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Research Article

A HOLISTIC VIRTUAL SCREENING TO FIND NOVEL INHIBITORS FROM *ALANGIUM SALVIFOLIUM* (ALANGIACEAE) FOR RECEPTOR TYROSINE KINASES INHIBITION

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A R T I C L E I N F O

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A B S T R A C T

Tyrosine kinase has important mediators of the signaling cascade, determining key roles in diverse biological processes like growth, differentiation, metabolism and apoptosis in response to external and internal stimuli. The inhibitors of the receptor tyrosine kinase (RTKs), have been used as the most modern and effective tools in the treatment of several types of cancer. Thus, there is a direct need for the search of novel inhibitors with fewer side-effects. Secondary metabolites obtained from *Alangium salvifolium* (Alangiaceae) an ayurvedic medicinal plant used for the treatment of hemorrhoids, rheumatic arthritis, loose stools, herpes, blood disorders etc. Therefore, the current study focuses on finding a common inhibitor from available natural products, which bind with both SRC-1 and ErbB1 types of receptor tyrosine kinases. A variety of virtual throughput screening approaches have been adopted in this study, including receptor ligands retrieving or preparation and structure analysis, 3D pharmacophore, docking studies, An in silico study confirmed the four phytochemicals, which need to be confirmed through in vivo studies.

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INTRODUCTION

Receptor tyrosine kinases (RTKs) is transmembrane glycoprotein that are activated by the binding of their cognate ligands, and they transduce the extracellular signal to the cytoplasm by phosphorylating tyrosine residues on the receptor themselves (autophosphorylation) and on downstream signaling proteins. The RTK family includes the receptors for insulin and for many growth factors, such as epidermal growth factor (EGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and nerve growth factor (NGF)[1]. In addition to the RTKs, there exists a large family of nonreceptor tyrosine kinases (NRTKs), which includes Src, the Janus kinases (Jaks), and Abl, among others. The NRTKs are integral components of the signaling cascades triggered by RTKs and by other cell surface receptors such as G protein-coupled receptors and receptors of the immune system. The specific reaction catalyzed by PTKs is the transfer of the γ phosphate of ATP to the hydroxyl group of a tyrosine in a protein substrate. The need for tight regulation of PTK catalytic activity is underscored by the numerous PTKs that have been identified as oncogenes (2, 3). Several examples are cited to illustrate the importance of PTKs in embryonic development, metabolism, and immune system function. The development of the vascular system relies on the concerted action of several subfamilies of RTKs and their cognate ligands (4).

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The vascular system is formed in a two-step process. In the first step, referred to as vasculogenesis, endothelial cells differentiate to form a crude network of interconnected vessels. In the second step, termed angiogenesis, the vessels are remodeled and extended, and non-endothelial support cells are recruited to the maturing vasculature. Vasculogenesis requires the growth factor VEGF and one of the RTKs through which it acts, KDR. Angiogenesis requires another VEGF receptor, Flt1, as well as the angiogenic factor angiopoietin 1, which is a ligand for the RTKs Tie2. More recently implicated in angiogenesis (in the demarcation of arteries and veins) is the ligand ephrinB2 and the RTK EphB4 (5). Ephrins and the Eph receptors are better known for their roles in axon guidance [6]. RTKs play an important role not only as key regulators of normal cellular processes, but also in the development and progression of various types of cancer.4 Generally, the inhibitors of the enzymes tyrosine kinase (ITK's), also known by "tinibs", compete for the ATP binding site at the catalytic site of various oncogenic tyrosine kinases, have a safe therapeutic profile, and can be combined with other chemotherapies or radiation.[7] There are currently no fully efficient therapies, but research regarding tyrosine kinase inhibitors (ITK's), targeting the neoangiogenesis of cancer, has shown good results, especially for progression-free survival.[8,9]

Ankol (*Alangium Salvifolium*) is an ayurvedic medicinal plant used for the treatment of hemorrhoids, rheumatic arthritis, loose stools, herpes, blood disorders etc. Each part of ankol tree has several medicinal values. For example, seeds are aphrodisiac and provide strength to the body. Athletes use

Ankol seeds to increase physical endurance and stamina for exercises.Ankol oil is beneficial in itching, eczema, herpes and other skin diseases due to its antipruritic characteristic [10]. Generally, Ankol root bark and Ankol oil are used in ayurvedic medicine. Other parts are rarely used. Seeds work as a general tonic and increase physical endurance and exercise stamina in athletes. Ankol (Alangium Salvifolium) has following healing properties. Various research studies have shown that Ankol has significant anticancer, antitumor, antibacterial, Antinociceptive and anti-inflammatory properties. Due to wide range of medicinal properties, Ankol (Alangium Salvifolium) is used for diabetes, epilepsy, pain disorders, and inflammatory diseases. The seeds are not used commonly in ayurveda[11]. The Ankol oil, whole fruits and root bark are more beneficial. The roots of Ankol have analgesic and anti-inflammatory action, which can help in arthritis and joint pains.The anti-inflammatory characteristic of Alangium Salvifolium In ayurveda, Ankol root bark is used for its pain relieving properties along with other herbs. In combination with following adjuvants, Ankol root bark powder helps reducing inflammation and pain [12]. The current study also follows the structural drug designing approach, that I we focus on *A. salvifolium* four phytocompounds as a inhibitor targeting both proteins. This approach was successfully implemented to find a naval medicinal plant based inhibitor for the receptor of tyrosine kinases (SRC-1 and ErbB1.

MATERIALS & METHODS

Protein primary sequence and structure retrieval

The primary sequences of SRC-1 (UniProt ID: P00233) and ErbB1 (UniProt ID: P00533) were retrieved from Universal Protein Resource (UniProt), which is a comprehensive resource for protein sequence and annotation data (www.uniprot.org). The three-dimensional structures of SRC-1 (PDB ID: 3GQL) and ErbB1 (PDB ID: IMP14) were obtained from Protein Data Bank (PDB) (www. rcsb.org), which is a single worldwide archive of structural data of biological macromolecules [13].

Sequence and structure analysis

Although SRC-1 has two isoforms produced by alternative splicing, only the first isoform is primarily involved in lung cancer (www.uniprot. org/uniprot/P00533) [14]. ErbB2 has four isoforms (www.uniprot.org/ uniprot/P04626). To understand the similarities and dissimilarities of the kinase domain of these isoforms, sequence comparison was performed for each protein separately using the Clustal Omega program of UniProt (www.uniprot.org/align/). The three-dimensional structures of both the proteins were compared by jCE algorithm [15] of RCSB PDB Protein Comparison Tool (www.rcsb.org/pdb/workbench/ workbench.do).

Ligand library construction

Natural products containing 6,160 compounds from marine sources and 18,151 compounds from medicinal plants were retrieved from previous extensive literature studies [16], Dr. Duke's Phytochemical library (www.ars-grin.gov/duke/), and PubChem BioAssay (www.ncbi.nlm.nih.gov/pcassay), which contains the bioactivity screens of chemical substances. If not found ,the structure of ligands draw with use of chem.-sketch software and its physical properties was depicted in table no.2., and deposited freely accessible, online database containing information on drugs and drug targets. Both the drugs bind irreversibly with the kinase domain of the targets [17].

3D pharmacophore modelling and virtual screening

A pharmacophore is defined as a 3D structural feature that illustrates the interaction of a ligand molecule with a target receptor in a specific binding site [16]. It is possible to compute the shared pharmacophore feature of a known drug when its three-dimensional structure is available. To this end, virtual screening of the ligand based 3D pharmacophore was performed using Argus lab and Discovery studio 3.1. [18]. Both the optimized structures were loaded onto the LigandScout, which were then aligned based on the pharmacophore features. Virtual screening was then performed with the generated shared feature against the natural products database and approved drug database created from the molecules obtained from the previous step. The "pharmacophore-fit" scoring function, "match all query features" screening mode, and "get best matching conformation" retrieval mode were used for the pharmacophore search. The screened molecules were further confirmed by docking study.

Molecular docking

Molecular docking studies were carried out for both the proteins separately with both the datasets natural product and approved drugs using PyRx (Autodock). It has two docking search algorithms: MolDock Optimizer and MolDock Simplex Evolution (SE). Mol Dock Optimizer is the default search algorithm in. In order to dock the receptor and ligand, the receptor was prepared from the "prepare molecule" option provided. Then, for grid searching, cavities were generated using the "detect cavity" option. Finally, the ligands obtained from the pharmacophore studies were provided in an sdf file format for docking using the docking wizard. During docking, the following parameters were fixed: number of runs 10, population size 50, crossover rate 0.9, scaling factor 0.5, maximum iteration 2,000, and grid resolution 0.30 [19]. Shared molecules capable of inhibiting both the proteins and which have better docking scores.

Visualization of results

Discovery studio3.1 software, which is an integrated platform for predicting protein–ligand interactions, was used to visualize the docked result. This software handles all aspects of the docking process from preparation of the molecules to determination of the potential binding sites of the target protein, and prediction of the binding modes of the ligands [20].

RESULTS AND DISCUSSION

Sequence and structure analysis

The retrieved sequences of SRC-1 and ErbB1 were aligned independently. The kinase domain of isoform1 of Src-1 (Figure 1). Previous studies have demonstrated that only the first isoform is essentially involved in lung cancer (www.uniprot.org/uniprot/P00533) [9]. On the contrary, the kinase domains of ErbB2 show significant similarities (Figure 2). The three-dimensional structures of both the proteins were compared by the jCE algorithm.

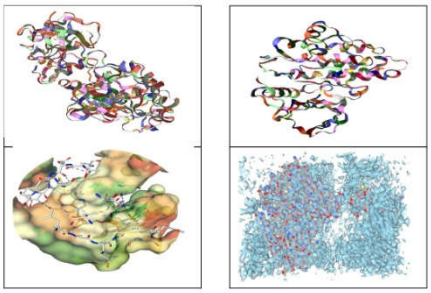

Figure1: Three dimensional structure alignments of src-1 (PDB ID: 3QEL) and ErbB1 (PDB ID: IML14).

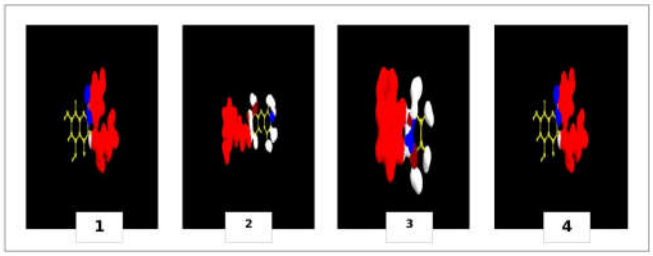

Figure:-2. Shared Pharmacophore feature of the reference drugs ***A. Salvifolium*** phytochemicals.

The kinase domains of both the proteins showed higher similarity with RMSD: 1.68, identities: 73% and similarities: 83% (Table 1), which indicates that a common inhibitor may be inhibiting both the proteins. Product molecules only 1,015 screened out were more poised. The significant reduction in the number of molecules could be attributed to the many stringent descriptors considered for this prediction.

surface area of polar nitrogen and oxygen atoms and carbonyl carbon atoms, predicted central nervous system activity, hexadecane/gas partition coefficient, octanol/gas partition coefficient, water/gas partition coefficient, octanol/water partition coefficient, aqueous solubility

3D pharmacophore modelling and virtual screening

The structurally optimized drug molecules A. salvifolium phytocompounds were based on their pharmacophore features using LigandScout. Three shared features-two hydrophobic and one hydrogen bond acceptor-were obtained from both the drugs (Figure 4), which were considered as a query for virtual screening. The ensued molecules were further confirmed by docking study.

Molecular docking and toxicity prediction

Molecular docking has played a key role in the identification of efficient binding of receptors and ligands. Compounds identified from docking studies with most favourable binding energy were considered as hits. The docking studies demonstrated that only 109 of the 201 natural product molecules and 125 of the 356 approved drugs have efficient binding with both the targets. Furthermore, only eighteen natural product molecules and five approved drugs were found to have a better docking score than the reference drug molecules. All docking results are concluded with RMSD in percentage duplicated in table no 3. The two-dimensional structure of the phytocompounds drug like molecules, four best natural product molecules aes are shown in Figures 2 and 3.

Table no 1 Receptor tyrosine kinases (RTSs) characterization and its homology modeling identity

S. No.	Target receptor characterization (RTK-SRC- 1)	Credits	Target receptor characterization (RTKs	Credits
	PDB ID	3GQL	1M14	
1		TYROSINE-PROTEIN KINASE	TRANSFERASE	
2	Gene Names: SRC	SRC (SRC1)	EGFR (ERBB, ERBB1, HER1)	
3	Protein code or type	EC: 2.7.10.2	EC: 2.7.10.1	
4	No of residue	452	333	
4	No of chain	A(1)	A(1)	
5	Nature of protein		Tyrosine Kinase Domain from Epidermal Growth Factor Receptor	
6	Total Structure Weight	7679.23	37875.75	
7	Total atom count	3646	2452	
8	Homology modeling identitity	86.17 (similarity index)	98.17 (similarity index)	
9	Percentage of amino acid			

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

The descriptors considered were number of rotatable bonds, molecular weight, computed dipole moment, total solvent accessible surface area, total solvent-accessible volume, number of hydrogen bond donor, number of hydrogen bond acceptor, number of likely metabolic reactions, Vander Waals

The PyRx docking score is shown in Table 3. The selected phytochemicals had a docking score ranging from −6.9Kcal/mol to -9.1 Kcal/mol with SRC-1 targets molecule, and the top ranked ERB1 drugs had a docking score ranging

from −6.8 Kcal/mol to −9.5 Kcal/mol, which is better than that of the reference drug molecules.

Figure:-3. Shared Pharmacophore feature of the reference drugs ***A. Salvifolium*** phytochemicals.

The docking result with Alangium-1 phytocompounds and both kinases receptor hydrogen bond interactions are shown in 2D map with 3D Visulaising with cavity shown in Figure 5,6,7 and 8. Docking results of four experimental phytodrugs with src-1 and ErbB1 are hit in same domain area that was shown in Figure 4. For better visualization, the hydrogen atoms of the proteins have been wireframe structure. The number of interacting pose between protein and phytocompounds are shown in Tables 3. Furthermore a detailed analysis of the docking results showed that all ligands bonded with the kinase domains of the target. Hyoscyamide is a nonalkaloidal component that is present in the seeds of Hyoscyamus niger [21]. Cannabisin F and Cannabisin E are acyclic bis-phenylpropane lignanamides existing in the fruits of Cannabis sativa [22]. It has been reported that another derivative of Cannabisin possesses considerable anticancer property by arresting the S phase of the cell cycle [23]. Cannabis sativa is cultivated for seed oil, food, and medicine. Historically, tinctures, tea, and ointments have also been common preparations. In traditional Indian medicine, C. sativa has been used as a hallucinogenic, hypnotic, sedative, an analgesic, and anti-inflammatory agent [24].

[29,30]. Heliotropamide from Heliotropium ovalifolium has oxopyrrolidine- 3-carboxamide central moiety [31]. A group of researchers from the United States of America synthesized Heliotropamide [32]. Although all five molecules are of plant source, they are not present worldwide and isolation of compounds is a very tedious procedure. Thus, it is paramount to perform their synthesis in a laboratory. Fesoterodine, which is an approved drug, is a prodrug. It is broken down in-vivo into its active metabolite, 5-hydroxymethyl tolterodine (5-HMT), by plasma esterases. 5-hydroxymethyl metabolite exhibits an antimuscarinic activity. Both urinary bladder contraction and salivation are mediated via cholinergic muscarinic receptors. Therefore, acting as a competitive muscarinic receptor antagonist, fesoterodine ultimately acts to decrease the detrusor pressure owing to its muscarinic antagonism, thereby decreasing bladder contraction, and consequently, the urge to urinate [33-36]. Antrafenine is a piperazine derivative drug that acts as an analgesic and anti-inflammatory with an efficacy similar to that of naproxen. It is not widely used as it has largely been replaced by newer drugs [37,38]. Fluspirilene is a relatively long-acting injectable depot antipsychotic drug used for schizophrenia. It does not differ greatly from other depot antipsychotics (fluphenazine decanoate, fluphenazine enathate, perphenazine onanthat, pipotiazineundecylenate) with respect to treatment efficacy, response, or tolerability [39]. Posaconazole exerts its antifungal activity through blockage of the cytochrome P-450 dependent enzyme, sterol 14α-demethylase, in fungi by binding to the heme cofactor located on the enzyme. This leads to the inhibition of the synthesis of ergosterol, a key component of the fungal cell membrane, and accumulation of methylated sterol precursors, which in turn results in the inhibition of fungal cell growth, and ultimately, cell death [40,41]. Iloprost is a second generation structural analog of prostacyclin (PGI) with about tenfold greater potency than the first generation stable analogs, such as carbaprostacyclin. It binds with equal affinity to human prostacyclin (Prostanoid IP) and prostaglandin EP1 receptors, and constricts the ilium and fundus circular smooth muscle as strongly as prostaglandin E2 (PGE). itself.

Table 3 Mean values of docking energies (kcal/mol) and standard deviation for each skeletal type of *Alangium salvifolium* phytochemicals as liagands with Receptor tyrosine kinases (RTSs)

Target	Ligands	Dimession Centre(x=25Ay=25z=25	No of pose	RSD %lower	RSD %upper	Mean binding energy
PROTEIN TYROKINASE (SRC-1)	ALANGIUM1	X=20.6447,Y=33.7682, Z=67.4240	9	57.39%	54.39%	-9.0
	2		9	84.95%	83.04%	-7.5
	3		9	51.86%	49.81%	-6.9
	4		9	40.71%	40.26%	-7.0
PROTEIN TYROSINE KINASE(ERBB1)	ALANGIUM1	X=20.6447,Y=33.7682, Z=67.4240	9	50.13%	55.31%	-9.5
	2		9	69.40%	66.09%	-7.6
	3		9	67.12%	61.06%	-6.9
	4		9	38.03%	39.05%	-7.0

Recently, a group of scientists from China synthesized cannabisin F from vanillin [25]. Cannabisin F has already been reported for its cytotoxic activity [26], and cell-growth inhibitory activities against human lung cancer and human cervical cancer [27] Cochinchinenene D from Dracaena cochinchinensis has already been reported for its antibacterial activities against Helicobacter pylori [28]. Dracaena cochinchinensis is predominant in China and its various other secondary metabolites are used to cure a variety of diseases, including neurodegenerative diseases, diabetes, and cancer

Iloprost inhibits the ADP, thrombin, and collagen-induced aggregation of human platelets. In whole animals, iloprost acts as a vasodilator, hypotensive, and antidiuretic, and prolongs bleeding time. All of these properties help to antagonize the pathological changes that take place in the small pulmonary arteries of patients with pulmonary hypertension [42-46].

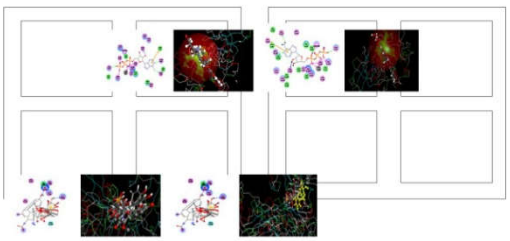

FIGURE 5:-Docking interaction between target and ligands[a] shr-1[b] ebbr1

FIGURE 6:-Docking interaction between target and ligands[a] shr-1[b] ebbr1

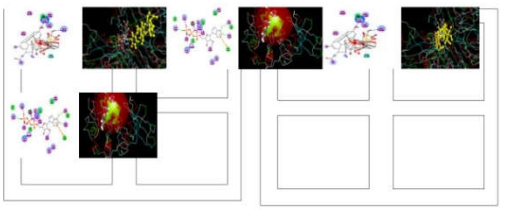

FIGURE 8:-Docking interaction between target and ligands[a] shr-1[b] ebbr1

Figure.7:- Docking interaction between target and ligands[a] shr-1[b] ebbr1

CONCLUSION

Although several previous studies have attempted at finding the best inhibitors, they have thus far failed to determine a common inhibitor targeting both the proteins. The current study achieved this by following an in silico approach. Four Ayurvedic phytochemicals (Drav or Rasa) Alagium-1,2,3,4 drug like molecules are capable of inhibiting both SRC-1 and ErbB1. The results obtained need to be confirmed biologically by conducting in-vitro and in vivo experiments.

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