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RESEARCH ARTICLE

STRUCTURE BASED DOCKING STUDIES TOWARDS EXPLORING POTENTIAL ANGIOTENSIN-I RECEPTOR BLOCKERS OF SELECTED *ALANGIUM SALVIFOLIUM* PHYTOCHEMICALS AGAINST PROTECTIVE VASCULAR REMODELING.

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Abstract

ACE is an important drug target in the treatment of vesicular diseses. ACE is primarily known for its ability to cleave Angiotensin -I to the vasoactive octa peptide Angiotensin-II, but is also able to cleave a number of other substrates including the vasodilator a physiological modulator of hematopoiesis. In present study virtual screening of *Alangium salvifolium* phytocompounds act as Angiotensin-I inhibitor and assess its molecular basis of inhibition.

The present research computationally emphases to Angiotensin-I protein receptor with four Alangium phytocompounds, using molecular docking and simulation studies. From the results showed the interactions between 4YAY (Angiotensin-I) receptor protein with *A. salvifolium* phytocompounds, a alangum1(Alangium-1(4(benzoyloxy)methyl-2hydroxyphenoxy tetrahydorxy hexoxone 1,2,3,4,5, pentaium) showed the best glide docking XP score -8.5 kcal/mol binding energy value with best fit simulation study .. Based on the result, the Alangium-1 and target were run on MD simulations stable at 10 ns. Finally, this study concludes the Alangium-1 is a more suitable drug for vesicular remodeling by blocking Angiotensin signaling cascade.

Introduction:-

The renin–angiotensin system (RAS) plays a pivotal role in regulating processes in participates significantly in the pathophysiology of hypertension, congestive heart failure, myocardial infarction, and diabetic nephropathy.[1] Angiotensin-I (Ang) , induces not only acute vasoconstriction by binding mainly to the Ang-I type 1 receptor (AT1) but also promotes vascular growth and proliferation, acts as a pro-inflammatory mediator and causes endothelial dysfunction, leading to cardiovascular disease. [2] Research focused on blocking the RAS led to the discovery of Angiotensin-converting-enzyme (ACE) inhibitors, which are effective in the treatment of hypertension and heart failure but are associated with a high frequency of cough and other adverse effects. AT-II-receptor blockers (ARBs) were developed as agents that would more completely block the RAS and decrease the adverse effects seen with ACE inhibitors. Although both classes of drugs (ACE inhibitors and ARBs) block the RAS, they differ in several important aspects [3] ACE inhibitors reduce the biosynthesis of Ang II by the action of ACE, but do not inhibit alternative non-ACE Ang-II-generating pathways. ARBs block the actions of Ang-II via the AT1 receptor regardless of the biochemical pathway leading to Ang-II formation.• ACE inhibitors may increase Ang (1–7) levels more than do ARBs[4]. Production of Angiotensin II can occur through non-ACE pathways as well as through primary ACE pathway, and these alternative pathways are unaffected by ACE inhibition (Figure1). Agents that can specifically

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and selectively inhibit the action of AT-II could completely block the RAS. Currently, two classes of drugs have the mechanistic potential to completely block the RAS: renin inhibitors and AT-II-receptor antagonists. ARBs displace Angiotensin-II from the Angiotensin I receptor and produce their blood pressure lowering effects by antagonizing Angiotensin-II actions (vasoconstriction, aldosterone release,catecholamine release, arginine vasopressin release, water intake and hypertrophic response.[5] Moreover, since ARBs block the effects of Angiotensin II, one would also expect that they could decrease the risk of coronary artery disease, cardiac failure, renal dysfunction, and cerebral artery diseases. In fact, studies have shown that ARBs, like ACE inhibitors, do significantly reduce these risks, and that the mechanisms of action may involve the blocking of Angiotensin II-related functions, such as by inducing growth factors and cytokines, in addition to their hypotensive effect. Various ARBs have been widely used to treat hypertensive patients [6].

Alangium salvifolium (Alangiaceae) is one of the most valuable drugs in traditional system of medicine from ancient time. The genus contains of 17 species of small trees, shrubs and lianas. It has common names as Sage-leaved Alangium (English), Angol, Dhera (Hindi) Ankolam(Malayalam), and Urgu (Telugu). It is native totropical Australia, Madagascar, Western AfricaSouthern and western Pacific Ocean islands Eastern Asia (China, Malaysia, Indonesia, India, and Philippines)and New Caledonia[7]. In India, it is found throughout the Hyderabadforests and Sitamata wildlife sanctuary, Rajasthan . Fruits 1-2 seeded berries, crowned by the calyx lobes2[8]. It Is anti-hypertensive, antidote for several poisons for rabies. Roots are used in rheumatism and inflammation as external application. Fruits are used in treatment of hemorrhages *Alangium salvifolium*, but this plant has not yet developed as a drug by pharmaceutical industries[9] . . *Alangium salviifolium* bioactive components can be further developed into naturally based cosmetic, externally used products and herbal drugs for treatment of dermatomycotic infections. The clinical studies with human subjects should be taken to investigate. Nutrient, bioavailability and bio-toxicity, positive effects on infections tuberculosis effects are claimed by traditional medicine in regard to diseases, such as: diabetes and cardiac disease , antioxidant properties in fighting diseases, such as: heart disease, cancer and Alzheimer's disease[10]. This research evaluates the ACE inhibitor activity of *A.Salvifolium* establishing the interaction of existing phytocompounds involved in this inhibition activity through a virtual screening and molecular docking analysis.

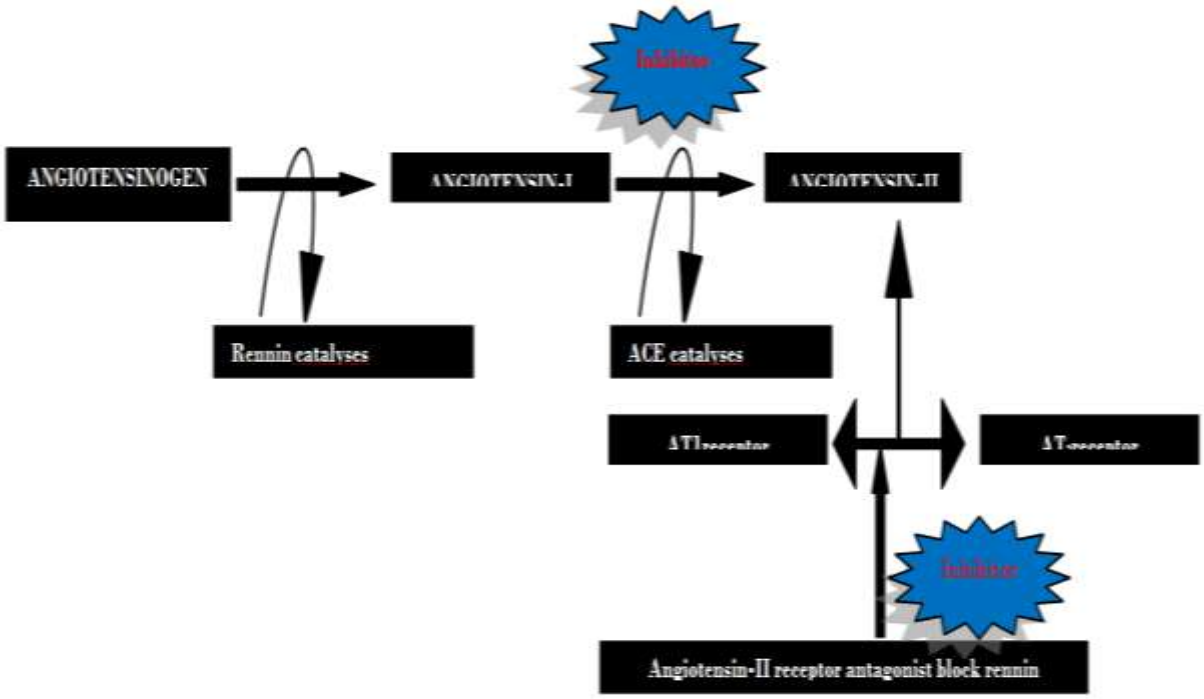

Figure-1 Angiotensin signaling cascade ray diagram

Methods:-

Molecular study was performed using different modules of Software. The schematic representation describes the work flow of the study followed by detailed description in the subsequent sections.

Modeling platform:-

All computational analysis was carried out on standard software at latest version (PyRx, glide Viana-docking, grid generation, free energy calculations, and simulations with help of discovery studio3.1 version). This software package programmed on DELL PRECISSION T1700 workstation machine running on Intel (R) Core (TM) i5-4590 CPU processor with 8GB RAM and 240 GB hard disk, with windows as the operating system. The schematic representation describes the work flow of the study followed by detailed description in the subsequent sections.[11]

Biological data:-

In this study four bioactive molecules were selected against the target of ARBs receptor. These bioactive molecules names and their medicinal plant phytochemicals were listed in Table 1.Later, these collected four bioactive molecules were retrieved and drawing from the chemical database. The Angiotensin receptor (AR) receptor was obtained from Protein Data Bank PDB ID: 4YAY [12]

Preprocessing and preparation of protein target structure:-

Protein X-ray crystal structures of SHBG was obtained from the Protein Data Bank after converted into PDB format with the help of Pymol and Rsmol software[13]. The protein preparation is using by the tool of protein preparation wizard on Schrodinger suite. In general, protein is commonly occupied the water molecules. But, this process was evacuating those water molecules for increasing the entropy of target.

Preprocessing and preparation of ligands:-

All the ligand molecules are prepared by the tool ChemSketch in *ACDlabs*.36 Later these ligand molecules optimized on various ionization states, tautomer, stereo chemistries and ring conformations to adding molecules. It was using ligand rotatable bonds can move freely on further process.[14,15]. The ligand drug like properties and pharmacophre energy optimization mapping was done by Arguslab.

Docking approach:-

To have a better understanding about the inhibitory mechanism as well as the mode of interactions of the phytcompounds of the *A. salvifolium*, docking analysis was accomplished using the PyRX-4.12package and discovery studio3.1. Two primary drug-target-pathways Force Field prior to docking using the Powell method with an initial Simplex [16] optimization and 1000 interactions or gradient termination at 0.01 kcal/(mol*A). The input ligand file format was mol2 for all docking programs investigated. The docking tool "AutoDock" utilizes genetic algorithm to explore the rotational flexibility of receptor hydrogen's and ligand conformational flexibility. Such PyRx docking was carried out using the wizard with default parameters population size(100); selection pressure (1.1); number of operations(10,0 00); number of islands (1); niche size (2); and operator weights for migrate (0), mutate (100), and crossover(100). The active site with a 10 Å radius sphere was defined by selecting an active site residue of protein. Default genetic algorithm settings were used for all calculations and a set of 10 solutions was saved for each ligand. Viana was used by a biding affinity score fitness function. Binding score is a molecular mechanism like function and has been optimized for the calculation of binding positions of ligand.

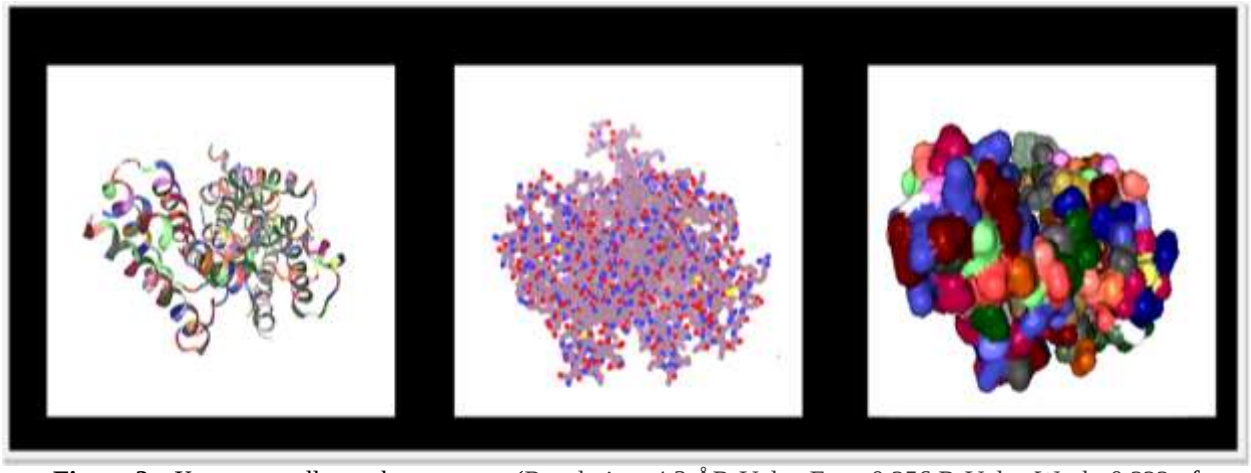

Figure 2:- X-ray crystallography structure (Resolution: 4.3 ÅR-Value Free: 0.256 R-Value Work: 0.222 of Angiotensin-I receptor and its [1] Ribbon structure [2] Electron density structure, [3] Residue type cartoon structure.

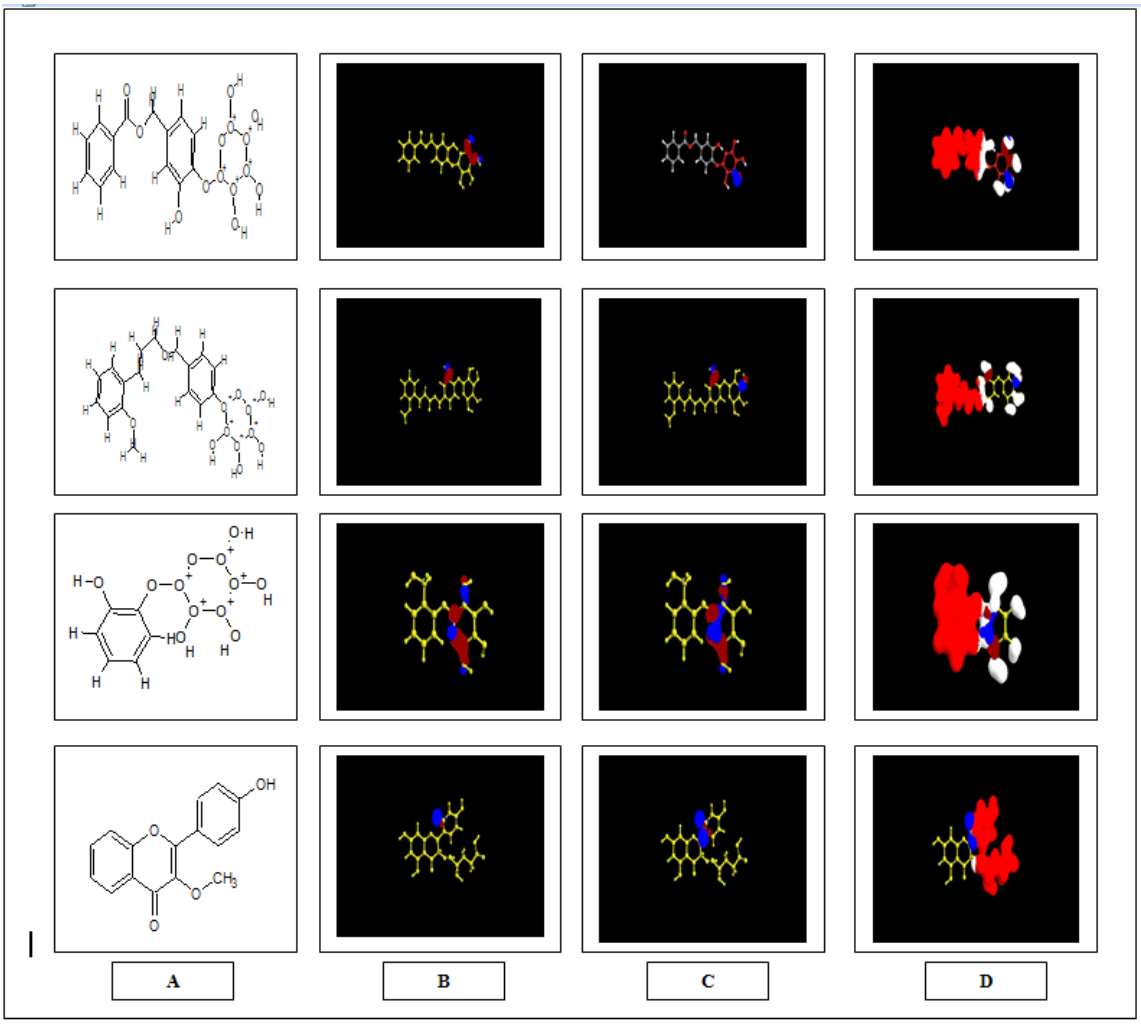

Figure 3:-[A] 2D structure generated by NMR projectile model [B] Simulation in highest energy occupied in ligands structure [C] Simulation as drug –like potency in lowest unoccupied structure [D] Pharmacophre simulation of ligands Esp mapping generated by Argus lab (www.arguslabs.org)

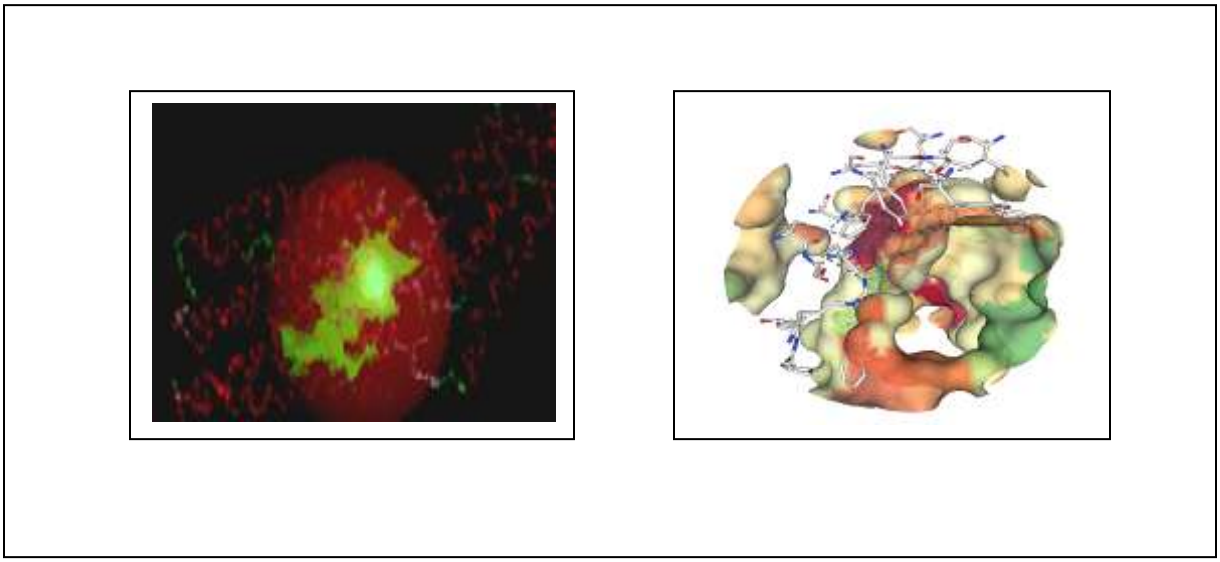

Figure 4:-3D structure generated by discovery studio3.1 projectile cavity force field simulation model.

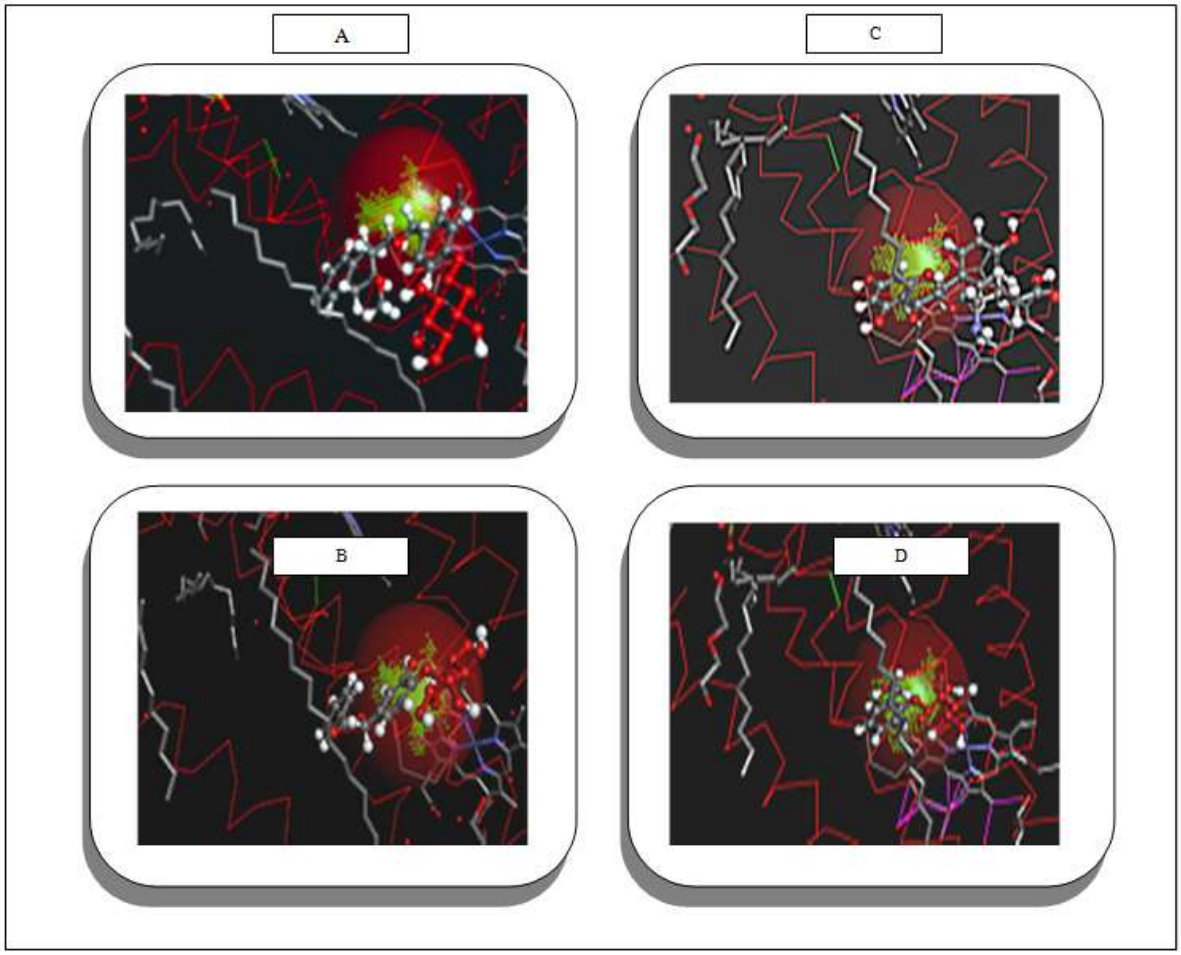

Figure 5:-3D structure generated by discovery studio 3.1 projectile cavity force field simulation model [A,B,C,D] 3D view of ligand cavity projectile in 72$A^{\cdot radius}$ of Alangium-1,2,3and4 phytocompounds. In this structure green color mesh and red spherical showed interaction region in ligand binding probability region in active binding cavity

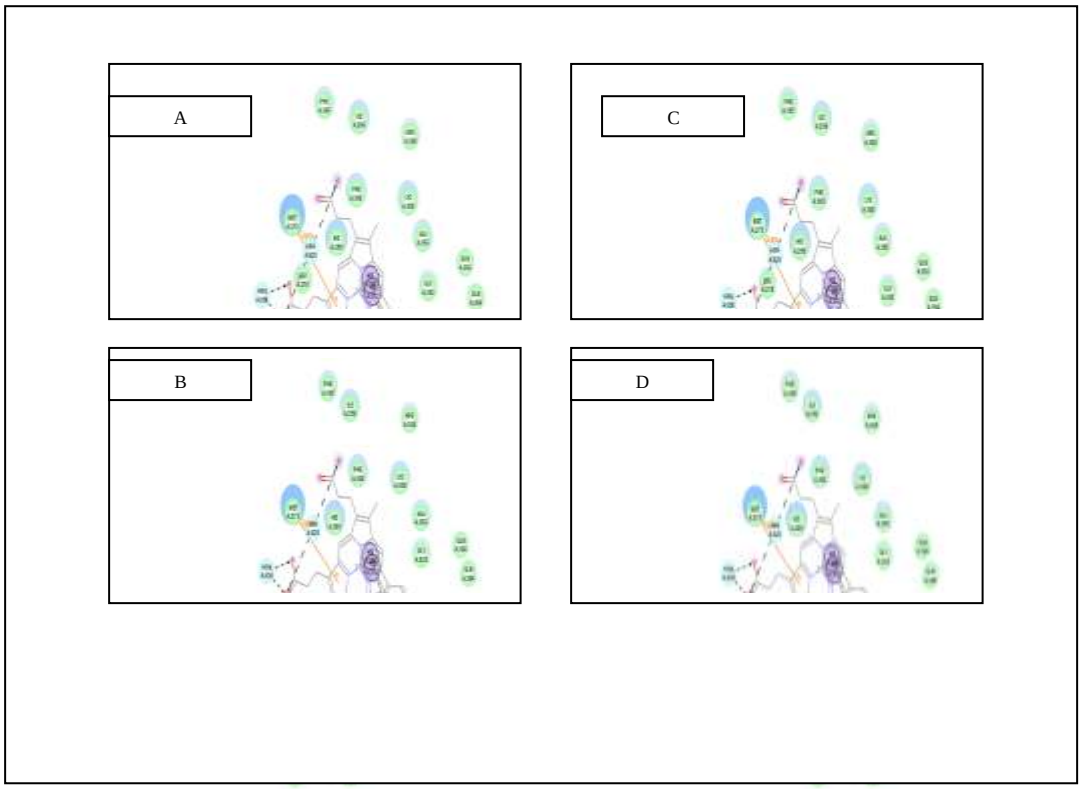

Figure 6:- Structure generated by discovery studio 3.1 projectile cavity force field simulation model .2D view of ligand cavity projectile in $72A^{\cdot\,radius}$. In this structure clear showed inside the cavity hydrogen bond and other binding interaction.

Table no:-1. Angiotensin-I receptor (ARs) characterization and its homology modeling identity

S. No.	Target receptor characterization (ANGIOTENSIN-I)	Credits
1	PDB, id	4YAY
2	Protein code or type	Membrane Protein
3	No of residue	414
4	No of chain	A(1)
5	Nature of protein	
6	Total structure weight	47679.23
7	Total atom count	3110
8	Homology modeling identitity	56.17 (similarity index)
9	Percentage of amino acid	33%(Acidic)

Table no 2:-General Properties of phytochemicals obtained from *Alangium salvifolium*

S.no.	Properties	Alangium 1	Alangium 2	Alangium 3	Alangium 4
1	Name of chemicals	4(benzoyloxy)methyl-2hydroxyphenoxy tetrahydorxy hexoxone 1,2,3,4,5, pentaium		Tetahydroxy(2hydroxy phenoxy)hexone 1,2,3,4,5 pentaium	Tetahydroxy(2hydroxy phenoxy)hexone 1,2,3,4,5 pentaium
2	Molecular formula	$C_{14}H_{15}O_{14}$	$C_{17}H_{23}O_{12}$	$C_6H_9O_{12}$	$C_{16}H_{12}O_4$
3	molecular weight	407.26	419.36	273.13	268.26
4	Composition				
5	Molar refractivity	81.88	94.46	46.12	76.43

Table 3:-Mean values of docking energies (kcal/mol) and standard deviation for each skeletal type of *Alangium salvifolium* phytochemicals as liagands with Angiotensin-I targets.

	Ligands (ALANGIUM PHYTOCOMPOUNDS)	Dimension Centre (x=25Ay=25z=25)	No of pose	RSD %lower	RSD %upper	Mean binding energy
Target (Angiotensin-I)	ALANGIUM 1	X=0.8353 Y=2.2958 Z=2.6955	9	87.13%	76.31%	-8.1
	ALANGIUM 2		9	132.88%%	112.81%	-7.5
	ALANGIUM 3		9	78.28%	69.52%	-5.8
	ALANGIUM 4		9	135.70%	86.94%	-5.1

Table 4:-Energy simulation score and ligand interaction results for the ***A. salvifolium*** phytocompounds

S. No.	Compound name (IUPAC name)	SCF simulation score	Uv simulation score	Ligand interaction
1	ALANGIUM 1	-231.767296889	-231.819691035	Ala,Glu,His, Leu ,Asp,Lys
2	ALANGIUM 2	-300.7076472584	-300.771772957	Lys, His, Asp, Ala ,Asn
3	ALANGIUM 3	47.3947768704	47.521422858	Ala,Glu,His, Leu ,Asp,Lys
4	ALANGIUM 4	213.3165388741	213.3165388741	Ala,Glu,His, Leu ,Asp,Lys

Results & Discussion:-

There were many crystal structures published in the Protein Data Bank (PDB) (www.rcsb.org/pdb) on Angiotensin-II in complexes with ligands and fragments developed by fragment-based design with resolutions ranging from 2.1 to 2.14 Å[17]. As we attempted to utilize the crystal structure of Ang-II in complex with an inhibitor (PDB ID: 4YAY) with 2.1 Å resolution and receptor protein related information depleted in Table no1.

In our present study, docking of tested compounds physical and chemical characteristics was summarized and determined as shown in Table-2 and Figure-3.The molecular dynamics simulation was carried out for the *A. salvifolium* phytocompounds. For evaluate the structural constancy of those molecules with the help of Arugus lab software. The final trajectory files were taken for calculating the SCF score of the ligand structures. At the same time as running MD simulation for phytocompounds for UV score both are summarized in Table-4 . Plot shows the stability of the complex structures. The period and the constant potential energy stable at ESp mapped. In addition, when performing the simulation for 10 ns, and it makes the stability of the complex structure during the entire simulation Figure2.

Angiotensin-I enzyme crystal structure complexed with Alangium-1(4(benzoyloxy)methyl-2hydroxyphenoxy tetrahydorxy hexoxone 1,2,3,4,5, pentaium) phytocompounds as a inhibitor was taken for our study to discover novel hit molecule for ACE inhibitor drug discovery. The reference ligand was docked into the active site of the enzyme, and the docking score was found to be –8.1 kcal/mol. The final trajectory files were taken for calculating the RMSD of the complex structures. At the same time as running MD simulation for receptor protein and phytocompound for 10 ns, the RMSD (Root Mean Square Deviation) plot shows the stability of the complex structures. The period and the constant potential energy stable at 1.2 ns to 10 ns. In addition, when performing the simulation [18] . The amino group of reference ligand was found to interact with positively charged amino acid Phe 368 and non-polar amino acid Leu270. Docking interaction showed in Figure- 5A,6A (3D,2D).

Later, the phytocompound selected for our study was made to dock into the active site pocket of the receptor closer analysis of the compound was analyzed and found that the compound was found to interact with the amino acid Met372 and the benzyl group is stacked with the non-polar amino acid Ala271. The 3-dimensional view of this molecule reveals that the compound was well fitted into the active site cavity which made this molecule more effective binding than the reference ligand. Furthermore, the nitro group and methoxyphenyl group was well surrounded by the non-polar amino acids. The binding analysis and the ligand interaction diagram was depicted in the Figure. 5B,6B.

The compound Tetahydroxy(2hydroxy phenoxy)hexone 1,2,3,4,5 pentaium which showed structure in Figure-2 . The docking score of –5.8 kcal/mol to further discuss about this compound binding analysis and interactions, the amino met 372 donates one hydrogen atom to the compound and the benzilic group was found to be interact with two stacking interaction with non-polar amino acids Trp409 and Phe584. Furthermore, the compound is fully surrounded by the non-polar amino acids such as Val567, Ala566, and Ile459 which made this compound possess least docking score than others because it was increase the bond length between receptor and ligand[19]. The binding analysis and the docking score of the compound were depicted in Fig. 5C,6C.

The compound Tetahydroxy(2hydroxy phenoxy)hexone 1,2,3,4,5 pentaium showed the docking score of –5.1 kcal/mol. Further, the structure-activity relationship of this compound reveals that the phenol group is showing a stacking interaction with Met372. Due to the presence of light ring of benzene present on the both the side of this compound, the compound tends to lose its activity on binding with the receptor [20]. 3-Dimensional representation of this molecule reveals that the compound is slightly away from the active site which made this compound lesser active than others [21]. The binding analysis and the ligand interaction of the compound,the binding analysis and the ligand interaction of the compound were depicted in Figure. 5D, 6D. The comparison with three compounds of *A. Salvifolium* compound -4 give less result that directly reflected to this phytocompounds showed not much good inhibitor of Angiotensin-1 receptor

Conclusion:-

As a result of this computational experiment Phytocompound of the Alangium-1(4(benzoyloxy)methyl-2hydroxyphenoxy tetrahydorxy hexoxone 1,2,3,4,5, pentaium) has shown efficient docking score and effective binding affinities. Hence, we concluded that the Alangium-1 phytocompounds may be a suitable potential to the Angiotensin-I inhibitor, which break the signaling cascade and play the important role vesicular remodeling. Based on this finding, we suggested that Alangium-1 bioactive molecule used for further drug development process,and this study will be addressed to further drug processing analysis.

References:-

1. Paul M, Poyan Mehr A, Kreutz R. (2006)Physiology of local reninangiotensinsystems. *Physiol Rev.*;86:747–803.
2. Stelings UM, Kaschina E, Unger T.(2005) The AT2 receptor – a matter oflove and hate. *Peptides*. ;26:1401–1409.
3. Norwood D, Branch E, Smith B(2002). Olmesartan Medoxomil forHypertension: A Clinical Review. *Drug Forecast* ;27:12.
4. Ruster C, Wolf G(2006) Renin-angiotensin-aldosteronesystem and progression of renal disease.*J Am Soc Nephrol* 17: 2985–2991.
5. Unger, T. (2002)The role of the renin-angiotensin system in the development ofcardiovascular disease. *Am. J Cardiol*. **2002,** *89* (2A), 3A-9A.
6. Kang, H.; Fan, Y.; Sun, A.; Jia, X.; Deng, X(2013). Simulated microgravity exposure modulates the phenotype ofcultured vascular smooth muscle cells. Cell Biochem. Biophys. . 66, 121–130
7. Cowan MM.(1999) Plant products asantimicrobial agents. Clin. Microbiol Rev.;12(4):564–582.
8. Chopra RN, Nayar SL, Chopra IC.(1996) Inglossary of Indian medicinal plants.Council of Scientific and IndustrialResearch New Delhi. ;1:197.
9. Jain VC, Patel NM, Shah DP, Patel PK,Joshi BH. (2010)Antioxidant and antimicrobialactivities of *Alangium salvifolium* (L.F) Wang root. Global Journal ofPharmacology. 4(1):13-18.
10. Subuhi SK, Prusty KB, Panda PK. (2012)Phytochemical and Antiulcer activity of petroleum ether and chloroform extracts of leaves of Alangium salvifolium Linn. (Family-Alangiaceae). Int. J. of Pharm. Res. and BioSci.. 1(2): 102-114.
11. Langer T, Hoffmann RD(2001). Virtual screening: An effective tool for lead structure discovery? Curr Pharm Des .7(7):509-27.
12. . Gohlke H, Klebe G.(2202) Approaches to the description and prediction of the binding affinity of small-molecule ligands to macromolecular receptors. Angew Chem Int Ed Engl 41(15):2644-76.
13. . Hajduk PJ, Greer J. (2007)A decade of fragment-based drug design: Strategic advances and lessons learned. Nat Rev Drug Discov ;6(3):211-9
14. Bajorath J. Integration of virtual and high-throughput screening. Nat Rev Drug Discov 2002;1(11):882-94
15. Ooms F.(2000) Molecular modeling and computer aided drugdesign. Examples of their applications in medicinal chemistry.Curr Med Chem. 7: 141-58.
16. Sahu S, Raja S, Kathiresan KP(2011). *In silico* docking analysis ofmangrove-derived compounds against breast cancer protein(BRCA1). Int Multidiscip Res J. 2011; 1.
17. Aathi M, Piramanayagam S. (2013) In silico validation of human N-myc downstreamregulated gene 2 protein against Alzheimer's disease using molecular modeling, docking and dynamics studies. Drug invent today. ;5(1):22-7.
18. Baig MH, Sudhakar DR, Kalaiarasan P, Subbarao N, Wadhawa G, Lohani M, (2014) Insight into the Effect of Inhibitor Resistant S130G Mutant on Physico-Chemical Properties of SHV Type Beta-Lactamase: A Molecular Dynamics Study. Plos one. ; 9(12): doi:10.1371/journal.pone.0112456.
19. Mohammad HB, Khurshid A, Sudeep R, Jalaluddin MA, Mohd A, Mohammad HS, (2016) Computer Aided Drug Design: Success and Limitations, Current pharma des. ;22(5):572-81.
20. Prime, version 3.1, Schrödinger, LLC, New York, 22 NY. (2012). 46. http://www.schrodinger.com/kb/1635,Schrodinger Prime User Manual
21. Subhani S, Archana J, Jamil K. (2015) Homology modelling and molecular docking of Multi Drug Resistance1 with chemotherapeutic agents in non-small cell lung cancer. Biomed Pharma. ;71:37-45.