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Review Article

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Role of Curcumin in Wound Healing

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Abstract

Wound healing implicates several biological and molecular events, such as coagulation, inflammation, migration-proliferation, and remodeling. 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 has been shown to possess significant anti-inflammatory, anti-oxidant, anti-carcinogenic, anti-mutagenic, anticoagulant 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.

Keywords: Curcumin, wound healing.

INTRODUCTION

Cell migration, cell proliferation, and the deposition of extracellular matrix are among the biological and molecular processes that are involved in wound healing. Obtaining tissue integrity and homeostasis is the immediate goal of wound healing (Eming et al., 2007).[1] Hemostasis, inflammation, proliferation, and remodelling are the four distinct but overlapping processes that make up the natural healing process for wounds.

Significant anti-inflammatory, antioxidant, anti-mutagenic, anti-carcinogenic, anti-clotting, and anti-infective properties of curcumin have been demonstrated. Additionally, strong wound healing abilities of curcumin have been demonstrated. It affects different stages of the body's natural wound-healing cycle to speed up healing.

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HISTORY

The turmeric plant, a herb from the ginger family, has long been utilised in Indian and Chinese cuisines as a culinary spice and food colour (Chattopadhyay et al., 2004).[2] The most useful portion of the plant for medicinal uses is the rhizome (root), which has been utilised for millennia in Chinese and Indian traditional remedies (Chattopadhyay et al., 2004; Patwardhan et al., 2005).[3]

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 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) Curcumin (diferuloylmethane) is the main curcuminoid present in turmeric and responsible for its yellow color.

The structure of curcumin (1,7-bis(4-hydroxy-3methoxyphenyl)-1,6hepadiene-3,5-dione) (Fig. 1) was first described by Milobedska et al.[4] (1910).

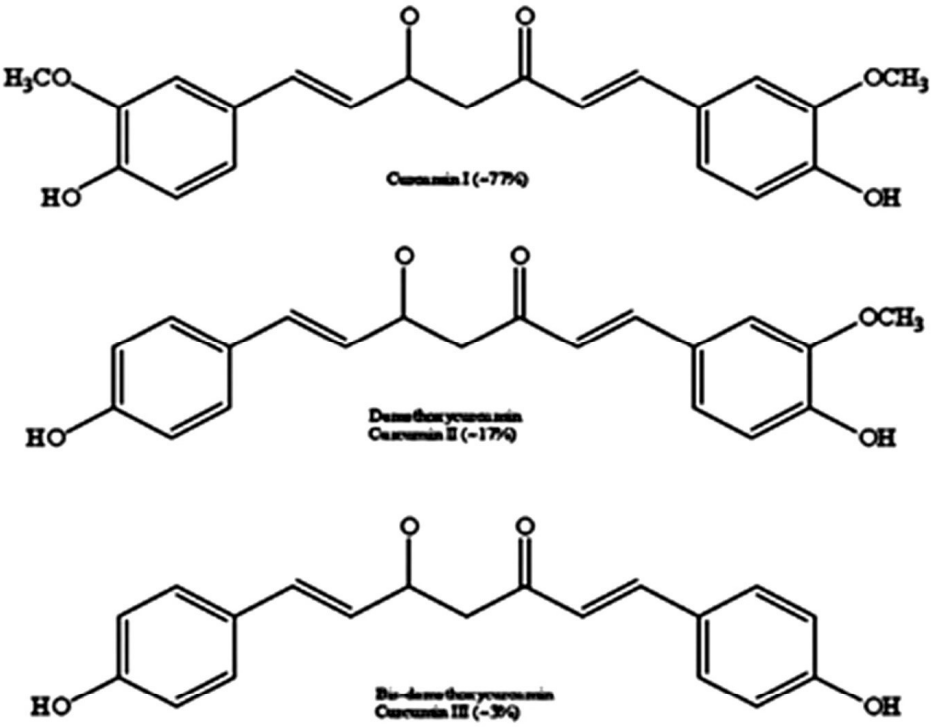


Fig. 1: Chemical structures of curcuminoids: Curcumin, demethoxycurcumin and bisdemetohxycurcumin that have shown antioxidant and/or anti-inflammatory properties.

PHYSIOLOGY

Wound healing Process

Skin acts as a natural barrier against the elements and performs a number of vital defensive tasks. The body starts a multi-step, dynamic process at the wounded location when the integrity of skin is disrupted by either acute or chronic injuries. This process results in partial repair of the tissue and restoration of the skin's barrier function. Obtaining tissue integrity and homeostasis is the immediate goal of wound healing (Eming et al., 2007). Hemostasis, inflammation, proliferation, and remodelling are the four distinct but overlapping processes that make up the natural healing process for wounds. Injury results in hemostasis, which causes platelet aggregation and the production of blood clots (Enoch et al., 2006).[5] A temporary extracellular matrix for cell motility is provided by the blood clot (Epstein et al., 1999). Blood cells, such as phagocytic neutrophils and macrophages, migrate to the site of the lesion during the inflammatory phase (Enoch et al., 2006). As the inflammatory phase comes to a conclusion, the phagocytes release cytokines to encourage fibroblast migration and proliferation in addition to initially removing foreign particles (Topman et al., 2013).[6] Within hours of the injury, the wound starts to reepithelialize, which is a stage of the proliferative phase (Epstein et al., 1999).[7] According to Topman et al. (2013), this phase is characterised by the development of new blood vessels (angiogenesis or neovascularization), which restores perfusion to support the developing tissues. It is also characterised by the production and deposition of extracellular matrix protein fragments like collagen fibres and granulation tissue (Enoch et al., 2006). Fibroblasts are essential to the wound healing process because they develop the new extracellular matrix required to promote cell ingrowth utilising collagen as the building block (Epstein et al., 1999).

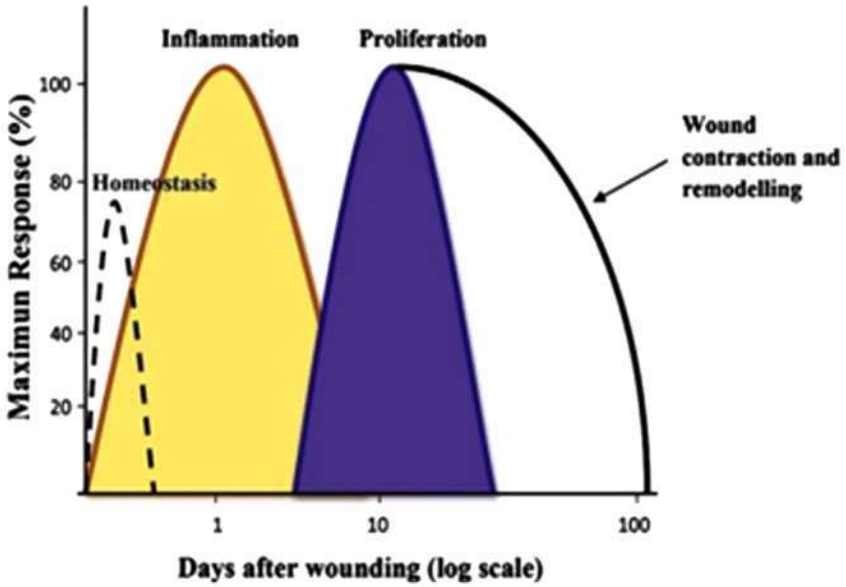


Fig. 2: The four phases of acute wound healing.

Collagen remodelling and the development of scar tissue are part of the last stage. Figure 2 highlights the overlapped nature of the process while also showing the length of each wound healing phase after injury (Epstein et al., 1999).

Wound healing Activities of Curcumin

An ideal wound dressing or agent prevents bacterial infection, lessens inflammation, and promotes cell proliferation to help the body repair injured tissue (Kulac et al., 2013).[8] Since free radicals are thought to be the primary cause of inflammation throughout the healing process of wounds, it would ideally also function as an antioxidant (Mohanty et al., 2012).[9] The biochemical properties of curcumin, such as its anti-inflammatory (Liang et al., 2009)[10], anti-infectious (Mun et al., 20131[11]; Singh et al., 2010[12]) and anti-oxidant (Ak and Gulcin, 2008; Meng et al., 2013) activities, are thought to contribute to its ability to heal wounds. Through its role in tissue remodelling, granulation tissue development, and collagen deposition, curcumin has also been proven to improve the healing of cutaneous wounds (Joe et al., 2004).[13] 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 topical curcuminin wound healing, focusing on its mechanisms of action and providing evidence for its effects on the various stages of wound healing process.

Mechanism of Action of Curcumin on the Phases of Wound Healing

Effects of Curcumin on Inflammation

Joe et al. (2004)[13] provided a thorough analysis of the several ways that curcumin affects inflammation. The two primary cytokines generated by monocytes and macrophages, tumour necrosis factor alpha (TNF-) and interleukin-1 (IL-1), which are crucial for controlling inflammatory responses, were demonstrated to be inhibited by curcumin.

Equally significant is curcumin's capacity to block the activity of NF-(B), a transcription factor that controls numerous genes linked to the start of inflammatory reactions. NF-(B) stands for nuclear factor kappa-light-chain-enhancer of activated B cells. Curcumin has an impact on a number of the pathways involved in the activation of NF-() B, which are often triggered by different kinases (AKT, PI3K, IKK).

According to Imlay (2003)[14] and Matés et al. (1999)[15], reactive oxygen species (ROS) are by products of aerobic respiration that are unavoidable and play a key role in a number of cellular and biochemical functions, including intracellular communication, differentiation, cell growth, apoptosis, and immunity. Since ROS are necessary for the immune system to defend against microorganisms, they are also implicated in wound healing. However, oxidative stress is produced when ROS are present for an extended period of time at high quantities, and this can seriously harm human cells

(Panchatcharam et al., 2006; Roy et al.[16], 2006). The wound healing process is significantly influenced by oxidative stress, which normally prevents tissue remodelling (Thangapazham et al.,[17] 2013). Superoxide (O_2) and hydrogen peroxide (H_2O_2), two ROS, can be utilised as indicators of how much oxidative stress is present in a system (Imlay, 2003). As free radicals, ROS cause oxidative damage that prevents optimum wound healing by causing lipid peroxidation, DNA damage, and enzyme inactivation. Inflammation during wound healing is thought to be mostly caused by ROS (Mohanty et al., 2012). Free radicals must be appropriately scavenged since they also target and harm tissue proteins (Kapoor and Priyadarsini, 2001). Human cells are shielded from harmful reactive oxygen species by anti-oxidant enzymes such catalase, glutathione peroxidase, and superoxide dismutase (Matés et al., 1999). When given topically, antioxidants with the ability to scavenge free radicals have been demonstrated to considerably increase wound healing (Martin, 1996).

Effects of Curcumin on the Pproliferative Phase of Wound Healing

In the proliferative phase of wound healing, granulation tissue is formed, collagen is deposited (creating the extracellular protein matrix), fibroblasts multiply, epithelialization occurs, and undesirable cells are killed by apoptosis (Epstein et al., 1999).

Effects of Curcumin on Fibroblast Proliferation

The most crucial factor in guaranteeing quick and aesthetically pleasing wound closure is likely the presence of fibroblasts in the wound environment. Fibroblasts naturally develop into myofibroblasts during the creation of granulation tissue (Petroll et al., 1993).[18] Numerous studies have demonstrated that curcumin treatment causes fibroblasts to invade wound sites. Myofibroblasts were deposited in the wound environment treated with the curcumin-loaded oleic acid based polymeric (COP) bandage as early as four days after wound excision, according to research by Mohanty et al. (2012) in a rat model. Numerous wounds, particularly diabetic ones, contained myofibroblasts (Sidhu et al., 1998; Sidhu et al., 1999).

It is important to note that curcumin's cytotoxicity limits the extent of increased fibroblast infiltration in groups that received curcumin treatment. In in vitro wound models, curcumin can induce fibroblast death at high dosages (25 M). At 48 hours after treatment, cell mortality at this concentration reached 60%. The fundamental cause of the observed fibroblast apoptosis in the curcumin-treated group is that curcumin becomes oxidising at high concentrations and generates ROS. In cells treated with curcumin, fibroblast shape was unaffected at lower concentrations (such as 5 and 10 M), and no apoptosis was seen (Scharstuhl et al., 2009).

Effects of Curcumin on Granulation Tissue formation

Four days after a skin injury, granulation tissue or new stroma start to form. It is distinguished by the development of tiny capillaries and fibroblast infiltration, which promote the creation of extracellular matrix (Epstein et al., 1999). Granulation tissue promotes re-epithelialization by giving epithelial cells the basal support they need to move and heal the wound gap (Sidhu et al., 1999). When compared to gauze treated wounds, excised wounds on rats treated with a curcumin-loaded chitosan alginate (CLCA) sponge had improved granulation tissue alignment (control group). In addition, Gopinath et al. (2004) found that rats treated with CICM (curcumin included collagen matrix) had higher wound hydroxyproline level than control rats. Protein markers like hydroxyproline are primarily produced through the formation of collagen. As a result, the presence of hydroxyproline points to a proliferation of myofibroblasts around the wound. Myofibroblasts are a good indicator of the production of granulation tissue since fibroblasts can differentiate into them throughout this process. Similar to this, Mohanty et al. (2012) shown that wounds treated with COP (curcumin loaded oleic acid based polymeric) had improved organisation of granulation tissue ten days after treatment, and little or poorly formed granulation tissue until four days post-treatment. Diabetic rats treated with curcumin also showed neovascularization, or an increased production of tiny capillaries (Sidhu et al., 1999).

Effect of Curcumin on Collagen Deposition

Collagen is the main protein in the extracellular matrix of skin, which makes up between 70 and 80 percent of skin (Shoulders and Raines, 2009). Scar tissue, primarily made of collagenous fibres, forms as the final outcome of wound healing (Sai and Babu, 2000).[19] In order to improve wound repair, sufficient collagen production and deposition in a wound site would be ideal. It was demonstrated in a rat model that the wounds treated with a CLCA sponge had a greater collagen content than the gauze-treated control group. The resulting collagen is more compact and well-aligned, and the collagen

bundles in the curcumin-treated group seemed to be thicker (Dai et al., 2009). In comparison to the collagen in the control group, Mohanty et al. (2012) showed that wounds treated with COP bandages had greater aldehyde contents. The production of a strongly cross-linked collagen bed in the wounds treated with COP bandages was thought to be caused by the high aldehyde content in collagen (Mohanty et al., 2012; George and Chandrakasan, 1996). When rats' wounds were topically treated with curcumin, Panchatcharam et al. (2006) demonstrated that collagen content increased and that collagen fibres also matured earlier. 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 crosslinked 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; Sidhuet al., 1999).

Effects of Curcumin on Apoptosis

A number of apoptotic mechanisms occur to remove undesired inflammatory cells from the wound site so that the wound can go onto subsequent phases of healing. This enables the wound to develop and enter the proliferative stage (Sidhu et al., 1998; Sidhu et al., 1999; Brown et al., 1997). Although the precise method of action is uncertain and varies depending on the cell type, it has been reported that curcumin can produce ROS, which can lead to apoptosis (Scharstuhl et al., 2009).[20] Given that DNA fragmentation experiments have shown the presence of dead cells as early as four days after treatment with the COP bandage in a rat wound model, curcumin is apoptotic in the early stages of wound healing (Mohanty et al., 2012). Curcumin was able to speed up the healing cycle into the proliferative phase with little prolonging of the inflammatory phase as compared to control treatments, where low apoptosis rates were found in the early stages of wound healing.

Effects of Curcumin on Wound Contraction

The last stage of healing, known as wound contraction, is characterised by complicated interactions between cells, extracellular matrix proteins, and cytokines (Epstein et al., 1999). Wound contraction starts roughly two weeks after the wound when fibroblasts transform into myofibroblasts (Welch et al., 1990). By promoting smooth muscle actin expression in the granulation tissue, myofibroblasts promote wound contraction (Desmouliere et al., 1993).[21] Transforming growth factor and platelet-derived growth factors are also necessary to stimulate wound contraction while cross-linking in collagen bundles takes place (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.

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).

Effects of Curcumin on Re-epithelialization and Remodeling

The epidermis, which is the top layer of skin, acts as a vital barrier between an organism and its surroundings, shielding the host from microbiological, chemical, and physical harm (Koivisto et al., 2011).[22] Keratinocytes migrate and divide during the process of epithelialization from the bottom layers of the skin (Panchatcharam et al., 2006). Re-epithelialization must be a robust process to restore appropriate barrier function of the epidermis as the final step of wound healing (together with remodelling) (Koivisto et al., 2011). In a rat model, topical application of curcumin to wounds led to full epithelialization. When compared to the control group, curcumin significantly shortened the time it took for the treated wounds to epithelialize, from 23 days to just 11 days (Panchatcharam et al., 2006).

INDICATIONS

In traditional medicine, curcumin was frequently used to treat biliary and hepatic problems, cough, diabetic ulcers, rheumatism, and sinusitis. Curcumin has recently been the subject of substantial research as an anti-cancer, anti-aging, and wound healing agent. For example, curcumin has been shown to have a positive impact on the course of endometriosis, a prevalent condition affecting women of reproductive age that shares several molecular processes with wound healing (i.e., adhesion and proliferation, cellular invasion and angiogenesis).

CONTRAINDICATIONS

People with blood disorders, diabetes, GERD, infertility, iron deficiency, liver illness, ailments that are hormone-sensitive, arrhythmia, and GERD shouldn't use turmeric.

Curcumin is contraindicated with antiplatelet, anticoagulant, non-steroidal anti-inflammatory medicines (NSAIDs), and selective serotonin reuptake inhibitors (SSRIs) medications (SSRIs).

ADVANTAGES

Through its role in tissue remodelling, granulation tissue development, and collagen deposition, curcumin has also been proven to improve the healing of cutaneous wounds (Joe et al., 2004). Numerous studies have demonstrated that applying curcumin to a wound also promotes epithelial regeneration, boosts fibroblast activity, and increases vascular density (Sidhu et al., 1998; Thangapazham et al., 2013).

DISADVANTAGES

Curcumin has a low rate of absorption after oral administration due to its hydrophobicity, and only traces of the substance can be found in blood serum (Ravindranath and Chandrasekhara, 1980). Additionally, curcumin is a light sensitive molecule and goes through significant first pass metabolism (Asai and Miyazawa, 2000). (Anand et al., 2007).[23] Curcumin is a good choice for topical applications due to its limited water solubility and significant first-pass metabolism.

RECENT ADVANCES

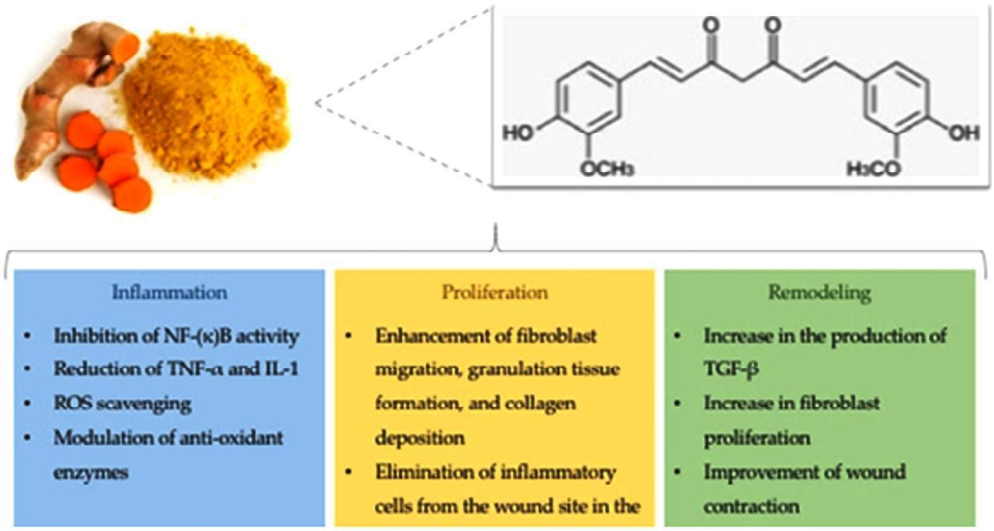
To improve the topical use of curcumin at the wound site, numerous groups have created novel curcumin formulations. These include of collagen films, chitosan alginate sponges, polymeric bandages, alginate foams, and creams (Dai et al., 2009; Mohanty et al., 2012; Hegge et al., 2011). (Durgaprasad et al., 2011).[24] It was discovered that adding curcumin to these formulations improved its bioactivity when compared to unformulated (raw) curcumin. However, because all of these formulations have similar wound healing profiles, there was no discernible difference in the way curcumin affected wound healing amongst them. The infiltration of curcumin into cells at the site of the wound might still be improved with curcuminnano formulation, even though the a fore mentioned formulations improved the topical application of curcumin. Curcumin has been successfully synthesised as nanoparticles in traditional Chinese medicines (TCM), which face comparable restrictions in the administration of curcumin. This has led to significantly better therapeutic results (Wang et al., 2011). Curcumin nanoparticles' therapeutic benefits result from their larger total surface area and smaller size, which make it easier for cells to absorb curcumin (Anand et al., 2007; Wang et al., 2011). Curcumin was discovered to have an improved cellular absorption into cancer cells and lessen their growth when it was created as nanoparticles as opposed to raw curcumin (Lee et al., 2014a; Lee et al., 2014b). Furthermore, curcuminnano-formulation showed improved bioavailability and longer half-life of curcumin (Anand et al., 2010). Curcuminnano-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).

CONCLUSION

In conclusion, it has been found that curcumin possesses powerful modulating effects on wound healing.

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-(k) B transcription factor, reducing the production of TNE-a 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)
Profileration	Enhancing fibroblat 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-B and therefore increasing fibroblast proliferation



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