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Phytochemical Investigation of *Annona Squamosa* Bark

Sandeep* and Abhilasha Mittal
*Department of Pharmacogonosy, Jayoti Vidyapeeth Women's University, Jaipur, Rajasthan-303122, India.
Faculty of Pharmaceutical Science, Jayoti Vidyapeeth Women's University, Jaipur, Rajasthan -303122, India.
Email: sandeepandcp@gmail.com

ABSTRACT
*In current study, phytochemical investigation of the bark of Annona squamosa L. (Annonaceae) yields three known alkaloids namely, two aporphine (anonaine (**A**) and asimilobine (**B**)), one oxoaporphine (lysicamine (**C**)) together with two unknown compounds 1,2-dihydroxy-7H-dibenzo-quinolin-7-one (**D**) and 1,2,9-trihydroxy-5,6,6a,7-tetrahydro-4H-dibenzo-quinoline (**E**). Structures of these alkaloid compounds were determined by spectral analysis. The structures of the isolated compounds have been confirmed on the basis of FT-IR, ^{1}H NMR and mass spectral studies as well as by comparison with literature data. Our findings revealed that bark of Annona squamosa species is an important source of aporphine and oxoaporphine alkaloids.*
KEY WORDS: *Annona squamosa L., Alkaloids, Aporphine, Oxoaporphine, FT-IR, ^{1}H NMR.*

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INTRODUCTION

The family (Annonaceae) is a vast family containing around 135 genera and more than 2500 species conveyed basically in tropical and subtropical areas [1]. The genus name, 'Annona' is from the Latin word 'anon', meaning 'yearly produce', referring to the production of fruits of the various species in this genus. A. squamosa has been named botanically from Jamaica [2-4]. *Annona squamosa* L. (Annonaceae), commonly known as the custard apple tree is cultivated throughout India, because of its edible nature [5]. The taste of the pulp of the fruit is really sweet because of its higher sugar content of about 58% of dry mass, and hence it is found clear that the fruit pulp possess a high calorie value [6]. This plant was reputed to contain several medicinal properties. Synthetically, this family is described by the nearness of isoquinoline alkaloids, for the most part aporphines.

Phytochemical examined on *Annona squamosa* have reported the nearness of 10-hydroxy-16-hentriacontanone [7]. The Squamocenin a new Acetogenin, Annotemoyin-2 and Reticulatain-2 were isolated first time from the plant [8]. Samaquasine A, benzoquinazoline, Annonacin, Annonacin-A and Annonastatin alkaloid has been isolated from the seeds of *Annona squamosa* [9, 10]. A new keto-monotetrahydrofuran acetogenin with a ketolactone terminus was also isolated and characterized by spectral analyses and named Squamone. The cytotoxicities of three compounds were increased significantly by reduction of the two keto group to hydroxyls [11], Annotemoyin-1, Annotemoyin-2, Squamocin, cholesteryl glycopyranoside, Anonin I and Anonin VI were isolated from seeds of *Annona squamosa*. Annonain I is identical with that of Squamosin [12, 13]. A new natural compound Squamosamide isolated from *Annona squamosa* and two bis- tetrahydrofuran acetogenins, Squamocin-O (1) and Squamocin-O (2) were isolated from the methanolic extract of seeds of *Annona squamosa* [14, 15]. Six new ent-kaurane diterpenoids Annomosin A, Annosquamosin C, Annosquamosin D, Annosquamosin E, Annosquamosin F, Annosquamosin G were isolated from stem of the *Annona squamosa* [16]. The bioactivity-directed fractionation work on the bark of *Annona squamosa* has resulted in the discovery of three new Annonaceous acetogenins, (2,4-cis and trans)-squamolinone (1), (2,4-cis and trans)-9-oxoasimicinone (2), and bullacin B (3) [17].

The present investigation of chemical constituents of *Annona squamosa* was attempted as a major aspect of a more extensive study to discover the active constituents present in this plant. In present study, we describe the isolation and structural elucidation of two new chemical compounds namely, *1,2-dihydroxy-*

7H-dibenzo-quinolin-7-one (D) and *1,2,9-trihydroxy-5,6,6a,7-tetrahydro-4H-dibenzo-quinoline* (E) together with three known alkaloids *anonaine* (A) and *asimilobine* (B), *lysicamine* (C) reported for the first time from bark of *Annona squamosa.*

EXPERIMENTAL

The melting points were determined in open capillary tubes and were uncorrected. The purity of all the isolated compounds were checked by TLC on precoated silica gel-G aluminum sheets (Type 60 GF_{254}, Merck) and the spots were detected by exposure to iodine vapors. The infrared (FT-IR) spectra were recorded on 470-Shimadzu infrared spectrophotometer using the KBr disc prepared by pressed pellet technique and υ_{max} is expressed in cm^{-1}. NMR spectra were measured in DMSO-d_6 as solvent at 300 MHz (^{1}H NMR) and 75 MHz (^{13}C NMR) on a BRUKER AVANCE-300 spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are given in parts per million (ppm). Spin multiplicities are given as s (singlet), d (doublet) and m (multiplet). Mass spectra were obtained on Shimadzu 2010A LC-MS spectrometer. All the solvents were distilled and dried with usual desiccant.

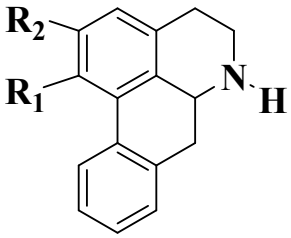
MATERIALS AND METHODS

The bark part of plant were collected from the herbal garden of Acharya Narendra Deo College of Pharmacy, Babhnan, Gonda, Uttar Pradesh, India in the month of September and identified by an expert taxonomist in Department of Taxonomy & Pharmacognosy, National Botanical Research Institute, Lucknow. The plant specimens were authenticated (Ref. No NBRI/CIF/413/2013). The areal part of plant was shade dried, reduced to coarse powder and stored in airtight container till further use.

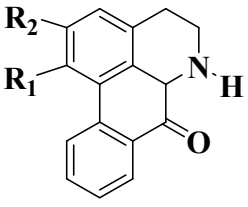
EXTRACTION AND ISOLATION

Dried and powdered bark of *A. squamosa* (950g) were defatted with hexane at room temperature for 24 h, dried and extracted with EtOH at room temperature for 72 h. The ethanolic extract was separated by filtration and concentrated under reduced pressure to yield 42.3g of crude extract. Small portion of the extract was analyzed chemically to determine the presence of different chemical constituents.

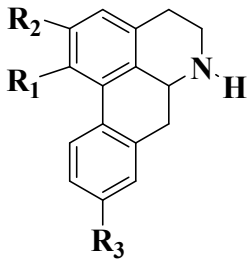
The ethanolic extract, was initially subjected to an acid–base extraction to give alkaloid (3.1 g) and neutral (5.7 g) fractions. The alkaloidal fraction was subjected to silica gel Column chromatography previously treated with a 10% $NaHCO_3$ solution, eluted with increasing concentrations of hexane, CH_2Cl_2 and EtOH, giving various fractions (30 ml each). These fractions were evaluated and pooled according to TLC analysis. Fraction F11-21 giving *anonaine* (**A**) and a mixture of alkaloids *asimilobine* (**B**) and new compound *1,2,9-trihydroxy-5,6,6a,7-tetrahydro-4H-dibenzo-quinoline* (**E**). The mixture was subjected to a preparative TLC eluted with CH_2Cl_2:EtOH (90:10, *v*/*v*, three times) giving compounds, Fraction 25-31 affording a mixture of two oxoaporphine alkaloids *lysicamine* (**C**) and a new compound *1,2-dihydroxy-7H-dibenzo-quinolin-7-one* (**D**) and the mixture was subjected to a preparative TLC eluted with CH_2Cl_2:EOtH (80:20, *v*/*v*, three times).



Compound A: R_1-R_2= O-CH_2-O
Compound B: R_1 = OCH_3; R_2= OH



Compound C: R_1= OCH_3; R_2 =OCH_3
Compound D: R_1 = OH; R_2= OH



Compound E: R_1 = OH; R_2= OH; R_3= OH

RESULT

Compound A

Anonaine (Compound **A)** was obtained as amorphous powder; brown solid; R_f = 0.63; Yield 39%; mp 132-133 ^oC**;** The FTIR (KBr, ν, cm^{-1}) spectrum of compound **A** showed absorption bands at: 3405.23 (N-H str), 3024.27 (Cyclic C-H, str), 1453.56 (Cyclic alkanes, C-H, ben), 1445.48 (C=C ring, str), 1205.23 (C-O-C asym., str), 1070.23 (C-O-C sym, str), 935.38 (C-O, str); The ^1H NMR spectrum (300 MHz, DMSO-d_6) δ (ppm) of compound **A** displayed the characteristic signals at 2.12 (s, 1H, NH, D_2O exchangeable), 2.63-3.44 (m, 6H, Ar-H), 4.34 (s, 1H, Ar-H), 5.93(s, 2H, -OCH_2O-), 6.43 (s, 1H, Ar-H), 7.12-7.96 (m, 4H, Ar-H); The ^{13}C NMR (75 MHz, DMSO-d_6) spectrum of compound **A** displayed the characteristic signals at: δ 30.2, 36.4, 37.5, 42.9, 101.5, 112.8, 115.2, 124.8 (2), 127.5 (2), 132.8, 134.4, 136.6, 142.5, 145.5, 148.4 The mass data EIMS (m/z) which showed 265.31 $[M]^+$, 266.37 $[M+1]^+$.(Calcd for $C_{17}H_{15}NO_2$).

Compound **A** was isolated and its molecular formula was determined as $C_{17}H_{15}NO_2$ {m/z = 265 (100) $[M^+]$}. The structure of the aporphine alkaloid was identified on the basis of extensive spectroscopic data analysis and by comparison of its spectral data with those reported in the literature.

Compound B

Asimilobine (compound **B**) was obtained as powder; white solid; R_f = 0.67; Yield 18%; mp 156-157 ^0C; The FTIR (KBr, ν, cm^{-1}) spectrum of compound **B** showed absorption bands at: 3603.29 (O-H, str), 3413.45 (N-H, str), 3012.45 (Cyclic aromatic, C-H, str), 1543.48 (C=C ring, str), 1455.42 (Cyclic alkanes, C-H, ben), 1195.33 (C-O-C asym., str), 1045.23 (C-O-C sym, str), 958.28 (C-O, str); The ^1H NMR spectrum (300 MHz, DMSO-d_6) δ (ppm) of compound **B** displayed the characteristic signals at 2.05 (s, 1H, NH, D_2O exchangeable), 2.33-3.04 (m, 6H, Ar-H), 3.62 (s, 3H, OCH_3), 4.22 (s, 1H, Ar-H), 5.03 (s, 1H, OH, D_2O exchangeable), 6.23 (s, 1H, Ar-H), 6.95-7.04 (m, 4H, Ar-H); The ^{13}C NMR (75 MHz, DMSO-d_6) spectrum of compound **B** displayed the characteristic signals at: δ 30.5, 37.8, 39.4, 42.6, 56.2, 58.6, 113.5, 119.2, 126.1(2), 127.4, 128.4 (2), 132.5, 144.5, 147.6, 151.5; The mass data EIMS (m/z) which showed m/z = 267.32 $[M]^+$, 268.43 $[M+1]^+$ (Calcd for $C_{17}H_{17}NO_2$).

Compound **B** was isolated and its molecular formula was determined as $C_{17}H_{17}NO_2$ {m/z = 267 (100) $[M^+]$}. The structure of the aporphine alkaloid was identified on the basis of extensive spectroscopic data analysis and by comparison of its spectral data with those reported in the literature.

Compound C

Lysicamine **(**compound **C)** was obtained as amorphous powder; brown solid; R_f = 0.53; Yield 23 %; mp 143-144 ^oC; The FTIR (KBr, ν, cm^{-1}) spectrum of compound **C** showed absorption bands at: 3398.25 (N-H str), 3048.34 (Cyclic aromatic, C-H, str), 1715.87 (Cyclic ketone, C=O, str), 1583.28 (C=C ring, str), 1445.24 (Cyclic alkanes, C-H, ben), 1177.45 (C-O-C asym., str), 1067.45 (C-O-C sym, str), 956.82 (C-O, str); The ^1H NMR spectrum (300 MHz, DMSO-d_6) δ (ppm) of compound **C** displayed the characteristic signals at 2.18 (s, 1H, NH, D_2O exchangeable), 2.67-2.87 (m, 4H, Ar-H), 3.77 (s, 6H, OCH_3), 5.62 (s, 1H, Ar-H), 6.44 (s, 1H, Ar-H), 6.75-7.12 (m, 4H, Ar-H); The ^{13}C NMR (75 MHz, DMSO-d_6) spectrum of compound **C** displayed the characteristic signals at: δ 41.6, 45.9, 58.2(2), 62.3, 112.6, 126.8 (2), 127.4, 133.3(2), 135.5, 145.6, 149.6, 196.5; The mass data EIMS (m/z) which showed m/z = 295.33 $[M]^+$, 296.45 $[M+1]^+$ (Calcd for $C_{18}H_{17}NO_3$).

Compound **C** was isolated and its molecular formula was determined as $C_{18}H_{17}NO_3$ {m/z = 295 (100) $[M^+]$}. The structure of the oxoaporphine alkaloid was identified on the basis of extensive spectroscopic data analysis and by comparison of spectral data with those reported in the literature.

Compound D

Compound **D** was obtained as powder; colourless solid; R_f = 0.63; Yield 23%; mp 138-139 ^0C; The FTIR (KBr, ν, cm^{-1}) spectrum of compound **D** showed absorption bands at: 3644.45(O-H, str), 3392.55 (N-H, str), 3012.44 (Cyclic aromatic, C-H, str), 1727.87 (Cyclic ketone, C=O, str), 1575.77 (C=C ring, str), 1435.44 (Cyclic alkanes, C-H, ben), 967.12 (C-O, str); The ^1H NMR spectrum (300 MHz, DMSO-d_6) δ (ppm) of compound **D** displayed the characteristic signals at 2.23 (s, 1H, NH, D_2O exchangeable), 2.77-3.12 (m, 4H, Ar-H), 4.74 (s, 1H, Ar-H), 5.16 (s, 2H, OH, D_2O exchangeable), 6.32 (s, 1H, Ar-H), 7.33-7.59 (m, 4H, Ar-

H); The ^{13}C NMR (75 MHz, DMSO-d_6) spectrum of compound **D** displayed the characteristic signals at: δ 31.2, 62.3, 113.2, 126.2 (2), 128.6 (2), 129.1, 133.2, 144.0, 146.2, 148.2, 157.2, 196.2. The mass data EIMS (m/z) which showed m/z = 267.28 $[M]^+$, 268.37 $[M+1]^+$ (Calcd for $C_{16}H_{13}NO_3$);

Compound **D** was isolated and its molecular formula was determined as $C_{16}H_{13}NO_3$ {m/z = 267 (100) $[M^+]$}. The structure of the Compound **D** (*1,2-dihydroxy-7H-dibenzo-quinolin-7-one)***,** a oxoaporphine alkaloid was identified on the basis of extensive spectroscopic data analysis and by comparison of spectral data with those reported in the literature.

Compound E

Compound **E** was obtained as amorphous powder; colourless solid; R_f = 0.67; Yield 32%; mp 167-168 ^oC; The FTIR (KBr, ν, cm^{-1}) spectrum of compound **E** showed absorption bands at: 3602.55 (O-H, str), 3407.24 (N-H, str), 3023.34 (Cyclic aromatic, C-H, str), 1563.57 (C=C ring, str), 1463.24 (Cyclic alkanes, C-H, ben), 936.72 (C-O, str); The ^1H NMR spectrum (300 MHz, DMSO-d_6) δ (ppm) of compound **E** displayed the characteristic signals at 2.66 (s, 1H, NH, D_2O exchangeable), 2.89-3.19 (m, 6H, Ar-H), 4.29 (s, 1H, Ar-H), 5.06 (s, 3H, OH, D_2O exchangeable), 6.55-7.23 (m, 5H, Ar-H); The ^{13}C NMR (75 MHz, DMSO-d_6) spectrum of compound **E** displayed the characteristic signals at: δ 30.3, 43.2, 53.4, 113.2(2), 115.3, 126.3 (2), 128.3(2), 129.8, 130.3, 141.8, 142.5, 146.9, 158.2; The mass data EIMS (m/z) which showed m/z = 269.3 $[M]^+$, 270.5 $[M+1]^+$. (Calcd for $C_{16}H_{15}NO_3$);

Compound **E** was isolated and its molecular formula was determined as $C_{16}H_{15}NO_3$ {m/z = 269 (100) $[M^+]$}. The structure of the Compound **E** (*1,2,9-trihydroxy-5,6,6a,7-tetrahydro-4H-dibenzo-quinoline*), an aporphine alkaloid was recognized on the premise of broad spectroscopic information examination and by correlation of ghastly information with those reported in the literature.

DISSCUSION

Compound **A** was assigned the molecular formula $C_{17}H_{15}NO_2$ by high resolution LC-MS, which showed a $[M]^{+1}$ peak at *m/z* 265.31. The IR spectrum suggested the presence of hydrogen bonded amine group at 3405.23 and methoxy asymmetric and symmetric stretch at 1205.23 and 1070.23 cm^{-1} respectively. The MS of **A** displayed an ion peak at *m/z* 221 which was due to the loss of $C_{17}H_{15}NO_2$ from the molecular ion. The fragment peak was observed at *m/z* 221, 133, 130, 122, 92 and 78. The ^1H-NMR spectrum of **A** showed singlet peak at 2.12 due to amine group D_2O exchangeable. The singlet peak was appeared at 5.93 for two protons of $-OCH_2O-$ group.

Compound **B** was assigned the molecular formula $C_{17}H_{17}NO_2$ by high resolution LC-MS, which showed a $[M]^+$ peak at *m/z* 267.32. The IR spectrum suggested the presence of free hydroxyl group at 3603.23 and hydrogen bonded amine group at 3413.45 and methoxy asymmetric and symmetric stretch at 1195.33 and 1045.23 cm^{-1} respectively. The MS of **B** displayed an ion peak at *m/z* 251 which was due to the loss of $C_{17}H_{17}NO_2$ from the molecular ion. The fragment peak was observed at *m/z* 251, 221, 133, 92 and 76. The ^1H-NMR spectrum of **B** showed a signal singlet at 2.05 due to a amine group D_2O exchangeable. The presence of hydroxyl group was confirmed by D_2O exchangeable signals for one proton at 5.03.

Compound **C** was assigned the molecular formula $C_{18}H_{17}NO_3$ by high resolution LC-MS, which showed a $[M]^+$ peak at *m/z* 295. The IR spectrum suggested the presence of hydrogen bonded amine group at 3398.25 and cyclic carbonyl group (ketone) at 1715.87 and methoxy asymmetric and symmetric stretch at 1177.45 and 1067.45 cm^{-1} respectively. The MS of **C** displayed an ion peak at *m/z* 265 which was due to the loss of $C_{18}H_{17}NO_3$ from the molecular ion. The fragment peak was observed at *m/z* 265, 235, 133, 106, 78 and 45. The ^1H-NMR spectrum of **C** showed a singlet for one proton at 2.18 due to a amine group and six aromatic protons showed singlet at 3.77.

Compound **D** was assigned the molecular formula $C_{16}H_{13}NO_3$ by high resolution LC-MS, which showed a $[M]^+$ peak at *m/z* 267.28. The IR spectrum suggested the presence of free hydroxyl group 3644.45 and hydrogen bonded amine group at 3392.55 and cyclic ketone group at 1727.87. The MS of **D** displayed an ion peak at *m/z* 235 which was due to the loss of $C_{16}H_{13}NO_3$ from the molecular ion. The fragment peaks were observed at *m/z* 235, 161, 133, 78 and 45. The ^1H-NMR spectrum of **D** showed a signal at one proton singlet for amine at 3.56 D_2O exchangeable signals. The presence of hydroxyl group was confirmed by D_2O exchangeable signals for two protons at 5.16.

Compound **E** was assigned the molecular formula $C_{16}H_{15}NO_3$ by high resolution LC-MS, which showed a $[M]^+$ peak at *m/z* 269.3. The IR spectrum suggested the presence of free hydroxyl group 3602.55 and hydrogen bonded amine group at 3407.24. The CH bending for cyclic alkanes is confirmed by the peak at 1463.24 cm^{-1}. The MS of **E** displayed an ion peak at *m/z* 221 which was due to the loss of $C_{16}H_{15}NO_3$ from the molecular ion. The fragment peak was observed at *m/z* 221, 147, 133, 103 and 78.

The ^1H-NMR spectrum of **E** showed a signal at one protons singlet for amine at 2.66 D_2O exchangeable. The presence of hydroxyl group was confirmed by D_2O exchangeable signals for three protons at 5.06.

The two new compounds were isolated by column chromatography from ethanol extract of the bark of A. squamosa. On the basis of TLC, IR, ^{1}H NMR, ^{13}C NMR and LC-MS spectroscopic analysis and by chemical transformation, structures and molecular formula of compounds D and E were elucidated as *1,2-dihydroxy-7H-dibenzo-quinolin-7-one* (**D**) and *1,2,9-trihydroxy-5,6,6a,7-tetrahydro-4H-dibenzo-quinoline* (**E**).

CONCLUSION

Present investigation was focused on isolation and characterization of two new along with three known alkaloid compounds were obtained from bark of A. squamosa. On the basis of TLC, IR, NMR and LC-MS spectroscopic analysis and by chemical transformation, structures and molecular formula of compounds.

LIST OF ABBREVIATIONS

Ar = Aromatic
UV = Ultra violet spectroscopy
FTIR = Fourier transform infrared spectroscopy
NMR = Nuclear magnetic resonance spectroscopy
str = Stretching
IR = Infrared spectroscopy
ppm = Parts per million
TLC = Thin layer chromatography

CONFLICT OF INTEREST

None of the author has any conflict of interest in the context of this work.

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