



A Review of the Biological Activity and Potential Applications of Compounds from *Elsholtzia ciliata* for the Treatment of Dermatological Diseases

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ABSTRACT:

In the context of increasing antibiotic resistance and associated adverse effects, treatments for dermatological conditions such as acne vulgaris and atopic dermatitis remain limited. This narrative review synthesises studies published mainly between 2010 and the first quarter of 2026, retrieved from PubMed, Scopus, Web of Science, ScienceDirect, and Vietnam Journals Online, with the aim of evaluating the potential dermatological applications of compounds isolated from *Elsholtzia ciliata*. The review identifies a total of 352 compounds from this species, classified principally into flavonoids, phenolic acids, terpenoids, alkaloids, and essential oil constituents. Experimental studies have identified several biological activities, including antioxidant, anti-inflammatory, antibacterial, and anti-allergic effects. However, direct evidence regarding the efficacy of *E. ciliata* against the skin-associated bacterium *Cutibacterium acnes*, as well as its clinical efficacy in dermatological diseases, remains limited. *E. ciliata* may represent a potential source of bioactive compounds for developing dermatological and cosmeceutical products; nevertheless, its therapeutic potential needs to be confirmed through appropriately designed pre-clinical and clinical studies.

KEYWORDS: anti-inflammatory activity, biological activity, cosmeceuticals, dermatological diseases, *Elsholtzia ciliata*

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1. INTRODUCTION

Dermatological conditions such as acne vulgaris and atopic dermatitis pose a substantial global healthcare burden (Karimkhani et al., 2017). Current therapeutic regimens rely predominantly on antibiotics and retinoids (Ramsis et al., 2024; Walsh et al., 2016); however, the long-term use of these treatments often leads to antibiotic resistance (Walsh et al., 2016) along with undesirable cutaneous adverse effects (Ramsis et al., 2024). For these reasons, contemporary dermatology is shifting toward the identification and standardisation of plant-derived bioactive compounds—laying the groundwork for nature-based therapeutic solutions. In this context, *Elsholtzia ciliata* represents a highly promising medicinal plant species, with preliminary evidence of antioxidant, anti-inflammatory, antibacterial, and anti-allergic activities, thereby suggesting potential applications in the supportive treatment of dermatological diseases and the development of cosmeceutical products (H.-H. Kim et al., 2011; Pudžiuvėlytė, Liaudanskas, et al., 2020; Wang et al., 2022).

Kinh giới (*Elsholtzia ciliata* (Thunb.) Hyl.) is a herbaceous species belonging to the Lamiaceae family, widely distributed across Asia, including Vietnam (Nguyen et al., 2020). In traditional medicine, the aerial parts have commonly been used to treat

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skin conditions (Wang et al., 2022; Q. Zhang et al., 2021). Recent studies have identified several groups of bioactive compounds in *E. ciliata*, including essential oils, flavonoids, and phenolic acids (Nguyen et al., 2020), which have shown antioxidant, anti-inflammatory, and antibacterial capacities in experimental models (Pudžiuvėlytė, Liaudanskas, et al., 2020). Given the growing trend of natural cosmetics development and its multi-component, multi-target profile, *E. ciliata* is expected to be a valuable source of bioactive ingredients for the formulation of modern cosmeceutical preparations. However, most of the available studies have assessed the activities of individual compounds independently, creating a research gap regarding an overarching view of the dermatological pharmacological activities of *E. ciliata* as well as the technological barriers to the formulation of cosmeceutical products derived from this species.

Based on the aforementioned reasons, this article aims to synthesize evidence regarding the bioactive compounds of *E. ciliata*, analyze their molecular mechanisms of action relevant to dermatological applications, and evaluate the prospects for the sustainable development of dermocosmetics.

2. METHODS

As a narrative review, this study synthesized the available evidence on the chemical composition, biological activities, mechanisms of action, and dermatological application potential of compounds from *Elsholtzia ciliata*. Scientific articles were retrieved from the PubMed, Scopus, Web of Science, ScienceDirect, and Vietnam Journals Online databases, mainly covering the period from 2010 to the first quarter of 2026. The search terms included the species name ("*Elsholtzia ciliata*" OR "Kính giới"), the extract components ("essential oil" OR "flavonoid" OR "extract"), and the skin-related pharmacological activities ("skin diseases" OR "wound healing" OR "anti-inflammatory" OR "acne" OR "tyrosinase").

In the selection process, studies that directly investigated *E. ciliata* or provided information relevant to its mechanism of action and dermatological application potential were included. Studies on other species of the genus *Elsholtzia* or on pure compounds such as rosmarinic acid were used only as supporting evidence. Articles were included in the analysis if they were *in vitro*, *in vivo*, *in silico*, or clinical studies that used *E. ciliata* extracts, essential oils, or pure compounds and measured dermatology-related outcomes, as well as reviews concerning bioactive compounds from *E. ciliata*. Documents that did not meet the objectives of the study or did not provide sufficient data on the methods and the outcomes described above were excluded.

Within the predefined analytical framework, data from the included articles were analyzed according to the following principal categories: chemical composition, anti-inflammatory activity, antimicrobial activity, antioxidant activity, anti-allergic activity, toxicity, and formulation technology. Owing to the heterogeneity across studies in terms of raw materials, extraction methods, experimental models, and assessment criteria, the findings were synthesized qualitatively. In interpreting the review findings, a clear distinction was made between direct and indirect evidence on the dermatological effects of the compounds of interest, as well as the hypotheses that need to be validated in further studies.

For language refinement, ChatGPT 5.5 and Gemini for Education were used to improve the manuscript's American English usage and grammar and to refine the presentation of the authors' ideas. The authors carried out all analytical content and final discussions.

3. RESULTS AND DISCUSSION

3.1. Phytochemistry of *Elsholtzia ciliata*

E. ciliata (family Lamiaceae) has a broad natural distribution across China, India, and other regions in Asia, Europe, and the United States (Stepanyan et al., 2021). Given its widespread geographical distribution, *E. ciliata* exhibits considerable chemotypic diversity depending on its origin, leading to differences in chemical composition (Chi et al., 2025), some of which may exhibit pharmacological activities relevant to dermatological therapy. Specifically, the limonene-dominant chemotype prevails (71%) in the highland areas of Northern Vietnam (Chi et al., 2025), whereas the Z-citral and carveol chemotypes are found in high concentrations in Đắk Lắk (Nhan et al., 2022). A review of existing studies has shown that a total of more than 352 compounds have been identified, including flavonoids, terpenoids, phenylpropanoids, and alkaloids (Wang et al., 2022). The pharmacological activities of *E. ciliata* have been evaluated primarily through *in vitro* assays and animal models; the available evidence largely focuses on antioxidant, anti-inflammatory, and antimicrobial activities (Nguyen et al., 2020; Wang et al., 2022). Table 1 systematically summarises the distribution of the main groups of bioactive constituents together with the pharmacological activities relevant to dermatology:

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Table 1. Distribution of bioactive compounds from *E. ciliata* and their potential dermatological applications

Compound/bioactive group	Plant material part/raw material form studied	Research findings	Research limitations
Chlorogenic acid	Ethanollic extract of leaves, stems, flowers and the whole plant	One of the predominant compounds in ethanollic extracts; extracts show antioxidant and anti-inflammatory activities at the extract level (Pudžiuvėlytė, Liaudanskas, et al., 2020)	The activity of chlorogenic acid alone cannot be determined from these data
Rosmarinic acid	Ethanollic extract of leaves, stems, flowers and the whole plant	Rosmarinic acid was identified as a dominant constituent; the extracts inhibited tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and prostaglandin E ₂ (PGE ₂) production in lipopolysaccharide (LPS)-stimulated macrophages (Pudžiuvėlytė, Liaudanskas, et al., 2020)	No <i>in vivo</i> testing to verify the actual therapeutic efficacy of the extracts in living organisms
Rutin	Ethanollic extract of leaves, stems, flowers and the whole plant	One of the predominant compounds in ethanollic extracts (Pudžiuvėlytė, Liaudanskas, et al., 2020)	The study did not separately assess the anti-inflammatory activity of rutin
Avicularin	Ethanollic extract of leaves, stems, flowers and the whole plant	Identified together with chlorogenic acid and rosmarinic acid as one of the outstanding free-radical scavengers in HPLC-ABTS assays (Pudžiuvėlytė, Liaudanskas, et al., 2020)	Results reflect the antioxidant activity of the compound or extract in the assay; do not demonstrate efficacy in human skin
Rosmarinic acid methyl ester	Phenolic glycoside compound isolated from <i>E. ciliata</i>	Inhibits NO production in RAW264.7 cells with an IC ₅₀ of 19.23 $\pm$ 1.30 μ M (Dung et al., 2023)	The findings are limited to <i>in vitro</i> data; <i>in vivo</i> efficacy requires further study
Methyl salicylate α -L-arabinopyranosyl-(1 $\rightarrow$ 6)- β -D-glucopyranoside	Phenolic glycoside compound isolated from <i>E. ciliata</i>	Inhibits NO production with an IC ₅₀ of 16.51 $\pm$ 1.56 μ M (Dung et al., 2023)	No direct data on dermatological efficacy
Glycosides from above-ground parts	Above-ground parts of the plant	Four glycosides were evaluated for their ability to inhibit sEH; butein-4'-O-glucoside reduced NO, PGE ₂ , iNOS, COX-2, IL-6 mRNA and sEH mRNA in poly(I:C)-stimulated RAW264.7 cells (J. H. Kim et al., 2024)	No evidence on skin barrier restoration or anti-acne activity
Ursolic acid and oroxylin	Compounds isolated in pharmacognostic studies of <i>E. ciliata</i>	Studies have reported anti-inflammatory, antioxidant, antimicrobial and anticancer activity of the species in the assays employed (Q. Zhang et al., 2021)	The above-mentioned bioactivities cannot be attributed to ursolic acid or oroxylin alone
<i>E. ciliata</i> essential oil	Whole plant; samples collected in the dry and wet seasons	Dry-season essential oil has an MIC of 200 μ g/mL against <i>E. coli</i> , <i>B. subtilis</i> , <i>S. aureus</i> and <i>C. albicans</i> . Wet-season essential oil has an MIC of 200 μ g/mL against <i>E. coli</i> , <i>B. subtilis</i> and <i>S. cerevisiae</i> , and 100 μ g/mL against <i>C. albicans</i> (Nhan et al., 2022)	Activity varies by season; adequate direct evidence against <i>C. acnes</i> is still lacking
Limonene-rich chemotype	<i>E. ciliata</i> essential oil surveyed in Northern Vietnam	Limonene constituted 71.0% of the reported chemotype; the essential oils exhibited activity against several microorganisms (Chi et al., 2025)	Insufficient data to confirm direct activity against skin-relevant microorganisms

Ethanol leaf extract obtained by mTPE	Leaves of <i>E. ciliata</i>	Under the reported extraction conditions (70 °C for 30 min, 60% ethanol, material-to-solvent ratio of 1:20, pH 5.6, and pressure of 24 psi), the extract contained total polyphenols at 28.05 ± 0.55 mg GAE/g dry weight, chlorogenic acid at 7.90 ± 0.07 mg/g dry weight, and DPPH activity at 320.22 ± 2.28 µmol TE/g; it also exhibited antibacterial activity (Truong et al., 2025)	<i>In vitro</i> scale; <i>in vivo</i> studies have not yet been carried out to confirm actual efficacy and biosafety
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The accumulation of bioactive compounds in *E. ciliata* displays significant geographical differentiation (Pudžiuvytė, Liaudanskas, et al., 2020) and is also closely dependent on extraction techniques. With respect to the essential oil, geographical characteristics directly influence the terpenoid profile (Phuc et al., 2023); for instance, a sample collected in Đắk Lắk showed that the main components were *Z*-citral (29.35%) and carveol (26.89%) (Nhan et al., 2022). *E. ciliata* essential oil exhibits pronounced chemotypic diversity. The review data identify the dominant compound in *E. ciliata* essential oil as carvacrol, reaching 73.48% in samples collected at Phú Lộc (Huế city) (Nguyễn et al., 2024). This chemical variability places demands on the pharmaceutical industry: establishing cultivation standards and raw material harvesting protocols, and using specific flavonoids as reference standards to ensure consistent therapeutic efficacy in dermatological applications. Thus, *E. ciliata* represents a promising source of bioactive compounds; however, compositional variability requires standardisation procedures with respect to cultivar, chemotype, harvesting, preservation and extraction techniques in order to ensure consistency in applied products.

3.2. Anti-inflammatory activity and prospects for acne control

The anti-inflammatory activity of *E. ciliata* depends on the plant part and the type of extract used. Experimental studies on ethanolic extracts from the leaves, stems, flowers, and the whole plant have reported significant reductions in pro-inflammatory mediators, including TNF-α, IL-6, and prostaglandin E₂, in murine peritoneal macrophages stimulated by lipopolysaccharide (LPS). Stem and flower extracts were more effective in reducing cytokine release, whereas the leaf extract exhibited a stronger effect on prostaglandin E₂ (Pudžiuvytė, Liaudanskas, et al., 2020). Because most of the available studies have focused on whole extracts, the observed findings cannot be directly attributed to single compounds such as chlorogenic acid, rosmarinic acid, or rutin, which represents a research gap that warrants further clarification.

At the pure-compound level, researchers isolated and evaluated 11 phenolic glycosides from *E. ciliata*. Rosmarinic acid methyl ester, methyl salicylate α-L-arabinopyranosyl-(1→6)-β-D-glucopyranoside, and methyl 2-O-β-D-glucopyranosyl benzoate inhibited nitric oxide production in LPS-activated RAW264.7 cells, with IC₅₀ values of 19.23 ± 1.30 µM, 16.51 ± 1.56 µM, and 13.73 ± 0.95 µM, respectively. The IC₅₀ value of the reference compound L-NMMA was 32.51 ± 3.70 µM, while the remaining compounds exhibited IC₅₀ values above 100 µM (Dung et al., 2023). These findings indicate that certain phenolic compounds isolated from *E. ciliata* may modulate NO production in a macrophage model, although evidence of efficacy in human epidermal cell models or in acne pathology models remains limited.

In additional mechanistic studies, evidence of the anti-inflammatory activity of *E. ciliata* has been reported for glycosides isolated from the aerial parts of the plant. Four compounds were assessed for their ability to inhibit soluble epoxide hydrolase (sEH); among them, butein-4'-O-glucoside reduced the sEH-related response, as well as NO and PGE₂ production, and the expression of iNOS, COX-2, IL-6 mRNA, and sEH mRNA in poly(I:C)-stimulated RAW264.7 cells (J. H. Kim et al., 2024). However, these results were obtained in an *in vitro* macrophage model, and studies in keratinocyte cell lines, reconstructed skin, or *in vivo* models have not yet been conducted.

From a pathobiological perspective, evaluating the anti-acne potential of *E. ciliata* should take into account the combination of its anti-inflammatory activity and its capacity to inhibit acne-related microorganisms. When hair follicles become blocked and sebum accumulates, *Cutibacterium acnes* can hydrolyse sebum into free fatty acids. This bacterium is also recognised by keratinocytes through Toll-like receptors, which subsequently activate NF-κB and AP-1, thereby promoting the release of pro-inflammatory mediators such as TNF-α, IL-1, IL-6, and IL-8 (Y. Zhang et al., 2025). Accordingly, formulations exhibiting synergistic effects against the inflammatory response and against *C. acnes* could be valuable in the search for acne-targeting therapies.

Nevertheless, a clear distinction between the direct evidence of anti-inflammatory activity of *E. ciliata* and evidence of anti-*C. acnes* activity from other species is necessary. For *E. ciliata*, the available studies have reported antibacterial activity against strains such as *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus*, *Candida albicans*, and several other microorganisms (Chi et al., 2025; Nhan et al., 2022). However, these studies have not provided sufficient direct evidence on the ability of the species to inhibit *C. acnes*. Within that context, the essential oil of a closely related species, *Elsholtzia splendens*, has been reported to exhibit antibacterial activity against *S. aureus*, *Cutibacterium acnes*, and *Staphylococcus epidermidis*, with the MIC value against *C. acnes*

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being 0.31 $\mu\text{L/mL}$ (Guo et al., 2012). This result provides a certain reference value and suggests that *E. ciliata* may possess anti-*C. acnes* activity.

At present, the anti-inflammatory activity of *E. ciliata* provides a basis for recognising its potential to support acne control, but it does not yet constitute evidence of acne-treating efficacy. Subsequent studies should directly evaluate the MIC and MBC values of the essential oil, the extracts, and the phenolic-rich fractions of *E. ciliata* against standardised strains of *C. acnes*. At the same time, keratinocytes or reconstructed skin should be used to evaluate the ability to reduce IL-1 β , IL-6, IL-8, TNF- α , COX-2, and PGE₂ after stimulation with *C. acnes*. This approach may enable the differentiation of direct antibacterial activity from secondary anti-inflammatory effects and provide a more appropriate foundation for pre-clinical acne studies.

3.3. Antibacterial and antifungal activity

The antibacterial activity of *E. ciliata* has been documented in both essential oil and extract preparations. This activity, however, varies notably with the harvest season and the chemical composition of the essential oil samples. Essential oil collected in the dry season inhibited *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus*, and *Candida albicans*, with a minimum inhibitory concentration (MIC) of 200 $\mu\text{g/mL}$. Essential oil collected in the wet season inhibited *E. coli*, *B. subtilis*, and *Saccharomyces cerevisiae* with an MIC of 200 $\mu\text{g/mL}$, and inhibited *C. albicans* with an MIC of 100 $\mu\text{g/mL}$ (Nhan et al., 2022). These results indicate that *E. ciliata* essential oil exhibits activity against several bacteria and fungi under the test conditions.

Studies within the genus *Elsholtzia* have also provided supporting evidence regarding antibacterial activity. The essential oils of four species were analysed: *E. blanda*, *E. ciliata*, *E. communis*, and *E. penduliflora*. The findings showed inhibitory activity against *S. aureus*, *E. coli*, and *C. albicans*, with MIC values ranging from 0.4% to 3.2% (Chi et al., 2025). However, the results were reported at the group level of the four species, and the available data have not provided separate MIC values of *E. ciliata* essential oil against each individual microorganism. The essential oil of *E. splendens* has been reported to inhibit the growth of *S. aureus*, *C. acnes*, and *S. epidermidis*, with an MIC of 0.31 $\mu\text{L/mL}$ against *C. acnes* (Guo et al., 2012). These results suggest considerable potential with respect to inhibiting acne-related microorganisms, particularly at the genus level. Nevertheless, further studies on the essential oil of *E. ciliata* are needed. The volatile constituents of both *E. ciliata* and *E. rugulosa* have also been reported to inhibit several bacterial strains; however, the results were presented jointly for both species, and no specific activity has been attributed to the compounds of each individual species (Guo et al., 2012).

In addition to the essential oil, the ethanolic extract from *E. ciliata* leaves obtained by mild thermal-pressure extraction has also shown antibacterial activity. In that study, *Penicillium chrysogenum* and Gram-positive bacteria exhibited distinct sensitivity to the extract (Truong et al., 2025). These findings support the antibacterial activity of the *E. ciliata* leaf extract, although they do not establish a specific inhibitory effect on *C. acnes* and therefore require further study.

Limonene was the dominant constituent in one chemotype of *E. ciliata* surveyed in Northern Vietnam, accounting for 71.0% of the oil (Chi et al., 2025). In a study on pure limonene, disruption of the cell membrane, leakage of macromolecules, reduction of adenosine triphosphate (ATP) content, and impairment of ATPase activity as well as of the respiratory chain complex were observed in *Listeria monocytogenes* (Han et al., 2019). However, this result was obtained with pure limonene and *L. monocytogenes*; studies adopting a comparable approach with limonene extracted from *E. ciliata* and targeting skin-relevant bacteria such as *C. acnes* are needed.

Some studies have also assessed the effects of *E. ciliata* essential oil on PC-3, A549, and HepG2 cell models. In an analysis of the essential oil collected in the dry season, IC₅₀ values on the PC-3 and A549 cell lines were 66.34 $\mu\text{g/mL}$ and 93.11 $\mu\text{g/mL}$, respectively. The essential oil collected in the wet season showed IC₅₀ values of 30.62 $\mu\text{g/mL}$, 22.78 $\mu\text{g/mL}$, and 85.35 $\mu\text{g/mL}$ on PC-3, HepG2, and A549, respectively (Nhan et al., 2022). These results indicate the effect of the essential oil on the cell models employed in the study, but they are not a substitute for toxicological assessment in human keratinocytes or dermal fibroblasts. These IC₅₀ values do not provide an adequate basis for establishing safe concentrations for topical dermatological applications, indicating a research gap that needs further study.

In subsequent studies, three models directly relevant to dermatological applications should be prioritised: (i) evaluation of *E. ciliata* essential oil and extracts against *Cutibacterium acnes* under appropriate anaerobic or microaerophilic conditions; (ii) the use of keratinocytes, particularly the HaCaT cell line, to examine the cytotoxicity and inflammatory response of epidermal cells; and (iii) verification of these findings on reconstructed skin. In the HaCaT model, *C. acnes* is recognised through Toll-like receptors, which activate nuclear factor kappa B (NF- κ B) and activator protein 1 (AP-1) and trigger the release of inflammatory mediators such as TNF- α , IL-1, IL-6, and IL-8 (Y. Zhang et al., 2025). This approach allows simultaneous assessment of antibacterial activity, epidermal cytotoxicity, and modulation of the inflammatory response in a system that more closely models the pathogenesis of acne.

On the basis of the experimental data, it is evident that *E. ciliata* essential oil and extracts exhibit activity against several bacteria and fungi, including *E. coli*, *B. subtilis*, *S. aureus*, *C. albicans*, and *S. cerevisiae* (Chi et al., 2025; Nhan et al., 2022). However, direct evidence on the ability of *E. ciliata* itself to inhibit *C. acnes* remains limited. Accordingly, considering this species

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as a potential source of antibacterial compounds is warranted, whereas its application potential in acne control requires confirmation through direct studies on *C. acnes*, keratinocytes, and reconstructed skin.

3.4. Anti-allergic potential

Evidence for the anti-allergic activity of *Elsholtzia ciliata* currently comes mainly from studies using the aqueous extract of this species. This extract inhibited the systemic anaphylactic reaction induced by compound 48/80, IgE-mediated local anaphylactic reactions, and histamine release in a mouse model. In the HMC-1 human mast cell line activated by phorbol 12-myristate 13-acetate in combination with the calcium ionophore A23187, the extract reduced intracellular calcium concentration, histamine release, as well as the expression and secretion of the pro-inflammatory cytokines TNF- α , IL-1 β , and IL-6. This effect may be related to the inhibition of the NF- κ B and p38 mitogen-activated protein kinase (MAPK) signalling pathways (H.-H. Kim et al., 2011). The above results indicate that *E. ciliata* has the potential to reduce several characteristic reactions of mast cell-mediated allergic inflammation; however, establishing clinical efficacy in atopic dermatitis or urticaria in humans needs further study.

In addition, the currently available data do not provide direct evidence that *E. ciliata* extracts or essential oils increase the expression of filaggrin, loricrin, or involucrin in human keratinocytes, nor do they improve functional indicators such as TEWL, skin surface pH, or ceramide content. Findings on rosmarinic acid and other herbal formulations should only be regarded as a reference basis for orienting further research, not as direct evidence of the restorative effect of *E. ciliata* on the epidermal barrier (Jung et al., 2022; Liu et al., 2021).

3.5. Antioxidant activity

In cosmeceutical applications, extracts from *E. ciliata* represent a promising source of raw material for antioxidant formulations owing to the diversity of their phytochemical constituents. Experimental data have confirmed that the aroma components of *E. ciliata* essential oil can inhibit lipid peroxidation in cell membranes (Jeong et al., 2005); compounds such as citral contribute to the overall antioxidant capacity of the essential oil (Nhan et al., 2022). The HPLC-ABTS method identified chlorogenic acid, rosmarinic acid, and avicularin as the three principal radical-scavenging constituents in extracts of this species (Pudžiuvėlytė, Liaudanskas, et al., 2020). In addition, the anti-inflammatory and antioxidant activities of this essential oil have been reported in a number of scientific studies (Phuc et al., 2023). However, no clinical data or specific photoaging models are currently available, and in particular, no study has evaluated photoaging-related biomarkers such as matrix metalloproteinases (MMPs), collagen, or the nuclear factor erythroid 2–related factor 2/antioxidant response element (Nrf2/ARE) pathway specifically for *E. ciliata* essential oil. Accordingly, although there is evidence that *E. ciliata* essential oil can neutralise free radicals and activate the endogenous antioxidant enzyme system, more specific clinical studies are needed in order to evaluate the application potential of bioactive compounds from *E. ciliata* in protecting the skin against ageing and against the harmful effects of solar radiation.

3.6. Prospects and challenges in cosmeceutical formulation technology

In the development of cosmeceutical applications from *E. ciliata*, three groups of closely interrelated barriers are encountered. First, the variability in chemical composition across chemotypes, geographical regions, and harvesting periods (Diep et al., 2026; Phuc et al., 2023) renders quality control across cultivation, harvesting, preservation, and processing an urgent requirement in order to ensure reproducibility between raw-material batches (Malik et al., 2021). The standardisation of these factors not only determines therapeutic efficacy but also carries particular safety implications for topical products, requiring the application of global cultivation standards such as Global GAP or VietGAP, together with the integration of chemotype identification and quantification of marker compounds for each batch in accordance with international guidance on the standardisation of herbal extracts (Heinrich et al., 2022). The fluctuation in limonene content (reaching up to 71% of the essential oil in wild populations of the highland areas of Northern Vietnam) (Chi et al., 2025; Diep et al., 2026) between production batches may directly alter the risk of allergic contact dermatitis in users. Therefore, simultaneous quantification of both the parent limonene and its oxidation products is required before introducing the material into cosmeceutical production.

Optimising the sustainability of the *E. ciliata* raw-material source requires a comprehensive consideration not only of the origin characteristics but also of the extraction processes, including parameters relating to solvent, treatment time, energy consumption, recovery yield of bioactive compounds, and the feasibility of scale-up. Green extraction techniques such as pressurised liquid extraction, supercritical fluid extraction, ultrasound-assisted extraction, microwave-assisted extraction, and pressurised hot water extraction have been developed to reduce solvent consumption and processing time, and may also improve the recovery of polyphenols (Ameer et al., 2017). However, the "green extraction" label does not necessarily guarantee a minimal environmental impact. Comprehensive assessment requires analysis of empirical indicators, including solvent usage, recovery efficiency, energy consumption, waste output, and yield of bioactive compounds.

Among extraction methods, mild thermal-pressure extraction (mTPE) is noteworthy for *E. ciliata*. In a study on *E. ciliata* leaves, the extraction conditions were established as follows: temperature 70 °C, time 30 min, 60% ethanol, raw material to solvent

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ratio of 1:20, pH 5.6, and pressure of 24 psi. The resulting extract showed total polyphenol content of 28.05 ± 0.55 mg GAE/g dry weight, chlorogenic acid content of 7.90 ± 0.07 mg/g dry weight, and DPPH antioxidant activity of 320.22 ± 2.28 μ mol TE/g. The extract also exhibited antibacterial activity, in which *Penicillium chrysogenum* and Gram-positive bacteria showed greater sensitivity to the extract (Truong et al., 2025). Accordingly, mTPE has the potential to support a green extraction orientation, but its sustainability advantage still needs to be confirmed by comparative studies and process evaluations at a larger scale.

Second, *E. ciliata* essential oil is susceptible to evaporation, oxidation, and degradation under exposure to light and heat (Pudžiuvėlytė et al., 2019). Microencapsulation technology using the spray-drying method combined with sodium caseinate, maltodextrin, skim milk, and beta-cyclodextrin has been demonstrated to increase encapsulation efficiency and maintain stable biological activity (Pudžiuvėlytė et al., 2019; Pudžiuvėlytė, Marksa, et al., 2020), which may provide a promising formulation direction for product forms derived from *E. ciliata* extract.

Third, regarding toxicity, data from studies on the intraperitoneal injection of *E. ciliata* extract in a BALB/c mouse model in the acute stage (single-dose, 24-h follow-up) and the sub-chronic stage (60 days) showed no significant histopathological changes or hepatotoxicity, nephrotoxicity, or haematotoxicity (Mačianskienė et al., 2023). However, systemic toxicity data from this intraperitoneal animal model remain insufficient to support cutaneous safety assessment, which requires a clear distinction between two target effects: (i) irritant contact dermatitis (ICD), which is a non-immunologically mediated inflammatory response, dose-dependent, occurring in any individual exposed to a sufficient concentration and limited to the site of contact; and (ii) allergic contact dermatitis (ACD), which is a Type IV hypersensitivity reaction mediated by antigen-specific memory T cells, expressed only in individuals previously sensitised and capable of spreading beyond the site of contact at very low doses (Peiser et al., 2011). Chemotypes with high limonene or (*Z*)- β -farnesene content are largely non-sensitising in their pure form but undergo natural air oxidation to form hydroperoxides. These are clinically confirmed contact allergens (Sköld et al., 2004) and pose a notable ACD risk. Accordingly, a separate safety-testing design is required for each target: ICD is assessed using OECD TG 439 or TG 431 (*in vitro* skin corrosion), whereas ACD is assessed using replacement methods such as OECD TG 442C (h-CLAT), TG 442D, or LLNA according to TG 429, combined with controlled patch testing on humans before broad use on hypersensitive skin.

In addition to microencapsulation technology, nanoemulsion technology is a promising formulation strategy for improving the dispersion, stability, and antibacterial efficacy of *E. ciliata* essential oil. In a study by Tinh et al., nanoemulsions from *E. ciliata* essential oil were developed by ultrasonic homogenisation. Compared with the original essential oil, the nanoemulsions exhibited higher growth-inhibitory activity against several surveyed strains, including *Staphylococcus epidermidis*; specifically, for *Bacillus subtilis* and *S. epidermidis*, the inhibitory efficacy of the *E. ciliata* nanoemulsion was 5-fold higher than that of the corresponding essential oil (Tinh et al., 2025). These results indicate that the enhanced efficacy may be related to improved dispersion of the essential oil in aqueous media and enhanced interaction of its hydrophobic components with bacterial cells. However, current data still display research gaps: direct activity against *Cutibacterium acnes* has not yet been evaluated, cytotoxicity on human keratinocytes or fibroblasts has not been examined, and there is insufficient evidence to confirm that the nanoemulsion reduces local toxicity. At a concentration of 500 μ g mL⁻¹, both nanoemulsions were reported to inhibit approximately 80% of HepG2 cells, whereas the commercial essential oil inhibited approximately 60% of HepG2 cells (Tinh et al., 2025). These results indicate activity on a liver cell line used in screening research, but do not provide evidence of cutaneous efficacy or safety. Therefore, additional testing on keratinocytes, fibroblasts, and reconstructed skin is required before assessing topical application potential. Furthermore, subsequent studies should optimise the technical parameters (droplet size, surfactant concentration, essential oil content), together with comprehensive evaluation of activity against *C. acnes*, cytotoxicity on skin cells, irritation potential, and formulation stability, before considering cosmeceutical product development.

Although *Elsholtzia ciliata* displays considerable potential in dermatological and cosmeceutical applications, realising these applications requires the integrated alignment of raw-material standardisation, advanced formulation technology, and in-depth clinical safety studies. This is necessary to establish a comprehensive efficacy and safety dossier in humans.

4. CONCLUSIONS

In phytochemical and pharmacological investigations, *Elsholtzia ciliata* is a plant species rich in bioactive compounds, including flavonoids, phenolic acids, terpenoids, alkaloids, and essential oil constituents. Current evidence indicates that extracts and isolated compounds derived from this species possess antioxidant, anti-inflammatory, antibacterial, and anti-allergic activities in various *in vitro* experimental models. These activities have been linked to the ability to attenuate oxidative stress, to inhibit pro-inflammatory cytokines, nitric oxide production, mast cell degranulation, and histamine release, as well as to modulate the NF- κ B and MAPK signalling pathways.

In antimicrobial evaluations, the essential oil and extracts from *E. ciliata* have demonstrated inhibitory activity against several microorganisms of relevance to dermatological diseases, particularly *S. aureus*, *E. coli*, and *C. albicans*. However, direct evidence regarding the ability of *E. ciliata* itself to inhibit *C. acnes* remains limited. Therefore, the currently available data indicate that the pharmacological potential of this species needs to be further validated by purpose-designed studies, in which the effects of

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whole extracts, essential oil, and individual pure compounds should be clearly differentiated. In addition, the effects of *E. ciliata* on keratinocytes and reconstructed skin need to be assessed independently in order to determine whether this species exerts any influence on epidermal barrier function.

The development of dermatological products from *E. ciliata* is further influenced by variations in raw-material source, growing conditions, harvesting time, processing methods, and extraction procedures. These factors may alter the composition of the extracts as well as the concentration of either bioactive or potentially toxic compounds. Accordingly, subsequent studies should focus on identifying and controlling chemotypes, on the standardisation of raw materials and extracts, on the selection of marker compounds for quality control, and on the optimisation of formulation technology to maintain stability and reproducibility between product batches.

Alongside efficacy evaluation, full assessments of local safety—covering irritant potential, sensitization potential, and cutaneous toxicity—need to be performed. *E. ciliata* therefore displays considerable potential for the development of cosmeceutical raw materials and supportive skin-care formulations; however, the establishment of human applications requires specific clinical evidence, a comprehensive safety dossier, and rigorous standardization procedures.

DECLARATION OF AI USE

In preparing this review, ChatGPT 5.5 and Gemini for Education were used as language-editing tools to improve the manuscript's American English usage and to refine the expression of the authors' ideas. The use of these tools was limited to language editing and stylistic improvement; they were not used to generate original scientific content, to interpret primary data, to formulate new conclusions, or to substitute for the authors' scientific judgment.

In this paper, all analytical content, including the interpretation of the chemical composition data, the synthesis of the biological activity findings, the mechanistic analysis of the anti-inflammatory, antibacterial, antioxidant, and anti-allergic evidence, and the formulation of the conclusions and the prospects for cosmeceutical development, was carried out by the authors. The authors take full responsibility for the integrity, accuracy, and originality of the manuscript.

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