, white inner cortical layer with thin bark containing numerous reddish resin cells; the wood wedges are narrow, while the medullary rays are broad (Remington et al. 1918; Sayre 1917). The average weight of wild root is 1.5-2 g. Wild roots are always sold intact.

Cut root: Cultivated American ginseng root is also traded in transversely cut slices or cut in pieces of various sizes. “Fiber,” “fibrous roots,” or “parts of root”: This is the finest fraction of the roots (usually cultivated) that is separated by means of a sieve while tumbling the whole roots and consists of pieces of rootlets and ends of main roots 2-25 millimeters long. Up to 20% of root harvest by weight consists of this fraction. While considered an inferior grade of American ginseng, the rootlets contain higher concentration of ginsenosides than the main roots (see Table 13).

Powder: Creamy white with flecks of light brown.

Organoleptic Profile

Aroma: Sweet, spicy, characteristic of Araliaceae.
Taste: Faintly aromatic, initially bitter and earthy, then slightly sweet, somewhat gelatinous.

Macroscopic and Organoleptic Differentiation of American Ginseng Roots Grown in Different Regions

Chinese-grown American ginseng roots compared to those cultivated in North America can often be differentiated by the surface color of the root and the color of the cross section. Chinese-grown roots tend to have skin that is smoother and lighter in color, while their cross section is often slightly more yellow and less creamy-white than American-grown roots. The above characteristics largely depend on soil type and post-harvest handling. Dried American-grown American ginseng roots tend to have a considerably more potent odor and a more bitter-earthly initial taste followed by sweetness, compared to Chinese-grown roots. Canadian and Chinese-grown American ginseng roots are characterized by a strong overall sweetness (see Qualitative Differentiation).
Figure 4  Macroscopic characteristics of field-cultivated American ginseng roots

4b. Three-year-old Canadian-grown American ginseng roots.
4c. Four-year-old Canadian grown American ginseng roots.
4d. Cut American ginseng roots, packaged in Taiwan.
4f. Transverse section of American ginseng root.

Photographs courtesy of: (4a-e) American Herbal Pharmacopoeia, Scotts Valley, CA; (4f) Reinhard Länger, AGES PharmMed, Vienna, Austria.
Macroscopic and Organoleptic Differentiation of American ginseng from Asian ginseng

American ginseng roots tend to have very dense and irregular striations on the root body while Asian ginseng tends to have more spaced out, straighter, and rounder striations. The neck of American ginseng is generally shorter than that of Asian ginseng. The taste and the aroma of the two species are similar, but both can be differentiated by appropriate training or by using botanical reference materials for comparison. Generally speaking, American ginseng has a stronger bitter aftertaste than Asian ginseng, while Asian ginseng has a more pronounced initial sweetness compared to American ginseng. American and Asian ginseng plants that are grown together can hybridize, and the hybrids cannot be easily differentiated. For a definitive determination of the root species, chemical differentiation is recommended (see Analytical section).

Figure 5 Macroscopic characteristics of woods-cultivated American ginseng roots

5a. Four-year-old, heavily fertilized, woods-cultivated roots.
5b. Older, high-grade, woods-cultivated roots.
5c. Close-up of a woods-grown American ginseng root.
5d. Seven-year-old wild-simulated roots, showing dense horizontal striations, a desirable characteristic.

Photographs courtesy of: (5a, b, d) Mark Haskett, from the collection of Dr. W. Scott Pearsons, Tuckasegee Valley Ginseng, used with permission; (5c) American Herbal Pharmacopoeia, Scotts Valley, CA.
Figure 6  Wild American ginseng roots
Photographs (6a-f) courtesy of © 2012 Steven Foster; (6g) American Herbal Pharmacopoeia, Scotts Valley CA.
Microscopic Identification

Transverse section: Cork thin, composed of thin-walled, regularly arranged parenchyma cells; phelloderm thin, consisting of tangentially elongated, slightly thickened cells; inside the phelloderm is a layer of parenchyma with no medullary rays; secondary phloem of narrow gray zones indicating sieve cells and companion cells, separated by broad medullary rays of large roundish parenchyma cells; secretory ducts up to 80 µm diameter, frequently filled with orange oil droplets or yellow-brown secretions, are scattered in the cortex and secondary phloem; secondary xylem of narrow strands of vessels separated by broad medullary rays; vessels up to 50 µm diameter; primary xylem of small vessels occurs in the center of the root; calcium oxalate cluster crystals up to 50 µm diameter or, occasionally, prisms present in parenchyma of all tissues except cork; fibers and sclereids are lacking throughout.

Longitudinal section: Vessels with reticulate or scalariform wall thickening.

Starch: Abundant in all parenchyma cells; granules simple or compound in aggregates of 2-4 granules, individual granules roundish or slightly angular in outline, up to 15 µm diameter; larger granules have a central hilum or slit.

Powder: Fragments of cork in surface view; parenchyma cells, some with yellow-brown secretions or calcium oxalate cluster crystals; occasional calcium oxalate prisms; secretory ducts in longitudinal section filled with orange-brown secretions; vessels with reticulate or scalariform wall thickenings; starch.

Wild, wild-simulated, woods-grown, and field-cultivated roots of American ginseng are microscopically identical. American ginseng roots are microscopically indistinguishable from Asian ginseng (P. ginseng) roots.

Figure 7 Microscopic characteristics of American ginseng roots

7a.  Root transverse section (ts): ck = cork; sd = secretory duct; sp = secondary phloem; cam = vascular cambium; sx = secondary xylem; px = primary xylem.
7b.  Root transverse section: cork (top), cork cambium, and phelloderm of somewhat thickened cells.
7c.  Secretory duct and surrounding parenchyma (ts).
7d.  Vessels in the secondary xylem (ts).
7e.  Starch granules.

Microscopic drawings courtesy of Reinhard Länger, AGES PharmMed, Vienna, Austria.
Figure 8  Microscopic characteristics of American ginseng roots

8a. Root transverse section: cork; parenchyma with secretory ducts; secondary phloem showing narrow strands of conducting tissue separated by broad medullary rays.

8b. Cork (red), cork cambium, phelloderm, and parenchyma with a secretory duct (ts).

8c. Root transverse section: secondary phloem (left); vascular cambium; and secondary xylem showing narrow strands of vessels separated by broad medullary rays.

8d. Cambial region with secondary phloem to the outside (top) and secondary xylem with vessels to the inside (ts).

8e. Secretory duct with orange contents in the parenchyma inside the phelloderm (ts).

8f. Calcium oxalate cluster crystal in the parenchyma inside the phelloderm (ts).

8g. Scalariform vessel (ls).

8h. Starch granules.

ls = longitudinal section; ts = transverse section.

Microscopic photographs courtesy of Reinhard Länger, AGES PharmMed, Vienna, Austria.
Commercial Sources and Handling

Commercially available American ginseng comes from wild and cultivated sources. The majority of marketed American ginseng roots are cultivated.

Wild American ginseng is native to eastern North America. The most expensive and highly regarded American ginseng is harvested from the wild. Wild and especially older, larger wild American ginseng roots are considered of superior quality in traditional Chinese medicine. It has long been assumed that wild roots have higher ginsenoside levels than cultivated roots, however, recent scientific data suggest that this is not always the case (see Constituents).

Wild-harvested roots account for less than 10% of total American ginseng roots exported from the United States (USFWS 2011b). Out of these, almost one fourth of the wild American ginseng harvested in the US comes from Kentucky, with smaller amounts coming from Tennessee, North Carolina, West Virginia, Indiana, Virginia, and Ohio, in descending order. Collection of wild American ginseng is currently illegal in Canada.

There are 3 different types of cultivated American ginseng roots: field-cultivated, woods-grown, and wild-simulated (Table 2). American ginseng is cultivated commercially in the US, Canada (mainly Ontario), northern and northeast China as well as throughout other parts of the world ranging from Australia to Poland to South America (Leung and Foster 1996; Ludwiczuk et al. 2002; Schweins and Sonnenborn 1994; Tyler et al. 1988; Wills and Stuart 2001). Ontario is the largest producer of field-cultivated American ginseng root in North America (6100 total acres). In the US, more than 90% of field-cultivated American ginseng comes from Marathon County, Wisconsin (USFWS 2010), while Michigan is the leading state in woods-cultivated American ginseng production (Hausbeck 2007).

There is a plethora of information on all aspects of American ginseng production readily available online (e.g., field-cultivated: BCMAFF 2003, OMAFRA 2011; woods-

grown: Beyfuss 2002; wild-simulated: Carroll and Apsley 2011; Hankins 2011). Following are the basic guidelines for harvesting, cultivation, and processing of American ginseng root.

Collection

The practices employed for collection of American ginseng root depend on the source of the roots: whether they are wild, woods-grown, or field-cultivated.

Wild American Ginseng

Wild roots are harvested from mature 5-year-old plants in the late summer to early fall, after the top growth begins to die back and the plant has produced viable seed, the primary means of reproduction. Wild roots should be gathered only from at least 3-pronged plants that are 5 or more years old (see Determining the Age of an American Ginseng Plant) to allow the plant to develop its complete reproductive maturity and contribute to the reseeding of native populations.

| Table 2 Sources of American ginseng roots by cultivation type and intensity |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Propagation                     | Naturally occurring | Seeds and rootlets planted, often from local plants only | Seeds and rootlets planted | Seeds, seedlings, and rootlets planted |
| Production site                 | Native habitat | Native habitat | In woods similar to native habitat | Grown in fields with artificial shading |
| Cultivation                     | None | None to minimal site preparation, e.g., clearing | Raised beds, tillage, herbicide and mulch application | Intensive cultivation, including soil fumigation, fertilization, and irrigation |
| Use of Fungicide                | None | None to minimal | Common | Extensive |
| Harvest Method                  | Dug by hand | Dug by hand | Dug by hand | Mechanical |
| Price (grade)                   | Highest | Highest to high | Medium | Low |

Determining the age of an American ginseng plant or root

Two methods can be employed for determining the approximate age of the plant. The first is by counting the number of branching leaf stalks (prongs), which increase in number with age. Seedlings have only a single prong consisting of 3 leaflets. The next phase has 2 prongs with 3-5 leaflets on each; mature plants have 3-4 prongs consisting of 5 leaflets each. The second method is by moving the soil away from the root crown and counting the number of bud scale scars at the top of the root, each scar representing one growing season. By the 5th year, the root is approximately the size of a little finger. There should be a minimum of 4 neck rings if roots are to be harvested. The point of attachment of the rhizome to the root crown counts for the 1st year of growth. However, under certain environmental conditions plants can go dormant and not grow out the aerial portion for 1 or more years (Persons and Davis 2005; USFWS 2011a).
However, typically, wild roots are gathered after 8 or more years to allow for the development of the root to a sufficient marketable size. The seeds from the harvested plants should be planted at the site of harvest (some states also specify the distance from the parent plant), to maintain the integrity of that population, at the soil depth of 20-25 mm (¾-1 inch) (McGraw et al. 2005). Another practice worthy of consideration is to break the stems of or remove the foliage from unharvested, fully senesced plants to prevent other pickers from removing the plants left by a previous picker.

When digging the root, a circle with an approximate radius of 12 cm (5 inches) is dug around the base of the plant. The root ball is lifted out, and the soil is loosened away from the root, taking care not to break the rootlets. If insufficiently mature roots are found, these should be replanted. Collection of wild roots is done by hand and should be conducted following federal and state laws and regulations as well as with a commitment to sustainability of the natural populations and habitat (see Checklist for American Ginseng Stewardship and Species Conservation).

Modification from AHPA (2011).

In addition to allowing plants to produce viable seeds, harvesting in late summer/fall allows the roots to fully develop their ginsenoside profile. The roots are also at their heaviest in the season. As the foliage senescence, it adds about 2% additional weight to the roots (Persons and Davis 2005). One study (Reynolds 1998a) suggested that roots harvested in late fall yield higher amounts of ginsenosides. Studies demonstrate that ginsenoside content increases with age and weight of roots, increasing from 3% in 1-year old roots to 8% in the 4th year (Court et al. 1996b) (see Table 3). Harvesting after the foliage has begun to die back is particularly significant for field-grown American ginseng, where harvests of 3000-4000 dry lbs/acre are not uncommon. Spring or early summer harvested roots also tend to have undesirable vertical creases, disparaged by buyers as “spring roots” (Persons and Davis 2005). Total ginsenoside levels have been shown to decline by as much as 14% after mid-September and by November (OMAFRA 2011).

### Table 3. Influence of root age on root weight and ginsenoside content in field-cultivated American ginseng roots

<table>
<thead>
<tr>
<th>Root age (years)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Root mass (g)*</td>
<td>0.29</td>
<td>1.89</td>
<td>3.79</td>
<td>12.09</td>
</tr>
<tr>
<td>Ginsenosides (mg/g dry weight)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rb1</td>
<td>4.75</td>
<td>11.37</td>
<td>13.65</td>
<td>19.27</td>
</tr>
<tr>
<td>mRb1</td>
<td>4.85</td>
<td>14.44</td>
<td>15.68</td>
<td>22.51</td>
</tr>
<tr>
<td>Rb2</td>
<td>0.44</td>
<td>0.40</td>
<td>0.39</td>
<td>0.43</td>
</tr>
<tr>
<td>mRb2</td>
<td>0.27</td>
<td>0.38</td>
<td>0.31</td>
<td>0.33</td>
</tr>
<tr>
<td>Rc</td>
<td>2.43</td>
<td>2.24</td>
<td>2.21</td>
<td>2.49</td>
</tr>
<tr>
<td>mRc</td>
<td>1.24</td>
<td>1.72</td>
<td>1.57</td>
<td>1.76</td>
</tr>
<tr>
<td>Rd</td>
<td>2.77</td>
<td>4.00</td>
<td>3.07</td>
<td>4.11</td>
</tr>
<tr>
<td>mRd</td>
<td>1.76</td>
<td>4.18</td>
<td>3.25</td>
<td>4.30</td>
</tr>
<tr>
<td>Re</td>
<td>8.24</td>
<td>11.23</td>
<td>12.50</td>
<td>15.34</td>
</tr>
<tr>
<td>Rg1</td>
<td>1.58</td>
<td>1.66</td>
<td>1.84</td>
<td>1.64</td>
</tr>
<tr>
<td>Ro</td>
<td>1.68</td>
<td>2.38</td>
<td>2.87</td>
<td>4.28</td>
</tr>
<tr>
<td>Total</td>
<td>30.30</td>
<td>54.30</td>
<td>57.75</td>
<td>77.10</td>
</tr>
</tbody>
</table>

*Average of 2 different harvest years.
Source: Court et al. (1996b).

### Field-Cultivated American Ginseng

Field-cultivated (or field-grown) American ginseng roots are typically harvested mechanically, with modified potato harvesters, at 3-4 years of age. Studies demonstrate that ginsenoside content increases with age and weight of roots, increasing from 3% in 1-year-old roots to 8% in the 4th year (Court et al. 1996b) (see Table 3). Harvesting after the foliage has begun to die back is particularly significant for field-grown American ginseng, where harvests of 3000-4000 dry lbs/acre are not uncommon. Spring or early summer harvested roots also tend to have undesirable vertical creases, disparaged by buyers as “spring roots” (Persons and Davis 2005). Total ginsenoside levels have been shown to decline by as much as 14% after mid-September and by November (OMAFRA 2011).

### Wild-Simulated American Ginseng

A subset of woods-cultivated American ginseng is referred to as “wild-simulated.” This production method accounts for some (or most) of what is marketed as wild American ginseng. Wild-simulated roots are harvested by hand. Yields of about 160 lbs/acre dry weight can be expected.

Current industry reporting mechanisms are insufficient to accommodate the complex range of husbandry practices used, which often result in “wild-appearing” roots (Burkhart 2011). American ginseng that is intentionally grown in a wild-simulated manner is usually reported as wild. It is often impossible to visually distinguish between the two. For export purposes, wild-simulated American ginseng roots are considered equivalent to wild (USFWS 2010).

### Woods-Grown American Ginseng

These roots are typically harvested at 6-9 years and are dug by hand. A yield of up to 600 dry lbs/acre is possible; however, it largely depends on a variety of factors, such as planting density, plant diseases, and pest control. Longer growth time will result in roots of a higher quality, with an intermediate dollar value between field-cultivated and wild roots (Persons and Davis 2005).
Concerns regarding dwindling populations of American ginseng due to overharvesting existed in the late 1800s (e.g., Kains 1899). This trend has continued throughout much of the 20th century. Since 1975, the international trade of wild and wild-simulated American ginseng has been subject to regulation under the Convention on International Trade in Endangered Species of Wild Flora and Fauna (USFWS 2009).

Collection of wild American ginseng is currently illegal in Canada. In the US, the Fish and Wildlife Service (FWS) of the Department of the Interior releases annual or biennial reports on the status of the species, including a statement whether the collection of wild American ginseng roots for export in the respective year(s) will be detrimental to the survival of the species. Non-detrimental finding in the report is required to legally export wild American ginseng roots in the respective year. The most recent finding (USFWS 2009) governs exports for the 2009 and 2010 harvest seasons and requires roots to be at least 5 years old to be lawfully harvested in one of the 19 states that have American ginseng harvest programs.

American ginseng is included in sensitive species (candidates for “endangered” or “threatened” status) lists of most Forest Service regions where it occurs (USFWS 2009). Few National Forests in the Eastern and Southern regions issue American ginseng harvest permits. On non-federal lands, the management of American ginseng is under jurisdictions of respective states. As of 2009, under state laws or regulations, American ginseng is considered “threatened,” “endangered,” or “rare” in Louisiana, Maine, Michigan, Nebraska, New Hampshire, Rhode Island, South Carolina, and Virginia (though, with the exception of Virginia, none of these states contribute to the export market). American ginseng is classed as “exploitable vulnerable” or “vulnerable” in New York and Pennsylvania, “a species of concern” in New Jersey, “of special concern” or “of regional concern” in Connecticut, Georgia, Massachusetts, Minnesota, North Carolina, South Carolina, and Tennessee, “a species of conservation” in Delaware, is on the watch list of Maryland, Mississippi, North Carolina, Oklahoma, Vermont, and Virginia, and “historical (possibly extirpated)” in the District of Columbia.

As of 2010, 19 US states, in which American ginseng occurs, had management programs in place governing the harvesting and sale of American ginseng, namely, Alabama, Arkansas, Georgia, Illinois, Indiana, Iowa, Kentucky, Maryland, Minnesota, Missouri, New York, North Carolina, Ohio, Pennsylvania, Tennessee, Vermont, Virginia, West Virginia, and Wisconsin (USFWS 2009). Regulations vary from state to state, but the majority of the states do not allow collection of the root on state lands and limit the harvest season to the fall and early winter. All states restrict harvesting to only mature plants and require seeds to be planted at the harvest site. Due to the high dollar value of the crop, poaching is a significant problem. Apart from poaching, habitat destruction remains the primary threat to the continued supply of wild plants.

NatureServe, a non-profit conservation organization, assigns conservation status to American ginseng at the global, national, and state levels. As of 2011, American ginseng had a “vulnerable” rounded global ranking, “vulnerable to apparently secure” in the US, and “imperiled to vulnerable” in Canada. Among the US states, the species was considered “critically imperiled” in Kansas, Louisiana, Nebraska, Oklahoma, Rhode Island, and South Dakota, “imperiled” in Delaware, New Hampshire, and New Jersey, and “imperiled to vulnerable” in Michigan. None of the above states are commercial sources of wild American ginseng. Further, American ginseng is listed as “vulnerable” in Connecticut, Georgia, Illinois, Indiana, Iowa, Maine, Maryland, Massachusetts, Minnesota, Mississippi, and Vermont, “vulnerable to apparently secure” in Kentucky, New York, Tennessee, Virginia, and West Virginia, and “apparently secure” in Alabama, Arkansas, Missouri, North Carolina, Pennsylvania, South Carolina, and Wisconsin (NatureServe 2011).

To preserve the existing populations, the seeds from the harvested plants should be reseeded directly into the same area at a soil depth of 20-25 mm (¾-1 inch) (McGraw et al. 2005). Traditionally, the Cherokee dug a small hole at the base of the plant prior to harvesting the root. They would bend the stalk, place the fruiting head in a hole at the base of the plant, and cover it with soil, before detaching the stem from the root (Harding 1908).

Market preference for wild American ginseng adds to the threat to wild populations of this species. Luckily, Asian users, in particular, believe that older, wild roots are more potent medicinally than cultivated roots, and this provides an economic incentive for allowing plants to grow and seed for long periods of time. The growing popularity of woods-grown and wild-simulated production methods may also lessen the demand for wild American ginseng by increasing the availability of more affordable high-grade roots. In addition, further research into the medicinal properties of the aerial, renewable, portions of the plant should be encouraged since the leaves are a significant source of several ginsenosides (see Constituents and Table 14 therein).

### Cultivation

American ginseng requires a certain level of shade and prefers deep, loamy, well-drained, moist, acidic soil (pH near 5.5) that is rich in organic matter and has calcium available at over 2000 lbs/acre (2240 kg/ha) (Persons and Davis 2005). There are 2 main systems for growing American ginseng commercially: field cultivation and woods-grown production. A third system, the wild-simulated production method, is gaining in popularity; however, since it is virtually impossible to distinguish between wild and high-quality wild-simulated roots, the amount of wild-simulated American ginseng roots currently produced cannot be assessed, and, for export purposes, wild-simulated roots are considered equivalent to wild.

#### Field-Cultivated American Ginseng

The soil for American ginseng growth should be very well drained. A slope can improve drainage, and a northern
or eastern exposure is ideal to minimize direct sun. Field-cultivated American ginseng typically utilizes raised beds with domed tops and artificial shade made from woven polypropylene plastic fabric or, less frequently, wood lathe. Occasionally, growers will grow a shade crop, such as birch trees, to provide the necessary shade. In North America American ginseng is grown primarily near Waterford, Ontario, in Canada and in Marathon County, Wisconsin.

Site preparation for field cultivation of American ginseng usually begins at least a year before the seed is planted. Fields are selected that are well drained and have no previous recent history of American ginseng being grown. Extensive soil tests are conducted to determine fertility, pH, and organic matter. Large amounts of cow manure are applied to the soil with more manure added in the spring of the planting year. Turkey manure is also used to supplement the soil. Typically, a cover crop, such as winter rye, is planted in late summer the year prior to planting American ginseng seed. The rye is allowed to grow until the following May when it is cut and either harvested as baled hay or plowed under to increase the levels of organic matter in the soil. Other cover crops include buckwheat, ryegrass, sweet clover, red clover, or hairy vetch (OMAFRA 2011). Another practice that has become popular is planting pearl millet a year prior to American ginseng to reduce nematode populations. The millet is mowed twice before fall frost.

Soil nutrient levels have a significant effect on the ginsenoside content of both the roots and leaves of American ginseng. Li TSC et al. (1996) analyzed variations in ginsenoside content of American ginseng root and leaf cultivated in 9 different locations in British Columbia. Their results indicated that levels of nitrogen (N) in the soil positively correlated with ginsenoside Rd and total ginsenosides in the root, while negatively correlating with ginsenoside Rb1, levels in the leaf. Leaf contents of ginsenosides Rb1 and Rc were negatively correlated with soil content of magnesium (Mg). Also, increased calcium (Ca) negatively affected Rb1 levels in the leaf only. The authors advise that N fertilization of American ginseng should be carried out cautiously.

Fertilizer is applied based on complete soil analyses of each individual field, and soil pH is adjusted to 5.5-6.5 by adding agricultural lime or sulfur, as necessary. Soil fumigation is usually performed 4-6 weeks prior to planting American ginseng seed, using vorlex Plus, dazomet (Basamid®), vapam, or 1,3-dichloropropene and chloropicrin (Telone®) (OMAFRA 2011). Raised beds are next formed with mechanical bed makers, and the shade-cloth-bearing posts and cables are erected.

Seeding is usually done from August to September (after the rye or wheat harvest) at a rate of 80-120 lbs of seed per acre, which approximately equals to 25 seeds per square foot of raised bed. Planted beds are immediately mulched with 2-4 inches of rye, wheat, or oat straw. Seedlings generally emerge in May. Due to its high planting density and intensive cultivation techniques, field-cultivated American ginseng is routinely treated with numerous applications of fungicides, insecticides, molluscicides, rodenticides, and herbicides throughout its 3-4 year growing cycle. Few agronomic practices, such as fumigation, are used to control pests and diseases. However, the use of herbicides is limited to prevent damage to the ginseng plants.

In the second system of growing American ginseng commercially called “wood-cultivated” or “woods-grown” and utilizes an existing tree canopy in a forested environment, to provide the required shade. Woodland sites are selected that may have previously harbored wild American ginseng, since American ginseng will usually grow better in such environments (Beyfuss 1998). Common forest types utilized for wood-cultivated American ginseng are sugar maple/beech forest associations in the northern part of the plant’s range, i.e., PA to Canada, and black walnut/tulip poplar/white oak/hickory in the south. In wooded areas where no American ginseng is present, potential growers often utilize an evaluation tool such as the Beyfuss’ “Visual Site Assessment and Grading Criteria for Potential Woodland Ginseng Growing Operation” (Beyfuss 2011). For optimal growth, American ginseng requires 100-125 cm (40-50 inches) of rain annually and a mean temperature of 15.5 ºC (60 ºF) with several weeks of cold for dormancy (Norfolk Ginseng Corp 1995).

Wood-cultivated American ginseng is also planted in late summer or fall, following as much as a year of site preparation that involves raised bed formation, frequent tillage to kill weeds, and herbicide applications. Soils for production of wood-cultivated American ginseng, however, are not usually fumigated, since the fumigant might kill or damage the shade-providing trees. Raised beds are also mulched with straw or other organic mulch, as in the case of field-cultivated American ginseng. Wood-cultivated American ginseng is rarely fertilized, since optimal rates of nutrients are not known for this crop under these growing conditions. Some growers will add lime to raise soil pH (Beyfuss 1998), phosphorus if that is a limiting factor in the soils (Davis 2011, personal communication to AHP, unreferenced), or gypsum if they want to increase calcium levels without affecting soil pH (Persons and Davis 2005).

Wood-cultivated American ginseng is often plagued by the same pests and diseases as field-cultivated American ginseng, and most large-scale growers routinely apply many of the same pesticides throughout the growing cycle. The crop is usually harvested by hand after 6-9 years of growth. Wood-cultivated American ginseng visually resembles wild American ginseng more than field-cultivated American ginseng does, and this appearance commands a higher price for the growers. Ginsenoside levels do not increase indefinitely, at least in the field-cultivated roots, and appear to level off after the 6th year (OMAFRA 2011). However, the root mass continues to increase and macroscopic characteristics of the roots continue to improve, so, older roots are considered subjectively to be of a higher quality (Persons and Davis 2005). Yields of wood-cultivated American ginseng roots
Figure 9 Field cultivation of American ginseng root

9a-c. Different growing stages of field-cultivated American ginseng at the production site in Canada.
9d. Harvesting of field-cultivated American ginseng root.
9e. Large-scale washer employed for field-cultivated American ginseng root.
9f. American ginseng roots packed in cardboard drums.

Photographs courtesy of: (9a, b, d, e) Ontario Ginseng Growers Association, Simcoe, Ontario, Canada; (9c) © 2012 Steven Foster; (9f) Roy Upton, Soquel, CA.
are significantly lower compared to the field-cultivated roots, ranging up to about 1200 lbs/acre (Persons and Davis 2005).

Wild-Simulated American Ginseng

Wild-simulated American ginseng is grown under a variety of methods that seek to mimic the natural cycle of the plant. In the simplest form, American ginseng harvesters revisit the sites they dig when the berries are ripe, and carefully plant the berries at optimal depth. This practice alone significantly improves survival of populations, since American ginseng berries are often consumed by deer and other forest animals (Farrington et al. 2009), and seeds will dry out and lose viability if they do not become covered by soil or leaf litter. In some situations commercial seed, either from field- or woods-cultivated operations, is used to supplement or expand the natural populations.

Wild-simulated growers utilize hand tillage tools to prepare sites and seed by hand, raking away leaves and removing brush and small trees. Seeds for wild-simulated operations are usually planted at much lower rates, e.g., 20 lbs/acre or even less (Persons and Davis 2005). Wild-simulated growers may still need to use pesticides, such as molluscicides and fungicides, but, generally, the lower planting density, lack of soil tillage, use of fewer soil amendments, and much slower growth rate allow for a much more “organic” approach. Yields of wild-simulated American ginseng are also much lower, ranging up to about 150 lbs/acre (Persons and Davis 2005).

Seed Propagation and Planting

American ginseng is usually propagated by seeds but can be propagated by root cuttings and by planting the “neck” (rhizome). American ginseng seeds do not sprout until the second spring after they are harvested. Unless stratified, the germination rates may not rise above 30%. Traditionally, depulped seed that has been kept in refrigerated conditions was mixed with clean sand and buried in a box, slightly below the soil level, in the fall, after the soil temperatures fell below 15 °C (59 °F). During stratification, a year-long process, the sand would be constantly kept moist, with adequate drainage provided. Several inches of straw could be added on top of the box to retain moisture and keep the temperatures more even (BCMAFF 2003). Despite the additional measures, the method is prone to fluctuations in moisture levels and temperature, which can result in stratification failures. Currently, large-scale growers are more likely to use controlled atmosphere facilities to ensure optimal stratification conditions.

Stratified seeds are planted in the fall and, generally, germinate in the spring of the following year. Some growers transplant young plants after 2 years. Lower density plantings help limit competition between plants for light, moisture, and nutrients and reduce disease spread. Konsler and Shelton (1984) found that roots of 4-, 5-, and 6-year-old plants were largest when grown with the widest distance between the plants (22.9 cm, compared to 15.2, 7.6, and 2.5 cm).

Once seeds are planted, mulching is required to keep the soil moist and cool. Some growers remove the flowers on

Figure 10 Production of woods-cultivated American ginseng root

10a. Dr. W. Scott Pearsons inspecting a mature American ginseng plant in a woods-cultivated lot.
10b. Small-scale washing of American ginseng roots, using a cement mixer.
10c. Drying rack for small-scale drying of American ginseng roots.

Photographs courtesy of: (10a) Mark Haskett; (10b) Tom Condon; (10c) Kim Fadiman.
Photograph (10a) from the collection of Dr. W. Scott Pearsons, Tuckasegee Valley Ginseng, used with permission.
Photographs (10b, c) from Growing & Marketing Ginseng, Goldenseal & Other Woodland Medicinals (Persons and Davis 2005), © 2005 Bright Mountain Books, Fairview, NC, used with permission.
3-year-old plants, so that they and the fruits do not deplete the root of nutrients (BCMAFF 2003; Foster and Yue 1992). Plants propagated by cuttings are ready for harvest approximately 2 years earlier than seed-grown plants (Eidus 1997).

Diseases of American Ginseng

Blight is the most common disease affecting both field-cultivated and woods-grown American ginseng and, if not controlled, is able to lead to crop loss (Hausbeck 2007; Weege 2011, personal communication to AHP, unreferenced). The disease is typically caused by the fungus Alternaria panax and affects leaves and stems of the plants, resulting in poor quality roots. The Alternaria leaf blight can be recognized by lesions with dark brown margins, light brown centers, and yellow-green halos (Figure 11a). Root rots caused by a variety of fungi are also of primary concern and, when present, may be most devastating (Bailey et al. 1995; Hausbeck 2007; MacDonald 1995; Proctor and Bailey 1987). Most growers in the major production areas consider themselves constrained to use fungicides to bring plants to maturity.

Pesticide Applications

There are a host of pesticides that are approved for use on American ginseng, and these differ with country of cultivation. US federal law requires specific approval of pesticides for specific crops and prohibits the use of pesticides unapproved for the crops. Tolerance levels for organochlorine and organophosphate pesticide residues in American ginseng products are strictly regulated in the US (Table 4). Nevertheless, the Food and Drug Administration (FDA 2008) reported that 5 out of 7 (71%) tested batches of American ginseng used by manufacturers had pesticide residues violating the stated tolerance levels.

Post-Harvest Handling

Wild roots are usually carefully washed immediately following harvest. Field-cultivated roots can be stored in a refrigerated area with relative humidity of more than 80% for up to 6 weeks before washing and drying. Some growers find that the storage helps to “condition” the roots, making their outer appearance more appealing, while others have not found any improvement in appearance and thus perceived quality. Storage temperature between 1-8 °C (34-46.4 ºF) is considered optimal. Diseased roots should be carefully sorted out before storage to avoid pathogen transmission to other roots in storage. If roots are harvested in wet weather or washed prior to storing, their surfaces should be completely dried before storing to prevent spoilage (BCMAFF 2003; OMAFRA 2011).

Washing is performed with a garden hose or in a commercial drum washer. A shaker chain and/or a soaking tank can be used prior to washing to remove excess dirt. While almost all soil generally should be removed for the product

### Table 4 EPA tolerances/FDA enforcement levels for chlorinated and phosphorus pesticides in ginseng (including American ginseng)

<table>
<thead>
<tr>
<th>Pesticide</th>
<th>Tolerance/Enforcement Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,4D</td>
<td>1.0 ppm*</td>
</tr>
<tr>
<td></td>
<td>0.1 ppm†</td>
</tr>
<tr>
<td>BHC (benzene hexachloride)</td>
<td>0.05 ppm††</td>
</tr>
<tr>
<td>Boscalid</td>
<td>0.70 ppm</td>
</tr>
<tr>
<td>Carfentrazone-ethyl</td>
<td>0.10 ppm</td>
</tr>
<tr>
<td>Clethodim</td>
<td>1.0 ppm</td>
</tr>
<tr>
<td>Chlorothalonil</td>
<td>0.1 ppm</td>
</tr>
<tr>
<td>(Zeta-)Cypermethrin</td>
<td>0.1 ppm</td>
</tr>
<tr>
<td>DCPA</td>
<td>2.0 ppm</td>
</tr>
<tr>
<td>Diazinon</td>
<td>0.75 ppm</td>
</tr>
<tr>
<td>Fenhexamid</td>
<td>0.3 ppm</td>
</tr>
<tr>
<td>Imidacloprid</td>
<td>0.40 ppm</td>
</tr>
<tr>
<td>Ipomdione</td>
<td>2.00 ppm (4.00 ppm dried root)</td>
</tr>
<tr>
<td>Myclobutanil</td>
<td>0.03 ppm</td>
</tr>
<tr>
<td>Lindane</td>
<td>0.50 ppm</td>
</tr>
<tr>
<td>(S-)Metolachlor acetamid (metolachlor related compound)</td>
<td>0.30 ppm</td>
</tr>
<tr>
<td>Pyraclostrobin</td>
<td>0.40 ppm</td>
</tr>
<tr>
<td>Sulfoate</td>
<td>0.15 ppm</td>
</tr>
<tr>
<td>Thiamthroxam</td>
<td>0.02 ppm</td>
</tr>
<tr>
<td>Zoximide</td>
<td>0.06 ppm</td>
</tr>
</tbody>
</table>

*Diethylamine salt from water hyacinth control; †diethylamine salt negligible residue tolerance; ††total of individual isomers alpha, beta, delta, gamma.

to be acceptable to buyers, care should be taken during washing so that not to damage the epidermis, since the cosmetic appearance of the roots contributes greatly to their economic value. In some cases, such as when processing small amounts of roots, dirt may simply be brushed off, using a soft brush, and the roots lightly rinsed. The exact washing/cleaning procedures often depend on the soil type.

According to one study, a gradient from very light to darker epidermis occurred as washing methods shifted from extensive washing under high pressure to light washing under low pressure to dry brushing (Bailey et al. 1995). A qualitative assessment of the resulting roots found that the extensively washed roots were considered of lower quality because they were overly white and often had damaged epidermis. However, the different treatments did not affect the internal root characteristics.

**Drying**

Drying is an important part of post-harvest handling of American ginseng roots as improper drying may greatly affect the final value of the raw material. Proper drying is best accomplished by sizing roots so that like sizes are dried in batches, to prevent over drying of smaller roots and insufficient drying of larger roots. Drying at a temperature of 38 °C (100.4 °F) to a moisture content of 8-10% is considered optimal (BCMAFF 2003; Li and Morey 1987; Reynolds 1998b; Wilhelm 1990). Though higher temperatures decrease drying time, they adversely affect macroscopic and chemical characteristics of the roots. Drying at temperatures below 38 °C may induce molding, especially on large roots. Roots dried below 30.5 °C (86.9 °F) exhibited a greening of the inner tissues, which is undesirable. Roots dried at temperatures above 40 °C (104 °F) turned dark-brown in color due to sugar caramelization (Van Hooren and Lester 1991). Ginsenosides, the primary active constituents of American ginseng, are thermally unstable (Ren and Chen 1999a). At the drying temperature of 44 °C (111.2 °F), total ginsenoside content was reduced by 16.7% compared to roots dried at 38 °C and by 26.4% compared to freeze-dried roots. Du et al. (2004) reported that increased drying temperatures decreased the concentration of total ginsenosides. Conversely, heat processing of American ginseng roots is associated with an increased content of phenolic compounds (Kang et al. 2007).

Humidity is controlled by constant air exchange between the chamber and the outside air. Relative humidity of up to 50% does not significantly affect the drying rate (BCMAFF 2003). Higher humidity will slow the drying process but will have no significant effect on root quality (BCMAFF 2003; Reynolds 1998b). Appropriate dryness has been reached when the root cannot be bent and breaks cleanly, revealing a white interior. This is often referred to as the “snap rating.” Alternatively, a convection laboratory oven can be used to monitor moisture content.

A variety of dryers can be used. One of the common configurations is a vertical stack of trays in a drying chamber, such as the one shown in Figure 10c. To ensure even drying, it is recommended to rotate the trays halfway through

---

**Figure 11 Diseases of American ginseng**

11a. Characteristic spot-like pattern of leaf blight (*Alternaria panax*).
11b. Leaf infection caused by *Phytophthora cactorum*, a root rot fungus.
11c. Root rot caused by *Fusarium* fungus.

the process and/or frequently turn the roots during drying. Large-scale dryers will take up to 2 weeks to dry a batch of material depending on weather conditions. In the investigation of Reynolds (1998b), it took approximately 192 hours at 38 °C (100.4 °F) to dry 1 kg of roots to a moisture content of 8%. Van Hooren and Lester (1991) recommended roots to be dried at a humidity of 4 kPa vapor pressure deficit (VPD), reduced from starting conditions (1 kPa) over a period of 48 hours (Van Hooren and Lester 1991). Combination of microwave radiation (60 W) and hot air for drying American ginseng roots to a moisture level of 10% decreased drying time by 28.7%-55.2%, compared to hot air alone, and had little negative effect on the roots color (Ren and Chen 1998). In both microwave-hot air combination and hot-air-alone methods, the temperatures were maintained at 40 °C (104 °F).

Simple small-scale drying operations done at lower temperatures are discussed by Persons and Davis (2005).

### Storage

Follow general guidelines for storage by packing in air-tight containers protected from light, heat, moisture, and insect infestation. Dried roots are generally stored in cardboard drums lined with plastic. Sealed plastic bags ensure that moisture content will be retained during shipping. Ginsenoside levels decline with exposure to temperatures above 40 °C (104 °F) (Du et al. 2004); thus, cool temperature storage is recommended.

### Qualitative Differentiation

There are both formal and informal criteria for grading American ginseng root as well as different grading parameters used in North America and China. None of these grading parameters have been verified to any objective criteria, e.g., efficacy or content of active ingredients. Some of the approaches to qualitative differentiation currently used are presented below.

#### United States Department of Agriculture (USDA) Grading and Classification System

The United States Department of Agriculture has applied a variety of grading criteria for cultivated American ginseng roots through the years, including size, form, color, degree of dryness, and texture (or degree of annulation). The most recent grading system was based on root size and internal and external defects ratio (USDA 2007). This grading system is currently under revision and being replaced by a new

| **Table 5** USDA grades for cultivated American ginseng roots |
|---------------------|---------------------|
| **Grade** | **Defects tolerances** |
| U.S. No. 1 | 1% |
| U.S. No. 2 | 1%-5% |
| U.S. No. 3 | 5%-10% |
| U.S. No. 4 | 10%-25% |
| U.S. No. 5 | 25%-50% |
| U.S. No. 6 | 50%-75% |
| U.S. No. 7 | >75% |


| **Table 6** USDA size classifications for cultivated American ginseng roots |
|---------------------|---------------------|
| **Classification** | **Description** |
| Premium | Consists of more than 50% short\(^1\) roots of any diameter |
| Select | Consists of more than 70% of short and medium\(^1\) roots of any diameter |
| Standard | Consists of more than 80% of short, medium, and long\(^1\) roots of any diameter |

\(^1\) For sizes definitions, see Table 7.

| **Table 7** Definitions of size categories used in USDA classifications of cultivated American ginseng roots |
|---------------------|---------------------|---------------------|
| **Diameter (inches)** | **Length (inches)** |
| Small | 3/16 to 3/8 |
| Medium | Larger than 3/8 to 5/8 |
| Large | Larger than 5/8 to 7/8 |
| Extra Large | Larger than 7/8 |

model that will be based strictly on the quality of the roots, i.e., percentage of defects (USDA 2011). The new grades will be numbered U.S. No. 1 through U.S. No. 7 (Table 5). Previously used terms “Premium,” “Select,” and “Standard” will now refer to size classifications (Table 6). Color and texture will apply to the lot as a whole and will be required to specify with the grade (see visual guides in Figure 12). While not a criterion of inherent quality, origin of the roots may be specified if this can be determined by a scientifically valid method. Additionally, the term “fiber” will be replaced by “rootlet” to describe small slender roots less than 1/8 inch in diameter.

### Table 8  Grading of American ginseng root by size according to the National Standard of the People’s Republic of China

<table>
<thead>
<tr>
<th>Grade</th>
<th>Diameter (cm)</th>
<th>Length (cm)</th>
<th>Average single root weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long roots</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Super large roots</td>
<td>1.5-2.0</td>
<td>7.5-10.0</td>
<td>≥ 10</td>
</tr>
<tr>
<td>Extra large roots</td>
<td>1.3-1.5</td>
<td>6.5-7.5</td>
<td>≥ 7</td>
</tr>
<tr>
<td>Large roots</td>
<td>1.0-1.3</td>
<td>5.5-6.5</td>
<td>≥ 5</td>
</tr>
<tr>
<td>Medium roots</td>
<td>0.9-1.0</td>
<td>4.5-5.5</td>
<td>≥ 3.5</td>
</tr>
<tr>
<td>Small roots</td>
<td>0.7-0.9</td>
<td>3.5-4.5</td>
<td>≥ 2.5</td>
</tr>
<tr>
<td>Short roots</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Special Grade</td>
<td>1.9-2.2</td>
<td>4.9-5.8</td>
<td>≥ 10</td>
</tr>
<tr>
<td>Short 1 Grade</td>
<td>1.6-2.0</td>
<td>4.6-5.6</td>
<td>≥ 7</td>
</tr>
<tr>
<td>Short 2 Grade</td>
<td>1.4-1.6</td>
<td>4.0-5.0</td>
<td>≥ 5</td>
</tr>
<tr>
<td>Short 3 Grade</td>
<td>1.3-1.4</td>
<td>3.6-4.2</td>
<td>≥ 3</td>
</tr>
<tr>
<td>Short 4 Grade</td>
<td>1.1-1.3</td>
<td>2.8-3.4</td>
<td>≥ 2</td>
</tr>
</tbody>
</table>

“Pao Shen” (round-shaped roots with a similar length and diameter)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Diameter (cm)</th>
<th>Length (cm)</th>
<th>Average single root weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>-</td>
<td>-</td>
<td>≥ 7</td>
</tr>
<tr>
<td>Grade 2</td>
<td>-</td>
<td>-</td>
<td>≥ 5</td>
</tr>
<tr>
<td>Grade 3</td>
<td>-</td>
<td>-</td>
<td>≥ 3</td>
</tr>
<tr>
<td>Grade 4</td>
<td>-</td>
<td>-</td>
<td>≥ 1.5</td>
</tr>
<tr>
<td>Grade 5</td>
<td>-</td>
<td>-</td>
<td>&lt; 1.5</td>
</tr>
</tbody>
</table>


### Table 9  Grading of American ginseng root by qualitative markers according to the National Standard of the People’s Republic of China

<table>
<thead>
<tr>
<th>Highest Grade</th>
<th>Grade 1</th>
<th>Acceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identity test</td>
<td>Contains Rb₁, Re, Rg₁, F₁₁</td>
<td>Contains Rb₁, Re, Rg₁, F₁₁</td>
</tr>
<tr>
<td>Water content</td>
<td>≤ 13%</td>
<td>≤ 13%</td>
</tr>
<tr>
<td>Total ash</td>
<td>≤ 4.0%</td>
<td>≤ 4.5%</td>
</tr>
<tr>
<td>Insoluble ash</td>
<td>≤ 0.4%</td>
<td>≤ 0.5%</td>
</tr>
<tr>
<td>Total saponins</td>
<td>≥ 6.5%</td>
<td>5.5-6.5%</td>
</tr>
<tr>
<td>Rb₁</td>
<td>≥ 1.5%</td>
<td>1.2-1.5%</td>
</tr>
</tbody>
</table>


**Other Criteria for American Ginseng Root Grading**

American ginseng root is additionally graded according to growing method and various macroscopic attributes of the roots. The criteria are often quite subjective and vary according to the market. The Asian market, in particular, considers wild American ginseng to have a stronger therapeutic effect than cultivated American ginseng. In turn, American ginseng cultivated in the forest is considered to be of higher quality than that grown in fields under artificial shade.

The Asian market also judges American ginseng root quality according to root size, shape, external color, surface texture, age, and taste. In Hong Kong, which imports the bulk of American ginseng, roots are graded into more than 40 categories based on these characters. High quality roots have characteristics indicative of older wild roots. Just as wild roots are considered more potent than cultivated roots, older roots are considered superior to younger ones. In general, the most highly prized roots have short, thick, round bodies shaped like a bubble or bullet. Larger roots are considered to be of higher quality than smaller roots of the same color and texture. The shorter roots are also preferred because they don’t need to be sliced when cooking to maximize the flavor. Lateral roots and rootlets are often sold as separate, lower-grade cut roots and trimmings. The external color of the root should approximate the beige color of older, wild American ginseng roots; in other words, it should have a medium degree of darkness, rather than be very light or very dark. In addition, high quality roots have many closely spaced annular wrinkles on the surface of the root. Older wild roots tend to have highly wrinkled surfaces, compared to the smoother surfaces of cultivated roots (Eidus 1997). Although roots are graded primarily based upon appearance, taste is also important. The highest quality roots are considered to have an earthy bitter taste with a slightly sweet aftertaste (Guo et al. 1995).
Adulterants

Authentication of American ginseng is very important due to the high incentive for adulteration, based on the high dollar value of the roots. In 1978, a study found that one third of ginseng products, examined using thin layer chromatography (TLC) and spectrophotometric analyses, contained no ginseng at all (Liberti and Der Marderosian 1978). All adulterants are readily distinguishable through morphological, microscopic, and/or chemical methodologies.

Asian ginseng is oftentimes disguised to look like American ginseng because the latter species commands a market price that is much higher than the former (Ma et al. 1995, 1996; Ngan et al. 1999; Weege 2011, personal communication to AHP, unreferenced).

*American Ginseng Leaf Extracts:* While the primary material of commercial value is American ginseng root, leaf material also contains ginsenosides (see Constituents). Because of this, American ginseng leaves may be used to make American ginseng extracts, standardized to ginsenosides. Occasionally, such extracts are declared as being made from American ginseng roots and thus are misbranded. Alternatively, American ginseng leaf extracts can be used to augment American ginseng root extracts.

*Adulterating Species:* In Asia, adulteration with three poisonous species *Mirabilis jalapa*, *Phytolacca acinosa*, and *Talinum paniculatum* has been reported (Shaw and But 1995). These have not been reported, nor are they likely, to adulterate the North American market when traded in their...
whole form, as they are readily distinguishable morphologically and organoleptically.

The name “ginseng” has been applied to a number of other plants in order to capitalize on the reputation of Panax species. These have included plants from various genera, e.g., Aralia californica (“California ginseng”), Oplopanax horridus syn. Echinopanax horridus (“Alaskan ginseng”), Pfaffia paniculata (“Brazilian ginseng”), Rumex hymenosepalus (“wild red desert ginseng”), and Withania somnifera (“Indian ginseng”). However, in 2004, the American ginseng industry of Wisconsin successfully lobbied for the passage of a law restricting the name “ginseng” to only the botanicals within the genus Panax. None of the above named species occur as adulterants of American ginseng in trade but, rather, are occasionally marketed as types of “ginseng” in the hopes of capturing some of the panache of the true Panax market. They are all easily distinguishable morphologically and chemically.

**Fillers:** In North America, both American and Asian ginseng have been subject to diminution with inert fillers or flow agents, such as dextrose, lactose, corn syrup, and caramel (Leung and Foster 1996). The presence of high amounts of these materials gives the powder a gritty texture that is noticeable upon mastication. Pure ginseng powder is soft, fine, and possesses a somewhat glutinous quality. In some cases a small amount of flow agent may be used in the grinding of whole or cut roots to powder. The amount of flow agent used should be declared. However, the presence of significant amounts of fillers and flow agents may indicate the intention to use these to increase the weight of the raw material. These ingredients can be observed microscopically.

**Extracted Root:** Extractors have been known to dry the marc (the material remaining after extraction) and sell it as ginseng powder (Upton 2011, personal communication to AHP, unreferenced). Roots that have already been extracted will generally lack the expected concentration of ginsenosides and can easily be rejected based on chemical analysis, unless the material was augmented with leaf ginsenosides. Extracted material can be discerned microscopically as the cell structures will appear swollen and deteriorated.

### Preparations

American ginseng is available in a variety of grades as crude root and in various preparations, including pills, tablets, capsules, teas, extracts, oils, various food products, and cosmetics.

Extraction of ginsenosides from dried root powder with aqueous-ethanol menstruums varies with the ethanol content. In the investigation of Du et al. (2004), maximum extraction of neutral ginsenosides was obtained with 70% ethanol, 40% ethanol for malonyl ginsenosides, and 60% ethanol for total ginsenosides (Table 10).

There is a widespread traditional practice of steaming Asian ginseng. In traditional Chinese medical terms, this increases the yáng or warming and vitalizing properties of the root. Steaming American ginseng at 100 °C (212 °F) results in an increase of neutral ginsenosides (Kim et al. 2007). However, experiments with American ginseng steamed at 120 °C (248 °F) showed a reduction in total ginsenosides and a significant increase in ginsenoside Rg3, which has marked anticancer activity. These changes were proportional to length of steaming time, with increases of ginsenoside Rg3 from 0.003% in unsteamed root to 1.225% after 4 hours of steaming (Wang et al. 2007, 2008, 2009).

According to traditional Chinese literature, use of metal cookware is forbidden in the preparation of ginseng products (Bensky et al. 2004). In traditional Chinese medicine, ginseng is typically cooked in a ceramic “ginseng cooker” and a double-boiler.

<table>
<thead>
<tr>
<th>Solvent (% ethanol)</th>
<th>Concentration of ginsenosides (mg/g)</th>
<th>Neutral</th>
<th>Malonyl</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>39.0b</td>
<td>11.8</td>
<td>50.8</td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>48.5</td>
<td>16.0</td>
<td>64.5</td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>51.1</td>
<td>17.2</td>
<td>68.2</td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>50.4</td>
<td>19.5</td>
<td>69.9</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>50.4</td>
<td>20.9</td>
<td>71.3</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>47.9</td>
<td>19.8</td>
<td>67.7</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>44.0</td>
<td>17.8</td>
<td>61.8</td>
<td></td>
</tr>
<tr>
<td>LSD&lt;sub&gt;0.05&lt;/sub&gt;</td>
<td>± 1.4</td>
<td>± 1.7</td>
<td>± 1.9</td>
<td></td>
</tr>
</tbody>
</table>

*Least significant difference.

Each value is the mean of three replicates.

Concentration was standardized against the weight of ginseng powder used.

Modified from Du et al. (2004).
**Constituents**

The constituents of American ginseng root have been investigated since the early 19th century (Garrigues 1854; Rafinesque 1828) and are some of the best studied among the medicinal plants. Several classes of active compounds have been identified, including triterpenoid saponins (ginsenosides), polyacetylenes, and proteins. American ginseng shares many of its main compounds with other medicinal *Panax* species.

**Ginsenosides**

Ginsenosides are considered to be the primary type of constituents associated with the activity of American ginseng root. These compounds are triterpene saponin glycosides and possess a 4-trans-ring steroid structure, with several modified side chains (Figure 13). They are commonly designated with an index Rx, where R stands for *radix* (Latin for root) and x = a, a’, b, b’, c, d, e, etc., roughly according to the mobility of the compounds on thin-layer chromatography plates, with polarity increasing from ‘a’ to ‘h’ (Ro being an exception as the least polar ginsenoside named after the unique triterpene skeleton it possesses).

As glycosides, ginsenosides can be classified either by the aglycone or by the glycone (sugar moiety attached to the aglycone) part of the molecule. There are 4 main types of ginseng saponins distinguished by their aglycone base:

- **20(S)-Protopanaxadiol type**: ginsenosides Rb₁, Rb₂,
- **Protopanaxatriol type**: ginsenoside Ro
- **Pseudoginsenoside F₁₁**: R = -Glc²-Rha

<table>
<thead>
<tr>
<th>Ginsenoside</th>
<th>R₁</th>
<th>R₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rb₁</td>
<td>-Glc²-Glc</td>
<td>-Glc³-Glc</td>
</tr>
<tr>
<td>mRb₁</td>
<td>-Glc²-Glc²-Ma</td>
<td>-Glc³-Glc</td>
</tr>
<tr>
<td>Rb₂</td>
<td>-Glc²-Glc</td>
<td>-Glc³-Ara(p)</td>
</tr>
<tr>
<td>mRb₂</td>
<td>-Glc²-Glc²-Ma</td>
<td>-Glc³-Ara(p)</td>
</tr>
<tr>
<td>Rc</td>
<td>-Glc²-Glc</td>
<td>-Glc³-Ara(f)</td>
</tr>
<tr>
<td>mRc</td>
<td>-Glc²-Glc²-Ma</td>
<td>-Glc³-Ara(f)</td>
</tr>
<tr>
<td>Rd</td>
<td>-Glc²-Glc</td>
<td>-Glc³-Rha</td>
</tr>
</tbody>
</table>

Glc – glucose; Ma – malonyl; Ara(p) – arabinose in pyranose form; Ara(f) – arabinose in furanose form; Rha – rhamnose.

*Figure 13  Main ginsenosides occurring in American ginseng root*
American ginseng roots are reported to typically have higher concentrations of total saponins by weight than Asian ginseng (*P. ginseng*) (e.g., Ma et al. 1995; Zhu et al. 2004; also see Table 11). The variation between individual roots, however, can be significant, from as little as 0.85% (Schlag and McIntosh 2006) and up to 9.5% (Li J et al. 1995, cited in Court 2000).

The profile of individual ginsenosides in American ginseng root is different from the other medicinal *Panax* species. Typically, saponins of the protopanaxadiol type are predominant in American ginseng roots (Samukawa et al. 1995a, 1995b; Wang et al. 1999), whereas protopanaxatriol-type saponins are predominant in both Asian ginseng and Tienchi ginseng (also known as *san qi* (*P. notoginseng* syn. *P. pseudoginseng* var. *notoginseng*)). Another unique property of American ginseng roots is high levels (up to 40%) of malonylated ginsenosides (mRb₁, mRb₂, mRe, mRd), which may or may not be present in the commercial samples as they are easily demalonylated during storage and processing. The major saponins present in the root are Rb₁, mRb₁, Rc, mRc, Rd, Re, and, occasionally, Rg₁ (Lang et al. 1993; Le Men-Olivier et al. 1995; Li X et al. 1995; Li TSC et al. 1996; Ma et al. 1995; Zheng et al. 1989; Zhu et al. 2004). Ginsenoside Rg₁, pseudoginsenoside F₁₁, and gypenoside XVII can also be present in considerable amounts (Court et al. 1996a; Le Men-Olivier et al. 1995; Qu et al. 2009). Ginsenosides Rb₁, mRb₁, and Re can comprise up to 75% of total glycosides in 4-year-old roots, with Rb₁ making up more than 50% of the total (Li TSC et al. 1996; Ma et al. 1995; Chen and Chen 1999b). Ginsenosides Ra, Rf, Rg₁, Rh₁, and Rh₂ are absent from American ginseng roots (Chuang et al. 1995; Lang et al. 1993; Lui and Staba 1980; Ma et al. 1996; Qu et al. 2009). The reported levels of the primary ginsenosides contained in American ginseng root can be seen in Table 12.

Compared to Asian ginseng, American ginseng has higher levels of ginsenosides Rb₁ and Re and lower levels of ginsenoside Rg₁. The ratio of ginsenosides Rg₁ and Rb₁ is often considered of major importance in both differentiating between the species and in explaining the differences in their therapeutic actions. Studies have shown that these 2 ginsenosides have opposing effects on postprandial glycemia (Sievenpiper et al. 2004) and vascular formation in neoplasms (Sengupta et al. 2004). Ma et al. (1996) reported the Rg₁/Rb₁ ratio to be 0.13 in American ginseng compared to 0.77 in Asian ginseng. Some reports, however, state that Rg₁ may be present in American ginseng at equal or higher amounts as compared to Rb₁, particularly, in very old wild roots (Awang 2000; Chuang et al. 1995; Ma et al. 1996). The content of ginsenoside Rg₁ in a 23-year-old wild American ginseng root analyzed by Ma et al. (1996) was reported to

---

Table 11 Differences in ginsenoside profiles of American ginseng root and leaf and roots and leaves of other medicinal *Panax* spp.

<table>
<thead>
<tr>
<th>Ginsenoside</th>
<th>American ginseng root</th>
<th>American ginseng leaf</th>
<th>Asian ginseng root, white</th>
<th>Asian ginseng root, red</th>
<th>Asian ginseng leaf</th>
<th>Tienchi (<em>P. notoginseng</em>) root</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rb₁</td>
<td>++++</td>
<td>+</td>
<td>++</td>
<td>++++</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td>Rb₂</td>
<td>tr</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>tr</td>
</tr>
<tr>
<td>Rb₃</td>
<td>++</td>
<td>++++</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Rb₄</td>
<td>++</td>
<td>++++</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Rb₅</td>
<td>++</td>
<td>++++</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Rb₆</td>
<td>++</td>
<td>++++</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Rg₁</td>
<td>++</td>
<td>++++</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Rg₂</td>
<td>tr</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Rg₃</td>
<td>++</td>
<td>++++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>F₁₁</td>
<td>++</td>
<td>++++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Total ginsenosides, % of root mass</td>
<td>~4-5(-9)%</td>
<td>~11-12%</td>
<td>~1-3%</td>
<td>~1-3%</td>
<td>~12%</td>
<td>~5-7(-20)%</td>
</tr>
</tbody>
</table>

Sources: *Asafu-Adjaye and Wong (2003);* Chan et al. (2000); *Dou et al. (1998);* Lang et al. (1993); *Lui and Staba (1980);* King and Murphy (2010); *Ma et al. (1995);* Wang et al. (1998); Zhu et al. (2004).

* Occasionally present in relatively high amounts.
### Table 12 Concentrations of individual and total ginsenosides in American ginseng roots as reported by different research groups

<table>
<thead>
<tr>
<th>Ginsenoside</th>
<th>Content range, mg/g</th>
<th>Mean content, mg/g</th>
<th>Method</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rb₁</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not reported</td>
<td>–</td>
<td>30.1</td>
<td>HPLC</td>
<td>Asafu-Adjaye and Wong 2003</td>
</tr>
<tr>
<td>7.7-18.6</td>
<td>–</td>
<td>27.4</td>
<td>HPLC</td>
<td>Brown 2011</td>
</tr>
<tr>
<td>6.4-27.6</td>
<td>–</td>
<td>12.2</td>
<td>HPLC</td>
<td>Li TSC et al. 1996</td>
</tr>
<tr>
<td>–</td>
<td>–</td>
<td>18.5</td>
<td>HPLC-ELSD</td>
<td>Ma et al. 1995</td>
</tr>
<tr>
<td>2.5-23.6</td>
<td>–</td>
<td>20.7</td>
<td>NIR</td>
<td>Qu et al. 2009</td>
</tr>
<tr>
<td>27.8-34.0</td>
<td>–</td>
<td>25.1</td>
<td>RP-HPLC</td>
<td>Ren and Chen 1999b</td>
</tr>
<tr>
<td>12.4-37.1</td>
<td>–</td>
<td>30.9</td>
<td>LC/MS/MS</td>
<td>Sengupta et al. 2004</td>
</tr>
<tr>
<td><strong>Rb₂</strong></td>
<td></td>
<td>0.5</td>
<td>HPLC</td>
<td>Asafu-Adjaye and Wong 2003</td>
</tr>
<tr>
<td>Not reported</td>
<td>–</td>
<td>0.7</td>
<td>HPLC</td>
<td>Brown 2011</td>
</tr>
<tr>
<td>0.2-0.3</td>
<td>–</td>
<td>0.2</td>
<td>HPLC</td>
<td>Li TSC et al. 1996</td>
</tr>
<tr>
<td>0.4-1.8</td>
<td>–</td>
<td>0.6</td>
<td>HPLC</td>
<td>Ma et al. 1995</td>
</tr>
<tr>
<td>–</td>
<td>–</td>
<td>0.4</td>
<td>HPLC-ELSD</td>
<td>Qu et al. 2009</td>
</tr>
<tr>
<td><strong>Rc</strong></td>
<td></td>
<td>3.2</td>
<td>HPLC</td>
<td>Asafu-Adjaye and Wong 2003</td>
</tr>
<tr>
<td>Not reported</td>
<td>–</td>
<td>3.9</td>
<td>HPLC</td>
<td>Brown 2011</td>
</tr>
<tr>
<td>1.4-2.4</td>
<td>–</td>
<td>1.8</td>
<td>HPLC</td>
<td>Li TSC et al. 1996</td>
</tr>
<tr>
<td>1.5-9.0</td>
<td>–</td>
<td>3.3</td>
<td>HPLC</td>
<td>Ma et al. 1995</td>
</tr>
<tr>
<td>–</td>
<td>–</td>
<td>2.9</td>
<td>HPLC-ELSD</td>
<td>Qu et al. 2009</td>
</tr>
<tr>
<td>1.2-11.8</td>
<td>–</td>
<td>5.4</td>
<td>NIR</td>
<td>Ren and Chen 1999b</td>
</tr>
<tr>
<td>5.5-6.7</td>
<td>–</td>
<td>6.2</td>
<td>LC/MS/MS</td>
<td>Wang et al. 1999</td>
</tr>
<tr>
<td>1.1-3.0</td>
<td>–</td>
<td>1.8</td>
<td>RP-HPLC</td>
<td>Zhu et al. 2004</td>
</tr>
<tr>
<td><strong>Rd</strong></td>
<td></td>
<td>6.3</td>
<td>HPLC</td>
<td>Asafu-Adjaye and Wong 2003</td>
</tr>
<tr>
<td>Not reported</td>
<td>–</td>
<td>4.4</td>
<td>HPLC</td>
<td>Brown 2011</td>
</tr>
<tr>
<td>2.3-4.0</td>
<td>–</td>
<td>2.9</td>
<td>HPLC</td>
<td>Li TSC et al. 1996</td>
</tr>
<tr>
<td>1.1-11.2</td>
<td>–</td>
<td>4.9</td>
<td>HPLC</td>
<td>Ma et al. 1995</td>
</tr>
<tr>
<td>–</td>
<td>–</td>
<td>2.2</td>
<td>HPLC-ELSD</td>
<td>Qu et al. 2009</td>
</tr>
<tr>
<td>0.1-3.0</td>
<td>–</td>
<td>2.3</td>
<td>NIR</td>
<td>Ren and Chen 1999b</td>
</tr>
<tr>
<td>1.4-2.0</td>
<td>–</td>
<td>1.7</td>
<td>RP-HPLC</td>
<td>Zhu et al. 2004</td>
</tr>
<tr>
<td><strong>Re</strong></td>
<td></td>
<td>12.3</td>
<td>HPLC</td>
<td>Asafu-Adjaye and Wong 2003</td>
</tr>
<tr>
<td>Not reported</td>
<td>–</td>
<td>10.0</td>
<td>HPLC</td>
<td>Brown 2011</td>
</tr>
<tr>
<td>7.4-13.8</td>
<td>–</td>
<td>11.0</td>
<td>HPLC</td>
<td>Li TSC et al. 1996</td>
</tr>
<tr>
<td>2.5-32.1</td>
<td>–</td>
<td>17.0</td>
<td>HPLC</td>
<td>Ma et al. 1995</td>
</tr>
<tr>
<td>–</td>
<td>–</td>
<td>20.5</td>
<td>HPLC-ELSD</td>
<td>Qu et al. 2009</td>
</tr>
<tr>
<td>1.8-16.5</td>
<td>–</td>
<td>10.2</td>
<td>NIR</td>
<td>Ren and Chen 1999b</td>
</tr>
<tr>
<td>16.8-24.9</td>
<td>–</td>
<td>21.3</td>
<td>LC/MS/MS</td>
<td>Wang et al. 1999</td>
</tr>
<tr>
<td>2.9-10.6</td>
<td>–</td>
<td>7.2</td>
<td>RP-HPLC</td>
<td>Zhu et al. 2004</td>
</tr>
<tr>
<td><strong>Rg₁</strong></td>
<td></td>
<td>1.7</td>
<td>HPLC</td>
<td>Asafu-Adjaye and Wong 2003</td>
</tr>
<tr>
<td>Not reported</td>
<td>–</td>
<td>1.3</td>
<td>HPLC</td>
<td>Brown 2011</td>
</tr>
<tr>
<td>1.1-3.3</td>
<td>–</td>
<td>1.8</td>
<td>HPLC</td>
<td>Li TSC et al. 1996</td>
</tr>
<tr>
<td>0.2-22.0”</td>
<td>–</td>
<td>3.8</td>
<td>HPLC</td>
<td>Ma et al. 1995</td>
</tr>
<tr>
<td>–</td>
<td>–</td>
<td>2.5</td>
<td>HPLC-ELSD</td>
<td>Qu et al. 2009</td>
</tr>
<tr>
<td>0.4-3.0</td>
<td>–</td>
<td>1.2</td>
<td>NIR</td>
<td>Ren and Chen 1999b</td>
</tr>
<tr>
<td>–</td>
<td>–</td>
<td>0.5</td>
<td>RP-HPLC</td>
<td>Sengupta et al. 2004</td>
</tr>
<tr>
<td>0.3-21.5”</td>
<td>–</td>
<td>4.9</td>
<td>RP-HPLC</td>
<td>Zhu et al. 2004</td>
</tr>
<tr>
<td><strong>F₁₁</strong></td>
<td></td>
<td>2.0</td>
<td>HPLC-ELSD</td>
<td>Qu et al. 2009</td>
</tr>
<tr>
<td>Total ginsenosides</td>
<td>25.2-38.8</td>
<td>30.0</td>
<td>HPLC</td>
<td>Li TSC et al. 1996</td>
</tr>
<tr>
<td></td>
<td>12.6-86.0</td>
<td>46.4</td>
<td>HPLC</td>
<td>Ma et al. 1995</td>
</tr>
<tr>
<td></td>
<td>13.6-75.2</td>
<td>43.9</td>
<td>HPLC-ELSD</td>
<td>Qu et al. 2009</td>
</tr>
<tr>
<td></td>
<td>29.0-75.4</td>
<td>40.1</td>
<td>NIR</td>
<td>Ren and Chen 1999b</td>
</tr>
</tbody>
</table>

* Or pseudoginsenoside, as in pseudoginsenoside F₁₁.

** The analyses by Ma et al. (1995) and Zhu et al. (2004) each include 1 root with an untypically high content of Rg₁.
Table 13  Concentrations of individual and total ginsenosides in different parts of American ginseng roots (means or range)

<table>
<thead>
<tr>
<th>Ginsenoside*</th>
<th>Content in rhizome, mg/g</th>
<th>Content in main roots, mg/g</th>
<th>Content in rootlets, mg/g</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rb₁</td>
<td>37.5</td>
<td>13.0-31.0</td>
<td>21.6-55.0</td>
<td>Lang et al. 1993</td>
</tr>
<tr>
<td></td>
<td>10.61</td>
<td>18.46</td>
<td>11.63</td>
<td>Qu et al. 2009</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>2.5-17.2</td>
<td>7.6-8.3</td>
<td>Ren and Chen 1999b</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>34.2</td>
<td>46.0</td>
<td>Wang et al. 2006</td>
</tr>
<tr>
<td></td>
<td>42.6</td>
<td>22.7</td>
<td>53.6</td>
<td>Zhang K et al. 2008</td>
</tr>
<tr>
<td>mRb₁</td>
<td>—</td>
<td>1.6-11.1</td>
<td>1.8-10.4</td>
<td>Ren and Chen 1999</td>
</tr>
<tr>
<td>Rb₂</td>
<td>0.91</td>
<td>0.44</td>
<td>2.34</td>
<td>Qu et al. 2009</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>1.7</td>
<td>5.5-5.6</td>
<td>Ren and Chen 1999b</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>0.6</td>
<td>2.2</td>
<td>Wang et al. 2006</td>
</tr>
<tr>
<td></td>
<td>1.11</td>
<td>0.69</td>
<td>2.94</td>
<td>Zhang K et al. 2008</td>
</tr>
<tr>
<td>mRb₂</td>
<td>—</td>
<td>1.1-1.3</td>
<td>8.0-9.0</td>
<td>Ren and Chen 1999b</td>
</tr>
<tr>
<td>Rb₃</td>
<td>2.54</td>
<td>0.38</td>
<td>3.62</td>
<td>Qu et al. 2009</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>1.1</td>
<td>3.5</td>
<td>Wang et al. 2006</td>
</tr>
<tr>
<td></td>
<td>3.43</td>
<td>1.17</td>
<td>5.24</td>
<td>Zhang K et al. 2008</td>
</tr>
<tr>
<td>Rc</td>
<td>3.90</td>
<td>3.61-7.07</td>
<td>7.14-17.1</td>
<td>Lang et al. 1993</td>
</tr>
<tr>
<td></td>
<td>2.49</td>
<td>2.88</td>
<td>10.68</td>
<td>Qu et al. 2009</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>1.2-3.3</td>
<td>9.9-11.7</td>
<td>Ren and Chen 1999b</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>5.2</td>
<td>16.0</td>
<td>Wang et al. 2006</td>
</tr>
<tr>
<td></td>
<td>3.56</td>
<td>2.41</td>
<td>23.5</td>
<td>Zhang K et al. 2008</td>
</tr>
<tr>
<td>mRc</td>
<td>—</td>
<td>1.0-2.8</td>
<td>9.4-10.2</td>
<td>Ren and Chen 1999b</td>
</tr>
<tr>
<td>Rd</td>
<td>1.22</td>
<td>0.25-4.42</td>
<td>0.81-15.2</td>
<td>Lang et al. 1993</td>
</tr>
<tr>
<td></td>
<td>4.61</td>
<td>2.19</td>
<td>9.48</td>
<td>Qu et al. 2009</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>0.1-1.6</td>
<td>2.1-3.0</td>
<td>Ren and Chen 1999b</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>8.7</td>
<td>20.3</td>
<td>Wang et al. 2006</td>
</tr>
<tr>
<td></td>
<td>10.4</td>
<td>2.42</td>
<td>16.5</td>
<td>Zhang K et al. 2008</td>
</tr>
<tr>
<td>mRd</td>
<td>—</td>
<td>3.0-2.6</td>
<td>4.4-5.3</td>
<td>Ren and Chen 1999b</td>
</tr>
<tr>
<td>Re</td>
<td>22.3**</td>
<td>5.61-18.8*</td>
<td>8.81-20.5*</td>
<td>Lang et al. 1993</td>
</tr>
<tr>
<td></td>
<td>17.80</td>
<td>20.54</td>
<td>19.07</td>
<td>Qu et al. 2009</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>1.8-14.0</td>
<td>9.0-9.7</td>
<td>Ren and Chen 1999b</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>12.0</td>
<td>16.8</td>
<td>Wang et al. 2006</td>
</tr>
<tr>
<td></td>
<td>21.0</td>
<td>16.4</td>
<td>28.7</td>
<td>Zhang K et al. 2008</td>
</tr>
<tr>
<td>Rg₁</td>
<td>see Re</td>
<td>see Re</td>
<td>see Re</td>
<td>Lang et al. 1993</td>
</tr>
<tr>
<td></td>
<td>8.81</td>
<td>2.45</td>
<td>8.32</td>
<td>Qu et al. 2009</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>0.4-2.0</td>
<td>2.6-3.0</td>
<td>Ren and Chen 1999b</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>1.6</td>
<td>2.0</td>
<td>Wang et al. 2006</td>
</tr>
<tr>
<td></td>
<td>2.68</td>
<td>2.14</td>
<td>3.04</td>
<td>Zhang K et al. 2008</td>
</tr>
<tr>
<td>Rg₂</td>
<td>not detected</td>
<td>not detected</td>
<td>not detected</td>
<td>Qu et al. 2009</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>not detected</td>
<td>0.1</td>
<td>Ren and Chen 1999b</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>0.1</td>
<td>0.2</td>
<td>Wang et al. 2006</td>
</tr>
<tr>
<td>Ro</td>
<td>8.76</td>
<td>1.98-3.81</td>
<td>2.22-4.22</td>
<td>Lang et al. 1993</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>1.4-2.8</td>
<td>1.5-2.6</td>
<td>Ren and Chen 1999b</td>
</tr>
<tr>
<td>F₁₁₁</td>
<td>3.25</td>
<td>2.03</td>
<td>3.95</td>
<td>Qu et al. 2009</td>
</tr>
<tr>
<td>Total ginsenosides</td>
<td>76.5</td>
<td>25.6-65.1</td>
<td>44.7-111.5</td>
<td>Lang et al. 1993</td>
</tr>
<tr>
<td></td>
<td>51.02</td>
<td>49.37</td>
<td>69.09</td>
<td>Qu et al. 2009</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>13.6-57.6</td>
<td>74.1-75.2</td>
<td>Ren and Chen 1999b</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>63.6</td>
<td>107.1</td>
<td>Wang et al. 2006</td>
</tr>
</tbody>
</table>

* Or pseudoginsenoside, as in pseudoginsenoside F₁₁₁.
** Reported together with Rg₂.

Data for the oldest roots, where multiple ages are reported (Zhang K et al. 2008, 1-4 years old).

Lang et al. (1993) data is mixed from both wild and cultivated sources, except for the rhizome, which is only wild. Cultivated levels are usually in the middle of the range, while wild specimens exhibit both the lowest and the highest values.
be 1.4 times higher than that of ginsenoside Rb1. Significant deviations from the typical ratios have been observed in roots sourced from less commercially common geographical locations within the natural distributional range of the species (Schlag and McIntosh 2006).

A unique saponin was isolated from American ginseng roots by Besso et al. (1982), which they identified as mono-O-acetyl-ginsenoside Rb1. The compound was given a name quinquenoside R. Several other acetylated ginsenosides were isolated by Jia et al. (2008). Yoshikawa et al. (1998) discovered 5 previously unknown dammarane-type glycosides in American ginseng root material, which were named quinquenosides I-V. The quinquenosides demonstrated hepatoprotective activity in mice. Also reported present in American ginseng roots are chikusetsusaponin IVa, pseudoginsenoside RC1, notoginsenosides A, C, and K, all occurring in the roots in small amounts (Yoshikawa et al. 1998).

Total and individual ginsenoside content in American ginseng roots differs depending on root age, size, harvest time, the exact part of the root, environmental conditions, geographical location, and genetic differences between individual plants. Li TSC et al. (1996) observed significant variations in total ginsenoside content between 9 different cultivation locations in British Columbia. The variations were mainly due to differences in the levels of ginsenosides Rb1, Re, and Rd. Ginsenoside Rb1 showed the greatest variation: 0.77-1.86% of total dry root mass. Roots from plants less than 3 years old contain very low amounts of ginsenosides and are generally not harvested (Court et al. 1996b; Schlag and McIntosh 2006). The amount of ginsenosides appears to decrease from rootlet to rhizome to tap root (Table 13). Larger roots contain higher levels of ginsenosides (Smith et al. 1996).

**Processing Effects on the Levels of Ginsenosides**

Drying and storage at high temperatures lead to reduced levels of ginsenosides (see Commercial Sources and Handling). Steaming at 100 °C (212 °F) resulted in the increase of total ginsenosides in American ginseng roots from 3.27% to 3.91% (30 minutes of steaming), 4.52% (60 minutes), 5.71% (90 minutes), and 5.72% (120 minutes), according to Kim et al. (2007). The increase correlated with higher levels of ginsenosides Rb1, Rb2, and Rd, but not Rg1, Re, or Rc. It is likely that the observed increase was due to the conversion of malonylated ginsenosides into their neutral counterparts by heat, thus making them detectable in the analysis. Steam treatment is a traditional processing method of Asian ginseng roots, however, it is not commonly employed for American ginseng.

When American ginseng roots were steamed at 120 °C (248 °F) for 0.5-4 hours, their total ginsenoside content gradually decreased from 7.95% in the unsteamed root down to 5.85% after 1 hour of steaming, 4.05% at 2 hours, and 2.42% at 4 hours of steam treatment (Wang et al. 2007). However, the content of ginsenoside Rg1, a compound with known anticarcinogenic activity, increased from 0.003% in the unsteamed root to 0.271% after 1 hour, to 0.664% after 2 hours, and to 1.225% at 4 hours of steam treatment.

Heating isolated ginsenosides results in their transfor-
roots) and ranged from $210 \pm 12 \text{ mg/kg}$ (wet weight) in main roots to $780 \pm 21 \text{ mg/kg}$ for panaxydol and $190 \pm 10 \text{ mg/kg}$ in “hairy roots” for panaxynol. The location of polyacetylenes within the root is usually restricted to the secretory ducts, which can be detected visually in the transverse section of the root as brownish spots in the phloem parenchyma tissue (Baranska et al. 2006).

A novel protein (54 kDa) isolated from the roots of American ginseng was named quinqueginsin (Wang and Ng 2000). The protein exhibited antifungal, anti-human-immunodeficiency-virus, ribonuclease, and cell-free-translation-inhibitory activities in vitro. Several proteoglycans, named quinquefolans A, B, and C, with molecular masses estimated to be more than 2000 kDa, were isolated from an aqueous extract of American ginseng roots (Oshima et al. 1987). The fraction represented < 1% of the total mass of the roots. The molecules elicited a hypoglycemic effect in normal and alloxan-induced mice. The neutral sugar components of the newly discovered molecules were determined as mannose and glucose (1.0:2.3 molar ratio in quinquefolan A, 1.0:5.5 in quinquefolan B) or xylose (quinquefolan C). The total content of the neutral sugar residues was determined by 3 different methods with equivocal results and was at least 54.3% in quinquefolan A and 61.6% in quinquefolan B, as determined by the phenol-H$_2$SO$_4$ method, and 27.2% in quinquefolan C, as determined by anthrone-H$_2$SO$_4$ method. The acidic sugar fraction was reported to be composed of glucuronic acid (10.8% by weight of quinquefolan A, 11.7% by weight of quinquefolan B, and 7.1% by weight of quinquefolan C). The presence of peptide moieties was determined by the Lowry method (2.7%, 2.9%, and 2.3%, respectively, for quinquefolans A, B, and C).

Other common ingredients of American ginseng root include proteins, carbohydrates, fats, organic acids, flavonoids, and minerals. Compounds of these classes are not considered to be significantly involved in the reported biological activities of the root.

Constituents of American Ginseng Aerial Parts

Ginsenosides have been reported in the stems, leaves, flowers, and flower buds of American ginseng (Lang et al. 1993; Li TSC et al. 1996; Ma et al. 1995, 1996). Concentration of ginsenosides in the leaves of American ginseng is significant and can be higher than that in the roots. Lang et al. (1993) estimated the total ginsenoside content of the leaves to be 11.54%. By another estimate, 1-month-old leaves contained 1.33-2.64 g total ginsenosides per 100 g of dry mass, while the ginsenoside content in 4-month-old leaves was 4.14-5.58 g per 100 g of dry mass (Li TSC et al. 1996). Wills et al. (2002) note that leaves may contain up to 30% of the total plant ginsenosides, therefore representing a valuable resource.

Some of the ginsenosides that are absent from the roots (e.g., Rh$_1$ and Rh$_2$) occur in the aerial parts of the plant. Other aerial ginsenosides include Rd, Rg$_1$, Re, Rg$_2$, F$_2$, and pseudoginsenoside F$_{11}$ (Lang et al. 1993). According to one report, the principal ginsenosides in mature, 4-month-old leaves are Rd and Re, each accounting for about 40% of the total ginsenosides (Li TSC et al. 1996). Starratt et al. (2001) reported Rb$_1$, mRb$_1$, Rd, mRd, and Re as the primary glycoside components of the leaves in the end of growing season (late September-early October). The Rg$_1$ content of the leaves may be 2-3 times higher than that of Rb$_1$ (Ma et al. 1996).

The seed oil of American ginseng was found to contain high amounts of sterols by one group of researchers (Matsumoto et al. 1986), while another team reported sesquiterpenes as the primary constituents, with β-farnesene being the most common (Meng et al. 2001).

Data on the content of ginsenosides in the aerial parts of American ginseng is included in Table 14.
<table>
<thead>
<tr>
<th>Ginsenoside*</th>
<th>Leaf content, mg/g</th>
<th>Stem content, mg/g</th>
<th>Berry content, mg/g</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rb₁</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.02</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.3</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.77 ± 0.42**</td>
<td>1.35 ± 0.02 (s)</td>
<td>—</td>
<td>Lang et al. 1993</td>
</tr>
<tr>
<td></td>
<td>1.02</td>
<td>—</td>
<td>1.75</td>
<td>Li TSC et al. 1996</td>
</tr>
<tr>
<td></td>
<td>1.45-4.32***</td>
<td>0.74-2.55</td>
<td>—</td>
<td>Qu et al. 2009*</td>
</tr>
<tr>
<td><strong>Rb₂</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15.9</td>
<td>—</td>
<td>—</td>
<td>Lang et al. 1993</td>
</tr>
<tr>
<td></td>
<td>6.2</td>
<td>—</td>
<td>—</td>
<td>Li TSC et al. 1996</td>
</tr>
<tr>
<td></td>
<td>18.22 ± 1.35</td>
<td>1.06 ± 0.06</td>
<td>—</td>
<td>Qu et al. 2009</td>
</tr>
<tr>
<td></td>
<td>11.94</td>
<td>—</td>
<td>14.16</td>
<td>Wang et al. 2006</td>
</tr>
<tr>
<td></td>
<td>14.2-17.9</td>
<td>1.32-1.88</td>
<td>—</td>
<td>Zhang K et al. 2008</td>
</tr>
<tr>
<td><strong>Rb₃</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>49.2</td>
<td>—</td>
<td>—</td>
<td>Lang et al. 1993</td>
</tr>
<tr>
<td></td>
<td>46.36 ± 0.28</td>
<td>3.75 ± 0.03</td>
<td>—</td>
<td>Li TSC et al. 1996</td>
</tr>
<tr>
<td></td>
<td>47.07</td>
<td>—</td>
<td>53.48</td>
<td>Qu et al. 2009</td>
</tr>
<tr>
<td></td>
<td>47.4-62.7</td>
<td>4.26-6.16</td>
<td>—</td>
<td>Wang et al. 2006</td>
</tr>
<tr>
<td></td>
<td>5.6</td>
<td>—</td>
<td>—</td>
<td>Zhang K et al. 2008</td>
</tr>
<tr>
<td><strong>Rc</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.2</td>
<td>—</td>
<td>—</td>
<td>Lang et al. 1993</td>
</tr>
<tr>
<td></td>
<td>5.60 ± 0.51</td>
<td>0.28 ± 0.03</td>
<td>—</td>
<td>Li TSC et al. 1996</td>
</tr>
<tr>
<td></td>
<td>3.84</td>
<td>—</td>
<td>6.8</td>
<td>Qu et al. 2009</td>
</tr>
<tr>
<td></td>
<td>6.84-9.90</td>
<td>0.84-1.36</td>
<td>—</td>
<td>Wang et al. 2006</td>
</tr>
<tr>
<td><strong>Rd</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>29.6</td>
<td>—</td>
<td>—</td>
<td>Lang et al. 1993</td>
</tr>
<tr>
<td></td>
<td>17.4</td>
<td>—</td>
<td>—</td>
<td>Li TSC et al. 1996</td>
</tr>
<tr>
<td></td>
<td>28.06</td>
<td>4.45 ± 0.43</td>
<td>—</td>
<td>Qu et al. 2009</td>
</tr>
<tr>
<td></td>
<td>37.01</td>
<td>—</td>
<td>8.47</td>
<td>Wang et al. 2006</td>
</tr>
<tr>
<td></td>
<td>18.9-41.2</td>
<td>2.87-6.16</td>
<td>—</td>
<td>Zhang K et al. 2008</td>
</tr>
<tr>
<td><strong>Re</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>13.1†</td>
<td>—</td>
<td>—</td>
<td>Lang et al. 1993</td>
</tr>
<tr>
<td></td>
<td>15.6</td>
<td>—</td>
<td>—</td>
<td>Li TSC et al. 1996</td>
</tr>
<tr>
<td></td>
<td>34.19 ± 1.93</td>
<td>5.52 ± 0.18</td>
<td>—</td>
<td>Qu et al. 2009</td>
</tr>
<tr>
<td></td>
<td>17.78</td>
<td>—</td>
<td>16.63</td>
<td>Wang et al. 2006</td>
</tr>
<tr>
<td></td>
<td>16.4-29.3</td>
<td>5.20-9.81</td>
<td>—</td>
<td>Zhang K et al. 2008</td>
</tr>
<tr>
<td><strong>Rg₁</strong></td>
<td>see Re</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.8</td>
<td>—</td>
<td>—</td>
<td>Lang et al. 1993</td>
</tr>
<tr>
<td></td>
<td>9.58 ± 0.12</td>
<td>0.45 ± 0.06</td>
<td>—</td>
<td>Li TSC et al. 1996</td>
</tr>
<tr>
<td></td>
<td>6.72</td>
<td>—</td>
<td>0.44</td>
<td>Qu et al. 2009</td>
</tr>
<tr>
<td></td>
<td>2.97-7.93</td>
<td>1.60-2.53</td>
<td>—</td>
<td>Wang et al. 2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Zhang K et al. 2008</td>
</tr>
<tr>
<td><strong>F₁₁</strong></td>
<td>19.41 ± 0.11</td>
<td>3.15 ± 0.03</td>
<td>—</td>
<td>Qu et al. 2009</td>
</tr>
<tr>
<td><strong>Ro</strong></td>
<td>trace</td>
<td>—</td>
<td>—</td>
<td>Lang et al. 1993</td>
</tr>
<tr>
<td><strong>Total ginsenosides</strong></td>
<td>115.4</td>
<td>—</td>
<td></td>
<td>Lang et al. 1993</td>
</tr>
<tr>
<td></td>
<td>41.8</td>
<td>—</td>
<td>—</td>
<td>Li TSC et al. 1996</td>
</tr>
<tr>
<td></td>
<td>165.25 ± 5.18</td>
<td>20.23 ± 0.87</td>
<td>—</td>
<td>Qu et al. 2009</td>
</tr>
<tr>
<td></td>
<td>126.2</td>
<td>102.5</td>
<td>—</td>
<td>Wang et al. 2006</td>
</tr>
</tbody>
</table>

* Or pseudoginsenoside, as in pseudoginsenoside F₁₁.
** Mean ± SD in 5-year-old leaves.
*** Where multiple ages are reported, data is a range covering all ages (Zhang K et al. 2008, 1-4 years old).
† Protopanaxatriols (Re and Rg₁) reported as a single value.
Analytical
The main analytes of interest in Panax spp. plants and products are ginsenosides (see Constituents). The metabolites of these steroidal saponins that result from interaction with mammalian gut flora following ingestion are hypothesized to be primarily responsible for the pharmacological activity of the plant. To date, there have been approximately 30 different ginsenosides identified. However, within the primary commercial species of ginseng (P. quinquefolius, P. ginseng, P. notoginseng) 6 ginsenosides predominate (Rb1, Rb2, Rc, Rd, Re, and Rg1). Cultivated American ginseng root is best characterized by the presence of ginsenosides Rb1 and Re and generally low amounts of Rg1, while wild and woods-grown American ginseng roots may have higher amounts of Rg1; neither have ginsenoside Rf, while both exhibit the presence of pseudoginsenoside F11. American ginseng leaf extract, which sometimes occurs as an adulterant in the American ginseng root market, is characterized by the presence of high amounts of ginsenoside Rb1 and low amounts of Rb2. In Asian ginseng (P. ginseng) root the total concentration of ginsenosides is lower than that in American ginseng, with multiple ginsenosides (Rb1, Rb2, Rc, Rd, Re, Rf, Ro) present in moderate amounts and often with slightly higher levels of Rg1. Tienchi ginseng (P. notoginseng) typically contains very high levels of both Rb1 and Rg1, with other ginsenosides present in relatively low amounts or undetectable.

High Performance Thin Layer Chromatography (HPTLC) for the Identification of American Ginseng Root
The HPTLC method was adapted from a method by Xie and Yan (1988), which forms the basis of the identification method included in the Pharmacopoeia of the People's Republic of China (2005). This was further optimized by CAMAG (Muttenz, Switzerland) for identification and differentiation of Asian ginseng, American ginseng, and Tienchi ginseng. The HPTLC fingerprint of American ginseng is relatively consistent and can be used for the positive identification of American ginseng root products as well as the detection of other species of Panax. Admixtures of the species are difficult to distinguish.

Sample Preparation:
Place 1 g of finely powdered sample in a centrifuge tube, add 10 mL of absolute ethanol, mix well, and sonicate for 10 minutes. Centrifuge or filter the extract through a syringe filter. The supernatant is the test solution. Liquid extracts can be applied to the plate directly following appropriate dilution with ethanol.

Standards Preparation:

   a) Botanical reference material.
   b) Chemical standards (optional).
Individually dissolve 1 mg of each ginsenoside standard (e.g., Rb1, Rb2, Rc, Rd, Re, Rf, Rg1, Rg2, and pseudoginsenoside F11 [ChromaDex, USA]) in 5 mL of methanol.

Reagent Preparation:
Sulfuric acid reagent: Carefully add 20 mL of sulfuric acid to 180 mL of ice-cold methanol. Mix well. Bring to room temperature.

Chromatographic Conditions:
Stationary Phase
HPTLC plates 10 × 10 cm or 20 × 10 cm silica gel 60 F254 (Merck or equivalent).
Relative Humidity
30-35%.
Mobile Phase

Sample Application:
Apply 10 µL of the sample, 10 µL of botanical standard preparation, or 5 µL of each chemical standard as 8 mm bands, 2 mm apart from each other. Application position should be 8 mm from the lower edge of the plate and at least 15 mm from the left and right edges of the plate.

Development:
Line a twin trough chamber with filter paper. Add 10 mL of developing solvent for a 10 × 10 cm chamber, 20 mL for a 20 × 20 cm chamber, or enough to cover the bottom with a 5 mm level if using a flat bottom chamber. Let saturate for 20 minutes. Measure and mark the developing distance 80 mm from the lower edge of the plate. Introduce the plate into the chamber with the developing layer towards the inside, close the chamber, and allow the solvent to reach the mark. Remove the plate and dry for 5 min in a stream of cool air.

Detection:
Immerse the plate in sulfuric acid reagent for 1 second or spray the reagent evenly on the plate surface. Heat to 100 °C for 5 minutes. Examine the plate under white light and then UV 366 nm.

Results:
Compare to the chromatograms provided.
Figure 15a  HPTLC chromatogram of cultivated American ginseng root (sulfuric acid reagent, white light)

Discussion of the chromatogram.

All standards in Lane 1 appear as purple bands. Bands of different intensities, matching ginsenosides Rb₁, Rc, Re, Rd, Rg₁, and Rg₂, are seen in the samples (Lanes 2-12). In the leaf sample (Lane 13), a strong band is also seen at the position of ginsenoside Rb₂. Ginsenoside Rf is notably missing from all American ginseng samples. Ginsenoside Rf is characteristic of Asian ginseng and is absent in American ginseng. A band located just below ginsenoside Rg₂ is detected in all samples and is particularly strong in the leaf sample (Lane 13). This band corresponds to pseudoginsenoside F₁₁, found only in American ginseng (also see Figure 18). The strongest bands are seen for ginsenoside Rb₁ and Re. All samples show a sharp purple band at R_f 0.5. At least one brownish and one pink zone are seen in the upper R_f region and two or more greenish zones occur close to the application position.

Lane 1: Ginsenoside standards (with increasing R_f value): Rb₁, Rb₂, Rc, Re, Rd, Rg₁, Rf, Rg₂.
Lane 2: Cultivated American ginseng root.
Lane 3: Cultivated American ginseng root.
Lane 4: Cultivated American ginseng root.
Lane 5: Cultivated American ginseng root.
Lane 6: Cultivated American ginseng root.
Lane 7: Cultivated American ginseng root.
Lane 8: Cultivated American ginseng root.
Lane 9: Cultivated American ginseng root.
Lane 10: Cultivated American ginseng root.
Lane 11: Cultivated American ginseng root.
Lane 12: Cultivated American ginseng root.
Lane 13: Cultivated American ginseng leaves.
Figure 16a  HPTLC chromatogram of wild and woods-grown American ginseng root (sulfuric acid reagent, white light)

Discussion of the chromatogram
All standards (Lane 7) appear as purple bands. Bands of different intensities, matching ginsenoside \( \text{Rb}_1 \), \( \text{Rc} \), \( \text{Re} \), \( \text{Rd} \), \( \text{Rg}_1 \), and \( \text{Rg}_2 \), are seen in all samples (Lanes 1-6 and 8-17). The band seen at the position corresponding to ginsenoside \( \text{Rb}_2 \) is of a different color than the standard. A band located just below ginsenoside \( \text{Rg}_2 \) is detected in all samples and is particularly strong in the wild ginseng samples on Lanes 1-6. This band corresponds to pseudoginsenoside \( \text{F}_{11} \), found only in American ginseng (also see Figure 18). In the wild ginseng samples (Lanes 1-6), the overall content of ginsenosides is very high; the strongest bands are seen for ginsenosides \( \text{Rb}_1 \), \( \text{Rg}_1 \), and pseudoginsenoside \( \text{F}_{11} \). The woods-grown samples in Lanes 12-17 are more similar in their profile to the cultivated samples (see Figure 15). The strongest bands are seen for ginsenosides \( \text{Rb}_1 \) and \( \text{Re} \). The samples in Lanes 8-11 have an overall content of ginsenosides similar to those on Lanes 12-17 but with a pattern that is more similar to that of the samples on Lanes 1-6. All samples show a sharp purple band at \( R_f = 0.5 \). At least one brownish and one pink zone is seen in the upper \( R_f \) region and two or more greenish zones occur close to the application position.

Figure 16b  HPTLC chromatogram of wild and woods-grown American ginseng root (sulfuric acid reagent, UV 366 nm)

Discussion of the chromatogram
All standards (Lane 7) appear as fluorescing bands. The protopanaxadiols (\( \text{Rb}_1 \), \( \text{Rb}_2 \), \( \text{Rc} \), \( \text{Rd} \)) appear bluish, and the protopanaxatriols (\( \text{Re} \), \( \text{Rg}_1 \), \( \text{Rf} \), \( \text{Rg}_2 \)) are more pinkish. Bands of different intensities, matching ginsenosides \( \text{Rb}_1 \), \( \text{Rc} \), \( \text{Re} \), \( \text{Rd} \), \( \text{Rg}_1 \), and \( \text{Rg}_2 \), are seen in all samples (Lanes 1-6 and 8-17). A brownish fluorescing band located just below ginsenoside \( \text{Rg}_2 \) is detected in all samples. This band corresponds to pseudoginsenoside \( \text{F}_{11} \), found only in American ginseng (see Figure 18). All samples show a sharp thin band at \( R_f = 0.5 \). Additional fluorescing broad bands are seen in the upper third of the chromatogram, and one blue and one brown zone below the ginsenosides.

Lane 1:  Wild American ginseng root.
Lane 2:  Wild American ginseng root.
Lane 3:  Wild American ginseng root (“body”).
Lane 4:  Wild American ginseng rhizome (“neck”).
Lane 5:  Wild American ginseng root (“body”).
Lane 6:  Wild American ginseng rhizome (“neck”).
Lane 7:  Ginsenoside standards (with increasing \( R_f \) value): \( \text{Rb}_1 \), \( \text{Rb}_2 \), \( \text{Rc} \), \( \text{Re} \), \( \text{Rd} \), \( \text{Rg}_1 \), \( \text{Rf} \), \( \text{Rg}_2 \).
Lane 8:  Woods-grown American ginseng root.
Lane 9:  Woods-grown American ginseng root.
Lane 10: Woods-grown American ginseng root.
Lane 11: Woods-grown American ginseng root.
Lane 12: Woods-grown American ginseng root.
Lane 14: Woods-grown American ginseng root.
Lane 15: Woods-grown American ginseng root.
Lane 16: Woods-grown American ginseng root.
Lane 17: Woods-grown American ginseng root.
Figure 17a  HPTLC comparison of different ginseng species (sulfuric acid reagent, white light)

Discussion of the chromatogram

All standards (Lanes 1-9) appear as purple bands. Bands of different intensities, matching ginsenoside Rb1, Rc, Re, Rd, Rg1, and Rg2, are seen in the American ginseng samples (Lanes 10-12). In the leaf sample (Lane 11), a strong band is also seen at the position of ginsenoside Rb2. A band located below ginsenoside Rg1 and above ginsenoside Rf is detected in all American ginseng samples. This band corresponds to pseudoginsenoside F11 found only in American ginseng. The amount and proportion of ginsenosides vary in the cultivated (Lane 10) and wild (Lane 12) American ginseng samples. In American ginseng leaf sample, the strongest band is seen at the position of ginsenoside Rb2 and likely represents ginsenoside Rb3. Bands of different intensities, matching all ginsenoside standards, are seen in the Asian ginseng samples (Lanes 13-16). Ginsenoside Rf is characteristic for Asian ginseng and is absent in American ginseng. In most Asian ginseng samples, the relative intensity of all ginsenosides is similar. Bands of different intensities, matching ginsenosides Rb1, Rc, Rd, Re, Rg1, and Rg2, are seen in the sample of Tienchi ginseng (Lane 17). In the same sample, very strong bands corresponding to ginsenosides Rb1, Re, and Rg1 are seen. The purple band seen in the sample above ginsenoside Rg1 possibly corresponds to notoginsenoside R1 found only in Tienchi ginseng. Additionally, in all samples, up to 3 purple-gray zones are located above the position of the ginsenoside standards. Diffuse zones are located in the upper third of the chromatograms, and a brown zone close to the application position.

Figure 17b  HPTLC comparison of different ginseng species (sulfuric acid reagent, UV 366 nm)

Discussion of the chromatogram

All standards (Lanes 1-9) appear as fluorescing bands. The propanaxadiols (Rb1, Rb2, Rc, Rd) appear bluish, and the propanaxatriols (Re, Rg1, Rf, Rg2) are more pinkish. For discussion of samples, refer to the previous chromatogram.

Lane 1: Ginsenoside Rb1.
Lane 2: Ginsenoside Rb2.
Lane 3: Ginsenoside Rc.
Lane 4: Ginsenoside Rd.
Lane 5: Ginsenoside Re.
Lane 6: Ginsenoside Rf.
Lane 7: Ginsenoside Rg1.
Lane 8: Ginsenoside Rg2.
Lane 9: Ginsenoside standards (with increasing Rf value): Rb1, Rb2, Rc, Re, Rd, Rg1, Rf, Rg2.
Lane 10: Cultivated American ginseng root.
Lane 11: Cultivated American ginseng leaves.
Lane 12: Wild American ginseng rhizome.
Lane 13: Kirin ginseng (Asian ginseng) root.
Lane 14: Shih Chu ginseng (Asian ginseng) root.
Lane 15: White ginseng (Asian ginseng) root.
Lane 16: Woods-grown Asian ginseng root.
Lane 17: Tienchi ginseng root.
**Figure 18a** HPTLC comparison of different ginseng species (sulfuric acid reagent, white light)

**Discussion of the chromatogram**

All standards (Lanes 1-4) appear as brownish bands. Bands of different intensities, matching ginsenoside $R_{b_1}$, $R_{b_2}$, $R_{c}$, $R_{d}$, $R_{g_1}$, and $R_{g_2}$, are seen in all samples. A band corresponding to ginsenoside $R_f$ is seen in Asian ginseng only. Pseudoginsenoside $F_{11}$ is detected only in American ginseng. Tienchi ginseng shows an intense band about the position of ginsenoside $R_{h_1}$ (probably notoginsenoside $R_i$). The intensity of all bands is similar in Asian ginseng, while American ginseng and Tienchi ginseng show prominent bands for ginsenosides $R_{b_1}$, $R_{e}$, and $R_{g_2}$. Additional brown to green bands are seen above ginsenoside $R_{h_2}$ and below ginsenoside $R_{b_1}$ in all samples.

Lane 1: Ginsenoside standards (with increasing $R_f$ value): $R_{b_1}$, $R_{b_2}$, $R_{c}$, $R_{d}$.
Lane 2: Ginsenosides $R_{b_2}$, $R_{e}$, $R_{f}$, $R_{g_2}$.
Lane 3: Ginsenosides $R_{g_1}$, $R_{g_2}$, $R_{h_1}$, $R_{h_2}$.
Lane 4: Pseudoginsenoside $F_{11}$, panaxatriol, panaxadiol.
Lane 5: Asian ginseng root.
Lane 6: American ginseng root (cultivated).
Lane 7: Tienchi ginseng root.

---

**Figure 18b** HPTLC comparison of different ginseng species (*Panax* spp.) (sulfuric acid reagent, UV 366 nm)

**Discussion of the chromatogram**

A similar picture is seen, but better differentiation of the compounds can be made, due to the coloration of the zones. Ginsenosides $R_{b_1}$, $R_{b_2}$, $R_{c}$, $R_{d}$, $R_{g_1}$, and $R_{g_2}$ (protopanaxadiol derivatives) are blue, and ginsenosides $R_{e}$, $R_{f}$, $R_{g_1}$, $R_{g_2}$, and $R_{h_1}$ (protopanaxatriol derivatives) and pseudoginsenoside $F_{11}$ are brownish.
High Performance Liquid Chromatography (HPLC) for Determination of Ginsenosides in American Ginseng Root

The following method was chosen after a comparative review of numerous ginsenoside methods \( n = 25 \) and was selected from the monograph for Asian ginseng included in the *United States Pharmacopeia* (USP34 2010b). The extraction protocol was subsequently optimized and the entire methodology was subjected to a single-laboratory-validation (SLV) study according to the guidelines of AOAC International using individual ginsenosides standards (Brown 2011). The study demonstrated that the method is suitable for quantitation of the 6 major ginsenosides (Rb\(_1\), Rb\(_2\), Rc, Rd, Re, and Rg\(_1\)) in *Panax* spp. roots and ginseng preparations, such as tablets, hard shell and soft gel capsules, glycerin extracts, and hydro-alcohol tinctures. The method was validated for assaying products with the ginsenoside content in the range of 1.49-10.32% (w/w). Additionally, the method can be used for determining the presence or absence of ginsenoside Rf. Ginsenoside Rf is commonly used to differentiate between Asian ginseng and American ginseng, being generally absent in American ginseng and present in Asian ginseng. Other sources (e.g., USP34 2010a) use various ginsenoside ratios as identifying characteristics. However, some reports suggest that American ginseng roots, both wild (Ma et al. 1996) and cultivated (Schlag and McIntosh 2006), may exhibit atypical ginsenoside ratios. Therefore, the use of ginsenoside ratios for species identification is not reliable.

One challenge with the analysis of ginseng species is the presence of neutral and acidic malonyl ginsenosides in crude root samples. The acidic malonyl ginsenosides are unstable and are susceptible to conversion to their demalonylated neutral counterparts. These malonyl ginsenosides make up a significant amount of the total ginsenosides in American ginseng (Awang 2000; Ren and Chen 1999a). Thus, uncontrolled hydrolysis of these compounds during analytical sample preparation could result in reporting inconsistent values for the levels of the neutral ginsenosides. The method described here includes a base hydrolysis step to force the conversion of the acidic ginsenosides to their neutral counterparts for a more accurate assay.

It should also be noted that ginsenosides possess a poor chromophore (Fuzzati 2004). Thus, their limited UV absorption can limit the sensitivity that can be achieved through UV detection. Despite this limitation, numerous methods have successfully employed UV detection for ginsenosides and UV detectors have sufficient sensitivity to detect and quantify the primary ginsenosides (Brown 2011). The common use of UV detectors in the industrial settings also allows for the broad applicability of this method.

Sample Preparation

Dry roots
Grind roots to 60 mesh. Weigh approximately 400 mg of powdered root material. Record the accurate weight. Transfer the powder into a 50 mL centrifuge tube. Add 10 mL of 70:30 methanol/water as the extraction solution. Mix the tube for 1 minute on a vortex mixer and then sonicate for 25 minutes at room temperature. Following sonication centrifuge the tube at 4000 rpm for 5 minutes. Transfer the supernatant into a 25 mL volumetric flask. Add 10 mL of extraction solution to the centrifuge tube and mix again for 1 minute then sonicate for 25 minutes. Centrifuge the tube and transfer the supernatant to the same 25 mL volumetric flask used to collect the first extract. Extract the sample in the tube one more time with 4 mL of extraction solvent. Mix the tube again with the vortex mixer for 1 minute and sonicate for 25 minutes. Centrifuge and transfer the supernatant to the 25 mL volumetric flask. Rinse the sample material in the tube by adding 1 mL of extraction solvent, mix the tube for 5 minutes on the vortex mixer, centrifuge for 5 minutes, and transfer the supernatant to the 25 mL volumetric flask. Prepare the flask up to volume with the 70:30 methanol-water solution, cap, and repeatedly invert to ensure complete mixing of the solution.

Hydrolysis Step
Transfer 1 mL of solution into a 2-mL microcentrifuge tube. Pipette 100 µL of 5% KOH solution into the tube and mix the tube with a vortex mixer for 5 seconds. Allow the tube to sit for 2 hours at room temperature, protected from direct light. Neutralize the solution by pipetting 100 µL of 14% KH\(_2\)PO\(_4\) solution into the tube and then mixing the tube with a vortex mixer for 5 seconds. Filter approximately 1 mL of the solution into an HPLC vial, using a syringe fitted with a 45-µm PTFE filter, and analyze as per the chromatography method described below.

Powdered Extracts
Follow the steps described above for crude roots using a sample weight of 200 mg. Extracts do not typically require a hydrolysis step, as conversion of malonylated ginsenosides usually occurs in the extraction process.

Capsules
Weigh and combine the contents of no fewer than 10 capsules. Follow the steps described above for crude roots using a sample weight of 400 mg for capsules containing root material and a sample weight of 200 mg for capsules containing extract material.

Tablets
Weigh and finely powder no fewer than 10 tablets. Follow the steps described above for crude roots using a sample weight of 400 mg.

Liquid extracts
Liquid extracts can be diluted with the appropriate solvent to the desired concentration and filtered if necessary.

Note: The method has not been validated on liquid extracts.

Standards Preparation
The 6 major ginsenosides of interest for quantification of American ginseng are Rb\(_1\), Rb\(_2\), Rc, Rd, Re, and Rg\(_1\). Ginsenoside Rf is not usually quantified, and only its presence or absence is typically recorded. As such, it is recommended that mixed standard solutions of the ginsenosides Rb\(_1\), Rb\(_2\), Rc, Rd, Re, and Rg be prepared for quantification. If required, Rf may be included in the standard mix or run separately (see below) for detection of this ginsenoside for
purposes of species differentiation or determining the potential for admixtures with other Panax species.

To prepare the quantification stock standard solutions, calculate, based on the stated purity of the standard, the required amount of each ginsenoside standard to be quantified (Rb₁, Rb₂, Rc, Rd, Re, and Rg₁) to obtain a concentration of about 1500 µg/mL of each compound when dissolved in 10 mL of solvent. Accurately weigh the calculated amount of each ginsenoside standard into a separate 10 mL volumetric flask. Bring to half volume with methanol and mix until the compounds are completely dissolved. Bring to volume using methanol and mix well to obtain separate 1000 µg/mL standard stock solution of ginsenoside Rf.

**Linearity Range**
The linear range of the method is 5-131 µg/mL for ginsenoside Rf, 16-396 µg/mL for ginsenoside Re, 39.993 µg/mL for ginsenoside Rb₂, 6-135 µg/mL for ginsenoside Rc, 7-166 µg/mL for ginsenoside Rb₁, and 8-200 µg/mL for ginsenoside Rd.

**Storage of Reference Standards**
Store at -20 °C, protected from light, when not in use.

**Chromatographic Conditions**

**Apparatus**
HPLC system equipped with an autosampler, binary pump, and diode array detector.

**Column**
Luna, C18(2), 5 µm, 4.5 mm × 150 mm, 100 Å pore size (Phenomenex, Torrance, CA).

Note: In addition to the column used above, an alternative column is the Luna, C18, 2.1 mm × 250 mm, 5 µm (Phenomenex, Torrance, CA). It is a smaller bore column that only uses approximately 25% of the required mobile phases of a 4.5 mm column and gives good resolution. Use of alternative columns will result in changes in the chromatography.

**Column temperature**
25 °C.

**Injection volume**
10 µL.

**Mobile phase**
Gradient:

<table>
<thead>
<tr>
<th>Time interval (min)</th>
<th>Acetonitrile aqueous solution (concentration %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-8</td>
<td>24</td>
</tr>
<tr>
<td>8-18</td>
<td>32</td>
</tr>
<tr>
<td>18-25</td>
<td>40</td>
</tr>
<tr>
<td>25-42</td>
<td>48</td>
</tr>
<tr>
<td>43-44</td>
<td>100</td>
</tr>
<tr>
<td>44-45</td>
<td>24</td>
</tr>
</tbody>
</table>

**Flow rate**
1.5 mL/min.

**Detection (diode array detector)**
203 nm.

**Run time**
45 min.

**Post time**
5 min.

**Quantitation**
Inject each standard preparation to generate a standard curve based on the peak area vs. concentration in µg/mL for each ginsenoside to be quantified. Figure 19 shows a typical chromatogram for a mixed ginsenoside standard. Simple linear regression analysis of the peak area of the analytes vs. the concentration of 1000 µg/mL of ginsenoside Rf when dissolved in 10 mL of solvent. Accurately weigh approximately the calculated amount of the ginsenoside Rf standard into a 10 mL volumetric flask. Bring to half volume with methanol and mix until the compounds are completely dissolved. Bring to volume using methanol and mix well to obtain separate 1000 µg/mL standard stock solution of ginsenoside Rf.
analyte concentrations can be used to generate the equation of the lines of each of the curves.

The concentration of each ginsenoside (µg/mL) as determined by HPLC is calculated using equation (i):

\[
(i) \quad X = \frac{\hat{Y} - b_0}{b_1}
\]

Where:
- \(X\) = the concentration of ginsenoside (µg/mL);
- \(\hat{Y}\) = the analyte peak area (mAu·s);
- \(b_0\) = the calculated intercept of the calibration curve;
- \(b_1\) = the calculated slope of the calibration curve.

The amount of each ginsenoside in the test sample in % (w/w) is calculated using equation (ii):

\[
(ii) \quad A = \frac{X \cdot V \cdot D}{W \cdot 10}
\]

Where:
- \(A\) = the amount of ginsenoside in the test sample in % (w/w);
- \(X\) = the concentration of ginsenoside (µg/mL) determined from equation (i);
- \(V\) = the final volume of the sample preparation (mL);
- \(D\) = the dilution factor of the sample preparation;
- \(W\) = the initial sample weight of the test sample (mg).

Calculate the percentage of total ginsenosides in the sample by adding the percentages of individual ginsenosides.

**Species Differentiation**

Identification of American ginseng root and quantification of ginsenosides by HPLC can be performed in a single analysis. The main identifying characteristic of American ginseng root detectable by HPLC is the absence of ginsenoside Rf. Detection of ginsenoside Rf in an American ginseng sample indicates the potential presence of other *Panax* species.

Detection of ginsenoside Rf is accomplished by comparison against a ginsenoside Rf calibration standard. An approximately 1 mL aliquot of the ginsenoside Rf stock standard solution is filtered through a 0.45 µm polytetrafluoroethylene (PTFE) syringe filter into a HPLC vial and analyzed using the chromatography methodology described above. The presence or absence of the ginsenoside Rf peak in a test sample can be established through comparison with the peak retention time and UV profile obtained from analysis of the ginsenoside Rf standard (Figure 20).

Representative chromatograms for American ginseng, Asian ginseng, and Tienchi ginseng root material are shown in Figures 21a-d.

**Limit Tests**

<table>
<thead>
<tr>
<th>Test</th>
<th>Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foreign Matter</td>
<td>Not more than 2.0% (USP34 2010a)</td>
</tr>
<tr>
<td>Total Ash</td>
<td>Not more than 8.0% (USP34 2010a)</td>
</tr>
<tr>
<td>Acid-insoluble Ash</td>
<td>Not more than 1.0% (USP34 2010b)</td>
</tr>
<tr>
<td>Loss on Drying</td>
<td>Not more than 10.0% determined when 1.0 g of the pulverized root is dried at 105 °C for 2 hours (USP34 2010a).</td>
</tr>
</tbody>
</table>
Therapeutics

There is a relative abundance of research on the medicinal properties of American ginseng and its constituents. However, there are only a few properly designed clinical trials, which makes it difficult to fully assess the therapeutic value of the herb.

Much of the pre-clinical research has focused on administration of single compounds, predominantly ginsenosides, found in American ginseng roots, or combinations of compounds. Although these data are not sufficient to establish clinical relevance, the action of individual compounds may provide mechanistic and physiological support for some of the herb’s putative actions. An important segment of pre-clinical studies focuses on biologically relevant metabolites of ginsenosides.

Pharmacokinetics

There is limited information on the pharmacokinetics of American ginseng. Most of the data come from studies in animals, performed using Asian ginseng (Panax ginseng), its extracts, or isolated ginsenosides from Panax spp., with a small selection of studies investigating the effects in humans. American and Asian ginsengs contain many of the same compounds and occur in very similar matrices, so the pharmacokinetics of the two species is expected to be similar.

Ginsenosides are the primary class of American ginseng’s active constituents. Pharmacokinetics of isolated ginsenosides has been studied in multiple models using various routes of administration (oral, intragastric, and i.v.). Hasegawa (2004) reported oral bioavailability of Rb1 to be in the range of 0.1-4.4%, Rb2 3.7%, and Rg2 1.9-18.4%. Xu et al. (2003) found that ginsenosides Rb1 and Rg1 from Tienci ginseng (P. notoginseng) followed a two-compartment model in the serum of rats. The bioavailability of ginsenoside Rb1, absorbed from the digestive tract, was 4.35%, with the half-life of the α-phase lasting 23.4 min and that of the β-phase 17.96 h. The oral bioavailability of Rg1 was 18.40%, and the half-lives of Rg2 were 24.2 min for the α-phase and 14.13 h for the β-phase. In the mini-pig, the terminal half-life of ginsenoside Rb1 was 16 hours, while for ginsenoside Rg1, it was 27 min (Jenny and Soldati 1985). Ginsenoside Rg1 administered to rats at 100 mg/kg via intragastric route reached a maximum serum concentration of 0.9 µg/mL after 30 minutes and was undetectable after 6 hours by thin layer chromatography (TLC) (Odani et al. 1983a). After 15 minutes, there were 42.3 ± 1.6% and 55.6 ± 4.3% of Rg1 left in the stomach and the small intestine, respectively. In fasting Wistar rats divided into three dosage groups (50, 100, or 200 mg/kg), ginsenosides Rb1 and Rd reached the maximum serum concentration at 6-8 hours, independent of the dose, while Rg1 and Re reached their maximum levels at 8 hours, independent of the dose (Lin et al. 2009). Half-life and area under the curve for all ginsenosides can be seen in Table 15.

Incubation of human intestinal bacteria with ginsenoside Rb1 resulted in its conversion into 20(S)-protopanaxadiol via ginsenoside Rd and 20-O-(β-D-glucopyranosyl)-20(S)-protopanaxadiol, also known as IH-901, ginsenoside M1, or compound K (Kobayashi et al. 1994, cited in Shibata 2001).

Compound K (Figure 23) was reported to be the main product of the bacterial metabolic pathway for the protopanaxadiol type of ginsenosides (e.g., Rb1, Rb2, Rc, Rd) in vivo (Hasegawa et al. 1996). Ginsenosides of the protopanaxatriol group (e.g., Re and Rg1) were shown to be metabolized into 20(S)-protopanaxatriol via ginsenoside Rh1 (Hasegawa et al. 1996; Kobayashi et al. 1994, cited in Shibata 2001).

Intragastric administration of radioactively labeled ginsenoside Rb1 to rats at 100 mg/kg resulted in the compound widely distributed to the liver, kidney, lung, heart, pancreas, and brain, with the liver containing the greatest concentration (Karikura et al. 1992). It was determined that ginsenoside Rb1 broke down in the rat large intestine into 6 different metabolites, including ginsenoside Rd. After 24 hours, urine and feces elimination were 2.3% and 84.3% of the dose, respectively. After 48 hours, urine and feces elimination were 3% and 87.3% of the dose, respectively. The elimination amount included both the parent compound and its metabolites (Karikura et al. 1990, 1991).

Complete characterization of the hydrolytic degradation of propanaxadiol ginsenosides by the intestinal bacteria was observed in rats. Six different metabolites of ginsenosides Rh1 (Qian and Cai 2010) and Rb1 (Karikura et al. 1992) were detected in rat feces, including ginsenosides Rd, Rg1, (3-O-(β-D-glucopyranosyl-(1→2)-β-D-glucopyranosyl)-20(S)-protopanaxadiol), F1, (3-O-(β-D-glucopyranosyl)-20-O-(β-D-glucopyranosyl)-20(S)-protopanaxadiol), Rh1 (3-O-(β-D-glucopyranosyl)-20(S)-protopanaxadiol), compound K, and protopanaxadiol (Figure 23).

Compound K and ginsenoside Rh1 were the only products of bacterial hydrolytic degradation of ginsenosides detected in the blood of 2 healthy human subjects administered 700 mg of Asian ginseng extract (Tawab et al. 2003). The extract contained 4% ginsenosides. Ginsenoside Rh1 appeared in the blood 1 hour after administration of the extract, while compound K was detected after 6 hours. Ginsenoside Rh1 was also observed in the blood from one of the subjects between 5 and 8 hours. Ginsenosides Rh2, Rd, Re, Rc, and Rb2 were excreted in the urine between 0 and 3 hours after administration of the extract. Since these ginsenosides were not detected in the plasma, their concentration in the blood was estimated to be very low: 2.8 ng/mL for Rg1, Rd, and Re and 5-20 ng/mL for Rb2, and Re. Ginsenoside Rh1 appeared in the urine after 3 hours, and compound K
and ginsenoside Rb₁ appeared in the urine after 6 hours. At 12-24 hours the excreted compounds were compound K and ginsenoside Rh₁ (Tawab et al. 2003). The amount of compound K detected in the urine of a human subject 16 hours after administration of 10 g of the Asian ginseng extract containing 9-11% of total saponins was 0.2 µg/mL (Hasegawa et al. 1996). Ginsenoside Rb₁ was detected in the plasma of a human subject who ingested 1.5 g of fermented red Asian ginseng product (Hyosam). The maximum concentration was 15.9 ng/mL and was reached in 3 hours (Ji et al. 2004).

Considerable variations have been observed in the intestinal bacterial enzymatic activity in mice (Hasegawa and Uchiyama 1998) and in microflora specimens from human subjects (Yim et al. 2004). The enzymatic potential for metabolizing Rb₁ in microflora specimens taken from 90 mice ranged from 0-83%, with 41% of the animals exhibiting less than 10% hydrolyzing activity. The bacterial enzymatic activity in mice was correlated between mothers and their litters (P < 0.01), suggesting a hereditary effect. Administration of Asian ginseng over 2 weeks caused a 2-fold increase in Rb₁ hydrolysis (P < 0.01) in mice with more than 10% hydrolyzing potential but not in mice with less than 10% hydrolyzing potential. Inoculation of mice with low hydrolyzing potential with the intestinal bacteria from mice with high hydrolyzing potential did not result in increased levels of metabolites, suggesting that genetic factors affecting the binding of bacteria to the intestinal epithelial wall may be involved. More studies are needed to establish the range of bioavailability of the intestinal ginsenoside metabolites in humans.

Based on the experiments performed using i.v. administration, Sawchuck et al. (1980) suggested that protopanaxadiol ginsenosides Rb₂ and Rd possessed plasma protein binding of > 99%, compared to 45.5% and 33.2% for protopanaxatriol ginsenosides Re and Rg₁. Using radioactively labeled ginsenosides, Joo et al. (1982) observed that the total recovery of the radioactivity in rats was only about 30% and concluded that the compounds are not readily extractable and remain in the body mostly bound to macromolecules. Subsequently, protein binding rates of ginsenoside Rg₁ in plasma, liver, testes, and brain of mice were determined in vitro to be 24%, 48%, 22%, and 8%, respectively (Huo et al. 1986). Very small recoveries of intact ginsenosides were made in the liver (0.25% dose) and heart (< 0.1% dose) of rats (Takino et al. 1982, cited in Jia et al. 2009).

A study of rats receiving Rb₁ at a dose of 5 mg/kg i.v. revealed that the ginsenoside followed a two-compartment pharmacokinetic model and was distributed mainly in the kidney (9.0 ± 1.6 µg/g), heart (5.3 ± 0.9 µg/g), lung (3.3 ± 0.5 µg/g), and liver (2.9 ± 0.6 µg/g), with less than 0.5 µg/g in the brain and pancreas (Odani et al. 1983b). The terminal half-life (t₁/₂β) was reported as 14.5 hours with excretion occurring primarily through the urine. Administered at the dose of 70.4 mg/kg i.v., ginsenoside Rb₁ followed a two-compartment model, with the central volume of distribution (Vc) of 0.2707 L, distribution half-life (t₁/₂α) of 0.8417 min, terminal half-life of 169.88 min, AUC of 67067.79 µg·min/mL, and clearance at 2.386 mL/min (Zhao et al. 2007).

Table 15  Half-life (t₁/₂) and area under the concentration-time curve (AUC) of ginsenosides administered p.o. to fasting Wistar rats

<table>
<thead>
<tr>
<th>Doses</th>
<th>Ginsenoside Rb₁</th>
<th>Ginsenoside Re</th>
<th>Ginsenoside Rd</th>
<th>Ginsenoside Rg₁</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg/kg</td>
<td>30.42 hours</td>
<td>n/d</td>
<td>11.09 hours</td>
<td>n/d</td>
</tr>
<tr>
<td>AUC, mg·h/L</td>
<td>506.34</td>
<td>2.928</td>
<td>240.56</td>
<td>7.725</td>
</tr>
<tr>
<td>100 mg/kg</td>
<td>19.38 hours</td>
<td>19.85</td>
<td>1241.10</td>
<td>72.66</td>
</tr>
<tr>
<td>AUC, mg·h/L</td>
<td>706.47</td>
<td>4.971</td>
<td>10108.36</td>
<td>288.42</td>
</tr>
<tr>
<td>200 mg/kg</td>
<td>31.34 hours</td>
<td>99.66</td>
<td>9.83</td>
<td>4.731</td>
</tr>
<tr>
<td>AUC, mg·h/L</td>
<td>12165.36</td>
<td>4.971</td>
<td>10108.36</td>
<td>288.42</td>
</tr>
</tbody>
</table>

Source: Lin et al. (2009).
A study of 3 groups of rats, receiving ginsenoside Re i.v. at the doses of 20, 30, and 40 mg/kg, followed a two-compartment kinetics with reported $t_{1/2\alpha}$ of 6.055, 6.817, 4.499 min, $t_{1/2\beta}$ of 28.96, 30.49, 27.57 min, and AUC of 599.31, 1025.65, 1415.7 min·mg/L, respectively. It was found that the AUC increased proportionally with the dose in a linear pharmacokinetic model (Peng et al. 2006).

Radioactively labeled ginsenoside Rg1, administered i.v. to mice, followed a three-compartment pharmacokinetics model with $t_{1/2\alpha}$ $t_{1/2\beta}$ $t_{1/2\gamma}$ of 25, 0.87, 0.07 hours, respectively (Huo et al. 1986). The compound was distributed, in descending order, to the kidneys, adrenal glands, liver, lung, spleen, pancreas, heart, testes, and brain.

**Clinical Efficacy and Pharmacodynamics**

**Effects on Blood Sugar**

**Human Clinical Trials**

**Effects in Normal Subjects**

A series of experiments compared the effects of different doses and times of administration of American ginseng root on glucose tolerance. In 10 non-diabetic subjects, administration of 3 g of American ginseng root powder 40 minutes prior to a 25-g oral glucose test resulted in a significant decrease of glycemic levels 45 minutes after administration of glucose ($1.7 \pm 1.2$ mmol/L vs. $2.8 \pm 1.0$ mmol/L; $P < 0.05$) and 60 minutes after administration of glucose ($0.1 \pm 0.8$ mmol/L vs. $0.8 \pm 1.1$ mmol/L; $P < 0.05$), compared to placebo (Vuksan et al. 2000a). The measurements were taken at 15, 30, 45, 60, and 90 minutes after the start of glucose intake. The decrease was also significant for the area under the curve (AUC) ($93 \pm 31$ mmol/L vs. $122 \pm 39$ mmol/L, an $18\% \pm 31\%$ reduction; $P < 0.05$). Similar decreases were observed in subjects ($n = 10$) with normal glucose tolerance with administration of 1, 2, 6, or 9 g of the root powder at 40 minutes before the glucose challenge (Vuksan et al. 2000c, 2001). Earlier time of administration relative to the glucose challenge (80 or 120 minutes prior to the intake of glucose) did not change the effect of 3, 6, or 9 g doses of the root (Vuksan et al. 2000c). However, no difference from placebo was observed when the powder was taken 10 or 20 minutes before the glucose challenge (Vuksan et al. 2001) or at the same time as the glucose (Vuksan et al. 2000a). The treatment was well-tolerated with no adverse effects except for 1 case of mild insomnia.

The ginsenoside content of the powder used in the above studies was 3.21% by weight (Rb, 1.53%; Re, 0.83%; Rd, 0.44%). To test the effect of variation in ginsenosides content of different batches of American ginseng root, Dascalu et al. (2007) compared the glycemia-lowering effect of 5 different batches of Ontario-grown American ginseng in 12 healthy volunteers. The total ginsenosides content in the batches differed from 5.16% to 6.56%, with the protopanaxadiol (PPD):protopanaxatriol (PPT) ratio ranging from 2.58 to 3.22. The subjects were administered 9-g doses of the different batches on separate days 40 minutes prior to 75-g oral glycemic tolerance test with a minimum 3-day washout period between treatments. The control treatment consisted of a glass of water in the same amount used for administration of the ginseng capsules. Blood samples were taken at baseline (-40 minutes), immediately before the consumption of the glucose drink (0 minutes), and at 15, 30, 45, 60, 90, and 120 minutes after the start of its consumption. Plasma glucose and insulin levels were determined for each time point. There was no effect of any of the treatments on premeal glycaemia (0 minutes), compared to the control. Three out of 5 batches caused reductions in glucose levels at 30 and 45 minutes, which were significantly different from placebo ($P < 0.05$ for all). Two out of those 3 batches additionally caused reductions at 60 minutes ($P < 0.05$ for both), and 1 of the 3 batches reduced plasma glucose at 15 minutes ($P < 0.05$). Although the remaining two batches did not cause a statistically significant reduction in plasma glucose when compared to the control, there was no significant difference between all 5 batches in their effect on incremental plasma glucose levels or glucose AUC when compared against each other. The mean reduction in glucose AUC of all treatments was 27.7% ($P < 0.05$). The PPD:PPT ratio showed no correlation with any of the outcomes of the treatments, possibly due to the lack of the statistical resolution. Additionally, a batch of American ginseng root with a low concentration of ginsenosides (1.66% total), administered at the dose of 6 g, did not reach a significant effect on plasma glucose ($P = 0.56$) or insulin ($P = 0.69$) levels in healthy individuals after a 75-g oral glucose tolerance test (Sievenpiper et al. 2003).

Another study compared the effects on glycemia of different types and species of ginseng (cultivated and wild American ginseng, dried or steam-treated Asian ginseng, Tienchi ginseng, *P. japonicus, P. vietnamensis* and Siberian ginseng (eleuthero) (*Eleutherococcus senticosus*) roots in 12 healthy, non-diabetic individuals (Sievenpiper et al. 2004). Three-gram doses of each root variety and two instances of placebo were randomly administered 40 minutes prior to a 75-g oral glucose tolerance test. Measurements of plasma glucose and plasma insulin were taken at 40 minutes before the glucose drink and 0, 15, 30, 45, 60, 90, and 120 minutes after the beginning of the glucose challenge. Incremental values, absolute peak values, and areas under the curves for plasma glucose and plasma insulin were compared. Additionally, whole body insulin sensitivity index and the early insulin secretion index were calculated for each different treatment. Cultivated American ginseng root had a glucose lowering effect on postprandial glucose, decreasing 90-minute plasma glucose, though this did not reach statistical significance ($P = 0.052$, compared to placebo).

**Effects in Subjects with Type 2 Diabetes**

Individuals with type 2 diabetes mellitus ($n = 9$), taking 3 g of American ginseng root 40 minutes before a 25-g oral glucose test, showed significant decrease of glycemic levels at 30 minutes ($3.8 \pm 1.2$ mmol/L vs. $4.8 \pm 0.9$ mmol/L; $P < 0.05$) and 45 minutes ($4.5 \pm 1.1$ mmol/L vs. $5.3 \pm 1.2$ mmol/L; $P < 0.05$) (Vuksan et al. 2000a). When American ginseng was taken at the same time with the glucose, the decreases were significant at 45 minutes ($4.2 \pm 1.3$ mmol/L vs. $5.3 \pm 1.3$ mmol/L; $P < 0.05$) and 60 minutes ($3.6 \pm 1.4$ mmol/L vs. $4.3 \pm 1.3$ mmol/L; $P < 0.05$).
mmol/L vs. 4.9 ± 1.5 mmol/L; P < 0.05). Higher doses of American ginseng root (6 g and 9 g) did not produce a stronger effect, and changes in time of administration (80 or 120 minutes before the glucose) did not significantly affect the results (Vuksan et al. 2000b).

In addition to the human clinical trials cited above, animal and in vitro studies (see below) have shown that the antidiabetic effects of American ginseng may be associated with compound K, a bioavailable intestinal metabolite of PPD ginsenosides. However, a few studies have investigated whether PPT ginsenosides have a similar effect. Ginsenoside Re, a PPT, is the second most prevalent ginsenoside in American ginseng root after ginsenoside Rb1, a PPD. In a recent trial in overweight and obese subjects with either impaired glucose tolerance or newly diagnosed type 2 diabetes, a subgroup of patients (n = 5) was prescribed ginsenoside Re (250 mg/day × 2 weeks followed by 500 mg/day × 2 weeks) (Reeds et al. 2011). The other subject groups were prescribed either red Asian ginseng (Panax ginseng) extract or placebo. The outcome parameters were based on a frequently sampled, modified oral glucose tolerance test (blood samples taken via a catheter at 15 minutes before the test, at the beginning of the test, and at 10, 20, 30, 60, 90, 120, 150, 180, 240, and 300 min after the glucose drink to record plasma glucose, C-peptide, and insulin levels) and measurements of glucose and fatty acid kinetics and insulin action in the muscle tissue via hyperinsulminemic-euglycemic clamp procedure. Body composition of the subjects, including body fat mass and fat-free mass, was assessed before and after the ginsenoside treatment. No changes in any measures, including glucose AUC, insulin AUC, total body insulin sensitivity index, the disposition index (measure of β-cell functionality), glucose rate of appearance, or hepatic insulin sensitivity, were observed after any treatment, compared to initial values. The study provides evidence that the effects of American ginseng on glycemia are unlikely due to ginsenoside Re.

Animal Studies
In studies of ICR mice, acute oral administration of compound K 30 minutes prior to an oral glucose tolerance test (1.5 g/kg) improved glucose tolerance by decreasing the rise in blood glucose and increasing insulin production (Han et al. 2007; Yoon et al. 2007). Long term (25 days to 8 weeks) administration of 10 or 20 mg/kg of compound K to diabetic (C57BL/KsJ db/db) mice resulted in a decrease in fasting blood glucose by 42% (P < 0.05) and 61% (P < 0.001), respectively, reduced inflammation, protected pancreatic islets from destruction, decreased insulin resistance, increased insulin levels (Han et al. 2007), decreased HbA1c levels (P < 0.01), and beneficially affected lipid levels in the liver (Yoon et al. 2007).

Beneficial effects of compound K were also observed on lipid metabolism, which is commonly disrupted in diabetes. Oral administration of 10-20 mg/kg of the compound for 6 weeks produced activation of adenosine monophosphate-activated protein kinase, which in turn reduced the hepatic expression of sterol regulatory element-binding protein and its target genes, fatty acid synthase, stearoyl-CoA desaturase 1, and glycerol-3-phosphate acyltransferase (Yuan et al. 2011). Additionally, compound K enhanced the expression of lipolytic genes peroxisome proliferator-activated receptors α (PPARα) and CD36 in the liver (Yuan et al. 2011), increased the expression of PPARγ, glucose transporter 4, and CD36 in adipocytes, and increased adiponectin levels (Han et al. 2007). When assessed with histological methods, the diabetic-control mice exhibited higher numbers of lipid droplets in the liver and the pancreas, compared to compound K-treated mice.

The involvement of PPARα and PPARγ in the hypoglycemic effect of American ginseng was confirmed by Banz et al. (2007) in rats. Additionally, the inclusion of American ginseng in the animals’ diet led to a significant decrease of the RNA for carnitine palmitoyltransferase 1 (CPT-1) and insulin receptor substrate (IRS) genes in the muscle tissue, and an increase in retinoid X receptor (RXR) RNA. The animals had no differences in body weight and total lipids, compared to controls.

A significant hypoglycemic effect was observed after intraperitoneal (i.p.) injection of American ginseng root polysaccharides quinquefolans A, B, and C (10, 50, and 100 mg/kg) into normal and diabetic mice (Oshima et al. 1987). Quinquefolan A produced the strongest effect in normal mice, causing a 53-55% reduction in plasma glucose levels at all doses 7 hours after administration and a 25% reduction at 10 mg/kg, 26% at 30 mg/kg, and 45% at 100 mg/kg 24 hours after administration (P < 0.01 for all changes). When injected into alloxan-induced hyperglycemic mice, quinquefolan A produced 62, 61, and 71% reduction in the glucose levels 7 hours after administration and 40, 48, and 77% reduction 24 hours after the administration, at the same respective doses (P < 0.01 for all changes). A water extract, injected at 10,000 mg/kg crude drug equivalent, only reduced the blood glucose significantly by 28% after 7 hours (P < 0.01). The effects from i.p. injections cannot be assumed to be duplicated following oral administration.

In Vitro Studies
In a screening procedure for sulfonylurea-like activity of several botanicals, a 70% ethanolic extract (1:40) of American ginseng inhibited the binding of radioactive ligand 3H-glibenclamide to SUR1 receptors (sulfonylurea target) by the average of 45.1%, suggesting a degree of sulfonylurea-like activity (Rotshteyn and Zito 2004). Moreover, treatment of cultured pancreatic β-cell line HIT-T15 with the extract resulted in a significant (P < 0.01) increase in insulin secretion by the cells (EC50 178.9 µg/mL), which was higher than that in the glibenclamide-treated cells used as the positive control.

Molecular effects of an aqueous extract of American ginseng root observed in vitro on islet cells include blocking of IL-1β-induced β-cell apoptosis, decrease in UCP-2 (a protein that regulates insulin secretion and reduces β-cell survival in pancreatic cells), increase of adenosine triphosphate (ATP) production by the cells, and enhanced cell survival via inhibition of caspase-9 (a pro-apoptotic protein) activation and increase in Bcl-2 (antiapoptotic protein) levels (Luo and Luo 2006). Additionally, compound K was
shown to increase glucose uptake in skeletal muscle cells by stimulating phosphorylation of both phosphatidylinositol-3 kinase (PI3K) and Akt (Yuan et al. 2011).

Immunological Effects

Human Clinical Trials

CVT-E002 (Alexa Life Sciences, Inc., Edmonton, Alberta, Canada) is a proprietary extract of American ginseng, reported to contain 80% polysaccharides and 10% protein. It is commercially available in Canada as COLD-IX®. The extract was used in several randomized, double-blind, placebo-controlled trials for prevention and treatment of respiratory infections.

Prevention of Respiratory Infections by American Ginseng Polysaccharide-Rich Extract

A study on the prevention of upper respiratory tract infections was conducted at University of Alberta, Canada (Predy et al. 2005). The study included 130 participants in the American ginseng group (average age 42.2, 61.5% females) and 149 participants in the placebo group (average age 43.1, 59.1% females) who completed the trial. In both groups, the mean reported number of colds in the previous year was ≥ 3. The treatment consisted of 2 capsules of American ginseng extract (200 mg/capsule) or placebo once a day after breakfast for 4 months during the influenza season. The primary endpoint of the study was the number of colds per person, verified according to Jackson et al. (1958). The secondary parameters were severity of symptoms, symptom duration, and duration of all colds. The mean number of Jackson-verified colds in the American ginseng group was lower than in the placebo group (0.68 vs. 0.93; P = 0.017). Significant difference was also found in the number of people having recurrent colds (10.0% vs. 22.8% in the American ginseng group and the placebo group, respectively; P = 0.004). American ginseng extract improved symptom severity (total symptom score of all colds 77.5 vs. 112.3 in the placebo group; P = 0.002) and decreased the total number of days when the symptoms were experienced (10.8 vs. 16.5 days in the placebo group; P < 0.001). The number of adverse events was low in both groups.

Three double-blind, randomized, placebo-controlled clinical trials assessed the effectiveness of the CVT-E002 extract for prevention of acute respiratory illness (ARI) in the elderly (McElhaney et al. 2004, 2006). The treatment, used in the first 2 studies (both reported in the 2004 publication), consisted of a twice-daily dosing of 1 capsule containing 200 mg of the extract or placebo (McElhaney et al. 2004). The first study lasted 8 weeks and enrolled 89 participants (average age 81), 78 of whom completed the trial. The second study lasted 12 weeks and enrolled 109 subjects (average age 83.5), with 105 included in the final analysis. The studies were conducted in nursing homes and assisted living facilities, and about 90% of participants in each of the studies had received influenza vaccines. The occurrence of ARI symptoms (coryza, sore throat, cough, or fever) in all participants was monitored by the study personnel, who also performed a viral throat or nasopharyngeal culture upon detection. When the intent-to-treat analysis corrected for drug exposure was done on the pooled data from both studies, the patients treated with the extract had a statistically significant reduction in the incidence of laboratory-confirmed influenza illness (1/97), compared with the placebo group (7/97; P = 0.03; odds ratio (OR) = 7.73). The treatment also resulted in a lower incidence of combined laboratory-confirmed influenza illness and laboratory-confirmed respiratory syncytial virus (RSV) illness (1/97 vs. 9/101 for placebo; P = 0.009; OR = 10.50), reducing the total relative risk of ARI by 89%. Results that did not reach statistical significance included the primary endpoint of clinically confirmed ARI and the secondary endpoints of severity and duration of respiratory illness and influenza. Adverse events were similar between the placebo and the treatment-groups, with more than 90% of the subjects reporting adverse events during the treatment. Most of the events, except 3 in the placebo group (parameters unspecified), were considered unrelated to the study medication. No changes in the laboratory tests, including biochemical and hematological analyses, were significant.

The third study of CVT-E002 on seniors involved 43 subjects, 21 in the placebo group (average age 67.8) and 22 in the extract group (average age 70.2), all of whom completed the study (McElhaney et al. 2006). The intervention consisted of 2 capsules, once daily, of the extract (200 mg/capsule) or placebo in the morning for 4 months during the fall-winter season. After the first 4 weeks, all subjects received an influenza vaccine. Significant differences between the groups were observed in the last 2 months of the study when only 32% of the subjects in the ginseng group reported having cold symptoms, compared to 62% in the placebo group (P = 0.05; 48% relative risk reduction). The duration of the symptoms in the American ginseng-treated group (5.6 days) was 55% shorter than in the control group (12.6 days, P = 0.04).

Treatment of Respiratory Infections by American Ginseng Polysaccharide-Rich Extract

A double-blind, randomized, placebo-controlled trial was conducted on the use of COLD-IX®, a product containing a polysaccharide-rich extract of American ginseng root, for the treatment of upper respiratory tract infection (URTI) in children (Vohra et al. 2008). Children 3-12 years of age were enrolled. The study consisted of 3 treatment arms: a standard dose group (26 mg/kg per day on day 1, 17 mg/kg per day on day 2, and 9 mg/kg per day on day 3, equivalent to 70-kg-adult doses of 600, 400, and 200 mg 3 times per day, respectively), low dose (half a standard dose), and placebo. The treatment was to be initiated within 48 hours of the onset of symptoms. Forty-five subjects, out of 75 enrolled, developed a URTI and were randomly assigned to treatment groups, 15 subjects per arm. The study results did not achieve statistical significance. The mean length of symptoms duration was 1.5 days in the standard treatment group, 1.9 days in the low dose group, and 1.9 days in the placebo group. All adverse events were mild or moderate, and there was no significant difference in the number of subjects experiencing adverse events between the groups.
Animal Studies

American ginseng powder enhanced immunization response against equine herpes virus in horses (Pearson et al. 2007). The treatment consisted of 55 mg/kg of the root powder and was administered to 5 horses, with 5 more horses being given vehicle placebo (a mixture of molasses and bread). In the treatment group, antibody titer achieved clinical significance on day 2 after vaccination, compared to day 6 in the control group (P < 0.05).

American ginseng constituents were shown to differentially affect various subsets of immune cells in animal models. Saponins from American ginseng roots, administered to mice at 50 and 100 mg/kg/day subcutaneously (s.c.) for 7 days, tripled the rate of spontaneous thymocyte proliferation (P < 0.02 and P < 0.001, respectively, for the 2 dosages) and enhanced ConA-induced proliferation of splenocytes by 2 to 2.4 times (no statistical data presented), while ConA-induced proliferation of thymocytes was increased by 51.9% (P < 0.05) and 48.3% (P < 0.05) by the 2 dosages, respectively (Yang and Yang 1992). The saponins partially restored proliferation of depressed bone marrow stem cells and splenocytes in mice treated with cyclophosphamide (Zhang et al. 1992). The ginsenoside fraction also increased the number of IgA+ cells in the jejunal lamina propria (P < 0.05) (Biondo et al. 2008).

The polysaccharide fraction of American ginseng root inhibited the decrease in white blood cell counts and in the weight of thymus and spleen cells and significantly enhanced the transformation of spleen lymphocytes in immunosuppressed mice (Li Y et al. 1996). The proprietary extract CVT-E002 administered by gavage reduced the level of eosinophilic inflammation of the airways otherwise seen in sham-treated, sensitized animals (Yang and Yang 1992). The saponins partially restored proliferation of depressed bone marrow stem cells and splenocytes in mice treated with cyclophosphamide (Zhang et al. 1992). The ginsenoside fraction also increased the number of IgA+ cells in the jejunal lamina propria (P < 0.05) (Biondo et al. 2008).

Effects on Inflammation

Animal Studies

American ginseng extract from Canadian-cultivated roots inhibited inflammation in a mouse model of chronic inflammatory intestinal colitis by inducing apoptosis in intestinal lymphoid cells via upregulation of p53, a pro-apoptotic protein (Jin et al. 2010). The extract was prepared with 75% ethanol (1:8), partially dried, mixed with maltodextrin to a final ginsenoside concentration of 10.1%, and administered to mice at 0.2625 mg/day, equivalent to 58 µg/day for a 60 kg human. Beginning with day 21 of the administration of the extract, p53-normal mice had significantly lower disease activity index (P < 0.005) and minimal histological damage to the intestinal tissue, while mice with a genetic deficiency for p53 gene were unresponsive to the treatment.

In contrast to the anti-inflammatory activity cited above, ginsenoside Rb1 enhanced burn wound healing in anesthetized mice by effectively increasing inflammation when applied topically to the wound area at doses up to 1 ng daily for 7 days (Kawahira et al. 2008). The saponin augmented the migration of mast cells to the wound sites, significantly increased the levels of monocyte chemo-attractant protein-1 (MCP-1), and stimulated histamine production in the damaged skin. At the same time, levels of substance P, a
neuropeptide associated with pain signaling and involved in wound healing, were drastically reduced by the treatment.

Ginsenoside Rb1 and compound K were topically applied to the ears of mice treated with oxazolone in a mouse model of skin inflammation to investigate potential use of the compounds from American ginseng in the treatment of psoriasis (Shin YW et al. 2005). After 13 days of administration, compound K at concentrations 0.02-0.05% significantly reduced swelling (P < 0.001) while inhibiting the expression of cyclooxygenase 2 (COX-2) gene by 73.1% and dose-dependently reducing mRNA levels for IL-1β, TNFα, IFNγ, and IL-4. Compound K additionally caused a decrease in the production of nitric oxide (NO) and prostaglandin E2, in an assay on RAW264.7 murine macrophage cells. Ginsenoside Rb1 had no significant effect.

Zymosan is a pro-inflammatory compound of fungal origin, known to overstimulate immune response, often leading to a septic shock and multiple organ failure. Zymosan treatment led to 100% death of animals 5 days after treatment, while co-treatment with compound K (30 mg/kg) led to 40% survival (Cuong et al. 2009). The levels of inflammatory markers in the serum were significantly decreased, and the damage to the spleen and liver due to excessive inflammation was reduced.

### In Vitro Studies

An ethanolic extract of American ginseng differentially affected the expression of inducible nitric oxide synthase (iNOS) and COX-2 in murine macrophage cell line RAW264.7 (Ichikawa et al. 2009). When co-administered with LPS, the extract inhibited the increase in the iNOS protein and mRNA levels in the cells. However, there was no effect on COX-2 levels. The action was likely due to the interruption of the macrophage-activation pathway by blocking phosphorylation of iNOS regulators STAT1 and STAT2. When administered without the addition of LPS, American ginseng extract caused a slight but significant increase in the levels of both iNOS and COX-2 proteins and mRNAs. The extract had no effect on the MAPK and NF-κB pathways of iNOS activation.

Compound K was shown to possess glucocorticoid receptor activity and ability to control zymosan-induced inflammation (Cuong et al. 2009). Compound K eliminated activation of TNFα, IL-6, and IL-12 subunit β by zymosan in murine macrophages on the protein and mRNA levels.

### Cardiovascular Effects

There are notable activities of American ginseng on the cardiovascular system, which include anti-ischemic and antilipidemic actions, reversal of hyperplasia, and protection against the effects of ischemia, hemorrhagic shock, and arrhythmia, while there is little to no effect on elevated blood pressure. The protective effect appears to involve induction of the antioxidant defense system in the cardiac cells, a blocking action against Ca2+ channels, and inhibition of NO production.

### Human Clinical Studies

In a novel application of constituents from American ginseng root, a controlled study was conducted in 30 patients undergoing open-heart surgery to evaluate the protective effect of panaxadiol ginsenosides on reperfusion injuries of the ischemic myocardium (Liu et al. 1997). The subjects were randomly divided into a control and verum group (n = 15 in each). The ginsenosides were added to the cold cardioplegic solution (80 mg/L) in the treated group. A standard solution was administered to controls. The serum levels of several key enzymes as well as lipid peroxidation levels were significantly improved by the addition of ginsenosides, as measured before operation, during ischemia and reperfusion period, and after operation (see Table 16). Marked changes in the ultra-minute structure of myocardial cells of the right auricle were observed by electron microscopy in the control group, while only slight changes were seen in the treatment group.

Effects of American ginseng root on blood pressure were investigated in 2 double-blind, randomized, placebo-controlled studies (Stavro et al. 2005, 2006). Sixteen hypertensive patients, 13 of whom were taking antihypertensive medication, were enrolled and randomly administered 3 g of 8 different batches of American ginseng root of variable ginsenoside content (6 days) or placebo (2 days) in the

### Table 16 Effects of panaxadiol ginsenosides added to cardioplegic solution on blood enzyme levels and oxidation parameters of patients undergoing open heart surgery for myocardial ischemia

<table>
<thead>
<tr>
<th>Time point</th>
<th>AST</th>
<th>LDH</th>
<th>HBDH</th>
<th>CK</th>
<th>CK-MB</th>
<th>LPD</th>
<th>SOD</th>
<th>GSH-Px</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 min after occlusion of</td>
<td>51.4*</td>
<td>79.1*</td>
<td>62.5*</td>
<td>42.3*</td>
<td>37.3*</td>
<td>72.4*</td>
<td>208.6*</td>
<td>136.9*</td>
</tr>
<tr>
<td>the aorta</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 min after reperfusion</td>
<td>72.6*</td>
<td>63.3*</td>
<td>38.9*</td>
<td>62.8*</td>
<td>48.6*</td>
<td>57.5*</td>
<td>185.1*</td>
<td>145.3*</td>
</tr>
<tr>
<td>20 min after reperfusion</td>
<td>64.8*</td>
<td>77.0*</td>
<td>67.1*</td>
<td>67.1*</td>
<td>43.9*</td>
<td>49.9*</td>
<td>190.1*</td>
<td>141.1*</td>
</tr>
<tr>
<td>12 hours after surgery</td>
<td>52.0*</td>
<td>74.6*</td>
<td>65.3*</td>
<td>62.8*</td>
<td>43.5*</td>
<td>55.2*</td>
<td>184.7*</td>
<td>141.4*</td>
</tr>
<tr>
<td>24 hours after surgery</td>
<td>47.3*</td>
<td>64.7*</td>
<td>73.6*</td>
<td>20.2*</td>
<td>50.6*</td>
<td>52.1*</td>
<td>244.2*</td>
<td>141.3*</td>
</tr>
</tbody>
</table>

*P < 0.05; † P < 0.01.


Source: Liu et al. (1997).
morning, on 8 different visits (Stavro et al. 2005). Blood pressure was recorded on each visit for a 2.5-hour period at 10-minute intervals. The individual batches of American ginseng root and their mean showed a neutral effect on systolic and diastolic blood pressure, with no difference from placebo in the overall mean blood pressure change. The mean systolic blood pressure was raised at 140 minutes and the mean diastolic pressure was lower at 100 minutes and higher at 160 minutes, compared to placebo (P < 0.05 for all 3 changes). All treatments were well tolerated with no adverse events. More prolonged intake of American ginseng (12 weeks of 3 g/day) did not cause any significant changes in blood pressure in 40 individuals with hypertension in a 24-hour period after the treatment, compared to placebo (Stavro et al. 2006). Additionally, the treatment did not alter plasma level of cystatin C, a measure of renal function.

Animal Studies

The effects of American ginseng extracts on the cardiovascular system were tested in various animal models. Most of the studies in this section used the term “American ginseng saponins” to refer to alcoholic extracts of various concentrations, evaporated to dryness.

Administration of American ginseng saponins (50 and 100 mg/kg/day p.o. for 7 days) reduced the scope of myocardial necrosis in rats, induced by injecting isoprenaline (2 mg/kg/day for 2 days s.c.), by 65.1% (P < 0.05) and 69.1% (P < 0.05), reduced the activity of creatine kinase in serum by 14.5% (P < 0.05) and 15.6% (P < 0.05), the activity of lactate dehydrogenase in serum by 13.6% (P < 0.05) and 17.3% (P < 0.01), the levels of free fatty acids in serum by 19.0% (P < 0.05) and 23.9% (P < 0.05), and lipid peroxide in myocardial tissue by 10.5% (P < 0.05) and 22.1% (P < 0.05), respectively, at 24 h after last injection of isoprenaline (Bian and Lu 1994). Xiangshen Fenghuangjiang koufuye, a compound liquor containing American ginseng and royal jelly, concentrated 3 times and administered to rats at 5 mL/kg daily for 7 days, reduced the S-T segment shift in the electrocardiogram at 5, 10, 20 and 30 minutes after the injection of isoprenaline (4 mg/kg s.c.) by 52.8%, 55.9%, 65.5%, and 72.4%, respectively (P < 0.05 for all values) (Gao et al. 1989).

Treatment with American ginseng saponins (50 mg/kg s.c.) for 2 weeks increased the percentage of rats that survived hemorrhagic shock from 27.27% in the control group to 81.81% (P < 0.01%) (Li et al. 1990). The content of malondialdehyde (MDA) in myocardium and that of nor-epinephrine in plasma were decreased by 26.0% (P < 0.05) and 42.2% (P < 0.005), respectively, and the contractility of the heart was enhanced. The content of lipid peroxide in the organs of rats with hemorrhagic shock, including hearts, livers, lungs, spleens, and kidneys, were reduced significantly (P < 0.05) by i.v. administration of 27 mg/kg of saponins (Guo et al. 1990). In dogs with hemorrhagic shock treated with American ginseng saponins (25 mg/kg i.v.), left ventricular pressure and maximal rate of left ventricular pressure rise (+dp/dt max) 5 hours after bleeding were only decreased by 58% (P < 0.01) and 33% (P < 0.05), respectively, compared to 61% and 51% in the control (Sun et al. 1991). In dogs with acute myocardial infarction, American ginseng saponins (50 mg/kg i.v.) inhibited the increase in left ventricular end-diastolic pressure down to 18.9%, compared to 42.5% in untreated animals (P < 0.01), and lessened the decrease in maximal rate of left ventricular pressure fall (+dp/dt max) from 53.7% to 21.2% (P < 0.05) (Lu et al. 1992a).

In several models of experimental arrhythmia, American ginseng saponins (dosage range from 150-187 mg/kg) significantly reduced ventricular arrhythmias and mortality (P < 0.01 and P < 0.05, respectively, for rats; P < 0.01 and P < 0.05 for guinea pigs; P < 0.01 for rabbits and mice) (Zhao et al. 1987). In another study on various animal models (rats, mice, and guinea pigs), American ginseng saponins (60 mg/kg and 80 mg/kg i.v.) effectively antagonized experimentally-induced arrhythmia evoked by chloroform in mice (P < 0.01 at 80 mg/kg), by BaCl2 in rats at 80 mg/kg (no statistical data given), by ouabain in guinea pigs (P < 0.01 and P < 0.05), by posterior pituitary (1 u/kg i.v.) in rats (P < 0.01) but had no effect on arrhythmia induced by aconitine (40 mg/kg i.v.) in rats (Zhang et al. 1985).

Negative inotropic effects of American ginseng saponins have been reported in animals. In anesthetized dogs, saponins (25 and 50 mg/kg i.v.) decreased the mean arterial pressure by 7.6% (no P value given) and 20.4% (P < 0.01), left ventricular pressure by 5.7% and 8.7% (P < 0.05 for both dosages), and dP/dt max by 13.3% and 16.7% (P < 0.05 for both dosages), respectively (Lu et al. 1992a). The results of another experiment showed that American ginseng saponins (50 mg/kg i.v.) remarkably increased myocardial blood flow and decreased coronary resistance, cardiac oxygen consumption, and myocardial minute oxygen consumption index (Lu et al. 1992b). Further details of this study were not available.

Hyperlipidemic rats were administered American ginseng saponins at 50, 100, and 200 mg/kg/day p.o. for 12 days. The content of serum low-density lipoprotein (LDL) was decreased by 32.6% (P value not available), 36.5% (P < 0.05), and 23.6% (P value not available); ratio of total cholesterol to high-density lipoprotein (TC/HDL) was decreased by 38.0% (P < 0.01), 46.8% (P < 0.001), and 35.0% (P < 0.01); LDL/HDL ratio was decreased by 57.0% (P < 0.001), 61.5% (P < 0.001), and 46.7% (P < 0.01); the content of serum HDL was increased by 58.0% (P < 0.05), 65.2% (P < 0.01), and 42.0% (P < 0.01); and the content of serum HDL1 was increased by 227.7%, 273.3%, and 146.7% (P < 0.01 for all 3 dosages) in the treatment groups, respectively, compared to control. Total cholesterol was not affected in any of the treatment groups. In addition, in all treatment groups, the levels of lipid peroxides in the liver were decreased by 20.1% (P < 0.05), 42.1% (P < 0.001), and 25.4% (P < 0.001); the serum levels of lipid peroxides decreased by 43.1%, 42.8%, and 37.9% (P < 0.001 for all 3 dosages); the activity of GSH-Px in the liver was increased by 54.9% (P value not available), 68.9% (P < 0.01), and 36.6% (P value not available); and the activity of serum GSH-Px increased by 10.4% (P value not available), 40.1% (P < 0.01), and 10.3% (P value not available), respectively (Li et al. 1993).

Increased antioxidant activity has been reported for
American ginseng saponins administered to rats with doxorubicin-induced myocardial injury (Ma et al. 1993). The saponins (50 mg/kg and 100 mg/kg i.p.) markedly increased the activities of glutathione peroxidase (GSH-Px) in the blood and myocardium (P < 0.05) and superoxide dismutase (SOD) in red blood cells and myocardium (P < 0.01) and decreased the content of MDA in serum and myocardium (P < 0.05). The saponins (100 mg/kg and 200 mg/kg) were also found to increase the activity of serum SOD in hyperlipidemic rats (Li JP et al. 1996).

In studies of individual ginsenosides, ginsenoside Rb1 (0.35 mM by continuous i.p.) attenuated the reduction in luminal diameter of the carotid artery (14.5%, compared to 45% in control mice, P < 0.05) in an animal model of intimal hyperplasia, at 4 weeks after injury (Chai et al. 2010). Additionally, compound K (10 mg/kg p.o.) reduced the size of the infarct area from 43.2 ± 7.0% to 22.4 ± 6.6% (P < 0.05) in hearts of mice subjected to ischemia-reperfusion injury, with the effect abolished by the inhibitor of phosphatidylinositol-3 kinase (PI3K) (Tsutsumi et al. 2011).

Li J et al. (2010) suggested a molecular mechanism of the protective effect of American ginseng on cardiomyocytes by demonstrating that the root extract (30 mg/kg) stimulated the expression of Nrf2 protein in the rat heart. The Nrf2 protein is a transcription factor that activates a variety of genes of cellular antioxidant protection. American ginseng extract partially reversed cardiomyocyte cell death associated with cytotoxicity resulting from the exposure to H2O2 in vitro, with the effect being blocked by the knockdown of the Nrf2 gene.

In Vitro Studies
American ginseng saponins were found to exert a bidirectional effect on the contractility of myocardium in vitro. The saponins reduced the contractility of papillary muscles in guinea pigs at the higher concentration of 0.6 mg/mL while enhancing the contractility at the lower concentration of 60 µg/mL (Zhao et al. 1987). In another study, the saponins (0.3, 0.6 mg/mL) decreased the contractility of the left atrium of guinea pigs by approximately 44% and 77%, respectively (no statistical data provided), at the higher frequency of electric stimulation (1 Hz), while 0.6 mg/mL increased the contractility at the lower frequencies (1/8, 1/4 Hz) by approximately 31% (P < 0.05) and 45% (P < 0.05), respectively (Yang et al. 1994a). The saponin fraction from American ginseng was found to stimulate contractions in dog mesenteric arteries stimulated in vitro by phenylephrine but had no effect on KCl-induced contractions (Kwan 1995).

A number of in vitro studies have reported on the effect of American ginseng saponins on the Ca2+ influx. The concentration of 0.1 mg/mL of saponins inhibited the pulse rate of the pacemaker in the right atrium from guinea pig (P < 0.01) (Yang et al. 1994a). This action was not affected by atropine (5 × 10^-7 mol/L) but was antagonized by increasing the Ca2+ concentration in Krebs-Henseleit solution. Studies in isolated aortic strips of rabbits have demonstrated the Ca2+ channel blocking effect of saponins at 0.2-2 mg/mL (Guan et al. 1996a, 1996b; Wu et al. 1995). The saponins antagonized the contractions induced by KCl, CaCl2, and norepinephrine (NE) in a non-competitive manner and inhibited the intracellular and extracellular Ca2+-dependent contractions induced by NE. Similar results were obtained in isolated rabbit ileum (Guan et al. 1996a, 1996b). Additionally, at 0.05-0.8 mg/mL the saponins inhibited the electric activities of isolated rabbit sinoatrial node and guinea pig papillary muscle (Ma et al. 1998; Wang et al. 1994).

Pseudoginsenoside F11 (PF11) at 3, 10, and 30 µg/mL increased electric parameters (the amplitude of action potential, overshooting, threshold potential, maximum diastolic potential, maximum rate of depolarization, and action potential duration) of cultured rat cardiomyocytes in a dose-dependent manner (Yang et al. 1994b). The effect of PF11 (10 µg/mL) was antagonized by verapamil (2 µmol/L). The effect was inhibitory at higher concentrations of 300 µg/mL and 500 µg/mL (P < 0.001 for all parameters at both concentrations). The activity was similar to that of MnCl2 (0.1 µg/mL) and that of verapamil (1.0 µmol/L). In addition, the inhibitory action of saponins (300 µg/mL) was reversed by Ca2+ (200 mMol/L), suggesting a modulation effect on calcium channels.

Pretreatment of human endothelial cells with American ginseng extract (1, 10, and 100 µg/mL) resulted in a significant decrease in thrombin-induced release of endothelin at 4 and 24 hours (Yuan et al. 1999). Nitroarginine, a known nitric oxide (NO) synthase inhibitor, reduced the effect, indicating that the action of the extract is at least partially mediated by NO. However, Wang et al. (2000) found that non-saponin constituents of American ginseng, namely, panaxydol and panaxynol, reduced accumulation of nitrite by C6 glioma cells stimulated by a combination of bacterial lipopolysaccharides and IFNγ by 45.48 ± 61.11% and 71.92 ± 3.07%, respectively.

The saponins (0.5 mg/mL) were found to have a protective effect against hypoxia (P < 0.05) and glucose deficiency (P < 0.01) in the isolated papillary muscle of guinea pigs (Yang et al. 1994c). Ginsenosides were also shown to protect cardiac cells from oxidative damage induced by xanthine/xanthine oxidase (X-XOD) (Yang et al. 1992). Electric activities were measured in cultured rat cardiac cells by conventional microelectrode technique. Changes in morphology were observed under electronic microscope. The exposure to saponins (250 µg/mL) inhibited the decreases in the electric parameters and reduced the percentage of beating clusters and the damage in microscopic structure caused by X-XOD.

Since protein tyrosine kinase (PTK) signal pathways play important roles in ischemia/reperfusion (I/R) injury, the inhibitory effects of ginsenosides on PTK activated by hypoxia/reoxygenation (an in vitro equivalent of I/R) were observed in cultured human umbilical vein endothelial cells by Dou et al. (2001). Ginsenosides Rb1, Rd, and Ro showed the highest activity, completely blocking the PTK activation at 10 µM. PPT-type ginsenosides (Re and Rg1) did not significantly interfere with the PTK activation.

The ability of ginsenosides to protect low-density lipoproteins (LDL) from oxidation was demonstrated by Li et al.
(1999). Native LDL (0.2 or 0.3 mg/mL) isolated from the plasma of healthy donors was incubated with saponins (0.25-1 mg/mL) for 30 minutes at 20 °C. The saponins reduced lipid peroxide levels in a concentration-dependent fashion, as measured by the amount of thiobarbituric acid-reactive substances formed, as compared to control (P < 0.05). The saponins in this concentration range also retarded the alterations in relative electrophoretic mobility of oxidized LDL (Ox-LDL) (P < 0.05 or P < 0.01). Furthermore, the saponins reduced the conversion of phosphatidylcholine to lysophosphatidylcholine by CuSO4 in Ox-LDL (P < 0.01).

Antioxidant Effects

Human Clinical Trials
The antioxidant effects of an alcoholic American ginseng extract were tested in a single-blind study that lasted 3 months (Cui and Chen 1991). Seventy-one subjects were randomly divided into two groups. The first group consisted of 32 male and 4 females (average age 62) and was treated with a compound liquid containing extracts of American ginseng, Epimedium grandiflorum, and Crataegus pinnatifida. The second group included 29 males and 6 females (average age of 61) and was treated with American ginseng extract only. A dose of 10 mL of either preparation was taken orally by the subjects twice daily for 3 months. The activity of superoxide dismutase (SOD) in erythrocytes increased in both groups by 71.3% and 81.8%, respectively, the content of lipid peroxide in serum decreased by 47.5% and 55.2%, and the ratio of lipid peroxide to lipid (SOD/LPO) increased by 178.0% and 266.7% (P < 0.001), respectively. The activity of monoamine oxidase B was decreased by 25.3% and 18.6%, while estradiol-to-testosterone ratio (E2/T) was decreased by 68.6% and 69.4%, respectively (P < 0.001 for all values), by the 2 preparations.

Animal Studies
Ginsenoside Rb1 administered to rats (5 mg/100 g/day) in drinking water for 2 weeks caused a 40% reduction (P < 0.05) in lipid peroxidation induced by an injection of puromycin aminonucleoside (PA) in plasma, liver, and kidneys, compared to animals treated with PA only (Lim et al. 1998). Elevated levels of glutathione peroxidase were observed in the ginsenoside-treated animals. Also, American ginseng extract administered by a single oral gavage at 30 mg/kg greatly increased activity of Nrf-2-driven transcriptional activity of genes encoding antioxidant and cytoprotective enzymes heme oxygenase-1, thioredoxin reductase-1, and NAD(P)H:quinone oxidoreductase in the heart (Li J et al. 2010).

In Vitro Studies
Reports have been made on protective effects of constituents from American ginseng against LDL oxidation (Li et al. 1999) and on protection of cardiomyocytes from induced oxidative damage by American ginseng compounds (Ma et al. 1993; Yang et al. 1992) (see Cardiovascular Effects). Additionally, American ginseng and an aqueous extract from its roots CNT2000 (Chai-Na-Ta, Langley, BC, Canada) reduced the formation of superoxide and hydroxyl radicals, concentration-dependently inhibited oxygen depletion in a linoleic acid emulsion test and in the ammonium thiocyanate assay, and effectively inhibited DNA damage by Fe2+-ions in vitro (Kitts et al. 1999, 2000). The CNT2000 extract additionally showed a metal-binding and reducing activity with Fe2+, Fe3+, and Cu2+ ions, exhibited a concentration-dependent DPPH radical scavenging activity, and protected rat brain proteins from oxidation by Fenton reactants (Kitts et al. 2000). A gastrointestinal (GI) fluid imitation extract and acidified methanol extract of American ginseng potently inhibited HOCl radical (IC50 < 2.5 μmol/L, gallic acid equivalent [GAE]) and had a moderate activity against peroxynitrite anion (IC50 < 15 μmol/L GAE) but were not very effective against superoxide anion and DPPH (IC50 ≥ 100 μmol/L GAE for both) (Chen et al. 2010). The GI fluid imitation was more effective than methanol or hexane at extracting phenolics from American ginseng, as measured by total phenolic assay (400 μmol/L gallic acid equivalent), and had the highest ORAC value among the 3 extracts and compared to Asian ginseng and Siberian ginseng (eleuthero) (Eleutherococcus senticosus).

Aqueous (500 μg/mL) and organic solvent (n-butanol) extracts from American ginseng roots weakly inhibited per-oxyl radicals-induced hemolysis of rat erythrocytes (by 16.9% ± 1.0% and 6.3% ± 1.7%, respectively, for the two types of extracts) and reduced lipid peroxidation in brain homogenates (by 10.5% ± 3.3% and 65.1% ± 1.9%, respectively) (Ng et al. 2004).

An ethanol (75%, 1.8) extract of American ginseng (1-50 μg/mL) time-dependently upregulated Nrf2 and was shown by chromatin immunoprecipitation assay to bind to promoters of several antioxidant response elements, including SOD-2, thioredoxin-1, and NAD(P)H:quinone oxidoreductase, in rat cardiomyocytes (Li J et al. 2010). A methanolic extract at the concentration of 10 μmol/L had an inducing effect on quinone reductase in rat cardiomyocytes (Chen et al. 2010).

Steamed American ginseng root powder protected Chinese hamster lung fibroblasts cells V79-4 from H2O2 toxicity, increasing cell viability from 22% (H2O2, only) to 48%, 65%, 72%, and 76% (30, 60, 90, and 120 minutes of steam treatment, respectively) (Kim et al. 2007). The dried, powdered, heat-treated American ginseng roots were also more effective, compared to “white” (not steamed) roots, in inhibiting lipid peroxidation and augmenting the activity of antioxidant enzymes catalase and superoxide dismutase and were more active radical scavengers in a cell-free environment.

Radioprotective Effects

In Vitro Studies
A series of reports by Lee TK et al. (2008, 2009, 2010) highlighted protective effects of a standardized American ginseng extract against radiation damage to lymphocytes. The extract (50-1000 μg/mL) containing 11.7% ginsenosides was applied to human peripheral blood mononuclear cells, subjected to 1 or 2 Gy (0.6 Gy/min) irradiation by 137Cs γ-rays, 90 min after irradiation. The effects of the treatments...
were measured using a cytokinesis-block micronuclei assay. The extract concentration-dependently reduced micronuclei counts in the irradiated cells, with a stronger protective effect observed at 750 µg/mL, at which concentration the micronuclei yield was reduced by 53.8% after 1 Gy and by 35.9% after 2 Gy, compared to irradiated cells not treated with American ginseng. The total antioxidant capacity (TAC) of human peripheral blood lymphocytes was significantly increased (P < 0.001) by the extract, reaching above pre-irradiation levels at 500-1000 µg/mL after 1 Gy irradiation (P < 0.01) (Lee TK et al. 2010). The increase in TAC correlated with the decrease in the levels of reactive oxygen species. Application of the extract 24 hours prior to irradiation was the most effective (Lee et al. 2006). The effect of American ginseng was greater than that of the biologically relevant form of amifostine (WR-1065) (1 and 3 mmol/L), the primary radioprotective agent approved by the US FDA for cancer patients undergoing radiation therapy.

Protection Against the Toxicity of Chemotherapeutic Drugs

Animal Studies
An extract from American ginseng (50 mg/kg and 100 mg/kg i.p.) improved antioxidant enzymatic activity in the heart muscle and blood of rats with doxorubicin-induced myocardial injury (Ma et al. 1993; see Cardiovascular Effects). Oral administration of American ginseng (50, 100 mg/kg p.o.) attenuated the toxicity of mitomycin C, a highly toxic chemotherapy drug often associated with myelosuppression, in a study on mice (Pawar et al. 2007). Pretreatment with 50 or 100 mg/kg of the root for 3-7 days reduced the number of micronucleated polychromatic erythrocytes, an indicator of myelosuppression, by 57%-87% in the bone marrow and by 46%-80% in the peripheral blood. Co-administration of the extract with the drug resulted in 63%-99.8% reduction of micronuclei in the bone marrow and 43%-64% reduction in the peripheral blood. Increase of the dose to 100 mg/kg further reduced the micronuclei by 87% and 86%.

Ginsenoside Rb1 protected mice from the toxicity associated with cyclophosphamide (Zhang et al. 2009). Administered at 25 and 50 mg/kg i.p., the ginsenoside significantly reduced the DNA damage in peripheral blood leukocytes and bone marrow cells, as measured by Comet assay (P < 0.05 and P < 0.001 for the 2 doses, respectively). At 50 mg/kg Rb1 also significantly reduced the number of apoptotic cells, and both doses restored the activity of antioxidant enzymes SOD and glutathione peroxidase (P < 0.01 or P < 0.001).

Ginsenoside Rg3, administered orally at 20 mg/kg to mice for 2 days, significantly reduced cyclophosphamide (100 mg/kg i.p.)-induced damage to the DNA of peripheral lymphocytes and bone marrow cells (P < 0.001 for both) and decreased bone marrow apoptosis after 6 hours (P < 0.001) and 12 hours (P < 0.05) (Zhang QH et al. 2008). The compound also significantly diminished the cyclophosphamide-induced reductions in the activities of serous SOD, MDA (P < 0.01 for both), and hepatic glutathione peroxidase (P < 0.001).

Anticancer Effects
Initial evidence on anticancer effects of American ginseng comes from studies of Asian ginseng, intake of which has been shown by epidemiological studies to decrease non-organ-specific cancer rates as well as to have direct anticancer effects in animal models (Shibata 2001). As of the date of this writing, there are no clinical data yet on the use of American ginseng root for the treatment of cancer. A phase II clinical trial on breast cancer is currently ongoing (see http://clinicaltrials.gov/ct2/show/NCT00631852), and a pilot study on cancer-related fatigue has been published. However, a significant amount of evidence has accumulated on the in vitro effects of American ginseng constituents and their metabolites on cancer cells. Of primary interest in this regard are studies on compound K, the main product of intestinal bacterial transformation of protopanaxadiol ginsenosides, which are typically prevalent in American ginseng root. Compound K and ginsenosides present in American ginseng root appear to affect different mechanisms involved in cancer progression, including cellular proliferation, cell cycle arrest, induction of apoptotic cascade, angiogenesis, formation of metastases, and expression of inflammatory factors. Synergistic effects were observed for combinations of American ginseng and chemotherapy drugs. A few reports also exist on the selectivity of the cytotoxic action of American ginseng on cancer cells, compared to normal cells. There is widespread use of ginsengs and other Chinese herbal tonics in cancer care for supporting immunocompetency and reducing side effects from conventional cancer therapies. These studies provide some mechanistic support for this strategy and warrant detailed human study.

Human Clinical Trials
A double-blind study with 282 randomized patients suffering from cancer-related fatigue compared 3 daily doses (750 mg, 1000 mg, and 2000 mg) of powdered American ginseng root to placebo (Barton et al. 2010). Dosing was twice daily for 8 weeks, during which time 57% of the patients were still receiving chemotherapy and 18% were treated with radiation. Prior to the study, 65% had received chemotherapy, and 38% had undergone radiation. A total of 175 patients completed the trial. Trends toward improvement in fatigue after 8 weeks of treatment with American ginseng were observed, based on area under the curve (AUC) analysis of Brief Fatigue Inventory mean scores. The increase was from 460 for placebo to 467 for 750 mg dosage, to 480 for 1000 mg dosage, and to 551 for 2000 mg dosage (P = 0.08 for the last dosage). As measured by the vitality subscale of the Medical Outcome Scale Short Form-36 (SF-36), the 94 patients taking 1000 or 2000 mg of the root were trending better in vitality improvements (10.5-14.6 from baseline; P = 0.06) than the 81 patients who were taking 750 mg root or placebo (changes of 7.3-7.8 from baseline). Of those patients who were receiving the 2 higher doses, 40% observed a benefit and were satisfied with the treatment, compared to 17% in the placebo group. No significant differences in toxicities occurred between any of the groups.
Animal Studies

A polysaccharide-rich extract of American ginseng CVT-E002 (Alexa Life Sciences, Inc., Edmonton, Alberta, Canada) was administered to juvenile or infant mice carrying Friend-leukemia-virus-induced erythroleukemia tumor, acquired via injection of the tumor cells into the lateral tail vein (Miller et al. 2009, 2011). In addition to the immunological effects of the treatment, described in the Immunological Effects section, the extract-treated mice exhibited prolonged survival and reduction of tumor cell counts to those statistically indistinguishable from the untreated, non-tumor-bearing controls. When the extract was administered p.o. to 10-week-old animals at 40 mg/day via the diet, the survival at 6 weeks was 30%-50%, compared to 0% in the untreated, tumor-bearing controls (P < 0.212) (Miller et al. 2009). At the dose of 120 mg/day, the survival was also increased, compared to the control, but less so than at the medium dose. The dose of 2 mg/day did not confer any survival benefits. In a separate investigation, in which the extract was administered i.p. to juvenile (7-day-old) mice bearing the same tumor, the dose of 20 mg/day was effective in prolonging survival, but not the higher (30, 40, and 50 mg/day) or the lower (5, 10 mg/day) doses (Miller et al. 2011). Moreover, mice receiving 30, 40, or 50 mg/day of the extract had reduced body weight, compared to those receiving 20 mg/day of the extract.

Compound K reduced the formation of metastases in several studies in animals. Metastases from the injection of hepatocellular carcinoma cells into the portal vein of mice were completely inhibited by intraperitoneal (i.p.) injection of compound K (10 mg/kg) every other day for 5 weeks (Song et al. 2010). When hepatocellular carcinoma cells were injected into mice s.c., administration of compound K by gastric perfusion at 50-100 µg/day significantly inhibited the formation of metastases, compared to cisplatin-treated control group (Ming et al. 2011). Additionally, pre-treatment of colon adenocarcinoma cells with compound K significantly reduced the formation of metastases after injecting the cells into the portal vein of the animals (Choo et al. 2008).

The potential for ginsenoside Rb1, hydrolysis, expressed by intestinal microflora (see Pharmacokinetics), appeared to affect the antimetastatic activity of Rb1 in mice after oral administration (25 mg/kg/day for 2 weeks) (Hasegawa and Uchiyama 1998). Significant antimetastatic activity (46.8 ± 10.3% inhibition) correlated with higher levels of compound K detected in the blood (7.5 ± 2.6 µg/mL) after oral administration of Rb1, compared with no detectable compound K in the blood of low-responders (4.8 ± 3.2% inhibition; P < 0.01). Oral administration of compound K (10 mg/kg/day) was superior (P < 0.01) to treatment with ginsenoside Rb1 (20 mg/kg/day) in the inhibition of lung metastases and was not statistically different from the results obtained with fluorouracil (10 mg/kg/day). However, treatment with compound K had no significant effect on the growth of the primary tumor (Lewis lung carcinoma injected s.c. into hind footpad).

Pre-treatment with 0.5 or 2.5 µmol of compound K reduced the incidence of skin tumors induced by 7,12-dimethylbenz[α]anthracene (DMBA) by 47% and 63%, respectively (Lee JY et al. 2005). In the same study, compound K significantly reduced parameters of acute inflammation, frequently co-occurring with cancer development, namely, expression of COX-2, production of PGE2, and DNA binding of NF-κB, and dose-dependently inhibited expression of ornithine carboxylase, a marker for tumor growth.

A combination of compound K with γ-radiation resulted in significant reduction in sizes of tumors formed from s.c. injection of cancer cells in mice, compared to both treatments alone (P < 0.05) (Chae et al. 2009).

Antiangiogenic Effects

Angiogenesis is the formation of new blood vessels and is a critical process for tumor growth and formation of metastases. Applied to subcutaneous implants in mice, an Rb1-predominant mixture of ginsenosides (20 µg Rg1, 50 µg Rb1) inhibited angiogenesis (P < 0.01, compared to control) (Sengupta et al. 2004). Significant inhibition of vascular endothelial growth factor (VEGF) (P < 0.05) and microvessel density (P < 0.01), measures of angiogenesis, was achieved by administration of ginsenoside Rg1 when used alone and when combined with cyclophosphamide (P < 0.01 vs. controls for both) (Xu et al. 2007). Ginsenoside Rg1 is formed from other ginsenosides after prolonged steam treatment of American ginseng root under specific conditions (Wang et al. 2007).

In Vitro Studies

Breast Cancer

A number of reports exist on the inhibition of breast cancer cell lines by American ginseng extracts in vitro. Varying concentrations of both aqueous and alcoholic extracts displayed greater or lesser degrees of antiproliferative effects. According to Duda et al. (1999, 2001), an aqueous extract significantly inhibited cell proliferation of MCF-7 cell line at 100 µg/mL or higher. Corbit et al. (2006) reported a significant 30-40% inhibition in cell proliferation at 500 µg/mL (P < 0.05) of an aqueous extract. In a screening of a variety of cell lines, a methanolic extract of American ginseng (50-2000 µg/mL) inhibited MCF-7, SKBr-3, and T47-D breast cancer cell lines (Peralta et al. 2009). In this study, the most responsive cell lines were SKBr-3 and MDA-MB-231, with 50-80% inhibition achieved at 250 µg/mL of the extract. In a study by Wang et al. (2008), an ethanolic extract of American ginseng roots steamed for 2 hours at 120 °C, which increased ginsenoside Rg3 content from 0.06% to 5.9%, completely inhibited growth of MCF-7 and MDA-MB-231 cells at 500 µg/mL, reducing cyclin A and cyclin D1 expression and arresting cancer cells in the G1 phase.

A number of biochemical mechanisms have been associated with the anticancer effects of American ginseng root preparations. Peralta et al. (2009) observed the reversed activation of p65 subunit of NF-κB and a decrease in proliferation markers Ki67 and cyclin D1. Duda et al. (2001) demonstrated that expression of the inflammatory...
mediator COX-2, associated with the majority of invasive breast cancers, was completely blocked by 100 μg/mL of American ginseng in the hormone-insensitive cell line MDA-MB-231 and, after induction by phorbol dibutyrate, in hormone-sensitive MCF-7 cells. In the same investigation, a dose-dependent (50-2000 μg/mL) increase in the mRNA expression of cytoplasmic p21, a cell cycle-regulating protein implicated in tumor growth inhibition, was observed in both MCF-7 and MDA-MB-231 cell lines (P = 0.0004 for MCF-7, P ≤ 0.0001 for MDA-MB-231, both at 2000 μg/mL). The increase in mRNA was not blocked by cycloheximide, a protein synthesis inhibitor, suggesting that the effect was happening at the gene level.

In one study, a standardized extract of American ginseng root (CNT2000) was found to be more effective in inhibiting proliferation of MCF-7 breast cancer cells than the chemotherapeutic drugs megace (10⁻⁴ M), fluorouracil (10⁻²⁴ M), and methotrexate (10⁻⁴ M) (Duda et al. 1999). Additionally, the effects of several chemotherapeutic drugs were potentiated when combined with American ginseng (60-100 mg). The cancer cell inhibitory effects of combinations of American ginseng with tamoxifen (10⁻⁶ M), cytoxan (10⁻⁴-10⁻³ M), taxol (10⁻⁶-10⁻⁴ M), doxorubicin (10⁻⁴-10⁻³ M), and methotrexate (10⁻⁸ M) were all significantly higher when compared to these agents or American ginseng alone. Additionally, ginsenoside Re, but not ginsenoside Rb₁, enhanced the cytotoxic effect of cisplatin in vitro (Aung et al. 2007). When MCF-7 cells were exposed to a 1:500 dilution of an alcoholic extract of American ginseng (Gaia Herbs, Inc., Brevard, NC) for 48 hours, cell proliferation rates increased 16-fold over untreated control cells (P < 0.05), as shown by the BrdU cell proliferation assay (Amato et al. 2002). However, no significant growth stimulation occurred at 1:1000 or 1:5000 dilutions. Also, no transactivation of estrogen receptor subtypes α or β could be detected. When given by gavage to ovariectomized mice at 500 μL/day for 4 days, no uterine growth was found, indicating a lack of estrogenic activity.

Other Cancers

Proliferation of HCT116 human colon cancer cells was inhibited by treatment with 1.0 mg/mL of American ginseng extract (6.89% ginsenosides), 0.15 mg/mL ginsenoside-rich fraction of the extract (22.2% ginsenosides), or 0.1 mg/mL polysaccharide fraction for 2-6 days (King and Murphy 2010). The increase in mRNA was not blocked by cycloheximide, a protein synthesis inhibitor, suggesting that the effect was happening at the gene level.

Compound K

The intestinal metabolite of American ginseng root ginsenosides, designated as compound K, has been shown to arrest the growth of multiple tumor-derived cells, including breast cancer cells (MDA-MD-231, Hs78T), hepatocellular carcinomas (HepG2, Hep3B), gastric cancer cells (MKN28, MKN45), cisplatin-resistant lung adenocarcinoma (PC-14), colon cancer cells (HT-29), and human myeloid leukemia cells (HL-60), with IC₅₀ values of 14.1-56.6 μM (Cho et al. 2009; Lee IK et al. 2010; Lee et al. 1999; Oh and Lee 2004; Yim et al. 2005). According to Oh and Lee (2004), the same concentrations of the compound were not cytotoxic to normal cells (hepatocytes).

Compound K promotes apoptosis in cancer cells via activation of pro-apoptotic factors Bid and Bax, generation of reactive oxygen species, loss of mitochondrial membrane potential, activation of caspases-3, -8 and -9, and release of cytochrome c from mitochondria into cytosol (Yim et al. 2005). In these cases induction of the expression of COX-2 was also observed. The cell-cycle-regulating proteins cyclin-dependent kinase and p27 were strongly induced by compound K in MDA-MB-231 and Hep3B cells, whereas p21 protein was not affected.

Compound K was also shown both to potentiate the effects of radiation and to have a tendency to a greater apoptotic effect on cancer cells than conventional radiation treatment. According to Chae et al. (2009), cell death rates were 32% with radiation alone, 37% with compound K alone, and 45% with radiation combined with compound K. However, these values were not considered to be statistically different.

In vitro research has provided additional evidence that compound K affects metastatic processes. In a model of murine colon adenocarcinoma, inhibition of TNFα-induced migration and invasion of cells and secretion of matrix metalloprotease-9, a protein associated with development of metastases in various cancers, were observed (Choo et al. 2008; Ming et al. 2011). The inhibition was considered to be at least partly due to the blocking of NF-kB activation.

Other Compounds

Panaxynol and panaxydol, polyacetylenes found in American ginseng root, reduced proliferation of Caco-2 colon cancer cells at concentrations above 2.5 μg/mL (P < 0.01) with IC₅₀ values between 5-10 μg/mL (Putup et al. 2009). However, at the concentrations below 1 μg/mL, a stimulation of cell proliferation occurred. Both compounds exhibited inhibition of normal intestinal epithelial cells at all doses. The polyacetylene fraction has also been associated with induction of quinone reductase, a phase 2 detoxification enzyme that may have further application in conventional cancer care (Chen et al. 2010; Lee et al. 2009).

Transformation of constituents in American ginseng roots steamed at 120 °C and the effect of this treatment on
the anticancer effects in vitro were studied by Wang et al. (2007, 2008, 2009) and Luo et al. (2008). Steaming was undertaken for 0.5-4 hours at 120 °C, resulting in gradual decrease in total ginsenosides from 7.95% in the unsteamed root down to 5.85% after 1 hour of steaming, 4.05% at 2 hours, and 2.42% at 4 hours of steam treatment, while the content of ginsenoside Rg₃, a compound with known anticarcinogenic activity, increased from 0.003% in the unsteamed root to 0.271% after 1 hour, to 0.664% after 2 hours, and to 1.225% after 4 hours of steam treatment. When screened for their antiproliferative activities, 70%-ethanol extracts of American ginseng roots steamed for 1 or 2 hours completely inhibited the growth of human colorectal cancer cell lines SW-480 and HT-29 and human non-small cell lung cancer cells at the concentration of 0.5 mg/mL. The antiproliferative effect of steamed American ginseng was significantly stronger than that of unsteamed American ginseng and that of steamed Asian ginseng extracts at the same concentrations. Isolated ginsenoside Rg₃ exhibited a 99.0 ± 1.3% inhibition of SW-480 cell growth at the concentration of 500 µg/mL, while ginsenosides Rb₁, Rd, and Re did not show a significant antiproliferative effect on this cell line.

Administration of ginsenoside Rg₃, i.p. to mice for 10 days after inoculation with SKOV-3 ovarian cancer cells prolonged the lives of the animals (P < 0.01) and reduced tumor weights (P < 0.05), compared to controls (Xu et al. 2007). When Rg₃ was combined with cyclophosphamide, these effects were enhanced for both agents (P < 0.01 vs. controls for both).

**Antiangiogenic Effects**

Compound K and ginsenoside Rb₁, inhibited proliferation, migration, and invasion of human umbilical vein endothelial cells, decreased the secretion of VEGF, and ameliorated tube formation by the cells (Jeong et al. 2010; Sengupta et al. 2004).

**Estrogenic Effects**

Water extracts of American ginseng roots were observed to possess estrogen receptor-binding activity (Gray et al. 2004). The activity, however, was traced to an estrogenic compound of fungal origin zearalenone. The compound is produced by certain species of *Fusarium* fungi, which commonly contaminate food and herbal products. Zearalenone is considered strongly estrogenic. In the study, a batch of wild-crafted American ginseng roots was confirmed positive for *Fusarium*. The zearalenone content of the root batch was estimated to be 680.1 ppb by enzyme-linked immunosorbent assay (ELISA) and 2.6 µg/g by high-performance liquid chromatography (HPLC). No *Fusarium* fungi were found in a batch of cultivated American ginseng roots. However, the cultivated batch possessed 177.4 ppb (ELISA) or 0.25 µg/g (HPLC) of zearalenone, possibly indicating earlier infestation.

King et al. (2006) reported that an alcohol extract of American ginseng has weak estrogenic activity, which was demonstrated by administrating American ginseng to estrogen-dependent MCF-7 cells grown in charcoal-stripped media. Low concentrations of the extract (5-100 µg/mL) had a stimulating effect on cell proliferation, which was blocked by estrogen receptor antagonists tamoxifen and ICI 182,780. However, higher concentrations of the extract (250-2000 µg/mL) produced an inhibitory effect on the cancer cell line, consistent with most other in vitro studies.

**Aphrodisiac Effects**

American ginseng was shown to possess significant effects on copulatory behavior in male rats (Murphy et al. 1998). When given at 10, 50, or 100 mg/kg for 28 days, American ginseng dramatically reduced latency to mount (P < 0.05), intromission latency (P < 0.05 for 100 mg/kg only), and latency to ejaculate (P < 0.05). The post-ejaculatory interval was not affected. Similar results were also obtained with 100 mg/kg dose administered for 14 days for mount latency (P < 0.05) and intromission latency (P < 0.05) but not for ejaculation latency, while an acute single dose administration of American ginseng produced significant reduction in ejaculation latency (P < 0.05). Hormone analyses revealed no effect of American ginseng on plasma luteinizing hormone or testosterone levels; however, plasma prolactin levels were reduced by approximately 50% from control values by all doses tested (P < 0.05 at all dosages).

**Hepatoprotective Effects**

Extracts of American ginseng exhibited a protective effect against liver injury induced by a mixture of D-galactosamine hydrochloride and lipopolysaccharide in mice (Yoshikawa et al. 1998). The methanolic extract (single dose 500 mg/kg) inhibited increases in the serum toxicity markers alanine aminotransferase (ALAT) by 93.4% (P < 0.01) and aspartate aminotransferase (AAT) by 90.8% (P < 0.01), while the 1-butanol-soluble fraction (single dose 200 mg/kg) inhibited the increases of the same markers by 73.2% (P < 0.05) and 82.0% (P < 0.01), respectively.

Administration of compound K (1 µM) significantly decreased cell killing by tert-butyl hydroperoxide in vitro (Lee HU et al. 2005). The results of the treatment were not statistically different from those of silybin at the same molecular concentration. When the toxic compound was administered to mice, co-treatment with ginsenoside Rb₁ or compound K (25 mg/kg) ameliorated the increase in the levels of ALAT by 91.7% and AAT by 86.8% (P < 0.05).

In a model of liver fibrosis, compound K (40 µM), but not the parent ginsenosides Rb₁ and Rb₂, induced apoptosis of rat hepatic stellate cells transformed by Simian virus 40 via activation of caspase-3, indicating the potential usefulness of American ginseng for liver regeneration (Park et al. 2006).

**Adaptogenic Effects: Effects on Performance and Stress Tolerance**

Panax spp., including American ginseng, have long been ascribed adaptogenic effects. Adaptogens are generally described as substances that help the body to adapt to physiological and psychological stresses and changes. Adaptogens are thought to work via the hypothalamic-pituitary-adrenal axis, resulting in enhanced athletic performance, motor
functions, stress thresholds, and compensatory actions, while having a normalizing effect on blood pressure, blood sugar, and immune responses and increasing feelings of general well being.

**Human Clinical Trials**

The effects of 4-week-long American ginseng supplementation on exercise performance were studied in 13 healthy, physically active volunteers by Hsu et al. (2005). The average age of the subjects was 23.0 ± 1.6 years old. The treatment consisted of daily intake of 4 capsules, each containing 400 mg of American ginseng root powder or placebo. The ginsenoside content of the American ginseng root was analyzed and was consistent with the typical profile of American ginseng, with ginsenosides Rb1 and Re predominating. Exercise performance was estimated when subjects were running on a treadmill at 80% of aerobic capacity. Blood was sampled before the exercise, at 15 and 30 min during exercise, immediately after, and at 20, 40, 60, and 120 min after exercise. After 4 weeks of daily supplementation with American ginseng, creatine kinase activity in the plasma, indicative of the level of muscle breakdown, was significantly lower in the American ginseng group at 30 minutes of exercise, immediately after, and 20, 60, and 120 minutes after exercise, compared to placebo group (P < 0.05 for all measures). Blood lactate concentration, an indicator of hypoxia due to muscle exertion, was significantly lower in the American ginseng group at 15, 30, and 120 minutes after exercise, compared to the placebo group (P < 0.05 for all measures). No difference was found between American ginseng and placebo groups in aerobic capacity, run time to exhaustion, and oxygen consumption.

**Animal Studies**

Tolerance to hypoxia and fatigue was improved by American ginseng in several animal experiments. Oral administration of the root powder to mice (50-100 mg/kg of “total saponins”) for 3 days resulted in 12.4±19.7% increases in survival time in hypoxia (P < 0.01) and 56.2±53.3% increases in swimming time (P < 0.01) (Kong et al. 1997). A single dosage of 3 g/kg i.p. prolonged the survival time of hypoxic mice by approximately 180% (P < 0.01) and prolonged the swimming time in 25 °C water by approximately 80% (P < 0.01) (Liu and Zhang 1997). An ethanol extract of American ginseng (0.33 g/kg calculated as root equivalent) i.p. for 7 days inhibited the drop in rectal temperature of cold-stressed mice (P < 0.05) (Liu and Zhang 1997).

Saponins extracted from American ginseng dry roots with 80% ethanol, yielding a total of 4.2±5.1%, including 0.48±0.52% Rb, and 0.21±0.22% Rg, were tested for their effects on cold tolerance (Wang and Lee 2000). When 10 mg/kg “total saponins” were injected i.p. in young rats (3-6 months old) 30 minutes prior to severe cold exposure (-10°C), both total and maximum heat production were elevated, but no benefits were found when Rb, and Rg were removed. Pretreatment with 2.5 and 5.0 mg/kg Rb, but not Rg, increased both cold tolerance and thermogenesis in young and old (26-28 months) rats.

The ability of American ginseng to affect exercise performance was demonstrated in a rat treadmill study (Wang and Lee 1998). Total ginsenosides extracted from American ginseng root were injected i.p. either acutely, 30 minutes prior to exercise, or chronically for 4 days. The experiment was repeated with all rats as their own controls, with a week between the tests to eliminate the learning factor. Acute treatment did not result in improved performance. However, after chronic administration, the endurance of rats estimated by running time was increased (P < 0.05). A separate control group, treated with saline only, had similar performance in both weeks, ruling out the training effect. Additionally, ginsenosides increased the end plasma levels of free fatty acids but did not increase the glucose levels.

Multiple studies have been performed on stress in animal models using American ginseng as either the main study treatment or the positive control. Two separate studies (Rasheed et al. 2008; Sheikh et al. 2007) report on normalizations of neurotransmitter levels in the cerebral cortex and the hypothalamus after treatment with American ginseng. Treatment of male Swiss albino mice with 200 mg/kg of American ginseng root powder p.o. for 7 days decreased plasma levels of corticosterone (P < 0.001), normalized levels of norepinephrine and 5-hydroxytryptophan in the hypothalamus (P < 0.01 for both neurotransmitters) and the brain cortex region (P < 0.001 and P < 0.05, respectively), and normalized dopamine levels in the hypothalamus (P < 0.001) (Rasheed et al. 2008). In the same study, American ginseng failed to restore the initial concentrations of dopamine in the brain cortex region of the animals under conditions of chronic unpredictable stress. The dose of 200 mg/kg also inhibited the increase in pro-inflammatory cytokines IL-2 and IL-6 in the brain cortical region and the hypothalamus of treated animals (P < 0.001) (Rasheed et al. 2008). According to Sheikh et al. (2007), the dose of 100 mg/kg of American ginseng root significantly inhibited elevation of corticosterone levels in the plasma of adult male Sprague-Dawley rats in both acute (P < 0.001) and chronic unpredictable (P < 0.001) stress models and reversed changes in concentrations of neurotransmitters norepinephrine (P < 0.001), dopamine (P < 0.001), and 5-hydroxytryptophan (P < 0.001) in the cortex and hippocampus of the stressed animals.

Several other physiological parameters associated with stress were normalized by treatment with American ginseng (Rai et al. 2003; Siripurapu et al. 2005). Administration of the root powder significantly decreased the ulcer index (P < 0.05), prevented the increase in the adrenal gland weight (P < 0.01) in chronically stressed mice and rats, prevented the increase in the levels of alanine aminotransferase in acutely stressed mice (P < 0.01), reduced the levels of aspartate aminotransferase in acutely stressed mice (P < 0.01), and decreased the levels of creatine kinase in acutely (P < 0.01) and chronically (P < 0.01) stressed mice and rats (P < 0.001). No significant effect was observed on triglycerides, which were decreased with stress, and American ginseng did not prevent the reduction in the weight of spleen and thymus in chronically stressed animals. However, administration of 60 mg/kg i.p. daily
for 6 consecutive days markedly inhibited the adrenocorticotropic hormone (ACTH)-induced atrophy of thymus (P < 0.05) and spleen (P < 0.01) in mice (Yan et al. 1987). The treatment also inhibited the ACTH-induced decrease in the content of vitamin C in adrenals of rats (P < 0.05). However, a single dose of American ginseng saponins (60 mg/kg i.p.) caused a 41% decrease in the content of vitamin C in adrenals of normal rats (Yan et al. 1987). The authors suggested that American ginseng facilitates the secretion of adrenal cortical hormones in normal rats but also elicits an effect against ACTH in ACTH-treated rats, thus exhibiting a potent anti-stress activity. Siripurapu et al. (2005) also reported the corticosterone-lowering effect of American ginseng as well as reduction in the increase of creatine kinase levels (P < 0.001) and prevention of acute stress-induced hyperglycemia (P < 0.01).

**Effects on Brain Function and Memory**

**Human Clinical Trials**

Neurocognitive effects of an acute treatment with the American ginseng extract Cereboost™ (Naturex, USA) were assessed in a double-blind, randomized, placebo-controlled, crossover trial (Scholley et al. 2010). The patented extract is prepared using 75% aqueous ethanol and is standardized to contain 11.65% ginsenosides. The study enrolled 32 participants (50% male) aged 18-40 years old. Each participant took 0 (placebo), 100, 200, and 400 mg of the extract once, with a 7-day washout period between tests. The participants were advised not to take any other vitamins, herbal supplements, or over-the-counter medicines during the duration of the study. A number of tests, shown to be sensitive to nutritional manipulations, were used to assess the subjects’ cognitive performance and mood. The tests were performed at 1, 3, and 6 h after administration of American ginseng. Significant effects were observed in a number of the tests, as shown in Table 17. No effect of any dose was observed in word presentation, picture presentation, face presentation, simple reaction time, four choice reaction time, Stroop color-word task, N-back, delayed word recall, delayed picture recognition, delayed face recognition, serial sevens subtraction task, serial three subtraction task, or rapid visual information processing tests. There was significant increase in self-rated calmness at 3 h (P = 0.002) and 6 h (P = 0.001) with the 100 mg dose.

**Animal Studies**

**Neuroprotective Effects**

Multiple animal studies point out that American ginseng and, specifically, protopanaxadiol-type ginsenosides can protect brain cells and memory function from toxicity associated with various chemical stressors. In early studies, ginsenoside Rb1, increased the depolarized release of acetylcholine from hippocampal cells (Benishin 1990), the number of molecular carriers for choline (Benishin 1992), and improved memory deficits caused by the anticholinergic agent scopolamine in mice (Benishin et al. 1991).

Oral administration of 100 and 500 mg/kg of American ginseng saponins to mice for 7 days reversed memory impair-
alone) or independently from NGF when the treatment was prolonged to 18 days ($P < 0.05$) (Rudakewich et al. 2001).

Expression of pro-inflammatory cytokines IL-1β, TNFα, IL-6, and NO in microglial cells of the rat was reduced by ginsenoside Rb$_1$ (50-250 µg/mL), with the dose of 500 µg/mL proving cytotoxic (Joo et al. 2005). Ginsenosides Rg$_1$ and Rb$_1$ exhibited neuroprotection from a toxic agent MPTP (Rudakewich et al. 2001), while Rb$_1$, but not Rg$_1$, suppressed Aβ-induced inhibition of acetylcholine release (Lee et al. 2001).

Ginsenoside Rb$_1$ increased the expression of nerve growth factor mRNA in the CA1 pyramidal layer ($P < 0.05$) and in the infrapyramidal blade of the dentate gyrus ($P < 0.05$) of the hippocampus (Salim et al. 1997). Tyrosine kinase A mRNA encoding the nerve growth factor receptor was increased by approximately 20% ($P < 0.05$) in the diagonal band of Broca, a cholinergic nerve bundle in the human brain, and only non-significantly in the medial septum. Rb$_1$ had no significant effect on the expression of brain-derived neurotrophic factor and neurotrophin-3.

**Table 17 Statistical significance of American ginseng root administration on subjects’ performance in various memory tests**

<table>
<thead>
<tr>
<th>Effective doses</th>
<th>Time after American ginseng administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 hour</td>
</tr>
<tr>
<td>200 mg</td>
<td>$P &lt; 0.003$</td>
</tr>
<tr>
<td>200 mg</td>
<td>$P &lt; 0.039$</td>
</tr>
<tr>
<td>100 mg</td>
<td>$P &lt; 0.041$</td>
</tr>
<tr>
<td>400 mg</td>
<td>$P &lt; 0.033$</td>
</tr>
<tr>
<td>100 mg</td>
<td>$P &lt; 0.006$</td>
</tr>
<tr>
<td>400 mg</td>
<td>$P &lt; 0.001$</td>
</tr>
<tr>
<td>100 mg</td>
<td>$P &lt; 0.037$</td>
</tr>
<tr>
<td>200 mg</td>
<td>$P &lt; 0.35$</td>
</tr>
<tr>
<td>400 mg</td>
<td>$P &lt; 0.027$</td>
</tr>
</tbody>
</table>

Source: Scholey et al. (2010).

**Modulation of the Activity of Neurotransmitters**

Compound K was found to increase spontaneous GABA release from isolated rat hippocampal CA3 pyramidal neurons (Bae et al. 2010). Its metabolic predecessor ginsenoside Rb$_1$ increased the expression of choline acetyltransferase by approximately 20% ($P < 0.05$) and by approximately 40% ($P < 0.05$) in the septum. At the concentrations of 10$^{-8}$-10$^{-7}$ M, ginsenoside Rb$_1$ facilitated the release of acetylcholine (ACh) from rat brain hippocampal slices by approximately 20% ($P < 0.05$) and 40% ($P < 0.05$). No increase was observed at the higher concentration (10$^{-6}$ M). At 10$^{-6}$ and 10$^{-5}$ M, Rb$_1$ also increased the uptake of choline (precursor of ACh) into synaptosomes by approximately 15% ($P < 0.05$) and 18% ($P < 0.05$), respectively. Rb$_1$ had no effect on the binding of quinuclidinyl benzylate, acetylcholinesterase activity, or calcium uptake into synaptosomes (Benishin et al. 1991).

Water extract of powdered American ginseng root (10:1 w/w) at a concentration of 3 µg/mL was found to inhibit GABAergic activity in 75% of nucleus tractus solitarius units in the caudal brainstem region of rats by 25.1 ± 4.4% when applied directly to the organ preparations ex vivo (Yuan et al. 1998a). The inhibition was not reversed by the known GABA$_A$ receptor antagonist bicuculline. However, a small percentage (14.3%) of units exhibited an activation response (21.0 ± 4.5%) to the treatment, indicating that American ginseng may have differential effects on brain activity. Pretreatment with American ginseng also reversed inhibition of GABA$_A$ neurons by muscimol, suggesting effects on the ligand binding.

**Protection from Ischemic Stroke and Alzheimer’s Disease**

American ginseng extract (3 mg/mL) and ginsenoside Rb$_1$ produced a tonic block of voltage-dependent sodium (Na$^+$) channels, resulting in 25% inhibition ($P < 0.01$), and slowed their recovery from inactivation, suggesting a beneficial effect on brain damage associated with ischemic stroke (Liu et al. 2001).

American ginseng root may be beneficial for protecting against one of the main histological characteristics of Alzheimer’s disease, the formation of neurofibrillary tangles, as treatment of several neural cell lines with ginsenoside Rb$_1$ (40 µM) prevented deterioration of the microtubular network after their exposure to β-amyloid peptide (Chen et al. 2008). Additionally, Rb$_1$ partially or completely prevented phosphorylation of the tau protein, induced by β-amyloid, which is thought to compromise the protein’s ability to control the integrity of microtubules, thus being the main contributor to the formation of the tangles.
Behavioral Effects

Animal Studies
A concentrated ginsenosides fraction from American ginseng root was compared to diazepam in its effect on anxiety levels in mice, using several previously confirmed experimental models for anxiety, including an elevated plus-maze test, light/dark test, hole-board test, and isolation-induced aggressive test (Wei et al. 2007). The ginsenosides were administered at 25-50 mg/kg 30 min before the tests. The 50 mg/kg dose resulted in an increase in the number of entries (P < 0.01) and time spent (P < 0.05) in the open arms of the maze in the elevated plus-maze test, indicating an anxiolytic effect. At the same time, ginsenosides did not increase total entry into the arms of the maze, indicating lack of the increase in locomotion, a known side effect of anxiolytic drugs, such as diazepam and benzodiazepines in general. Similar effects were observed in the light/dark test and the hole-board test with the relevant parameters reaching significance at the 50 and 100 mg/kg dosages (P < 0.05 and P < 0.01, respectively). In the isolation-induced aggression test, the fighting time was significantly decreased with 50 and 100 mg/kg of the ginsenosides (P < 0.01 both dosages).

A few preclinical studies report on constituents in American ginseng root being potentially useful in the treatment of drug addiction. Ginsenoside Rb1 (100-200 mg/kg) administered i.p. 1 hour prior to administration of cocaine (15 mg/kg s.c.) dose-dependently inhibited cocaine-induced hyperactivity (P < 0.05 at 100 mg/kg and P < 0.01 at 200 mg/kg) and reduced drug-associated conditioned place preference (P < 0.01 at 100 mg/kg), a measure of cocaine’s psychological effects, in mice (Kim et al. 1999). Mice pretreated with 100 and 200 mg/kg of ginsenosides Rb1 or Rg1 i.p. demonstrated significant inhibition of methamphetamine-induced hyperactivity (P < 0.01 for all) (Kim et al. 1998). Also, significant inhibition of methamphetamine-induced conditioned place preference occurred in those pretreated with 100 mg/kg of ginsenosides Rb1 (P < 0.01) or Rg1 (P < 0.05) as well as an inhibition of the accompanying dopamine supersensitivity (P < 0.05 for both ginsenosides). The inhibition of methamphetamine-induced hyperlocomotion and conditioned place preference by 50 and 150 mg/kg i.p. of unspecified ginsenosides was associated with stimulation of adenosine A2A receptors in mice (Shin EJ et al. 2005). Pseudoginsenoside F11, another constituent of American ginseng root, at the low dose of 4 mg/kg ameliorated anxiety-like behavior and memory impairment induced by methamphetamine in mice and partially restored dopamine levels depleted with methamphetamine in the brains of the animals (Wu et al. 2003). The latter compound at the same dose prevented an increase in locomotor activity in mice induced by chronic morphine intake (10 mg/kg/day for 7 days) (P < 0.001), while 8 mg/kg, but not 4 mg/kg, of F11 inhibited a decrease in extracellular glutamate levels in the brain after a single (10 mg/kg) as well as chronic morphine dosing (Hao et al. 2007). When administered by itself, the saponin did not significantly affect behavior or biochemical parameters measured in either study.

Other Effects
Ginsenoside Rb1 (50 mg/kg) as well as its intestinal metabolite compound K inhibited scratching when administered orally 6 hours prior to application of an irritant compound 48/80 to the skin of mice (Shin and Kim 2005).

An early report (Kurokawa et al. 1988) claims that treatment with ginsenoside Rb1 had a depressive effect on feeding patterns in mice, resulting in decreased meal sizes.

Summary
Despite its broad use as an herbal supplement and herbal medicine, there is not a lot of clinical research on American ginseng. There is a large amount of preclinical data, some supporting the traditional uses of the herb (nervine and tonic) and others supporting novel applications (e.g., blood sugar regulation). Far more research has been done on the close relative of American ginseng, Asian ginseng. Both species contain similar active constituents. Thus, some actions associated with Asian ginseng may overlap with American ginseng actions. Nevertheless, the differences in the content of individual ginsenosides and in their ratios need to be taken into consideration, as different ginsenosides have been shown to differ in their physiological effect (e.g., Sengupta et al. 2004; Sievenpiper et al. 2004; see Constituents).

Physiological effects of American ginseng have been correlated with the compounds known as ginsenosides as well as their intestinal metabolites. Hydrolyzing enzymatic activity of the bacteria associated with the digestive tract results in the degradation of protopanaxadiol ginsenosides primarily into compound K, while protopanaxatriol ginsenosides are mainly metabolized into ginsenoside Rh1. These 2 compounds are the primary metabolites of ginsenosides that have been found in the human plasma for at least up to 24 hours after ingestion. Some pre-clinical investigations have been conducted with these metabolites.

Clinically, American ginseng root and its compounds have been found to possess adaptogenic, antioxidant, cardiovascular, hypoglycemic, immunological, and neurocognitive effects. One of the most significant clinically relevant findings is the hypoglycemic and insulinoergic action, demonstrated in both type-2 diabetic and non-diabetic subjects. This action is considered to involve peroxisome proliferator-activated α (PPARα) and γ (PPARγ) receptors and is correlated primarily with the action of the ginsenoside metabolite compound K, as shown in vitro and in animal studies. Markers of improvement relevant to type 2 diabetes include an increase in insulin production, reduced inflammation, pancreatic islet cell preservation, decreased insulin resistance, and improved liver lipid levels.

Immunologically, a patented polysaccharide-rich extract of American ginseng marketed in Canada was found to possess substantial preventive activity against upper respiratory tract viral infections in several clinical trials. The results achieving statistical significance included lowering the incidence, symptom severity, and symptom duration of the common cold and reduced risk of laboratory-confirmed acute respiratory illness among the elderly. The same preparation reduced airway inflammation in an induced asthma
Cardiovascular benefits have been demonstrated for American ginseng, resulting in clinical improvement in ischemia, hemorrhagic shock, arrhythmia, hyperlipidemia, and hyperplasia. These benefits are associated with enhanced action of antioxidant enzymes, such as SOD, as demonstrated in humans, and glutathione peroxidase, the increase of which activity has been observed in animals. American ginseng had a neutral effect on blood pressure in the few studies reporting on it. Animal data suggests American ginseng improves arrhythmias, increases coronary output, has negative inotropic and calcium channel blocking activity, and improves HDL/LDL ratios.

In cancer care, the only effect of American ginseng demonstrated in humans was a non-significant subjective feeling of greater well-being reported by cancer patients. However, pre-clinical research suggests a number of anticancer benefits. Compound K, the main intestinal metabolite of protopanaxadiol ginsenosides detected in human plasma, has been shown to have selective cytotoxic activity against multiple cancer types in vitro, possess antiangiogenic effects, inhibit metastases of colon, liver, and lung cancers, reduce the incidence of experimentally induced skin cancer, potentiate tumor-reducing activity of γ-radiation, and attenuate the toxicity of the chemotherapeutic agents cyclophosphamide and mitomycin C.

Adap tonic effects of American ginseng have been minimally addressed by clinical trials, with one study reporting on its effects in humans during and after prolonged exercise and one study investigating its effects on cancer-related fatigue. In the former investigation, the intake of American ginseng by healthy volunteers improved markers of exercise stress (plasma creatine kinase and lactate levels) but did not have a marked effect on performance. Multiple animal studies have demonstrated increased resistance to stress in various extreme conditions, adding credence to the adaptogenic effects of the herb. Immunological effects reported above may be considered as part of the constellation of adaptogenic effects. Additionally, self-reported anxiety levels were reduced with American ginseng administration during memory tests in healthy human volunteers.

The improvement of several memory parameters by American ginseng root was observed in a clinical trial. Combined with the multiple neuroprotective effects of American ginseng and its constituents, observed in preliminary studies, this suggests that American ginseng root may be useful for protecting, improving, and restoring the mental function. In animals, ginsenosides of the protopanaxadiol fraction (Rb1, Rb3, Rd) and their intestinal bacterial metabolite compound K were shown to be neuroprotective against multiple agents and enhance neuronal activity. Positive effects were observed on the neurotransmitter acetylcholine.

The molecular pathways found to be affected by compound K in vitro include activation of phosphatidylinositol-3 kinase (PI3K)/Akt pathway. PI3K is an important regulatory protein involved in numerous diverse signaling pathways and controlling the main functions of the cell (Krasilnikov 2000). Additionally, compound K has been shown to exert anti-inflammatory action via inhibition of TNFα and several cytokines.

Overall, American ginseng appears to elicit a variety of physiological responses, with many effects indicating that it is a valuable agent for protecting human health against a number of diseases associated with aging and modern lifestyle, including stress, common colds and influenza, memory decline, diabetes, cardiovascular diseases, and cancer. Such uses, in general, are consistent with the traditional use of Asian ginseng, which historically spurred interest in American ginseng.

Medical Indications Supported by Clinical Trials

Several clinical trials suggest the efficacy of American ginseng root for the control of postprandial hyperglycemia, both in healthy subjects and subjects with type 2 diabetes. However, batch-to-batch variation in the ginsenoside content may affect the outcome of the treatment. A proprietary extract of American ginseng root standardized to 80% poly-furanosyl-pyranosyl-saccharides is indicated for the prevention of acute respiratory illnesses in adults and as an influenza vaccine adjunct in the elderly. Limited evidence suggests benefit of the root for subjective perception of cancer-related fatigue.

Medical Indications Supported by Traditional or Modern Experience

The use of American ginseng in traditional American herbal practice is mostly limited to the geographic region where it is most common, the southeastern United States. In using American ginseng for “coughs, consumptions, and spasmodic disorders,” Stearns (1801) recommended the decoction to be prepared from 2 drachms (approximately 7 g) of the sliced root in 1 quart of water, boiled down to 8 ounces, also noting that the roots can be used for a second boiling. The decoction was dosed at 2 ounces, morning and evening. Alternatively, 1 scruple (approximately 1.3 g) of the whole root was to be consumed twice a day.

Samuel Thomson (1833) regarded American ginseng as a nerve, suggesting the root to be dug in the fall, dried, and ground to a fine powder. Thomson recommended the dose of ½-1 teaspoon added to hot water.

While the plant had limited use by orthodox, botanic, and Eclectic practitioners, it found popular favor as a panacea and tonic remedy amongst Appalachian and Ozark mountain people. Richard Foreman in his book The Cherokee Physician (1857) suggests using the root for “weakly females and for weakness of the womb and nervous afflictions; convulsions, palsy, vertigo, and dysentery.” He also mentions it can be taken in spirits if preferred. The practice of macerating American ginseng roots in corn liquor to make a tonic remedy is still common throughout the rural south. One account mentions a man with rheumatism that was not responding to treatment: “…he got somebody to slip him a half-gallon of whiskey with a handful of ginseng in it. He took it and swore that it run the rheumatism out of him” (Crellin and Philpott 1990).
Francis Porcher, in his *Resources of the Southern Fields and Forests* (1863), quotes numerous sources including a Dr. Jones stating that American ginseng is useful for “all cachetic and consumptive cases and in those arising from debility of any kind.” Dr. Healde is mentioned as using this herb as “a restorative after great fatigue, an antispasmodic in nervous affections, and as an aphrodisiac.”

King and Newton (1852) in their early edition of the *Eclectic Dispensatory of the United States* described American ginseng root as a mild tonic and stimulant that was employed for “loss of appetite, slight nervous debility, and weak stomach.” They reported that others considered the root beneficial for “asthma, gravel, convulsions, paralysis, to invigorate the vital powers, etc., etc.” According to this source, doses of the powder from 10-60 grains (0.6-3.8 g) and 2-4 ounces of the infusion were given.

The Physiomedicalist Cook (1869) stated the following regarding American ginseng:

The root of ginseng (often supposed to be the same with gentian) is a very mild tonic, somewhat aromatic and diffusive, principally relaxant, and making its chief impression upon nervous structures. As a soothing and nerve tonic, it answers a fair purpose in simple forms of dyspepsia, nervousness, hysteria, and similar cases of nervous sensitiveness with debility. Its powers are altogether too light to be of service in depressed cases. As its qualities are easily dissipated by heat, it should be used in substance or as a wine tincture.

For these purposes, Cook recommended a dose of the powder of approximately 1 scruple to 1 drachm (3.9 g) and noted that many prefer to chew the root itself.

In the later edition of *King’s American Dispensatory* (Felter and Lloyd 1905), American ginseng is recommended as an important remedy for mental exhaustion from overwork and “cerebral anemia.” This mirrors the most common uses of the root today for its tonic, adaptogenic properties. Scudder in his *Specific Medication* (1890) reported he had limited experience with American ginseng but was convinced of its utility in nervous dyspepsia. Conversely, he reported: “I have obtained more benefits from it in my own person, than from any other remedy, and I have employed it with others with equal advantage.” Scudder noted that it produces no immediate benefit but that marked improvements are observed over a period of weeks. The primary preparation used was a tincture of the fresh root. Felter, in his *The Eclectic Materia Medica* (1922), repeated similar indications and noted: “As a medicine it acts kindly and quietly, giving a graceful sense of comfort to the stomach.”

In the rural south, African American root doctors have used and still use American ginseng as an important tonic remedy. It is not uncommon to hear that American ginseng is good “for a man’s nature.” John Lee, a well-respected herbalist from eastern North Carolina, used the root for kidney and liver problems, lack of libido, poor appetite, prostate problems, back, chest, and stomach pains, diabetes, “bad blood,” and nervous conditions (Payne-Jackson 1993).

Tommie Bass (1908-1996), the renowned northern Alabama “Herb Doctor,” called this plant the “King of Herbs.” He believed it was an alterative, tonic, and male aphrodisiac (Patton 2004). He felt it was especially useful for treating people who were debilitated by long-term illness.

In agreement with classifying American ginseng as an adaptogen, the root of it is commonly used for treating stress-induced diseases, including mild depression, chronic fatigue immune deficiency syndrome, stress-induced asthma, impaired cognitive function, and post-performance immune depletion in athletes (Kuhn and Winston 2001). The American species of ginseng is believed to be less stimulating than Asian ginseng, so it is also seen as appropriate for anxiety, attention deficit hyperactivity disorder, “white coat” (stress-induced) hypertension, and nervous insomnia (Awang 1998; Kuhn and Winston 2001).

There is curious absence of the use of American ginseng root in the early-to-mid-20th century American herbal literature. Classic and influential texts, such as *Nature’s Healing Agents* by Clymer (1905), *Advanced Treatise on Herbolology* by Shook (ca. 1948), Otto Mausert’s *Herbs For Health* (1932), and Dr. Christopher’s *School of Natural Healing* (1976), do not mention American ginseng at all. However, American ginseng was listed in a few key herbal references of the era. The Dominion Herbal College Master Herbology program (1926) cited American ginseng as a tonic stimulant that tones the appetite and is used in digestive troubles. Maude Grieve, in her classic work *A Modern Herbal* (1931), reported on the use of the root for digestive disturbances, such as loss of appetite due to nervous exhaustion. Jethro Kloss, in his remarkably popular book *Back to Eden* (1939), stated that it is frequently used in hot, moist climates as a preventative “against all manner of illnesses.” Kloss further noted the root promotes appetite, benefits digestive and respiratory problems, enhances sweating, when taken as a hot tea, and relieves inflammation of the lungs and urinary tract. Kuts-Cheraux (1953), similarly, included American ginseng in his *Naturae Medicina and Naturopathic Dispensatory* as an equivalent of the Chinese species, listing it as a “soothing, mild and gentle gastric tonic, improving digestion and stimulating the circulation of the stomach and intestines.” Kuts-Cheraux reported that American ginseng improved assimilation, increased the appetite and digestion, was a tonic for the nervous system, especially for exhaustion due to overwork, and noted that it needed to be used for extended periods of time to obtain its benefits, all attributes ascribed to adaptogens.

Most often the use of American ginseng by modern Western herbalists mirrors its folk use in Appalachia as a tonic remedy for fatigue, stress, old age, and impotence. It is rare to find other variant uses for the plant. One exception is in James Green’s *Male Herbal* (1991) where he suggests that the root can be used to normalize blood pressure, especially low blood pressure, as well as to treat anemia and circulatory problems.

**Actions**

**Traditional:** Adaptogenic, nervine, tonic, sedative.
Clinically confirmed: Antioxidant, cardioprotective, hypoglycemic, immune modulator (polysaccharide-rich fraction), nerve, nootropic.

Preclinical support: Adaptogenic, antiaddictive, anticarcinogenic, aphrodisiac, hepatoprotectant, neuroprotective, sedative.

Indications
American ginseng root can be used for general fatigue, nervous exhaustion, memory support, prevention of common colds, as an adjunct in cancer therapies, and for blood sugar regulation.

Substantiated Structure and Function Statement
American ginseng root promotes healthy blood sugar levels, increases antioxidant activity, and supports normal cognitive functions. Traditionally used as a restorative and to help relieve nervousness and nervous dyspepsia.

Dosages
Root (whole or powder):
1-3 grams daily.

Tincture (1:5, 50-80% ethanol):
5-15 mL daily.

Fluid extract (1:1, 50-80% ethanol):
1-3 mL daily.

Safety Profile
Based on a critical review of the available traditional and scientific literature, American ginseng root appears to be a very safe herb when consumed within a wide range of dosages and in a wide array of dosage forms.

Adverse Effects
In several clinical trials of American ginseng root, adverse events were similar in the American ginseng and placebo-treated groups in healthy adults (Hsu et al. 2005; Predy et al. 2005; Sievenpiper et al. 2004), cancer patients (Barton et al. 2010), hypertensive individuals (Stavro et al. 2005, 2006), the elderly (McElhaney et al. 2004), and children (Vohra et al. 2008). Clinical trials have included doses ranging from 400 mg to 6000 mg daily for up to 12 weeks.

Articles written in 1979 and 1980 (Siegel 1979, 1980) spurred what are now recognized as erroneous concerns that American ginseng may cause high blood pressure. In the first of these observational studies of “ginseng users,” taking a variety of doses (up to 15 g/day with an average of 3 g daily) in different dosage forms (roots, extracts, teas, capsules, cigarettes) and via different routes of administration (primarily oral but also intranasal and intravenous) together with long term use (at least 13 weeks) and concurrent consumption of caffeine sources was associated with hypertension in one person out of six. All told, 22 out of 133 of the study participants experienced adverse events such as hypertension often accompanied by nervousness, sleeplessness, skin eruptions, and diarrhea (Siegel 1979). The second study of people using American ginseng products (teas, capsules, extracts, roots, and cosmetic creams) included a group of 10 drug addicts and a group of 8 normal ginseng users. Adverse events like those observed in the earlier study were observed only in the group comprised of drug addicts (Siegel 1980). An earlier article by the same author noted the prevalence of adulteration of ginseng products around the time that the studies were being published (Siegel 1977). As reported in the Therapeutics section of this monograph, more recent studies with American ginseng have shown a lack of effect on blood pressure (Stavro et al. 2005, 2006) suggesting that concern for use of American ginseng in contributing to hypertension is not warranted.

Interactions
Based on reviews of clinical studies, American ginseng may interact with warfarin and blood sugar medications.

The interaction of American ginseng and warfarin was tested in a 4-week study with 20 healthy volunteers (Yuan et al. 2004). Patients were randomly assigned to receive either 1.0 g of powdered American ginseng or cornstarch placebo p.o. in capsules twice daily during weeks 2 through 4. For the first 3 days of weeks 1 and 4 of the study, 5 mg daily of warfarin was administered p.o. After 2 weeks of ginseng administration, the decrease from baseline in peak international normalized ratio (INR) was significantly greater, compared with placebo. The INR area under the curve, peak plasma warfarin level, and warfarin area under the
curve were also more reduced from baseline values in a statistically significant manner in the American ginseng group as compared with placebo (Table 18). Peak INR and peak plasma warfarin levels were positively correlated. Based on these results, caution is advised in the concomitant administration of warfarin and American ginseng preparations.

Human studies have demonstrated that American ginseng may modify glucose regulation (Sotaniemi et al. 1995; Vukan et al. 2000a, 2000b) with inconsistent glycemic impacts reported between cultivated and wild roots (Sievenpiper et al. 2004) and roots with different ginsenoside profiles (Sievenpiper et al. 2003) (see Therapeutics). Therefore, people with diabetes are advised to monitor their blood sugar closely if using American ginseng and to discuss this use with a qualified healthcare practitioner.

A lack of interaction between American ginseng and the HIV protease inhibitor indinavir, a cytochrome P450 (CYP) 3A4 isoenzyme substrate, was shown in healthy volunteers. The subjects were administered 800 mg indinavir 3 times daily for 3 days before each of 3 weekly visits. For the 3 days prior to the final visit, the volunteers consumed capsules containing 1 g American ginseng every 8 hours while continuing to take indinavir. At the final visit, no difference in the indinavir area under the plasma-concentration-time curve was observed (Andrade et al. 2008).

An in vitro study in rat liver microsomes indicated that metabolites of selected compounds from American ginseng (ginsenoside Rg₂, 20(S)-panaxatriol, and 20(S)-protopanaxatriol) exhibited competitive inhibitory activity against the drug metabolizing isoenzyme CYP3A, while compounds such as ginsenosides Rb₁, Rb₂, Rc, Re, and Rg₁ and metabolite compound K had no inhibitory activity against the drug metabolizing isoenzyme CYP3A. Therefore, people with diabetes are advised to monitor their blood sugar closely if using American ginseng and to discuss this use with a qualified healthcare practitioner.

| Table 18 Changes in peak international normalized ratio, international normalized ratio area under the curve, peak plasma warfarin level, and warfarin area under the curve in a study of American ginseng interaction with warfarin |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------|
| From weeks 1 to 4 | American ginseng group | Placebo group | American ginseng vs. placebo |
| (n = 12) | (n = 8) | Estimated difference in medians (95% CI) | P value‡ |
| Peak INR* | -0.16 | -0.02 | -0.19 | 0.0012 |
| (-2.41/0.02) | (-0.07/0.22) | (-0.36 to -0.07) | |
| INR AUC* | -0.46 | -0.09 | -0.43 | 0.025 |
| (-6.36/0.36) | (-0.51/0.72) | (-1.00 to -0.09) | |
| Peak plasma warfarin level, μg/mL | -0.20 | 0.00 | -0.20 | 0.026 |
| (-0.70/0.20) | (-0.10/0.27) | (-0.35 to 0.00) | |
| Warfarin AUC, μg/mL per d | -0.40 | 0.18 | -0.64 | 0.0069 |
| (-1.20/0.20) | (-0.35/1.40) | (-1.25 to -0.13) | |

* AUC = area under the curve, INR = international normalized ratio.
† Median and range (min/max).
‡ Wilcoxon rank-sum test.
Source: Yuan et al. (2004).

When 200 mg of an American ginseng extract (8.5% ginsenosides) was given twice daily for 2 weeks to 10 healthy humans, the pharmacokinetic profiles of 500 mg of zidovudine, a nucleoside reverse transcriptase inhibitor, given at the end of the 2-week period did not differ significantly from baseline values (Lee LS et al. 2008). Zidovudine, used in combination therapy for HIV infections, is not metabolized by phase I CYP isoenzymes and is cleared from the body by phase II enzyme uridine diphosphate (UDP)-glucuronosyltransferase (UGT). However, the extract induced the phase II enzyme glucuronide reductase in vitro.

Beneficial interactions include reduction of side effects of the chemotherapeutic drugs cyclophosphamide (Zhang QH et al. 2008, 2009), doxorubicin (Ma et al. 1993), and mitomycin C (Pawar et al. 2007) by American ginseng root or isolated ginsenosides, as shown in studies in animals (see Therapeutics). The administration of the root or its constituents reduced bone marrow damage and enhanced the activity of various antioxidant enzymes.

Reproductive and Developmental Effects

No studies on reproductive or developmental effects of American ginseng root were identified.

Carcinogenicity

In tests for the mutagenic potential of American ginseng root in Salmonella typhimurium strain TM677, analyses of a water extract prepared by a procedure similar to that used in traditional medicine and of a “total ginsenosides” extract were completed (Chang et al. 1986). At concentrations up to 36 mg of the extracts per mL of culture media (approxi-
mately 9 g ginseng solids/300 mL water or 1-butanol), neither water nor 1-butanol extracts of ginseng were found to produce a mutagenic response with or without metabolic activation (Chang et al. 1986). Furthermore, anticancer activity has been reported for American ginseng root and its metabolite compound K (see Therapeutics).

**Toxicology**
No significant toxic effects were observed after intraperitoneal administration of 450 mg/kg of American ginseng root daily for 7 days in animals (Chen and Chen 2004).

**Contraindications**
There are no known contraindications for American ginseng root.

**Precautions**
Allergic reactions to American ginseng root, including drug rash and asthma, have been reported (Bensky et al. 2004) but appear to be rare. A primary reference text on traditional Chinese medicine indicates that “inappropriate use” of American ginseng root may cause headache, weakness, apathy, aversion to cold, distended abdomen, vomiting, and delayed menstruation (Bensky et al. 2004). No further details are given, and these adverse events have not been reported in Western literature on American ginseng. Use with caution in conjunction with conventional anticoagulants and blood-sugar-lowering medications.

**Lactation**
No safety concerns of using American ginseng in lactation have been reported. Modern midwives may recommend American ginseng to lactating mothers in cases of depression/deficiency (Bove, Romm 2011, personal communications to AHP, unreferenced). Nursing women are advised to discuss the possible benefits and risks of botanical medicines and supplements with a qualified healthcare practitioner prior to use.

**Influence on Driving**
Specific data are lacking. Based on a review of the available literature and the experience of modern herbal practitioners, no negative effects are to be expected.

**Overdose**
No reports of overdose associated with American ginseng were identified. No adverse effects have been observed at doses of 3000 mg for up to 12 weeks (Stavro et al. 2006).

**Treatment of Overdose**
Specific data are lacking.

**Classification of the American Herbal Products Association**
The forthcoming 2nd edition of the Botanical Safety Handbook (Gardner et al. 2012) lists American ginseng root as safety class 1, “herbs that can be safely consumed when used appropriately,” and interaction class B, “herbs for which clinically relevant interactions are biologically plausible,” noting an interaction with conventional anticoagulants.

**Conclusion**
American ginseng root has a long history of safe use. Based on both the extensive traditional and available scientific literature, it appears to be lacking in adverse effects and overt toxicity. An interaction has been confirmed in which concomitant use of American ginseng root with warfarin (Coumadin®) reduces the drug’s anticoagulant effect, therefore appropriate care must be taken by patients and practitioners. American ginseng root has been shown to have blood-sugar-lowering effects with and without concurrent oral hypoglycemic drug use, suggesting that diabetics should consult their primary health care provider prior to American ginseng root use and monitor their blood sugar levels if using American ginseng root with blood-sugar-lowering medications. Previous reports of American ginseng root contributing to hypertension appear to be unsubstantiated; formal clinical studies have demonstrated that American ginseng root lacks a hypertensive effect.
**International Status**

**United States**
Regulated as both a food (EPA, FDA, and USDA) and as a dietary supplement (FDA and FTC). American ginseng root and/or its preparations can be labeled and marketed as dietary supplement products (USC 1994) and require FDA notification and substantiation to support structure/function claim statements. The harvest and export of wild collected American ginseng root is regulated by the United States Fish and Wildlife Service (USFWS) under the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) (USFWS 2009). Inspections for the issuance of phytosanitary certificates for export of American ginseng are regulated by the United States Department of Agriculture (USDA) Animal and Plant Health Inspection Service (APHIS) (USDA 2010). Tolerances for pesticide residues in cultivated American ginseng root are regulated by the Environmental Protection Agency (EPA 2010) and enforced by the Food and Drug Administration (FDA 2008).

**Australia**
May be used as an active ingredient in “Listed” medicines in the Australian Register of Therapeutic Goods (ARTG) for supply in Australia (TGA 2007). **Quality:** For active ingredients of listed medicines, the quality standards of the British Pharmacopoeia are the minimum standards that must be applied in their entirety (TGA 2006). The monographs of the European Pharmacopoeia and the United States Pharmacopeia have also been adopted as additional default standards under the Therapeutic Goods Act (PCA 2009). **Specific Indications:** Various American ginseng root mono-preparations have been granted marketing authorization with approved indications including, among others: (1) helps improve physical stamina and physical endurance (TGA 2010a); (2) traditionally the wild root was consumed by American Indians as a general tonic, as a natural restorative for the weak and wounded, and to help the mind; and (3) as an adaptogenic to increase yin energy for calming effect (TGA 2010b).

**Canada**
American ginseng root is regulated as an active ingredient of Natural Health Products (NHPs) requiring pre-marketing authorization and issuance of a product license for over-the-counter (OTC) human use. **Quality:** The finished product must comply with the minimum specifications outlined in the current NHPD Compendium of Monographs (NHPD 2007a). For active ingredient specifications, pharmacopoeial standards, currently accepted by the NHPD, are the British Pharmacopoeia, the European Pharmacopoeia, and the United States Pharmacopeia (NHPD 2007b). **Specific Indications:** Several American ginseng root mono-preparations have received marketing authorization with approved indications including, among others: (1) powdered root in capsules: Traditional Chinese medicine [that] helps benefit the qi, generate fluids, nourish the yin & remove heat (NHPD 2006); (2) tincture (1:4): Used in herbal medicine as supportive therapy for the promotion of healthy glucose levels; (3) Traditionally used in herbal medicine to help relieve nervousness (as mild sedative); (4) traditionally used in herbal medicine to help relieve nervous dyspepsia/to help digestion in cases of nervousness and/or stress; (5) traditionally used in herbal medicine to help maintain a healthy immune system (NHPD 2010a); (6) Powdered extract in capsules standardized to 80.0% poly-furanosyl-pyranosyl-saccharides: helps reduce the frequency, severity, and duration of cold and flu symptoms by boosting the immune system (NHPD 2010b).

**China**
American ginseng root is regulated as both a health food and as an active ingredient of Traditional Chinese Medicines. **Quality:** For use as health food (e.g., chewing chips, freeze-dried roots, non-medicinal teas), the National Standards of the People’s Republic of China for the grade and quality standards of products of processed American Ginseng are in force (NSPRC 1998). For therapeutic use, the Pharmacopoeia of the People’s Republic of China (PPRC) specifies the minimum quality standards as well as therapeutic indications for use, action and dosage. **Action:** To tonify qi and nourish yin, remove heat, and promote the production of body fluids. **Indications:** Used for deficiency of qi and yin, internal-heat, cough and asthma, bloody phlegm, fire in the deficiency syndrome, dysphoria and tiredness, diabetes, dry and thirsty mouth and throat. **Usage and dosage:** 3-6 g (PPRC 2005).

**European Community**
Although there are no known registered products, a medicinal American ginseng preparation would presumably be regulated as Traditional Herbal Medicinal Product (THMP) requiring pre-marketing authorization and product registration (EPCEU 2004).
**Xī yáng shèn**

**Radix Panacis Quinquefolii**

**Therapeutics**

**Historical Overview**

*Bencao Congxin* (Thoroughly Revised Materia Medica, 1751): “Tonifies the lungs, directs fire downward, generates fluid, eliminates irritability and fatigue, and is most appropriate for deficiency accompanied by fire.”

*Yaoxing Qieyong* (The Right Use of Medicine, date unknown): “Nourishes qi and clears the lung.”

*Yaoxing Kao* (Investigation of Medications, 1795): “Nourishes yīn and calms heat. When made with ginger, it benefits the vitality; paired with other herbs, it returns the body back to balance.”

*Bencao Zaixin* (Renewed Materia Medica, 1820): “Treats the lung that is vigorous with fire, manifesting in coughs with much phlegm; weak in qi and tend to gasp for air; loss of blood due to injury and fatigue. The herb firms the essence and calms the mind, creating the potentials to defend the body.”

*Bencao Qiuyuan* (Search for the Origins of Materia Medica, Qing Dynasty): “Clears the lung and the kidney, cools the heart and mind to lower fire. It eliminates summer heat and relieves intoxication.”

*Bencao Biandu* (Convenient Reader of Materia Medica, 1887): “Benefits qi and cultivates the spleen.”

*Yixue Zhongzhong Canxi Lu* (A Record of Medical Science in Consultation with the East and the West, 1909): “American ginseng is cool in nature but nourishing. For those who would like to use ginseng but could not bear the warm nourishment of the herb, they can all use American ginseng instead.”


*Pharmacopoeia of the People’s Republic of China* (PPRC 2005): “Tonifies qi, nourishes yīn, removes heat, promotes the production of body fluids.”

**Flavor and Nature**

Sweet, slightly bitter, cold.

**Channels of entry**

Kidney, heart, lung (Chen and Chen 2004).

**Functions**

Benefits qi (Bensky et al. 2004; Chen and Chen 2004; Chen and Li 1993; PPRC 2005); nourishes yīn, clears fire from vacuity, generates body fluids (Bensky et al. 2004; Chen and Chen 2004; Hsu 1986; PPRC 2005; Yen 1992; Wiseman and Ellis 1996); clears and discharges stomach fire and nourishes stomach yīn (Bensky et al. 2004; Chen and Li 1993; Hsu 1986; Wiseman and Ellis 1996); clears heat in the intestines and stops bleeding (Bensky et al. 2004; Chen and Chen 2004).

**Actions and Indications**

**Benefits Qi and Nourishes Yīn**

*Xī yáng shèn* is used in the treatment of qi vacuity (deficiency), especially of the lung, due to enduring illness or in the wake of a febrile disease. It is primarily used to treat generalized weakness, enduring cough, and tiredness (Bensky et al. 2004; PPRC 2005; Yen 1992). Although Asian ginseng (*rén shēn*) is most often used for vacuity of qi, *xī yáng shèn* is especially useful when enduring disease has damaged the qi and yīn of the lung with symptoms of prolonged wheezing and enduring cough with scanty blood streaked sputum (Bensky et al. 2004; Chen and Chen 2004). Modern applications fitting these actions and indications are pulmonary tuberculosis, asthma, and diabetes (Hsu 1986; PPRC 2005). Although Wiseman and Ellis (1996) categorize this medicinal in the "Qi Supplemetting" section of their translation, they make no mention of such properties in their brief monograph.
**Traditional Processing (Pao Zhi)**

In Chinese herbal medicine, specific processing techniques are employed to alter the nature and therapeutics of medicinals. There is a large number of prepared medicinals used in Chinese medicine. Probably owing to its relative infancy in the Chinese materia medica, vị dương shên seems to be used mostly unprocessed.

The only reference to vị dương shên being prepared using traditional methods of pao zhi comes from a short translated piece in Bensky et al. (2004) where the author states: “Prepared with ginger it augments the qi.”

Vị dương shên is also used as a simple and in formulae prepared as tinctures in the treatment of qi and yin vacuity (Nong 1996).

**Standard Combinations**

In Chinese medicine, there are medicinals that are commonly, almost by standard, paired to enhance the function of each other. The method of this system is called dui yao in Chinese, which loosely translates to “the art of combining medicinals.” These common combinations are the basis for many traditional formulas and for modifications of formulas. For a more complete discussion of this subject, see Dui Yao: The Art Of Combining Chinese Medicinals by Philippe Sionneau (1997). This system embodies the philosophy of polypharmacy, which is the most common way in which medicinals are used within the Chinese medical paradigm. As mentioned above, vị dương shên is a relatively new medicinal in the materia medica of Chinese medicine. It is likely due to this fact that there are very few standard combinations or formulae and no pairs found in the literature.

**Qing Shu Yi Tăng (Summer Heat-Clearing Qi-Boosting Decoction)**: Clears summer heat, boosts the qi, nourishes yin, and generates fluids. Treats fever, profuse sweating, irritability, thirst, scanty and dark urine, a desire to curl up, shortness of breath, apathy, and a vacuous, rapid pulse (Bensky and Barolet 1990).

Vị dương shên with huáng qì (Radix Astragali), shān yào (Rhizoma Dioscoreae oppositae), and tiān huā fěn (Radix Trichosanthis); Treats yin and qi vacuity and thirst. Vị dương shên benefits the qi and nourishes yin; at the same time, it cools heat from vacuity, which is often associated with this pattern. Huáng qì supplements the qi of the lung and spleen and secures the exterior, stopping sweating from yin vacuity. Shān yào supplements the qi and yin of the lung, stomach, and kidney. Together these three herbs strongly supplement the three burners and nourish and stabilize the yin, especially of the lung. Tiān huā fěn clears heat from the lungs and stomach and generates fluids. In this combination, it augments the effects of vị dương shên by treating heat from yin vacuity and generating fluids.

Vị dương shên with shèng di huāng (Radix Rehmanniae), shí hú (Herba Dendrobii), and wú wèi zǐ (Fructus Schizandrae chinensis): This combination treats yin vacuity with heat state that vị dương shên should be steamed with lóng yàn ròu for this purpose.

**Nourishes Yìn, Clears Fire from Vacuity, Generates Body Fluids**

Vị dương shên is used in the treatment of lung and kidney yin vacuity with vacuity heat as evidenced by symptoms of cough, thirst, dry throat, mouth and tongue, and other yin vacuity heat signs (Bensky et al. 2004; Chen and Chen 2004; Hsu 1986; PPRC 2005; Wiseman and Ellis 1996; Yen 1992). Common symptoms of yin vacuity with vacuity fire are heart vexation (often translated as irritability) and difficulty sleeping (Wiseman and Ye 1998). Vị dương shên treats these symptoms very effectively (Bensky et al. 2004; Chen and Chen 2004; Wiseman and Ellis 1996; Yen 1992).

**Clears and Discharges Stomach Fire and Nourishes Stomach Yīn**

Vị dương shên treats stomach fire with yin vacuity. When there is stomach fire, heat travels up the hand and foot yang ming channels to cause upper burner signs and symptoms (Wiseman and Ye 1998). Vị dương shên is indicated for tooth-ache due to stomach fire (Wiseman and Ellis 1996) and various other symptoms associated with this pattern, including thirst, dry throat, and dry mouth and tongue (Bensky et al. 2004; Chen and Chen 2004).

**Clears Heat in the Intestines and Stops Bleeding**

Vị dương shên in combination with lóng yàn ròu (Arillus Lóngán) is used for the passage of red blood in the stool due to yin vacuity (Chen and Chen 2004). Bensky et al. (2004)
signs. 阴虚火旺 and 石斛 both nourishes 阴, clears heat from 阴虚 vacuity, and generates fluids. These two herbs combine with 赤芍 to create a very powerful combination to nourish 阴, clear heat from vacuity, and generate fluids. 乌贼骨 enriches the kidney 阴, generates fluids, and stops sweating. Since night sweats are a common symptom of 阴虚 vacuity with heat signs, the inclusion of this medicinal helps to stop further loss of fluids and thus further damage to 阴虚 humors. Furthermore, 乌贼骨 generates fluids, strengthening the other three medicinals action in the combination.

**Safety Profile**

**Contraindications**

赤芍 is contraindicated for those with cold-damp in the spleen and stomach (Bensky et al. 2004; Chen and Chen 2004; Yen 1992) and for fire due to depressive disorders and stagnation (Bensky et al. 2004; Chen and Chen 2004).

**Precautions**

In Traditional Chinese Medicine, 赤芍 is considered incompatible with 乌贼 (Veratri Radix et Rhizoma) (Chen and Chen 2004; PPRC 2005).

Note: Portions of these sections were derived from *Chinese Medical Herbology and Pharmacology* (Chen and Chen 2004) and *Chinese Herbal Medicine: Materia Medica 3rd Ed.* (Bensky et al. 2004) with permission of Art of Medicine Press, Inc., City of Industry, CA and Eastland Press, Seattle, WA, respectively.
REFERENCES


(AHPA) American Herbal Pharmacopoeia®. • American Ginseng Root • 2012. 67


Benishin CG. 1990. Ginsenoside Rb1 increases central nervous system cholinergic...

Furche F. 1863. Resources of the southern fields of Ohio, Tennessee, Kentucky, and Tennessee, agricultural, and farming, also being a medical bot- 


Qian T, Cai Z. 2010. Biottmation of ginsenosides Rb1, Rg2 and Rg3 in rat gut 


Rufnesque CS. 1850. Medical flora, or manu-

chemical Biochem Behav 75:825-30.

Rashid N, Tsvu E, Ahmad A, Siripurapu R, Lin H, Shukla S, Palit G. 2008. Involvement of monoamines and pros-


Reeds DN, Patterson BW, Okunade A, Hollosy JO, Polonsky KS, Klein S. 2011. Ginsenosides and ginseng: Do not improve B-cell function or insulin sensitiv-
ity in overweight and obese subjects with impaired glucose tolerance or diabetes. Diabetes Care 34:1071-6.


Ren G, Chen F. 1999b. Simultaneous quant-
ificiation of ginsenosides in American gins-
eng (Panax quinquefolium) root powder by visible/near-infrared reflectance spec-

Reynolds LB. 1998a. Effects of harvest date 

Shin YW, Bae EA, Kim SS, Lee YC, Kim DH. 2005. Effect of Rb1 and compound K in chronic ox-


Shook EE. 1948 [ca.]. Advanced treatise on herbology—Course lessons. Los Angeles (CA): Edward E Shook. [no pagination].

Siegel RK. 1977. Kola, ginseng, and mind-


seng saponin potentates attenuates metat-


Sumner J. 2004. American household horta-


Takano Y. 2002. Antioxidant and in vitro screening procedure 
of modified in vitro screening procedure 


Tohda G, Hashimoto I, Kurokawa T, Komata K. 2006. Metabolite 1 of pro-
topanaxadiol-type saponins, an axonal regenerative factor, stimulates tenui-
risin-2 linked by PI3-kinase cascase. Neuropsychopharmacology 31:1158-64.

Tohda G, Matsutomo N, Zhou Z, Meselyi MR, Konnoa K. 2004. APr(25-35)-induced memory impairment, axonal atrophy, and synaptic degeneration in mice by MA, a metabolite of protopanaxadiol-type sap-


American Herbal Pharmacopoeia® — American Ginseng Root • 2012


American ginseng

Source: Millspaugh, American Medicinal Plants; An Illustrative Guide (1887).
# Table of Contents

## Nomenclature  1
- Botanical Nomenclature
- Botanical Family
- Pharmaceutical Nomenclature
- Pharmacopoeial Definition
- Common Names

## History  1

## Identification  4
- Botanical Identification
- Macroscopic Identification
- Microscopic Identification

## Commercial Sources and Handling  13
- Sources
- Collection
- Species Conservation
- Cultivation
- Post-harvest Handling
- Drying
- Storage
- Adulterants
- Qualitative Differentiation
- Preparations

## Constituents  25

## Analytical  32
- High Performance Thin Layer Chromatography (HPTLC)
- High Performance Liquid Chromatography (HPLC)
- Limit Tests

## Therapeutics  40
- Pharmacokinetics
- Clinical Efficacy and Pharmacodynamics
  - Effects on Blood Sugar
  - Immunological Effects
  - Effects on Inflammation
  - Cardiovascular Effects
  - Antioxidant Effects
  - Radioprotective Effects
  - Protection Against the Toxicity of Chemotherapeutic Drugs
  - Anticancer Effects
  - Estrogenic Effects
  - Aphrodisiac Effects
  - Hepatoprotective Effects
  - Adaptogenic Effects: Effects on Performance and Stress Tolerance
  - Effects on Brain Function and Memory
  - Behavioral Effects
  - Other Effects
- Summary
- Medical Indications Supported by Clinical Trials
- Medical Indications Supported by Traditional or Modern Experience
- Actions
- Indications
- Substantiated Structure and Function Statement
- Dosages

## Safety Profile  60
- Adverse Reactions
- Interactions
- Reproductive and Developmental Effects
- Carcinogenicity
- Toxicology
- Contraindications
- Precautions
- Lactation
- Influence on Driving
- Overdose
- Treatment of Overdose
- Classification of the American Herbal Products Association
- Conclusion

## International Status  63

## Traditional Chinese Medicine Supplement  64

## References  67