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Review Article

A REVIEW ON CURCUMIN: WOUND HEALING PROPERTIES AND BIOMARKERS OF WOUND HEALING

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ABSTRACT

Turmeric (*Curcuma longa*), a rhizomatous perennial herb has been used from centuries for the treatment of rheumatism, diabetes, skin diseases, protozoal and fungal infections. Curcumin (diferuloylmethane), is the main curcuminoid responsible for imparting yellow color. It has caught attention since it is relatively safe, economical and owing to its multifaceted biological effects viz., anti-inflammatory, anti-oxidant, anti-carcinogenic and anti-infectious effects. Furthermore, wound healing properties of curcumin has received tremendous attention. It accelerates wound healing by exerting its action on various stages of wound repair. This review includes the in-vivo studies on the effect of curcumin. There is sufficient evidence on the wound healing effect of curcumin which provide proof for its positive effect on granulation tissue formation, collagen deposition and wound contraction. Further, the article includes various biomarkers used in the prediction of wound healing and wound infection. Thus, application of curcumin preferably topical application through modulation and optimization of formulation can confirm its therapeutic effects on skin wounds. Identification of a specific biomarker for wound healing could be a innovation in this field and for the treatment of impaired wound healing.

Keywords: Curcumin, Topical, In-vivo studies, Wound healing, Biomarkers.

INTRODUCTION

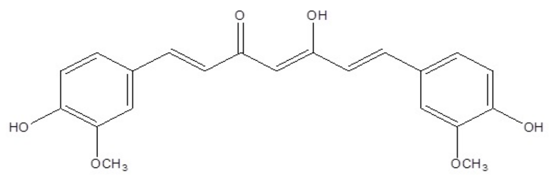

Figure 1: Chemical structure of curcumin.

Curcumin (cur, $C_2H_{20}O_6$, Figure I) is a spice from the herb *Curcuma longa,* belonging to Ginger family which has been used for long time since traditional Ayurvedic and Chinese medicine. It is a popular spice used in diet and as coloring agent. *Curcuma longa* is composed of group of natural yellow pigments called as curcuminoids. The biological activity of turmeric is mainly due to curcumin. Curcumin or diferuloyl methane, is a low molecular weight, lipophilic molecule. It was first isolated in 1815, then its crystalline form was obtained in 1910 but the final structure was elucidated by Lampe in 1913. It is hydrophobic drug, but soluble in organic solvents ethanol and acetone. There are many evidences supporting curcumin status as safe and effective. U.S. Food and Drug Administration has classified the curcumin molecule as 'Generally Regarded As Safe' (GRAS). In addition, curcumin at a dose of daily intake of 0.1–3 mg/kg-BW has been approved as an acceptable dose by the Joint FAO/WHO Expert Committee on Food Additives, 1996.[1] Curcumin has been used commonly for the treatment of biliary disorders, diabetic ulcers, rheumatism and sinusitis. The combination of cur paste and lime has been used for treating inflammation and wounds.[2]

Skin acts as first line of defense and provides various protective functions against the environment. The skin integrity is impaired due to acute and chronic injuries; then the body undergoes complex dynamic process to achieve healing of tissue with re-establishment of skin function as barrier. The wound healing process consists of four overlying phases viz., haemostasis, inflammation, proliferation and remodelling. Hemostasis phase is the immediate phase post-injury. It includes platelet aggregation and blood clot formation.[3] Thus the formed blood clot favors cell migration.[4] The inflammatory phase includes the migration of neutrophils and macrophages near wound site.

The phagocytes functions to remove foreign particles and simultaneously releases cytokines which in-turn aid fibroblast migration and proliferation in the inflammatory phase.[5] Re-epithelization phase includes angiogenesis i.e., formation of new blood vessels thereby providing perfusion to withstand the formed new tissues.[5] Further, extracellular matrix proteins are synthesized and deposited subsequently and formation of granulation tissue is formed in this phase. [3] Collagens are synthesized by fibroblasts. They play important role in wound repair since they provide strength and integrity to the tissues.[4] The final phase includes synthesis and breakdown of collagen followed by remodelling and formation of scar tissue.

The wound healing activity of curcumin is due to its multifaceted effects viz., anti-inflammatory[6], anti-infectious[7,8] and antioxidant [8,9] activities. An ideal wound healing agent shields the wound from infection and reduce inflammation. Besides this, it should be able to induce cell proliferation for the re-establishment of the damaged tissue and should essentially be an anti-oxidant since free radicals are the main cause of inflammation in wound repair. Literature studies indicate that topically applied curcumin on wounds has positive effects. Curcumin enhances cutaneous wound healing by granulation tissue formation, synthesis of matrix proteins, re-epithelialization and by laying down of collagen. Topical application of curcumin has been found to promote re-epithelialization and improves neovascularization.

Biomarkers are the substances used as indicators of biological state, pathological process or for pharmacological response meant for therapeutic treatment.[10] The measurement of these ensure well-being of an individual's mental and physical health. They can serve as important guides in determining the wound healing potential and wound infection. This review summarizes the literature on the curcumin and its effects on cutaneous wound healing. Further, it includes the various biomarkers used in the prediction of wound healing.

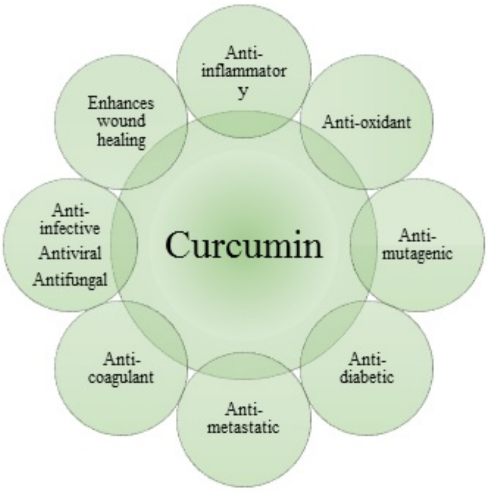

Figure 2: A glimpse of the multifaceted activities of curcumin

Biological properties of curcumin and its effects on phases of wound healing

Anti-inflammatory activity

It is the first step for optimal skin wound healing and hence considered as the vital phase. Inflammation is important in fighting against infections. It arises due to series of complex reactions and produced by host immune response. Such uncontrolled, sustained inflammatory responses triggers undesirable effects and leads to tissue damage as seen in rheumatoid arthritis.[11] Following injury, control of inflammation should be of importance thereby wound repair can be improved to certain extent.

Curcumin-treated burn wounds in rats showed raised inflammatory cell infiltration.[12] Curcumin-treated excision wounds in mice exposed to gamma radiation showed increased nitric oxide (NO) production.[13] This increased NO production is helpful since it promotes wound healing by enhancing inflammation.[14] Contrastingly, curcumin-treated in mouse model, it was found that increase in NO for wound healing was responsible only to a limited extent.[15] The injured skin readily enters the penultimate healing stages viz., proliferation and remodeling only when there is decreased inflammatory response whereas prolonged and uncontrolled inflammation tends to delay its progression to its subsequent stages and eventually leads to impaired and slow healing.

Anti-oxidant activity

Oxidative stress plays vital role in the pathogenesis of diseases such as myocardial ischemia, cerebral ischemia, hemorrhage, shock, and cancer. Reactive oxygen species are necessary for intracellular messaging, cell progression, apoptosis and immunity. Oxidative stress plays important role in the wound repair and inhibits tissue remodeling. Hydrogen peroxide and superoxide are used as markers of oxidative stress. Though, oxidative stress is important in wound repair, but prolonged presence of reactive species produces oxidative stress which is dangerous to human cells.[16] Curcumin possess strong antioxidant activity and scavenges superoxide radicals and hydrogen peroxide species.

Curcumin protects human keratinocytes from xanthine oxidase injury by its antioxidant nature.[17] When rats were fed curcumin (30mg/kg body weight) for 10 days, the iron-induced hepatic damage was decreased by lowering lipid peroxidation.[18] Protection from radiation by curcumin administration to mice is also due to its antioxidant property. Interestingly, apart from its anti-oxidative and free radical scavenging properties, it is also able to enhance the activities of other antioxidants viz., superoxide dismutase and catalase.[18] Phenolic and methoxy-functional groups on benzene rings and the 1,3-diketone system contribute together to its antioxidant properties.[19]

Gopinath et al. (2004)[20] synthesized curcumin incorporated collagen matrix (CICM) and tested its in-vitro antioxidant efficiency using the lipid peroxidation method.[20] Results indicate that curcumin was found to exhibit free radical scavenging activity against peroxy radicals. Transdermally applied curcumin on excision wounds in rats showed inhibition of H_2O_2-induced damage to keratinocytes and fibroblasts.[21]

Curcumin action on the proliferative phase

The proliferative phase consists of fibroblast proliferation, synthesis of extracellular matrix, formation of granulation tissue, epithelialization and apoptosis of undesirable cells.[4]

Fibroblast migration

Fibroblasts cells play important role in wound healing. Following injury, fibroblasts first appear at wound site in about 2-4 days followed by endothelial cells. Fibroblasts presence into the wound is a pre-requisite for the initiation of the proliferative phase.[4] After fibroblast migration, fibroblasts proliferate and starts to produce the skin extracellular matrix proteins fibronectin, hyaluronan and, subsequently, collagen and proteoglycans. These proteins help for construction of the extracellular matrix, which provides integrity and support essential for the wound repair. Studies indicate that wounds which fail to heal within anticipated duration often have impaired fibroblast proliferation and migration.[22,23] Hence, the infiltration of fibroblasts in the wound area is important factor to ensure faster wound closure. As the proliferative phase progresses, new granulation tissue starts to develop on the fibronectin matrix. Epithelialization of the wound marks the end point of the proliferative phase.

Formation of granulation tissue involves differentiation of fibroblasts into myofibroblasts.[23] Curcumin-loaded oleic acid based polymeric (COP) bandage treated excision wounds in rats showed the presence of myofibroblasts as early as four days.[24] Myofibroblasts were also observed in diabetic and various types of wounds. [25,26]

Granulation tissue formation

Formation of granulation tissue indicates optimal healing. It appears as pink, soft with granular look. This phase includes formation of new blood vessels from pre-existent vessels. The process includes proteolytic degradation of the basement membrane; migration and proliferation of endothelial cells; and maturation of endothelial cells. The appearance of the granulation tissue can be related to wound status. Healing wounds appear moist, shiny, hyperaemic, and reddish whereas poor healing wounds are often soft and friable with beefy red colour. [27]

Gopinath et al. (2004)[20] found elevated levels of hydroxyproline content in CICM (curcumin incorporated collagen matrix) treated wounds. Hydroxyproline, a protein marker is produced due to collagen synthesis. Therefore, presence of hydroxyproline indicates sufficient amount of myofibroblasts in the wound milieu. Curcumin was found to enhance wound healing by increasing the formation of granulation tissue, biosynthesis of matrix proteins, and TGF-β1 in wounds in rats and guinea pigs.[25]

Collagen deposition

The extracellular matrix undergoes reorganization and remodeling for prolonged periods, which is a criterion for wounds to heal entirely. The extracellular matrix includes various proteins such as granulation tissue and collagen. Collagen, the abundant protein accounts for about 70–80% of skin. It is synthesised by fibroblasts and provides strength, integrity to tissues and thus play important role in wound healing.

Curcumin-loaded chitosan-alginate sponge (CLCA) treated wounds in rats showed higher collagen content compared to gauze-treated as control group.[28] Topical application of curcumin in rats reported an increase in collagen and matured collagen fibres.[16] Increase in tensile strength and decrease in temperature of the wound tissue may have resulted in collagenization. In contrast to oral administration, topical application of curcumin resulted in compact, well-aligned and thicker collagen fibers at wound areas in diabetic mice, rats and in guinea pigs.[25,26].

Apoptosis

Apoptosis is essential to occur since it helps in the removal of unwanted inflammatory cells. This permits the wound to mature and progress to later stages of healing.[25,26] Curcumin causes apoptosis by the virtue of its ability to induce reactive oxygen species. Curcumin loaded-oleic acid polymeric bandage (COP) treatment in a rat showed dead cells in initial four days post-treatment. The dead cells presence was confirmed through DNA fragmentation studies. These observations indicate that curcumin is apoptotic in the initial phase of wound healing. [24]

Wound contraction

Wound contraction represents the last stage of healing. It occurs through interactions between fibroblasts, extracellular matrix and cytokines.[4] It actually begins around two weeks post-wounding, when fibroblasts start differentiating into myofibroblasts.[29] Myofibroblasts, by induction of α-smooth muscle actin expression enhance wound contraction in the granulation tissue.[30]

Curcumin-loaded sponge treated wounds in rats showed 90% wound contraction in 12 days post-injury whereas the gauze treated as control contracted by 74%. [28] In contrast, Mohanty et al. (2012)[24] demonstrated that only eight-day period is required for wound contraction between curcumin and control groups in a rat model. In another study, oral administration of curcumin in mice showed maximum wound contraction between day 6 to day 12 post-irradiation.[15]

Epithelialization and remodeling

Within few hours post-wounding, epidermal cell layer starts to migrate from the wound edges to form delicate covering on the outer fresh area. The epithelial cells further undergo growth and differentiation to form the stratified epithelium. Wet wound environment, sufficient nutrition and bacteria control are the ideal requirements for epithelialization.[27] Synthesis and remodelling process occurs in parallel with the granulation tissue formation and continues for longer period of time. Remodelling includes synthesis, breakdown of collagen since the extracellular matrix undergoes constant remodelling until it attains steady state about for about 21 days post-injury.[27]

Curcumin reduced the epithelization period of the wounds significantly from 23 days to 11 days.[16] Curcumin-treated wounds showed significant increase in re-epithelization, whereas curcumin treatment for 12 days continuously shown optimum re-epithelization.

Biomarkers of wound healing

Erythrocyte sedimentation rate (ESR), C-reactive protein, and albumin levels are usually used as indicators or biomarkers to determine both wound healing potential and wound infection.[10] Among these cytokines and proteases are of utmost importance and currently hold most potential. Current ongoing studies on wound effects gives conclusions which can be correlated with the changes in the levels of proteins, cytokines, chemokines, MMPs and other proteases. These serves as guide and further could be developed as a prognostic tool to help the health-care professionals in anticipating wound outcome.[31]

Cytokine levels

Cytokine, TNF-α, IL-1 and IL-6 levels are used as diagnostic tool for assessment of wound healing. Usually, their levels are higher in non-healing wounds than healing wounds.[32] IL-1 levels were found to be higher in non-healing wounds in comparison to healing wounds.[32] IL-8 values were found to be very high in chronic non-healing wounds.[33]

Matrix metalloproteinases (MMPs)

MMPs help in the degradation of extracellular matrix and play vital role in each of the stages of healing process. They require zinc ions for their activity. Serum MMP-2 and MMP-7 levels helps in the prediction of wound outcome.[34] Lower the level, higher the chances of successful healing. In such scenarios biomarkers prove to be reliable for healing[34]. The wound fluid MMP-9/TIMP ratios, wound levels of MMPs and elastase could also prove to be good prognosticators of wound repair.[35] Lower the level of MMP and MMP-9/TIMP ratio, greater the chance of wound healing. These biomarkers are convenient, suitable for estimating the outcome of wound repair.

Tissue bacterial levels

Tissue bacterial levels, another biological marker serves in prediction of healing in both acute and chronic wounds. Though, high levels have been found to impair all the processes of wound healing and prevent healing.[10]

CONCLUSION

From the literature review, it can be concluded that curcumin possess plethora of various biological effects. It exhibits powerful modulating effects on wound healing by acting on the various phases of wound healing; thereby reduces the time required for wound repair. But, its use is limited by poor aqueous solubility, rapid metabolism and low bioavailability. Therefore, to overcome the aforementioned problems and to use curcumin for its maximum ability, novel pharmaceutical formulations should be explored. A combined effort is required in the field of biomarker discovery. The currently used biomarkers do not possess the required characteristics. Identification of new biomarkers with desired characteristics to determine the extent of wound healing is essential and important since it will serve for the management of wound and have impact on patient's wellbeing.

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