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Review Article

A systematic review of the effects of *Curcuma longa* topical formulations on wound healing

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ABSTRACT

Topical herbal formulations are gaining more attention in wound healing due to their safety and efficacy. This is a systematic review of the effects of *Curcuma long* topical formulations on wound healing. *C. longa* is a traditional medicinal plant used due to its antimicrobial, antioxidant, anti-inflammatory, and wound healing properties. Studies carried out as randomized control trials and clinical trials were included for the analysis of this review. Searches were conducted in Pub Med, Scopus, Cochrane Central Register of Controlled Trials, and Google scholar (up to March 2022) with 04 studies meeting the inclusion criteria. All randomized control trials and clinical trials have shown a significant improvement in wound healing. The topical formulations containing *C. longa* as an ingredient have reportedly improved wound healing in cases of eczema, radio dermatitis, acne vulgaris, atopic dermatitis, ichthyosis vulgaris, senile pruritis, and xerotic skin conditions, according to the studies covered in this review. This review identified some evidence that *C. longa* on wound healing, including complications, larger, well-designed randomized control trials are required.

Key words: Curcuma longa, wound healing, topical preparations, clinical trials, randomized control trials

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INTRODUCTION

The skin serves as a barrier between individuals and the outside environment. Loss of the integrity of large portions of the skin as a result of injury or illness may lead to major disability¹. A wound is a physical lesion to any of the body's tissues that causes the continuity of soft body components to be disrupted. Wound healing is an important biological reaction that occurs spontaneously in the body throughout life². Wound healing is a highly regulated complex biological process mainly divided into 3 phases: hemostasis and inflammation, proliferation, and tissue remodeling^{3,4}. These three phases are sometimes overlapped and will happen for a long period of time depending on the nature of the wound.

Herbal or natural medicine has seen tremendous growth in recent years, and these formulations are gaining popularity all over the world^{5,6}. The World Health Organization (WHO) states that about 65 - 80 % of the world's population which lives in developing countries depends fundamentally on medicinal plants for their primary healthcare⁷. Herbal preparations used in wound management involve disinfection, debridement and providing a moist environment to restore the natural healing process⁸. Various herbal preparations have been

shown to expedite wound healing by increasing epithelialization, neovascularization, granulation tissue development, collagen production, wound contraction, and tensile strength^{9,10}.

Curcuma longa L., also known as turmeric, is a member of the Zingiberaceae (ginger)family. Turmeric is the most widely traded species, and its rhizomes are primarily grown in India, China, and Sri Lanka. The plants are grown for 7 to 9 months after which the rhizomes are harvested, boiled, processed, and crushed into powder¹¹. The extraction of powder is carried out by using solvents, water or both. C. longa is utilized in a variety of medicinal preparations as a preservative, spice and coloring agent, especially for ointments and creams. C.longa has been reported to possess anticancer, antidiabetic, antimicrobial, hepatoprotective, neuroprotective and anti-inflammatory $activities^{12}$. Curcuminoids are the primary polyphenolic chemicals found in turmenric rhizomes. Curcuminoids include curcumin, demethoxy curcumin, and bisdemethoxy curcumin. Among the curcuminoids, curcumin is the powerful substance which possesses anti-inflammatory, analgesic and wound healing properties^{13,14}. Curcumin was widely utilized in traditional Indian medicine to treat biliary diseases, cough, diabetic ulcers, hepatic disorders, arthritis, and sinusitis. Curcumin paste combined with lime has long been used as a home medicine for inflammation and wound healing^{15,16}. The volatile oil extracted from C. longa also has antibacterial and anti-inflammatory properties. Protein, lipids, and vitamins are all found in C. longa, and they all have a part in wound healing and regeneration^{17,18}

Curcumin in *C.longa* is known to cause improvements in wound healing at all three stages. During the inflammation stage, curcumin is known to suppress the activity of the NF-(κ) B (nuclear factor kappa-light-chain-enhancer of activated B cells) transcription factor, lowering the production of tumour necrosis factor alpha (TNF- α) and interlukin-1 (IL-1) cytokines and hence inflammation^{19,20}. Reactive oxygen species (ROS) helps immune system to fight against micro-organisms in wound healing. Curcumin has a scavenging effect on ROS while also increasing the generation of ROS^{21,22}. Curcumin will accelerate fibroblast migration, granulation tissue creation, collagen deposition, and, in general, re-epithelization during the proliferation stage of wound healing^{23,24}. During the proliferation stage, curcumin also induces apoptosis and remove undesired inflammatory cells from the wound site^{25,26}. Re-modeling is the final step of wound healing, in which curcumin improves wound contraction by boosting transforming growth factor beta (TGF- β) production and thus fibroblast proliferation^{27,28}.

C. longa extract or the active chemical curcumin is used to develop a variety of topical formulations such as creams, ointments, pastes, emulsions, hydrogels, films, fibers, and nanoformulations (nanoparticle, nanovesicle, micelle, and nanofiber)²⁹⁻³¹. A number of animal studies investigating the effect of C. longa on wound healing have been published, both in vitro and in vivo32,33. The efficacy of topical treatments prepared with C. longa has been shown to have a significant impact on wound healing. However, clinical trials on its influence on wound healing, or any of the parameters affecting wound healing in patients are still lacking. Furthermore, no systematic review or quantitative synthesis appears to have been conducted in this field of research and practice, which is essential to provide researchers and practitioners with an evidence base. The aim of this systematic review is to evaluate the effectiveness of C. longa topical herbal formulations in the treatment of wound healing.

Methods

The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement was used to conduct this systematic review³⁴. Moreover, this systematic review adheres to the Population, Intervention, Comparison, and Outcome (PICO) classification.

Search strategy

The literature on topical formulations of *C. longa* for wound healing treatments was searched in March 2022, via the MEDLINE (Pub Med), Scopus, Cochrane Central Register of Controlled Trialsand Google scholar databases. The search was based on a wide range of key word combinations:"*Curcuma longa*", "*C. longa*","Topical formulations", "cream", "ointment", "Inflammation", "gel", "herbal formulation", "wound healing", "scar treatment", "randomized control trials" and "clinical trials" (Table 1).

Table 1 Search terms and search strategy
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Patient/ population	Intervention	Outcome	Study design	Combination search terms
Acute wounds patients OR chronic wounds patients OR burn wounds patients	<i>Curcuma longa</i> OR <i>C.</i> <i>longa</i> ORturmeric OR Topical formulations	Inflammation OR Healing OR Wound OR Cytokines OR Skin	Randomized control trial OR clinical trial	Column 1 AND Column 2 AND Column 3 AND Column 4

Study selection

Eligibility criteria

1. Inclusion criteria: All randomized control trials or clinical trials conducted in humans using *C. longa* topical formulations published as full research papers, that

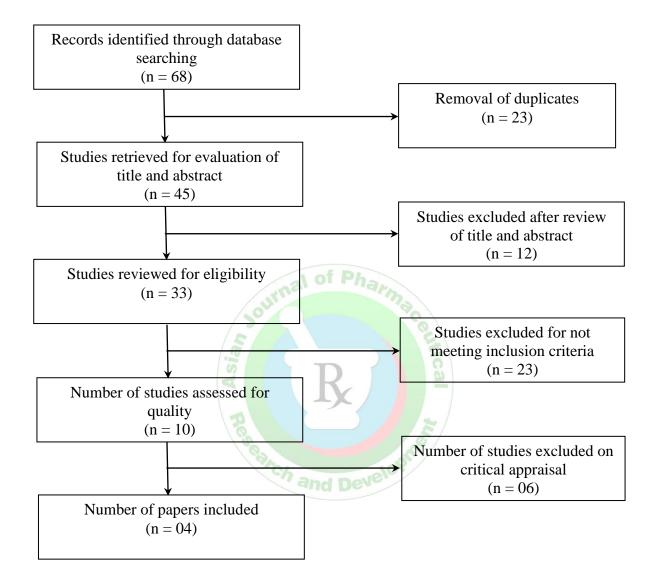
included a control group with placebo or comparison with other treatments were included in the study.

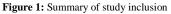
2. Exclusion criteria: Studies that were not done on humans or that did not include topical therapy with *C. longa* or any of its extracts were excluded. The review excluded studies written in languages other than English, as well as those with non-original or incomplete data.

Figure 1 represents the study selection procedure of this review. Titles and abstracts were screened to assess against the inclusion and exclusion criteria. Primary research studies investigating the use of topical herbal formulations to treat wound healing were included.

Data retrieval

The following information was extracted for the systematic review: Type of study; authors involved in the study; year of publication; type of wound treated; sample sizes; interventions and controls; treatment duration and follow-up periods; measurement of outcomes.





Quality assessment

The Cochrane risk of bias assessment technique was used to assess the quality of each included study. To assess the quality of each study, random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias were all employed. Each study was classified as low risk, high risk, or unknown danger based on the authors' evaluations³⁵.

RESULTS

Search process

After an extensive search, 68 studies were selected from the references of relevant publications in this topic. After filtering duplicates and screening studies based on titles and abstracts, 10 studies were left for full-text review. Finally, four studies either clinical trials or randomized control trials were included in the ten studies (Figure 1). Table 2 shows the baseline characteristics of the four studies.

Author and year of the study conducted	Study topic	Duration of treatment	Patient model	n	Topical preparation	Control group	Outcome/s of the study
Ranjan CR et al. 2009 ³⁶	Clinical Evaluation of an Indian Polyherbal Topical Formulation in the Management of Eczema	4 weeks	Patients with eczema	150	Herbavate® cream	Untreated	The efficacy and tolerability of Herbavate® cream in the treatment of eczema were tested. Patients' eczema symptoms like erythema, scaling, thickness, and itching had significantly improved. Only four patients reported moderate burning at the application site which improved with continued therapy.
Chatterjee S et al. 2005 ³⁷	Emollient and antipuretic effect of Itch cream in dermatological disorders: randomized control trial.	4 weeks	Patients with Xerotic and puritis disorders	64	Itch cream	Moisturex cream	The findings concluded that Itch cream had antipuritic and emollient properties in patients with moderate xerotic disorders including atopic dermatitis, ichthyosis vulgaris, and others. Few patients reported to have adverse events like minor localized skin irritation and burning sensations, but no significant adverse events were seen.
Palatty PL et al. 2014 ³⁸	Topical application of a sandal wood oil and turmeric based cream prevents radiodermatitis in head and neck cancer patients undergoing external beam radiotherap.	2 weeks	Radiodermatitis in patients with head and neck cancer undergoing radiotherapy	50	Turmeric- and sandal wood oil-containing cream Vicco® turmeric cream	Topical application of Johnson's® baby oil	Cohorts using Vicco turmeric cream experienced a significant decline in the severity of dermatitis at all time periods. Vicco turmeric cream had positive effects on cancer patients receiving radiation therapy in head and neck regions, and it also lowers the incidence and occurrence of Grade 3 dermatitis.
Lalla JK et al. 2001 ³⁹	Clinical trials of ayurvedic formulations in the treatment of acne Vulgaris.	4 weeks	Patients with acne vulgaris	53	Herbal extracts incorporated gel (Group 1) and cream (Group 2)	Placebo (Group 3 and 4)	In group I (Gel), 31.58% of patients had lesions that had improved "good to excellent," 63.16% had lesions that had improved "slight to fair," and 5.26% had responses that were variable. In group II (Cream), 57.89% demonstrated "good to excellent," 26.32% shown "slight to fair," and 15.79% demonstrated varied. None of the patients in group III had shown a "good to excellent response," although all of them improved their lesions in a "slight to fair," manner. Group IV's lesions did not get any better.

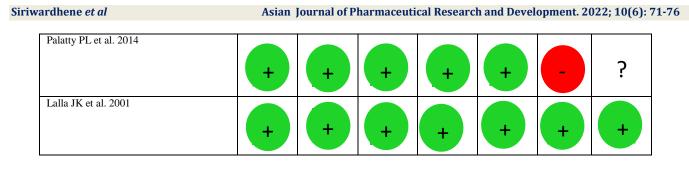
Table 2: Studies evaluating the effect of C. longa treatment on wound healing and reported outcomes.

n: number of sample included in the study (study population)

Assessment of risk of bias of included studies

Table 3: Risk of bias analysis for the studies on Curcuma longa that were included.

	Random sequence generation (Selection bias)	Allocation concealment (Selection bias)	Blinding of participants and personnel (Performance bias)	Blinding of outcome assessment (Detection bias)	Incomplete outcome data (Attrition bias)	Selective reporting (Reporting bias)	Other bias
Ranjan CR et al. 2009	?	+	-	+	+	-	+
Chatterjee S et al. 2005	+	+	?	+	+	+	+



Low risk of bias (+), unclear risk of bias (?), and high risk of bias (-)

The risks of bias summary in the included studies on C. longa are shown in Table 3. Notably, 100% of the studies reported low risk of bias with regard to allocation concealment, blinding of outcomes, and incomplete outcome data. However, in terms of random sequence generation and other biases, 75% of the trials showed a low risk of bias. Only 50% of studies showed low risk bias in blinding of participants and personnel and selective reporting. In the blinding of participants and personnel, a high bias was observed in Ranjan et al.³⁵ and an unclear risk of bias in Chatterjee et al.³⁶ Except for Chatterjee et al.³⁶ and Palatty et al.³⁷, which revealed a high risk of bias with regard to selective reporting, half of the studies displayed a low risk of bias. nal of

DISCUSSION

The findings of this systematic review provide some evidence for C. longa extract's efficacy in wound healing. The use of C. longa extract in wound care has long been practiced in Indian and Chinese medicine. The primary compound in C. longa that promotes wound healing is curcumin. According to studies, curcumin accelerates wound healing by influencing the inflammatory, proliferative, and remodelling stages of the process, which significantly reduces the time needed for wound healing. This review compiles the most recent data for its use in in vivo wound care management. According to the randomized control trials and clinical studies addressed in this review, topical formulations using C. longa as an ingredient have improved wound healing in cases of eczema, radiodermatitis, acne vulgaris, atopic dermatitis, ichthyosis vulgaris, senile pruritis, and xerotic skin conditions.

The commercial polyherbal Herbavate® cream's advantages in treating eczema were shown in the study by Ranjanet al^{35} . The cream contains C.longa extract as one of its major constituents. After one week of use, the severity of major eczema symptoms such as erythema, scaling, itching, and thickness were dramatically reduced (p < 0.001). In 36/44 cases, local tolerance was reported to be good or very good. Herbavate® cream was well tolerated; merely 4 patients experienced of mild burning when it was applied, and only 1 patient complained of hyperpigmentation, all of which subsided with continuing use. In a study by Chatterjeeet al.36 polyherbal Itch cream contained 16% w/w C.longa extract as the main constituent was used to treat many xerotic disorders. When compared to baseline mean scores, patients with atopic dermatitis, ichthyosis vulgaris, senile pruiritus, and xerotic skin disorders had a statistically significant reduction in mean pruiritus and patient's global assessment of wellbeing scores (p < 0.005). This study's findings indicated that atopic dermatitis, ichthyosis vulgaris, and other moderate xerotic illnesses could benefit greatly from the drug's good antipuritic and emollient characteristics. Patients with radiodermatitis and acne vulgaris demonstrated significant improvements in their symptoms in the trials by Palattyet al.³⁷ and Lalla et al.³⁸, respectively. Vicco turmeric cream lessens the prevalence and occurrence of Grade 3 dermatitis and has positive effects in preventing radiodermatitis in patients with head and neck cancer receiving radiation therapy. Acne vulgaris treated with turmeric topical and oral preparation has significantly improved the outcomes compared to placebo treatment. All of this clinical research has demonstrated that C. longa extract can be administered in a variety of settings to treat a wide range of skin conditions.

Almost all the turmeric topical preparations used in these randomized control trials are commercial products, and most of them contain other herbal extracts as well. It is therefore hard to ascertain whether the outcomes are due to the pharmacological action of turmeric alone or to the combined action of turmeric and other herbs. This systematic review only included four studies, which may restrict how widely the findings may be applied. A meta-analysis to determine the impact of C. longa on the outcomes examined could not be done since there were insufficient studies providing data on the same parameters. Therefore, more investigation is required to accurately determine how C. longa affects wound healing. The physical properties of C. longa make it tough to formulate into a dosage form, despite the fact that it possesses great wound healing effects. The hydrophobic nature of curcumin renders it less suitable for oral delivery, although numerous animal and human studies have shown outstanding topical application outcomes. Curcumin's poor bioavailability, quick metabolism, and light sensitivity are unfortunate additional drawbacks.

CONCLUSION

This systematic review has clearly expressed that C. longa topical preparations were excellent sources of wound healing in tested groups. C. longa treatment has shown better wound healing due to greater angiogenesis and its anti-microbial and anti-inflammatory effects. However, most of the formulations are combined herbal preparations, therefore the evidence is insufficient to prove the antiinflammatory and anti-microbial effect of C. longa in those topical preparations. Notably, the outcomes of topical delivery can be modified by incorporating C. longa in novel drug delivery systems.

Data availability

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

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Conflict of Interest

The authors declare no conflicts of interest.

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