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Volatile Components and Bioactivity of n-Hexane Extract of *Ixeris japonica* Nakai Leaves

Thành phần bay hơi và hoạt tính sinh học của dịch chiết *n*-hexane từ lá của *Ixeris japonica* Nakai

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Abstract

The *n*-hexane extract of *Ixeris japonica* leaves collected in Quang Ngai Province, Vietnam, was chemically characterized by GC–MS and evaluated for α-glucosidase inhibition, nitric oxide (NO) production inhibition, cytotoxicity, and molecular docking. The extract was dominated by two chromene derivatives, precocene I (6-demethoxyageratochromene) (41.8%) and precocene II (ageratochromene) (46.8%), representing the first report of these compounds in the genus *Ixeris*. The extract exhibited strong α-glucosidase inhibitory activity (IC_{50} = 8.61 ± 0.67 μg/mL), markedly more potent than acarbose (IC_{50} = 198.5 ± 6.25 μg/mL). It inhibited NO production in LPS-stimulated RAW 264.7 cells (IC_{50} = 213.33 ± 10.02 μg/mL) without reducing cell viability (>80% at tested concentrations) and showed no cytotoxicity toward KB, HepG2, A549, or HEK293 cells (IC_{50} > 256 μg/mL). Docking suggested that precocene I and II occupy a hydrophobic pocket near the α-glucosidase active site, supporting the observed enzyme inhibition. These findings indicate that *Ixeris japonica* may be a promising natural source of lead compounds for antidiabetic development.

Keywords: Precocene I, precocene II, chromene derivatives, α-glucosidase inhibition, molecular docking

Tóm tắt

Dịch chiết n-hexane từ lá *Ixeris japonica* thu tại tỉnh Quảng Ngãi (Việt Nam) được phân tích thành phần bằng GC–MS và đánh giá ức chế α-glucosidase, ức chế tạo nitric oxide (NO), độc tính tế bào và docking phân tử. Kết quả cho thấy dịch chiết giàu hai dẫn xuất chromene là precocene I (6-demethoxyageratochromene) (41,8%) và precocene II (ageratochromene) (46,8%), lần đầu ghi nhận trong chi *Ixeris*. Dịch chiết ức chế α-glucosidase mạnh (IC_{50} = 8,61 ± 0,67 μg/mL), mạnh hơn acarbose (IC_{50} = 198,5 ± 6,25 μg/mL). Dịch chiết ức chế tạo NO trên tế bào RAW 264.7 kích thích

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LPS (IC_{50} = 213,33 ± 10,02 µg/mL) mà không làm giảm sống sót tế bào (>80%) và không gây độc trên các dòng KB, HepG2, A549 và HEK293 (IC_{50} > 256 µg/mL). Docking cho thấy precocene I và II chiếm một túi kỵ nước gần trung tâm hoạt động của α-glucosidase, phù hợp với kết quả ức chế enzyme. Các dữ liệu cho thấy *Ixeris japonica* có tiềm năng là nguồn hợp chất định hướng phát triển tác nhân hỗ trợ điều trị đái tháo đường.

Từ khóa: precocene I, precocene II, dẫn xuất chromene, ức chế α-glucosidase, docking phân tử

1. Introduction

Globally, diabetes is one of the four major non-communicable diseases, affecting 463 million people (9.3% of the population aged 20–79) in 2019, with the prevalence increasing annually (International Diabetes Federation). According to data from the International Diabetes Federation (IDF), the number of people with diabetes worldwide is estimated to be around 537 million in 2022 and is projected to reach around 643 million (11%) in 2030 [21]. Of these, type 2 diabetes (T2DM) is the most common, accounting for around 90% of the diabetic population and is closely linked to lifestyle factors. Diabetes is associated with many potential health complications, including cardiovascular disease, kidney disease, neuropathy, visual impairment, and foot ulcers. In Vietnam, diabetes mellitus (DM) is increasing by 6.23% per year, causing significant health and economic challenges [10]. Since the 1990s, antidiabetic drugs with the ability to inhibit α-glucosidase, such as acarbose, miglitol, and voglibose, have been commercialized for the treatment of postprandial hyperglycemia. Because the inhibition of α-glucosidase enzymes leads to a delay in glucose production, reducing postprandial hyperglycemia (PPHG) contributes to its therapeutic role in T2DM. However, repeated intake of them will cause bloating, severe stomach discomfort, allergic reactions.

Many studies have shown the promising potential of herbs to support the treatment of T2DM [6,17] through α-glucosidase inhibition. The fact that plant-based preparations have fewer side effects than current conventional drugs, coupled with their lower cost, is encouraging both the general population and national healthcare organizations to consider natural health products as alternatives to synthetic drugs. Therefore, research on compounds derived from traditional medicinal herbs has become increasingly important.

The sage plant, *Ixeris japonica* Nakai, is widely distributed in Vietnam, and is commonly used as a wild vegetable. The availability and ease of cultivation of this species make it a good source of cheap medicinal materials if it has good biological activities. Traditional medicine often uses herbs to treat diabetes in the form of daily decoctions. In this study, we focus on *in-vitro* and *in-silico* α-glucosidase inhibition by *I. japonica* collected in Vietnam to demonstrate the promising potential in diabetes treatment.

2. Materials and methods

2.1. Plant material

Leaves of *Ixeris japonica* were collected in Quang Ngai Province in August 2024. The leaves were chopped, dried in air at 25°C under air conditioning.

2.2. Gas chromatographic-mass spectral analysis

A Shimadzu Technologies GCMS-QP2010 Plus (Shimadzu, Kyoto, Japan), equipped with a fused silica Equity-5 capillary column (30 m × 0.25 mm, film thickness 0.25 µm, Supelco, USA), was used to analyze the chemical composition. The analysis was conducted under the following conditions: helium was used as the carrier gas at a flow rate of 1.5 mL/min. The injector and interface temperatures were set at 270°C. The GC oven temperature was programmed as follows: an initial temperature of 50°C, held for 1.5 min, then increased at

4°C/min to 250°C (held for 9 min), followed by an increase at 5°C/min to a final temperature of 270°C, which was also held for 9 min. A split ratio of 9:1 was applied during sample injection, with an inlet pressure of 93.2 kPa and an injection volume of 1.0 µL.

For mass spectrometry (MS) analysis, the ionization voltage was set at 70 eV, the detector voltage at 0.82 kV, and the mass scan range covered 40–500 amu at a sampling rate of 0.5 scan/s. The retention index (RI) was determined by comparing the obtained data with a homologous series of n-alkanes (C7–C40). Chemical identification was performed by matching the RI values and MS fragmentation patterns of the samples with the published libraries, Adams [1], FFNSC3 [8], NIST20 [12], and Satyal [13] libraries. The relative abundance of each volatile compound was quantified based on the total ion chromatogram (TIC) peak areas.

2.3. Inhibition activity of α-glucosidase enzyme

The method for determining α-glucosidase inhibitory activity was performed on a 96-well plate. The test samples were diluted with DMSO and deionized water into a series of concentrations, with final concentrations in the reaction being 256, 64, 16, 4 and 1 µg/mL, or further diluted for samples with lower activity. Acarbose was used as a positive control.

The reaction components included 100 mM phosphate buffer (pH 6.8), 0.2 U/mL α-glucosidase, the test sample, and 2.5 mM p-nitrophenyl α-D-glucopyranoside. In the control sample, the test sample was replaced with the reaction buffer. The experiment was incubated at 37°C. After 30 minutes, the reaction was terminated by Na_2CO_3. The optical density of the reaction was measured using a BIOTEK spectrophotometer at a wavelength of 410 nm (A).

The percentage inhibition of α-glucosidase activity was calculated using the following equation:

Percentage inhibition (%) = [(ODc– ODs) / ODc] × 100%

Where:

ODc: optical density of the control reaction (without inhibitor)

ODs: optical density of the reaction containing the test sample

The IC_{50} (half-maximal inhibitory concentration), representing the sample concentration that inhibited 50% of α-glucosidase activity, was calculated using TableCurve software. Each concentration was tested in triplicate.

2.4. Cytotoxic activity

The MTT assay was used to evaluate the cytotoxicity of *n*-hexane extract against human cancer cell lines (KB, Hep-G2, and A549) and healthy HEK293 from ATCC. Cells were cultured in DMEM with 10% FBS, 1% Penicillin-Streptomycin, and 1% L-glutamine at 37°C with 5% CO_2. The extract was dissolved in DMSO (20 mg/mL) and diluted to final concentrations of 256, 64, 16, and 4 µg/mL. Cells (3×10^4 cells/mL) were seeded in 96-well plates and treated with different concentrations. After 72 h, MTT solution (10 µL, 5 mg/mL) was added for 4 h, then replaced with 100 µL DMSO. Optical density was measured at 540 nm using a BIOTEK plate reader, and the inhibition ratio was calculated from three replicate tests [11].

2.5. Inhibitory activity of nitric oxide (NO) production

2.5.1. NO production inhibitory activity assay

RAW 264.7 cells were seeded into 96-well plates at a density of 2×10^5 cells/well and incubated at 37°C with 5% CO_2 for 24 hours. The culture medium was then replaced with

DMEM without FBS for 3 hours. Cells were incubated with the test samples at different concentrations for 2 hours before being stimulated with LPS (10 µg/mL) for NO production over 24 h. Nitrite (NO_2^-), an indicator of NO production, was determined using the Griess reagent. Specifically, 100 µL of the culture medium was transferred to a new 96-well plate and mixed with 100 µL of the reagent. The mixture was incubated at room temperature for 10 minutes, and nitrite levels were measured at 540 nm using a spectrophotometer. Wells containing only the culture medium served as the negative control, while wells with LPS-stimulated cells were used as the positive control. L-NMMA was used as the reference compound. The nitrite level of each sample was quantified using a $NaNO_2$ standard curve. The percentage inhibition of NO production was calculated relative to the positive control. The NO production inhibition percentage (IP) was calculated using the formula:

% NO production inhibition = [(ODpc– ODs) / (ODpc – ODnc)] × 100%

Where:

ODpc: optical density of the LPS-stimulated cells (positive control)

ODs: optical density of test sample

ODnc: optical density of unstimulated cells (negative control)

The experiment was repeated three times for accuracy, and the IC_{50} value (concentration inhibiting 50% NO production) was determined using Excel software.

2.5.2. Determination of cell viability

The cells on the plate were incubated with 10 µL of MTT reagent (5 mg/mL). After 4 hours, the medium was removed, and formazan crystals were dissolved in 100 µL of DMSO. The optical density (OD) was measured using a spectrophotometer at a wavelength of 540 nm. Wells containing only the culture medium were considered negative controls, while wells with 100% cell growth were regarded as positive controls.

The test sample concentration with cell viability >80% was used to calculate the NO production inhibition percentage.

2.6. Molecular docking

Molecular docking was carried out using Molegro Virtual Docker (Version 6.0.1, Molegro ApS, Aarhus, Denmark) [16]. The X-ray crystal structures of Saccharomyces cerevisiae α-glucosidase, PDB 3AXI [20] and 3A4A [19], were obtained from the Protein Data Bank (PDB). The water molecules and co-crystallized ligands were removed from the structures and a sphere (15 Å radius) was centered on the binding site of each structure. Standard protonation states at neutral pH were used for the proteins. The structures of the ligands were built using Spartan ’24 for Windows (version 2.0, Wavefunction Inc., Irvine, CA, USA). A total of 50 runs per ligand were carried out and the ligand poses were sorted by MolDock re-rank scores. The re-rank scores were then normalized to account for molecular weight bias using the formula [15]:

DSnorm = 7.2 Edock/MW⅓

Where:

DSnorm is the normalized docking score

Edock is the MolDock re-rank score

MW is the molecular weight

7.2 is a scaling constant

3. Results

3.1. Chemical composition

The chemical composition of the *n*-hexane extract was dominated by two chromene compounds: precocene I (6-Demethoxyageratochromene) (41.8%) and precocene II (ageratochromene) (46.8%) (Table 1).

Chromene compounds have been reported as constituents of essential oils and various extracts from species of the genus *Ageratum* (Asteraceae), with the highest content observed in *Ageratum conyzoides* [9]. This is the first time that precocene I and precocene II compounds are reported in the genus *Ixeris*.

Table 1. Volatile components of the *n*-hexane extract of *Ixeris japonica*

RT (min)	RI(db)	RI(calc)	Compounds	%
4.876	855	877	(2*E*)-Hexenal	tr
4.943	859	878	(3*Z*)-Hexenol	0.1
7.122	932	930	α-Pinene	tr
7.618	946	942	Camphene	0.3
8.586	974	975	β-Pinene	tr
9.059	988	986	Myrcene	0.1
9.452	1001	995	δ-2-Carene	0.3
9.673	1004	1000	(3*Z*)-Hexenyl acetate	0.1
10.549	1024	1020	Limonene	0.1
19.276	1229	1223	Bornyl formate	0.2
21.875	1287	1284	Bornyl acetate	0.7
24.119	1330	1336	Bicycloelemene	tr
25.811	1374	1375	α-Copaene	tr
26.199	1387	1384	β-Bourbonene	tr
26.424	1387	1389	β-Cubebene	0.4
26.501	1389	1391	*trans*-β-Elemene	0.2
27.683	1417	1418	(*E*)-β-Caryophyllene	4.0
28.318	1432	1433	Coumarin	0.2
28.630	1440	1440	(*Z*)-β-Farnesene	0.1
29.090	1454	1452	α-Humulene	0.6
29.265	1454	1456	(*E*)-β-Farnesene	0.1
29.483	1461	1462	Precocene I (6-Demethoxyageratochromene)	41.8
29.754	1465	1468	*cis*-Muurola-4(14),5-diene	0.2
30.254	1484	1481	Germacrene D	0.6
30.370	1486	1484	*trans*-β-Bergamotene	0.2
30.689	1493	1492	*trans*-Muurola-4(15),5-diene	0.3
30.791	1493	1494	*epi*-Cubebol	0.2
30.876	1500	1497	Bicyclogermacrene	0.4
31.011	1500	1500	α-Muurolene	0.1
31.320	1505	1508	β-Bisabolene	0.1
31.933	1521	1523	β-Sesquiphellandrene	1.1
33.476	1561	1562	(*E*)-Nerolidol	0.1
34.134	1577	1578	*trans*-Sesquisabinene hydrate	0.1
34.295	1582	1582	Caryophyllene oxide	0.1
36.810	1646	1646	Desmethoxyencecalin	0.1
37.242	1658	1656	Precocene II (Ageratochromene)	46.8

RIcalc = Retention index determined with respect to a homologous series of n-alkanes on a ZB-5ms column. RIdb = Reference retention index obtained from databases. tr = trace (< 0.05%).

3.2. α-Glucosidase inhibitory activity

The n-hexane extract exhibited excellent α-glucosidase inhibitory activity, with an IC_{50} value of 8.61 ± 0.67 µg/mL.

Table 2. The α-glucosidase inhibitory activity of n-hexane extract from *Ixeris japonica* leaves

Concentration	**n-Hexane extract**	**Acarbose**
	Inhibition percentage (%)	**Inhibition percentage (%)**
256	100	63
64	100	38
16	90	0
4	25	0
1	12	0
IC_{50} value (µg/mL)	**8.61 ± 0.67**	**198.5 ± 6.25**

3.3. Inhibition of nitric oxide production

The *n*-hexane extract inhibited NO production with IC_{50} of 213.33 ± 10.02 µg/mL (Table 3).

Table 3. Inhibitory activity of nitric oxide (NO) production of n-hexane extract

Concentration	***n*-Hexane extract**	**L-NMMA**
	Percentage of surviving cells (%)	**Percentage of surviving cells (%)**
256	100	160
64	100	40
16	100	10
4	100	2.5
IC_{50} (µg/mL)	213.33 ± 10.02	4.08 ± 0.5

3.4. Cytotoxic activity

The n-hexane extract exhibited no cytotoxicity against cancer cell lines (KB, HepG2, A549) or healthy HEK293 cells (IC_{50} > 256 µg/mL) (Table 4).

Table 4. Percentage inhibition of cell lines by *n*-hexane extract

Concentration	**Percentage of cell line inhibition**	**Percentage of cell line inhibition**	**Percentage of cell line inhibition**	**Percentage of cell line inhibition**
	KB	**HepG2**	**A549**	**Healthy Hek293**
256	38	35	30	29
64	15	11	12	11
16	2	0	3	5
4	0	0	0	0
IC_{50}	> 256	> 256	> 256	> 256
Ellipticine (IC_{50})	0.45 ± 0.02	0.45 ± 0.02	0.44 ± 0.02	1.52 ± 0.04

3.5. Molecular docking

In-silico molecular docking revealed both precocene I and precocene II to bind with α-glucosidase with docking scores comparable to the co-crystallized ligand, glucose, but less exothermic than acarbose (Table 5).

Table 5. Molecular docking of precocene I and precocene II to Saccharomyces cerevisiae α-glucosidase

Ligand	MW	Rerank, Edock (kJ/mol)		Normalized, DSnorm (kJ/mol)	
		3AXI	3A4A	3AXI	3A4A
Precocene I	190.238	-67.8	-65.1	-84.9	-81.5
Precocene II	220.264	-66.8	-66.3	-79.6	-79.1
Glucose[a]	180.156	-58.9	-60.7	-75.1	-77.4
Acarbose	645.605	-112.2	-134.2	-93.5	-111.8

[a]: co-crystallized ligand

The precocene ligands occupy a hydrophobic pocket near the active site of α-glucosidase, surrounded by the hydrophobic residues Lys156, Tyr158, Phe314, and Ser240 (Figure 1).

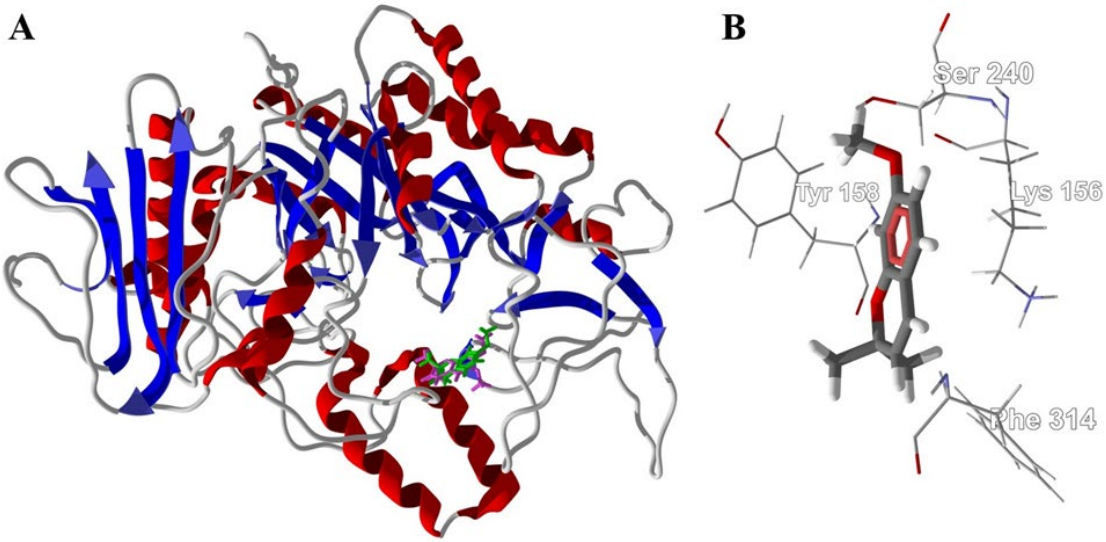


Figure 1. Lowest-energy docked poses of precocene I and precocene II with Saccharomyces cerevisiae α-glucosidase (PDB 3AXI). A: Ribbon structure of α-glucosidase with precocene I (green) and precocene II (magenta) in the binding site. B: Precocene I in the hydrophobic pocket of the binding site of α-glucosidase.

4. Discussion

The α-glucosidase inhibitory activity of *Ixeris japonica* may have been attributed to the presence of precocene I and precocene II. This was supported by the fact that the ethanol extract of *Ixeris japonica*, which lacked these two compounds, exhibited weaker α-glucosidase inhibition than the n-hexane extract. Extracts of Ageratum conyzoides containing chromene compounds have been reported to display anti-diabetic activity in a rat model [18]. Several previous studies have also reported the α-glucosidase inhibitory activity of chromene compounds [3,4].

A large body of evidence has been recorded, indicating that Type 2 diabetes is closely associated with chronic inflammation. These observations have paved the way for the development of new pharmacological strategies aimed at reducing silent inflammation. In addition to specific anti-inflammatory agents, the anti-inflammatory effects of hypoglycemic drugs have also been reported, which may have contributed to improved outcomes in diabetic patients. Diabetic vascular complications have at least partially been mediated by inflammatory processes; therefore, targeting inflammation has been proposed as an approach to prevent, slow down, and mitigate complications such as retinopathy, nephropathy, and cardiovascular disease. The anti-inflammatory effects of glucose-lowering drugs in preventing both

macrovascular and microvascular diabetic complications have been regarded as clinically significant [14].

Ageratum conyzoides essential oil, with a precocene I content of 82.09%, has been proven to exhibit anti-inflammatory activity through the inhibition of the lipoxygenase enzyme at a concentration of 8000 µg/mL, with an inhibition rate recorded at 48.3% [2]. Thus, the anti-inflammatory activity of the extracts has been confirmed to be reliable.

The *Ixeris japonica n*-hexane extract was found to exhibit no cytotoxicity against either healthy cells or cancer cell lines (Table 4). The extract demonstrated anti-inflammatory activity, furthermore it was less toxic to cell lines including healthy Hek293. These results were consistent with the cytotoxicity findings on RAW 264.7 cells (Table 3). A previous study by Li et al. (1999) also reported that the compound precocene II was minimally cytotoxic to human liver cells [7].

5. Conclusion

The n-hexane extract of *Ixeris japonica* was dominated by two chromene compounds, precocene I and precocene II. The extract demonstrated potential α-glucosidase inhibitory activity when compared to the positive control acarbose. In addition, the extract also demonstrated anti-inflammatory activity and showed low toxicity toward tested cell lines, including healthy HEK293 cells. Molecular docking of precocene I and precocene II with α-glucosidase corroborates the α-glucosidase inhibitory activity observed for *I. japonica* hexane extract. Further studies are needed to evaluate the α-glucosidase enzyme inhibitory activity of the two compounds precocene I and precocene II at in-vitro and in-vivo levels to evaluate their potential application in the treatment of diabetes.

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