Original Article

Triterpenoids Isolated from Stem Bark of Glochidion lanceolarium (Roxb.), Voigt

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Abstract

This paper presents the chemical investigation of the stem barks of *Glochidion lanceolarium* (Roxb.) Voigt, Euphorbiaceae. Classic phytochemical investigation of organic extracts of the aerial parts of *Glochidion lanceolarium* together with spectroscopic methods led to the isolation and characterization of three triterpenes, namely Epilupeol (1) Glochidonol (2), Glochidone (3). [Journal of Science Foundation, January 2020; 18(1): 13-18]

Keywords: Triterpenes; Epilupeol; Glochidonol; Glochidone; Phyllanthus; Glochidion

[Reviewed: 3 November 2019; Accepted on: 1 December 2019; Published on: 1 January 2020]

Introduction

Glochidion was regarded as a genus of the family Euphorbiaceae, which consists of monoecious, rarely dioecious trees or shrubs. But molecular phylogenetic studies have shown that Phyllanthus is paraphyletic over Glochidion. A recent revision of the family Phyllanthaceae has subsumed Glochidion into Phyllanthus (Hoffmann et al., 2006). Glochidion lanceolarium (Roxb.) Voigt, locally known as Keetchua, Bhauri, kakra, Anguti is a small to medium-sized evergreen tree usually 1-3m tall, rarely 7-12 m tall. The plant grows in Chittagong, Cox’s Bazaar and Sylhet of Bangladesh. It is also available in Bhutan, India, Myanmar and Nepal (Rahman, 2008).

Traditionally many Phyllanthus species are used in haemorrhoids, diarrhoea, dysentery, anaemia, jaundice, dyspepsia, insomnia etc. and some of them can induce diuresis (Ghani, 1998). In Chinese traditional medicine *Glochidion puberum* is used in dysentery, jaundice, leukorrhagia, common cold, sore throat, toothache, carbuncle, furuncle, rheumatic arthralgia (Fenglin et al., 2004). Recent investigation showed that *Glochidion multilculare* possess antitumor, analgesic and anti-inflammatory potential (Kabir et al., 2015).

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Biological investigations of *Phyllanthus* species revealed that many members of the genus possess anti-tumor promoting ability (Huang et al., 2006; Rajeshkumar et al., 2002; Tanaka et al., 2004), apoptosis inducing ability (Huang et al., 2004; Puapairoj et al., 2005), antiviral activity against hepatitis B virus (Lam et al., 2006; Venkateswaran et al., 1987), anti-angiogenic effect (Huang et al., 2006), analgesic effect (Santos et al., 1994, 2000), diuretic effect (Srividy and Periwal, 1995), lipid lowering activity (Khanna et al., 2002), hypocholesterolemic activity (Adeneye et al., 2006), antioxidative effect (Harish and Shivanandappa, 2006; Raphael et al., 2002; Sabir and Rocha, 2008), antidiabetic effect (Adeneye et al., 2006; Raphael et al., 2002; Srividy and Periwal, 1995), antitherpeptic activity (Alvarez et al., 2009; Yang et al., 2007), hepatoprotective effect (Harish and Shivanandappa, 2006; Sabir and Rocha, 2008), anti-inflammatory action (Kassuya et al., 2006; Kiemer et al., 2003), antiatherogenic effect (Duan et al., 2005), anti-HIV activity (Notka et al., 2003, 2004; Ogata et al., 1992); antiplasmodial activity (Luyindula et al., 2004), antibacterial activity (Meléndez and Capriles, 2006), hypotensive activity (Leeya et al., 2010; Srividy and Periwal, 1995).

Many secondary metabolites were isolated from *Glochidion* species, including tannins (Chen et al., 1995), glycosides (Otsuka et al., 2003), lignans (Otsuka et al., 2000), terpenoids (Hui and Li, 1976). Glochidiol, glochilocudiol, glochidone and dimedone were isolated from *G. multiloculare* (Talapatra et al., 1973). Previous phytochemical investigations of *G. lanceolarium* led to the isolation of triterpenes 3-epilupeol, glochidone and glochidiol from the bark and roots (Asolkar et al., 1992). We describe here the chemical characterization of triterpenes obtained from *G. lanceolarium* along with a small review regarding the importance of these compounds.

**Methodology**

General experimental procedures: Mass measurements were conducted on a Micromass Q-TOF Ultima Gloval Tandem mass spectrometer. 1H- and 13C- NMR spectra were acquired with a Bruker AMX-500 (500 MHz for 1H and 100 MHz for 13C) spectrometer and the spectra were referenced to the residual non-deuterated solvent signals. J-modulated 13C spectra were acquired with a relaxation time (d1) of 4 s. Vacuum liquid chromatography (VLC) was done over silica gel (Kieselgel 60H, mesh 70-230, Merck). while TLC and preparative TLC (pTLC) were performed by using silica gel 60 PF254 on glass plates (5 x 20 cm, thickness 0.5 mm) and the compounds were visualized under UV light (254 and 366 nm) and by spraying the developed plates with vanillin-sulfuric acid, followed by heating at 1100°C for 5-10 mins.

Plant material: The stem bark of *G. lanceolarium* was collected from Mirpur, Dhaka in the month of April, 2009 and identified by Mr. Sarder Nasir Uddin, Scientific Officer, Bangladesh National Herbarium, Dhaka, where a voucher specimen (DACB-34199) representing this collection has been deposited. Stem bark of this plant was air-dried for several days followed by oven-drying for 24 hours and then ground to a coarse powder.

Extraction and Isolation: The air dried powdered plant material (900 g) was successively cold extracted with methanol (7 days) at room temperature with occasional shaking and stirring. The extractives were filtered through fresh cotton plug and followed by whatman no. 1 filter paper. The filtrate were then concentrated by a Buchii rotavapor at low temperature and pressure and afforded methanol (MEGL) extract (36.8199g). The air dried powdered plant material (900 g) was successively cold extracted with methanol (7 days) at room temperature with occasional shaking and stirring. The extractives were filtered through fresh cotton plug and followed by whatman no. 1 filter paper. The filtrate were then concentrated by a Buchii rotavapor at low temperature and pressure and afforded methanol (MEGL) extract (36.8199g). The cold methanol extract (10 g) was subjected to Solvent-Solvent partitioning using the protocol designed by Kupchan and modified by Wagene (Vanwagenen et al., 1993). The extract was partitioned successively with petroleum ether, carbon tetrachloride and chloroform. Evaporation of solvents afforded petroleum ether (PEFGL, 3.5 g), carbon tetrachloride (CTFGL, 2.6 g), chloroform (CFFGL, 700 mg) and aqueous (AQFGL, 1.9 g). A portion of the carbon tetrachloride soluble fraction (1 g) was subjected to Vacuum Liquid Chromatography (VLC) for fractionation. The column was filled with fine TLC grade silica gel (kieselgel 60H, mesh 70-230) and eluted with petroleum ether, followed by petroleum ether and ethyl acetate mixtures of increasing polarities and finally with ethyl acetate and methanol in order of increasing polarities. A total of 28 fractions were collected. The VLC fractions 5A and 5B were combined together on the basis of TLC analysis. Preparative TLC of the VLC fractions developed with 5% EtOAc in toluene afforded compound 1 (2.5 mg). Depending on the TLC behavior, fractions 6B and 7A were bulked together and Preparative Thin Layer Chromatography (PTLC) developed with 10% EtOAc in toluene afforded compound 2 (3.5 mg). The
VLC fractions 9B and 10(A+B) were mixed together on the basis of the similar TLC feature and subjected to Preparative Thin Layer Chromatography (PTLC) with 12% EtOAc in toluene yielded compound 3 (5mg).

**Results and Discussion**

![Image of Epilupeol structure]

**Figure I: Structure of Epilupeol**

Epilupeol (I): white crystals; *ESI-MS*: \textit{m/z} 427 [M + H]^+ (C_{30}H_{50}O, M = 426); \textit{^1}H NMR (500 MHz, CDCl$_3$): \(\delta\) (ppm) 3.39 (1H, t, H-3), 2.39 (1H, ddd, \(J = 11.2, 11.2, 6.0\) Hz, H-19), 0.83 (3H, s, H-23), 0.94 (3H, s, H-24), 0.85 (3H, s, H-25), 1.04 (3H, s, H-26), 0.96 (3H, s, H-27), 0.79 (3H, s, H-28), 4.69 (1H, d, \(J = 2.4\) Hz, H$_{a}$-29), 4.57 (1H, dd, \(J = 2.4, 1.6\) Hz, H$_{b}$-29), 1.68 (3H, s, H-30); \textit{^13}C NMR (100 MHz, CDCl$_3$): \(\delta\) (ppm) 33.2 (C-1), 25.4 (C-2), 76.2 (C-3), 38.0 (C-4), 49.7 (C-5), 18.3 (C-6), 34.1 (C-7), 40.0 (C-8), 50.2 (C-9), 38.0 (C-10), 19.2 (C-11), 25.1 (C-12), 38.0 (C-13), 43.0 (C-14), 27.4 (C-15), 35.6 (C-16) 42.9 (C-17), 49.0 (C-18), 49.0 (C-19), 150.9 (C-20), 28.2 (C-21), 40.0 (C-22), 27.4 (C-23), 22.1 (C-24), 15.9 (C-25), 15.9 (C-26), 14.6 (C-27), 18.0 (C-28), 109.2 (C-29), 19.3 (C-30)

![Image of Glochidonol structure]

**Figure II: Structure of Glochidonol**

Glochidonol (II): white crystal, *ESI-MS*: \textit{m/z} 441[M + H]^+ (C$_{30}$H$_{48}$O$_2$, M = 440); \textit{^1}H NMR (500 MHz, CDCl$_3$): \(\delta\) (ppm) 3.89 (1H, dd, \(J = 8.0, 3.6\) Hz, H$_a$-1), 2.99 (1H, dd, \(J = 14.4, 8.0\) Hz, H$_{ax}$-2), 2.21 (1H, dd, \(J = 14.4, 3.6\), Heq-2), 2.38 (1H, dt, \(J = 11.2, 5.6\) Hz, H-19), 4.69 (1H, d, \(J = 2.0\) Hz, H$_{a}$-29), 4.57 (1H, br. S, H$_{b}$-29), 1.06 (3H, s, H-23), 1.04 (3H, s, H-24), 0.84 (3H, s, H-25), 1.06 (3H, s, H-26), 0.98 (3H, s, H-27), 0.80 (3H, s, H-28), 1.68 (3H, s, H-30)
Figure III: Structure of Glochidone

Glochidone (III): Oily substance, ESI-MS: m/z 422.69 [M + H]+, (C_{30}H_{46}O); 1H NMR (500 MHz, CDCl₃): δ (ppm) 7.10 (1H, d, J = 10.0, H-1), 5.79 (1H, d, J = 10.0, H-2), 2.40 (1H, dt, J = 11.0, 6.0, H-19), 4.71 (1H, d, J = 2.0, H-29), 4.59 (1H, m, H-29), 1.07 (3H, s, H-23), 1.08 (3H, s, H-24), 1.13 (3H, s, H-25), 1.12 (3H, s, H-26), 0.96 (3H, s, H-27), 0.81 (3H, s, H-28), 1.69 (3H, s, H-30)

Compound I was isolated as white crystal from the carbon tetrachloride soluble fraction of the stem bark of *G. lanceolarium*. The high-resolution ESI mass spectrum of Compound 1 showed the pseudo-molecular ion peak, [M + H]+ at m/z 427 which was consistent with a molecular formula (C_{30}H_{46}O, M = 426) for this compound. The 1H NMR (CDCl₃, 500 MHz) and 13C NMR (CDCl₃, 100 MHz) spectrum revealed typical signals for 50 protons and 30 carbons including seven tertiary methyls, one oxymethine and one terminal disubstituted double bond (Thu et al., 2010).

The 1H NMR spectrum (500 MHz, CDCl₃) of compound 1 showed a triplet (J = 2.8) of one proton intensity at δ 3.39 typical for an oxymethine proton at C-3 of a triterpene type carbon skeleton. The absence of a double doublet and the appearance of a triplet suggested that the hydroxy group was at the α (alpha)-position, thus confirming the β (beta) orientation of C-3 proton (Alam et al., 2009). The spectrum displayed a doublet at δ 4.69 (J = 2.4) and a double doublet at δ 4.57 (2.4, 1.6) assignable to the vinlyc protons at C-29. Triple doublet at δ 2.39 (11.2, 11.2, 6.0) could be ascribed to proton at C-19. The spectrum also displayed seven singlets at δ 0.83, 0.94, 0.85, 1.04, 0.96, 0.79 and 1.68 (3H each) for methyl protons at C-4 (H-23, H-24), C-10 (H-25), C-8 (H-26), C-14 (H-27), C-17 (H-28) and C-20 (H-30), respectively. On this basis and by comparing these 1H NMR and 13C NMR data with literature values (Thu et al., 2010; Alam et al., 2009), compound 1 was identified as epilupeol. The identity of compound 1 was further substantiated by co-TLC with an authentic sample. This is the first report of this compound from *G. lanceolarium*.

Compound II was isolated as white crystal from the carbon tetrachloride soluble fraction of the stem bark of *G. lanceolarium*. The high-resolution ESI mass spectrum of Compound II showed the pseudo-molecular ion peak, [M + H]+ at m/z 441 which was consistent with a molecular formula (C_{30}H_{46}O, M = 440) for this compound (Thu et al., 2010). The 1H NMR (CDCl₃, 500 MHz) spectrum of Compound 2 displayed methyl group resonances at δ 1.06, 1.04, 0.84, 1.06, 0.98, 0.80 and 1.68 were attributed to H-23, H-24, H-25, H-26, H-27, H-28 and H-30 respectively. The spectrum showed a doublet at δ 4.69 (2.0) and a singlet at 4.57 assignable to protons at C-29. A doublet of triplets at δ 2.38, (11.2, 6.0) integrating one proton intensity is indicative of H-19. A double doublets at δ 3.89 (8.0, 3.6) integrating one proton, is indicative of Hα-1. Two doublets of doublets at δ 2.99 (14.4, 8.0) and δ 2.21 (14.4, 3.6) are assignable to Hα-2 and Hα-2 respectively. On this basis and by comparing these 1H NMR data with literature values (Hui et al., 1976; Thu et al., 2010), compound II was identified as glochidonol. The identity of Compound 2 was further substantiated by co-TLC with an authentic sample. This is the first report of this compound from *G. lanceolarium*.
Compound III was isolated as oily substance from carbon tetrachloride soluble fraction of the stem bark of *G. lanceolarium*. The high-resolution ESI mass spectrum of Compound III showed the pseudo-molecular ion peak at *m/z* 422.69 which was consistent with a molecular formula, C_{30}H_{46}O for this compound. The $^1$H NMR (CDCl$_3$, 500 MHz) spectrum of Compound III showed a doublet at $\delta$ 7.10, integrating for one proton, is indicative of H-1. A doublet at $\delta$ 5.79, d (10.0) was assigned to H-2. A doublet of triplets at $\delta$ 2.40, dt (11.0, 6.0), integrating one proton was indicative of H-19. The spectrum exhibited two doublets at $\delta$ 4.71, d (2.0) and 4.59, m was assigned to protons at C-29. The spectrum also displayed seven singlets at $\delta$ 1.07, 1.08, 1.13, 1.12, 0.96, 0.81 and 1.69 (3H each) for methyl protons at C-4 (H$_2$-23, H$_3$-24), C-10 (H$_3$-25), C-8 (H$_2$-26), C-14 (H$_2$-27), C-17 (H$_2$-28) and C-20 (H$_3$-30), respectively. These spectral features are in close agreement to those observed for glochidonol (Hui et al., 1976; Neto et al., 1995). This is the first report of this compound from this plant.

Glochidonol and glochidiol show strong antiproliferative activity against three human tumor cell lines, MCF-7, NCI-H-460 and SF-268, through the involvement of apoptosis (Puapairoj et al., 2005). Glochidone shows pronounced antinociceptive properties in mice (Krogh et al., 1999). Lupeol is reported to exhibit a spectrum of pharmacological activities against various disease conditions such as inflammation, arthritis, diabetes, cardiovascular ailments, renal disorder, hepatic toxicity, microbial infections and cancer (Saleem, 2009; Siddique and Saleem, 2011).

**Conclusion**

In conclusion Glochidonol and glochidiol show strong anti-proliferative activity against three human tumor cell lines, MCF-7, NCI-H-460 and SF-268, through the involvement of apoptosis.

**Conflict of interest statement:** We declare that we have no conflict of interest.

**Acknowledgements:** The authors are thankful to the Department of Pharmaceutical Chemistry, University of Dhaka, and Department of Applied Chemistry & Chemical Engineering, University of Dhaka, Bangladesh for providing laboratory facilities to carry out this research work. The Bose Centre for Advanced Study and Research in Natural Sciences, University of Dhaka, Bangladesh is gratefully acknowledged for partial financial support to carry out the research work.

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