Life Sciences 116 (2014) 1–7

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Review article

Curcumin as a wound healing agent

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ARTICLE INFO

Article history:
Received 22 July 2014
Accepted 25 August 2014
Available online 6 September 2014

Keywords:
Curcumin
Turmeric
Topical administration
Nanoparticle
Wound healing
Skin regeneration

ABSTRACT

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 (diferuloylmethane) is the main curcuminoid present in turmeric and responsible for its yellow color. Curcumin has been shown to possess significant anti-inflammatory, anti-oxidant, anti-carcinogenic, anti-mutagenic, anti-coagulant 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. This review summarizes and discusses recently published papers on the effects of curcumin on skin wound healing. The highlighted studies in the review provide evidence of the ability of curcumin to reduce the body's natural response to cutaneous wounds such as inflammation and oxidation. The recent literature on the wound healing properties of curcumin also provides evidence for its ability to enhance granulation tissue formation, collagen deposition, tissue remodeling and wound contraction. It has become evident that optimizing the topical application of curcumin through altering its formulation is essential to ensure the maximum therapeutical effects of curcumin on skin wounds.

Contents

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http://dx.doi.org/10.1016/j.lfs.2014.08.016
0024-3205/

Introduction

Curcumin

The turmeric plant is a herb belonging to the ginger family and has been used throughout history as a dietary spice and coloring agent in Indian and Chinese cuisines (Chattopadhyay et al., 2004). The rhizome (root) part of the plant has also been used for centuries in Indian and Chinese traditional medicines and is the most valuable part of the plant for medicinal purposes (Chattopadhyay et al., 2004; Patwardhan et al., 2005). Curcumin became commonly used in Indian traditional medicine in the treatment of bilary disorders, cough, diabetic ulcers, hepatic disorders, rheumatism and sinusitis. The paste of curcumin mixed with lime has been a popular home remedy for the treatment of inflammation and wounds (Anamika, 2012). 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) was first described by Milobedska et al. (1910). In more recent times, curcumin has been studied extensively for its use as an anti-cancer (Agrawal and Mishra, 2010; Shehzad et al., 2013; Shishodia et al., 2007), anti-aging (Lima et al., 2011; Bala et al., 2006) and wound healing agent (Maheshwari et al., 2006).

Wound healing process

Skin provides a natural barrier against the environment and exerts a variety of essential protective functions. When the integrity of skin is compromised, either by acute or chronic injuries, the body initiates a multi-step and dynamic process at the injured site, leading to partial healing of the tissue and restoration of the skin's barrier function. The immediate goal in wound repair is to achieve tissue integrity and homeostasis (Eming et al., 2007). The natural process of wound healing is comprised of four overlapping but well-defined phases: hemostasis, inflammation, proliferation and remodeling. Hemostasis occurs upon injury, which constitutes platelet aggregation and thereby blood clot formation (Enoch et al., 2006). The blood clot provides a provisional extracellular matrix for cell migration (Epstein et al., 1999). The inflammatory phase involves the migration of blood cells, such as phagocytic neutrophils and macrophages, to the wound site (Enoch et al., 2006). The phagocytes initially remove foreign particles, while also releasing cytokines to promote fibroblast migration and proliferation towards the end of the inflammatory phase (Topman et al., 2013). Re-epithelialization of wounds begins within hours of injury and is a part of the proliferative phase (Epstein et al., 1999). This phase is characterized by the formation of new blood vessels (angiogenesis or neovascularization), which re-establishes perfusion to sustain the new tissues (Topman et al., 2013) and the synthesis and deposition of fragments of extracellular matrix proteins such as collagen fibers and granulation tissue (Enoch et al., 2006). Fibroblasts produce the new extracellular matrix necessary to support cell ingrowth using collagen as the building blocks (Epstein et al., 1999) and thus play a crucial role in the wound healing process. The final phase involves collagen remodeling and scar tissue formation. Fig. 2 illustrates the time span of each wound healing phase following injury while also importantly depicting the overlapping nature of the process (Epstein et al., 1999).

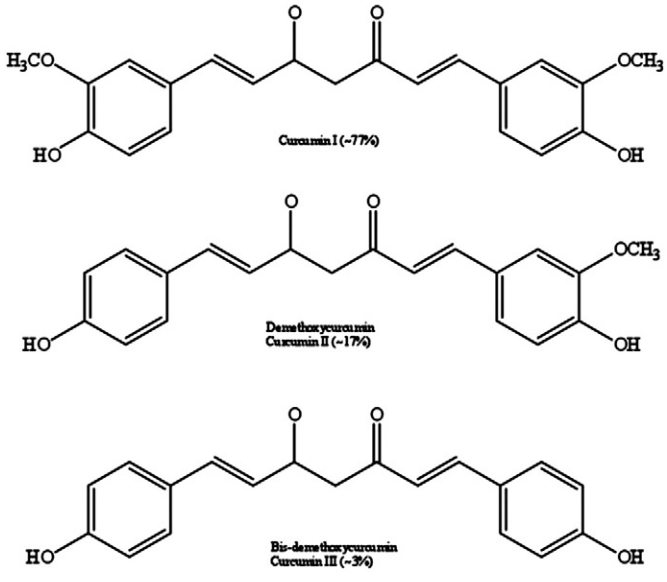

Fig. 1. Chemical structures of curcuminoids: curcumin, demethoxycurcumin and bis-demetohxycurcumin that have shown antioxidant and/or anti-inflammatory properties.

Wound healing activities of curcumin

An optimum wound healing dressing or agent protects the wound tissue from bacterial infection, reduces inflammation and induces cell proliferation to aid in the reconstruction of damaged tissue (Kulac et al., 2013). It would ideally also act as an anti-oxidant as free radicals are considered the major cause of inflammation during wound healing process (Mohanty et al., 2012). The wound healing potential of curcumin is attributed to its biochemical effects such as its anti-inflammatory (Liang et al., 2009), anti-infectious (Mun et al., 2013; Singh et al., 2010) and anti-oxidant (Ak and Gulcin, 2008; Meng et al., 2013) activities. Curcumin has also been found to enhance cutaneous wound healing through involvement in tissue remodeling, granulation tissue formation, and collagen deposition (Joe et al., 2004). 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 curcumin in wound healing, focusing on its mechanisms of action and providing evidence for its effects on the various stages of wound healing process. Precedence is given to the topical skin application of curcumin in vivo while also examining in vitro studies of curcumin in wound healing models.

Mechanisms of action of curcumin on the phases of wound healing

Effects of curcumin on inflammation

Inflammation is the crucial second phase of the wound healing process, often described as the first step in optimum skin regeneration (Epstein et al., 1999). Uncontrolled inflammatory responses may lead

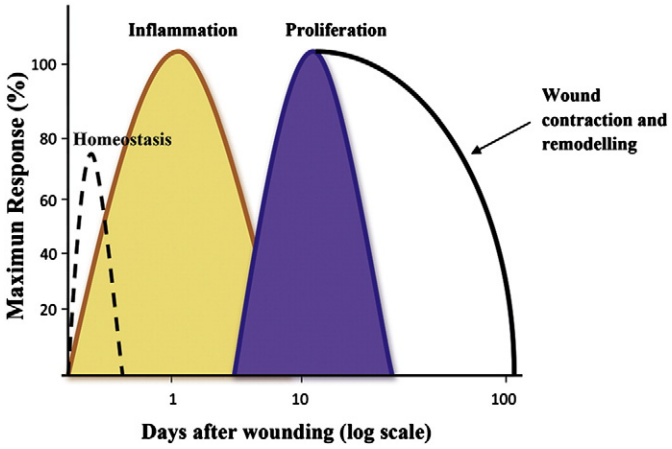

Fig. 2. The four phases of acute wound healing.