

**MINISTRY OF EDUCATION
AND TRAINING**

**VIETNAM ACADEMY OF SCIENCE
AND TECHNOLOGY**

ACADEMY OF SCIENCE AND TECHNOLOGY



Le Thi Giang

**"STUDY ON THE CHEMICAL CONSTITUENTS AND
HEPATOPROTECTIVE EFFECTS OF *SYMPLOCOS COCHINCHINENSIS*
(LOUR.) S. MOORE AND *ECLIPTA PROSTRATA* (L.) L."**

SUMMARY OF DOCTORAL THESIS IN MATERIAL SCIENCE

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INTRODUCTION

Studies have shown that many species belonging to the genera *Symplocos* and *Eclipta* are traditionally used for the treatment of tumors, diarrhea, dysentery, menorrhagia, cough, and inflammatory conditions, among others. Phytochemical investigations on species of these two genera have revealed a wide diversity of compound classes, including triterpenoids, flavonoids, phenolics, thiophenes, and more. Research on *S. cochinchinensis* and *E. prostrata* has demonstrated their hepatoprotective potential through anti-inflammatory and antioxidant activities, reduction of hepatic fat accumulation thereby lowering the risk of liver-related diseases-protection of hepatocytes from harmful effects such as toxins and free radicals, and support of liver function. However, *S. cochinchinensis* has been little studied in Vietnam, with only one phytochemical investigation and a few studies on its antioxidant, anti-inflammatory, and α -glucosidase inhibitory activities reported to date.

With the aim of conducting a more in-depth investigation into the chemical constituents and biological activities of *Symplocos cochinchinensis* and *Eclipta prostrata* in Vietnam, we have selected the research topic: **"Study on the chemical constituents and hepatoprotective effects of *Symplocos cochinchinensis* (Lour.) S. Moore and *Eclipta prostrata* (L.) L."**

Research objectives:

To identify the chemical constituents of *S. cochinchinensis* (Lour.) S. Moore and *E. prostrata* (L.) L.

To evaluate the hepatoprotective effects *in vitro* of the extracts and isolated compounds.

Research content:

1. To isolate compounds from the leaves and small branches of *Symplocos cochinchinensis* (Lour.) S. Moore and the aerial parts of *Eclipta prostrata* (L.) collected in Vietnam using chromatographic methods.
2. To elucidate the chemical structures of the isolated compounds by means of physicochemical and spectroscopic techniques.
3. To evaluate the *in vitro* hepatoprotective effects of the extracts and the isolated compounds from *Symplocos cochinchinensis* (Lour.) S. Moore and *Eclipta prostrata* (L.).

CHAPTER 1: RESEARCH OVERVIEW

1.1. Introduction to the genus *Symplocos*

1.1.1. Plant characteristics of the genus *Symplocos*

1.1.2. Introduction to the species *Symplocos cochinchinensis*

Family: Symplocaceae (Dung)

Genus: *Symplocos*

Scientific name: *Symplocos cochinchinensis* (Lour.) S. Moore

Common Vietnamese names: Trà dung, Dung đắng, Bôm, Dung bộp, Dung nam bộ

1.1.3. Research on the chemical composition of the genus *Symplocos*

Chemical composition studies of species within the genus *Symplocos* have shown that they primarily contain compounds from the classes of triterpenoids, flavonoids, iridoids, and lignans.

1.1.4. Research on Biological Activity

Species of the genus *Symplocos* have demonstrated a range of biological activities, including inhibiting the growth of various types of cancer cells, hypoglycemic effects, anti-inflammatory, analgesic, antimicrobial, and antioxidant properties.

1.2. Introduction to the *Eclipta* genus

1.2.1. Botanical characteristics of the *Eclipta* genus

1.2.2. Introduction to *Eclipta prostrata*

Family: Asteraceae (Daisy)

Genus: *Eclipta*

Scientific name: *Eclipta prostrata* (L.) L

Common Vietnamese names: Cỏ nhọ nồi, hàn liên thảo

1.2.3. Research on the chemical composition of *E. prostrata*

A review of research on the *Eclipta* genus shows that most studies focus on *E. prostrata*. This species contains a wide variety of compounds, particularly characterized by thiophene derivatives.

1.2.4. Research on the biological activities of *E. prostrata*

Studies have demonstrated that *E. prostrata* possesses valuable biological activities, such as anti-cancer properties, HIV resistance, hypoglycemic effects, anti-inflammatory properties, pain relief, and liver protection.

CHAPTER 2: RESEARCH SUBJECTS AND METHODS

2.1. Research subjects

2.1.1. *Symplocos cochinchinensis* (Lour.) S. Moore

Leaf and small stem samples of *S. cochinchinensis* (Lour.) S. Moore were collected in June 2022 from Ngọc Thành, Phúc Yên, Vĩnh Phúc, Vietnam.



Figure 2.1. Image of *S. cochinchinensis* (Lour.) S. Moore

2.1.2. *Eclipta prostrata* (L.) L

The above-ground parts of *E. prostrata* (L.) were collected in March 2022 from Khoái Châu, Hưng Yên, Vietnam



Figure 2.2. Image of *E. prostrata* (L.) L.

2.2. Research methods

2.2.1. Isolation of compounds

2.2.2. Structural identification methods

2.2.3. Methods for determining biological activity

The selection of the experimental method is a crucial factor in evaluating the biological activity of plant-derived compounds. In this study, the assay methods were selected according to each plant species, based on the characteristic chemical properties and biological mechanisms of the corresponding compound groups. The compounds isolated from *S. cochinchinensis* are mainly triterpenoid saponins, phenolics, and lignans. These groups of compounds possess antioxidant properties, enzyme - regulating activities, and interact with intracellular metabolic processes. Therefore, the Resazurin reduction assay - which evaluates cellular metabolic activity through the reduction of resazurin to resorufin - was chosen. Compounds isolated from *E. prostrata*,

characterized by thiophenes and coumestans, have been demonstrated to exert hepatoprotective effects against toxic agents and oxidative stress. The MTT assay, which is based on the conversion of MTT to formazan, was selected as a suitable method to assess the ability of these compounds to protect cells from toxicity

2.2.3.1. Methods for assessing hepatocyte viability

Principle: The Resazurin reduction assay was performed to evaluate the effects of the compounds isolated from *S. cochinchinensis* on the viability of HepG2 hepatocytes.

Experiment to determine cell viability

Step 1: Cell culture method

HepG2 liver cells were cultured in high-glucose DMEM medium supplemented with 10% (v/v) fetal bovine serum (FBS) and 100 µg/mL penicillin-streptomycin, under conditions of 37°C and 5% CO₂.

Step 2: Method for determining hepatic cell viability

HepG2 cells were seeded into 96-well plates at a density of 10⁴ cells per well and incubated at 37°C, 5% CO₂ for approximately 15 to 20 hours. The cells were then treated with the test compounds at two concentrations: 1 µM and 10 µM, using high-glucose DMEM medium supplemented with 1% (v/v) FBS and 100 µg/mL penicillin-streptomycin. On the same plate, several wells containing 0.5% (v/v) DMSO were included to assess the maximum viability of the cells (considered 100% viable), and wells containing 0.01% (v/v) Triton X-100 were included to determine the minimum cell viability (complete cytotoxicity). Paracetamol and Silymarin was used as a positive control. After 15 hours of incubation, each well was treated with 20% (v/v) Resazurin reagent (#G8080, Promega, USA) and further incubated for 1.5 hours. The fluorescence intensity of Resorufin was measured at an emission wavelength of 590 nm. Cell viability was calculated using the following formula:

$$\% \text{ Cell Viability} = \frac{\text{OD}_{\text{sample}} - \text{OD}_{\text{Triton X-100}}}{\text{OD}_{\text{DMSO}} - \text{OD}_{\text{Triton X-100}}} \times 100$$

Step 3: Data processing methods

2.2.3.2. Hepatoprotective activity assay

Principle: To evaluate the in vitro hepatoprotective activity of *E. prostrata*, the test samples were assessed using a HepG2 cell culture model in the presence of CCl₄.

Hepatoprotective activity experiment

Step 1: Cell culture method

The HepG2 cell line was cultured in DMEM medium containing 2 mM L-glutamine, 10 mM HEPES, and 1.0 mM sodium pyruvate, supplemented with 10% fetal bovine serum (FBS, GIBCO), under standard conditions at 37°C with 5% CO₂.

Step 2: Method for determining hepatoprotective activity

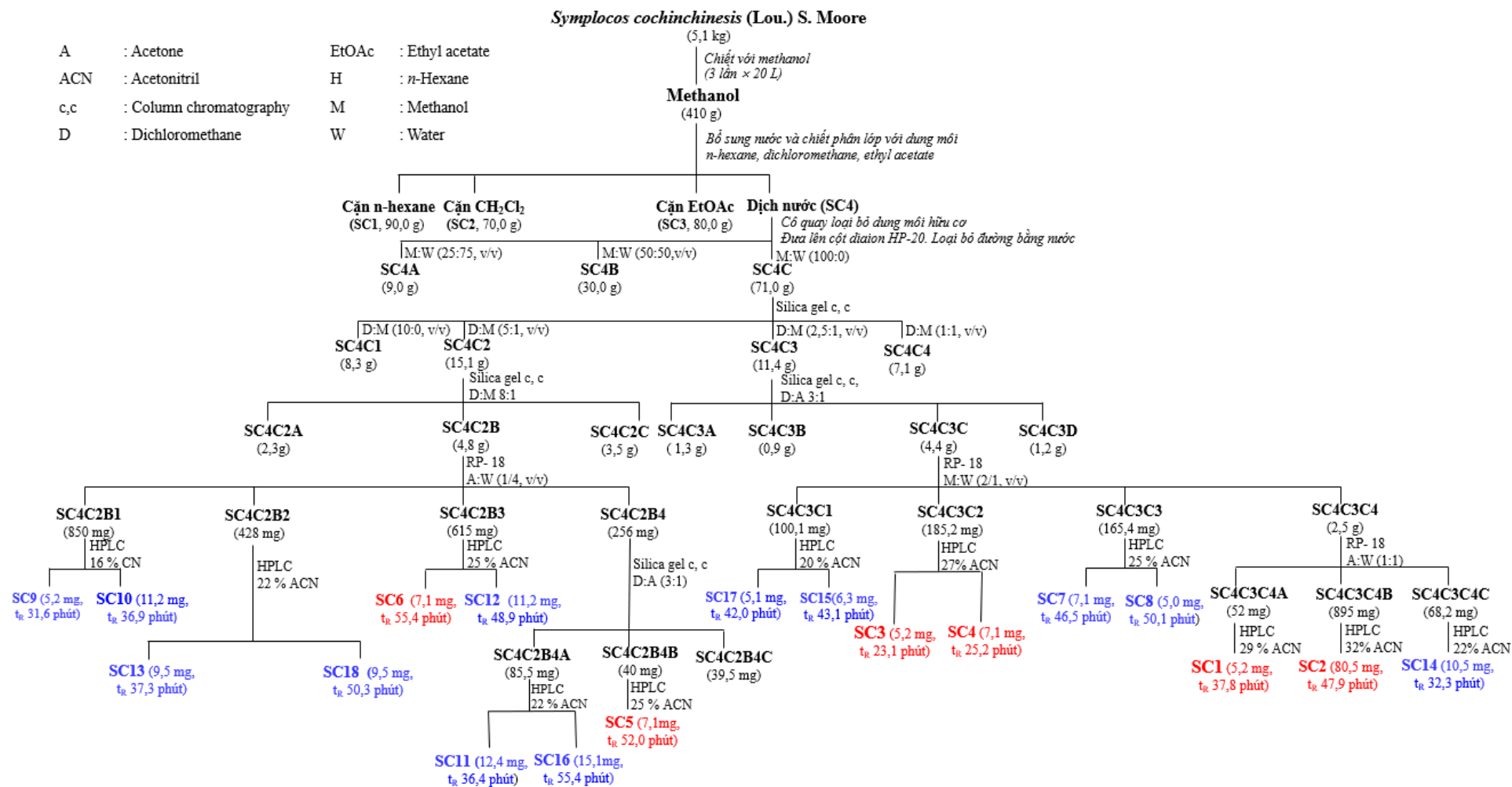
HepG2 cells were seeded into 96-well plates at a density of 3×10^4 cells/well and incubated for 24 hours at 37°C with 5% CO₂. The test samples or the reference compound quercetin were added to the wells at concentrations of 20 µM and 100 µM (for pure compounds), or 20 µg/mL and 100 µg/mL (for crude extracts), in the presence of 40 µM CCl₄. The plates were then further incubated for 2 hours. On the same assay plate, control wells without test samples were also included. Cell viability under CCl₄-induced toxicity was assessed using the MTT assay. After removing the culture medium, 50 µL of MTT solution (1 mg/mL) was added to each well. The plate was incubated at 37°C for 4 hours. The resulting formazan crystals were dissolved in DMSO, and the optical density (OD) was measured at 540 nm. The hepatoprotective effect was calculated using the following formula:

$$\% \text{ Protection} = \frac{OD_{\text{sample}} - OD_{\text{CCl}_4}}{OD_{\text{DMSO}} - OD_{\text{CCl}_4}} \times 100$$

Step 3: Data processing method

2.3. Isolation of compounds

2.3.1. Compounds isolated from *S. cochinchinensis*



2.3.2. Compounds isolated from *E. prostrata*

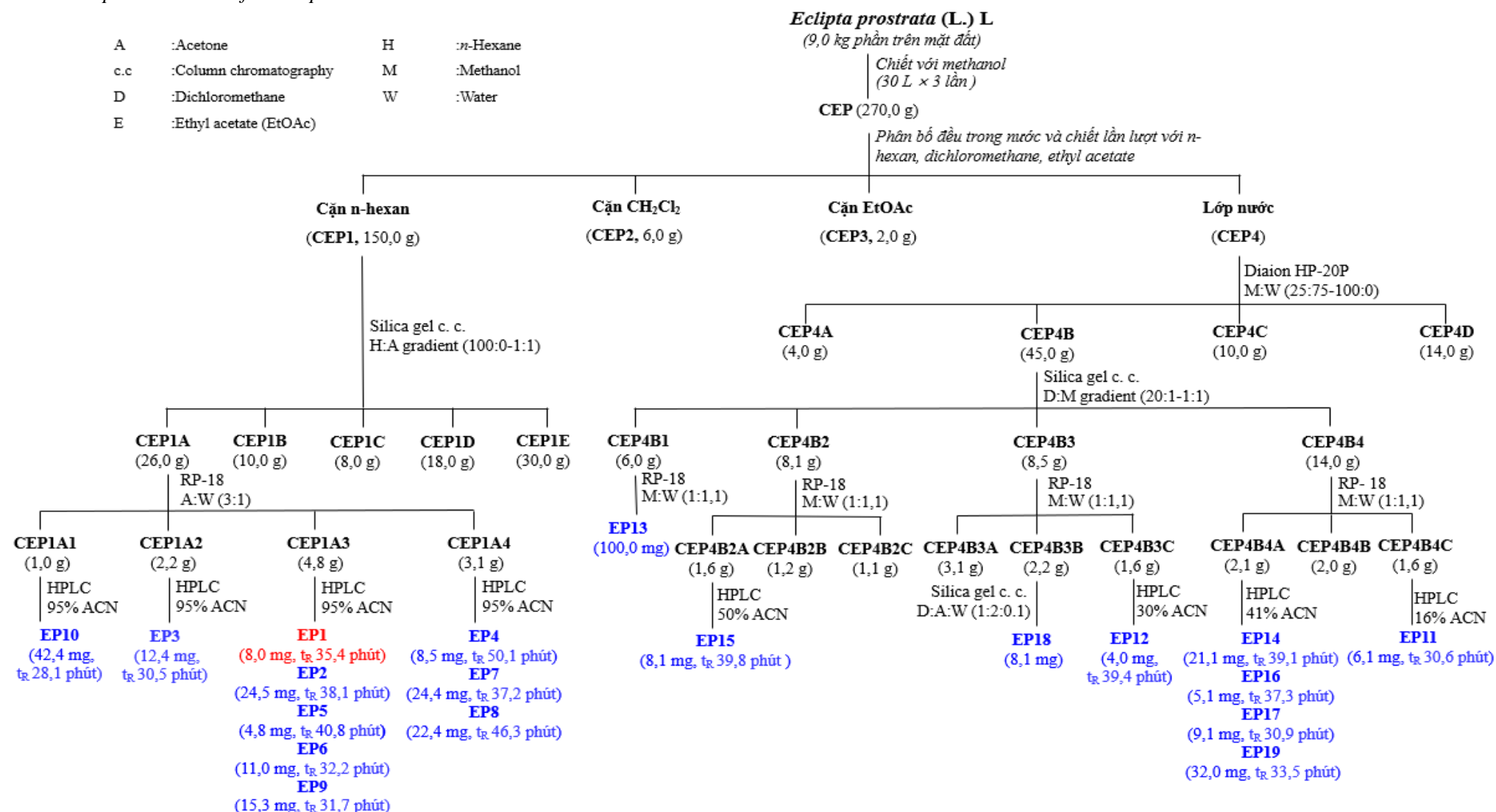


Figure 2.4. Schematic diagram of the isolation of compounds from *Eclipta prostrata*

CHAPTER 3. RESULTS AND DISCUSSION

3.1. Physical parameters and spectral data of the compounds

3.2. Structural elucidation of the isolated compounds

In the search for hepatoprotective compounds from *S. cochinchinensis* and *E. prostrata*, a total of 37 compounds were isolated and structurally elucidated, including:

18 compounds from *S. cochinchinensis*, consisting of:

- Four novel oleanane-type triterpenoid compounds, named symplosaponin A (**SC1**), symplosaponin B (**SC2**), symplosaponin C (**SC3**), and symplosaponin D (**SC4**).
- Ten lignan compounds, including two new compounds, symplolignan A (**SC5**) and symplolignan B (**SC6**), along with eight known compounds: secoisolariciresinol 9'-*O*- β -D-glucopyranoside (**SC11**), matairesinol 4-*O*- β -D-glucopyranoside (**SC12**), nortracheloside (**SC13**), nortrachelogenin 4-*O*- β -D-glucopyranoside (**SC14**), lariciresinol 4'-*O*- β -D-glucopyranoside (**SC15**), balanophonin 4-*O*- β -D-glucopyranoside (**SC16**), dehydrodiconiferyl alcohol 4-*O*- β -D-glucopyranoside (**SC17**), and dihydrodehydrodiconiferyl alcohol 9-*O*- β -D-glucopyranoside (**SC18**).
- Four known phenolic compounds: 1-*O*-[β -D-apiofuranosyl-(1 \rightarrow 6)- β -D-glucopyranosyl]-2-methoxy-4-propenylphenol (**SC7**), 1-*O*-[β -D-xylopyranosyl-(1 \rightarrow 6)-*O*- β -D-glucopyranosyl]-2,6-dimethoxy-4-propenylphenol (**SC8**), 6-*O*-p-coumaroyl- β -D-fructofuranosyl-(2 \rightarrow 1)- α -D-glucopyranoside (**SC9**), and arillatose B (**SC10**).

19 compounds from *E. prostrata*

- 10 thiophene compounds, including one new compound, 5-(but-3-en-1-yn-1-yl)-5'-(methoxymethyl)-2,2'-bithiophene (**EP1**), and 9 known thiophene compounds, including senecioester (**EP2**), tiglinsaurester (**EP3**), 5'-acetoxymethyl-5-(3-butene-1-ynyl)-2,2'-bithiophene (**EP4**), 5-(4-isovaleroyloxybut-1-ynyl)-2,2'-bithiophene (**EP5**), 5-hydroxymethyl-(2,2':5',2'')-terthienyl tiglate (**EP6**), 5-hydroxymethyl-(2,2':5',2'')-terthienyl angelate (**EP7**), 5-hydroxymethyl-(2,2':5',2'')-terthiophene dimethylacrylate (**EP8**), 5-methoxymethyl-2,2':5',2'')-terthiophene (**EP9**), and α -terthiophene (**EP10**).

- 3 known coumestan compounds: wedelolactone (**EP11**), demethylwedelolactone (**EP12**), and 1,3,8,9-tetrahydroxycoumestan 3-sulfate (**EP13**).
- 6 known triterpenoid compounds: eclalbasaponin I (**EP14**), eclalbasaponin II (**EP15**), eclalbasaponin III (**EP16**), eclalbasaponin IV (**EP17**), eclalbasaponin V (**EP18**), and eclalbasaponin VI (**EP19**). The chemical structures of these compounds are presented in Figure 3.2. The chemical structures of these compounds are depicted in Figure 3.1."

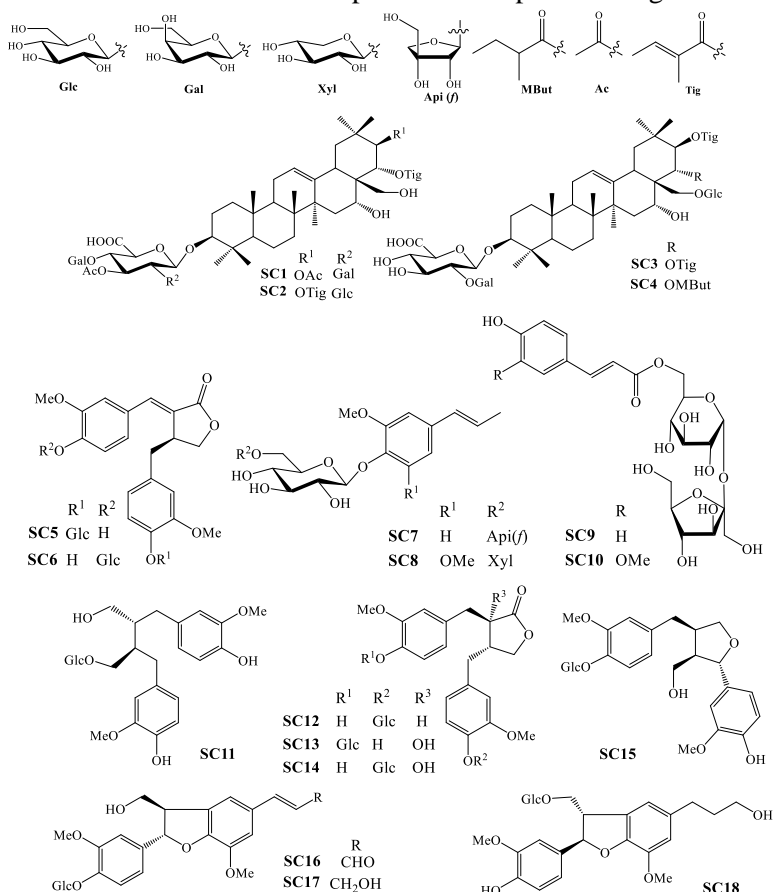


Figure 3.1. Chemical structure of compounds isolated from *S. cochinchinensis* species.

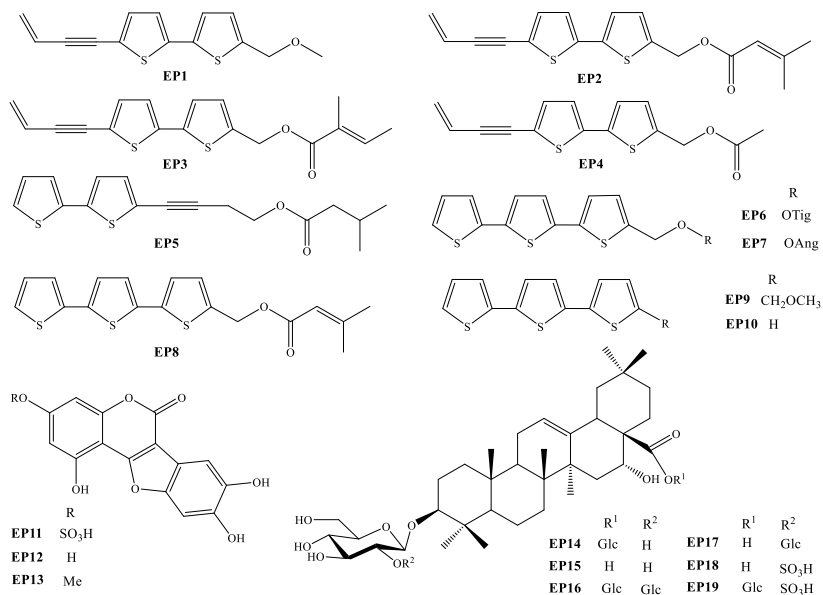


Figure 3.2. Chemical structure of compounds isolated from *E. prostrata* species.

3.2.1. Determination of the structure of compounds isolated from *S. cochinchinensis*

3.2.1.1. Compound **SC1**: Symplosaponin A (new compound)

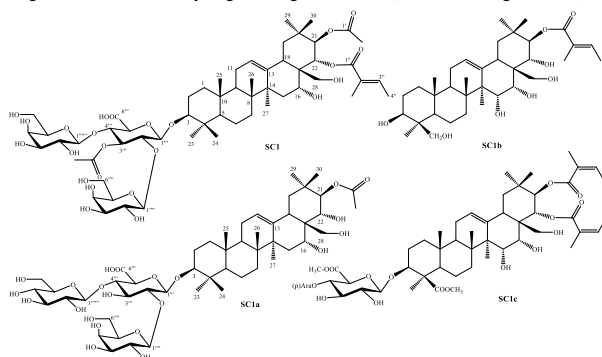


Figure 3.3. The chemical structure of **SC1** and the reference substance.

The compound **SC1** was obtained as a white powder. Its molecular formula was determined to be C₅₇H₈₈O₂₄ based on the pseudo-molecular

ion peak at m/z 1179.5538 $[M+Na]^+$ in the HR-ESI-MS spectrum (theoretically calculated formula for $[C_{57}H_{88}O_{24}Na]^+$, 1179.5558). The 1H -NMR spectrum of **SC1** shows proton signals for seven methyl groups at δ_H 0.88, 0.89, 0.96, 1.00, 1.07, 1.09, and 1.50 (each group, 3H, s), and one olefinic proton at δ_H 5.40 (1H, t, $J = 3.0$ Hz), characteristic of the presence of an oleanane-type triterpene framework. Additionally, there is the presence of another olefinic proton at δ_H 6.92 (1H, dq, $J = 1.8, 7.2$ Hz) and two methyl groups appearing in the high-field region at δ_H 1.81 (3H, dd, $J = 1.8, 7.2$ Hz) and 1.84 (3H, d, $J = 1.8$ Hz), suggesting the presence of a tigloyl group. Two acetyl methyl groups appear at δ_H 1.92 and 2.14 (each group, 3H, s). Three anomeric protons at δ_H 4.37 (1H, d, $J = 6.6$ Hz), 4.41 (1H, d, $J = 7.2$ Hz), and 4.59 (1H, d, $J = 7.8$ Hz) indicate the presence of three monosaccharide units. The relatively large coupling constants (J) suggest that these monosaccharide units are all linked via β -glycosidic bonds. The ^{13}C -NMR and HSQC spectra reveal signals for 57 carbon atoms, including four carbonyl carbons at δ_C 170.1, 172.9, 172.9, and 176.0, eight quaternary carbons at δ_C 36.7, 37.8, 40.4, 41.0, 42.4, 49.0, 129.6, and 143.0, twenty-four methine carbons at δ_C 40.8, 48.0, 57.0, 69.7, 70.1, 70.1, 72.5, 72.7, 74.9, 74.9, 75.2, 76.7, 76.7, 76.8, 77.8, 78.3, 79.4, 80.5, 91.8, 104.5, 105.0, 105.3, 125.3, and 139.3, ten methylene carbons at δ_C 19.3, 24.7, 27.0, 34.0, 34.9, 40.0, 47.8, 62.3, 62.5, and 64.5, and eleven methyl carbons at δ_C 12.1, 14.4, 16.2, 16.9, 17.3, 19.9, 21.0, 21.7, 27.7, 28.4, and 29.5 (Table 3.1). NMR data analysis suggests that the structure of **SC1** is similar to that of aesculiside D (**SC1a**) [114], except for differences in the sugar unit chain at C-3 and the tigloyloxy group at C-22.

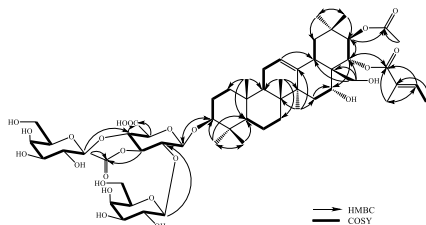


Figure 3.4. Main HMBC and COSY interactions of compound **SC1**.

Table 3.1. NMR spectral data of compound *sc1* and the reference compound

C	$\delta_c^{\#}$	$\delta_c^{a,b}$	$\delta_H^{a,c}$ mult., J=Hz)	C	$\delta_c^{\#}$	$\delta_c^{a,b}$	$\delta_H^{a,c}$ (mult., J=Hz)
1	38,7	40,0	1,01 (m)	21-O-Ac			
			1,63 (m)				
2	26,6	27,0	1,72 (m)	1'	171,4	172,9	-
			1,96 (m)				
3	89,2	91,8	3,22 (dd, 4,8, 11,4)	2'	21,4	21,0	1,92 (s)
4	39,2	40,4	-	22-O-Tig			
5	55,7	57,0	0,80 (br d, 12,0)	1''		170,1	-
6	18,4	19,3	1,42 (m)	2''		129,6	-
			1,59 (m)				
7	33,1	34,0	1,35 (m)	3''		139,3	6,92 (dq, 1,8, 7,2)
			1,62 (m)				
8	40,0	41,0	-	4''		14,4	1,81 (dd, 1,8, 7,2)
9	46,9	48,0	1,70 (m)	5''		12,1	1,84 (d, 1,8)
10	36,7	37,8	-	3-O-GlA			
11	23,8	24,7	1,92 (m)	1'''	105,5	105,3	4,59 (d, 7,8)
12	123,3	125,3	5,40 (t, 3,0)	2'''	82,3	78,3	3,84 (m)
13	143,5	143,0	-	3'''	75,8	76,8	5,21 (t, 9,0)
14	41,8	42,4	-	4'''	81,8	79,4	3,90 (d, 9,6)
15	34,4	34,9	1,37 (m)	5'''	75,5	77,8	3,82 (m)
			1,69 (m)				
16	67,8	69,7	3,97 (br s)	6'''	172,2	176,0	-
17	48,1	49,0	-	2'''-O-Gal I			
18	40,4	40,8	2,64 (br d, 11,4)	1''''	106,7	105,0	4,41 (d, 7,2)
19	47,5	47,8	1,20 (m)	2''''	74,6	72,5	3,47*
			2,68 (d, 11,4)				
20	36,1	36,7	-	3''''	74,8	74,9	3,45 (m)
21	81,9	80,5	5,90 (d, 10,2)	4''''	69,5	70,1	3,82 (br s)
22	72,8	75,2	5,48 (d, 10,2)	5''''	76,9	76,7	3,47*
23	28,0	28,4	1,09 (s)	6''''	61,3	62,5	3,67 (dd, 5,4, 11,4)
							3,76 (m)
24	16,7	16,9	0,89 (s)	3'''-OAc			
25	15,7	16,2	1,00 (s)	1'''''		172,9	-
26	16,9	17,3	0,96 (s)	2'''''		21,7	2,14 (s)
27	27,4	27,7	1,50 (s)	4'''-O-Gal/Glc	Glc	Gal II	
28	66,0	64,5	2,94 (d, 11,4)	1'''''	104,5	104,5	4,37 (d, 6,6)
			3,27 (d, 11,4)				
29	29,8	29,5	0,88 (s)	2'''''	74,8	72,7	3,42 (m)
30	20,2	19,9	1,07 (s)	3'''''	78,0	74,9	3,50 (m)
				4'''''	71,5	70,1	3,82 (br s)
				5'''''	78,7	76,7	3,47*
				6'''''	62,4	62,3	3,67 (dd, 5,4, 11,4)
							3,76 (m)

^aMeasured in CD₃OD, at 150 MHz and 600 MHz
¹³C chemical shifts (δ_c) of aesculiside D (**SC1a**, measured in pyridine-d₅) [114]
Abbreviations: GlA-glucuronopyranosyl, Glc-glucopyranosyl, Gal-galactopyranosyl, Tig tigloyl
Ac - acetyl.*overlapping signals.

Therefore, the substituent group was identified as a tigloyl group, and the position of the tigloyloxy group at C-22 was confirmed by the HMBC interaction from H-22 (δ_{H} 5.48) to C-1'' (δ_{C} 170.1). Hydrolysis of compound **SC1** under acidic conditions yielded monosaccharides. Based on the measurement of specific optical rotation and comparison with reference data, these monosaccharides were identified as D-glucuronic acid and D-galactose. Specifically, D-glucuronic acid exhibited a specific rotation value of +9.9 (c 0.1, H₂O), consistent with the reported value (+10.2) [117]. D-galactose exhibited a specific rotation value of +79.8 (c 0.1, H₂O), in agreement with the reported value (+80.1) [118]. To elucidate the substitution patterns and linkage sequence of the monosaccharide units, HSQC, COSY, and HMBC spectra were recorded, yielding the following characteristic spectral data for D-glucuronic: H-1''' (δ_{H} 4.59)/C-1''' (δ_{C} 105.3), H-2''' (δ_{H} 3.84)/C-2''' (δ_{C} 78.3), H-3''' (δ_{H} 5.21)/C-3''' (δ_{C} 76.8), H-4''' (δ_{H} 3.90)/C-4''' (δ_{C} 79.4), H-5''' (δ_{H} 3.82)/C-5''' (δ_{C} 77.8) và C-6''' (δ_{C} 176.0); the first D-galactose unit: H-1'''' (δ_{H} 4.41)/C-1'''' (δ_{C} 105.0), H-2'''' (δ_{H} 3.47)/C-2'''' (δ_{C} 72.5), H-3'''' (δ_{H} 3.45)/C-3'''' (δ_{C} 74.9), H-4'''' (δ_{H} 3.82)/C-4'''' (δ_{C} 70.1), H-5'''' (δ_{H} 3.47)/C-5'''' (δ_{C} 76.7) và H-6'''' (δ_{H} 3.67 và 3.76)/C-6'''' (δ_{C} 62.5); the second D-galactose unit: H-1''''' (δ_{H} 4.37)/C-1''''' (δ_{C} 104.5), H-2''''' (δ_{H} 3.42)/C-2''''' (δ_{C} 72.7), H-3''''' (δ_{H} 3.50)/C-3''''' (δ_{C} 74.9), H-4''''' (δ_{H} 3.82)/C-4''''' (δ_{C} 70.1), H-5''''' (δ_{H} 3.47)/C-5''''' (δ_{C} 76.7) và H-1''''' (δ_{H} 3.67 và 3.76)/C-6''''' (δ_{C} 62.3). On the other hand, the positions of the two D-galactose units at C-2''' and C-4''' were determined through HMBC correlations between H-1'''' (δ_{H} 4.41) and C-2''' (δ_{C} 78.3), and between H-1''''' (δ_{H} 4.37) and C-4''' (δ_{C} 79.4). The HMBC correlation between H-1''' (δ_{H} 4.59) and C-3 (δ_{C} 91.8) suggested the presence of an O- β -D-galactopyranosyl-(1 \rightarrow 2)-[β -D-galactopyranosyl-(1 \rightarrow 4)]- β -D-(3-acetyl)-glucuronopyranosyl chain linked at the C-3 position (Figure 3.4). The β -configuration of H-16 and H-22 was also established by NOE correlations between H-28 (δ_{H} 2.94 and 3.27) and H-16 (δ_{H} 3.97)/H-22 (δ_{H} 5.48). The α -configuration of H-21 was determined by NOE correlations between H-29 (δ_{H} 0.88) and H-21 (δ_{H} 5.90), and between H-30 (δ_{H} 1.07) and H-22

(δ_{H} 5.48). The α -configuration of H-3 was elucidated by NOE correlations between H-3 (δ_{H} 3.22) and H-5 (δ_{H} 0.80), between H-3 (δ_{H} 3.22) and H-23 (δ_{H} 1.09), as well as between H-24 (δ_{H} 0.89) and H-25 (δ_{H} 1.00) (Figure 3.5). Based on the spectroscopic evidence described above, the structure of **SC1** was determined as 21 β -acetoxy-22 α -tigloyloxy-3 β ,16 α ,28-trihydroxyolean-12-ene 3-*O*- β -D-galactopyranosyl-(1 \rightarrow 2)-[β -D-galactopyranosyl-(1 \rightarrow 4)]- β -D-(3-acetyl)glucuronopyranoside. This is a new compound and was named symplosaponin A (Figure 3.3).

Compound SC2: *Symplosaponin B (new compound)*

Compound SC3: *Symplosaponin C (new compound)*

Compound SC4: *Symplosaponin D (new compound)*

Compound SC5: *Symplolignan A (new compound)*

Compound SC6: *Symplolignan B (new compound)*

Compound SC7: 1-*O*-[β -D-apiofuranosyl-(1 \rightarrow 6)- β -D-glucopyranosyl]-2-methoxy-4-propenylphenol

Compound SC8: 1-*O*-[β -D-xylopyranosyl-(1 \rightarrow 6)-*O*- β -D-glucopyranosyl]-2,6-dimethoxy-4-propenylphenol

Compound SC9: 6-*O*-*p*-coumaroyl- β -D-fructofuranosyl-(2 \rightarrow 1)- α -D-glucopyranoside

Compound SC10: *Arillatose B*

Compound SC11: *Secoisolariciresinol 9'-O- β -D-glucopyranoside*

Compound SC12: *Matairesinol 4-O- β -D-glucopyranoside*

Compound SC13: *Nortracheloside*

Compound SC14: *Nortrachelogenin 4-O- β -D-glucopyranoside*

Compound SC15: *Lariciresinol 4'-O- β -D-glucopyranoside*

Compound SC16: *Balanophonin 4-O- β -D-glucopyranoside*

Compound SC17: *Dehydrodiconiferyl alcohol 4-O- β -D-glucopyranoside*

Compound SC18: *Dihydrodehydrodiconiferyl alcohol 9-O- β -D-glucopyranoside*

Conclusion: Previous global studies have shown that the chemical composition of *S. cochinchinensis* has not been extensively investigated. The compounds isolated so far mainly belong to the triterpenoid class, along with iridoids, lignans, and several other constituents. In our analysis

of the chemical composition of *S. cochinchinensis*, we isolated six new compounds, including four triterpenoids (**SC1–SC4**) and two lignans (**SC5, SC6**). Furthermore, based on a SciFinder search, among the twelve known compounds, eleven were isolated from the *Symplocos* genus for the first time (**SC7, SC9–SC18**), and one compound was isolated from *S. cochinchinensis* for the first time (**SC8**). These findings contribute to enriching the list of newly identified chemical constituents of *S. cochinchinensis*.

3.2.2. Structural elucidation of compounds isolated from *Eclipta prostrata*

3.2.2.1. Compound **EPI**: 5-(but-3-en-1-yn-1-yl)-5'-(methoxymethyl)-2,2'-bithiophene (new compound)

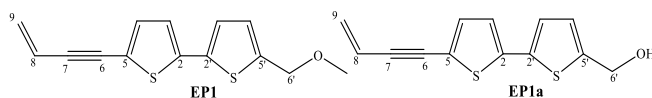


Figure 3.6. Chemical structure of compound **EPI** and the reference compound.

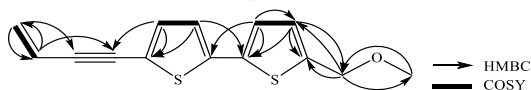


Figure 3.7. Key HMBC and COSY correlations of compound **EPI**.

Compound **EPI** was obtained as a brown oil. Its molecular formula was determined to be $C_{14}H_{12}OS_2$ by HR-ESI-MS spectroscopy, with the appearance of an ion peak at m/z 261.0405 $[M+H]^+$ (theoretical calculation for the formula $[C_{14}H_{13}OS_2]^+$: 261.0402). The 1H -NMR spectrum of **EPI** exhibited signals corresponding to four aromatic protons at δ_H 6.89 (1H, d, $J = 3.6$ Hz), 7.00 (1H, d, $J = 4.2$ Hz), 7.03 (1H, d, $J = 3.6$ Hz), and 7.08 (1H, d, $J = 4.2$ Hz); three olefinic protons of a vinyl group at δ_H 5.55 (1H, dd, $J = 1.8, 11.4$ Hz), 5.72 (1H, dd, $J = 1.8, 17.4$ Hz), and 6.02 (1H, dd, $J = 11.4, 17.4$ Hz); a methylene group directly bonded to an oxygen atom at δ_H 4.58 (2H, s); and a methoxy group at δ_H 3.40 (3H, s). The ^{13}C -NMR and HSQC spectra of **EPI** revealed the presence of 14 carbon atoms, including six non-protonated carbons at δ_C

83.2, 93.1, 121.8, 137.1, 139.0, and 140.8; five methine carbons at δ_C 116.8, 123.5, 123.7, 127.2, and 132.8; two methylene carbons at δ_C 69.1 and 127.0; and one methoxy carbon at δ_C 57.8. Analysis of the NMR spectroscopic data indicated that the structure of **EP1** closely resembled that of 5-(but-3-en-1-yn-1-yl)-5'-hydroxymethyl-2,2'-bithiophene (**EP1a**) (Figure 3.6) [130], except for the addition of a methoxy group in **EP1**. The presence of the bithiophene moiety was confirmed by HMBC correlations between H-3 (δ_H 7.00) and C-2 (δ_C 139.0)/C-4 (δ_C 132.8)/C-5 (δ_C 121.8)/C-2' (δ_C 137.1), and between H-3' (δ_H 7.03) and C-2 (δ_C 139.0)/C-2' (δ_C 137.1)/C-4' (δ_C 127.2)/C-5' (δ_C 140.8), as well as by COSY correlations between H-3 (δ_H 7.00) and H-4 (δ_H 7.08), and between H-3' (δ_H 7.03) and H-4' (δ_H 6.89). HMBC correlations between H-9 (δ_H 5.55 and 5.72) and C-7 (δ_C 93.1)/C-8 (δ_C 116.8), and between H-8 (δ_H 6.02) and C-6 (δ_C 83.2)/C-7 (δ_C 93.1) confirmed the presence of the but-3-en-1-yn-1-yl group. The location of this group at the C-5 position of the bithiophene ring was established by the HMBC correlation between H-4 (δ_H 7.08) and C-6 (δ_C 83.2). Furthermore, HMBC correlations from the methoxy proton (δ_H 3.40) to C-6' (δ_C 69.1), and from H-6' (δ_H 4.58) to C-4' (δ_C 127.2)/C-5' (δ_C 140.8) and the methoxy carbon (δ_C 57.8), confirmed the attachment of a methoxymethyl group at the C-5' position of the bithiophene moiety. Thus, the structure of the new compound **EP1** was elucidated as 5-(but-3-en-1-yn-1-yl)-5'-(methoxymethyl)-2,2'-bithiophene.

Table 3.19. NMR spectral data of compound **EP1** and reference

C	δ_C^a	$\delta_C^{a,b}$	$\delta_H^{a,c}$ (mult., J=Hz)	C	δ_C^a	$\delta_C^{a,b}$	$\delta_H^{a,c}$ (mult., J=Hz)
2'	138,9	137,1	-	4	132,8	132,8	7,08 (d, 4,2)
3'	123,8	123,7	7,03 (d, 3,6)	5	121,9	121,8	-
4'	126,1	127,2	6,89 (d, 3,6)	6	83,1	83,2	-
5'	143,8	140,8	-	7	93,0	93,1	-
6'	60,1	69,1	4,58 (s)	8	116,8	116,8	6,02 (dd, 11,4, 17,4)
2	138,5	139,0	-	9	126,9	127,0	5,55 (dd, 1,8, 11,4)
							5,72 (dd, 1,8, 17,4)
3	123,4	123,5	7,00 (d, 4,2)	6'-OMe		57,8	3,40 (s)

^ađo trong CDCl₃, ^b150 MHz, ^c600 MHz, ^d δ_C của hợp chất 5-(but-3-en-1-yn-1-yl)-5'-hydroxymethyl-2,2'-bithiophene (đo trong CDCl₃).

Compound EP2: *Senecioester*

Compound EP3: *Tiglinsaureester*

Compound EP4: *5'-Acetoxymethyl-5-(3-butene-1-ynyl)-2,2'-bithiophene*

Compound EP5: *5-(4-Isovaleroyloxybut-1-ynyl)-2,2'-bithiophene*

Compound EP6: *5-Hydroxymethyl-(2,2':5',2'')-terthienyl tiglate*

Compound EP7: *5-Hydroxymethyl-(2,2':5',2'')-terthienyl angelate*

Compound EP8: *5-Hydroxymethyl-(2,2':5',2'')-terthiophene dimethylacrylate*

Compound EP9: *5-Methoxymethyl-2,2':5',2'')-terthiophene*

Compound EP10: *α -Terthiophene*

Compound EP11: *1,3,8,9-Tetrahydroxycoumestan 3-sulfate*

Compound EP12: *Demethylwedelolactone*

Compound EP13: *Wedelolactone*

Compound EP14: *Eclalbasaponin I*

Compound EP15: *Eclalbasaponin II*

Compound EP16: *Eclalbasaponin III*

Compound EP17: *Eclalbasaponin IV*

Compound EP18: *Eclalbasaponin V*

Compound EP19: *Eclalbasaponin VI*

Conclusion: *E. prostrata* has been found to contain a wide variety of compounds, notably thiophenes—a rare class of natural products in other plant species. In our study, consistent with previous findings, we isolated 19 compounds, including one new thiophene (**EP1**) and eighteen known compounds (**EP2–EP19**), which fall into three main groups: nine thiophenes, three coumestans, and six triterpenoids. Notably, compounds **EP2**, **EP3**, and **EP9** are reported here for the first time with their NMR spectroscopic data, and compounds **EP11–EP13** have previously been reported to possess significant anti-inflammatory and hepatoprotective activities.

3.3. Results of biological activity evaluation

3.3.1. Evaluation of the viability of hepatocyte cells from *S. cochinchinensis*

The compounds isolated from the leaves of *S. cochinchinensis* (**SC1-SC18**) were assessed for hepatocyte cell viability in vitro using the HepG2 cell line at concentrations of 1 μ M, and 10 μ M.

Table 3.2. Results of the assessment of the viability of liver cells of the species *S. cochinchinensis*.

Compound	Concentration ^s		Compound	Concentration ^s	
	1 μ M	10 μ M		1 μ M	10 μ M
SC1	91.1 \pm 3.3	75.9 \pm 3.3	SC10	88.5 \pm 1.0	87.4 \pm 1.9
SC2	82.5 \pm 4.4	56.1 \pm 2.8	SC11	108.1 \pm 3.1**	107.4 \pm 0.9*
SC3	89.5 \pm 1.6	83.7 \pm 2.6	SC12	107.9 \pm 1.9	109.2 \pm 3.3
SC4	85.9 \pm 8.3	84.7 \pm 4.4	SC13	102.2 \pm 3.5	106.5 \pm 2.0
SC5	105.4 \pm 2.9	107.4 \pm 0.4	SC14	86.8 \pm 4.0	88.3 \pm 4.6
SC6	90.1 \pm 0.9	82.8 \pm 3.8	SC15	90.7 \pm 1.4	90.7 \pm 1.0
SC7	107.3 \pm 6.0	103.6 \pm 6.6	SC16	103.9 \pm 1.6	105.0 \pm 2.6
SC8	108.7 \pm 2.9	111.4 \pm 2.2*	SC17	105.5 \pm 1.7	106.5 \pm 1.5
SC9	98.3 \pm 1.5	100.7 \pm 1.6	SC18	95.7 \pm 1.7	87.4 \pm 2.2
Mẫu trắng	100.0 \pm 6.0				
Silymarin	106.0 \pm 2.9				

^s% cell viability at experimental concentration, * P <0.1 and ** P <0.01 indicate significant differences compared to control, [#]concentration 6.32 μ M

The study results showed that the two phenolic compounds **SC7** and **SC8**, together with six lignan compounds **SC5**, **SC11**, **SC12**, **SC13**, **SC16**, and **SC17**, were able to increase the viability of HepG2 hepatocytes (above 100%), indicating a positive biological effect on healthy liver cells. Notably, **SC8**, **SC11**, and **SC12** exhibited consistent and pronounced effects, with **SC8** showing the strongest activity at a concentration of 10 μ M, achieving a viability of 111.4%, surpassing both silymarin (106.0%) and the control (100%). In addition, **SC7**, **SC11**, and **SC12** also demonstrated effects comparable to Silymarin at 1 μ M. Compared with Paracetamol (89.2%), these compounds not only

protected hepatocytes from toxicity but could also support the recovery or stimulate the growth of healthy cells. Therefore, further studies are warranted to investigate the effects of **SC7**, **SC8**, **SC11**, and **SC12** on hepatocyte viability.

3.3.2. Results of evaluating the hepatoprotective activity of *E. prostrata*

Based on the evaluation of the hepatoprotective activity of the extract residues, 19 compounds were isolated with a focus on biological activity from *E. prostrata*. The results of the in vitro evaluation of the hepatoprotective potential on the HepG2 cell line of the extract residues and the isolated compounds (**EP1-EP13**) at concentrations of 20 μ M and 100 μ M (for pure compounds) and 20 μ g/mL and 100 μ g/mL (for extract residues) are presented in Table 3.3.

Table 3.3. Results of evaluation of hepatoprotective activity of *E. prostrata*

Compound	% protection		Compound	% protection	
	Concentration 20 ^{a,b}	Concentration 100 ^{a,b}		Concentration 20 ^{a,b}	Concentration 100 ^{a,b}
EP1	17.97 \pm 0.94	25.38 \pm 1.75	EP11	15.97 \pm 1.01	38.68 \pm 1.57
EP2	12.92 \pm 0.37	10.06 \pm 0.47	EP12	22.7 \pm 1.50	48.54 \pm 1.22
EP3	19.96 \pm 0.94	28.87 \pm 0.23	EP13	20.67 \pm 1.94	45.16 \pm 1.31
EP4	17.19 \pm 1.17	21.98 \pm 2.03	MeOH	12.25 \pm 0.94	20.74 \pm 1.24
EP5	13.19 \pm 0.76	12.49 \pm 1.34	<i>n</i>-hexane	5.86 \pm 0.68	10.67 \pm 1.16
EP6	9.06 \pm 0.69	15.58 \pm 1.33	CH₂Cl₂	14.92 \pm 1.07	27.34 \pm 1.34
EP7	13.04 \pm 0.47	18.51 \pm 0.23	EtOAc	15.14 \pm 1.01	32.33 \pm 1.20
EP8	15.69 \pm 0.94	17.37 \pm 0.70	H₂O	16.69 \pm 1.33	21.59 \pm 1.89
EP9	6.41 \pm 0.39	17.13 \pm 1.76	Quercetin	31.39 \pm 1.22	72.31 \pm 3.70
EP10	12.38 \pm 0.47	15.20 \pm 0.70			

^aconcentration in μ M for pure compounds, and concentration in μ g/mL for extract residues.

The results of the evaluation of hepatoprotective activity showed that the MeOH extract exhibited moderate hepatoprotective effects, with a protection rate of 20.74% at a concentration of 100 μ g/mL. The EtOAc fraction demonstrated the highest hepatoprotective activity, with a protection rate of 32.33%, followed by the CH₂Cl₂ fraction and the aqueous extract, with protection rates of 27.34% and 21.59%, respectively. However, the EtOAc and CH₂Cl₂ fractions were not further

investigated due to the limited quantity of the extracts. At a concentration of 100 μ M, the bithiophene compounds **EP1**, **EP3**, and **EP4** exhibited moderate hepatoprotective activities, with protection rates of 25.38%, 28.87%, and 21.98%, respectively. In contrast, the coumestan-based compounds **EP11–EP13** demonstrated the highest hepatoprotective effects, with protection rates of 38.68%, 48.54%, and 45.16%, respectively.

CONCLUSIONS AND RECOMMENDATIONS

CONCLUSIONS

1. From *Symplocos cochinchinensis* collected in Vĩnh Phúc and *Eclipta prostrata* collected in Hưng Yên, after processing, extraction, and isolation using chromatographic techniques and modern spectroscopic methods, combined with comparison of spectral data with related compounds reported in the literature, we have achieved the following results:

- Eighteen compounds were isolated and structurally elucidated from *S. cochinchinensis*. Among them, six are newly identified compounds: symplosaponin A (**SC1**), symplosaponin B (**SC2**), symplosaponin C (**SC3**), symplosaponin D (**SC4**), symplolignan A (**SC5**), and symplolignan B (**SC6**), along with twelve previously known compounds (**SC7–SC18**). Notably, eleven compounds were isolated for the first time from the genus *Symplocos*, including 1-*O*-[β -D-apiofuranosyl-(1 \rightarrow 6)- β -D-glucopyranosyl]-2-methoxy-4-propenylphenol (**SC7**), 6-*O*-p-coumaroyl- β -D-fructofuranosyl-(2 \rightarrow 1)- α -D-glucopyranoside (**SC9**), arillatose B (**SC10**), secoisolariciresinol 9'-*O*- β -D-glucopyranoside (**SC11**), matairesinol 4-*O*- β -D-glucopyranoside (**SC12**), nortracheloside (**SC13**), nortrachelogenin 4-*O*- β -D-glucopyranoside (**SC14**), lariciresinol 4'-*O*- β -D-glucopyranoside (**SC15**), balanophonin 4-*O*- β -D-glucopyranoside (**SC16**), dehydrodiconiferyl alcohol 4-*O*- β -D-glucopyranoside (**SC17**), and dihydrodehydrodiconiferyl alcohol 9-*O*- β -D-glucopyranoside (**SC18**), along with one compound first isolated from *S. cochinchinensis*: 1-*O*-[β -D-xylopyranosyl-(1 \rightarrow 6)- β -D-glucopyranosyl]-2,6-dimethoxy-4-propenylphenol (**SC8**).

- Nineteen compounds were isolated and structurally elucidated from *E. prostrata*, including one new compound, 5-(but-3-en-1-yn-1-yl)-5'-(methoxymethyl)-2,2'-bithiophene (**EP1**), and eighteen known compounds (**EP2–EP19**). Notably, the NMR spectral data for three compounds, namely senecioester (**EP2**), tiglinsaurester (**EP3**), and 5-methoxymethyl-2,2':5',2''-terthiophene (**EP9**), were reported for the first time.

2. The effects of the isolated compounds from *S. cochinchinensis* on hepatocyte viability and the hepatoprotective activity of *E. prostrata* on HepG2 cells were evaluated. The results are as follows:

- For *S. cochinchinensis*, compounds **SC7**, **SC8**, **SC11**, and **SC12** demonstrated stabilizing effects on liver function. At a concentration of 10 μM , compound **SC8** exhibited the most potent activity, enhancing hepatocyte viability to 111.4%. Meanwhile, at a concentration of 1 μM , compounds **SC7**, **SC11**, and **SC12** increased hepatocyte viability to 107.3%, 108.1%, and 107.9%, respectively. In addition, compounds **SC5**, **SC13**, **SC16**, and **SC17** also showed significant enhancement of HepG2 cell viability.

- For *E. prostrata*, at a concentration of 100 $\mu\text{g/mL}$, the EtOAc and CH_2Cl_2 extracts exhibited the highest hepatoprotective activities, with protection rates of 32.3% and 27.34%, respectively. The MeOH extract and aqueous extract showed moderate hepatoprotective activities with protection rates of 20.74% and 21.59%, respectively. At a concentration of 100 μM , compounds **EP11–EP13** demonstrated the highest hepatoprotective effects, with protection rates of 38.68%, 48.54%, and 45.16%, respectively.

RECOMMENDATIONS

Studies on the chemical composition and biological activities of *S. cochinchinensis* and *E. prostrata* have contributed to the identification of new compounds, thereby enriching the chemical profiles of these species. Notably, biological activity assays of compounds **SC7**, **SC8**, **SC11**, and **SC12** demonstrated stabilizing effects on liver function. Therefore, it is recommended to conduct further in vivo experiments to comprehensively

evaluate these effects and to explore the potential applications of these compounds.

NEW CONTRIBUTIONS OF THE DISSERTATION

1. Isolation and structural elucidation of compounds from *Symplocos cochinchinensis* (Lour.) S. Moore and *Eclipta prostrata* (L.) L.

For *Symplocos cochinchinensis* (Lour.) S. Moore: Six new compounds were isolated and structurally elucidated, namely symplosaponin A (**SC1**), symplosaponin B (**SC2**), symplosaponin C (**SC3**), symplosaponin D (**SC4**), symplolignan A (**SC5**), and symplolignan B (**SC6**).

In addition, eleven compounds were isolated and reported for the first time from the genus *Symplocos*, including 1-O-[β -D-apiofuranosyl-(1 \rightarrow 6)- β -D-glucopyranosyl]-2-methoxy-4-propenylphenol (**SC7**), 6-O-*p*-coumaroyl- β -D-fructofuranosyl-(2 \rightarrow 1)- α -D-glucopyranoside (**SC9**), arillatose B (**SC10**), secoisolariciresinol 9'-O- β -D-glucopyranoside (**SC11**), matairesinol 4-O- β -D-glucopyranoside (**SC12**), nortracheloside (**SC13**), nortrachelogenin 4-O- β -D-glucopyranoside (**SC14**), lariciresinol 4'-O- β -D-glucopyranoside (**SC15**), balanophonin 4-O- β -D-glucopyranoside (**SC16**), dehydrodiconiferyl alcohol 4-O- β -D-glucopyranoside (**SC17**), and dihydrodehydrodiconiferyl alcohol 9-O- β -D-glucopyranoside (**SC18**).

Furthermore, one compound, 1-O-[β -D-xylopyranosyl-(1 \rightarrow 6)-O- β -D-glucopyranosyl]-2,6-dimethoxy-4-propenylphenol (**SC8**), was isolated and reported for the first time from the species *S. cochinchinensis*.

For *Eclipta prostrata* (L.): One new compound, 5-(but-3-en-1-yn-1-yl)-5'-(methoxymethyl)-2,2'-bithiophene (**EP1**), was isolated and structurally elucidated.

In addition, NMR spectroscopic data of three compounds, namely senecioester (**EP2**), tiglinsaurester (**EP3**), and 5-methoxymethyl-2,2':5',2''-terthiophene (**EP9**), were reported for the first time.

2. Evaluation of hepatoprotective effects *in vitro*

For *Symplocos cochinchinensis* (Lour.) S. Moore: Eight compounds, including symplolignan A (**SC5**), 1-O-[β -D-apiofuranosyl-

(1→6)-β-D-glucopyranosyl]-2-methoxy-4-propenylphenol (**SC7**), 1-O-[β-D-xylopyranosyl-(1→6)-O-β-D-glucopyranosyl]-2,6-dimethoxy-4-propenylphenol (**SC8**), secoisolariciresinol 9'-O-β-D-glucopyranoside (**SC11**), matairesinol 4-O-β-D-glucopyranoside (**SC12**), nortracheloside (**SC13**), balanophonin 4-O-β-D-glucopyranoside (**SC16**), and dehydrodiconiferyl alcohol 4-O-β-D-glucopyranoside (**SC17**), were found to increase the viability of HepG2 hepatocytes compared with the control group (over 100%). Among these, compounds **SC7**, **SC8**, **SC11**, and **SC12** exhibited pronounced hepatoprotective effects, contributing to the stabilization and improvement of hepatic cell function comparable to, or stronger than, that of the reference compound silymarin (106.0%). In particular, at a concentration of 10 μM, compound **SC8** demonstrated the highest hepatocyte viability, reaching 111.4%.

For *Eclipta prostrata* (L.): The hepatoprotective activities of the extracts and isolated compounds were evaluated against CCl₄-induced cytotoxicity. The results indicated that, at a concentration of 100 μg/mL, the EtOAc and CH₂Cl₂ extracts exhibited the strongest hepatoprotective effects, with protection rates of 32.33% and 27.34%, respectively. Among the isolated compounds, the coumestans wedelolactone (**EP11**), demethylwedelolactone (**EP12**), and 1,3,8,9-tetrahydrocoumestan 3-sulfate (**EP13**) displayed the most potent hepatoprotective effects at 100 μM, with protection rates of 38.68%, 48.54%, and 45.16%, respectively. Several bithiophene derivatives, including 5-(but-3-en-1-yn-1-yl)-5'-(methoxymethyl)-2,2'-bithiophene (**EP1**), tiglinsaurester (**EP3**), and 5'-acetoxymethyl-5-(3-butene-1-ynyl)-2,2'-bithiophene (**EP4**), also exhibited moderate hepatoprotective activities, with protection rates ranging from 21.98% to 28.87%.

3. For the first time, this study directly evaluated the *in vitro* effects of compounds isolated from *Symplocos cochinchinensis* on the viability of HepG2 hepatocytes.

LIST OF PUBLISHED WORKS

1. **L.T. Giang**, S. Lee, Y. Seo, N.T. Cuong, B.H. Tai, P. Van Kiem, N.T.M. Hang, N.T.T. Oanh, P. Van Cuong, N.K. Ban, S. Park, N.X. Nhiem, *Symplosaponins A–D: New acylated oleanane-type triterpene saponins from *Symplocos cochinchinensis* and their hepatoprotective effect*, Fitoterapia, 2024, Article 106056.
2. **L.T. Giang**, S. Park, S. Lee, Y. Seo, P. Van Kiem, B.H. Tai, N.T.M. Hang, V.M. Thao, P. Van Cuong, N.K. Ban, N.X. Nhiem, *Hepatoprotective lignan glycosides from the leaves and stems of *Symplocos cochinchinensis* (Lour.) S. Moore*, Chemistry & Biodiversity, 2024, 21, e202400896.
3. **L.T. Giang**, S. Park, N.T. Cuc, B.H. Tai, P.V. Kiem, N.T.M. Hang, N.K. Ban, P.V. Cuong, N.X. Nhiem, *Bithiophene and coumestan derivatives from *Eclipta prostrata* (L.) L. and their hepatoprotective activity*, Journal of Asian Natural Products Research, 2024, 1–7.
4. **Le Thi Giang**, Vu Mai Thao, Nguyen Tu Oanh, Vu Phuong Nhung, Nguyen Thi Minh Hang, Ninh Khac Ban, Nguyen Xuan Nhiem, *Review: The traditional uses, secondary metabolites, and pharmacology of *Symplocos* species*, Vietnam Journal of Science and Technology, 63(5) (2025) 823–848.
5. **Le Thi Giang**, Nguyen Xuan Nhiem, Ninh Khac Ban, Nguyen Thi Anh Tuyet, *Lignan compounds from the leaves of *Symplocos cochinchinensis**, TNU Journal of Science and Technology, 2024, 10, 344–349.