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ORIGINAL PAPERS

The Role of Vitamin A on the Histology of Skin of Adult Rats After Exposure to UVB

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Abstract

Background: long-term exposure of skin to sun (UV light) may produce different dermatological changes. The aim of this experiment is to explore the protective effects of oral vitamin A on skin subjected to UVB.
Methods: twenty rats were separated into: group 1 (without UVB exposure), group 2 (exposed to single daily increasing dose of UVB for one week), group 3 (exposed to UVB with oral daily administration of vit A 10000 IU for one week), group 4 (received vit A for one week). The daily doses of UVB were respectively 0.24, 0.36, 0.48, 0.6, 0.72, 0.84 and 0.96 J/cm^2. Skin samples were stained with hematoxylin-eosin and Masson's trichrome stains, in addition to Melan-A stain for melanocytes.
Results: histopathological results in skin of group 2 demonstrated loss of normal architecture with increase in thickness of epidermis, hyperkeratosis and parakeratosis, moreover, skin sections detected increased number of inflammatory cells with damaged hair follicles. The basal layer shows an increase in mitotic division and necrosis, besides, epidermal edema and vascular congestion. Furthermore, collagen fibers were degraded. Immunohistochemical reaction revealed intense positive expression of Melan-A with increased proliferation and activity of melanocytes, while sections of groups 1 and 4 show normal healthy skin and negative Melan-A expression. In contrast, skin of group 3 reveals mild hyperkeratosis with normal keratin layer, in addition, the infiltration of inflammatory cells was dropped and hair follicles were preserved. Collagen bundles were slightly degraded with normal arrangement. Immunohistochemical results of this group show mild positive expression of Melan A.
Conclusion: oral administration of vitamin A decreases the toxic effect of UVB radiation on skin and reduces its induced pigmentation.

Keywords: UVB, skin, melanocytes, vitamin A, Melan-A.

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INTRODUCTION

The skin is an important organ that covers the whole body as a protective shield from harmful factors like light, heat, injury, and microbes. Also, it regulates the body temperature, as well as it allows a sense of warmth, cold and touch[1].

There are several factors affecting the skin, these include: intrinsic factors (e.g. genetics, cellular metabolism, and hormones) and extrinsic factors (e.g. pollution, ionizing radiation, UV light, chemicals, and toxins). Exposure to sun light for longed period is associated with aging changes like rough as well as dry skin, dark patches and wrinkles[2]. Long-term exposure of skin to sun may produce different photoaging changes of the skin[3].

UV light is categorized as UVA, UVB, and UVC, depending on its electro-physical characteristics, the wavelength of UVC is (100–280 nm), whereas of UVB is (280–320 nm), and that of UVA is (320–400 nm)[4]. Ultraviolet radiation is an electro-magnetic spectrum found between visual light and X-rays. The UV radiation that reaches the earth is made of 90% UVA and 10% UVB[5].

UVA light infiltrates deeply into the dermis which results in vascular destruction, necrosis of endothelium, and collagen fibers degradation[6]. UVB is riskier on the skin than UVA as it has a greater chance of damaging different tissues[7]. UVB light is completely absorbed in the epidermis which may lead to increase cytokines production and neuroactive and vasoactive mediators which may cause inflammation, photoaging, sunburn, hyperpigmentation and cancer of skin[8-11].

Avoiding long-term exposure to sunlight is essential to protect skin from UV-related damage[12]. The hairless mice were considered as a photoaging models during the last decades[13].

The microscopical investigation of healthy skin shows oval or fusiform dendritic mature melanocytes that are smaller in size than keratinocytes. The cytoplasm of these cells contains special organelles bounded to their cell membrane called melanosomes which are producing melanin[14]. Melanocytes are located in the stratum basali of epidermis, every melanocyte is related to (30-40) keratinocytes and this relationship is referred to as epidermal melanin units[15].

Vitamin A (retinoic acid) has an influence on the differentiation and proliferation of human keratinizing epithelium and hence it has a beneficial effect on different dermatological diseases such as psoriasis, genodermatosis and acne[16]. Etretinate (a second-generation retinoid) had been found to be beneficial in treating psoriasis when used in combination with psoralen ultraviolet A (PUVA)[17].

The aim of this work is to explore the protective effects of using vitamin A on skin subjected to high doses of UVB.

MATERIALS AND METHODS

All experiments were performed in the animal breading house of College of Veterinary Medicine/ University of Mosul.

Adult rats used in this experiment were obtained from post graduate laboratory of College of Veterinary Medicine, they were saved under standard conditions, normal diet and 24 hrs. light-dark cycles. Twenty animals were randomly divided into four equal groups, including: group 1 (control group without UVB exposure), group 2 (exposed to UVB light as suberythemal single daily increasing dose for 1 week), group 3 (exposed to UVB light as suberythemic single daily increasing dose for 1 week with the administration of oral dose of vitamin A), group 4 (received oral dose of vitamin A for one week).

The UV source was a 311 narrow band wand lamp UVB with comb KN-4003LB. The distance between the back skin of rats and light's source was 3 cm using a plastic translucent comb of machine.

Vitamin A capsules of 10000 IU were from 21st century Drugs Company. It was mixed with olive oil and given orally at a dose of 10000 IU per day through gavage syringe immediately before UVB exposure[18].

Each rat before its exposure to UVB light was anesthetized by intra-peritoneal injection of 2% Xylazine and 10% Ketamine, and shaved to remove the back hair. UVB radiation protocol was carried out by giving the animal a daily progressive increasing dose, which is calculated according to the following formula[19]:

Time of radiation (min.) = dose (J/cm^2 *1000/ intensity (mW/cm^2)*60

The daily doses of UVB were 0.24 J/cm^2 in first day, 0.36 J/cm^2 in second day, 0.48 J/cm^2 in third day, 0.6 J/cm^2 in fourth day, 0.72 J/cm^2 in fifth day, 0.84 J/cm^2 in sixth day and 0.96 J/cm^2 in seventh day.

The measurement of erythema was estimated by observing the red patches of skin in the dorsal area of rats 24 hours after radiation[20].

Twenty-four hours following the last radiation, rats were sacrificed by cervical dislocation. Two $cm^3$of skin tissue of rat's back was extracted, harvested and fixed in formalin. The specimens were then processed, paraffinized and sectioned for histological stain. Skin samples were stained with hematoxylin-eosin stain to observe epidermal and dermal cells[21], and Masson trichrome stain to detect collagen fibers[22].

For immunohistochemical staining, the sections of all groups were stained via the method of "streptavidin biotin alkaline-phosphate". The 1ry antibodies "mouse monoclonal Melan-A and A103 clone" were from (Novocastra Laboratories Ltd., United Kingdom)[23].

All slides were evaluated using the light microscope and the photos were taken by the digital camera.

RESULTS

In this study the histopathological observations of skin layers in groups 1 and 4, show normal healthy skin with normal architecture. There were no changes noticed in the epidermis, the stratum corneum and keratin layers observed normal thickness, there were no histological changes in stratum granulosum and stratum spinosum, the basal layer show no mitotic changes. Moreover, there were no infiltration of polymorphonuclear leukocytes and inflammatory cells, similarly the dermis as well as the hair follicles were normal and collagen fibers show no degradation (Figures 1-4).

The result of the immunohistochemical stain of group 1 and group 4 showing a negative expression to

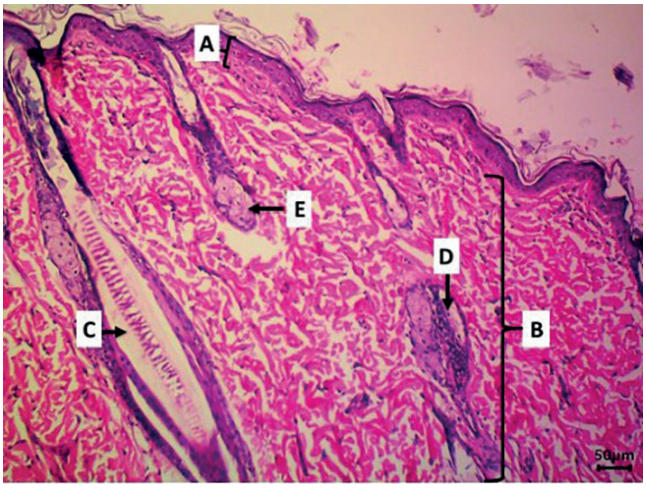

Figure 1: Hematoxylin-eosin-stained skin tissue slide of control group showing, normal histological structure. Epidermis (A), dermis (B), hair follicle (C), sweat gland (D) and sebaceous gland (E). 100X

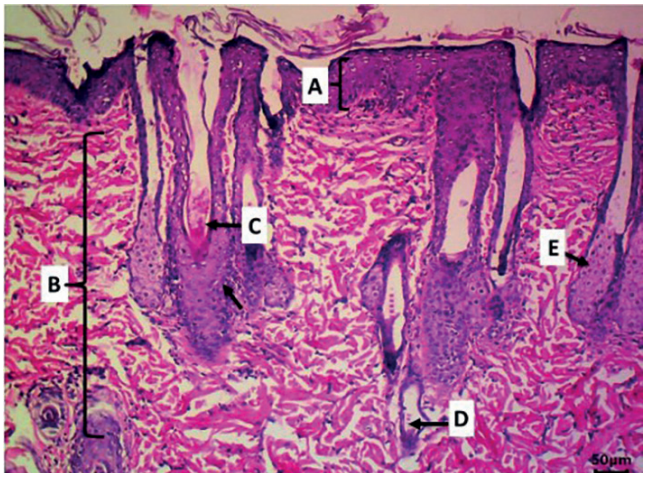

Figure 2: Hematoxylin-eosin stained skin tissue slide of group 4 showing normal histological structure. Epidermis (A), dermis (B), hair follicle (C), sweat gland (D) and sebaceous gland (E). 100X

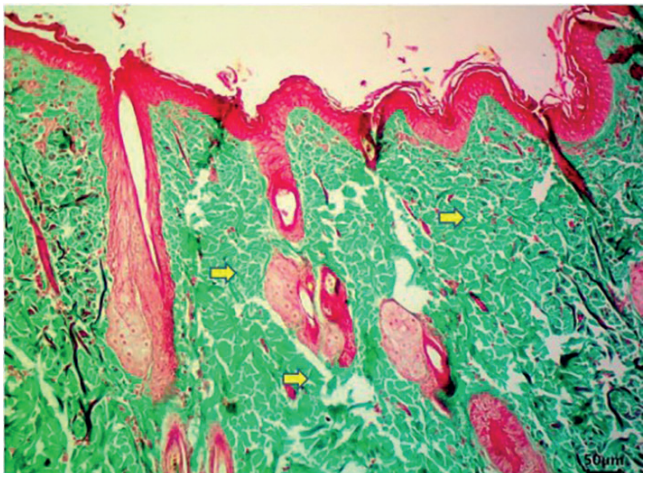

Figure 3: Skin tissue slide of control group showing, normal collagen fibers in the dermis (arrows). Masson Trichrome stain, 100X

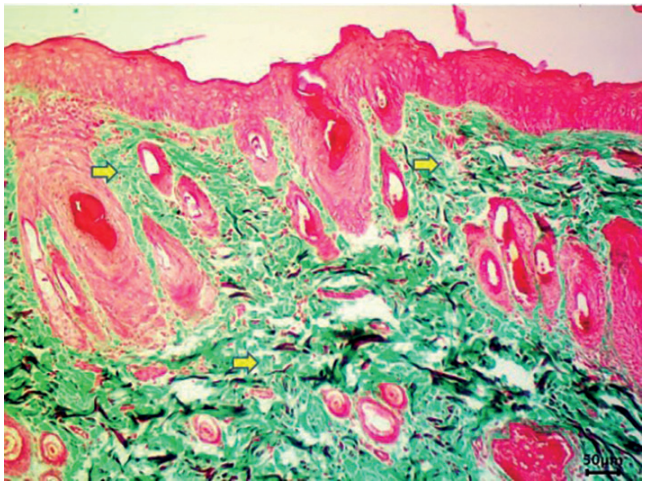

Figure 4: Skin tissue slide of group 4 showing, normal collagen fibers in the dermis (arrows). Masson Trichrome stain, 100X

Melan-A with normal shape and activity of melanocytes (Figures 5, 6).

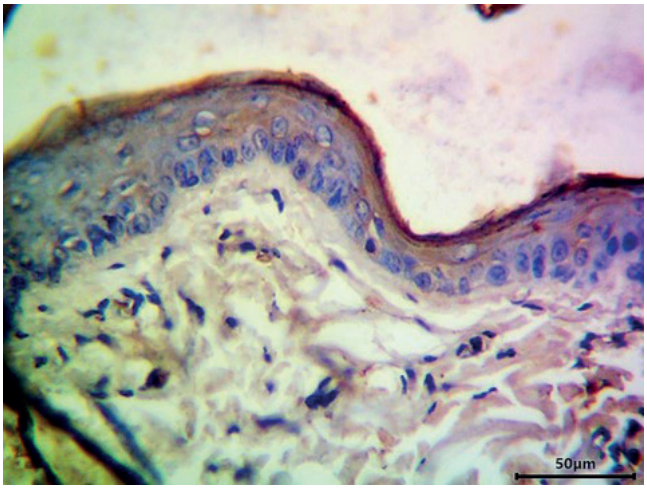

Figure 5: Immunohistochemical expression for Malan-A in the rat skin of control group, showing negative expression. Hematoxylin stain. 400X

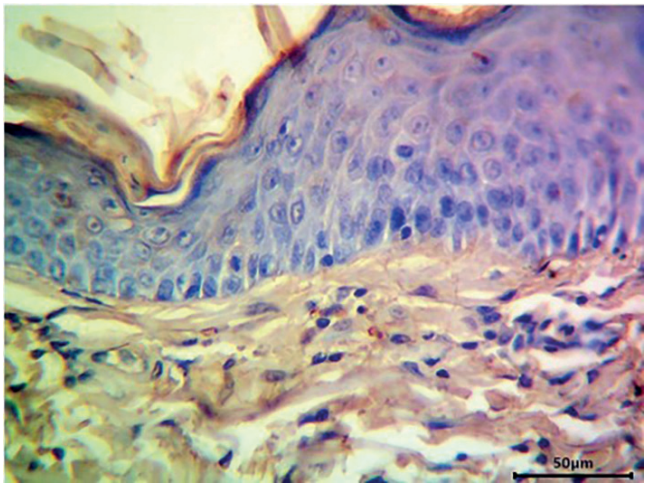

Figure 6: Immunohistochemical expression for Malan-A in the rat skin of group 4, showing negative expression. Hematoxylin stain. 400X

In comparison, the histopathological results in skin of group 2 demonstrated loss of normal architecture with obvious increase in thickness of epidermis, hyperkeratosis and parakeratosis with thick stratum corneum, granulosum and spinosum layers. Moreover, skin section revealed an increased number of polymorphonuclear leukocytes and lymphocytes inflammatory cells with damaged hair follicles (Figure 7). The basal layer shows abnormal activity including an increase in mitotic division, vacuolar degeneration and necrosis, besides, epidermal edema (spongiosis) and vascular congestion (Figure 8). Furthermore, thickness of

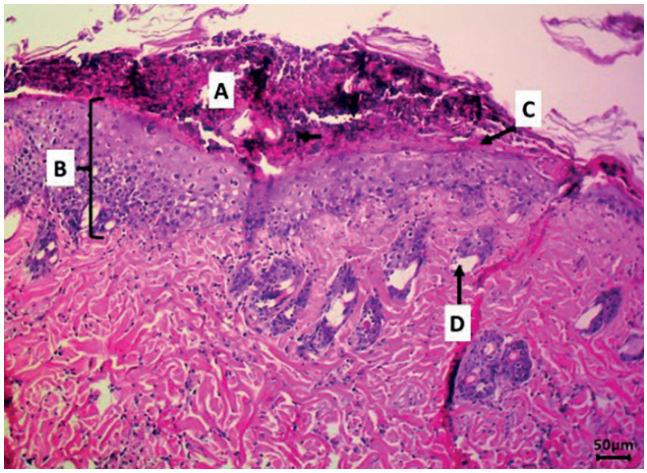

Figure 7: Hematoxylin-eosin stained skin tissue slide of group 2 showing parakeratosis (A), increased thickness of epidermis (B), hyperkeratosis (C) and damaged hair follicles (D). 100X

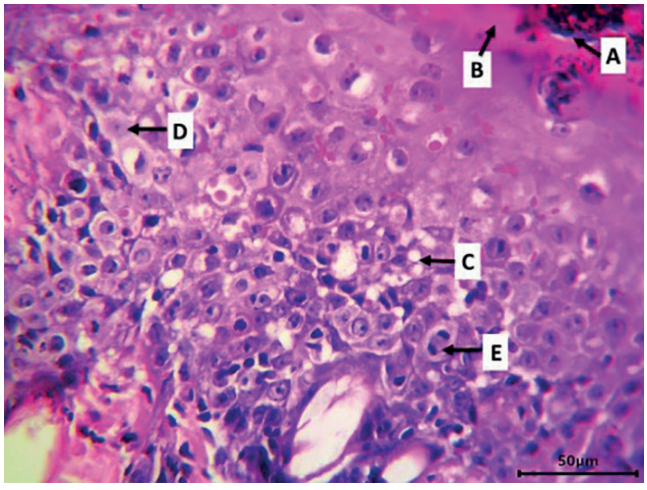

Figure 8: Hematoxylin-eosin stained skin tissue slide of group 2 showing parakeratosis (A), hyperkeratosis (B), vacuolar degeneration (C), necrosis (D) and mitotic division (E) of epithelial cells in addition to epidermal edema (spongiosis) and vascular congestion. 400X

dermis was raised and collagen fibers were degraded with irregular arrangement (Figure 9).

In this group the immunohistochemical reaction showed an intense positive expression of Melan-A with increased proliferation and activity of melanocytic cells (Figure 10).

In contrast, the skin of group 3 conserves normal architecture with mild histopathalogical changes in epidermis and dermis. There was mild hyperkeratosis, mild vacuolar degeneration with normal keratin layer. In addition, the infiltration of inflammatory cells was dropped and the hair follicles were preserved (Figure 11). The collagen bundles were slightly degraded with normal arrangement (Figure 12).

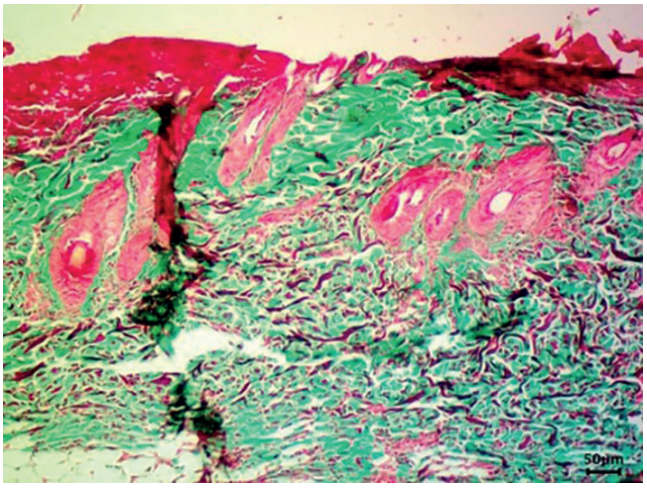

Figure 9: Skin tissue slide of group 2 showing degradation of the collagen fibers in the dermis. Masson Trichrome stain, 100X

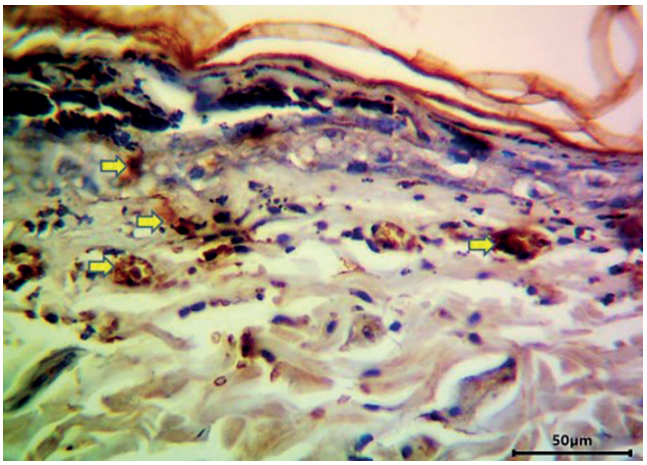

Figure 10: Immunohistochemical expression for Malan-A in the rat skin of group 2 showing intense positive reaction (arrows) in the dermal melanocytes. Hematoxylin stain. 400X

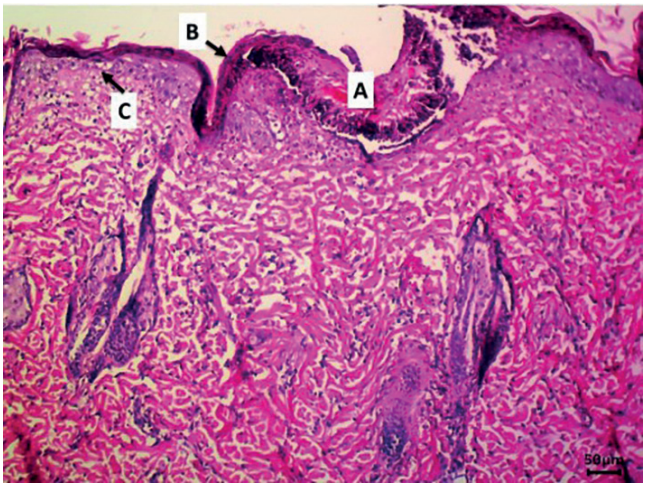

Figure 11: Hematoxylin-eosin stained skin tissue slide of group 3 showing mild parakeratosis (A) mild hyperkeratosis (B) mild vacuolar degeneration of epithelial cells (C) and presence of the hair follicle. 100X

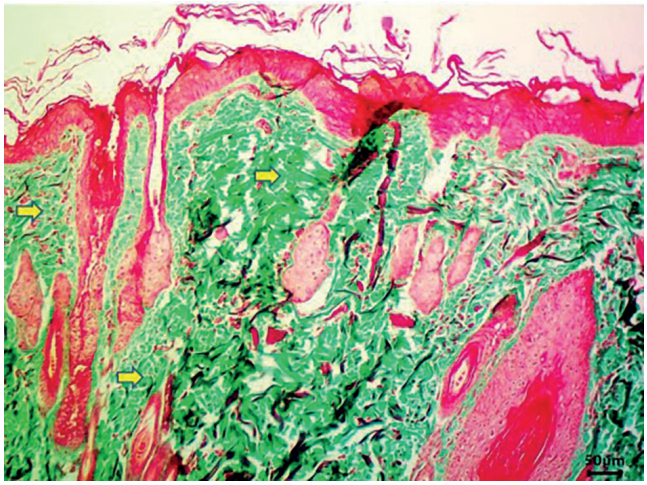

Figure 12: Skin tissue slide of group 3 showing slight degradation of the collagen fibers in the dermis (arrows). Masson Trichrome stain, 100X

Immunohistochemical result of this group shows mild positive expression of Melan-A with normal proliferation and activity of melanocytes (Figure 13).

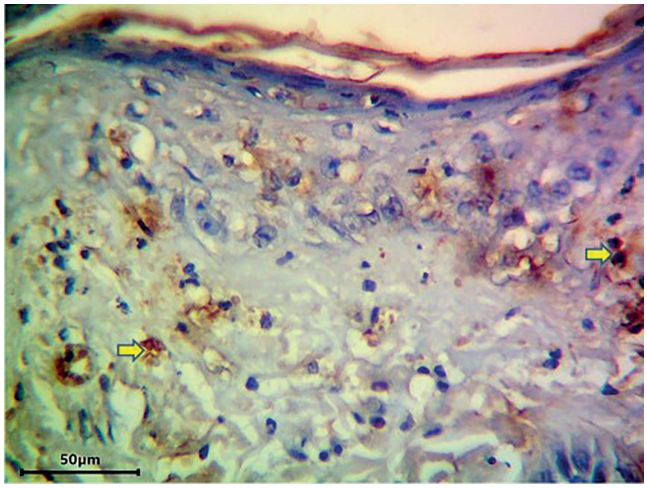

Figure 13: Immunohistochemical expression for Malan-A in group 3 showing mild to moderate positive expression (arrows) in the dermal melanocytes. Hematoxylin stain, 400X

DISCUSSION

The expanding interest concerning skin aging, cancer, care and cosmetics has increased the in vivo and in vitro studies on skin and its exposure to sun[24]. Exposure to sunlight is necessary for human being, but long-term exposure leads to various histopathological changes in skin, since sunrays contain UV light that can harm the skin[25].

In the current and previous studies[26,27] exposure to UV light and specifically UVB causes histological skin changes, there were epidermal thickness, obvious hyperkeratosis with an obvious increase in number of polymorphonuclear leukocytes and lymphocyte inflammatory cells. Furthermore, there were an increased thickness of dermis with vascular congestion and absence of hair follicles.

Different mechanisms explain these changes. Lohani and Morganti stated that, exposure to UV light will trigger the formation of free radicles within the skin where they cause biochemical changes and histological damage[28]. De Jager et al. reported that, besides the potential of elaborating ROS by the UV light, UVB is almost completely absorbed by epidermal layer and has a high energy that can stimulate inflammation and produce damage to DNA of skin cells[29]. Others illustrate the cutaneous damage by the alteration of keratinocyte proteome and subsequent degradation of proteins leading to variation of proteins' expression, thus alter the intracellular redox balance causing inflammation, reduction of cellular proliferation and apoptosis[30,31].

To prevent or reduce such damage, several studies regarding skin repair using different methods and ingredients were accomplished. Some of these ingredients were applied locally while others were given orally. Of these ingredients used we have plants like (sea buckthorn, Buddleja cordata, Gayo coffee)[27,32,33] and vitamins like E, C and A[34,35].

The photoprotective effect of vit A (retinol) and its metabolites (retinoids) is considered to be a field for researches, since this vitamin is essential for maintaining healthy skin and hair, it influences the growth as well as differentiation of keratinocytes and regulates keratins production[36,37].

In earlier studies, pre or post UV irradiation the vit A were applied locally to the exposed skin in order to determine its beneficial effect, and no data or literature is available discussing the effect of oral vit A.

In the present study, we used daily oral vit A at a dose of 10000 IU with the exposure to UVB light. The skin reveals normal architecture with mild histopathalogical changes in epidermal and dermal layer, there were mild hyperkeratosis with normal keratin layer. In addition, the infiltration of inflammatory cells was markedly dropped. Moreover, mild congestion of dermal blood vessels, as well as hair follicles were seen. It is indicated that exposure to UVB light with concomitant administration of oral form of vit A will protect the skin from the toxic effect of UVB light.

Similar protective effect was reported by many authors who used topical form of vit A in their studies. Sorg et al. mentioned that vit A acts as an antioxidant that scavenge free radicals produced by UV light, likewise it absorbs UV light in the exposed region of the body thus minimizing the adverse effects following sun exposure[38]. Antille et al. found that epidermal retinyl esters (vit A) that can be accumulated in sufficient amount in the skin by local application can save the DNA from UV damage[39]. The studies of Tran et al., and Sorg et al. indicate that UV rays exposure decreases the concentration of retinol as well as retinyl ester in animal skin and the local delivery of vit A will partially neutralize this deficiency and conserve the skin[40,41].

In this study the collagen fibers were degraded and irregularly arranged following UVB radiation. Lestari et al. found that UVB exposure will cause a reduction in the collagen density and thickness in the skin of rats which supports our result, and they explain this reduction by the deceased synthesis of collagen[27]. Varani et al. mentioned that local vit A application will trigger collagen production and will stabilize the collagen structure in the skin[42], thus in the current experiment the use of oral vit. A after UVB exposure will retain the normal synthesis and structure of collagen.

In addition to the improving effect on skin histology, vit A also affects skin pigmentation. This work found a rising in the expression of melan- A marker with increased proliferation and activity of melanocytes post irradiation to UVB light, which means a hyperpigmentation state. On the contrary, receiving oral vit A with UVB light will show a less expression with normal proliferation and activity of the cells, indicating preservation of pigmentation by the vitamin. This finding comes in consistence with Lee et al. and Dhaliwal et al. who declared that UVB induces hyperpigmentation, whereas, topical retinol can reduce it[43,44]. The increment in pigmentation following UV exposure is owing to the elevation in the count of multinucleated melanocytic cells and the activation of melanin pigment production with subsequent accumulation of melanosomes in the epidermis[45,46], an adverse effect which can be counteracted by topical retinol therapy[44].

Probably oral vit A will have the same mechanisms for protecting the skin and reducing hyperpigmentation as topical one on exposure to UV light, but in our opinion oral formulation is easier to use, more available and cheaper than topical application[47-49].

CONCLUSION

Oral administration of vitamin A has an ameliorative effect on skin damage, it minimizes the toxic effect of UVB radiation on skin and reduces its induced pigmentation.

In future it is recommended to study the ameliorative effect of oral form of other chemicals and vitamins (like E, C, and D) on skin.

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Conflict of interest
All authors declare that there are no conflicts of interest concerning the publication and/or funding of this manuscript.

Ethics Statements
The research was approved by College of Medicine Ethics Committee/ University of Mosul.

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