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Chemical and Biological Studies on *Cichorium intybus* L

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Abstract

Cichorium intybus L. (Asteraceae family) is a worldwide grown plant known as chicory. In traditional medicine, this plant is used as diuretic, anti-inflammatory, digestive, cardiotonic and liver tonic. Chromatographic purification of the supercritical fluid extract of aerial parts of *C. intybus* on silica gel column led to isolation of three compounds: new compound, 28*β*-hydroxytaraxasterol (**I**), and two known compounds usnic acid (**II**), and *β*-sitosterol (**III**). Purification of the ethanolic extract of aerial parts of this plant on silica gel column chromatography yielded four compounds: 1,3-dioleylglycerate (**IV**), sitoindoside II (**V**), 11*β*-13-dihydrolactucin (**VI**), and *β*-sitosterol-3-O-glucoside (**VII**). The structures of the isolated compounds were determined by their 1D, 2D NMR and MS spectral data. All the fractions and isolated compounds were tested for cannabinoid and opioid receptor binding, as well as antibacterial, antifungal, and antimalarial activities. Compound **I** showed moderate activity (60.5 % displacement) towards CB1 receptor.

Keywords

Cichorium intybus; isolation; cannabinoid receptor; opioid receptor

1. Introduction

Genus *Cichorium* belongs to Asteraceae family consists of ten species that grow widely in many parts of the world (Sastri et al. 1950). *Cichorium intybus* is commonly known as chicory. It is a perennial herb distributed in the temperate parts of the world. This plant is a medicinal herb, used in Unani, Ayurveda and Siddha systems of medicine for treating diseases of renal system, hepatobiliary system, anorexia and dyspepsia (Crellin & Philpatt 1990; Tyler, Brady & Robbers 1988). It is also used as an appetizer as well as in the treatment of jaundice, hepatic failure, intermittent fever and skin diseases. The plant

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exhibited antibacterial, antipyretic antidiabetic, antihepatotoxic, antioxidant, anti-inflammatory, anticancer and antimalarial activities (Najib et al. 2014; Rahman et al. 2008).

Recent studies on *C. intybus* have found some of the important constituents such as caffeic acid derivatives, phenylacetic acid esters, fructooligosaccharides, flavonoids, coumarins, polyphenol, cichoriosides, sonchuside A, ixerisosides, magnolialide, eudesmanolides, bitter sesquiterpene lactones, inulin, and vitamins (El-Lakany et al. 2004; Hussain et al. 2011; Kumari, Ali, & Aeri 2012; Kirillov et al. 2017; Lulu et al. 2016). In this paper, we report the isolation and characterization of one new 28β-hydroxytaraxasterol besides six known compounds from the aerial parts of *C. intybus*.

2. Results and discussion

Compound **I** was obtained as a white solid and its FTMS showed a molecular ion at *m*/*z* 443.3882 $[M+H]^+$ (calcd for $C_{30}H_{51}O_2$ 443.3889), another ionic fragment peak at 425.3777, indication for loss of hydroxyl group $[M-OH]^+$, indicating six double bond of equivalent. FT-IR spectrum of the compound exhibited peaks at 3397 (ν O-H), 2866 (ν C-H), 1034 (ν C-O), and 883 cm^{-1} (δ_{oop} $=CH_2$). The ^1H NMR spectrum ($CDCl_3$, 400 MHz) of **1** showed five methyl singlets at δ 0.76, 0.84, 0.96, 0.99, and 1.00, which were assigned to the C-24, C-25, C-23, C-27, and C-26 methyl protons, respectively. While a methyl doublet at δ 1.04 (J= 8.0 Hz) was assigned to the C-29 methyl protons. While, a characteristic downfield double-doublet at δ 3.0 (dd, J=5.1, 11.1 Hz) attributable to hydroxylated methine proton at C-3 position. Further downfield two doublets at δ 3.69 (d, J=10.9 Hz), and 3.78 (d, J=10.9 Hz) were assigned to C-28 hydroxylated methylene protons. Most downfield two singlets at δ 4.65, δ 4.63 were assigned to the *exo*-cyclic C-30 olefinic protons.

The ^{13}C NMR spectrum of **1** ($CDCl_3$, 100 MHz) showed resonances for 30 carbon atoms including six methyl, 12 methylene, six methine, and six quaternary carbons. The downfield resonances at δ 154.53 and 107.70 were assigned to the C-20 and C-30 olefinic carbons, respectively. One oxygenated methine carbon at δ 79.14 and one oxygenated methylene carbon at δ 61.25 were assigned to the OH-bearing C-3 and C-28, respectively. The resonances at δ 28.13, 25.87, 16.42, 16.05, 15.52, and 15.12, were ascribed to the methyl carbons (C-23, C-29, C-25, C-26, C-24, and C-27, respectively). The overall NMR data were in good agreement with a taraxastane-type skeleton (Rahman et al. 2008; Mukhtar et al. 2005; Patra, Mukhopaclhyay, & Mitra. 1981). The HMBC spectrum of **1** showed the following correlations: The C-23 methyl group at δ 0.96 showed correlations with C-3 (δ 79.14), C-4 (δ 37.27), C-5 (δ 55.49), and C-24 (δ 15.12). The C-24 methyl group (δ 0.76) showed correlations with C-3 (δ 79.14), C-4 (δ 37.27), C-5 (δ 55.49), and C-23 (δ 28.13). The C-25 methyl group (δ 0.84) showed correlations with C-1 (δ 38.90), C-5 (δ 55.49), C-9 (δ 50.58), and C-10 (δ 39.01). The C-26 methyl group (δ 1.00) showed connectivity with C-7 (δ 34.17), and C-9 (δ 50.58). The C-27 methyl group (δ 0.97) showed correlations with C-16 (δ 31.80). The C-28 oxy methylene protons δ 3.69 (d, 10.9 Hz), 3.78 (d, 10.9 Hz) showed correlations with C-16 (δ 31.80). The C-29 proton (δ 1.04) correlated with C-18 (δ 48.51) C-19 (δ 39.28), and C-20 (δ 154.53). The C-30 *exo*-methylene protons exhibited correlations with C-19 (δ 39.28) and C-21 (δ 25.60). Hence, compound **1** could be identified

as 28β-hydroxytaraxasterol (Figure 1) and to our knowledge this is the first time reporting from nature.

Compound **II**, NMR data, matched with a naturally occurring benzofuran derivative, usnic acid. This is the first time reporting from this plant and it had been previously isolated from lichen *Parmelia subrudecta* (Ivanova et al. 2010). Compound **III** was identified as β-sitosterol as its spectral data matched with the reported data (El-Lakany et al. 2004). Compound **IV** identified as glyceryl-1,3-dioleate, reported from several plants and is reporting first time from this plant. Compound **V** spectral data were identical to those of fatty acid ester of steroidal glucopyranoside, sitoindoside II, its first time isolated from this plant, previously reported from *Musa paradisiaca* (Ghosal & Saini 1984). Compound **VI** coincides with data for a sesquiterpene, 11β-13-dihydrolactucin, had been previously isolated (Fan et al. 2017) from *Lactuca mucronata* (Sarg et al. 1982). Compound **VII** spectral data matched with the data for a steroidal glycoside β-sitosterol-3-O-glucoside (Wang et al. 2009; El-Lakany et al. 2004). Compound **I** showed a moderate activity (60.5% displacement) towards CB1 receptor. None of the extracts and isolated compounds showed activity towards antimicrobial**,** antimalarial and antileishmanial activities at 20 μg/mL concentration.

2.1 28β-hydroxytaraxasterol (I)

White amorphous powder, FTMS *m*/*z* 443.3882 $[M+H]^+$ (calcd for $C_{30}H_{51}O_2$ 443.3889). FT-IR: 3397 (ν O-H), 2866 (ν C-H, 1034 (ν C-O), and 883 cm^{-1} (δ_{oop} $=CH_2$). ^1H NMR (400 MHz, $CDCl_3$): δ 4.65 (1H, s, H-30a), 4.63 (1H, s, H-30b), 3.78 (1H, d, *J*=10.9 Hz, H-28b), 3.69 (1H, d, *J*=10.9 Hz, H-28a), 3.00 (1H, dd, 5.1 11.1 Hz, H-3), 2.45 (1H, m H-21b), 2.19 (1H, m H-21a), 2.12 (1H, m H-19), 1.70 (1H, m H-1b), 1.63 (1H, m H-16a), 1.61 (2H, m H-2), 1.58 (1H, m, C-13), 1.52 (1H, m H-6b), 1.50 (1H, m H-11b), 1.37 (2H, m H-7), 1.36 (1H, m H-6a), 1.29 (1H, m H-9), 1.26 (1H, m H-11a), 1.25 (2H, m H-22), 1.17 (1H, m H-18), 1.09 (1H, m H-12b), 1.09 (1H, m H-15b), 1.07 (1H, m H-16a), 1.04 (3H, d, *J*=8.0 Hz, H-29), 1.00 (3H, s, H-26), 0.93 (1H, m H-1a), 0.98 (1H, m H-12a), 0.98 (1H, m H-15a), 0.97(3H, s, H-27), 0.96 (3H, s, H-23), 0.84 (3H, s, H-25), 0.76 (3H, s, H-24), 0.69 (1H, m H-5). ^{13}C NMR (100 MHz, $CDCl_3$): 154.53 (C-20), 107.70 (C-30), 79.14 (C-3), 55.49 (C-5), 50.58 (C-9), 38.90 (C-1), 37.27 (C-4), 61.25 (C-28) 41.11 (C-8) 48.51 (C-18) 39.01 (C-10) 42.07 (C-14) 34.17 (C-7) 38.56 (C-13) 27.53 (C-2) 39.17 (C-17) 39.28 (C-19) 31.80 (C-16) 26.62 (C-12) 18.43 (C-6) 26.53 (C-15) 21.52 (C-11) 29.85 (C-22) 28.13 (C-23) 25.60 (C-21) 25.87 (C-29) 15.52 (C-24) 16.42 (C-25) 16.05 (C-26) 15.12 (C-27).

3. Conclusion

Chromatographic purification of supercritical fluid extract of *C. intybus* aerial parts over silica gel yielded three compounds (**I**–**III**): 28β-hydroxytaraxasterol (**I**, new), benzofuran derivative, usnic acid (**II**), and β-sitosterol **(III**). Four compounds were obtained from the ethanolic extract of aerial parts of *C. intybus*: glyceryl-1,3-dioleate **(IV**), sitoindoside II (**V**), 11β-13-dihydrolactucin (**VI**), β-sitosterol-3-O-glucoside (**VII**). Compound **I** was isolated for the first time from nature. Compounds **II**, **IV**, and **V** were reported for the first time from this plant. Only compound **I** showed moderate activity (60.5% displacement) towards CB1

receptor. Both the extracts and isolated compounds showed no activity towards antimicrobial, antimalarial and antileishmanial activities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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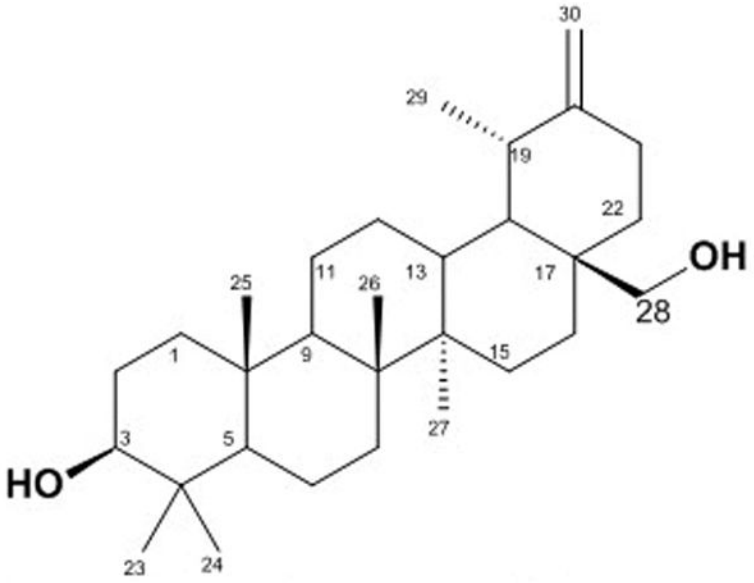

Figure 1.
Structure of compound I (28β-hydroxytraraxasterol)