

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

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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 sistematis 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.



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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.

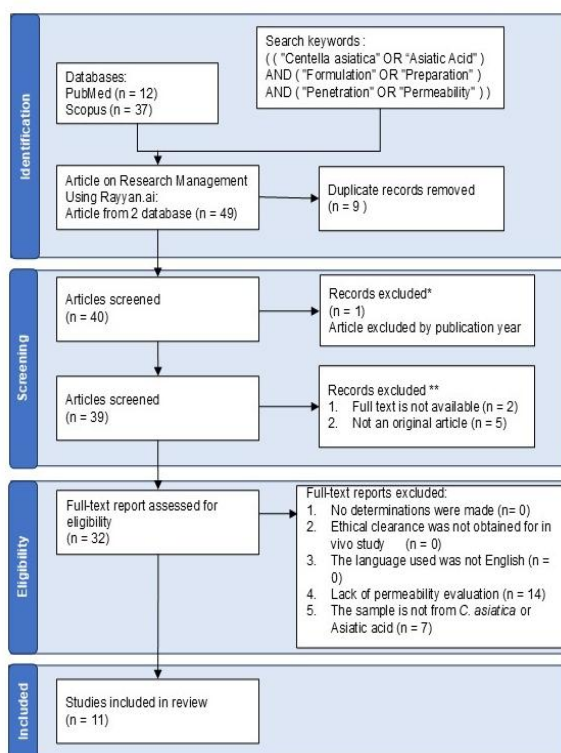


Figure 1. PRISMA flow diagram of the literature selection process.

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

The findings of this study demonstrate a strong and statistically significant relationship between caregiver preparedness and fall risk in older adults ($p = 0.0001$; $r = -0.697$). The negative direction of the correlation indicates that higher levels of caregiver preparedness are associated with lower fall risk in older adults. This finding reflects a clinically consistent pattern, in which caregivers with low levels of preparedness tend to care for older adults with a higher risk of falls, whereas those with higher preparedness are more commonly associated with older adults at lower risk [5].

From a theoretical perspective, these results are consistent with the concepts of patient safety and fall prevention, which consider falls as preventable events [15]. Recent evidence suggests that fall in older adults are influenced by a complex interplay of physical, psychological, and social factors, thereby requiring a comprehensive and multifactorial approach to prevention [16]. In this context, caregiver preparedness and fall risk appear to be associated with each other; however, this relationship should not be interpreted as a causal relationship. The findings indicate an association between the two variables but do not demonstrate that caregiver preparedness directly influences or causes changes in fall risk among older adults [17]. These findings are further supported by previous studies indicating that caregivers play a strategic role in fall prevention through the implementation of evidence-based strategies, such as environmental modifications and improvements in home safety. In addition, nursing interventions that focus on caregiver empowerment have been shown to be effective in enhancing caregiver preparedness and their ability to manage fall risk in older adults [18]. Moreover, experimental studies have demonstrated that caregiver preparedness enhancement programs can significantly improve balance

in older adults and reduce the risk of falls [19].

However, these findings should also be interpreted with caution. First, although a strong association was identified, the cross-sectional design of this study does not allow for definitive conclusions regarding causality. Second, other factors, such as the health status of older adults, cognitive impairment, depression, and social conditions (e.g., living alone), have also been shown to contribute to fall risk [17]. These findings suggest that caregiver preparedness is an important factor, but not the sole factor associated with fall risk in older adults.

Furthermore, qualitative studies have shown that caregivers often experience concerns related to the risk of falls (fear of falling) [20] which may influence their behavior, either through overprotective actions or limitations in supporting older adults' activities [17], [21]. This condition may act as a double-edged sword, whereby preparedness that is not supported by adequate knowledge may inadvertently reduce the independence of older adults [17]. The implications of these findings highlight that improving caregiver preparedness should be approached comprehensively, not only through enhancing knowledge but also through practical skills training, simulation-based learning, and continuous support from healthcare professionals. A family-centered care approach is therefore essential in fall prevention in older adults, as caregivers constitute an integral component of the community-based care system [22], [23].

These findings further indicate that caregiver preparedness plays a crucial role in determining the level of fall risk in older adults. Empirically, caregivers with low preparedness are less likely to provide optimal supervision, implement environmental modifications, and respond promptly to emergency situations, thereby increasing the likelihood of falls. Caregiver preparedness encompasses knowledge,

attitudes, and skills in preventing and managing emergency conditions in older adults, particularly fall-related incidents [24]. Older adults experience physiological changes, including decreased muscle strength, impaired balance, reduced visual function, and slower protective reflexes [25]. These conditions place them at a higher risk of falling, particularly in the absence of a safe environment and adequate supervision. From a patient safety perspective, falls are considered adverse events that can be prevented through strategies such as risk identification, environmental modification, and enhancement of caregiver competence. In this context, caregiver preparedness functions as a primary protective mechanism within family-based care, thereby serving as a key protective factor against fall in older adults [26].

The findings of this study are consistent with previous research indicating that caregivers with limited knowledge and skills tend to care for older adults with a higher risk of falls compared to those with better education and training [15]. A systematic review of intervention studies has demonstrated that home-based fall prevention programs involving family members and caregivers significantly reduce the incidence of fall in older adults. Furthermore, a study by Phelan et al. showed that caregiver education on home environment modification and safe mobility assistance techniques can significantly reduce fall risk [27]. In addition, other studies have reported that caregiver vigilance is associated with older adults' adherence to the use of assistive devices and safe behaviors during daily activities. Psychosocial factors affecting caregivers, such as fatigue and stress, have also been shown to influence their ability to effectively supervise older adults [17], [28]. Caregivers with a high caregiving burden are more likely to experience decreased preparedness, which in turn increases the risk of falls among older adults [22].

Therefore, the results of this study reinforce previous evidence that caregivers are key determinants in fall incidents in older adults, both directly through physical assistance and indirectly through decision-making in daily care. The high proportion of caregivers with moderate and low levels of preparedness suggests that many caregivers have not yet achieved optimal capacity in fall prevention. This may be influenced by limited access to health information, lack of specific training in fall prevention, and the perception that falls are a normal part of the aging process [29].

The belief that falls are a natural phenomenon in older adults may reduce caregiver vigilance toward environmental hazards, such as slippery floors, poor lighting, and inappropriate footwear. In fact, falls can lead to serious consequences, including fractures, head injuries, and long-term dependency, ultimately increasing the burden on families and healthcare systems [17]. This study also found that although some older adults were categorized as low risk, the proportion of moderate- and high-risk individuals remained substantial. This indicates that the older adult population in this study is in a vulnerable condition, emphasizing the importance of caregiver-based interventions [19]. These findings suggest that fall prevention strategies should target not only older adults but also their caregivers [18].

Educational and training programs for caregivers focusing on early detection of fall risk, safe mobility techniques, and home environment modification should be integrated into primary healthcare services, such as community health centers and elderly integrated service posts. By improving caregiver preparedness, it is expected that fall risk in older adults can be significantly reduced.

Overall, this study demonstrates that caregiver preparedness is significantly associated with fall risk in older adults [30]. These findings are consistent with gerontological nursing theories and

previous studies that position caregivers as central actors in fall prevention. High levels of caregiver preparedness function as a protective factor, whereas low preparedness increases the vulnerability of older adults to falls. Therefore, enhancing caregiver preparedness represents a key strategy in promotive and preventive efforts in elderly healthcare [31].

CONCLUSION

This study demonstrates a significant association between caregiver preparedness and fall risk in older adults. Higher levels of caregiver preparedness are associated with a lower risk of falls. Caregiver preparedness is associated with fall prevention through effective supervision, environmental modification, and prompt responses to emergency situations. Therefore, enhancing caregiver preparedness may be considered an important component of elderly care and can be supported through structured education and training programs focusing on fall prevention, safe mobility techniques, and home environment modification. Primary healthcare services, such as community health centers (Puskesmas) and integrated service posts for older adults (Posyandu Lansia), may consider incorporating caregiver-based approaches into elderly healthcare programs.

Future research is recommended to develop and evaluate the effectiveness of caregiver preparedness intervention models in reducing fall incidence in older adults using longitudinal study designs.

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