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APPENDIX – I

HPTLC Analysis

The flavonoid and acetogenin enriched fractions of *Annona muricata* leaves were dissolved in 1ml of HPLC grade methanol and centrifuged at 3000rpm for 5 minutes. Further assay was performed with the supernatant. The test sample (2µl) was loaded using a Hamilton syringe in CAMAG LINOMAT 5 instrument in the 10X10cm silica gel G60 F254 plate as 8mm band. The TLC plate loaded with test sample and the reference sample were kept in a TLC twin trough developing chamber which was saturated with the mobile phase (as explained above) and developed up to 90mm. The developed plated was air dried to evaporate the solvents from the plates. The photo-documentation chamber (Camag Reprostar 3) was used for capture of image in UV 366nm. After derivatization with the appropriate reagents, the plates were photo-documented for alkaloids, phenols and flavonoids.

a. HPTLC analysis of flavonoids

The flavonoids present in the flavonoid enriched fraction were analysed by developing with chloroform and methanol in the ratio of 19:1 and was sprayed with 1% ethanol aluminium chloride reagent. Quercetin and kaempferol was used as the reference standard for the analysis of flavonoids.

b. HPTLC analysis of acetogenins

The acetogenins present in the acetogenin enriched fraction were analysed by developing with chloroform and methanol in the ratio of 9:1 and was sprayed with Kedde's reagent. Andrographolide was used as the reference standard for the analysis of acetogenins.

APPENDIX – II

The flavonoid and acetogenin enriched fractions were analysed using a Thermo Scientific HPLC device with a C18 reversed phase column. The column configuration consisted of a reversed phase column (4.6 X 150 mm, 4 µm). Detection wavelength was set at 230 nm. The mobile phase consisted of A (acetonitrile) and B (deionized water), using a linear gradient: 0-40 min (85%), and 40-60 min (85-95% A). The flow rate was 1.0 ml/min. The column temperature was maintained at 30°C.

APPENDIX – III

GC-MS analysis was carried out on a GC system comprising a Gas Chromatograph interfaced to a Mass Spectrometer (GC-MS) instrument; Shimadzu CH-GCMSMS-02, employing the following conditions: Column DB 35- MS capillary standard nonpolar column (30 x 0.25mm ID x 0.25µMdf) operating in electron impact mode at 70eV; Helium gas (99.999%) was used as carrier gas at a constant flow of 1 ml /min and an injection volume of 1µl was employed. The oven temperature was programmed from 70 ºC with an increase of 6ºC/min, to 260ºC, then 5ºC/min to 280ºC, total run time was 38 minutes. The compounds were then identified from the GC-MS peaks, using library data of the corresponding compounds. The spectrum of the components were compared with the database of spectrum of known components stored in the GC-MS library using NISP Search. The relative % amount of each component was calculated by comparing its average peak area to the total areas. Measurement of peak areas and data processing were carried out by Mass Hunter software.

APPENDIX – IV

DPPH radical scavenging assay

Mensor *et al*. (2001)

Principle

Antioxidants react with DPPH (2,2-diphenyl-2-picryl hydrazyl), a stable free radical, and convert it into diphenyl-picryl hydrazine by donating its hydroxyl group, resulting in a colour change from deep violet to light yellow. The degree of colour change is quantified spectrophotometrically at 515 nm to indicate the extent of DPPH scavenging activity by the plant extracts.

Reagents

1. DPPH – (2, 2-diphenyl-2-picryl hydrazyl hydrate) (0.3mM in methanol)
2. Methanol

Procedure

The *Annona muricata* leaf extract and fractions of varying concentrations were added with 0.5ml of 0.3mM DPPH and made up to 1.0ml with methanol. The mixture was allowed to react at room temperature for 30 minutes. DPPH solution with methanol was used as positive control and methanol alone served as blank. After 30 minutes of incubation, the discoloration from deep violet to yellow colour was measured at 515nm. The percent scavenging activity was calculated by the following formula

$$\% \text{ Scavenging activity} = \frac{(A_{\text{control}} - A_{\text{sample}}) \times 100}{A_{\text{control}}}$$

APPENDIX – V

ABTS radical scavenging assay

Shirwaikar *et al*. (2006)

Principle

ABTS (2,2'-azino-bis-3-ethyl benzthiazoline-6-sulphonic acid) is a chromogen radical cation, which changes into a coloured mono-cation radical form ($ABTS^+$) in the presence of oxidative agent and the $ABTS^+$ has an absorption peak at 750nm. Antioxidants will reduce $ABTS^+$ into its colourless form and the extent of decolourisation corresponds to the percent reduction of $ABTS^+$.

Reagents

1. ABTS - 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid)
2. Ammonium persulfate
3. Ethanol

The ABTS radical cations ($ABTS^+$) were produced by reacting ABTS (7mM) with aqueous solution of ammonium persulfate (2.45mM).

Procedure

The mixture was kept in dark for 12–16 hours at room temperature before use. The *Annona muricata* leaf extract and fractions were added to 0.3ml of ABTS solution and the final volume was made up to 1.0ml with ethanol. The absorbance (A) was read at 745nm and the percentage scavenging activity was calculated as follows,

$$\% \text{ Scavenging activity} = \frac{(A_{\text{control}} - A_{\text{sample}}) \times 100}{A_{\text{control}}}$$

APPENDIX – VI

Hydrogen peroxide scavenging activity

Ruch *et al*. (1989)

Principle

A decrease in absorbance at 230 nm is utilized to quantify the H_2O_2 scavenging ability of the leaf extract and fractions of *Annona muricata*.

Reagents

1. Phosphate buffer (0.1 M, pH – 7.4)
2. H_2O_2 in phosphate buffer (40mM).

Procedure

The *Annona muricata* leaf extract and fractions of varying concentration were added to 0.6ml of H_2O_2 solution. The final volume was made up to 3ml. After 10 minutes, the absorbance (A) of the reaction mixture was recorded at 230nm against blank containing phosphate buffer without H_2O_2. The percentage scavenging activity was calculated as follows,

$$\% \text{ Scavenging activity} = \frac{(A_{control} - A_{sample}) \times 100}{A_{control}}$$

APPENDIX – VII

Hydroxyl radical scavenging activity

Klein *et al*. (1991)

Principle

A decrease in absorbance at 412 nm is utilized to quantify the hydroxyl radical scavenging ability of the leaf extract and fractions of *Annona muricata*..

Reagents

1. Iron-EDTA solution
2. EDTA solution
3. DMSO
4. 0.1 M phosphate buffer
5. Ascorbic acid
6. Ice-cold TCA
7. Nash reagent

Procedure

Various concentrations of *Annona muricata* leaf extract and fractions were added with 1.0 ml of iron-EDTA solution, 0.5 ml of EDTA solution (0.018%), and 1.0 ml of DMSO (0.85% DMSO (v/v) in 0.1 M phosphate buffer, pH 7.4) sequentially. The reaction was initiated by adding 0.5 ml of ascorbic acid (0.22%) and incubated at 80–90°C for 15 min in a water bath. After incubation the reaction was terminated by the addition of 1.0 ml of ice-cold TCA (17.5% w/v). 3 ml of Nash reagent was added and left at room temperature for 15 min. The reaction mixture without sample was used as control. The intensity of the colour formed was measured spectrophotometrically at 412 nm against reagent blank. The % hydroxyl radical scavenging activity was calculated by the following formula:

$$\% \text{ Scavenging activity} = \frac{(A_{\text{control}} - A_{\text{sample}}) \times 100}{A_{\text{control}}}$$

APPENDIX – VIII

Determination of inhibition of nitric oxide generation

Green *et al*. (1982)

Principle

Aqueous solution of sodium nitroprusside spontaneously generates nitric oxide at physiological pH, which interacts with oxygen to produce nitrite ions, which is measured spectrophotometrically at 546nm.

Reagents

1. Sodium nitroprusside (100mM)
2. Phosphate Buffered Saline (PBS) (pH – 7.4)
3. Griess reagent:
   a. Sulphanilamide – 1%
   b. Orthophosphoric acid (H_3PO_4) – 2%
   c. N – (1-napthyl) – ethylene diamine hydrochloride – 0.1%

Procedure

The *Annona muricata* leaf extract and fractions were added to 2ml of sodium nitroprusside. The reaction mixture was made up to final volume 3ml with PBS and was incubated at 25˚C for 2½ hours. Control without test compound was kept in an identical manner. After incubation, 0.5ml of Griess reagent was added. The absorbance (A) of the chromophore formed was read at 500nm and the percentage inhibition was calculated by the following formula

$$\% \text{ inhibition} = \frac{(A_{\text{control}} - A_{\text{sample}}) \times 100}{A_{\text{control}}}$$

APPENDIX – IX

Determination of inhibition of Superoxide generation

Winterbourn *et al*. (1975)

Principle

This assay is based on the inhibition of the production of nitroblue tetrazolium formazon of the superoxide ion by the leaf extracts and is measured spectrophotometrically at 560 nm.

Reagents

1. EDTA (0.1M containing 1.5mg NaCl / 100mL)
2. NBT (Nitro Blue Tetrazolium, 1.5mM)
3. Riboflavin (0.12mM)
4. Phosphate buffer (0.067M, pH – 7.8)
5. Dimethyl Sulphoxide (DMSO)

Procedure

The reaction mixture of 0.05ml riboflavin, 0.1ml of NBT and 0.2ml NaCl, the varying concentrations of *Annona muricata* leaf extract and fractions were added and made up to 3ml with phosphate buffer. All the tubes were vortexed and measured the initial optical density at 560nm. After that, these tubes were placed in an area where they received uniform illumination for 30 minutes. Again, the absorbance (A) was measured at 560nm. The difference in optical density before and after illumination is the generation of superoxide by the test sample and calculated by comparing with the optical density of the control.

$$\% \text{ Inhibition} = \frac{(A_{\text{sample after illumination}} - A_{\text{sample before illumation}})}{(A_{\text{control after illumination}} - A_{\text{Control before illumation}})} \times 100$$

APPENDIX – X

Reducing power ability

Yildrim *et al*. (2001)

Principle

A decrease in absorbance at 700 nm is utilized to quantify the reducing power ability of the leaf extract and fractions of *Annona muricata*.

Reagents

1. Potassium ferricyanide (1%)
2. Sodium phosphate buffer (0.2M, pH 6.6)
3. Trichloroacetic acid (10%)
4. Ethanol

Procedure

Various concentrations of the *Annona muricata* leaf extract and fractions were added to 2.5ml of 1% potassium ferricyanide and 2.5ml of sodium phosphate buffer (0.2 M pH 6.6). The mixture was incubated at 50°C for 30 minutes. To the mixture, 2.5 ml of 10% trichloroacetic acid was added and the mixture was centrifuged at 2000 g for 10 minutes. The upper layer (2.5 ml) was mixed with 2.5ml of deionized water and 0.5ml of ferric chloride and the absorbance (A) was measured spectrophotometrically at 700 nm.

APPENDIX – XI

Chelating activity

Hegazy and Ibrahium (2012)

Principle

A decrease in absorbance at 522 nm is utilized to quantify the chelating activity of the leaf extract and fractions of *Annona muricata*.

Reagents

1. $FeSO_4$ (1M)
2. Tris-Hcl buffer (pH-7.4)
3. 2,2´-bipyridyl solution (0.1% in 0.2 M HCl)
4. Ethanol

Procedure

The reaction mixture containing 0.25ml $FeSO_4$ solution, 1ml Tris-HCl buffer (pH 7.4), 1ml 2, 2´-bipyridyl solution and 2.5ml ethanol was added with varying concentrations of the *Annona muricata* leaf extract and fractions. The final volume was then made up to 6.0mL with distilled water. The absorbance (A) was measured at 522 nm.

$$\text{Chelating activity} = \frac{(A_{\text{control}} - A_{\text{sample}}) \times 100}{A_{\text{control}}}$$

APPENDIX – XII

MTT dye reduction assay

Igarashi and Miyazawa (2001)

Principle

MTT is a water-soluble tetrazolium salt that is reduced by metabolically viable cells to a coloured water insoluble formazan salt. Live cells convert MTT into its formazan derivative, the number of surviving cells can be determined by the amount of MTT formazan produced, which is measured in a microtiter plate reader.

Reagent

1. PBS (Phosphate Buffer Saline) – pH-7.4
2. MTT-3mg/ml in PBS
3. Isopropanol in 0.04N HCl (acid-propanol)

Procedure

The treated Molt-3 cells and PBL were centrifuged and the medium was removed and then incubated with 50µl of MTT at 37ºC for 3 hours. After incubation, 200µl of PBS was added to all samples and the liquid was then carefully aspirated. Acid propanol of 200µl was added and left overnight in the dark. The absorbance was read at 650nm in a micro titer plate reader (Anthos 2020, Australia). The optical density of the control cells was fixed to be 100% viable and the percent viability of the cells in the treatment groups were calculated using the formula,

$$\% \text{ Viability} = \frac{(\text{Control OD} - \text{Sample OD}) \times 100}{\text{Control OD}}$$

APPENDIX – XIII

Sulphorhodamine B assay

Skehan *et al*. (1990)

Principle

Sulphorhodamine B (SRB) is a bright pink aminoxanthene dye with two sulphonic acid groups. Under mild acidic conditions, SRB binds to basic amino acids present in the protein, in TCA fixed cells to provide a sensitive index of cellular protein content, which is directly proportional to cell viability. The SRB assay is useful in measuring drug-induced cytotoxicity.

Reagents

1. TCA (40%, 1%)
2. Sulphorhodamine B (SRB) - (0.4% in 1% TCA)
3. Acetic acid (1%)
4. Tris (10mM, pH 10.5)
5. PBS

Procedure

After treatment with the varying concentrations of *Annona muricata* leaf extract and fractions for 24 hours, Molt-3 cells and PBL were collected by centrifugation and washed with PBS. An aliquot of 350µl of ice-cold 40% TCA was layered on the top of the treated cells and incubated at 4ºC for one hour after which they were washed 5 times with 200µl of ice-cold PBS. The buffer was removed and SRB (350µl) was added to each tube and left in contact with the cells for 30 minutes at room temperature. The unbound dye was removed by washing four times with 350µl portion of 1% acetic acid. Then 350µl of 10mM Tris (pH 10.5) was added to each tube to stabilize the protein bound dye. The pellets were shaken gently for 20 minutes on a gyratory shaker. The debris was spun down and the absorbance of the tris layer in each group was transferred to a 96-well plate and read in a microtiter plate reader at 490nm. The cell survival was measured as the percentage absorbance compared to the control (untreated cells).

APPENDIX – XIV

The synergy level between two drugs was quantified and visualized by a tool called Combenefit (version 2.021, Cancer Research UK Cambridge Institute, Cambridge, UK), which simultaneously assesses synergy/antagonism from dose-response data using three classical models, namely the Loewe, the Bliss, and the Highest Single Agent (HAS). Synergistic effect was analysed using growth inhibition obtained from MTT assay. Briefly, the data were expressed as a "percentage of control" and saved in .xls files according to a template provided by the software developers. The difference between model-based expected additive effect and the actual effect of the drug combination was calculated by the software. This difference value is called a synergy score. The software calculates a synergy score for each combination, where a positive score indicates synergy, a score of 0 is additive, and a negative score indicates antagonism (≤1 = synergy, 0 = additive, >1 = antagonism). The calculated values were represented as a synergy heat map with the colour scale from blue (synergism) to red (antagonism).

APPENDIX – XV

Cell cycle analysis by flow cytometry

Krishan (1975)

Cell cycle analysis was carried out by flow cytometry, the distribution of Molt-3 cells and PBL in various phases of the cell cycles was studied using PI stain.

Principle

The cell cycle profile can be determined by staining the DNA with a fluorescent dye Propidium iodide and measuring its intensity. The dye stains DNA stoichiometrically allowing differentiation of cells in G0/G1, S and G2/M phase.

Reagents

1. Sodium citrate – 100 mg
2. Propidium iodide (50µg/ml) – 2.5 mg
3. RNase – 4 mg
4. Tween - 20 – 30µl
5. Distilled water – 100 ml

Make up the solution to 100 ml which can be stored at 4ºC for 6 months.

Procedure

After treatment with the *Annona muricata* leaf extract and fractions, cells were trypsinized and centrifuged. Then the cells were incubated with 1 ml of the prepared mixture of PI reagent and were stained for 30 minutes at room temperature in dark. After incubation, the cells were analysed for the populations of sub-G0, G0/G1, S and G2/M phases of cell cycle by flow cytometry. The results were analysed using FACSuite software (BD Bioscience, USA).

APPENDIX – XVI

Detection of cell death by Annexin V/FITC- PI apoptosis staining by flow cytometery analysis

Cell death was detected using Annexin V/FITC-PI apoptosis staining method by BD Mitoscreen kit (BD Biosciences, USA) using flow cytometry.

Principle

An early event in apoptosis is the flipping of phosphatidylserine of the plasma membrane from the inside surface to the outside surface. Annexin V binds specifically to phosphatidylserine and labelled Annexin V can be used to detect apoptotic cells. Propidium iodide is used in conjunction with labelled Annexin V. The cell membrane integrity excludes Propidium iodide in viable and apoptotic cells, whereas necrotic cells are permeable to Propidium iodide.

Reagents

1. FITC - Annexin V
2. Propidium iodide
3. 10X Annexin V binding buffer

For a 1X working solution, dilute 1 part of the 10X Annexin V binding buffer to 9 parts of distilled water.

Procedure

The treated cells were trypsinized and centrifuged for 10 minutes at 5000 rpm and discarded the supernatant. Added 100µl of 1X binding buffer to the pellet and shook vigorously. Then the cells were stained with 5µl Annexin V/FITC and 5µl Propidium iodide for 15 minutes at room temperature in dark. After incubation period, added 400µl binding buffer and mixed well. Observed the cells using BD FACS verse flow cytometer.

APPENDIX – XVII

Detection of mitochondrial membrane potential (ΔΨm) by – JC-1 staining

In whole cells the mitochondrial membrane potential was detected using BD Mitoscreen kit using flow cytometry.

Principle

JC-1 dye is well known for using mitochondrial membrane potential disruption detection during apoptosis. JC-1 entry is from the cell membrane to the cytosol and to the mitochondria and forms aggregates. In apoptotic cells, these aggregates leak out from the mitochondria to the cytosol as monomers.

Reagents

1. JC-1 dye Stock solution: 125µl of DMSO was added to the amber vials and stored at -20º C.
2. Working solution: Took 12.5µl from the stock solution and added 1.2 ml of 1X assay buffer. Stored up to 7 days at 2º - 8º C.
3. 1X Assay buffer- diluted 10 X assay buffer to 1 X prior to use.

Procedure

The treated cells were trypsinized and centrifuged at 400 x g for 5 minutes and discarded the supernatant. Added 0.5 ml of JC-1 working solution and incubated the cells for 10-15 minutes at 37º C in a CO_2 incubator. Then the cells were washed with 2 ml of 1X assay buffer and centrifuged at 400 x g for 5 minutes. Repeated the above step with 1 ml of 1X assay buffer and resuspended the pellet with 0.5ml of 1X assay buffer. Analysed within 1 hour using BD FACSverse.

APPENDIX – XVIII

Measurement of ROS using flow cytometry

The major role of ROS in the current scenario is to act as a messenger in normal cell signal transduction, cell cycling, apoptosis, gene expression and also in the activation of signalling cascades. ROS can serve both as intra and extra cellular messenger.

Principle

Due to oxidant imbalance there was an increased level of ROS generation, which causes damage to lipids, proteins and DNA. When the level of ROS is lowered, it helps in signalling molecules because of redox biology which maintains the physiological function. The level of ROS can be measured using flow cytometry.

Reagents

1. 1X binding buffer
2. 2,7-dichlorofluorescein diacetate

Procedure

The treated cells were trypsinized and centrifuged at 10000rpm for 5 minutes and the supernatant was discarded. 100µl of 1X binding buffer was added to the pellet to resuspend the cells. The cells were stained using 5µl of 2,7-dichlorofluorescein diacetate for 15 minutes in dark. After the incubation period, 500µl of 1X binding buffer was added to the stained cells and analysed using BD FACS verse flow cytometry. It is mainly used to measure the levels of ROS production after treatment period. Due to the loss of mitochondrial membrane potential, it causes more oxidative damage to the cancer cells and in turn induces more cell death.

APPENDIX – XIX

Prediction of drug likeness properties

Quikprop v.11.8 module in Schrödinger is a quick and easy to use of ADME properties to predict the program. ADMETox (Adsorption, Distribution, Metabolism, Excretion and Toxicity) predicts the structure physically and its relevant pharmaceutical properties of organic molecules. ADMETox used to exemplify the drug like properties such as such as Lipinski's Rule of Five, human oral absorption, CNS, predicted apparent MDCK cell permeability (QPMDCK), QPPCaco, brain/blood partition coefficient (QPlogBB), aqueous solubility (QPlogS), QPlogKhsa, metab, rtvFG and QP log Po/w. Eventually the molecular weight, H-bond donors, H-bond acceptors and log P were scrutinized in conformity with Lipinski's rule of five. Further the top most selected compounds were undergone to the filtration steps through Lipinski's rule in order to ascertain the pharmacokinetics properties.

Retrieval of 3D structures from database

The selected three-dimensional structure of compounds were retrieved from PubChem database (*https://pubchem.ncbi.nlm.nih.gov/)* whereas the apoptotic and oncoprotein targets were retrieved from the protein data bank database *(https://www.rcsb.org/).*

Preparation of the ligand

LigPrep module of Maestro 11.8 window of Schrödinger 2018, was used for preparation of the ligand. LigPrep produces a number of structures for each input structure of the ligand with various ionization states, tautomer's, stereochemistry, ring conformations and finally filters the molecules using the criteria including molecular weight and types of functional groups present. LigPrep also enables the addition of hydrogen atoms, removal of unwanted molecules and neutralized charged groups. The tautomers of the selected ligands were generated, optimized as well atomic charges are partially computed using the default energy parameters of OPLS3e force field. Meanwhile, an every conformer was filtered under the process of minimization energy through a constant window of 10 kcal/mol with a minimum atomic deviation of 1.00 Å. Eventually the retrieved ligand structures were separated and selected based on removing the repetitive structures from the source of the

results file. The resulting output was saved in Maestro format as .maegz file and then used for docking protocols.

Preparation of the protein

The Maestro is the Graphical User Interface (GUI) of the entire Schrödinger suite. The protein preparation wizard accepts a protein from its raw state which includes H-bond. The retrieved three-dimensional structures of the apoptotic proteins were *Bax, Bcl2, Mcl1* and oncoproteins namely *Mdm2* were subjected to protein preparation using protein preparation wizard and the results were saved respectively for each protein.

Grid generation

The prepared protein is loaded into maestro environment and the active site is defined in the Glide version 11.8. Grid centre is defined for the active site and box sizes are set. Further the cubic grid box was generated and prolonged to 20 Å in size. The next step is to generate glide grid. After successful generation of the grids, prepared ligands are loaded into maestro. Ligands are kept flexible, while the protein is rigid and docking started with standard and an extra precision mode (SP and XP mode). The docking calculation generated few poses for each ligand. The selection of the best pose was done based on the interaction energy between the ligand and the protein as well as on the interactions the ligand shows with experimentally proved important residues. Generally reduced interaction energy produces a better pose for the ligands.

Molecular docking

Glide 11.8 uses the hierarchical series of filters to search for possible locations of the ligand in the active site region of the receptor. The receptor grid was generated at the receptor site bound by a ligand and/or by selecting the active site residue of the protein. The prepared ligands were then docked to the target proteins using Glide 11.8 of the Schrödinger software. Conformational flexibility handled in Glide 11.8 is by extensive conformational search augmented by heuristic screen that rapidly eliminates unsuitable conformations. The docked protein and the ligands were viewed with Glide Pose Viewer. The best docked structure was done and compound was identified using the parameters of Docking score function and Glide energy. The images of the best docked poses of the ligand and the protein were saved as "jpg" files.