

Nanoemulsion-Based Delivery of Centella Asiatica: Formulation, Characterization, And Antioxidant Efficacy

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ABSTRACT

Centella asiatica (CA), a traditional medicinal herb rich in triterpenoids such as asiaticoside, madecassoside, asiatic acid, and madecassic acid, has been widely explored for its pharmacological properties, particularly its antioxidant, wound healing, neuroprotective, and anti-aging effects. However, poor solubility, limited permeability, and chemical instability of its bioactive constituents hinder therapeutic efficacy in conventional formulations. Nanoemulsion-based delivery systems offer a promising approach to overcome these challenges by enhancing solubility, stability, skin penetration, and bioavailability. This review provides a comprehensive overview of CA phytochemistry, pharmacology, and limitations of traditional delivery, followed by an in-depth analysis of nanoemulsion formulation strategies, characterization methods, and antioxidant efficacy assessments. Comparative advantages over conventional formulations, limitations, regulatory considerations, and future perspectives are also discussed. Collectively, the review highlights nanoemulsion-based systems as an advanced platform for unlocking the therapeutic potential of CA in pharmaceutical and cosmeceutical applications.

Keywords: *Centella asiatica*(CA); nanoemulsion; triterpenoids; antioxidant efficacy; drug delivery; phytopharmaceuticals.

INTRODUCTION

Centella asiatica (CA), also known as Gotu kola, has been used for centuries in Ayurveda, Chinese, and other traditional medicine systems for its healing, anti-inflammatory, and rejuvenating properties. Modern pharmacological research attributes these benefits mainly to its triterpenoid constituents—asiaticoside, madecassoside, asiatic acid, and madecassic acid—which contribute to collagen synthesis, antioxidant protection, and skin repair [1,2]. Despite their therapeutic potential, these compounds suffer from poor water solubility, instability under heat and light, and susceptibility to oxidative degradation. Conventional preparations such as crude extracts, tinctures, or creams are therefore limited in their ability to provide consistent and reliable outcomes, restricting their clinical and commercial applications [3].

Advances in nanotechnology, particularly the development of nanoemulsion-based systems, have created new opportunities to overcome these

challenges. Nanoemulsions—nanoscale oil–water dispersions—enhance the solubility and stability of CA’s triterpenoids while facilitating deeper skin penetration and controlled release. Unlike traditional formulations, these systems offer improved bioavailability, predictable therapeutic profiles, and better patient acceptability. Recent studies have reported that CA-loaded nanoemulsions not only boost antioxidant efficacy *in vitro* but also demonstrate enhanced wound healing, anti-aging, and neuroprotective effects *in vivo*, outperforming conventional formulations [4-7]. Their scalability, relatively simple preparation methods, and versatility for both topical and oral applications position them as a practical delivery system. Collectively, nanoemulsion-based formulations provide a bridge between the historical use of CA and modern therapeutic requirements, holding promise for next-generation pharmaceutical, nutraceutical, and cosmeceutical products.

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***Centella asiatica*: A Phytopharmacological Overview**

Centella asiatica (CA), or Gotu kola, has been treasured in Ayurvedic, Chinese, and Thai medicine for centuries for its wound healing, memory-enhancing, anti-inflammatory, and skin rejuvenating effects. Modern research has now confirmed that these therapeutic benefits are mainly attributed to its triterpenoid compounds, such as asiaticoside, madecassoside, asiatic acid, and madecassic acid. These bioactives play vital roles in collagen synthesis, tissue repair, and antioxidant defense. Additionally, CA contains flavonoids, phenolic acids, and volatile oils, which provide further anti-inflammatory and free-radical scavenging properties [8-10]. Recent findings suggest asiaticoside and madecassoside are particularly effective in skin repair, while asiatic and madecassic acids exert stronger neuroprotective and antioxidant effects [11].

Over the past few years, CA has gained recognition for its diverse pharmacological activities, including skin regeneration, anti-aging, and wound healing, owing to its ability to promote fibroblast growth and stimulate collagen production [12,13]. Its antioxidant potential has also been highlighted through the upregulation of key enzymes such as superoxide dismutase and catalase, alongside reductions in oxidative damage markers [14]. Beyond dermatology, CA shows promise in neurological health by enhancing cognitive performance, reducing oxidative stress in neurons, and demonstrating anxiolytic properties [15]. Despite these benefits, poor solubility, instability to light and heat, and susceptibility to oxidation continue to limit its efficacy in conventional preparations. Nanoemulsion-based delivery systems have emerged as a promising solution, offering improved solubility, stability, dermal penetration, and controlled release of CA bioactives. This nanotechnology-driven approach is increasingly seen as the key to transforming CA into a more effective and reliable therapeutic and cosmeceutical agent [16,17].

Nanoemulsion as a Novel Drug Delivery System

In recent years, nanoemulsions (NEs) have gained significant attention as an advanced delivery system for bioactive compounds, especially plant-derived

molecules like those in *Centella asiatica* (CA). Unlike conventional emulsions, NEs are colloidal dispersions with nanoscale droplets (typically 20–200 nm) stabilized using specific surfactants and co-surfactants [18]. This minute droplet size imparts unique physicochemical properties, including transparency, low viscosity, and an extremely high surface area, which collectively enhance the solubilization of poorly water-soluble compounds. This is particularly relevant for CA, as its main triterpenoids—asiaticoside, madecassoside, asiatic acid, and madecassic acid—exhibit poor water solubility, limited bioavailability, and susceptibility to degradation in conventional formulations [19]. Beyond solubility, the nanoscale nature of NEs facilitates better penetration through biological barriers such as the stratum corneum, improving dermal delivery for wound healing and anti-aging applications, while also enhancing oral bioavailability through improved dissolution and lymphatic transport, bypassing first-pass metabolism [20,21]. Encapsulation within NE droplets further protects CA's delicate phytoconstituents from degradation due to light, heat, and oxygen, maintaining their therapeutic potency during storage and application [22].

In addition to enhanced solubility and protection, NEs provide the advantage of controlled and sustained release of active compounds. By optimizing the oil phase, surfactant/co-surfactant ratios, and droplet size, the release profile of CA triterpenoids can be finely tuned, prolonging their therapeutic effect and reducing dosing frequency [23]. This is especially valuable in chronic wound healing and skin rejuvenation, where continuous exposure to asiaticoside and madecassoside supports collagen synthesis, angiogenesis, and fibroblast proliferation [24]. NEs are also relatively easy to manufacture using methods like high-pressure homogenization, ultrasonication, or low-energy emulsification, making them scalable for commercial production [25]. Overall, NEs represent a versatile and effective platform to overcome the limitations of traditional CA preparations, offering enhanced solubility, stability, bioavailability, and controlled delivery, thereby bridging traditional herbal benefits with modern nanopharmaceutical applications.



Formulation Aspects of *Centella asiatica* Nanoemulsion

Centella asiatica (CA), commonly referred to as Gotu kola, is enriched with bioactive triterpenoids, including asiaticoside, madecassoside, asiatic acid, and madecassic acid, which contribute to its well-documented wound-healing, antioxidant, and skin-rejuvenating properties. Despite their therapeutic potential, these compounds face challenges such as poor water solubility, chemical instability, and susceptibility to degradation under light, heat, and oxygen exposure. To address these limitations, nanoemulsion (NE) technology has emerged as a promising delivery approach. NEs are nanoscale oil-in-water dispersions, generally ranging from 20 to 200 nm, stabilized using carefully selected surfactants and co-surfactants. The nanosized droplets improve the solubility and bioavailability of CA triterpenoids, protect them from environmental degradation, and allow enhanced penetration into the skin, making NEs particularly advantageous for cosmeceutical and dermatological applications.

The successful formulation of CA nanoemulsions requires meticulous selection of the oil phase, surfactants, and preparation techniques. Oils such as medium-chain triglycerides and chia seed oil are favored for their ability to solubilize triterpenoids while also contributing skin benefits like hydration and barrier support. Non-ionic surfactants (e.g., Tween-80, Span-20) combined with co-surfactants (e.g., propylene glycol, PEG 400) are employed to reduce interfacial tension, stabilize droplets, and prevent aggregation. The surfactant-to-co-surfactant ratio (S_{mix}) is optimized using pseudo-ternary phase diagrams to ensure formulation stability. Preparation techniques, including high-energy methods like ultrasonication and high-pressure homogenization or low-energy spontaneous emulsification, are chosen based on their ability to generate uniform nanosized droplets while preserving the integrity of CA bioactives. Post-formulation characterization is crucial, with parameters such as droplet size, polydispersity index, zeta potential, viscosity, pH, and encapsulation efficiency being routinely assessed. Recent studies have shown that optimized CA nanoemulsions can achieve droplet sizes as small as 40–50 nm with high encapsulation efficiency and

enhanced antioxidant activity. For instance, Tanjungsari et al. (2024) reported a SNEDDS-based CA nanoemulsion with a droplet size of 43.2 ± 2.0 nm exhibiting superior DPPH radical scavenging activity, while Kinanti et al. (2025) developed a CA-containing sunscreen nanoemulsion with stable droplet distribution, high SPF, and favorable physicochemical properties for topical application. These findings underscore that careful formulation and characterization not only protect the bioactives but also ensure consistent therapeutic efficacy, establishing CA nanoemulsions as a versatile and effective platform for modern pharmaceutical and cosmeceutical applications. [26-27].

Characterization of *Centella asiatica* Nanoemulsions

The development of nanoemulsions for delivering *Centella asiatica* (CA) bioactives requires careful characterization to ensure optimal stability, uniformity, and therapeutic efficacy. Unlike conventional herbal formulations, nanoemulsions rely on nanoscale droplets that improve solubility, penetration, and bioavailability of active compounds, making the evaluation of their physicochemical properties essential. Recent studies have emphasized the importance of parameters such as droplet size, polydispersity index (PDI), zeta potential, viscosity, pH, encapsulation efficiency, stability, and in vitro release in assessing the quality and performance of CA nanoemulsions. Droplet size, in particular, is a crucial factor as it affects surface area, solubilization of triterpenoids, and absorption. Reported droplet sizes range from 50 to 175 nm, with PDI values reflecting particle uniformity. For example, one study reported a droplet size of 57.8 ± 0.03 nm with a PDI of 0.50 ± 0.03 , indicating moderate uniformity, while another formulation achieved 174.8 nm with a PDI of 0.274, suggesting a more homogeneous particle distribution [29,30]. Zeta potential is also significant, as values around -26.5 mV indicate good electrostatic stability and minimal aggregation, especially for topical applications.

Viscosity and pH are critical for ease of application and compatibility with skin. CA nanoemulsions often exhibit pseudoplastic, shear-thinning behavior, allowing smooth spreadability, and pH is typically



adjusted to around 6.0 to match skin's natural pH and prevent irritation. Encapsulation efficiency (EE) indicates how effectively bioactive triterpenoids, such as asiaticoside and madecassoside, are retained within the nanoemulsion droplets, with studies reporting values up to 99.8%, demonstrating protection against degradation [31]. Stability studies under various storage conditions confirm the structural integrity, droplet size, and bioactive content over time. In vitro release studies further reveal controlled and sustained release profiles, which maintain effective antioxidant concentrations at the target site, enhancing wound healing and skin rejuvenation [32]. Collectively, these characterization parameters ensure that CA nanoemulsions are physically stable, therapeutically effective, and suitable for both pharmaceutical and cosmeceutical applications.

In Vitro and Ex Vivo Evaluation of *Centella asiatica* Nanoemulsions

Assessment of *Centella asiatica* (CA) nanoemulsions through in vitro and ex vivo studies is vital to confirm their therapeutic efficiency, especially in enhancing antioxidant activity and improving dermal delivery. Unlike conventional formulations, nanoemulsions create a protective nanoscale environment that increases solubility, shields bioactive compounds from degradation, and facilitates their passage across biological barriers. These preclinical models provide critical insights into formulation stability, release behavior, and bioactivity under controlled conditions before advancing to in vivo or clinical testing. In vitro antioxidant assays, including DPPH, ABTS, and FRAP, are routinely used to quantify the free radical scavenging potential of CA nanoemulsions. Research indicates that nanoemulsified CA consistently shows higher antioxidant activity compared to crude or aqueous extracts, largely due to improved solubility, enhanced protection of triterpenoids, and controlled release mechanisms. For instance, self-nanoemulsifying CA formulations exhibited markedly higher DPPH scavenging activity than conventional extracts, suggesting sustained antioxidant delivery. Similarly, prolonged antioxidant activity in nanoemulsified CA, confirming that nanoscale encapsulation maintains effective concentrations of bioactives over extended periods [32].

Ex vivo skin permeation studies further highlight the advantages of CA nanoemulsions for topical applications. Using porcine or rat skin, which closely mimics human skin, researchers can evaluate the penetration efficiency of triterpenoids across the stratum corneum into deeper tissue layers. Studies show that nanoemulsions significantly enhance the dermal permeation of CA bioactives compared to aqueous solutions or crude extracts. The nanosized droplets, typically ranging from 50 to 200 nm, efficiently traverse skin pores and hair follicles, aided by surfactants that transiently disrupt the lipid barrier. For example, Lala and Patel observed a more than two-fold increase in cumulative permeation with CA nanoemulsions compared to aqueous extracts, improving local antioxidant delivery and supporting wound healing and anti-aging effects. Stability assessments and in vitro release studies complement these findings by confirming retention of bioactives and controlled release profiles, which sustain therapeutic activity. CA nanoemulsions with droplet sizes of 50–175 nm, moderate polydispersity indices, and stable zeta potential values, demonstrating efficient encapsulation and sustained release of triterpenoids, thereby enhancing antioxidant efficacy and overall therapeutic potential [33].

In Vivo Evaluation and Antioxidant Efficacy of *Centella asiatica* Nanoemulsions

Moving from bench models to living organisms reveals how *Centella asiatica* (CA) nanoemulsions actually behave under physiological conditions—how they distribute, how they're metabolized, and how their bioactive triterpenoids perform in tissue repair, immune modulation, and oxidative stress control. While in vitro and ex vivo assays set the stage, animal studies allow us to see healing in context: interactions with inflammatory pathways, systemic antioxidant defenses, and real wound healing dynamics. For example, NanoSECA, a nanoemulsion of CA ethanolic extract, improved memory and biochemical markers in rats when given orally: increased glutathione, lowered malondialdehyde and other oxidative mediators, and reduced pro-inflammatory cytokines compared to unformulated extract, supporting its neuroprotective and antioxidant potential in vivo.



In wound healing and skin health models, CA formulations accelerate closure, re-epithelialization, and collagen deposition, outperforming many conventional preparations. Histological analyses often show thicker epithelial layers, enhanced fibroblast activity, more organized collagen, and reduced markers of inflammation such as TNF- α and IL-6, indicating that nanoemulsion delivery helps keep oxidative stress and damaging inflammation in check. Furthermore, improved antioxidant enzyme activities (e.g., superoxide dismutase, catalase, glutathione peroxidase) and reduced lipid peroxidation are frequently observed, which correlate with better tissue integrity, reduced scar formation, and overall enhanced skin barrier function. These *in vivo* results strongly suggest that nanoemulsified CA can deliver more sustained, potent antioxidant effects *in vivo* than non-nano forms, making them promising for wound care, skin aging, and oxidative stress-related conditions. [34].

Comparative Analysis

When assessing different nanocarrier platforms for the delivery of *Centella asiatica* (CA), it becomes evident that each system has its own advantages and limitations, depending on the therapeutic objective, formulation stability, and route of administration. Among these, **nanoemulsions (NEs)** have consistently gained attention for striking a balance between efficiency and feasibility. They enhance the solubility and dermal penetration of CA's bioactive triterpenoids while also being relatively straightforward to prepare and scale up using techniques such as ultrasonication and high-pressure homogenization [35,36]. This practicality, along with their ability to provide rapid action at an affordable cost, makes NEs particularly suitable for cosmeceutical and dermatological applications where consumer compliance and market adaptability are crucial. In contrast, **nanostructured lipid carriers (NLCs) and solid lipid nanoparticles (SLNs)** are more effective in cases requiring longer residence time and controlled release, such as in chronic wound healing. Their lipidic matrices safeguard CA compounds from degradation and enable gradual release, although their large-scale production can be technically challenging [37,38]. Similarly, **liposomes and deformable vesicles** offer strong potential for

deeper dermal penetration and dual drug loading but require careful optimization to overcome their tendency toward instability and leakage [39].

Beyond these systems, **polymeric nanoparticles (PNPs)** hold promise for targeted or systemic delivery where controlled pharmacokinetics are essential, but their higher cost and complex regulatory requirements can hinder broader use in everyday skincare formulations. In comparison, traditional dosage forms such as creams, gels, or ointments remain common due to their simplicity but generally fail to deliver CA's triterpenoids effectively into deeper skin layers because of solubility and stability limitations. Taken together, comparative analyses suggest that while multiple nanocarriers can add therapeutic value to CA delivery, NEs remain the most versatile and scalable option, bridging laboratory research with commercial applications. Other systems may find relevance in specialized or advanced therapeutic contexts, but the future of CA-based nanoformulations is likely to depend on tailoring the delivery strategy to meet specific treatment goals rather than adopting a one-size-fits-all approach. [40].

Challenges and Limitations

Although nanoemulsion-based delivery systems for *Centella asiatica* (CA) offer considerable therapeutic promise, several challenges must be addressed to ensure their effective clinical and commercial application. A primary concern is **formulation stability**. Nanoemulsions, while kinetically stable, are thermodynamically unstable and thus prone to droplet growth, coalescence, and phase separation over time. This is particularly critical for sensitive CA bioactives such as asiaticoside and madecassoside, which are easily degraded by light, heat, or oxidative conditions. While the inclusion of surfactants and co-surfactants can enhance stability, excessive use may cause toxicity, skin irritation, or long-term compatibility issues, especially in daily cosmetic or topical formulations [41,42].

Beyond stability, **scale-up and manufacturing** present significant hurdles. Laboratory techniques like ultrasonication and high-pressure homogenization yield consistent nanoemulsions, but replicating these results on an industrial scale is challenging. Minor variations in droplet size,



surfactant concentration, or mixing parameters can compromise stability, efficacy, and shelf life, while stringent quality control and specialized equipment increase production costs. Furthermore, regulatory challenges limit rapid commercialization, as advanced drug delivery systems such as nanoemulsions require extensive toxicological and clinical validation, particularly when novel excipients are employed. Adding to these concerns, the **limited in vivo and clinical data** means that although in vitro and ex vivo studies show enhanced antioxidant activity and skin penetration, real-world therapeutic efficacy and safety remain less established. Variations in human skin physiology, age, and environmental factors further complicate outcome predictability [43,44]. Collectively, these limitations emphasize that while CA nanoemulsions are a promising delivery platform, addressing stability, scalability, regulatory compliance, and clinical validation is crucial to fully realize their therapeutic and cosmeceutical potential.

Future Prospects

The future of nanoemulsion-based delivery systems for *Centella asiatica* (CA) looks exceptionally promising, fueled by recent advances in extraction and formulation technologies. Current research is focusing on refining extraction methods to increase both the yield and bioactivity of crucial triterpenoids like asiaticoside and madecassoside. Innovative approaches, such as microwave-assisted extraction and other eco-friendly techniques, have demonstrated the ability to preserve antioxidant activity while concentrating bioactive compounds, providing a robust foundation for more efficient nanoemulsion formulations [45,46]. In parallel, self-nanoemulsifying drug delivery systems (SNEDDS) have emerged as a reliable strategy to produce stable CA nanoemulsions capable of sustaining antioxidant activity and improving bioavailability, outperforming conventional extracts [47].

Beyond formulation efficiency, the development of multifunctional nanoemulsions is opening new possibilities for therapeutic and cosmetic applications. Incorporating oils rich in essential fatty acids, such as chia seed oil, can enhance skin hydration and strengthen the skin barrier, demonstrating synergistic effects in cosmeceutical

products [48]. Additionally, targeted delivery systems are being explored to improve the bioavailability of CA triterpenoids in the brain, showing potential for neurological applications such as epilepsy management [49]. Computational tools, including in silico modeling, are increasingly guiding formulation design by predicting interactions between bioactives and carriers, streamlining the creation of effective and safe nanoemulsions [50]. Together, these advancements suggest that CA nanoemulsions may soon transition from traditional herbal remedies to scientifically validated and technologically advanced therapeutics, offering improved stability, bioavailability, and targeted delivery in pharmaceutical, nutraceutical, and cosmeceutical applications.

CONCLUSION

Nanoemulsion-based delivery systems have emerged as a promising strategy to fully exploit the therapeutic benefits of *Centella asiatica* (CA). Conventional formulations often face significant limitations due to the poor water solubility, low bioavailability, and instability of key triterpenoids like asiaticoside, madecassoside, asiatic acid, and madecassic acid. By encapsulating these bioactives in nanoscale oil–water droplets, nanoemulsions enhance solubility, protect sensitive compounds from degradation, and enable controlled, sustained release. This nanoscale approach also promotes deeper skin penetration, ensuring that the active compounds reach target tissues more effectively. Careful evaluation of critical parameters such as droplet size, polydispersity index, zeta potential, encapsulation efficiency, and release kinetics is essential to confirm the stability, safety, and consistent therapeutic performance of these formulations.

Findings from in vitro, ex vivo, and in vivo studies consistently demonstrate that CA nanoemulsions outperform conventional preparations, exhibiting superior antioxidant activity, accelerated wound healing, enhanced skin hydration, and even potential neuroprotective effects. Compared with other nanocarrier platforms, nanoemulsions strike a practical balance between efficacy, ease of production, and scalability, making them particularly suitable for dermatological and cosmeceutical



applications. Although challenges such as long-term stability, large-scale manufacturing, and regulatory compliance remain, advances in green extraction methods, multifunctional formulation design, and targeted delivery approaches are paving the way for the next generation of CA nanoemulsions. Altogether, these advanced delivery systems hold considerable promise for transforming the traditional therapeutic value of *Centella asiatica* into safe, effective, and modern pharmaceutical and cosmetic applications

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