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A new isoquinoline and ceramide from the stem barks of Discoglypremna caloneura (Pax) Prain (Euphorbiaceae) with antiproteinase and cytotoxic activities

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ABSTRACT

Two new compounds, an isoquinoline (1) and caloneuramide (2), a ceramide were isolated from the stem bark of *Discoglypremna caloneura* together with seven known compounds namely aurantiamide acetate (3), acetylaleuritolic acid (4), 3α-hydroxylaleuritolic acid 2 α-p-hydroxybenzoate (5), mixture of stigmasterol (6) and β-sitosterol (7), mixture of 7-oxo-stigmasterol (8) and 7-oxo- β-sitosterol (9). Their structures were determined based on data from literature and spectroscopic methods. Derivatization reactions on the isoquinoline led to two new compounds, the methylated (10) and acetylated (11) derivatives. Some compounds and extracts were evaluated for their cytotoxic and antiproteinase activity. Antiproteinase effect of compounds 1, 10 and 11 exhibited IC_{50} values of 10.77, 1.19 and 3.61 µg/mL respectively; significantly low compared to the standard drug, acetyl salicylic acid (IC_{50} = 20.28 µg/mL). Ethyl acetate and methanol extract exhibited moderate cytotoxicity activity on Chang liver cells with CC_{50} values of 167.90±2.20 and 106.30 ±2.03 µg/mL compared to the reference drug cucurmin (CC_{50} = 11.05 ± 1.04 µg/mL).

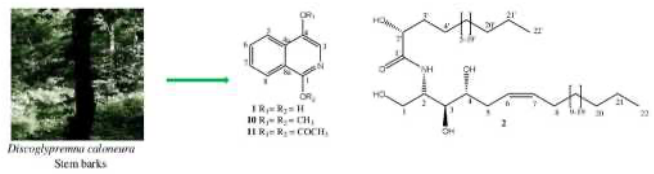
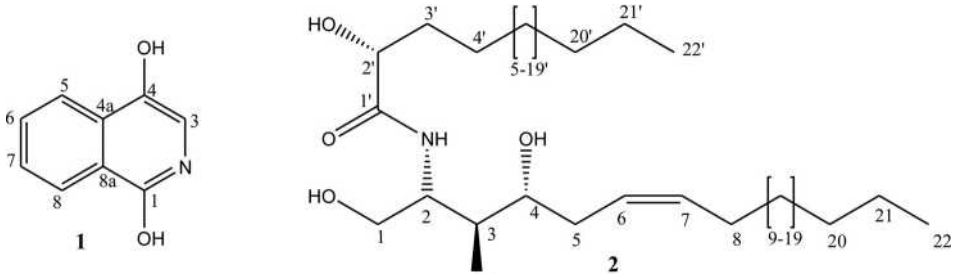


***Figure 1**. Structures of compounds 1 and 2.*



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1. Introduction

Discoglypremna caloneura is a single species genus belonging to the Euphorbiaceae family with one known synonym, Alchornea caloneura Pax. It is native to tropical regions of Africa, particularly the geographical zone of Guinea to Uganda and Democratic Republic of Congo. D. caloneura is a large, dioecious tree up to 45 m tall. In West Africa, the leaves are traditionally used as expectorant for bronchial problems and to get rid of lice on human head. Its seeds or seeds oil are used as emetic and purgative against dysentery, diarrhea, edema, abortive during difficult childbirth and poison for unwanted animals. The stem bark of the plant is used to relieve cough and painful bowel caused by food poisoning (Schmelzer and Gurib-Fakim 2008). Some communities in Southern Ghana also use the leaves and roots to treat stroke and female infertility (Boadu and Asase 2017). Previous research works on this plant showed that crude ethanol leaves extract had moderate in vitro bacteriostatic effects against Staphylococcus aureus and Enterococcus faecalis (Atindehou et al. 2002). Additionally, 3-O-acetyl aleuritolic acid isolated from the hexane extract of the stem bark was considered as promising naturally occurring filaricide (Nyasse et al. 2006).

In our efforts to discover bioactive substances from medicinal plants, a new isoquinoline (1) and a new ceramide (2) (Figure 1) were isolated from the stem bark of D. *caloneura,* along with seven known compounds (3-9) (Figure S1, Table $S1_{c-g}$). Compound 1 was derivatized to afford two new derivatives (10-11). The present study aimed at describing the isolation, structure elucidation and *in vitro* antiproteinase and cytotoxic activities of some compounds and extracts of *D. caloneura*.

2. Results and discussion

Compound 1 was isolated as a yellowish powder. Its molecular formula $C_9H_7NO_2$ was generated from the HRESI-MS (Figure S2) which showed the quasi-molecular ion $[M + H]^+$ at *m/z* 162.0542 (calcd. For C9H8NO2, 162.0555) revealing seven degrees of unsaturation.

The IR absorption band (Figure S3) at 3298.15 cm^{-1} shows the presence of phenolic hydroxyl groups.

The ^1H NMR spectrum (Figure S4a) displayed signals of two doublet of doublet at δ_H 8.06 (1H, dd, *J* = 6.70, 1.28 Hz; H-8) and 7.43 (1H, dd, *J* = 7.22, 1.55 Hz, H-5), one singlet at δ_H 7.95 (1H, s, H-3) and a quintet doublet-like (Figure S4b) at δ_H 7.18 (2H, qd, H-6 and H-7).

The COSY spectrum (Figure S5) showed characteristic correlations of an ABCD spin system typical of the non-substituted non heterocyclic ring of quinoline or isoquinoline (Osborne et al. 1992; Nelson and Davis 1991).

The APT spectrum (Figure S6, Table S1a) in conjunction with the HSQC spectrum (Figure S7) displayed four quaternary carbons at δ_C 169.2 (C-1), 138.2 (C-4), 127.6 (C-4a) and 108.7 (C-8a); and five methine carbons at δ_C 133.4 (C-3), 123.6 (C-6), 122.0 (C-7), 121.7 (C-8) and 112.8 (C-5). However, the carbon C-8a of quinoline which appears at δ_C 136.9-149.5 (Sun et al. 2014; Kouam et al. 2017; Gao et al. 2020) is absent since carbons at δ_C 169.2 and 138.2 are for the two oxymethine carbons respectively at C-1 and C-4. The presence of the two hydroxyl functions was confirmed by methylation. This suggested the presence of an isoquinoline skeleton where C-8a usually appears at δ_C 115.0-122.3 (Chung-Yi et al. 2001; Mona et al. 2013; Hai-Yan et al. 2015).

Two α-positions (1 and 3) to the nitrogen atom are available for the singlet observed at δ_H 7.95. The fact that the long range (^4J) correlation was observed on the HMBC spectrum (Figure S8) between the singlet and C-5 allowed us to position the singlet at C-3. This was in agreement with the NOESY spectrum (Figure S9) which did not display any correlation between the singlet and H-8.

Finally, compound 1 was characterized as isoquinoline-1,4-diol, which is a new compound (Figure 1). However, its analogues 4-hydroxyisoquinolone and 1-chloro-4-hydroxyi-soquinoline were encountered in a synthetical scheme by Kapatsina et al. (2008).

Compound 2 was isolated as white powder. Its molecular formula $C_{44}H_{87}NO_5$ was deduced from HRESI-MS (Figure S10) which showed the pseudo-molecular ion peak $[M + Na + 2H]^+$ at *m/z* 734.6749 (calcd. For $C_{44}H_{89}NaNO_5$, 734.6638). Its IR spectrum (Figure S11) showed absorption bands at û 3332 and 3211 cm^{-1} indicating the presence of hydroxyl groups, 1619 and 1542 cm^{-1} suggesting

the presence of secondary amide group. The ^{1}H NMR spectrum (Figure S12a-d) of 2 displayed signals of NH- group at δ_H 8.60 (1H, d, *J* = 8.8 Hz); -OH groups at δ_H 7.67 (1H, d, *J* = 4.9, HO-2'), 6.75 (2H, d, *J* = 6.2 Hz, HO-1,3) and 6.28 (1H, d, *J* = 6.6 Hz, HO-4); olefinic group at δ_H 5.53 (1H, dt, J = 6.3, 6.2 Hz, H-6) and 5.49 (1H, dt, J = 6.3, 6.2 Hz, H-7); oxymethine protons at δH 4.62 (1H, dd, J = 8.1, 4.4 Hz, H-2'), 4.38 (1H, dd, J= 11.3, 6.2 Hz, H-3) and 4.29 (1H, m, H-4); diastereotopic oxymethylene protons at δ_H 4.50 (1H, dd, *J*= 10.8,4.6Hz,H-1a) .43(1H,dd,*J*= 10.5, 4.6 Hz, H-1b); diastereotopic methylene protons at δ_H 2.28 (1H, m, H-5a), 1.96 (1H, m, H-5b), 2.25 (1H, m, H-3'a) and 1.93 (1H, m, H-3'b) with several other methylene protons at δ_H 1.91 - 1.21 and two terminal methyls at δ_H 0.85 (6H, t, *J*=6.8 Hz).

The smaller coupling constant *J* = 6.3 and 6.2 Hz observed between the two olefinic protons H-6 and H-7 respectively at δ_H 5.53 and 5.49 suggested the Z geometry. The chemical shifts for the corresponding allylic carbons for the Z configuration are usually less than d 29.0 (Kondo et al. 1992; Su and Takaishi 1999; Poumale et al. 2011). The discrepancy observed with carbon C-5 at dc 34.6 could be due to its proximity with the oxymethine at C-4 (Gunstone et al. 1977).

The HSQC spectrum (Figure S13) showed two olefinic carbons at δc 131.3 (C-6) and 131.1 (C-7), three oxymethine carbons [dc 77.2 (C-3), 73.4 (C-4), 72.9 (C-2^0)], one oxymethylene at dc 62.5 (C-1), one nitromethyne carbon at dc 53.4 (C-2), methylenic carbons in the range dc 34.16-23.4 and two methyl carbons at δc 14.8 (C-22, C-220). The HSQC spectrum also well displayed the diastereotopic methylene protons beared by C-1 (δH 4.50 and 4.43), C-3^0 (δH 2.25 and 1.93), C-5 (δH 2.28 and 1.97) and C-8 (δH 1.93 and 1.71).

The amide function was confirmed by the presence of a conjugated carbonyl at δ_c 175.8 (C-1^0) in the APT spectrum (Figure S14).

All these data were in agreement of a ceramide type skeleton (Jian et al. 2001).

The COSY spectrum (Figure S15) showed correlation between one vinylic proton H-6 and an allylic proton H-5; H-5 also displayed a COSY correlation with the oxymethine proton H-4. These allowed us to position the double bond at C-6 and C-7. This was approved by the correlations observed on the HMBC spectrum (Figure S16a, Table S1b) between H-5a/C-3, H-5a/C-4, H-5b/C-3, H-5b/C-6, H-5b/C-7, H-8a/C-4, H-8a/C-5, H-8b/C-5, H-6/C-5, H-6/C-8, H-7/C-5 and H-7/C-8 (Figure S16b).

Compound 2 was methanolyzed with 5% HCl in MeOH for 24 h under reflux at 70 °C, extracted with hexane to furnish the fatty acid methyl ester (FAM) chain. The rest of the reacting mixture was neutralized with Na_2CO_3 to pH 7 and extracted with ethyl acetate to furnish the long-chain base (LCB).

The LC-MS (Figure S17) of LCB displayed the pseudo-molecular ion peak $[M + Na]^+$ at *m/z* 394, 3079 from which the molecular formula C22H45NO3 was generated and LCB identified as (Z)-2-aminodocos-6-ene-1,3,4-triol.

A meaningful interpretation of the EIMS (Figure S18a) helped to establish the lengths of the side chains. The length of the fatty acid was determined by the characteristic ions at *m/z* 357 $[CH_3(CH_2)_{19}CH(OH)CONH + 3H]^+$ (base peak), 339 $[CH_3(CH_2)_{19}CH(OH)CO]^+$, 308 $[CH_3(CH_2)_{19}CH(OH)]^+$ and 281 $[CH_3(CH_2)_{19}]^+$; and the length of the long chain base was confirmed by the characteristic ions at m/z 370 $[CH_3(CH_2)_{14}CH = CHCH_2CH(OH)CH(OH)CH(NH)CH_2OH]^+$ (Figure S18b).

We observed much closed similarity of chemical shift at asymmetric centers of Compound 2 with benjaminamide described in the literature (Simo et al. 2008). Based on this, the stereochemistry of compound 2 was established.

Finally, compound 2 was characterized as (2 *R*)-2-hydroxy-*N*-*((Z,2S,3S,4R*)-1,3,4-trihy- droxydocos-6-en-2-yl)docosamide (Figure 1) which is a new ceramide to which we attributed the trivial name caloneuramide.

Compound 1 was derivatized to afford a methylated and an acetylated product respectively 1,4-dimethoxyisoquinoline (10) and 1,4-diacetoxyisoquinoline (11) which are all new derivatives. The success of each reaction was confirmed by the TLC, ^1H and ^{13}C NMR analyses.

The ^1H NMR spectrum (Figure S19) of compound 10 displayed two groups of methoxy protons at δ_H 3.85 whereas its APT spectrum (Figure S20) showed two methoxy carbons at δ_C 51.3 and 33.5. These low chemical shifts could be explained by the mesomeric and anisotropic effects induced by lone pair of electrons of *N*-atom.

The ^1H NMR spectrum (Figure S21) of compound 11 in addition to signals observed on spectrum of compound 1 displayed singlet of a-methyl protons at δ_H 2.72. Its APT spectrum (Figure S22) showed the methyl and the two carbonyl carbons at δ_C 22.2, 165.5 and 169.8.

Crude extracts and some isolated compounds were screened for antiproteinase and cytotoxicity activity. The most significant antiproteinase activity (Table S2) was observed for the hexane extract (DC-Hex), compounds 1, 10 and 11 which exhibited IC_{50} values of 0.02, 10.77, 1.19 and 3.61 µg/mL respectively compared to the reference drug, acetyl salicylic acid (20.28 µg/mL). This plant D. caloneura has already shown anti-inflammatory activities (BSA denaturation) through his hexane, ethyl acetate and methanol\dichloromethane (1:1) extracts (Toukam et al. 2017). Moreover, several other plants belonging to the Euphorbiaceae family have shown portent anti-inflammatory activities such as Euphorbia species, Phyllanthus species, Bridelia retura, Alchornea cordifolia

(Borges et al. 2013). The methylated derivative (10) displayed the highest activity suggesting that the methoxy groups in this structure seem to increase the activity more than the acetyl groups in compound 11. Comparing the structures of compounds 1, 10 and 11 with the reference (acetylsalicylic acid), it appeared that the absence of the bicyclic pyridine group on the reference might be responsible for the observe decrease in activity.

Slight cytotoxicity to Chang liver cells was revealed with ethyl acetate and methanol extract of D. caloneura with CC_{50} values of 167.9 ± 2.20 µg/mL and 106.3 ± 2.03 µg/ mL respectively. All other tested samples were not cytotoxic to Chang liver cells up to CC50 > 200 mg/mL (Table S3).

3. Experimental

3.1 General experimental procedures

Electrothermal IA 9000 series digital melting point device was used for melting point determination. IR measurements were achieved with a Perkin-Elmer 1750 FTIR spectrophotometer.

MS detection was carried out using Micromass ESI-Q-TOF II instrument using ESI ionization in the positive mode (Waters).

NMR spectra were recorded in $CDCl_3$, MeOH-d_4 or $CDCl_3$/MeOH-d_4 on a Bruker 500 MHz for ^{1}H and 125 MHz for ^{13}C, with TMS as an internal reference.

Ordinary column chromatography was performed using silica gel 60 (Merck, 0.040-0.063 mm) as stationary phase. The mobile phase consisted of binary - gradient solvent system of hexane/ethyl acetate, ethyl acetate/methanol and dichloromethane/methanol.

TLC was performed on pre-coated Merck kieselgel 60 F_{254} aluminium plates (20 x 20 cm, 0.25 mm). After development of the plate, spots were checked under UV - 254 nm and by spraying with diluted sulphuric acid followed by gentle heating.

3.2 Plant material

Stem bark of *D*. caloneura was harvested in July 2013 in Mefoup, South region of Cameroon by Mr Nana, botanist of the National Herbarium of Cameroon. The plant was authenticated on the voucher number N°4207/SRFK at the National Herbarium in Yaoundé (Cameroon).

3.3 Extraction and isolation

The stem bark was chopped into small pieces, air-dried and grounded to powder. The resulting

powder was successively extracted by percolation with hexane, ethyl acetate and mixture MeOH/DCM (1:1) in increasing polarity.

After the successive extraction of the plant powder by percolation, the hexane and ethyl acetate extracts were chromatographed over silica gel column chromatography to give a series of fractions and compounds. Based on the TLC profile, some fractions were purified and an overall of fourteen compounds were isolated.

The hexanic extract (19.5 g) was chromatographed over silica gel eluting with a gradient solvent system Hex/EtOAc to afford 95 fractions of 150 mL each. Fractions 12-15 crystallized in hexane; they were filtered and washed with the same solvent to give acetyl aleuritolic acid (4, 50 mg). Fractions 30 and 31 crystallized in 5% Hex/EtOAc; their filtration and washing led to the isolation of the mixture stigmasterol/β-sitosterol (5/6, 30 mg). Fractions 58 and 59 crystallized in 15% Hex/EtOAc and provided the mixture 7-oxo-stigmasterol/7-oxo-β-sitosterol (7/8, 20 mg). Fractions 72 and 73 precipitated in 20% Hex/EtOAc, after simple filtration, aurantiamide acetate (2, 05 mg) was isolated. Fractions 87-104 crystallized in 35% Hex/EtOAc to afford a compound (75 mg) not yet characterized.

The ethyl acetate extract (86.0 g) was subjected to column chromatography over silica gel eluting with gradient solvent system Hex/EtOAc, EtOAc/MeOH and MeOH to furnish 225 fractions of 250 mL each. Based on the TLC profile, those fractions were grouped into ten pooled fractions DCAE1 - DCAE10

DCAE1, DCAE2, and DCAE3 were oily and fatty fractions containing mostly compounds isolated in hexane extracts and were not purified.

Pooled fractions DCAE4 and DCAE5 were purified over silica gel column chromatography eluting with gradient solvent system Hex/EtOAc to furnish 3α-hydroxyaleuritolic acid 2α-*p*-hydroxybenzoate (5, 15 mg) and 05 mg of compound (not yet characterized) respectively.

DCAE6 was also purified through column chromatography over silica gel eluting with Hex/EtOAc in increasing polarity to afford DC9 (10 mg) within fractions 19-25 and DC14 (15 mg) within fractions 28-34, they all crystallized in the eluting solvent system and were recovered with simple filtration and washing.

Pooled fraction DCAE7was purified with solvent system DCM/MeOH in increasing polarity over silica gel with normal phase column chromatography. Precipitations in fractions 48-56 led to the isolation of isoquinoline-1,4-diol (**1**, 120 mg) after simple filtration. Likewise, fractions 68-69 and 81-83 led to the isolation of DC15 (80 mg) and DC11 (15 mg) respectively.

DCAE8 and DCAE9 were also purified with gradient solvent system of DCM/MeOH. Compounds DC16 (17 mg) and caloneuramide (**2**, 65 mg) were isolated from DCAE8 in fractions 16-22 and 48-54 respectively; and DC17 (7 mg) was isolated from DCAE9.

DCAE10 has not yet been purified.

3.3.1 1,4-Dihydroxyisoquinoline (1)

C9H7NO2, yellowish powder, mp: 216-218 °C; IR *umax* 3298, 1621, 1579, 1519 cm^{-1}; ^{1}H NMR (CD_3OD, 600 MHz) δ_H: 8.06 (1H, dd, *J* = 6.70, 1.28 Hz, H-8), 7.95 (1H, s, H-3), 7.43 (1H, dd, *J* = 7.21, 1.55 Hz, H-5), 7.20 (1H, ov, H-6), 7.18 (1H, ov, H-7); 13C-NMR (CD3OD, 125 MHz) δC: 169.2 (C-1), 133.4 (C-3), 138.2 (C-4), 127.6 (C-4a), 112.9 (C-5), 123.6 (C-6), 122.0 (C-7), 121.7 (C-8), 108.7 (C-8a); HR-ESI-MS *m/z* 162.0542 [M + H] (calcd. For C9H8NO2, 162.0555).

3.3.2 Caloneuramide (2)

C44H87NO5, white powder, mp: 141-143 °C; IR *umax* 3332, 3211, 2915, 2848, 1619, 1542, 1466 cm^{-1}; ^{1}H NMR (C5D5N, 600 MHz) δ_H: 8.60 (1H, d, *J* = 8.9 Hz, N-H), 7.67 (1H, d, *J* = 4.9, HO-20), 6.75 (2H, d, *J* = 6.2 Hz, HO-1,3), 6.28 (1H, d, *J* = 6.6 Hz, HO-4), 5.53 (1H, dt, *J*=6.3, 6.2 Hz, H-6), 5.49 (1H, dt, *J*=6.3, 6.2 Hz, H-7), 5.12 (1H, ov, H-2), 4.62 (1H, dd, *J*=8.1, 4.4 Hz, H-2^0), 4.50 (1H, dd, J = 10.8, 4.6 Hz, H-1a), 4.43 (1H, dd, *J* = 10.5, 4.6 Hz, H-1b), 4.36 (1H, dd, *J* = 11.3, 6.2 Hz, H-3), 4.29 (1H, m, H-4), 2.28 (1H, m, H-5a), 2.24 (1H, m, H-3'a), 2.05 (1H, m, H-3'b), 1.97 (1H, m, H-5b), 1.95 (1H, m, H-8a), 1.71 (1H, m, H-8b), 1.69 (2H, m, H-4^0), 1.34-1.27 (22H, br s, H-9 to H-19), 1.27-1.25 (30H, br s, H- 5^0 to H-19^0); 1.23 (4H, ov, H-21, H-21^0); 1.21 (4H, ov, H-20, H-20^0); 0.83 (6H, ov, H-22, H- 22^0); ^{13}C-NMR (C5D5N, 125MHZ) δC: 175.8 (C-1^0), 131.3 (C-6), 131.1 (C-7), 77.2 (C-3), 73.4 (C-4), 72.9 (C-2^0), 62.5 (C-1), 53.4 (C-2), 36.2 (C-3^0), 34.6 (C-5), 32.6 (C-20, C-20^0), 30.8-30.5 (C-9 to C-19), 30.5-30.1 (C-5'to C-19^0), 27.1 (C-8), 26.3 (C-4^0), 23.4 (C-21 and C-210), 14.8 (C-22 and C-220); HR-ESI-MS *m/z* 734.6749 [M + Na + 2H]$^+$ (calcd. For C44H89NaNO5, 734.6638).

3.4 Antiproteinase assay

The in vitro antiproteinase test was carried out as per the method described by Oyedepo and Femurewa (1995) and Sakat et al (2010) with slight modification. The reaction mixture (1000 µL) consisted of 0.03 mg trypsin, 500 µL 20 mM Tris HCl buffer (pH 7.4) and 500 µL test sample/reference drug (acetyl salicylic acid) of different concentrations (250 - 15.625 µg/mL). The mixture was incubated at 37 °C for 5 min and 500µL of 0.8% (w/v) casein was added. The mixture was incubated for an additional 20 min and 1000 µL of 70% perchloric acid was added to terminate the reaction. Cloudy suspension was centrifuged and the absorbance of the supernatant was read

at 210 nm against buffer as blank. The experiment was performed in triplicate.

The percentage inhibition of proteinase inhibitory activity was calculated as

$$\% \text{ inhibition} = (1 - Vc=Vt) \times 100$$

3.5 CYTOTOXICITY ASSAY

In vitro cytotoxicity activity was carried out on Chang liver cell line using the colorimetric resazurin assay (Süzgec-Selcuk et al. 2011). A sub-confluent cell culture in 75cm^2 culture flask was trypsinized, and cells were counted and suspended in DMEM supplemented with 10% (Fetal bovin serum) FBS and 1% penicillin-streptomycin. Cells were seeded into a 96-well plate (100 µL per well) at concentrations of 1 x 10^5 cells per mL and incubated overnight with 5% CO_2 at 37 °C, to allow cells to attach to the surface of the plate. The cells were then treated in triplicate with 10 µL of each sample (5-fold serially diluted 3.2-2000 µg/mL) in the culture medium. After 48 h of incubation, 10 µL of 2.5 mM resazurin solution were added to each well and further incubated for 4h at 37 °C. Fluorescence was measured using the microplate reader (TECAN Infinite M200 Pro Plate Reader, Austria) at excitation and emission wavelengths of 530 nm and 590 nm respectively. Medium seeded with cells without treatment served as negative control. Curcumin was used as positive control, while medium without cells served as blank. Experiments were conducted in triplicate. The percentage growth inhibition was calculated from the absorbances with respect to the negative control. The concentration of extract that inhibited 50% cell (CC_{50} values) was determined using GraphPad Prism 7.0 (GraphPad Prism software Inc. San Diego, CA).

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