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Oral administration of resveratrol ameliorates epidermal hyperplasia in ultraviolet B irradiated BALB/c mice

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ABSTRACT

Commercial sunscreens contain cosmetic preservatives which could exert phototoxic effect when exposed to sunlight. Natural sources, such as resveratrol, have gain attention in the cosmetic world as it has higher antioxidant capacity than vitamins C and E. Resveratrol also possesses strong anti-inflammatory, anti-cancer, and anti-aging properties. It also has proven to reduce epidermal hyperplasia and skin thickness. The aim of the study was to evaluate the ameliorative effect of resveratrol in reducing epidermal hyperplasia of mouse skin exposed to UVB irradiation. Eighteen female BALB/c mice were randomly divided into three groups: control group (n = 6), without Ultraviolet B irradiation and resveratrol administration; UVB exposure group (n = 6), irradiated with UVB dose of 250 mJ/cm^2 for 3 minutes; and treatment group (n = 6), irradiated with UVB and treated with 0.02 ml of 200 mg/kg of resveratrol by oral gavage. Treatment was given for 14 days and UVB exposure was given on day 9, 11, and 13. On day 15, skin morphology was observed and skin-fold thickness was measured to evaluate edema. The mice were then sacrificed to obtain dorsal part of skin for histopathological observation using hematoxylin and eosin (H&E) stain. Resveratrol reduced skin scaling and erythema in UVB induced mice. Skin-fold thickness of resveratrol decreased significantly (p = 0.001) as compared to UVB irradiated group. H&E staining showed that resveratrol group reduced leukocyte infiltration and epidermal hyperplasia as compared to UVB exposure group. Hence, oral resveratrol was able to reduce skin thickness and epidermal hyperplasia and it has the potential to be developed as a natural alternative for photoprotection.

INTRODUCTION

Skin is the largest and outermost organ which protects the internal organs of the body by acting as a shield against environmental carcinogens and xenobiotic agents (D'Orazio *et al*., 2013). However, the skin is more likely to be exposed to oxidative stress due to environmental insults which include UV radiation or pollution. Besides, it can be the consequences of any specific impairment in antioxidant status resulting from pathological or aging condition (Soeur *et al*., 2015). Solar UV radiation, particularly UVB (290–320 nm) is known as the "burning rays" and it constitutes only 4%–5% of UV light. However, UVB is 1,000 times more capable of causing skin sunburn than UVA. Besides, UVB is also more genotoxic than UVA. UVB acts mainly in the epidermal basal cell layer (Svobodová *et al*., 2003). The basal cell layer able to divide new cells and UVB radiation may alter and distort the proliferation, differentiation, and metabolism (Vostálová *et al*., 2010). Hence, the skin is the most susceptible organ to be affected by UVB radiation due to its direct contact with the sunlight. Acute exposure to UVB radiation may cause erythema, sunburn, edema, epidermal hyperplasia, and actinic keratosis (Gregoris *et al*., 2011; Ichihashi *et al*., 2003). Meanwhile, chronic UVB radiation may lead to skin carcinogenesis. This occurs due to the formation of pyrimidine dimer in DNA and also point mutation on p53 caused by UVB radiation (De Gruijl, 2002).

One of the mandatory strategies to prevent UVB exposure on the skin is to use sunscreens. These commercial sunscreens contain preservatives such as parabens which supposedly to

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increase the half-life and prevent microbial contamination (Rodford, 1997; Sambandan and Ratner, 2011). In certain circumstances, the cosmetic excipients can react with sunlight and give phototoxic effects on the human skin (Harber and Baer, 1969). In addition, researchers discovered methylparaben was able to induce oxidative stress, nitric oxide production, cellular lipid peroxidation, and cell death (Handa *et al*., 2006).

Over the past years, naturally occurring plant products have been the growing interest in cosmeceutical field due to their broad biological activities (Ouhtit *et al*., 2000). Resveratrol is a naturally occurring plant polyphenol that is present in grapes, berries, peanuts, and a variety of plants (Nichols and Katiyar, 2010). Resveratrol possesses many pharmacological activities which include analgesia, anti-oxidant, anti-inflammation, anti-aging, anti-hyperpigmentation, and chemoprevention (Bazzo *et al*., 2013; Hasiah *et al*., 2011; Hsu *et al*., 2014; Lanzilli *et al*., 2012; Lee *et al*., 2014; Zhu *et al*., 2014). Furthermore, it was also reported that resveratrol is a promising agent to reduce the occurrence of cutaneous malignancies (Polonini *et al*., 2013). The aim of the current study is to determine the effect of oral administration of resveratrol in reducing the epidermal thickness on UVB irradiated BALB/c mice skin.

MATERIALS AND METHODS

Animal model

Eighteen female BALB/c mice (5–6 weeks old) were obtained from the Faculty of Veterinary Medicine, University Putra Malaysia, 43400 Serdang, Selangor, Malaysia. The animals were housed in the animal house in the Department of Biomedical Science, Centre of Health and Applied Sciences, Universiti Kebangsaan Malaysia, Jalan Raja Muda Aziz, Wilayah Persekutuan, 50300 Kuala Lumpur, Malaysia, under 12 hours light/dark cycles at the controlled room temperature condition. All mice were fed standard pellet diet and provided with water *ad libitum*. Animals were randomly divided into three groups: vehicle control group (n = 6), which were not exposed to UVB irradiation and not treated with resveratrol; exposure group (n = 6), which were exposed to UVB irradiation only; and treatment group (n = 6), which were exposed to UVB irradiation and also treated with resveratrol. The treatment was given for 14 successive days (Park *et al*., 2012).

The animal usage had been approved by the Universiti Kebangsaan Malaysia Ethics Committee (UKMAEC) (UKMAEC NO: FSK/2017/AHMAD ROHI/22-NOV./887-NOV.-2017-JULY-2018) and the guidelines were strictly followed.

Treatment of mice with resveratrol

Mice were treated with resveratrol (Tokyo Chemical Industry, Japan) with a dose of 200 mg/kg (Kim *et al*., 2010). These doses were freshly prepared daily by dissolving in corn oil and then vortexed until the powder dissolved completely. All mice fasted for 4 hours before treated with 0.2 ml of dissolved resveratrol by an oral gavage.

UVB irradiation

The source of irradiation was a lamp with 312 nm of wavelength, 15 W (UVP, USA). Mice from both groups (exposure and treatment group) were exposed to UVB irradiation for 3 minutes at a dose of 250 mJ/cm^2 on 9th, 11th, and 13th day of treatment after shaving the dorsal part of the skin using an electric shaver (Phillips, Malaysia; Park *et al*., 2012).

Skin morphological changes

The dorsal part of the skin was observed before the mice were euthanized by cervical dislocation for any morphological changes of skin damage, such as scaly and thickening of the skin.

Evaluation of skin edema

The skin edema was assessed by measuring the skin-fold thickness (Kim, 2016). The mid-line dorsal skin of the mouse was lifted up at the neck pinching and skin-fold thickness was measured mid-way between the shoulder and hip using a Harpenden skin-fold caliper (Baty, UK).

Histopathological observation

At the end of the experiment, the animals were anesthetized by ketamine and xylazine and were euthanized by cervical dislocation. Tissue samples were taken from the dorsal part of the skin. The tissue specimens were fixed using 10% neutral buffered formalin for 24 hours and embedded in a paraffin block. The sections were cut at 5-µm thickness for histopathology observation. Hematoxylin & Eosin (H&E) staining was performed to assess the structural alteration, leukocyte infiltration, and epidermal hyperplasia.

Statistical analysis

Data were presented as mean ± standard error mean (SEM). One-way analysis of variance was used to determine skin-fold thickness between groups. The differences among means were compared using a *post-hoc* Tukey test and were considered to be significant at $p < 0.05$.

RESULTS

Effects of resveratrol on skin morphology in UVB irradiated skin damage

The results of skin morphology changes of various groups are shown in Figure 1. Skin scaling was obvious in UVB exposure group when compared with the vehicle control group. Moreover, mice in the UVB exposure group responded to strong erythema, hardening, and thickening of the skin as compared with mice in the vehicle control group. However, oral administration of 200 mg/kg resveratrol markedly reduced the redness on the skin with no obvious scaly skin in the treatment group.

Effects of resveratrol on cutaneous edema in UVB irradiated skin tissue

Figure 2 shows the results of skin-fold thickness which indicated edema in various groups. The skin-fold thickness of the UVB exposure group (1.725 ± 0.079 mm) increased approximately by 1.7-fold compared with the vehicle control group (1.0 ± 0.035 mm; p = 0.001). Oral administration of 200 mg/kg of resveratrol significantly inhibited the UVB induced edema, showing skin-fold thickness (1.0 ± 0.000 mm; p = 0.001) compared to UVB exposure group (1.725 ± 0.079 mm).

Effect of resveratrol on histopathological changes in UVB irradiated skin tissue

The result of the histopathological changes in the skin tissues of various groups is shown in Figures 3 and 4. In Figure 3, the vehicle control group has a normal skin histology which constitutes of thin epidermis, dermis, and hypodermis. However, the UVB exposure group showed epidermal hyperplasia and hyperkeratosis, where the keratinocytes and epidermal layers increased dramatically. In contrast, the treatment groups developed a less severe epidermal hyperplasia within the same experimental period. Furthermore, the keratinocyte proliferation was also not prominent as compared to the UVB exposure group.

Figure 4 shows that UVB exposure group resulted in an induction of infiltration of leukocytes in the dermis as compared with the vehicle control group. However, UVB with 200 mg/kg of resveratrol was found to cause a marked

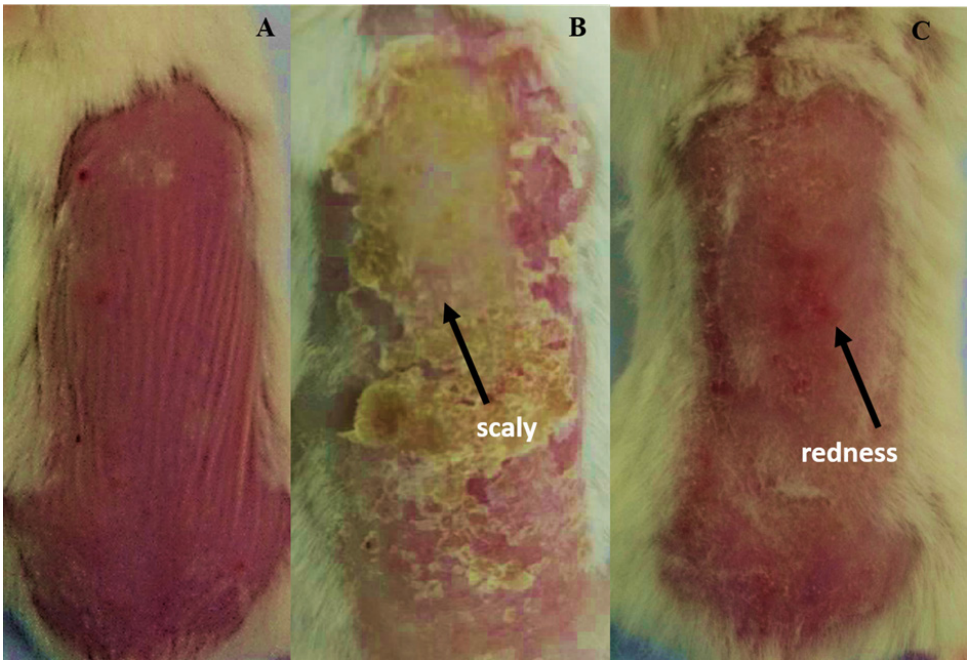

Figure 1. (A) Skin of the vehicle control group showed normal thickness and not scaly skin; (B) UVB irradiated group showed obvious scaly and redness on skin; and (C) treatment group showed not scaly and less redness on the skin.

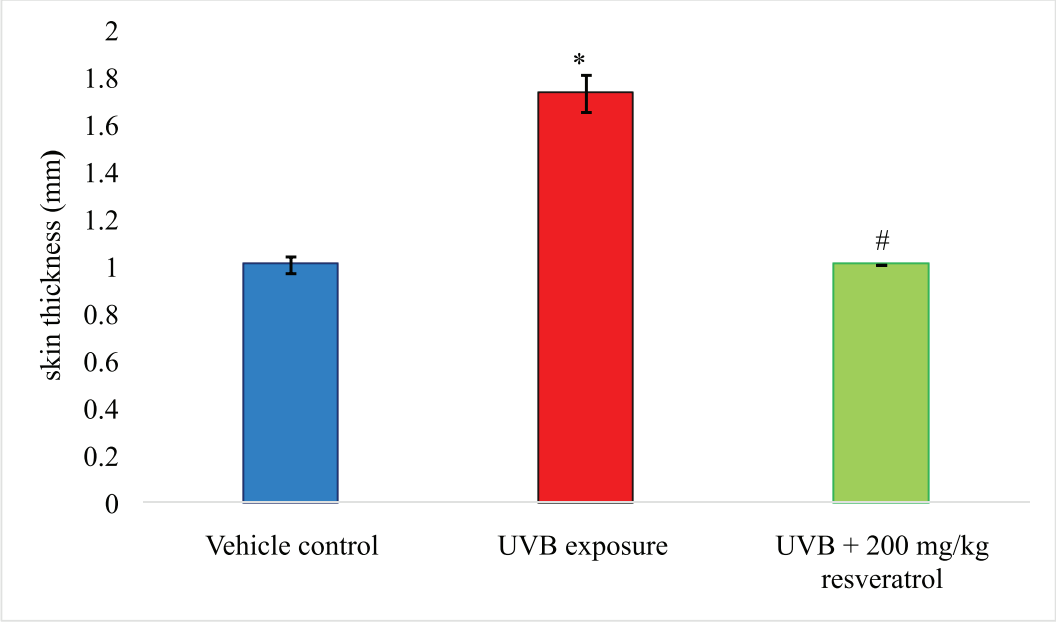

Figure 2. Bar chart showed results of skinfold thickness in different groups represented by the mean ± SEM ($n = 6$). *Statistically significant difference in comparison to the vehicle control group ($p = 0.001$). #Statistically significant difference in comparison to the UVB exposure group ($p = 0.001$).

reduction in the number of infiltrating leukocytes compared to the UVB-exposure group.

DISCUSSION

UVB radiation is believed to be the major cause of cutaneous malignancies. This environmental carcinogen has the ability to alter the cellular function, production of free radicals, oxidation of macromolecules, DNA damage, and alternation of signaling pathways (Kim, 2016; Katiyar and Meeran, 2007; Schneider *et al*., 2006). Moreover, its effect on the skin's biology plays a major role in keratinocyte proliferation, epidermal hyperplasia, edema, erythema, and carcinogenesis (Ichihashi *et al*., 2003). Natural antioxidants are regarded as a promising agent that can reduce the UVB induced cutaneous malignancies (Maruki-Uchida *et al*., 2013). In recent years, naturally occurring compounds such as resveratrol and dietary polyphenol gain considerable attention in modifying the cellular response to UVB irradiation (Park *et al*., 2012). The previous study reported that oral

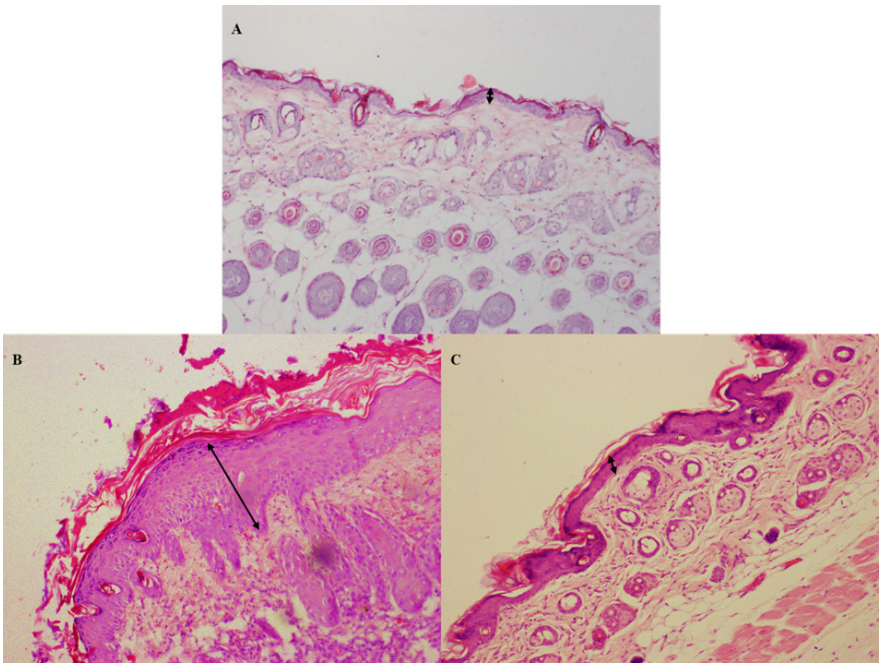

Figure 3. Epidermal hyperplasia (double sided arrow). (A) Vehicle control group; (B) UVB exposure group; and (C) UVB with 200 mg/kg resveratrol treatment group. Hematoxylin-eosin staining; magnification ×10. Scale bar: 100 µm.

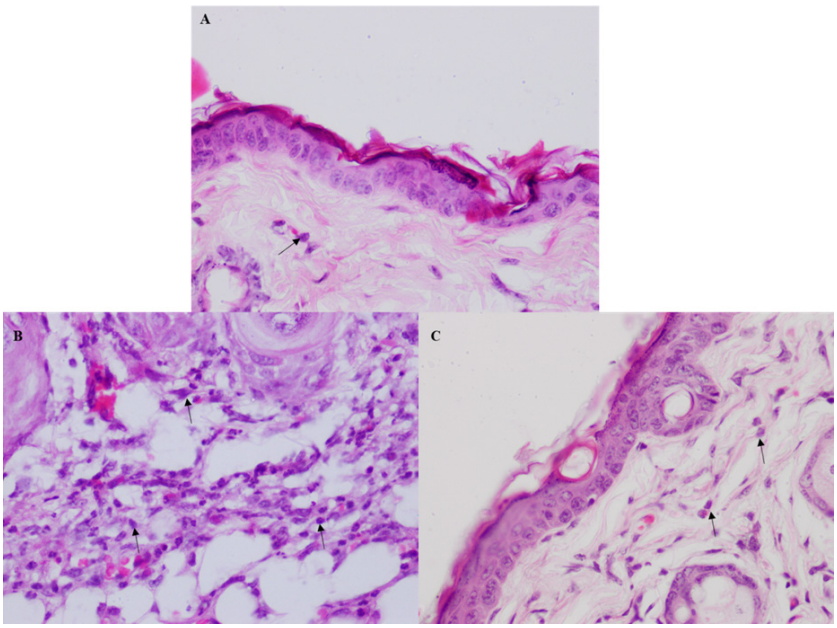

Figure 4. Leukocyte infiltration (arrow) in mice; (A) vehicle control group; (B) UVB exposure group; (C) UVB with 200 mg/kg resveratrol treatment group. Hematoxylin-eosin staining; magnification × 40. Scale bar: 100 µm.

supplements can protect the skin through multiple mechanisms (González *et al*., 2016).

Prolong exposure of skin to UVB irradiation may increase the skin scaling that would results in hyperkeratinization and hyperplasia on epidermal layer of the skin (Lee *et al*., 2013). Furthermore, skin scaling is one of the earliest signs of many skin disorders such as hyperpigmentation and skin cancer (Ichihashi *et al*., 2003). These finding revealed that oral resveratrol prevented the formation of skin scaling. From the present study, resveratrol-treated mice showed less erythema as compared to UVB exposure group. We could suggest that oral administration of resveratrol as natural polyphenol with antioxidant and anti-inflammation activity was able to protect the skin from UVB induced skin scaling and erythema. The antioxidant capacity was able to combat the excess production of reactive oxygen species (ROS) against UVB irradiation; and hence, strengthened the skin integrity and defense insult from the UVB irradiation (Afaq *et al*., 2003). Our study was in agreement with a study that reported oral epigallocatechin gallate (EGCG), a polyphenol increases the minimal erythema dose (MED) on UVB induced HWY/Slc hairless rats. MED is a measure of the ability of a sunscreen to protect against erythema (Jeon *et al*., 2009).

Cutaneous edema is also indicated as a marker for skin damage. Edema is caused by the accumulation of extracellular fluid due to excess leakage from hyperpermeable blood vessels and by a failure of lymphatic vessels to sufficiently drain the fluid from the interstitium (Kajiya *et al*., 2006). Edema can be determined by measuring the skin-fold thickness (Afaq *et al*., 2003). Our study demonstrated that oral resveratrol reduced the skin-fold thickness significantly as compared to the UVB exposure group. Our finding suggested that oral administration of resveratrol was able to reduce skin edema induced by the UVB irradiation. Previous literature supported that topical application of resveratrol significantly inhibited the UVB-mediated increase in skin-fold thickness in SKH-1 hairless mice (Afaq *et al*., 2003).

Acute UV exposure is also known to cause infiltration of leukocytes, especially in dermis layer (Reagan-Shaw *et al*., 2004). These cells could produce large amounts of pro-inflammatory cytokines and ROS that would enhance the inflammatory response (Martinez *et al*., 2015). Our study reported that oral resveratrol markedly reduced the infiltration of leukocyte as compared to the UVB exposure group. We suggested that oral resveratrol had the ability to inhibit the generation of inflammatory cells. Thus, resveratrol proved that it could inhibit the UVB-mediated leukocyte infiltration. Previous studies on the topical application of resveratrol on UVB induced SKH-1 hairless mice reported that it minimized the leukocyte infiltration (Afaq *et al*., 2003). In addition to this, the polyphenols such as EGCG and silymarin could also block the UV induced leukocyte infiltration significantly (Svobodová *et al*., 2003).

Acute UVB exposure triggers the epidermal hyperplasia due to the continuation of epidermal growth factor receptor which would lead to keratinocyte proliferation and inhibition of apoptosis (El-Abaseri and Hansen, 2007; El-Abaseri and Putta, 2006). Present study showed that UVB exposure group demonstrated a prominent epidermal hyperplasia as compared with the vehicle control group. However, oral resveratrol pretreatment group showed a marked reduction in epidermal hyperplasia as compared to the UVB exposure group. These result indicated that oral administration of resveratrol was able to inhibit the proliferation of epidermal layer. Evidence also showed that polyphenols such as curcumin also had the photo-preventive effect on UVB induced epidermal hyperplasia (Khandelwal *et al*., 2016).

We demonstrated that oral administration of resveratrol prior to UVB irradiation could protect the skin from the photo damage. Oral resveratrol was also able to reduce the skin scaling, erythema, cutaneous edema, and leukocyte infiltration. It also improved the hyperplasia of the epidermal skin layer induced by the UVB irradiation.

CONCLUSION

Oral administration of resveratrol could influence the cutaneous response and provide photoprotection against UVB-induced hyperplasia. Therefore, resveratrol has the potential as a natural alternative for photoprotection.

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CONFLICT OF INTEREST

The author declares no conflict of interest in the data/research.

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