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Photoprotective Effect of Red Ginseng against Ultraviolet Radiation-induced Chronic Skin Damage in the Hairless Mouse

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To evaluate the ability of red ginseng (RG) to protect the skin from photodamage, the gross and microscopic changes in the skin of hairless mice and RG-treated mice exposed chronically to UV were examined. The skin of the UV-irradiated mice showed characteristic signs of photoaging, such as deep wrinkles across the back, increased epidermal thickness, numerous cell infiltration, and many enlarged keratinizing cysts. The RG-treated mice showed a significantly decreased wrinkling score, minimal epidermal hyperplasia, slightly increased dermal cellularity and lack of proliferation of cysts. By week 22, 88.9% (i.p. with saline) or 60.0% (topical administration with cream base) of the UV-irradiated mice developed at least one tumor. RG delayed tumor onset significantly. RG was also effective in reducing the occurrence of UV radiation-induced skin tumors and reduced the number of tumors per mouse. After 22 weeks of treatment, 57.1% (i.p.) or 85.7% (topical administration) of the mice treated with RG were tumor-free. Tumor multiplicity was reduced by 89.3% (i.p.) or 92.2% (topical administration) in the RG treated groups. It is noted that skin that is chronically exposed to UV is subject to photoaging and photocarcinogenesis and the regular use of RG would prevent these photodamaging effects of UV. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: Panax ginseng; ultraviolet; chronic skin damage; photocarcinogenesis.

INTRODUCTION

Sunlight is composed of a continuous spectrum of electromagnetic radiation that is divided into three main regions of wavelengths: ultraviolet (UV), visible and infrared. UV radiation is further divided into three sections, each of which has distinct biological effects: UVA (320–400 nm), UVB (280–320 nm) and UVC (200–280 nm). Studies have demonstrated that solar UV radiation, particularly its UVB component, is the major cause of skin cancer (Gailani *et al.*, 1996). UV radiation is also known to elicit a variety of other adverse effects, such as erythema, sunburn cells, inflammation, hyperplasia, hyperpigmentation, immunosuppression, premature skin aging and photocarcinogenesis (Goihman-Yahr, 1996; Mukhtar and Elmets, 1996; Naylor, 1997; Young, 1990). The effects elicited by UV radiation are collectively known as the UV response (Fisher *et al.*, 1996; Kraemer, 1997). UVB radiation is regarded as a complete carcinogen, with tumor-initiating as well as tumor-promoting potential (Scharffetter-Kochanek *et al.*, 1997).

The SKH hairless mouse has been used as a model to study the photoaging effects of chronic UV radiation on the skin. These effects include dramatic changes in the appearance of the skin surface, which have been described as wrinkling and sagging (Bissett *et al.*, 1987, 1990b), in addition to the appearance of skin tumors (Forbes *et al.*, 1981). Histologically, there are a number of alterations in the epidermis and dermis, which are similar to those observed in sun-exposed human skin. These visible and histological changes in the mouse have been used as photodamage markers for evaluation of chronic photoprotection by sunscreen (Bissett *et al.*, 1987; Plastow *et al.*, 1988) and antioxidants (Bissett *et al.*, 1990a).

Panax ginseng, also known as Korean or Chinese ginseng, has been used as a general tonic in traditional Oriental medicine to increase vitality, health and longevity, especially in older persons (Tang and Eisenbrand, 1992; Sonnenborn and Propert, 1991). Commercially available ginseng is classified into fresh, white and red ginseng. White ginseng is made by peeling the fresh ginseng roots and drying them without steaming. To preserve ginseng for an extended period of time, red ginseng is made by steaming and drying the fresh ginseng, suggesting chemical transformation by heat (Park, 1996). In Oriental medicine, ginseng is extracted with boiling water and used for medicinal purposes. Aqueous extracts of ginseng are composed of a mixture of glycosides, ginsenosides, trace minerals and a variety of complex carbohydrates as well as proteins, peptides and amino acids (Park, 1996). The main pharmacologically active constituents of ginseng are believed to be ginsenosides, derivatives of the

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triterpene dammarane structure (Gillis, 1997; Park, 1996). The pharmacological effects of ginseng have been demonstrated in the CNS and in cardiovascular, endocrine and immune systems. In addition, ginseng and its constituents have been ascribed to possess antineoplastic, antistress, radioprotective, and antioxidant activities (Attele *et al.*, 1999; Gillis, 1997; Lee *et al.*, 2006; Shin *et al.*, 2000).

In this report we described the photoprotective effect on hairless mice of red ginseng (RG) against chronic skin damage induced by UV radiation. To the knowledge of the authors this is the first study showing prevention of UV-mediated damages in skin by red ginseng.

MATERIALS AND METHODS

Animals. Seven-week-old female SKH-1 hairless mice were obtained from a specific pathogen-free colony at Oriental Inc. (Seoul, Korea) and allowed 1 week for quarantine and acclimatization. The Institutional Animal Care and Use Committee at Chonnam National University approved the protocols used in this study, and the animals were cared for in accordance with the Guidelines for Animal Experiments. The animals were housed in a room that was maintained under the following conditions: 23 ± 2 °C, a relative humidity of 50 ± 5%, with artificial lighting from 08:00 to 20:00 h and with 13–18 air changes per hour. The animals were housed five per polycarbonate cage, and were given tap water and commercial rodent chow (Samyang Feed Co, Korea) *ad libitum*.

Irradiation and RG treatment. The UV apparatus consisted of four UV lamps (GL20SE, Sankyo denki, Japan). The spectral irradiance for the UV lamps was 280–360 nm, providing 80% UVB and 20% UVA. The peak intensity of the light source was 306 nm. The radiant dose was quantified with a Solarmeter® (Solartech Inc., USA). The fluence at 40 cm from the dorsal surface of the mice was 0.48–0.50 mJ/cm^2/s. The mice were placed in individual compartments in an open plastic cage on a rotating base to abrogate any differences in fluence across the UV light bulbs. Mice were exposed to 90 mJ/cm^2 three times per week and the dose was increased by 10% per week until the dose reached 175 mJ/cm^2. UV treatment was stopped at 22 weeks. At the completion of the experiment, the mice were killed by CO_2 asphyxiation. The freeze-dried RG extract powder was kindly provided by the Korea Ginseng Corporation (Daejon, Korea). The percentage of ginseng saponins from red ginseng was about 3.3%. Ginseng saponins contained Rb1 (15.8%), Rb2 (7.8%), Rc (8.1%), Rd (7.6%), Re (3.2%), Rf (4.7%), Rg1 (1.9%), Rg2 (22.2%), Rg3 (24.2%), Rh1 (4.7%) and other minor ginsenosides. A total of 100 mice (20 mice/group) were divided into (a) untreated control, (b) UV-irradiated control (i.p. with saline vehicle), (c) RG i.p. administration in combination with UV-irradiation, (d) UV-irradiated control (topical administration with cream base vehicle), (e) RG topical administration in combination with UV-irradiation. For mice receiving an i.p. injection, the RG (25 mg/kg of body weight) or vehicle (saline) was given i.p. at 24 h prior to each UV irradiation. For mice receiving topical treatment with a vehicle (cream base, Kolma Korea Co., Korea) or RG cream, the RG cream (0.2% RG in cream base) or vehicle was applied evenly to the skin of the back at a rate of 0.2 mg/cm^2 at least 15 min before UV irradiation. The cream base contained 1,3-butylene glycol, aloe vera gel, cyclopentasiloxane, decamethylcyclopentasiloxan, dimethicone copoyol crospolymer, glycerin, imidazolidinyl urea, methyl parahydroxybenzoate, sodium meta bisulfate as major ingredients and other minor ingredients.

Visual skin evaluation. Skin wrinkling in mice was assessed as described previously (Bissett *et al.*, 1987, 1990b). For con-venience in grading, the mice were held perpendicular by the tail with their feet resting against a solid surface to diminish movement. Skin lesions were recorded as tumors if they were circular, red, raised, greater than 1 mm in diameter, and persisting for 2 or more weeks. These lesions were counted. An individual not involved in the treatment and irradiation work carried out the visual evaluations blind, based on group number.

Histology. All mice were euthanized and their dorsal skins were dissected using a rectangular template (2.5 × 5 cm) to include the entire treated areas. The skin was stapled to cardboard, fixed in 10% neutral-buffered formalin, embedded in paraffin, and sectioned at 5 μm. Sections were stained with hematoxylin and eosin. The histological parameters and grading scales were as follows: epidermal thickness, 0–3 scale; dermal cellularity, 0–3 scale; and dermal cyst changes, 0–5 scale. These histological changes in mice were assessed as described previously (Bissett *et al.*, 1987, 1990b). The skin with tumors was processed for microscopic evaluation of tumor type (papilloma or squamous cell carcinoma).

Statistics. The statistical significance of differences between the results in RG-treated and untreated groups was determined by two-tailed Student's *t*-test and the Chi-square test by use of the Graph PAD In Plot computer program (GPIP, Graph PAD Software Inc., USA). A value of $p < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

The UV exposure induced heavy wrinkling in the mouse skin. The degree of wrinkling was reduced by previous treatment with RG. At treatment week 12, the mean wrinkle grade of the RG-treated group was 1.50 (i.p. treatment) or 1.25 (topical treatment), and that of the vehicle-treated group was 1.88 or 1.85, respectively. The difference in mean wrinkle grade between the two groups was significant. However, at treatment weeks 18 and 20, the means of the wrinkle grades of the topical treatment of RG were 2.14 and 2.36, and those of the control group were 2.31 and 2.44 (Fig. 1). No improvement in the grade was detected at this time as skin penetration of RG was inhibited due to increased epidermal thickness.

Skin was taken for histological evaluation at week 22 in the experiment. Irradiated mice showed strikingly better histological scores for epidermal thickening, dermal cellularity and cysts than non-irradiated mice. The RG (i.p. group) showed reduced damage as assessed by a number of parameters (Table 1).

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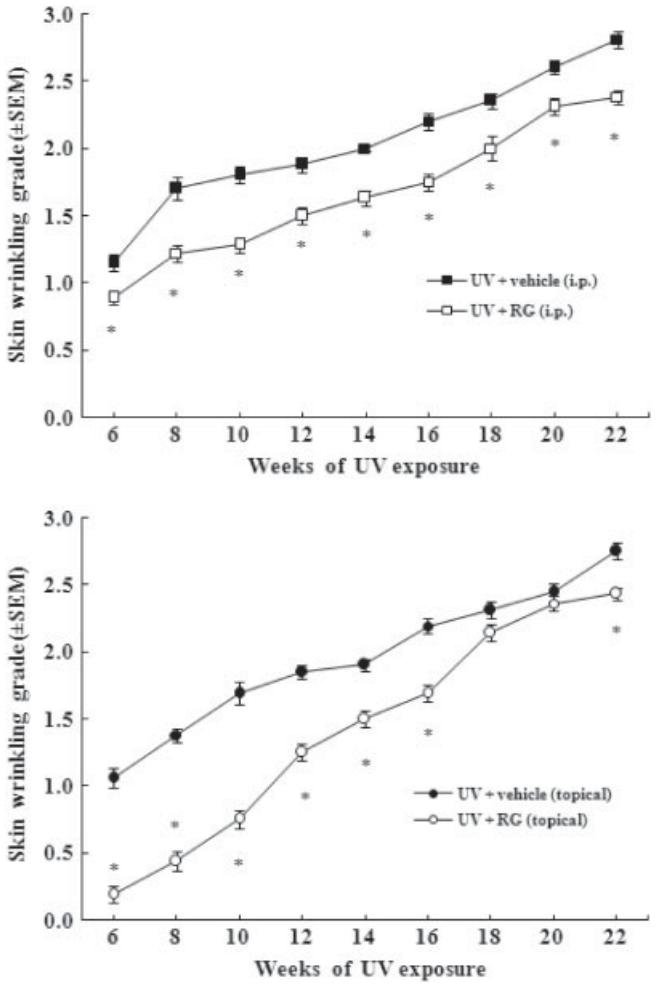

Figure 1. Sequential changes of wrinkle grade in the skin of UV-irradiated mice and red ginseng (RG)-treated mice. The mice were graded using a scale of mouse wrinkling. The scale ranges from 0 for the normal skin to 3 for the heavily fixed wrinkling skin. Half-grade increments can be used with this scale. * $p < 0.01$ compared with corresponding UV + vehicle group.

The tumor data were calculated in terms of incidence (percentage of mice bearing tumors) and multiplicity (average number of tumors per mouse). The tumors were first observed after 14 weeks of UV irradiation and continued to appear throughout the course of the experiment. The mice treated with RG were substantially protected against the carcinogenic effects of UV radiation. After 22 weeks of treatment, when the experiment was terminated, 88.9% (i.p. with saline vehicle) or 60.0% (topical administration with cream base vehicle) of the animals in the UV-irradiated groups had developed tumors, while 57.1% (i.p. with RG) or 85.7% (topical administration with RG cream) of the mice treated with RG were tumor-free. Similarly, tumor multiplicity was reduced by 89.3% (i.p. with RG) or 92.2% (topical administration with RG cream) in the RG treated groups (Table 2). The overall effect of treatment on tumor incidence and multiplicity was highly significant. In addition to the reduction in tumor incidence and multiplicity, there was a significant delay in tumor appearance (Table 3).

Human skin is constantly exposed to numerous noxious physical, chemical and environmental agents. Some of these agents directly or indirectly adversely affect the skin. Among several environmental and xenobiotic factors, exposure to solar UV radiation is the key factor in the initiation of skin disorders, such as wrinkling, scaling, dryness, mottled pigment abnormalities consisting of hypopigmentation and hyperpigmentation, and skin cancers (deGruijl and Van der Leun, 1994; Ichihashi *et al.*, 2003). Chronic exposure to UV irradiation leads to photoaging, immunosuppression and ultimately photocarcinogenesis. Photocarcinogenesis involves the accumulation of genetic changes, as well as immune system modulation, and ultimately leads to the development of skin cancers. UVB exposure to the skin has been shown to produce excessive generation of ROS, which if not counteracted by the antioxidant defense ability of the living system, creates oxidative stress in the skin (Black *et al.*, 1997). This oxidative stress is shown to be responsible for a variety of pathological conditions, including immunosuppression, inflammation, aging and skin cancer (Black *et al.*, 1997; Scharffetter-Kochanek *et al.*, 1997; Trenam *et al.*, 1992). Therefore, prevention/intervention with antioxidant agents is often regarded as a plausible strategy for the management of these oxidative stress conditions.

In recent years, there has been great interest in the use of dietary supplements that are derived from naturally occurring botanicals for the photoprotection of the skin, including protection from skin cancers. Dietary botanicals, which possess antiinflammatory, immunomodulatory and antioxidant properties, are among the most promising groups of compounds that can be exploited as ideal chemopreventive agents for skin

Table 1. Effects of red ginseng (RG) on UV-induced histological changes

Group	Histological score (± SD)		
	Epidermal thickening	Dermal cellularity	Dermal cyst changes
NC (n = 20)	0	0	0.83 ± 0.79
UV + vehicle (n = 18)[a]	2.83 ± 0.35	2.67 ± 0.50	3.50 ± 0.50
UV + RG (n = 14)[a]	1.79 ± 0.49[c]	1.57 ± 0.84[c]	2.07 ± 0.84[c]
UV + vehicle (n = 20)[b]	1.97 ± 0.58	1.40 ± 0.44	2.10 ± 0.59
UV + RG (n = 14)[b]	1.93 ± 0.78	1.64 ± 0.48	1.93 ± 1.02

SKH-1 hairless mice were exposed to 90 mJ/cm^2 three times per week and the dose was increased by 10% per week until the dose reached 175 mJ/cm^2. UV treatment was stopped at 22 weeks after first irradiation and the mice were killed.
The histological parameters and grading scales were as follows: epidermal thickness, 0–3 scale; dermal cellularity, 0–3 scale; dermal cyst changes, 0–5 scale.
[a] RG (25 mg/kg of body weight) or vehicle (saline) was given i.p. at 24 h prior to each irradiation.
[b] RG cream (0.2% in cream base) or vehicle (cream base) was topically treated at 15 min prior to each irradiation.
[c] $p < 0.01$ compared with corresponding UV + vehicle group.

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Table 2. Incidence and number of tumors by type in the skin of UV-irradiated mice and red ginseng (RG)-treated mice

Group	No. of tumors by type (± SD)		
	Papilloma	Carcinoma	Total
NC (n = 20)	0 (0)	0 (0)	0 (0)
UV + vehicle (n = 18)[a]	4.78 ± 3.19 (88.9)	0.56 ± 0.88 (33.3)	5.33 ± 3.57 (88.9)
UV + RG (n = 14)[a]	0.57 ± 0.79[c] (42.9)[c]	0[d] (0)[c]	0.57 ± 0.79[c] (42.9)[c]
UV + vehicle (n = 20)[b]	1.70 ± 1.83 (60.0)	0.10 ± 0.32 (10.0)	1.80 ± 1.99 (60.0)
UV + RG (n = 14)[b]	0.14 ± 0.38[c] (14.3)[c]	0 (0)[c]	0.14 ± 0.38[c] (14.3)[c]

SKH-1 hairless mice were exposed to 90 mJ/cm^2 three times per week and the dose was increased by 10% per week until the dose reached 175 mJ/cm^2. UV treatment was stopped at 22 weeks after first irradiation and the mice were killed. The percentages of mice with tumors are shown in parentheses.

[a] RG (25 mg/kg of body weight) or vehicle (saline) was given i.p. at 24 h prior to each irradiation.

[b] RG cream (0.2% in cream base) or vehicle (cream base) was topically treated at 15 min prior to each irradiation.

[c] $p < 0.01$ compared with corresponding UV + vehicle group.

[d] $p < 0.05$ compared with corresponding UV + vehicle group.

Table 3. Effect of red ginseng (RG) on onset time of tumor

Treatment	Average week of tumor onset (± SD)
UV + vehicle (n = 16)[a]	15.06 ± 0.75
UV + RG (n = 6)[a]	16.67 ± 0.65[c]
UV + vehicle (n = 12)[b]	16.88 ± 0.81
UV + RG (n = 2)[b]	17.64 ± 0.67[d]

SKH-1 hairless mice were exposed to 90 mJ/cm^2 three times per week and the dose was increased by 10% per week until the dose reached 175 mJ/cm^2. UV treatment was stopped at 22 weeks after first irradiation and the mice were killed.

[a] RG (25 mg/kg of body weight) or vehicle (saline) was given i.p. at 24 h prior to each irradiation.

[b] RG cream (0.2% in cream base) or vehicle (cream base) was topically treated at 15 min prior to each irradiation.

[c] $p < 0.01$ compared with corresponding UV + vehicle group.

[d] $p < 0.05$ compared with corresponding UV + vehicle group.

cancer (Afaq *et al.*, 2002; Baliga and Katiyar, 2006). The strong free radical scavenging effects of *P. ginseng* have been extensively documented (Kim *et al.*, 2002; Kitts *et al.*, 2000; Kitts and Hu, 2000; Valli and Giardina, 2002). The 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 (Kim *et al.*, 1993, 2003). 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 (Kim *et al.*, 2002; Kitts *et al.*, 2000; Kitts and Hu, 2000; Valli and Giardina, 2002), leading to the prevention of DNA degradation (Kitts *et al.*, 2000; Kitts and Hu, 2000; Zhang *et al.*, 1996).

Since free radicals play an important role in UV-induced damage, the underlying protective mechanism of ginseng could be linked, either directly or indirectly, to its antioxidative capability by the scavenging of free radicals responsible for DNA damage. In addition, ginseng's photoprotective potential may also be related to its immunomodulating capabilities. The results of the present study indicate that RG is protective against chronic damage induced by UV radiation in the hairless mouse. Protection against visible changes (wrinkling and tumor formation) and histological alterations were demonstrated. The RG provides broad solar UV protection of the skin. Ginseng is a natural product with worldwide distribution, and in addition to its antitumor properties, it appears to be a promising photoprotector capable of attenuating the deleterious effects of UV on human skin.

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