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Comparative Docking Studies of Aristolochic Acid B Against Lung Cancer Protein PTEN

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Abstract

Aristolochia bracteolate (A. bracteolate) is a main subdivision in the family of *Aristolochiaceae*. *A.bracteolata* is commonly called "worm killer". *A.bracteolate* is used in conventional medicine for gastric stimulant, tumor, lung cancer, diarrhea, and snakebites. Lung inflammation or lung tumor is a major reason death for similar to both male and female. SCLC is a threatening neoplasm, for ~25-30% of all lung cancer patients. Molecular mechanisms (MM) adapt in SCLC incorporate induced utterance of oncogene, and loss of cancer defeat genes such as PTEN Tumor Suppressor Protein. The overexpression of PTEN proteins in SCLC is mostly effect of gene amplification. These over expression leads to swift proliferation and loss of terminal distinction. Alteration or deletion of PTEN canister lead to more swift proliferation and minimized apoptosis. The potential ligand candidate was identified from Pubchem database. *A. bracteolata* is derived compounds such as Aristolochic acid A, Aristolochic acid B, Aristolochic acid C, Aristolochic acid D and Aristolochic acid E. Lipinski rule was employed to check the ligand likeliness of the compound. The 3D crystallographic structure of PTEN Tumor Suppressor Protein (ID.1D5R) fetched from the PDB (Protein Data Bank) and protein target sites of the ligands were identified. Comparative docking studies was executed using Schrodinger Maestro 11.9. Hence it has been concluded Aristolochic acid B as a potent inhibitor for Lung cancer.

Keywords
Lung cancer, PTEN, Pubchem, Aristolochic acid B, PDB and Docking.

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INTRODUCTION:

Aristolochia bracteolata is an herbaceous perennial medicinal plant. The plant commonly called as "Worm killer" in English and "Aadutheendapalai" in Tamil [1].

Scientific classification
Kingdom: Plantae
Phylum: Tracheophyta
Class: Magnoliopsida
Order: Piperales
Family: *Aristolochiaceae*

Subfamily: *Aristolochioideae*
Genus: *Aristolochia*
Species: *A. bracteolate*
Binomial name: *Aristolochia bracteolate*

India has one of the oldest, richest, and most diverse cultural traditions associated with the use of medicinal plants. Medicinal plants have provided the basic building blocks for a number of highly effective drugs [2]. Medicinal plants play a vital role in preventing various diseases such as antidiuretic, anti-inflammatory, antianalgesic, anticancer, antiviral, antimalarial, antibacterial, and antifungal activities [3]. The plant contain Aristolochic acid has many medicinal properties in various disease condition. The phytochemical screening revealed the presence of alkaloids, triterpenoids, steroids, flavanoids, tannins, phenolic compounds and cardio glycosides [4]. *A.bracteolata* is derived compounds such as Aristolochic acid A, Aristolochic acid B, Aristolochic acid C, Aristolochic acid D and Aristolochic acid E etc. Aristolochic acid A is a benzylisoquinoline obtained from *A. bracteolate* plant.

Cancer is a disease with abnormal cell growth and uncontrolled multiplication of the cells within the body. Cancer therapy is currently modeled by surgery, radiotherapy and chemotherapy. Most of the cancers are treated with chemotherapy [5]. Lung cancer is the leading cause of cancer-related deaths in the United States [6]. The global distribution of lung cancer has undergone major changes, with reduction in the number of cases in the developed world. However, the proportion of lung cancer patients in developing nations has increased from 31% to 49.9% in the last two decades. It has recently been estimated that 15% of men and 53% of all women with lung cancer worldwide are never smokers [7]. Smoking, particularly of cigarettes, is far the main contributor to lung cancer [8]. Cigarette smoke contains at least 73 known carcinogens, including benzo [α] pyrene [9,10]. About 8% of lung cancer is due to inherited factors [11]. In relatives of people with lung cancer, the risk is doubled. This is likely due to a combination of genes [12]. Polymorphism on chromosomes 5, 6, and 15 are known to affect the risk of lung cancer [13].

Phosphatase and tensin homolog deleted on chromosome 10 (PTEN) is a protein that can modulate cell survival and cell cycle progression [14]. In healthy physiological conditions, PTEN can control smooth muscle differentiation [15], mediate angiogenesis [16], maintain cell stability [17], and coordinate retinal neurogenesis [18]. However, PTEN is a tumor suppressor that is commonly down-regulated in many types of cancer [19], including nonsmall cell lung cancer (NSCLC) [20,21]. Small cell lung carcinoma (SCLC) is a highly metastatic neuroendocrine tumor that results in the deaths of >20,000 people per year in the USA alone. It has been known that the p53 tumor suppressor genes are mutated in the majority of SCLCs and they are frequently amplified (22,23). Alterations in the PTEN pathway have also been reported in SCLC, through direct PTEN mutation/deletion (24,25) or through PIK3CA activation (26). PIK3CA and/or PTEN mutations were more recently found in two recent next generation sequencing studies of SCLC (27,28). The huge number of somatic mutations in human SCLC (27-29) necessitates the functional evaluation of key SCLC-mutated genes. As inhibition of PI3-kinase or of the downstream effectors AKT and mTOR can be achieved using targeted therapies, the importance of the PTEN pathway in SCLC is particularly critical to elucidate. Murine models for SCLC have been generated that accurately recapitulate the cardinal features of human SCLC, including recapitulating key secondary alterations (30-33).

DATABASE AND METHODOLOGY:

Uniprot:

Uniprot is a comprehensive, high quality and free online database of protein sequence and functional information, mainly derived from genome sequencing projects. It contains a large amount of information about the biological function of proteins derived from the research literature [(https://www.ncbi.nlm.nih.gov/pubmed/25348405). The primary sequence of PTEN Tumor Suppressor protein, has been retrieved and the accession number of is P60484 [34].

Preparation of Protein Structure:

The protein data bank (PDB) web contains a collection of 3D structure of large biological molecules including proteins and nucleic acids. The structure of PTEN Tumor Suppressor protein having PDB ID 1D5R with resolution of 2.1A° respectively was retrieved from the protein data bank [(http://www.rcsb.org/pdb/)]. All the interacting heavy atoms, water molecules, metal ions are removed and added with hydrogen atoms, stabilized with minimized energy using "Protein Preparation Wizard" of Schrodinger Maestro 11.9.

Ligand Preparation:

Drug compounds of Aristolochic acid A, Aristolochic acid B, Aristolochic acid C, Aristolochic acid D and Aristolochic acid E were obtained from the PubChem website [(https://pubchem.ncbi.nlm.nih.gov/)][35] as SDF format were converted from 2D to 3D structures

by including stereo chemical, ionization, tautomeric variations, as well as energy minimization and optimized for their geometry, desalted and corrected for their chiralities and missing hydrogen atoms. The bonds orders of these ligands were fixed and the charged groups were neutralized. The ionization and tautomeric states were generated between pH of 6 to 8 using Epik module. In the LigPrep module, the compounds were minimized by Optimized Potentials for Liquid Simulations-2005 (OPLS-2005) force field. A single low energy ring confirmation per ligand was generated and the optimized ligands were used for docking analysis [36].

Receptor grid generation:

The ligand Tartaric Acid was retained in the crystal structure of the prepared protein which was used for the receptor grid construction.

Glide ligand docking:

The glide docking of the designed molecules was carried out using the receptor grid and the ligand molecules. The favorable interactions between ligand molecules and the receptor were scored using Glide module of ligand docking program. All the docking calculations were performed using standard precision (SP) and extra precision (XP) mode. The docking process was run in a flexible docking mode which automatically generates conformations for each input ligand. The ligand poses generated were passed through a series of hierarchal filters that evaluate the ligand's interaction with the receptor. The spatial fit of the ligand to the defined active site, and examines the complementarity of the ligand receptor interactions using grid-based method by the empirical ChemScore function. Poses that pass these initial screens enter the final stage of the algorithm, which involves evaluation and minimization of grid approximation OPLS non bonded ligand-receptor interaction energy. Finally, the minimized poses were re-scored using Glide Score scoring function. The XP-Glide score of active compounds were summarized and the fitness scores for each ligand in PTEN Tumor Suppressor Protein are compared. When compared with the G-score, D-score and prime energy of standard compound of gemcitabine and pemetrexed which is used as anti tumour agent, as well as potent PTEN Tumor Suppressor Protein [37].

RESULT AND DISCUSSION:

Molecular Docking Analysis:

The molecular docking studies of the designed ligands with protein active sites were performed by an advanced molecular docking program Schrodinger Maestro 11.9 version to determine the various binding affinities of the compounds. The designed compounds are docked towards the PTEN Tumor Suppressor Protein (1D5R) inhibition activity. The compounds Aristolochic acid B (Figure 2) showed good affinity to the receptor when compared with standard gemcitabine and pemetrexed. The compounds Aristolochic acid A, Aristolochic acid B, Aristolochic acid C, Aristolochic acid D and Aristolochic acid E have more Glide scores when compared with standard drug. This is due to more lipophilic evidence and hydrogen bonding. The results are summarized in the Table 1. The best affinity modes of the top one docked compound (Aristolochic acid B) with PTEN Tumor Suppressor Protein having good Glide score are shown in Figure 2 [36].

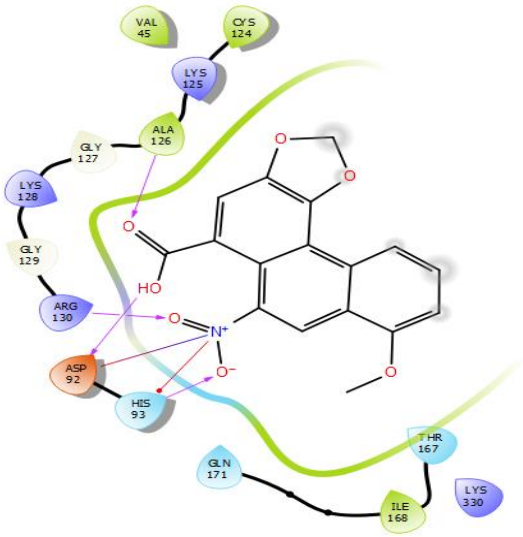

Fig 1. Protein ligand interaction profile of PTEN Tumor Suppressor Protein with Aristolochic acid A

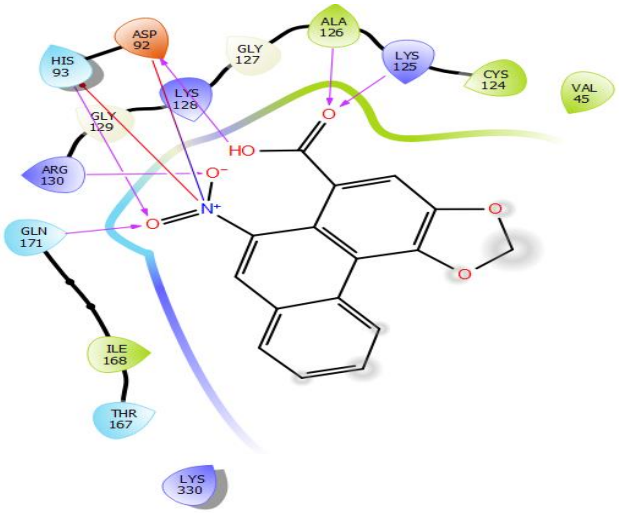

Fig 2. Protein ligand interaction profile of PTEN Tumor Suppressor Protein with Aristolochic acid B

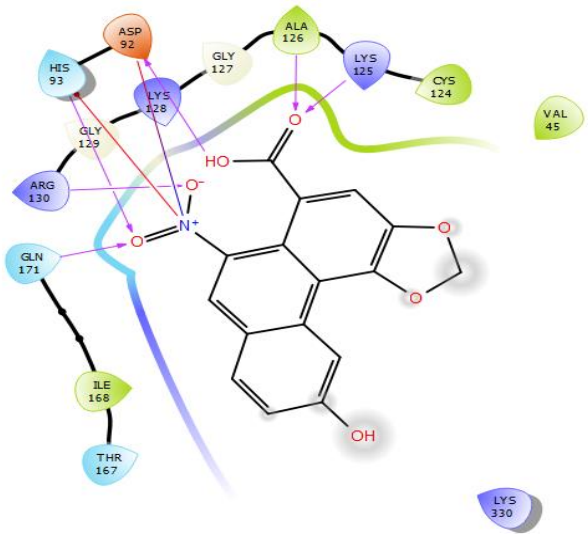

Fig 3. Protein ligand interaction profile of PTEN Tumor Suppressor Protein with Aristolochic acid C

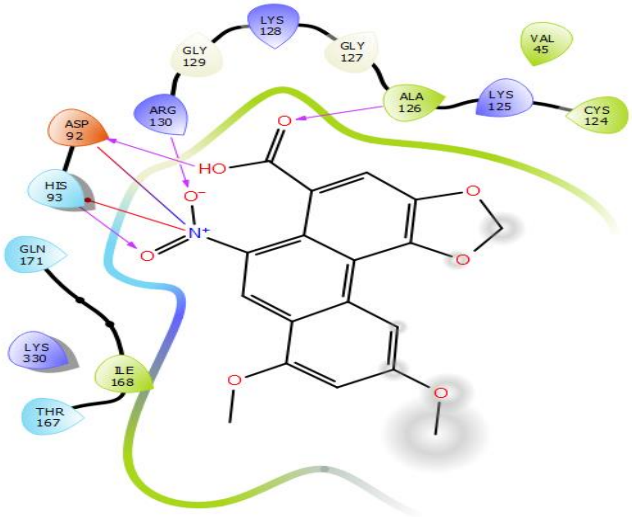

Fig 4. Protein ligand interaction profile of PTEN Tumor Suppressor Protein with Aristolochic acid D

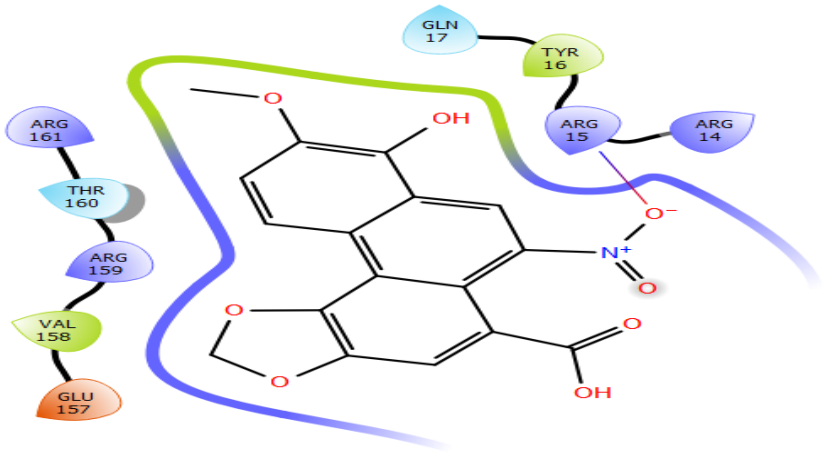

Fig 5. Protein ligand interaction profile of PTEN Tumor Suppressor Protein with Aristolochic acid D

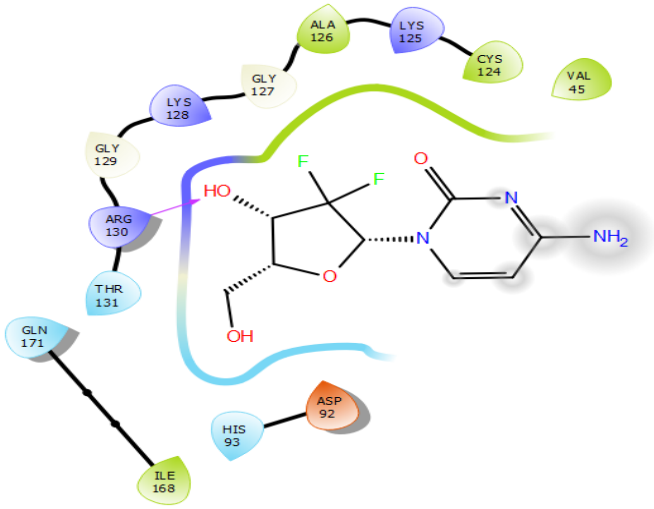

Fig 6. Protein ligand interaction profile of PTEN Tumor Suppressor Protein with Gemcitabine

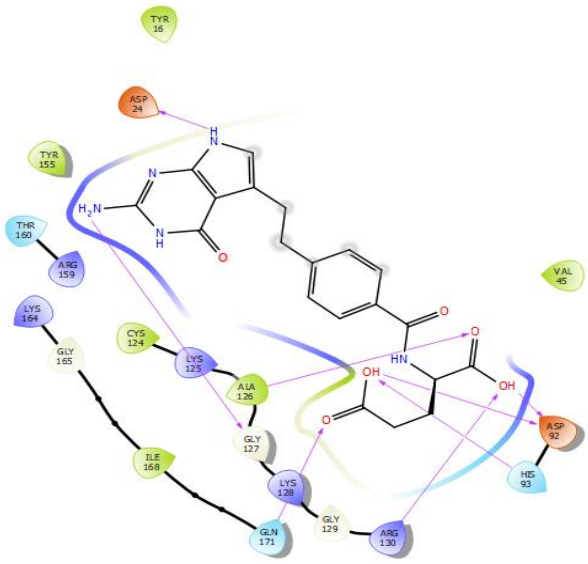

Fig 7. Protein ligand interaction profile of PTEN Tumor Suppressor Protein with Pemetrexed

Table 1: Results of Docking analysis of *A.bracteolatais* and Standard Drug against PTEN Tumor Suppressor Protein.

TITLE	DOCKING SCORE	GLIDE SCORE	XP SCORE	MMGBSA DG BIND
Aristolochic acid A	-3.908	-3.908	-3.908	-28.54
Aristolochic acid B	-4.765	-4.765	-4.765	-36.83
Aristolochic acid C	-3.782	-3.782	-3.782	-32.71
Aristolochic acid D	-3.323	-3.323	-3.323	-28.06
Aristolochic acid E	-3.634	-3.634	-3.634	-34.06
Gemcitabine	-4.111	-4.111	-4.111	-14.6
Pemetrexed	-4.223	-4.223	-4.223	-34.14

CONCLUSION:

Aristolochic acid B compound are eco-friendly, safer and cheaper for the treatment of Lung Cancer. The intention of this study is focused to examine the comparative molecular docking studies on the target protein PTEN Tumor Suppressor Protein which is responsible for Lung Cancer with the ligand of Aristolochic acid A, Aristolochic acid B, Aristolochic acid C, Aristolochic acid D, Aristolochic acid E and standard drugs for Gemcitabine and Pemetrexed. The comparative docking studies was done by "Schrodinger Maestro 11.9". Aristolochic acid B is having best binding score (-4.765 Kcal/mol) than the other standard drugs. The ligand Aristolochic acid B with the Glide score -4.765, shows the binding affinity with the amino acid (AA) residues LYS 125, ALA 126, ASP 92, HIS 93, ARG 130 and GLN 171. These residues are acting as a conclusive pocket for the potential ligand. Hence it has been concluded Aristolochic acid B as a potent inhibitor for PTEN Tumor Suppressor Protein in Lung Cancer.

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REFERENCES:

[1] Samia HA, Elmalik KH, Khalid HS. Therapeutic effect of Aristolochia bracteolate. extract against experimental Trypanosoma evansi infection. Int J Trop Med. (4):170-2, (2006).

[2] Alluri N, Majumdar M. Phytochemical analysis and in vitro antimicrobial activity of Calotropis gigantea, Lawsonia inermis and Trigonella foecum-graecum. Int J Pharm Pharm Sci. 6(4):524-7 (2014).

[3] Tiwari P, Kumar H, Kaur M, Kaur G, Kaur H. Phytochemical screening and extraction: A review. Int Pharm Sci. 1(1):98-106 (2011).

[4] Kalpana Devi.B, Kanimozhi.S, Suganyadevi. P.* Phytochemical screening and biological property of Aristolochia bracteata. Journal of Pharmacy Research, 4(5), 1509-1514 (2011).

[5] Wilken R, Veena MS, Wang MB, Srivatsan ES. Curcumin: A review of anti-cancer properties and therapeutic activity in head and neck squamous cell carcinoma. Molecular cancer. 10(1):12 (2011).

[6] Jemal A, Murray T, Ward E, et al: Cancer statistics, 2005. CA Cancer J Clin 55:10-30, (2005).

[7] Parkin DM, Bray F, Ferlay J, et al: Global cancer statistics, 2002. CA Cancer J Clin 55:74-108, (2005).

[8] Biesalski HK, Bueno de Mesquita B, Chesson A, etal. European Consensus Statement on Lung Cancer: risk factors and prevention .Ling Cancer Panel.CA Cancer J Clin. 48(3):167-76; discussion 164-66 (1998).

[9] HechSS. Lung carcinogenesis by tobacco smoke. Int J Cancer. 131(12):2724-32 (2012).

[10] Kumar V, Abbas AK, Aster JC. Chapter 5. Robbins Basic Pathology (9th ed.) Elsevier Saunders.p.199.ISBN 978-1-4377-1781-5 (2013).

[11] Yang IA, Holloway JW, Fong KM. Genetic susceptibility to lung cancer and co-morbidities. JThorac Dis. 5(Suppl 5):S454-S462 (2013).

[12] Dela Cruz CS, Tanoue LT, Matthay RA. Chapter 109: Epidemiology of lung cancer. In Grippi.MA Elias JA, Kotlooff RM, Pack AL Senior RM. Fishman's Pulmonary Diseases and Disorders (5th ed.) McGraw -Hill.p.1673.ISBN 978-0-07-179672-9 (2015).

[13] Larsen JE, MinnaD. Molecular biology of lung cancer: clinical implications. Clinics nChest Medicine. 2 (4):703-740 (2011).

[14] S un H, Lesche R, Li DM, Liliental J, Zhang H, Gao J, Gavrilova N, Mueller B, Liu X, Wu H. PTEN modulates cell cycle progression and cell survival by regulating phosphatidylinositol 3,4,5-trisphosphate and Akt/protein kinase B signaling pathway. Proc Natl Acad Sci USA. 96:6199–6204 (1999).

[15] Horita H, Wysoczynski CL, Walker LA, Moulton KS, Li M, Ostriker A, Tucker R, McKinsey TA, Churchill ME, Nemenoff RA, Weiser-Evans MC. Nuclear PTEN functions as an essential regulator of SRF-dependent transcription to control smooth muscle differentiation. Nat Commun 7:10830 (2016).

[16] Serra H, Chivite I, Angulo-Urarte A, Soler A, Sutherland JD, Arruabarrena- Aristorena A, Ragab A, Lim R, Malumbres M, Fruttiger M, Potente M, Serrano M, Fabra A, et al. PTEN mediates Notch-dependent stalk cell arrest in angiogenesis. Nat Commun. 6:7935 (2015).

[17] Shrestha S, Yang K, Guy C, Vogel P, Neale G, Chi H. Treg cells require the phosphatase PTEN to restrain TH1 and TFH cell responses. Nat Immunol. 16:178–187 (2015).

[18] Jo HS, Kang KH, Joe CO, Kim JW. Pten coordinates retinal neurogenesis by regulating Notch signalling. EMBO J. 31:817–828 (2012).

[19] Song MS, Salmena L, Pandolfi PP. The functions and regulation of the PTEN tumour suppressor. Nat Rev Mol Cell Biol. 13:283–296 (2012).

[20] Maeda M, Murakami Y, Watari K, Kuwano M, Izumi H, Ono M. CpG hypermethylation contributes to decreased expression of PTEN during acquired resistance to gefitinib in human lung cancer cell lines. Lung Cancer. 87:265–271 (2015).

[21] Noro R, Gemma A, Miyanaga A, Kosaihira S, Minegishi Y, Nara M, Kokubo Y, Seike M, Kataoka K, Matsuda K, Okano T, Yoshimura A, Kudoh S. PTEN inactivation in lung cancer cells and the effect of its recovery on treatment with epidermal growth factor receptor tyrosine kinase inhibitors. Int J Oncol. 31:1157–1163 (2007).

[22] Johnson BE, Ihde DC, Makuch RW, Gazdar AF, Carney DN, Oie H, et al. myc family oncogene amplification in tumor cell lines established from small cell lung cancer patients and its relationship to clinical status and course. J Clin Invest. 79:1629–34 (1987) [PubMed: 3034978].

[23] Jackman DM, Johnson BE. Small-cell lung cancer. Lancet. 366:1385–96 (2005) [PubMed: 16226617].

[24] Forgacs E, Biesterveld EJ, Sekido Y, Fong K, Muneer S, Wistuba, et al. Mutation analysis of the PTEN/MMAC1 gene in lung cancer. Oncogene. 17:1557–65 (1998) [PubMed: 9794233].

[25] Yokomizo A, Tindall DJ, Drabkin H, Gemmill R, Franklin W, Yang P, et al. PTEN/MMAC1 mutations identified in small cell, but not in non-small cell lung cancers. Oncogene. 17:475– 9 (1998). [PubMed: 9696041].

[26] Shibata T, Kokubu A, Tsuta K, Hirohashi S. Oncogenic mutation of PIK3CA in small cell lung carcinoma: a potential therapeutic target pathway for chemotherapy-resistant lung cancer. Cancer letters. 283:203–11 (2009). [PubMed: 19394761].

[27] Peifer M, Fernandez-Cuesta L, Sos ML, George J, Seidel D, Kasper LH, et al. Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer Nature genetics (2012).

[28] Rudin CM, Durinck S, Stawiski EW, Poirier JT, Modrusan Z, Shames DS, et al. Comprehensive genomic analysis identifies SOX2 as a frequently amplified gene in small-cell lung cancer Nature genetics (2012).

[29] Pleasance ED, Stephens PJ, O'Meara S, McBride DJ, Meynert A, Jones D, et al. A small-cell lung cancer genome with complex signatures of tobacco exposure. Nature. 463:184–90 (2010). [PubMed: 20016488].

[30] Meuwissen R, Linn SC, Linnoila RI, Zevenhoven J, Mooi WJ, Berns A. Induction of small cell lung cancer by somatic inactivation of both Trp53 and Rb1 in a conditional mouse model. Cancer Cell. 4:181–9 (2003). [PubMed: 14522252].

[31] Dooley AL, Winslow MM, Chiang DY, Banerji S, Stransky N, Dayton TL, et al. Nuclear factor I/B is an oncogene in small cell lung cancer. Genes & development. 25:1470–5 (2011). [PubMed: 21764851].

[32] Park KS, Martelotto LG, Peifer M, Sos ML, Karnezis AN, Mahjoub MR, et al. A crucial requirement for Hedgehog signaling in small cell lung cancer. Nature medicine. 17:1504–8 (2011).

[33] Schaffer BE, Park KS, Yiu G, Conklin JF, Lin C, Burkhart DL, et al. Loss of p130 accelerates tumor development in a mouse model for human small-cell lung carcinoma. Cancer research. 70:3877–83 (2010). [PubMed: 20406986].

[34] Premila J., R. Sangeetha and Vijayalakshmi K. Insilico Docking Analysis of Capsaicin Alkaloids from Red chilli against Breast Cancer. Int. J. Curr. Res. Aca. Rev. Special Issue-4: 145-157.

[35] Rathinasabapathy Pushpalatha*, Subramanian Selvamuthu Kumar, Duraisamy Kilimozhi Comparative Insilico Docking Analysis of Curcumin and Resveratrol on Breast Cancer Proteins and their Synergistic Effect on MCF-7 Cell Line. J Young Pharm, 9(4): 480-485 (2017).

[36] Kalirajan R*, Pandiselvi M, Sankar S and Gowramma B Kalirajan R, Pandiselvi M, Sankar S and Gowramma B. SF Journal of Pharmaceutical and Analytical Chemistry 1(1) (2018).

[37] Halperin I, Ma B, Wolfson H, Nussinov R. Principles of Docking: An Overview of Search Algorithms and a Guide to Scoring Functions. Proteins: St Fun Gen. 47: 409-443 (2002).