UNIVERSITAT DE BARCELONA

Facultat de Farmàcia
i Ciències de l'Alimentació

TREBALL FINAL DE GRAU

Grau de Farmàcia

The immunomodulatory potential of *Centella asiatica* in low-grade skin inflammation

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Universitat de Barcelona

Barcelona, Abril del 2026

ABBREVIATIONS

AD: *Atopic dermatitis*

AKT: *Protein kinase B*

COX-2: *Cyclooxygenase-2*

ECa 233: *Standardized extract of Centella asiatica*

ERK1/2: *Extracellular signal-regulated kinases 1 and 2*

IL-1α: *Interleukin-1 alpha*

IL-1β: *Interleukin-1 beta*

IL-4: *Interleukin-4*

IL-6 : *Interleukin-6*

IL-10: *Interleukin-10*

iNOS: *Inducible nitric oxide synthase*

JAK: *Janus kinase*

LPS: *Lipopolysaccharide*

MAPK: *Mitogen-activated protein kinase*

MCP-1: *Monocyte chemoattractant protein-1*

MMP-1: *Matrix metalloproteinase-1*

MMP-9: *Matrix metalloproteinase-9*

NF-κB: *Nuclear factor kappa B*

NO: *Nitric oxide*

PGE2: *Prostaglandin E2*

RAW 264.7: *Murine macrophage cell line*

ROS: *Reactive oxygen species*

STAT: *Signal transducer and activator of transcription*

TECA: *Titrated extract of Centella asiatica*

TNF-α: *Tumor necrosis factor alpha*

UVB: *Ultraviolet B*

ABSTRACT

The immunomodulatory potential of *Centella asiatica* in low-grade skin inflammation

Low-grade skin inflammation was recognized as an important contributor to the development and persistence of several chronic dermatological conditions, like atopic dermatitis. Unlike acute inflammation, this state involves persistent but mild immune activation that may occur even in the absence of visible lesions. Continuous activation of intracellular signaling pathways and sustained cytokine production can contribute to alterations in skin homeostasis and barrier function. Understanding the mechanisms involved in this process has raised interest in therapeutic strategies that are capable of modulating inflammatory responses while also preserving normal immune function.

The aim of this work was to explore the potential immunomodulatory role of *Centella asiatica* in low-grade skin inflammation. The work is based on a narrative literature review, using PubMed as the main database, complemented by additional searches in Google Scholar and ScienceDirect. Studies investigating the effects of *C. asiatica* extracts or its main triterpenoid compounds on inflammatory mediators and signaling pathways were also included, especially those using experimental models relevant to skin inflammation.

The reviewed studies show that *C. asiatica* extracts reduced the expression of pro-inflammatory mediators such as TNF-α, IL-1β and IL-6, along with decreased activity of COX-2, iNOS and PGE_2. These effects were frequently associated with the modulation of intracellular pathways including NF-κB and MAPK, which play an important role in the regulation of inflammatory responses in the skin.

Overall, the available evidence suggests that *Centella asiatica* may influence inflammatory signaling involved in cutaneous inflammation. However, most of the current data derives from preclinical studies, and further clinical research is required to determine its potential relevance in clinical practice.

Key words: *Centella asiatica,* low-grade skin inflammation, atopic dermatitis, NF-κB, MAPK, triterpenoids.

RESUM

El potencial immunomodulador de la *Centella asiatica* en la inflamació cutània de baix grau

La inflamació cutània de baix grau ha estat reconeguda com un factor important en el desenvolupament i la persistència de diverses afeccions dermatològiques cròniques, com la dermatitis atòpica. A diferència de la inflamació aguda, aquesta implica una activació del sistema immune persistent però lleu que pot produir-se fins i tot en l'absència de lesions visibles. Una contínua activació de vies de senyalització intracel·lulars i una producció sostinguda de citocines poden contribuir a alteracions en l'homeòstasi de la pell i en la funció de la barrera cutània. Entendre els mecanismes implicats en aquest procés ha despertat cert interès en trobar estratègies terapèutiques capaces de modular les respostes inflamatòries i alhora preservar la funció immunitària normal.

L'objectiu d'aquest treball ha estat explorar el possible paper immunomodulador de *Centella asiatica* en la inflamació cutània de baix grau. El treball es basa en una revisió narrativa de la literatura, utilitzant PubMed com a base de dades principal, complementada amb cerques addicionals a Google Scholar i ScienceDirect. També es van incloure estudis que investigaven els efectes dels extractes de *C. asiatica* o dels seus principals compostos triterpenoides sobre mediadors inflamatoris o vies de senyalització, especialment aquells que utilitzaven models experimentals rellevants per a la inflamació cutània.

Els estudis revisats mostren que els extractes de *C. asiatica* redueixen l'expressió de mediadors proinflamatoris com TNF-α, IL-1β i IL-6, així com l'activitat de COX-2, iNOS i PGE_2. Aquests efectes s'associen sovint amb la modulació de vies intracel·lulars com NF-κB i MAPK, que tenen un paper important en la regulació de les respostes inflamatòries a la pell.

En conjunt, l'evidència disponible suggeriria que la *Centella asiatica* podria influir en els processos de senyalització inflamatòria implicats en la inflamació cutània. No obstant això, la major part de les dades actuals provenen d'estudis preclínics, i serien necessaris més estudis clínics per determinar la seva possible rellevància en la pràctica clínica.

Paraules clau: *Centella asiatica*, inflamació cutània de baix grau, dermatitis atòpica, NF-κB, MAPK, triterpenoides.

INTEGRATON OF DICIPLINES

This work is mainly related to **Pharmacognosy and Phytotherapy**, as it focuses on the potential of *Centella asiatica* in regulating low-grade skin inflammation and helping maintain skin balance. However, the topic cannot be fully understood from only one perspective as it involves concepts from different disciplines.

On the one hand, it is connected to pharmacognosy and phytotherapy, since it looks at the plant origin of the active compounds and the role of its main triterpenoids, such as asiaticoside, madecassoside, asiatic acid and madecassic acid, in its biological activity. Looking at how these compounds are naturally present in the plant extract helps explain the interest in using whole extracts rather than isolated components.

At the same time, the work also relates to **Immunology**, as it considers how *Centella asiatica* may influence inflammatory responses by acting on pro-inflammatory cytokines and signaling pathways like NF-κB and MAPK, which are involved in chronic skin inflammation. This perspective is especially relevant when studying conditions linked to persistent low-grade inflammation.

Lastly, it is linked to **Pharmaceutical Technology**, as it considers how formulation affects treatment effectiveness, especially considering that the physicochemical properties of these compounds can limit their penetration through the skin. This highlights the importance of developing topical formulations that allow the active compounds to reach their site of action within the skin.

Looking at the topic from these different areas helps to better understand both how *Centella asiatica* works and how it could potentially be used in dermatological practice.

SUSTAINABLE DEVELOPMENT GOALS

This work is mainly related to SDG 3 (Good Health and Well-being) and SDG 9 (Industry, Innovation and Infrastructure), as it explores potential new approaches for managing chronic low-grade skin inflammation.

SDG 3 focuses on promoting health and well-being. This study looks at the immunomodulatory potential of *Centella asiatica* in low-grade skin inflammation, which is involved in chronic conditions such as atopic dermatitis. These disorders often require long-term anti-inflammatory treatment, usually based on topical corticosteroids, whose prolonged use may lead to adverse effects. This reflects the need for safer complementary treatment options.
Exploring plant-derived compounds that can influence inflammatory pathways such as NF-κB and MAPK without causing immunosuppression, this work aims to contribute to the exploration of alternative strategies that could complement existing treatments.

Secondly, this work is also related to **SDG 9**, which focuses on innovation in science and healthcare. Studying *Centella asiatica* is a good example of how traditional medicinal knowledge can be revisited using modern research to better understand its possible therapeutic values. Exploring how its main active compounds interact with inflammatory pathways may contribute to developing new dermatological approaches.
At the same time, the importance of extract standardization and the development of suitable topical formulations shows how pharmaceutical research is needed to move from theoretical knowledge to applications that could eventually be useful in clinical practice.
Standardizing extracts and working on appropriate topical formulations also shows how pharmaceutical research helps move from theoretical knowledge to something that could actually be used in real treatments.

Overall, this work aims to contribute to both improving health and encouraging new developments in pharmaceutical research.

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INTRODUCTION

Low-grade inflammation and skin homeostasis

Beyond its known role in wound healing and tissue repair, recent dermatological research highlights the relevance of low-grade inflammation in the development of chronic skin conditions such as mild atopic dermatitis (AD) and sensitive skin syndromes.

Chronic inflammatory skin conditions like AD used to be understood as acute flare-up episodes. More modern articles describe AD as a dynamic disorder associated with persistent alterations in skin homeostasis, epidermal barrier dysfunction and fragility, immune imbalance, microbial dysbiosis, exogenous environmental and genetic susceptibility (1-3). The skin barrier may appear unaffected with symptoms being absent or very minimal, while still remaining functionally weakened and imbalanced, which may contribute to a persistent state of low-level inflammatory activity (3).

Barrier alteration is no longer viewed merely as a consequence of inflammation but rather as a key element in the pathology's development (4). When the skin barrier is damaged, it allows irritants, allergens and other microorganisms to penetrate more easily, activating immune pathways and inflammatory responses, through interactions between keratinocytes and tissue-resident immune cells (5,6). These interactions promote type 2 inflammation and the expression of genes involved in epidermal barrier components, including structural proteins, lipids and junctional elements (6). Reduced levels of certain structural proteins like filaggrin, increased trans-epidermal water-loss and higher permeability to exogenous agents make the skin more reactive and more likely to respond to triggers (7).

Recent studies indicate that, at a cellular level, stressed keratinocytes release signaling cytokines that recruit immune cells and maintain low-level inflammatory activity, even in the absence of visible flare-ups (5), suggesting that early cellular alterations may occur before lesions become clinically apparent (8).

The continuous activation of these intracellular signaling pathways, nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK), plays an important role in maintaining inflammatory responses. When these pathways stay active, they keep triggering the continuous production of pro-inflammatory genes, leading to a continued cytokine release (9). In the skin, this increased NF-κB activity contributes to the production of Interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α) and interleukin-1 beta (IL-1β), promoting chronic inflammation (10). The mechanisms involved in low-grade skin inflammation are summarized in Figure 1.

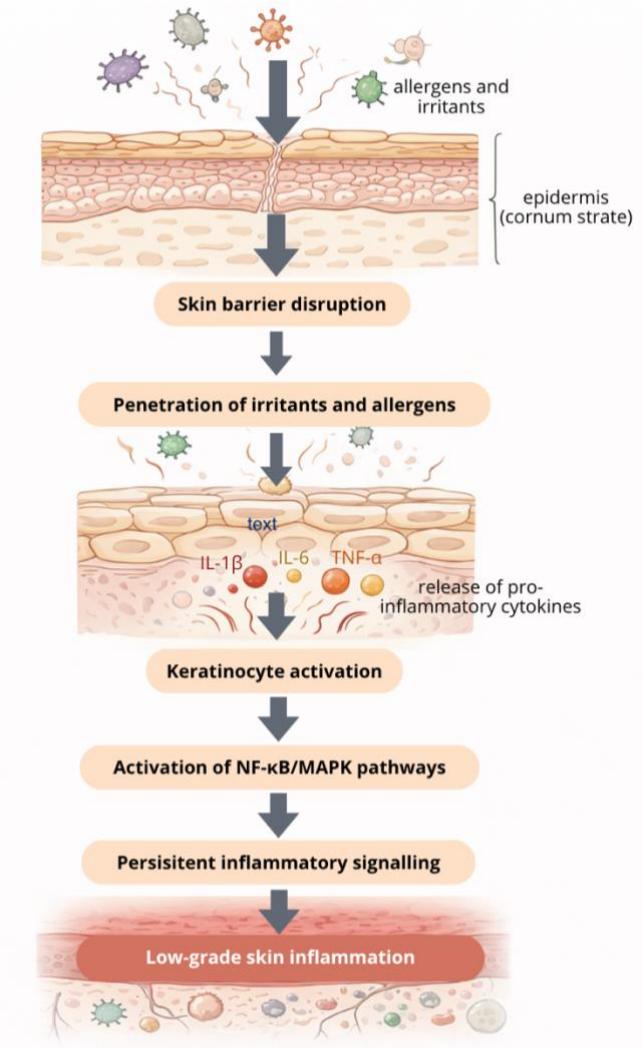

Figure 1. Representation of the mechanisms involved in low-grade skin inflammation. The disruption of the epidermal barrier allows the penetration of irritants and allergens, leading to keratinocyte activation and the release of pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α. These mediators activate intracellular signaling pathways including NF-κB and MAPK, contributing to persistent inflammatory signaling in the skin.

All these findings help justify exploring the potential immunomodulatory role of *Centella asiatica* not only in acute skin repair, but also in conditions characterized by chronic low-level inflammation and altered barrier function such as AD.

Cutaneous immune regulation in low-grade inflammation

The skin is not only a physical barrier but also an active immunological organ that can sense and respond to environmental stress. Keratinocytes, are the predominant cells in the epidermis, where they play a central role by producing cytokines and other mediators that regulate local immune responses (11).

When the skin barrier is disrupted or exposed to environmental stress, keratinocytes activate intracellular signaling pathways such as NF-κB and MAPK. These pathways regulate the expression of pro-inflammatory cytokines, including IL-1β, IL-6 and TNF-α, which maintain inflammatory signaling in chronic inflammatory conditions (9).

In low-grade inflammation, this activation does not necessarily cause visible inflammatory symptoms, but it may promote persistent subclinical immune activity[1] (9). These processes are thought to contribute to the development of chronic dermatological conditions such as AD (4,11).

Low-grade inflammation as a chronic cutaneous state

Low-grade inflammation is a mild but long-lasting inflammatory state that is different from acute inflammation in both intensity and duration (12). Instead of resulting from an acute immune response, it is linked to changes in barrier function and low cytokine production (13).

[1] Subclinical immune activity refers to a low level of immune response that occurs without obvious clinical symptoms. It may not be visible, but it can still affect how the skin functions over time (9).

Recent studies suggest that this type of chronic low-level inflammation may also be related to age-associated changes in the skin, a process commonly referred to as “inflammaging” (10). In the skin, this persistent inflammatory signaling may lead to slower repair processes and increased sensitivity to environmental stressors (10, 14).

Relevance of targeting intracellular inflammatory pathways

Intracellular signaling pathways such as NF-κB and MAPK play an important role in regulating inflammatory responses in the skin. These pathways control the transcription of multiple pro-inflammatory cytokines and mediators involved in epidermal immune activation and are implicated in the molecular pathogenesis of AD (4,5).

A persistent activation of these signaling pathways contributes to the maintenance of type 2 inflammation and is closely associated with epidermal barrier dysfunction in AD (6).

Modulating these pathways could help restore immune balance instead of relying on immunosuppression, particularly now that recent discoveries have helped us better understand the mechanisms that sustain the disease and have contributed to identifying new therapeutic targets (7).

Chronic inflammatory skin disorders such as AD are are associated with persistent alterations in skin homeostasis (1-3). Even when visible lesions are absent, the skin may remain in a state of low-grade inflammatory activity. At a molecular level, several intracellular signaling pathways, including NF-κB and MAPK, contribute to the regulation of pro-inflammatory mediators involved in this process (9-10).

Because these conditions often require long-term treatment, there is an increasing interest in approaches that can help regulate inflammatory responses while avoiding the adverse effects associated with prolonged corticosteroid use (15,16). For this reason, plant-derived compounds are being explored as potential complementary strategies.

About Centella asiatica

Centella asiatica (L), commonly known as *Gotu Kola* or *Pegaga*, is a perennial herbaceous plant native to the wetlands of Southeast Asia that has long been used in Ayurvedic and Chinese traditional medicine (17-19). Historically, the whole plant has been used for medicinal purposes, being wildly used for wound healing and other skin-related conditions (18). In recent years, its potential in dermatological applications has received growing scientific interest (20).

Commonly regarded as a medicinal plant with properties that support tissue repair and skin recovery, *C. asiatica*'s extracts are prepared mostly from the aerial parts and formulated as aqueous or hydroalcoholic preparations for topical use. These have been applied to boost wound healing and assist in restoring the skin barrier. The long-standing use of these preparations in different Asian medical models has encouraged further scientific investigations into their therapeutic properties (17,20).

Advances in pharmacognosy and phytochemical analysis methods have helped define the plant's composition more clearly and get a deeper insight into the phytochemical's pharmacodynamics (19). *C. asiatica* contains a rich and diverse range of secondary metabolites, dominated by pentacyclic triterpenoid saponins, thought to be its principal bioactive components (21-23). These are mainly classified into two major groups: asiaticosides and madecassosides[2], along with their corresponding aglycones, asiatic acid and madecassic acid (21,23). These four compounds are widely used as reference markers for the extract's standardization and quality control, and play a central role in *C. asiatica*'s biological activity (21,22).

Together with their aglycones, these triterpenoids are thought to act synergistically in the plant's overall activity, supporting skin repair and tissue regeneration. Whole-extract formulations have been suggested to offer greater effectiveness than isolated constituents, likely due to the combined contribution of multiple bioactive components involved in skin repair processes (23).

[2] Asiaticosides and madecassosides are triterpene saponins consisting of a triterpenoid central structure, known as an aglycone, linked to one or more glycosyl groups. These aglycones represent the non-glycosidic core of the molecule, with asiaticosides containing asiatic acid and madecassosides containing madecassic acid as their respective aglycones (19).

Alongside these saponins*, C. asiatica* contains other metabolites, flavonoids, phenolic acids, alkaloids, phytosterols, volatile constituents and polyacetylenes, believed to also contribute to the plant's biological activity (19). However, the triterpenoids appear to have a much more dominant role in skin-related applications (21,22).

Experimental and preclinical studies increasingly report that *C. asiatica* extracts and their main terpenoids can help improve skin condition in situations where the skin barrier is altered and inflammation is present, such as in wounds or sensitive skin. These studies describe effects related to collagen production, tissue repair, and the modulation of inflammatory mediators, supporting its dermatological relevance (20). This activity is especially relevant in conditions characterized by persistent low-grade inflammation, such as sensitive or reactive skin and mild forms of dermatitis. In these cases, botanical ingredients with a long history of topical use and favorable safety profiles like *C. asiatica* have gained attention as supportive approaches for maintaining skin balance.

Its effectiveness in topical use also depends strongly on the formulation, since the physicochemical properties of its active components can limit skin penetration (24). This has led to growing interest in optimizing galenic forms to improve local availability and therapeutic efficacy.

Overall, the traditional use of *C. asiatica*, along with its well-characterized triterpenoid content and its documented role in skin repair, have positioned it as a candidate for further investigation in skin conditions associated with chronic low-level inflammation (20).

OBJECTIVES

General objective

This work aims to explore the potential immunomodulatory role of *Centella asiatica* in low-grade skin inflammation and its possible relevance in dermatological conditions associated with chronic inflammatory processes.

Specific objectives

- To describe the main mechanisms involved in low-grade skin inflammation and its role in chronic skin disorders such as atopic dermatitis.
- To review the phytochemical composition of *Centella asiatica*, focusing on its main triterpenoid compounds.
- To examine the available evidence on the anti-inflammatory effects of *Centella asiatica* and its main components in cellular and animal models.
- To analyse how *Centella asiatica* may influence key inflammatory signalling pathways, particularly NF-κB and MAPK.
- To discuss the possible dermatological implications of these mechanisms in skin conditions characterized by persistent inflammation.

METHODOLOGY

This work was carried out as a narrative bibliographic review focused on the potential role of *Centella asiatica* and its main triterpenoid components in skin inflammation, particularly in conditions associated with low-grade inflammatory processes.

The search relied mainly on PubMed as the primary scientific database. Also, some targeted studies were found through additional researches in Google Scholar and scientific journal websites such as ScienceDirect and MDPI. There was also particular emphasis on reviewing the reference lists of selected articles to identify other relevant publications. Even though the search started by prioritizing studies published within the last 5 years, to understand certain concepts, some older publications were needed since some topics are still under investigation or have not been studied further. Despite that, more recent articles were important for understanding the current direction of research in this field and providing a more updated perspective.

The search terms used included *Centella asiatica*, triterpenoids, asiaticoside, madecassoside, skin inflammation, low-grade inflammation, inflammatory pathways, NF-κB, MAPK, atopic dermatitis and topical formulation.

The search terms were adapted for each database to find studies that could be suitable for the research. The review included *in vivo, in vitro*, and clinical studies about the effects of *C. asiatica* extracts or its main triterpenoids on cutaneous effects, as well as studies providing insight into inflammatory pathway mechanisms. The studies that were found to be relevant focused mainly on skin inflammation, barrier function, dermatological conditions like AD and topical formulation development. Studies that addressed other medical uses and therapeutical areas were excluded, unless they provided relevant mechanistic evidence applicable to cutaneous inflammation.

Reviews that focused exclusively on systemic administration were also excluded when they showed no relevance to skin inflammation. The findings were then grouped based on their main

topic, mostly regarding immunomodulatory effects, low-grade inflammation, and topical formulations.

All 46 references were cited following the Vancouver citation style, as required for Pharmacy degree thesis.

RESULTS

1. *Immunomodulatory effects of Centella asiatica relevant to low-grade skin inflammation*

Across the reviewed studies, the strongest evidence comes from preclinical models showing that *Centella asiatica* extracts and their main triterpenoids modulate inflammatory mediators and signaling pathways that are also relevant to chronic cutaneous inflammation. The most relevant findings come from keratinocyte and skin models, whereas macrophage and wound-healing studies provide supportive mechanistic evidence. Taken together, the results suggest a potential immunomodulatory role in low-grade skin inflammation, although the evidence remains mainly indirect and preclinical.

1.1. *Modulation of inflammatory mediatiors*

In LPS-stimulated keratinocyte inflammatory models[3], using a standardized *Centella asiatica* extract (ECa 233) showed a significant reduction in the release of pro-inflammatory cytokines like IL-1β and TNF-α, while also lowering cyclooxygenase-2 (COX-2) expression and prostaglandin E_2 (PGE_2) production, suggesting a reduction of inflammatory signaling activity at the cellular level (25). Because keratinocytes are key regulators of cutaneous immune signaling, these findings are especially relevant to the topic of low-grade skin inflammation.

Other supportive evidence from LPS-stimulated macrophages showed a similar pattern, where a 70% ethanolic extract of *C. asiatica*, very rich in asiaticosides, was observed to decrease IL-6, TNF-α, monocyte chemoattractant protein-1 (MCP-1) and nitric oxide (NO) levels while also down-regulating the gene expression of inflammatory markers iNOS[4] and COX-2 (26).

Although these findings were not based on epidermal cell models, they add additional mechanistic understanding on how *C. asiatica* and its main triterpenoids may help regulate inflammatory processes at a cellular level. Although they do not provide direct evidence of an

[3] LPS-stimulated keratinocytes inflammatory models are an *in vitro* system with keratinocytes where inflammation was induced using lipopolysaccharides (LPS), a bacterial component used to trigger an inflammatory response in skin cells (29).

[4] iNOS[4], inducible nitric oxide synthase, an enzyme that produces nitric oxide during inflammatory processes (26).

effect in the skin, they support the anti-inflammatory properties of the plant and help identify mediators that are also involved in chronic skin inflammation.

Additional supportive mechanistic evidence comes from diabetic wound models, in which treatment with *C. asiatica* lowered IL-1β, IL-6, TNF-α and NO levels and reduced iNOS expression, while increasing interleukin-4 (IL-4) and interleukin-10 (IL-10), anti-inflammatory cytokines that contribute to reducing inflammation and enhancing wound healing (27). Since wound models mainly reflect processes of tissue injury and repair, they do not directly represent low-grade skin inflammation. However, they can still provide useful insight into how the extract may affect inflammatory responses in damaged tissue.

Studies using individual triterpenoids have also shown similar effects. Asiatic acid in LPS-stimulated RAW 264.7 macrophages[5] proved its role as a modulator of the inflammatory response, reducing IL-6, NO and iNOS, while increasing levels of IL-10 (28). Other articles on madecassosides also proved a decrease in IL-6, TNF-α and IL-1β, along with suppressing iNOS and COX-2 (30). These findings highlight that both of *C. asiatica*'s main triterpenoids, asiatic acid and madecassosides, may independently act as modulators of inflammatory cytokines and mediators.

1.2. *Modulation of intracelular inflammatory signaling pathways*

Beyond alterations in cytokine production, several studies suggest that the anti-inflammatory effects of *C. asiatica* are linked to the modulation of intracellular signalling pathways involved in the regulation of inflammatory responses.

The ECa 233 extract in keratinocyte models, reduced ERK1/2[6] phosphorylation and NF-κB activation. The extract also lowered intracellular reactive oxygen species (ROS) levels, suggesting

[5] RAW 264.7 is a murine macrophage cell line isolated from a mouse tumor and widely used for immune and inflammatory response studies (29).
[6] ERK1/2: Extracellular signal-regulated kinases 1 and 2, involved in the MAPK signalling pathway (25).

that its anti-inflammatory effects may be somehow related to the modulation of oxidative stress (25).

In LPS-stimulated RAW 264.7 macrophages, *C. asiatica* extracts reduced intracellular ROS levels and the expression of inflammatory mediators while inhibiting MAPK and NF-κB signalling. This was associated with decreased phosphorylation and reduced nuclear translocation of the p65 subunit, indicating a lower activation of inflammatory signalling and reduced entry of NF-κB into the nucleus, where it normally promotes the expression of pro-inflammatory genes (26).

Findings from *in vivo* models also point in the same direction, supporting the involvement of intracellular signalling pathways in the regulation of inflammation at a tissue level. In a diabetic wound model, a treatment with *C. asiatica* lowered phosphorylation levels in the AKT (Protein kinase B)/MAPK/NF-κB pathway, indicating a lower activation state. Since this pathway is involved in macrophage-mediated inflammation, its modulation may contribute to both reducing inflammation and improving wound healing in treated animals (27). This model does not directly represent low-grade dermatitis, but it still supports the idea that *C. asiatica* may act on key regulatory points of the inflammatory cascade.

Together, these findings suggest that *C. asiatica* may influence inflammatory responses by modulating key intracellular signalling pathways rather than by affecting only one isolated mediator. This is particulary relevant in low-grade skin inflammation, where inflammation is often maintained by persistent low-level signalling rather than by strong acute responses. The mechanism through which *C. asiatica* may modulate inflammatory pathways is shown in Figure 2.

NF-κB and MAPK pathways are not independent processes. They act as central key regulators that integrate signals from different sources of inflammatory stimuli, such as barrier disruption, oxidative stress, and cytokine signalling (9,25). For this reason, the modulation of these pathways may help explain the anti-inflammatory effects observed across the different experimental

models. By targeting these regulatory points in the signalling cascade instead of single inflammatory mediators, *C. asiatica* may help modulate the overall immune response in the skin (27,30).

Overall, this suggests that it may have a modulatory effect rather than a purely suppressive one. This could be important in chronic low-grade inflammatory conditions, where the therapeutic goal is to restore homeostasis and barrier-immune balance without completely suppressing the immune response (12).

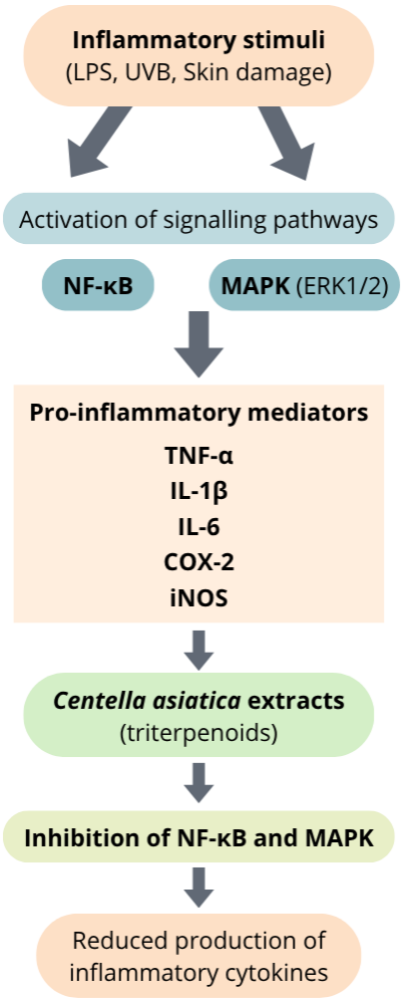

Figure 2. Anti-inflammatory mechanism of *Centella asiatica*. Activation of NF-κB and MAPK signalling pathways promotes the production of pro-inflammatory mediators such as TNF-α, IL-1β and IL-6. *Centella asiatica* extracts have been shown to inhibit these pathways and reduce inflammatory signalling.

2. *Experimental evidence*

2.1. Evidence from cellular models

Low-grade skin inflammation is closely linked to signalling processes in the epidermis, making keratinocyte models particularly relevant for studying the cutaneous immunomodulatory effects of *C. asiatica*.

In LPS-stimulated keratinocytes, ECa 233 extract reduced the release of pro-inflammatory cytokines together with COX-2 expression and PGE_2 production. The extract also lowered intracellular ROS levels, reducing oxidative stress and decreasing the activation of ERK1/2 and NF-κB signalling pathways, which are involved in the regulation of inflammatory gene expression in epidermal cells (25).

Other recent studies in keratinocytes have also shown anti-inflammatory effects after treated with *C. asiatica* extracts. These effects include reduced NF-κB activity and changes in other inflammatory signalling pathways such as MAPK and JAK/STAT[7], supporting the idea that epidermal cells are direct targets of the extract's action (31).

These findings suggest that *C. asiatica* acts by influencing inflammatory signalling in keratinocytes and that the epidermis may be an important target.

2.2. Evidence from in vivo skin models

Recent *in vivo* studies also point to *C. asiatica* as a modulator of skin inflammation.

In UVB-induced (ultraviolet B) skin inflammation models, oral supplementation with a standardized *C. asiatica* extract has shown an ability to help attenuate both inflammatory and structural skin damage. The treatment prevented the increase in IL-6 and TNF-α triggered by UVB exposure. These changes were associated with improved skin structure, including some recovery

[7]JAK (Janus kinase) are intracellular tyrosine kinases involved in cytokine signalling.
STAT (Signal Transducer and Activator of Transcription) are transcription factors activated by JAK that regulate immune and inflammatory gene expression (31).

of collagen and reduced MMP-1, with MMP-9[8] also showing a slight decrease. At the same time, antioxidant activity and skin barrier function improved, suggesting that the extract may have helped protect the skin from UVB damage (32). Although this involves a systemic route of administration, these results provided additional evidence of the plant's ability to modulate the inflammatory response at the cutaneous level.

Similarly, a topical treatment with *C. asiatica*-based formulations has demonstrated protective effects in acute UVB exposure models. The study reported that a C. asiatica leaf extract cream reduced interleukin-1 alpha (IL-1α) expression and decreased the number of sunburn cells[9] in irradiated skin, suggesting attenuation of early inflammatory responses caused by UV-induced damage (33).

Further *in vivo* evidence from UV damage models suggests that *C. asiatica* may influence both skin structure and inflammatory responses. In a UVB-induced mouse model, a treatment with a topical gel containing extracellular vesicles derived from *C. asiatica* helped reduce epidermal thickening and the infiltration of inflammatory cells in UV-damaged skin. In parallel, *in vitro* experiments showed that these vesicles also lowered COX-2 expression in UV-irradiated keratinocytes and fibroblasts (34).

Other earlier animal models of dermatitis have also shown that a treatment with titrated extracts of *C. asiatica* (TECA)[10] can reduce skin signs of inflammation and inflammatory cell infiltration[11] in the affected tissue, as well as decrease IL-1β, TNF-α and iNOS and COX-2 levels along with a decreased NF-κB activity (35).

[8] MMP-1 and MMP-9 (Matrix metalloproteinase-1 and Matrix metalloproteinase-9) are enzymes involved in extracellular matrix breakdown. MMP-1 primarily degrades collagen, while MMP-9 contributes to dermal matrix remodeling. In the referenced study, MMP-1 was significantly reduced, whereas MMP-9 decreased, although not significantly (32)

[9] Sunburn cells is the term used for keratinocytes undergoing apoptosis induced by UVB exposure (33).

[10] TECA is a standardized extract of *C. asiatica* that contains defined proportions of the main triterpenoids (35).

[11] Cell infiltration refers to the migration and accumulation of immune cells within the skin that contribute to inflammation (35).

Outside of classical skin inflammation models, similar effects have also been observed in diabetic wound models.. In a diabetic wound model, treatment with *C. asiatica* was associated with lower levels of IL-1β, IL-6 and TNF-α in the wound tissue, together with faster wound closure and collagen deposition and increased angiogenesis (33).

All these *in vivo* observations suggest that *C. asiatica* may help modulate inflammatory responses both at a cellular and at a tissue level.

3. Mechanistic synthesis

Across the studies reviewed, there seems to be a similar pattern in the modulation of inflammatory mediators. *C. asiatica* repeatedly reduces mediators like TNF-α, IL-1β, IL-6, COX-2, iNOS and PGE2 while also affecting NF-κB and MAPK pathways, and in some models, AKT-related signalling (25-35). This overlap is important because these mediators and pathways play a key role in maintaining inflammatory activity in the skin.

Many studies connected these changes to alterations in intracellular signalling pathways. The most involved pathway appeared to be NF-κB, often acting alongside components of the MAPK pathway such as ERK1/2 and p38 (25-27). This is particularly relevant in the skin, because these pathways regulate the production of cytokines and inflammatory mediators released by keratinocytes and other cells found in the epithelium.

At the tissue level, specially in wound-healing models, changes in AKT/MAPK/NF-κB pathways were observed together with lower cytokine levels and improved repair (27). These findings suggest a potential immunomodulatory effect, but their implications in chronic low-grade dermatoses remain uncertain.

Taken together, the recurring modulation of cytokines and intracellular pathways across different experimental models supports the idea that *C. asiatica* may function not only as a wound-healing agent, but also as a regulator of inflammatory activity the skin. Together, these findings suggest

that *C. asiatica* may have wider anti-inflammatory effects, which could be relevant in skin conditions characterized by persistent low-grade immune activity like chronic dermatoses (12).

As shown in Table 1, the most frequently observed pattern across the reviewed models is the reduction of TNF-α, IL-1β and IL-6, together with the modulation of NF-κB and MAPK signalling. However, direct evidence on low-grade skin inflammation is still limited and this should be taken into account when interpreting the overall results.

Studies	Models	Intervention	Key markers	Main reported findings
Moolsap et al. (25)	LPS-stimulated keratinocytes	Standardized extract (ECa 233)	IL-1β, TNF-α, COX-2, ROS, PGE_2, ERK1/2, NF-κB	Reduced cytokine release, decreased COX-2/PGE_2 and ROS levels, associated with ERK1/2 and NF-κB activation.
Shin et al. (26)	LPS-stimulated RAW 264.7 macrophages	70% ethanolic extract	IL-6, TNF-α, MCP-1, iNOS, COX-2, MAPK, NF-κB	Reduced pro-inflammatory mediators and gene expression, linked to inhibition of MAPK and NF-κB signalling.
Xiao et al. (27)	Diabetic wound model (*in vivo*)	*C. asiatica* extract	IL-1β, IL-6, TNF-α, NO, iNOS, IL-4, IL-10, AKT/MAPK/NF-κB	Reduced pro-inflammatory cytokines and NO, increased anti-inflammatory IL-4 and IL-10, modulation associated with inhibition of MAPK and NF-κB signalling.
Han et al. (28)	LPS-stimulated RAW 264.7 macrophages	Asiatic acid	IL-6, NO, iNOS, IL-10,	Reduced pro-inflammatory mediators, increased IL-10.
Wang et al. (30)	LPS/D-GalN mouse model	Madecassosides	IL-6, TNF-α, IL-1β, iNOS, COX-2,	Reduced cytokine levels and inflammatory mediators.
Ko et al. (31)	Keratinocytes model	*C. asiatica* extract	NF-κB; MAPK, JAK/STAT	Reduced NF-κB activity and modulation of inflammatory signalling pathways.
Choi et al. (32)	UVB-induced photoaging (mouse)	Oral extract	IL-6, TNF-α, MMP-1, MMP-9	Reduced cytokine and MMPs, improved collagen preservation.

Sari et al. (33)	UVB-induced skin inflammation (mouse)	Topical cream with *C. asiatica*	IL-1α, sunburn cells	Reduced IL-1α expression and inflammatory tissue damage.
Chang et al. (34)	Diabetic wound model	Extracellular vesicle gel	COX-2, epidermal thickness, inflammatory infiltration	Reduced epidermal thickning, inflammatory cell infiltration and COX-2 expression.
Park et al. (35)	Mouse atopic dermatitis model	TECA	IL-6, TNF-α, IL-1β, iNOS, COX-2, NF-κB	Reduced inflammatory markers and tissue inflammation.

Table 1. Summary of experimental evidence on inflammatory mediators and pathways modulated by *Centella asiatica*

4. Low-grade skin inflamation in dermathology

The inflammatory mechanisms described above play an important role in dermatological conditions where barrier dysfunction and persistent immune signalling coexist. AD is a good example, because it involves the alteration of the barrier function, cytokine dysregulation and chronic inflammatory activity even in the absence of clear flare-ups (4,11). In that sense, it offers a useful perspective for discussing low-grade skin inflammation in relation to the topic of this work.

At the pathophysiological level, this sustained inflammatory state contributes to a further weakening of the epidermis, reinforcing a cycle in which tissue fragility and immune activation perpetuate one another (11). Several mediators repeatedly identified in the reviewed *C. asiatica* studies, such as IL-1β, IL-6, TNF-α, COX-2 and NF-κB/MAPK signalling, are also implicated in this inflammatory context.

Clinically, the treatment follows a stepwise strategy: emollients are used to support barrier function for maintenance, while topical anti-inflammatory therapies are applied during flares (15). Topical corticosteroids are still the main treatment for controlling flares and reducing inflammation (16), and are typically used alongside other barrier-supportive treatments to

prevent a prolonged use (11). This highlights the need to find complementary strategies that can control inflammation while preserving the skin's natural repair mechanisms.

Since the NF-κB and MAPK pathways are also involved in AD inflammation and related chronic skin diseases (35), targeting them may be relevant in chronic skin inflammation. However, current evidence does not yet show efficacy in low-grade dermatitis in humans and should mainly be understood as preclinical support for a possible biological effect.

5. Dermatological implications

The immunomodulatory mechanisms described in both cellular and animal models suggest that *C. asiatica* may help regulate inflammatory pathways involved in chronic inflammatory skin disorders. Current evidence identifies several targets and mediators that are highly relevant to this condition.

In AD, persistent inflammation contributes to barrier damage and helps sustain the disease's chronicity. It develops through an interaction between barrier dysfunction, immune imbalance and changes in the skin microbiome, with inflammatory cytokines playing a key role in the process (36). The NF-κB and MAPK pathways modulated by *C. asiatica* in experimental studies are also involved in these local immune responses (36,37).

In practice, topical corticosteroids remain the first-line treatment to control inflammation in AD, but they need to be applied carefully to avoid local side effects such as skin atrophy or other structural changes when used for a long time (4). For this reason, alternative approaches that help reduce reliance on steroid use continue to attract attention.

In chronic dermatological conditions, therapeutic strategies do not only focus on controlling acute flare-ups, but also on maintaining skin balance over time (35). Several experimental studies

using *C. asiatica* have shown anti-inflammatory and tissue-protective effects in UVB-induced skin damage models (32,33) and in dermatitis-related inflammation models (35).
Although these models mainly represent acute inflammatory situations, they involve intracellular pathways such as NF-κB and MAPK that are also relevant in chronic inflammatory dermatoses. For that reason, they can be used as supportive models, but they do not fully reflect low-grade inflammatory disease.

Overall, the consistent reduction of inflammatory mediators together with the improvements in skin structure observed in these studies may support the hypothesis that *C. asiatica* has a broader anti-inflammatory role beyond acute inflammation. For now, it could be especially relevant in persistent low-grade inflammation, particularly during maintenance or non-acute phases, rather than as a proven treatment.

6. Topical galenic formulations

Beyond its biological effects, *C. asiatica*'s dermatological potential depends on how it is administered and formulated.

Experimental studies of skin inflammation have mainly relied on topical applications of *C. asiatica,* typically in the form of creams or standardized plant extracts. In UVB-induced models, topical treatment reduced the expression of IL-1α and decreased the formation of sunburn cells, suggesting that its anti-inflammatory effects happen locally within the skin (35).

In dermatitis models, the use of topical *C. asiatica* formulations was associated with decreased inflammatory markers and visibly improved tissue inflammation, indicating that it could be beneficial in conditions where the skin barrier is disrupted, and local immune responses are triggered (31).
In wound-related inflammatory models, extract-based formulations also delivered active triterpenoids directly to the injured tissue and were associated with both a modulation of

inflammatory mediators and improvements in tissue repair processes like collagen formation and angiogenesis (27).

These findings highlight the importance of formulation in enabling local bioactivity. *C. asiatica's* main triterpenoids, asiaticoside and madecassoside, have certain physicochemical characteristics, like relatively high molecular weight and low lipophilicity, that may restrict passive diffusion through the stratum corneum (24). So their therapeutic effectiveness depends strongly on how efficiently topical formulations can deliver and maintain enough concentrations of the active compound at the inflammation site.
Another aspect that seems relevant is extract standardization. Formulations such as TECA or ECa 233 have been used in experimental models of cutaneous inflammation and contain a defined composition of triterpenoids (25,35).

Other topical formulations like gels or extracellular-vesicle-based formulations, may improve the delivery of triterpenoids into the skin. In UV-induced skin damage models, extracellular vesicle gels showed anti-inflammatory effects and reduced epidermal thickening, suggesting that formulation strategy could significantly influence its performance in the skin (34).

These observations indicate that the dermatological effects of *C. asiatica* depend not only on its own properties but also on whether the formulation can ensure good local availability in the skin, how effectively the active compounds are delivered into the skin and how these remain once applied.

7. Limitations of the available evidence

Despite recent interest in the anti-inflammatory potential of *C. asiatica*, the available evidence has important limitations that should be taken into consideration when interpreting the findings.

An important limitation is that most of the evidence supporting the anti-inflammatory effects of *C. asiatica* is derived from *in vitro* and animal studies, and although these help us understand how the plant works at a biological level, offering mechanistic insight, they do not accurately reproduce the pathophysiology and complexity of inflammatory skin disorders in humans. Regulatory evaluations[12] by the European Medicines Agency, also note that most available pharmacological evidence is mainly based on preclinical studies, with very limited robust clinical studies. This lack of data raises uncertainty about the real therapeutic impact in humans (38).

Another limitation is variability in extract composition. Different plant origins, processing methods and triterpenoid concentration may influence the biological activity (19). Changes in the phytochemical content of the extracts can affect both reproducibility and standardization of phytopharmaceutical formulations (40). Although some studies included in this review used standardized extracts such as TECA and ECa 233, none of them provided a detailed characterization of the phytochemical composition of the extracts used (25, 35).

Model selection is also another important limitation. Many experimental models are based on wound repair or UV-induced skin damage (29), but these may not accurately reflect the mechanisms involved in chronic skin disorders like AD, as they focus on acute rather than the persistent inflammatory processes proposed in the title of this work.

Most studies focus only on short-term outcomes, so long-term impact on chronic skin inflammation is still rather unclear. Also, the use of herbal therapies in clinical practice is limited by the lack of robust clinical studies (41).

Finally, botanical preparations contain different active compounds, which makes their effects more unpredictable. However, better standardization, improved formulation control and well-designed clinical trials are still needed before clear therapeutic conclusions can be made (19,42).

[12] Regulatory evaluations are scientific assessments carried out by official authorities, like the EMA in this case, to determine whether a treatment or its active compunds, are safe, effective, and suitable for human use (39).

8. Therapeutic context and emerging needs

Recent research has shown a growing interest in finding alternatives to reduce the long-term use of topical corticosteroids for treating inflammatory skin conditions. This reflects the need for therapies that can control inflammation while avoiding the adverse effects associated with prolonged corticosteroid use.

Different corticosteroid-sparing strategies[13] have been explored, highlighting the need for alternative therapies that can effectively control inflammation while minimizing side effects associated with a chronic treatment (43).

In recent years, nonsteroidal therapies have become more available, including topical calcineurin inhibitors and other targeted treatments that control inflammation without directly suppressing the immune system (44). Topical calcineurin inhibitors such as tacrolimus and pimecrolimus are widely used as steroid-sparing agents in clinical practice (45). Supportive measures that help restore the skin barrier, such as emollients, can improve skin function and may reduce the need for topical corticosteroids (46).

These developments point to a growing interest in managing inflammation without relying solely on corticosteroids.

[13] Steroid-sparing strategies refers to treatments that help reduce the need for corticosteroids while still keeping the disease under control, lowering the risk of side effects (43).

DISCUSION

Taken together, the evidence reviewed in this work suggests that *Centella asiatica* and its main triterpenoid components may regulate inflammatory responses through multiple mechanisms. Rather than targeting single inflammatory mediators, the plant seems to act on key signalling pathways, in particular NF-κB and MAPK, that coordinate the expression of pro-inflammatory gene transcription.

Across both cellular and *in vivo* models, there was a consistently observed reduction of TNF-α, IL-1β and IL-6. These mediators are relevant because they contribute to the persistence of inflammatory activity in the skin. However, the evidence is not uniform; keratinocyte and dermatitis-related models are the most directly relevant to the title, whereas macrophage and wound studies mainly provide supportive mechanistic information.

The involvement of NF-κB and MAPK provides a mechanistic explanation for these effects. These pathways function as key regulators of inflammatory gene expression and are related to the development of chronic inflammatory dermatoses. Results observed in keratinocyte models suggest that the epidermis could be a direct target of *C. asiatica* and the similar patterns in cytokine regulation and signalling pathways observed across different experimental systems support the idea that the plant may have broader anti-inflammatory effects. The similarity in the mechanisms does not mean that the disease model is equivalent; it's important that we make this distinction when discussing low-grade skin inflammation.

From a dermatological perspective, these findings are most relevant in conditions with barrier dysfunction and persistent immune activation, like AD. Evidence shows that this chronic skin disorder is not only driven by acute inflammatory episodes but also by persistent alterations in homeostasis, barrier function and cytokine signalling that may help sustain a low-level inflammatory state.

Within this context, the interest in *C. asiatica* comes from its potential as a complementary strategy capable of influencing inflammatory pathways without the immunosuppressive effects associated with many conventional treatments. This is particularly relevant because long-term treatments for chronic dermatoses often seek strategies that reduce the use of corticosteroids. However, the current evidence is still limited and does not firmly support these therapeutic claims; it mainly points to the need for further research.

Overall, it is important to interpret these findings carefully, since most of the available evidence is still preclinical, and the variability in extract composition and formulation may affect biological responses. Therefore, better clinical studies using topical formulations are still necessary to determine how these experimental observations may translate into real therapeutic relevance in humans.

CONCLUSION

The reviewed evidence supports the potential role of *C. asiatica* in modulating inflammatory responses in the skin.

Results from experimental research consistently show effects on key inflammatory mediators such as TNF-α, IL-1β and IL-6, along with intracellular pathways including NF-κB and MAPK. These mechanisms are involved in the pathophysiology of chronic inflammatory skin conditions characterized by persistent low-grade inflammation.

Overall, these findings suggest that *C. asiatica* may act at key regulatory points within the inflammatory cascade while also contributing to tissue repair. However, the current evidence is still insufficient to consider it an established treatment for low-grade skin inflammation but instead it points to a possible immunomodulatory effect that requires further investigation.

Chronic inflammatory skin conditions such as AD need long-term anti-inflammatory control, commonly treated with topical corticosteroids. In this context, findings suggest that *C. asiatica* could be used as a complementary strategy in mild disease or maintenance phases. For now, this idea is still a hypothesis that is supported mainly by preclinical evidence.

Additional clinical studies using standardized extracts and suitable cutaneous models are needed to determine whether these experimental findings translate into real benefits in human dermatology.

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