International Journal of Dermatology

Review

# Signaling pathways targeted by curcumin in acute and chronic injury: burns and photo-damaged skin

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## Abstract

Phosphorylase kinase (PhK) is a unique enzyme in which the spatial arrangements of the specificity determinants can be manipulated to allow the enzyme to recognize substrates of different specificities. In this way, PhK is capable of transferring high energy phosphate bonds from ATP to serine/threonine and tyrosine moieties in serine/threonine kinases and tyrosine kinases, thus playing a key role in the activation of multiple signaling pathways. Phosphorylase kinase is released within five minutes following injury and is responsible for activating inflammatory pathways in injury-activated scarring following burns. In photo-damaged skin, PhK plays an important role in promoting photocarcinogenesis through activation of NF-kB-dependent signaling pathways with inhibition of apoptosis of photo-damaged cells, thus promoting the survival of precancerous cells and allowing for subsequent tumor transformation. Curcumin, the active ingredient in the spice, turmeric, is a selective and non-competitive PhK inhibitor. By inhibition of PhK, curcumin targets multiple PhK-dependent pathways, with salutary effects on a number of skin diseases induced by injury. In this paper, we show that curcumin gel produces rapid healing of burns, with little or no residual scarring. Curcumin gel is also beneficial in the repair of photo-damaged skin, including pigmentary changes, solar elastosis, thinning of the skin with telangiectasia (actinic poikiloderma), and premalignant lesions such as actinic keratoses, dysplastic nevi, and advanced solar lentigines, but the repair process takes many months.

## Introduction

Injury to the skin triggers a cascade of injury-induced inflammatory and repair processes. Acute injuries such as burns and scalds frequently result in undesirable consequences, such as blistering and bullae formation, swelling, and erythema, inflicting considerable pain to the sufferer, and resulting in loss of function. Sunlight may also cause acute sunburns, resulting in pain, erythema, and blistering. Burns from ultraviolet light injury are due mainly to the ultraviolet B spectrum (290–320 nm wavelength).

Burns and scalds are caused by heat injury to the cellular proteins, with resultant coagulative necrosis of the cells, and damage to cellular proteins both within the cytoplasm and nucleus. Damage to the DNA in the nucleus sets up the well-known DNA damage response (DDR) in an attempt to repair the DNA. However, the accompanying inhibition of cell proliferation, i.e. cell cycle arrest, associated with the DDR impairs the ability of the cells to regenerate new cells, thus slowing down the repair process. Furthermore, the inflammatory process in burns and scalds induces cytokines, such as TGFβ1, which results in hypertrophic scar formation, which is commonly observed with second- and third-degree burns and scalds. The formation of hypertrophic scars involves the conversion of fibroblasts to myofibroblasts, which is induced by secretion of excessive TGFβ.[1–4]

The damaging wavelengths in sunlight are usually attributed to wavelengths in the ultraviolet range, i.e. ultraviolet B or UVB (290–320 nm wavelength), and ultraviolet A or UVA (320–400 nm wavelength). The ultraviolet C component of solar radiation (200–290 nm), which is filtered off by clouds, humidity, dust particles, and the ozone layer, was previously believed not to be a significant factor on planet Earth. However, because of the current depletion of the ozone layer, UVC may play an increasing role in photocarcinogenesis. Although UVB wavelengths are more prone to cause sunburn, current evidence suggests that UVA radiation, which makes up 95% of the solar ultraviolet light reaching the earth,[5] may be the more damaging of the two with regard to photocarcinogenesis and photoaging. Additionally, other wavelengths, such as infrared rays that produce heat, may

also contribute to the injury observed in acute sunburns and chronic dermal injury.[6,7]

Radiation in the UVB range is less penetrating than wavelengths in the UVA range. Thus, UVB radiation exerts its effects maximally in the upper half of the epidermis, with tapering effects on the basal cell layer, papillary, and upper reticular dermis.[8] Consequently, UVB may be more important in the induction of squamous cell carcinomas from epidermal keratinocytes, as these cells are situated more superficially than basal cells and melanocytes. On the other hand, UVA, which penetrates deep into the dermis with tapering effects down to the subcutaneous tissue, may contribute more significantly to the induction of basal cell carcinomas and malignant melanomas,[9,10] as well as to the induction of dermal changes of photoaging, such as wrinkling and loss of elasticity associated with solar elastosis. Clothing and sunscreens that block UVB may not completely block UVA. Consequently, these agents should not be totally relied upon for prevention of photodamaged skin.[11–13]

Point mutations and mutagenic cyclobutane pyrimidine dimmers (CPDs) have been associated with both UVA and UVB exposure.[14–16] However, the CPDs produced by UVB tend to be pyrimidine dimers containing thymine–cytosine, cytosine–thymine, and cytosine–cytosine, which are easily removed and produce limited injury to the DNA. On the other hand, the CPDs produced by UVA tend to be predominantly thymine–thymine pyrimidine dimers, which are difficult to remove and tend to produce damage to large segments of the DNA. The damage induced by the large double-stranded DNA breaks, which induce the DNA response pathways, are difficult to repair[17] and frequently result in errors of replication that cause cells to transform into their malignant counterparts.[17,18] In addition, it has been observed that the bystander effect, which results in tissue damage outside the areas exposed, was only observed with UVA radiation but not with UVB.[19]

Because sunscreens have been shown to be somewhat ineffective in the prevention of photocarcinogenesis,[11–13] attention has been focused on certain botanicals, in particular curcumin for the treatment of photoaging skin and prevention of photocarcinogenesis.[20–22] Curcumin, diferuloylmethane, is an active ingredient in the spice, turmeric. The effectiveness of curcumin administered orally is hindered by its poor bioavailability due to the fact that the unconjugated curcumin molecule, which is hydrophobic, is poorly absorbed when taken orally, with poor bioavailability in blood and tissues. However, the curcumin product in a topical gel base has been found to be effective in skin disease.[23] In this paper, we explore the differences and similarities between the signaling pathways in acute injury such as burns, resulting mainly in scarring, and chronic solar damage, resulting in photodamaged skin and photocarcinogenesis, pointing out the common signaling targets blocked by curcumin in its ability to repair both acute and chronic injury.

## Signaling pathways induced by acute and chronic injury

### Nuclear factor kappa B (NF-kB)-dependent signaling pathways

In acute burns and sunburns, the injury stimulus results in inflammatory processes, such as T-cell activation. The repair processes, resulting in the production of new blood vessels and fibroblastic proliferation, lead to dermal scarring (Fig. 1a). With repeated insults to the skin with chronic solar injury, damage to the epidermis results in epidermal proliferation and scaly skin, and melanocytic proliferation leading to the formation of premalignant solar lentigenes and dysplastic nevi. Additionally, with chronic solar damage, DNA injury may result in photocarcinogenesis,[23–26] with dysregulated cell cycling and malignant transformation, leading to squamous cell carcinomas, basal cell carcinomas, and malignant melanomas (lentigo maligna, superficial spreading melanomas, and nodular melanomas). The above pathways, mediated by

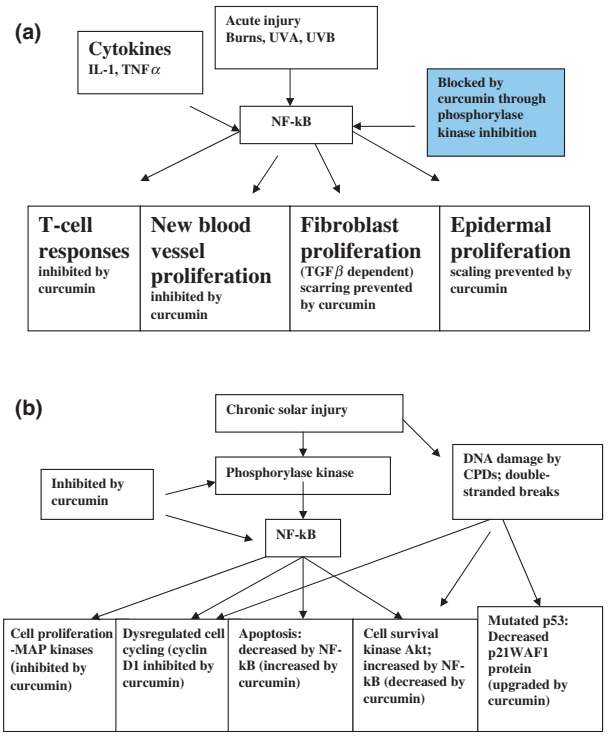


**Figure 1** (a) Signaling targets blocked by curcumin in NF-kB-dependent signaling in acute injury. (b) Signaling targets in chronic solar injury inhibited by curcumin. CPD, cyclobutane pyrimidine dimer

 

NF-kB-dependent signaling pathways and inhibited by curcumin are shown in Fig. 1a,b.

### Role of NF-kB in injury pathways

Curcumin, the active ingredient in the spice, turmeric, is an indirect but potent inhibitor of NF-kB activation.[27] Following injury, gene transcription is induced by the activation of transcription regulators. One of the major transcription regulators is NF-kB.[28,29] NF-kB belongs to a family of related protein dimers that bind to a common sequence on the DNA known as the kB site. In the unactivated state, NF-kB exists as a pair of dimers (p50 and p65) located within the cytoplasm. After activation by injury, these dimers translocate to the nucleus,[28] where they bind to the DNA and are responsible for activation of multiple genes related to cell proliferation, cell migration, neovascularization, scar tissue formation, inhibition of apoptosis, stimulation of cell survival kinase (Akt), enhancement of dysregulated cell cycling, and decreased expression of the p53 suppressor gene[30] (Fig. 2). The p53 suppressor gene encodes the p21WAF1 protein,[31] which binds to both strands of the DNA during DNA replication, thus stabilizing the DNA, and prevents dysregulated proliferation.[30] DNA damaged by UV radiation results in decreased expression of p53, resulting in decreased production of p21WAF1 protein, with decreased ability to stabilize DNA strands during replication. This results in dysregulated proliferation and malignant transformation.[26–31] Curcumin has been shown to inhibit cell cycle progression by upregulating p21WAF-1 and p53.[32]

### Activation of NF-kB and IkBα kinase

The activation of NF-kB is triggered by injurious stimuli, including ultraviolet light radiation. In the unactivated state, NF-kB exists as a pair of dimers located within the cytoplasm. Following injury, activation of NF-kB involves phosphorylation at three serine-specific sites[33] (Ser-276, Ser-529, and Ser-536). In addition, before the NF-kB can translocate to the nucleus, the inhibitory molecule, IkBα, needs to be removed by activation of the enzyme, IkBα kinase. IkBα kinase consists of three subunits (α,β subunits, and γ subunit [NEMO], which contains a zinc finger, with an ubiquitin-ligase binding site).[34] Activation of IkB kinase requires activation of sites that are both serine-specific and tyrosine-specific: Ser-171, Ser-181,[35] and Tyr-188, Tyr 199,[36] on the β subunit, as well as phosphorylation of the zinc finger[37] on the γ subunit. In ultraviolet light-induced injury, additional sites (Ser-32, Ser-36, Ser-68) are also phosphorylated.[38] The zinc finger of the γ subunit (NEMO) is selectively required for NF-kB activation by ultraviolet light radiation.[39] The removal of the inhibitory IkBα molecule through activation of its kinase, IkBα kinase, enables the activated NF-kB dimers to translocate to the nucleus, where they are responsible for activating genes such as mitogen-activated protein kinases (MAP kinases), which cause proliferation of damaged cells. Ultraviolet light injury may also activate several MAP kinase signaling pathways.[40,41] Besides activating NF-kB, UV light injury may also induce the activation of transcription factors such as AP-1 (fos and jun), resulting in activation of the p38 MAPK pathway.[42,43] Curcumin has also been shown to inhibit the c-jun N-terminal kinase (JNK) signaling.[44,45] In addition, curcumin also blocks NF-kB and ERK signaling.[46]

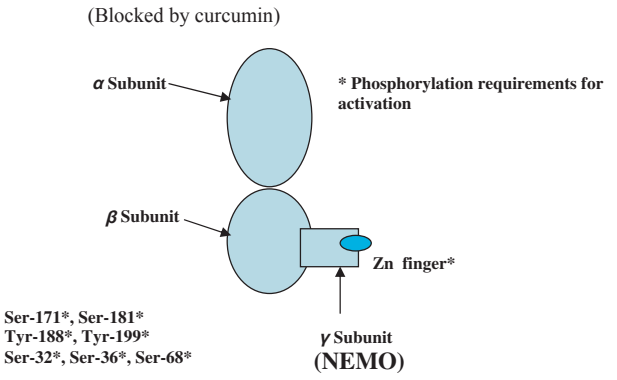


**Figure 2** Details of sites of phosphorylation involved in activation of IkB kinase. This kinase contains three subunits, α, β and γ (also called NEMO). The γ subunit (NEMO) contains a zinc finger and ubiquitin ligase site, which is involved in the DNA response pathway. Activation of IkB kinase is blocked by curcumin

NF-kB promotes carcinogenesis in skin and tissues by increasing the cell survival kinase (Akt),[47,48] a serine–threonine kinase, and other NF-kB-dependent cell survival genes including survivin, $TRAF_1$, and $TRAF_2$, which block apoptosis of photo-damaged cells. Activation of NF-kB allows DNA-damaged and potentially malignant cells to survive. By inhibiting Akt[49] and cell survival proteins, curcumin induces apoptosis[50–54] of the DNA-damaged cells, with resultant anticarcinogenic effect.

### Activation of IkB kinase

#### *Role of phosphorylase kinase in NF-kB and IkB kinase activation: blocked by curcumin*

Phosphorylase kinase is a unique kinase[22,23,55–58] in which the spatial arrangements of the specificity determinants can be manipulated to allow phosphorylase kinase to transfer high-energy phosphate bonds from ATP to substrates of different specificities, such as serine/threonine and tyrosine. This is achieved by the presence of a hinge joint between the subunits of phosphorylase kinase, which allow changes in the substrate binding site, as well as the ability to change the shape of the substrate binding

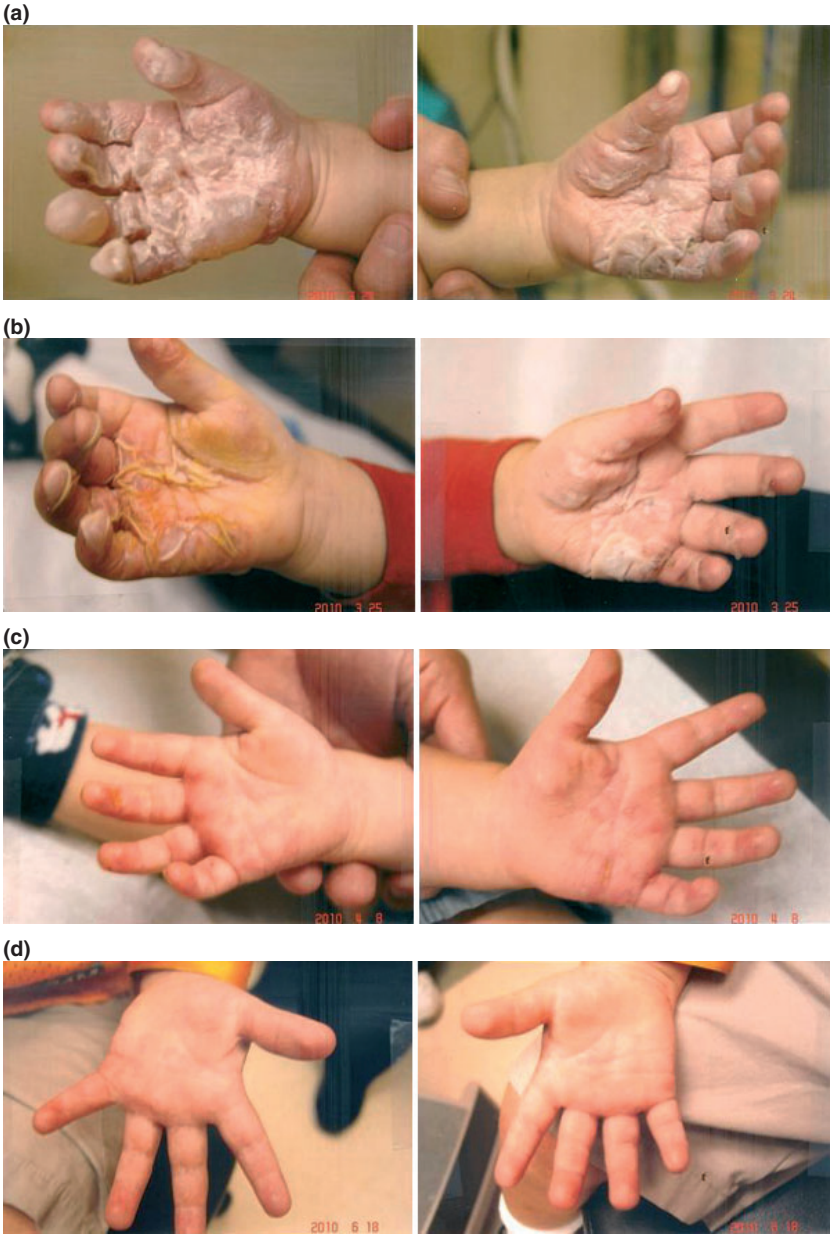


**Figure 3** (a) Two-year-old with at least second-degree burns on both hands after falling into a campfire. He was seen 4 d later and treated with silvadene cream. (b) Improvement was seen 24 h later after hourly application of curcumin gel. The patient was also put on oral prednisone for 2 weeks. (c) Rapid healing with curcumin gel treatment (frequent applications) when seen 2 weeks later. Oral corticosteroid therapy had been stopped by his parents by this time. (d) The same patient with burns treated by frequent applications of curcumin gel, showing complete healing without erythema or scarring when seen 2 months later

site by binding either to $Mg^{2+}$ or $Mn^{2+}$ ions.[57,58] Phosphorylation of multiple serine-specific sites (Ser276, Ser529, and Ser536) on the NF-kB molecule is necessary for the initial partial activation of NF-kB.[34] Additionally, phosphorylation of multiple serine-specific (Ser171, Ser181), and tyrosine-specific (Tyr188, Tyr198) sites on the IkBα kinase molecule is necessary for the removal of the inhibitory molecule (IkBα),[34–39] in order that the activated NF-kB may translocate to the nucleus to bind to the DNA for gene transcription. The multiple phosphorylations of differing moieties such as serine–threonine and tyrosine may thus be achieved through the activity of

 

phosphorylase kinase alone. In addition, the use of one enzyme ensures that the phosphorylation reactions are synchronized. Activation of NF-kB is associated with transcription of multiple genes related to inflammation, cell proliferation, scarring, and malignant transformation. The effects of phosphorylase kinase activation are therefore responsible for much of the aftermath of injury-triggered disease. The utilization of a single enzyme (PhK) for phosphorylation of multiple serine/threonine and tyrosine-specific sites has the advantage for synchronization of phosphorylation of multiple sites of different specificities,[23,55–60] required for the activation of NF-kB and its inhibitor protein, IkB kinase. It is possible that phosphorylase kinase may also be involved in inhibition

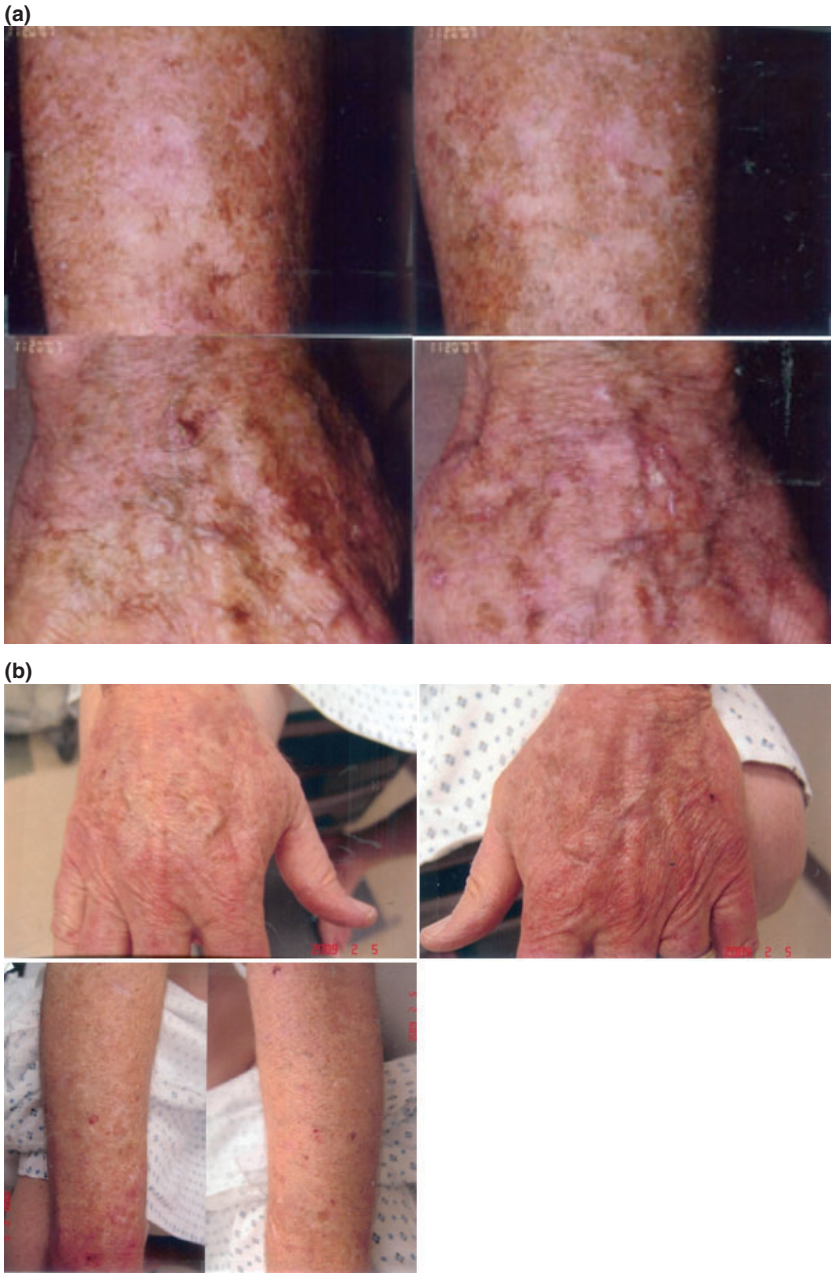


**Figure 4** (a) Photo-damaged skin with multiple confluent solar lentigenes and actinic keratoses on the dorsum of both hands and forearms before curcumin gel treatment. (b) Improvement in the photo-damaged skin over the dorsum of both hands and extensor aspects of both forearms after 15 months of curcumin gel treatment

 

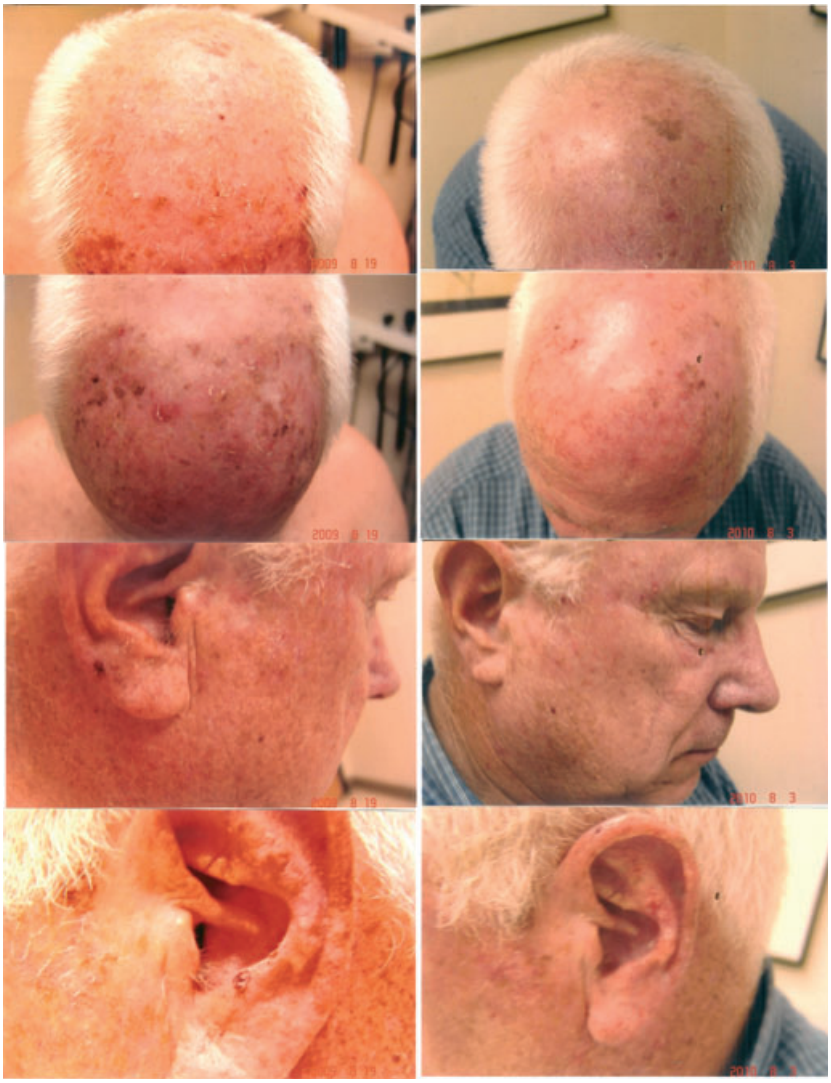

**Figure 5** Severely photo-damaged skin before (left panels) and 12 months following application of extra-strength curcumin gel (right panels). Note improvement in texture, solar lentigenes, actinic keratoses of large sheets of skin following treatment with curcumin gel (right panels)

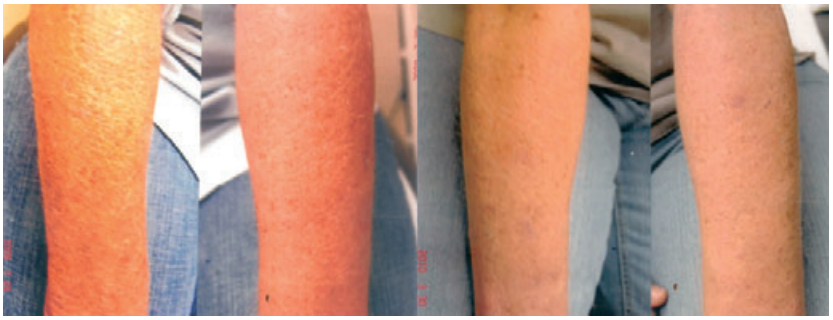

**Figure 6** Photo-damaged skin with severe solar elastoses before curcumin gel treatment (left panel). Note improvement in solar elastoses, with increased smoothness of the skin 8 months after curcumin gel therapy (right panel)

 

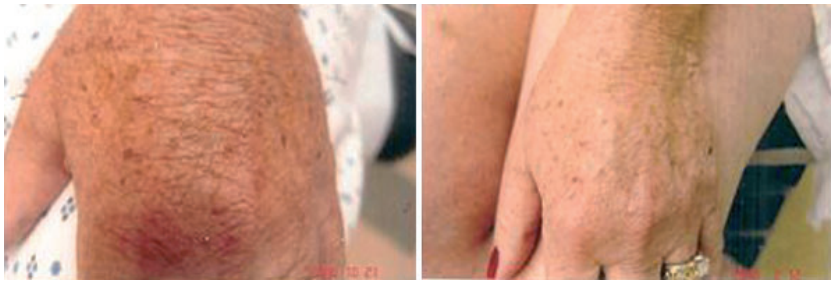

**Figure 7** Photo-damaged skin with severe wrinkling and solar elastosis before curcumin gel treatment (left panel). Note improvement in wrinkling and solar elastosis after 16 months with curcumin gel and sunscreen (right panel)

of cyclin D1 by curcumin,[20,61] leading to enhancement of its anti-carcinogenic properties.[62,63]

Curcumin, the principal ingredient in the spice, turmeric, is a specific and non-competitive inhibitor of phosphorylase kinase.[60] Its clinical use in a wide range of different skin diseases is achieved through its inhibitory effect on phosphorylase kinase.[22,23,60] It, thus, appears that curcumin, through PhK inhibition, may function as an indirect inhibitor of NF-kB activation and NF-kB-dependent injury pathways kinase.[22,23] This includes blockade of cell proliferation by inhibition of MAP kinases (which are made of both serine/threonine kinases [MAP kinase, kinase kinase, and MAP kinase kinase] and tyrosine kinase [MAP kinase]). Curcumin also induces apoptosis by blockade of Akt (a serine/threonine cell survival kinase).[47–49] This removes potentially malignant cells from the damaged tissue. Apoptosis of damaged cells by curcumin[50–54] is necessary to allow the space for new cells to be formed. In photodamaged skin, the formation of new cells replaces the damaged cells, thus allowing slow repair of the damaged tissue.

*Use of curcumin gel in the repair of burns and photo-damaged skin*

In acute burns, the removal of damaged cells by apoptosis allows room for more rapid healing by replacement of the damaged cells with new healthy cells. In addition, blockade of the NF-kB-dependent signaling prevents overgrowth of excessive scar tissue, which usually accompanies severe burns. With curcumin gel, the burns are observed to heal rapidly with no scarring and apparent perfect regeneration (Fig. 3).

Similarly, the removal of damaged cells in chronically solar-damaged skin by apoptosis prevents the DNA-damaged cells from surviving to develop into precancerous and cancer cells. The replacement of the damaged cells by new healthy cells allows the skin to repair photodamaged areas (Fig. 4). This modality also allows for the successful repair of large areas of photodamaged skin without surgical

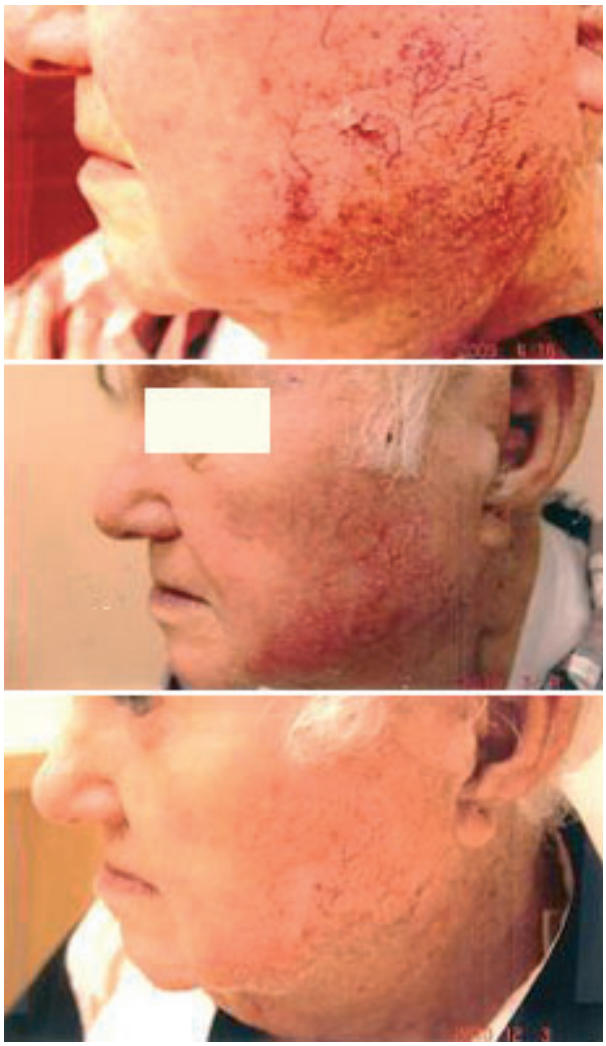

**Figure 8** Severely photo-damaged skin with marked thinning and telangiectasia (actinic poikiloderma) before the use of curcumin gel (top panel). Improvement is observed with curcumin gel applied twice daily after 3 months (middle panel), with greater improvement 9 months after curcumin gel therapy (bottom panel)

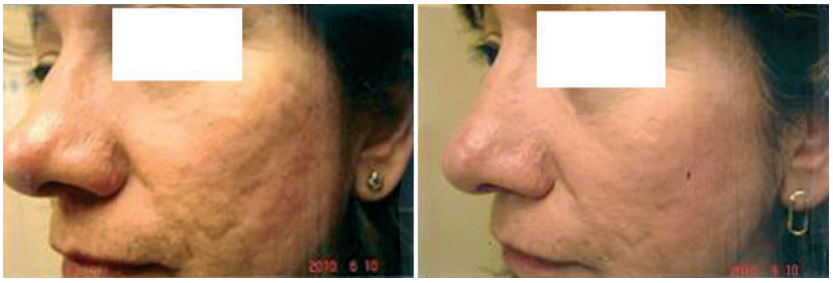

**Figure 9** Melasma, i.e. hyperpigmentation in sun-exposed distribution of cheeks and face (upper panel) induced by cytokine-induced photosensitivity associated with underlying lactose intolerance is improved (lower panel) with a lactose free diet, topical curcumin during the day, and more sunscreen on the dark areas than over the light areas

intervention (Fig. 5). The obvious advantage of removal of precancerous cells produced by chronic solar damage by curcumin-induced apoptosis allows for potential treatment of precancerous lesions, including actinic keratoses and solar lentigenes, by non-surgical methods (Figs. 4 and 5).

Furthermore, curcumin gel may also be useful in the repair of many of the features found in chronic solar injury (photodamaged skin), including improvement in texture and solar elastosis (Figs. 6 and 7). It has also been observed that application of curcumin gel results in improvement in actinic poikiloderma (thinning of the skin and telangiectasia; Fig. 8). Furthermore, application of curcumin gel over the entire face, with application of sunscreen over the areas of melasma, has been observed to result in improvement of the areas of hyperpigmentation (Fig. 9).

In patients with dysplastic nevi and advanced solar lentigenes, the use of a good camera (Sony 8 megapixels digital camera with Leica lens) capable of taking close-up shots may be used to reveal erythema (Figs. 10a, 11a, and 12a) due to the presence of inflammatory response directed against premalignant cells within the dysplastic nevi/advanced solar lentigenes. Resolution of the erythema within six months (Figs. 10b, 11b, and 12b) was observed after curcumin gel was applied twice daily for six months.

In a patient who elected not to be treated with curcumin gel, an irregular nevus monitored by sequential photography was observed to worsen to a full-blown clinically dysplastic nevus over five months of observation (Fig. 13a,b). The dysplastic nevus was excised, and the pathology (Fig. 13c) showed the presence of a lentiginous compound nevus, with moderate atypical melanocytic hyperplasia, with clear margins.

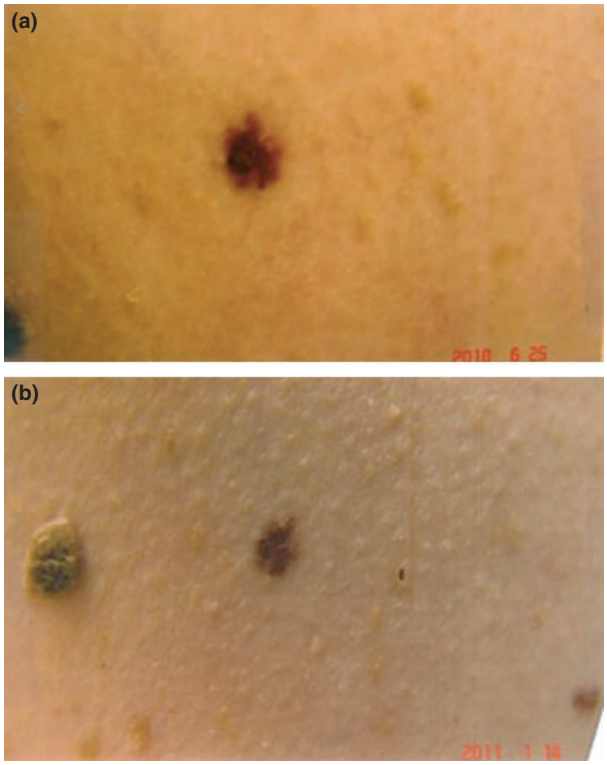


**Figure 10** (a) Dysplastic nevus showing irregular outline with irregular pigmentation within the nevus. Note the erythema due to dilated blood vessels associated with an inflammatory response directed against the premalignant cells. (b) Note resolution of the erythema and improvement in the irregularity of the nevus as well as resolution of the hyperpigmented areas within the nevus following 6 months of therapy with curcumin gel applied twice daily

## Discussion and summary

The mechanism of ultraviolet-induced photoaging has been the intense interest of many investigators over the last two decades.[64–69] Although UVB-induced free radical formation[64,65] has been initially thought to be important in photoaging and photocarcinogenesis, it is currently believed that photocarcinogenesis originating from mutagenic bipyrimidine photo-products rather than oxidative lesions are the main type of DNA damage involved in

 

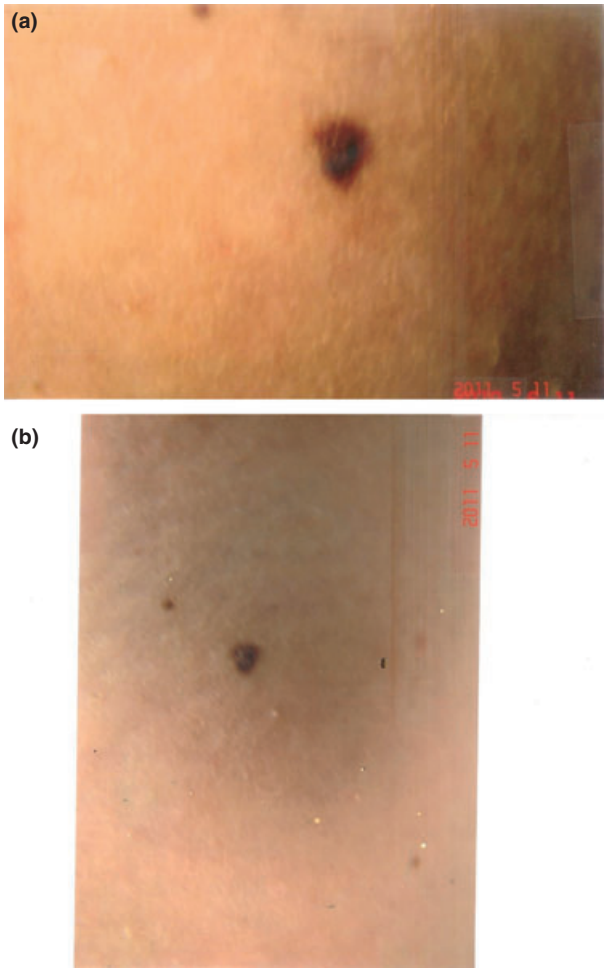


**Figure 11** (a) Dysplastic nevi with irregularity in shape and pigmentation showing erythema from an inflammatory response directed against the precancerous cells. Photographed prior to curcumin gel treatment. (b) Note resolution of erythema and improvement of pigmentation and irregularity after 6 months of curcumin gel applied twice daily

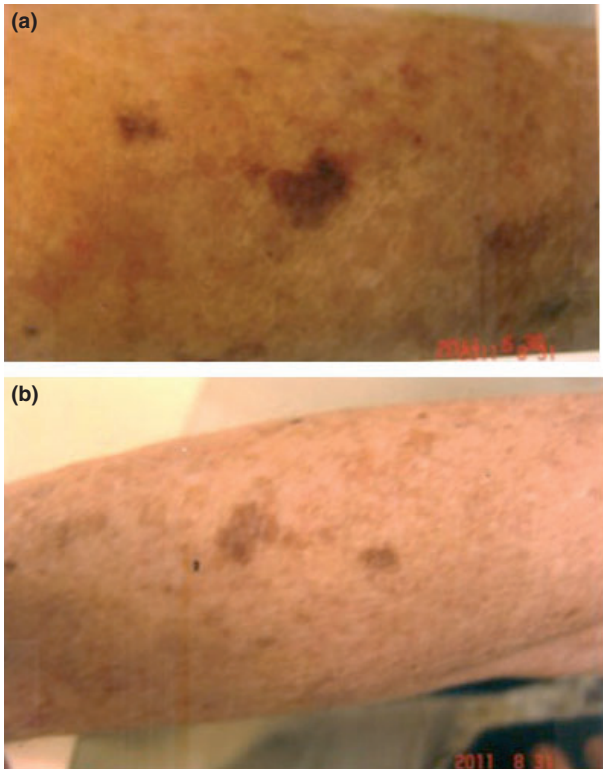


**Figure 12** (a) The forearm of a patient with severely photo-damaged skin with multiple solar lentigenes. The central lesion, which may represent early prelentigo maligna, shows irregularity in shape and pigmentation, demonstrating erythema. (b) Note improvement in erythema, irregularity and pigmentation of the treated lesions after 6 months of curcumin gel applied twice daily. Also note general improvement in skin texture with the treatment

UVA-induced damage.[16–18] CPDs are prominent in DNA lesions in whole human skin exposed to UVA radiation.[15] Moreover, the UVA-induced CPDs, which were observed to form mainly at the thymine–thymine dipyrimidines, have been found to be particularly mutagenic because they cause double-stranded DNA breaks and produce damage to large segments of the DNA that are difficult to repair. When the damaged DNA in these cells involve the p53 suppressor sequence, the depletion in the p21WAF-1 protein leads to failure to bind the two strands of the DNA during replication, leading to dysregulated gene function. These functional defects include dysregulated transcription factor (AP-1/c-jun)-mediated proliferation and NF-kB-dependent ERK 1/2/p38 MAP kinase proliferation, resulting in keratotic lesions, pigmentary changes, and skin malignancies, as well as dysregulated formation of metalloproteinases in solar elastosis and photoaging skin.

Retinoids, which are considered the mainstay for the prevention and treatment of photoaging skin, are thought to function by inhibiting UV light induction of c-jun, Ap-1, and MMP.[67–70] However, retinoids have also been shown to accelerate the recovery of RAR-γ and RXR-α following UV exposure.[71] Retinoids have been observed to induce apoptosis through the RXR nuclear receptor,[72,73] and there is evidence that retinoids may induce apoptosis via the synergism induced by the binding of selected ligands to the RAR and RXR nuclear receptors.[74] It is possible that the beneficial effects of retinoids in photoaging skin may be achieved through induction of apoptosis of photo-damaged cells via the PPAR/RXR pathway.

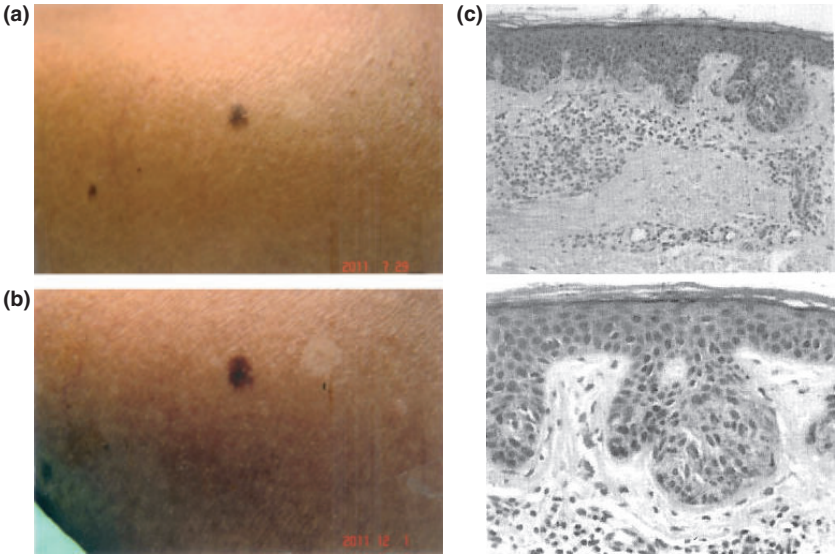


**Figure 13** (a) An irregular nevus with mild erythema at the lower pole, photographed for observation. The patient elected not to use curcumin gel. (b) The same nevus followed for 5 months, with worsening and frank clinical dysplastic change with marked erythema. Curcumin gel had not been used on this lesion. (c) Histopathology of irregular nevus in (b) with dysplastic changes and erythema, showing a compound nevus with early to moderate atypical melanocytic proliferation and inflammatory dermal infiltrate. (a, 20× magnification; c, 40× magnification.) Sections were stained with hematoxylin and eosin

The mechanism for achieving apoptosis is thought to be achieved through suppression of phosphorylation of the RXR nuclear receptors. It has been observed that when certain ligands suppress phosphorylation of the RXR receptor, this step allows for the subsequent binding of its endogenous ligand (9-cis-retinoic acid), resulting in induction of apoptosis.[73] Thus, apoptosis that is achieved via suppression of the Akt (cell survival kinase, also known as protein kinase B) may also be achieved through the PPAR/RXR pathway. Suppression Akt-induced phosphorylation inhibits the binding of PPARβ to its RXR receptor, which allows the RXR receptor to accept its endogenous ligand (9-cis-retinoic acid), with resultant induction of apoptosis. Akt is a serine/threonine kinase, activated by phosphorylase kinase and inhibited by curcumin. Inhibition of Akt results in induction of apoptosis. By killing off photodamaged cells in the dermis engaged in dysregulated activity, including increased MMP-2 production and formation of elastotic collagen (abnormal collagen that stain blue resembling elastic tissue), both the collagen and MMP content may be improved, resulting in clinical improvement of solar elastosis.

In summary, topical curcumin is an anti-inflammatory agent with the ability to block the inflammatory response following acute and chronic skin injury by blocking NF-kB signaling pathways through inhibition of phosphorylase kinase. In acute injury such as burns, there is abrogation of the inflammatory response with inhibition of NF-kB/TGFβ signaling pathways with the use of curcumin gel, resulting in rapid healing of the burn injury without residual scarring. In chronic injury from repeated ultraviolet light damage, the photodamaged skin may be repaired by curcumin-induced apoptosis of DNA-damaged precancerous cells, allowing for a more gradual replacement of the damaged cells by new healthy, undamaged cells. We provide clinical evidence of rapid repair of burn injury without scarring following curcumin gel therapy, as well as slow improvement of photodamaged skin with actinic keratoses, solar elastoses, actinic poikiloderma (thinning of the skin with telangiectasia), dysplastic nevi, and solar lentigines with the same treatment.

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