A majority of potential radioprotective synthetic compounds have demonstrated limited clinical application owing to their inherent toxicity, and thus, the seeking of naturally occurring herbal products, such as ginseng, for their radioprotective capability has become an attractive alternative. In general, ginseng refers to the roots of the species of the genus Panax. As a medicinal herb, ginseng has been widely used in traditional Chinese medicine for its wide spectrum of medicinal effects, such as tonic, immunomodulatory, antimutagenic, adaptogenic and antiaging activities. Many of its medicinal effects are attributed to the triterpene glycosides known as ginsenosides (saponins). This review addresses the issue of the radioprotective effects of ginseng on mammalian cells both in vitro and in vivo. Results indicate that the water-soluble extract of whole ginseng appears to give a better protection against radiation-induced DNA damage than does the isolated ginsenoside fractions. Since free radicals play an important role in radiation-induced damage, the underlying radioprotective mechanism of ginseng could be linked, either directly or indirectly, to its antioxidative capability by the scavenging free radicals responsible for DNA damage. In addition, ginseng’s radioprotective potential may also be related to its immunomodulating capabilities. Ginseng is a natural product with worldwide distribution, and in addition to its antitumor properties, ginseng appears to be a promising radioprotector for therapeutic or preventive protocols capable of attenuating the deleterious effects of radiation on human normal tissue, especially for cancer patients undergoing radiotherapy.

Introduction

Although efforts have been directed to mitigate radiation-induced normal tissue damages since the discovery of the deleterious effects of radiation (1), the expanding role of radiotherapy (RT) in cancer treatment along with the potential threat of nuclear or radiological terrorism creates new imperatives for developing safe and effective agents for prophylaxis and treatment of ionizing radiation-induced normal tissue damage (2–4). By definition, radioprotectors are chemical compounds that have the ability to reduce the biological effects of ionizing radiation on normal tissues, including lethality, mutagenicity and carcinogenicity (5,6), and have applications in clinical oncology, space travel, radiation site clean-up, radiological terrorism and military scenarios (7). An ideal radioprotector is relatively non-toxic to normal cells, easy to administer and does not degrade performance nor compromise the therapeutic effects of radiation treatment for cancer patients (8,9). Many radioprotective compounds have been developed over the years, a majority of them designed to reduce the levels of radiation-induced free radicals within the cell (4,6,10–12). In this regard, thiol compounds like Amifostine (WR-2721), which are efficient free radical scavengers, have been studied extensively. Indeed, Amifostine, the only Food and Drug Administration (FDA) approved radioprotector in use, is currently employed in the clinic for reducing the incidence and severity of xerostomia in head and neck cancer patients undergoing RT. Unfortunately, application of this drug has so far been less than hoped for, owing to untoward toxicity often being evidenced at optimal radioprotective doses (1,3–5,13). Thus, the search to identify or develop less toxic or non-toxic agents to counter the effects of ionizing radiation remains an area of intense focus (1,14).

In recent years, it has become well known that antioxidant phytochemicals are present in plants, fruits and vegetables (6,15,16). Indeed, herbal medicine (phytomedicine), is generally considered a well-established form of complementary medicine. It is estimated that within the population of USA, use of complementary medicine has increased from 33.8% in 1990 to 42.1% in 1997 (17,18). In an attempt to find potent natural antioxidants, some herbal medicines have recently gained recognition as biological response modifiers (1,19). In particular, the use of herbal plants for their potential as possible modifiers of the radiation response is receiving considerable attention (1,20–23). Ginseng ranks as having the second highest annual sales of any herbal medicine in the recent USA marketplace (18,24–27). Reports have shown that, in addition to its significant antineoplastic (28–30) and other pharmacological activities (16,27,28,31,32), ginseng and its partially purified constituents have potential radioprotective properties (19,23,28,33–37). However, reports on the radioprotective effects of ginseng, have primarily been done in non-human models. Data from human studies are very limited, although one clinical study from Korea suggests that partially purified Panax ginseng components may reduce radiotherapy-related morbidities and stimulate the recovery of hematopoietic functions in cancer patients (33). In addition, although it is well known that G0 stage peripheral blood lymphocytes (PBL) are particularly suitable for quantifying the role of radioprotective compounds to radiation response (38), scanty information regarding the effect of ginseng on human PBL exists (39–42). Recently, however, our laboratory demonstrated the unambiguous capacity of P.ginseng crude water extract to protect against 137Cs-induced micronuclei in human PBL ex vivo in a dose-dependent manner (37).
Despite the increasing interest in the potential clinical applications of ginseng, an in-depth analysis of the radioprotective potential of ginseng is yet to be carried out, and it is unclear as to what extent ginseng meets the characteristic requirements of an applicable radioprotector. Since we believe that ginseng administration may have the potential to counter radiation-induced normal tissue damage either in cancer patients undergoing RT or in individuals under risk scenarios, such as accidental exposure or nuclear attack, the following review, which is based on the information of adequately focused and controlled ex vivo and in vivo research in mammalian cells, attempts to link together suggestive strands of important evidence that ginseng, as a natural product, combines both low toxicity and radioprotective potential against radiation-induced normal tissue damage.

What is ginseng and what is its active component?

Ginseng, a low-growing, deciduous, shade-loving perennial herb, usually refers to the dried root of several species in the plant genus *Panax*, which belongs to the Araliaceae family (24,26,29,43). *Panax* is derived from the word panacea, which means cure-all and longevity (28,43,44), and ginseng means ‘essence of the earth in the form of a man’ (17,24,35,43). The two major commercial forms are *P. ginseng* C. A. Meyer (Asian ginseng) and *P. quinquefolius* (North American ginseng) (15,16,24). Both are commonly referred to as ginseng (15,45). They are cultivated in China, Korea, Japan, United States and Canada (15,16,24,31,32,46–50). *P. ginseng* is the most commonly used and extensively researched species, particularly in China and Korea (15,16,23,27,31,47,48,50–52). For more than 5000 years (24,28,42,50), *P. ginseng* has been highly treasured in Chinese traditional medicines, with the belief that the mysterious ‘man-shaped’, bifurcated herbal root promotes longevity (24,31,47,50,53), enhances disease resistance (15,16,29,51) and helps to maintain the equilibrium of the human body under stress, usually known as the adaptogenic effect (48,54). For these reasons, *P. ginseng* is one of the most sought after medicines in the world. Indeed, ginseng now ranks as having the second highest annual sales of any herbal medicine in the USA marketplace (18,24–27).

Investigating the efficacy of herbal therapy is a complex process, because many herbal remedies contain mixtures of components and exist in a variety of forms (53). This is particularly true for ginseng, as its different varieties have subtle differences in activity (50). To date, approximately 200 substances have been isolated and characterized from *P. ginseng* (55), and, although it is not completely understood which component(s) is pharmacologically active, the consensus, based on many studies, is that the putative bioactive components of *P. ginseng* are believed to be a mixture of over 30 heterogeneous glycosidal saponins (glycosylated steroids) known as ginsenosides (15–17,26,28,31,32,45,50,52,56,57), which are derivatives of the triterpene dammarane structure (32). Hence, the majority of published research on the medicinal activity of *P. ginseng* has focused on ginsenosides present in the plant’s leaf, stem, berries, as well as the traditionally harvested root (15,45,57,58).

The nomenclature of ginsenoside molecules, on thin-layer chromatography, denotes whether they are derived from the root. For example, root variants are labeled as Ra, Rb, Rc, etc., and the subsets of each variant are labeled 1, 2 and 3 (28,59). Rg1, Re, Ro, Rc, Rb2 and Rd are present in both Asian and North American ginsens in different proportions (46). In 1993, according to a Ginseng Evaluation Program led by the American Botanical Council of Austin, Texas, the ginsenosides Rb1, Rb2, Rc, Rd, Re and Rg1 account for >90% of the total ginsenoside content of the *P. ginseng* root (28,34,35,55). As of 2003, more than 60 different ginsenosides have been isolated from various *Panax* species (28), and 29 of them are of the Rb series (59). Ginsenosides are associated with a variety of important pharmacological effects in the human body, including antioxidant (15,16,31,32,51,56,60), antistress (15,16,25,31,58), antidiabetic (27,31,48), antihypertensive (26,27,31,48,49,58) and antineoplastic activity (29,30,43,44,51,52,60–64). Ginsenosides have also been demonstrated in both humans and rodents to possess bio- modulating and immunomodulating action, and have produced beneficial effects within the cardiovascular, hematopoietic, endocrine, immune and central nervous systems (15,16,24,25,27,31,48,54,58).

Radioprotective potential of *P. ginseng* (Asian ginseng) and *P. quinquefolius* (North American ginseng)

Since the 1980s, the radioprotective effects of both *P. ginseng* and its partially purified constituents have been documented in experimental models (19–23,36,65–68). Based on the information of adequately focused and controlled ex vivo and in vivo research in various mammalian cells, Table I summarizes the evidence that *P. ginseng* has significant radioprotective potential. Ben-Hur and Fulder (20) demonstrated that in the presence of partially purified *P. ginseng* saponin mixture, Chinese hamster V79 fibroblasts are significantly more resistant to subsequent γ-irradiation as determined by the ex vivo colony forming assay. In the studies of cultured spleen lymphocytes from mice, application of *P. ginseng* water extract 48 h before γ-ray-irradiation has been shown to reduce the frequency of DNA double strand breaks (68), and it also has been demonstrated to reduce the degree of radiation-induced apoptosis in both jejunal crypt cells and hair follicles (21,22,66,69). In addition, Hsu et al. (36) found in ICR mice that the intraperitoneal injection of a Chinese herbal medicine that contains 25% of *P. ginseng* root before whole-body X-ray exposure (0–5 Gy) markedly enhanced the radiotolerance of bone marrow stem cells and peripheral hematocytes. Moreover, in Swiss albino mice, *P. ginseng* extract has been shown to significantly decrease testicular acid phosphatase activity and lipid peroxidation levels and thereby, protect against γ-ray-induced testicular damage (70).

In contrast to the research in rodents, however, reports on the radioprotective effects of ginseng in human populations are very limited, although, as stated above, one clinical study from Korea suggests that partially purified *P. ginseng* components may reduce RT-related morbidities and stimulate the recovery of hematopoietic functions in cancer patients (33). Moreover, since unrepaired or misrepaired DNA damage in PBL may be responsible for micromun colony (MN) formation (71), we recently assessed the effect of *P. ginseng* dried root crude water extract on the radiation-induced MN formation in human G0 PBL ex vivo using the cytokinesis-blocked micromun colony assay (37). We found that treatment with ginseng 24 h before 137Cs exposure (2 Gy) resulted in a linear decline of MN yields as ginseng concentration increased ($R^2 = 0.7$, $P = 0.0001$, Figure 1), with the best-fitting line being $Y = 31.2 - (6.9 \times 10^{-3})D$, where $Y$ is the percentage of MNs and $D$ is the ginseng concentration in mg/mL.

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a 6.9 MN per 1000 binucleated (BN) cells decline per 1000 μg/ml increase in ginseng crude water extract concentration. Our findings of the radioprotective effect of ginseng crude water extract was further supported by the results obtained from analysis of the micronucleated BN index (MN BN) in PBL. The MN BN index indicates the magnitude of the DNA-damaged cell fraction in BN cells, and thus, has comparable biological significance as the MN yield. We found that the MN BN index in irradiated PBL showed a similar corresponding pattern of decline as a function of increasing ginseng concentration as did the MN yields (Figure 1 and Table II). In addition, we also found that increasing concentrations of ginseng crude water extract reduced the number of binucleated (BN) cells with /C21/2 MN (Table II), indicating the efficacy of ginseng in reducing radiation–induced DNA damage. These findings suggest that the ginseng crude water extract may contain a potential radioprotective constituent with therapeutic value in dampening the damaging effects of ionizing radiation on normal tissues without exhibiting any negative effects on PBL. Finally, ginsenoside Rh2 has been shown to suppress the formation of sister chromatid exchanges in human PBL (42), findings which appear to support the idea that ginseng has antimutagenic effect and offers protection against DNA damage (48). Unfortunately, although the ex vivo radioprotective effect of P.ginseng (Asian ginseng) in rodents has been well studied, to the best of our knowledge, the radioprotective effect of P.quinquefolius (North American ginseng) has never been reported. Obviously, experimental studies on the radioprotective potential of this important ginseng compound are critically needed.

Which preparation of P.ginseng—aqueous extracts or isolated compounds—is more effective in free radical scavenging and radioprotection?

Historically, whole herbs or mixtures of herbs, have been demonstrated to be superior to active compounds isolated in the laboratory. In oriental medicine, P.ginseng root is extracted with boiling water when used for medicinal purposes (47). The aqueous extracts of P.ginseng roots are composed of a mixture

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<th>Table I. Summary of reported radioprotection in mammalian experimental models following P.ginseng administration</th>
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<td>Water extract</td>
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*In vivo.
*Cytokinesis-blocked micronuclei assay.
*Mortality rate within 60 days.
*Colony-forming-units of spleen.
of glycosides, essential oils and a variety of complex carbohydrates and phytosterols, as well as various amino acids, peptides and trace elements (15,16,23,32,47). Gamma rays, similar to many cytotoxic agents, incite normal tissue toxicity by inducing an oxidative stress. Zhang et al. (2004) found that both P. ginseng gave better protection against γ-rays than the isolated protein and carbohydrate fractions, suggesting a possible synergistic action between the different constituents of ginseng extracts (15,16,23).

When compared with purified ginsenosides, such as Rb1 and Rg1, the crude water extract of P. ginseng root has proven to be more effective in free radical scavenging (16). Liu et al. (72) found that ginsenosides P. ginseng, as a proper additive agent of cardioprotective solution, could protect SOD activity and decrease oxygen free radical levels in rats with heart transplantation, suggesting that ginsenosides have the potential to play an important role in protection against myocardial ischemia and reperfusion injury. In a placebo-controlled trial of 30 patients receiving mitral valve surgery, Zhan et al. (73) found that both ginseng and ginsenoside Rb showed protective effects on myocardial ischemia and reperfusion injury; however, the whole ginseng extract provided greater benefit than the isolated Rb. To elicit protection against radiation-induced damage resulting from the generation of hydroxyl radicals, high concentrations of scavengers must be present at critical target sites within the DNA. Importantly, we found that a 24 h preirradiation incubation of ginseng water extract is necessary to confer radioprotection inside the PBL before and during the time of radiation exposure (37).

**Possible mechanisms underlying ginseng’s radioprotective potentials**

Ginseng’s radioprotective ability is related to its antioxidant properties.

The strong free radical scavenging effects of P. ginseng have been extensively documented (15,16,23,47,53,58,61,74). The radioprotective effect of P. ginseng has been closely linked to its antioxidative capability through both the chelating of transition metal ions and the scavenging of free radicals responsible for DNA damage (21,22,70). Studies have demonstrated that ginseng root extracts exhibit both lipid-soluble and water-soluble antioxidant activity *ex vivo*, and that this antioxidant action occurs both directly through free radical scavenging and indirectly through upregulation of antioxidant enzymes (15,16,47,53,74), leading to the prevention of DNA degradation (15,16,61,74). Both Cu,Zn-superoxide dismutase (Cu,Zn-SOD or SOD1) and catalase (CAT) are key enzymes involved in the metabolism of oxygen free radicals, and ginsenosides have been associated with the upregulation of these two enzymes at the level of gene expression and transcription (15,48,75). In addition, lipid peroxidation leads to altered lysosomal membrane permeability and results in the release of hydrolytic enzymes in response to radiation-induced damage *in vivo*: both P. ginseng extract and *P. quinquefolius* extract have been shown to inhibit lipid peroxidation through transition metal chelation and scavenging of hydroxyl and superoxide radicals (15,16). Kumar et al. (70) found that administration of P. ginseng root extract before irradiation significantly decreased lipid peroxidation levels and reduced the radiation damage in mice testes. Percutaneous transluminal coronary angioplasty, which has been extensively utilized in the treatment of coronary heart disease, has been demonstrated to result in excessive free radical generation by the balloon-injured endothelial cells, leading to restenosis of the artery. However, Wu et al. (76), using an *in vivo* assay administering standardized P. ginseng extract (termed G115), have shown that this excessive free radical generation, early after arterial balloon injury, can be effectively reduced by the administration of G115, thereby preventing vascular restenosis in animal models.

The root of *P. quinquefolius*, although not investigated as extensively as the *P. ginseng*, also possesses antioxidant properties. Fu and Ji (77) found that *P. quinquefolius* supplementation could prevent age-associated increases in oxidant production and oxidative protein damage in the homogenates of various tissues in rats. *P. quinquefolius* is known to directly scavenge hydroxyl radicals, 1-diphenyl-2-picrylhydrazyl (DPPH) and to chelate metal ions (15,16). Kitts et al. (15,16) have shown that the North American ginseng extract (NAGE) exhibits antioxidant activity by both chelating transition metal...
ions as well as by scavenging radicals. To further understand the mechanism of *P. quinquefolius* in suppressing the generation of lipid hydroperoxides by means other than metal chelation, a linoleic acid emulsion system free of metal ions was used. Kitts et al. (15, 16) found that the concentration-dependent inhibition of lipid peroxidation by *P. quinquefolius* over an extended incubation period was a strong indicator of its affinity to scavenge peroxy radicals. They also found that the *ex vivo* antioxidant activity of NAGE is directly related to its affinity to scavenge hydroxyl radicals in the non-site-specific assay. In addition to the ginseng root extract NAGE, American ginseng berry extract (AGBE) is also a potent antioxidant (15). Shao et al. (57) demonstrated the significant antioxidant effects of AGBE in chick cardiomyocytes exposed to oxidant stress generated by antimycin-A.

**Ginseng’s radioprotective potential may also be related to its immunomodulating capabilities**

Although the number of published clinical reports is limited, studies have shown in humans that the immunomodulating benefits of *P. ginseng* include the following:

(i) Both ginseng aqueous extract and ginsenoside Rg1 promote DNA synthesis and mitosis in PHA-stimulated PBL *ex vivo* (39, 40, 78).

(ii) Ginseng aqueous extract increases the chemotaxis and phagocytic index of neutrophils obtained from healthy males (78).

(iii) Oral intake of standardized *P. ginseng* preparation significantly increases the CD4+ and CD8+ T cell counts, as well as natural killer cell function, of both healthy volunteers and HIV-1 (human immunodeficiency virus-1) infected patients (78, 79).

(iv) In gastric cancer patients during postoperative chemotherapy, oral intake of *P. ginseng* powder capsules restores CD3+ and CD4+ activity and also demonstrates a significantly higher overall survival rate than controls (80).

Moreover, studies have demonstrated the immunomodulating effects of *P. ginseng* on radiation exposure in different animal models. For example, Hsu et al. (36) have shown in mice that the application of *P. ginseng* before whole body irradiation significantly protected both bone marrow stem cells and peripheral hematocytes, thereby reducing the magnitude of radiation-induced regression in the immunohematopoietic system. In addition, recent reports have demonstrated that, in irradiated mice, the polysaccharide fraction isolated from the aqueous extract of *P. ginseng* (termed Ginsan) reported by Song et al. (19, 81) and *P. quinquefolius* (termed CVT-E002) reported by Wang et al. (82), significantly increased GM-CSF (granulocyte and monocyte colony stimulating factor), CFU-S (colony-forming unit in spleen) and GM-CFC (granulocyte-macrophage colony-forming cells) marrow precursor populations, and circulating neutrophils, lymphocytes and platelets. Finally, a growing body of recent evidence suggests that cytokines and growth factors can influence the cellular response to ionizing radiation (10) and that the introduction of recombinant hematopoietic growth factors has the potential to reduce the hematopoietic toxicity associated with radiation therapy or chemotherapy (19). Hence, ginseng may be exerting its radioprotective effects through upregulation of these immunomodulating cytokines. For instance, *P. ginseng* and *P. quinquefolius* have been reported to upregulate the production of cytokines, such as IL-1, IL-2, IL-4, IL-6, IL-10, IL-12, GM-CSF, interferon (IFN)-γ and tumor necrosis factor (TNF)-α in animal models (17, 19, 28, 81, 83, 84). Further studies to fully investigate this potential mechanism are certainly warranted.

**Conclusion**

The studies described in this review have indicated that *P. ginseng* and *P. quinquefolius*, which appear to radioprotect through mechanisms involving their antioxidative and immunomodulating properties, have the potential to be effective, systemic radioprotectors that can be used to ameliorate radiation-induced toxicity to normal tissues both in cancer patients undergoing radiotherapy and in individuals under the risk of radiation exposure from occupational accidents or nuclear terrorism. Furthermore, in contrast to amifostine (WR-2721), both *Panax* species have the benefit of being natural products with worldwide distribution and a long history of safety. We believe that ginseng should be further evaluated for its radioprotective potential in a clinical setting.

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