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Reviewing the Potential Use of Curcumin Extract for Topical Therapy Supporting Burn Wound Healing

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ABSTRACT

Introduction: Wound dressing is a fundamental aspect of modern healthcare, encompassing a diverse range of materials and techniques aimed at optimizing the healing process while safeguarding against infection and further injury. By understanding the specific benefits of different types of wound dressings, healthcare professionals can optimize the healing process and improve patient outcomes

Methods: This literature review was compiled using information from numerous open access web databases. Data were compiled and analyzed.

Results and Discussions: Curcumin has the ability to improve burn wound healing. Curcumin can reduce inflammation by inhibiting proinflammatory cytokines. It also helps cell proliferation, and has an antimicrobial effect, therefore it speeds up burn wound healing and prevents keloid formation.

Conclusion: Curcumin has potential activity in speeding up burn wound healing, thanks to its anti-inflammation, antioxidant, and antimicrobial activity. However, due to low solubility in water of curcumin and its instability, further research must be done to find out better form for curcumin

KEYWORDS: curcumin, burn, wound healing, infection, proliferation, antiinflammation, antioxidant, antimicrobial, dressing, form.

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INTRODUCTION

Burn injuries are often overlooked as a significant form of trauma, yet they can affect anyone, at any time, and in any location. These injuries can result from various sources, including friction, cold, heat, radiation, chemicals, or electricity, though the majority are caused by heat from hot liquids, solids, or flames. Burn injuries are a major health concern, contributing to considerable morbidity and mortality, with an estimated 180,000 deaths annually, predominantly in low- and middle-income countries. While the incidence of burn injuries is declining in high-income nations, the prevalence remains high in other regions. The direct medical costs associated with burn treatment can vary widely, but they tend to be quite high. A 2014 systematic review reported an average healthcare cost of US$ 88,218 per burn patient, with costs ranging from US$ 704 to US$ 717,306[1, 2].

Burn injuries are among the most severe and complex forms of trauma. In addition to causing visible skin damage, such as scars, thermal injuries disrupt the body's hormonal balance. During the acute phase, the body experiences a significant increase in stress hormones and an intense activation of proinflammatory cells and their cytokines. While this hypermetabolic stress response is beneficial in the early stages to maintain circulatory stability, prolonged activation can have detrimental effects, leading to a range of late complications. Burn injuries cause coagulative necrosis in various skin layers and underlying tissues. The skin, serving as a protective barrier, typically limits the damage to deeper tissues, but the extent of injury depends on factors such as temperature, the energy transferred by the causative agent, and exposure duration. Dampening the initial hypermetabolic response helps minimize nonviable tissue and improves outcomes, including faster healing and reduced scarring[3-5].

Burn wound healing is a complex process including inflammation, granulation, and remodeling of the tissue. When treating burn wounds, we should retain the blister skin as a biofilm to protect the wound surface, maintain a moist wound environment, and reduce the risk of infection. This approach helps prevent the wound from deepening and supports recovery. For cases where caregivers cannot

preserve blister skin, numerous artificial dressings are available. These include biosynthetic (skin substitute) dressings, silver-containing dressings, and silicone-coated dressings, as well as gauze, hydrocolloids, and hydrogels. Among natural antioxidants, curcumin stands out as one of the most powerful anti-inflammatory agents used in clinical medicine. Derived from the plant Curcuma longa, turmeric is a golden spice commonly used in both health care and food preservation. The diferuloyl-methane component of curcumin has antioxidant and anti-inflammatory effects, remaining non-toxic even at high doses. Curcumin exerts its antioxidant action by regulating various enzymes, transcription factors, growth factors, and inflammatory cytokines [6, 7]. Picture of *Curcuma longa* as the main source of curcumin can be seen in figure 1.

Figure 1. Rhizome of *Curcuma longa*[8]

METHODS

We conducted this literature review by analyzing data from various web databases. The inclusion criteria include: (1) journals that were openly accessible, and (2) choosing articles that corresponded the subject matter covered in this review. For this literature review, we utilized keywords such as "curcumin extract for burn wound healing", "active ingredients of curcumin extract for burn wound healing", and "mechanism of action of active ingredients in curcumin extract for burn wound healing" on platforms including PubMed, Google Scholar, and Elsevier. We collected, organized, and summarized the data obtained from these sources.

REVIEW RESULTS AND DISCUSSIONS

Active Ingredients of Curcumin and Their Mechanisms of Action

1. Curcumin
   a. Antiinflammation

      Curcumin has the ability to reduce inflammation. Curcumin reduces inflammation by regulating the signaling pathway of inflammation. Complete mechanism of anti-inflammatory effect of curcumin can be seen in figure 2.

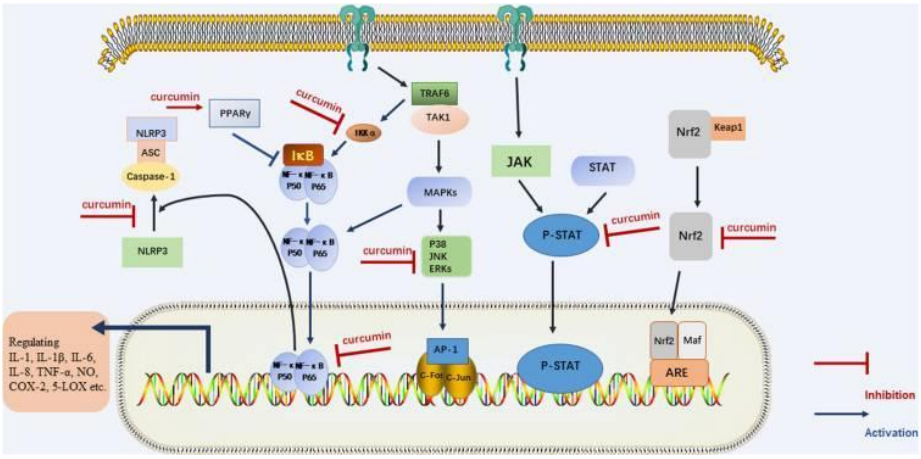

Figure 2. The regulatory effect of curcumin on inflammatory signaling pathway[9]

Curcumin can bind to Toll Like Receptors (TLR) and downregulates Factor kappa-B (NF-κB), Mitogen-activated protein kinases (MAPK), and Activator Protein 1 (AP-1), to control inflammatory mediators and treat inflammatory diseases. It downregulates NF-κB by interacting with

Peroxisome proliferator-activated receptor gamma (PPARγ). Additionally, curcumin exerts anti-inflammatory effects by modulating the Janus kinase/Signal transducer and activator of transcription (JAK/STAT) pathway. Moreover, the NOD-like receptor pyrin domain-containing 3 (NLRP3) inflammasome, a cytosolic multiprotein complex, plays a role in several inflammatory diseases. The NLRP3 inflammasome consists of three components: a sensor protein, an apoptosis-associated speck-like protein containing a caspase recruitment domain, and the protease caspase-1. Curcumin directly inhibits the assembly of the NLRP3 inflammasome or suppresses its activation through the NF-κB pathway, which may be one of the mechanisms by which curcumin treats inflammatory conditions. Interestingly, studies suggest that in the absence of infection, inflammation might not be required for tissue repair. While inflammation is crucial for wound healing, excessive or prolonged inflammation and edema can worsen pain and hinder the healing process.[9, 10]

b. Antioxidant

Low levels of reactive oxygen species (ROS) form during normal wound healing to defend against invading pathogens and facilitate intracellular signaling, particularly for angiogenesis. To counteract the toxic effects of ROS, mammalian cells are equipped with an antioxidant enzyme system and small antioxidant molecules that detoxify radicals and repair oxidized molecules at the wound site. However, when oxidative stress becomes excessive, these agents cannot be produced in sufficient amounts to restore the redox balance, leading to oxidative stress and prolonged inflammation, which is a key factor in the development of chronic nonhealing wounds[1].

Antioxidant therapy targets ROS by introducing antioxidants to the wound area, aiming to eliminate ROS and thereby promote the healing of chronic wounds. Curcumin demonstrates potent antioxidant activity due to its ability to transfer electrons or donate H-atoms from its two methoxy phenol groups. Additionally, curcumin contains functional groups like b-diketone and several π-electrons that enhance its electron transfer capacity. The phenolic hydroxyl groups contribute to its ROS-scavenging ability, while the di-ketone structure helps bind to metals. The molecular mechanisms behind curcumin's antioxidant activity involve the activation of cytoprotective signaling pathways, such as the nuclear factor erythroid 2-related factor (Nrf2) pathway[11]

c. Fibroblast Activation and Collagen Synthesis

Wound healing is associated with normalization of vascularization, reduced leukocytic movement and edema, and fibroblast proliferation. This process is related to Keratinocytes Growth Factor (KGF-1). KGF-1 binds to the keratinocyte growth factor receptor (KGFR), mainly expressed on keratinocytes and epithelial cells, with high affinity. KGF-1 controls several cellular processes, such as cell proliferation, differentiation, migration, and survival. KGF-1 stimulated keratinocyte proliferation and migration during the reepithelialization stage[12].

d. Angiogenesis

Angiogenesis inhibitors fall into two categories. The first category, known as direct angiogenesis inhibitors, includes those that are more selective for endothelial cells than tumor cells. The second category, indirect inhibitors, do not directly affect endothelial cells but regulate angiogenesis by downregulating angiogenesis stimulators. Curcumin acts as a direct angiogenesis inhibitor and also downregulates several proangiogenesis factors. It influences the entire angiogenesis process by suppressing transcription factors like NF-κB and proangiogenesis factors such as VEGF, bFGF, and MMPs[13].

e. Anti-microbial Activity

A lot of researches stated that curcumin has potential antimicrobial activity. Curcumin has antimicrobial activity against several bacteries such as *S. agalactiae, S. intermedius, S. epidermidis, S. aureus, A. hydrophila, B. subtilis, B. cereus,* and *E. tarda*. Study stated that turmeric oil as a derivative product from curcumin manufacture also was found effective against *B. subtilis, B. coagulans, B. cereus, Staph. aureus, E. coli,* and *P. aeruginosa.* Curcumin also was stated has significant effect in inhibiting Methicillin-Resistant *S. aureus* strains (MRSA) with Minimum Inhibitory Concentration (MIC) value of 125–250 μg/mL. Antimicrobial activity of curcumin is caused by its activity in inhibiting formation of FtsZ, a protein encoded by the ftsz gene. The FtsZ protein, called Z ring as well, has a significant role in cell division of bacteria. Curcumin inhibits coding of this protein so bacteria can't do cell division properly[14].

2. Other Active Compounds in Curcumin Extract:

Demethoxycurcumin (DMC) and Bisdemethoxycurcumin (BDMC) are also found in curcumin extract. These curcuminoids, along with curcumin, synergistically contribute to wound healing through enhanced anti-inflammatory and antioxidant effects. DMC and BDMC can inhibit COX-1 and COX-2, thus reducing inflammation and helping wound healing. Studies also reported that DMC and BDMC reduced inflammation by

inhibiting LPS-induced NF-kB activation. DMC and BDMC have more potent anti-inflammatory effect but have less antioxidative effect than curcumin. Their combined actions may improve the overall healing process[15].

Accelerated Burn Wound Healing: Evidence and Mechanism

Controlling inflammation is desirable and can accelerate the wound healing process since tissue injury produces practically a rapid start of acute inflammation. Inflammation in wound is an immune response initiated by injury-induced signals, damage-associated molecular patterns (DAMPs) released by necrotic cells and damaged tissue, and pathogen-associated molecular patterns (PAMPs) from microbial components. These signals will activate inflammatory cells such as mast cells, Langerhans cells, T cells and macrophages, by binding pattern recognition receptors and releasing inflammatory cytokines. The inflammatory response is a complex mechanism and has various benefits, but excessive inflammation can delay burn wound healing. Therefore, the immune cell response must be situational, increasing to respond to infection, yet still being effective enough to allow wound healing[16].

Curcumin is an anti-inflammatory and anti-microbial agent. The anti-inflammatory effect is due to its capability to inhibit inflammatory mediators. Curcumin can bind to Toll-like receptors (TLRs) and regulates nuclear factor kappa-B (NF-κB), mitogen-activated protein kinase (MAPK), Activator Protein 1 (AP-1) and other signaling pathways. Therefore, reducing inflammatory response. In vitro study also stated that curcumin can decrease levels of pro-inflammatory mediators such as Interleukin-1 (IL-1), IL-1β, IL-6, IL-8, IL-17, IL-27, Tumor necrosis factor-α (TNF-α), Inducible nitric oxide synthase (iNOS), NO, Regulated upon activation normal T cell expressed and secreted factor(RANTES), Granulocyte colony-stimulating factor (G-CSF), and Monocyte chemotactic protein-1 (MCP-1)[7].

In order to coordinate wound closure, matrix deposition, and angiogenesis, keratinocytes, fibroblasts, macrophages, and endothelial cells are extensively activated during the proliferative phase of healing. Changes in electrical gradients and mechanical strain, as well as exposure to hydrogen peroxide, pathogens, growth factors, and cytokines, can activate keratinocytes as early as 12 hours after injury. Keratinocytes along the wound edge undergo a partial epithelial–mesenchymal transition as a result of this stimulation, taking on a more invasive and migrating appearance. The leading-edge keratinocytes can move laterally across the wound to reform the epidermal layer, a process known as re-epithelialization, when front-to-rear polarity takes the place of top-to-bottom polarity[16].

Curcumin promoted collagen production and enhanced cellular proliferation at the wound site, as seen by increased DNA, total protein, and type III collagen content in wound tissues. Curcumin-increased cytokine production causes fibroblasts to migrate to wound sites, resulting in enhanced fibroblast and collagen proliferation. Fibroblasts naturally develop into myofibroblasts during the creation of granulation tissue. Curcumin sped up cell proliferation by reducing inflammation in wounds. The antioxidant effect of curcumin is also playing a role in collagen deposition and fibronectin production, resulting in quick re-epithelialization in wound healing[17].

Keloids is one of many dermatological challenges, marked by excessive collagen deposition and abnormal proliferation of fibroblast sequel to skin injury or trauma. Study said that curcuminoids such as curcumin or DMC have the ability to prevent keloid formation. Keloids can be formed via the STAT3 signaling pathway, a signaling pathway that causes cell proliferation and differentiation. Curcumin and DMC prevent keloid formation by blocking STAT3 signaling pathways. Curcumin also has the ability to suppress the synthesis of cytokines linked to inflammation, including interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6), all of which are essential for the development of keloid. Furthermore, curcumin has shown that it can inhibit the overgrowth of fibroblasts, which are the main cell type linked to keloid development. By regulating fibroblast activity, curcumin may lessen the development of keloids and hypertrophic scars, which are frequent side effects of burn wound healing. Curcumin facilitates balanced collagen synthesis, which results in a less hypertrophic and more malleable scar[18].

Side Effects and Anticipated Challenges

Despite having a lot of benefits, curcumin as topical treatment for burn wound healing also has many side effects, such as[19, 20].

1. Allergic Reactions
   As a topical treatment, curcumin has the chance of being allergen to some people. Some individuals may experience skin irritation, allergic dermatitis, or rash upon topical application of Curcumin extract. Testing for sensitivities before widespread application is recommended.
2. Limited Skin Penetration
   Curcumin has poor solubility in water and limited bioavailability in topical formulations. It may reduce its effectiveness in accelerating burn wound healing. Formulation improvements, such as using liposomal encapsulation or other nanotechnology-based delivery systems, are required to enhance skin penetration and bioavailability.
3. Interaction with Other Medications:
   Curcumin can affect the metabolism of certain drugs by interacting with cytochrome P450 enzymes. Patients on concurrent medications should be monitored for potential drug interactions, especially in burn patients requiring pain management and antibiotics.
4. Irritation on Sensitive Skin
   Burn wounds, especially in the acute phase, are highly

sensitive skin. Curcumin is considered as foreign object. Therefore it may cause irritation or exacerbation of the inflammatory response if not appropriately diluted or combined with soothing agents.

Barriers to the Development of Curcumin as a Standard Topical Therapy

Curcumin has low water solubility and poor absorption. It is also metabolized rapidly in the body. The low water solubility and rapid metabolism of Curcumin reduce its effectiveness in topical wound therapies. For improving its efficacy, the need for stable, bioavailable formulations such as microemulsions, hydrogels, or nanostructured lipid carriers is crucial[21].

Despite curcumin's historical use in traditional medicine, regulatory and standardization should be required to substantiate its claims and establish standardized safe dosages for topical use in burn treatments. It is important to note that most research evaluating the safety profile of curcumin has only been carried out for brief periods of time. There is currently no reliable information on the effects of prolonged usage of this substance. Supplements containing curcumin are freely accessible to the general people and are becoming more and more popular, despite the fact that the dosages advised for over-the-counter curcumin are typically lower than those in the clinical research previously stated. In this sense, the medical community's attention was drawn to the potential liver toxicity of curcumin by recent reports of liver disorders associated with this chemical[22].

Although Curcumin is derived from a common plant, large-scale production of pharmaceutical-grade Curcumin may be cost-prohibitive, especially in low-resource settings. Availability of high-quality Curcumin could limit its widespread adoption in clinical practice[20].

Potential for Future Development

Curcumin is naturally water-insoluble, unstable, and has low bioavailability. Combination between curcumin and piperine (black pepper natural alkaloid) has proven to be effective in increasing curcumin's bioavailability[21]. Besides, study stated that adding hyaluronic acid to topical curcumin increases its ability in wound healing. Wounds which are treated with curcumin conjugated to hyaluronic acid have faster healing time than topical curcumin without hyaluronic acid[17].

One area of medicine that has shown promise is nanotechnology (nanomedicine). The inherent physical and chemical characteristics of nanoscale structures have been used as tools for diagnosis and treatment. The presence of nanotechnology helps increase the solubility of curcumin in water. Besides, nano formulation of curcumin is also increasing its antimicrobial effect[23].

Although curcumin has a wide safety threshold, toxicity caused by curcumin can occur. Lethal dose 50 (LD50) of curcumin is about 2g/kg/day. Research stated that consuming curcumin 100 mg/kg/day for 90 days in a row can cause side effects such as overproduction of Reactive Oxygen Species (ROS). Therefore, a lot of research must be carried out to find its effective dose without causing side effects[24].

CONCLUSION

Curcumin is one of the natural compounds that has a lot of benefits in speeding up burn wound healing. Its anti-inflammation, antioxidant, and antimicrobial effect are the main reasons for its effectiveness in burn wound healing. Nevertheless, curcumin is not soluble in water and has low bioavailability. These problems make curcumin be less effective as a burn wound healing treatment. But it can be combined with other substances to make curcumin more soluble, more stable, and increase its bioavailability, thus improving its effectiveness. However, a lot of research must be done to make sure its safety to the human body.

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