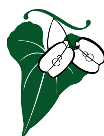
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Original Scientific Report

The chemical composition and anti-inflammatory effect of the essential oil obtained from *Abeliophyllum distichum* flowers

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ABSTRACT:
In the present study, the chemical composition of the essential oil (EO) obtained from the flowers of *Abeliophyllum distichum*, commonly known as white forsythia, was examined by gas chromatography–mass spectrometry (GC/MS). Thirty-five components including epoxy linalool, methyl salicylate, linalool oxide (pyranoid), and L-linalool were identified in the EO of *A. distichum* flowers (AfEO). In addition, the AfEO exhibited a remarkable anti-inflammatory effect in lipopolysaccharide (LPS)-stimulated RAW 264.7 cells. We found that this anti-inflammatory effect was mediated by inhibiting the expression of pro-inflammatory mediators, including *IL-1β*, *IL-6*, and *IL-18*. Taken together, these results confirm the potential use of the AfEO as an anti-inflammatory agent for topical application.

Keywords:
Abeliophyllum distichum, anti-inflammation, essential oil, pro-inflammatory mediator

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Essential oils (EOs) obtained from several plant organs are a mixture of various aromatic chemicals belonging to different chemical families, including terpenes, aldehydes, alcohols, esters, phenolic, ethers, and ketones (Leyva-López *et al*. 2017). In plants, the synthesis, storage, and secretion of EOs occur in various organs, e.g. oil cells, ducts, lysigenous and schizolysigenous cavities, or glandular trichomes, according to the botanical families (Feijó *et al*. 2014). Although EOs are known to play a crucial role in protecting against many pathogens and arthropod pests as well as in facilitating communication between plants (Kumar *et al*. 2018), they have been extensively utilized in the perfume, cosmetics, pharmaceutical, and food industries because of their unique flavour and fragrance and biological activities (Swamy *et al*. 2016). So far, several hundred plant EOs have been found to exhibit antimicrobial, antioxidant, anti-inflammatory, and anticancer activities in various cell and animal models, suggesting that plant EOs are promising natural alternatives to many chemical drugs.

Abeliophyllum distichum Nakai (family: Oleaceae) is a monotypic genus, and is endemic to Korea (Oh *et al*. 2003). Although *A. distichum* has been used as a landscape plant due to its horticultural value, phytochemical studies have revealed that it contains biologically active compounds, including rutin, chlorogenic acid, kaempferol, ferulic acid, and quercetin (Yoo *et al*. 2020). In addition, the pharmaceutical properties of *A. distichum*, such as anticancer (Park *et al*. 2014; Yoo *et al*. 2020), anti-inflammatory (Choi *et al*. 2017), antidiabetic (Li *et al*. 2013), and antihypertensive (Oh *et al*. 2003) effects, have also recently been disclosed. Although 20 volatile components, including aliphatic compounds, isoprenoid compounds, and others, have been identified from *A. distichum* flowers (Shen *et al*. 2017), the chemical composition and bioactivities of the EO of *A. distichum* flowers (AfEO) have not been simultaneously analyzed so far.

The present study aimed to investigate the chemical composition of the AfEO and to evaluate its anti-inflammatory properties using lipopolysaccharide (LPS)-

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Table 1. Primer sequences for Real-time PCR analysis.

Primer	Sequences (5`-3`)
IL-1β-F	TGTGAAATGCCACCTTTTGA
IL-1β-Rev	TGAGTGATACTGCCTGCCTG
IL-6-F	CCACTTCACAAGTCGGAGGCTTA
IL-6-Rev	GTGCATCATCGCTGTTCATACAATC
IL-18-F	ACTTTGGCCGACTTCACTGT
IL-18-Rev	GGGTTCACTGGCACTTTGAT
β-actin-F	CCCACTCCTAAGAGGAGGATG
β-actin-Rev	AGGGAGACCAAAGCCTTCAT

stimulated RAW 264.7 cells, in addition to exploring its underlying molecular mechanism.

Plant materials and EO preparation. Blossoming flowers were harvested from *A. distichum* cultivated at the research forest at Chungbuk National University in South Korea. AfEO was extracted from 500 g fresh flowers using the hydro-distillation method with Clevenger apparatus, as described by Samadi *et al.* (2017). The hydro-distilled oils were dried over anhydrous sodium sulfate. The yield of the AfEO was 0.32%, and it was stored in sealed vials in the dark, at 4°C, until used.

Gas chromatography–mass spectrometry (GC/MS) analysis of volatile components. The composition of the AfEO was analyzed by GC/MS using an Agilent 6890 gas chromatograph (Agilent Technologies, Santa Clara, CA, USA) equipped with an Agilent 5973i inert mass selective detector. A DB-5 fused-silica capillary column (30 m × 250 µm, 0.25 µm film thickness) was used to separate the compounds. The initial temperature of the column oven was held constant at 50°C for 2 min. The temperature was then increased to 250°C at a rate of 10 °C/min, followed by holding at 250°C for 10 min. Helium was used as the carrier gas at a constant flow rate of 1 ml/min, and the mass spectrometer was operated in the electron impact (EI) mode (ionization energy, 70 eV; ion source temperature 230°C). The components of EO were identified by their retention time and computer matching with the W10N11 full library and Wiley/7n mass spectral database (Hewlett Packard, Palo Alto, CA, USA).

LPS-induced inflammation assay. The RAW 264.7 macrophage cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% FBS and antibiotics (100 U/ml penicillin and 100 µg/ml streptomycin) at 37°C in a 5% CO_2 humidified environment. The cells were plated at a density of 1.5×10^5 cells/ml in 96-well plates. After overnight incubation in the medium, the cells were treated with LPS (1 µg/ml) and various concentrations of EO for 24 h. The culture supernatant (100 µl) was used to determine the nitric oxide (NO) levels, and the cultured cells were used to determine the cell viability. In order to determine the NO levels, 100 µl of the culture supernatant was transferred

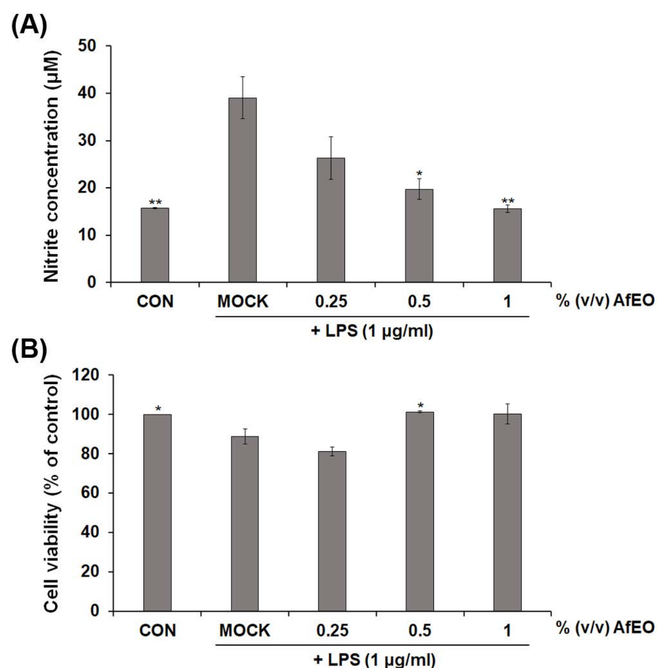

Figure 1. Effect of the essential oil obtained from *Abeliophyllum distichum* flowers (AfEO) on nitric oxide production (A) and cell viability (B) in lipopolysaccharide (LPS)-stimulated RAW 264.7 cells. Values are the mean ± SE of triplicate experiments. $*p < 0.05$ and $**p < 0.01$ represent significant differences compared with the MOCK (DMSO with LPS). CON, non-treated control.

to another 96-well plates and 100 µl of Griess reagent [1% sulfanilamide (w/v) and 0.1% (w/v) naphthylethylenediamine in 2.5% phosphoric acid (v/v)] was added. After incubation for 10 min, the absorbance at 540 nm was measured and the NO levels were calculated with reference to the standard curve generated using sodium nitrite. For the cell viability assay, 10 µl MTT (5 mg/ml in PBS) solution was added to each well and the plates were further incubated for 4 h at 37°C. After removing the supernatant, 200 µl DMSO was added to each well in order to solubilize the formazan crystals. The optical density was measured at 520 nm using an iMARK microplate reader (BIO-RAD, CA, USA). The percentage of viable cells compared with that of the mock-treated control cells was then calculated.

Western blotting. The cells were treated with various concentrations of EO with LPS (1 µg/ml). After incubation for 24 h, the cells were harvested, washed three times with cold PBS, and lysed with RIPA buffer containing a protease inhibitor cocktail. Western blot analyses were performed as described previously (Choi *et al.* 2017). The membranes were hybridized with primary antibodies specific for β-actin and inducible nitric oxide synthase (iNOS). The signal blot was developed using the enhanced chemiluminescence (ECL) system (SuperSignal™ West Pico PLUS Chemiluminescent Substrate;

Table 2. GC/MS result of the chemical composition of the essential oil obtained from *Abeliophyllum distichum* flowers.

No.	Compound	Group	Ref[1)]	RI[2)]	RT (min)
1	Leaf aldehyde	aldehyde	6924	617	3.64
2	*cis*-3-Hexen-1-ol	alcohol	8362	619	3.66
3	*trans*-2-Hexen-1-ol	alcohol	8338	639	3.82
4	N-Heptanal	aldehyde	15522	805	4.43
5	3-(Methylthio)propionaldehyde	aldehyde	10020	810	4.50
6	Benzaldehyde	aldehyde	10683	868	5.45
7	Octanal	aldehyde	24736	907	6.15
8	*trans*-2-*trans*-4-Heptadienal	aldehyde	12139	915	6.28
9	Benzenemethanol	alcohol	11343	940	6.69
10	β-Isophorone	ketone	33831	946	6.80
11	Benzeneacetaldehyde	aldehyde	18806	948	6.84
12	O-Cresol	phenol	11301	960	7.05
13	Epoxy linalool	terpene	73777	977	7.35
14	*cis*-Linaloloxide	terpene	73891	987	7.55
15	L-Linalool	terpene	53281	999	7.77
16	Phenethyl alcohol	alcohol	19944	1011	7.96
17	1H-Pyrazole, 4,5-dihydro-5,5-dimethyl-4-isopropylidene-	alkaloid	33730	1020	8.10
18	4-Oxoisophorone	terpene	49139	1043	8.47
19	Linalool oxide (pyranoid)	terpene	73571	1069	8.91
20	Methyl salicylate	ester	48606	1088	9.25
21	4-Vinyl phenol	phenol	18856	1104	9.54
22	Benzaldehyde, 2-amino-	aldehyde	19203	1107	9.58
23	Indole	alkaloid	17360	1159	10.6
24	2-Methoxy-4-vinylphenol	phenol	46395	1173	10.88
25	Methyl anisate	ester	67058	1207	11.20
26	3-Allyl-6-methoxyphenol	phenol	64566	1217	11.46
27	2,4,4-Trimethyl-3-carboxaldehyde-5-hydroxy-1-cyclohexanone 2,5-diene	phenol	86239	1234	11.91
28	Vanillin	aldehyde	48701	1238	12.02
29	α-Ionone	ketone	103650	1251	12.39
30	β-Ionone	ketone	103445	1276	13.11
31	Ethyl 4-ethoxybenzoate	ester	105823	1293	13.64
32	Nerolidol	terpene	148268	1420	14.09
33	Cyclopentaneacetic acid, 3-oxo-trans-2-(cis-2-pentenyl), methyl ester	ester	151048	1494	15.05
34	Benzyl benzoate	ester	133592	1611	16.47
35	Hexahydrofarnesyl acetone	ketone	211395	1676	17.20

[1)] Ref: Library search purity value.
[2)] Retention index on DB-5 fused-silica capillary column

Thermo Fisher Scientific, CA, USA) and analyzed using the Azure c280 gel imaging system (Azure Biosystems, Inc., CA, USA).

Quantitative real-time polymerase chain reaction (qRT-PCR). Total RNA was isolated from the RAW 264.7 cells treated with EO in the presence or absence of 1 μg/ml of LPS using TRI Reagent (Molecular Research Center, Cincinnati, USA). cDNA was synthesized using the ReverTra Ace® qPCR RT Master Mix with qDNA Remover (TOYOBO, Co., Ltd, Osaka, Japan), according to the manufacturer's instructions. Following this, the relative gene expression levels were quantified using the CFX96™ Real-Time System (BIO-RAD, CA, USA). The specific primer pairs are listed in Table 1.

Statistical analysis. The data were expressed as the mean ± standard error (SE) of three independent experiments. The significance of between-group differences was determined by Student's t-test or Duncan's multiple range test. The values of $p < 0.05$ were considered statistically significant.

Chemical composition of EO. The AfEO obtained by the hydro-distillation method using Clevenger apparatus was analyzed by GC/MS to investigate its chemical

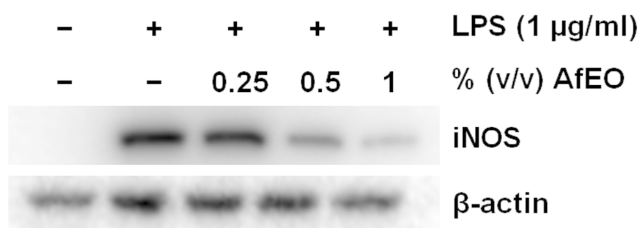

Figure 2. Effect of the essential oil obtained from *Abeliophyllum distichum* flowers (AfEO) on the expression of the inducible nitric oxide synthase (iNOS) protein in lipopolysaccharide (LPS)-stimulated RAW 264.7 cells. The iNOS protein level was analyzed by western blotting after the treatment of the AfEO with LPS.

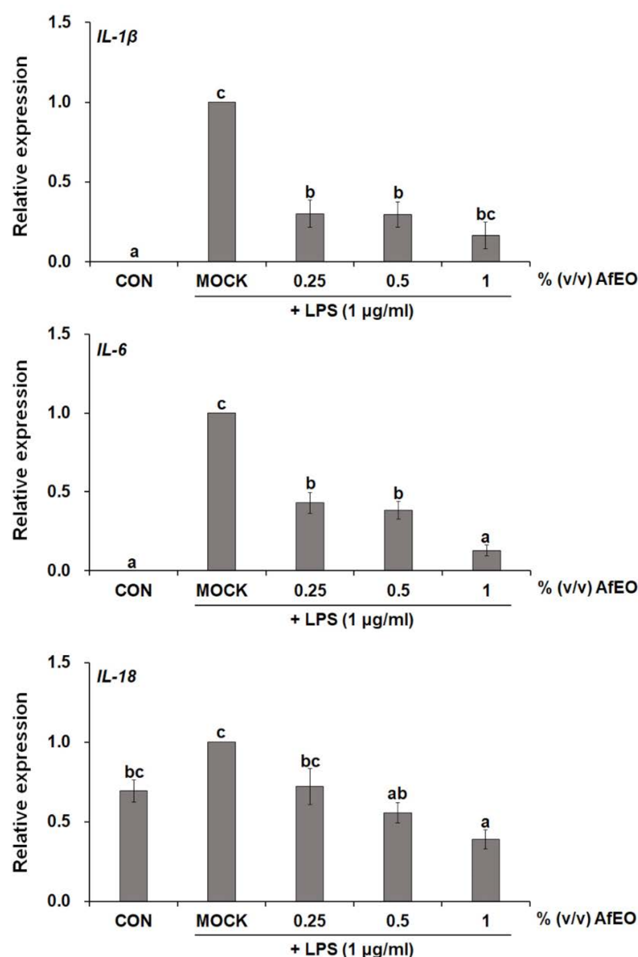

Figure 3. Effects of the essential oil obtained from *Abeliophyllum distichum* flowers (AfEO) on the expression of interleukin (*IL*)-*1β*, *IL-6*, and *IL-18* in lipopolysaccharide (LPS)-stimulated RAW 264.7 cells. The transcription levels of these genes were analyzed by qRT-PCR. The data are expressed as the mean ± SE of triplicate experiments. Values with different superscripted letters are significantly different ($p < 0.05$). CON, non-treated control; MOCK, treated control.

composition (Supplementary Fig. 1). A total of 35 components including epoxy linalool, methyl salicylate, linalool oxide (pyranoid), and L-linalool were identified from the AfEO (Table 2). Chloroplast genome analysis has shown that *A. distichum* has a close genetic relationship with the *Forsythia* species, suggesting that the genus *Abeliophyllum* has evolutionarily separated from the *Forsythia* clade (Min *et al.* 2019). L-linalool has been found to be the main volatile compound in *F. suspense* flowers (Shen *et al.* 2017). Moreover, linalool has also been found to be the main oxygenated component in *F. forsythiae* EO (Jiao *et al.* 2012). Similarly, the EO of *F. koreana* leaves has proved to be rich in linalool (Yang *et al.* 2015), which has various biological properties, such as analgesic, anti-inflammatory, and antioxidant effects (Seol *et al.* 2016). Although the composition of EO differs according to the growth conditions, harvesting time, and extraction method (Daferera *et al.* 2000), linalool should be a characteristic compound of the *Abeliophyllum* and *Forsythia* species. In addition, linalool oxide, methyl salicylate, L-linalool, benzaldehyde, benzenemethanol, and epoxy linalool have been identified as significantly different volatiles between five variants of *A. distichum* in partial least squares discriminant analysis (Lee *et al.* 2021).

Effects of the AfEO on NO production in LPS-stimulated RAW264.7 cells. NO is an intercellular messenger which serves as an indicator of cellular inflammation (Sharma *et al.* 2007). Excess NO production under pathological conditions induces host tissue damage associated with acute and chronic inflammation (Nagy *et al.* 2007; Tripathi *et al.* 2007). Therefore, the inhibition of NO production under inflammatory stimuli is the main goal in the discovery of anti-inflammatory drugs. In the present study, we studied the inhibitory effect of the AfEO on NO production in the LPS-stimulated RAW 264.7 cells. As shown in Fig. 1A, the AfEO significantly inhibited LPS-induced NO production in a dose-dependent manner. To investigate whether this inhibitory effect was mediated by cell viability, we analyzed the cytotoxicity of the EO-treated RAW 264.7 cells using the MTT assay (Fig. 1B). The results suggested that the AfEO did not affect cell viability regardless of the presence of LPS for 24 h, indicating that the inhibitory effect of the AfEO on LPS-induced NO production is not attributed to cytotoxicity.

As NO production in the LPS-stimulated RAW264.7 cells is regulated by the iNOS level (Aktan 2004), we assessed whether the AfEO modulated the expression of the iNOS protein. As shown in Fig. 2, iNOS was not detectable in the unstimulated RAW 264.7 cells. However, it was significantly induced by LPS treatment. The induction of iNOS by LPS treatment was strongly suppressed on incubation with the AfEO in a dose-dependent manner, indicating that the inhibitory effect of AfEO on LPS-induced NO production in the RAW 264.7 cells is due to

the suppression of iNOS protein expression. Linalool has been found to dose-dependently decrease the iNOS levels in lung tissues (Huo *et al.* 2013) and inhibit LPS-induced iNOS enzyme activity, interleukin-6 (IL-6) activity, and tumor necrosis factor-α (TNF-α) activity in RAW264.7 cells (Peana *et al.* 2006; Huo *et al.* 2013), indicating that the anti-inflammatory effect of the AfEO should be mediated by linalool together with the volatile components.

The inflammatory response is controlled by the balance between pro- and anti-inflammatory cytokines, which are known to be the intercellular messengers in the immune system (Zhang & An 2007). Pro-inflammatory cytokines, such as IL-1β, IL-6, and IL-18, are responsible for the induction of early responses and the amplification of inflammatory reactions, whereas anti-inflammatory cytokines, such as IL-4, IL-10, and IL-13, are a series of immunoregulatory molecules responsible for controlling the pro-inflammatory cytokine response (Zhang & An 2007; Wojdasiewicz *et al.* 2014). In the LPS-stimulated RAW264.7 cells, the AfEO inhibited the expression of LPS-induced *IL-1β*, *IL-6*, and *IL-18* (Fig. 3). Thus, the anti-inflammatory effect of the AfEO is mediated by inhibiting the production of the LPS-induced inflammatory mediator (iNOS) and pro-inflammatory cytokines (IL-1β, IL-6, and IL-18).

To sum up, we analyzed the chemical composition and anti-inflammatory effect of the AfEO. Based on GC/MS analysis, we identified thirty-five components including epoxy linalool, methyl salicylate, linalool oxide (pyranoid), and L-linalool. In addition, our results also suggested that the anti-inflammatory effect of the AfEO depends on its ability to inhibit the expression of iNOS, *IL-1β*, *IL-6*, and *IL-18*. These findings should contribute to improving ethnobotanical knowledge, in addition to indicating the potential therapeutic applications of the AfEO as an anti-inflammatory agent.

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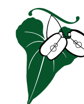

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Hemijski sastav i anti-upalno dejstvo esencijalnog ulja dobijenog iz cvetova *Abeliophillum distichum*

Hyun Ju Ju, Heung Bin Lim i Tae Kyung Hyun

U radu je pomoću gasne hromatografije-masene spektrometrije (GC/MS) istraživan hemijski sastav esencijalnog ulja (EO) dobijenog iz cvetova *Abeliophyllum distichum*, poznatog kao bela forzicija. Trideset pet komponenata, uključujući epoksi linalool, metil salicilat, linalool oksid (piranoid) i L-linalool, identifikovano je u EO cvetova *A. distichum* (AfEO). Uz to, AfEO je pokazao izvanredan protivupalni učinak u RAW 264,7 ćelijama stimuliranim lipopolisaharidima (LPS). Otkrili smo da je ovaj protivupalni učinak posredovan inhibiranjem ekspresije protivupalnih medijatora, uključujući IL-1β, IL-6 i IL-18. Zajedno, ovi rezultati potvrđuju potencijalnu upotrebu AfEO kao protivupalnog sredstva za lokalnu primenu.

Ključne reči: *Abeliophillum distichum*, protivupala, esencijalno ulje, protivupalni medijator