Curcumin as a wound healing agent

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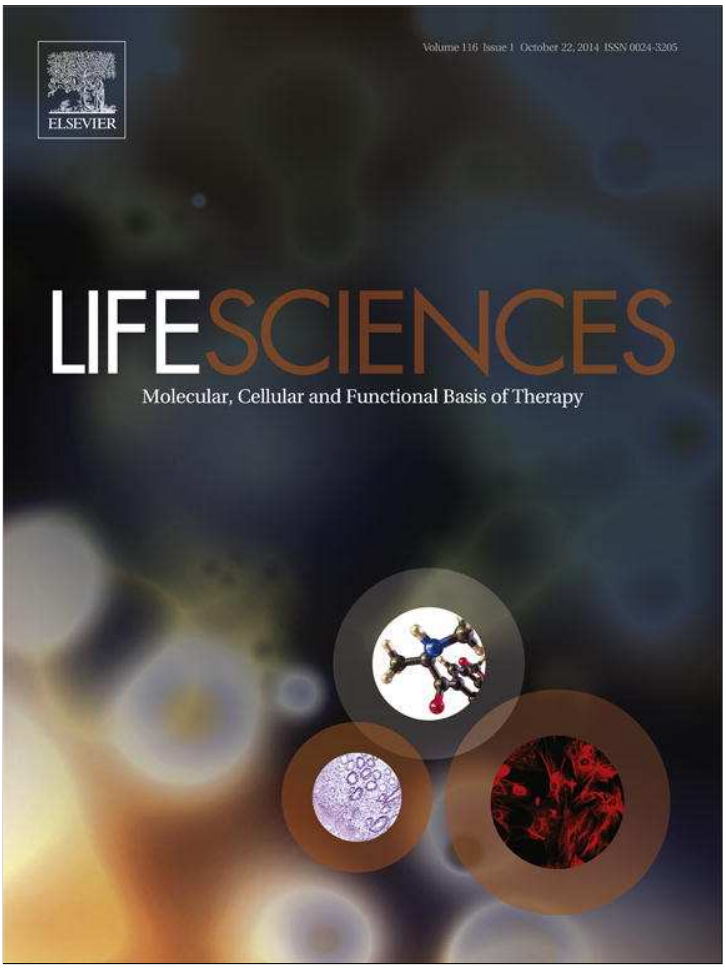
Life Sciences



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Review article

Curcumin as a wound healing agent

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ABSTRACT

Turmeric (*Curcuma longa*) is a popular Indian spice that has been used for centuries in herbal medicines for the treatment of a variety of ailments such as rheumatism, diabetic ulcers, anorexia, cough and sinusitis. Curcumin (diferuloylmethane) is the main curcuminoid present in turmeric and responsible for its yellow color. Curcumin has been shown to possess significant anti-inflammatory, anti-oxidant, anti-carcinogenic, anti-mutagenic, anti-coagulant and anti-infective effects. Curcumin has also been shown to have significant wound healing properties. It acts on various stages of the natural wound healing process to hasten healing. This review summarizes and discusses recently published papers on the effects of curcumin on skin wound healing. The highlighted studies in the review provide evidence of the ability of curcumin to reduce the body's natural response to cutaneous wounds such as inflammation and oxidation. The recent literature on the wound healing properties of curcumin also provides evidence for its ability to enhance granulation tissue formation, collagen deposition, tissue remodeling and wound contraction. It has become evident that optimizing the topical application of curcumin through altering its formulation is essential to ensure the maximum therapeutical effects of curcumin on skin wounds.

Contents

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Introduction

Curcumin

The turmeric plant is a herb belonging to the ginger family and has been used throughout history as a dietary spice and coloring agent in Indian and Chinese cuisines (Chattopadhyay et al., 2004). The rhizome (root) part of the plant has also been used for centuries in Indian and Chinese traditional medicines and is the most valuable part of the plant for medicinal purposes (Chattopadhyay et al., 2004; Patwardhan et al., 2005). Curcumin became commonly used in Indian traditional medicine in the treatment of bilary disorders, cough, diabetic ulcers, hepatic disorders, rheumatism and sinusitis. The paste of curcumin mixed with lime has been a popular home remedy for the treatment of inflammation and wounds (Anamika, 2012). Curcumin is one of the three curcuminoids present in turmeric, making up 2 to 5% of the spice (Anamika, 2012) and approximately 77% of a singular extract (Chutima, 2012). The structure of curcumin (1,7-bis(4-hydroxy-3methoxyphenyl)-1,6-hepadiene-3,5-dione) (Fig. 1) was first described by Milobedska et al. (1910). In more recent times, curcumin has been studied extensively for its use as an anti-cancer (Agrawal and Mishra, 2010; Shehzad et al., 2013; Shishodia et al., 2007), anti-aging (Lima et al., 2011; Bala et al., 2006) and wound healing agent (Maheshwari et al., 2006).

Wound healing process

Skin provides a natural barrier against the environment and exerts a variety of essential protective functions. When the integrity of skin is compromised, either by acute or chronic injuries, the body initiates a multi-step and dynamic process at the injured site, leading to partial healing of the tissue and restoration of the skin's barrier function. The immediate goal in wound repair is to achieve tissue integrity and homeostasis (Eming et al., 2007). The natural process of wound healing is comprised of four overlapping but well-defined phases: hemostasis, inflammation, proliferation and remodeling. Hemostasis occurs upon injury, which constitutes platelet aggregation and thereby blood clot formation (Enoch et al., 2006). The blood clot provides a provisional extracellular matrix for cell migration (Epstein et al., 1999). The inflammatory phase involves the migration of blood cells, such as phagocytic neutrophils and macrophages, to the wound site (Enoch et al., 2006). The phagocytes initially remove foreign particles, while also releasing cytokines to promote fibroblast migration and proliferation towards the end of the inflammatory phase (Topman et al., 2013). Re-epithelialization of wounds begins within hours of injury and is a part of the proliferative phase (Epstein et al., 1999). This phase is characterized by the formation of new blood vessels (angiogenesis or neovascularization), which re-establishes perfusion to sustain the new tissues (Topman et al., 2013) and the synthesis and deposition of fragments of extracellular matrix proteins such as collagen fibers and granulation tissue (Enoch et al., 2006). Fibroblasts produce the new extracellular matrix necessary to support cell ingrowth using collagen as the building blocks (Epstein et al., 1999) and thus play a crucial role in the wound healing process. The final phase involves collagen remodeling and scar tissue formation. Fig. 2 illustrates the time span of each wound healing phase following injury while also importantly depicting the overlapping nature of the process (Epstein et al., 1999).

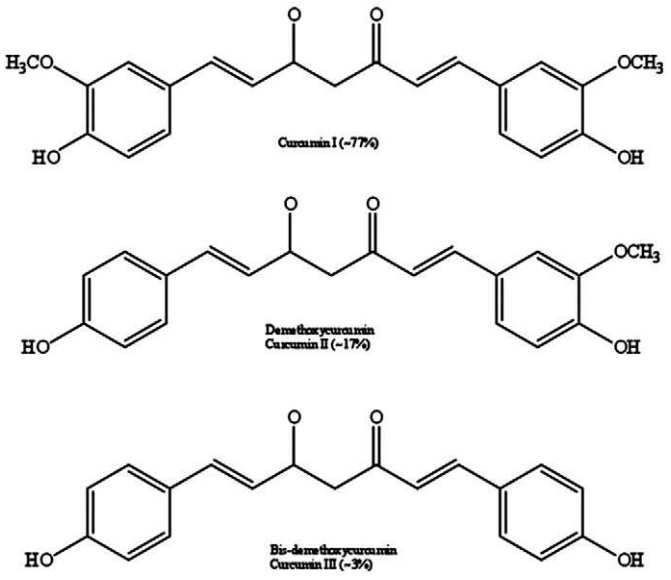

Fig. 1. Chemical structures of curcuminoids: curcumin, demethoxycurcumin and bis-demetohxycurcumin that have shown antioxidant and/or anti-inflammatory properties.

Wound healing activities of curcumin

An optimum wound healing dressing or agent protects the wound tissue from bacterial infection, reduces inflammation and induces cell proliferation to aid in the reconstruction of damaged tissue (Kulac et al., 2013). It would ideally also act as an anti-oxidant as free radicals are considered the major cause of inflammation during wound healing process (Mohanty et al., 2012). The wound healing potential of curcumin is attributed to its biochemical effects such as its anti-inflammatory (Liang et al., 2009), anti-infectious (Mun et al., 2013; Singh et al., 2010) and anti-oxidant (Ak and Gulcin, 2008; Meng et al., 2013) activities. Curcumin has also been found to enhance cutaneous wound healing through involvement in tissue remodeling, granulation tissue formation, and collagen deposition (Joe et al., 2004). Various studies have shown that curcumin's application on wound also enhances epithelial regeneration and increases fibroblast proliferation and vascular density (Sidhu et al., 1998; Thangapazham et al., 2013). This review critically evaluates the literature addressing the current applications of curcumin in wound healing, focusing on its mechanisms of action and providing evidence for its effects on the various stages of wound healing process. Precedence is given to the topical skin application of curcumin in vivo while also examining in vitro studies of curcumin in wound healing models.

Mechanisms of action of curcumin on the phases of wound healing

Effects of curcumin on inflammation

Inflammation is the crucial second phase of the wound healing process, often described as the first step in optimum skin regeneration (Epstein et al., 1999). Uncontrolled inflammatory responses may lead

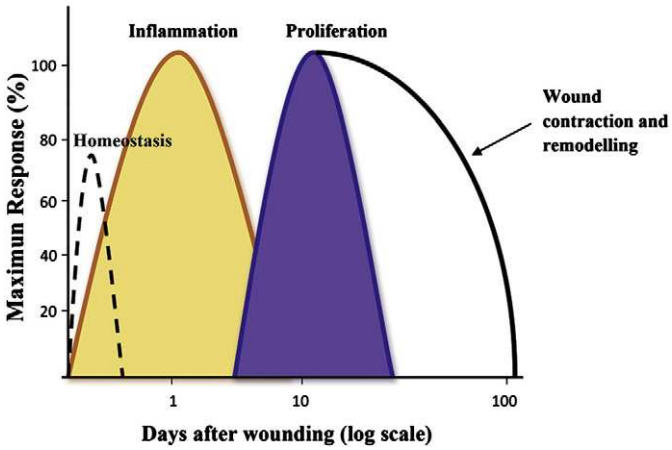

Fig. 2. The four phases of acute wound healing.

to undesirable effects and subsequently tissue damage, which is evident in inflammatory disorders such as rheumatoid arthritis (Joe et al., 2004). Considering that tissue injury causes almost immediate onset of acute inflammation, controlling inflammation is therefore desirable and can optimize the wound repair process. Joe et al. (2004) thoroughly reviewed the numerous mechanisms by which curcumin modulates inflammation. Most notably, curcumin was shown to inhibit the production of tumor necrosis factor alpha (TNF-α) and interleukin-1 (IL-1), two main cytokines released from monocytes and macrophages that play important roles in the regulation of inflammatory responses. Of equal importance is curcumin's ability to inhibit the activity of NF-(κ)B (nuclear factor kappa-light-chain-enhancer of activated B cells), a transcription factor that regulates many genes implicated in the initiation of inflammatory responses. NF-(κ)B is normally activated by various kinases (AKT, PI3K, IKK) and curcumin affects a variety of the pathways implicated in this activation (Fig. 3). For a while, NF-(κ)B has been considered oxidant responsive (Frey and Malik, 2004), highlighting the correlation between oxidation and inflammation in wound healing.

Mohanty et al. topically applied a curcumin-loaded oleic acid based polymeric bandage (COP) on the back of wounded rats and found a downregulation in the expression of various kinases in the PI3K/AKT/NF-(κ)B pathway (Mohanty et al., 2012). Application of the COP bandage also resulted in the downregulation of the expression of P13K and pAKT kinases, which in turn leads to less activation of the NF-(κ)B gene and reduced inflammation. An upregulation in I-(κ)B-(α) protein, which is involved in the inhibition of NF-(κ)B pathway, was also observed. Hence, Mohanty et al. demonstrated that curcumin reduces inflammation at wounded sites caused by the activation of the NF-(κ) B pathway (Mohanty et al., 2012).

Contrastingly to the Mohanty's findings, an in vivo study reported an increase in inflammatory cell infiltration to burn wounds on rats in curcumin-treated groups compared to untreated groups (Kulac et al., 2013). However, the study did not mention the type of inflammatory cells measured; hence further works are needed to establish pro-inflammatory effects of curcumin on wound. Interestingly, curcumin was also found to enhance nitric oxide (NO) production on the excision wounds of mice exposed to gamma radiation (Jagetia and Rajanikant, 2012). It has been shown that increased NO production promotes wound healing in patients by enhancing inflammation (Bernatchez et al., 2013). Contrary to most studies that show that curcumin enhances wound healing by inhibiting the inflammatory response; using a mouse model Jagetia and Rajanikant (2012) concluded that an increase in NO was partially responsible for the improvement in wound healing using curcumin treatment. Although this study suggested that enhancing the natural inflammatory response caused by curcumin treatment improved wound healing, the majority of papers provided evidence that curcumin indeed reduces inflammation. By reducing inflammatory response, the damaged skin can more readily enter the later stages of healing such as proliferation and remodeling. Prolonged and uncontrolled inflammation delays the later stages of healing and thereby slows down the wound healing process.

Curcumin reduces oxidation: a major cause of inflammation

Reactive oxygen species (ROS) are inevitable by-products of aerobic respiration and are important in some cellular and biochemical processes including intracellular messaging, differentiation, cell progression, apoptosis and immunity (Imlay, 2003; Matés et al., 1999). ROS are also involved in wound healing as they are required for immune system defense against micro-organisms. However, the prolonged presence of ROS at high concentrations generates oxidative stress, which can critically injure human cells (Panchatcharam et al., 2006; Roy et al., 2006). Oxidative stress is a significant factor in the wound healing process and generally inhibits tissue remodeling (Thangapazham et al., 2013). ROS such as hydrogen peroxide (H_2O_2) and superoxide (O_2^-) can be

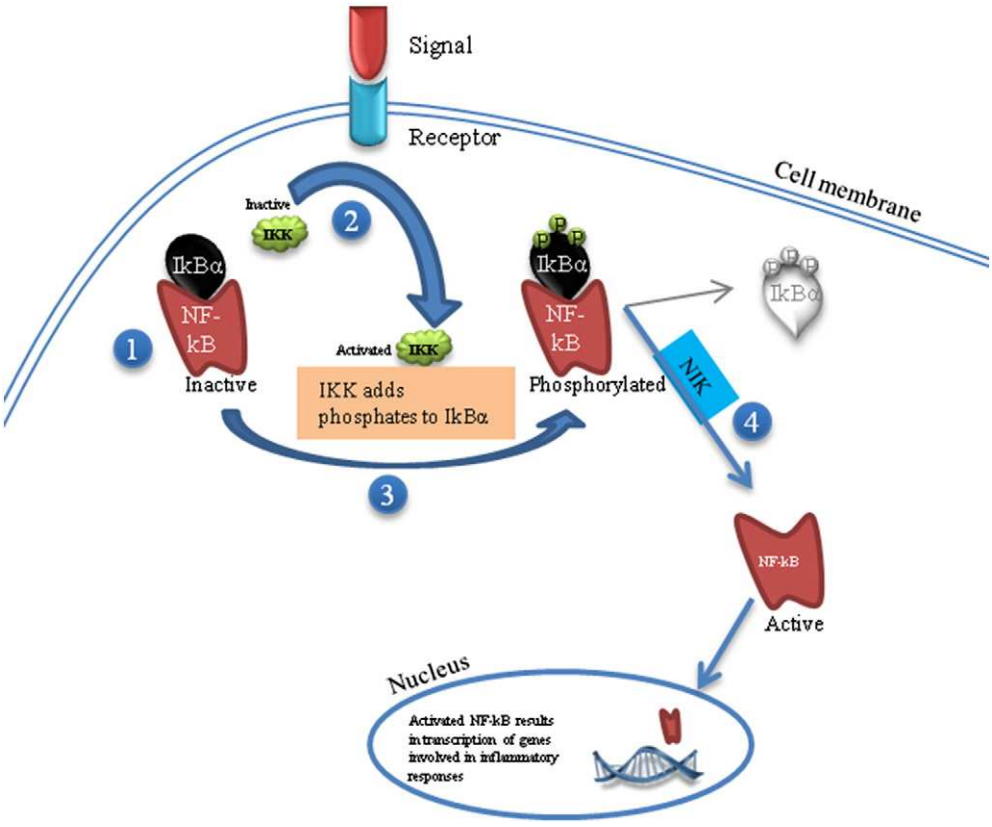

Fig. 3. A scheme showing curcumin interferes with inflammatory pathways by blocking the transcription factor NF-[κ]B. The numbers 1, 2 and 3 represent the pathways that curcumin inhibits NF-[κ]B (Joe et al., 2004).

used as markers for the amount of oxidative stress present in a system (Imlay, 2003). As free radicals, ROS result in oxidative damage, leading to lipid peroxidation, DNA breakage and enzyme inactivation, all of which inhibit optimum wound healing. ROS are considered to be the major cause of inflammation during wound healing activity (Mohanty et al., 2012). Free radicals also target and damage proteins in tissue (Kapoor and Priyadarsini, 2001) and for this reason they must be sufficiently scavenged. Anti-oxidant enzymes such as superoxide dismutase, glutathione peroxidase, and catalase protect human cells against toxic reactive oxygen species (Matés et al., 1999). It has been found that anti-oxidants with free radical scavenging potential can significantly improve wound healing when applied topically (Martin, 1996).

Gopinath et al. (2004) tested the in vitro antioxidant efficiency of curcumin incorporated collagen matrix (CICM) using the lipid peroxidation method, where curcumin was found to exhibit scavenging action against the peroxy radicals. In another study, transdermally applied curcumin on the excision wounds on rats produced marked inhibition of H_2O_2-induced damage to keratinocytes and fibroblasts (Gadekar et al., 2012). Similarly, in vitro studies of curcumin on keratinocytes and fibroblasts showed optimal protection against hydrogen peroxide (Phan et al., 2001). Although Gadekar et al. (2012) did not detail the methodology from which these results were obtained, Phan et al. (2001) used the MTT cell viability assay for the analysis of H_2O_2-induced damage to the skin cells. Curcumin was found to exhibit toxic effects on fibroblasts at a concentration of 5 μg/mL (Fig. 4). The authors also found curcumin to be toxic to keratinocytes at a concentration of 25 μg/mL. Similarly, an in vitro wound contraction assessment showed that curcumin significantly increased ROS formation compared to untreated fibroblasts at high concentrations (25 μg/mL), resulting in fibroblast apoptosis (Scharstuhl et al., 2009).

In orally-administered curcumin in rat studies, curcumin treatment has been found to enhance the activity of anti-oxidant enzymes including superoxide dismutase, catalase and glutathione peroxidase (Reddy and Lokesh, 1994; Subudhi and Chainy, 2010). Topically applied curcumin on excised wounds on the back of rats resulted in a significant increase in the anti-oxidant enzymes catalase, superoxide dismutase and glutathione peroxidise compared to control (Panchatcharam et al., 2006). When incorporated into the collagen matrix (CICM) and collagen films (CF) designed for use as topical wound healing materials, curcumin was found to slightly raise catalase activity in a rat wound model. However, there was a highly significant decrease ($p < 0.01$) in the level of superoxide dismutase (SOD) in tissues in both CF and CICM groups compared to control. This decrease in SOD was attributed to the inherent anti-oxidant activities of curcumin. Curcumin is known to non-enzymatically reduce superoxide radicals and hence decrease oxidative stress (Ghoneim et al., 2002). A decrease in superoxide radicals would therefore cause a decrease in the extent of anti-oxidant enzymes. The scavenged superoxide radicals were converted into hydrogen peroxide, which explains the slight increase in the activity of catalase in CICM and CF groups (Gopinath et al., 2004). Similarly, Mohanty et al. (2012) also reported a substantial downregulation in the expression of the common anti-oxidant enzymes such as SOD, CAT and GPx following the treatment of excised wounds in a rat model using curcumin-loaded polymeric bandage. This was also due to the ROS scavenging ability of curcumin, which reduces lipid peroxidation and therefore reduces activation of anti-oxidant enzymes. Controversially, as it was mentioned above, it was reported that curcumin treatment in a rat model enhanced the level of anti-oxidant enzymes in the wound tissue, which would be in theory ideal for enhancing wound healing process (Panchatcharam et al., 2006). It should be noted that the broader view in the literature suggests the opposite effect, as topical application of curcumin on wounds has been shown to cause a significant reduction in the expression of anti-oxidant enzymes and curcumin reduces oxidation through non-enzymatic mechanisms.

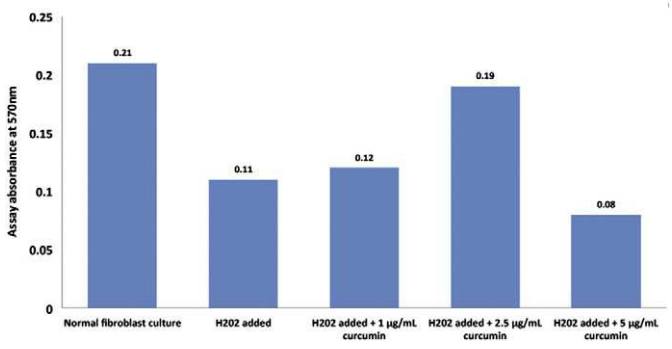

Fig. 4. Protective effect of curcumin on hydrogen peroxide induced damage to human dermal fibroblasts (Phan et al., 2001).

Effects of curcumin on the proliferative phase of wound healing

The proliferative phase in wound healing involves granulation tissue formation and collagen deposition (the formation of the extracellular protein matrix), fibroblast proliferation, epithelialization and apoptosis of unwanted cells (Epstein et al., 1999). As discussed below, various studies have assessed the effects of curcumin on these processes while also studying time for wound closure in curcumin-treated animals compared to controls.

Effects of curcumin on fibroblast proliferation

The infiltration of fibroblasts into wound site is essential for granulation tissue formation/remodeling, collagen production and deposition (Epstein et al., 1999; Loughlin and Artlett, 2011; Martin, 1997). Studies have shown that cutaneous wounds that fail to heal within the expected time period have impaired fibroblast proliferation and migration within the wound area (Blakytny and Jude, 2006; Hasan et al., 1997; Hehenberger et al., 1998). Therefore, the presence of fibroblasts in the wound environment is arguably the most important mediator in ensuring fast and esthetically acceptable wound closure. During granulation tissue formation, fibroblasts naturally differentiate into myofibroblasts (Petroll et al., 1993). Various studies have shown the infiltration of fibroblasts into wound sites when treated with curcumin. Mohanty et al. (2012) showed in a rat model that myofibroblasts were deposited in the wound environment treated with the curcumin-loaded oleic acid based polymeric (COP) bandage as early as four days following wound excision. Myofibroblasts were detected in a variety of wounds, including diabetic wounds (Sidhu et al., 1998; Sidhu et al., 1999). Contrastingly, in in vitro wound healing model (by scratching a line through the cell layer), curcumin showed no influence on the migration kinematics of fibroblasts to the wound area (scratch line). This contradictory result was attributable to the difficulty in adequately mimicking the complex wound healing process in an in vitro setting. Fibroblast migration depends on various factors that cannot be entirely mimicked in in vitro assays. These include interactions between cells and the environment as well as homeostatic mechanisms (Topman et al., 2013). It is worth noting that enhanced fibroblast infiltration in curcumin-treated groups is limited due to the cytotoxicity of curcumin. At high doses (25 μM), curcumin can cause fibroblast apoptosis in in vitro wound models. At this concentration, cell death was as high as 60% at 48 h post-treatment. At high concentrations, curcumin becomes oxidizing and produces ROS, the underlying reason for observed fibroblast apoptosis in curcumin-treated group. At lower concentrations (e.g., 5 and 10 μM), fibroblast morphology was not affected and no apoptosis was observed in curcumin-treated cells (Scharstuhl et al., 2009).

Effects of curcumin on granulation tissue formation

Granulation tissue or new stroma begins to grow approximately four days after skin injury. It is characterized by the formation of small capillaries as well as the infiltration of fibroblasts, which facilitate the

production of extracellular matrix (Epstein et al., 1999). Granulation tissue enhances re-epithelialization by providing basal support for epithelial cells to migrate and close the wound gap (Sidhu et al., 1999). Excised wounds on rats treated with a curcumin-loaded chitosan–alginate (CLCA) sponge showed better alignment of granulation tissue compared to gauze-treated wounds (control group). Gopinath et al. (2004) also measured an increase in hydroxyproline content of wound in CICM (curcumin incorporated collagen matrix) treated rats compared to control. Hydroxyproline is a protein marker, which is predominantly due to collagen synthesis. Hence, the presence of hydroxyproline is suggestive of an abundance of myofibroblasts in the wound environment. Fibroblasts differentiate into myofibroblasts during granulation tissue formation so the presence of myofibroblasts is an adequate marker of granulation tissue formation. Similarly, Mohanty et al. (2012) showed that COP (curcumin-loaded oleic acid based polymeric) treated wounds in rates had better organization of granulation tissue ten days following treatment, and little or ill-formed granulation tissue until four day post-treatment. The delay before granulation tissue formation is expected, considering that the tissue begins to grow approximately four days after injury. Organization of granulation tissue was also more advanced and myofibroblasts were more abundant when topical curcumin was applied to heal puncture wounds in diabetic rats. Neovascularization or the increased formation of small capillaries was also observed in curcumin-treated diabetic rates (Sidhu et al., 1999).

Effect of curcumin on collagen deposition

The reorganization and remodeling of the extracellular matrix are a prerequisite for wounds to completely heal. The extracellular matrix provides support to cells and is composed of various proteins and polysaccharides including granulation tissue and collagen. Collagen is the major protein in the skin extracellular matrix, comprising 70–80% of skin (Shoulders and Raines, 2009). The ultimate result of wound repair is the formation of scar tissue, composed mostly of collagenous fibers (Sai and Babu, 2000). For this reason, adequate collagen formation and deposition in a wound site would be optimal for enhancing wound repair. In a rat model, it was shown that collagen content of wounds treated with a CLCA sponge was higher compared to the gauze-treated control group. The resulting collagen is more compact and well-aligned and the bundles of the collagen appeared to be thicker in the curcumin-treated group (Dai et al., 2009). Mohanty et al. (2012) demonstrated in a rat model an increase in collagen content in COP bandage treated wounds with a higher aldehyde content compared to the collagen in control group. The high level of aldehyde in collagen was suggested to be the cause of formation of highly cross-linked collagen bed in the COP bandage treated wounds (Mohanty et al., 2012; George and Chandrakasan, 1996). Panchatcharam et al. (2006) not only showed an increase in collagen content, but that collagen fibers also mature earlier when wounds in rats were topically treated with curcumin. This was concluded to be due to the significant increase in tensile strength and shrinkage temperature of the wound tissue treated with curcumin. An increase in the aldehyde content of collagen was also detected in this study, confirming a highly cross-linked nature of these newly formed collagen fibers. When compared to the oral administration, it was found that the topically administered curcumin resulted in a higher synthesis of compact and well-aligned collagen fibers in wound site in diabetic mice as well as in rats and guinea pigs (Sidhu et al., 1998; Sidhu et al., 1999). Curcumin treatment on the excision wounds of mice exposed to gamma radiation showed a maximum collagen synthesis eight days after the start of the treatment (Jagetia and Rajanikant, 2012). Collagen produced by fibroblasts begin migrating into the wound site three days after a wound appears and they will be transformed into myofibroblasts by the end of the seventh day. Myofibroblasts contract wound to finalize the healing process at which point collagen deposition is no longer required.

Effects of curcumin on apoptosis

In order for wound to progress onto proceeding stages when it heals, a series of apoptotic processes happen to eliminate unwanted inflammatory cells from the wound site. This allows the wound to mature and advance into the proliferative phase (Sidhu et al., 1998; Sidhu et al., 1999; Brown et al., 1997). It has been suggested that curcumin is able to cause apoptosis because of its capability to induce ROS, although the exact mechanism of action is unclear and differs as a function of cell type (Scharstuhl et al., 2009). Curcumin is apoptotic in the early phase of wound healing, as DNA fragmentation studies have confirmed the presence of dead cells as early as four days post-treatment with the COP bandage in a rat wound model (Mohanty et al., 2012). Compared to control treatments, where low apoptosis rates were detected in the early phase of wound healing, curcumin was able to accelerate the healing cycle into the proliferative phase with minimal prolongation of the inflammatory phase. Mohanty et al. (2012) and Sidhu et al. (1999) provided evidence for increased level of apoptosis at eleven days post-wounding in the control group whereby curcumin-treated wounds showed no apoptotic cells at this point. This indicates that untreated wounds are still in the early phases of wound healing in the control group whereas curcumin treated wounds had progressed into the proliferation phase.

Effects of curcumin on wound contraction

Wound contraction is a part of the final stage of healing and involves complex interactions between cells, extracellular matrix proteins and cytokines (Epstein et al., 1999). When fibroblasts differentiate into myofibroblasts around two weeks post-wounding, wound contraction begins (Welch et al., 1990). Myofibroblasts increase wound contraction by inducing α-smooth muscle actin expression in the granulation tissue (Desmouliere et al., 1993). Wound contraction also requires stimulation by transforming growth factor β and platelet derived growth factors as cross linking in collagen bundles occurs (Montesano and Orci, 1988; Clark et al., 1989; Woodley et al., 1991). Many studies have been able to provide evidence for curcumin's ability to increase the wound contraction rate and hence accelerating wound healing. By measuring wound area planimetrically in a rat model, the size of a wound was traced and it was found that topical curcumin application significantly increased the percentage of wound contraction by 20% compared to control (Durgaprasad et al., 2011). Similarly, Dai et al. (2009) showed that wounds in rats treated with curcumin-loaded sponge contracted by 90% 12 days after injury compared to the gauze treated (control) group, which showed a 74% contraction in wound. Mohanty et al. (2012) showed similar results in a rat model and illustrated that an eight day period is needed post-wounding to ensure an accurate comparison of wound contraction between curcumin and controls as little contraction occurs before this time. Jagetia and Rajanikant (2012) also reported that maximum wound contraction was observed during 6 to 12 days post-irradiation when mice were treated with oral curcumin.

TGF-β is an important cytokine that is involved in the repair, chemotaxis and deposition of collagen in a wound site (Slavin, 1996). It is released by a variety of cells including fibroblasts. Curcumin-treated wounds consistently showed a greater number of fibroblasts, which were positive for TGF-β staining compared with untreated wounds (Sidhu et al., 1998). The granulation tissues of wounds in diabetic mice also showed a significant increase in the expression of TGF-β when topically treated using curcumin. Only a faint expression of TGF-β was seen in control-treated wounds (Sidhu et al., 1999).

Effects of curcumin on re-epithelialization and remodeling

The epidermis is the outermost layer of the skin and serves as an important barrier between an organism and its environment, protecting the host from physical, chemical and microbial damages (Koivisto et al., 2011). Epithelialization is the process where keratinocytes

migrate from the lower skin layers and divide (Panchatcharam et al., 2006). As the final stage of wound healing (along with remodeling), re-epithelialization must be a robust process to restore adequate barrier function of the epidermis (Koivisto et al., 2011).

Curcumin has been shown to result in a complete epithelialization when topically applied to wounds in a rat model. Curcumin reduced the epithelialization period of the treated wounds significantly from 23 days to 11 days when compared to the control group (Panchatcharam et al., 2006). Re-epithelialization of wounds was significantly increased when treated with curcumin, where optimum re-epithelialization was observed after 12 days of continued curcumin treatment. Similarly, in a diabetic rat model, Sidhu et al. (1999) showed that in the curcumin-treated diabetic wounds the rate of re-epithelialization was accelerated eleven days after curcumin treatment compared to the seven day treatment. They also showed an enhanced migration of the epithelium and a decrease in the wound gap and width in the curcumin-treated group. On the eleventh day post-wounding, wound organization (remodeling) was more advanced in the curcumin-treated wounds. The untreated wounds in rat and guinea pig models showed impaired epitheliums and the epithelial cells adjacent to the wounded area did not exhibit hyperplasia compared to the curcumin-treated wounds in these animals (Sidhu et al., 1998).

Challenges and improvements in the topical delivery of curcumin

Due to its hydrophobicity, curcumin is poorly absorbed following oral administration and only traces of the compound appear in the blood serum (Ravindranath and Chandrasekhara, 1980). Curcumin also undergoes extensive first-pass metabolism (Asai and Miyazawa, 2000) and is a light-sensitive molecule (Anand et al., 2007). Because of its low water-solubility and extensive first-pass metabolism, curcumin makes a suitable candidate for topical applications. Studies to date have demonstrated that topical application of curcumin has more pronounced effects on wound healing compared to its oral administration owing to the greater accessibility of the drug at the wound site (Sidhu et al., 1998; Sidhu et al., 1999; Merrell et al., 2009; Mani et al., 2002). With this in mind, many groups have developed new formulations of curcumin to achieve better topical application at the wound site. These include: chitosan–alginate sponges (Dai et al., 2009), polymeric bandages (Mohanty et al., 2012), alginate foams (Hegge et al., 2011), collagen films (Gopinath et al., 2004), and creams (Durgaprasad et al., 2011). Compared to unformulated (raw) curcumin, it was found that the bioactivity of curcumin increased when incorporated into these formulations. However, no significant difference in curcumin's wound healing effect was found between these different formulations as they all exhibit similar wound healing profiles. While the above-mentioned formulations enhanced the topical application of curcumin, the infiltration of curcumin into cells at the wound site can still potentially be improved through nano-formulation of curcumin. In traditional Chinese medicines (TCM) that confront similar limitations in curcumin application, curcumin has successfully been formulated as nanoparticles, resulting in substantially improved therapeutical effects (Wang et al., 2011). Therapeutic advantages of curcumin nanoparticles are due to the higher total surface area and smaller size that facilitate the cellular uptake of curcumin (Anand et al., 2007; Wang et al., 2011). When formulated as nanoparticles, curcumin was found to have an enhanced cellular uptake into cancer cells and reduce their proliferation compared to raw curcumin (Lee et al., 2014a; Lee et al., 2014b). Furthermore, curcumin nano-formulation showed improved bioavailability and longer half-life of curcumin (Anand et al., 2010). Curcumin nano-formulation also enhances its water dispersibility (Lee et al., 2014b) and allows curcumin to be made into an aqueous formulation such as cream (Durgaprasad et al., 2011). No studies to date have tested the effect of curcumin nanoparticles on wound healing. This warrants future studies to focus on this formulation in order to improve curcumin delivery to wound sites.

Table 1
Summarizing the effects of curcumin topical treatment on different stages of wound healing.

Wound healing stage	Effects of curcumin topical treatment
Inflammation	• Inhibiting the activity of NF-(κ)B transcription factor, reducing the production of TNF-α and IL-1 cytokines, and thereby reducing inflammation • Scavenging action against ROS (at lower dose of curcumin) • Increasing ROS formation (at higher dose of curcumin) • Increasing or decreasing the production of anti-oxidant enzymes (dose dependent)
Proliferation	• Enhancing fibroblast migration, granulation tissue formation, collagen deposition, and in general re-epithelialization • Being apoptotic in the early phase of wound healing, thereby eliminating unwanted inflammatory cells from the wound site
Remodeling	• Improving wound contraction by increasing the production of TGF-β and therefore increasing fibroblast proliferation

Conclusion

In conclusion, it has been found that curcumin possesses powerful modulating effects on wound healing. The effects of curcumin on different wound healing phases are summarized in Table 1. Studies have demonstrated that curcumin does this by acting on the inflammatory, proliferative and remodeling phases of the wound healing process and in doing so, reduces the time needed for wound healing. Unfortunately, curcumin is limited by its low bioavailability, rapid metabolism, poor solubility and light sensitivity. In order to minimize these effects and to be able to use curcumin to its maximum capability, novel formulations such as nanoparticles should be explored.

Conflict of interest

There is no conflict of interest in this work.

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