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Evaluating the efficacy of topical *Centella asiatica* in accelerating burn healing in animal models: A systematic review

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Abstract

Centella asiatica (CA), a medicinal plant with historical use in traditional medicine, is rich in bioactive compounds like asiaticoside, madecassoside, and asiatic acid, which are known for their anti-inflammatory, antioxidant, and collagen-boosting properties. These compounds are especially beneficial in addressing the complexities of burn healing, which involves a balance between inflammation, tissue regeneration, and scarring. The review covers experimental studies focusing in CA in burn animal model from 2014 to 2024, focusing on various outcomes in the aspects of gross, histology, and markers. Results indicate that CA significantly accelerates healing by enhancing tissue repair processes and improving wound quality while reducing scar formation. However, variations in experimental methods, including differences in burn induction, CA formulation, and outcome measurements, highlight a need for standardized research protocols. Findings suggest that CA holds promise as a low-cost, effective therapeutic option for burn treatment, particularly valuable in low-resource settings. This review underlines the importance of further clinical trials to confirm CA's therapeutic potential, with the goal of developing accessible and effective treatments for burn injuries in humans.

Keywords: *Centella asiatica*; Burn healing; Wound healing; Animal models; Topical application

1. Introduction

1.1. Burn Injuries and Healing Process

Burn injury remains a significant global health concern, with an estimated 11 million people requiring medical attention for burns each year, the majority of which occur in low- and middle-income countries with limited access to advanced burn care [1, 2]. Burn wounds are complex and challenging to treat due to the dynamic healing process involving inflammation, tissue formation, and remodeling [3]. Prolonged inflammation during the crucial inflammatory phase can lead to delayed wound closure and increased scarring, and might be the precursor of skin cancer [4]. Current treatment modalities, such as silver sulfadiazine and other topical agents, have limitations in their ability to modulate inflammation and promote rapid tissue repair [5], highlighting the need for alternative therapies that can effectively accelerate burn healing while minimizing complications such as scarring and infection.

1.2. *Centella asiatica* (CA): Traditional Uses and Bioactive Compounds

Centella asiatica, a perennial herbaceous plant native to Asia, Africa, and the Pacific Islands, has been used for centuries in traditional medicine systems, such as Ayurveda, Traditional Chinese Medicine, and Indonesian folk medicine, to treat various skin conditions, including wound healing [6, 7]. In Ayurvedic medicine, CA is used to treat skin ulcers, burns, and leprosy [8], while in Chinese medicine, it is employed to treat traumatic injuries, burns, and scalds [9]. In Indonesia,

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CA is known as "Pegagan" and has been used for cosmetical purpose and medicinal purpose. The ethnopharmacological use of CA for wound healing has also been documented in several African countries, such as Madagascar, where it is applied topically to promote skin regeneration [10].

The therapeutic potential of CA is attributed to its rich content of bioactive compounds, primarily triterpene saponins such as asiaticoside, madecassoside, and asiatic acid [11]. These compounds have been extensively studied for their anti-inflammatory, antioxidant, and collagen-stimulating properties, which are crucial for effective wound healing [12]. Asiaticoside has been shown to enhance collagen synthesis, promote angiogenesis, and inhibit inflammation in both in vitro and in vivo models [13], while madecassoside has demonstrated significant anti-inflammatory and antioxidant activities, which can help to reduce oxidative stress and accelerate wound closure [14]. Asiatic acid, another key component of CA, has been reported to stimulate collagen production, including collagen-1 and collagen-3, hence it improves skin tensile strength, aiding in the wound healing process [15].

1.3. Mechanisms of Action of *Centella asiatica* in Burn Healing

Recent studies have extensively investigated the mechanisms of action of CA relevant to burn healing. One of the key properties of CA is its ability to modulate inflammatory pathways, which is crucial in the context of burn injuries. Asiaticoside, a major active compounds of CA, has been found to inhibit the NF-kB signaling pathway and reduce the production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 in macrophages [16]. Similarly, asiatic acid, another bioactive compound in CA, has been shown to reduce inflammation in a burn wound model by suppressing the NLRP3 activation and reducing IL-1β secretion [17]. Moreover, CA has been demonstrated to reduce oxidative stress, a critical component of burn wound pathology, by enhancing antioxidant enzyme activities and eliminating free radicals [18].

In addition to its anti-inflammatory properties, CA has been reported to promote angiogenesis and collagen synthesis, both of which are essential for effective wound healing. A study by Ruszymah *et al.* [19] revealed that a topical application of CA extract significantly increased collagen synthesis and accelerated wound closure in a rat burn model, attributing these effects to the upregulation of transforming growth factor-beta 1 (TGF-β1) and vascular endothelial growth factor (VEGF) expression, which are key mediators of collagen deposition and angiogenesis, respectively. Similarly, Somboonwong *et al.* [20] found that asiaticoside enhanced angiogenesis by increasing VEGF expression and promoting endothelial cell proliferation and migration in vitro.

Furthermore, CA has been investigated for its antimicrobial properties, which could be beneficial in preventing and treating infections in burn wounds. A study by Samy *et al.* [21] demonstrated that CA extract exhibited significant antibacterial activity against common wound pathogens, including Staphylococcus aureus, Pseudomonas aeruginosa, and Escherichia coli, suggesting that the antimicrobial effects of CA could be attributed to its ability to disrupt bacterial cell membranes and inhibit biofilm formation. Ling *et al.* [22] reported that asiaticoside, in combination with other antimicrobial agents, effectively reduced the bacterial load and promoted wound healing in a rat burn model infected with Pseudomonas aeruginosa.

1.4. Animal Models in Burn Research and Ethical Considerations

Animal models have been widely used in burn research to investigate the pathophysiology of burn injuries and to evaluate the efficacy of potential therapeutic interventions. The use of animal models is justified by their physiological similarities to humans in terms of skin structure and healing mechanisms. Porcine models, in particular, have been considered the gold standard for burn research due to the comparable thickness and composition of their skin to that of humans [23], and their similar healing processes, including epithelialization, granulation tissue formation, and scarring [24]. Rodent models, such as rats and mice, have also been extensively employed in burn studies due to their cost-effectiveness, ease of handling, and the availability of various transgenic strains that allow for the investigation of specific molecular pathways involved in burn healing [25].

However, the use of animal models in research has important ethical considerations. The principles of the 3Rs (Replacement, Reduction, and Refinement) have been increasingly emphasized in animal research to minimize animal suffering and improve the quality of scientific findings [26]. In the context of burn research, efforts have been made to develop alternative methods, such as in vitro models using human skin equivalents, to reduce the reliance on animal testing [27]. Moreover, advancements in imaging technologies, such as laser Doppler imaging and thermography, have allowed for non-invasive monitoring of burn wound progression, thereby reducing the number of animals required in studies [28].

Systematic reviews play a crucial role in consolidating the existing evidence from animal studies and identifying areas where further research is needed. By critically appraising and synthesizing the available data, systematic reviews can help to reduce animal studies and promote the implementation of the 3Rs [28]. Furthermore, systematic review can help in the design of more effective and targeted clinical trials and further studies [29].

1.5. Recent Findings and Limitations in *Centella asiatica* Research for Burn Healing

In recent years, there has been vast research supporting the efficacy of *Centella asiatica* (CA) in wound and burn healing. Somboonwong *et al.* [30] investigated the wound healing activities of various CA extracts in incision and burn wound models in rats, finding that topical application of an ethanolic extract of CA significantly increased the rate of wound healing and reduced scar formation. Similarly, Ju Ho *et al.* [31] demonstrated that a titrated extract of CA (TECA) enhanced the healing of burn wounds in rats by promoting angiogenesis, collagen synthesis, and re-epithelialization, while also reducing the expression of pro-inflammatory cytokines, such as TNF-α and IL-1β. In a more recent study, Singkhorn *et al.* [32] evaluated the efficacy of a CA-containing hydrogel in promoting burn wound healing in rats. Moreover, the CA hydrogel was found to exhibit antimicrobial activity against common burn wound pathogens, such as Staphylococcus aureus and Pseudomonas aeruginosa.

Despite the promising findings, there are limitations and gaps in the current literature on CA in burn healing. One major issue is the lack of standardized methodologies across studies, which makes it difficult to compare and interpret the results. The burn models employed in different studies vary in terms of the method of burn induction and the duration of the study [33]. Another limitation is the variation in CA formulations used in different studies. The composition and concentration of bioactive compounds in CA extracts can vary depending on the plant source, extraction method, and formulation process [34], making it challenging to determine the optimal dosage and formulation for burn healing applications.

1.6. Purpose and Scope of the Systematic Review

The purpose of this systematic review is to comprehensively evaluate the efficacy of topical *Centella asiatica* (CA) in accelerating burn healing, with a specific focus on animal models. By critically appraising and synthesizing the available preclinical evidence, this review aims to provide a clear understanding of the therapeutic potential of CA in burn wound management. The findings of this review could have significant translational implications for improving burn treatments in humans, particularly in settings where affordable and accessible interventions are needed. Burn injuries disproportionately affect low- and middle-income countries, where the majority of burn-related deaths occur [35]. Therefore, identifying cost-effective and readily available treatments, such as CA, could have a substantial impact on reducing the global burden of burn injuries.

The scope of this systematic review will include a comprehensive search of multiple electronic databases for studies investigating the effects of topical CA on burn healing in animal models. The selection of studies will be based on predefined eligibility criteria. The key outcomes assessed will include burn wound healing viewed from gross examination, histological, and also with healing or inflammatory markers. By evaluating these outcomes, the review will provide a holistic understanding of the mechanisms underlying CA's effects on burn healing and its potential to improve clinical outcomes.

This systematic review aims to rigorously evaluate the efficacy of topical *Centella asiatica* (CA) in accelerating burn healing in animal models, providing valuable insights for clinical and pharmacological fields. By synthesizing existing preclinical evidence, it will guide future drug development, optimize the use of CA in burn wound management, and contribute to the creation of affordable and effective treatments, ultimately improving patient outcomes and reducing the global burden of burn injuries.

2. Methods

2.1. Study Selections

- P (Population) : Animal models with induced burn injuries
- I (Intervention) : Topical application of *Centella asiatica*.
- C (Comparison) : Placebo or conventional treatments for burn healing.
- O (Outcome) : Rate of burn healing, measured through parameters such as wound closure time, degree of epithelialization, and overall recovery.

Moreover, we use exclusion and inclusion criteria to make sure the research articles selected are in line with the purpose of this study as followed in Table 1.

Table 1 Inclusion and Exclusion Criteria

Inclusion Criteria	**Exclusion Criteria**
Articles in English Experimental studies comparing *Centella asiatica* with placebo or conventional treatments Research focusing on the topical application of *Centella asiatica* Studies conducted on animal models with induced burn injury of any degree. Studies published in peer-reviewed journals in 2014-2024.	Articles published in peer-reviewed journals or in language other than English Non-experimental study or study with no control groups Studies involving human subjects Studies conducted *in vitro* only Studies not focused on burn healing Studies not focused on *Centella asiatica* or active compounds extracted from *Centella asiatica*

2.2. Search Strategy

This systematic review was meticulously conducted in accordance with the esteemed Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement. The review also faithfully adhered to the Population, Intervention, Comparison, and Outcome (PICO) framework, ensuring a comprehensive and focused approach to the research question at hand.

To cast a wide net and capture all relevant literature, a thorough search strategy was employed across multiple reputable databases, including Pubmed, Proquest, and Semantic scholar. The search terms were carefully crafted, combining keywords from predetermined PICO and each terms' synonyms, then creating search strings using the Boolean operators OR and AND (Table 2). This approach allowed for a comprehensive yet targeted exploration.

Table 2 Search Terms and Strategy based on PICO

Population(P)	**Intervention (I)**	**Comparison (C)**	**Outcome (O)**	**Search Strings Combinations**
"burn" OR "laser" OR "heat" OR "thermal" OR "flame" OR "sunburn"	"*Centella asiatica*" OR "Gotu Kola" OR "Indian pennywort" OR "Bua-bok" OR "Pegagan" OR "Centella" OR "asiaticoside" OR "madecassoside" OR "asiatic acid" OR "madecassic acid"	"control group" OR "placebo group"	"healing" OR "epithelialization" OR "treatment efficacy" OR " recovery" OR "scar formation" OR "scarring" OR "wound contraction" OR "wound size reduction" OR "healing time" OR "contraction" OR "inflammation" OR "wound" OR "cytokines" OR "interleukin" OR "collagen" OR "infection" OR "skin" OR "histology" OR "angiogenesis" OR "regeneration" OR	Combining P AND I Combining P AND O

Then, references of articles were diligently examined by writer to identify any additional studies that may have been missed, ensuring a truly exhaustive review of the literature. The searches were conducted with great care and attention to detail by one researcher (S.M), and the data from the selected articles were extracted. To ensure the utmost accuracy and reliability, a second researcher (K.H.) independently cross-checked the search results and data extraction to verify.

2.3. Quality Assessments

The risk of bias assessment was assessed by the SYRCLE's Risk of Bias tool [42]. SYRCLE's Risk of Bias Tool is specifically designed for animal studies, adapted from the Cochrane Risk of Bias Tool, making it more suitable for experiments involving animals. This tool provides a more detailed focus on methodological risks of bias, such as allocation sequence generation, allocation concealment, blinding, and selective outcome reporting. We also use Mixed Methods Appraisal Tool (MMAT) 2018 version with minimum score of 4/7 to assess the quality of quantitative experimental research [43].

Table 3 SYRCLE's risk of bias tool for animal studies

	Was the allocation sequence adequately generated and applied? (selection bias)	**Were the groups similar at baseline or were they adjusted for confounders in the analysis? (selection bias)**	**Was the allocation adequately concealed? (selection bias)**	**Were the animals randomly housed during the experiment? (performance bias)**	**Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment? (performance bias)**	**Were animals selected at random for outcome assessment? (detection bias)**	**Was the outcome assessor blinded? (detection bias)**	**Were incomplete outcome data adequately addressed? (attrition bias)**	**Are reports of the study free of selective outcome reporting? (reporting bias)**	**Was the study apparently free of other problems that could result in high risk of bias? (other)**
Hou (2016)	?	V	?	V	X	?	X	V	V	V
D. A. Swastini (2021)	?	V	?	V	X	?	X	V	V	V
F. I. Armadany (2023)	?	V	?	V	X	?	X	V	V	V
Thanusha (2018)	?	V	?	V	X	?	X	V	V	V
Thanusha (2020)	?	V	?	V	X	?	X	V	V	X
Zhu (2016)	?	V	?	V	X	?	X	V	V	V

"V": Yes; "X": No; "?": Not mentioned or unknown

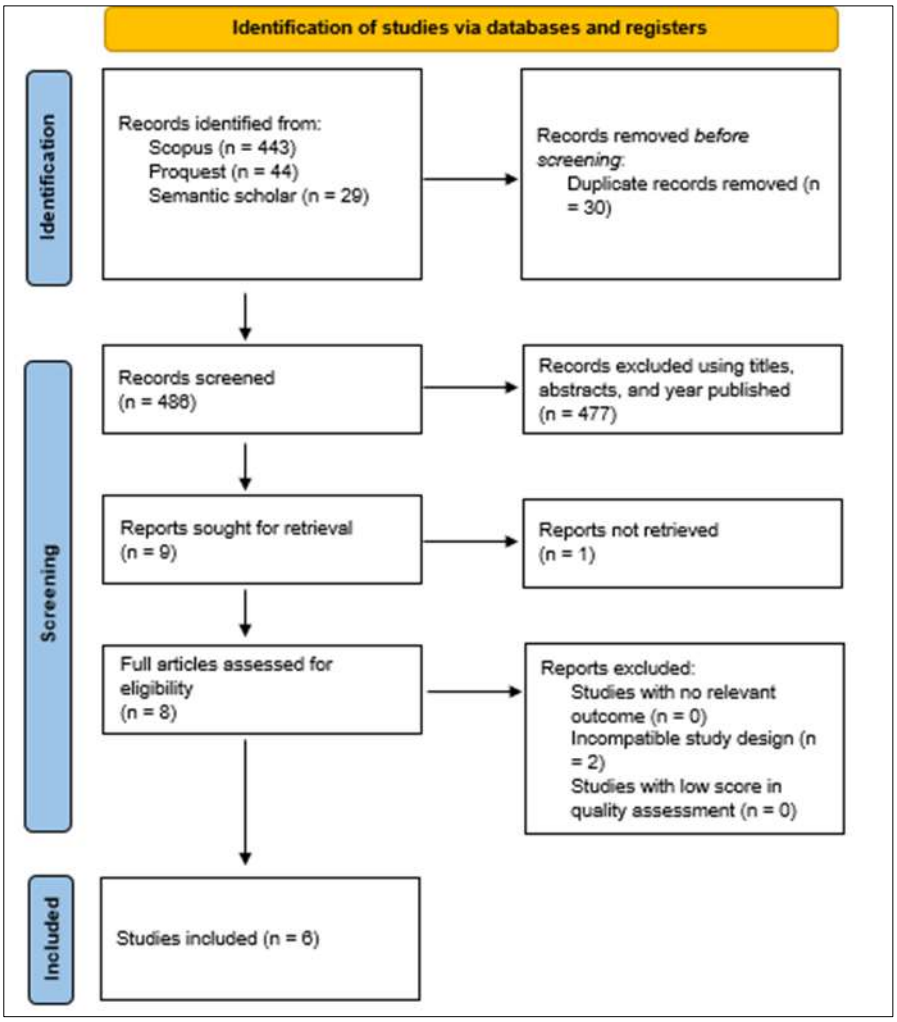

Figure 1 PRISMA Flow diagram of the search strategy conducted

Based on the PRISMA flow diagram shown, we initially identified 516 records from three databases (443 from Pubmed, 44 from Proquest, and 29 from Semantic Scholar). After removing 30 duplicate records, 486 records were screened. Of these, 477 unrelated records were excluded based on titles, abstracts reviews, and year of publications. Of the remaining 9 reports sought for retrieval, 1 report could not be retrieved. Among the 8 full articles assessed for eligibility, 2 were excluded due to incompatible study design, while no studies were excluded due to irrelevant outcomes or low quality MMAT score. This systematic review process ultimately yielded 6 studies that met all inclusion criteria for final analysis.

3. Results and Discussions

From study selections methods above, we compile 6 studies as shown in Table 4.

Centella asiatica has been traditionally used for wound healing, and recent studies have investigated its efficacy in burn injury management. These findings align with other recent studies supporting *Centella asiatica*'s wound healing properties. Ruszymah *et al.* found that *Centella asiatica* promoted fibroblast proliferation and collagen synthesis in vitro [19]. Sh *et al.* reported enhanced wound contraction and epithelialization in excisional rat wound models treated with *Centella asiatica* extract [41].

Table 4 Studies evaluating the effect of topical *Centella asiatica* on burn injury and reported outcomes

Study	Duration	Burn Lesion		Animal Model	n	Compound	Control Group		Outcomes		
		Induction	Degree of burn				(-)	(+)	Gross	Histology	Marker
Hou (2016) [35]	14 days	Hot plate (75 °C for 10 seconds)	2nd degree	Sprague-Dawley rats	8 per group (total 150)	asiaticoside, madecassoside	vaseline	-	↑ wound contraction	= re-epithelialization, = tissue organization	↑ VEGF, ↓ MCP-1,
D. A. Swastini (2021) [36]	21 days	Heated cylindrical metal (75° C for 10 seconds)	2nd degree	Wistar rats	5 per group (total 45)	*Garcinia mangostana* L. extract, *Anredera cordifolia* extract, CA extract	saline solution	silver sulfadiazine	↑ wound healing	↑ angiogenesis, ↓ inflammatory cell infiltration, ↑ collagen	-
F. I. Armadany (2023) [37]	21 days	Heated metal coin to skin (5 seconds, unknown temperature)	2nd degree	Mus musculus (male mice)	4 per group (total 28)	CA extract combined with VCO	Tween 20 solution	commercial burn healing gel (ingredients unexplained)	↑ wound contraction, ↓ burn diameter	↑ fibroblast cell count	-
Thanusha (2018) [38]	28 days	Heated metallic brass bar (90 ± 5 °C for 20 seconds)	2nd degree	Wistar rats	16 total	Nano hydrogel composite include gelatin, hyaluronic acid, chondroitin sulfate, asiatic acid (derived from CA), zinc oxide, and copper	gauze	commercial skin graft NeuSkin™	↑ wound contraction ↓ scar formation	↑ tissue regeneration, ↓ inflammatory cell infiltration, ↑ collagen	↑ MMP-2, ↓TNF-α,

						oxide nanoparticles					
Thanusha (2020) [39]	28 days	Custom design metallic punch (120 + 5°C for 20 seconds)	2nd degree	Wistar rats	6 per group (total 30)	Biopolymeric scaffold with 10 mm in size, made of gelatin, hyaluronic acid, chondroitin sulfate, and asiatic acid	no treatment	commercial burn healing gel Kollagen-D	↑ wound contraction	↑ tissue regeneration, ↑ dermis formations	↑ collagen, ↑ DNA, ↑ protein content, ↑ hydroxyproline, ↑ hydroxylamine, ↑ MMP-2, ↓TNF-α
Zhu (2016) [40]	21 days	Circular burn instrument with constant pressure	2nd degree	Sprague-Dawley rats	6 per group (30 in total)	Asiaticoside in coaxial nanofibers composed of sodium alginate, chitosan, and polyvinyl alcohol	no treatment	commercial asiaticoside 2,5% cream.	↑ wound healing,	↑ re-epithelialization, ↓ inflammatory cell	↑ collagen, ↑ VEGF, ↑ CD31, ↑ PCNA, ↓ IL-6 ↓ TNF-α

CA: *Centella asiatica*; MCP-1: Monocyte Chemoattractant Protein-1 (MCP-1); VEGF: Vascular Endothelial Growth Factor; TNF-α: Tumour Necrosis Factor-alpha; MMP-2: Matrix Metalloproteinase 2; IL-6: Interleukin-6; CD31: Platelet Endothelial Cell Adhesion Molecule-1; PCNA: Proliferating Cell Nuclear Antigen, ↑: increases, ↓: decreases, = not significant

Centella asiatica has been shown to accelerate burn healing in animal models through various molecular mechanisms that influence key processes such as wound contraction, angiogenesis, tissue regeneration, dermis formation, re-epithelialization, collagen production, growth marker expression, and inflammation. Wound contraction is enhanced by *C. asiatica* through its effects on the transforming growth factor-beta (TGF-β) signaling pathway. The plant's active compounds, particularly asiaticoside and madecassoside, have been found to upregulate the expression of TGF-β1, which stimulates the differentiation of fibroblasts into myofibroblasts [44]. Myofibroblasts are responsible for generating the contractile forces necessary for wound closure. Additionally, *C. asiatica* increases the expression of alpha-smooth muscle actin (α-SMA), a marker of myofibroblast differentiation [45].

Angiogenesis, the formation of new blood vessels, is crucial for providing oxygen and nutrients to the healing wound. *C. asiatica* promotes angiogenesis by upregulating the expression of vascular endothelial growth factor (VEGF) and its receptor, VEGFR-2 [46]. VEGF is a key signaling protein that stimulates the proliferation, migration, and tube formation of endothelial cells. The plant's compounds, particularly asiatic acid, have been shown to activate the PI3K/Akt/mTOR pathway, which is involved in the transcriptional regulation of VEGF [47].

Tissue regeneration and dermis formation are enhanced by *C. asiatica* through its effects on fibroblasts and keratinocytes. The plant's compounds stimulate the proliferation and migration of these cells by modulating the expression of growth factors such as epidermal growth factor (EGF) and fibroblast growth factor (FGF) [48]. Additionally, *C. asiatica* increases the production of extracellular matrix components, particularly collagen, by upregulating the expression of genes involved in collagen synthesis, such as COL1A1 and COL3A1 [49].

Re-epithelialization, the process by which keratinocytes migrate and proliferate to cover the wound surface, is accelerated by *C. asiatica* through its effects on matrix metalloproteinases (MMPs). The plant's compounds, particularly asiaticoside, have been shown to increase the expression and activity of MMP-2, which is involved in the degradation of the extracellular matrix, facilitating keratinocyte migration [49]. Additionally, *C. asiatica* upregulates the expression of integrin β1, a cell surface receptor that mediates keratinocyte adhesion and migration [7].

Collagen production is enhanced by *C. asiatica* through its effects on the TGF-β/Smad signaling pathway. The plant's compounds, particularly asiaticoside and madecassoside, have been found to increase the phosphorylation of Smad2 and Smad3, which are key transcription factors involved in the regulation of collagen synthesis [47]. Additionally, *C. asiatica* upregulates the expression of growth markers such as hydroxyproline and hydroxylamine, which are indicative of increased collagen production [49].

Inflammation is reduced by *C. asiatica* through its effects on pro-inflammatory cytokines and immune cells. The plant's compounds, particularly asiatic acid and madecassic acid, have been shown to inhibit the production of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) by macrophages and neutrophils [50]. This is achieved through the modulation of signaling pathways such as NF-κB and MAPK, which are involved in the transcriptional regulation of pro-inflammatory genes. Additionally, *C. asiatica* has been found to promote the polarization of macrophages towards the anti-inflammatory M2 phenotype [47].

In conclusion, the molecular mechanisms by which *Centella asiatica* accelerates burn healing in animal models involve a complex network of signaling pathways and cellular processes. The plant's active compounds modulate the expression and activity of various growth factors, cytokines, enzymes, and transcription factors involved in wound contraction, angiogenesis, tissue regeneration, dermis formation, re-epithelialization, collagen production, growth marker expression, and inflammation. Further research is needed to fully elucidate the molecular targets and interactions of *C. asiatica* compounds in the context of burn healing.

The author notices that some researches above do not include standardized burn-conduction model, hence the burn degree may not be reliable for it may vary or uneven burn injury in each sample – there might be first degree burn in some samples because the heat induction is not enough. The temperature set for inducing metal instrument varies, from minimum 75 °C to 125°C with the duration of 5-20 seconds to induce second degree burns. Some conductions also require measurable pressure, and some not. All the studies use rodents as animal models, as known that rodents are cost-effective and representatives although they're not the gold standard for burn injury animal model. All the studies present minimum 2 kinds of outcomes, gross evaluation and histological evaluation. But some of the studies only describe the gross outcome such as the presence of re-vascularization and re-epithelialization, not using quantified study. So, in writer's opinion, the gross outcome may not be reliable.

While these studies provide promising evidence, further research is needed to fully elucidate *Centella asiatica*'s optimal dosing, toxicity, and potential synergistic effects with other compounds. Larger, well-designed clinical trials are necessary to confirm its efficacy and safety in human burn injury management.

4. Conclusion

This systematic review highlights the potential of *Centella asiatica* (CA) as a promising therapeutic agent for burn healing, supported by its bioactive compounds—asiaticoside, madecassoside, and asiatic acid—which exhibit significant anti-inflammatory, antioxidant, and collagen-stimulating effects. Findings from multiple animal studies suggest that topical CA application accelerates wound closure, enhances tissue regeneration, and improves overall wound quality, with reduced scarring. Despite these promising results, variations in study methodologies, such as burn induction methods, CA formulations, and outcome assessments, suggest a need for standardized protocols to improve the reliability of findings. Future clinical studies are necessary to validate these preclinical outcomes and determine optimal CA formulations and dosages for safe and effective human use. Ultimately, CA presents a valuable, cost-effective option, particularly in low-resource settings, for improving burn treatment and reducing complications associated with healing.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that there is no conflict of interest.

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