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ORIGINAL ARTICLE

Nitric oxide inhibitory compounds from Thai medicinal plants *Averrhoa bilimbi* and *Schinus terebinthifolia*

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ABSTRACT: Nitric oxide (NO) overproduction by activated macrophages drives inflammatory responses *via* iNOS activation, prompting the search for natural NO inhibitors. A bioassay-guided investigation targeting NO inhibition was conducted on *Averrhoa bilimbi* and *Schinus terebinthifolia*, two Thai medicinal plants. The most active fractions, derived from the branches of *A. bilimbi* and the stems of *S. terebinthifolia*, were subjected to chemical analysis. Seventeen compounds were isolated, five (**ABS1–ABS5**) from *A. bilimbi* and twelve (**ST1–ST12**) from *S. terebinthifolia*, with bilimoside A (**ABS1**) identified as a new compound. Structural elucidation of all isolated compounds was accomplished through detailed spectroscopic analysis, including NMR and HRESIMS. Their *in vitro* NO inhibitory activity was evaluated, revealing 3-oxoursolic acid (**ST2**) as the most potent compound (IC_{50} 28.00 µg/mL), surpassing the positive control L-NMMA (IC_{50} 41.30 µg/mL), while exhibiting minimal cytotoxicity. These findings suggest that **ST2** could serve as a promising candidate for further development as an anti-inflammatory agent.

Keywords: *Averrhoa bilimbi*, *Schinus terebinthifolia*, bilimoside A, nitric oxide inhibition

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1 Introduction

Averrhoa bilimbi L. is an edible plant with diverse traditional medicinal uses. In India, its fruit has been employed for antidiabetic (Kurup & M, 2017) and anti-obesity purposes (Alhassan & Ahmed, 2016; Seebaluck-Sandoram, 2019), as well as for treating whooping cough, acne, and hypertension (Alhassan & Ahmed, 2016). The leaves are traditionally used for fever and skin infections, recognized for their antiscorbutic and astringent properties (Alhassan & Ahmed, 2016; Seebaluck-Sandoram, 2019). Fruit decoctions are applied in the treatment of hepatitis, fever, and diarrhea (Seebaluck-Sandoram, 2019). Despite its ethnopharmacological significance, its phytochemical profile remains incompletely characterized. An Indonesian study reported 15 compounds from the leaves, including two novel flavonoid glycosides with potent CYP3A4 and CYP2D6 inhibitory activity (Auw et al., 2015). In India, myricetin and dihydromyricetin were identified *via* HPLC from various plant parts (Kurian et al., 2018; Chau et al., 2023), and GC-MS has been used to analyze volatile constituents (Wong & Wong, 1995; Pino et al., 2004). Biological studies report

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antioxidant (Fidrianny et al., 2018; Rosyada et al., 2023), xanthine oxidase inhibitory (Ahmed et al., 2018), antibacterial (Siddique, 2013; Iwansyah et al., 2021; Mohammed Atiyah et al., 2022), cytotoxic (Seebaluck-Sandoram, 2019), and thrombolytic activities (Mokhtar & Aziz, 2016). *In vivo* evaluations support its antidiabetic (Kurup & M, 2017) and anti-ulcerative colitis potential (Suluvoy et al., 2017). Furthermore, ethanol extract has been shown to enhance serum nitric oxide (NO) levels and vasodilation in hypertensive rats (Solfaine et al., 2021).

Schinus terebinthifolia Raddi (Brazilian peppertree), a perennial species in the Anacardiaceae family, is native to South America and traditionally used to treat inflammation, infections, and gastrointestinal issues. It contains essential oils, polyphenols, flavonoids, and lectins across various plant organs (Dettweiler et al., 2020; Alqathama et al., 2023; Abbas et al., 2024), exhibiting antimicrobial, antioxidant, anti-inflammatory, insecticidal, and cytotoxic properties. The fruits and leaves show strong antioxidant (Guimarães et al., 2023) and antibacterial activity, including against multidrug-resistant strains (Dettweiler et al., 2020; Blandón Pardo et al., 2024), and lectins contribute to immunomodulation (de Lima et al., 2022; de Lima et al., 2023; Santos et al., 2023). Extracts and oils also possess insect-repellent and ovicidal activity (Abbas et al., 2024; de Campos Añaña et al., 2022). While research has focused on aerial parts, roots remain understudied. Given organ-specific metabolic profiles (Carneiro et al., 2024), root-derived compounds may offer novel bioactivities. Notably, methanolic fruit extracts and isolated apigenin inhibited NO production in LPS-stimulated macrophages (Bernardes et al., 2014), and a leaf lectin (SteLL) modulated NO and monoaminergic signaling, yielding antidepressant-like effects in mice (de Lima et al., 2022).

This study investigated the chemical constituents of *A. bilimbi* branches and *S. terebinthifolia* stems through a NO inhibition-guided isolation approach, highlighting their potential in managing oxidative stress and inflammation-related conditions.

2 Materials and Methods

2.1 General Experimental Procedures

All reagents and solvents used in this study were purchased from commercial sources and employed directly without additional purification. Column chromatography (CC) was conducted using Merck Kieselgel 60 silica gel (46–60 Å), while analytical thin-layer chromatography (TLC) utilized Merck pre-coated silica gel 60 F-254 plates. NMR spectra were recorded on a Bruker Avance III spectrometer operating at 500 MHz for ^{1}H NMR and at 125 MHz for ^{13}C NMR, depending on instrument availability. High-resolution electrospray ionization mass spectrometry (HRESIMS) of **ABS1** was performed in positive ion mode using a MicrOTOF-Q mass spectrometer coupled with an Agilent 1100 LC-MSD Trap system. Prior to analysis, **ABS1** was dissolved in MeOH and introduced into the liquid chromatography system.

2.2 Plant Materials

Plant materials, specifically the branches of *Averrhoa bilimbi* L., were obtained from Uttaradit Province, Thailand, in October 2023. The species was authenticated by Asst. Prof. Dr. Kanit Wangwasit, Department of Biology, Faculty of Science, Mahasarakham University, Thailand. A voucher specimen (K. Wangwasit 240807-1) has been deposited at the same institution for future reference.

Stems of *Schinus terebinthifolia* Raddi were collected in January 2025 from Kalasin Province, Thailand. The plant was also identified by Asst. Prof. Dr. Kanit Wangwasit, and a voucher specimen (TUNPCB250107) was deposited at the Natural Products Chemistry and Bioactivities Research Laboratory, Faculty of Science and Technology, Thammasat University Lampang Campus, Thailand.

2.3 Extraction and Isolation

Isolation of A. bilimbi branches: Branches of *A. bilimbi* (17 kg) were extracted three times with MeOH (40 L each time, 12 h per extraction) at ambient temperature. The combined filtrates were concentrated under reduced pressure to obtain a crude MeOH extract (280 g). This extract was sequentially partitioned using *n*-hexane, a 1:1 mixture of *n*-hexane and EtOAc (v/v), and then EtOAc, yielding four fractions: *n*-hexane (32 g, H), *n*-hexane:EtOAc (47 g, HEA), EtOAc (82 g, EA), and a water-soluble fraction (112 g). The EA fraction was further separated by column chromatography (CC) on Sephadex LH-20 using MeOH, resulting in five major fractions (EA1–EA5). Fraction EA1 (31.0 g) underwent additional Sephadex LH-20 CC (MeOH as mobile phase) to afford three subfractions (EA1.1–EA1.3). From EA1.2 (5.1 g), silica gel CC was performed using a gradient of *n*-hexane:EtOAc:MeOH (10:9:1 to 0:9:1, v/v/v), yielding five subfractions (X1–X5). Further separation of subfraction X2 (1.4 g) on normal-phase silica gel using the same solvent gradient provided subfractions X2.1–X2.3. Subsequent purification of subfraction X2.3 (200 mg) led to the isolation of compounds **ABS4** (3.5 mg) and **ABS5** (5.0 mg). Additionally, fraction EA4 (20.0 g) was subjected to Sephadex LH-20 CC with MeOH, yielding four subfractions (EA4.1–EA4.4). EA4.2 (4.5 g) was purified on silica gel CC using a gradient of *n*-hexane:EtOAc:MeOH (3:9:1 to 0:9:1, v/v/v), producing subfractions Y1–Y4. Further purification of subfraction Y2 (480 mg) by silica gel CC with EtOAc:MeOH (15:1 to 0:1, v/v) afforded three pure compounds, **ABS1** (10.0 mg), **ABS2** (2.5 mg), and **ABS3** (5.0 mg).

Isolation of S. terebinthifolia stems: Air-dried stems of *S. terebinthifolia* (1.9 kg) were extracted twice by maceration with MeOH (2 × 20 L) at room temperature. The combined methanolic extracts were concentrated under reduced pressure to yield a crude MeOH extract (257.6 g). This extract was then subjected to liquid–liquid partitioning using a 1:1 (v/v) mixture of *n*-hexane and EtOAc, producing a crude *n*-hexane:EtOAc fraction (22.1 g). Upon dissolution in acetone, the extract separated into a soluble phase and an insoluble solid residue (10.0 g). The acetone-soluble portion was fractionated *via* silica gel CC using a gradient of *n*-hexane:EtOAc (2:1 to 0:1, v/v), resulting in

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22 fractions (ST1–ST22). Fraction ST15 (1.2 g) was further separated by silica gel CC using a solvent gradient of *n*-hexane:EtOAc:MeOH (40:9:1 to 0:9:1, v/v/v), yielding four subfractions (S1–S4). Subsequent purification of subfraction S4 (400 mg) on silica gel using $CHCl_3$:acetone (300:25 to 50:50, v/v) afforded three fractions (S41–S43), from which compounds **ST1** (5.0 mg), **ST2** (2.1 mg), and **ST3** (6.0 mg) were isolated. In parallel, fraction ST22 (2.2 g) underwent silica gel CC with EtOAc:MeOH:H_2O (9:1:0.01, v/v/v) as the mobile phase, producing four fractions (R1–R4). Further separation of fraction R1 (80 mg) using a solvent system of *n*-hexane:EtOAc:MeOH:H_2O (4:9:1:0.01, v/v/v/v) afforded compound **ST7** (4.0 mg). Fraction R4 (500 mg) was purified by silica gel CC using *n*-hexane:EtOAc:MeOH:H_2O (2:9:1:0.01, v/v/v/v) to give three subfractions (R41–R43). Further purification of these subfractions with the same solvent system resulted in the isolation of compounds **ST4** (10.0 mg), **ST5** (2.0 mg), and **ST6** (6.0 mg). Detailed isolation of compounds **ST8**–**ST12** was described in Scheme S1.

2.4 Cytotoxicity

The methodology employed was in accordance with the protocol reported by Nguyen et al. (2024). Briefly, RAW 264.7 cells were seeded in a 96-well plate at a density of 5×10^4 cells per well, using a complete medium containing DMEM and 10% fetal bovine serum (FBS). Subsequently, the cells were incubated at 37°C with 5% CO_2. For the positive control, Doxorubicin was used, while dimethyl sulfoxide (DMSO) served as the negative control. The absorbance of the samples was measured at 570 nm using an ELISA Reader (BioTek, USA). Cell death (% inhibition) was estimated by the following formula: % Inhibition = 100 – [100 × (A_{Sample} – A_{B1})/(A_{DMSO} – A_{B2})]. Where, A_{Sample}: Absorbance of sample, A_{DMSO}: Absorbance of negative control, A_{B1}: Absorbance of blank of sample, A_{B2}: Absorbance of blank of DMSO. The IC_{50} value and the inhibitory chart were respectively calculated and built using GraphPad Prism software.

2.5 Nitric Oxide Inhibition

Following cytotoxicity testing, NO production inhibition was evaluated. Cells were prepared as previously reported, and test substances (in DMSO), L-NMMA as the positive control, and DMSO as the negative control were applied in serum-free medium. After 1 hour of pre-incubation, lipopolysaccharide (LPS; Sigma-Aldrich, Germany) was added at a final concentration of 1 µg/mL to stimulate NO production, and incubation proceeded for 24 hours. An aliquot (50 µL) of the supernatant was then mixed with 50 µL of Griess reagent in a 96-well plate and incubated at room temperature for 10 minutes. The absorbance at 540 nm was recorded using a BioTek microplate reader (USA), and IC_{50} values were calculated using GraphPad Prism software (version 8.0.1; Insightful Science LLC, USA). Three independent experiments were conducted to evaluate NO inhibitory and cytotoxic activities. Data are presented as mean ± standard deviation.

3 Results and Discussion

By employing a bio-guided procedure that targets nitric oxide inhibition, the most active extract from the stems of *S. terebinthifolia* was chemically analyzed. For the branches of *A. bilimbi*, three extracts: HEA, EA, and a water-soluble fraction exhibited similar NO inhibition with IC_{50} values ranging from 17.37 to 22.28 µg/mL. The EA extract was selected for further chemical analysis due to its ease of isolation and non-cytotoxic properties.

From *A. bilimbi* branches, five compounds, bilimoside A (**ABS1**), (+)-syringaresinol (**ABS2**) (Tu & Chen, 2012), ciwujiatone (**ABS3**) (Tu & Chen, 2012), gallic acid (**ABS4**) (Sánchez et al., 2013), and 3,4-dihydroxycinnamic acid (**ABS5**) (Duong et al., 2024), were isolated. From *S. tereb inthifolia* stems, twelve compounds, *epi*-α-amyrin (**ST1**) (Dekebo et al., 2002), 3-oxoursolic acid (**ST2**) (de Campos Añaña et al., 2022; Carneiro et al., 2024; Alghonaim et al., 2024; Locali-Pereira et al., 2020; Nocchi et al., 2016), α-amyrone (**ST3**) (Dekebo et al., 2002), β-sitosterol (**ST4**) (Uttu et al., 2023), β-sitosterol-3-*O*-β-D-glucoside (**ST5**) (Peshin & Kar, 2017), luteolin (**ST6**) (Lin et al., 2015), catechin (**ST7**) (Naceiri Mrabti et al., 2018), amentoflavone (**ST8**) (Ryu et al., 2010), agathisflavone (**ST9**) (Nascimento & David, 2022), methyl gallate (**ST10**) (Sánchez et al., 2013), 4-*O*-methylgallic acid (**ST11**) (Sun et al., 2007), and protocatechuic acid (**ST12**) (Nguyen et al., 2015) were isolated. To the best of our knowledge, compounds **ABS1**–**ABS3** and **ST1**–**ST3** are reported here for the first time in the genera *Averrhoa* and *Schinus*, respectively. It is noteworthy that limited chemical information is available regarding the polar, water-soluble extract of *A. bilimbi* branches. Compounds **ST6**–**ST9** are known as major flavonoids that have been previously identified in the leaves and fruits of *S. terebinthifolia*. Bilimoside A (**ABS1**) is a new compound, and its structure was elucidated as follows:

Compound **ABS1** was isolated as colorless oil. In the negative-ion HREIMS, a molecular ion peak at *m/z* 495.1507 $[M\text{-}H]^-$ (calcd. for $C_{23}H_{27}O_{12}^-$ 495.1503), was observed which is consistent with a molecular formula $C_{23}H_{28}O_{12}$. The combined ^{1}H NMR and HSQC spectra of compound **ABS1** reveal the presence of a 1,3,5-trisubstituted benzene ring (A-ring), indicated by *meta*-coupled aromatic protons at δ_H 6.37 (1H, t, J = 2.0 Hz, H-2′), 6.41 (1H, t, J = 2.0 Hz, H-4′), and 6.43 (1H, t, J = 2.5 Hz, H-6′) and a 1,3,4,5-tetrasubstituted benzene ring (B-ring) characterized by two symmetric aromatic protons at δ_H 7.32 (2H, s, H-2‴/H-6‴). Other observed ^{1}H NMR signals include a methylene group at δ_H 2.57 (2H, m, H-1a/H-1b), an oxymethylene group at δ_H 3.64 (2H, m, H-2a/H-2b), two methoxy groups (δ_H 3.85) and signals of a D-glucopyranose unit that are evident: an anomeric proton at δ_H 4.97 (1H, d, J = 7.5 Hz, H-1″), four oxymethine protons at δ_H 3.87, 3.54, 3.57, and 3.49, and two diastereotopic oxymethylene protons at δ_H 4.72 and 4.40. The ^{13}C NMR and HSQC spectra display an ester carboxyl carbon (δ_C 165.7), five aromatic methine carbons (δ_C 109.9, 108.4, 101.4, 107.3, and 107.2), two methylene carbons (δ_C 39.4 and 62.7), and two methoxy carbons (δ_C 55.9 × 2). Futher seven quaternary aromatic carbons (δ_C 158.1, 141.8, 154.5, 121.4, 147.6 × 2, and 141.8) were identified based on HMBC correlations (Figure 1).

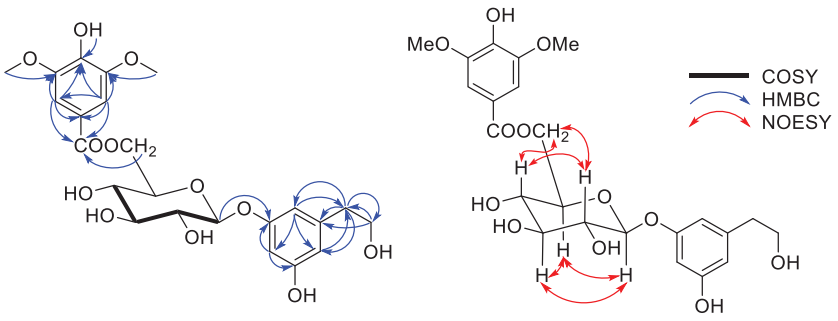

Figure 1. Key COSY, HMBC, and NOESY correlations of **ABS1**

The hexose unit was identified by oxygenated carbons at δ_C 100.8 (C-1″), 73.8 (C-2″), 76.9 (C-3″), 70.6 (C-4″), 74.2 (C-5″), and 64.0 (C-6″). HMBC correlations of H_2-1 (δ_H 2.57) with the oxymethylene carbon C-2 (δ_C 62.7) and with aromatic carbons C-2′, C-3′, and C-4′ and of H_2-2 (δ_H 3.64) with C-1 and C-3′, supporting the connectivity of the ethan-1-ol-2-yl moiety at C-3′. The anomeric proton H-1″ (δ_H 4.97) showed a key HMBC correlation with C-1′ (δ_C 158.1), confirming a glycosidic linkage between the hexose unit and ring A at C-1′. Additionally, a hydroxy proton at δ_H 8.22 correlates with aromatic carbons C-4′, C-5′, and C-6′, suggesting its attachment at C-5′. HMBC correlations of the methoxy groups at δ_H 3.85 with C-3‴ and C-5‴ and of the hydroxy proton at δ_H 8.04 correlates with C-3‴, C-4‴, and C-5‴, indicating their locations in B-ring. Symmetric protons H-2‴/H-6‴ (δ_H 7.32) and the oxymethylene H_2-6″ (δ_H 4.72 and 4.40) of the hexose unit exhibit HMBC correlations with the ester carbonyl carbon (δ_C 165.7), indicating that the B-ring is linked to the sugar unit *via* an ester bond at C-6″. The ^{1}H-^{1}H COSY spectrum reveals the chemical shifts of hydroxy groups of the sugar units.

The stereochemistry of **ABS1** is supported by NOESY interactions and vicinal *J*-coupling constants. The *J*-value of 7.5 Hz for H-1″ suggests an axial orientation. NOESY cross-peaks: H-2″/H-4″, H-2″/H-6″, H-1″/H-5″, and H-3″/H-5″, establishing that all involved protons are on the same face and axially oriented, confirming the presence of a β-glucopyranose unit. Comparison of NMR data of **ABS1** (Table 1) and clemomandshuricoside A strengthened the structural elucidation of **ABS1**. Naturally occurring glycosides in higher plants almost exclusively contain D-glucose as the sugar unit (Kytidou et al., 2020). Flavonoid glycosides previously reported from *Averrhoa* species also contained a D-glucose unit (Luan et al., 2021). From a biogenetic perspective, the β-glucopyranose unit of **ABS1** was therefore proposed to be a D-glucopyranose. Accordingly, the structure of **ABS1** was elucidated as shown in Figure 2, namely bilimoside A.

3.1 In vitro Inhibitory Activity on Nitric Oxide Production

The isolated compounds **ABS1–ABS3**, **ST1–ST3**, **ST8**, and **ST9** were evaluated for their NO inhibitory activity, with L-NMMA serving as the positive control (IC_{50} 41.30 ± 3.60 μg/mL) (Table 2). The results presented

Table 1. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectral data (acetone-d_6) of **ABS1** (δ in ppm, *J* in Hz)

No.	δ_H	δ_C	No.	δ_H	δ_C
1	2.57 (2H, *m*)	39.4	1‴		121.4
2	3.64 (2H, *m*)	62.7	2‴	7.32 (1H, *s*)	107.3
1′		158.1	3‴		147.6
2′	6.37 (1H, *t*, 2.0)	109.9	4‴		141.8
3′		141.8	5‴		147.6
4′	6.41 (1H, *t*, 2.0)	108.4	6‴	7.32 (1H, *s*)	107.2
5′		154.5	-COO-		165.7
6′	6.43 (1H, *t*, 2.5)	101.4	-OCH_3	3.85 (6H, *s*)	55.9
1″	4.97 (1H, *d*, 7.5)	100.8	2″-OH	4.55 (1H, *d*, 4.0)	
2″	3.49 (1H, *m*)	73.8	3″-OH	4.62 (1H, *d*, 4.0)	
3″	3.54 (1H, *m*)	76.9	4″-OH	4.47 (1H, *d*, 4.0)	
4″	3.57 (1H, *m*)	70.6			
5″	3.87 (1H, *m*)	74.2			
6″	4.72 (1H, *dd*, 11.5, 2.0) 4.40 (1H, *dd*, 11.5, 6.5)	64.0			

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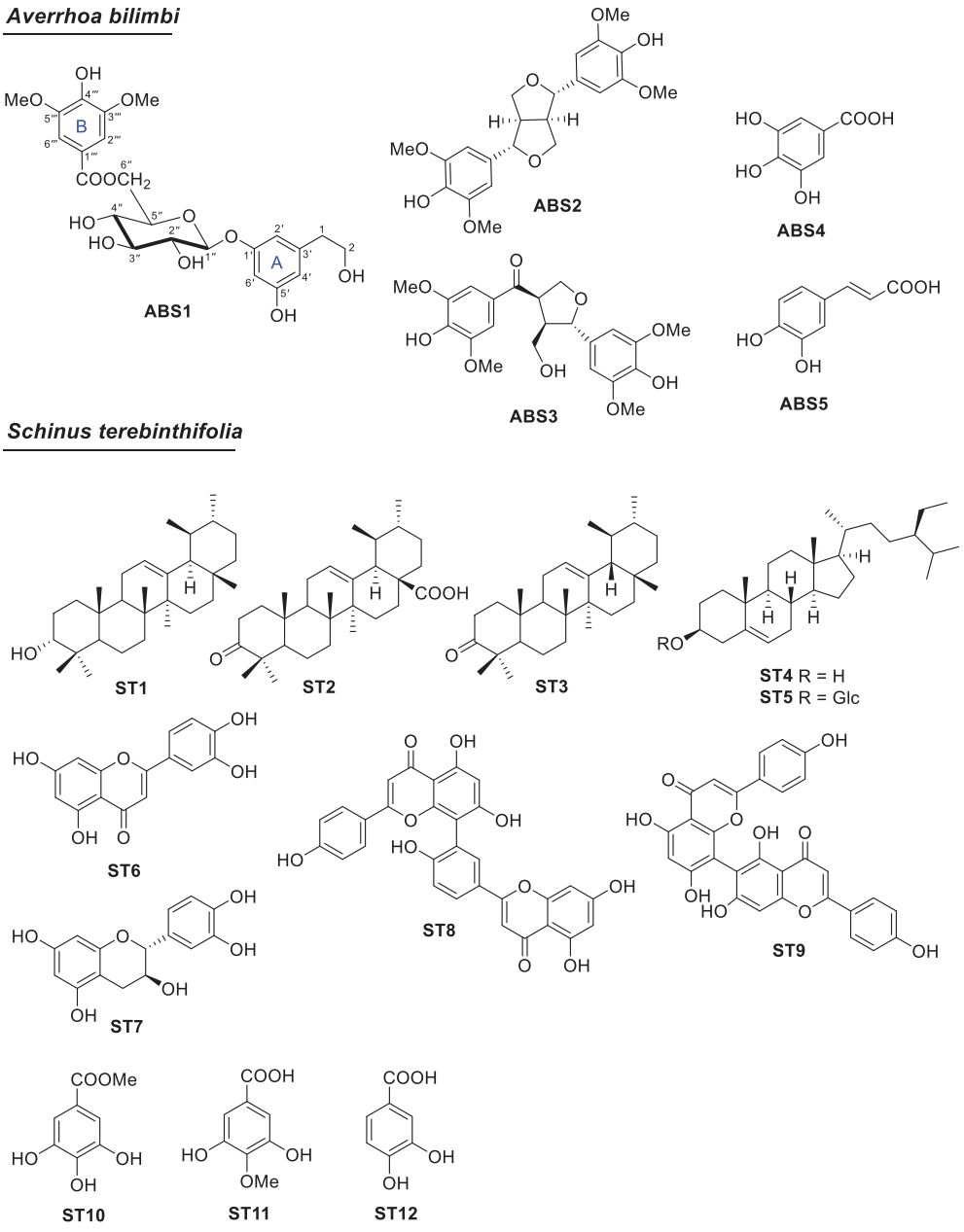

Figure 2. Chemical structures of **ABS1–ABS5** and **ST1–ST12**

in Table 2 demonstrate NO inhibitory activity and cytotoxicity among the extracts and selected compounds from *A. bilimbi* branches and *S. terebinthifolia* stems, with most samples exhibiting low cytotoxicity (IC_{50} > 200 µg/mL), except for a few compounds showing moderate cell toxicity. Among the *A. bilimbi* branch extracts, the *n*-hexane: EtOAc (1:1, v/v) extract exhibited the strongest NO inhibitory activity (IC_{50} 17.36 ± 0.82 µg/mL), followed by the water-soluble extract (IC_{50} 18.99 ± 1.29 µg/mL) and the EtOAc fraction (IC_{50} 22.28 ± 0.33 µg/mL). These findings suggest that active compounds may be distributed across both polar and non-polar extracts. Notably, the higher potency of the *n*-hexane:EtOAc fraction could be attributed to the enrichment of moderately non-polar triterpenoids and biflavonoids, which are known to exert anti-inflammatory effects via inhibition of inducible nitric oxide synthase (iNOS) and NF-κB signaling (Mlala et al., 2019; Deng et al., 2024). The water-soluble fraction, likely rich in tannins and polyphenols, also showed significant activity, which aligns with previous findings on polyphenol-rich extracts exerting NO scavenging and iNOS suppression (Mal & Pal, 2021). The crude MeOH and n-hexane extracts also exhibited NO inhibitory effects (IC_{50} values of 46.16 ± 1.31 and 39.23 ± 1.12 µg/mL, respectively), but their activity was comparatively weaker. Although both the EA and water-soluble extracts demonstrated low cytotoxicity, the EA extract was prioritized for further chemical analysis due to its simplified isolation process and its lower sugar and tannin contents compared to the water-soluble extract.

The crude methanolic extract of *S. terebinthifolia* stems exhibited no significant NO inhibitory activity (IC_{50} >

Table 2. NO production inhibitory effect of isolated compounds (**ABS1–ABS3**, **ST1–ST3**, **ST8**, and **ST9**) and extracts of *A. bilimbi* branches and *S. terebinthifolia* stems

Sample	IC_{50} (μg/mL)[a]	
	NO inhibition	Cytotoxicity in RAW 264.7 cells
A. bilimbi crude MeOH extract	46.16 ± 1.31	>200
A. bilimbi n-hexane extract	39.23 ± 1.12	>200
A. bilimbi n-hexane:EtOAc extract	17.36 ± 0.82	69.05 ± 2.48
A. bilimbi EtOAc extract	22.28 ± 0.33	>200
A. bilimbi water-soluble extract	18.99 ± 1.29	>200
S. terebinthifolia crude MeOH extract	>200	45.27 ± 3.98
S. terebinthifolia n-hexane:EtOAc extract	23.15 ± 0.17	>200
S. terebinthifolia water-soluble extract	35.83 ± 2.26	>200
Bilimoside A (**ABS1**)	45.22 ± 6.30	>200
(+)-Syringaresinol (**ABS2**)	67.03 ± 4.03	>200
Ciwujiatone (**ABS3**)	53.18 ± 3.28	>200
epi-α-Amyrin (**ST1**)	>200	55.84 ± 1.50
3-Oxoursolic acid (**ST2**)	28.00 ± 0.48	143.48 ± 1.27
α-Amyrone (**ST3**)	>200	23.35 ± 2.29
Amentoflavone (**ST8**)	34.63 ± 1.27	>200
Agathisflavone (**ST9**)	34.57 ± 2.25	>200
L-NMMA[b]	41.30 ± 3.60	>200
Doxorubicin[b]		2.43 ± 0.03

Note: [a]Data presented as mean ± standard deviation (SD). [b]Positive control.

200 μg/mL), yet showed moderate cytotoxicity (IC_{50} 45.27 ± 3.98 μg/mL). Among the solvent-partitioned fractions, the *n*-hexane:EtOAc (1:1, v/v) extract displayed the most potent NO inhibition (IC_{50} 23.15 ± 0.17 μg/mL), which is comparable to the active extracts of *A. bilimbi* branches (IC_{50} 17.36–46.16 μg/mL) and more effective than the water-soluble extract of *S. terebinthifolia* stems (IC_{50} 35.83 ± 2.26 μg/mL). This fraction is also presumed to concentrate semi-polar flavonoids and triterpenoids, two classes of compounds consistently reported to suppress LPS-induced NO production (Mlala et al., 2019; Deng et al., 2024).

Regarding the isolated compounds, 3-oxoursolic acid (**ST2**) exhibited the strongest NO inhibitory effect (IC_{50} 28.00 ± 0.48 μg/mL) among the pure compounds, accompanied by weak cytotoxicity (IC_{50} 143.48 ± 1.27 μg/mL). Its superior activity compared to **ST1** (*epi*-α-amyrin) and **ST3** (α-amyrone), which lack the 17-carboxyl (17-COOH) group, suggesting that the presence of the 17-COOH group plays a critical role in iNOS interaction, thereby enhancing NO inhibitory activity, as supported by structure-activity relationship (SAR) studies on pentacyclic triterpenes (Mlala et al., 2019; Deng et al., 2024).

Both amentoflavone (**ST8**) and agathisflavone (**ST9**) showed similar NO inhibitory activity (approximately 34.6 μg/mL) and low cytotoxicity (IC_{50} > 200 μg/mL), highlighting their potential as safe anti-inflammatory agents. These biflavonoids possess multiple hydroxylated aromatic rings, enabling both radical scavenging and inhibition of pro-inflammatory transcription factors (Goossens et al., 2021). Their activity corresponds closely to prior studies describing biflavonoids as dual regulators of NO and cytokine expression. In contrast, other compounds isolated from *A. bilimbi* branches, including bilimoside A (**ABS1**), (+)-syringaresinol (**ABS2**), and ciwujiatone (**ABS3**), exhibited weaker NO inhibitory effects (IC_{50} > 45 μg/mL) than some of the corresponding crude fractions. This trend may reflect the loss of synergistic interactions present in the original extract matrix, rather than being solely attributable to structural features such as glycosylation. Similar observations have been widely reported, where purified constituents from bioactive extracts show reduced activity *in vitro* despite their structural relevance (Williamson, 2001; Uto et al., 2012; Wrońska et al., 2022).

4 Conclusions

In this study, a bioassay-guided approach targeting NO inhibition led to the successful isolation and identification of bioactive constituents from the branches of *A. bilimbi* and the stems of *S. terebinthifolia*. Seventeen compounds were isolated, five from *A. bilimbi* branches and twelve from *S. terebinthifolia* stems, with bilimoside A (**ABS1**) assigned as a new compound. Notably, compounds **ST1–ST3** and **ABS1–ABS3** were reported for the first time from their respective genera. Among them, 3-oxoursolic acid (**ST2**) exhibited the most potent NO inhibitory activity (IC_{50} 28.00 ± 0.48 μg/mL) with low cytotoxicity, followed by compounds **ST8** and **ST9**, both of which showed favorable activity profiles. Although individual constituents from *A. bilimbi* branches were less active, the pronounced NO inhibition of its fractions suggests synergistic phytochemical interactions. These findings provide valuable chemical and pharmacological insights into

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the anti-inflammatory potential of *A. bilimbi* and *S. terebinthifolia*, validating their traditional medicinal uses and establishing a chemical foundation for future investigations into their therapeutic applications and mechanisms of action.

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Conflicts of Interest

The authors declare that they do not have any conflict of interest.

Supporting Information

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