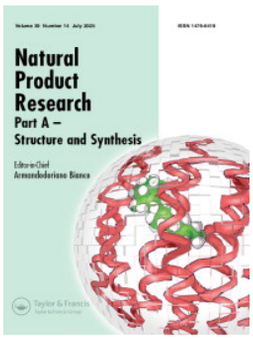

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In vitro and *in silico* evaluation of anti-inflammatory triterpene saponins from *Elsholtzia penduliflora* W.W. Smith (Lamiaceae)

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In vitro and *in silico* evaluation of anti-inflammatory triterpene saponins from *Elsholtzia penduliflora* W.W. Smith (Lamiaceae)

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ABSTRACT

Elsholtzia penduliflora W.W. Smith (Lamiaceae), a medicinal herb traditionally used in Vietnam, was investigated for its anti-inflammatory potential. Phytochemical analysis of its aerial parts, extracted using 80% ethanol, yielded 15 oleanane-type saponins (**1**–**15**) using chromatographic techniques. Among these, penduloside E (**4**), penduloside C (**5**), and kajiichigoside F1 (**10**) were prioritised for bioactivity testing based on structural characteristics and preliminary anti-inflammatory screening. These compounds at a concentration of 3 µM reduced PGE2 production by 48.9–54.3% and downregulated COX-2 mRNA expression by 36.6–42.4% in LPS-stimulated RAW 264.7 cells. Their effects were comparable to dexamethasone, which reduced PGE2 production by 59.8%, reaching 40.2% of the LPS control, and COX-2 mRNA to 33.3%. The compounds demonstrated low cytotoxicity, with cell viability consistently >80%. Molecular docking using AutoDock Vina revealed favourable binding interactions with COX-2 and iNOS enzymes, with compound **5** showing the highest binding affinities (−9.2 kcal/mol for COX-2; −8.7 kcal/mol for iNOS). Structural analysis revealed the triterpenoid backbone with feature functional groups may enhance bioactivity, suggesting structure-activity relationships. These findings suggest that *E. penduliflora* is a promising source of novel COX-2/iNOS inhibitors, with potential implications for the development of anti-inflammatory therapeutics.

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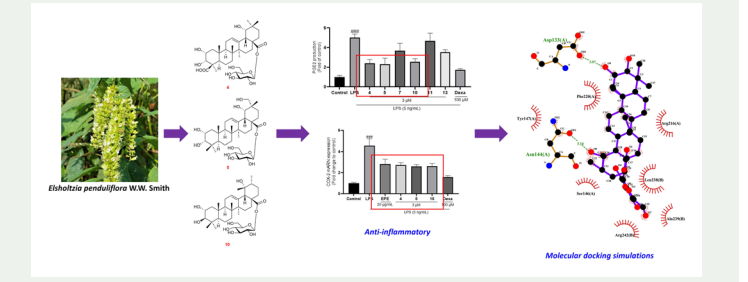

1. Introduction

Natural products derived from plants, fungi, and marine organisms have long been recognised for their potential therapeutic properties, particularly for the treatment of inflammatory diseases (Cao et al. 2021; Liu et al. 2023). By targeting specific molecules or signalling pathways involved in inflammation, some natural products can mitigate the inflammatory process while showing minimal adverse effects commonly associated with conventional treatments, such as non-steroidal anti-inflammatory drugs (NSAIDs) (Viet Phong et al. 2022). NSAIDs, including aspirin, ibuprofen, and celecoxib, are widely used to inhibit cyclooxygenase (COX) enzymes and reduce the production of prostaglandins, key mediators of inflammation (Chaiamnuay et al. 2006). However, prolonged use of NSAIDs is often associated with gastrointestinal side effects, cardiovascular risks, and renal toxicity (Domper Arnal et al. 2022; Hijos-Mallada et al. 2022). Therefore, there is an increasing demand for safer and more effective alternatives, and natural products offer a promising avenue for the development of such anti-inflammatory agents.

Elsholtzia penduliflora W.W. Smith, belonging to the genus *Elsholtzia* in the family Lamiaceae, is found across various Asian countries, including Vietnam, Thailand, and China. *E. penduliflora* is a small annual plant characterised by a square, smooth stem and lanceolate leaves measuring 5–15 cm in length. Its flowers are arranged in spike-like clusters, and the fruit is small, oblong, and grayish-black (Chi 2012). In northern Vietnam, particularly in Lai Chau and Lao Cai provinces, local communities traditionally use the aerial parts of *E. penduliflora* to treat symptoms associated with inflammation, such as fever, cough, and painful urination, which may involve inflammatory responses (Chi 2012; Hoang et al. 2022). These ethnopharmacological uses provide a relevant foundation for investigating its anti-inflammatory properties.

Phytochemical studies have revealed the presence of flavonoids, terpenoids, and triterpenoid saponins in this plant (Hoang et al. 2022; Zhang et al. 2022). Notably, a prenylated 3-benzazepine derivative named elsholtzioxin has been isolated from various organs of *E. penduliflora*, exhibiting promising anti-influenza virus activity against strain A/WSN/33/2009 (H1N1) with an inhibition rate of 47.19% (Zhang et al. 2022). Additionally, previous research identified several bioactive compounds from the EtOAc fraction of this plant (**EPE**), which demonstrated potential cytotoxic effects

against human lung cancer (A549) and breast cancer (MCF-7) cell lines (Hoang et al. 2022).

Despite these findings, there have been limited studies evaluating the chemical constituents of *E. penduliflora* and their anti-inflammatory effects. While NSAIDs remain the cornerstone of anti-inflammatory therapy, their limitations—such as gastrointestinal ulcers, cardiovascular risks, and renal toxicity—necessitate the exploration of alternative agents with comparable or superior efficacy and improved safety profiles. Triterpenoid saponins, a class of secondary metabolites widely distributed in plants, have gained attention for their diverse pharmacological activities, particularly anti-inflammatory effects, along with antioxidant and immunomodulatory properties (Miranda et al. 2022; Bildziukevich et al. 2023; Sharma et al. 2023; Avunduk 2024; Mantiniotou et al. 2025). Importantly, many triterpenoid saponins exhibit favourable safety profiles, with lower toxicity compared to conventional NSAIDs. For instance, glycyrrhizin, a well-known triterpenoid saponin derived from liquorice root, has demonstrated potent anti-inflammatory activity through the inhibition of COX-2 and nitric oxide synthase (iNOS), with efficacy comparable to that of certain NSAIDs but with reduced risk of adverse effects such as gastrointestinal damage (Akamatsu et al. 1991; Hu et al. 2022).

Given the promising pharmacological profile and improved safety of triterpenoid saponins, this study aims to investigate the anti-inflammatory potential of saponins isolated from *E. penduliflora* and compare their efficacy and safety with known anti-inflammatory agents. By evaluating both their bioactivity and cytotoxicity, this study aims to identify new, safe, and effective anti-inflammatory natural candidates that could serve as viable alternatives to current therapies. We reported the potential anti-inflammatory effects of 15 triterpenoid saponins (**1–15**), from the aerial parts of *E. penduliflora*. Furthermore, the *in vitro* underlying mechanisms of PGE2 and iNOS were also evaluated. Finally, the molecular docking simulation of bioactive compounds was also discussed.

2. Results and discussion

2.1. Structural elucidation of compounds from E. penduliflora

Three times over the course of 3 days, 10.0 kg of dried *E. penduliflora* plant material was extracted using 80% ethanol (30 L) at room temperature (20–25 °C). After the extract was mixed, filtered, and evaporated at low pressure, a green-brown residue (400.0 g, **EP**) was produced. Four fractions were derived from the residue, after it was suspended in distilled water and then fractionated with solvents of increasing polarity, including *n*-hexane, DCM to EtOAc (each 20 L), followed by concentration. The resulting fractions were: *n*-hexane (78.0 g, **EPH**), DCM (100.0 g, **EPD**), EtOAc (30.3 g, **EPE**), and a water-soluble layer (180.0 g, **EPW**) (Scheme S1).

Fifteen saponins (**1**–**15**) were separated from the EtOAc layer using a variety of column chromatography (CC) separation techniques. These compounds, shown in Figure 1, are as follows: sericoside (**1**), 2*α*,3*α*,19*α*,24-tetrahydroxyolean-12-en-28-oic acid 28-*O*-*β*-D-glucopyranosyl ester (**2**), penduloside F (**3**), penduloside E (**4**), penduloside C (**5**), penduloside D (**6**), penduloside A (**7**), penduloside B (**8**), rosamultin (**9**), kajiichigoside F1 (**10**), officinoterpenoside B (**11**), onjisaponin B (**12**), pruvuloside B (**13**), 24-hydroxytormentic acid ester glucoside (**14**), and niga-ichigoside F1 (**15**) (Hoang

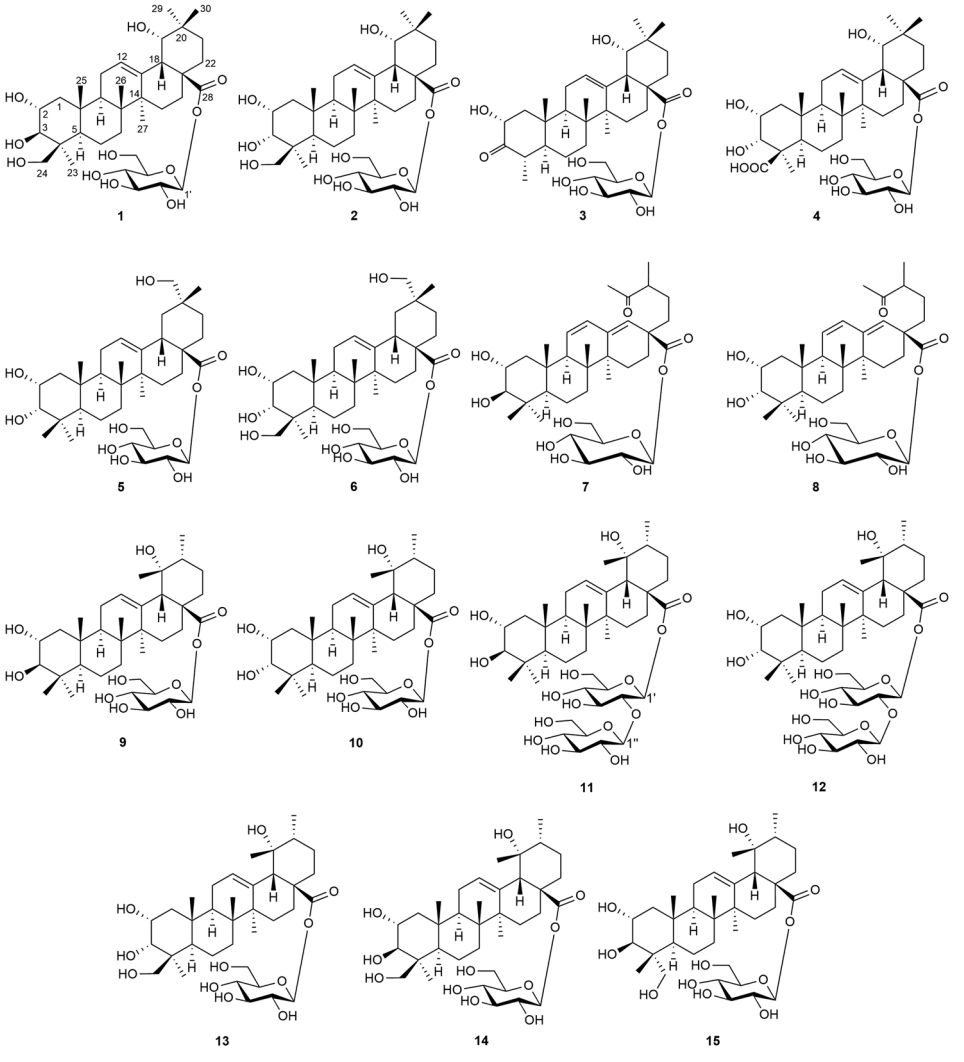

Figure 1. Chemical constituents (**1**–**15**) isolated from the aerial part of *E. penduliflora*.

et al. 2022). Their structures were characterised by NMR spectroscopy and compared with structures reported in the literature (Table S3–S5).

2.2. Cytotoxic effect of isolated compounds in RAW 264.7 cells

All compounds isolated from the **EPE** extract (**1–15**) were evaluated to test their cytotoxicity in RAW 264.7 cells using the MTT method, with a test dose of 3 µM.

Compounds **4**, **5**, **7**, **10**, **11**, and **13** demonstrated minimal cytotoxicity at a concentration of 3 µM, with cell viability rates exceeding 80% ($p < 0.001$ vs. control, Figure S2A). This suggests that these compounds are safe for use in *in vitro* anti-inflammatory assays. In contrast, compounds **1**, **6**, **9**, **12**, **14**, and **15** showed cytotoxicity, with cell viability rates below 70% ($p < 0.001$ vs. control, Figure S2A). These results highlight

the differential biological activities of the isolated saponins and underscore the importance of safety screening in drug discovery.

2.3. Impact of the potential compounds on PGE2 production in RAW 264.7 cells

Based on this information, the major compounds **4**, **5**, **7**, **10**, **11**, and **13** were evaluated for their ability to inhibit PGE2 production in RAW 264.7 cells stimulated with lipopolysaccharide (LPS; 5 ng/mL) using the ELISA method. These compounds were tested at a concentration of 3 µM. Dexamethasone (100 nM) was used as a positive control. The results are depicted in Figure S2B.

PGE2 is a widely distributed endogenous molecule known to play essential roles in both physiological and pathological pathways. However, excessive production of PGE2 has been associated with various disorders such as diabetes, circulatory shock, atherosclerosis, cancer, and chronic inflammatory diseases. Consequently, regulating PGE2 secretion emerges as a critical pharmacological strategy in drug development efforts. Furthermore, PGE2 is a key mediator of inflammation, contributing to the initiation and perpetuation of inflammatory responses in various tissues and organs. Excessive PGE2 production can lead to tissue damage and exacerbation of inflammatory conditions, underscoring the importance of targeting its secretion for therapeutic intervention in inflammatory diseases.

When cells were stimulated with LPS (5 ng/mL) to induce inflammation, the ratio of PGE2 in the cell culture supernatant increased to 502.91 ± 36.05% compared to the blank control sample. However, treatment with dexamethasone at 100 nM resulted in a lower increase of PGE2 in the cells, reaching only 174.13 ± 10.30% compared to the blank control sample. At a concentration of 3 µM, saponins **4**, **5**, and **10** significantly reduced the production of PGE2 by 52.2%, 54.3%, and 48.9%, respectively, compared to the LPS-induced inflammation control group ($p < 0.01$). Compared with the blank control sample, the levels of PGE2 ratios of compounds **4**, **5**, and **10** were 240.58 ± 37.20%, 229.69 ± 62.82%, and 256.99 ± 30.19%, respectively, with **5** exhibiting the strongest effect among them.

In contrast, compounds **7**, **11**, and **13** at a concentration of 3 µM did not significantly reduce the production of PGE2 compared to the LPS-induced inflammation control group, with ratios of PGE2 compared to the blank control sample being 367.44 ± 75.85%, 470.27 ± 76.78%, and 354.05 ± 24.54%, respectively ($p < 0.05$). Overall, all tested compounds demonstrated weaker effects compared to dexamethasone at a concentration of 100 nM. Indeed, dexamethasone showed 182.97 ± 11.78%.

2.4. Impact of the extract and potential compounds on the mRNA expression level of COX-2

Based on the screening results for PGE2, the **EPE** extract and compounds **4**, **5**, and **10**, which exhibited the highest activity, were selected to evaluate their influence on the mRNA expression of COX-2. The experimental concentrations were 20 µg/mL for the extract and 3 µM for the test compounds. The inflammatory control used was LPS at a concentration of 5 ng/mL. Dexamethasone at 100 nM was used as a

positive control. The assessment results of the potential impact of the **EPE** extract and these compounds on the mRNA expression level of COX-2 are depicted in Figure S2C.

As shown in the figure, when RAW 246.7 cells were stimulated with LPS (at a concentration of 5 ng/mL) to induce inflammation, the mRNA expression level of COX-2 increased to 455.74 ± 63.32% compared to the blank control sample. However, when treated with dexamethasone at 100 nM, the mRNA expression level of COX-2 only increased to 159.29 ± 13.55% compared to the blank control sample ($p < 0.001$ compared to LPS-induced inflammation control).

At a concentration of 20 µg/mL, **EPE** extract and compounds **4**, **5**, and **10** at a concentration of 3 µM significantly reduced the mRNA expression level of COX-2 compared to the LPS-induced inflammation control group ($p < 0.01$). The increases in COX-2 expression were 282.99 ± 45.66%, 272.65 ± 22.99%, 259.59 ± 17.95%, and 261.82 ± 25.43% for the **EPE** extract and compounds **4**, **5**, and **10**, respectively. Additionally, these compounds downregulated the mRNA expression of COX-2 by 38.0%, 42.4%, and 36.6%, respectively, demonstrating a strong anti-inflammatory effect. However, all test samples exhibited weaker effects compared to dexamethasone at a concentration of 100 nM.

2.5. Molecular docking simulations

Molecular docking-based virtual screening has been a widely used approach for structure-based drug discovery since the early 1980s (Meng et al. 2011; Gioia et al. 2017; Agu et al. 2023). By employing molecular docking models, researchers can analyse how small molecules interact with specific protein-binding sites at the atomic level (Meng et al. 2011; Trang et al. 2022). This method helps in gaining insights into fundamental biochemical processes by mapping out these interactions. Based on our *in vitro* results, we performed molecular docking simulations to determine if the ligands would dock to the receptor.

As iNOS and COX-2 are key enzymes involved in the inflammatory response, playing crucial roles in the production of inflammatory mediators, such as NO and PGs, targeting the iNOS and COX-2 proteins has emerged as a promising strategy for the treatment of inflammatory diseases. Understanding the molecular mechanisms underlying the regulation of iNOS and COX-2 expression and activity is essential for the development of effective therapeutic interventions aimed at modulating the inflammatory process and mitigating associated pathological conditions. The crystal structures of iNOS (PDB ID: 4NOS) and COX-2 (PDB ID: 5KIR) were obtained from the Protein Data Bank (PDB). These structures reveal the active sites, key interactions, and molecular mechanisms of inhibitors targeting inflammation. For instance, S-ethylisothiourea (SEITU), a potent and selective inhibitor of iNOS, binds in a narrow cleft within the larger active site containing tetrahydrobiopterin (H4B) and haem, forming hydrogen bond interactions with conserved residues such as Glu377 (Trp194, Cys200, Met355, Phe369, Trp372, Trp463, and Tyr489) (Fischmann et al. 1999). Similarly, rofecoxib, a COX-2-selective nonsteroidal anti-inflammatory drug (NSAID), binds to the hydrophobic channel of COX-2, interacting with key residues such as Val349, Tyr385, Arg513, Phe518, Val523, Ala527, Ser530, and Leu531 (Orlando and Malkowski 2016). The docking results are presented in Figures S3 and S4, and Tables S1 and S2.

The active compounds **4**, **5**, and **10** were then docked into the active site of the iNOS and COX-2 proteins using the same reported procedure. According to our docking results, compounds **4**, **5**, and **10** can bind to the active sites of iNOS and COX-2 proteins, with docking scores ranging from −6.5 to −9.8 kcal/mol. This reflects a potentially strong binding affinity between the ligands (bioactive saponins) and the target inflammation proteins (Tables S1 and S2). In other words, it suggests that the ligand is predicted to bind tightly to the protein, forming stable interactions at the binding site. Interestingly, Arg242 (2.95), Asp133 (2.77), Gln457 (2.85, 3.23), Tyr147 (3.12, 3.17), Asn144 (3.14), Asp133 (3.07), Glu140 (2.74, 3.00), and Glu236 (3.12) (Figure S3). Although these active compounds did not show direct interactions with Val349 and Ser530, which are critical for time-dependent inhibition and high-affinity binding of traditional inhibitors like rofecoxib and diclofenac (Orlando and Malkowski 2016), they instead interacted with other residues such as Arg242, Gln457, and Glu140, which are also located near the active site and contribute to enzyme stability and substrate binding. Specifically, Arg242 is part of the hydrophobic channel and plays a role in stabilising the enzyme's conformation, while Gln457 and Glu140 form hydrogen bonds that may help anchor the ligand in the binding pocket, potentially disrupting substrate access to the active site. These interactions suggest that compounds **4**, **5**, and **10** may inhibit COX-2 through a mechanism distinct from traditional NSAIDs, which typically rely on interactions with Val349 and Ser530. This alternative mode of binding highlights the unique inhibitory potential of our compounds and provides a foundation for further exploration of their anti-inflammatory effects.

With the iNOS protein, the sugar moieties of **4**, **5**, and **10** established hydrogen bond interactions with Arg199 (3.16), Tyr489 (3.04), Asp382 (2.80, 3.20), Glu377 (3.32), Arg199 (3.14), Tyr489 (2.84), Asp382 (2.91, 2.97), and Glu377 (2.87, 3.09) from the active site, respectively (Figure S4). These residues are known to play important roles in stabilising the active conformation of iNOS. For example, Glu377 is a conserved residue critical for inhibitor binding, as demonstrated by the loss of activity when Glu377 is replaced with glutamine, leucine, or alanine (Fischmann et al. 1999). The involvement of these residues in stabilising the binding of compounds **4**, **5**, and **10** suggests a potential mechanism of iNOS inhibition.

3. Experimental

See Supplementary Material.

4. Conclusion

Triterpenoid saponins exhibit diverse pharmacological effects, including anti-inflammatory and cytotoxic activities (Vinh et al. 2017; Cao et al. 2021; Vinh et al. 2024). A phytochemical analysis of the aerial parts of *E. penduliflora* led to the isolation of 15 saponins (**1–15**). Their structures were identified based on spectroscopic data, including HR-ESI-MS and 1D and 2D NMR (Tables S3–S5). The findings of this study highlight the significant potential of the EPE extract and its isolated triterpenoid saponins as effective anti-inflammatory agents.

Among the isolated compounds, penduloside C (**5**) emerged as particularly promising, showing substantial inhibition of PGE2 production by 54.3% ($p < 0.01$) and downregulation of COX-2 mRNA expression by 42.4% ($p < 0.01$) in LPS-stimulated RAW 264.7 cells. Additionally, compounds **4** and **10** exhibited strong anti-inflammatory properties, consistent with previous studies supporting their efficacy. Cytotoxicity screening revealed that compounds **4**, **5**, and **10** demonstrated minimal toxicity at 3 µM, with cell viability exceeding 80% ($p < 0.001$), highlighting their safety for therapeutic investigation.

Structure-activity relationship (SAR) analysis revealed that structural modifications significantly influenced bioactivity. Compounds **1**, **2**, **6**, **13**, **14**, and **15**, which possess an additional methylene group at C-24 of the aglycone, as well as compounds **11** and **12**, which have two sugar moieties, exhibited cytotoxicity or weak inhibition of PGE2 production. Similarly, compounds **3**, **7**, and **8**, which feature additional carbonyl groups at C-3 and C-19, also showed reduced anti-inflammatory activity. In contrast, compounds **4**, **5**, and **10**, which have an α-configuration at C-2 and C-3, methyl groups at C-23 and C-24, fewer sugar moieties, and a lack of carbonyl groups, demonstrated strong anti-inflammatory activity, underscoring the importance of these structural features in enhancing bioactivity. Furthermore, compound **9**, which has a different configuration of the hydroxyl group at C-3 compared to compound **10**, demonstrated decreased anti-inflammatory activity, highlighting the critical role of specific conformations in modulating biological activity.

When compared to known anti-inflammatory drugs such as dexamethasone and rofecoxib, the isolated saponins demonstrated moderate but significant activity. For instance, while dexamethasone reduced PGE2 levels to $182.97 \pm 11.78\%$ ($p < 0.001$) and downregulated COX-2 mRNA expression to $159.29 \pm 13.55\%$ ($p < 0.001$), compound **5** achieved reductions of $229.69 \pm 62.82\%$ ($p < 0.01$) for PGE2 and $259.59 \pm 17.95\%$ ($p < 0.01$) for COX-2 mRNA expression at a concentration of 3 µM. Although these effects were weaker than those of dexamethasone, they are comparable to the activity of rofecoxib in terms of binding affinity to COX-2 and iNOS, as evidenced by molecular docking results. These compounds exhibited interactions with key amino acid residues, suggesting a high binding affinity that may enhance their therapeutic potential. However, this study has limitations, including reliance on a single cell line (RAW 264.7) and the absence of *in vivo* validation, which are critical for assessing translational potential. Additionally, molecular docking simulations, while informative, have limitations such as the lack of solvation effects and dynamic conformational changes, and further experimental validation (e.g. Western blotting or ELISA) is needed to confirm mechanistic insights. Thus, further studies should explore the efficacy of compound **5** in animal models to establish its therapeutic potential and establish its safety and pharmacokinetic profile. Overall, these findings underscore the potential of *E. penduliflora* saponins, particularly compound **5**, as leads for developing novel anti-inflammatory agents.

Disclosure statement

No potential conflict of interest was reported by the authors.

Author contributions

CRediT: **Le Thi Kim Van**: Data curation, Formal analysis, Investigation; **Hoang Thi Dieu Huong**: Investigation; **Vinh Le Ba**: Investigation, Writing – original draft; **Nguyen Viet Phong**: Formal analysis, Investigation, Writing – original draft; **Nguyen Thi Thu**: Investigation; **Vu Thi Diep**: Investigation; **Nguyen Thi Hang**: Investigation; **Nguyen Thi Hong Anh**: Investigation; **Thi Ha Do**: Writing – review & editing; **Viet Dung Le**: Conceptualization, Methodology, Supervision, Writing – review & editing; **Seo Young Yang**: Conceptualization, Methodology, Supervision, Writing – review & editing.

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