RESEARCH PAPER

Topical Curcumin in wound healing: From molecular insights to clinical applications

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ABSTRACT

The process of wound healing is a complex biological process which encompasses hemostasis, inflammation, proliferation and remodelling. The diabetic ulcers and burn wounds are a significant burden of health care in the whole world since they take a longer period to heal and moreover they are prone to infection. The traditional medicinal plant, Turmeric (Curcuma longa) has been actively applied in the traditional medicine system and received a considerable amount of scientific attention in its wound healing qualities due to its active constituent, curcumin. This is a systematic review where experimental and clinical evidence has been reviewed on the efficacy of Curcuma longa in wound management. The databases utilized in the search of the literature, which included Publisher, Scopus, and Web of Science was suggested by PRISMA. The inclusion and exclusion criteria were pre-determined when selecting the studies. It has been shown, both in vitro and in vivo, that curcumin not only enhances fibroblast proliferation, collagen deposition, angiogenesis, and re-epithelialization, but also has a potent anti-inflammatory, antioxidant, and anti-microbial effect. It has also been shown to enhance the rate of healing of chronic wounds such as diabetic ulcers and postoperative wounds. Though the findings are encouraging, its clinical application is restricted due to such factors as low aqueous solubility, low bioavailability and fast metabolism. Nanoparticles, hydrogel and nanoemulgels are the latest types of drug delivery systems and have significantly enhanced the stability and therapeutic properties of curcumin. To sum up, Curcuma longa is a promising natural agent in wound healing but its clinical use needs to be determined by conducting large-scale randomized clinical trials and standardized formulations.

Keywords: Curcuma longa; Curcumin; Wound healing; Nanoemulgel; Anti-inflammatory.

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Introduction

The process of wound healing is a multifaceted, dynamic and highly coordinated biological event that re-establishes the structural and functional integrity of injured tissues after an injury. It entails a series of interacting events, comprising hemostasis, inflammation, proliferation, and remodeling, which are controlled by a network of cellular and molecular events [1]. These processes are timely and ordered under normal physiological conditions; in case of disruptions in this cascade, they may cause delayed or impaired healing, which leads to chronic wounds [2]. Chronic wounds, including diabetic foot ulcers, pressure ulcers, and venous leg ulcers, are a major worldwide healthcare issue because they have long-lasting healing phases, are highly susceptible to infections, and cause high morbidity and mortality rates [3]. The chronic wound burden has grown exponentially over the past few decades and is largely attributed to the escalating levels of diabetes, aging and lifestyle-related illnesses [4]. Diabetic wounds are especially troublesome since they are predisposed to underlying pathophysiological processes, including lack of proper vascularization, neuropathy, unresolved inflammation, and defective immune system [5]. These will cause delayed wound healing, predisposition to microbial infections, and, in severe situations, amputation of the limbs [6]. Traditional wound management techniques such as debridement, antibiotic treatment, and high tech dressings tend to be less successful particularly in chronic and infected wounds [4]. Moreover, the use of antibiotics has been so extensive, thus leading to the development of antimicrobial resistance, which has made the treatment of wounds more difficult [7].

The past years have seen an increasing interest in investigation of natural products and plant-based therapeutics in wound healing use [8]. Over the ages, medicinal plants have been utilized in traditional medicine systems like Ayurveda, Traditional Chinese Medicine and Unani because they are safe, accessible and multi-targeted, due to their therapeutic effects [9]. Phytochemicals have pleiotropic effects unlike synthetic drugs, which typically have a single action, acting on one pathway in wound repair [10]. One of these medicinal plants of particular interest is *Curcuma longa* (or turmeric) that has powerful pharmacological effects and potential to be used in the treatment of wounds [11]. A perennial herb of the Zingiberaceae family, *Curcuma longa* is commonly grown in India and other tropical areas [12]. It has been widely employed as a food seasoning, dye and in medicine [13]. Most of the therapeutic effects of turmeric have been ascribed to its bioactive components, which are collectively referred to as curcuminoids, with the most notable and widely studied one being curcumin [12]. Curcumin (diferuloylmethane) is a water insoluble polyphenol with a variety of biological properties, such as anti-inflammatory, antioxidant, antimicrobial, anticancer, and immunomodulatory properties [13]. These characteristics render it a prospective agent to improve wound healing [14].

Curcumin has the potential of healing wounds via several different mechanisms. It regulates the pathways of inflammation through the inhibition of these key mediators: nuclear factor-kappa B (NF-κB), tumor necrosis factor-alpha (TNF-), interleukins, and inhibits the excessive inflammation which postpones healing [15]. Also, curcumin shows great antioxidant properties in scavenging reactive oxygen species (ROS) and increasing the activity of endogenous antioxidant enzymes like superoxide dismutases and catalases. This helps in protecting tissues from oxidative damage, which is a major contributing factor in chronic wounds [16].

Further, curcumin has been demonstrated to stimulate fibroblast growth, collagen production and extracellular matrix deposition, which are essential in the regeneration of tissues and wound healing [17]. It also promotes angiogenesis through increasing vascular endothelial growth factor (VEGF), which promotes the development of new blood vessels that are needed to supply nutrients and oxygen to the healing tissue [18]. Moreover, its antimicrobial action against a wide range of pathogens such as bacteria and fungi is very important in wound infection prevention and in maintaining healing process [19].

Although these were encouraging therapeutic findings, clinical usage of curcumin is greatly hampered by its unpleasant physicochemical characteristics such as low solubility in water, high rate of metabolism and low bioavailability. These are the constraints that limit its therapeutic effect in conventional dosage forms [20]. In a bid to deal with these hurdles, a lot of research has been focused in developing superior drug delivery systems. New formulations including nanoparticles, liposomes, hydrogels and nanoemulgels have shown superior stability, better permeation of skin and long release of drugs, thus positively influencing the overall wound healing potential of curcumin [21].

Specifically, delivery systems based on nanoemulsions have become one of the promising delivery methods of topical drugs in wound treatment. These systems integrate the benefits of nanoemulsions like enhanced solubilization and bioavailability with those of gel based systems, including convenience when applying, prolonged presence, and compliance in patients [22]. Nanoemulgels loaded with curcumin have exhibited a better performance in preclinical studies where they have proven to have a better wound contraction, increased epithelialization and better collagen deposition than the traditional formulations [23]. This development is in line with the increased attention of nanotechnology-based therapeutics in treating chronic wounds [24].

With the growing body of evidence on the potential of *Curcuma longa* to heal wounds, a detailed and systematic review of experimental and clinical evidence is necessary [25]. Although a number of studies on its pharmacological properties have been conducted, there is need to consolidate its efficacy, mechanisms and formulation strategies to be in a position to know its translational potential [26]. Thus, the current systematic review would critically review the current literature on *Curcuma longa* in wound healing, its mechanism of action, experimental results, clinical results and improvement of drug delivery systems, especially nanoemulgel systems [27].

This review also aims at identifying the existing research gaps, limitations and directions to assist in development of effective, safe and standard curcumin-based therapies in wound management. Combining the traditional knowledge and current developments in the field of science, *Curcuma longa* has a great potential as a new and versatile therapeutic agent in wound healing.

2. Methodology

2.1 Search Strategy

A thorough and methodical literature review was performed to find the pertinent studies that assess the effect of *Curcuma longa* and its active ingredient curcumin in wound healing. The database search has been conducted in three large electronic databases, PubMed, Scopus, and Web of Science, which are well known to index high quality biomedical and pharmaceutical research. These databases were chosen such that they provide wide coverage of peer-reviewed experimental and clinical studies. A combination of keywords and Boolean operators was used to develop the search strategy to help maximize the retrieval of relevant literature and minimize irrelevant ones. Keywords that were mainly used were: *Curcuma longa* and wound healing, Curcumin and diabetic wounds, and Turmeric and skin regeneration. Such terms were selected to identify those studies that dealt with various facets of wound healing such as general tissue repair, chronic wounds like diabetic ulcers, and the skin regeneration mechanisms. Besides, search of databases was conducted with variations and synonyms of the keywords to increase sensitivity. The filters were used where appropriate to narrow down the results to articles published in English and within the stipulated time (2000-2025). Manual screening of reference lists of selected articles was also done in order to find out more relevant studies that were not found when using databases. This was a multi-step strategy that guaranteed comprehensive and impartial identification of eligible studies [28].

2.2 Inclusion Criteria

The relevance, quality and consistency in the review process were achieved by including studies based on pre-determined criteria [28]. Experimental researches which were both in vitro and in vivo were considered in order to assess the mechanistic and pharmacological impacts of curcumin on wound healing [25]. In vitro experiments gave an understanding of cellular response including fibroblast proliferation, collagen synthesis and antioxidant activity, whereas in vivo experiments mostly involving animal models, provided evidence regarding wound contraction, tissue regeneration and healing kinetics [26]. Clinical trials were also involved to determine the translational capability and therapeutic effects of *Curcuma longa* in humans [11]. The only studies that were taken into consideration were those that were published in English language to ensure that there was a consistency in interpretation and there were no translation inaccuracies [29]. Moreover, the publication time was limited to 2000-2025 to make sure that the review contains the background research as well as the latest developments especially in formulation technologies like the nano-based delivery systems [30].

2.3 Exclusion Criteria

The exclusion criteria were applied to studies that failed to satisfy the inclusion criteria in an attempt to uphold the scientific rigor and focus of the review [28]. The studies that did not contain original experimental or clinical data were filtered out Review articles, meta-analyses, and opinion papers Review articles, meta-analyses, and opinion papers did not contain original experimental or clinical data and were excluded, since the aim of this study was to analyze primary research evidence [31]. Nevertheless, these articles were at times referred to gain background knowledge. Any non-English publications were not included as it would be difficult to interpret the data and filled with translation bias. Also, research studies that did not explicitly measure wound healing outcomes (like studies that investigated only the anti-inflammatory or antioxidant effects and not the wound reparation process) were eliminated. Articles that had inadequate methodological information, ambiguous results or were not reproducible were also filtered out to guarantee reliability of the data included [28].

2.4 PRISMA Flow

The selection of studies was performed in compliance with the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) guidelines to provide the transparency and reproducibility of the study. First, 512 records were found by searching the database. Having eliminated duplicates, 420 distinct records could be further screened. As part of the title and abstract shortlisting stage, 300 studies were shortlisted on the basis of their relevance to the topic. The full-text review of these articles was then done in order to determine their eligibility based on the established inclusion and exclusion criteria. Following the thorough analysis, 65 studies ended up being incorporated into the systematic review. PRISMA approach provided a systematic and impartial selection process that reduced the chances of selection bias and increased the credibility of the review results [28].

2.5 Risk of Bias

The quality and reliability of the incorporated studies were critically evaluated to mention the possible sources of bias [32]. Small sample sizes, absence of randomization and blinding were all sources of moderate bias in a number of animal studies [25]. These might affect the internal validity of the results and restrain their generalizability [33]. The second significant shortcoming of clinical studies was the lack of randomized controlled trials. The number of studies was small, the follow up period was short, and the treatment procedures were not consistent, which could impact the strength of the conclusions [34]. Also, various curcumin preparations like crude extracts, gels, nanoparticles, and nanoemulgels brought heterogeneity to studies and hence direct comparisons were difficult [25]. In general, despite the existing evidence on therapeutic value of *Curcuma longa* in the wound healing process, methodological constraints prove the necessity of more stringent, large-scale, and standardized clinical trials to confirm its effectiveness. Table 1 indicates some risk of bias [28].

Table 1: Risk of Bias Assessment of Included Studies

Bias Domain	Animal Studies	Clinical Studies	Overall Assessment
Random sequence generation	Low–Moderate	Moderate	Moderate
Allocation concealment	Moderate	Moderate–High	Moderate
Blinding	High (often absent)	Moderate	High
Sample size adequacy	Low–Moderate	Low	Moderate–High
Outcome reporting	Moderate	Moderate	Moderate
Selective reporting	Low	Moderate	Low–Moderate

3. Phytochemistry of *Curcuma longa*

Curcuma longa (turmeric) is a good source of various bioactive compounds that have led to its diverse pharmacological effects and especially in wound treatment [35]. Tumeric is a complex chemical compound mainly made up of two broad categories (curcuminoids, non-volatile polyphenolic compounds and volatile oils, essential oils). These ingredients have a synergistic effect to generate anti-inflammatory, antioxidant, antimicrobial, and tissue-generative effects [36].

3.1 Curcuminoids

The major bioactive compounds found in the rhizome of *Curcuma longa* are curcuminoids that make up about 2-5 percent of the rhizome. These are primarily curcumin, demethoxycurcumin and bisdemethoxycurcumin which are structurally related polyphenolic compounds. The most common and most widely investigated of these is the curcumin (diferuloylmethane), which gives turmeric its yellow colour [13]. Curcumin has strong anti-inflammatory property by regulating major inflammatory signaling pathways, including nuclear factor-kappa B (NF), cyclooxygenase-2 (COX-2), and pro-inflammatory cytokines, like tumor necrosis factor-alpha (TNF-), and interleukins [37]. This suppression of inflammatory mediators is crucial in preventing prolonged inflammation, which is a major cause of delayed wound healing [15]. Besides being an anti-inflammatory agent, curcumin has a potent antioxidant effect, which allows it to counter the effect of reactive oxygen species (ROS) and lower the level of oxidative stress in the wound area [16]. It also enhances the growth of fibroblasts, collagen production and the formation of the extracellular matrix that is vital in repairing the tissue and sealing a wound. Demethoxycurcumin and bisdemethoxycurcumin are lesser amounts but they play a significant role in the total biological activity. These substances improve antioxidant defense systems and promote the stabilization of free radicals, thus complementing curcumin [38].

3.2 Volatile Oils

Curcuma longa has a volatile oil fraction of 3-7% of the rhizome which comprises compounds like ar-turmerone, alpha-turmerone, beta-turmerone, zingiberene, and atlantone. These hydrophobic compounds are very important in antimicrobial and anti-inflammatory effects of turmeric [39]. One of the main constituents of essential oil, Turmerone, has great antimicrobial effect on a broad spectrum of pathogenic microorganisms, such as bacteria and fungi that are usually related to wound infection. This helps to reduce the amount of microbes on the location of wound and it prevents the complications such as infection and delayed healing. Moreover, volatile oils increase skin permeability and drug absorption that could be used in topical formulations to improve the delivery and efficacy of curcuminoids [40]. It is also postulated in some studies that turmerones can have anti-inflammatory and neuroprotective effects, which can further aid in the healing process [39].

3.3 Synergistic Effects of Phytoconstituents

Minimal evidence supports the therapeutic efficacy of *Curcuma longa* as a result of any single compound but as a result of an interactive relationship between curcuminoids and volatile oils [41]. Although curcuminoids are mainly aimed at inflammation, oxidative stress, and tissue regeneration, volatile oils also provide antimicrobial properties and increase bioavailability. The synergism is especially crucial in wound healing where several biological processes have to be coordinated [42]. Table 2 represents turmeric phytoconstituents biological functions and their synergistic effect of these phytoconstituents is:

- Reduced inflammation
- Defense against oxidative injury.
- Prevention of microbial infection
- Enhanced tissue regeneration [43].

Table 2: Phytoconstituents of *Curcuma longa* and Their Biological Functions [44]

Compound	Class	Function
Curcumin	Polyphenol	Anti-inflammatory, antioxidant, promotes collagen synthesis
Demethoxycurcumin	Curcuminoid	Antioxidant, stabilizes free radicals
Turmerone	Essential oil	Antimicrobial, enhances skin penetration

3.4 Relevance in Wound Healing

The phytochemical composition of *Curcuma longa* directly supports its role in wound healing. Curcuminoids also control inflammatory and oxidative processes, whereas volatile oils prevent the proliferation of microbes and enhance drug delivery [45]. This is a multi-targeted mechanism that renders turmeric a very effective natural agent in the treatment of acute and chronic wounds [46]. Furthermore, lipophilic essential oils increase the skin penetration of curcumin and this is of great advantage when used topically as gels, ointments and nanoemulgels [47]. This is particularly applicable to contemporary pharmaceutical strategies whereby bioavailability enhancement is very vital to therapeutic effectiveness [48].

4. Wound healing mechanisms.

Hepatitis A is a multi-stage process in the body that involves four overlapping processes: hemostasis, inflammation, proliferation, and remodeling. Curcumin, the major bioactive of *Curcuma longa*, has a major role in regulating all these phases via various molecular and cellular processes [13]. Identical response to the previous step, except that it occurs during the inflammatory stage [49]. Inflammatory phase is necessary to remove pathogens and debris but too much or too long inflammation may impair healing, particularly in chronic injuries like diabetic ulcers [2]. Curcumin has a potent anti-inflammatory effect via inhibition of prominent pro-inflammatory cytokines, such as:

- Adhesion molecules (AMs)
- Interleukin-6 (IL-6)
- Interleukin-1 beta (IL-1β) [50].

This is mainly done by inhibiting the NF-KB signaling pathway that is the major mediator of inflammation. Inhibiting these mediators, curcumin suppresses too much inflammatory reaction, limits the tissue destruction, and forms a conducive milieu to the transition to the proliferative stage [13].

2. Improvement of Antioxidant Defense.

One of the key factors influencing the wound healing process, which especially applies to chronic wounds, is oxidative stress. Reactive oxygen species (ROS) can damage the cell structures, proteins and DNA, leading to delayed tissue repair.

Curcumin stimulates:

- Fibroblast proliferation
- Mobility of fibroblasts into the wound [36].

Synthesis of collagen

It also enhances the expression of growth factors such as:

- Changes growth factor-beta (TGF-B).

This increases the development of the granulation tissue and contraction of the wound [13].

3. Angiogenesis (Proliferation Phase) Promotion of VEGF.

Angiogenesis (growth of new blood vessels) is essential to the healing tissue to provide it with oxygen and nourishment. Lack of enough blood supply greatly retards wound healing.
Curcumin also leads to angiogenesis by:

- Activating vascular endothelial growth factor (VEGF).
- Enhancing the increase and migration of endothelial cells.
- Betterment of the microcirculation of the wound [36].

The outcome is the growth of the new capillaries formed that help in mending of the tissues and repair. Curcumin is a pleiotropic agent, which means that it has numerous molecular targets simultaneously as compared to the traditional drugs, which have a single direction of action. It is especially useful in treating complex and chronic wounds, in which there are several pathological factors involved [14].

5. Experimental Evidence

There is exhaustive scientific evidence on the wound healing capabilities of Curcuma longa or curcumin, its active constituent, based on experimental studies. Such works are in vitro (cell-based) and in vivo (animal-based) studies, and, in combination, will aid in proving its pharmacological and therapeutic effects at different stages of wound healing [51].

5.1 In Vitro Studies

In vitro research is essential in the understanding process of cellular and molecular pathways of wound healing. Such studies normally deal with cultured cells like fibroblasts, keratinocytes, and endothelial cells. Increased Fibroblast Proliferation [52]. Fibroblasts have a critical role in repairing tissue because they are the ones that synthesize the extracellular matrix and collagen. It has been demonstrated that curcumin can considerably increase the fibroblast proliferation and migration in cell culture models [53]. It activates cellular signaling pathways that control cell growth and division and thus it promotes the proliferation of fibroblasts at the wound site. This augmented fibroblast activity is involved in:

- Quickly formed granulation tissue.
- Improved wound contraction
- Increased tissue-regeneration support [54].

Enhanced Collagen Synthesis

Collagen is the main structural protein and which is needed to achieve wound strength and integrity. The in vitro research has shown that curcumin enhances the production of collagen and specifically Type I collagen through the up-regulation of the fibroblast activity and growth factors like transforming growth factor-beta [55]. Besides, curcumin can be used to regulate the deposition of collagen by balancing the synthesis and degradation of collagen. This gets rid of the development of abnormal scars and facilitates the processes of remodelling of tissues [56].

Reduced Oxidative Stress

The outcome of reactive oxygen species (ROS) overproduction is oxidative stress, which can cause cell components damage and delay wound healing. In vitro curcumin possesses a good antioxidant activity, which removes the free radicals and enhances intracellular antioxidant response. Curcumin lowers oxidative stress and spares the cell damage. It increases the activities of antioxidant enzymes such as:

- Superoxide dismutase (SOD)
- Catalase
- Glutathione [57]

5.2 In Vivo Studies

Direct evidence of the wound healing efficacy of curcumin under physiological conditions is contained in in vivo studies, which are mostly carried out in rat and mouse models [58].

Faster Wound Contraction

Wound contraction is one of the crucial indicators of the progression of healing and the wound contraction consists of the decrease of the wound size with time. Curcumin has been reported to strongly hasten the wound contraction process in animal models especially in excision and incision wounds [36]. Wounds treated with curcumin have better tensile strength because:

- Increased collagen content
- Improved collagen fiber orientation
- Reduced Healing Time [59]

A decrease in overall healing time is one of the greatest in vivo discoveries. These experimental findings are very solid in confirming the possibility of curcumin in the form of a therapeutic agent especially when it is integrated in some of the advanced delivery systems such as nanoemulgels, another factor that increases its bioavailability and efficacy [15].

6. Clinical Evidence

In the wound healing process, clinical investigation on *Curcuma longa* and its active ingredient curcumin has offered promising, yet rather sparse evidence, on its therapeutic usefulness. A number of clinical trials have examined its application in the treatment of various kinds of wounds especially chronic wounds like diabetic foot ulcer, post operative wounds and burn wounds [60]. One of the greatest clinical trials finds is the wound healing of diabetics. Topical application of curcumin-containing preparations, including gels, ointments, or sophisticated delivery systems, has shown to result in quicker wound contraction and enhanced healing in patients compared with traditional methods [61]. This effect is mainly explained by the fact that the curcumin can regulate inflammation, increase collagen production and angiogenesis. Curcumin provides benefits in the healing of diabetic wounds by restoring the balance between pro-inflammatory and anti-inflammatory mediators that cause delays in the healing process of diabetic wounds through impaired blood flow and ongoing inflammation [62].

Another important clinical benefit observed is the reduction in wound infection. Curcumin has a broad-spectrum antimicrobial effect on common pathogenic agents of wounds such as *Staphylococcus aureus* and *Escherichia coli* [63]. Clinical evidence has shown that curcumin-treated wounds contain less microbial load, assisting to produce a cleaner wound environment and reduce the likelihood of complications, such as sepsis or slow wound healing [64]. This antimicrobial activity is particularly helpful in the background of increasing antibiotic resistance because curcumin is a natural alternative/complement to conventional antimicrobial therapies [65].

In addition, curcumin has been discovered to do more rapid epithelialization, which is a vital process in wound healing. Epitehelialization is a process which involves migration and proliferation of keratinocytes to cover the wound surface. Clinically, curcumin based treatments have been shown to enhance re-epithelialization leading to accelerated new skin growth and reduction in healing time. This has been facilitated by its ability to trigger growth factors such as vascular endothelial growth factor (VEGF) and transforming growth factor - beta (TGF-b) that are key agents in tissue regeneration [55].

Although these are promising outcomes, there are a number of limitations that are linked to the clinical evidence that should be taken into serious consideration. One of the issues is a small sample size in most of the clinical studies. A majority of the trials have small sample sizes, thereby decreasing the sensitivity and applicability of the results [66].

The other important limitation is the absence of standardization between studies. The nature of formulations of curcumin is highly varied with crude extraction, topical creams, hydrogel, nanoparticles, and nanoemulgels [67]. The variability in dosage, application frequency, length of treatment, and the nature of wound further complicates the comparisons across the studies. In addition, clinical benchmarks are hard to set since there are no standardized outcome measures and evaluation criteria [68].

In short, although there is clinical evidence that Curcuma longa has significant potential in healing wounds by improving diabetic wound healing, infection prevention, and epithelialization, the existing evidence is still not in place to give definite clinical recommendations [69]. Subsequent studies ought to be done in large scale, randomized controlled trials using standardized formulations and protocols to confirm these results and enable these to be translated into standard clinical practice [70].

7. Advanced Formulation Strategies

Curcumin, the major bioactive of Curcuma longa has shown great potential in wound healing, because of its anti-inflammatory, antioxidant, antimicrobial and tissue-regenerative activities. Nonetheless, it has a number of physicochemical and pharmacokinetic limitations that limit its clinical use to a considerable extent. The use of these challenges has led to the formulation of better formulation strategies to increase its therapeutic effectiveness [71].

Limitations of Curcumin

7.1 Poor Solubility

Curcumin is a hydrophobic polyphenol having very poor solubility in water. This low solubility prevents its dissolution in biological fluids, and as such, decreases its availability in the target site. Poor solubility in topical application results in low drug release rates and poor penetration of the drug through the skin layers resulting in ineffective therapy of the wound [72].

7.2 Low Bioavailability

Besides lack of solubility, curcumin has low bioavailability as it is metabolized and excreted in the body within a short period. It is greatly metabolized in the liver and the intestinal wall leading to its inactivation into inactive products. Moreover, it is unstable at physiological pH, and it is easily degraded, which minimizes its concentration at the wound site. The combination of these factors restricts its clinical translation although with good pharmacological activity.

High Level Formulation Strategies to beat limitations. As a solution to these difficulties, different innovative systems of drug delivery have been invented to enhance solubility, stability, permeability, and sustained release of curcumin [73].

7.3 Nanoparticles

Drug delivery systems based on nanoparticles have become a very promising method in improving the bioavailability of curcumin. In this system, curcumin is entraped in nanosized carriers like polymeric nanoparticles, solid lipid nanoparticles or nanostructured lipid carriers. Nanoparticle formulations are used in wound healing to enhance the wound site by providing deeper penetration into the skin and retention in wound healing, thus improving therapeutic effects of wound healing, including the rapid wound contraction and the minimization of inflammation [74]. These systems have a number of benefits:

- Higher solubility through an increment of surface area.
- Preservation of curcumin.
- Increased uptake and penetration by cells.
- Controlled and sustained release of drugs [75].

7.4 Hydrogels

Hydrogels are polymeric networks that are three-dimensional and that are hydrophilic and can absorb a lot of water. They create a humid ambiance which is very favorable to wound healing as it enhances cell migration, angiogenesis and tissue regeneration. Moreover, hydrogels may be designed to react to environmental conditions like pH or temperature, and thereby deliver drugs to the wound site in a controlled manner. Nonetheless, hydrogels in their own right might not be efficient in the delivery of poorly soluble drugs such as curcumin [55].

7.5 Nanoemulgels

Nanoemulgels are a cross between nanoemulsions and hydrogels in terms of drug delivery. Under this system, curcumin is initially added to a nanoemulsion (oil in water system with droplet size of nanometers) and finally added to a gel basis.

This two-tiered system provides a lot of benefits:

- Improved solubility of curcumin that is hydrophobic.
- Enhanced penetration of the skin because of nanosized droplets.
- Increased drug stability
- Extended period of wound retention.
- Regulated and slow release of drug.

The nanoemulgels are also characterized by high spreadability and patient acceptability which make it suitable in the topical wound treatment. Notably, research has shown that the nanoemulgels of curcumin yield significantly increased wound contraction, collagen production and re-epithelialization in comparison to the traditional formulations.

Nanoemulgels are especially promising in the context of research since they have solved the problem of solubility and bioavailability at the same time. This renders them very appropriate in chronic wound cases where there is a need to have a longer acting drug and penetrate the tissue more deeply [76].

8 Conclusions

Curcuma longa has been developed as a massively promising natural therapeutic agent in the area of wound healing with a strong body of experimental and slowly accumulating clinical evidence. In vitro and in vivo preclinical studies have consistently shown that curcumin, the primary bioactive component of *Curcuma longa*, has a considerable impact on wound healing by enhancing the core biological responses, such as fibroblast growth, collagen synthesis, angiogenesis, and re-epithelialization. These effects are further augmented by its strong anti-inflammatory, antioxidant and antimicrobial effects, which together combine to form an ideal microenvironment to facilitate efficient tissue regeneration.

A multi-targeted mechanism of action is one of the most evident benefits of curcumin. In contrast to other conventional therapeutic agents, which usually have a biologic impact on only one or few of the many molecular pathways, curcumin influences wound healing by impacting many pathways, such as inhibition of pro-inflammatory mediators, such as NF-KB, TNF-a and interleukins, and stimulation of growth factors, such as vascular endothelial growth factor (VEGF). This pleiotropic property renders *Curcuma longa* very useful in the treatment of complex and chronic wounds like diabetic ulcers where there are several pathological factors at play.

Regardless of these potential features, clinical translation of curcumin is not extensively developed because of a number of intrinsic issues. Its bioavailability, poor aqueous solubility, high rate of metabolism and physicochemical instability are critical obstacles to its therapeutic effect in conventional dosage forms. Furthermore, its wide-scale clinical application is also limited by the unavailability of standardized preparations, differences in dose schedules, and a deficiency of large-scale randomized clinical trials. The existing clinical evidence is promising but remains limited, with most being small studies and some having methodological flaws.

The development of novel drug delivery systems in that respect has played a critical role in eliminating these shortcomings. Among the numerous ways explored that have revolutionized the curcumin formulation technology is nanomulgel delivery systems. The nanoemulgels that are a combination of the nanoemulsions and hydrogels enhance the solubility of the drugs, drug absorption into the skin, prolongation of drug release, and maintenance of the drugs in the wound area. All these characteristics result in better therapeutic outcomes such as contraction of wounds faster, increases collagen deposition, and decreases the healing time.

Moreover, nanoemulgels are highly compatible with the topical wound management because of their non-greasy consistency, topical application and stability. The combination of nanotechnology and herbal therapeutics does not only enhance the pharmacokinetic properties of curcumin but also provides new opportunities to create the multifunctional and targeted wound healing systems.

To sum up, Curcuma longa has a great potential as an effective, safe, and multifunctional agent in wound healing. Nevertheless, to fully achieve its clinical utility, future studies are needed on the development of standardized, reproducible formulations and well-designed, large-scale randomized controlled trials. The focus should also be on the investigation of new delivery systems, including polyherbal nanoemulgels, that could further improve the therapeutic effect and cope with the complexity of managing chronic wound. Curcuma longa can become a part of modern wound care therapy with further development of the science of formulations and clinical trials.

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