Phytochemistry Letters 3 (2010) 238–241

Contents lists available at ScienceDirect

Phytochemistry Letters

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

Identification of novel fatty acid glucosides from the tropical fruit *Morinda citrifolia* L.

Hye-Kyeong Kim [a], Min-Kyong Kwon [a], Jin-Nam Kim [a], Chang-Kwon Kim [b], Yeon-Ju Lee [b], Hee Jae Shin [b], Joongku Lee [c,*], Hyi-Seung Lee [b,*]

[a] Department of Food Science & Nutrition, The Catholic University of Korea, Republic of Korea
[b] Marine Natural Products Laboratory, Korea Ocean Research & Development Institute, Republic of Korea
[c] Natural Medicines Research Center, Korea Research Institute Bioscience & Biotechnology, Republic of Korea

ARTICLE INFO

Article history:
Received 1 July 2010
Received in revised form 12 September 2010
Accepted 14 September 2010
Available online 28 September 2010

Keywords:
Morinda citrifolia L. (noni)
Rubiaceae
Fatty acid glucoside
Copper-induced LDL oxidation

ABSTRACT

Two new fatty acid glucosides, 1,6-di-*O*-octanoyl-β-D-glucopyranose (**1**) and 6-*O*-(β-D-glucopyranosyl)-1-*O*-decanoyl-β-D-glucopyranose (**2**), were isolated from a methanol extract of the fruit of *Morinda citrifolia* L. along with five known saccharide fatty acid esters. The structures of these compounds were determined by combination of spectral and chemical analyses. These fatty acid glucosides exhibited inhibitory effect against copper-induced low-density lipoprotein oxidation. Compound **2** had the strongest effect, which was almost comparable to that of butylated hydroxytoluene.

1. Introduction

The tropical plant *Morinda citrifolia*, commonly known as noni, is widely distributed in the areas of Micronesia, Hawaii, Australia, and Southeast Asia. The genus *Morinda*, belonging to the family Rubiaceae, is indigenous to tropical countries and is considered as an important traditional folk medicine. The fruits, roots, barks, and leaves of *M. citrifolia* have been used as folk medicine for the treatment of various illnesses (Chan-Blanco et al., 2006). In particular, noni juice, which is obtained from the *M. citrifolia* fruit, is in high demand in the field of alternative medicine for the treatment of various illnesses such as arthritis, diabetes, high blood pressure, and cancers as well as cardiovascular diseases (Wang et al., 2002). Thus far, the functions of *M. citrifolia* have not been elucidated in detail. However, there is some evidence for biological activities in various assay systems. The anticancer activity of *M. citrifolia* fruits was evident from the prolonged survival of mice infected with Lewis lung carcinoma (Wang et al., 2008). In addition, a number of biological activities have been reported, such as anti-inflammation (Akihisa et al., 2007), antioxidant (Hemwimon et al., 2007; Kamiya et al., 2004), lipoxygenase inhibition (Deng et al., 2007a,b), inhibition of cell transformation (Liu et al., 2001), and quinone reductase-inducing activity (Deng et al., 2007a,b; Pawlus et al., 2005). In previous studies conducted to ascertain the chemical constituents of *M. citrifolia*, several types of compounds have been isolated from the fruits, such as fatty acid derivatives (Akihisa et al., 2007; Dalsgaard et al., 2006; Wang et al., 2000, 1999), flavonol glycosides (Su et al., 2005), iridoids (Su et al., 2005; Kamiya et al., 2005; Samoylenko et al., 2006), anthraquinones (Akihisa et al., 2007; Hemwimon et al., 2007; Deng et al., 2007a,b; Pawlus et al., 2005; Kamiya et al., 2005), and lignans (Kamiya et al., 2004; Deng et al., 2007a,b).

In the course of our search for biologically active constituents that can be obtained from tropical organisms (Lee et al., 2009), we tested a crude extract of the *M. citrifolia* fruits found in the Federated States of Micronesia. The extract exhibited moderate antioxidant activity. Guided by the results of the ^{1}H NMR analysis, fractions were obtained from the crude extract by solvent partitioning followed by the isolation and purification of compounds using different chromatographic methods including reversed-phase vacuum flash chromatography and C_{18} HPLC. Seven fatty acyl glucosides, members of a group of glycolipids, were isolated as a result. It has previously been indicated that these compounds possess interesting biological properties (Dembitsky, 2004). We focused on the effect of the compounds isolated from the noni fruit on the prevention of atherosclerosis. Low-density lipoprotein (LDL) particles are susceptible to oxidation in the presence of free radicals and transition metal ions such as copper. Oxidized LDL particles can be taken up by scavenger receptors on

* Corresponding authors. Tel.: +82 31 400 6179; fax: +82 31 400 6170.
E-mail addresses: jklee@kribb.re.kr (J. Lee), hyiseung@ymail.com, hslee@kordi.re.kr (H.-S. Lee).

1874-3900/$ – see front matter © 2010 Phytochemical Society of Europe. Published by Elsevier B.V. All rights reserved.
doi:10.1016/j.phytol.2010.09.002

macrophages, resulting in the formation of foam cells. These foam cells are the key components of the fatty streak lesions that are symptomatic of atherosclerosis (Young and McEneny, 2001). In this paper, we elucidated the structures of the major compounds isolated from the methanolic extract of the noni fruit and evaluate their inhibitory effects on copper-induced LDL oxidation.

2. Results and discussion

Extracts were obtained from frozen *M. citrifolia* fruits (dry wt 370 g) using MeOH and CH_2Cl_2. The combined extract was partitioned between *n*-BuOH and H_2O. The *n*-BuOH layer was dissolved in 15% aqueous MeOH and extracted with hexane. Further separation of the methanolic phase by ODS flash chromatography, followed by reversed-phase HPLC, afforded two new (**1** and **2**) (Fig. 1) and five known fatty acid glucosides (**3**–**7**).

Compound **1** was obtained as a white powder (7.5 mg). The molecular formula was deduced from the HRFABMS and the ^{13}C NMR data to be $C_{22}H_{40}O_8$. The ^1H and ^{13}C NMR spectra of **1** showed signals consistent with a glucose and two fatty acid ester moieties. The characteristic ^1H NMR signal at δ_H 5.44 (1H, d, J = 8.0 Hz) and ^{13}C NMR signals at δ_C 95.6 (d), 77.9 (d), 76.1 (d), 73.9 (d), 71.3 (d), and 64.2 (t) indicated the presence of an anomeric proton from a monosaccharide moiety with β configuration. The carbonyl carbons at δ_C 175.4 and 173.9 in the ^{13}C NMR data, coupled with the absorption band at 1742 cm^{-1} in the IR spectrum, revealed the presence of two octanoic acid esters in the molecule. The presence of two octanoic acid esters was supported by ^1H NMR signals at δ_H 2.39 (2H), 2.33 (2H), 1.61 (4H), 1.28–1.36 (16H), and 0.90 (6H) and by ^{13}C NMR signals at δ_C 175.4 (s), 173.9 (s), 35.0 (t), 34.9 (t), 32.9 (×2, t), 30.2 (t), 30.1(×2, t), 30.0 (t), 26.0 (t), 25.7 (t), 23.7 (t), 23.6 (t), and 14.4 (×2, q). The fatty acyl chain length was determined by generating the octanoic acid through alkaline hydrolysis and LC–MS analysis. The linkages of the two fatty acid moieties and the glucose were established on the basis of HMBC correlations (Fig. 2). Long-range correlations of H-1′ (δ_H 5.44) to C-1 (δ_C 173.9), and of H-6′ (δ_H 4.37, 4.19) to C-1″ (δ_C 175.4) showed that two fatty acids were attached to the glucose. Compound **1** is therefore identified as 1,6-di-*O*-octanoyl-β-D-glucopyranose and is reported here for the first time.

Compound **2** was obtained as a white powder (12.4 mg). The molecular formula was deduced from the HRFABMS and the ^{13}C NMR data to be $C_{22}H_{40}O_{12}$. The ^1H and ^{13}C NMR spectra of **2** demonstrated a fatty acid ester moiety and the presence of decanoyl group was supported by ^1H NMR signals at δ_H 2.39 (2H, m), 1.62 (2H, pent, J = 6.9 Hz), 1.26–1.36 (12H, m), and 0.90 (3H, t, J = 6.8 Hz) and by ^{13}C NMR signals at δ_C 174.1 (s), 34.9 (t), 33.0 (t), 30.5 (t), 30.4 (×2, t), 30.1 (t), 25.6 (t), 23.7 (t), and 14.4 (q). A combination of the COSY, HSQC, and HMBC data allowed assignment of the ^{13}C NMR signals from the disaccharide. The characteristic features of the two glucose moieties appeared in the ^{13}C NMR spectra, which exhibited at δ_C 95.6 (d), 77.8 (d), 77.7 (d), 73.9 (d), 70.9 (d), and 69.5 (t) for the inner glucose and signals at δ_C 104.6 (d), 78.0 (×2, d), 75.1 (d), 71.5 (d), and 62.7 (t) for the second glucose. The ^1H NMR signals at δ_H 5.44 (1H, d, J = 7.8 Hz) and 4.31 (1H, d, J = 7.8 Hz), and the ^{13}C NMR signals at δ_C 104.6 (d) and 95.6 (d) indicated the presence of anomeric protons and carbons in the disaccharide moiety having a β configuration. The HMBC correlation between anomeric proton δ_H 4.31 (H-1″) and δ_C 69.5(C-6′) connected the terminal glucose to the inner glucose. The linkage between the fatty acid ester moiety and the disaccharide was also established by the HMBC correlation between anomeric proton δ_H 5.44 (H-1′) and the carbonyl δ_C 174.1 (C-1). Important HMBC interactions of compound **2** are shown in Fig. 2. On the basis of the above data, the structure of **2** was deduced to be 6-*O*-(β-D-glucopyranosyl)-1-*O*-decanoyl-β-D-glucopyranose, a new fatty acid ester disaccharide.

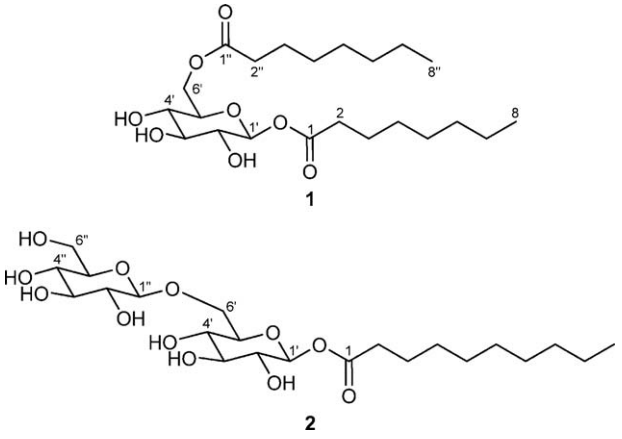

Fig. 1. Chemical structures of new fatty acid glucosides (**1** and **2**).

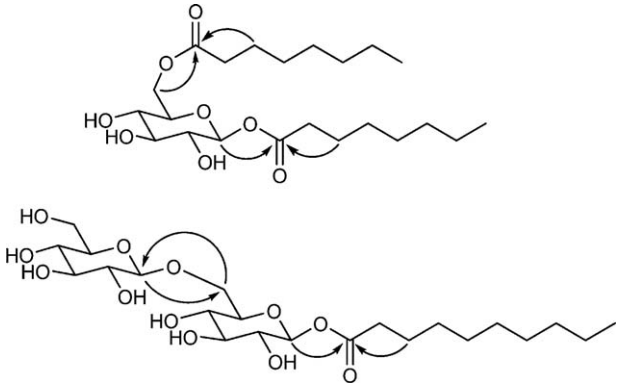

Fig. 2. Key HMBC correlations (H → C) of compounds **1** and **2**.

Compounds **3** and **4** were deduced to have the molecular formulas $C_{20}H_{36}O_{12}$ and $C_{18}H_{32}O_{12}$ based on the HRFABMS and ^{13}C NMR data, respectively. The ^1H NMR spectra of **3** and **4** resembled those of **2**, except for the integrations of protons in the region δ_H 1.26–1.36. The ^{13}C NMR spectra of **3** and **4** suggested that compounds **3** and **4** contained the octanoyl and hexanoyl group, respectively, instead of the decanoyl group found in **2**. On the basis of these data, compound **3** and **4** were identified as 6-*O*-(β-D-glucopyranosyl)-1-*O*-octanoyl-β-D-glucopyranose and 6-*O*-(β-D-glucopyranosyl)-1-*O*-hexanoyl-β-D-glucopyranose, respectively. These compound were previously isolated from *M. citrifolia* (Wang et al., 2000).

In addition, a disaccharide fatty acid ester, 2-*O*-(β-D-glucopyranosyl)-1-*O*-octanoyl-β-D-gluropyranose (**5**), and two trisaccharide fatty acid esters, 2,6-di-*O*-(β-D-glucopyranosyl)-1-*O*-octanoyl-β-D-glucopyranose (**6**) and 2,6-di-*O*-(β-D-glucopyranosyl)-1-*O*-hexanoyl-β-D-glucopyranose (**7**) were isolated from the other fraction of the MeOH extract and were identified as the known compounds (Akihisa et al., 2007). All these compounds have been fully characterized and their purity was checked by HPLC.

The noni fruit juice has been promoted for the prevention and cure of various diseases. We have focused on the potential effect of the compounds obtained from the noni fruit on atherosclerosis. The development of atherosclerosis is closely related to the oxidation of LDL. Kamiya et al. tested several different fractions of noni fruit and the MeOH extract, and it was found that the EtOAc- and n-BuOH soluble phases had a remarkable inhibitory effect on copper-induced LDL oxidation. Six lignans were isolated from

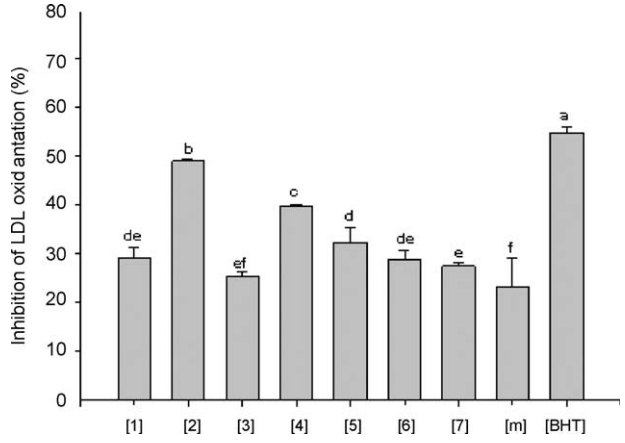

Fig. 3. Inhibition of LDL oxidation by methanol extract [M] and fatty acid glucosides [**1**–**7**] from noni fruit. LDL (100 μg/ml) was incubated with 25 μM $CuSO_4$ at 37 °C for 6 h in the presence of each sample and BHT (50 μg/ml). Values are means ± SEM of triplicate incubation ($n = 3$) and means with different letters are different by Duncan's multiple range test, $p < 0.05$.

EtOAc-soluble phase and identified as biologically active compounds (Kamiya et al., 2004). Based on our preliminary data on antioxidant activity of the crude MeOH extract, we tested the effect of the seven fatty acid glucosides purified from the MeOH extract on copper-induced LDL oxidation. All the compounds exhibited an inhibitory effect against copper-induced LDL oxidation and the effect was significantly stronger than that of the crude MeOH extract alone. Compound **2** had the strongest effect, almost comparable to that of BHT (Fig. 3). Considering that the MeOH extract had an activity comparable to that of the EtOAc-soluble fraction, our results demonstrated that the fatty acid glucosides from MeOH extract as well as the lignin from the EtOAc-soluble fraction had significant inhibitory effect on LDL oxidation.

3. Materials and methods

3.1. General experimental procedure

The melting points were measured with a Fisher-Johns melting point apparatus and were uncorrected. The IR spectra were recorded using a JASCO FT/IR-4100 spectrophotometer as thin films. Optical rotations were measured using a JASCO DIP-370 automatic polarimeter. The ^{1}H NMR spectra were recorded using a Varian Unity 500 spectrometer at 500 MHz and the ^{13}C NMR spectra were recorded on the same instrument at 125 MHz. Chemical shifts were expressed on a δ (ppm) scale and CD_3OD (^{1}H, 3.30 ppm; ^{13}C, 49.0 ppm) was used as internal standards. Mass spectra were obtained with a Micromass Auto Spec spectrometer.

3.2. Plant material and chemicals

The specimens of *M. citrifolia* (Sample No. 07KS-NF) were collected from Kosrae, Federated States of Micronesia, in July 2007. A voucher specimen is currently deposited at the Natural Medicines Research Center, Korea Research Institute of Bioscience and Biotechnology, Korea under the curatorship of J. Lee.

Trichloroacetic acid (TCA), 2-thiobarbituric acid (TBA), and LDL from human plasma were purchased from Sigma–Aldrich Co. (St. Louis, MO).

3.3. Extraction and isolation

The fruit of *M. citrifolia* (noni) was crushed immediately after collection and stored at −25 °C until the time of the analysis. The air-dried fruit (dry wt 370 g) of *M. citrifolia* was extracted twice with 600 mL portions of MeOH and once with 700 mL of CH_2Cl_2. The resulting extracts were pooled, filtered, and concentrated under reduced pressure to yield a residue of 35.6 g (9.6%) of crude extract. This residue was partitioned between H_2O and *n*-BuOH to yield 7.9 g of organic-soluble material. The *n*-BuOH phase was re-partitioned with 15% aqueous MeOH (4.82 g, 1.3%) and *n*-hexane (2.73 g, 0.74%). The residue of the aqueous MeOH layer was subjected to C_{18} reversed-phase flash chromatography using a gradient mixture of MeOH and H_2O. The fraction eluted with 10% aqueous MeOH was dried (100 mg) and separated by reversed-phase HPLC (YMC ODS-A column, 1 cm × 25 cm) with a mobile phase of 20% aqueous MeOH to give 7.5 mg of compound **1** as a major product. The fraction eluted with 30% aqueous MeOH was dried (0.75 g) and separated by reversed-phase HPLC (YMC ODS-A column, 1 cm × 25 cm) with a mobile phase of 40% aqueous MeOH to give 12.4 mg of compound **2** as a major product. The fraction eluted with 40% aqueous was dried (1.05 g) and separated by reversed-phase HPLC (YMC ODS-A column, 1 cm × 25 cm, 50% aqueous MeOH) to give 98.1 mg of compound **6** and 116 mg of a mixture. Further purification of the mixture was carried out by reversed-phase HPLC (YMC ODS-AQ column, 1 cm × 25 cm, 65% aqueous CH_3CN) to give 17.1 and 31.9 mg of pure compounds **3** and **5**, respectively. An aliquot (1.67 g) of the fraction eluted with 50% aqueous MeOH (2.45 g) was dried and separated by reversed-phase HPLC (YMC ODS-A column, 1 cm × 25 cm, 70% aqueous MeOH) to give 35.4 mg of pure compound **7** and 105 mg of pure compound **4**.

3.3.1. 1,6-Di-O-octanoyl-β-D-glucopyranose (1)

White powder; mp 68–70 °C; $[\alpha]_D$ +22.3° (*c* 0.16 MeOH); IR (film) 3355 (OH), 2927, 2857, 1742 (CO), 1168, 1065 cm^{-1}; ^{1}H NMR (CD_3OD, 500 MHz) δ 5.44 (1H, d, J = 8.0 Hz, H-1′), 4.37 (1H, dd, J = 11.5, 1.0 Hz, H-6′), 4.19 (1H, dd, J = 11.5, 5.0 Hz, H-6′), 3.55 (1H, m), 3.39 (1H, m), 3.34–3.31 (2H, m), 2.39 (2H, m), 2.33 (2H, m) 1.61 (4H, m), 1.28–1.36 (16H, m), 0.90 (6H, m); ^{13}C NMR (CD_3OD, 125 MHz) δ 175.4 (C-1″), 173.9 (C-1), 95.6 (C-1′), 77.9 (C-3′), 76.1 (C-5′), 73.9 (C-2′), 71.3 (C-4′), 64.2 (C-6′), 35.0, 34.9, 32.9 (×2), 30.2, 30.1(×2), 30.0, 26.0, 25.7, 23.7, 23.6, 14.4 (×2, C-8, C-8″); HRESIMS(+) m/z 455.2614 (M+Na), (calcd for $C_{22}H_{40}O_8Na$, m/z 455.2615).

3.3.2. 6-O-(β-D-glucopyranosyl)-1-O-decanoyl-β-D-glucopyranose (2)

White powder; mp 150–152 °C; $[\alpha]_D$ +24.0° (*c* 0.13 MeOH); IR (film) 3367 (OH), 2927, 2857, 1742 (CO), 1168, 1065 cm^{-1}; ^{1}H NMR (CD_3OD, 500 MHz) δ 5.44 (1H, d, J = 7.8 Hz, H-1′), 4.31 (1H, d, J = 7.8 Hz, H-1″), 4.14 (1H, dd, J = 11.7, 2.0 Hz, H-6′), 3.84 (1H, dd, J = 12.2, 2.2 Hz, H-6″), 3.76 (1H, dd, J = 11.2, 4.9 Hz, H-6′), 3.66 (1H, dd, J = 11.7, 5.4 Hz, H-6″), 3.53 (1H, m, H-5′), 3.43 (1H, m, H-4′), 3.41 (1H, m, H-3′), 3.34 (1H, m, H-3″), 3.32 (1H, m, H-2′), 3.28 (1H, m, H-4″), 3.25 (1H, m, H-5″), 3.20 (1H, m, H-2″), 2.39 (2H, m, H-2), 1.62 (2H, pent, J = 6.9 Hz, H-3), 1.26–1.36 (12H, m, H-4, H-5, H-6, H-7, H-8, H-9), 0.90 (3H, t, J = 6.8 Hz, H-10); ^{13}C NMR (CD_3OD, 125 MHz) δ 174.1 (C-1), 104.6 (C-1″), 95.6 (C-1′), 78.0 (×2, C-3″, C-5″), 77.8 (C-3′), 77.7 (C-5′), 75.1 (C-2″), 73.9 (C-2′), 71.5 (C-4″), 70.9 (C-4′), 69.5 (C-6′), 62.7 (C-6″), 34.9 (C-2), 33.0 (C-8), 30.5 (C-7), 30.4 (×2, C-5, C-6), 30.1 (C-4), 25.6 (C-3), 23.7 (C-9), 14.4 (C-10); HRFABMS(+) m/z 519.2416 (M+Na), (calcd for $C_{22}H_{40}O_{12}Na$, m/z 519.2417).

3.4. Basic hydrolysis of compound 1

Compound **1** (2.3 mg) was dissolved in 2 mL of methanol and treated with 5% NaOH-H_2O solution (1.0 mL) under stirring at room temperature for 24 h. The solvent was evaporated and the aqueous suspension acidified with dilute HCl. Extraction with

CH_2Cl_2 gave octanoic acid. The octanoic acid was identified by LC–MS based on the comparison with an authentic sample: ESIMS(−) *m/z* 143.25 (M−H).

3.5. Copper-induced LDL oxidation

3.5.1. Evaluation of inhibitory effects against copper-induced LDL oxidation

The inhibition of LDL oxidation was measured by the reported method (Kamiya et al., 2004). LDL (100 μg/mL) was incubated in a phosphate-buffered saline (pH 7.4, 1 mL) containing 25 μM $CuSO_4$, in the absence (control) or presence of purified fatty acid glucosides (50 μg/mL) for 6 h at 37 °C. The reaction mixture (1 mL) (15% TCA, 0.375% TBA and 0.25 N hydrochloric acid) was added to the LDL mixture prepared as above. The resultant mixture was heated for 30 min at 95 °C. After cooling, the absorbance of the pink chromophore was measured at 515 nm. A similar amount of 2,6-di-tert-butyl-4-methylphenol (BHT) was used as a reference compound.

3.5.2. Statistical analysis

Data were analyzed using SAS software (version 9.1; Cary NC). Values are expressed as means ± SEM and one-way ANOVA was used to determine significant difference of compound treatments. Differences among treatment means were determined by Duncan's multiple range test and a p value of <0.05 was considered significant.

Acknowledgements

We are grateful to the Department of Agricultural and Marine Resources, State of Kosrae, Federated States of Micronesia, for granting tropical plant research. And we thank In-Ho Jung, Special Advisor to Governor for Industrial Development, for providing noni fruit collected in Kosrae, FSM. This study was supported by the Catholic University of Korea, Research Fund, 2009, and the Ministry of Land, Transport and Maritime (PM55420), and the Ministry of Education, Science and Technology (PN64540), Korea.

References

Akihisa, T., Matsumoto, K., Tokuda, H., Yasukawa, K., Seino, K., Nakamoto, K., Kuninaga, H., Suzuki, T., Kimura, Y., 2007. Anti-inflammatory and potential cancer chemopreventive constituents of the fruits of *Morinda citrifolia* (Noni). J. Nat. Prod. 70, 754–757.

Chan-Blanco, Y., Vaillant, F., Perez, A.M., Reynes, M., Brillouet, J.-M., Brat, P., 2006. The noni fruit (*Morinda citrifolia* L.): a review of agricultural research, nutritional and therapeutic properties. J. Food Compos. Anal. 19, 645–654.

Dalsgaard, P.W., Potterat, O., Dieterle, F., Pauluat, T., Kuhn, T., Hamburger, M., 2006. Nonioside E-H, new trisaccharide fatty acid esters from the fruit of *Morinda citrifolia* (Noni). Planta Med. 72, 1322–1327.

Dembitsky, V.M., 2004. Astonishing diversity of natural surfactants: 1. Glycosides of fatty acids and alcohols. Lipids 39, 933–953.

Deng, S., Palu, A.K., West, B.J., Su, C.X., Zhou, B.-N., Jensen, J.C., 2007a. Lipoxygenase inhibitory constituents of the fruits of noni (*Morinda citrifolia*) collected in Tahiti. J. Nat. Prod. 70, 859–862.

Deng, Y., Chin, Y.-W., Chai, H., Keller, W.J., Kinghorn, A.D., 2007b. Anthraquinones with quinone reductase-inducing activity and benzophenones from *Morinda citrifolia* (Noni) roots. J. Nat. Prod. 70, 2049–2052.

Hemwimon, S., Pavasant, P., Shotipruk, A., 2007. Microwave-assisted extraction of antioxidative anthraquinones from roots of *Morinda citrifolia*. Sep. Purif. Technol. 54, 44–50.

Kamiya, K., Tanaka, Y., Endang, H., Umar, M., Sadake, T., 2004. Chemical constituents of *Morinda citrifolia* fruits inhibit copper-induced low-density lipoprotein oxidation. J. Agric. Food. Chem. 52, 5843–5848.

Kamiya, K., Tanaka, Y., Endang, H., Umar, M., Satake, T., 2005. New anthraquinone and iridoid from the fruits of *Morinda citrifolia*. Chem. Pharm. Bull. 53, 1597–1599.

Lee, H.-S., Lee, J.H., Won, H., Park, S.-K., Kim, H.M., Shin, H.J., Park, H.S., Sim, C.J., Kim, H.K., 2009. Identification of novel acetylenic alcohols and a new dihydrothiopyranone from the tropical sponge *Reniochalina* sp. Lipids 44, 71–75.

Liu, G., Bode, A., Ma, W.-Y., Sang, S., Ho, C.-T, Dong, Z., 2001. Two novel glycosides from the fruits of *Morinda Citrifolia* (Noni) inhibit AP-1 transactivation and cell transformation in the mouse epidermal JB6 cell line. Cancer Res. 61, 5749–5756.

Pawlus, A.D., Su, B.-N., Keller, W.J., Kinghorn, A.D., 2005. An anthraquinone with potent quinone reductase-inducing activity and other constituents of the fruits of *Morinda citrifolia* (Noni). J. Nat. Prod. 68, 1720–1722.

Samoylenko, V., Zhao, J., Dunbar, D.C., Khan, I.A., Rushing, J.W., Muhammad, I., 2006. New constituents from noni (*Morinda citrifolia*) fruit juice. J. Agric. Food. Chem. 54, 6398–6402.

Su, B.-N., Pawlus, A.D., Jung, H.-A., Keller, W.J., McLaughlin, J.L., Kinghorn, A.D., 2005. Chemical constituents of the fruits of *Morinda citrifolia* (Noni) and their antioxidant activity. J. Nat. Prod. 68, 592–595.

Wang, M.-Y., Nowicki, D., Anderson, G., Jensen, J., West, B., 2008. Liver protective effect of *Morinda citrifolia* (Noni). Plant Foods Hum. Nutr. 63, 59–63.

Wang, M.-Y., West, B.J., Jensen, C.J., Nowicki, D., Su, C., Palu, A.K., Anderson, G., 2002. *Morinda citrifolia* (Noni): a literature review and recent advances in noni research. Acta Pharmacol. Sin. 23, 1127–1141.

Wang, M., Kikuzaki, H., Csiszar, K., Boyd, C.D., Maunakea, A., Fong, S.F.T., Ghai, G., Rosen, R.T., Nakatani, N., Ho, C.-T., 1999. Novel trisaccharide fatty acid ester identified from the fruits of *Morinda citrifolia* (Noni). J. Agric. Food. Chem. 47, 4880–4882.

Wang, M., Kikuzaki, H., Jin, Y., Nakatani, N., Zhu, N., Csiszar, K., Boyd, C., Rosen, R.T., Ghai, G., Ho, C.-T., 2000. Novel glycosides from noni (*Morinda citrifolia*). J. Nat. Prod. 63, 1182–1183.

Young, I.S., McEneny, J., 2001. Lipoprotein oxidation and atherosclerosis. Biochem. Soc. Trans. 29, 359–362.