Food Chemistry 115 (2009) 558–562

Contents lists available at ScienceDirect

Food Chemistry

journal homepage: www.elsevier.com/locate/foodchem

Antioxidant prenylflavonoids from *Artocarpus communis* and *Artocarpus elasticus*

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ARTICLE INFO

Article history:
Received 29 April 2008
Received in revised form 10 December 2008
Accepted 18 December 2008

Keywords:
Antioxidant activity
Artocarpus communis
Artocarpus elasticus
Prenylflavonoids

ABSTRACT

Two new prenylflavonoids, cyclogeracommunin **(1)** and artoflavone A **(2),** were isolated from the cortex of roots of *Artocarpus communis*. Their structures were determined by spectroscopic methods. Compounds **1**, **2** and known compounds, artomunoisoxanthone **(3)**, artocommunol CC **(4)**, artochamin D **(5)**, artochamin B **(6)**, and dihydroartomunoxanthone **(7),** isolated from *A. communis,* and known compounds, cycloartelastoxanthone **(8)**, artelastoheterol **(9)**, cycloartobiloxanthone **(10)** and artonol A **(11),** isolated from *Artocarpus elasticus*, all showed inhibition of oxidative DNA damage. Compounds **2** and **8**-**10** significantly showed 1,1-diphenyl-2-picrylhydrazyl (DPPH·)-scavenging activity with IC_{50} values of 24.2 ± 0.8, 18.7 ± 2.2, 42.2 ± 2.8 and 26.8 ± 1.2 μM, respectively, while compounds **1** and **11** significantly displayed inhibitory effects on xanthine oxidase (XO) activity with IC_{50} values of 73.3 ± 19.1 and 43.3 ± 8.1 μM, respectively. These findings indicate that **1**–**11** are promising antioxidants.

1. Introduction

Artocarpus plants are distributed over tropical and subtropical regions and have been used as traditional medicine in Indonesia against inflammation and malarial fever (Nomura, Hano, & Aida, 1998). In a previous paper, we have reported the isolation of flavonoids from the acetone and $CHCl_3$ extracts of the cortex of roots of *Artocarpus communis* Forst. (Moraceae) (Weng et al., 2006) and their antiplatelet, cytotoxic and anti-inflammatory effects (Lin, Shieh, Ko, & Teng, 1993; Liou, Shieh, Cheng, Won, & Lin, 1993; Wei et al., 2005; Weng et al., 2006). Prenylflavonoids isolated from *Artocarpus elasticus* revealed significant cytotoxic effects against human cancer cell lines (Cidade et al., 2001; Ko, Lu, Yang, Won, & Lin, 2005).

Flavonoids are present in both lower and higher plants and form a group of naturally occurring antioxidants. Several flavonoids are reported as scavengers of free radicals. Free radicals are implicated in certain pathological disorders, including inflammation, metabolic disorders, cellular ageing, arteriosclerosis and carcinogenesis (Rajendran, Manisankar, Gandhidasan, & Murugesan, 2004). Flavonoids, such as liquiritigenin, isoliquiritigenin and apigenin-4′-*O*-(2″-*O*-12″-*O*-*P*-coumaroyl)-*β*-D-glucopyranoside were reported as xanthine oxidase inhibitor (Jias, Ge, Shi, & Tan, 2006; Kong, Zhang, Pan, Tan, & Cheng, 2000). Hence, for isolation of free radicals, scavenging agents and xanthine oxidase inhibitors from naturally occurring prenylflavonoids from *Artocarpus* plants, we have further investigated the constituents of the cortex of roots of *A. communis* and have isolated two additional new prenylflavonoids, cyclogeracommunin **(1)** and artoflavone A **(2)** (Fig. 1). In the present paper, the structure elucidation of **1** and **2** and the antioxidant activity of **1**, **2** and known compounds, artomunoisoxanthone **(3)**, artocommunol CC **(4)**, artochamin D **(5)**, artochamin B **(6)** and dihydroartomunoxanthone **(7)** isolated from *A. communis* and known compounds, cycloartelastoxanthone **(8)**, artelastoheterol **(9)**, cycloartobiloxanthone **(10)** and artonol A **(11)** (Fig. 1) isolated form *A. elasticus* (Ko et al., 2005; Weng et al., 2006) are reported.

2. Materials and methods

2.1. Instruments

Optical rotations were recorded on a Jasco-370 polarimeter, UV spectra on Jasco-UV–vis spectrophotometer, IR spectra on a Hitachi 260–30 spectrometer, NMR spectra on a Varian-Unity 400 spectrometer, operating at 400 MHz for ^1H NMR and 100 MHz for ^{13}C NMR spectra and EIMS spectra on a JMS HX-100 mass spectrometer; *m/z* (rel.%).

2.2. Plant material

The roots of *A. communis* (13.5 kg) were collected at Kaohsiung Hsien, Taiwan, during November, 2001 and a voucher specimen (2001–3) has been deposited in the Department of Medicinal Chemistry.

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doi:10.1016/j.foodchem.2008.12.059

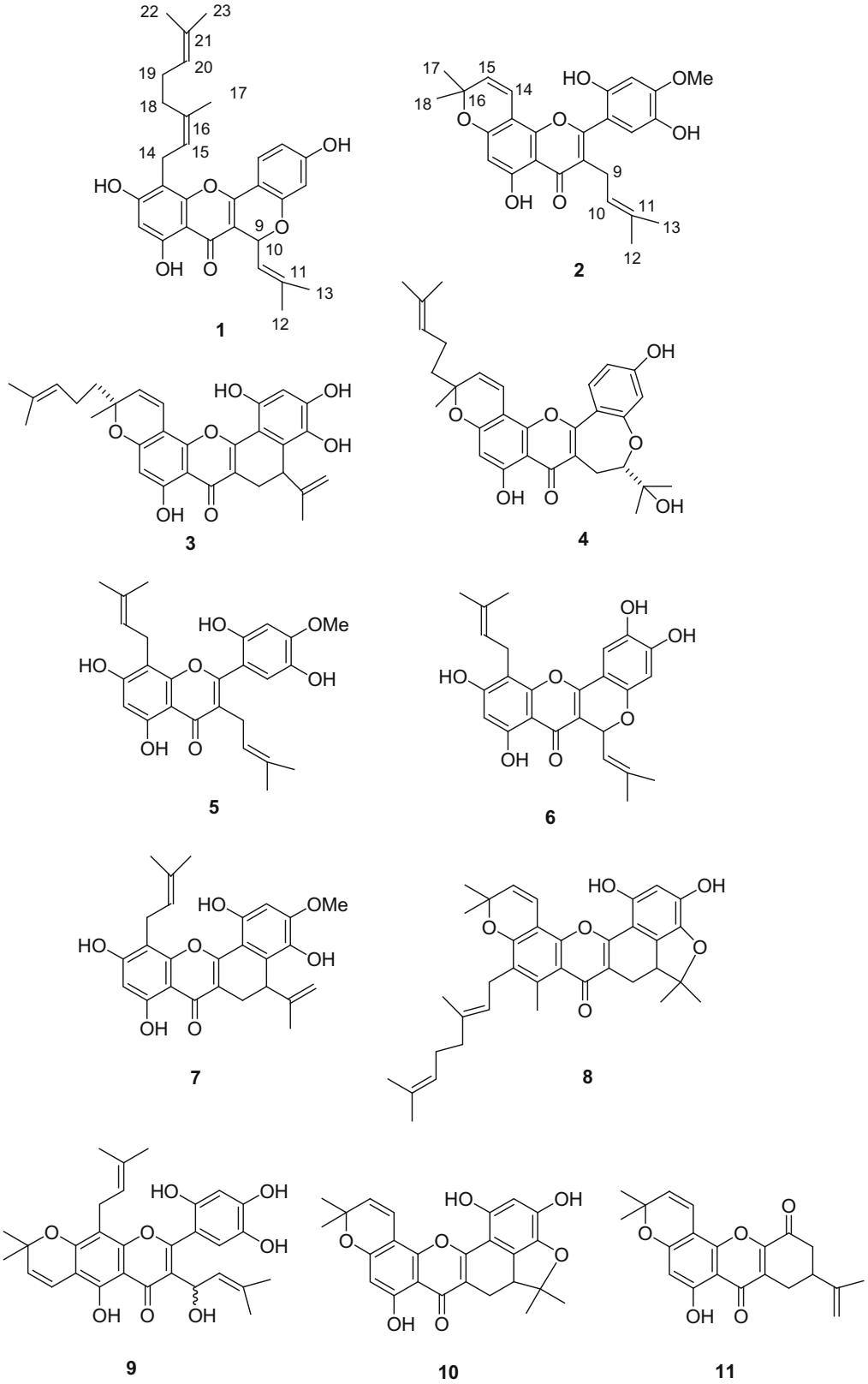

Fig. 1. Structures of prenylflavonoids.

2.3. Extraction and isolation

The cortex of the roots (0.52 kg) of *A. communis* was chipped and extracted with $CHCl_3$ at room temperature. The $CHCl_3$ extracts of cortex of roots were chromatographed over silica gel, eluted with *n*-hexane-EtOAc (6:1, 5:1 and 7:3), $CHCl_3$–EtOAc (15:1 and 4:1) and EtOAc to yield fractions 1-10. Fraction 6 was applied to a RP-18 column and eluted with acetone-H_2O (4:1) to yield **1** (15 mg) and **2** (8 mg).

Table 1
1H and ^{13}C NMR spectroscopic data (δ in ppm, J in Hz) of **1** and **2** (in acetone- d_6).

	1		**2**	
	δ_H	δ_C	δ_H	δ_C
2		159.1		163.4
3		108.3		122.4
4		180.1		183.9
4a		106.2		106.3
5	12.81 (s, OH)	156.0	13.22 (s, OH)	162.6
6	6.33 (s)	100.0	6.15 (s)	100.4
7	9.58 (s, OH)	162.6		160.6
8		109.3		102.3
8a		161.6		153.9
9	6.19 (d, J = 9.2)	71.0	3.14 (d, J = 6.8)	25.3
10	5.47 (d, J = 9.2)	122.8	5.13 (t, J = 6.8)	123.1
11		132.3		133.0
12	1.94 (s)	26.4	1.45 (s)	26.5
13	1.68 (s)	18.3	1.57 (s)	18.3
14	3.52 (dd, J = 14.8, 6.8)	22.8	6.60 (d, J = 10.0)	116.1
	3.59 (dd, J = 14.8, 6.8)			
15	5.32 (t, J = 6.8)	124.1	5.65 (d, J = 10.0)	128.7
16		132.3		79.5
17	1.50 (s)	17.2	1.44 (s)	28.9
18	1.54 (m) 1.64 (m)	27.9	1.44 (s)	28.9
19	2.00 (m)	41.0		
20	5.03 (t, J = 6.8)	125.7		
21		136.3		
22	1.55 (s)	26.5		
23	1.85 (***s***)	19.3		
1'		110.3		112.8
2'		139.3		150.1
3'	6.45 (d, J = 2.4)	105.6	6.67 (s)	102.2
4'	9.58 (s, OH)	164.6		151.9
5'	6.64 (dd, J = 8.4, 2.4)	111.4		141.2
6'	7.72 (d, J = 8.4)	126.9	6.88 (s)	117.2
OMe			3.88 (s)	56.9
OH			7.45 (s), 8.37 (s)	

2.4. Spectral measurements

Cyclogeracommunin (**1**): orange powder; UV (MeOH) λ_{max} (log ε): 220 (4.34), 270 (4.32), 370 (3.88) nm, (MeOH–$AlCl_3$): 250, 370, 410 nm, (MeOH–NaOAc): 275, 285, (MeOH–NaOMe): 265, 405 nm, (MeOH–NaOAc–H_3BO_3): unchanged; IR νmax (KBr): 3306, 2915, 1646, 1620, 1559; ^1H NMR and ^{13}C NMR see Table 1; EIMS (probe) 70 eV, *m/z* (rel. int.): 488 $[M]^+$ (6), 473 $[M - Me]^+$ (9), 433 $[M - 55]^+$ (14), 365 (6), 189 (27), 165 (12), 137 (16); HRESIMS: 489.2278 ($[M + 1]^+$, $C_{30}H_{33}O_6$; calc. 489.2277).

Artoflavone A (**2**): yellow powder; UV (MeOH) λ_{max} (log ε): 270 (4.15), 300 (sh) (3.45), 350 (3.45) nm, (MeOH–$AlCl_3$): 225, 225, 275, 405 nm, (MeOH–NaOAc): unchanged, (MeOH–NaOMe): unchanged, (MeOH–NaOAc–H_3BO_3): unchanged; IR νmax (KBr): 3400, 2974, 1654, 1560; ^1H NMR and ^{13}C NMR see Table 1 ; EIMS (probe) 70 eV, *m/z* (rel. int.): 450 $[M]^+$ (21), 435 $[M - Me]^+$ (37), 407 (11), 203 (58), 189 (19), 91 (25), 69 (45); HRESIMS: 451.1758 ($[M + 1]^+$, $C_{26}H_{27}O_7$; calc. 451.1757).

Compound identification of **3–11**: the physical and spectral data of these compounds have been described in previous reports. (Chan, Ko, & Lin, 2003; Deshpande, Parthasarathy, & Venkataraman, 1968; Wang et al., 2004; Weng et al., 2006).

2.5. Inhibition of oxidative DNA damage

The inhibition of supercoiled plasmid pBR322 DNA (ABgene, Advanced Biotechnologies Ltd, UK) strand breaks induced by $O_2^{\cdot-}$ (generated by XA/XO system) by prenylflavonoids was studied in phosphate buffer (pH 7.4). The migration rates of supercoiled (SC) DNA and open circle (OC) DNA were studied by agarose gel electrophoresis. A mixture of supercoiled plasmid pBR322 DNA (1 μg/ml) and XA (2 mM)/XO (0.7 U/ml) in 10 mM phosphate buffer (pH 7.4) was incubated for 20 min with 500 μM SOD, quercetin acting as positive control and **1–11** in a total volume of 20 μl in a 1.5 ml microfuge tube at 37 °C. After the incubation (20 min at 37 °C) was over, a 15 μl aliquot of mixture was loaded onto 1.0% agarose gel containing ethidium bromide (0.05 μg/ml) in Tris–acetate–ethylenediaminetetraacetic acid (EDTA) buffer. The electrophoresis was carried out for 0.5 h at 100 V. After the electrophoresis, the gels were illuminated with UV light and photographed. DNA, subjected to electrophoresis in the absence of SOD, quercetin and **1–11,** under identical conditions, served as the control. The gel electrophoretic motility of the various forms of DNA was compared with the control (Rajendran et al., 2004).

2.6. Free radical-scavenging activity

Radical-scavenging activities of **1**, **2**, **8–10**, BHT and TOC were determined, using DPPH· as a reagent (Kabouche, Kabouche, Öztürk, Kolak, & Topcu, 2007), with modification by using 96-well plates. A 0.1 mM solution of DPPH radical in MeOH was prepared and then 150 μl of this solution was mixed with 50 μl of sample solution. The mixture was incubated for 30 min in a dark room at room temperature. Scavenging capacity was read spectrophotometrically by monitoring the decrease in absorbance at 490 nm using a MRX Microplate Reader (Dynex MRX II, Dynex Technologies, 14340 Sullyfield Circle, Chantility, VA 20151-1683, USA). BHT and TOC were used as standards. The percent DPPH·-scavenging effect was calculated using the following equation:

$$\text{DPPH}^{\cdot}\text{-scavenging effect}\ (\%) = \frac{\text{A control- A sample}}{\text{A control}} \times 100 \qquad (1)$$

A control is the absorbance of control and A sample is the absorbance of the sample.

2.7. Assay of XO activity

The XO activity with xanthine as the substrate was measured at 25 °C, according to the protocol of Kong et al. (2000), with modification. The assay mixture, consisting of 50 μl of test solution, 60 μl of 70 mM phosphate buffer (pH 7.5) and 30 μl of enzyme solution (0.1 unit/ml in 70 mM phosphate buffer (pH 7.5)) was prepared immediately before use. After preincubation at 25 °C for 15 min, the reaction was initiated by addition of 60 μl of substrate solution (150 μM xanthine in the same buffer). The reaction was monitored for 5 min at 295 nm. The XO activity was expressed as micromoles of uric acid per minute.

2.8. Statistical analysis

Data are presented as means ± s.e.m. from four to six separated experiments. Statistical analyses were performed using the Bonferroni *t*-test method after ANOVA for multigroup comparison and the student's *t*-test method for two-group comparison. $P < 0.05$ was considered significant. Analysis of linear regression (at least three data within 20–80% inhibition) was used to calculate IC_{50} values.

3. Results and discussion

Compound **1** was obtained as an orange power, $[\alpha]_D^{25}$ 134 (c = 0.016, acetone). Its IR spectrum showed absorption bands for hydroxyl (3306 cm^{-1}), conjugated carbonyl (1646 cm^{-1}) and aromatic ring (1559 cm^{-1}). The UV spectrum of **1** was similar to that of cyclomulberrin (Lin & Shieh, 1992). It suggested that **1** possessed a 5, 7, 2′, 4′-tetraoxygenated flavone moiety. HRESIMS suggested a molecular formula of $C_{30}H_{33}O_6$ ($[M + 1]^+$, 489.2278, △ −0.0001 mmu).

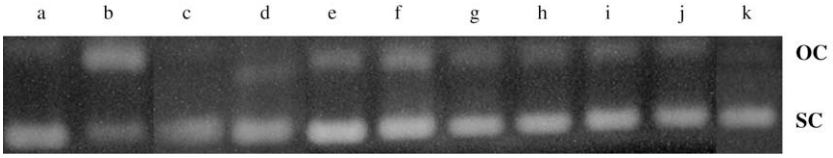

Fig. 2. Inhibition of DNA strand breaks induced by $O_2^{\cdot-}$ (generated by XA/XO) in the presence of prenylflavonoids (75 μM), studied by gel electrophoresis. Supercoiled plasmid pBR322 DNA (500 ng) in phosphate buffer (pH 7.4) solution was incubated for 20 min with XA/XO acting as the control. Lane a, DNA (without XA/XO); Lane b, control; lane c, control + **1**; lane d, control + **2**; lane e; control + **3**; lane f, control + **4**; lane g, control + **5**; lane h, control + **6**; lane i, control + **7**; lane j, control + SOD (300 μM); lane k, control + quercetin (300 μM).

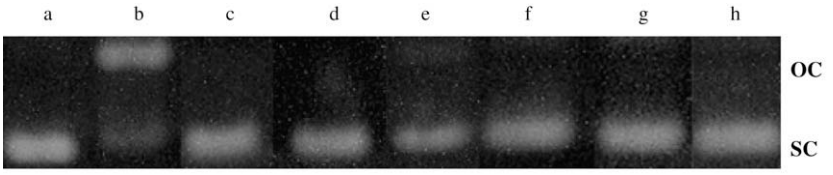

Fig. 3. Inhibition of DNA strand breaks induced by $O_2^{\cdot-}$ (generated by XA/XO) in the presence of prenylflavonoids (75 μM), studied by gel electrophoresis. Supercoiled plasmid pBR322 DNA (500 ng) in phosphate buffer (pH 7.4) solution was incubated for 20 min with XA/XO acting as the control. Lane a, DNA (without XA/XO); Lane b, control; lane c, control + **8**; lane d, control + **9**; lane e; control + **10**; lane f, control + **11**; lane g, control + SOD (300 μM); lane h, control + quercetin (300 μM).

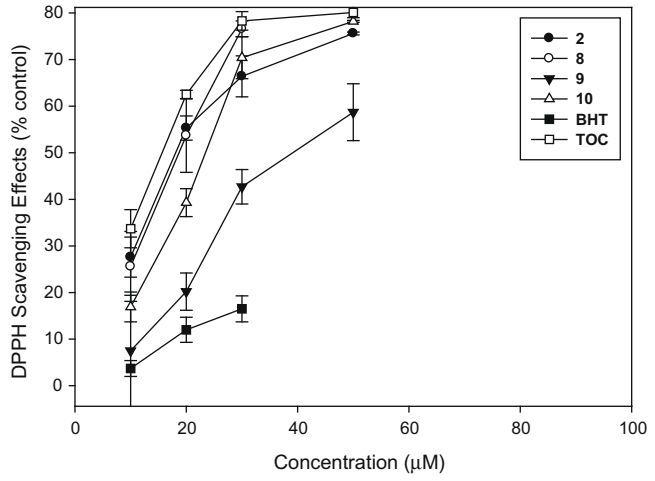

Fig. 4. Free radical-scavenging avtivity of **2**, **8**-**10**, BHT, and TOC by DPPH radical. Values are means ± S. D., $n = 3$.

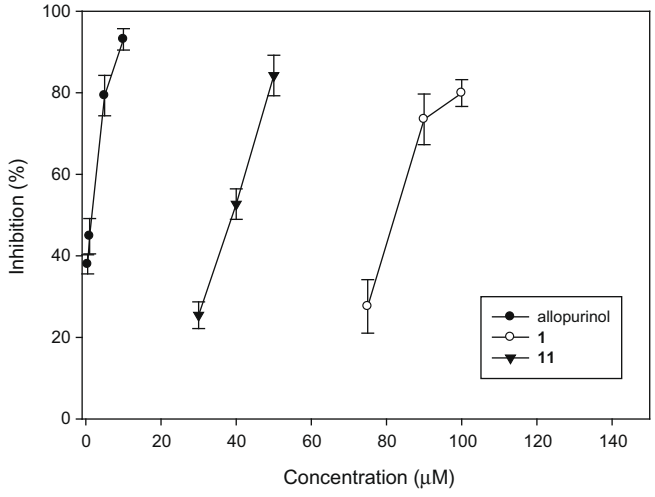

Fig. 5. Dose-dependent inhibition of XO by **1**, **11** and allopurinol. Data are presented as mean ± S. D. $n = 3$. $P < 0.05$, significantly different with student's *t*-test.

In the ^{1}H NMR spectrum of **1** (Table 1), the chemical shift values and coupling patterns of all proton signals were similar to those of the relevant protons of mulberrin (Lin & Shieh, 1992) except for the absence of a 3,3-dimethylallyl group and the presence of a geranyl group [δ(H) 5.32 (t, $J = 6.8$ Hz), 5.03 (t, $J = 6.8$ Hz), 3.59 (dd, $J = 14.8$, 6.8 Hz), 3.52 (dd, $J = 14.8$, 6.8 Hz), 2.00 (m), 1.64 (m), 1.54 (m), 1.85 (s), 1.55 (s) and 1.50 (s). In the ^{13}C NMR spectrum of **1** (Table 1), the chemical shift values were almost identical to those of mulberrin (Lin & Shieh, 1992), except for C-14 to C-23. In addition, the UV spectrum of **1** showed bathochromic shifts upon addition of $AlCl_3$, NaOAc and NaOMe. Based on the above results, the structure of cyclogeracommunin was elucidated as **1**.

Compound **2** was obtained as a yellow powder. Its IR spectrum showed absorption bands for hydroxyl (3400 cm^{-1}), conjugated carbonyl (1654 cm^{-1}) and aromatic ring (1560 cm^{-1}). The UV spectrum of **2** was similar to that of artochamin D (Wang et al., 2004). This suggested that **2** possessed a 5, 7, 2′, 4′, 5′-pentaoxygenated flavone moiety. HRESIMS suggested a molecular formula of $C_{26}H_{26}O_7$ ([M + 1] $^+$, 451.1758, △ −0.0001 mmu). The ^{1}H NMR spectrum of **2** (Table 1) showed signals for a prenyl group at δ(H) 1.45, 1.57 (each s), 3.14 (d, $J = 6.8$ Hz) and 5.13 (1H, t, $J = 6.8$ Hz), a 2,2-dimethylpyran ring at δ(H) 1.44 (6H, s), 5.65 (d, $J = 10.0$ Hz) and 6.60 (d, $J = 10.0$ Hz), three aromatic proton signals at δ(H) 6.15 (s), 6.67 (s) and 6.88 (s), a methoxyl proton signal at δ(H) 3.88 (s) and three phenolic proton signals at δ(H)7.45, 8.37 and 13.22 (each s). In the ^{13}C NMR spectrum of **2** (Table 1), the chemical shift values of carbon signals of C-2 to C-6, C-9 to C-13, C-1′ to C-6′ and OMe-4′ were almost identical to those of corresponding carbon signals of artochamin D, except for the absence of an additional prenyl group and the presence of a 2,2-dimethypyran ring. In addition, the UV spectrum of **2** showed no bathochromic shifts upon addition of NaOAc, NaOAc + H_3BO_3 or NaOMe and the presence of a bathochromic shifts upon addition of $AlCl_3$. Thus, the structure of artoflavone A was elucidated as **2**.

Reactive oxygen species (ROS) have been known to damage DNA in many biological macromolecules. ROS produced by both endogenous and exogenous sources are able to cause oxidative DNA damage and abnormal cell signalling, which may ultimately lead to carcinogenesis (Hsu & Li, 2002).The ability of **1**–**11** to inhibit the supercoiled (SC) plasmid pBR322 DNA to relaxed open circles (OC), caused by $O_2^{\cdot-}$ (generated by xanthine (XA)/xanthine oxidase (XO), was investigated by the agarose gel electrophoresis method. As shown in Figs. 2 and 3, all prenylflavonids, **1**–**11,** at

the dose of 75 μM showed protective effect on DNA damage caused by $O_2^{-\cdot}$. Among them, compounds **1**, **2**, **8**, **9**, **10** and **11** (each at 75 μM) showed potent protective effects on DNA damage caused by $O_2^{-\cdot}$. Addition of quercetin (300 μM) and superoxide dismutase (SOD) (300 μM) to the XA/XO system inhibited the DNA damage. Prenylflavonoids with a xanthone moiety, such as **8**, **10** and **11,** showed potent protective effects on DNA damage caused by $O_2^{-\cdot}$. This behaviour indicated that compounds with a xanthone moiety had lower oxidation potential than had those compounds with a flavone moiety. Compounds with a lower oxidation potential had a higher inhibitory effect on oxidative DNA damage (Rajendran et al., 2004).

These compounds may protect against carcinogenesis by inhibiting oxidative DNA damage induced by ROS.

DPPH· is a stable free radical and accepts an electron to become a stable molecule (Kabouche et al., 2007). Selective compounds, **2** and **8**–**10,** with potent protective effects on DNA damage caused by $O_2^{-\cdot}$ showed significant DPPH·-scavenging activity in a concentration-dependent manner with IC_{50} values of 24.2 ± 0.8, 18.7 ± 2.2, 42.2 ± 2.8 and 26.8 ± 1.2 μM, respectively (Fig. 4), while selective compounds **1** and **11,** also with potent protective effect against DNA damage caused by $O_2^{-\cdot}$, did not show DPPH·-scavenging activity. Compounds **1** and **11** may display inhibitory effects on xanthine oxidase. The positive controls, butylated hydroxytoluene (BHT) and α-tocopherol (TOC) also showed DPPH·-scavenging activity in a concentration-dependent manner with IC_{50} values of 80.0 ± 10.9 and 18.1 ± 1.5 μM, respectively (Fig. 4). The above result clearly indicates that **8** has the same DPPH·-scavenging activity as has TOC. As shown in Fig. 4, compounds with a 2,2-dimethylpyran ring substituted at C-7 and C-8 of the flavonoid, such as **2**, **8** and **10,** enhanced the DPPH·-scavenging activity of prenylflavonoids.

XO, an enzyme, catalyses the oxidation of XA and hyoxanthine into uric acid (Thi Nguyen et al., 2006) and is responsible for the disease known as gout. XO is also related to important biological sources of oxygen-derived free radicals that induce oxidative damage in many pathological processes, such as inflammation, atherosclerosis, cancer and ageing (Sweeney, Wyllie, Shalliker, & Markham, 2001). Thus, *in-vitro* bioassays were used to investigate **1** and **11** for XO inhibition. As shown in Fig. 5, compounds **1**, **11** and allopurinol (positive control) significantly inhibit the XO in a concentration-dependent manner with IC_{50} values of 73.3 ± 19.1, 43.3 ± 8.1 and 2.0 ± 0.7 μM, respectively. Compound **11,** with a xanthone moiety, showed stronger XO inhibition than did **1** with a flavone moiety.

4. Conclusion

Two additional prenylflavonoids, cyclogeracommunin (**1**) and artoflavone A (**2**) were further isolated from the cortex of roots of *A. communis*. Compounds **1**, **2** and known compounds **3**–**7,** isolated from *A. communis* and known compounds **8**–**11,** isolated form *A. elasticus,* exhibited significant inhibitory effect on oxidative DNA damage. Among them, compounds **2** and **8**–**10** significantly showed DPPH·-scavenging activity while compounds **1** and **11** displayed significant inhibitory effect on XO activity. These compounds may serve as antioxidant agents for the treatment of free radical-induced disease.

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