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Research Article
Anti-inflammatory Activity of Biphenyls from *Streptomyces* sp. BO07 in LPS-induced RAW 264.7 Cells

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Abstract

Background and Objective: Two new biphenyls, 3'-hydroxy-5-methoxy-3,4-methylenedioxybiphenyl (1) And 3'-hydroxy-5,5'-dimethoxy-3,4-methylenedioxybiphenyl (2) Have been isolated from *Streptomyces* sp. BO07, an endophyte in the root tissue of *Boesenbergia rotunda* (L.) Mansf A. Although, there are many biphenyls on anti-inflammatory activity have been reported. This study investigated the anti-inflammatory property of these biphenyls on LPS-induced macrophage RAW 264.7 cells. **Materials and Methods:** The effects of the two biphenyl compounds were investigated on the formation of NO, PGE_2, TNF-α, IL-1β, IL-6, IL-10 and also on inducible nitric oxide synthase (iNOS) and cyclo-oxygenase-2 (COX-2) in LPS-induced murine macrophage RAW 264.7 cells. **Results:** The data obtained were consistent with the modulation of TNF-α, IL-1β, IL-6, IL-10 production by these biphenyls at concentration of 5-20 μg mL^{-1}. A similar effect was also observed when LPS-induced NO release, iNOS and COX-2 enzyme expression were tested. The inhibitory effects were shown in concentration-dependent manners. However these compounds did not significantly reduce the formation of PGE_2. **Conclusion:** From the obtained results, it is concluded that these biphenyls possess anti-inflammatory activity on LPS-induced RAW 264.7 cells.

Key words: Anti-inflammatory activity, biphenyls, *Streptomyces* sp., RAW 264.7 cells

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Competing Interest: The authors have declared that no competing interest exists.

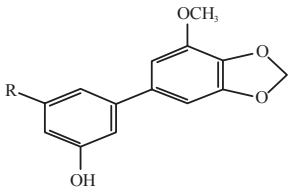
Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Inflammation is one of the defense mechanisms of the immune system which is characterized by pain, swelling, redness and sensation of heat. The inflammatory responses play an important role in host survival although it can also lead to chronic inflammatory diseases such as rheumatoid arthritis[1], asthma[2], cancer[3], Crohn's disease[4] and ulcerative colitis[5]. Inflammation can be initiated by micro-organisms such as lipopolysaccharide (LPS) from Gram-negative bacteria. The LPS is an endotoxin which can directly activate macrophages[6]. The production of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1b (IL-1β), interleukin-6 (IL-6), interleukin-10 (IL-10) and other inflammatory mediators including nitric oxide (NO) and prostaglandin E_2 (PGE_2) is increased during the processes of inflammation in activated macrophages[7].

In previous study the organism *Streptomyces* sp. BO07 was isolated from root tissue of *Boesenbergia rotunda* (L.) Mansf A. (Zingiberaceae). Cultures produced 3'-hydroxy-5-methoxy-3,4-methylenedioxybiphenyl (1) and 3'-hydroxy-5,5'-dimethoxy-3,4-methylenedioxybiphenyl (2) (Fig. 1), which had antibacterial, antioxidant and anti-cancer activities[8]. Biphenyls and substituted derivatives form a large class of secondary metabolites isolated particularly from plants[9] but also from fungi and bacteria[10,11]. Phenolic compounds display a wide variety of pharmacological and biochemical properties[12-16]. In particular some have been found to be potent against inflammation and edema and/or to affect enzymes and chemical mediators involved in the inflammation process. Biphenyls are particularly active but systems with groups such as methoxy, prenyl, geranyl, etc., can also be active[17,18]. Biphenyl-type neolignan derivatives isolated from the twigs of *Magnolia denudata* have shown anti-inflammatory activity by inhibiting N-formyl-L-methionyl-L-leucyl-L-phenylalanine/cytochalasin B (fMLP/CB)-induced elastase released from human neutrophils[19]. Of the new biphenyls, 3-hydroxy-2',5-dimethoxybiphenyl and 2',3-dihydroxy-5-methoxybiphenyl isolated from the roots of *Rhaphiolepis indica* have also exhibited inhibitory effects on fMLP-induced superoxide production by human neutrophils[20]. For these reasons it was of interest to further explore the bioactivity profiles of biphenyls 1 and 2.

Therefore, the objective of the present study was to evaluate the anti-inflammatory activities of biphenyls on LPS-activated macrophage RAW 264.7 cells by investigating their effect on the inhibition of production of NO, PGE_2, TNF-α, IL-1β, IL-6 and IL-10. It is known that during inflammatory processes large amounts of proinflammatory mediators inter alia NO and PGE_2 are generated by the inducible NO synthase (iNOS) and cyclo-oxygenase-2 (COX-2) enzymes, respectively[21,22] and cytokines (e.g., TNF-α, IL-1β, IL-6 and IL-10) are also involved. Therefore, the effects of biphenyls on the expression of iNOS and COX-2 enzyme in LPS-activated macrophage RAW 264.7 cells are also reported.



1 R = H
2 R = H_3CO

Fig. 1: Chemical structures of 3'-hydroxy- 5-methoxy-3, 4-methylenedioxybiphenyl (1) and 3'-hydroxy-5, 5'-dimethoxy-3,4-methylenedioxybiphenyl (2)

MATERIALS AND METHODS

Extraction and isolation: *Streptomyces* sp. BO-07 was isolated from the root tissue of *Boesenbergia rotunda* (L.) Mansf A. by the surface-sterilization technique and identified as described in our previous study[8]. Strain BO07 was grown on ISP-2 agar at 30°C for 14 days and then the culture medium was cut into small pieces that were extracted with ethyl acetate (3×500 mL). This organic solvent was pooled and then taken to dryness under rotary evaporation to give a dark brown solid (1.68 g). The solid was separated by column chromatography using silica gel 60 (Merck, 0.040-0.063 mm) and petroleum/ethyl acetate (2:1 and 1:1) as the eluent to give five main fractions (F1-F5). Only fraction F3 (0.54 g) displayed antibacterial activity by disk diffusion method. This fraction was further separated by TLC (Merck, Si gel 60, 0.5 mm, hexane/ethyl acetate (3:2) to give 157 and 96 mg of pure compounds 1 and 2, respectively. The structural determination of the compounds was made by spectral analyses as described in the previous report[8].

Cell culture and sample treatment: The RAW 264.7 murine macrophage cell line was obtained from the Korean Cell Line Bank (Seoul, Korea). These cells were grown at 37°C in DMEM medium supplement with 10% FBS, penicillin (100 units mL^{-1}) and streptomycin sulfate (100 μg mL^{-1}) in a humidified atmosphere of 5% CO_2. Cells were incubated with compounds 1 and 2 at increasing concentrations and stimulated with LPS 1 μg mL^{-1} for 24 h.

MTT assay for cell viability: Cytotoxicity studies were performed on a 96-well plate. RAW 264.7 cells were mechanically scraped and plated 2×10^5 per well on 96-well plate containing 100 µL of DMEM medium with 10% FBS and incubated overnight. The compounds 1 and 2 were dissolved in dimethyl sulfoxide (DMSO) for stock solution. The DMSO concentrations in all assays did not exceed 0.1%. About 24 h after seeding, 100 µL new media or test compound was added and the plates were incubated for 24 h. Cells were washed once before adding 50 µL FBS-free medium containing 5 mg mL^{-1} MTT. After 4 h of inoculation at 37°C, the medium was discarded and the formazan blue, which formed in the cells was dissolved in 50 µL DMSO. The optical density was measured at 450 nm. The concentration required for reducing the absorbance by 50% (IC_{50}) compared to the control cells was determined.

Nitrite assay: Nitrite accumulation, an indicator of NO synthesis was measured in the culture medium by Griess reaction[21]. Briefly, 100 µL of cell culture medium was mixed with 100 µL of Griess reagent [equal volumes of 1% (w/v) sulfanilamide in 5% (v/v) phosphoric acid and 0.1% (w/v) naphthylethylenediamine-HCl] and incubated at room temperature for 100 min and then the absorbance at 550 nm was measured in a micro-plate reader. Fresh culture medium was used as the blank in all experiments. The amount of nitrite in the samples was calculated from a sodium nitrite standard curve freshly prepared in culture medium.

PGE_2, TNF-α, IL-1β, IL-6 and IL-10 assay: The PGE_2, TNF-α, IL-1β, IL-6 and IL-10 level in macrophage culture medium were quantified by ELISA kits (PeproTech, NJ, USA) according to the manufacturer's instructions.

Western blot assay: Cellular proteins were extracted from control and test compound-treated RAW 264.7 cells as described in our previous study[22]. Protein concentration was determined by BioRad protein assay reagent according to the manufacturer's instructions, 40-50 µg of cellular proteins from treated and untreated cell extracts were electro-blotted onto nitrocellulose membrane followed by separation on 10% SDS-polyacrylamide gel electrophoresis. The immunoblot was incubated overnight with blocking solution (5% skim milk) at 4°C, followed by incubation for 4 h with a 1:500 dilution of monoclonal anti-iNOS or COX-2 antibody (Santacruz, CA, USA). Blots were washed 2 times with PBS and incubated with a 1:1000 dilution of horseradish peroxidase-conjugated goat anti-mouse IgG secondary antibody (Santacruz, CA, USA) for 1 h at room temperature. Blots were again washed three times in Tween 20-Tris-buffered saline and then developed with the colorimetric substrate 3,3',5,5'-tetramethylbenzidine (SurModics, MN, USA).

Data analysis: Data are reported as Mean±SEM values of three independent determinations. Statistical analysis was performed by Student's t-test.

RESULTS

Effects of biphenyl compounds on cell viability in RAW 264.7 cells: In this study, biphenyl compounds at concentrations of 40 and 80 µg mL^{-1} caused a significant reduction in cell viability ($p<0.05$). However, these compounds at concentrations of 5, 10 and 20 µg mL^{-1} did not show any cytotoxic activity in MTT assays. In detail, the cell viability in RAW 264.7 cells which were incubated with compound 1 at concentrations of 5, 10, 20, 40 and 80 µg mL^{-1} for 24 h were 103.36±3.86, 101.24±4.56, 98.86±5.55, 81.36±7.32 and 57.32±6.98%, while the cell viability of compound 2 at different concentrations were 101.15±4.25, 99.65±3.94, 97.82±4.70, 78.61±6.78 and 52.41±7.26% of the control group treated with media only, respectively (Fig. 2). Therefore, the non-toxic concentrations of up to 20 µg mL^{-1} were chosen for subsequent experiments.

Effects of biphenyl compounds on NO and PGE_2 production in LPS-induced RAW 264.7 cells: The LSP caused a significant increase in NO and PGE_2 production when compared with the

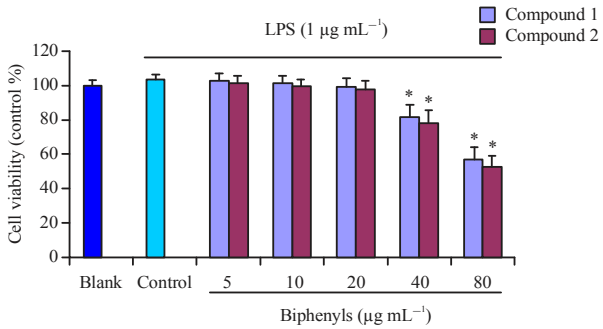


Fig. 2: Effects of biphenyl compounds on cell viability in LPS-induced RAW 264.7 macrophage cells. RAW 264.7 cells were cultured with increasing concentrations (5-80 µg mL^{-1}) of biphenyl compounds in the presence of LPS (1 µg mL^{-1}) for 24 h. Cell viability was tested by MTT assays
The values are the means of at least three determinations±SEM

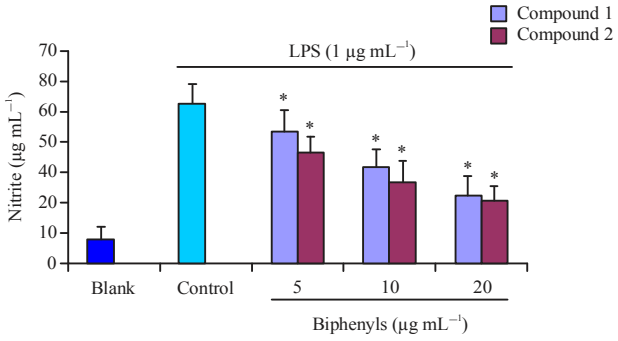


Fig. 3: Evaluation of nitrite production by RAW 264.7 cells stimulated for 24 h with LPS alone or in combination with increasing concentrations (5-20 μg mL^{-1}) of biphenyl compounds

The values are the means of at least three determinations±SEM. Probability level (Student's t-test): *p<0.05 vs. LPS-treated group

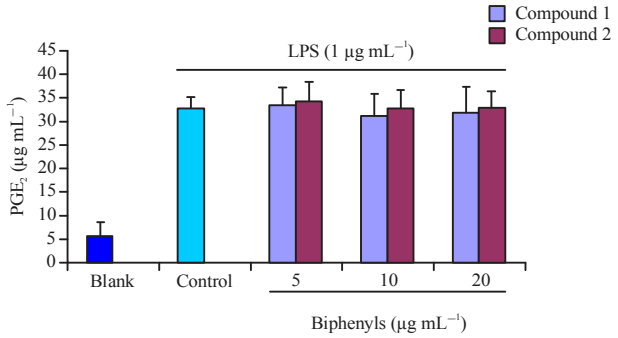


Fig. 4: Effect of biphenyl compounds on PGE2 production in LPS-induced RAW 264.7 macrophage for 24 h

The values are the means of at least three determinations±SEM. Probability level (Student's t-test)

blank control, biphenyl compounds at concentrations of 5, 10 and 20 μg mL^{-1} caused a significant reduction in NO production when compared with LPS-induced control group ($p<0.05$) but did not cause a significant reduction in PGE_2 production. In detail, the production of NO in LPS-induced RAW 264.7 incubated with compound 1 at concentrations of 5, 10 and 20 μg mL^{-1} for 24 h were 43.67±6.11, 31.86±5.46 and 22.13±6.76 μM, respectively, the production of NO in LPS-induced RAW 264.7 incubated with compound 2 at different concentrations were 36.74±5.05, 26.67±6.81 and 20.87±4.38 μM, respectively, while the production of NO in the group treated with LPS only was 52.64±6.11 μM. The production of PGE_2 in LPS-induced RAW 264.7 incubated with compound 1 at concentrations of 5, 10 and 20 μg mL^{-1} for 24 h were 34.15±4.25, 32.65±3.94 and 32.82±3.70 ng mL^{-1}, respectively, the production of PGE_2 in LPS-induced RAW

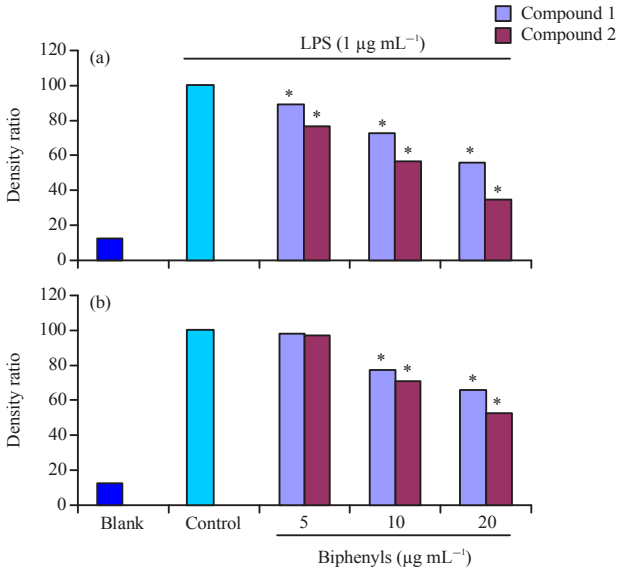


Fig. 5(a-b): Effect of biphenyl compounds on iNOS protein production (a) COX-2 protein expression and (b) LPS-induced RAW 264.7 macrophage for 24 h

Probability level (Student's t-test): *p<0.05 vs. LPS-treated group

264.7 incubated with compound 2 at different concentrations were 33.36±3.86, 31.24±4.56 and 31.86±5.55 ng mL^{-1}, respectively, while the production of PGE_2 in the group treated with LPS only was 32.66±2.56 ng mL^{-1}. Therefore, the inhibitory levels of biphenyl compounds on NO production also showed a dose-dependent pattern, while these compounds did not significantly reduce the formation of PGE_2 (Fig. 3, 4).

Effects of biphenyl compounds on iNOS and COX-2 production in LPS-induced RAW 264.7 cells: The effects of biphenyl compounds on iNOS and COX-2 production in LPS-induced RAW 264.7 cells were also carried out by Western blot analysis. Results of relative density ratio from Western blot analysis further indicated that iNOS and COX-2 production in LPS-induced RAW 264.7 cells were significantly reduced when treated with biphenyl compounds in different concentration. In detail, the relative density ratio of iNOS production in LPS-induced RAW 264.7 incubated with compound 1 at concentrations of 5, 10 and 20 μg mL^{-1} for 24 h were 88.86, 72.28 and 55.68, respectively and the relative density ratio of iNOS production in LPS-induced RAW 264.7 incubated with compound 2 at different concentrations were 75.83, 56.77 and 34.32, respectively (Fig. 5a). The relative density ratio of COX-2 production in LPS-induced RAW 264.7 incubated with compound 1 at concentrations of 5, 10 and 20 μg mL^{-1}

for 24 h were 97.99, 76.98 and 65.79, respectively and the relative density ratio of COX-2 production in LPS-induced RAW 264.7 incubated with compound 2 at different concentrations were 96.69, 70.86 and 52.63, respectively (Fig. 5b). Therefore, the inhibitory levels of biphenyl compounds on iNOS and COX-2 production in LPS-induced RAW 264.7 cells also showed a dose-dependent pattern.

Effects of biphenyl compounds on pro-inflammatory cytokine production in LPS-induced RAW 264.7 cells: In this study data showed that biphenyl compounds decreased production of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6 and IL-10 in LPS-induced RAW 264.7 cells ($p<0.05$) (Fig. 6-9). Treatment with LPS alone in RAW 264.7 cells resulted in a significant increase of pro-inflammatory cytokine productions compared with the blank control group. The detailed results of this assay were as follows: TNF-α productions in LPS-induced RAW 264.7 cells incubated with compound 1 at concentrations of 5, 10 and 20 μg mL^{-1} for 24 h were 30.56±4.51, 21.87±3.20 and 13.97±3.32 ng mL^{-1}, respectively, TNF-α productions in LPS-induced RAW 264.7 incubated with compound 2 at different concentrations were 24.75±4.02, 16.09±2.74 and 11.85±2.32 ng mL^{-1}, respectively, while the production of TNF-α in the group treated with LPS only was 38.73±3.78 ng mL^{-1}, IL-1β productions in LPS-induced RAW 264.7 cells incubated with compound 1 at different concentrations were 30.58±6.26, 16.86±7.24 and 11.56±4.56 ng mL^{-1}, respectively, IL-1β productions in LPS-induced RAW 264.7 cells incubated with compound 2 at different concentrations were 25.03±4.60, 10.60±4.28 and 8.58±3.32 ng mL^{-1}, respectively, while the production of IL-1β in the group treated with LPS only was 42.39±5.48 ng mL^{-1}, IL-6 productions in LPS-induced RAW 264.7 cells incubated with compound 1 at different concentrations were 24.68±3.76, 16.01±3.46 and 12.42±2.53 ng mL^{-1}, respectively, IL-6 productions in LPS-induced RAW 264.7 cells incubated with compound 2 at different concentrations were 20.01±2.68, 10.61±2.34 and 6.86±1.31 ng mL^{-1}, respectively, while the production of IL-6 in the group treated with LPS only was 30.78±5.96 ng mL^{-1}, IL-10 productions in LPS-induced RAW 264.7 cells incubated with compound 1 at different concentrations were 21.81±3.66, 16.61±2.56 and 12.32±2.83 ng mL^{-1}, respectively, IL-10 productions in LPS-induced RAW 264.7 cells incubated with compound 2 at different concentrations were 17.01±2.67, 9.61±2.84 and 7.86±2.39 ng mL^{-1}, respectively, while the production of IL-10 in the group treated with LPS only was 25.79±4.97 ng mL^{-1}. Therefore, treatment with biphenyl compounds (5, 10 and 20 μg mL^{-1}) remarkably inhibited in a LPS-induced TNF-α, IL-1β, IL-6 and IL-10 production in a dose-dependent manner.

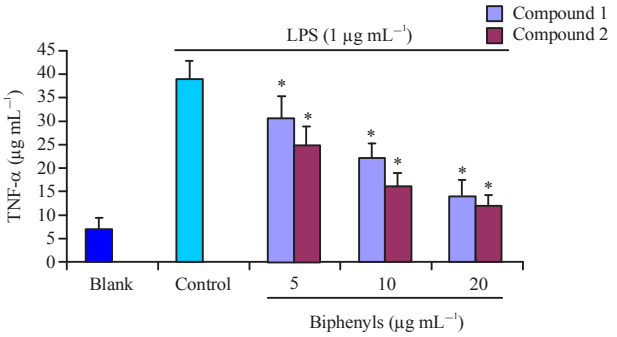


Fig. 6: Effect of biphenyl compounds on LPS-induced TNF-α production by RAW 264.7 cells
The values are the means of at least three determinations±SEM. Probability level (Student's t-test): *p<0.05 vs. LPS-treated group

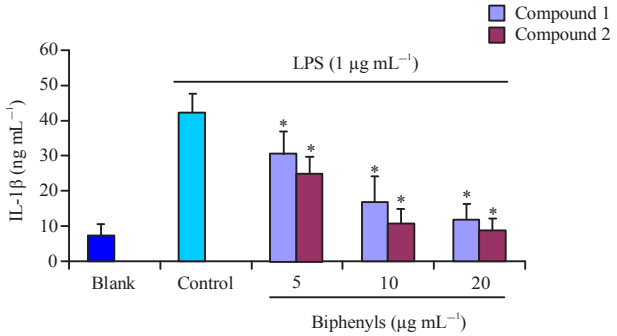


Fig. 7: Effect of biphenyl compounds on LPS-induced IL-1β production by RAW 264.7 cells
The values are the means of at least three determinations±SEM. Probability level (Student's t-test): *p<0.05 vs. LPS-treated group

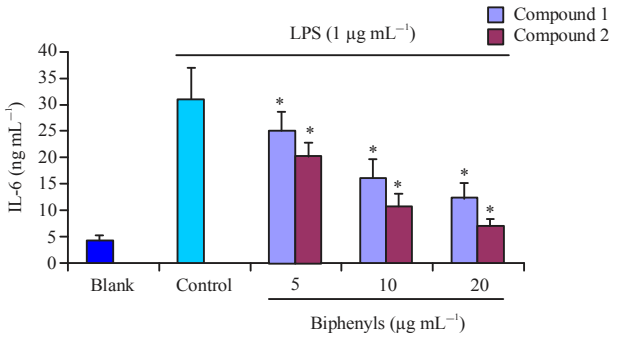


Fig. 8: Effect of biphenyl compounds on LPS-induced IL-6 production by RAW 264.7 cells
The values are the means of at least three determinations±SEM. Probability level (Student's t-test): *p<0.05 vs. LPS-treated group

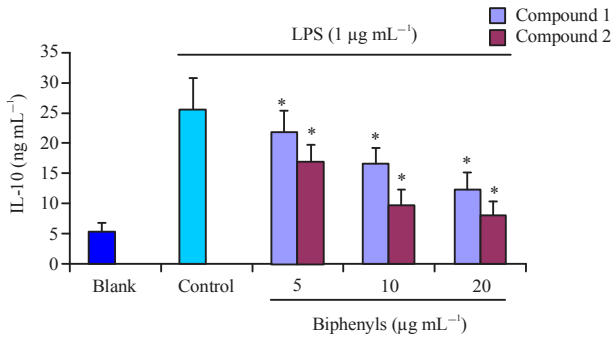


Fig. 9: Effect of biphenyl compounds on LPS-induced IL-10 production by RAW 264.7 cells

The values are the means of at least three determinations±SEM. Probability level (Student's t-test): *p<0.05 vs. LPS-treated group

DISCUSSION

Chronic inflammation is one of the major inducers of various diseases. Many pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6 and IL-10 as well as other inflammatory mediators including NO and PGE_2 are produced during the inflammation process[3]. It is well known that macrophages play a crucial role in both non-specific and acquired immune responses and macrophage activation by LPS leads to a functionally diverse series of responses including the production of proinflammatory cytokines (TNF-α, IL-1β, IL-6 and IL-10)[23], the activation of phospholipase A2 producing lipid metabolites of arachidonic acid such as PGs and NO production[24,25]. These mediators drive the recruitment and initiation of macrophages and other immune cells to complete a full cycle of inflammation and interfere with metabolic functions[26,27]. TNF-α, IL-1β, IL-6 and IL-10 are pro-inflammatory cytokines produced by various immune cells including macrophages, monocytes and lymphocytes in response to inflammation and infection[28]. Growing evidence demonstrated that TNF-α, IL-1β, IL-6 and IL-10 played a central role in the inflammatory process during cancer development, leading a new direction of therapeutics, the pro-inflammatory cytokines blocking agents[27]. NO and PGE_2 also work as pro-inflammatory mediators that are produced by inducible nitric oxide synthase (iNOS) and cyclo-oxygenase (COX-2) respectively, which are involved in the innate response in activating macrophages[29].

The LPS (1 μg mL^{-1}) highly induced NO_2 production in murine macrophage RAW 264.7 cells. Treatment of biphenyl compounds (5-20 μg mL^{-1}) prevented NO production in dose-dependent fashion and cell viability was observed to be over 90% by the MTT assay. Results from Western blotting analysis further indicated that LPS-induced expression in RAW 264.7 macrophages was significantly reduced by these compound treatment. The enzyme iNOS is responsible for long-lasting NO production and it is strikingly induced by LPS as shown in this study. Therefore, these results suggested that inhibition of LPS-induced NO production is due to iNOS gene expression. Mechanism of various anti-inflammatory action is at least shared by the inhibition of prostaglandin synthesis, which is mediated by COX. This exists in two isoforms, COX-1 and 2, each with distinct expression pattern in various cell types. COX-1 has been suggested to provide a physiologic level of prostaglandins for normal platelet, stomach and kidney function[30]. In contrast, COX-2 has been found to be highly induced at inflammatory sites in animals as well as patients with inflammatory diseases[24,31] and it is considered to be responsible for proinflammatory prostaglandin formation[32,33]. In addition to inhibition of NO release and iNOS induction, biphenyl compounds also significantly inhibited COX-2 gene expression in LPS-treated RAW 264.7 macrophages but they did not inhibit PGE_2 production. The reason for this phenomenon is due to PGE_2 production by the other pathways for example COX-1 and prostaglandin synthases with a relatively contribution of the isoprostane pathway[34,35].

It has been reported that cytokines such as TNF-α, IL-1β, IL-6 and IL-10 are pro-inflammatory *in vitro* as well as *in vivo*[36-38]. The present study also demonstrated that biphenyl compounds have inhibitory effects on the production of TNF-α, IL-1β, IL-6 and IL-10 in LPS-stimulated RAW 264.7 macrophages. The LPS-induced productions of TNF-α, IL-1β, IL-6 and IL-10 were significantly inhibited by biphenyl compounds in a concentration-dependent manner. In addition, cytotoxic effect of biphenyl compounds was evaluated in the absence or presence of LPS. When treated alone, these compounds did not affect the cell viability at all concentrations used (5-20 μg mL^{-1}). The potencies of the inhibitory activities of biphenyl compounds on RAW 264.7 macrophage cells are expected that these compounds would be useful for the treatment of inflammatory diseases that show the increased expression of COX-2 and iNOS enzyme.

CONCLUSION

The results obtained here demonstrate that biphenyl compounds, 3'-hydroxy-5-methoxy-3,4-methylenedioxybiphenyl (1) and 3'-hydroxy-5,5'-dimethoxy-3,4-methylenedioxybiphenyl (2), isolated from the culture of *Streptomyces* sp. BO07, an endophyte in *Boesenbergia*

rotunda (L.) Mansf A are able to inhibit various pro-inflammatory mediators in LPS-activated macrophages, except PGE_2 and also shows a capacity to attenuate cytokine-mediated inflammation. The limitation of this study is an *in vitro* experiment, thus an *in vivo* experiment can be considered in further studies.

SIGNIFICANCE STATEMENT

This study has demonstrated that biphenyl compounds, isolated from endophytic *Streptomyces* sp. BO07, showed significantly suppression in the releases of TNF-α, IL-1β, IL-6 and IL-10 and the production of NO and expression of COX-2 and iNOS enzyme in LPS-stimulated macrophages in a dose-dependant manner. These results suggest that biphenyl compounds can inhibit inflammatory response and may be a potential therapeutic candidate for the treatment of chronic inflammatory diseases.

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