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Inhibitory effects of *Angelica sinensis* ethyl acetate extract and major compounds on NF-κB trans-activation activity and LPS-acetate inflammation

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**A B S T R A C T**

**Aim of the study:** Previous study showed that the ethyl acetate (EtOAc) fraction from *Angelica sinensis* (Oliv.) Diels (Apiaceae) (AS) inhibited nitric oxide (NO) and prostaglandin E\(_2\) secretions in vitro. This study was to evaluate anti-inflammatory activity of AS EtOAc extract and its major compounds in vivo and in vitro.

**Materials and methods:** NF-κB luciferase activity and pro-inflammatory cytokine secretions from lipopolysaccharide (LPS) plus interferon (IFN)-γ-stimulated RAW 264.7 cells pre-treated with EtOAc extract or compounds were analyzed. For further in vivo study, BALB/c mice were tube-fed with 1.56 (AS1 group), 6.25 (AS2 group) mg/kg body weight/day in 100 μl soybean oil, while the control and PDTC (pyrrolidine dithiocarbamate, an anti-inflammatory agent) groups were tube-fed with 100 μl soybean oil/day only. After 1 week of tube-feeding, the PDTC group was injected with 50 mg/kg BW PDTC and 1 h later, all of the mice were injected with 15 mg/kg BW LPS. The pro-inflammatory cytokine levels and lifespan of LPS-challenged mice were determined.

**Results:** The results showed that AS EtOAc extract significantly inhibited NF-κB luciferase activity and TNF-α, IL-6, macrophage inflammatory protein-2 (MIP-2) and NO secretions from LPS/IFN-γ-stimulated RAW 264.7 cells. The AS1 and PDTC groups, but not AS2, had significantly higher survival rate than the control group. This was characterized by the inhibition of the serum TNF-α and IL-12p40 levels after LPS injection (p < 0.05). The major compounds of AS, ferulic acid and Z-ligustilide, also significantly decreased NF-κB luciferase activity, which may contribute to the anti-inflammatory activity of AS.

**Conclusions:** Low dose of AS EtOAc extract that inhibits the production of inflammatory mediators alleviates acute inflammatory hazards and protect mice from endotoxic shock.

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1. Introduction

Inflammation, an important component of innate immunity, is dependent on the activation of nuclear factor kappa B (NF-κB). Expression of various pro-inflammatory cytokines and chemokines, such as TNF-α, IL-6, IL-12, macrophage inflammatory protein-2 (MIP-2) and nitric oxide (NO) are induced by NF-κB activation. The proper production of these mediators helps the innate immune response, but excessive inflammation may cause conditions such as chronic inflammation, sepsis and even death (Das, 2000). Sepsis is generally considered a systemic inflammatory disorder and a serious clinical problem with high mortality (Bone et al., 1997).

Traditional Chinese medicine herbs are used in many medicines as well as in dietary supplements in Asia. Our previous study on pre-screening of 22 commonly used Chinese herbs by NF-κB-dependent activity implies that the EtOAc fraction of *Angelica sinensis* (Oliv.) Diels (Apiaceae) (AS), or Dang gui in Chinese, exerts an anti-inflammatory effect (Chao et al., 2007). Further in vivo study indicates that NF-κB-dependent luciferase reporter assay may serve as pre-screen tool to identify anti-inflammatory Chinese medicine herbs (Chao et al., 2009a). AS, one of the herbs screened out by the suppression of NF-κB luciferase activity, decreased NO and PGE\(_2\) production in LPS/IFN-γ-stimulated peritoneal macrophages (Chao et al., 2009b), suggesting that AS is worthy of further in vivo evidence-based research on anti-inflammation.

The main chemical constituents of *Angelica* roots are ferulic acid, Z-ligustilide (the main lipophilic component of the essential oil...
of AS), angelicile, butylidenephthalide and butyphthalide. Ferulic acid has been suggested as one of the major bioactive components in AS (Zhao et al., 2003; Dong et al., 2005). The components of AS EtOAc extract, which showed higher inhibitory activity of NF-κB transactivation than hexane or water fractions in our previous study (Chao et al., 2007), were also identified as ferulic acid and Z-ligustilide. The amounts of ferulic acid and Z-ligustilide in AS EtOAc fraction were calculated as 3.75 and 15.95 mg/g dry weight of whole plant (Chao et al., 2009b). Therefore, we further evaluated the pharmacological effects of the EtOAc extract from AS, ferulic acid and Z-ligustilide for their ability to modulate NF-κB trans-activation activity in this study. In addition, a murine model of LPS-induced endotoxic shock was used to evaluate in vivo anti-inflammatory effect of AS EtOAc extract.

2. Materials and methods

2.1. Extraction and semi-purification of Angelica sinensis

*Angelica sinensis* (Oliv.) Diels (Apiaceae) (AS) was purchased from a licensed Chinese herbal drug store in Taipei City (voucher no. 05-03-10, Yong-Sheng Pharmacy) and was authenticated (Sheng Chang Pharmaceutical, Co., Ltd., Taiwan) (Chao et al., 2009b). In total, 10 g of AS was extracted with 300 ml of 95% ethanol at 50 °C for 3 h. The total crude extract was evaporated under vacuum to yield a residue, and then the residue was suspended in 0.9% saline and successively partitioned with hexane and ethyl acetate to obtain hexane, EtOAc and water fractions, respectively. The EtOAc extract (6% of ethanol extract) was used in this study due to its higher bioactivity than the hexane and water extract (Chao et al., 2007).

Ferulic acid (3-(4-hydroxy-3-methoxyphenyl)-2-propenonic acid) and Z-ligustilide (3-butylidene-4,5-dihydro-1(3H)-isobenzofuranone, solution), two marker substances of AS were purchased from Fluka (St. Louis, MO, USA) and Chroma-Dex (Santa Ana, CA, USA), respectively, for NF-κB reporter gene assay and for HPLC analysis standards.

2.2. NF-κB reporter gene assay

The NF-κB-promoted luciferase reporter was used to investigate the activity of NF-κB trans-activation. A reporter plasmid, 3x-κB-tk-luc, had three copies of an NF-κB binding site in the upstream thymidine kinase promoter and a luciferase reporter gene in the pGL3 vector (mock) (Promega Corp., Madison, WI, USA) (Kashiwada et al., 1998). The RAW 264.7 cells were seeded on 24-well plates (Nunc, Roskilde, Denmark) at 5 x 10⁴ cells/well in Dulbecco’s modified Eagle’s medium with 10% fetal bovine serum (GIBCO, Grand Island, NY, USA). The cells were co-transfected with 0.3 µg 3x-κB-tk-luc reporter gene plasmid and 0.1 µg of Renilla luciferase reporter plasmid pRL-tk (Promega) for 48 h using the ExGen 500 in vitro transfection reagent (Fermentas, Hanover, MD, USA).

After transfection, the cells were pre-incubated with AS EtOAc extract, the NF-κB-DNA binding inhibitor helenalin (10 µM, Calbiochem-Novabiochem Corp., San Diego, USA), ferulic acid and Z-ligustilide or its solvent dimethyl sulfoxide (DMSO), for 1 h, and then stimulated with LPS (100 ng/ml, Sigma) plus IFN-γ (1000 units/ml, Sigma) for 8 h. The supernatant was collected for cytokine and NO assays. Luciferase expression was analyzed using the Dual-Glo™ luciferase reporter assay system (Promega) (Chao et al., 2007). There was no cytotoxicity of the extract or compounds at the concentrations used in this study as confirmed by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT, Sigma) assay for cell viability (Chao et al., 2009b).

2.3. AS supplement prior to LPS-induced inflammation in mice

Four-week-old female BALB/c mice were purchased from the Animal Center of the College of Medicine at National Taiwan University (Taipei, Taiwan). At age of 8 weeks, mice (20±2 g) were divided into five groups: the PBS group (n=8), the LPS group (n=8, as a control) and the PDTC group (n=8, as a positive control) were tube-fed with 100 µl soybean oil/day, while the AS groups (n=8/group) were tube-fed with different doses of AS EtOAc extract (AS1, 1.56 mg/kg BW; AS2, 6.25 mg/kg BW) in 100 µl soybean oil/day. The mice had free access to AIN-76 diet and water and additionally tube-fed with either soybean oil or AS EtOAc extract daily. After 1 week of tube-feeding, all of the mice were injected i.p. with 15 mg/kg BW LPS to induce acute inflammation. Mice in the PDTC group were injected i.p. with 50 mg/kg BW PDTC (Sigma) 1 h before LPS challenge. This PDTC dose was referred to previous studies showing anti-inflammatory effects in LPS-challenged model (Hong et al., 2009; Chao et al., 2009a). Sera were collected by orbital bleeding at 2 and 9 h after LPS challenge for cytokine assay. The life spans of these mice that continued on AIN-76 diet ad lib were recorded. Animal care and handling conformed to accepted guidelines (NRC, 1996), and approved by the Institutional Animal Care and Use Committee NTU (IACUC Approval No. 95-072).

2.4. Cytokine measurements

The productions of TNF-α, IL-6, IL-12p40, MIP-2 and NO in RAW 264.7 macrophage cell supernatants, and serum of LPS-challenged mice were measured by commercial ELISA kits. IL-6 ELISA kit (PharMingen, San Diego, CA, USA) and TNF-α, IL-12p40, MIP-2 kits (R&D Systems, Inc., Minneapolis, MN, USA) were used and the cytokine concentration was calculated according to the manufacturer’s cytokine ELISA protocol.

2.5. NO determination by Griess assay

Griess reagent was freshly prepared from reagents A (1% sulfanilamide in 2.5% phosphoric acid) and B (0.1% N-1-naphthylethylene diamide dihydrochloride in 2.5% phosphoric acid) at a ratio of 1:1. Each liquor of 50 µl of cell supernatant was incubated with 50 µl Griess reagent in a 96-well plate for 10 min and the plate was read on an ELISA reader at 540 nm. The NO concentrations were determined using a standard curve (Calixto et al., 2004).

2.6. Statistical analysis

The data are expressed as the mean±S.D. The significant difference compared to the control group was statistically analyzed by the Student’s t-test using the SAS software program (SAS/STAT version 8.2; SAS Institute, Cary, NC, USA). Statistical comparison between different survival curves was analyzed by Cox’s proportional hazards regression test (STATA version 9.0; Stata Corp., TX, USA). The relationship was analyzed by the simple correlation of the SAS program. Statistical significance is expressed as p<0.05.

3. Results and discussion

3.1. AS EtOAc extract suppresses NF-κB transcriptional activity and pro-inflammatory mediators production in LPS/IFN-γ-activated macrophages

Activation of RAW 264.7 macrophages with LPS/IFN-γ resulted in a significant increase in NF-κB trans-activation activity (Fig. 1). Addition of helenalin, a naturally occurring cell permeable pseudoguainolide sesquiterpenoid lactone that inhibits NF-κB-DNA
binding activity (Siedle et al., 2004), thoroughly suppressed reporter activity. AS ETOAc extract pre-treatment significantly and dose-dependently reduced LPS/NF-κB-activated NF-κB luciferase activity. No cytotoxicity of AS ETOAc extract up to 20 μg/ml was confirmed by cell viability (data not shown).

The levels of TNF-α, IL-6, MIP-2 and NO in LPS/NF-κB-stimulated RAW 264.7 macrophages cell supernatants were also measured (Table 1). Pre-treatment with AS ETOAc extract, as well as the NF-κB inhibitor helenalin, significantly decreased TNF-α, IL-6, MIP-2 and NO productions in LPS/NF-κB-stimulated RAW 264.7 macrophages (An et al., 2006). There was a significant correlation between NF-κB luciferase activity and TNF-α level \( r = 0.62, p < 0.01 \). Our results show that AS ETOAc extract attenuates inflammatory mediator synthesis, the mechanism of which, at least in part, might involve the inhibition of NF-κB.

### 3.2. Low doses of AS ETOAc extract significantly improved survival of LPS-challenged mice

To investigate whether suppression of pro-inflammatory mediators production in vitro may benefit survival of LPS-challenged mice, the life spans were recorded (Fig. 2). The survival rate in the positive control PDTC group (64%) was significantly higher than that in the control LPS group (12%). The survival rate in the AS1 group (44%) was also significantly higher than the LPS group. However, the AS2 group did not increase the survival rate (18%). Our data show that AS ETOAc extract in low dose, but not high dose, significantly protect mice against lethal endotoxia. Although further studies are required to clarify the reasons, it is known that traditional Chinese medicine have their optimal effective dosage and overdose may cause side-effect or toxicity.

Our previous studies have suggested that the anti-inflammatory effect of food components screened by in vitro NF-κB trans-activation activity in RAW 264.7 macrophage cells also can exert anti-inflammatory effect in an LPS-induced inflammatory murine model (Hong et al., 2009; Chao et al., 2009a). In the present study, again, we show that PDTC and AS1 groups have higher survival rates than the LPS group (Fig. 2), suggesting that in vivo anti-inflammatory effect can be pre-screened by in vitro fast reporter bioassay.

### 3.3. Suppression of TNF-α, IL-12p40, MIP-2 levels in serum from LPS-challenged mice pre-treated with AS ETOAc extract

To investigate the in vivo anti-inflammatory action of AS ETOAc extract, serum levels of pro-inflammatory mediators were determined at 2 and 9 h after LPS challenge in mice (Table 2). The mice injected with LPS had marked increase of serum TNF-α, IL-12p40-activated NF-κB trans-

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**Table 1**

Effects of AS ETOAc extract on pro-inflammatory mediators production from LPS/NF-κB-stimulated RAW 264.7 macrophages.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>TNF-α (pg/ml)</th>
<th>IL-6 (ng/ml)</th>
<th>MIP-2 (ng/ml)</th>
<th>NO (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medium only</td>
<td>n.d.</td>
<td>n.d.</td>
<td>n.d.</td>
<td>1.90 ± 0.10</td>
</tr>
<tr>
<td>L/I (LPS/NF-κB)</td>
<td>786 ± 158</td>
<td>0.48 ± 0.10</td>
<td>2.43 ± 0.20</td>
<td>7.00 ± 1.00</td>
</tr>
<tr>
<td>L/I + helenalin</td>
<td>0.14 ± 0.04</td>
<td>n.d.</td>
<td>2.94 ± 0.42</td>
<td></td>
</tr>
<tr>
<td>L/I + AS 2.5</td>
<td>743 ± 51</td>
<td>0.51 ± 0.17</td>
<td>2.61 ± 0.42</td>
<td>6.57 ± 0.40</td>
</tr>
<tr>
<td>L/I + AS 5</td>
<td>490 ± 115</td>
<td>0.43 ± 0.06</td>
<td>2.16 ± 0.23</td>
<td>5.10 ± 0.17</td>
</tr>
<tr>
<td>L/I + AS 10</td>
<td>341 ± 63</td>
<td>0.32 ± 0.08</td>
<td>1.71 ± 0.21</td>
<td>4.43 ± 0.40</td>
</tr>
<tr>
<td>L/I + AS 20</td>
<td>75 ± 5</td>
<td>0.18 ± 0.03</td>
<td>0.52 ± 0.01</td>
<td>3.88 ± 0.50</td>
</tr>
</tbody>
</table>

The data are expressed as the mean ± S.D. from three independent experiments \( p < 0.05 \) compared to L/I. RAW 264.7 macrophages transient transfection with a NF-κB reporter plasmid were pre-treated with AS ETOAc extract or helenalin and then stimulated with L/I for 8 h. Supernatant was collected for analysis of pro-inflammatory mediators production. n.d.: not detectable.

**Table 2**

Effects of AS ETOAc extract on serum levels of pro-inflammatory mediators at 2 and 9 h after LPS injection.

<table>
<thead>
<tr>
<th>Groups</th>
<th>TNF-α (ng/ml)</th>
<th>IL-12p40 (ng/ml)</th>
<th>MIP-2 (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PBS</td>
<td>n.d.</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>LPS</td>
<td>2.60 ± 0.30</td>
<td>4.10 ± 0.67</td>
<td>78.2 ± 6.16</td>
</tr>
<tr>
<td>PDTC</td>
<td>0.47 ± 0.06</td>
<td>1.71 ± 0.30</td>
<td>70.7 ± 6.96</td>
</tr>
<tr>
<td>AS 1</td>
<td>1.60 ± 0.24</td>
<td>2.20 ± 0.45</td>
<td>69.8 ± 7.06</td>
</tr>
<tr>
<td>AS 2</td>
<td>2.80 ± 0.52</td>
<td>3.30 ± 0.64</td>
<td>74.4 ± 5.88</td>
</tr>
<tr>
<td>9h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PBS</td>
<td>n.d.</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>LPS</td>
<td>0.32 ± 0.06</td>
<td>3.43 ± 0.64</td>
<td>12.8 ± 2.04</td>
</tr>
<tr>
<td>PDTC</td>
<td>0.11 ± 0.03</td>
<td>1.82 ± 0.33</td>
<td>7.25 ± 0.87</td>
</tr>
<tr>
<td>AS 1</td>
<td>0.14 ± 0.03</td>
<td>2.03 ± 0.59</td>
<td>10.2 ± 1.97</td>
</tr>
<tr>
<td>AS 2</td>
<td>0.21 ± 0.03</td>
<td>2.11 ± 0.66</td>
<td>10.5 ± 3.40</td>
</tr>
</tbody>
</table>

Treatments were administrated orally 7 days before LPS injection. Data are expressed as mean ± S.D. of eight mice \( p < 0.05 \) compared to the LPS group. n.d.: not detectable.
and MIP-2. The AS1 and PDTC groups showed significantly lower serum TNF-α levels at both 2 and 9 h after LPS challenge compared to the LPS group. There are significantly negative correlations between serum TNF-α levels and life spans ($r = -0.3$, $p = 0.0006$ for 2 h; $r = -0.3$, $p = 0.03$ for 9 h). Our study suggests that the suppression of serum TNF-α at 2 and 9 h may prolong life span of the mice suffering from endotoxic shock.

TNF-α is a representative cytokine capable of initiating systemic inflammatory response syndrome, endotoxin shock and multiple organ failure, which are all correlated with a high mortality. The development of therapies directed towards the inhibition of TNF-α production has been an important goal in improving the management of endotoxic shock.

IL-12p40, a subunit of the heterodimeric cytokine increased in serum after LPS challenge (Table 2), was decreased in the PDTC and AS1 groups, significantly at 2 h. The cytokine IL-12 is a heterodimer of the p40 and p35 subunits and is secreted by macrophages, dendritic cells and B cells. IL-12 promotes the differentiation of naïve T cells and generates memory Th1 cells in response to antigenic stimulation. IL-12p40 was reported to enhance the expression of TNF-α and iNOS, and up-regulate NO production via the activation of NF-kB in BV-2 glial cells, mouse primary microglia and mouse peritoneal macrophages (Jana et al., 2003; Pahan et al., 2001).

In the LPS-induced toxic shock model, the in vivo half-life of IL-12 is much longer than that of other cytokines and may maintain high serum levels of IL-12 for several hours while the production of most other pro-inflammatory cytokines from macrophages has been down-regulated. Thus the excessive production of IL-12 seems to contribute to septic shock and autoimmune diseases (Wysocka et al., 1995).

MIP-2, a critical chemokine for neutrophils recruitment secreted by macrophage and epithelial cells in response to inflammatory stimuli such as LPS, rose in serum at 2 h and dropped at 9 h after LPS challenge (Table 2). Both PDTC and AS EtOAc extract had no significant effect on the serum level of MIP-2. However, serum MIP-2 level at 9 h negatively correlated with life span ($r = -0.46, p = 0.0001$) suggesting that down-regulating MIP-2 secretion during late phase of inflammation is important for endotoxin shock.

MIP-2 expression induced by LPS is dependent on NF-kB activation (Kim et al., 2003; De Plaen et al., 2006). A low molecular weight (<10 kDa) fraction of AS water extract was shown to significantly attenuate a late pro-inflammatory cytokine induced by endotoxin and protected mice against lethal endotoxemia (Wang et al., 2006). Furthermore, Sakai et al. (1997, 1999) reported that ferulic acid and isoferulic acid inhibited MIP-2 production by RAW 264.7 cells, indicating this major compound plays a role in anti-inflammatory activity of AS.

### 3.4. Effects of ferulic acid and Z-ligustilide on NF-kB trans-activation activity

To investigate whether the two major compounds of AS contribute to its anti-inflammatory effect, ferulic acid and Z-ligustilide were tested by NF-kB reporter gene bioassays. As shown in Fig. 3, either ferulic acid, Z-ligustilide, or ferulic acid plus Z-ligustilide significantly suppressed NF-kB activation in a dose dependent manner. In addition, ferulic acid plus Z-ligustilide showed the highest activity ($IC_{50} = 1.20 \mu g/ml$), indicating that ferulic acid plus Z-ligustilide have synergistic effect in the inhibition of LPS/IFN-γ-induced NF-kB trans-activation. The anti-inflammatory effects of ferulic acid and Z-ligustilide were associated with their strong inhibition of NF-kB activity.

Since herbal medicines are becoming popular throughout the world, pharmacological evidence that help an understanding of the action of these medicines and their underlying mechanisms is needed. The active principles of AS have been found to include...
a number of anti-inflammatory substances including polysaccharides and ferulic acid (Yang et al., 2006; Kim et al., 2007).

Ferulic acid is abundant in rice bran, wheat, barley, tomato, sweet corn and toasted coffee. It has been demonstrated to exhibit against Alzheimer’s disease, antioxidant, anti-inflammatory, anti-cancer, anti-hyperlipidemic, antimicrobial, and anti-carcinogenic properties (Yan et al., 2001; Ou et al., 2003; Ronchetti et al., 2006; Kan et al., 2008; Sudheer et al., 2008). Ferulic acid is also shown to have hypotensive activity in experimental animals (Suzuki et al., 2002). Thereby, this hypotensive effect may contribute to the reason for not increasing survival rate by high dose of AS EtOAc fraction (AS2 group) in our study.

Phytochemical studies indicate that Z-ligustilide is a highly lipophilic compound that can facilitate blood circulation, penetrate the blood–brain barrier, act to limit ischemic brain damage in rats, and attenuate pain behavior in mice (Du et al., 2007; Peng et al., 2007; Kuang et al., 2008). Z-ligustilide was shown a significant anti-inflammatory effect that is probably related to an inhibition of TNF-α and NF-κB activity (Liu et al., 2005). Recent study also showed that Z-ligustilide inhibits TNF-α activated NF-κB signaling pathway, which may contribute to its protective effect against β-amyloid peptide-induced neurotoxicity in rat (Kuang et al., 2009). Recent therapeutic interest has focused on AS’s cardiovascular, hepatoprotective, antioxidant and immunomodulatory properties.

The most active compounds in AS appear to be the phthalides, polysaccharides and ferulic acid. Its strong aromatic odor is related to the presence of Z-ligustilide. Preclinical studies indicate that AS and Z-ligustilide may also relax smooth muscle in the circulatory, respiratory and gastrointestinal systems (Wedge et al., 2009). Our data suggested that AS EtOAc extract inhibited the production of inflammatory mediators and alleviated acute hazards especially at its optimal dosages.

In conclusion, our data provide evidence that, in a murine model of LPS-induced endotoxemia, low dose of AS EtOAc extract significantly decreases the serum TNF-α and IL-12p40 levels and thus increases the survival rate in endotoxic shock mice. Two major compounds of AS, ferulic acid and Z-ligustilide, do possess anti-inflammatory properties probably through down-regulating NF-κB activation.

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