

FORMULATION APPROACHES TO ENHANCE DERMAL DELIVERY OF *CENTELLA ASIATICA* EXTRACT AND ASIATIC ACID: A SYSTEMATIC NARRATIVE REVIEW

Arini Nur Yunia Puspitaningrum Rahmawati^{1*}, Muhammad Khafi²

¹Pharmacy Bachelor Program, Universitas Pembangunan Nasional Veteran Jakarta, Indonesia

²Master's Program in Pharmaceutical Science, Universitas Gadjah Mada, Yogyakarta,

ABSTRACT

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Abstract:

Centella asiatica, is a medicinal plant that exhibits a wide range of pharmacological activities, particularly in inflammatory and skin-related diseases. One of its major bioactive compounds is asiatic acid. However, its application as a topical formulation is often limited by unfavorable physicochemical properties, which hinder its penetration through the skin. This systematic review aimed to evaluate pharmaceutical formulation strategies that can enhance the dermal delivery of *C. asiatica* extract and asiatic acid. The literature search followed PRISMA guidelines with predefined inclusion and exclusion criteria. A total of 49 articles were identified, of which 11 met the eligibility criteria and were included in this review. The findings indicate that vesicle and nanocarrier-based delivery systems, such as ethosomes, transfersomes, liposomes, and nanostructured lipid carriers, are effective in improving the dermal delivery of *C. asiatica* extract by enhancing solubility, vesicle deformability, and interactions with skin lipids. Meanwhile, formulation approach for asiatic acid are generally aimed at improving its solubility and modifying the stratum corneum barrier using chemical penetration enhancers or flexible carrier systems such as transfersomes. Overall, these approaches highlight that formulation design plays a crucial role in enhancing the dermal delivery of *C. asiatica* extract and asiatic acid.

Abstrak:

Centella asiatica, adalah tanaman obat yang memiliki aktivitas farmakologis yang luas, terutama pada penyakit terkait inflamasi dan penyakit kulit. Salah satu senyawa bioaktif utamanya adalah asiatic acid. Namun, penaplikasiannya sebagai sediaan topikal seringkali terbatas oleh sifat fisikokimia yang tidak menguntungkan dan pada akhirnya menghambat penetrasi kulit. Tinjauan sistematik ini bertujuan untuk mengevaluasi strategi formulasi farmasi yang dapat meningkatkan permeabilitas kulit ekstrak *C. asiatica* dan asam asiatica. Pencarian literatur dilakukan mengikuti pedoman PRISMA dengan kriteria inklusi dan eksklusi yang telah ditentukan sebelumnya. Sebanyak 49 artikel diidentifikasi, di mana 11 memenuhi kriteria kelayakan dan dimasukkan dalam tinjauan ini. Temuan menunjukkan bahwa sistem penghantaran berbasis vesikel dan nanokarier, seperti etosom, transfersom, liposom, dan pembawa lipid nanostruktur, efektif dalam meningkatkan permeabilitas ekstrak *C. asiatica* melalui kulit dengan meningkatkan kelarutan, deformabilitas vesikel, dan interaksi dengan lipid kulit. Sebaliknya, strategi formulasi untuk asam asiatica sebagai senyawa utama dari ekstrak ini umumnya bertujuan untuk meningkatkan kelarutan dan memodifikasi penghalang stratum corneum menggunakan peningkat penetrasi kimia atau sistem pembawa fleksibel seperti transfersome. Secara keseluruhan, pendekatan ini menunjukkan bahwa desain formulasi memainkan peran penting dalam meningkatkan pengiriman ekstrak *C. asiatica* dan asiatic acid ke kulit.



*Corresponding Author:

Arini Nur Yunia Puspitaningrum Rahmawati,
Pharmacy Bachelor Program,
Universitas Pembangunan Nasional Veteran
Jakarta, Indonesia,
email: arini.nur.yunia@upnvj.ac.id

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INTRODUCTION

Centella asiatica is widely used as a traditional medicine in Indonesia [1]. This plant has been empirically reported to be used for a wide range of dermal problems, including itching, smallpox, tuberculosis, stomach ulcers [2], and wound healing [3]. In line with these activities, experimental studies have shown this plant exhibits anti-inflammatory, antioxidant activities and promotes wound healing [4]. One of the predominant phytochemical in this plant is asiatic acid, a pentacyclic triterpenoid, which also shows anti-inflammatory and antioxidant activities [5]. Notably, in the cosmetic industry, extracts and isolated compounds from *C. asiatica* have been formulated for wound repair, barrier support, scar modulation, and photoaging applications. Examples include Madecassol®, Centellase®, and Blastoestimulina®, which contain 40% asiaticoside and a 60% mixture of asiatic and madecassic acids [6], [7].

Limitations arise in the development of *C. asiatica* products due to their poor aqueous solubility and low permeability [8]. Increasing the administered dose may enhance the exposure to bioactive compounds; however, excessive exposure may increase the risk of adverse effects, including skin irritation or allergic reactions associated with topical use of *Centella asiatica* [9]. Therefore, two principal strategies can be employed to address these challenges, namely drug design and drug delivery approaches [10]. The drug design approach is generally more suitable for formulations containing isolated or pure compounds. Nevertheless, structural modification may alter biological activity, as the removal or addition of functional groups can influence drug–receptor interactions [11]. In contrast, drug delivery system–based strategies are more versatile and can be applied to both plant extracts and pure compounds, for example through the development of micro- or nanoscale delivery systems [7].

In this systematic review, a search was conducted to identify the most appropriate formulation methods to enhance the dermal delivery of *C. asiatica* extract and its compound, asiatic acid. The search strategy adhered to the PRISMA guidelines, which emphasize inclusion and exclusion criteria to ensure that only relevant and high-quality articles were selected. The findings are expected to serve as guidance in selecting suitable formulation approaches for *C. asiatica*, contributing to the downstream development of natural and sustainable products that are environmentally friendly as cosmetic and pharmaceutical products.

RESEARCH METHOD

Dermal Delivery terminology

In this review, dermal delivery refers to the delivery and localization of active compounds within or across skin layers. The reported outcomes were categorized according to their specific evaluation parameters. Permeation refers to the movement of compounds across the skin membrane into the receptor compartment, commonly assessed by cumulative permeated amount or flux [12]. Penetration refers to the distribution of compounds into specific skin layers, while skin retention refers to the amount of compound remaining within skin tissue after application [13]. These parameters represent different aspects of dermal delivery and were not considered interchangeable.

Search Strategy

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure 1) [14]. The Rayyan.ai software was used for reference management, duplicate removal, and article screening [15]. A systematic literature search was performed in two electronic databases, PubMed and Scopus. The search was conducted on March 2026, covering publications from 2015 to 2025. The

keywords used were: (("Centella asiatica" OR "Asiatic Acid") AND ("Formulation" OR "Preparation") AND ("Penetration" OR "Permeability")). The search strategy was developed using a combination of free-text keywords related to *Centella asiatica*, asiatic acid, formulation approaches, and skin delivery-related outcomes. The search terms were adapted according to the requirements of each database. PubMed searches were performed using the Title/Abstract field, while Scopus searches were performed using the TITLE-ABS-KEY field. No additional filters were applied during database searching.

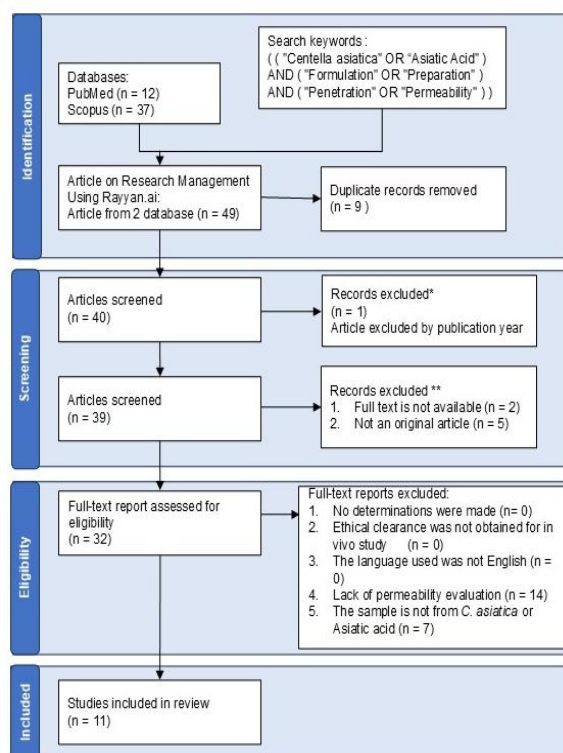


Figure 1. PRISMA flow diagram of the literature selection process.

Study Selection

The keywords used were limited to titles and abstracts. The collected articles were screened based on inclusion and exclusion criteria. The inclusion criteria were as follows:

1. Original Articles: Only original research articles were included, excluding books or review articles.

2. Article Freshness: Articles included in the study were limited to those published in the last ten years (from 2015 to 2025).

The exclusion criteria were as follows:

1. Lack of Plant Determination: Studies that did not specify the plant material up to the taxonomic level of genus and species by a university or research institution were excluded.
2. No Ethical Clearance for Animal Testing: Studies using animal testing methods were included only if they had received proper approval and ethical clearance from a university or research institution, as evidenced by ethical clearance documentation.
3. Lack of permeability evaluation: Studies that did not provide substantial evidence of permeability evaluation through in vitro, in vivo or ex vivo approaches were excluded.
4. Non-Utilization of *C. asiatica* or Asiatic acid: Research that did not utilize *C. asiatica* or Asiatic acid as active ingredients was excluded.
5. Lack of Free Full-Text Access and/or Available in Languages Other Than English: Studies that did not offer free access to full-text articles and/or were available in languages other than English were excluded.

Data Extraction and Management

The data extracted from the selected articles consisted of information related to *Centella asiatica* and Asiatic acid formulations developed to enhance dermal permeability. The extracted data included the type of delivery system, active compound used (either *C. asiatica* extract or Asiatic acid), key formulation components, membrane or skin model, experimental method, outcome parameters, and the reported results. The delivery systems identified from the literature included nanocrystal suspensions, bicelles, liposomes, ethosomes, nanoemulsions, transfersome gels, film-forming polymeric systems, nanostructured lipid carriers, solid

lipid microparticles, and hydrogel systems with chemical enhancers. Experimental models used in the studies included synthetic membranes, porcine skin, pig ear skin, rat skin, cadaver skin, and nasal mucosa, while permeation studies were generally conducted using the Franz diffusion cell method. Outcome parameters reported in the studies included cumulative permeation, percentage penetration, penetration depth, and skin retention.

Methodological Quality and Reporting Quality Assessment

The methodological quality and reporting quality of the included experimental studies were assessed using the Science in Risk Assessment and Policy (SciRAP) in vitro assessment framework [16]. The SciRAP framework separately evaluates reporting quality (RQ), methodological quality (MQ), and study relevance. The in vitro tool comprises 24 criteria for reporting quality, 16 criteria for methodological quality, and four items for relevance assessment. Each applicable RQ and MQ criterion was rated as fulfilled, partially fulfilled, or not fulfilled. Criteria that were not applicable to dermal permeation experiments, such as those specifically related to cell passage number or cell-culture conditions, were removed from the assessment in accordance with the flexibility of the SciRAP framework. Because the included studies primarily investigated in vitro/ex vivo dermal permeation rather than toxicity, the SciRAP criteria were applied with consideration of the experimental characteristics of dermal permeation studies, including the formulation/test substance, skin or membrane model, exposure conditions, Franz diffusion system, replication, analytical methods, sampling time points, and statistical analysis. Removed criteria were not included in the calculation of the reporting and methodological quality. Study relevance was evaluated separately based on the identity of the tested

substance, test system, investigated endpoint, and concentration used. Detailed study-level assessments are provided in Supplementary Table S1.

RESULTS AND ANALYSIS

A total of 49 records were identified from two databases (PubMed, $n = 12$; Scopus, $n = 37$). After removing 9 duplicate records, 40 records remained for title and abstract screening. One record was excluded based on publication year, leaving 39 records for full-text eligibility assessment. Seven records were further excluded due to unavailable full texts ($n = 2$) and non-original articles ($n = 5$), resulting in 32 reports assessed for eligibility. Twenty-one reports were excluded during eligibility assessment because they lacked permeability evaluation ($n = 14$) or did not investigate samples derived from *Centella asiatica* extract or asiatic acid ($n = 7$). Finally, 11 studies were included in this review. All included studies evaluated dermal or transdermal permeability using Franz diffusion cell systems under in vitro or ex vivo conditions. Various membrane models were employed, including porcine skin, rat abdominal skin, pig ear skin, cadaver skin, and synthetic membranes. The outcome parameters used to assess permeation varied considerably across studies, encompassing cumulative permeation ($\mu\text{g}/\text{cm}^2$), percentage penetration (%), and skin retention ($\mu\text{g}/\text{g}$). Due to this heterogeneity in membrane models and outcome measurements, a quantitative meta-analysis was not performed. Instead, findings were synthesized narratively to allow comparative evaluation of formulation approaches while accounting for methodological variability (Figure 1).

The methodological quality and reporting quality of the included studies were assessed using the SciRAP in vitro framework. Overall, the included studies demonstrated high reporting quality and adequate methodological quality. Reporting quality scores ranged from 84.38% to

100%, whereas methodological quality scores ranged from 79.17% to 100%.

Most studies fulfilled the majority of applicable reporting criteria, particularly regarding the description of test compounds, experimental procedures, diffusion systems, and analytical methods. However, some limitations were observed in specific studies, including experimental administration procedures.

The methodological assessment showed that most studies adequately described the experimental design, including formulation characteristics, membrane selection, exposure conditions, and analytical evaluation. The lowest

methodological score observed was 79.17%, mainly associated with incomplete information regarding test compounds, administration procedures, and data analysis. These variations may influence the comparability of permeability outcomes among studies.

Since the included studies focused on in vitro/ex vivo dermal permeation rather than toxicity evaluation, the SciRAP assessment was interpreted as an evaluation of reporting transparency and methodological rigor rather than a formal risk-of-bias assessment. Detailed criterion-level assessments are provided in *Supplementary 1*.

Delivery system	Active compound	Key Components	Membrane	Model	Outcome parameter	Result	References
Nanocrystal suspension	CA extract 10%	PVP K30 stabilizer	Porcine skin	Fran z cell	Skin retention ($\mu\text{g/g}$)	19.7 $\mu\text{g/g}$	[17]
Transfersome gel	CA extract 2%	Lecithin + Tween 80 + PG	Porcine skin	Fran z cell	Deformability index	1.31 $\pm$ 0.21	[18]
Liposom	CA 1%	SPC + Chol	Intestinal skin	Fran z cell	% Penetration	97.9 $\pm$ 4.3%	[19]
Ethosom	CA 1%	Phospholipon + ethanol 20%	Rat abdomen skin	Fran z cell	Cumulative permeation ($\mu\text{g/cm}^2$)	3809.73 $\pm$ 17.20	[20]
Film forming polymeric Nanoemulsion lotion	CA extract 10%	Tween 80 + IPM + ethanol	Porcine skin	Fran z cell	% Penetration	21.63%	[21]
	CA extract 1%	Stearic acid + oleic acid	Rat abdomen	Fran z cell	Cumulative permeation ($\mu\text{g/cm}^2$)	1558.64 $\pm$ 566.93	[22]
Transfersome gel	CA extract equivalent to asiaticoside 0,5%	Phospholipon + Tween 80	Rat skin	Fran z cell	% Penetration	51.80% $\pm$ 0.97	[23]
Transfersome gel	Asiatic acid 0,3%	Lecithin 4% + Tween 80 (50:50), AA 0.3%	Synthetic membrane	Fran z cell	Skin retention ($\mu\text{g/g}$)	14.20 $\pm$ 0.47%	[24]
Transfersome gel	Asiatic acid 0,3%	Lecithin 2% + Tween 2% + Ethanol 5%, AA 0.3%	Synthetic membrane	Fran z cell	Skin retention ($\mu\text{g/g}$)	41.27 $\pm$ 0.04%	[25]
Solid lipid microparticle	Asiatic acid 0,01%	Cetyl alcohol 15% + Poloxamer 188 3% + AA 0.01%	Newborn pig skin	Fran z cell	Skin retention ($\mu\text{g/g}$)	18.13 $\pm$ 0.11%	[26]
Hydrogel + chemical enhancer + microneedle	Asiatic acid 2%	HA/CS/P407/C940 base + amine, solvent, lipid-disrupting enhancers	Rat skin	Fran z cell	Skin retention ($\mu\text{g/g}$)	70.80 $\pm$ 14.07	[27]

DISCUSSION

Formulation Approaches for *Centella asiatica* Extract

The triterpenoids present in *Centella asiatica*, such as madecassoside, asiaticoside, and asiatic acid, possess relatively high molecular weights and limited chemical stability, which may limit their absorption through the skin following topical administration [9]. These physicochemical characteristics result in suboptimal passive penetration into the stratum corneum layer. Therefore, the development of formulation systems capable of enhancing the stability and permeability of *C. asiatica* extracts is required. Various approaches have been developed, ranging from polymer-based systems to lipid-based systems, to optimize the dermal delivery of these active compounds. Vesicular systems represented the most extensively investigated strategy for enhancing dermal permeability of *Centella asiatica* extract. Various vesicle-based carriers, including liposomes, transfersomes, ethosomes, and bicelles, were developed to improve the penetration of bioactive triterpenoids across the stratum corneum. These systems are primarily composed of phospholipid bilayers, often combined with cholesterol, surfactants, or ethanol to enhance membrane flexibility and interaction with skin lipids. All permeation outcomes discussed in this section were obtained using Franz diffusion cell systems under in vitro or ex vivo conditions. Of the different skin models used in Franz diffusion experiments, porcine skin is widely preferred because its histological structure closely mimics that of human skin [28].

Ethosomal Delivery System for Extract

Among the evaluated formulations, a study conducted [20] with ethosomal systems demonstrated the highest cumulative permeation, reaching approximately $3809.73 \pm 17.20 \mu\text{g}/\text{cm}^2$ (Table 1). The superior performance of ethosomes in drug delivery may be

attributed to multiple synergistic mechanisms and likely contributed to enhanced penetration through the lipid bilayer of the stratum corneum. Smaller vesicles facilitate closer interaction with intercellular lipid domains and improve translocation across the skin barrier.

The presence of propylene glycol in the formulation may have further enhanced permeation by acting as a chemical penetration enhancer, promoting lipid fluidization and increasing drug partitioning into the skin. The high ethanol content in the ethosomal system enhances skin permeability by disrupting and fluidizing the lipid structure of the stratum corneum. This process facilitates the delivery of drugs with both hydrophilic and lipophilic properties. Furthermore, when formulated as a cream, lower viscosity of the ethosomal cream compared to non-ethosomal formulations may have reduced diffusional resistance, thereby facilitating drug movement across the skin. A higher concentration of active ingredients in the ethosomal system would also increase the concentration gradient across the membrane, in accordance with Fick's law of diffusion, the higher concentration of active constituents within the ethosomal system increases the concentration gradient across the membrane, which directly contributes to enhanced permeation.

Transfersome Delivery System for Extract

Transfersome-based formulations demonstrated a marked improvement in dermal permeation compared to non-vesicular control gels. A study by [23] that formulated *C. asiatica* extract equivalent to asiaticoside 0.5% in the form of a transethosomal gel for subcutaneous delivery reported that cumulative amount of asiaticoside permeated over 24 hours reached $51.80\% \pm 0.97$ for the transfersomal gel, whereas the control gel achieved only $26.63\% \pm 0.60$. The steady-state flux further confirmed this enhancement, with transfersomes exhibiting 47.92

$\pm 1.74 \mu\text{g}/\text{cm}^2/\text{h}$ versus $26.57 \pm 0.77 \mu\text{g}/\text{cm}^2/\text{h}$ for the non-transfersomal gel. These findings indicate that incorporation of asiaticoside into deformable vesicles significantly increased transdermal transport. The improved permeation observed in transfersomes can be attributed to their unique elastic and deformable structure. Unlike conventional liposomes and niosomes, transfersomes contain edge activators that destabilize the lipid bilayer and increase membrane flexibility. Comparative studies evaluating different edge activators such as Tween, Span, and sodium deoxycholate demonstrated variable permeation performance. Formulations containing sodium deoxycholate exhibited the most rapid initial penetration within the first 0.5 hours, which may be associated with its stronger surfactant activity and ability to transiently disrupt lipid packing within the stratum corneum. However, formulations incorporating Span 80 yielded the highest overall penetration percentage which is $9.80 \pm 0.77\%$, suggesting that surfactant type significantly influences vesicle deformability and drug transport efficiency.

In addition to surfactant selection, viscosity was identified as a critical factor affecting permeation. Lower viscosity formulations facilitated faster drug release and enhanced diffusion across the membrane. Reduced viscosity likely minimizes diffusional resistance within the formulation matrix, thereby increasing the concentration gradient at the skin interface. According to Fick's law of diffusion, an increased concentration gradient directly enhances permeation rate, explaining the higher flux observed in lower-viscosity transfersomal systems. When compared with other vesicular carriers, transfersomes consistently demonstrated superior penetration relative to liposomes and niosomes. This enhanced performance is primarily due to their elastic bilayer structure, which allows them to deform and pass through intercellular lipid channels that are smaller than their original vesicle

diameter. In contrast, liposomes and niosomes possess relatively rigid bilayers, limiting their ability to traverse narrow intercellular pathways and resulting in comparatively lower permeation. In transfersome formulations, the presence of an edge activator also promotes elasticity and deformability within the lipid bilayer structure, thereby facilitating rapid penetration through the intercellular lipids of the stratum corneum [29].

Liposomes Delivery System for Extract

Liposomes are spherical vesicles composed of one or more phospholipid bilayers surrounding an aqueous core and are capable of encapsulating both hydrophilic and lipophilic compounds [30]. Based on the synthesis of studies reported in [19], liposomal formulations demonstrate significant potential in enhancing the topical delivery of *Centella asiatica* (CA) extracts. One study reported that *Centella asiatica* formulated in a liposomal system achieved a penetration rate of $97.9 \pm 4.3\%$, indicating a higher delivery efficiency compared with non-liposomal formulations. The formulation used in that study employed soybean phosphatidylcholine (SPC) combined with cholesterol to enhance membrane fluidity and reduce the rigidity of the liposomal structure. Research conducted by [31] reported that liposomal formulations containing SPC and cholesterol exhibit high flexibility, enabling their lipid components to penetrate the membrane interface between the dermis and epidermis [32]. Furthermore, [33] explained that the ability of liposomes to penetrate the skin largely depends on the extent to which the liposomal membrane can undergo deformation or structural changes. The more flexible and deformable the membrane, the greater its capacity to enhance penetration into deeper layers of the skin. This finding is consistent with the study by [34], which reported that liposomal systems do not always increase penetration in a linear manner. Under certain conditions, liposomes may instead

enhance drug retention within the skin layers while slowing transdermal diffusion. These variations in outcomes indicate that the effect of liposomes on permeation is influenced by multiple factors, including the molecular weight of the active compounds, their lipophilicity, as well as the lipid composition and the flexibility of the vesicles.

Nanoparticle-Based Delivery System for Extract

In the advancement of drug delivery systems, the role of nanotechnology has become increasingly significant. Nanoparticles often exhibit improved pharmacokinetic profiles due to their small size and unique physicochemical properties. They are capable of targeting specific cells, entering intracellular compartments, and modulating cellular functions, making them promising candidates for the treatment of chronic diseases such as diabetes, cancer, and kidney disorders [35]. Several nano-based formulations have been developed, and in this review the discussion focuses on nanosuspension and nanoemulsion. A study conducted by [17] utilizing a nanocrystal suspension formulation with *Centella asiatica* (CA) extract reported that under sink condition testing, asiatic acid, asiaticoside, and madecassoside were not detected. Asiatic acid possesses lipophilic characteristics ($\log P \approx 5.7$) and a relatively high molecular weight, which limits its ability to penetrate the skin and results in its tendency to be adsorbed or deposited primarily within the stratum corneum. The presence of asiatic acid was only detected after the application of a 1% nanosuspension formulation. Due to the low aqueous solubility of asiatic acid, a portion of the active compound remains in a solid state within the formulation. Consequently, the amount of asiatic acid deposited in the skin was not significantly different from that observed with a commercial cream formulation (9.5 vs 6.4 $\mu\text{g/g}$). This phenomenon may be attributed to the rapid dissolution or adsorption of the

active compound within the skin layers, leading to the formation of a high concentration gradient between the hydrogel formulation and the stratum corneum, which subsequently promotes the diffusion of the active compound into the skin.

In another study conducted by [36], dried and glycolic extracts containing asiatic acid were encapsulated in nanostructured lipid carriers (NLC-D and NLC-G) to improve skin delivery performance. In vitro release and skin permeation studies demonstrated that asiatic acid release from NLC-D reached approximately 23.7%, while NLC-G produced nearly a two-fold higher release during the same period. Electron paramagnetic resonance (EPR) analysis further showed that both formulations were able to increase the fluidity of the stratum corneum membrane, with a more pronounced effect observed in NLC-G. As a result, NLC-G facilitated faster penetration of asiatic acid into deeper skin layers, with detectable levels in the epidermis and dermis ($9.14 \pm 0.54 \mu\text{g/cm}^2$) within 24 hours, whereas a similar permeation level from NLC-D was only achieved after 48 hours ($10.42 \pm 1.41 \mu\text{g/cm}^2$). The enhanced permeation observed with NLC-G was attributed to the faster release of asiatic acid from the carrier system as well as the increased stratum corneum fluidity induced by the formulation, suggesting that NLC-G may represent a promising topical delivery system for improving asiatic acid penetration into deeper skin layers and for potential therapeutic applications such as the treatment of scleroderma.

Film-Forming Polymeric for Extract

Another type of formulation containing *Centella asiatica* (CA) extract was reported by [21] which developed a film-forming polymeric formulation. The study used an optimized formulation consisting of Eudragit, glycerin, and ethanol. In the skin permeation test, neither

madecassoside nor asiaticoside was detected in the receptor medium during the 12-hour observation period. This indicates that both compounds did not penetrate into the dermal layer. Instead, the compounds were predominantly retained within the upper layers of the skin, suggesting that this formulation is more suitable for localized topical delivery rather than systemic transdermal administration. In the CA extract used in the study, the concentration of madecassoside was $4.95 \pm 2.66\%$, while asiaticoside was $5.85 \pm 2.85\%$. Madecassoside exhibits higher polarity, which allows it to dissolve more readily in the release medium and diffuse out of the formulation more easily compared with asiaticoside. This finding indicates that the developed formulation provides a sustained release profile for madecassoside and asiaticoside. In other words, the active compounds are released more slowly and in a more controlled manner from the formulation system compared with the free extract. Furthermore, the formulation demonstrated approximately five-fold higher accumulation within the skin, with retention values of about 4.95% for madecassoside and 5.85% for asiaticoside. This suggests that the formulation enhances the retention or accumulation of active compounds within the skin compared with the crude extract. Asiaticoside showed slightly higher skin accumulation than madecassoside due to its lower polarity. More lipophilic compounds tend to interact more readily with the lipid components of the stratum corneum, which facilitates their retention within the skin layers. In addition to the formulation type, the presence of ethanol also plays an important role as a penetration enhancer, which facilitates drug permeation through the skin. Madecassoside and asiaticoside possess relatively large molecular weights, approximately 975.12 Da and 959.12 Da, respectively, whereas the ideal molecular weight for effective skin delivery is generally below 500 Da. Due to their large

molecular sizes, both compounds exhibit limited ability to penetrate deeply into the skin. Consequently, they are more suitable for producing localized therapeutic effects on the skin rather than for transdermal drug delivery into systemic circulation.

Formulation Approaches for Asiatic Acid

Asiatic acid (AA) is a pentacyclic triterpenoid that contains several active hydroxyl and carboxyl functional groups. Evidence suggests that AA functions as a chemopreventive compound and may enhance the effectiveness of other therapeutic agents [5]. A study conducted by [37] reported that in *Centella asiatica* (CA) extract, asiatic acid is one of the major components and plays an important role in the wound-healing process associated with various skin disorders. With the advancement of drug delivery systems, AA has been formulated into various dosage forms to improve its penetration into the skin.

Transfersomes Delivery System for Asiatic Acid

A study conducted by [24] formulated asiatic acid into transfersomes and reported that the highest penetration value was obtained when the lipid to edge activator ratio was 50:50, reaching $14.20 \pm 0.47\%$. In this formulation, the deformability of the vesicles increased, allowing them to change shape and penetrate through skin pores or intercellular gaps. The selection of edge activator also plays a crucial role in drug penetration in transfersome-based delivery systems. When the edge activator has a low hydrophilic-lipophilic balance (HLB), it tends to be more lipophilic. Since AA is also lipophilic, this similarity increases the affinity between the drug and the vesicle membrane, causing the drug to be retained within the vesicles for a longer period and resulting in a slower drug release profile.

These findings are consistent with a study by [25] that compared asiatic acid transfersome formulations with a

conventional gel formulation without vesicular modification for the treatment of hypertrophic scars. In this study, three edge activators were used in the transfersome formulation, namely Tween 80, Span 80, and sodium deoxycholate, while a hydroethanolic asiatic acid solution served as the control. The results demonstrated that transfersome formulations containing edge activators significantly enhanced the penetration of asiatic acid, reaching $41.27 \pm 0.04\%$, compared with the conventional dispersion. In addition to acting as drug carriers, transfersome vesicles can also penetrate the intercellular lipid regions of the stratum corneum and interact with the skin lipid structure, thereby increasing lipid fluidity. As a result, the skin barrier becomes more permeable, allowing drug molecules to diffuse deeper into the skin. In this study, it is likely that both mechanisms occurred simultaneously. After 8 hours, the highest permeation was observed in the formulation containing Tween 80 as the edge activator, which may be attributed to its high vesicle deformability.

Solid Lipid Microparticles Delivery System for Asiatic Acid

Another drug delivery approach involving AA was reported by [26] using solid lipid microparticles. In this study, permeation tests were conducted using Franz diffusion cells, where asiatic acid permeation was compared between formulations containing 10% and 15% cetyl alcohol, with hydroethanolic solution and asiatic acid dissolved in water used as comparators. The results showed that after 3 and 24 hours of testing, the highest permeation was observed in the formulation containing 15% cetyl alcohol and in the hydroethanolic solution, although the difference between the two was not statistically significant. The high permeation observed in the hydroethanolic solution is likely attributed to the presence of ethanol, which can dissolve asiatic acid more effectively, with a solubility of approximately 10 mg/mL. This increased solubility enhances the drug concentration

in the donor phase, thereby increasing the concentration gradient that drives drug diffusion across the skin barrier. On the other hand, the increased permeation observed in the formulation containing a higher concentration of cetyl alcohol may be attributed to the role of cetyl alcohol as a long-chain fatty alcohol (C16–C18), which can disrupt the tightly packed lipid arrangement within the stratum corneum, thereby increasing skin permeability. Interestingly, even when asiatic acid was dissolved only in water, a small degree of permeation through the stratum corneum was still observed. This phenomenon may be explained by the molecular weight of asiatic acid, which is below 500 Da, along with its lipophilic nature, allowing it to penetrate the skin to some extent through passive diffusion mechanisms.

Chemical enhancer and microneedle approach for Asiatic Acid

Interestingly, a study by [27] developed a novel hydrogel formulation for AA to investigate several pharmaceutical strategies aimed at improving its dermal delivery, including chemical enhancers and microneedle pretreatment. A hydrogel containing 3.5% hyaluronic acid (HA) was selected as the optimal base due to its favorable drug release profile as well as its suitable morphological and rheological properties. To further enhance skin penetration, different counterions and chemical penetration enhancers were evaluated. Among the tested counterions, AA–DETA (Diethylenetriamine) demonstrated the most significant enhancement effect on AA penetration, while L-menthol was identified as the most effective chemical enhancer for promoting drug delivery into deeper skin layers. In addition, microneedle pretreatment was optimized at 6 minutes of application time, 5 N of force, and a needle length of 0.5 mm. The results indicated that each of these approaches could individually increase drug retention within the skin. Moreover, different counterions and chemical enhancers exhibited distinct

effects, either enhancing drug retention within the stratum corneum or facilitating penetration into deeper skin layers. Notably, combining enhancers with microneedles or using multiple enhancers together was able to induce transdermal absorption of AA. Among the evaluated strategies, the combination of DEtA and L-menthol provided the highest drug accumulation in deep skin layers, reaching $70.80 \pm 14.07 \mu\text{g/g}$. These findings suggest that the synergistic use of counterions and chemical enhancers represents a promising strategy for improving topical and transdermal delivery of AA and other drugs with similar physicochemical characteristics.

Cross-Comparative Mechanistic Interpretation

Although many formulation approaches have been investigated to improve the dermal delivery of *Centella asiatica* extract and asiatic acid (Table 1), comparing permeation results between studies is often difficult. This limitation arises because each study commonly uses different experimental setups, such as variations in skin models, receptor media, and permeation parameters. Even so, examining the mechanisms behind each formulation strategy still provides useful insight into how different delivery systems can enhance skin permeation. The physicochemical properties of the active compounds strongly influence which formulation strategy is most appropriate.

For *Centella asiatica* extract, the presence of several triterpenoid constituents, including madecassoside, asiaticoside, and asiatic acid, presents a particular challenge. These compounds generally have relatively high molecular weights and different polarity characteristics, which restrict their ability to passively diffuse through the stratum corneum. As a result, many studies employ vesicular or nanocarrier-based systems to improve dermal delivery. These systems can enhance drug solubility, increase vesicle deformability, and promote stronger

interactions with skin lipids. Delivery platforms such as ethosomes, transfersomes, liposomes, and bicelles (Figure 2) mainly improve permeation through mechanisms related to membrane flexibility, interaction with lipid bilayers, and targeting through follicular pathways. In addition, the inclusion of ethanol, surfactants, or edge activators within these vesicular systems can further increase lipid fluidity in the skin barrier, facilitating the transport of active compounds across the stratum corneum.

In contrast, asiatic acid as an isolated compound has a molecular weight below 500 Da and relatively high lipophilicity, allowing it to penetrate the skin to some extent through passive diffusion. Therefore, formulation strategies for asiatic acid are often directed toward improving solubility and modifying the lipid structure of the stratum corneum to increase permeation. Chemical penetration enhancers such as ethanol or fatty alcohols can increase the solubility of the compound and strengthen the concentration gradient across the skin, thereby accelerating diffusion in accordance with Fick's law. Moreover, vesicular carriers such as transfersomes (Figure 2) can also enhance penetration by improving vesicle flexibility and facilitating transport through intercellular lipid pathways. Overall, these findings suggest that nanocarrier and vesicular systems are particularly beneficial for delivering complex plant extracts like *Centella asiatica*, whereas the dermal permeation of single lipophilic compounds such as asiatic acid can be effectively improved through solubilization techniques, chemical penetration enhancers, and flexible vesicular systems. This highlights the importance of designing formulation strategies that align with the physicochemical characteristics of the active compounds in order to achieve optimal dermal delivery. Furthermore, combining advance drug delivery system with chemical and physical enhancers, such as diethylenetriamine (DEtA) and

microneedles, may result in transdermal delivery (Figure 2). While this approach may enable the drug to bypass first-pass metabolism, it may also increase the risk of adverse effects if the formulation is intended primarily for topical skin therapy.

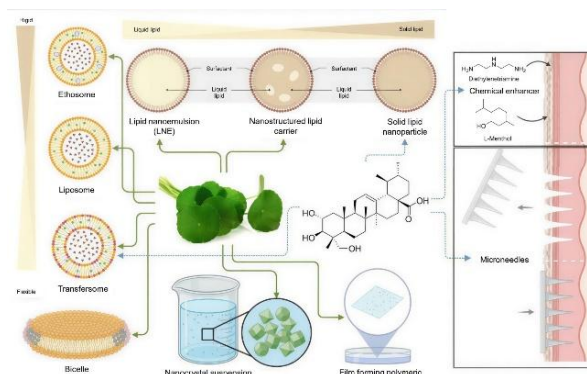


Figure 2. Combining Advance Drug Delivery System With Chemical And Physical Enhancers

Implications and Research Gaps

The findings presented in this review emphasize the importance of choosing formulation strategies that correspond to the physicochemical properties of the active compounds found in *Centella asiatica*. Vesicular and nanocarrier-based delivery systems have shown considerable potential for improving the dermal delivery of plant extracts that contain multiple triterpenoid components. Formulation systems such as ethosomes, transfersomes, liposomes, and bicelles are capable of enhancing skin permeation through several mechanisms, including improved drug solubilization, increased vesicle flexibility, and stronger interaction with lipid structures within the skin barrier. Because of these characteristics, such systems may be particularly suitable for delivering phytoconstituents with relatively high molecular weight or limited permeability, including madecassoside and asiaticoside. On the other hand, when the target compound is a single molecule such as asiatic acid, formulation approaches tend to focus more on improving solubility and modifying the lipid barrier of the stratum corneum. Strategies such as the incorporation of chemical penetration

enhancers or the use of flexible vesicular carriers can facilitate the transport of the compound across the skin, thereby improving dermal absorption.

Limitation

Although these formulation approaches show encouraging results, several limitations in the current body of research remain apparent. A key issue is the substantial variation in experimental design across studies. Differences in the type of skin model used, the composition of receptor media, permeation parameters, and the duration of diffusion experiments make it difficult to directly compare permeation outcomes between studies. Moreover, most studies rely on in vitro or ex vivo models, particularly Franz diffusion cell systems, while in vivo investigations that assess the clinical relevance of these formulations are still relatively scarce. Another notable limitation is the lack of studies that directly compare multiple formulation strategies under the same experimental conditions. Conducting such comparative studies would help clarify which delivery systems are most effective for enhancing the dermal permeation of *Centella asiatica* constituents. Therefore, future research should prioritize the use of more standardized permeation models and well-structured comparative studies in order to better determine the most suitable formulation strategies for improving the dermal delivery of *Centella asiatica* extract and its major active compound, asiatic acid.

CONCLUSION

In general, the enhancement of dermal permeability of active compounds derived from *Centella asiatica* is strongly influenced by the physicochemical characteristics of its constituents. Triterpenoid compounds with relatively large molecular weights, such as madecassoside and asiaticoside, exhibit limited ability to penetrate the stratum corneum. Consequently, vesicular and nanocarrier-based systems, including

liposomes, transfersomes, ethosomes, and bicelles, represent promising strategies for improving their dermal delivery. In contrast, for single compounds such as asiatic acid, which possesses lipophilic properties and a relatively smaller molecular weight, enhanced permeation may be achieved through improved solubility and the use of penetration enhancers such as ethanol, as well as deformable vesicular systems like transfersomes. Therefore, formulation strategies should be tailored to the molecular characteristics of the active compounds in order to achieve optimal dermal delivery.

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