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COMPREHENSIVE STRATEGY FOR INVESTIGATING THE ANTI-BREAST CANCER EFFICACY OF AYURVEDIC BOTANICALS TARGETING EPIDERMAL GROWTH FACTOR RECEPTOR THROUGH NETWORK ETHNOPHARMA-COLOGY, MOLECULAR DOCKING, AND ADMET ANALYSIS

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ABSTRACT
There is enough evidence to suggest that the epidermal growth factor receptor contributes to the onset and metastasis of breast cancer. Consuming sufficient amounts of natural chemicals produced from plants has been shown in both in vitro and in vivo studies to reduce the mortality and recurrence rates of breast cancer. Data for the network was gathered from the databases Dr. Duke's, IMPPAT, PubChem, Binding DB, UniProt, and DisGeNET. The network was designed using the Cytoscape tool. PyRx software was used to conduct docking studies with EGFR on bioactives that were screened using a polypharmacology approach and had a similarity index greater than 0.6. Following that, the ligands that had a sufficient docking score were examined further for the investigation of molecular docking interactions. Ashwagandh, Shatavari, Neem, Alsi seeds, Methi, Haldi, Ghritkumari, Yashtimadhu, and Kadi Patta were the sources of 3, 11, 3, 5, 14, 14, 4, 19, and 2 bioactives, respectively that interacted with EGFR with a similarity value of 0.6 or higher. The binding energies and interactions of the ligands were found to be reasonably good when the top molecules with apigenin (-6.56 kcal/mol), campesterol (-8.43 kcal/mol), diosgenin (-7.82 kcal/mol), genistein (-6.81 kcal/mol), prunetin (-6.87 kcal/mol), quercetin (7.28 kcal/mol), racemolol (-7.30 kcal/mol), beta-sitosterol (-7.47 kcal/mol), sominone (-7.66 kcal/mol), and syringetin (-6.87 kcal/mol) were docked against the target EGFR. An in silico molecular mechanism of EGFR inhibition by a variety of bioactive phytoconstituents from certain botanicals was clarified by the study.

KEYWORDS: Breast Cancer, Epidermal Growth Factor Receptor, Network Pharmacology, Molecular docking, Ayurvedic Botanicals.

INTRODUCTION

Originating from ancient wisdom found in the Rigveda and Atharvaveda, Ayurveda encompasses a scientific legacy of harmonious life. An ancient Indian medical method, Ayurveda has been used for centuries. Numerous Ayurvedic medications have been used to treat and control a range of human illnesses. From ancient Ayurveda to present practice as "tradition to trend," a number of medications have been created and used. For better therapeutic leads, the potential of Ayurvedic medicine needs to be further investigated using contemporary scientific validation techniques [1]

The prevalence of breast cancer keeps rising in spite of decades of laboratory, epidemiological, and clinical study. One in 20 women worldwide and up to one in eight in high-income nations are affected by breast cancer (BC), which continues to be the most common cancer-related cause of disease burden for women. Both a population-based strategy to lower exposure to modifiable risk factors and a precision-prevention strategy to identify women at higher risk and target them for particular interventions, like risk-reducing medication, are probably needed to lower the incidence of breast cancer [2].

Because the etiology of BC is complex, therapy is difficult. A number of cancer forms, including breast cancer, frequently exhibit changes in the cell division cycle. Hormonal therapy, radiation, chemotherapy, and surgery are common therapies; however, difficulties and noncompliance are caused by side effects and multidrug resistance. As a result, demand for natural products made from foods and medicinal plants is rising [3].

Scientists are looking to agents with more efficacies, including natural chemicals, for the treatment and prevention of BC because the majority of chemotherapeutic medicines are linked to adverse effects, drug resistance, and cancer recurrence. Certain natural compounds—substances produced from living things—inhibit metastasis and encourage apoptosis, which

stops the spread of cancer. These substances may therefore be able to slow the progression of BC, improving patient outcomes and lowering the number of fatalities from BC [4].
As a type I receptor tyrosine kinase, the epidermal growth factor receptor (EGFR) and its ligands regulate a variety of cellular processes. The pharmacological and pathological roles of EGFR and its signaling pathway in both health and illness have been thoroughly investigated. There is sufficient data to conclude that EGFR has a role in the etiology and development of a number of malignancies [5]. In women with early-stage breast cancer, EGFR overexpression seems to be linked to a lower overall and disease-free survival rate. Compared to patients with triple negative tumors and normal EGFR expression, those with triple negative tumors with over expressed EGFR have a worse overall and disease-free survival rate [6].
Targeting known breast cancer targets using in-silico techniques, the study aims to investigate the anti-breast cancer activity of a number of Ayurvedic botanicals that are traditionally recognized for their anti-cancerous action. The design employs a network ethnopharmacological approach to the initial screening of phytochemicals from reputable botanicals, a molecular docking tool [8] to further explore the screened bioactives for binding affinity and interaction analysis, and an ADMET prediction of the top 10 molecules in order to identify bioactives that target EGFR.
In comparison to conventionally manufactured chemicals, large-scale research will identify leads as naturally occurring, bioactive compounds that efficiently block EGFR in the treatment and prevention of breast cancer.

MATERIAL AND METHODS
NETWORK PHARMACOLOGICAL STUDIES

Data mining for Phytochemicals
This study utilized use of phytoconstituents from particular botanicals that have been shown to have anti-breast cancer qualities in the past. Data were collected using Dr. Duke's Phytochemical and Ethnobotanical Databases web platform, Indian Medicinal Plants, Phytochemistry and Therapeutics 2.0 9, and literature mining to learn more about the phytoconstituents of specific botanicals [10].
The study made advantage of the publicly available SDF (Structure Data File) formats that are present in the three-dimensional structures of phytoconstituents. Search PubChem for the precise structures and common names of the phytoconstituents found in a few chosen plants [11].

Establishment of Target
Information about EGFR and its function in the development of cancer was gathered using the RCSB Protein Data Bank (RCSB PDB). The target's UniProt ID at RCSB PDB identifies the species, which is limited to human sources [12]. The DisGeNET database was used to identify the EGFRas therapeutic target associated with breast cancer [13]. The standard name for the protein target was found using the UniProt database [14].

Screening of bioactives by polypharmacology
To predict the binding of bioactives to EGFR for the therapy of breast cancer, the SDFs which comprised the structures of phytoconstituents from specific botanicals were submitted to the Binding DB [15]. Binding DB suggests a similarity index greater than 0.4 when examining compound target-association. The bioactives used for the investigation had similarity indices ranging from 0.6 to 1. The numerous databases to which Binding DB is connected were used to learn more about the target. The protein symbols were retrieved from UniProt using the UniProt IDs given in the Binding DB. We searched for associations between the bioactive target and breast cancer using DisGeNET.

Network Construction
The network was updated, the data was assessed, and it was visually represented using Cytoscape software [16]. Excel programmed files were used to create the data pairings of specific botanicals with bioactive PCIDs (PubChem Compound Identification), bioactive PCIDs with EGFR, and EGFR with breast cancer. A network map of the illness target and therapy components was produced after the data pairs were loaded.
The nodes, which represent breast cancer, EGFR, bioactives, and confident botanicals, are connected by edges on the network map. The 'Network Analyzer' tool was used to evaluate the network.

DOCKING STUDIES
Selection of ligand
For in-silico research, the ligands with a high docking score were examined further. The network pharmacology approach's screened bioactives that had a similarity index higher than 0.6 and were linked to EGFR (3POZ) for breast cancer activity were then put through docking tests against EGFR using the AutoDockv.4.2 program [17]. EGFR (3POZ) was chosen for investigation because it is a transcription inhibitor, it is a human organism, and it does not show any signs of mutation. The EGFR (3POZ) protein can imitate its shape to facilitate docking.

Preparation of ligand
Together with their matching PCID, the inhibitors' three-dimensional structures were redeemed and saved in '.sdf' format. Additionally, all of the ligands' 3D structures were converted from the.sdf to the.pdb format using Pymol software during the ligand production process. The generated ligands were saved in PDB format [19] for further docking studies. The

Discovery Studio 2020 Client and Chimera software are used to effectively visualize docking, and 2D and 3D images of hydrogen bonds and protein-ligand interactions are displayed [20].

Preparation of protein

The Discovery Studio 2020 Client and Chimera software are used to create 2D and 3D representations of protein-ligand interactions and hydrogen bonds for an efficient docking visualization.

Molecular docking

Molecular docking is an essential component of computer-assisted drug discovery. It helps predict the intermolecular framework that arises between a protein and ligand and creates the right connection between the molecules. The docking procedure was managed by the AutoDock 4.2.6 application. The top ten conformations with the lowest docked energy were chosen from the docking search. Utilizing Pymol, UCSF Chimera, and Accelrys Discovery Studio Visualizer, the interactions of complex protein-ligand conformations, such as hydrogen bonds and bond lengths, were investigated.

CASTp Identification

Concave surface areas on three-dimensional protein structures can be found, defined, and measured using an online application called CASTp (Computed Atlas of Surface Topography of proteins). These include pockets visible on the surface of proteins and cavities concealed within them [21].

ADMET ANALYSIS

Computational ADMET predication (absorption, distribution, metabolism, excretion, and toxicity) is one of the fundamental methodologies used in contemporary drug discovery to forecast drug pharmacokinetics and toxicity. ADMET properties are essential for the selection and development of drug candidates [22]. The ADMET properties of the top 10 substances were calculated using ADMETlab 2.0. When consumed orally, a drug with a greater HIA may be more easily absorbed from the digestive tract. The BBB Penetration, or penetration of the blood-brain barrier, was determined to be the most promising therapeutic candidate. However, understanding a chemical compound's toxicity is necessary to determine its detrimental effects on humans, animals, plants, or the environment. Here, we used ADMETlab 2.0 to confirm the ADMET property prediction.

RESULTS AND DISCUSSION

NETWORK PHARMACOLOGY STUDIES

Phytochemical data mining

52 phytoconstituents have been reported to be present in the botanical plant *Withania somnifera.* According to reports, *Asparagus racemosus* contains 28 phytoconstituents. According to reports, *Linum usitatissimum* contains 60 phytoconstituents, while *Azadirachta indica* contains 23. According to reports, *Trigonella foenum-graecum* contains 65 phytoconstituents, while *Curcuma longa* contains 98 phytoconstituents. According to reports, *Murraya koenigii* has 86 phytoconstituents, *Glycyrrhiza glabra* contains 100, and *Aloe barbadensis* contains 21.

Establishment of Target

Regarding EGFR data with PDB ID 3POZ, The gene names are EGFR, ERBB1, ERBB, and HER1, the protein name is epidermal growth factor receptor, the organism or organisms are Homo sapiens, the sequence length is 327, and the Uniprot ID is -P00533.

Screening of bioactives by polypharmacologyfor target

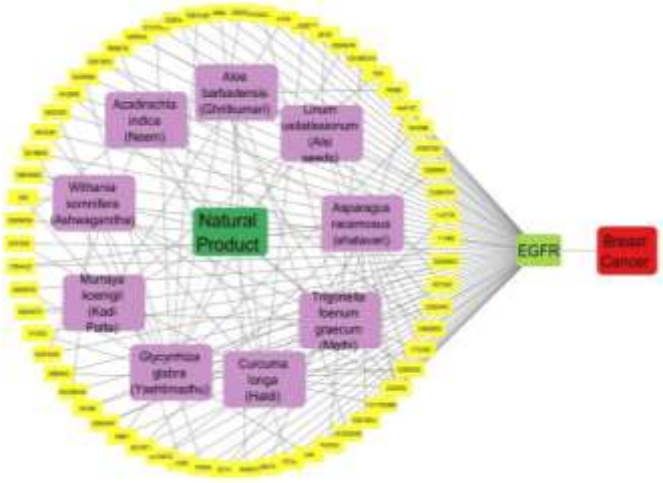

Figure 1. Interaction network of bioactives from selected botanicals with EGFR in breast cancer

Three bioactives from *Withania somnifera*, 11 from *Asparagus racemosus*, 3 from *Azadirachta indica*, 5 from Linum usitatissimum, 14 from Trigonella foenum-graecum, 14 from *Curcuma longa,* 4 from *Aloe barbadensis*, 19 from *Glycyrrhiza glabra*, and 2 from *Murraya koenigii* were high scoring bioactives with an interaction with EGFR of 0.6 or higher (high scoring bioactives) **(Figure 1)**. Cytoscape v.3.2.1 software was used to generate and analyze networks from the bioactives that were screened from a selection of botanicals utilizing a polypharmacology method.

MOLECULAR DOCKING STUDIES

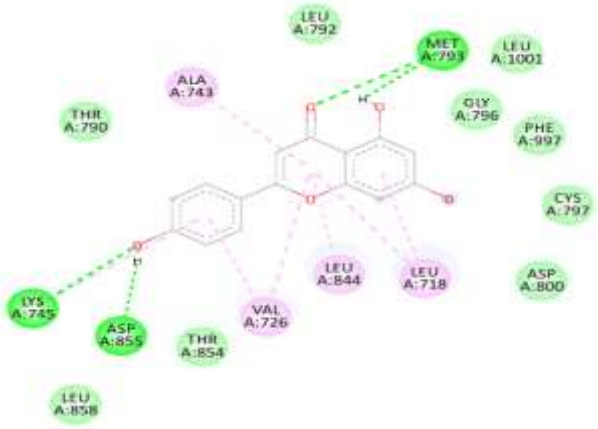

Figure 2. Docking poses of Apigenin against EGFR) 2D model

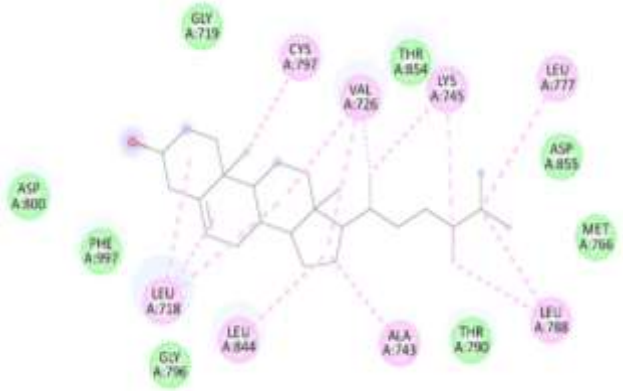

Figure 3. Docking poses of Campesterol against EGFR 2D model

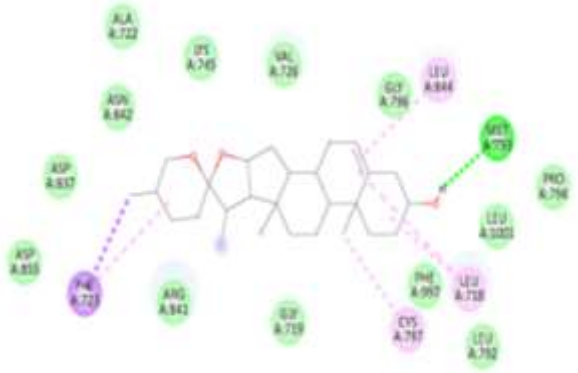

Figure 4. Docking poses of Diosgenin against EGFR2D model

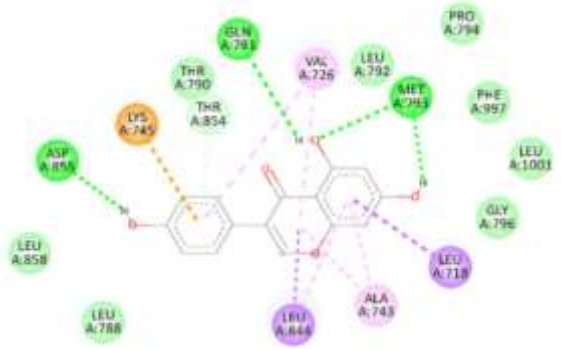

Figure 5. Docking poses of Genistein against EGFR2D model

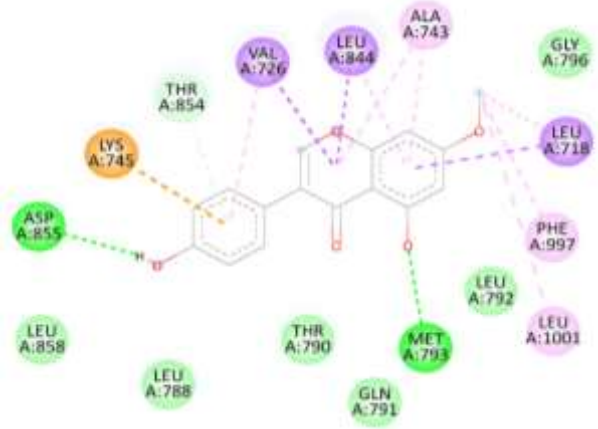

Figure 6. Docking poses of Prunetin against EGFR2D model

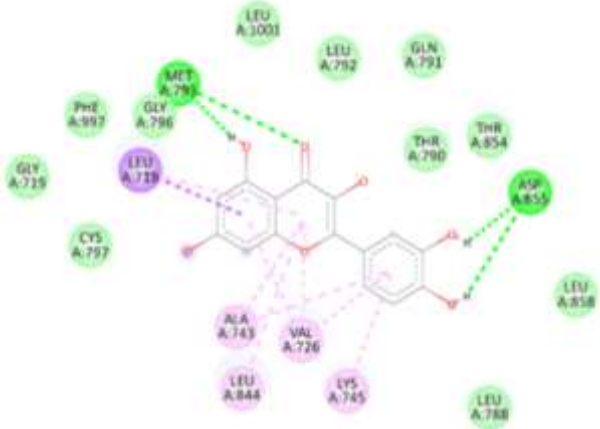

Figure 7. Docking poses of Quercetin against EGFR 2D model

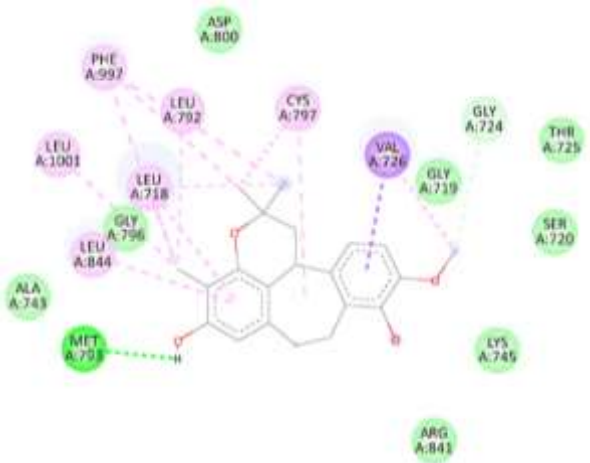

Figure 8. Docking poses of Racemosol against EGFR 2D model

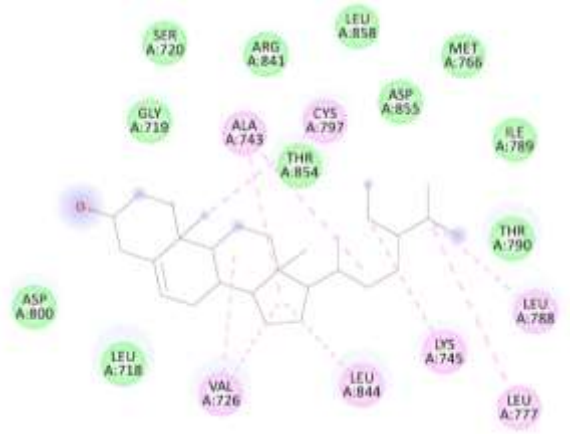

Figure 9. Docking poses of Beta-Sitosterol against EGFR 2D model

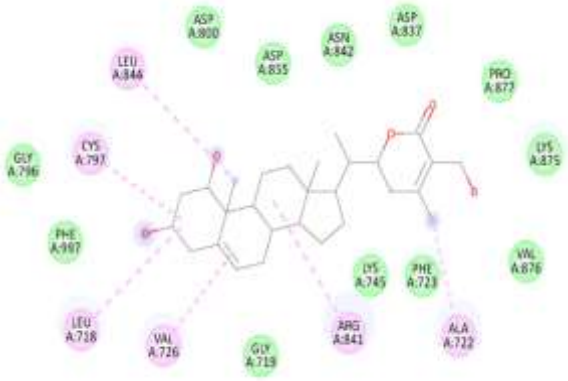

Figure 10. Docking poses of Sominone against EGFR2D model

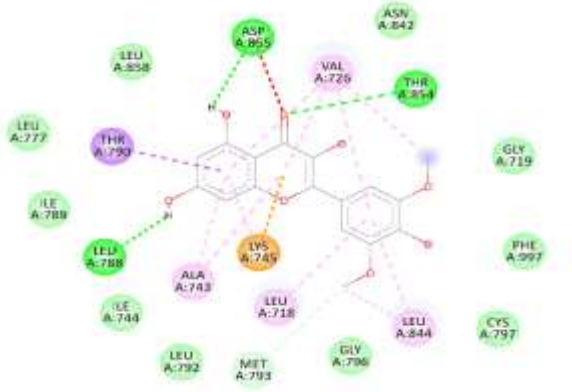

Figure 11. Docking poses of Syringetin against EGFR2D model

From the docking search, the top ten conformations with the lowest docked energy were selected. Apigenin (-6.56kcal/mol) (**Figure 2**), campesterol (-8.43kcal/mol) (**Figure 3**), diosgenin (-7.82kcal/mol) (**Figure 4**), genistein (-6.81kcal/mol) (**Figure 5**), prunetin (-6.87kcal/mol) (**Figure 6**), quercetin (7.28kcal/mol) (**Figure 7**), racemolol (-7.30kcal/mol) (**Figure 8**), beta-sitosterol (-7.47kcal/mol) (**Figure 9**), sominone (-7.66kcal/mol) (**Figure 10**), and syringetin (-6.87kcal/mol) (**Figure 11**) were used for docking against the target epidermal growth factor receptor (3POZ). There was not a single comp
ound that surpassed Lipinski's rule of five.

Table 1. EGFR inhibition by screened top bioactive ligands

Protein Name	Ligand Name	Binding Energy (kcal/mol)	No. of H Bonds	Interacting residue	Final Intermolecular Energy (kcal/mol)	vdW + Hbond + desolv Energy (kcal/mol)	Electrostatic Energy (kcal/mol)	Torsional Free Energy (kcal/mol)
3POZ	Apigenin	-6.56	03 H1:3.22Å H2:2.05Å H3:2.14Å	LYS:745(H1), ASP:855(H2), MET:793(H3), VAL:726, LEU:844, LEU:718, ALA:743	-7.10	-6.88	-0.22	+1.19
	Campesterol	-8.43	00	LEU:718, LEU: 844, ALA:743, CYS:797, VAL:726, LYS:745, LEU:777, LEU:788.	-10.27	-10.23	-0.04	+1.79
	Diosgenin	-7.82	01 H1:2.03Å	MET:793(H1), LEU:718, CYS:797, LEU:844, PHE:723.	-8.12	-8.11	-0.00	+0.30
	Genistein	-6.81	03 H1:2.12 Å H2:2.92 Å H3:2.88 Å	ASP:855(H1), GLN:791(H2),MET:793(H3)	-7.34	-7.14	-0.20	+1.19
	Prunetin	-6.87	02 H1:2.12 Å H2:2.97 Å	ASP:855(H1), MET:793(H2), LYS:745, THR:854, VAL:726, LEU:844, ALA:743, PHE:997, LEU:1001.	-7.39	-7.26	-0.13	+1.19

	Quercetin	-7.28	02 H1:2.45Å H2:1.99Å	MET:793(H1), ASP:855(H2), ALA:743, VAL:726, LYS: 745, LEU: 844, LEU:718.	-7.25	-7.05	-0.21	+1.79
	Racemosol	-7.30	01 H1:2.22Å	MET:793(H1), LEU:844, LEU:1001, LEU:718, PHE:997, CYS:797, VAL:726, GLY:724.	-7.67	-7.57	-0.09	+0.89
	Beta-Sitosterol	-7.47	00	VAL:726, LEU:844, ALA:743, CYS:797, LYS:745, LEU:777, LEU: 788.	-9.37	-9.34	-0.03	+2.09
	Sominone	-7.66	00	LEU:718,VAL:726, CYS:797, LEU: 844,ARG: 841,ALA:722.	-8.87	-8.92	+0.06	+1.79
	Syringetin	-6.87	03 H1:1.87Å H2: 2.21Å H3:3.39Å	LEU:788(H1), ASP:855(H2), THR:854(H3), ALA:743, LEU:718, LEU: 844, MET: 793, LYS:745, THR:790, VAL: 726.	-7.56	-7.53	-0.03	+2.09

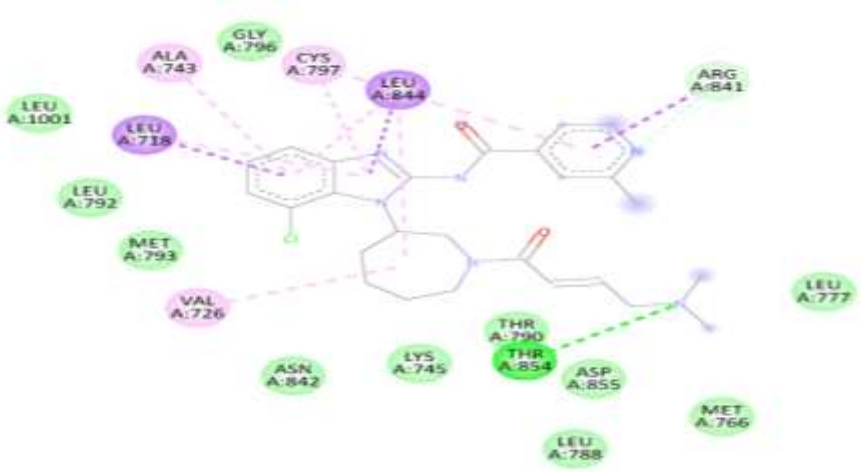

Figure 12. Docking poses of Standard Synthetic Nazartinib against EGFR 2D model

Table 1 shows the docking analysis for EGFR inhibition using the standard synthetic Nazartinib ligand and the top 10 bioactives that were evaluated. Nazartinib (**Figure 12**) was used as standard synthetic ligand for docking against the target epidermal growth factor receptor (3POZ).

CASTp Identification

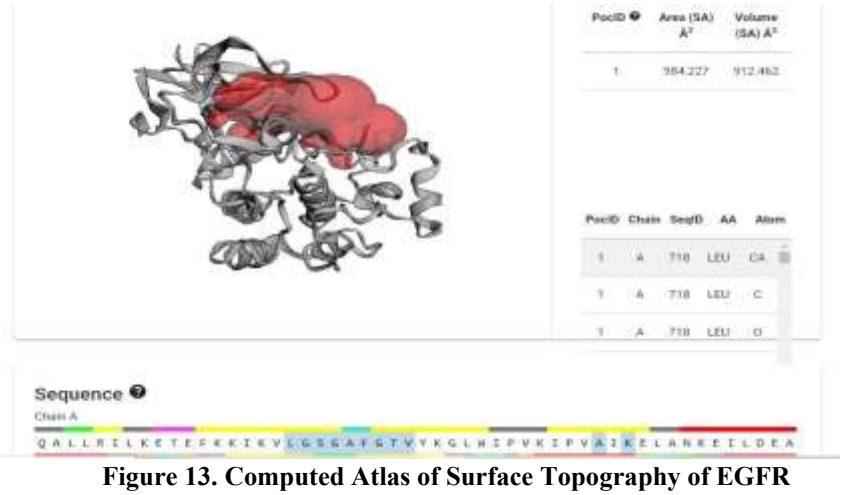

Figure 13. Computed Atlas of Surface Topography of EGFR

On the basis of CASTp server we have selected the pocket 1 with area 984.227 and volume 912.462 and in the pockets total 64 numbers of amino acids were included **(Figure 13)**. The number of amino acids are 718, 719, 720, 721, 722, 723, 724, 725, 726, 742, 745, 766, 775, 776, 777, 788, 790, 791, 792, 793, 795, 796, 797, 799, 800, 801, 803, 804, 805, 836, 837, 839, 841, 842, 844, 854, 855, 856, 858,859, 863, 864, 866, 867, 875,876, 877, 878, 879, 880,881, 891,906, 912,913,914, 916, 920,990, 995, 996, 997, 1001.

ADMET ANALYSIS

Table 2: Performance of the classification models incorporated into the ADMETlab 2.0 platform for tested bioactives

Category	Model	Points									
		1	2	3	4	5	6	7	8	9	10
Absorption	Caco-2 Permeability	-4.847	-4.740	-4.805	-4.764	-4.764	-5.204	-4.897	-4.756	-4.756	-5.149
	MDCK Permeability	1.2e-05	8.9e-06	4.7e-05	7.8e-06	7.8e-06	7.7e-06	2.1e-05	8.6e-06	3.4e-05	1.1e-05
	Pgp-inhibitor	---	-	--	---	---	---	+	-	---	--
	Pgp substrate	++	---	---	+	+	---	---	---	---	---
	HIA	---	---	---	---	---	---	---	---	--	--
Distribution	PPB (%)	97.255%	98.676%	97.743%	97.558%	97.558%	95.496%	99.560%	98.314%	93.074%	92.020%
	VD	0.510	1.842	1.695	0.471	0.471	0.579	1.395	1.963	1.084	0.799
	BBB Penetration	---	++	++	---	---	---	---	++	-	--
	Fu (%)	3.668%	1.790%	1.872%	2.088%	2.088%	7.423%	1.016%	1.485%	3.826%	14.299%
Metabolism	CYP1A2 inhibitor	+++	---	---	+++	+++	+++	--	---	---	+++
	CYP1A2 substrate	--	+	-	--	--	--	+++	-	--	+++
	CYP2C19 inhibitor	+	---	---	+	+	---	+	---	---	---
	CYP2C19 substrate	---	+++	+++	---	---	---	+++	+++	-	---
	CYP2C9 inhibitor	+	---	--	+	+	+	-	---	---	+
	CYP2C9 substrate	+++	--	---	+++	+++	+	+++	-	--	++
	CYP2D6 inhibitor	++	---	---	++	++	-	-	---	---	-
	CYP2D6 substrate	++	-	++	++	++	--	++	-	-	-
	CYP3A4 inhibitor	++	--	--	++	++	-	--	--	--	-
	CYP3A4 substrate	--	++	+	--	--	---	++	++	+ +	--
Excretion	CL	7.022	17.948	23.332	7.844	7.844	8.284	6.986	16.686	16.277	6.437
	T1/2	0.856	0.015	0.023	0.876	0.876	0.929	0.278	0.013	0.079	0.925
Toxicity	hERG Blockers	---	---	---	---	---	---	---	---	---	--
	H-HT	---	--	--	---	---	---	+	--	--	---
	DILI	++	--	---	+	+	+++	---	--	---	+++
	AMES Toxicity	-	---	---	--	--	+	---	---	---	-
	Rat Oral Acute Toxicity	---	---	++	-	-	---	-	---	--	---
	FDAMDD	-	+	+	--	--	-	+++	++	+ +	++
	Skin Sensitization	+++	--	--	+++	+++	+++	++	--	---	++
	Carcinogenicity	--	---	--	-	-	---	--	---	--	---
	Respiratory Toxicity	--	+	+	---	---	---	+	+	+ +	--
	BF	0.975	3.141	3.319	1.033	1.033	1.017	2.161	2.963	0.821	1.038
	IGC50	4.588	4.855	4.719	4.558	4.558	4.231	5.035	4.984	4.313	4.071

	LC50FM	5.208	4.972	4.955	5.275	5.275	5.222	5.749	5.365	4.680	4.835
	LC50DM	5.209	5.897	5.748	5.632	5.632	5.331	6.779	6.231	5.133	5.724
Physicochemical Properties	MW	270.050	400.370	414.310	270.050	270.050	302.040	340.170	414.390	458.300	346.070
	Volume	265.186	464.772	447.944	265.186	265.186	282.767	356.888	482.068	486.104	326.149
	Density	1.018	0.861	0.925	1.018	1.018	1.068	0.953	0.860	0.943	1.061
	nHA	5	1	3	5	5	7	4	1	5	8
	nHD	3	1	1	3	3	5	2	1	3	4
	nRot	1	5	0	1	1	1	1	6	3	3
	nRing	3	4	6	3	3	3	4	4	5	3
	MaxRing	10	17	20	10	10	10	17	17	17	10
	nHet	5	1	3	5	5	7	4	1	5	8
	fChar	0	0	0	0	0	0	0	0	0	0
	nRig	18	20	30	18	18	18	21	20	27	18
	Flexibility	0.056	0.250	0.000	0.056	0.056	0.056	0.048	0.300	0.111	0.167
	Stereo Centers	0	9	11	0	0	0	1	9	10	0
	TPSA	90.900	20.230	38.690	90.900	90.900	131.360	58.920	20.230	86.990	129.590
	logS	-3.606	-7.006	-5.869	-3.440	-3.440	-3.671	-4.148	-7.052	-4.853	-3.817
	logP	3.307	7.308	5.556	2.506	2.506	2.155	5.054	7.663	3.775	2.463
	logD	2.704	6.163	4.972	2.577	2.577	1.767	3.597	6.329	3.769	2.095

Since campesterol showed the highest suppression of the anti-breast cancer target EGFR, according to docking studies, it was investigated further to estimate the computational ADMET prediction using ADMETlab v.2.0. The ADMET analysis results for the top ten compounds are listed in detail in **Table 2.** The prediction probability values are transformed into six symbols: 0-0.1(---), 0.1-0.3(--), 0.3-0.5(-), 0.5-0.7(+), 0.7-0.9(++), and 0.9-1.0(+++). 1: Apigenin, 2: Campesterol, 3: Diosgenin, 4: Genistein, 5: Prunetin, 6: Quercetin, 7: Racemosol, 8: Beta-Sitosterol, 9: Sominone, 10: Syringetin

CONCLUSION

The study showed how different bioactive phytoconstituents from different Ayurvedic botanicals influence the inhibition of EGFR through in silico studies of the cellular mechanisms. This study also shows that by focusing on the EGFR protein, historically used Ayurvedic herbs with proven anti-cancer properties may be used to treat breast cancer. Bioactives from identified phytoconstituents from reputable Ayurvedic botanicals were discovered using ehanopharmacological screening using a networking technique.The network findings' experimental validation will help bioactive formulation-based drug discovery and provide insight into the mechanism underlying the anti-breast cancer effect.

The docking score showed that, in comparison to a typical synthetic ligand, the evaluated bioactives inhibited the target with good binding energies and interactions. Docking studies showed that natural bioactive chemicals that have been screened have better ligands because of their stronger molecular interactions. The ADMET profiles of all the phytochemicals that were analyzed were satisfactory. Using additional in silico tools, in vitro and in vivo research, and other approaches the screened ligands can be thoroughly characterized for to breast cancer treatment and prevention.

DECLARATIONS

No declarations

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest

REFERENCES

1. Mukherjee PK, Harwansh RK, Bahadur S, Banerjee S, Kar A, Chanda J, Biswas S, Ahmmed SM, Katiyar CK. Development of Ayurveda-Tradition to trend. J Ethnopharmacol. 2017;197:10-24.
2. Britt KL, Cuzick J, Phillips KA. Key steps for effective breast cancer prevention. Nat Rev Cancer. 2020;20(8):417-436.

3. KüpeliAkkol E, Bardakci H, Barak TH, Aschner M, ŞekerKaratoprak G, Khan H, Hussain Y. Herbal Ingredients in the Prevention of Breast Cancer: Comprehensive Review of Potential Molecular Targets and Role of Natural Products. Oxid Med Cell Longev. 2022; 2022:6044640.
4. Noel B, Singh SK, Lillard JW Jr, Singh R. Role of natural compounds in preventing and treating breast cancer. Front Biosci (Schol Ed). 2020; 12(1):137-160.
5. Rajaram P, Chandra P, Ticku S, Pallavi BK, Rudresh KB, Mansabdar P. Epidermal growth factor receptor: Role in human cancer. Indian J Dent Res. 2017; 28(6):687-694.
6. Gonzalez-Conchas GA, Rodriguez-Romo L, Hernandez-Barajas D, Gonzalez-Guerrero JF, Rodriguez-Fernandez IA, Verdines-Perez A, Templeton AJ, Ocana A, Seruga B, Tannock IF, Amir E, Vera-Badillo FE. Epidermal growth factor receptor overexpression and outcomes in early breast cancer: A systematic review and a meta-analysis. Cancer Treat Rev. 2018; 62:1-8.
7. Sowjanya A, Kumar GS. In-silico and In-vitro Studies on Targeting Tumor Apoptosis by Activating Caspase-3. International Journal of Pharmaceutical Quality Assurance. 2023; 14(3):661-670.
8. Kohli K, Sharma N, Mazumder A. Docking: A Powerful Approach for the Discovery of Anti-cancerous Drugs. International Journal of Drug Delivery Technology. 2021; 11(4):1138-1145.
9. Vivek-Ananth RP, Mohanraj K, Sahoo AK, Samal A. IMPPAT 2.0: An Enhanced and Expanded Phytochemical Atlas of Indian Medicinal Plants. ACS Omega. 2023 Feb 23; 8(9):8827-8845.
10. U.S. Department of Agriculture, Agricultural Research Service. 1992-2016. Dr. Duke's Phytochemical and Ethnobotanical Databases. Home Page, http://phytochem.nal.usda.gov/ http://dx.doi.org/10.15482/USDA.ADC/1239279
11. Kim S, Chen J, Cheng T, Gindulyte A, He J, He S, Li Q, Shoemaker BA, Thiessen PA, Yu B, Zaslavsky L, Zhang J, Bolton EE. PubChem 2023 update. Nucleic Acids Res. 2023 Jan 6; 51(D1):D1373-D1380.
12. Berman HM, Westbrook J, Feng Z, Gilliland G, Bhat TN, Weissig H, Shindyalov IN, Bourne PE. The Protein Data Bank. Nucleic Acids Res. 2000; 28(1):235-42.
13. Gene-disease association data retrieved from DisGeNET v7.0 (https://www.disgenet.org/), Integrative Biomedical Informatics Group GRIB/IMIM/UPF
14. UniProt: the Universal Protein Knowledgebase in 2023 Nucleic Acids Res. 2023; 51:D523–D531.
15. Gilson MK, Liu T, Baitaluk M, Nicola G, Hwang L, Chong J. BindingDB in 2015: A public database for medicinal chemistry, computational chemistry and systems pharmacology. Nucleic Acids Res. 2016; 44(D1):D1045-53.
16. Doncheva NT, Morris JH, Gorodkin J, Jensen LJ. CytoscapeStringApp: Network Analysis and Visualization of Proteomics Data. J Proteome Res. 2019; 18(2):623-632.
17. Morris GM, Huey R, Lindstrom W, Sanner MF, Belew RK, Goodsell DS, Olson AJ. AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. J Comput Chem. 2009; 30(16):2785-91.
18. Wang W, Liu R, Zhu Y, Wang L, Tang Y, Dou B, Tian S, Wang F. YuNü-Jian attenuates diabetes-induced cardiomyopathy: integrating network pharmacology and experimental validation. Front Endocrinol (Lausanne). 2023; 14:1195149.
19. Kumar A, Sharma A, Handu S, Singh J, Naithani M. Molecular docking analysis of piperlongumine with different apoptotic proteins involved in Hepatocellular Carcinoma. Bioinformation. 2021; 17(9):829-833.
20. Cali K, Persaud KC. Modification of an Anopheles gambiae odorant binding protein to create an array of chemical sensors for detection of drugs. Sci Rep. 2020; 10(1):3890.
21. Kashid S, Suttee A, Kadam P, Kasarla R. In-silico Assessment of Potent Immunomodulators from Pimpinellaanisum and its Antioxidant Potential. International Journal of Drug Delivery Technology. 2023; 13(3):864-868.
22. Grewal, A.S., Sharma, N. and Singh, S. (2019). Grewal, A.S., Sharma, N. and Singh, S. (2019). Molecular Docking Investigation of Compounds from SapiumEllipticum (Hochst) Pax as Allosteric Activators of Human Glucokinase. International Journal of Pharmaceutical Quality Assurance 10(4): 571-577.