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Original Article

Cucumol A: a cytotoxic triterpenoid from *Cucumis melo* seeds

Sabrin Ibrahim[a,b,*], Rwaida Al Haidari[a], Gamal Mohamed[c,d], Ehab Elkhayat[d], Mohamed Moustafa[e]

[a] *Department of Pharmacognosy and Pharmaceutical Chemistry, College of Pharmacy, Taibah University, Al Madinah Al Munawwarah, Saudi Arabia*
[b] *Department of Pharmacognosy, Faculty of Pharmacy, Assiut University, Assiut, Egypt*
[c] *Department of Natural Products and Alternative Medicine, Faculty of Pharmacy, King Abdulaziz University, Jeddah, Saudi Arabia*
[d] *Department of Pharmacognosy, Faculty of Pharmacy, Al-Azhar University, Assiut Branch, Assiut, Egypt*
[e] *Department of Pharmaceutical Chemistry, Faculty of Pharmacy, King Abdulaziz University, Jeddah, Saudi Arabia*

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ABSTRACT

Phytochemical investigation of the MeOH extract of *Cucumis melo* L. var. *reticulates*, Cucurbitaceae, seeds led to the isolation of a new triterpenoid: cucumol A (27-hydroxy taraxerol-3β-o1), along with three known compounds: α-spinasterol and D:B-friedoolean-5-ene-3-β-ol. Their structures were established by extensive 1D (^{1}H, ^{13}C, and DEPT) and 2D (^{1}H–^{1}H COSY, HMQC, and HMBC) NMR, as well as IR and HRESIMS spectral analyses. Compound **3** displayed cytotoxic activity against L5178Y and Hela cancer cell lines with ED_{50} of 1.30 and 5.40 μg/ml, respectively compared to paclitaxel (0.07 and 0.92 μg/ml, respectively).

Introduction

Cucumis melo L. (cantaloupe) belonging to Cucurbitaceae family, is cultivated in temperate, subtropical, and tropical regions worldwide (Yasar et al., 2006; Ibrahim, 2010). Its fruits are consumed in the summer period because the pulp of the fruit is very refreshing, high nutritional, and sweet with a pleasant aroma, which may be used as an appetizer, a dessert or as salad (Melo et al., 2000; Baghaei et al., 2008). In Chinese folk medicine, the seeds of *C. melo* are used as digestive, febrifuge, antitussive, demulcent, and vermifuge (Duke and Ayensu, 1985; De Marino et al., 2009). Their extract can be used as an anti-diabetic and is useful in chronic eczema (Lal and Lata, 1980; Teotia and Ramakrishna, 1984). Seed kernel is commonly used in renal disorders such as kidney and bladder stones, ulcers in the urinary tract and stomach, painful and burning micturation, jaundice, vitiligo, ascites, suppression of urine, chronic fevers, inflammation of the liver and kidney, and in general debility in the Indian traditional medicine (Nayar and Singh, 1998; Baitar, 2003; Gill et al., 2011; Milind and Kulwant, 2011; Ibrahim, 2014; Ullah et al., 2015). The fruit's pulp possesses diuretic and anthelmintic properties (Ullah et al., 2015). Its lotion is employed for acute and chronic eczema. Roots are emetic agents. The fruits are used as a first aid treatment for burns and abrasions. Peduncle is used to manage anasarca and indigestion (Milind and Kulwant, 2011). *C. melo* revealed a wide range of biological activities such as antioxidant, analgesic, anti-inflammatory, and antimicrobial (Vouldoukis et al., 2004; Mariod and Matthaus, 2008; Gill et al., 2011; Ibrahim, 2014). Previous phytochemical studies on *C. melo* L. var. *reticulates* seeds resulted in the isolation of chromone derivatives, triterpene, and sterols (Ibrahim, 2010; Ibrahim, 2014, Ibrahim and Mohamed, 2015a,b). In the present work, investigation of the MeOH extract of *C. melo* L. var. *reticulates* seeds afforded a new triterpenoid: cucumol A (27-hydroxy taraxerol-3β-o1) (**3**), along with α-spinasterol (**1**) and D:B-friedoolean-5-ene-3-β-ol (**2**). The new compound was evaluated for its cytotoxic activity against L5178Y, PC12, and Hela cancer cell lines.

Materials and methods

General experimental procedures

Melting point was carried out using an Electrothermal 9100 Digital Melting Point apparatus (Electrothermal Engineering Ltd, Essex, England). Optical rotation was recorded on a Perkin-Elmer

* Corresponding author.
E-mail: sribrahim@taibahu.edu.sa (S. Ibrahim).

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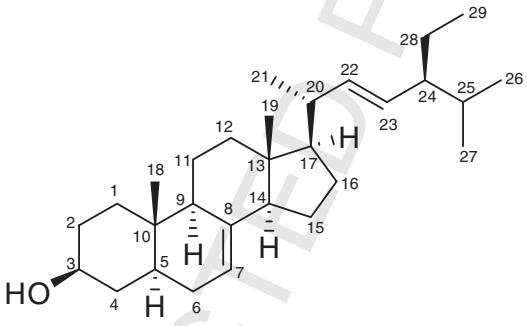
Model 341 LC Polarimeter (Perkin-Elmer, Waltham, MA, USA). EIMS was recorded on JEOL JMS-SX/SX 102A mass spectrometer (Joel, Peabody, MA, USA). HRESIMS spectrum was recorded on a LTQ Orbitrap (Thermo Finnigan, Bremen, Germany). 1D and 2D NMR spectra were recorded on a Bruker DRX400 NMR spectrometer using standard Bruker software and C_5D_5N and $CDCl_3$ as solvents, with TMS as the internal reference (Bruker, Rheinstetten, Germany). Column chromatographic separations were performed on silica gel 60 (0.04–0.063 mm, Merck, Darmstadt, Germany). TLC was performed on precoated TLC plates with silica gel 60 F_{254} (layer thickness 0.2 mm, Merck, Darmstadt, Germany). The chromatograms were developed using the following solvent systems: hexane:EtOAc (95:5, S_1) and hexane:EtOAc (90:10, S_2). The compounds were detected by spraying with *p*-anisaldehyde/H_2SO_4 reagent and heating at 110 °C for 1–2 min.

Plant material

Seeds of *C. melo* L. var. *reticulates*, Curcubitaceae, were obtained from the cultivated plants El-Galaa Village, Samalout, Minia, Egypt. The plant material was identified and authenticated (voucher specimen 2014-5) by Prof. Dr. Mohamed A. Farghali, Professor of Horticulture (Vegetable Crops), Faculty of Agriculture, Assiut University.

Extraction and isolation

Fruits were cut and seeds were removed from stringy piths. The seeds were rubbed by hand and washed quickly with tap water, then transferred to a colander and dried at room temperature. Dried seeds (200 g) were triturated in a ball mill and screened through a mesh of 0.5 mm diameter. The triturated seeds (175 g) were packed in a Soxhlet apparatus and defatted using hexane (3 × 1 l), then extracted with MeOH several times (4 × 1 l). The MeOH extract was evaporated and concentrated under reduced pressure to afford a dark brown residue (9.3 g). The latter was subjected to VLC (vacuum liquid chromatography) using hexane:EtOAc and EtOAc:MeOH gradients to afford five fractions: CA-I to CA-V; CA-I (2.6 g, hexane:EtOAc 75:25), CA-II (1.3 g, hexane:EtOAc 50:50), CA-III (2.1 g, hexane:EtOAc 25:75), CA-IV (0.7 g, EtOAc 100%), and CA-V (1.2 g, MeOH 100%). Fraction CA-I (2.6 g) was subjected to silica gel column chromatography (120 g × 50 × 2 cm) using hexane:EtOAc gradient to afford four subfractions CA-IA:CA-ID. Silica gel column chromatography (80 g × 50 × 2 cm) of subfraction CA-IB (0.55 g) using hexane:EtOAc as an eluent gave compound **1** (15 mg, white crystalline needles). Subfraction CA-IC (0.67 g) was chromatographed over silica gel column (90 g × 50 × 2 cm) using hexane:EtOAc gradient to yield compound **2** (10 mg, white crystals). Subfraction CA-ID was subjected to silica gel column using hexane:EtOAc (95:5–80:20) to afford compound **3** (7.5 mg, white needles)



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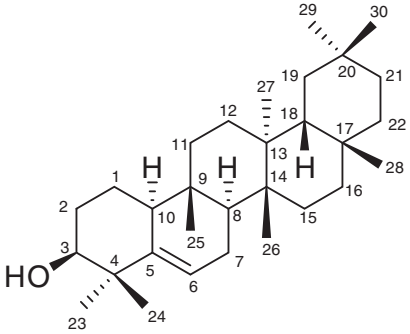

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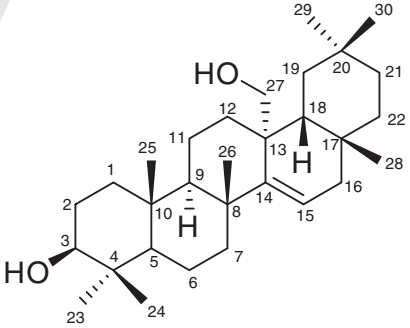

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