

Antioxidant and Anti-inflammatory Activities of *Arundina graminifolia* Leaf Extract

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Abstract

Arundina graminifolia (D.Don) Hochr. has been used as a traditional medicine for detoxification, anti-arthritis, and antidote for many years. This study aimed to determine the biological property of *Arundina graminifolia* leaf extract (ALE) for antioxidant and anti-inflammatory activities. *Arundina graminifolia* leaves were extracted with 70% ethanol, and antioxidant activity was evaluated by DPPH and ABTS assay. The iron-binding capacity of ALE was measured by spectrophotometric technique. Lipid peroxidation assay was determined using the thiocyanate method. Moreover, the production of TNF- α and IL-6 was measured by an ELISA kit. Our results showed that ALE containing total phenolic and flavonoid contents exhibited antioxidant activity by scavenging free radicals. The IC₅₀ values of ALE by DPPH and ABTS radical scavenging assay were 155.17 $\pm$ 3.61 and 13.82 $\pm$ 0.38 μ g/mL, respectively. Furthermore, ALE could inhibit free radical production via the Fenton reaction by complex formation with Fe³⁺-NTA. The scavenging activity of ALE in hemoglobin-induced lipid peroxidation resulted in 42% inhibition. Besides, ALE significantly inhibited LPS-induced pro-inflammatory mediators, including the production of NO and IL-6. These findings suggest that ALE could be used as a functional food or pharmaceutical product containing antioxidant and anti-inflammatory activities and providing therapeutic potential for treating inflammatory diseases.

Keywords: Anti-inflammatory, Antioxidant, *Arundina graminifolia*, Free radicals

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Introduction

Arundina graminifolia (D.Don) Hochr. (Bamboo orchid) does a terrestrial perennial plant belong to the orchid family (Orchidaceae)⁽¹⁾. This plant is widespread in Asian countries, including Thailand, Sri Lanka, India, Vietnam, and China⁽²⁾. The plant has been used in traditional medicine, especially Chinese folk medicine, as a detoxifying agent, diuretic agent, antidote, demulcent, and for treating arthritis^(1,3). A previous study found that the phytochemical composition of *Arundina graminifolia* was rich in stilbenoids, triterpenes, flavonoids, and lignans⁽⁴⁾. The phenolic compound of *Arundina graminifolia* exhibited anti-HIV, anti-tobacco mosaic virus (anti-TMV), and anti-hepatitis activity⁽⁵⁻⁶⁾.

Arundina graminifolia has a long history of use as a traditional medicine in China. It is known in China as “Bai-yang-jie” and is widely distributed in Yunnan province. In folk medicine, it was used to detoxify, remove blood stasis, relieve pain, and treat hepatic fibrosis and liver injury in Dai Hospital⁽⁶⁾. In Thailand, the bamboo orchid is found in the forests and is used as an ornamental plant. Although *Arundina graminifolia* has long been used as a traditional medicine for the treatment of disease in many countries, the other bioactivities of *Arundina graminifolia* have not been studied, and its mechanism of action is unclear. Therefore, we have to study the bioactivity of *Arundina graminifolia* and the underlying mechanism of its action, including antioxidant and anti-inflammatory activities, to be developed as supplementary foods or pharmaceutical products for health benefits.

Methods

Chemicals and Reagents

Folin, 2, 2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2'-casino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) reagents were purchased from Merck KGaA (Darmstadt, Germany). Dulbecco's modified eagle medium (DMEM), fetal bovine serum (FBS), penicillin (50 U/mL), and streptomycin (50 µg/mL) were obtained from Gibco, Invitrogen™ (Grand Island, NY, USA).

Plant material

Arundina graminifolia leaves were collected from Mae Suai district, Chiang Rai province, Thailand. The voucher specimen number QBG No.114805 was deposited in Queen Sirikit Botanic Garden Herbarium, Chiang Mai, Thailand.

Extraction

The fresh leaves of *Arundina graminifolia* were mixed with 70% ethanol with continuous stirring overnight. Then, filter paper (Whatman No.1) filtered the ethanolic solution. Next, the solution was evaporated by a rotary evaporator and using freeze-drying to obtain a powder of *Arundina graminifolia* leaf extract (ALE).

Phytochemical analysis

Quantification of total phenolic content

The Folin-Ciocalteu method was used to determine the total phenolic contents (TPC) of ALE with slight modification⁽⁷⁾. Briefly, the extract was mixed with Folin-Ciocalteu reagent (10% v/v) and sodium carbonate (Na_2CO_3) (7.5% w/v). The reaction was incubated for 15 min at room temperature in the dark. After that, the absorbance was measured at 760 nm using a microplate reader. The TPC was expressed in milligrams of gallic acid equivalents (GAE) per gram dry weight of extract (mg GAE/g extract) using a calibration gallic acid standard curve. All measurements were performed in triplicate.

Quantification of total flavonoid content

The aluminum chloride colorimetric technique was used to measure the total flavonoid contents (TFC) of ALE⁽⁷⁾. Concisely, the extract was mixed with deionized water and sodium nitrite (NaNO_2) (5% w/v). The reaction mixture was incubated at room temperature for 5 min. After that, aluminum chloride (AlCl_3) (10% w/v) was added to the mixture at room temperature in the dark for another 6 min. Then, 1 M sodium hydroxide (NaOH) was added, and the mixture was further incubated for 15 min. The absorbance of the sample was measured at 510 nm using a microplate reader. The TFC was expressed in milligrams of catechin equivalents (CE) per gram dry weight of extract (mg CE/g extract) using a calibration catechin standard curve. All measurements were accomplished in triplicate.

Determination of phytochemical constituent by using LC-MS analysis

The phytochemical constituents in ALE were determined using a Liquid Chromatography-Mass Spectrometry instrument, LC-MS/MS 1260 Infinity II, QTOF Model 6545 (Agilent Technology Co., Ltd., USA). Poroshell 120 EC-C18 column (2.1 x 100 mm, 2.7 μ m) was used for chromatographic separation. Gradient elution condition was arranged for the mobile phase with A: B (0.1% formic acid in water: 0.1 % formic acid in acetonitrile), continuing a flow rate of 0.35 mL/min. Gradient elution was A: B at a ratio of 90:10% in 0–15.0 min, 40:60% in 15.0–30.0 min, 10:90% in 30.0–45.0 min, and 90:10% in 45.0–50.0 min. The Injection volume of the sample is 10 μ L. The ion source is Dual AJS ESI (seg), and the ionization was carried out in positive ion mode.

Antioxidant activity

DPPH radical scavenging assay

The 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay was used to assess the antioxidant activity of ALE⁽⁸⁾. In brief, the mixture of ALE at various concentrations and DPPH reagent (0.2 mM) were added to 96-well plates and incubated in the dark for 15 min at room temperature. After that, the absorbance of the mixture was measured at 540 nm using an ELISA plate reader. All measurements were conducted in triplicate. The percentage of scavenging activity was calculated. The antioxidant activity was expressed as the half-maximal inhibitory concentration (IC_{50}), and vitamin C was used as a positive control.

ABTS radical scavenging assay

The slight modification of 2,2'-azino-bis (3-ethylbenzthiazoline-6-sulphonic acid) (ABTS) radical scavenging assay was used to evaluate the antioxidant activity of ALE⁽⁸⁾. Briefly, the ALE mixture at various concentrations and working ABTS solution were incubated for 6 min at room temperature in the dark. After that, the absorbance of the reaction sample was measured at 734 nm using a UV-visible spectrophotometer. All measurements were performed in triplicate. The percentage of scavenging activity was calculated. The antioxidant activity was expressed as the half-maximal

inhibitory concentration (IC_{50}), and vitamin C was used as a positive control.

Iron binding assay

A spectrophotometric technique was used to determine iron-binding capacity with slight modifications⁽⁸⁾. In brief, the mixture of ALE (500 μ g/mL) and ferric nitrilotriacetate (Fe^{3+} -NTA) (0-400 μ M) was incubated for 60 min at room temperature. The iron-ALE complexes measured the absorbance at wavelengths ranging from 350 to 900 nm using a scanning UV-visible spectrophotometer (Double-beam). All measurements were performed in triplicate. Deferoxamine and deferiprone were used as a positive control.

Lipid peroxidation assay

Lipid peroxidation assay was determined using the thiocyanate method with slight modifications⁽⁸⁾. Hemoglobin suspension was used as an inducer for lipid peroxidation, and linoleic acid was used as a lipid membrane model. ALE (20 mg/mL) was incubated with 1 mM linoleic emulsion, 40 mM phosphate buffer, pH 6.5, and hemoglobin suspension (0.0016% v/w) at 37 °C for 45 min. After that, 0.6% hydrochloric acid (HCl) in ethanol was added for the termination reaction. Then, 0.02 M Ferrous chloride ($FeCl_2$) in 7.5% HCl and 300 mg/mL ammonium thiocyanate (NH_4SCN) were added to color the reaction. The absorbance of the mixture was measured at 480 nm using a UV-visible spectrophotometer, and vitamin C (4 mg/mL) was used as a positive control. All measurements were performed in triplicate.

Anti-inflammatory activity

Cell lines and culture condition

The macrophage cell line, RAW 264.7 cells, was obtained from American Type Culture Collection (ATCC). The RAW 264.7 cell lines were grown in Dulbecco's Modified Eagle Medium (DMEM), 10% (v/v) fetal bovine serum (FBS), penicillin (50 U/mL), and streptomycin (50 μ g/mL) in 5% CO_2 with humidified incubator at 37°C.

Cell viability assay

The 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was used to determine the cell viability of ALE against RAW 264.7 cells⁽⁹⁾. In brief, RAW

264.7 cells (7.5×10^3 cells/well) were added in 96-well plates in DMEM, supplemented with 10% FBS for 24 h. After that, the cells were treated with different concentrations of ALE (0-400 $\mu\text{g/mL}$) for 24 h or pre-treated with ALE for 2 h, and the cells were incubated with or without LPS (1 $\mu\text{g/mL}$) for a further 22 h. Then, MTT dye (5 mg/mL) was added and incubated at 37°C for 4 h. All solutions were removed, and dimethyl sulfoxide (DMSO) dissolved the formazan crystal. The absorbance of formazan dye was measured at 540/630 nm using an ELISA plate reader. All measurements were performed in triplicate.

Determination of nitric oxide (NO) production

The Griess reagent test was used to determine NO production with slight modifications⁽⁹⁾. Briefly, the RAW 264.7 cells (3.5×10^5 cells/well) were added in 12-well plates in DMEM supplemented with 10% FBS for 24 hr. After that, the RAW 264.7 cells were pre-treated with or without different concentrations of ALE (0-200 $\mu\text{g/mL}$) for 2 h. Then, the cells were incubated with or without LPS (1 $\mu\text{g/mL}$) for 22 h. The cultured medium was collected and measured NO production by Griess reaction. The absorbance of the mixture was measured at 540 nm by an ELISA plate reader. All measurements were accomplished in triplicate.

Determination of pro-inflammatory cytokines production

Pro-inflammatory cytokines production, Tumor necrotic factor-alpha (TNF- α), and interleukin-6 (IL-6) were measured by ELISA kit (Biolegend, USA) following the manufacturer’s instructions⁽⁹⁾. The RAW 264.7 cells (6.0×10^5 cells/well) were added in 12-well plates in

DMEM supplemented with 10% FBS for 24 h. After that, the cells were pre-treated with or without different concentrations of ALE (0-200 $\mu\text{g/mL}$) for 2 h. The cells were incubated with or without LPS (1 $\mu\text{g/mL}$) for 22 h. The cultured medium was collected, and IL-6 and TNF- α production in the medium were then measured using an ELISA kit. An ELISA plate reader was used to measure the absorbance at 450/570 nm. All measurements were performed in triplicate.

Statistical analysis

The results were displayed as mean $\pm$ standard deviation (SD) values that analyze the difference between the test and control using one-way analysis of variance (ANOVA) with Dunnett’s test. Prism version 6.0 software was used for all analyzed multiple comparisons. The p-value < 0.05 were considered significant.

Results

Extract yield and phytochemical constituents of ALE

The yield of ALE was 5.60% by weight. The TPC and TFC were 114.08 ± 9.69 mg GAE/g extract and 8.35 ± 1.45 mg CE/g extract, respectively. The phytochemical constituents in ALE were determined using LC-MS analysis. The results are shown in Table 1. It was found that the detected compounds in ALE were assigned as 11-amino-undecanoic acid, delphinidin 3-rhamnoside 5-glucoside, C16 sphinganine, militarinone A, sorbitan oleate, and pheophorbide a. The LC-MS chromatogram of the detected compounds is shown in as shown in Figure 1.

Table 1 The tentatively identified compound found in the ALE, based on LC-MS analysis

Tentatively identified compound	Retention time (min)	Molecular formula	Molecular weight	Measured (m/z)	Error (ppm)
11-amino-undecanoic acid	2.114	C ₁₁ H ₂₃ NO ₂	201.31	202.1810	-4.01
Delphinidin 3-rhamnoside 5-glucoside	9.956	C ₂₇ H ₃₁ O ₁₆	611.50	611.1608	-0.44
C16 Sphinganine	16.992	C ₁₆ H ₃₅ NO ₂	273.45	274.2732	2.28
Militarinone A	19.718	C ₂₆ H ₃₇ NO ₆	459.60	460.2702	-1.64
Sorbitan oleate	28.387	C ₂₄ H ₄₄ O ₆	428.60	429.3199	2.96
Pheophorbide a	32.187	C ₃₅ H ₃₆ N ₄ O ₅	592.70	593.2769	-1.58

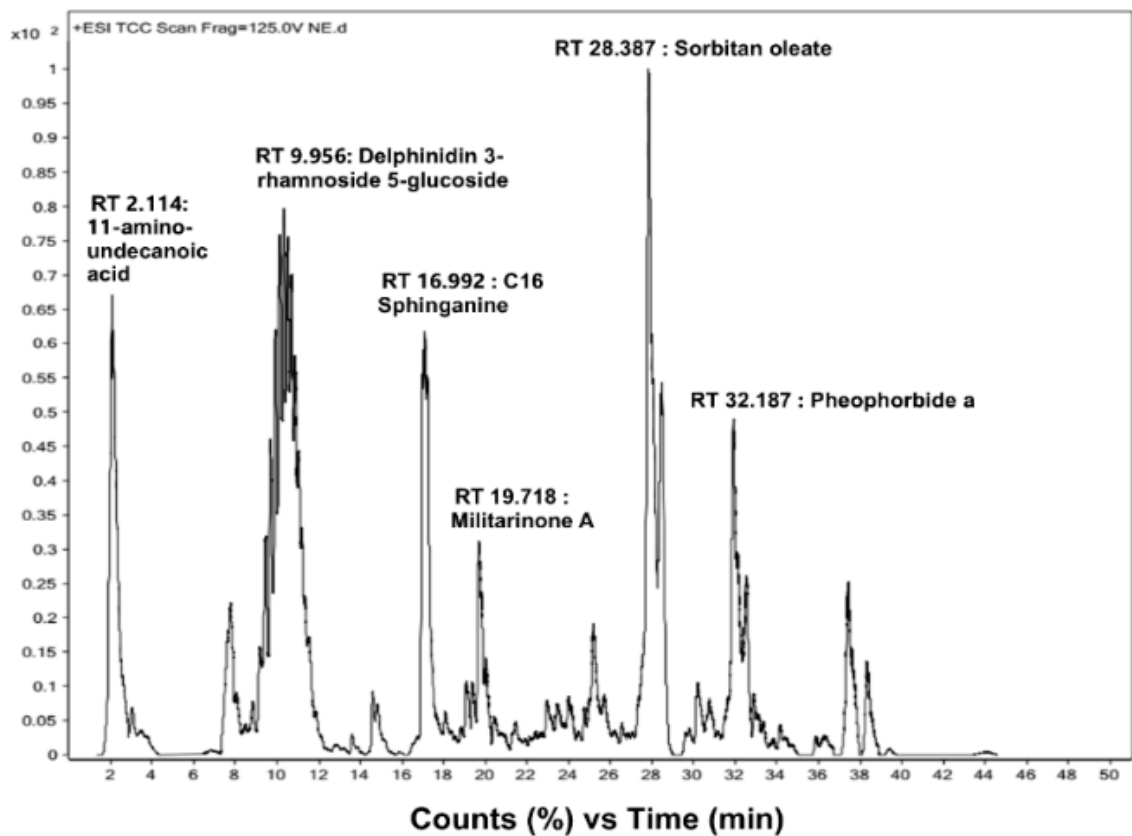


Figure 1 LC-MS chromatogram representation of ALE

Antioxidant capacities of ALE

DPPH radical scavenging activity with IC₅₀ of ALE was 155.17±3.61 µg/mL. Likewise, ABTS radical scavenging activity with IC₅₀ of ALE was 13.82±0.38 µg/mL. The spectral analysis of the iron-ALE extract complexes revealed the maximum absorption at 395 and 675 nm, the respective major and minor peaks as shown in Figure 2A.

Effect of ALE on lipid peroxidation inhibition

As shown in Figure 2B, ALE (20 mg/mL) significantly inhibited lipid peroxidation by approximately 42% compared with the control (p-value <0.001). The positive control, vitamin C, at a concentration of 4 mg/mL, exhibited approximately 89% inhibition compared with the control (p-value < 0.001).

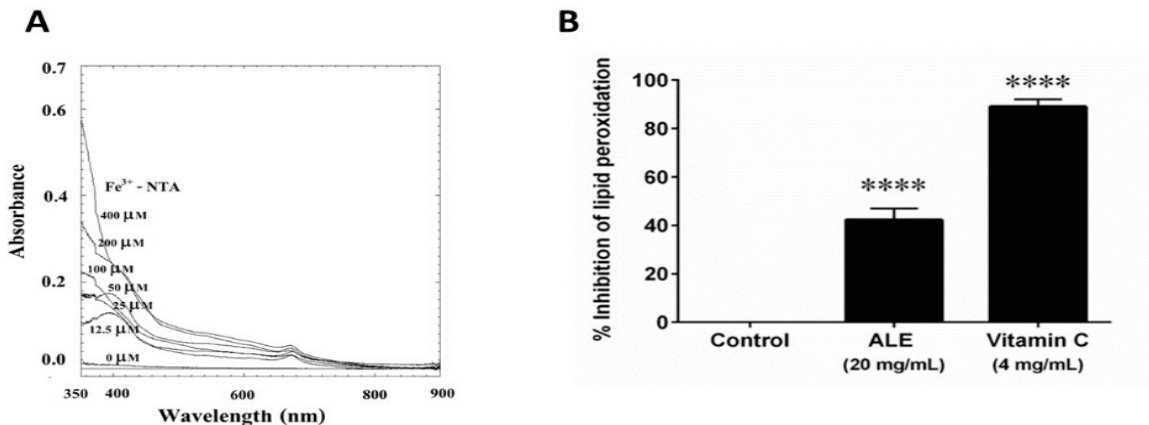


Figure 2 The spectral analysis of the iron-ALE complex resulting from the complexation of Fe³⁺-NTA (A) and the Inhibitory effects of ALE on lipid peroxidation (B). Data represent the mean of three independent experiments performed in triplicate (n = 3). The mean ± standard deviations (SD) are revealed as **** p-value < 0.001 versus control.

Effects of ALE on the viability of RAW 264.7 cells

Our results showed no significant effect on the cell viability of RAW 264.7 cells after treatment with ALE for 24 h. However, after the cells were pre-treated with ALE (400 µg/mL) for 2 h and incubated with LPS (1 µg/mL) for a further 22 h, they significantly decreased cell viability compared with LPS alone as shown in Figure 3A. The 20% inhibitory concentration (IC₂₀) of ALE with LPS was 215.21±8.71 µg/mL, and the 50% inhibitory concentration (IC₅₀) was more than 400 µg/mL. Therefore, a non-toxic dose of ALE (0-200 µg/mL) was used for further experiments.

Effect of ALE on NO production in LPS-induced Raw 264.7 cells

As shown in Figure 3B, NO production was

significantly increased after the cells were treated with LPS (1 µg/mL). However, after the cells were pre-treated with different concentrations of ALE (12.5-200 µg/mL) after being treated with LPS, NO production was significantly decreased in a dose-related manner.

Effect of ALE on pro-inflammatory cytokine production in LPS-induced Raw 264.7 cells

The production of IL-6 and TNF-α was significantly increased after the cells were treated with LPS (1 µg/mL). However, when pre-treated the cells with ALE (200 µg/mL) found that the IL-6 production from RAW 264.7 cells was significantly decreased as shown in Figure 3C, while TNF-α production did not change after pre-treatment of the cells with ALE as shown in Figure 3D.

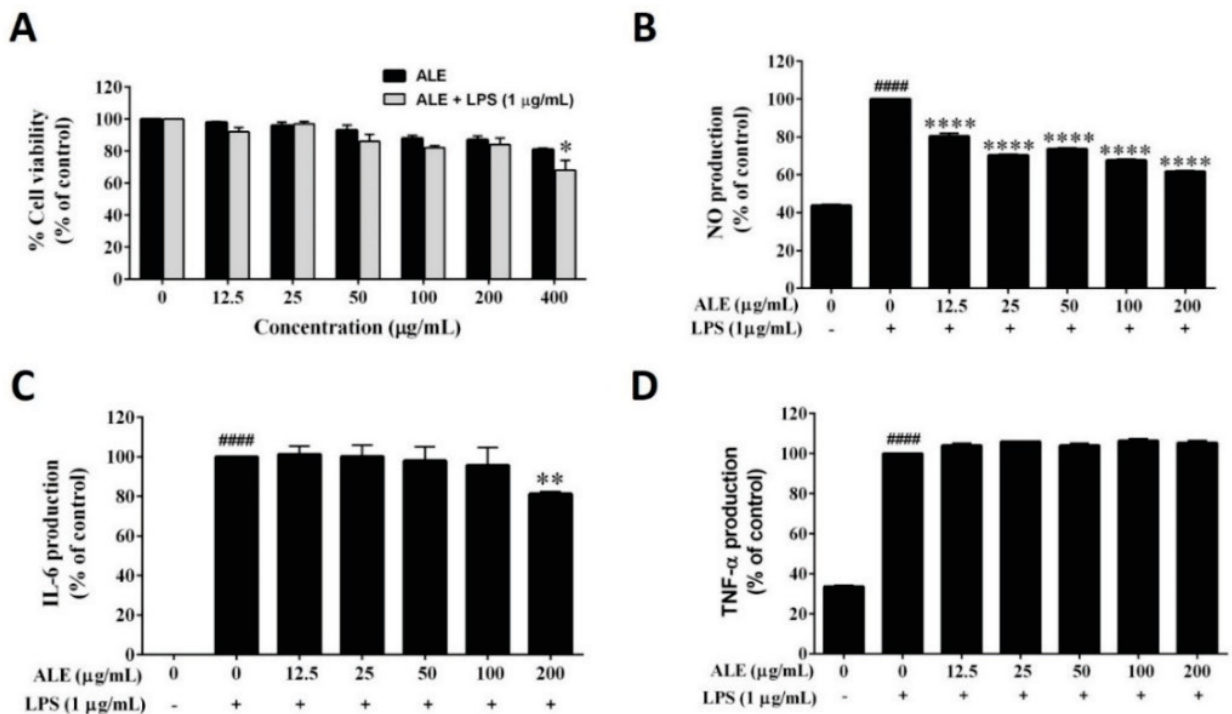


Figure 3 The cytotoxic effect of ALE on LPS-induced RAW 264.7 cells was determined by MTT assay (A). The NO production was determined using the Griess reagent system (B). The pro-inflammatory cytokine production, including IL-6 (C) and TNF-α (D), was determined by ELISA kit. Data represent the mean of three independent experiments performed in triplicate (n=3). The mean ± standard deviations (SD) are revealed as ##### p-value < 0.001 versus non-treated cells, and * p-value < 0.05, ** p-value < 0.01, and **** p-value < 0.001 versus LPS alone.

Discussion

This study has demonstrated the effect of *Arundina graminifolia* leaf extracts on antioxidant and

anti-inflammatory activities. Ethanol (70%) was used to extract the fresh *Arundina graminifolia* leaves to obtain ethanolic extract (ALE). ALE contained phenolic and

flavonoid contents. The phytochemical composition of ALE contained alkaloids such as militarinone A. Not only alkaloids found in ALE but also flavonoids such as delphinidin 3-rhamnoside 5-glucoside and fatty acids such as 11-amino-undecanoic acid, C16 sphinganine, and sorbitan oleate. The results are similar to a previous study showing that *Arundina graminifolia* contained phytochemical constituents, including alkaloid, terpenoid, phenol, sugar, saponin, flavonoid, quinoline, and steroid⁽¹⁰⁾.

The ALE had no cytotoxic effect on RAW 264.7 cells that were considered clinically safe. However, the high dose (400 µg/mL) tends to decrease cell viability, suggesting that an overdose of ALE may be toxic. Moreover, when co-treated ALE (400 µg/mL) with LPS (1 µg/mL) in RAW 264.7 cells, significantly reduced cell viability may be due to the effect of LPS that is known to reduce cell viability. Therefore, the synergistic effect between ALE and LPS may decrease cell viability⁽¹¹⁾.

ALE with phenolic and flavonoid content exhibited the antioxidative effect *via* inhibiting free radicals as determined using DPPH and ABTS assay. The reducing power of ALE may have a mutual correlation with the antioxidant properties. Free radicals are reactive oxygen species (ROS), the by-products of the cellular redox process. An imbalance between the induction of ROS and a decrease of intracellular antioxidants or radical scavengers leads to oxidative stress⁽¹²⁾. Oxidative stress can harmfully affect numerous cellular structures, such as membranes, deoxyribonucleic acid (DNA), lipids, and proteins⁽¹³⁾.

Furthermore, oxidative stress plays an important role in developing chronic diseases such as autoimmune disorders, cancer, aging, cardiovascular diseases, and arthritis⁽¹⁴⁾. Many naturally occurring compounds have been identified as antioxidants or radical scavengers. Therefore, ALE which contains phenolic and flavonoids as antioxidants, could scavenge free radicals through the action mediated by their functional hydroxyl groups⁽¹⁵⁾.

Moreover, the results showed that ALE significantly inhibited lipid peroxidation. Membrane lipid peroxidation was generated by methemoglobin comprising oxidizing form and ferric ions⁽¹⁵⁾. Additionally, ALE revealed an

iron-binding activity, as determined by the iron-binding assay. ALE obstructed the formation of the ferrozine complex and ferrous. An antioxidant molecule exhibited a chelating effect on ferrous ions, preventing free radical generation. Thus, the chelating ability significantly decreased the transition metal (TM) catalysis concentration in lipid peroxidation⁽¹⁶⁾.

Excess ROS production has been found to oxidize biomolecules, for example, proteins, lipids, and genes, as well as trigger signaling cascades, leading to the development of inflammatory diseases⁽¹⁷⁾. Our study showed that the anti-inflammatory effect of ALE was revealed *via* the reduction of NO and IL-6 production, which is an important pro-inflammatory mediator in the inflammatory cascade. NO, a pro-inflammatory mediator, is a signaling molecule that plays a vital role in the progression of inflammation owing to its overproduction in unusual conditions⁽¹⁸⁾. Hence, ALE's inhibition of NO production could prevent the inflammation process. In addition, another pro-inflammatory cytokine, IL-6, plays a crucial role in chronic inflammation related to chronic inflammatory diseases, autoimmune diseases, and cancer⁽¹⁹⁾. Suppose the ALE could decrease IL-6 production, leading to the prevention of chronic inflammation-induced chronic diseases. The signaling pathway involved with ALE could inhibit NO, and IL-6 production may be due to the diminished expression of inducible nitric oxide synthase (iNOS) *via* NF-κB suppression in RAW 264.7 cells⁽²⁰⁾.

The antioxidant and anti-inflammatory activities of ALE may be related to the active compound found in ALE, such as 11-amino-undecanoic acid (Ursolic acid), same as a previous study of this compound showed antioxidant activity by inhibiting DPPH⁽²¹⁾. Furthermore, 11-amino-undecanoic acid and Pheophorbide exhibited an anti-inflammatory effect like the prior reports^(20, 22).

In conclusion, this study suggested that ALE which contained high phenolic and flavonoid contents, exhibited antioxidant and anti-inflammatory activities. ALE played an important role in antioxidant activity by radical scavenging and iron chelating activities and subsequently prevented lipid peroxidation from

preventing oxidative stress-induced RBC hemolysis. The anti-inflammatory effect of ALE was revealed via the reduction of NO and IL-6 production, which is an important pro-inflammatory mediator in the inflammatory cascade. It could then be concluded that the biological and phytochemical characterization of the ALE supports the use of this plant for the treatment of inflammatory diseases. However, ALE's active compound should be evaluated as an antioxidant and anti-inflammatory activity. Further investigation of the anti-inflammatory effects of ALE on a molecular level is necessary, and an *in vivo* study could be done to prove the activities.

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