Original article

In vitro anti-inflammatory, cytotoxic properties and quantification of total triterpenoids in *Gymnosporia chevalieri* Tard. leaves

Doan Thi Ai Nghia[1,4*], Hoang Thi Nhu Hanh[2], Le Tuan Anh[3], Le Thi Hong Van[4], Nguyen Thi Hoai[1], Ho Viet Duc[1]

[1]Faculty of Pharmacy, University of Medicine and Pharmacy, Hue University

[2]Faculty of Engineering & Food Technology, University of Agriculture and Forestry, Hue University

[3]Mien trung Institute for Scientifc Research, Vietnam National Museum of Nature, VAST

[4]School of Pharmacy, University of Medicine and Pharmacy at Ho Chi Minh City

Abstract

Background: *Gymnosporia chevalieri* is a native species of Vietnam, belonging to the genus *Gymnosporia*, known for its potential anti-inflammatory and cytotoxic properties. **Objectives:** This study is the first report on *in vitro* anti-inflammatory and cytotoxic activities and quantification of total triterpenoids from leaves of *G. chevalieri*. **Materials and methods:** The leaves of *G. chevalieri* were collected from Dakrong district, Quang Tri Province, Vietnam. The extraction procedure involved maceration at room temperature and liquid-liquid partitioning. Anti-inflammatory activity was assessed by measuring the inhibition of nitric oxide (NO) production in RAW 264.7 cells. Anticancer activity was evaluated using a spectrophotometric method with Sulforhodamine B (SRB) dye. Quantification of triterpenoids by UV-Vis. **Results:** Among the tested extracts, the total methanol extract exhibited an inhibitory effect on NO production, with an IC_{50} value of 69.57 ± 2.46 µg/mL, while the *n*-hexane extract showed the strongest anti-inflammatory activity, with an IC_{50} value of 46.92 ± 2.07 µg/mL. The methanol extract exhibited strong inhibitory activity against the cancer cell lines HepG2 (human lung carcinoma), A549 (human cervical carcinoma) and MCF7 (human breast carcinoma); with IC_{50} values of 2.12 ± 0.16, 4.78 ± 0.74 and 28.79 ± 4.21 *µg*/mL, respectively. The *n*-hexane extract demonstrated the most remarkable inhibitory effects against these cell lines, with IC_{50} values of 14.11 ± 2.52; 27.74 ± 3.77 and 18.32 ± 1.77 *µg*/mL, respectively. The *n*-hexane extract contained the highest amount of triterpenoids with equivalent value of 629.76 ± 13.13 mgUA/g extract. **Conclusion:** Both methanol and *n*-hexane extracts of *G. chevalieri* leaves demonstrated significant biological activities, particularly anti-inflammatory and cytotoxic effects. The higher triterpenoid content in the *n*-hexane fraction may contribute to its pronounced bioactivity.

Keywords: *Gymnosporia chevalieri*, *anti-inflammatory, HepG2, A549, total triterpenoid.*

1. INTRODUCTION

The genus *Gymnosporia* (Celastraceae family), comprising approximately 116 species worldwide [1]. Approximately 80 compounds have been isolated from the *Gymnosporia* genus. Triterpenoid is among the key compound groups present in various species of this genus [2-5]. The review also highlights that, this is a group of plants with significant potential for anticancer and anti-inflammatory properties [6-13]. Triterpenoids represent the most structurally diverse group of natural products, and this remarkable diversity underpins their broad range of biological activities including anticancer, hepatoprotective, antidiabetic, anti-inflammatory, antioxidant, and antimicrobial properties; making them highly valuable in pharmaceuticals and industry [14]. Triterpenoids, along with anticancer and anti-inflammatory properties, are key defining features associated with the *Gymnosporia* genus.

Gymnosporia chevalieri ("Loã Châu Chevalier") is one of eight species of *Gymnosporia* genus found in Vietnam [15]. This publication reports for the first time the *in vitro* anti-inflammatory and anti-cancer activities as well as the quantification of total triterpenoids of *G. chevalieri* leaves.

2. MATERIALS AND METHODS

2.1. Materials

The leaves of *G. chevalieri* were collected from Dakrong district, Quang Tri Province, Vietnam, in October 2023 (Figure 1). Sampling coordinates are 16°38'20.8"N 106°48'08.7"E. The plant name was identified by Dr. Anh Tuan Le (Mien trung Institute for Scientific Research, Vietnam National Museum of Nature, VAST, Vietnam). The authenticated sample (GC-01) has been deposited at the Faculty of Pharmacy, Hue University of Medicine and Pharmacy, Hue University, Vietnam.

*Corresponding Author: Doan Thi Ai Nghia. Email: dtanghia@huemed-univ.edu.vn
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Figure 1. *Gymnosporia chevalieri* in the field

2.2. Methods

2.2.1. Herbal extraction

The powdered material was extracted with methanol (MeOH) using maceration at room temperature. The obtained crude extracts were fractionated using liquid-liquid partitioning with *n*-hexane, ethyl acetate (EtOAc). The total extract (GCM) along with the *n*-hexane (GCH), EtOAc (GCE) fractions and the remaining aqueous extract (GCW) were concentrated using rotary evaporation under reduced pressure to fully eliminate the solvent.

2.2.2. Anti-inflammatory and anticancer assays

The extracts were tested for their ability to inhibit LPS-induced NO production in RAW 264.7 cells, with the nitrite concentration in the culture medium, serving as a marker for NO levels, quantified using the Griess assay [16-18]. Additionally, their cytotoxic effects on three human cancer cell lines (HepG2, A549, MCF7) were assessed using the Sulforhodamine B (SRB) assay. The detail protocols have been carefully described in our previous reports [16-17].

2.2.3. Quantification of total triterpenoids

The total triterpenoid content (TPL) was determined according to the previously published method by Lei et al. [19]. First, 0.2 mL of a diluted extract solution was taken, followed by the addition of 0.2 mL of 5% vanillin-acetic acid reagent (w/v) and 1.8 mL of 72% sulfuric acid. The solution was then mixed and incubated in a water bath at 70 °C for 30 minutes. After cooling for 15 minutes, the mixture was adjusted to a final volume of 10 mL with acetic acid. Absorbance was measured at 573 nm using a UV-Vis spectrophotometer. Ursolic acid was used as the standard for the calibration curve [19].

Sample preparation: T - GC: *G.chevalieri* leaf powder (100 mg) was extracted with 2.0 mL of methanol by ultrasonication at 50 °C for 30 min. The mixture was then centrifuged at 4000 rpm for 5 minutes to separate solids. T – GCM, T – GCH, T – GCE, T – GCW: were prepared by dissolving 10 mg of extract GCM, GCH, GCE, GCW (prepared in section 2.2.1) in 2 mL of methanol. The extract was diluted to the appropriate concentration and triterpenoid content was measured via UV-Vis spectroscopy. Each experiment was conducted in triplicate, and the results were expressed as the mean of three replicates with standard deviations within acceptable limits. Total triterpenoid content (TPL) was expressed as milligrams of ursolic acid equivalent per 1 g dry weight for powder samples; or milligrams of ursolic acid equivalent per 1 g extract for extract samples.

3. RESULTS

3.1. Extraction

The dried leaves of *G.chevalieri* were ground into a powder (4 kg). The powdered material was subjected to maceration with MeOH (10 L x 3 times x 7 days), and the solvent was removed under reduced pressure to obtain a total extract (GCM, 930 g). This crude extract was then partitioned with water (2 L) and sequentially extracted with *n*-hexane and EtOAc (each 4 L x 3 times). The solvents were evaporated under reduced pressure to yield the corresponding extracts: *n*-hexane (GCH, 201.8 g), EtOAc (GCE, 97.9 g) and the aqueous extract (GCW, 525 g).

3.2. Anti-inflammatory activity of extracts

Among the extracts, the *n*-hexane extract exhibited the strongest anti-inflammatory activity, with IC_{50} values of 46.92 ± 2.07 µg/mL; while the EtOAc and aqueous extracts showed the weakest activity, with IC_{50} values of 84.44 ± 3.95 and 84.68 ± 4.31 µg/mL, respectively. The total methanol extract also demonstrated inhibitory activity against NO production with IC_{50} values of 69.57 ± 2.46 µg/mL. The positive control Dexamethasone remained stable in the study, with an IC_{50} value of 4.89 ± 0.45 µg/mL (Table 1).

Table 1. Anti-inflammatory activity of *G. chevalieri* leaf extracts

ExtractS	IC_{50} ± SD (µg/mL)	% living cells ± SD (at extract concentration of 100 µg/mL)	% living cells ± SD (at extract concentration of 20 µg/mL)
GCM	69.57 ± 2.46	86.93 ± 2.41	89.41 ± 2.46
GCH	46.92 ± 2.07	87.04 ± 2.20	90.82 ± 3.64
GCE	84.44 ± 3.95	85.56 ± 1.31	90.41 ± 1.94
GCW	84.68 ± 4.31	86.53 ± 1.19	92.97 ± 1.81
Dexamethasone	4.89 ± 0.45	93.71 ± 2.10	98.98 ± 1.17

3.3. Anticancer cell activity of extracts

The total extract exhibited potent inhibitory effects on the cancer cell lines HepG2, A549 and MCF7; with IC_{50} values of 2.12 ± 0.16, 4.78 ± 0.74 and 28.79 ± 4.21 µg/mL, respectively. Among the three fractions tested, the *n*-hexane extract demonstrated stronger inhibitory activity against all three cancer cell lines compared to the EtOAc and aqueous extracts, with IC_{50} values of 14.11 ± 2.52, 27.74 ± 3.77 and 18.32 ± 1.77 µg/mL, respectively. The EtOAc extract showed inhibitory effects on HepG2 and A549 cell lines with IC_{50} values of 49.57 ± 5.68 and 57.83 ± 7.38 µg/mL, respectively; but did not inhibit the MCF7 cell line. The aqueous extract displayed no inhibitory effects on any of the cancer cell lines in this study. The positive control Ellipticine was stable in the study, inhibiting three cancer cell lines HepG2, A549 and MCF7; with IC_{50} values of 0.081 ± 0.005, 0.102 ± 0.005 and 0.095 ± 0.007 µg/mL, respectively (Table 2).

Table 2. Anticancer cell line activity of *G. chevalieri* leaf extracts

Extracts	IC_{50} ± SD (µg/mL)		
	HepG2	A549	MCF7
GCM	2.12 ± 0.16	4.78 ± 0.74	28.79 ± 4.21
GCH	14.11 ± 2.52	27.74 ± 3.77	18.32 ± 1.77
GCE	49.57 ± 5.68	57.83 ± 7.38	> 100
GCW	> 100	> 100	> 100
Ellipticine	0.081 ± 0.005	0.102 ± 0.005	0.095 ± 0.007

3.4. Quantification of total triterpenoids

The leaf powder of *G. chevalieri* extracted by ultrasonic and maceration methods yielded comparable total triterpenoid contents of 58.36 ± 2.13 and 61.39 ± 4.37 mg UA/g dry weight, respectively. In the extracts, the *n*-hexane extract contained the highest amount of triterpenoids with equivalent value of 629.76 ± 13.13 mgUA/g extract. Total triterpenoid content of *G. chevalieri* leaf extracts were shown in Table 3 and Figure 2.

Table 3. Triterpenoid content of extracts from *G. chevalieri*

Sample	Total triterpenoid content (TPL)	
	mgUA/g dry weight	mgUA/g extract
T - GC	58.36 ± 2.13	
T - GCM	61.39 ± 4.37	264.05 ± 18.78
T - GCH		629.76 ± 13.13
T - GCE		223.30 ± 8.45
T - GCW		247.86 ± 20.23

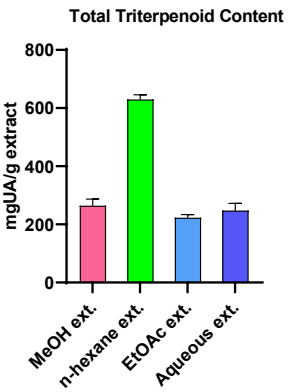

Figure 2. Total triterpenoid content of *G. chevalieri* leaf extracts

4. DISCUSSION

4.1. Anti-inflammatory activity of extracts

The anti-inflammatory activity of *Gymnosporia* species has been studied at both *in vitro* and *in vivo* levels, focusing on extracts and isolated pure active ingredients. The methanol extract of *G. montana* leaves exhibits anti-inflammatory and pain-relieving properties in experimental animals [6]. The methanol extract of *G. senegalensis* root bark, at doses of 400 and 800 mg/kg, reduced mouse paw edema by 51.92 ± 2.34% and 54.66 ± 1.35%, respectively; while the polar fraction, at doses of 200 and 300 mg/kg, demonstrated inhibitory effects of 57.12 ± 3.35% and 58.22 ± 2.90%, respectively [7]. The ethanol extract of *G. senegalensis* exhibited notable anti-inflammatory properties but proved toxic to adult male CD-6 mice at a dose of 1200 mg/kg, which is 10 times higher than the effective anti-inflammatory dose [8].

Compounds isolated from the aerial parts of *G. heterophylla* were tested for *in vitro* anti-inflammatory effects in COX-1 and COX-2 inhibition models, and most of the tested compounds exhibited non-selective inhibitory effects; except for 3-acetoxy-1*β*-hydroxylupe-20(29)-ene, lup-20(29)-ene-1*β*,3*β*-diol which showed selective inhibition of COX-2 at mM concentrations (selectivity index) of 0.54 (1.85) and 0.45 (2.22), respectively. These findings further support the anti-inflammatory properties of this species [20]. In a recent domestic study, acteoside and isoacteoside isolated from *G. stylosa* demonstrated anti-inflammatory activity by inhibiting NO production in RAW264.7 macrophages, with IC_{50} values of 17.8 ± 0.4 µM and 19.3 ± 0.3 µM, respectively [21].

Anti-inflammatory activity has been widely investigated in various species of the genus *Gymnosporia*, and this study is the first to evaluate such activity in extracts of *G. chevalieri*.

4.2. Anticancer cell activity of extracts

The genus *Gymnosporia* is well-known for its notable anticancer activity, with studies exploring this effect conducted on both extracts and purified compounds derived from various species within the genus. In particular, maytansine, a macrolide belonging to the ansamycin group, isolated from *G. diversijolia* and *G. emarginata*, demonstrated strong antitumor activity [9]. In 1979, it entered phase II clinical trials owing to its promising effects on breast carcinoma and melanoma [10].

The methanol extract from *G. diversifolia* showed significant inhibition of P-388 lymphocytic cell growth in BDK mice (treated/control ratio = 180%) at a dose of 50 mg/kg/day [11]. Similar results were also observed for the ethanol extract of *G. trilocularis* [12]. The DMSO and ethanol extracts of *G. senegalensis* were both moderately toxic to U87 glioma cells (U87CD4CXCR4), with CC_{50} values of 70.2 µg/mL and 90.0 µg/mL, respectively [13].

The active ingredient (GCE) from *G. rothiana* showed strong anti-cancer properties by prolonging the "S" phase of the cell cycle, a feature that has been utilized to develop new combination chemotherapy with "S" phase-sensitive drugs [6], [22]. Emargiatine A and emargiatine B, isolated from *G. emarginata*, showed strong inhibitory effects on KB cancer cells (human nasopharyngeal carcinoma), with ED_{50} values of 4.0 to 0.4 µg/mL, respectively [12], [23]. Emarginatine F, a new alkaloid isolated in 1994, showed very strong effects on KB, HCT-8 (human colon adenocarcinoma), P-388 (mouse lymphocytic leukemia), RPMI-7951 (human metastatic melanoma) and TE-671 (human rhabdomyosarcoma) cell lines, with ED_{50} values ranging from < 0.1 to 1.29 µg/mL, but exhibited weaker effects on A549 cells (ED_{50} = 5.5 µg/mL) [24]. Two compounds, (-)-syringaresinol and syringaldehyde, isolated from the CH_2Cl_2-methanol extract of *G. trigyna*, exhibited DNA strand-scission in the presence of Cu^{2+}, suggesting their great potential in the development of anticancer drugs with a mechanism of action similar to bleomycin [25]. Pristimerin, a triterpenoid from the Celastraceae family (e.g., *G. montana*), exhibited anticancer activity against pancreatic cancer cell lines (MiaPaCa-2 and Panc-1) by inducing apoptosis via inhibition of Akt/NF-κB/mTOR signaling and anti-apoptotic Bcl-2 [26], [27]. The compound (2S)-9-benzoyl-1-methyl-2-phenyl-1,5,9-triazacyclotridecan-4-one is a new

alkaloid containing a macrolactam ring, isolated from *G. arenicola* species, showing a stronger inhibitory effect on breast cancer cells (MCF7) than on normal cells (MCF10A) [28]. The compounds quercetin, quercetin 3-O-*α*-L-arabinofuranoside, (2S)-1-O-(4′Z,7′Z,10′Z-octadecatrienoyl)glycerol, *β*-sitosterol, and *β*-sitosterol glucoside, isolated from *G. senegalensis*, at a concentration of 50 µM, showed the ability to reduce the survival rate of cells from weak to moderate in cytotoxicity tests on DLD1 (*colorectal adenocarcinoma*), MCF7 and MKN45 *(gastric adenocarcinoma)* cancer cell lines [29].

The genus *Gymnosporia* holds great potential as a source of anticancer compounds, and preliminary findings from this study indicate that *G. chevalieri* also demonstrates significant anticancer activity, warranting further investigation.

4.3. Quantification of total triterpenoids

We have isolated some pentacyclic triterpenoids from the *n*-hexane fraction including mixture of *α*-amyrin and *β*-amyrin, *β*-amyrenonol, 3-oxofriedelan-29-ol, taraxastane-3*β*,20*R*-diol and taraxastane-3*β*,20*S*-diol [30]. Triterpenoids, especially pentacyclic types, exhibit notable biological effects, including the inhibition of NO production in inflammatory models and the suppression of pro-inflammatory mediator expression in LPS-stimulated macrophages [31]. Moreover, triterpenoids such as ursolic acid, oleanolic acid, and their semi-synthetic derivatives have been reported to exhibit cytotoxic effects against tumor cells by inducing cell cycle arrest, activating apoptotic pathways and inhibiting proliferative signaling cascades, including Akt/mTOR and NF-κB [32]. Therefore, the high triterpenoid content observed in the *n*-hexane extract of *G. chevalieri* may account for its pronounced anti-inflammatory and anticancer activities.

This is the first publication on the total triterpenoid content of *G. chevalieri* leaves.

5. CONCLUSION

This is the first report on *in vitro* anti-inflammatory and anti-cancer activities as well as the quantification of total triterpenoids of *G. chevalieri* leaves. The methanol extract showed NO inhibitory activity (IC_{50} = 69.57 ± 2.46 µg/mL) and strong effects against HepG2, A549 and MCF7 cell lines (IC_{50} = 2.12 ± 0.16, 4.78 ± 0.74 and 28.79 ± 4.21 µg/mL, respectively). Among the fractions, the *n*-hexane fraction was most effective, with the strongest anti-inflammatory activity (IC_{50} = 46.92 ± 2.07 µg/mL) and the best inhibitory effects against HepG2, A549 and MCF7 cell lines (IC_{50} = 14.11 ± 2.52, 27.74 ± 3.77 and 18.32 ± 1.77 µg/mL, respectively). The *n*-hexane fraction exhibited the highest total triterpenoid content, corresponding to 629.76 ± 13.13 mg UA/g extract.. This is reasonable as *G. chevalieri* exhibits potential activity similar to other species in the genus and highlighting the need for further research to identify effective anti-inflammatory and anticancer compounds from this species, especially the triterpenoids.

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