International Journal of Botany Studies
ISSN: 2455-541X; Impact Factor: RJIF 5.12
Received: 25-08-2020; Accepted: 10-09-2020: Published: 26-09-2020
www.botanyjournals.com
Volume 5; Issue 5; 2020; Page No. 287-292

In-silico evaluation of phytochemicals from adiantum latifolium lam. As an anticancer agents through docking analysis

Ramya Roselin I[1], S Catharin Sara[2]*, S Sujatha[3], M Gayathiri[4]
[1, 3, 4] PhD, Scholars, PG and Research Department of Botany Holy Cross College Autonomous, Bharathidasan University, Tamil Nadu, India
[2] Assistant Professor, PG and Research Department of Botany, Holy Cross College Autonomous, University, Tamil Nadu, India

Abstract
Herbs are widely used in treatments of various ailments from time immemorial. Compound isolation, drug discovery from herbals and molecular docking to analyse ligand receptor interaction by Phytochemists and drug developers evolve new molecules which is more effective than conventional drugs. *Adiantum latifolium* Lam.is a plant which is employed in folk medicine Worldwide for its anti-inflammatory, anti-infectious, diuretic and analgesic properties. Frond extracts was studied for its active biomolecules through phytochemical studies. The present molecular docking study was carried out with compounds isolated through GCMS analysis. The four selected compounds from *A.latifolium* were docked with target proteins such as IGSK3P,Bcl-2 and Bax which are known structure of apoptotic and proapoptotic cancer pathway proteins. Among the four compounds, Androst-5-en-3-one,19-acetoxy-4,4-dimethyl-oxime, compound interact with all cancer pathway receptor proteins. The rest of the ligand of the compound interacted with three and two receptor protein molecules, respectively. All the computation finding shows lot of bioactive ligands having neutral docking score above 90 which displayed phytocompound having anticancer compound for future anticancer drug discovery.

Keywords: adiantum latifolium lam., bioactive compounds, cancer pathway protein, docking studies

1. Introduction
Molecular docking is a bioinformatics tool used to study and analyse ligand receptor interaction. It is a method of modeling, which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex. In modern drug designing molecular docking is routinely used for understanding drug information about drug receptor interactions and is frequently used to predict the binding orientation of small molecule drug candidates to their protein targets in order to predict the affinity and activity of the small molecule [1].

India has different frameworks of wellbeing like Ayurveda, Unani, Siddha, Homeopathy and Naturopathy that mentioned even in the Vedas and different sacred writings [2]. These systems existed one next to the other with allopathy containing long, protected, and continuous use of numerous herbal drugs [3]. Nearly 80% of the total population depends on traditional medicines for essential social health care, the majority of which include the utilization of plant extracts [4] Plants interact with hectic environments by physiological adaptation and altering the biochemical profile of plant tissues and produce a spectrum of secondary metabolites. Secondary metabolites are of special interest to scientists because of their unique pharmacophores and medicinal properties. *Adiantum latifolium* Lam. belongs to the family Adiantaceae. It has been used in Latin American traditional medicine as anxiolytic, analgesic and anti-inflammatory, for many years [5]. This plant is popularly called as “broad leaf maidenhair fern” because of the shiny black rachis of the leaves. The target proteins for anticancer was selected from Pubchem and its characteristic features were mainly explored for the present studied. The target protein Glycogen synthase kinase-3 beta (1GSK3β) is an enzyme encoded by the *GSK3B* gene.

GSK3B is involved in energy metabolism, neuronal cell development, and body pattern formation. Also target protein Cysteine-Aspartic Proteases (CASP9) which is a family of protease enzymes playing essential roles in programmed cell death (apoptosis, pyroptosis and necroptosis) and inflammation. They are named caspases due to their specific cysteine protease activity and they perform programmed cell death, occurring widely during development, and throughout life to maintain cell homeostasis. The target protein *B-cell lymphoma 2*, (Bcl-2) is also known as 1G5M that regulate cell death (apoptosis), by either inhibiting (anti-apoptotic) or inducing (pro-apoptotic) apoptosis. Bcl-2-is a target protein associated with X protein (Bax) which is regulated by the tumor suppressor P53 and has been shown to be involved in P53-mediated apoptosis. The *in-silico* evaluation studies realizes the significance of the enormous medicinal plant wealth and the vital necessity of discovering new anticancer drug, by using computational techniques. Thus this research work deals with the receptor and ligand interaction and its analysis by retrieving the target protein from PDB and performing molecular docking for cancer pathway protein receptors like IGSK3β, CASPG, Be12 and Bax with the GCMS obtained compounds from the present experimental plant *A.latifolium* Lam.

2. Methodology

2.1 Molecular Docking Studies

Molecular docking of bioactive compound isolated from *A.latifolium* Lam. whole plant extract was carried out with apoptotic and proapoptotic cancer pathway proteins like IGSK3B, CASP9, Bcl2 and BAX using docking systems. The molecular interaction patterns between the receptor and the ligand molecular were represented by *in silico* molecular docking analysis using Discovery Studio2.1 Version Software.

2.2 Preparation of receptors (targets protein)

The X-ray crystallographic structures of selected known structure of apoptotic and pro-apoptotic cancer pathway proteins are, (Glycogen synthase kinase-3 beta (1GSK3β), PDB ID – IGNG, Cysteine-aspartic proteases (CASP9), PDB ID - INW9, *B-cell lymphoma 2*, (Bcl-2) PDB ID - IG5M and Bcl-2-associated X protein (Bax) PDB ID – 4UF2). These were downloaded from Protein Data Bank (PDB) resources as a *mol format and distribution of the selected proteins are collected. The receptors are opened in the software window, then water molecules, heteroatom and unwanted amino acid chains were removed, missing hydrogen atoms were added, corrections were made for unfilled valence atoms using alternate conformations from 3D downloaded structures of the receptor. Following the above steps of preparation, the protein was subjected to energy minimization using the CHARMm force field.

2.3 Preparation of ligands (small chemical molecules)

The selected GCMS structure of Pregnane-3, 20-dione, 17, 21-[(methylborylene) bis(oxy)]-, (5a)-,10-Phenanthrenedione,1,2,3,4,4a,10a-hexahydro-6-hydroxy-1,1,4a-trimethyl-7-(1-methylethyl)-, (4aS-cis)-, Androst-5-en-3-one,19-acetoxy-4,4-dimethyl-oxime, 2-Hexyldecanoic acid selected phytochemical compounds of *A.latifolium* was retreived from pubchem online data resources and the properties were also predicted by using chemsketch. The chemical molecule was developed as 2D structure and generated into 3D molecule.

2.4 Active site prediction and receptor grid generation

The shape and properties of receptor are repented on a grid by several different sets of fields that provide progressively more accurate scoring of the ligand poses. The functional sites of the identified protein were searched using CD search on CDD webserver [6, 7] at three interfaces including protein active site. The binding pockets or active sites in the receptor were explored using grid/sphere generation which is based on the cavity detection algorithm combined with Monte Carlo conformational search for evaluating candidate poses and protein-ligand interaction energies.

2.5 Ligand Docking

The receptor and ligand interaction and its analysis were done with LibDock module in the Discovery Studio 2.1 version software. The hits were displayed in the output page with total poses of interaction, LibDock score, absolute energy values, hydrogen bond interactions, their bond length and interacting amino acid residues/atoms.

3. Result and Discussion

Molecular docking has been proved very efficient tool for novel drug discovery for targeting protein. Among different types of docking, protein-ligand docking is of special interest, because of its application in medicine industry [8]. Protein-ligand docking refers to search for the accurate ligand confirmations within a targeted protein when the structure of proteins is known. Docking procedures are basically the combination of search algorithms and scoring function. The largest number of search algorithms and scoring functions are available. Search algorithms predict the ligand binding orientation and conformations commonly referred to as posing [9].

3.1 Interaction of selected Ligand and Receptor Proteins

To predict the interaction between the selected phytochemical compounds (ligand) and selected cancer pathways proteins (Receptor), the Phytochemical compound is selected from GCMS studies based on the high peak of the compounds, biological properties and literature based.

3.2 Molecular Docking

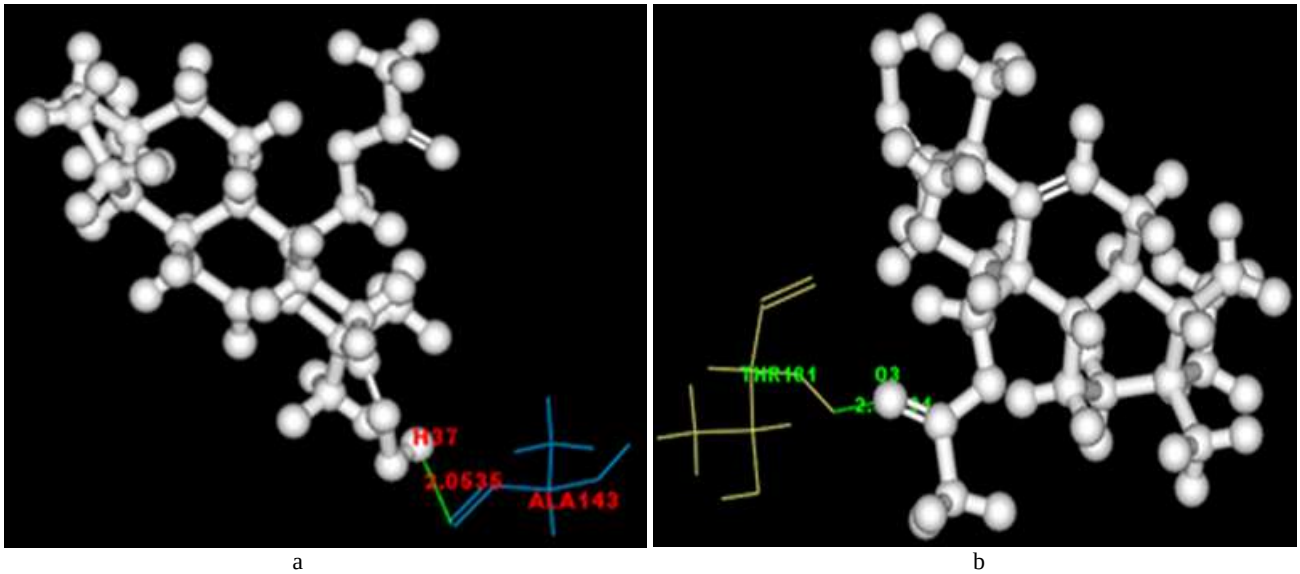
In molecular docking, the active sites of four model proteins of *A. latifolium* Lam. were predicted and identified. The result was interpreted as poses which refers to the binding mode. In the present study, the maximum poses of 1GSK3β protein showed 99, CASP9 protein showed 100, Bcl-2 protein showed 100 and BAX protein 100 was noticed. The hydrogen bonds of four proteins were found out and these hydrogen bond formations contribute to the interaction of ligand and protein. Maximum three hydrogen bonds were noted in BAX protein and two hydrogen in 1GSK3β, CASP9 and Bcl- 2 protein. The ligand protein interaction details were given in Table - 1. The Phytocompound Androst-5-en-3-one, 19-acetoxy-4,4-dimethyl-oxime interacted with all receptor protein such as 1GSK3β, CASP9, Bcl-2 and BAX (Figure-1a-d). Other two molecules Pregnane-3, 20-dione, 17, 21-[(methylborylene) bis(oxy)]-, and Hexyldecanoic acid of *A. latifolium* Lam. the covalent interaction with 1GSK3β protein is missing (Figure-2&3a-c). Interaction with 1GSK3β protein and CASP9 receptor proteins were missing by the compound 9,10 Phenan threnedi one,1,2,3,4,4a,10a-hexahydro-6-hydroxy-1,1,4a-trimethyl-7-(1-methylethyl)-,(4aS-cis) (Figure-4 a&b) during docking studies. Docking algorithm based on the tetrahedral grid model of proteins allows a more precise description of shape complementarity [10]. Maximum Lib Dock scoring could be seen in the Table-1 with 126 by Autogrid for the molecule Androst-5-en-3-one, 19-acetoxy-4,4-dimethyl-oxime. The present computational finding on ligand target protein interaction of *A.latifolium* Lam. showed effective binding affinities and Androst-5-en-3-one, 19-acetoxy-4,4-dimethyl-oxime had superior docking score then other ligands. In our compilation finding other compounds like Pregnane-3, 20-dione, 17, 21-[(methylborylene) bis(oxy)]-, Hexyldecanoic acid and Phenanthrenedione,1,2,3,4,4a,10a-hexahydro-6-hydroxy-1,1,4a-trimethyl-7-(1-methylethyl)-,(4aS-cis) also shows lot of bioactive ligands having central docking score above 90 (Table-1). The experimental molecules also contributed to the ligand flexibility of target. Moreover the ligand molecule generated their consequent glide energy after completion of docking analysis. The results indicate that the target protein possess enzymes that have been docked with the bioactive molecules of *A.latifolium* Lam. possessing

anticancer remedial properties based on these reactions. The present finding displayed phytocompound having anticancer property and hence further antiproliferative work could be continued on cell lines or animal studies.

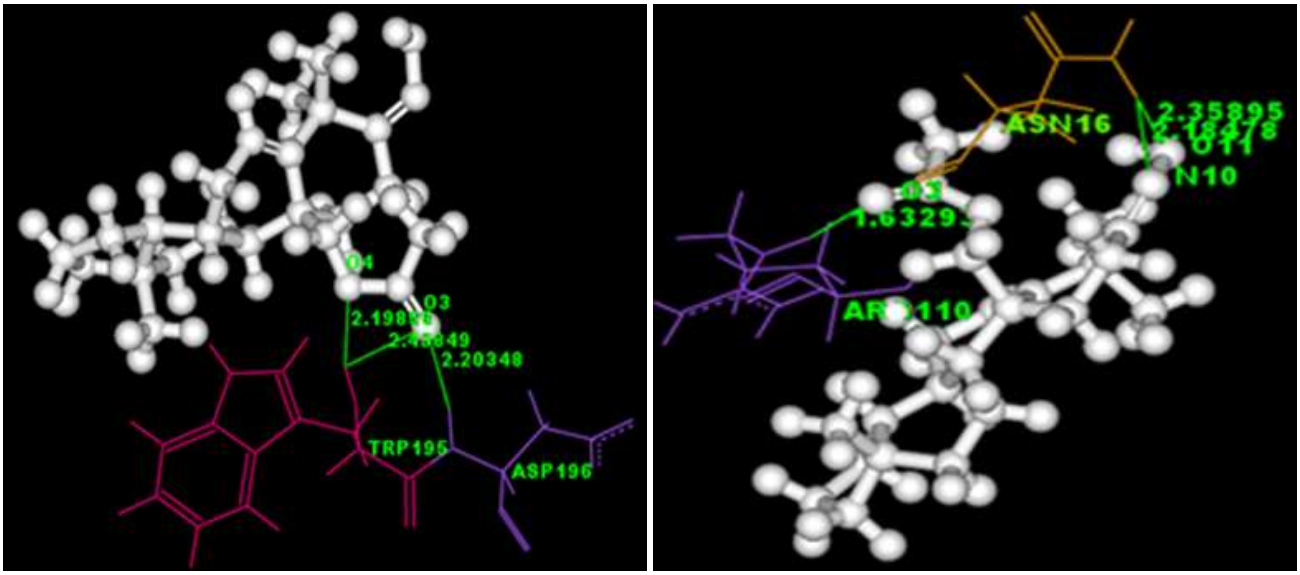
Also the results of the present work done on experimental plant *A.latifolium* coincide with the works done earlier[11] and it shows that the active principles studied from *A.latifolium* Lam, found to be useful in the primary treatment of antitumor and antioxidant activity.

Table 1: Hydrogen bond interaction between Selected compounds of *A. latifolium*Lam. and of Selected Target protein

Compounds	Receptors	PDB-ID	No. of Posses	Absolute energy	LibDock scores	No. of H bonds	Bond Length (Å)	Interacting Amino acids	Interacting atoms
Pregnane-3,20-dione,17,21-[(methylborylene)bis(oxy)]-,(5a)-	1GSK3β	IGNG	2	No Covalent Interactions					
	CASP9	INW9	95	51.935	98.102	2	2.43551	ARG178	O23
							1.91573	ARG180	O5
	Bcl 2	IG5M	85	62.649	116.648	2	2.16466	TRY9	O5
							2.44192	ARN11	
	BAX	4UF2	95	53.324	93.688	1	2.296	ARG110	O5
9,10-Phenanthrenedione,1,2,3,4,4a,10a-hexahydro-6-hydroxy-1,1,4a-trimethyl-7-(1-methylethyl)-,(4aS-cis)-	1GSK3β	IGNG	0	-	-	-	-	-	-
	CASP9	INW9	97	No Covalent Interactions					
	Bcl 2	IG5M	100	38.692	100.927	2	2.24987	Gly190	O13
							2.38027	Trp105	O23
	BAX	4UF2	100	57.653	85.792	2	2.4626	Trp105	O49
							2.10551	ARG110	O11
Androst-5-en-3-one,19-acetoxy-4,4-dimethyl-oxime	1GSK3β	IGNG	5	48.787	49.565	1	2.0535	ACA143	H37
	CASP9	INW9	98	55.127	106.115	1	2.0524	THR181	O3
	Bcl 2	IG5M	99	59.448	125.384	2	2.19856	TRP195	O4
							2.43849	ASP195	O3
	BAX	4UF2	100	49.935	98.214	3	2.35895	ASN16	O11
							2.18478	ARG110	N10
							1.63293		O3
2-Hexyldecanoic acid	1GSK3β	IGNG	99	No Covalent Interactions					
	CASP9	INW9	100	19.692	101.034	2	2.4976	THYR179	010
							2.26713	THR181	O8
	Bcl 2	IG5M	99	23.295	104.813	2	2.35252	TRP196	O18
							1.2093	ASP195	O4
	BAX	4UF2	100	20.194	95.023	2	1.80506	ARG110	O18
							1.95794		119

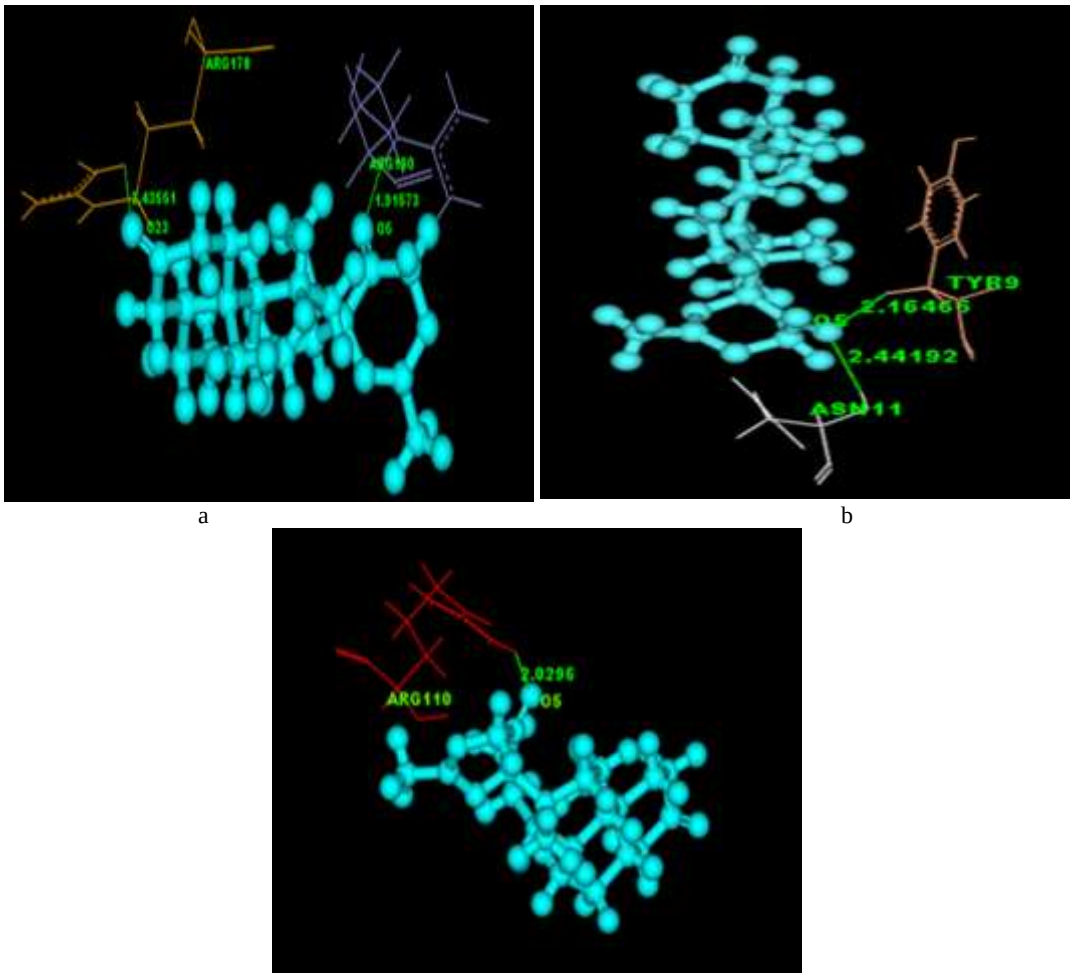


a b



a b

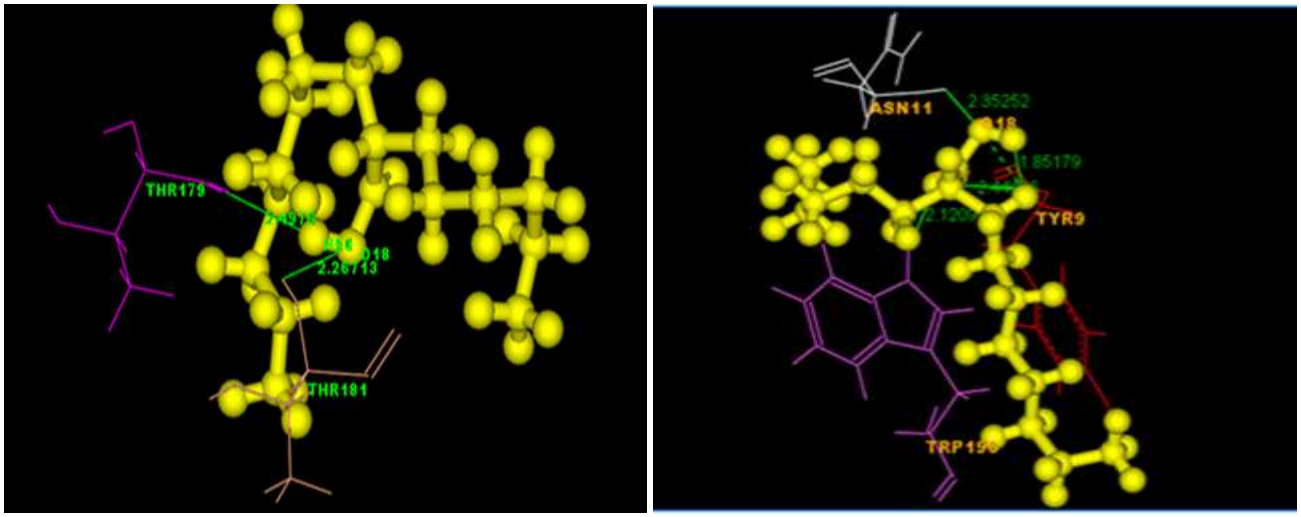
Fig 1: Interaction of Androst-5-en-3-one, 19-acetoxy-4, 4-dimethyl- oxime with pro-and anti-apoptotic proteins 1a. Interactions between Androst-5-en-3-one, 19-acetoxy-4,4-dimethyl-oxime - 1GSK3β receptor with hydrogen bond(s) (indicated as green line) 1b. Interactions between Androst-5-en-3-one, 19-acetoxy-4,4-dimethyl-oxime - casp9 receptor with hydrogen bond (s) (indicated as green line) 1c. nteractions between Androst-5-en-3-one, 19-acetoxy-4, 4-dimethyl-oxime - Bcl2 receptor with hydrogen bond (s) (indicated as green line) 1d. Interactions between Androst-5-en-3-one, 19-acetoxy-4,4-dimethyl-oxime - BAX receptor with hydrogen bond(s) (indicated as green line)



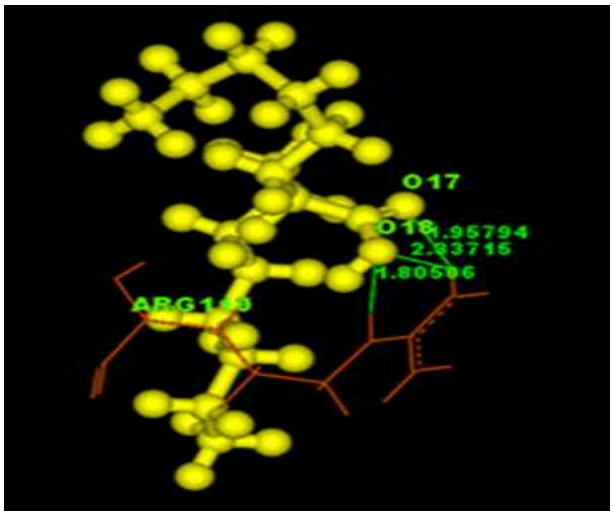
a b

c

Fig 2: Interaction of Pregnane-3, 20-dione, 17, 21-[(methylborylene)bis(oxy)] with pro-and anti-apoptotic proteins 2a. Interactions between Pregnane-3, 20-dione, 17, 21-[(methylborylene) bis(oxy)] and receptor (CASP9) with hydrogen bond(s) (indicated as green line)**.** 2b. Interactions between Pregnane-3, 20-dione, 17, 21-[(methylborylene)bis(oxy)] and receptor (Bcl 2) with hydrogen bond (s) (indicated as green line). 2c. Interactions between Pregnane-3, 20-dione, 17, 21-[(methylborylene)bis(oxy)] and receptor (BAX) with hydrogen bond(s) (indicated as green line).

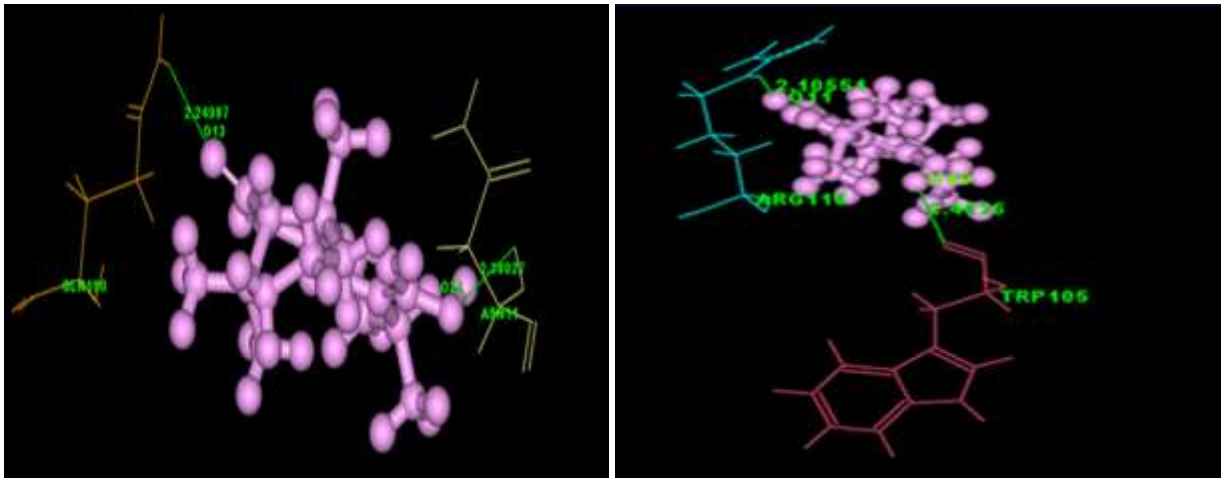


a b



c

Fig 3: Interaction of 2-Hexyldecanoic acid with pro-and anti-apoptotic proteins 3a. Interactions between 2-Hexyldecanoic acid - and receptor (Casp9) with hydrogen bond(s) (indicated as green line) 3b. Interactions between 2-Hexyldecanoic acid - and receptor (Bcl2) with hydrogen bond(s) (indicated as green line) 3c. Interactions between 2-Hexyldecanoic acid - and receptor (BAX) with hydrogen bond(s) (indicated as green line)



a b

Fig 4: Interaction of 9, 10-Phenanthrenedione, 1, 2, 3, 4, 4a, 10a-hexahydro-6-hydroxy- 1, 1, 4a-trimethyl-7-(1-methylethyl)-(4aS-cis) - with pro-and anti-apoptotic proteins 4a. Interactions between 9,10-Phenanthrenedione,1,2,3,4,4a,10a-hexahydro-6-hydroxy-1,1,4a-trimethyl-7-(1-methylethyl) - (4aS-cis)and receptor (BCL2) with hydrogen bond(s) (indicated as green line) 4b. Interactions between 9,10-Phenanthrenedione,1,2,3,4,4a,10a-hexahydro-6-hydroxy-1,1,4a-trimethyl-7-(1-methylethyl) - (4aS-cis)and receptor (BAX) with hydrogen bond(s) (indicated as green line)

4. Conclusion

The current *in silico* molecular docking-based study, revealed that all bioactive compounds of *A.latifolium* Lam. can effectively bind with cancer pathway target proteins selected. Docking on ligands concludes that compounds extracted from *A.latifolium* Lam. are having Anticancer attributes. Among the four selected phyto compounds, Androst-5-en-3-one, 19-acetoxy-4, 4-dimethyl-oxime inter acted with all receptor proteins and satisfying most of the conditions, and rest of the three compounds interacted with three and two protein receptor. Hence the above studies support the identification of compound which inhibited the cancer receptor protein pathway. Based on the results all these factors are very helpful for categorization and identification of their toxicity prediction in human body. Such studies reduce the time and costs involved in drug discovery process and have no adverse effect on the environment. The present finding displayed phytocompound having anticancer property, so that the future experimental designing for cell culture and *in-vitro* studies could be carried out with these phytocompounds.

5. Acknowledgement

The authors would like to express their gratitude to Management and Principal Dr. (Sr) A. Christina Bridget, Head of the Department, Dr. P. Shanthi for the support rendered during this work in a successful manner. We express our gratitude to Dr. Miss. P Rajalakshmi Assistant professor in Biotechnology for helping us to complete the Docking studies.

References

1. Radha R, Ravi Kumar Y, Sakar M, Rohith Vinod K, Balakumar S. Understanding the lattice composition directed in situ structural disorder for enhanced visible light photocatalytic activity in Bismuth iron niobate pyrochlore, Applied Catalysis B: Environmental. 2018; 225:386-396.
2. Gyanranjan Mahalik, Pallavi Jali, Sabuj Sahoo, Kunja Bihari Satapathy. Ethnomedicinal, phytochemical and pharmacological properties of Mangiferaindica L: A review, International Journal of Botany Studies. 2020; (2):01-05
3. Subramanian V, Gautam V, Raman V, Prahalathan S, Ashish K. Foreword in Road Beyond Boundaries (The Case of Selected Indian Healthcare Systems). Export-Import Bank of India Mumbai. 2003; 1:7-9.
4. Sandhya B, Thomas S, Isabel W, Shenbagarathai R. Ethnomedicinal plants used by the Valaiyan community of Piranmalai hills (reserved forest), Tamilnadu, India.-a pilot study. African Journal of Traditional, Complementary and Alternative Medicines. 2006; 3(1):101-14.
5. Nonato FR, Nogueira TM, de Almeida Barros TA, Lucchese AM, Oliveira CE, dos Santos RR, Soares MB, Villarreal CF. Antinociceptive and antiinflammatory activities of Adiantum latifolium Lam.: evidence for a role of IL-1β inhibition. Journal of ethnopharmacology. 2011; 14; 136(3):518-24.
6. Marchler-Bauer A, Derbyshire MK, Gonzales NR, Lu S, Chitsaz F, Geeret LY, *et al*. CDD: NCBI's conserved domain database. *Nucleic Acids Res.* 2015; 43:222-226.
7. Marchler-Bauer A, Bo Y, Han L, He J, Lanczycki CJ, Lu S, *et al*. CDD/SPARCLE: functional classification of proteins via subfamily domain architectures. *Nucleic Acids Res.* 207; 45:200-203.
8. Muegge I, Rarey M. Small molecule docking and scoring. Rev Comp Chem. 2001; 17:1-60.
9. Sousa SF, Fernandes PA, Ramos MJ. Protein-ligand docking: current status and future challenges. Proteins: Struct Funct Bioinf. 2006; 65:15-26.
10. Chitra P, Jeyanthi GP. In silco drug designing approaches for latent autoimmune diabetes in adults. Int J Pharma Bio Sci. 2011; 2:16-27.
11. Ramya Roselin I, Sujatha S, Gayathiri M, Catharin Sara S. Gas chromatography and mass spectroscopy analysis of bioactive compounds of *Adiantum latifolium*Lam. *International Research Journal of Pharmacy*. 2018; 9(10):125-130
12. Bhosale AA. Importance of bioanalysis in drug discovery and development: A review. matrix.;16:17.