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Inhibition of interleukin-8 production in interleukin-1 stimulated human monocytic THP-1 cells by *N,N*-didesmethylgrossularine-1 obtained from an Ascidian *Polycarpa aurata* collected in North Sulawesi

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Abstract. *N,N*-Didesmethylgrossularine-1 (DDMG-1) has a rare β -carboline structure and was isolated from an Indonesian ascidian *Polycarpa aurata* as an active component against tumor necrosis factor (TNF)- α production in lipopolysaccharine (LPS)-stimulated murine macrophage-like RAW 264.7 cells as reported in our previous paper. Further investigation on the inhibitory activity of DDMG-1 against the production of inflammatory cytokines in human monocytic THP-1 cells, we found that DDMG-1 reduced the excess production of IL-8 in LPS-stimulated THP-1 cells through inhibition of the mRNA level of IL-8 1 κ B- α degradation, and binding of NF- κ B to the target DNA site. The THP-1 cells used in this study showed the high production of IL-8 by the stimulation with TNF- α , IL-1 β , and 12-O-tetradecanoylphorbol-13-acetate (PMA) as similar to LPS. DDMG-1 inhibited the IL-8 production in IL-1 β -stimulated THP-1 cells but did not show an inhibitory activity in the cells stimulated by TNF- α and PMA. Therefore, DDMG-1 was specific to the IL-1 β signalling pathway. These results suggested that DDMG-1 could be a useful drug candidate lead compound to control the excess production of IL-8.

1. Introduction

In the previous paper [1], we described the inhibitory activity of *N,N*-didesmethylgrossularine-1 (DDMG-1) on the production of tumor necrosis factor (TNF)- α in lipopolysaccharide (LPS)-stimulated murine macrophage-like RAW 264.7 cells. To compare the difference in the response to DDMG-1 between murine and human immune cells, studies on the effects of DDMG-1 against the production of inflammatory cytokines were performed using human monocytic THP-1 cells, which produced large amounts of interleukin (IL)-8 (abt. 220 ng/ mL) by the stimulation with LPS.

THP-1 cells were derived from an acute monocytic leukemia patient and can be differentiated into macrophage-like cells by for example 12-O-tetradecanoylphorbol-13-acetate (PMA) [2], and, therefore, this cell line is used for the studies on monocyte/macrophage functions, immune modulations [3]. LPS is a component of the Gram-positive bacterial cell wall and frequently used as an inflammatory model because of its property to activate macrophages [4]. Macrophages play important roles in immune reactions, inflammation, and allergy [5]. In response to LPS and other

stimulants, macrophages secrete many kinds of inflammatory cytokines such as IL-1 and IL-6, chemokines such as IL-8, and (TNF)- α via the activation of nuclear factor-kappa B (NF- κ B) [6]. IL-8 is a member of the superfamily of C-X-C chemokines and is a chemotactic factor for T cells, neutrophils, and basophils. Expression of IL-8 has been detected in various human cancers and it has been suggested to be a factor in tumor progression and metastasis [7][8][9]. Regulation of IL-8 production is, therefore, an important target for therapeutic research. In this study, we found that DDMG-1 reduced the IL-8 production in LPS-stimulated THP-1 cells through the inhibition of the messenger RNA (mRNA) level of IL-8, NF- κ B inhibitor (I κ B)- α degradation, and binding of NF- κ B to the target DNA site, which was specific to the IL-1 β signaling pathway.

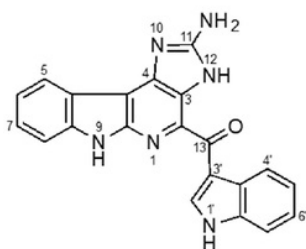


Figure 1. Structure of *N,N*-didesmethylgrossularine-1 (DDMG-1) isolated from *Polycarpa aurata* collected in North Sulawesi.

2. Materials and Methods

2.1. General experimental procedures.

EI mass spectra were obtained by a JEOL JMS-MS 700 mass spectrometer (Tokyo, Japan). ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-AL-400 NMR spectrometer at 400 MHz for ^1H and 100 MHz for ^{13}C in CD_3OD (δH 3.30, δC 49.0). Preparative HPLC was carried out with a Hitachi L-6200 system.

2.2. Materials.

Fetal bovine serum (FBS) and other culture materials were purchased from Invitrogen (Carlsbad, CA, USA). β -actin was purchased from Santa Cruz Biotechnology (Santa Cruz, CA, USA). All other chemicals, including endotoxin LPS (*Escherichia coli* 055-85) and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), were purchased from Sigma-Aldrich (St. Louis, Mo., USA).

Isolation of *N,N*-didesmethylgrossularine-1 (DDMG-1).

The solitary ascidian *P. aurata* (978 g, wet weight) was collected by scuba diving in the coral reef at Manado, North Sulawesi, on September 19th 2008, cut into small pieces, and soaked in EtOH on a boat immediately after collection. The EtOH extract was evaporated, and the residue was dissolved in MeOH-H₂O (4:1) and washed with n-hexane. The methanolic solution was concentrated and diluted with water to a MeOH content of 40%, and the solution was extracted with CHCl_3 . The CHCl_3 extract (5.3 g) was separated by a SiO_2 column with CHCl_3 -MeOH (gradient elution) into six fractions. The 7:3 eluate (3.2 g) was subjected to ODS column chromatography (eluted with 50, 70, 85, and 100% MeOH) to give four fractions. DDMG-1 (5.2 mg) was purified from the second fraction (70% MeOH elution, 0.3 g) by preparative HPLC (ODS, 70% MeOH).

DDMG-1: a yellow pigment; ^1H NMR; ^{13}C -NMR EIMS m/z 366 [M]⁺; 249 [M - indole]⁺; 221 [M - indole - CO]⁺. Table 1 [14].

Table 1. NMR Data for DDMG-1 [14]

C	¹ H, δ		¹³ C	
		δ	mult ^b	HMBC corr
1				
2		146.6	C	
3		132.4	C	
4		126.5	C	
4a		105.4	C	
4b		119.8	C	
5	8.19 (d, 7.8)	122.7	CH	C-7 ⁵⁴
6	7.21 (td, 7.8, 1.2)	118.9	CH	C-4b/C-7/C-8
7	7.41 (td, 7.8, 1.2)	127.4	CH	C-6/C-8a
8	7.51 (d, 7.8)	110.6	⁴⁵ C	C-4b
8a		137.5	C	
9	11.6 (s)			C-4a/C-4b
11			159.4	C
12	11.3 (s)			
13		187.0	C	
1'	12.2 (s)			²⁸
2'	9.6 (s)	139.7		C-3'/C-7a'
3'		114.5		C
3a'		125.7		C
4'	8.54 (m)	122.3	CH	C-4'/C-9' C-3a'/C-7a'
4b				
5'	7.26 (m)	121.8 ^c	CH	
6'	7.27 (m)	121.9 ^c	CH	
7'	7.57 (m)	112.2	CH	C-6'/C-7a'
7a'		135.9	C	

2.3. Cell culture ³⁴

The culture of THP-1 cells was performed in the RPMI medium containing 10% FBS. THP-1 cells were pretreated with DDMG-1 for 5 min ²⁷ After addition of each stimulant (LPS, TNF- α , IL-1 β , ³³ PMA at the final concentration of 1 $\mu\text{g}\cdot\text{mL}^{-1}$, 20 $\text{ng}\cdot\text{mL}^{-1}$, 5 $\text{ng}\cdot\text{mL}^{-1}$, and ¹⁹ nM, respectively), the cells were cultured for 24 h at 37 °C. The concentration of inflammatory cytokines in each culture supernatant was measured by enzyme-linked immunosorbent assay (ELISA). A control experiment was carried out without the addition of a stimulant.

2.4. Measurement of IL-8 mRNA expression. ⁴⁴

THP-1 cells were incubated with 5 or 10 μM ³ DDMG-1 for 1 h, and then 1 μg of LPS was added. After incubation for 6 h, the cells were recovered and washed twice with phosphate-buffered saline (PBS) (-). The total RNA was extracted with an RNeasy Mini Kit (Qiagen Co., Tokyo, Japan). An iScript cDNA synthesis Kit was used to synthesize the first-strand cDNAs from 1 μg of the total RNA. ³⁹ Polymerase chain reaction (PCR) was performed using the CFX96/384 real-time PCR system (BIO-RAD, California, USA). Primers (human IL-8 and GAPDH) for quantitative PCR were purchased from BIO-RAD (USA).

2.5. Western blot analysis. ⁴¹

THP-1 cells were treated with DDMG-1 ⁵³ for 15 min and then stimulated with LPS (1 $\mu\text{g}/\text{mL}$) for 5–30 min. Cytoplasmic extracts of cells were subjected to Western blot analysis with an anti-I κ B antibody.

The blots were finally reacted with the ECL reagent (Amersham-Pharmacia, San Francisco, CA, USA) and exposed to X-ray film [10].

2.6. Determination of cell cytotoxicity.

Cell proliferation was evaluated by enumerating viable cells using the MTT formazan production method [11]. THP-1 cells were incubated with various concentrations (0.1, 1, 3, and 10 μ M) of DDMG-1 for 24 h. The cells were treated with MTT solution and, after incubation for 3 h, production of formazan was assessed by measuring optical density (OD) at 570 nm.

2.7. Preparation of nuclear extracts and electrophoretic mobility shift assay (EMSA).

Nuclear extracts were prepared from THP-1 cells as described previously [12]. EMSA was conducted on 5% polyacrylamide gels in 1 x Tris-borate/EDTA electrophoresis buffer. The other experimental conditions were the same as described in the previous report [12].

2.8. Statistical analysis.

Each experiment was performed at least three times, and representative data are shown. Means were checked for statistical differences using Student's t-test with error probabilities of $p < 0.1$.

3. Results and Discussion

3.1. Isolation of DDMG-1.

DDMG-1 was obtained as a yellow pigment from *P. aurata* collected in the coral reef at Manado, North Sulawesi. The structure (Fig. 1) was confirmed by the direct comparison of chromatographic and spectroscopic properties with those of the compound isolated and identified previously [13].

DDMG-1 was first isolated from *P. aurata* collected in Chuuk Atoll [14], and we isolated this compound from an Indonesian *P. aurata* and reported the inhibitory activity against the production of TNF- α in LPS-stimulated RAW 264.7 [1]. Three α -carboline alkaloids, grossularines-1 (*N,N*-dimethylamino derivative at C-11 of DDMG-1) and -2 (4-hydroxyphenyl derivative at C-13 of grossularine-1) [15] and DDMG-1 [14], have thus far been isolated from ascidians. Grossularines-1 and -2 showed the weak cytotoxicity against murine leukemia L1210 cells and more potently to human colon (WiDr) and breast (MCF7) tumor cell lines [15][16]. Interestingly, the mechanisms of cytotoxicity by these compounds were suggested to be different [16]. On the other hand, the biological activity of DDMG-1 has not been reported, and we found for the first time the inhibitory activity of DDMG-1 against TNF- α [1].

3.2. Inhibition of LPS-induced IL-8 production by DDMG-1 in THP-1 cells.

We first examined the effect of DDMG-1 on LPS-stimulated THP-1 cells in order to compare the experimental results from the previous study using murine RAW 264.7 cells [1]. In LPS-stimulated THP-1 cells, large amounts of IL-8 (ca 220 ng/mL) were detected in the culture supernatant, but the production of TNF- α was small. Therefore, the effects of DDMG-1 on the inflammatory cytokine production system were observed for the IL-8 production. The results of the quantitative analysis of IL-8 in the culture supernatant detected by ELISA are shown in Fig. 2A, and Fig. 2B shows the effects of DDMG-1 on the IL-8 mRNA expression detected by real-time PCR analysis. These results indicated that DDMG-1 inhibited the IL-8 production in LPS-stimulated THP-1 cells, although the inhibitory effects at lower concentrations of DDMG-1 were smaller than those in RAW cells [1]. Since the transcription factor NF- κ B is also greatly involved in the production of IL-8, we examined the effects of DDMG-1 (10 μ M) on the induction of NF- κ B using Western blot analysis (Fig. 2C) and EMSA (Fig. 2D). These experiments revealed that DDMG-1 suppresses the activation of NF- κ B transcription factor. Consequently, DDMG-1 (10 μ M) had a very similar inhibitory activity against the TNF- α and IL-8 production in LPS-stimulated RAW 264.7 and THP-1 cells, respectively.

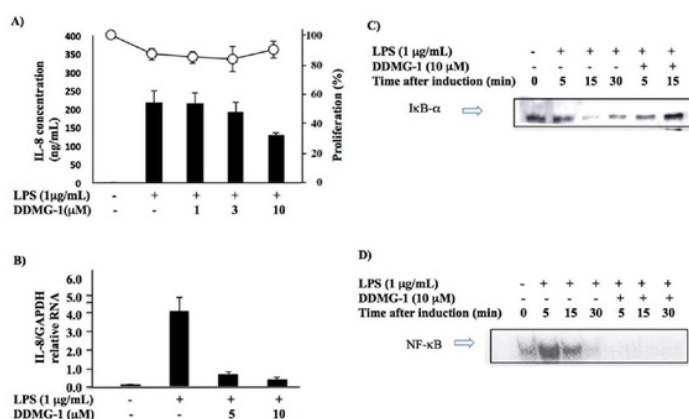


Figure 2. Effects of DDMG-1 on IL-8 production and intracellular signaling molecules in LPS-stimulated THP-1 cells. A): Effects of DDMG-1 on IL-8 production (solid bar) and cell proliferation (open circle). Concentration of IL-8 was measured by ELISA. Statistical difference compared to the control, $p < 0.1$. The effect on cell proliferation was measured by the MTT assay, and data are the means relative (%) to the control value. B): Effects of DDMG-1 on IL-8 mRNA induction. The relative ratio is shown as a percentage, whereby the IL-8 signal was normalized to the GAPDH signal. C): Effects of DDMG-1 on NF-κB transcription by IκB-α degradation. Total proteins were extracted at the indicated times, resolved by 10% SDS-PAGE, blotted, and examined by Western blotting using polyclonal anti-serum against IκB-α. D): Effects of DDMG-1 on DNA 20 binding activities of NF-κB transcription factor. EMSA was performed using 32P-labeled probes that possessed NF-κB binding sites. The NF-κB/probe complex is indicated.

3.3. Effects of DDMG-1 on IL-8 production in THP-1 cells stimulated with IL-1β, TNF-α and PMA
 Since the production of IL-8 was also induced in THP-1 cells by IL-1β, PMA, and TNF-α as similar to the stimulation by LPS, we examined the effects of DDMG-1 on the IL-8 production in THP-1 cells stimulated with IL-1α, PMA, and TNF-α (Fig. 3). Interestingly, DDMG-1 showed the different effects on the IL-8 production in THP-1 cells with the different stimulants. DDMG-1 inhibited the IL-8 production in a dose-dependent manner in IL-1β-stimulated THP-1 cells (Fig. 3A). On the other hand, an inhibitory activity of DDMG-1 on the IL-8 production in THP-1 cells stimulated with PMA and TNF-α was not detected (Fig. 3B and C), and increased production was observed in PMA-stimulated THP-1 cells (Fig. 3B). It will be suggested that DDMG-1 enhanced the activation of THP-1 cells by PMA.

These results indicated that the suppressive activity on IL-8 production by DDMG-1 will be specific to the IL-1β signaling pathway.

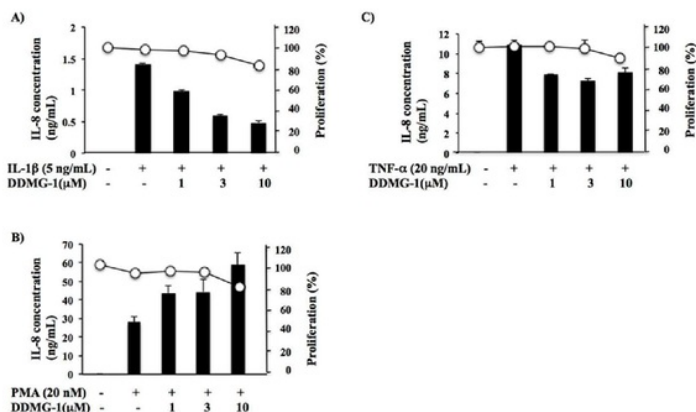


Figure 3. Effects of DDMG-1 on IL-8 production (solid bar) and cell proliferation (open circle) in THP-1 cells stimulated with IL-1 β (A), PMA (B), and TNF- α (C). Concentration of IL-8 was measured by ELISA. Statistical difference compared to the control, $p < 0.05$ (A) and 0.1 (B and C). The effect on cell proliferation was measured by the MTT assay, and data are the means relative (%) to the control value.

4. Conclusions.

DDMG-1 (Fig. 1), a rare α -carboline alkaloid, has been obtained from an Indonesian ascidian *P. aurata* as an active component against the production of TNF- α from LPS-stimulated murine RAW 364.7 cells [1]. In this study, we examined the effects of DDMG-1 on the inflammatory cytokine production using human monocytic THP-1 cells to compare the results from RAW 264.7 cells. THP-1 cells used in this study produced large amounts of IL-8 by the stimulation with LPS, IL-1 β , PMA, and TNF- α . DDMG-1 inhibited the excess production of IL-8 in LPS-stimulated THP-1 cells by the inhibition of the mRNA level of IL-8, I κ B- α degradation, and binding of NF- κ B to the target DNA site (Fig. 2). These results were very similar to those obtained with RAW 264.7 cells. Therefore, the effects of DDMG-1 on the production of TNF- α in RAW 264.7 cells and IL-8 in THP-1 cells were ascribable to the resemble mechanism. Furthermore, the inhibitory activity of DDMG-1 was specific to the IL-1 β signaling pathway, because DDMG-1 reduced the IL-8 production in THP-1 cells by the stimulation with IL-1 β but not with PMA and TNF- α .

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