Chapter 5
Panax Quinquefolius (American Ginseng) and *Panax Notoginseng* (Notoginseng) in Cancer Chemoprevention

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Abstract The clinical management of cancer invariably involves diverse conventional modalities, including surgery, radiation, and chemotherapy. However, the complexity of human cancer requires some alternative management to improve the therapeutic efficacy of conventional treatment and/or the quality of life of cancer patients. Medicinal botanicals have recently gained more attention for cancer management. Numerous effective anticancer drugs have been developed from botanicals, and identifying new herbal sources to develop ideal chemoprevention remains an essential step in advancing the treatment of cancer. In this chapter, potential roles of ginseng herbs, especially American ginseng and notoginseng, in cancer chemoprevention are presented. The major pharmacologically active constituents of ginsengs are ginsenosides, which can be mainly classified into protopanaxadiol and protopanaxatriol groups. The recognized active anticancer compounds from American ginseng and notoginseng are ginsenosides Rg3, Rh2, and protopanaxadiol. The structure-activity relationship between their chemical structures and pharmacological activities is discussed. Sugar molecules within a ginsenoside have a high impact on cancer cells. Anticancer activities increase with the decrease of sugar number. In addition, various steaming temperatures and time treatments of the ginseng herbs can change their ginsenoside profiles and enhance their anticancer activities. This heat treatment process may increase the role and efficacy of American ginseng and notoginseng in cancer chemoprevention.

5.1 Introduction

Cancer is a leading cause of death worldwide. In the United States, a total of 1,529,560 new cancer cases and 569,490 deaths from cancer are projected to occur in 2010 (Jemal et al. 2010). Although early diagnosis with rigorous screening may

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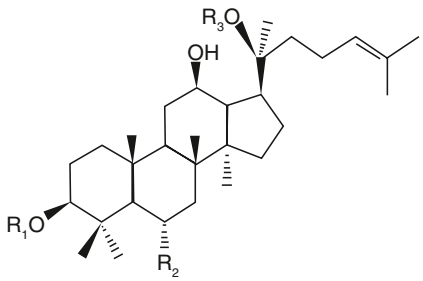
have reduced its incidence compared to a few years ago, the prognosis associated with metastatic disease remains bleak. Current cancer treatment generally employs surgical resection combined with chemotherapy, using cytotoxic drugs and radiation therapy. Because this therapy is only moderately successful for late stage cancers, novel approaches to the treatment of cancer are required. The data from several controlled clinical trials supports a multimodal and multidisciplinary approach, including combinations of treatments and schedules in which they are administered, for treating both early and advance stage cancers (Goldberg et al. 2004; Hurwitz et al. 2004; Ma and Adjei 2009). Studies also showed that patients with cancer often resort to complementary and alternative medicine for the treatment of cancer-related symptoms and/or to reduce the adverse effects of chemotherapy (Shumay et al. 2001; Ott 2002; Lee et al. 2006; Wu et al. 2007).

There is compelling evidence that patients in this country resort to supplements or substitute them for conventional pharmacotherapy. Several national surveys indicate that at least one third of American adults take some form of dietary supplement, and botanicals comprise approximately 25% of the supplement market (Barnes et al. 2004). Botanicals have also been the major source of therapy in many traditional medical systems and have been used clinically for the treatment of a variety of diseases (Mashour et al. 1998; Wang et al. 2007a, c; Wicks et al. 2007; Xie et al. 2006). Botanical ingredients in natural products contain bioactive constituents with medical benefits (Akerele 1993; Leung 2007; Zhou et al. 2007; Li and Zhang 2008). Furthermore, botanicals have contributed significantly to cancer therapy, and it is likely that extracts and active constituents from herbal medicine will continue to play an important role in cancer therapeutics (Liu and Jiang 2006; Ng et al. 2006; Shieh et al. 2006; Ozaslan et al. 2007). In this chapter, we will discuss the potential roles of ginseng herbs in the chemoprevention of cancer.

5.2 Medicinal Use of Botanicals in Ginseng Family

Panax L. is a small genus in the family Araliaceae. Nearly all species in the genus *Panax*, such as *Panax ginseng* C.A. Meyer (Asian ginseng), *Panax quinquefolius* L (American ginseng), and *Panax notoginseng* (Burk) F.H. Chen (notoginseng), are important herbs used for different medical conditions (Chen et al. 2001; Wang et al. 2007c). Asian ginseng and notoginseng are considered Chinese herbal medicines, and American ginseng is one of the most commonly used botanicals in the US (Wang et al. 1999, 2006c).

It is generally believed that the active compounds in Asian ginseng, American ginseng, and notoginseng are triterpene glycosides or dammarane saponins, commonly referred to as ginseng saponins (ginsenosides and notoginsenosides). These ginseng saponins are the major active ingredients in the herbs, and their levels can be used to develop quality controls for these herbs (Fuzzati 2004; Chao et al. 2006; Wang et al. 2006a). There are over 100 different known ginseng saponins,



Compound	R_1	R_2	R_3
Notoginsenoside R1	-H	-O-glc$^{2-1}$xyl	-glc
Ginsenoside Rb1	-glc$^{2-1}$glc	-H	-glc$^{6-1}$glc
Ginsenoside Rb2	-glc$^{2-1}$glc	-H	-glc$^{6-1}$ara(pyr)
Ginsenoside Rb3	-glc$^{2-1}$glc	-H	-glc$^{6-1}$xyl
Ginsenoside Rc	-glc$^{2-1}$glc	-H	-glc$^{6-1}$ara(fur)
Ginsenoside Rd	-glc$^{2-1}$glc	-H	-glc
Ginsenoside Re	-H	-O-glc$^{2-1}$rha	-glc
Ginsenoside Rg1	-H	-O-glc	-glc
Ginsenoside Rg2	-H	-O-glc$^{2-1}$rha	-H
Ginsenoside Rg3	-glc$^{2-1}$glc	-H	-H

Fig. 5.1 Chemical structures of saponins from American ginseng and notoginseng

and they are characterized by a four *trans*-ring rigid steroid aglycone skeleton and attached sugar moieties. Based on the aglycone skeleton, all representative ginseng saponins can be divided into protopanaxadiol group and protopanaxatriol group, except for the ginsenoside Ro, which is derived from the oleanolic acid group (Fig. 5.1).

Ginseng has many reported health benefits (Attele et al. 1999; Liu et al. 2006; Yamakage et al. 2006; Yoo et al. 2006). Regarding its anticancer effects, a case-control study on over one thousand subjects in Korea showed that Asian or Korean ginseng intakers had a decreased risk for many different cancers compared with nontakers (Yun and Choi 1995, 1998). It also suggested that ginseng has a non-organ specific preventive effect against cancer (Yun 2003).

Regarding the responsible anticancer constituents from Asian ginseng, published studies showed that some saponins could reduce the proliferation of cancer cells and sensitize cancer cells to chemotherapeutic agents *in vitro* (Lee and Huemer 1971; Kim et al. 2007; Koo et al. 2007). Several investigators found antitumor properties and other pharmacological activities of ginseng, and ginsenosides Rg3 and Rh2 are recognized as active anticancer saponins (Helms 2004). Jia et al. (2004) noted that ginsenoside Rh2 inhibited proliferation and induced apoptosis in cancer cell lines, and sensitized drug-resistant breast cancer cells to paclitaxel. Kim et al. (2004) studied 11 ginsenosides and determined that Rg3 and Rh2 inhibited the proliferation

of prostate cancer cells. Iishi et al. (1997) used a rat model to determine the effects of ginsenoside Rg3 on inhibiting colon cancer cell proliferation.

5.3 American Ginseng

Ginseng root has been used for centuries in Oriental medicine as a panacea that promotes longevity (Yun 2003; Fuzzati 2004). However, relatively few studies focus on American ginseng, which is a popular herbal supplement in the US with consumers and patients (Attele et al. 1999; Helms 2004).

American ginseng is an obligate shade perennial plant native to eastern North America. The most commonly used part of the plant is the root, which is harvested after several years' cultivation. The largest ginseng growing area in the US is in Wisconsin. The bioactive constituents of American ginseng are ginsenosides, which are present in the root, leaf, stem, and berry of the plant. More than 60 ginsenosides, such as Rb1, Rb2, Rb3, Rc, Rd, Re, Rg1, Rg2, and Rg3 have been identified (Wang et al. 1999, 2006b; Assinewe et al. 2003; Qi et al. 2010) in American ginseng (Fig. 5.1). Previous studies of American ginseng focused on its activities on the cardiovascular system, such as its anti-ischemic, anti-arrhythmic, and antihypertensive effects (Yuan and Dey 2001; Kim and Park 2003). These pharmacological effects are, to a significant extent, considered to be linked to the antioxidant properties of the herb (Kitts et al. 2000; Wang et al. 2007c).

American ginseng extracts were found to inhibit the growth of breast cancer cells (Corbit et al. 2006). We investigated the effects of several herbal extracts on reducing chemotherapeutic side effects and found that American ginseng and one of its major constituents, ginsenoside Re, can attenuate cisplatin-induced nausea and vomiting in a rat model, while not affecting its anticancer properties in human cancer cells (Aung et al. 2007; Mehendale et al. 2005). In addition, the extract from American ginseng enhanced the anti-proliferation effect of cisplatin on human breast cancer cells, suggesting that it possesses its own anticancer activity (Aung et al. 2007). Our group also showed that after steaming American ginseng, its antiproliferative effects improved significantly, possibly due to the altered ginsenoside profile (Wang et al. 2006c, 2007a, 2008).

To explore the mechanisms involved in cancer cell inhibition, we observed the effects of American ginseng on the gene expression and apoptotic pathways. From the analysis of microarray hybridization, we found that the anticancer mechanism of American ginseng extract and its representative compound, ginsenoside Rg3, have many of the same characteristics and the alterations in gene expression level imply important information for exploring this mechanism. The two recognized genes regulated by the extract and Rg3 (AKAPA8L and PITPNA) suggest that American ginseng takes effect through the regulation of cell mitosis and an intracellular singling pathway (Luo et al. 2008). In a separate study, the observed expression profiling of the selected pathways revealed various apoptotic related genes that inhibited growth in human colorectal cancer cells treated

with American ginseng. The mitochondrial apoptotic pathway was a key target in cancer chemoprevention by steamed American ginseng extract (Wang et al. 2009a; Li et al. 2010). These expression analyses may lead to the identification of markers that predict the responsiveness of human cancer cells to American ginseng treatment.

Chronic inflammation is associated with increased cancer risk (Aggarwal et al. 2009). Ginseng has been observed to play a role in reducing inflammation, and suppressing colitis through p53-mediated apoptosis of inflammatory cells (Hofseth and Wargovich 2007; Jin et al. 2010). Ginsenoside compound K [20-O-beta-D-glucopyranosyl-20(S)-protopanaxadiol] exerts immunomodulatory and anti-inflammatory effects by deactivating the inflammatory response through the inhibition of COX-2 (cyclooxygenase-2) expression (Kimura et al. 2006; Hofseth and Wargovich 2007). Ginsenoside Rg3 attenuates COX-2 expression, NF-κB (nuclear factor-κB) activation, and activator protein-1 transcription factors (Lee et al. 2005). PPD inhibits inducible nitric oxide synthase and COX-2 expression through the inactivation of NF-κB (Kim et al. 2010).

For the clinical study, to investigate whether American ginseng might help cancer-related fatigue, in a randomized, double-blind study, 290 cancer patients received American ginseng in doses of 750, 1,000, or 2,000 mg/day or a placebo given twice daily over 8 weeks. Overall, this study suggested that American ginseng, at a dose of 750 mg/day, did not provide any benefit over that seen with a placebo. However, the two highest doses of ginseng (1,000 and 2,000 mg/day) did appear to decrease fatigue more than a placebo, as measured by various scales of fatigue, vitality, and well being. Data suggested that the higher doses studied may be helpful in cancer-related fatigue (Barton et al. 2010).

5.4 Notoginseng

Notoginseng is a Chinese herbal medicine that has a long history of use in China and other Asian countries. This herb is distributed in southwest China, Burma, and Nepal. Notoginseng is cultivated commercially in southwest China, especially in the Yunnan Province. The root is commonly used in remedies and it is dug up after the fruit has ripened.

The earliest scientific description of notoginseng was in Compendium of Materia Medica, a dictionary of Chinese herbs, written by Li Shi Zhen (1518–1593 AD). In Compendium of Materia Medica, notoginseng was described as “more valuable than gold,” indicating the significance of this herb in traditional Chinese medicines. Notoginseng is regarded as the emperor herb in the treatment of different types of wounds because it is favored for the treatment of both internal and external hemorrhage (Ng et al. 2006; Wang et al. 2006c).

Modern pharmacological research on notoginseng has found that notoginseng exerts various effects on the cardiovascular system, central nervous system, endocrine system, and the inflammation response (Sun et al. 2005; Wang et al. 2006a, c).

Consistent with the hemostatic effect of notoginseng reported in ancient China, recent studies showed that the alcohol extract of notoginseng resulted in a reduction of the extent of bleeding and provides better hemostatic effects than no treatment, placebo treatment, or treatment with hydrophilic or lipophilic extracts (White et al. 2001). Notoginseng can also decrease blood pressure, improve blood supply, protect against shock, and protect the cardiovascular system and brain vasculature. Its protective mechanism could work by conferring protection against damage by oxygen free radicals, and also by binding to the estrogen receptor, since ginsenosides share many of the protective actions of estrogen in various body systems. Pharmacokinetic and pharmacodynamic studies have shown that the intranasal preparation of notoginseng saponins is a promising development and may be beneficial for the treatment of Alzheimer's disease. Notoginseng extracts were also found to possess the capacity to adjust energy metabolism and treat diabetes (Ng 2006).

Notoginseng has a very distinct saponin profile compared to that of American ginseng (Chen et al. 2001; Sun et al. 2005). The main bioactive compounds in notoginseng are dammarane saponins. Oleanane-type saponins, present in Asian ginseng and American ginseng, are not found in notoginseng. To date, 56 saponins have been isolated from the notoginseng plant. 35 of these notoginseng saponins belong to the protopanaxadiol group, while 21 of them belong to the protopanaxatriol group (Sun et al. 2005; Wang et al. 2006a). Ginsenosides Rb1, Rg1, Rd, and notoginsenoside R1 are the main saponins in the notoginseng root (Fig. 5.1).

Some studies have shown that notoginseng has antitumor effects (Chen et al. 2001; Wang et al. 2006c). We observed that the notoginseng root extract and its constituents have significant antiproliferative effects on human colorectal cancer cells (Wang et al. 2007a). Other plant parts of notoginseng also displayed potential antiproliferative effects on colorectal cancer cells (Wang et al. 2009b). The flower extract's most potent cancer cell growth inhibitory effects were shown within special chemical compositions (Wang et al. 2009b).

Ginsenosides Rb1 and Rd are major constituents in American ginseng and notoginseng. After oral administration, protopanaxadiol-type ginsenosides such as Rb1 and Rd are mostly metabolized by intestinal bacteria to a protopanaxadiol monoglucoside, compound K. In humans, compound K is detected in plasma 7 hours after the intake of ginsenosides and in urine 12 hours after the intake, indicating that compound K is the final metabolite of this type of ginsenoside (Ren et al. 2008). Ginsenoside Rb1 was not detectable in serum for 24 hours, indicating a major intestinal bacterial metabolism (Wakabayashi et al. 1997). Compound K has been recognized as an potential anticancer compound (Jeong et al. 2010).

Recently, we performed a steaming treatment on notoginseng root. We observed that there was a significant difference in the ginsenoside content after steaming the notoginseng root. No differences were observed in total ginsenoside content and antiproliferative effect between steaming the root for 4 hours or 6 hours. After steaming, ginsenoside Rg3 content increased significantly, an increase that was partially responsible for the increase in anticancer activity. On the other hand, ginsenoside Rh2 content increased only slightly after steaming. Thus, some other active anti-

cancer components, in addition to Rg3 and Rh2, may form in the notoginseng root extract after the steaming process (Sun et al. 2010).

Our group also found that the notoginseng extract can increase the effects of cancer chemotherapy. Using the HCT-116 human colorectal cancer cell line, the antiproliferative effect of notoginseng extract combined with 5-FU was investigated. Compared to the control, when cells were treated with 5-FU or notoginseng separately, cell proliferation was reduced by 31% and 25%, respectively. The combination of 5-FU and notoginseng reduced cell proliferation by 59%, suggesting that combining notoginseng with 5-FU can reduce the dose of 5-FU, while significantly increasing the overall anti-proliferation effect on the cancer cells. Since it is well known that 5-FU has cytotoxic effects on primary cells, this synergistic effect between notoginseng and 5-FU makes it possible to reduce the dose of 5-FU in combination with notoginseng and thereby further decrease dose-related toxicity (Wang et al. 2007b).

In another study, notoginseng's potential to enhance the effects of irinotecan without affecting irinotecan's activity was observed. It appears that irinotecan-induced toxicity can be reduced by using notoginseng as a chemo-adjuvant (Wang et al. 2007a). When notoginseng potentiates the tumoricidal effects of chemotherapeutic agents, smaller chemotherapy doses can be used. Data obtained from our studies will have the potential to advance treatment regimens and improve the quality of life for patients suffering from cancer.

5.5 Saponin Structure-activity Observation and Heat-treatment of Ginsengs

Ginseng saponins belong to a family of triterpene glycosides or triterpene saponins. Ginseng saponins (except ginsenoside Ro) possess the four *trans*-ring rigid steroid skeleton, with a modified side chain at C-20. Sugar residues are attached to the -OH of the aglycon. As mentioned above, ginsenosides can be mainly classified into protopanaxadiol and protopanaxatriol groups. For the protopanaxadiol group, sugar residues are attached to the β-OH at C-3 and another -OH at C-20 of the aglycon, e.g. ginsenosides Rb1, Rb2, Rc, Rd, Rg3, and Rh2. For the protopanaxatriol group, sugar residues are attached to the α-OH at C-6 and another -OH at C-20 of the aglycon, e.g. ginsenosides Re, Rg1, Rh1, and notoginsenoside R1 (Fig. 5.1).

The structure-activity relationship elucidates the relations between chemical structure and the pharmacological activity for a series of compounds (Ooi et al. 2006; Benjamin et al. 2008). The anticancer activities of ginseng saponins are related to their aglycons and sugar residues (Helms 2004; Wang et al. 2007d). Sugar molecules within a ginsenoside have a high impact on cancer cells. Anticancer activities increase with a decrease in sugar number. The main anticancer saponins so far identified are from the protopanaxadiol group. The three most potent compounds in this group are Rg3, Rh2, and their aglycon, protopanaxadiol, and the latter two may have stronger effects (Popovich and Kitts 2002; Wang et al. 2007d).

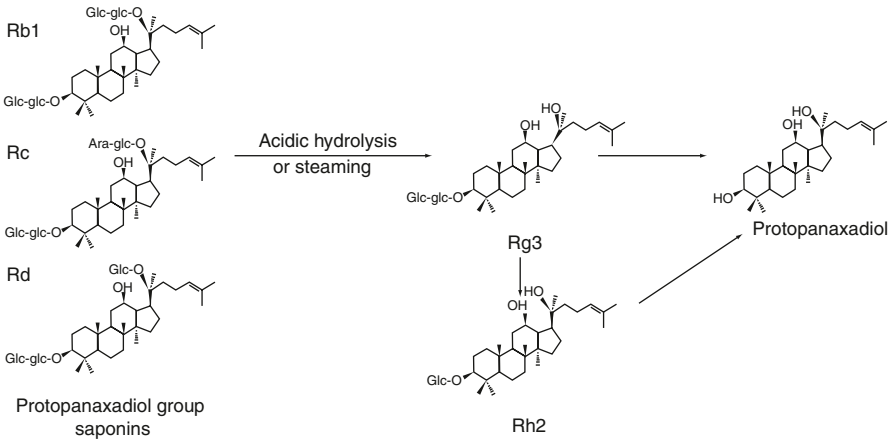


Fig. 5.2 Chemical conversions starting from protopanaxadiol group saponins using acidic hydrolysis or steaming process

Other compounds in the protopanaxadiol group showed less or no anticancer activities, probably due to the fact that their sugar residues are attached to the -OH at C-20 (Wang et al. 2006c).

Ginsenoside Rg3 was isolated from Asian ginseng, American ginseng, and notoginseng (Chen et al. 2002; Xu et al. 1987). However, Rg3 is only a trace saponin in different species of the genus *Panax* (Fuzzati 2004). Rg3 can also be obtained from a mild acidic hydrolysis of protopanaxadiol group saponins, such as Rb1, Rb2, and Rc (Fig. 5.2). Since Rg3 was found to effectively inhibit the growth of cancer cells (Mochizuki et al. 1995), studies of Rg3 sources were emphasized. In 2003, Rg3 was approved as a new anticancer drug in China (Lu et al. 2008). Although this saponin can be obtained by biological transformation and chemical synthesis, the process is complicated, the yield is limited and thus, the cost of the product is high. As shown in Fig. 5.2, Rh2 and protopanaxadiol are also derived from the protopanaxadiol group saponins. In Asia, Asian ginseng root can be prepared as (1) air-dried to white ginseng, or (2) steamed at approximately 100°C to red ginseng. Red ginseng has stronger anticancer activities than white ginseng (Yun et al. 2001) due to its relatively high Rg3 content. It seems likely that the steaming process or heat-treatment of ginseng is a good approach to transform inactive ginsenosides to active anticancer compounds, such as Rg3, Rh2, and protopanaxadiol.

Our laboratory treated the American ginseng berry at various temperatures and heating times to observe the changes in ginsenoside content and anticancer activities on human colorectal cancer cells. We found that steaming the American ginseng berry extract very significantly augmented the content of Rg3. When human colorectal cancer cells were treated with steamed berry extract (120°C, 2 hours), the anti-proliferation effects were 98% for HCT-116 and 99% for SW-480 cells. At the same treatment concentration, the effects of unsteamed extract were 34% for HCT-116 and 5% for SW-480 cells. This suggests that the steamed American gin-

seng berry augmented Rg3 content and anticancer activity significantly (Wang et al. 2006b). We also steamed American ginseng root and found a comparable change to its chemical constituent and antiproliferative activities (Wang et al. 2007a). Recent studies suggested that increasing the steaming time resulted in additional chemical changes and an increase in cancer cell growth inhibitory effects (Wang et al. 2009a).

Constituent changes of notoginseng after steaming treatment have also been reported (Lau et al. 2004). After the treatment, the content of Rb1, Rg1, Rd, and notoginsenoside R1 decreased, while Rg3 had increase, and this trend is similar to what we observed after the steaming treatment of American ginseng. Recently, we performed steaming treatment on the notoginseng root. After the treatment, the content of Rg3 was found to have increased remarkably, and the antiproliferative effects on cancer cells significantly increased (Sun et al. 2010).

After assaying the chemical structure-functional relationship of ginsenosides, we propose that the number of sugar molecules, structure of hydroxyl groups, and stereoselectivity in ginsenosides affect their anticancer activity. An understanding of this relationship is a prerequisite for purposeful modifications to produce novel agents for use in medical oncology (Qi et al. 2010).

5.6 Perspectives and Challenges

Previous studies suggested that American ginseng and notoginseng possess anticancer activities. We recently observed that after using a special heat-preparation or steaming process, the content of Rg3, a previously identified anticancer ginsenoside, increased significantly and became the main constituent in the steamed American ginseng. As expected, using the steamed extract increased anticancer activity significantly. Notoginseng has a very distinct saponin profile compared to that of American ginseng. Steaming notoginseng also significantly increased its anticancer effect.

The next logical step would be to characterize the effects of the two ginseng herbs (unsteamed and steamed) and their active constituents on cancer, and their mechanisms of action. Data obtained from future studies will help develop useful products for complementary and alternative therapies in oncology and expand our understanding about the biological mechanism behind the antitumor activity of ginseng and its active compounds.

Although ginseng plants have been extensively studied, much more knowledge is required to answer the questions regarding the observed effects of American ginseng and notoginseng in cancer chemoprevention. Thus, looking to the future, the widespread research of American ginseng and notoginseng seems certain to ensure continued interest in the development of this herb. With the trend of interdisciplinary research and the development of modern combinatorial techniques, it appears promising that new insights will be gained into novel cancer chemopreventive agents from ginseng in drug discovery.

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References

Aggarwal, B. B., Van Kuiken, M. E., Iyer, L. H., et al. (2009). Molecular targets of nutraceuticals derived from dietary spices: Potential role in suppression of inflammation and tumorigenesis. *Experimental Biology and Medicine (Maywood), 234,* 825–849.

Akerele, O. (1993). Nature's medicinal bounty: Don't throw it away. *World Health Forum, 14,* 390–395.

Assinewe, V. A., Baum, B. R., Gagnon, D., et al. (2003). Phytochemistry of wild populations of *Panax quinquefolius* L. (North American ginseng). *Journal of Agricultural and Food Chemistry, 51,* 4549–4553.

Attele, A. S., Wu, J. A., & Yuan, C. S. (1999). Ginseng pharmacology: Multiple constituents and multiple actions. *Biochemical Pharmacology, 58,* 1685–1693.

Aung, H. H., Mehendale, S. R., Wang, C. Z., et al. (2007). Cisplatin's tumoricidal effect on human breast carcinoma MCF-7 cells was not attenuated by American ginseng. *Cancer Chemotherapy and Pharmacology, 59,* 369–374.

Barnes, P. M., Powell-Griner, E., McFann, K., et al. (2004). Complementary and alternative medicine use among adults: United States, 2002. *Advance Data, 22,* 1–19.

Barton, D. L., Soori, G. S., Bauer, B. A., et al. (2010). Pilot study of *Panax quinquefolius* (American ginseng) to improve cancer-related fatigue: A randomized, double-blind, dose-finding evaluation: NCCTG trial N03CA. *Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer, 18,* 179–187.

Benjamin, M., Kaiser, E., & Milz, S. (2008). Structure-function relationships in tendons: A review. *Journal of Anatomy, 212,* 211–228.

Chao, Z., Shoyama, Y., & Tanaka, H. (2006). Pharmacokinetic study of ginsenosides Rb1 and Rg1 in rat by ELISA using anti-ginsenosides Rb1 and Rg1 monoclonal antibodies. *The American Journal of Chinese Medicine, 34,* 1069–1081.

Chen, F. D., Wu, M. C., Wang, H. E., et al. (2001). Sensitization of a tumor, but not normal tissue, to the cytotoxic effect of ionizing radiation using *Panax notoginseng* extract. *The American Journal of Chinese Medicine, 29,* 517–524.

Chen, Y., Zhan, E., Chen, H., et al. (2002). Saponins with low sugar chain from the leaves of *Panax notoginseng* (Burk) F. H. Chen. *Zhong Yao Cai Zhongyaocai (Journal of Chinese Medicinal Materials), 25,* 176–178.

Corbit, R., Ebbs, S., King, M. L., et al. (2006). The influence of lead and arsenite on the inhibition of human breast cancer MCF-7 cell proliferation by American ginseng root (*Panax quinquefolius* L.). *Life Sciences, 78,* 1336–1340.

Fuzzati, N. (2004). Analysis methods of ginsenosides. *Journal of Chromatography. B: Analytical Technologies in the Biomedical and Life Sciences, 812,* 119–133.

Goldberg, R. M., Sargent, D. J., Morton, R. F., et al. (2004). A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 22,* 23–30.

Helms, S. (2004). Cancer prevention and therapeutics: *Panax ginseng. Alternative Medicine Review: A Journal of Clinical Therapeutic, 9,* 259–274.

Hofseth, L. J., & Wargovich, M. J. (2007). Inflammation, cancer, and targets of ginseng. *The Journal of Nutrition, 137,* 183S–185S.

Hurwitz, H., Fehrenbacher, L., Novotny, W., et al. (2004). Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *The New England Journal of Medicine, 350,* 2335–2342.

Iishi, H., Tatsuta, M., Baba, M., et al. (1997). Inhibition by ginsenoside Rg3 of bombesin-enhanced peritoneal metastasis of intestinal adenocarcinomas induced by azoxymethane in Wistar rats. *Clinical & Experimental Metastasis, 15,* 603–611.

Jemal, A., Siegel, R., Xu, J., et al. (2010) Cancer statistics, 2010. *CA: A Cancer Journal For Clinicians, 60,* 277–300.

Jeong, A., Lee, H. J., Jeong, S. J., et al. (2010). Compound K inhibits basic fibroblast growth factor-induced angiogenesis via regulation of p38 mitogen activated protein kinase and AKT in human umbilical vein endothelial cells. *Biological & Pharmaceutical Bulletin, 33,* 945–950.

Jia, W. W., Bu, X., Philips, D., et al. (2004). Rh2, a compound extracted from ginseng, hypersensitizes multidrug-resistant tumor cells to chemotherapy. *Canadian Journal of Physiology and Pharmacology, 82,* 431–437.

Jin, Y., Hofseth, A. B., Cui, X., et al. (2010). American ginseng suppresses colitis through p53-mediated apoptosis of inflammatory cells. *Cancer Prevention Research (Philadelphia, Pa.), 3,* 339–347.

Kim, S. H., & Park, K. S. (2003). Effects of *Panax ginseng* extract on lipid metabolism in humans. *Pharmacological Research: The Official Journal of the Italian Pharmacological Society, 48,* 511–513.

Kim, H. S., Lee, E. H., Ko, S. R., et al. (2004). Effects of ginsenosides Rg3 and Rh2 on the proliferation of prostate cancer cells. *Archives of Pharmacal Research, 27,* 429–435.

Kim, S. J., Jeong, H. J., Yi, B. J., et al. (2007). Transgenic *Panax ginseng* inhibits the production of TNF-alpha, IL-6, and IL-8 as well as COX-2 expression in human mast cells. *The American Journal of Chinese medicine, 35,* 329–339.

Kim, S. M., Lee, S. Y., Cho, J. S., et al. (2010). Combination of ginsenoside Rg3 with docetaxel enhances the susceptibility of prostate cancer cells via inhibition of NF-kappaB. *European Journal of Pharmacology, 631,* 1–9.

Kimura, Y., Sumiyoshi, M., Kawahira, K., et al. (2006). Effects of ginseng saponins isolated from red ginseng roots on burn wound healing in mice. *British Journal of Pharmacology, 148,* 860–870.

Kitts, D. D., Wijewickreme, A. N., & Hu, C. (2000). Antioxidant properties of a North American ginseng extract. *Molecular and Cellular Biochemistry, 203,* 1–10.

Koo, H. N., Jeong, H. J., Choi, I. Y., et al. (2007). Mountain grown ginseng induces apoptosis in HL-60 cells and its mechanism have little relation with TNF-alpha production. *The American Journal of Chinese Medicine, 35,* 169–182.

Lau, A. J., Seo, B. H., Woo, S. O., et al. (2004). High-performance liquid chromatographic method with quantitative comparisons of whole chromatograms of raw and steamed *Panax notoginseng*. *Journal of Chromatography, 1057,* 141–149.

Lee, K. D., & Huemer, R. P. (1971). Antitumoral activity of *Panax ginseng* extracts. *Japanese Journal of Pharmacology, 21,* 299–302.

Lee, J. Y., Shin, J. W., Chun, K. S., et al. (2005). Antitumor promotional effects of a novel intestinal bacterial metabolite (IH-901) derived from the protopanaxadiol-type ginsenosides in mouse skin. *Carcinogenesis, 26,* 359–367.

Lee, T. I., Chen, H. H., & Yeh, M. L. (2006). Effects of chan-chuang qigong on improving symptom and psychological distress in chemotherapy patients. *The American Journal of Chinese Medicine, 34,* 37–46.

Leung, P. C. (2007). The efficacy of Chinese medicine for SARS: A review of Chinese publications after the crisis. *The American Journal of Chinese Medicine, 35,* 575–581.

Li, X. J., & Zhang, H. Y. (2008). Western-medicine-validated anti-tumor agents and traditional Chinese medicine. *Trends in Molecular Medicine, 14,* 1–2.

Li, B., Wang, C. Z., He, T. C., et al. (2010). Antioxidants potentiate American ginseng induced killing of colorectal cancer cells. *Cancer Letters, 289,* 62–70.

Liu, X. S., & Jiang, J. (2006). Molecular mechanism of matrine-induced apoptosis in leukemia K562 cells. *The American Journal of Chinese Medicine, 34,* 1095–1103.

Liu, R., Xing, D., Lu, H., et al. (2006). Pharmacokinetics of puerarin and ginsenoside Rg1 of CBN injection and the relation with platelet aggregation in rats. *The American Journal of Chinese Medicine, 34,* 1037–1045.

Lu, P., Su, W., Miao, Z. H., et al. (2008). Effect and mechanism of ginsenoside Rg3 on postoperative life span of patients with non-small cell lung cancer. *Chinese Journal of Integrative Medicine, 14*(1), 33–36.

Luo, X., Wang, C. Z., Chen, J., et al. (2008). Characterization of gene expression regulated by American ginseng and ginsenoside Rg3 in human colorectal cancer cells. *International Journal of Oncology, 32,* 975–983.

Ma, W. W., & Adjei, A. A. (2009). Novel agents on the horizon for cancer therapy. *CA: A Cancer Journal for Clinicians, 59,* 111–137.

Mashour, N. H., Lin, G. I., & Frishman, W. H. (1998). Herbal medicine for the treatment of cardiovascular disease: Clinical considerations. *Archives of Internal Medicine, 158,* 2225–2234.

Mehendale, S., Aung, H., Wang, A., et al. (2005). American ginseng berry extract and ginsenoside Re attenuate cisplatin-induced kaolin intake in rats. *Cancer Chemotherapy and Pharmacology, 56,* 63–69.

Mochizuki, M., Yoo, Y. C., Matsuzawa, K., et al. (1995). Inhibitory effect of tumor metastasis in mice by saponins, ginsenoside-Rb2, 20(*R*)- and 20(*S*)-ginsenoside-Rg3, of red ginseng. *Biological & Pharmaceutical Bulletin, 18,* 1197–1202.

Ng, T. B. (2006). Pharmacological activity of sanchi ginseng (*Panax notoginseng*). *The Journal of Pharmacy and Pharmacology, 58,* 1007–1019.

Ng, L. T., Chiang, L. C, Lin, Y. T., et al. (2006). Antiproliferative and apoptotic effects of tetrandrine on different human hepatoma cell lines. *The American Journal of Chinese Medicine, 34,* 125–135.

Ooi, L. S., Li, Y., Kam, S. L., et al. (2006). Antimicrobial activities of cinnamon oil and cinnamaldehyde from the Chinese medicinal herb *Cinnamomum cassia* blume. *The American Journal of Chinese Medicine, 34,* 511–522.

Ott, M. J. (2002). Complementary and alternative therapies in cancer symptom management. *Cancer Practice, 10,* 162–166.

Ozaslan, M., Didem Karagoz, I., Kalender, M. E., et al. (2007). In vivo antitumoral effect of *Plantago major* L. extract on Balb/C mouse with Ehrlich ascites tumor. *The American Journal of Chinese Medicine, 35,* 841–851.

Popovich, D. G., & Kitts, D. D. (2002). Structure-function relationship exists for ginsenosides in reducing cell proliferation and inducing apoptosis in the human leukemia (THP-1) cell line. *Archives of Biochemistry and Biophysics, 406,* 1–8.

Qi, L. W., Wang, C. Z., & Yuan, C. S. (2010). American ginseng: Potential structure-function relationship in cancer chemoprevention. *Biochemical Pharmacology, 80,* 947–954.

Ren, H. C., Sun, J. G., Wang, G. J., et al. (2008). Sensitive determination of 20(*S*)-protopanaxadiol in rat plasma using HPLC-APCI-MS: Application of pharmacokinetic study in rats. *Journal of Pharmaceutical and Biomedical Analysis, 48,* 1476–1480.

Shieh, D. E., Cheng, H. Y., Yen, M. H., et al. (2006). Baicalin-induced apoptosis is mediated by Bcl-2-dependent, but not p53-dependent, pathway in human leukemia cell lines. *The American Journal of Chinese Medicine, 34,* 245–261.

Shumay, D. M., Maskarinec, G., Kakai, H., et al. (2001). Why some cancer patients choose complementary and alternative medicine instead of conventional treatment. *The Journal of Family Practice, 50,* 1067.

Sun, H., Ye, Y., & Pan, Y. (2005). Immunological-adjuvant saponins from the roots of *Panax notoginseng*. *Chemistry & Biodiversity, 2,* 510–515.

Sun, S., Wang, C. Z., Tong, R., et al. (2010). Effects of steaming the root of *Panax notoginseng* on chemical composition and anticancer activities. *Food Chemistry, 118,* 307–314.

Wakabayashi, C., Hasegawa, H., Murata, J., et al. (1997). In vivo antimetastatic action of ginseng protopanaxadiol saponins is based on their intestinal bacterial metabolites after oral administration. *Oncology Research, 9,* 411–417.

Wang, C. Z., McEntee, E., Wicks, S., et al. (2006a). Phytochemical and analytical studies of *Panax notoginseng* (Burk.) F.H. Chen. *Journal of Natural Medicines, 60,* 97–106.

Wang, C. Z., Wu, J. A., McEntee, E., et al. (2006b). Saponins composition in American ginseng leaf and berry assayed by high-performance liquid chromatography. *Journal of Agricultural and Food Chemistry, 54,* 2261–2266.

Wang, C. Z., Zhang, B., Song, W. X., et al. (2006c). Steamed American ginseng berry: Ginsenoside analyses and anticancer activities. *Journal of Agricultural and Food Chemistry, 54,* 9936–9942.

Wang, C. Z., Aung, H. H., Ni, M., et al. (2007a). Red American ginseng: Ginsenoside constituents and antiproliferative activities of heat-processed *Panax quinquefolius* roots. *Planta Medica, 73,* 669–674.

Wang, C. Z., Luo, X., Zhang, B., et al. (2007b). Notoginseng enhances anti-cancer effect of 5-fluorouracil on human colorectal cancer cells. *Cancer Chemotherapy and Pharmacology, 60,* 69–79.

Wang, C. Z., Mehendale, S. R., & Yuan, C. S. (2007c). Commonly used antioxidant botanicals: Active constituents and their potential role in cardiovascular illness. *The American Journal of Chinese Medicine, 35,* 543–558.

Wang, W., Zhao, Y., Rayburn, E. R., et al. (2007d). In vitro anti-cancer activity and structure-activity relationships of natural products isolated from fruits of *Panax ginseng*. *Cancer Chemotherapy and Pharmacology, 59,* 589–601.

Wang, C. Z., Aung, H. H., Zhang, B., et al. (2008). Chemopreventive effects of heat-processed *Panax quinquefolius* root on human breast cancer cells. *Anticancer Research, 28,* 2545–2551.

Wang, C. Z., Li, X. L., Wang, Q. F., et al. (2009a). The mitochondrial pathway is involved in American ginseng-induced apoptosis of SW-480 colon cancer cells. *Oncology Reports, 21,* 577–584.

Wang, C. Z., Xie, J. T., Fishbein, A., et al. (2009b). Antiproliferative effects of different plant parts of *Panax notoginseng* on SW480 human colorectal cancer cells. *Phytotherapy Research: PTR, 23,* 6–13.

Wang, X., Sakuma, T., Asafu-Adjaye, E., et al. (1999). Determination of ginsenosides in plant extracts from *Panax ginseng* and *Panax quinquefolius* L. by LC/MS/MS. *Analytical Chemistry, 71,* 1579–1584.

White, C. M., Fan, C., Song, J., et al. (2001). An evaluation of the hemostatic effects of hydrophilic, alcohol, and lipophilic extracts of notoginseng. *Pharmacotherapy, 21,* 773–777.

Wicks, S. M., Tong, R., Wang, C. Z., et al. (2007). Safety and tolerability of *Ganoderma lucidum* in healthy subjects: A double-blind randomized placebo-controlled trial. *The American Journal of Chinese Medicine, 35,* 407–414.

Wu, H., Yang, F., Cui, S., et al. (2007). Hematopoietic effect of fractions from the enzyme-digested colla corii asini on mice with 5-fluorouracil induced anemia. *The American Journal of Chinese Medicine, 35,* 853–866.

Xie, J. T., Chang, W. T., Wang, C. Z., et al. (2006). Curry leaf (*Murraya koenigii* Spreng.) reduces blood cholesterol and glucose levels in ob/ob mice. *The American Journal of Chinese Medicine, 34,* 279–284.

Xu, S. X., Chen, Y. J., Cai, Z. Q., et al. (1987). Studies on the chemical constituents of *Panax quinquefolius* Linn. *Yao Xue Xue Bao, 22,* 750–755.

Yamakage, M., Hattori, J., Satoh, J., et al. (2006). Effects of the Chinese herbal medicines Bupleuri radix, Ginseng radix, and Zingiberis rhizoma on lymphatic vessel activity in rats. *The American Journal of Chinese Medicine, 34,* 1063–1068.

Yoo, H. H., Yokozawa, T., Satoh, A., et al. (2006). Effects of ginseng on the proliferation of human lung fibroblasts. *The American Journal of Chinese Medicine, 34,* 137–146.

Yuan, C. S., & Dey, L. (2001). Multiple effects of American ginseng in clinical medicine. *The American Journal of Chinese Medicine, 29,* 567–569.

Yun, T. K. (2003). Experimental and epidemiological evidence on non-organ specific cancer preventive effect of Korean ginseng and identification of active compounds. *Mutation Research, 523/524,* 63–74.

Yun, T. K., & Choi, S. Y. (1995). Preventive effect of ginseng intake against various human cancers: A case-control study on 1987 pairs. *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology, 4,* 401–408.

Yun, T. K., & Choi, S. Y. (1998). Non-organ specific cancer prevention of ginseng: A prospective study in Korea. *International Journal of Epidemiology, 27,* 359–364.

Yun, T. K., Lee, Y. S., Lee, Y. H., et al. (2001). Anticarcinogenic effect of *Panax ginseng* C.A. Meyer and identification of active compounds. *Journal of Korean Medical Science, 16*(Suppl), S6–S18.

Zhou, X., Lin, J., Yin, Y., et al. (2007). Ganodermataceae: Natural products and their related pharmacological functions. *The American Journal of Chinese Medicine, 35,* 559–574.