EXPERT OPINION

1. Introduction
2. Curcumin overview
3. Curcumin as an antiinflammatory: potential for wound healing
4. Potential barriers to curcumin bioavailability
5. Curcumin delivery vehicles
6. Conclusion
7. Expert opinion

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Curcumin: a novel therapeutic for burn pain and wound healing

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Introduction: Managing burn injury-associated pain and wounds is a major unresolved clinical problem. Opioids, nonsteroidal antiinflammatory drugs (NSAIDs), antidepressants and anticonvulsants remain the most common forms of analgesic therapy to treat burn patients. However, prolonged treatment with these drugs leads to dose escalation and serious side effects. Additionally, severe burn wounds cause scarring and are susceptible to infection. Recent encouraging findings demonstrate that curcumin, a major bioactive component found in turmeric, is a natural pharmacotherapeutic for controlling both severe burn pain and for improved wound healing.

Areas covered: This article covers current pr-clinical and clinical studies on the analgesic and wound healing effects. Particular emphasis has been placed on studies aimed at developing improved curcumin delivery vehicles that increase its bioavailability. Based on the available evidence, a hypothesis is proposed that the dual beneficial effects of curcumin, analgesia and enhanced wound healing are mediated through common anti-inflammatory mechanisms.

Expert opinion: Emerging studies have demonstrated that curcumin is a promising investigational drug to treat both pain and wounds. The adequate control of severe burn pain, particularly over the long courses required for healing, as well improvements in burn wound healing are unmet clinical needs.

Keywords: curcumin, inflammatory pain, painful neuropathy, wound dressing, wound healing

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1. Introduction

According to the American Burn Association, around 500,000 burn patients seek medical attention every year [1]. Burn injury causes pain and damage to the skin and underlying tissues. Additionally, uncontrolled acute burn pain contributes to several sensory abnormalities including chronic pain, allodynia, hyperalgesia, paresthesia, phantom skin syndrome and dysesthesia [2,3]. Burn patients report intense pain during procedures such as wound debridement, dressing changes and strenuous physical and occupational therapy. In fact, procedural pain is the most common grievance reported by the burn population [4,5]. Opioids, antidepressants, anticonvulsants and antiinflammatory drugs are the major analgesics used to control pain [6]. Wound healing and reepithelialization are delayed in burn patients, increasing the opportunity for infection or sepsis, a major cause of mortality and morbidity [7].

Burn wounds are managed with surgery, autografts, topical dressings, corticosteroids, laser therapy and topical therapeutic agents including silver sulfadiazine [3]. Despite the availability of these treatments, and continued research in the field, the clinical outcomes for burn patients, including those related to chronic pain

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Article highlights.

- Burn injury causes pain and damage to the skin and underlying tissues. Additionally, uncontrolled acute burn pain contributes to several sensory abnormalities including chronic pain, allodynia, hyperalgesia, paresthesia, phantom skin syndrome and dysesthesia.
- Despite the availability of multiple treatments, for burn wounds, such as surgery, autografts, topical dressings, corticosteroids, laser therapy and topical therapeutic agents and continued research in the field, the clinical outcomes for burn patients, including those related to chronic pain and wound management, are generally not satisfactory.
- Curcumin (diferuloylmethane) is the major bioactive constituent of turmeric (*Curcuma longa*), which is a common spice that has been used in South Asian countries in food preparations and folk medicine for centuries.
- A growing body of evidence from preclinical studies indicates that curcumin is effective as an analgesic and as an aid to wound healing, and both of these effects are linked to its antiinflammatory properties.
- Due to the relatively low bioavailability of curcumin, current research is focused on improved delivery systems for this agent.
- Reports from several laboratories strongly support the consideration of curcumin in various drug delivery forms as an antiinflammatory analgesic and as an aid to wound healing for thermal injury.

This box summarizes key points contained in the article.

and wound management, are generally not satisfactory. For instance, the major concern with chronic use of most analgesics is their side effects, which include addiction and adverse effects on various organ systems [8]. As a result, the search continues to identify therapies with reduced side effects to treat both acute and chronic pain following burn injury. Novel biologic drugs [9], stem cells [10] and alternative medicine approaches including acupuncture, botanical medicine, massage and neuroreflexotherapy are some of the cost-effective and promising complementary and alternative approaches for treating pain and improving wound healing [8,11].

Wound healing after a burn is a complex process that balances inflammation and proliferation of injured tissues. The challenges of wound healing are highlighted in multiple reviews [12,13]. Potentiated inflammation inhibits healing and is thought to aid in the formation of scars; however, some level of inflammation is also required for wound healing and to control infection. Currently, burn centers try to impact wound healing through selection of dressings (silver infused, etc.), placement of wound vacs [14], application of topical medications and treatment with human growth hormone [15]. These practices have improved survival after large burns and decreased length of stay in the hospital; however, pain remains largely undercontrolled.

Among the botanical medicines for burn treatments, one of the promising and currently most intensively studied is curcumin (diferuloylmethane), the major bioactive constituent of turmeric (*Curcuma longa*), which is a common spice used in South Asian countries in food preparations and folk medicine. This article focuses on the potential of curcumin as a therapeutic for pain and wound treatment, and also discusses the prospects of developing curcumin as a novel therapeutic for burn injuries.

2. Curcumin overview

Curcumin (diferuloylmethane) is a low-molecular-weight, lipophilic molecule, with the chemical structure 1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione (**Figure 1**). In the past three decades, extensive modern research has demonstrated that curcumin can alter gene expression, modulate several signaling pathways and interact directly with target molecules to produce antiinflammatory effects [16] and numerous health benefits [17].

2.1 The effects of curcumin on pain: evidence from animal models

Table 1 summarizes recent research reports on the use of curcumin in multiple rodent pain models. One of these models is for diabetic painful neuropathy, a common complication in patients suffering from diabetes mellitus. The affected peripheral nerves exhibit slower impulse conduction, axonal degeneration and impaired regeneration. Peripheral neuropathy patients frequently experience sharp spontaneous pain, allodynia and hyperalgesia [18]. Analgesics used to treat painful neuropathy include opioids, anticonvulsants and tricyclic antidepressants (TCAs); however, their use is often unsatisfactory because of limited efficacy and negative side effects [18,19]. Curcumin administration significantly attenuates pain associated with diabetic neuropathy, thus curcumin may provide an alternative to current therapies [20].

In rat models of diabetic neuropathy, tumor necrosis factor-alpha (TNF-α), a proinflammatory cytokine, may play a role in neuropathic pain. TNF-α levels are increased in neuronal and non-neuronal cells, and also in plasma in animal models of neuropathic pain [21,22]. In a streptozotocin-induced diabetic neuropathy mouse model, oral administration of curcumin for four weeks significantly decreased serum TNF-α levels and also reduced thermal hyperalgesia [20]. Another recent study showed that coadministration of curcumin and gliclazide, an oral hypoglycemic agent, elevated thresholds of mechanical and thermal hyperalgesia by suppressing the production of serum TNF-α in a rat model of diabetic neuropathy [23]. These results suggest that curcumin may be effective against pain associated with diabetic neuropathy.

The mechanism of action of curcumin on neuropathic pain may be due to its peripheral antiinflammatory activity. In addition to TNF-α, several other cytokines (IL-1β, 6, 8), interferon (IFN)-γ, bradykinins, prostaglandins and sympathetic amines are also altered in serum by neuropathy and may contribute to the associated pain. The effects of

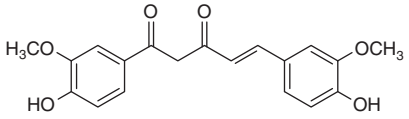

Figure 1. Chemical structure of curcumin, a major component present in turmeric (*Curcuma longa*) powder with diverse biological activities.

curcumin on these inflammatory mediators have yet to be studied. A large body of evidence suggests that the TNF-α level is also increased in dorsal root ganglia (DRG) neurons and glial cells following nerve injuries [22]. Nerve injury induces up-regulation of the TNF-α receptor (TNFR1) in both DRG and dorsal horn neurons, and inhibition of TNF signaling pathways attenuates hyperalgesia and allodynia [24]. Therefore, additional studies are needed to explore the effects of curcumin treatment on TNF-α signaling in DRG and the spinal dorsal horn in diabetic painful neuropathy.

The antinociceptive mechanisms of curcumin have also been studied in a chronic constriction injury (CCI) neuropathic pain model [25]. Three weeks of oral curcumin treatment resulted in dose-dependent attenuation of mechanical allodynia and thermal hyperalgesia in this model. Interestingly, the antinociceptive effects of curcumin were maintained 10 – 12 days after cessation of curcumin treatment. Further, curcumin mediated antiallodynic and antihyperalgesic effects through multiple neurotransmitter systems: descending serotonergic, noradrenergic and opioidergic. Because neuropathic pain is a complex disease state involving alterations in several neurotransmitter systems, this study indicates that curcumin can target multiple pain-relevant target sites to abrogate neuropathic pain symptoms. Additionally, another recent study using the same CCI model has demonstrated that the decreased allodynia and hyperalgesia induced by curcumin is linked to reversal of astrocyte activation and suppression of extracellular-signal-regulated kinase (ERK) signaling in the spinal cord dorsal horn [26]. Current treatments for chronic neuropathic pain often include TCA drugs, which function by modulating the descending monoaminergic system [27]. However, long-term treatment with TCAs can cause severe side effects, including several cardiovascular and neurological problems [28]. Therefore curcumin, which is safe to use in a wide range of concentrations in both humans and animals [17], may be an effective alternative for the treatment of neuropathic pain.

Additional evidence demonstrates antinociceptive efficacy for curcumin in rat models of inflammatory pain. Intrathecal administration of curcumin reduced formalin-induced inflammatory pain behaviors [29]. Curcumin (i.p.), given as an adjuvant with the nonsteroidal antiinflammatory drug (NSAID) diclofenac, reduces spontaneous pain behaviors in a formalin-induced orofacial pain model [30]. There is also preclinical evidence that curcumin acts on a subpopulation of nociceptors expressing the transient receptor potential vanilloid 1 (TRPV1) channel, a member of a family of transmembrane cation channels. TRPV1 is predominantly expressed in primary sensory neurons with unmylinated C-fibers and is activated by heat, protons and vanilloids, such as capsaicin. TRPV1 participates in the transduction of mechanical, thermal and chemical stimuli [31]. Intraperitoneal (i.p.) injection of curcumin attenuates TRPV1-mediated hyperalgesia in a capsaicin-induced pain model [32]. Recently, it was shown in rodent studies that curcumin could suppress three of the primary adverse effects of long-term opioid use; opioid-induced hyperperalgesia, dependence and tolerance [33,34]. Curcumin exerted this effect, at least in part, through an epigenetic mechanism involving inhibition of histone acetylation. Thus curcumin could be a promising adjuvant to opioid treatment that would reduce its side effects, in addition to exerting its own analgesic effects.

Further, emerging clinical studies show that curcumin is effective in controlling pain associated with various diseases. For instance, oral curcumin treatment improved postoperative pain in patients who underwent laparoscopic cholecystectomy [35] and reduced joint pain in osteoarthritis patients [36].

The burn patient population also experiences several psychological comorbidities, including posttraumatic stress disorder, depression, suicidal thoughts, fear and anxiety, that complicate pain management [3,37-39]. Studies have shown that pain and depression are closely linked. For example, depression can be accompanied by unexplained physical symptoms such as back pain or headaches. Depression may also increase the response to pain, or intensify the suffering associated with pain, and chronic pain is stressful and depressing in itself. Curcumin may be effective at treating these comorbidities, as well. Curcumin was shown to be effective in ameliorating comorbid symptoms of pain and depression in a rat model for reserpine-induced pain-depression [40]. This raises the possibility that curcumin could have a dual function as a suppressor of both pain and depression.

Together, these studies indicate that curcumin is effective at reducing pain behaviors in several rodent models of pain, potentially by reducing systemic inflammatory mediator release, and by altering pain processing in the peripheral and central nervous system. Importantly, curcumin is effective as an analgesic in several disease models associated with chronic pain and no negative side effects for curcumin have been reported.

3. Curcumin as an antiinflammatory: potential for wound healing

Inflammation, cell proliferation, matrix remodeling and matrix contraction are important stages of wound healing that can be affected by curcumin [41]. Several studies have reported positive effects of curcumin on wound healing. One recent study demonstrated that topical application of

Table 1. Antinociceptive effects of curcumin in various animal models of pain.

Study/Refs.	Animal	Animal models of pain	Doses tested	Route	Treatment	Pain tests	Results
Sharma *et al.* (2006, 2007) [16,20]	Mouse	Streptozotocin-induced diabetic neuropathy	15 – 60 mg/kg	p.o.	Once per day for 4 weeks	Tail immersion; hot plate	Dose-dependent antinociceptive effects
Mittal *et al.* (2009) [30]	Rat	Formalin-induced orofacial pain	25 – 600 mg/kg	i.p.	Single	Nocifensive behavioral scoring	Inhibits facial grooming
Yeon *et al.* (2010) [32]	Rat	Capsaicin-induced thermal hyperalgesia	5 – 50 mg/kg	i.p.	Single	Thermal	Dose-dependent reversal of thermal hyperalgesia
Attia *et al.* (2012) [23]	Rat	Streptozotocin-induced diabetic neuropathy	100 mg/kg	p.o.	Once per day for 5 weeks	Hot plate; tail flick; tail pinch	Increased thermal latency and mechanical threshold
Arora *et al.* (2011) [40]	Rat	Reserpine-induced pain-depression dyad	100 – 300 mg/kg	i.p.	Single	Randall Sellitto; Von Frey	Dose-dependent increase in mechanical threshold
Zhao *et al.* (2012) [25]	Rat	Chronic constriction injury (CCI)	5 – 45 mg/kg	p.o.	Twice per day for 3 weeks	Von Frey; thermal	Dose-dependent increase in mechanical threshold and thermal latency
Han *et al.* (2012) [29]	Rat	Formalin-induced spontaneous pain	62.5 – 500 µg	i.t.	Single	Nocifensive behavioral scoring	Dose-dependent suppression of flinching behavior in Phase II
Liang *et al.* (2013) [33]	Mouse	Morphine-induced hyperalgesia	50 mg/kg	i.p.	Once per day for 4 days	Von Frey; thermal	Reduced allodynia and thermal hyperalgesia
Feng-tao *et al.* (2013) [26]	Rats	Chronic constriction injury (CCI)	50 – 100 mg/kg	i.p.	Once per day for 7 – 14 days	Von Frey; thermal	Decreased allodynia and thermal hyperalgesia

p.o.: Per os; i.p.: Intraperitoneal; i.t.: Intrathecal.

curcumin significantly improved the healing time of rats with thermal injury wounds [42]. Curcumin treatment increased collagen deposition, angiogenesis, and reepithelialization processes. In another study, oral administration of curcumin for 5 – 20 days dose-dependently increased collagen synthesis, enhanced vascular and fibroblast densities and improved contraction by decreasing healing time in a mouse model for full-thickness wounding caused by fractionated irradiation exposure [43]. Also, intravenous (i.v.) delivery of 1 – 3 µg/kg of curcumin was found to reduce injury progression in a rat burn model as measured by the percentage of unburned interspaces that underwent necrosis [44]. Thus curcumin improved wound healing in these studies regardless of the route of administration.

Inflammation-induced production of cytokines, such as transforming growth factor-β (TGF-β), plays a key role in scar development and formation. Siddu *et al.* have shown that oral and local administration of curcumin improved healing in diabetic mice with full thickness cutaneous wounds [45]. The action of curcumin in this model was found to be mediated through increased production of TGF-β at both the protein and mRNA levels. Additionally, enhanced epithelial regeneration and neovascularization was also observed at the wound site of curcumin-treated animals. Further, recent clinical and laboratory studies indicate that curcumin has potent antiinflammatory activity that involves suppression of signaling through the nuclear factor κB-(NF-κB) pathway [46-49].

While not all of these studies have been performed using identical wound models, routes of curcumin administration or *in vitro* tests, one common conclusion emerges: curcumin is effective in treating a range of different wound types, and therefore has great therapeutic potential. Together, these data support curcumin as a naturally occurring antiinflammatory agent that could act as an analgesic and have prohealing effects, as a result of suppression of inflammation at the site of burn injury.

4. Potential barriers to curcumin bioavailability

The bioavailability of curcumin depends on concentration and route of administration. For example, curcumin is poorly absorbed from the gastrointestinal tract when given orally [50-52], primarily due to its hydrophobicity and insolubility in physiological media, as indicated by its octanol:water partition coefficient of log P = 2.5 and its water solubility of about 0.1 µg/ml [53,54]. Hence, therapeutic curcumin dosages are difficult, albeit not impossible, to achieve *in vivo* by either parenteral or topical delivery routes. Pan *et al.* reported relatively high plasma levels of 2.25 µg/ml curcumin when injected i.p. into mice, in comparison to only 0.13 µg/ml following oral administration [55]. Another comparative study in rats has shown similarly higher serum concentrations of curcumin after i.v. injection in contrast to oral administration [56].

Both animal and clinical studies have shown low levels of tissue deposition of curcumin when given orally, with trace

amounts detected in lung, kidney, spleen and brain. [51-53]. However, by using various advanced drug delivery systems the bioavailability and tissue distribution of curcumin have been greatly improved. The delivery systems include nanoparticles [57], microparticles [58] and liposomes [59]. Orally administered curcumin undergoes metabolism to form glucuronide and sulphate conjugates. On the other hand, systemic and i.p. injected curcumin reduces to tetrahydrocurcumin, hexahydrocurcumin and octahydrocurcumin [60-62]. There is some speculation that the degradation products of curcumin may have pharmacological effects [63,64]. Importantly, in all studies to date curcumin is found to be safe and well-tolerated in animals and in humans irrespective of concentration and route of administration [17,65].

5. Curcumin delivery vehicles

The hydrophobicity and insolubility of curcumin present substantial limitations to its effective *in vivo* delivery by either oral or parenteral routes. To overcome these limitations, adjuvants like piperine, which interferes with glucuronidation, have been used with some success [53]. In addition, novel delivery vehicles have been studied including topical wound dressings, implantable depot devices and injectable nanoparticle dispersions. Topical wound dressings have long been a standard procedure in wound management to prevent bacterial infection, avoid accidental contact with external noxious stimuli, and maintain a moist environment to facilitate faster healing [66,67]. Several novel polymeric wound dressing materials have been developed including hydrogels, alginates, hydrocolloids, foams and films that can provide controlled delivery of therapeutic agents [66].

Burn wounds require frequent dressing changes, which are associated with high ratings for procedural pain have (7/10 on the numeric rating scale of 0 – 10) [68]; thus the ideal dressing would deliver pain therapy for several days or weeks, while also enhancing wound healing. For example, Li *et al.* have incorporated block copolymer poly(ε-caprolactone)-*b*-poly (ethylene glycol) (PEG) nanoparticle complexes of curcumin into *N*,O-carboxymethyl chitosan/oxidized alginate hydrogel (CCS–OA hydrogel) and studied its efficacy in a mouse with full-thickness wounds. This modified biocompatible dressing accelerated wound healing by increasing reepithelialization and collagen deposition processes in the wound tissue [69]. Another study showed that by embedding curcumin in a biodegradable sponge composed of chitosan and sodium alginate produced a positive effect on wound healing [70].

The advantage of this technology is that curcumin could be released to the wound area in a sustained and controlled manner. Along similar lines, Mohanty and Sahoo have shown that dressing thermal injury wounds with a polymeric bandage containing a formulation of curcumin and oleic acid enhanced the wound healing process in a rat thermal injury wound model. Biochemical studies showed that curcumin treatment reduced free radicals and inflammation mediated through the NF-κB pathway [71]. A device in which curcumin was embedded in a solid mixture of poly(ε-caprolactone) and PEG was delivers significant dosages of curcumin over 3 months when implanted subcutaneously in rats [72]. A polymer drug approach has also been demonstrated in which curcumin was covalently polymerized along with poly(ethylene glycol) and a tyrosine-derived monomer to form a hydrogel containing up to 75 mol% curcumin [73]. This hydrogel underwent controlled hydrolysis under physiological conditions, resulting in the release of biologically active curcumin for up 80 days.

A sustained delivery of curcumin using poly (ε-caprolactone) (PCL) nanofibers showed higher efficacy in wound closure in the streptozotocin-induced diabetic mouse model [74]. Further *in vitro* studies showed cytoprotective and antiinflammatory activity for the curcumin-loaded nanofibers [74]. These experiments used low doses of curcumin (released from 17% w/w curcumin nanofibers), indicating that with an appropriate delivery vehicle even low-dose curcumin has the potential to treat wounds. Further, a clinical report showed that curcumin gel was effective in preventing early stage scar formation in patients, and the mechanism was hypothesized to be a curcumin-mediated inhibition of phosphorylase kinase/NF-κB-based fibroblast proliferation [47].

Nanoparticles, typically composed of polymeric hydrophobic cores and hydrophilic shells, can solubilize a variety of hydrophobic drugs and phytochemicals and provide sustained delivery of these agents *in vitro* and *in vivo* [75-77]. Incorporation of curcumin in an aqueous solution of nanoparticles comprised of hydrophobic poly(lactic-co-glycolic acid) and hydrophilic PEG resulted in controlled *in vitro* release of curcumin for 9 days under physiological conditions and improved the bioavailability of curcumin by > 50 fold as compared to aqueous curcumin suspensions after oral administration in an *in vivo* rat pharmacokinetics study [78]. Similarly, a solution of nanoparticles comprised of PEG and zein, a plant protein, increased the aqueous solubility of curmumin by a factor of 2,000 and provided sustained release for up to 24 h *in vitro* [54]. In this case, curcumin delivery to cancer cells was increased by a factor of 2 – 3 by the PEG-zein nanoparticles compared to free curcumin. Finally, the effective solubility of curcumin has been enhanced through formation of a colloidal suspension using a component of vegetable gum derived from the ghatti tree. Investigators demonstrated a 40-fold increase in bioavailability of curcumin in the colloidal formulation, relative to orally administered powder, in rats [79].

Accumulating evidence indicates that integrating curcumin into biocompatible dressing materials may be the most effective way to increase its bioavailability, and therefore its efficacy.

6. Conclusion

In this article, we have focused on published studies demonstrating the efficacy of curcumin for controlling pain and wound healing. Several reports clearly demonstrate that curcumin can directly act on nociceptive neurons and inhibit

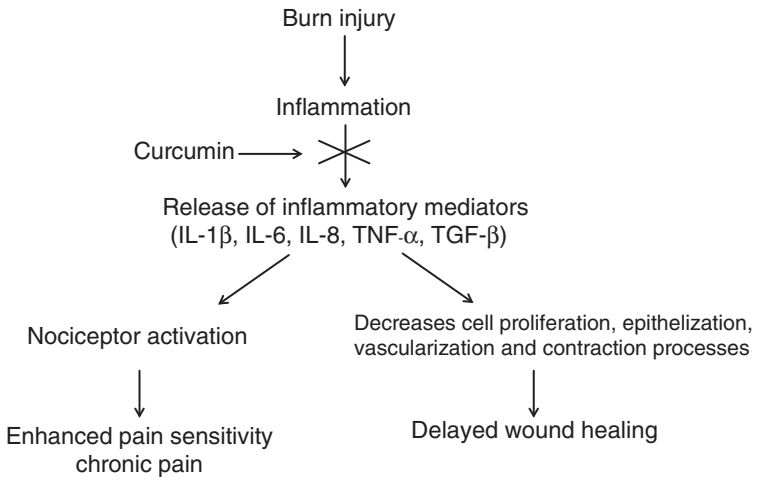

Figure 2. Inflammatory mediators released at the site of burn continuously stimulate nocicepptors evoking hyperalgesia and allodynia. Additionally, these same proinflammatory mediators delay wound healing processes. We propose that curcumin suppresses the release of proinflammatory mediators to simultaneously attenuate pain and enhance wound healing.

inflammatory signaling, and thereby can both attenuate pain and enhance wound healing processes. Further, curcumin is well-tolerated and has a favorable safety profile. Although low bioavailability is still a concern, several preclinical studies using advanced drug delivery systems have demonstrated improved efficacy of curcumin. Taken together with the many observations of the antiinflammatory and antinociceptive properties of curcumin, we conclude that curcumin formulations should be fully developed and tested clinically for patients suffering with chronic pain and wounds.

7. Expert opinion

Management of the intense pain that accompanies burn wounds currently relies heavily on opioids, which produce many CNS side-effects such as tolerance, hyperalgesia, hemodynamic instability respiratory depression and, perhaps the most costly, addiction [3]. Interestingly, conflicting results over the years have shown that opioids can have both positive and negative effects on wound healing, with the latter being attributed to immunosuppressive effects of long-term opioid treatment [13]. There is therefore a critical need in the burn care field for both effective nonopioid analgesic therapies, as well as treatments that can enhance wound healing and reduce scarring.

The central role for inflammation in both wound healing and pain signaling has led us to propose a model in which curcumin impacts both of these processes simultaneously through its antiinflammatory action (**Figure 2**). This is admittedly a simplified model, which necessarily omits a great deal of detail. However, we believe that is can serve as a starting point for mechanism-based development of this drug. It has been previously hypothesized that this same antiinflammatory function is a mechanism for skin tumor suppression by curcumin [80,81]. In regards to burn wounds, the first-line inflammatory response is initiated within minutes of burn injury and persists for days [82]. An important component of this response includes activation of sensory neurons and immune cells found at the site of injury, initiating pain signaling to the spinal cord and the release of inflammatory mediators. Nociceptors innervating the injured site, sensory cell bodies of the DRG, and spinal dorsal horn neurons express several types of pain-relevant ion channels and receptors targeted by these inflammatory mediators [83,84]. The continuous stimulation of these cells results in allodynia and hyperalgesia, the major symptoms of chronic pain [85]. In addition, the receptor proteins and downstream signaling pathways are altered following burn injury, and these changes likely contribute to both physiological and emotional components of burn pain and to the transition from acute to chronic pain states [86]. Over time, the balance between the release of both pro- and antiinflammatory cytokines, as well as algesic and analgesic mediators contributes to the chronicity of pain [87]. Also, inflammatory mediators decrease epithelization, vascularization, cell proliferation and contraction processes, which can lead to delays in wound healing. Thus inflammation is central to both burn-induced pain and wound healing [88]. Studying the action of curcumin on the inflammatory process at the site of burn injury, and at the three levels of the neuroaxis (peripheral, spinal and supraspinal) will provide important insight into the relationship between pain signaling and wound healing, which to our knowledge has not been explored.

Author's contributions

BP Cheppudira, D Devore and JL Clifford wrote the initial draft of the manuscript. A Greer, A Mares, DR Loyd, M Fowler, L McGhee and L Petz contributed text and proofread the manuscript.

Declaration of interest

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