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
**Title:** Curcumin: a novel therapeutic for burn pain and wound healing.

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**ABSTRACT**

**SUBJECT TERMS**

**SECURITY CLASSIFICATION OF**

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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 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 vats [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
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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.

<table>
<thead>
<tr>
<th>Study/Refs.</th>
<th>Animal</th>
<th>Animal models of pain</th>
<th>Doses tested</th>
<th>Route</th>
<th>Treatment</th>
<th>Pain tests</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sharma et al. (2006, 2007) [16,20]</td>
<td>Mouse</td>
<td>Streptozotocin-induced diabetic neuropathy</td>
<td>15 – 60 mg/kg</td>
<td>p.o.</td>
<td>Once per day for 4 weeks</td>
<td>Tail immersion; hot plate</td>
<td>Dose-dependent antinociceptive effects</td>
</tr>
<tr>
<td>Yeon et al. (2010) [32]</td>
<td>Rat</td>
<td>Capsaicin-induced thermal hyperalgesia</td>
<td>5 – 50 mg/kg</td>
<td>i.p.</td>
<td>Single</td>
<td>Hot plate; tail flick; Randall-Sellitto</td>
<td>Thermal</td>
</tr>
<tr>
<td>Attia et al. (2012) [23]</td>
<td>Rat</td>
<td>Streptozotocin-induced diabetic neuropathy</td>
<td>100 mg/kg</td>
<td>i.p.</td>
<td>Single</td>
<td>Tail pinch; Randall-Sellitto</td>
<td>Increased thermal latency and mechanical threshold</td>
</tr>
<tr>
<td>Arora et al. (2011) [40]</td>
<td>Rat</td>
<td>Reserpine-induced pain-depression dyad</td>
<td>100 – 300 mg/kg</td>
<td>i.p.</td>
<td>Single</td>
<td>Von Frey; thermal</td>
<td>Dose-dependent increase in mechanical threshold and thermal latency</td>
</tr>
<tr>
<td>Zhao et al. (2012) [25]</td>
<td>Rat</td>
<td>Chronic constriction injury (CCI)</td>
<td>5 – 45 mg/kg</td>
<td>i.t.</td>
<td>Twice per day for 3 weeks</td>
<td>Nocifensive behavioral scoring</td>
<td>Dose-dependent increase in mechanical threshold and thermal latency</td>
</tr>
<tr>
<td>Han et al. (2012) [29]</td>
<td>Rat</td>
<td>Formalin-induced spontaneous pain</td>
<td>62.5 – 500 µg</td>
<td>i.p.</td>
<td>Once per day for 4 days</td>
<td>Von Frey; thermal</td>
<td>Decreased allodynia and thermal hyperalgesia</td>
</tr>
<tr>
<td>Liang et al. (2013) [33]</td>
<td>Mouse</td>
<td>Morphine-induced hyperalgesia</td>
<td>50 mg/kg</td>
<td>i.p.</td>
<td>Once per day for 7 – 14 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feng-tao et al. (2013) [26]</td>
<td>Rats</td>
<td>Chronic constriction injury (CCI)</td>
<td>50 – 100 mg/kg</td>
<td>i.p.</td>
<td></td>
<td>Von Frey; thermal</td>
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p.o.: Per os; i.p.: Intraperitoneal; i.t.: Intrathecal.
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 [55]. 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, alginate, 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,N-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 curcumin 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
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 it 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.
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Declaration of interest

This work was supported by the United States Army Medical Research and Materiel Command Combat Casualty Care Research and the Clinical and Rehabilitative Medicine Research programs. B Cheppudira is supported by National Research Council (NRC) Senior Research Associate Fellowship. The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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* An up to date review of molecular signaling related to burn injury scarring.


** A thorough review of the effects of opioids, the most widely used analogics, on wound healing.


* See Table 1.


** An authoritative review of the entire range of biological effects of curcumin.


* See Table 1.


* See Table 1.


* See Table 1.


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28. Rosenberg LB, Whang W, Shimbo D, et al. Exposure to tricyclic antidepressants is associated with an increased risk of


• See Table 1.


• See Table 1.


This article describes the landmark discovery of TRPV1.


• See Table 1.


This study showed that topically applied curcumin could enhance healing of burn wounds in a rat model, supporting the utility of this mode of administration.


• See Table 1.


• See Table 1.


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84. Bopaiah Cheppudira1 PhD, Marcie Fowler1 PhD, Laura McGhee3 PhD, Angie Greer3 BS, Alberto Mares1 MS, Lawrence Petz1 PhD, David Devore2 PhD, Dayna R Loyd1 PhD & John L Clifford1 PhD

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This study showed the feasibility of delivering a therapeutically effective dose of curcumin over an extended period of time in a rat wound healing model.