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Anti-inflammatory Activity of Norisoprenoids from the Aerial Parts of *Celosia cristata* L.

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Abstract : *Celosia cristata*, belongs to Amaranthaceae family, has been utilized in many traditional medicinal systems to treat hemostasis, eye and mouth inflammation, and gynecological diseases. The various physiological investigations on *C. cristata* have documented its antibacterial, antioxidant, antifungal, and antihepatotoxic properties. During the research program aimed at isolating bioactive constituents from the medicinal plants, the aerial parts of *C. cristata* were extracted using 80% EtOH, then sequentially partitioned with *n*-hexane, CH_2Cl_2, and EtOAc. The CH_2Cl_2-soluble fraction demonstrated inhibitory effects on nitric oxide production in LPS-induced RAW 264.7 cells, with an IC_{50} value of 24.7 μg/mL. The CH_2Cl_2-soluble fraction was subjected to a series of chromatographic techniques, such as Sephadex LH-20 column chromatography, MPLC, and preparative HPLC. As a result, seven known norisoprenoids (**1**–**7**) were isolated, and the structures were determined through the analysis of spectroscopic data, especially 1D NMR, 2D NMR, and HR-ESI-MS. Dehydrovomifoliol (**2**), 3-hydroxy-4,7-megastigmadien-9-one (**6**), and 9-hydroxy-4,7-megastigmadien-3-one (**7**) exhibited inhibitory effects on LPS-induced nitric oxide production in RAW 264.7 macrophages with IC_{50} values of 17.7–24.4 μM.

Keywords : *Celosia cristata*, Amaranthaceae, Norisoprenoids, Anti-inflammation

Introduction

Celosia cristata L. (Amaranthaceae) is an herbaceous annual plant widely distributed in the tropical and subtropical regions around the world including Asia, South America, India, and Africa.[1] There are approximately 60 species of genus *Celosia*, and among them, *C. cristata*, *C. argentea*, *C. isertii*, and *C. spicata* are considered significantly as dietary leaf vegetables.[2] *C. cristata* is an ornamental plant, and is commonly known as cock's comb flower, since the flower looks like the head on a cock.[3] It has traditionally been used to treat hemostasis, eye and mouth inflammation, and gynecological ailments, such as severe menstrual pain and leukorrhea, based on its astringent action.[4] *C. cristata* has been reported with various bioactive constituents, such as phenolic compounds, terpenoids, saponins, and carotenoids.[4,5]

Norisoprenoids, the carbonyl compounds with 13, 12, 11, 10 or 9 carbon atoms, are the breakdown products of carotenoids. This decomposition process involves enzymatic reactions activated by carotenoid cleavage dioxygenase (CCD) and non-enzymatic reactions such as exposure to light, oxygen, fluctuations in temperature, and acid hydrolysis.[6] In previous research from plant biotechnology, two classes of CCDs (CCD1 and CCD4) enzymes are involved in species such as petunia, tomato, crocus, grape, citrus, and rose.[7] Further investigation on food-nutritional studies have shown that norisoprenoids influences the aroma and taste of fruit.[8] It also has been revealed that it significantly affects the scents produced during the aging process of wine.[9] Additionally, in a pharmacological study, it was reported various bioactivities such as anti-cancer, anti-tumor, and anti-inflammation.[10,11,12]

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In the course of phytochemical search of aerial parts of *C. cristata*, seven known compounds (**1**–**7**) (Fig. 1) were isolated from the ethanol extract. The structures were determined by comparing their physical and spectroscopic characteristics with previously published data, particularly 1D and 2D NMR data such as COSY, HSQC, HMBC, and NOESY, in addition to HR-ESI-MS.

Experimental

General experimental procedures – UV spectra were recorded on a JASCO UV-550 spectrophotometer (JASCO, Tokyo, Japan). 1D and 2D NMR spectra were recorded on Bruker AVANCE 400 spectrometer (Bruker, MA, USA). HR-ESI-MS and LC-HR-MS/MS analyses were conducted with an Orbitrap Exploris 120 mass spectrometer, connected to a Vanquish UHPLC system and diode array detector (Thermo Fisher Scientific, MA, USA). Open column chromatography was performed on Sephadex LH-20 (25-100 μm, Pharmacia, New Jersey, USA). MPLC was conducted utilizing the Biotage Isolera Prime chromatography system. Semi-preparative HPLC was carried out using a Waters HPLC system, equipped with two Waters 515 pumps, a 2996 photodiode array detector, and three semi-preparative columns, such as YMC J'sphere ODS-H80 (4 μm, 250 × 20 mm, I, d., flow rate 10 mL/min), YMC J'sphere ODS-H80 (4 μm, 150 × 20 mm, I, d., flow rate 6 mL/min), and YMC J'sphere ODS-H80 (4 μm, 150 × 10 mm, I, d., flow rate 3 mL/min). TLC was performed on silica gel 60 F_{254} plates (0.25 mm, Merk), and the spots were visualized using a spray regent consisting of 10% vanillin solution in sulfuric acid.

Plant materials – The aerial parts of *C. cristata* was harvested from wild cultivation at Chungbuk National University, in 2019. A voucher specimen (CBNU-2019-CC) was identified by Professor Moon-Soon Lee and stored in the natural chemistry laboratory of the College of Industrial Plant Science and Technology, Chungbuk National University.

Extraction and isolation – The dried aerial parts of *C. cristata* (2 kg) were extracted with 80% EtOH (15 × 2 L). The extract was filtered and evaporated under reduced pressure, and the resulting residue (170 g) was suspended in water and sequentially partitioned with *n*-hexane (4 × 1 L), CH_2Cl_2 (4 × 1 L), and EtOAc (4 × 1 L). The CH_2Cl_2-soluble fraction (8.6 g) was fractionated using normal-phase MPLC (silica) with a CH_2Cl_2-MeOH step gradient system (100:0 to 84:16) to give six fractions, CCAC1–CCAC6. CCAC2 (1.58 g) and CCAC3 (2.27 g) were subject to Sephadex LH-20 open column chromatography with *n*-hexane-CH_2Cl_2 isocratic system (1:4) to obtain fractions CCAC2C, CCAC2D and CCAC3C, CCAC3D, respectively. CCAC3D (1.2 g) was separated using reverse-phase MPLC (C_{18}) with a H_2O-MeOH gradient system (80:20 to 20:80), and six subfractions (CCAC3D-1–CCAC3D-6) were obtained. CCAC3D-3 (149.5 mg) was separated using normal-phase MPLC with a CH_2Cl_2-MeOH step gradient system (99:1 to 91:9), and three subfractions (CCAC3D-3-1–CCAC3D-3-3) were obtained. CCAC3D-3-1 (55.8 mg) was further purified by preparative HPLC [YMC J'sphere ODS-H80 (4 μm, 150 × 20 mm, I, d., flow rate 6 mL/min)] using a H_2O-CH_3CN

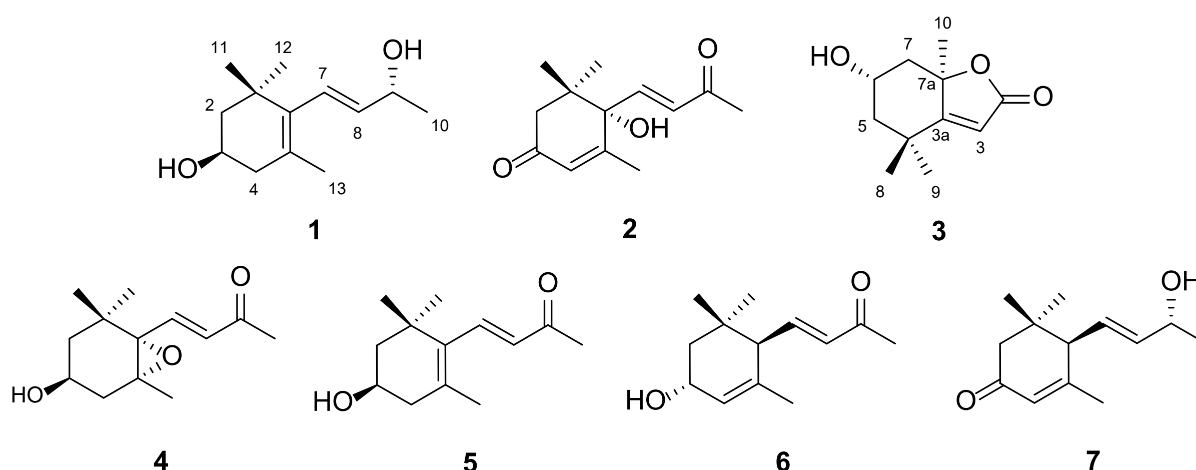

Fig. 1. Chemical structures of the isolated compounds (**1**–**7**).

isocratic system (70:30) to afford compound **1** (1.42 mg; t_R = 18.8 min). CCAC2D (0.81 mg) was separated using semi-prep HPLC [YMC J'sphere ODS-H80 (4 μm, 250 × 20 mm, I, d., flow rate 10 mL/min)] and fraction collector with a H_2O-CH_3CN gradient system (80:20 to 20:80), and twenty-two subfractions (CCAC2D-1–CCAC2D-22) were obtained. CCAC2D-5 (50 mg) was purified by preparative HPLC [YMC J'sphere ODS-H80 (4 μm, 150 × 10 mm, I, d., flow rate 3 mL/min)] using a H_2O-CH_3CN isocratic system (82:18) to afford compounds **2** (4.46 mg; t_R = 15.6 min), **3** (11.59 mg; t_R = 17.5 min), and **4** (7.08 mg; t_R = 22.0 min). CCAC2D-8 (39.6 mg) was purified by preparative HPLC [YMC J'sphere ODS-H80 (4 μm, 150 × 10 mm, I, d., flow rate 3 mL/min)] using a H_2O-CH_3CN isocratic system (75:25), and two subfractions (CCAC2D-8-1–CCAC2D-8-2) were obtained. CCAC2D-8-2 (22.24 mg) was purified by preparative HPLC [YMC J'sphere ODS-H80 (4 μm, 150 × 10 mm, I, d., flow rate 3 mL/min)] using a H_2O-CH_3CN isocratic system (83:17) to afford compounds **5** (3.22 mg; t_R = 65.2 min), **6** (3.57 mg; t_R = 69.9 min), and **7** (1.07 mg; t_R = 75.8 min).

3,9-Dihydroxy-5,7-megastigmadiene (1) – Brown amorphous powder; $[\alpha]^{20}_{D}$ −38.6 (*c* 0.48, CH_2Cl_2); HR-ESI-MS *m/z* 211.1694 $[M+H]^+$ (calcd. for $C_{13}H_{23}O_2$, 211.1693); ^1H NMR (400 MHz, CD_3OD): δ 1.02 (3H, s, 12-CH_3), 1.05 (3H, s, 11-CH_3), 1.25 (3H, d, *J* = 6.3 Hz, 10-CH_3), 1.40 (1H, t, *J* = 12.0 Hz, H-2ax), 1.65 (1H, dd, *J* = 12.0, 2.1 Hz, H-2eq), 1.69 (3H, s, 13-CH_3), 1.95 (1H, m, H-4ax), 2.28 (1H, dd, *J* = 5.9, 16.3 Hz, H-4eq), 3.88 (1H, m, H-3), 4.28 (1H, dd, *J* = 6.5, 6.3 Hz, H-9), 5.44 (1H, dd, *J* = 6.5, 16.1 Hz, H-8), 5.99 (1H, d, *J* = 16.1 Hz, H-7); ^{13}C NMR (100 MHz, CD_3OD): δ 21.5 (13-CH_3), 23.9 (10-CH_3), 28.7 (11-CH_3), 30.6 (12-CH_3), 37.7 (C-1), 42.8 (C-4), 48.4 (C-2), 65.5 (C-3), 69.7 (C-9), 126.9 (C-5), 127.2 (C-7), 138.0 (C-6), 140.0 (C-8).

Dehydrovomifoliol (2) – Brown syrup; $[\alpha]^{20}_{D}$ −5.2 (*c* 0.11, CH_2Cl_2); HR-ESI-MS *m/z* 223.1328 $[M+H]^+$ (calcd. for $C_{13}H_{19}O_3$, 223.1329); ^1H NMR (400 MHz, $CDCl_3$): δ 1.02 (3H, s, 12-CH_3), 1.11 (3H, s, 11-CH_3), 1.88 (3H, s, 13-CH_3), 2.30 (3H, s, 10-CH_3), 2.34 (1H, dd, *J* = 0.9, 17.2 Hz, H-2ax), 2.50 (1H, dd, *J* = 0.6, 17.2 Hz, H-2eq), 5.96 (1H, s, H-4), 6.46 (1H, d, *J* = 15.7 Hz, H-8), 6.83 (1H, d, *J* = 15.7 Hz, H-7); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.8 (13-CH_3), 23.0 (12-CH_3), 24.5 (10-CH_3), 28.6 (11-CH_3), 41.5 (C-1), 49.7 (C-2), 79.4 (C-6), 127.9 (C-4), 130.4 (C-8), 145.0 (C-7), 160.3 (C-5), 197.0 (9-C=O), 197.5 (3-C=O).

(−)-Loliolide (3) – Yellow amorphous powder; $[\alpha]^{20}_{D}$ −13.3 (*c* 0.001, CH_2Cl_2); HR-ESI-MS *m/z* 197.1171 $[M+H]^+$ (calcd. for $C_{11}H_{17}O_3$, 197.1172); ^1H NMR (400 MHz, $CDCl_3$): δ 1.27 (3H, s, 9-CH_3), 1.47 (3H, s, 8-CH_3), 1.53 (1H, dd, *J* = 3.7, 14.5 Hz, H-7ax), 1.77 (4H, overlap, H-5ax, 10-CH_3), 1.98 (1H, dt, *J* = 2.6, 14.5 Hz, H-7eq), 2.46 (1H, dt, *J* = 2.5, 14.5 Hz, H-5eq), 4.33 (1H, m, H-6), 5.69 (1H, s, H-3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.5 (9-CH_3), 27.0 (10-CH_3), 30.7 (8-CH_3), 36.0 (C-4), 45.6 (C-7), 47.3 (C-5), 66.8 (C-6), 86.8 (C-7a), 112.9 (C-3), 172.0 (C-2), 182.6 (C-3a).

(7*E*)-5,6-Epoxy-3-hydroxy-7-megastigmen-9-one (4) – Brown syrup; $[\alpha]^{20}_{D}$ −13.6 (*c* 0.39, CH_2Cl_2);HR-ESI-MS *m/z* 225.1484 $[M+H]^+$ (calcd. for $C_{13}H_{21}O_3$, 225.1485); ^1H NMR (400 MHz, $CDCl_3$): δ 0.97 (3H, s, 12-CH_3), 1.19 (6H, overlap, 11-CH_3 and 13-CH_3), 1.26 (1H, dd, *J* = 10.4, 12.9 Hz, H-2ax), 1.65 (2H, overlap, H-2eq and H-4ax), 2.28 (3H, s, 10-CH_3), 2.39 (1H, dd, *J* = 5.1, 14.1 Hz, H-4eq), 3.90 (1H, m, H-3), 6.29 (1H, d, *J* = 15.6 Hz, H-8), 7.02 (1H, d, *J* = 15.6 Hz, H-7); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.9 (13-CH_3), 25.0 (11-CH_3), 28.3 (10-CH_3), 29.4 (12-CH_3), 35.1 (C-1), 40.6 (C-2), 46.7 (C-4), 64.0 (C-3), 67.3 (C-5), 69.5 (C-6), 132.6 (C-8), 142.4 (C-7), 197.4 (9-C=O).

3-Hydroxy-5,7-megastigmadien-9-one (5) − Yellow syrup; $[\alpha]^{20}_{D}$ −4.3 (*c* 0.5, CH_2Cl_2); HR-ESI-MS *m/z* 209.1536 $[M+H]^+$ (calcd. for $C_{13}H_{21}O_2$, 209.1536); ^1H NMR (400 MHz, $CDCl_3$): δ 1.11 (6H, overlap, 11-CH_3 and 12-CH_3), 1.49 (1H, t, *J* = 12.0 Hz, H-2ax), 1.79 (4H, overlap, H-2eq and 13-CH_3), 2.08 (1H, dd, *J* = 9.6, 17.4 Hz H-4ax), 2.30 (3H, s, 10-CH_3), 2.43 (1H, dd, *J* = 5.1, 17.4 Hz, H-4eq), 4.00 (1H, m, H-3), 6.11 (1H, d, *J* = 16.5 Hz, H-8), 7.20 (1H, d, *J* = 16.5 Hz, H-7); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6 (13-CH_3), 27.3 (10-CH_3), 28.6 (12-CH_3), 30.0 (11-CH_3), 36.9 (C-1), 42.8 (C-4), 48.4 (C-2), 64.6 (C-3), 132.2 (C-7), 132.4 (C-5), 135.6 (C-6), 142.3 (C-8), 198.5 (9-C=O).

3-Hydroxy-4,7-megastigmadien-9-one (6) − Yellow syrup; $[\alpha]^{20}_{D}$ +1.0 (*c* 0.21, CH_2Cl_2); HR-ESI-MS *m/z* 209.1536 $[M+H]^+$ (calcd. for $C_{13}H_{21}O_2$, 209.1536); ^1H NMR (400 MHz, $CDCl_3$): δ 0.89 (3H, s, 12-CH_3), 1.03 (3H, s, 11-CH_3), 1.41 (1H, dd, *J* = 6.3, 13.5 Hz, H-2ax), 1.62 (3H, s, 13-CH_3), 1.84 (1H, dd, *J* = 6.1, 13.5 Hz, H-2eq), 2.26 (3H, s, 10-CH_3), 2.50 (1H, d, *J* = 10.0 Hz, H-6), 4.27 (1H, m, H-3), 5.63 (1H, br s, H-4), 6.10 (1H, d,

J = 15.8 Hz, H-8), 6.54 (1H, dd, J = 10.0, 15.8 Hz, H-7); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.7 (13-CH_3), 24.7 (12-CH_3), 27.2 (10-CH_3), 29.7 (11-CH_3), 33.8 (C-1), 43.8 (C-2), 54.3 (C-6), 65.5 (C-3), 125.8 (C-4), 133.6 (C-8), 135.5 (C-5), 147.1 (C-7), 198.0 (9-C=O).

9-Hydroxy-4,7-megastigmadien-3-one (7) – Yellow syrup; $[\alpha]_D^{20}$ −6.1 (c 0.42, CH_2Cl_2); HR-ESI-MS m/z 209.1537 $[M+H]^+$ (calcd. for $C_{13}H_{21}O_2$, 209.1536); ^{1}H NMR (400 M Hz, $CDCl_3$): δ 0.96 (3H, s, 12-CH_3), 1.03 (3H, s, 11-CH_3), 1.30 (3H, d, J = 6.5 Hz, 10-CH_3), 1.91 (3H, d, s, 13-CH_3), 2.09 (1H, br d, J = 16.5 Hz, H-2ax), 2.33 (1H, br d, J = 16.5 Hz, H-2eq), 2.50 (1H, d, J = 9.2 Hz, H-6), 4.35 (1H, dd, J = 6.0, 6.5 Hz, H-9), 5.53 (1H, dd, J = 9.2, 15.3 Hz, H-7), 5.68 (1H, dd, J = 6.0, 15.3 Hz, H-8), 5.90 (1H, s, H-4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.5 (13-CH_3), 23.7 (10-CH_3), 27.2 (11-CH_3), 27.9 (12-CH_3), 36.2 (C-1), 47.5 (C-2), 55.5 (C-6), 68.3 (C-9), 125.9 (C-4), 126.7 (C-7), 138.6 (C-8), 161.8 (C-5), 199.1 (3-C=O).

Assessment of LPS-induced NO production and cell viability – RAW 264.7 cells (ATCC, Manassas, VA, USA) were cultured in DMEM (Sigma-Aldrich, St Louis, MO, USA) supplemented with 10% FBS, 100 U/mL penicillin, and 100 μg/mL streptomycin. The cells were maintained in a humidified atmosphere with 5% CO_2 at 37°C. As previously described,[13] the cells were seeded into the 96-well microplates (2 × 10^5 cells/ well) and incubated for 24 h. Subsequently, the cells were treated with the tested compounds and extracts, initially dissolved in DMSO, and further diluted with the DMEM medium to obtain a range of working concentrations. The cells were then stimulated with LPS (1 μg/mL) to trigger NO production. After 24 h of incubation at 37°C, 100 μL of cell-free supernatant was mixed with 100 μL of Griess reagent (Sigma-Aldrich, St Louis, MO, USA) for 10 min, for nitrite production assessment. The absorbance was measured at 550 nm against a calibration curve established with sodium nitrite standards. The viability of the remaining cells was assessed using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) colorimetric assay (Sigma Chemical Co., St. Louis, MO).

Results and Discussion

Phytochemical investigation of the aerial parts of *C. cristata* resulted in the isolation of seven known compounds (**1**–**7**), which were identified as 3,9-dihydroxy-5,7-megastigmadiene (**1**),[14] dehydrovomifoliol (**2**),[15] (-)-loliolide (**3**),[16] (7*E*)-5,6-epoxy-3-hydroxy-7-megastigmen-9-one (**4**),[14] 3-hydroxy-5,7-megastigmadien-9-one (**5**),[14] 3-hydroxy-4,7-megastigmadien-9-one (**6**),[14] and 9-hydroxy-4,7-megastigmadien-3-one (**7**),[14] respectively, by comparing their physicochemical and spectroscopic data with those of published values.

Inducible NO synthase (iNOS) in macrophages generates NO. The overexpression of iNOS increases NO levels, and excessive NO production may cause various inflammatory disease such as rheumatoid arthritis and inflammatory bowel disease.[17] Therefore, inhibition of NO production is known as one of important strategies in controlling inflammatory disease under various pathological conditions. Although research on the antitumor, antioxidant, and antinociceptive activities of *C. cristata* has been reported, studies on its anti-inflammatory effects have not been documented.[18-20] In previous study, several C_{13}-norisoprenoids such as 3-oxo-α-damascone (IC_{50}: 2.0 ± 0.9 μM), 4-oxo-β-damascone (IC_{50} : 1.8 ± 0.9 μM), and β-damascone (IC_{50}: 3.0 ± 0.7

Table 1. Inhibitory effects of compounds **1–7** on LPS-induced NO production in RAW 264.7 Cells[a]

Compound	IC_{50} (μM)	Compound	IC_{50} (μM)
1	> 100	**5**	> 100
2	17.7 ± 2.1	**6**	17.8 ± 2.3
3	> 100	**7**	24.4 ± 2.5
4	> 100	Aminoguanidine	17.6 ± 1.9

[a] Results are expressed as the mean IC_{50} values in μM from triplicate experiments.

μM) isolated from the apples (*Malus* sp., Rosaceae), have been reported to inhibit NO production.[21] Therefore, all isolated norisoprenoids (**1**–**7**) were assessed for their anti-inflammatory activity on LPS-induced NO production in RAW 264.7 macrophage cells, with aminoguanidine utilized as a positive control (IC_{50}: 17.6 μM). Among them, only dehydrovomifoliol (**2**), 3-hydroxy-4,7-megastigmadien-9-one (**6**), and 9-hydroxy-4,7-megastigmadien-3-one (**7**), which have a double bond between C-4 and C-5, showed significant activity effects with IC_{50} values of 17.7, 17.8, and 24.4 μM (Table 1), respectively. Furthermore, the presence of a carbonyl group at C-9 in **2** and **6** instead of a hydroxy group in **7** might enhance the inhibitory effects. This study has confirmed for the first time that *C. cristata* contains norisoprenoids. Additionally, norisoprenoids isolated from *C. cristata* were found to exhibit anti-inflammatory activity. These results suggest that norisoprenoids contribute to the anti-inflammatory effects of *C. cristata*. Therefore, it is suggested that *C. cristata* might have potential for further research for the anti-inflammatory agents.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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