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Review Article

Topical Curcumin: A Review of Mechanisms and uses in Dermatology

Abstract

Curcumin, the active ingredient in the spice turmeric, has been used in many Eastern countries for its known anti-inflammatory activity. Recently, analysis of multiple studies have cast doubt with regard to the efficacy of oral curcumin in several diseases. While the effectiveness of oral curcumin is hindered by its low bioavailability and poor absorption by the oral route, this is not the case for topical curcumin. In this review, we discuss the mechanisms for its anti-inflammatory and anti-apoptotic activity based on its inhibitory activity on the enzyme, phosphorylase kinase, and present evidence for its salutary effects on burns, wounds, surgical scars, photo-damaged skin and psoriasis.

Introduction

Curcumin (diferuloylmethane) is one of the ingredients found in the spice, turmeric. Turmeric has been used for centuries in many Eastern countries both as a spice and as a medicine. In recent years, extensive studies have been done on the potential medicinal value of curcumin, particularly when taken orally. The effectiveness of oral curcumin, however, is hindered by poor bioavailability because the unconjugated curcumin molecule, which is hydrophobic, is poorly absorbed by the gastrointestinal tract. Very low curcumin levels are detected in blood and tissues following curcumin ingestion [1-3]. The molecule is mainly absorbed as water-soluble curcumin glucuronate or sulfate metabolites, which are largely inactive products. In contrast, topical curcumin can be formulated to be better absorbed through the skin, particularly when the skin barrier becomes defective in the presence of skin injury and disease. Largely because of the unfavorable pharmacokinetics of oral curcumin, the extensive literature on therapeutic potential of oral curcumin in clinical trials has been disappointingly negative [4]. There have been much fewer studies with topical curcumin despite the fact that the use of topical curcumin is not hindered by issues of gastrointestinal absorption.

In this review, we will present our clinical experience with topical curcumin in several dermatologic disorders, and discuss the mechanisms that may underlie the biologic basis of how topical curcumin may potentially be useful in these conditions. We found topical curcumin to be effective in a number of conditions associated particularly with skin injury and inflammation. We believe that the most likely mechanism responsible for these results is related to the unique ability

of curcumin to inhibit the enzyme, phosphorylase kinase. In addition, topical preparations can be more easily formulated to increase penetration of the hydrophobic curcumin through the skin, unlike the problems encountered with curcumin bioavailability in the gut. Skin penetration of topical curcumin may also be enhanced in dermatologic disorders because of inflammation and loss of the normal skin barrier function. These factors make the potential therapeutic value of topical curcumin much more promising than that found so far with oral curcumin.

Anti-inflammatory Properties

Curcumin is widely known to have anti-inflammatory properties [5]. In cell cultures, it has been shown to suppress the proliferation of a wide variety of tumor cells, downregulate transcription factors (NF- κ B, AP-1), downregulate the expression of cytokines (TNF- α), cell surface adhesion molecules and cyclin D, and inhibit the activity of c-Jun N-terminal kinase, protein tyrosine kinase, and protein serine/threonine kinases [5].

How curcumin may have therapeutic benefits became better understood after discovery that curcumin is a selective inhibitor of phosphorylase kinase [6]. Phosphorylase kinase is an enzyme responsible for breaking down glycogen, eventually to form ATP, and plays an important role in phosphorylation reactions [7]. Phosphorylase kinase is released within 5 mins after injury and plays a key role in the injury pathway with significant effect on activation of inflammatory cells [7-9], wound healing and scar tissue formation [10]. Inhibition of phosphorylase kinase activity by curcumin results in modulation of the inflammatory response because of downregulation of transcription factors,

cytokines, adhesion molecules, cyclin kinases, and a variety of protein kinases.

Curcumin-Induced apoptosis

Curcumin has been reported to induce apoptosis in damaged cells [11-13]. The process may allow more rapid replacement of the injured cells by normal healthy cells [11]. This may be the mechanism for our clinical observations of improved healing of burns and sun-burns. Curcumin-induced apoptosis may also function in the improvement observed with the application of curcumin gel on sun-damaged skin. The removal of damaged premalignant cells by apoptosis allows the space for replacement by new, healthy cells without the potential of malignant transformation [11]. By blocking phosphorylation, curcumin may block the DNA Damage Repair (DDR) pathway through histone-mediated DNA repair, and as a consequence, accelerate apoptosis [11]. Curcumin-mediated apoptosis has been shown to occur through the mediation of the mitochondrial pathway [12].

The mechanism of curcumin-induced apoptosis may also be achieved by inhibition of phosphorylase kinase. Georgoussi et al., has reported that phosphorylase kinase also exhibits phosphatidylinositol kinase activity [14]. This is significant since the early participants in the DDR pathway include a family of phosphatidylinositol kinases responsible for Cell Cycle Arrest, Nucleotide Excision and Repair and DNA replication [11]. It is probable that curcumin induces apoptosis by blocking phosphorylation of the phosphatidylinositol kinases through phosphorylase kinase inhibition.

Injury Pathway and NF-KB Activation in the Inflammatory

Response: The key molecule in the tissue injury pathway (Figure 1) is a transcription activator, nuclear factor-kB, which is expressed as early as 30 mins after injury [15,16]. In the non-activated state, NF-kB exists as a pair of dimers (p50/p65) within the cytoplasm. When activated by injury, phosphorylation occurs at several serine specific sites (Ser276; Ser529, Ser536), and the dimers translocate to the nucleus,

where they bind to the kB site on the DNA, resulting in turning on over 200 genes related to inflammation, cell migration, cell cycling, and cell proliferation [7-10]. Before the dimers are able to translocate to the nucleus, the inhibitory molecule, I κ B α is removed, and the removal requires the activation of its kinase, I κ B α kinase. Activation of the I κ B α kinase requires phosphorylation of both serine (Ser171, Ser181) and tyrosine (Tyr188, Tyr199) moieties [7-10]. Phosphorylation of both Serine and Tyrosine moieties is achieved by the dual specificity kinase, phosphorylase kinase.

Phosphorylase Kinase: A Dual-Specificity Kinase/Multi-specificity Kinase: Protein kinases usually catalyze the transfer of high energy phosphate bonds to either serine/threonine or tyrosine moieties. This is because protein kinases, with the exception of phosphorylase kinase, allow only one configuration in their substrate binding site. In the case of phosphorylase kinase, however, the substrate binding site may be altered by utilizing a hinge joint between the subunits to alter the size of the substrate binding site. In addition, the substrate binding site may be made to alter its shape and swivel in one plane by binding to magnesium, or in another by binding to manganese. In this way, phosphorylase kinase is able to phosphorylate substrates of multiple specificities i.e. both serine/threonine and tyrosine. Graves [17], reported that in the phosphorylase kinase molecule, the spatial arrangement of the specificity determinants can be manipulated so that phosphorylase kinase can utilize several substrates. Yuan et al. [18], provided evidence of dual specificity of phosphorylase kinase, depending on ion binding i.e., manganese or magnesium. There is evidence that phosphorylase kinase also activates phosphatidylinositol kinase [14].

Curcumin, a Selective Phosphorylase Kinase Inhibitor: Curcumin has been shown to be a selective, non-competitive phosphorylase kinase inhibitor [6]. By inhibiting phosphorylase kinase in the injury pathway, curcumin blocks the activation of NF-kB, the transcription activator [5,19,20]. NF-kB is responsible for activating 200 genes related to proliferation of inflammatory cells (T cells and macrophages), cell migration, cell cycling (including cyclin D), epidermal proliferation and fibroblast proliferation. The growth factor (TGF β 1) secreted by macrophages is responsible for conversion of fibroblasts to myofibroblasts, which are responsible for hypertrophic scarring [10,21,22]. Blocking the activation of NF-kB-mediated TGF-beta1 is likely to be mechanistically relevant to the therapeutic efficacy of topical curcumin in skin injury and healing.

Clinical effects of topical curcumin in skin disorders

Acute Injury: Burns, Wounds and Surgical Scars: We have observed that topical curcumin can be used to heal acute skin injuries more rapidly, often with less or no scarring. The cases presented include burns, wounds and surgical wounds.

Burns from a Barbeque Fire: Figure 2a shows a patient who sustained secondary degree burns after pouring lighter fluid on a barbeque fire. He was engulfed in flames and sustained burns over his forehead, eyelids, cheeks, ears, nose, lips and neck. He also singed his hair and eyelashes. He was seen 4 days after

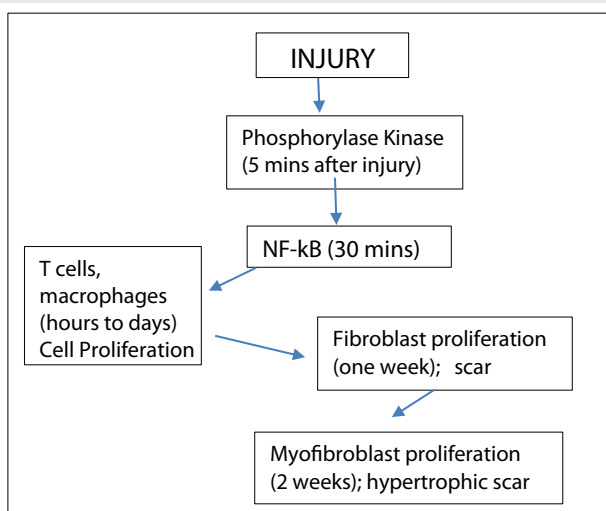


Figure 1: Injury Pathway showing the sequence of events leading to Scar tissue formation.

sustaining the burns, and was much improved 5 days later (Figure 2b) after topical curcumin use at frequent intervals for the first few days (Figure 2c), and appeared fully healed without detectable scarring two months later.

Wounds: We have also observed beneficial effects on knife wounds on a finger nail and tip of the finger sustained while cooking. The tip of the little finger was severed. This was stitched in place by the Emergency Room doctors, but the tissue was ischemic when seen one week later (Figure 3a). Curcumin gel dressings were applied and changed several times a week. The finger eventually healed without scarring (Figure 3b) and without nail deformity. Furthermore, she had normal sensation in the little finger.

Crush Injury: The patient's fingers of her right hand were crushed by a garage door. Concentrated curcumin gel was applied every 5 mins to the crushed fingers, which were photographed 15-20 mins later. Gel application was repeated frequently, and 3 hours later, the swelling had resolved (Figure 3c, left panels, 12 noon) and the only change was the presence of subungual hemorrhage.

Surgical Wounds and Scars: The patient developed scarring following excision of a basal cell carcinoma situated over the right chin. The scar resolved with application of concentrated topical curcumin twice daily (Figure 4 a-c).

Figure 5 shows a patient with a basal cell carcinoma right alar nose, treated with excision and graft repair (Figure 5, left panels). The graft was taken from the adjacent skin over the right paranasal cheek. The wound was treated with twice daily applications of concentrated topical curcumin. She had good graft survival and the scar healed with minimal scarring (Figure 5, right panels).

Inflammatory Skin Conditions

Rosacea: The patient had rosacea probably secondary to cytokine (TNF α)-induced photosensitivity associated with underlying lactose intolerance (Figure 6a (upper panel). In addition, she had sebaceous hyperplasia (enlarged sebaceous glands) (Figure 6a (upper panel) from growth



Figure 3a,b: a. (left panels): Knife wound while cooking. The tip of the finger was severed and sewed back by ER doctor. Treated with curcumin gel dressings; b. (right panels). When seen many months later, the finger had healed completely without scarring, nerve dysfunction or nail dystrophy.

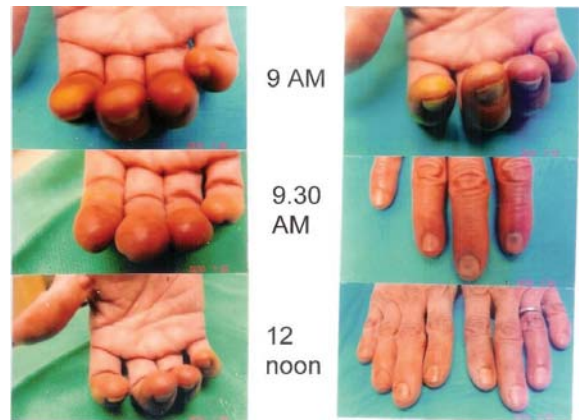


Figure 3c,d: c. (left panels) shows fingers of right hand mins after being crushed; d. (right panels): Improvement 3 hours later after frequent applications of high concentration topical curcumin gel.



Figure 2: a. (left panels): Second degree burns seen 4 days later; b. (middle panels): Rapid healing 5 days later with frequent application of topical curcumin gel; c. (right panels): healing with no detectable scarring with mild post-inflammatory pigmentation 6 weeks later.



Figure 4: a. (top panel): Excision of basal cell carcinoma right chin; b. (middle panel): Residual scarring; c. (lower panel): Improvement of scar following application of concentrated topical curcumin twice daily.

factors (transforming growth factor α) secreted by colonic inflammatory cells. The rosacea was much improved (Figure 6b (lower panel) with the use of topical curcumin gel and a lactose free diet.

Improvement of Scarring in Acneiform Conditions: Figure 7a (left panels) shows a acne patient with severe follicular plugging. She was put on a regimen aimed at unplugging the plugged follicles with high dose oral vitamin A (100,000 IU tid) for 9 months, retinoic acid gel 0.025% at bed-time and curcumin gel during the day. For control of the pustules, she was put on oral minocycline 100 mg daily. Curcumin gel helped healing without residual scarring. Figure 7b (right panels) show significant improvement after 12 months of treatment.

Psoriasis: Psoriasis is a genetic disease with lesions usually precipitated by injury (trauma, allergic contact allergens and bacterial superinfection). Psoriatic activity has been associated with elevated levels of phosphorylase kinase [7]. Suppression of phosphorylase kinase by topical curcumin has been shown to correlate with resolution of psoriasis [8]. We have developed a protocol aimed at inhibition of phosphorylase kinase activity [23]. by the use of topical curcumin, avoidance of contact allergens, treatment of bacterial infections and avoidance of lactose in the diet. Figure 8 shows a patient with chronic psoriasis for 60 years, aggravated by black hair dye and clothing dye allergy, elastic underwear, MRSA infection and lactose intolerance. Figure 8a,b (left panels) show the patient with generalized psoriasis before treatment with the protocol, and figure 8c,d (right panels) show complete clearance following 16 weeks of treatment including intravenous vancomycin, clobetasol solution 0.05% for the scalp., clobetasol cream 0.05% mixed with ketoconazole cream 2% for the trunk and limbs during the day, and topical curcumin gel in the evenings. She was also put on oral Diflucan 200 mg weekly for candida intertrigo, lactose free diet and daily bleach baths. Figure 8c,d (right panels) show complete clearance after 16 weeks fo treatment with no recurrence for many years.

Sunburns and photo-damaged skin

Ultraviolet light (both UVA and UVB) induces the formation of cyclobutane pyrimidine dimers (CPDs) which damage the



Figure 6: a (upper panel): Rosacea due to cytokine (TNF α)-induced photosensitivity, with sebaceous hyperplasia from increased TGF α secretion; b (lower panel): Improvement following application of curcumin gel twice daily and strict lactose-free diet.



Figure 7: a (left panels) showed an acne patient with severe follicular plugging; b (right panels) show improvement following topical curcumin and current treatment for acne, including high dose oral vitamin A.



Figure 8: a,b (left two panels): Generalized psoriasis present for 60 years; c,d (right two panels) shows clearance in 4 months after treatment with antibiotics, topical steroid creams, curcumin gel and lactose free diet. She avoids black hair dyes and clothing, elastic clothing and nickel from coins and keys. Taken from Heng MCY: JCDSA 2011)- ref 23.



Figure 5: a. (left panels): Basal cell carcinoma treated with excision and graft repair; b. (right panels): healing with minimal scarring with topical curcumin.

DNA [24-27]. CPDs formed by UVB tend to be easily repaired and may only cause point mutations on the DNA and squamous cell carcinomas, while CPDs formed by UVA exposure are less easily repaired and usually result in more extensive DNA damage

[24-27]. Mistakes are made when large segments of the DNA are involved, or when both strands of DNA are affected. The DNA repair pathway involves a family of phosphatidylinositol kinases [28-31]. These are involved in Cell Cycle Arrest (CCA), Nucleotide Excision Repair (NER) and replacement by newly synthesized nucleotide strands. The repair mechanisms involving the DNA Repair Pathway [25-28], are laborious and slow [11], with residual damaged cells resulting in a potential for tumor transformation. Topical curcumin, by induction of curcumin-induced apoptosis [11-14], results in the rapid repair of sun-burns, leaving space necessary for replacement by normal cells without malignant potential. This may prevent or potentially reduce future development of premalignant and malignant lesions.

Sunburns: Although UVB rays have less penetrating property and usually do not cause basal cell carcinomas and malignant melanomas, they do cause painful sunburns. Figure 9a (upper panel) showed severe sunburn with early blistering. The burns were much improved two days later with frequent applications of topical curcumin (Figure 9b (lower panel)).

Photo-damaged skin: Actinic dermatitis and keratosis: Figure 10a (upper panel) shows photo-damaged skin (actinic dermatitis) with multiple confluent actinic keratoses involving the ear. He had previous surgery for squamous cell carcinoma. After the use of concentrated topical curcumin for over a year, there was improvement with significant resolution of his photo-damaged skin (Figure 10b (lower panel)).

Photo-damaged skin: Actinic keratosis: Figure 11 shows photo-damaged skin with multiple actinic keratoses over the vertex scalp (upper panel). After 15 months of concentrated curcumin gel, there was resolution of the actinic keratoses and improvement in the surrounding photo-damaged skin (Figure 10b – lower panel).

Comment

Therapeutic effects of topical curcumin

In the above discussion, we show examples of the clinical



Figure 9: a. (upper panel) showed severe sunburn with early blistering; b. (lower panel) shows rapid healing with aborted blister formation with frequent applications of topical curcumin.



Figure 10: a. (upper panel): photo-damaged skin (actinic dermatitis) with confluent actinic keratoses before treatment with curcumin gel; b. (lower panel): Improvement with concentrated curcumin gel applied twice daily.



Figure 11: a. (upper panel): Photo-damaged skin with multiple actinic keratoses vertex scalp before treatment with topical curcumin; b. (lower panel). Improvement of photo-damaged skin and resolution of actinic keratoses after 15 months of concentrated topical curcumin applied twice daily.

effects of topical curcumin on a spectrum of dermatologic conditions. We emphasize these are clinical cases treated with topical curcumin usually in association with other standard therapy, including antibiotics. They were not part of a protocol designed to systematically investigate the clinical efficacy of topical curcumin. Instead, we used them as examples of results in our experience with the goal of informing other investigators of the potential therapeutic value of topical curcumin, and to encourage future proof of concept studies into its use for skin disorders. We believe that from the viewpoint of having preliminary proof of clinical benefit, and of biologic plausibility for these benefits from preclinical studies of biologic mechanisms [7,8], there are sufficient grounds to regard topical curcumin as a potential effective therapy for a number of dermatologic disorders [5-11], and as rationale for further clinical trials to evaluate its efficacy.

In contrast to the extensive investigations with oral curcumin [4], there have been relatively few reports of

preclinical and clinical studies on the therapeutic efficacy of topical curcumin [8,23,32-36]. Most of these were performed on animal models. Partoazar et al. [32], studied the effect of topical curcumin on second degree burns in a rat and found a favorable outcome with its use. Li et al. [33], reported the protective effect of curcumin in ultraviolet light B induced photo-damage in hairless mice and cell cultures. Kant et al. [34], found that topical curcumin hastened wound healing in diabetic rats, while Lopez-Jornet et al. [35], noted that topical curcumin increased healing after carbon dioxide laser damage in mice. In a randomized double-blind placebo-controlled trial performed in patients, Afshariani et al. [36], found topical curcumin to be effective in treating mastitis of breast-feeding women. Kant et al. [37], also proposed that the anti-inflammatory and antioxidant properties of curcumin may be responsible for increased wound healing in diabetic rats. The investigators [47] observed that curcumin decreased TNF- α , IL-1 β and MMP-9, and increased superoxide dismutase and catalases in their animals. Kant et al. [37], also found elevated glutathione peroxidase levels, but did not measure reduced glutathione values. Reduced glutathione is usually measured together with superoxide dismutase and catalases in evaluating the anti-oxidant properties of tissues.

Topical Curcumin may have Pleotropic Effects: In the cases above, we showed clinical benefits of topical curcumin in a fairly diverse variety of dermatologic conditions, including heat related injuries, solar damage and burns, skin wounds, skin healing after surgery, and chronic inflammatory skin conditions like psoriasis, acne, and rosacea. The range of skin conditions that appear to respond to use of topical curcumin suggests that more than one mechanistic effect may be operating with topical curcumin use, i.e. topical curcumin may have pleotropic effects. The extensive literature on biologic effects of curcumin has provided plausible evidence for the potential pleiotropic effects of curcumin [6-8,11-14]. These include its primary effect as a phosphorylase kinase inhibitor [8,23], with particular benefit in psoriasis, and the secondary NF- κ B-dependent anti-inflammatory effect that results in improved wound healing and less scarring [8-10,21-23]. The less well-known curcumin-induced apoptosis appear to involve phosphorylase kinase-dependent inhibition of phosphatidylinositol kinase [11-14]. The family of phosphatidylinositol kinases play a key role in the DNA Damage Repair (DDR) pathway [11,24-31], including ATM, ATR which affect Cell Cycle Arrest, Nucleotide Excision Repair, and DNA-protein kinase that is involved in DNA replication. By blocking phosphorylation and repair in this pathway, curcumin induces apoptosis of damaged cells [11-14,24-31]. Although inhibition of phosphorylase kinase may be key in both the anti-inflammatory and anti-apoptotic pathways, other kinases, such as phosphatidylinositol kinases, may also be involved in curcumin-induced apoptosis.

In our clinical experience and studies, topical curcumin is an effective therapy for psoriasis [8,23], an observation that is likely related to curcumin being a potent and selective inhibitor of phosphorylase kinase [6-8]. Our previous laboratory and clinical studies have suggested that psoriatic patients may have a defective mechanism, genetic in origin, in switching

off phosphorylase kinase activity after the enzyme has been activated by injury [8,23]. Phosphorylase kinase plays a crucial role in the inflammatory process related to wound healing, activating NF- κ B which in turn activates 200 genes related to the initiation of inflammation [5,9,10,19,20]. Activation of NF- κ B has been shown to be blocked by curcumin [19,20]. Our studies suggest that psoriatic patients may have a genetic defect that results in the inability to switch off phosphorylase kinase, and accordingly, an inability to reduce the inflammatory process triggered by external precipitating or aggravating factors [7,8,23]. The clinical result is the development of psoriatic lesions that tend to persist rather than heal. We have reported that inhibition of phosphorylase kinase activity by topical curcumin results in decreased phosphorylase kinase activity and significant clinical improvement of psoriasis [8,23].

The other chronic inflammatory disorders – rosacea and acne – that involve inflammatory processes that lead to residual scarring [10, 21,22] also appear to respond well to topical curcumin treatment. The beneficial effects of curcumin in these probably result from inhibition of NF- κ B-mediated inflammatory response and fibroblastic proliferation, with resultant decrease in residual scarring. Chronic inflammation is a pathophysiologic feature present in acneiform lesions, and the anti-inflammatory effect of topical curcumin is the likely mechanism for results noted with its use. Similarly, the benefits after topical curcumin use after surgical and traumatic injuries, and heat and solar damage, are likely the result of its anti-inflammatory effects. While there are other anti-inflammatory medications available, e.g. topical corticosteroids, the therapeutic benefit of topical curcumin lies in its safety and absence of observable side-effects. The clinical outcome of the use of topical curcumin on surgical scars and wounds are of particular interest. In our clinical experience, we observed that surgical wounds healed more rapidly and with less scarring with topical curcumin than without [10]. The anti-inflammatory effects of topical curcumin also appear to reduce fibroblast and myofibroblast formation in surgical wounds, with less scarring and keloid formations [10].

Studies showing that curcumin induces apoptosis in damaged cells show yet another aspect of the curcumin pleiotropy [11-14]. This mechanism may assist wound healing in accelerating removal of dead or dying cells and replacement by normal ones. We observed more rapid healing in traumatic wounds and heat or solar damage which may, in part, be due to this property of the curcumin [11].

Newer Strategies involving Nano-encapsulation in Wound healing: Because of its hydrophobic properties, curcumin is known to be poorly absorbed by tissues. For this reason, a host of strategies involving curcumin nano-encapsulation [38-42], have been attempted to increase the effectiveness of delivery of curcumin into tissues for wound healing. These strategies [38-42], include nanovesicles, polymeric micelles, conventional liposomes and hyalurosomes, nanocomposite hydrogels [41], electrospun nanofibers [42], nano-hybrid scaffolds [40], nanoconjugates, nanostructured lipid carriers, nanoemulsion, nanodispersion and polymeric nanoparticles [39]. These have yet to be clinically tested in human wounds, and have been

mainly studied in hairless mice [41], and diabetic rats [42]. In addition, the long-term benefits and side-effects of each technique are yet to be evaluated.

Topical versus Oral Curcumin: The use of curcumin for medicinal purpose has long been deeply embedded in many Eastern cultures, most prominently in South Asia. Mainly because of this, curcumin has been the focus of extensive studies into its possible medicinal value for a wide variety of diseases. The comprehensive review by Nelson et al. [4], reported that in 2015, the Curcumin Resource Database listed over 9000 publications and 500 patents on potential therapeutic value curcumin for a number of unrelated diseases. The great majority of these were related to studies with oral curcumin. The review noted that despite over 120 clinical trials of curcumin done, no double-blinded, placebo controlled trial has been reported successful [4]. There appears to be at least two important reasons for this. Curcumin has been demonstrated to be an unstable, reactive compound that interferes with assay readout, providing a misleading experimental outcome from this false activity rather than through real compound-target interaction [4]. Many of the preclinical studies showing initial promise that led to the unsuccessful clinical trials were attributed to this phenomenon. Probably more importantly, oral curcumin is poorly absorbed and has very low bioavailability, which essentially renders curcumin a poor candidate as an effective oral agent [1-3].

The issues detailed above with oral curcumin do not appear applicable to topical curcumin. Both the interference with assay readout encountered after oral curcumin and low bioavailability were not reported in the context of topical curcumin use. The negative results of clinical trials with oral curcumin are also unlikely to be pertinent to topical curcumin because the pharmacology and therapeutics of oral and topical medications are extremely different. In addition, our studies with topical curcumin suggest biologic mechanisms for topical curcumin efficacy in dermatologic disorders related to phosphorylase kinase inhibition and secondary downstream NF- κ B-mediated anti-inflammatory effects [7-9]. We postulate that these effects are highly plausible biologic mechanism for the clinical improvement noted after topical curcumin use in the cases presented above.

It is clear from the extensive literature on curcumin that oral administration of curcumin is not likely to be productive in the search for new medicinal products from the compound. Instead, the search should be changed to find uses for curcumin without the need for systemic absorption. Nelson et al. [4], suggested "As an alternative approach, it may be possible for compound 1 (*i.e.* curcumin) to have an effect on human health without being absorbed" [4]. While the authors referred to its use for gastrointestinal disorders, we believe that it is just as important, and also because it may be more productive, that topical curcumin be investigated more extensively in skin disorders.

Disclosures

Dr. Heng has shares in Omnicure, Inc., a company that manufactures and markets topical curcumin gel.

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