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Anti-inflammatory and Anti-oxidative Activities of Polyacetylene from *Dendropanax dentiger*

Shih-Chang Chien^{a,b}, Yen-Hsueh Tseng^a, Wei-Ning Hsu^a, Fang-Hua Chu^c, Shang-Tzen Chang^c, Yueh-Hsiung Kuo^{d,e,*} and Sheng-Yang Wang^{a,b,f,g,*}

^aDepartment of Forestry, National Chung-Hsing University, Taichung, Taiwan

^bExperimental Forest Management Office, National Chung-Hsing University, Taichung, Taiwan

^cSchool of Forestry and Resource Conservation, National Taiwan University, Taipei, Taiwan

^dGraduate Institute of Chinese Pharmaceutical Science, China Medical University, Taichung, Taiwan

^eDepartment of Biotechnology, Asia University, Taichung, Taiwan

^fAgricultural Biotechnology Research Center, Academia Sinica, Taipei, Taiwan

^gAgricultural Biotechnology Center, National Chung-Hsing University, Taichung, Taiwan

taiwanfir@dragon.nchu.edu.tw (Prof. S.Y. Wang)

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Dendropanax dentiger has been used as a folk medicine since ancient times. In our current study, we observed that *D. dentiger* exhibited a significant anti-inflammatory activity, which could efficiently inhibit nitric oxide (NO) production in the lipopolysaccharide (LPS)-induced macrophage inflammation assay. (9Z,16S)-16-Hydroxy-9,17-octadecadiene-12,14-diynoic acid (HODA) was isolated from the leaves of *D. dentiger* following a bioactivity guided fractionation protocol. Our data indicated that HODA significantly inhibited the NO production in LPS-induced RAW 264.7 murine macrophage cells ($IC_{50} = 4.28 \mu\text{M}$). Consistent with these observations, the mRNA and protein expression levels of iNOS were also inhibited by HODA in a dose-dependent manner. HODA also reduced the translocation of NF- κ B into nuclear fractions. Meanwhile, HODA enhanced Nrf-2 activation and its downstream antioxidant gene HO-1. We concluded that HODA possessed significant anti-inflammatory and anti-oxidative activity; the compound may have a potential for development as a chemoprevention agent.

Keywords: *Dendropanax dentiger*, Araliaceae, Chemoprevention, Anti-inflammation, Anti-oxidative activity, Polyacetylene.

Dendropanax dentiger Merr. (Araliaceae) is distributed in Taiwan, southwest China, and Indo-China [1]. The roots, bark, and leaves are used as a folk medicine for treating migraine headaches, rheumatism, and rheumatoid arthritis; it is also claimed to have muscle relaxing activity, stimulating blood circulation, and strengthening muscles and bones [2]. With regard to its chemical constituents, Zheng *et al.* isolated 24 known compounds from *D. dentiger* stems [3]. Recently, Lai and Lee identified 21 compounds from the leaves and twigs, among them syringin, which was the most abundant, along with 6'-*O*-apiofuranosyl dendranthemoside A, a new megastigmane glycoside, and 3-methoxy-D-mannono-1,4-lactone, a new hexono-1,4-lactone [4]. Recently, a polyacetylene, (9Z,16S)-16-hydroxy-9,17-octadecadiene-12,14-diynoic acid (HODA) (Figure 1), a potent anti-inflammatory compound with anti-oxidative properties, was isolated for the first time from the leaves of *D. dentiger* by using a bioactivity guided fractionation protocol. The content of HODA in the crude extract was determined by HPLC to be 23.4 mg/g.

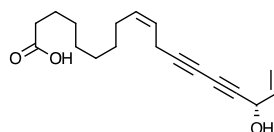


Figure 1: HODA, obtained from *D. dentiger*.

HODA significantly inhibited the production of NO in LPS-induced RAW 264.7 murine macrophage cells ($IC_{50} = 4.28 \mu\text{M}$), without causing cytotoxicity at this dosage; the IC_{50} value of the reference compound (curcumin) was $17.4 \mu\text{M}$ ($6.4 \mu\text{g/mL}$). The possible

mechanism of HODA as an anti-inflammation agent was further studied. As shown in Figure 2, we found that quiescent RAW 264.7 cells expressed either low or undetectable levels of iNOS, mRNA and protein expression. In contrast, strong mRNA and iNOS expression were observed after treatment with $1 \mu\text{g/mL}$ LPS. HODA suppressed LPS-induced mRNA and protein iNOS expression in a dose-dependent manner for the translation and transcription stages.

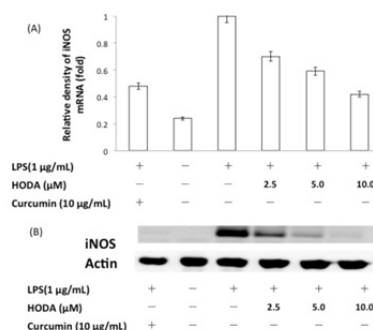


Figure 2: Effects of HODA on iNOS in RAW264.7 cells. (A) The mRNA expression of iNOS. (B) The protein expression of iNOS. RAW264.7 cells were treated with HODA (2.5 ~10 μM) for 1 h, then inflammation was induced by treatment with $1 \mu\text{g/mL}$ LPS for 16 h to obtain protein and mRNA.

Figure 3 demonstrates that both p50 and p65 NF- κ B expressions in nuclear fractions were lowered in a concentration-dependent manner by HODA. This suggests that pre-treating cells with HODA blocks the translocation of p50 and p65 NF- κ B subunits into the nuclear compartment. HODA inhibited NF- κ B translocation into the

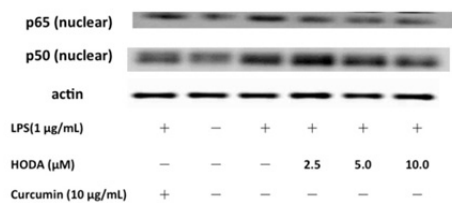


Figure 3: Effects of HODA and curcumin on the expression of NF-κB protein in LPS-stimulated RAW264.7 cells.

nucleus, thereby inhibiting the expression of iNOS protein downstream, resulting in reduction of the amount of generated NO.

Heme oxygenase 1 (HO-1) is a major antioxidant enzyme, which plays an essential role in the antioxidant defense system when cells are damaged by ethanol-induced stress [5]. We observed that 2.5 - 10 μM of HODA notably increased HO-1 expression levels in ethanol-induced RAW 264.7 cells in a dose dependent manner (Figure 4). Curcumin (10 μg/mL) also enhanced the HO-1 protein expression level.

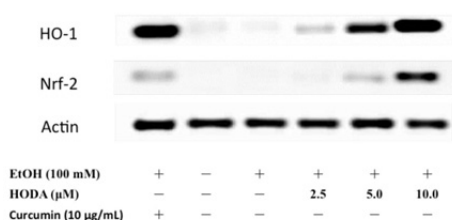


Figure 4: Effects of HODA on HO-1 and Nrf-2 expression in EtOH-induced cell damage. RAW264.7 cells were treated with HODA (2.5 ~ 10 μM) for 1 h, then cell damage was induced by treatment with 100 mM EtOH to obtain protein. Proteins were determined by Western blotting.

It has been proved that HO-1 can be activated by nuclear factor E2-related factor 2 (Nrf-2), a major transcription factor regulating antioxidant response element (ARE)-driven phase-II gene expression [6]. We, therefore, attempted to determine whether HODA up regulates HO-1 expression in association with Nrf-2 activation. Activation of Nrf-2 was determined by Western blot using nuclear extracts from cultured RAW 264.7 cells. As illustrated in Figure 4, HODA boosted Nrf-2 accumulation in the nuclear fraction. These results support that HODA against oxidative stress in cell through activation of Nrf-2 and induction of HO-1 expression. HODA possesses significant anti-inflammatory and anti-oxidative activity and might have potential as a chemoprevention agent; further study is needed to explore this.

Experimental

Materials: *Dendropanax dentiger* was collected in May 2011 from Nantou County, Taiwan, and was identified by Professor

Yen-Hsueh Tseng (NCHU). The voucher specimen (TCF13519) was deposited in the herbarium of the same university.

General: Compound structure elucidation was achieved using UV, IR, and NMR spectroscopic, and MS analysis, as described previously [7]. The EtOH extract of *D. dentiger* was dissolved in MeOH and quantification was based on the measured integration area applying the calibration equation. The concentration of HODA used for calibration was 0.025–1.0 mg/mL. The linear regression equation, $y = 0.3642x + 7.0329$, revealed a good linearity ($R^2 = 0.99326$).

Extraction and purification: Air-dried leaves of *D. dentiger* (560 g) were extracted with EtOH (10 L) at ambient temperature and concentrated under vacuum to yield the EtOH extract (51.2 g). This was partitioned between EtOAc-H₂O to give EtOAc-soluble (28.35 g) and H₂O-soluble fractions. The EtOAc-soluble fraction was further chromatographed over silica gel eluted with *n*-hexane and a gradient of *n*-hexane-EtOAc. The eluent was collected in constant volumes, and combined into 19 fractions based on TLC properties. Fraction 10 (obtained with *n*-hexane: EtOAc = 70:30, amount 3.6 g) displayed the strongest NO inhibition activity and was further separated by HPLC with a mixture of *n*-hexane: EtOAc = 70:30 at a flow rate of 3 mL/min to obtain (9*Z*,16*S*)-16-hydroxy-9,17-octadecadiene-12,14-dienoic acid (HODA) (retention time 12.2 min). HODA was isolated earlier from *D. moribifera* [8], but this is the first record of this compound for *D. dentiger*.

Anti-inflammatory and anti-oxidative activities evaluation of HODA:

Nitric oxide production inhibitory activity assay was measured indirectly by analysis of nitrite levels using the Greiss reaction [7]. The cytoplasmic and nuclear fractions were obtained using commercially available nuclear and cytoplasmic extraction reagent kits (Pierce Biotechnology, Rockford, IL, USA). Oxidative stress was then induced by the addition of ethanol (100 mM) to the culture medium for 12 h. At the end of incubation, cells were lysed with cytoplasmic and nuclear extraction reagent. For Western blot analysis, 20 μg protein fractions were separated by 7% to 12% SDS-polyacrylamide gel electrophoresis and transferred onto a PVDC membrane. Western blots were performed with appropriate antibodies using the ECL Western blotting reagent (Millipore, Billerica, MA, USA) and the image was visualized by a VL Chemi-Smart 3000 (Viogene Biotek, Sunnyvale, CA, USA) imaging device.

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