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Original Article

MOLECULAR DOCKING AND INVESTIGATION OF *BOSWELLIA SERRATA* PHYTOCOMPOUNDS AS CANCER THERAPEUTICS TO TARGET GROWTH FACTOR RECEPTORS: AN *IN SILICO* APPROACH

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ABSTRACT

Objective: *Boswellia serrata* is a plant with a long history of use in traditional medicine, particularly for its anti-inflammatory and anti-cancer properties. Growth factors and their receptors are significant components in the initiation and progression of malignancy, and aberrant functioning of these pathways can result in unrestrained cell division and expansion.

Methods: In this study, an *in silico* approach was used to explore the potential of *Boswellia serrata* phytochemicals as cancer therapeutics to target growth factor receptors. The virtual screening involved molecular docking simulations (PyRx) to predict the binding affinity between the phytochemicals and the receptors.

Results: The seventy-four phytocompounds identified from *Boswellia serrata* were preliminarily screened based on their binding towards growth factor receptors. The ligands demonstrated better binding with the GFR targets, and the binding score less than-7 kcal/mol was considered for further investigation results demonstrated that Alpha-boswellic exhibited strong binding affinity to the receptors, suggesting their potential as targeted cancer therapies. This study provides a foundation for future *in vitro* and *in vivo* experiments to validate the efficacy of these phytochemicals as cancer treatments.

Conclusion: The results suggest that Boswellic acid derivatives from *Boswellia serrata* could be a promising source of new cancer therapies.

Keywords: EGFR, FGFR, ILGFR, PDGFR, VEGFR, Cancer, Phytocompounds

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INTRODUCTION

Cancer is an alarming major health problem, and its burden is escalating globally. Cancer is an intricate condition that can damage different anatomical organs and tissues and can be extremely traumatic for both patients and their families. The World Health Organization (WHO) estimates that cancer will be accountable for around 15 million deaths worldwide by 2025. Cancer represents the second major cause of mortality in India following cardiovascular diseases. It is anticipated that approximately 1.7 million new instances of cancer will be diagnosed in India by 2025. A multifaceted strategy that incorporates tumor mitigation, early diagnosis, and efficient diagnosis is suggested to resolve this dilemma [1].

Growth factors are signaling molecules that are essential for controlling cell growth, differentiation, and survival. These growth factors attach to cell surface proteins called growth factor receptors (GFRs), which transmit signals inside the cell to stimulate cellular activity. While these signaling pathways are critical for normal cellular function, cancer cells may undergo abnormalities of these pathways, which results in uncontrollable proliferation and expansion of the malignant cells. Overexpressed or mutant GFRs activate signaling pathways that promote tumor development and survival in cancer. Overexpressed or mutant GFRs activate signaling pathways that promote tumor development and survival in cancer [2].

Growth factor receptors, such as the EGFR (Epidermal Growth Factor Receptor) [2], FGFR (Fibroblast Growth Factor Receptor) [3], IGF1R (Insulin-like Growth Factor 1 Receptor) [4], PDGFR (Platelet-Derived Growth Factor Receptor) [5], and VEGFR (Vascular Endothelial Growth Factor Receptor) [6], all play critical roles in balanced cellular processes, including cell growth, differentiation, and their deregulation, however, can promote the onset and advancement of cancer. The discovery of chemotherapeutics progressively targets the GFRs and the signal transduction pathway proteins. Prevailing cancer therapeutics include immunotherapies and specific molecular inhibitors that directly target respective GFRs and their ligands. Even though these treatments have shown promising results in terms of strengthening immune response, the emergence of drug sensitivity is a significant obstacle to the effective and sustainable treatment of cancer [7].

It has been demonstrated that plant-based chemicals with anti-cancer potential include flavonoids, carotenoids, and polyphenols. These substances alter several signaling pathways involved in cell viability, development, and death to prevent the growth and metastasis of tumors. Plant-based substances are a compelling substitute as they have demonstrated fewer adverse effects than conventional treatments [8]. The capability to address numerous signaling pathways, as opposed to just one, is one of the benefits of plant-based medicines over synthetic pharmaceuticals. As a result, cancers are less likely to become resistant to substances derived from plants. Plant-based substances are more readily available and less expensive than many synthetic medications since they are frequently sold as dietary supplements or herbal treatments. The ability of plant-based substances to be used with other therapeutic modalities, like chemotherapy and radiation therapy, are their additional benefits. This method can improve the effectiveness of conventional cancer medicines while minimizing their adverse effects [9, 10].

Boswellia serrata is an Indian native tree, and its resin contains phytochemicals that have been demonstrated to have anti-cancer potential. By blocking multiple signaling pathways associated with the initiation and progression of cancer, the active components, known as boswellic acids, can cause apoptosis (programmed cell death) in cancer cells. It has been discovered that boswellic acids reduce the activity of several transcription factors, including NF-B, AP-1, and STAT3, which are responsible for controlling the expression of genes that support cancer cell survival, proliferation, and metastasis. According to studies, *Boswellia serrata* extracts can

impede the development of several cancer cell types, including breast, prostate, and colorectal cancer [11, 12]. *Boswellia serrata* extracts have also been demonstrated in clinical research to enhance the quality of life and alleviate pain in cancer patients. Therefore, in the present research, we have investigated the therapeutic efficacy of *Boswellia serrata* phytocompounds through *in silico* docking and pharmacological studies as a potential inhibitor of growth factor receptors as these metabolites hold potential as a safe and effective approach to cancer treatment, and their ability to target multiple signaling pathways makes them a promising area of research for the future.

MATERIALS AND METHODS

Retrieval of ligands

The secondary metabolites of the medicinal plant *Boswellia serrata* were retrieved from IMPPAT [13] (Indian Medicinal Plants, Phytochemistry and Therapeutics) (https://cb.imsc.res.in/imppat/home) database. A total of seventy-four metabolites were retrieved after removing the duplicates. The canonical SMILES (Simplified Molecular Input Line Entry System) and the 2D SDF (Standard Data Files) were retrieved from the PubChem [14] (https://pubchem.ncbi.nlm.nih.gov/) database for further investigations.

Protein retrieval and purification of the proteins

Owing to the potential role in cell signaling and proliferation the GFRs, including EGFR, FGFR, ILGFR, PDGFR, and VEGFR were appraised as molecular targets in the present study. The 3-dimensional structures of the proteins were downloaded from the RCSB PDB (https://www.rcsb.org/) database [15]. The crystal structure of EGFR (PDB ID: 5UGB), FGFR (PDB ID: 6LVM), ILGFR (PDB ID: 3NW5), PDGFR (PDB ID: 5K5X), and VEGFR (PDB ID: 6GQO) was resolved through X-Ray diffraction techniques at a resolution of 2.53 Å, 2.53 Å, 2.14 Å, 2.17 Å, and 1.87 Å respectively.

All the crystal structures were purified in DS Biovia Discovery Studio Visualizer by eliminating the non-structural water molecules and heteroatoms. To avoid the complexity of the structure only A chains were retained for the present investigation. The structure was further optimized by adding polar hydrogen atoms and the purified structure was used for further analysis.

Protein structure validation

Understanding the 3-dimensional structures is essential for molecular docking as they determine how the ligands interact with the proteins. Therefore, the purified structures of GFRs were validated through web servers, including PDBsum generate [16] (http://www.ebi.ac.uk/thornton-srv/databases/pdbsum/Generate.html), ProSA [17] (https://prosa.services.came.sbg.ac.at/prosa.php), and DS Biovia Discovery Studio.

Molecular docking

The interaction between a small molecule and the protein targets can be evaluated through computational techniques like Molecular docking simulation. The present study has utilized the virtual screening software PyRx to perform molecular docking of *Boswellia serrata* phytocompounds with GFRs. The purified protein structures were assigned as macromolecules as the docking was performed through the AutoDock Vina plugin of PyRx. The 2D SDF files of the ligands were subjected to energy minimization by applying universal force filed (_uff) using OpenBabel chemical file converter tools. The prepared proteins and ligand files were saved in. pdbqt format and the docking parameters were set by setting the GPF (Grid Parameter Files) files. The GPF parameters for the GFRs are documented in table 1. The molecular docking was analyzed based on the binding affinity exhibited by the ligands at zero RMSD (Root Mean Square Deviation) towards the target GFRs [18]. The best-docked complexes were further visualized in DS Biovia Discovery Studio Visualizer for the molecular interaction at the binding pocket of the target proteins [19].

Table 1: GPF parameters for the GFRs

Protein	Grid dimensions (Angstrom)
EGFR	X=56.4491, Y=49.7363, Z=-24.8580
FGFR	X=49.7518, Y=59.6079, Z=52.10.9913
ILGFR	X=61.3457, Y=61.3722, Z=51.8915
PDGFR	X=53.8489, Y=53.6268, Z=39.6648
VEGFR	X=56.3868, Y=60.7911, Z=11.2543

Pharmacological studies

Drug discovery and development can be expedited, making it quicker and more affordable, by identifying the pharmacological and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties of small compounds through *in silico* investigations. Also, it is possible to find drug candidates with a greater probability of success using *in silico* techniques, thereby decreasing the possibility of drug failure [20]. The physicochemical properties, drug-likeness properties, and ADMET properties of the small molecules were evaluated using the ADMETlab 2.0 webserver (https://admetmesh.scbdd.com/) [21]. While the bioactivity of the small molecules toward six major drug classes was predicted with the Molinspiration Cheminformatics server (https://molinspiration.com/cgi-bin/properties) [22].

RESULTS

Retrieval of ligands

Boswellia serrata is an Indian tree that has been employed for decades in Ayurvedic remedies for its anti-inflammatory and analgesic effects. Boswellic acids and terpenoids are the major metabolites present in the tree's resin that have been demonstrated to possess several medicinal properties. Recent findings indicate that the bioactive substances in *Boswellia serrata* have anti-inflammatory and anti-cancer characteristics, suggesting that they may be useful in treating diseases including rheumatoid arthritis and other malignancies. The bioactive compounds have also been shown to have advantageous impacts on the immune system, which may enhance general health and wellness. The ligands from *Boswellia serrata* were retrieved from the IMPPAT database and the structure of the ligands which have exhibited better binding with GFRs are depicted in fig. 1.

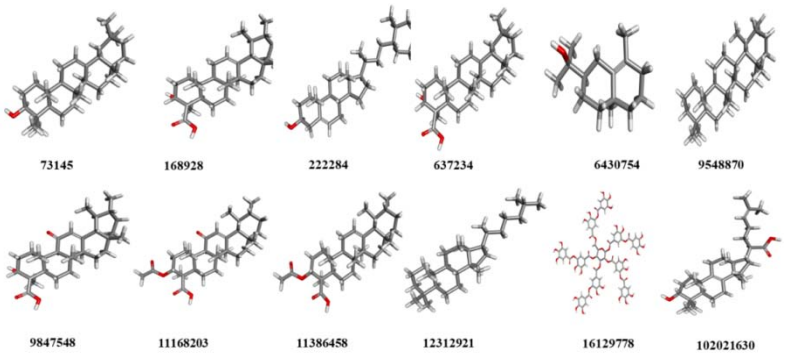

Fig. 1: Structure of top GFR inhibitors of *Boswellia serrata*

Protein structure validation

To successfully perform the molecular docking process, the quality of the protein structures must be determined. To find prospective therapeutic candidates, molecular docking predicts how ligands interact with target proteins. Therefore, the purified protein structures were validated by the following analysis.

Secondary structure and ramachandran plots

The distribution of the dihedral angles is critical in determining protein stability and folding. The Ramachandran plot analysis provides valuable insights into the structural architecture, topology, and irregularities in the protein. Therefore, it is imperative to assess the protein structures before docking. The purified structure (fig. 2a) of EGFR has 85.4% of its residues in the most favored regions, 13.5% in additionally allowed regions, 0.7% in generously allowed regions, and 0.4% in the disallowed regions (fig. 2b). The purified structure of FGFR (fig. 3a) has 89.3% of its residues in the most favored regions, 9.4% in additionally allowed regions, 0.8% in generously allowed regions, and 0.4% in the disallowed region (fig. 3b). The purified structure of ILGFR (fig. 4a) has 88.6% of its residues in the most favored regions, 9.8% in additionally allowed regions, 1.5% in generously allowed regions, and 0.0% in the disallowed region (fig. 4b). The purified structure of PDGFR (fig. 5a) has 94.4% of its residues in the most favored regions, and 5.6% in additionally allowed regions (fig. 5b). The purified structure of VEGFR (fig. 6a). Has 90.7% of its residues in the most favored regions, 9.3% in additionally allowed regions, 0.0% in generously allowed regions, and 0.0% in disallowed regions of the Ramachandran plot (fig. 6b). The secondary structures of the GFRs predominantly have hairpins, beta bulges, sheets, helix-helix interacts, strands, and beta and gamma turns (fig. 2c, 3c 4c, 5c, and 6c).

Hydropathy plots

While identifying druggable proteins it is critical to determine the hydrophobic and hydrophilic amino acids in the targets as the binding affinity of the drug majorly depends on the hydropathicity of the binding pocket. Hydrophobic drugs usually bind to hydrophobic regions of proteins, whereas medications that are hydrophilic bind to hydrophilic areas. A medication may bind securely to hydrophobic areas of proteins if it is too hydrophobic, making it challenging to eliminate from the body and possibly hazardous. On the other hand, overly hydrophilic medications may not attach to their target protein with sufficient vigor, resulting in diminished efficacy. A protein's shape and stability can be impacted by its hydropathicity, which may also have an impact on how well medicines bind to it. For instance, a protein's hydrophobic portions might be hidden within its structure, making them less accessible to medications. The hydropathy graphs typically range from-3 to+3, wherein the positive values represent hydrophobic regions and the negative values represent hydrophilic regions. In the graphs (fig. 2d, 3d, 4d, 5d, and 6d), the peaks above X-axis are more hydrophobic regions. It is evident that GFRs have more hydrophobic regions in them.

ProSA model quality assessment

An online tool for analyzing and validating protein structures based on statistical potentials is the ProSA (Protein Structure Analysis) web server. The Z-score plot, one of the server's outputs, can be used to assess the quality of a protein structure based on how significantly it deviates from the parameters that would be predicted for a protein. Negative Z-scores show areas of the protein that are less structured than projected, whereas positive Z-scores show regions of the protein that is more highly organized than expected. The Z-score plot can be used to discover potential inconsistencies in the protein structure by identifying peaks and valleys. A Z-score of zero denotes a protein region that conforms to the predicted structure for a protein of that size and amino acid makeup. The Z-scores for all the GFRs were between-4.21 to-5.34 and these structures were further considered for docking.

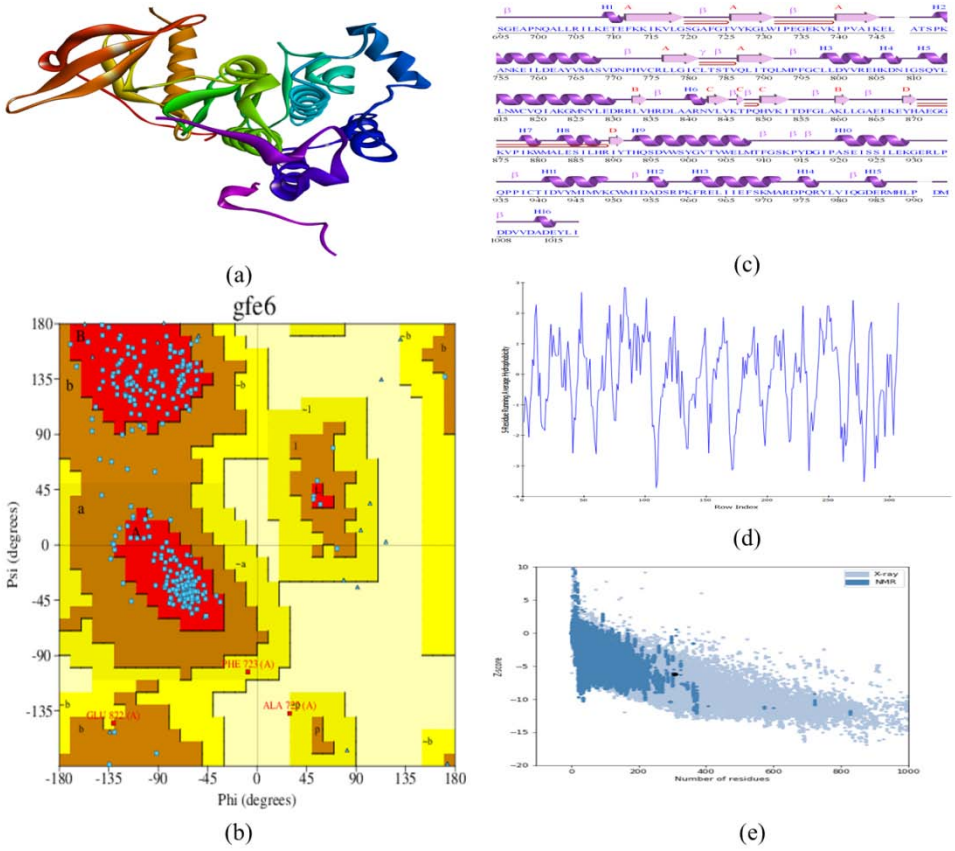

Fig. 2: Secondary structure evaluation of EGFR protein, (a) 3D structure of EGFR (b) Ramachandran plot (c) Secondary structures EGFR (d) Hydropathy plot for EGFR (e) Z-score analysis

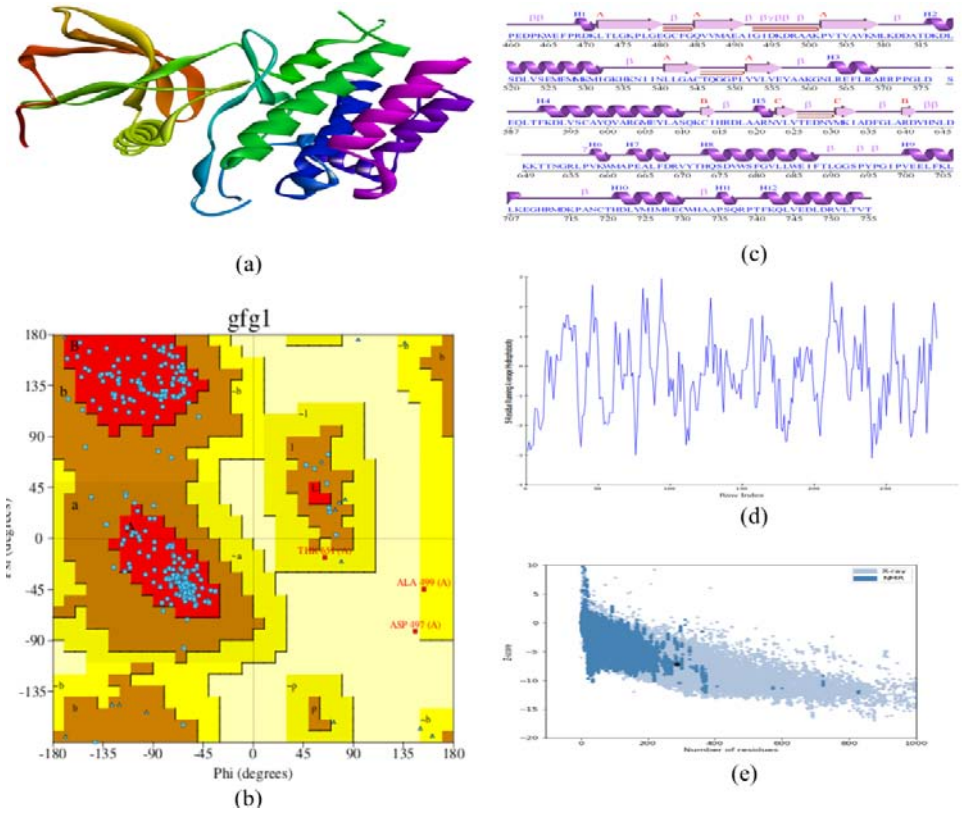

Fig. 3: Secondary structure evaluation of FGFR protein, (a) 3D structure of FGFR (b) Ramachandran plot (c) Secondary structures FGFR (d) Hydropathy plot for FGFR (e) Z-score analysis

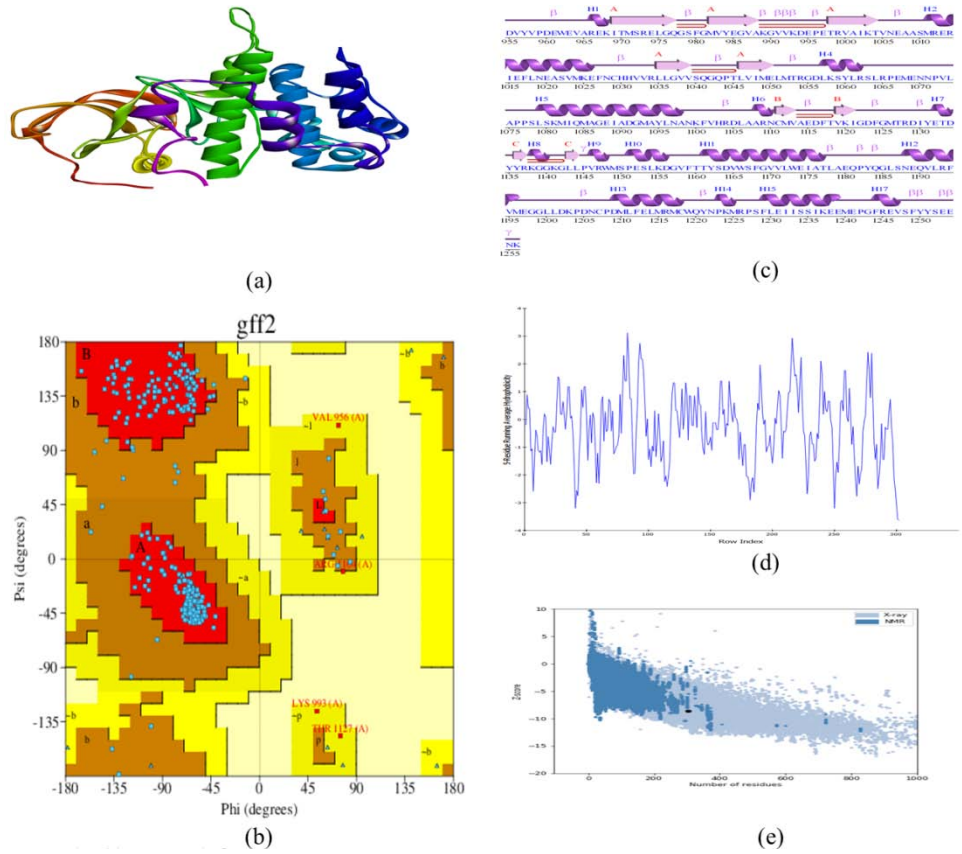

Fig. 4: Secondary structure evaluation of ILGFR protein, (a) 3D structure of ILGFR (b) Ramachandran plot (c) Secondary structures ILGFR (d) Hydropathy plot for ILGFR (e) Z-score analysis

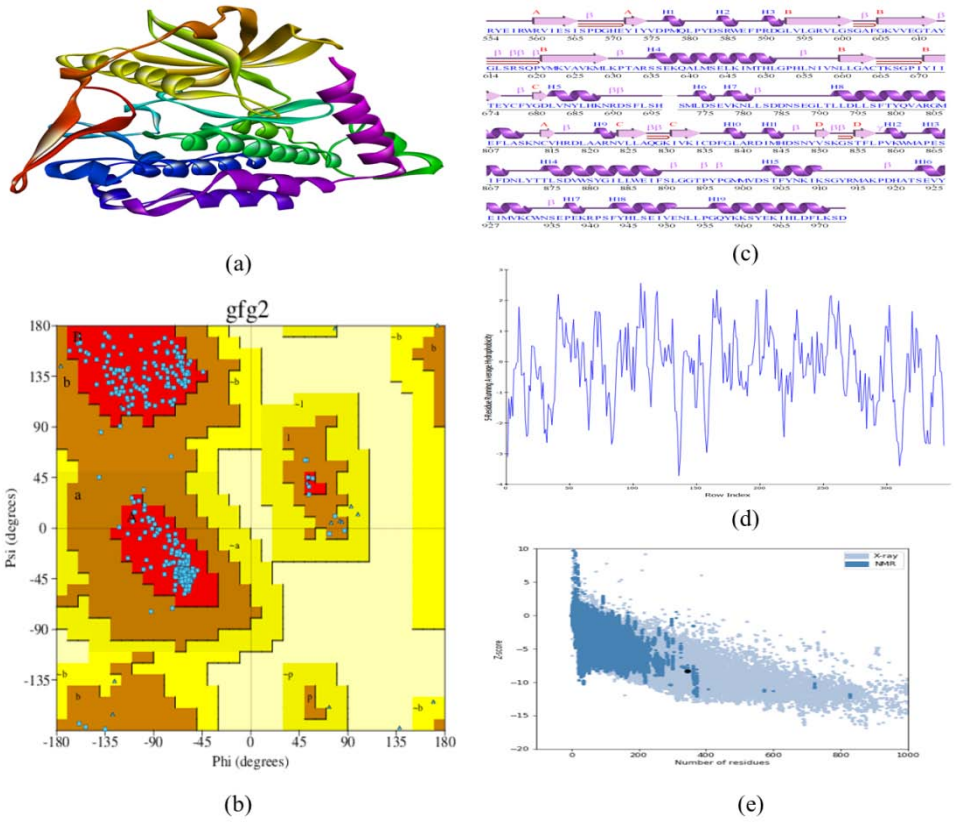

Fig. 5: Secondary structure evaluation of PDGFR protein, (a) 3D structure of PDGFR (b) Ramachandran plot (c) Secondary structures PDGFR (d) Hydropathy plot for PDGFR (e) Z-score analysis

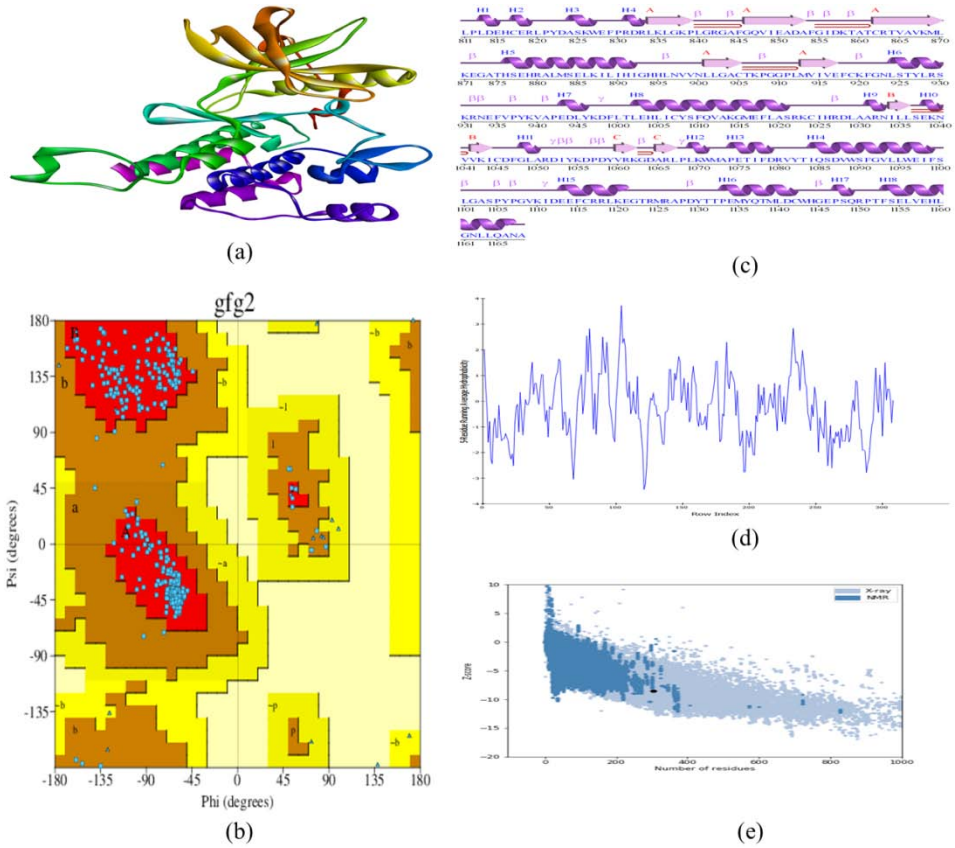

Fig. 6: Secondary structure evaluation of VEGFR protein, (a) 3D structure of VEGFR (b) Ramachandran plot (c) Secondary structures VEGFR (d) Hydropathy plot for VEGFR (e) Z-score analysis

Table 2: Molecular of *Boswellia serrata* phytocompounds with target GFRs

S. No.	Ligand	Pubchem ID	EGFR	FGFR	ILGFR	PGF	VEGFR
1	10-epi-gamma-Eudesmol	6430754	-8.8	-10.5	-9.9	-8.9	-10.7
2	11-Keto-beta-boswellic acid	9847548	-9.7	-10.1	-8.7	-7.4	-9.2
3	3-Acetyl-11-keto-beta-boswellic acid	11168203	-9.7	-9	-8.6	-8.8	-8.9
4	3-Acetyl-beta-boswellic acid	11386458	-14.2	-15.1	-14.3	-13	-13.2
5	3-Hydroxytirucalla-8,24-diene-21-oic acid	102021630	-9.4	-8.7	-7.8	-7.9	-8.9
6	Alpha-Boswellic acid	637234	-14.6	-15.9	-14.8	-13.4	-16.5
7	Beta-Amyrin	73145	-9.1	-9.5	-7. 9	-8.6	-10.6
8	Beta-Boswellic acid	168928	-9.6	-9.6	-8.4	-9.1	-9.6
9	Beta-Sitosterol	222284	-7.8	-9.2	-7.7	-8.3	-9.1
10	Euphane	12312921	-8.3	-8.7	-7.2	-8.4	-8.6
11	Tannic acid	16129778	-9.5	-9.0	-9.1	-9.4	-10
12	Ursane	9548870	-9.2	-10.5	-8.9	-9.4	-8.9

Molecular docking

The docking in PyRx assumes ligands and flexible and the macromolecules as rigid. The efficacy of the ligand is determined in terms of binding affinity at zero RMSD. In the present research, as the ligands demonstrated better binding with the GFR targets, a binding score less than-7 was considered for further investigation (table 2). It was found that Alpha-boswellic acid has a better binding with all the target GFRs.

Visualization

The top 6 ligands that demonstrated the best binding were visualized in DS Biovia Discovery Studio Visualizer. For EGFR the ligand with PubChem CID: 168928, 637234, 9847548, 11168203, 11386458, and 16129778 demonstrated binding less than-9.5 kcal/mol (table 2). From the visualization, it is evident the ligands majorly bonded by establishing hydrogen bonding and other non-covalent interactions predominantly with PHE 723, VAL 726, ALA 743, LEU 844, LYS 745, and ARG 841 (fig. 7).

In the case of FGFR, it was noticed that the ligands with PubChem CID: 168928, 637234, 6430754, 9548870, 9847548, and 11386458 demonstrated binding less than-9.6 kcal/mol (table 2). From the visualization, it was observed that the ligands majorly bonded with VAL 486, ALA 506, LYS 508, ILE 539, VAL 555, GLY 561, and ARG 621 (fig. 8).

For ILGFR it was observed that the ligands with PubChem ID: 647234, 6430754, 9548870, 9847548, 11386458, and 16129778 displayed binding better than-9.0 kcal/mol (table 2). In the visualization, it was observed that ARG 1034, ILE 1130, TYR 1131, GLU 1332, TYR 1135, and LEU 1143 were the major interaction (fig. 9).

The docking studies of PDGFR revealed that the ligands with the PubChem CID: 168928, 637234, 6430754, 9548870, 11386458, and 16129778 demonstrated a binding of-9.1 kcal/mol (table 2). In the visualization, it was noticed that the TRP 586, LEU 615, LEU 661, ASP 836, PHE 969, and SER 972 were the prevalent interactions (fig. 10).

Similarly, VEGFR the ligands with PubChem CID: 73145, 168928, 637234, 6430754, 16129778, and 11386458 demonstrated binding less than-9.6 kcal/mol (table 2). From the visualization, it was evident that VAL 848, ALL 866, HIS 1026, LEU 1035, ASP 1046, and PHE 1047 were the major interactions.

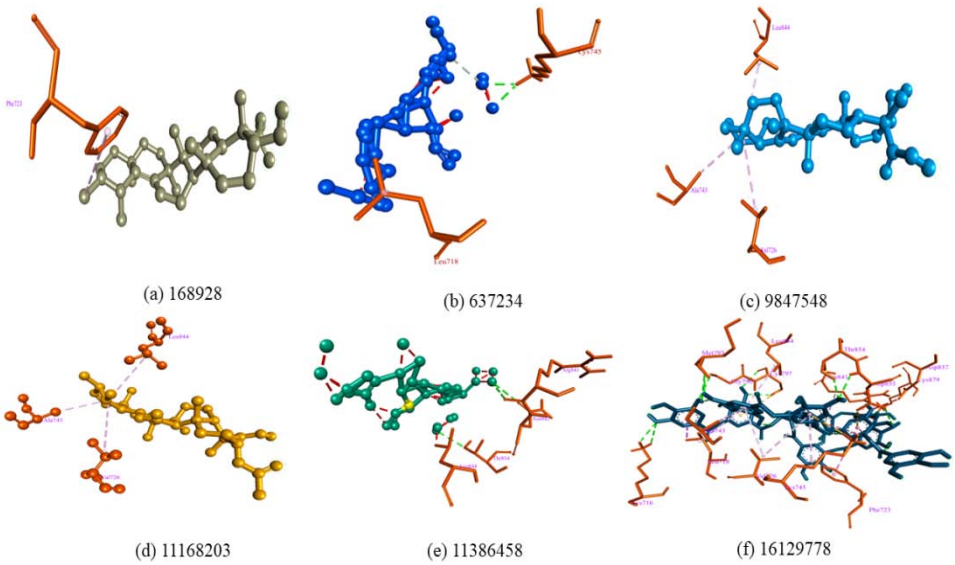

Fig. 7: Molecular interactions of *Boswellia serrata* phytocompounds with target EGFR

Pharmacological studies

The therapeutic potential of *Boswellia serrata* phytocompounds is studied through ADMT properties as the bioactive compounds should possess favorable drug-likeness properties. The top 12 as appraised through docking, were investigated for their physicochemical (table 3), absorption (table 4), Distribution (table 5), medicinal chemistry (table 6) metabolism and excretion (table 7), toxicity properties (table 8) and bioactivity (table 9). From the phrenological assessment, it is evident all the compounds showed advantageous pharmacological properties and bioactivity except compound 16129778.

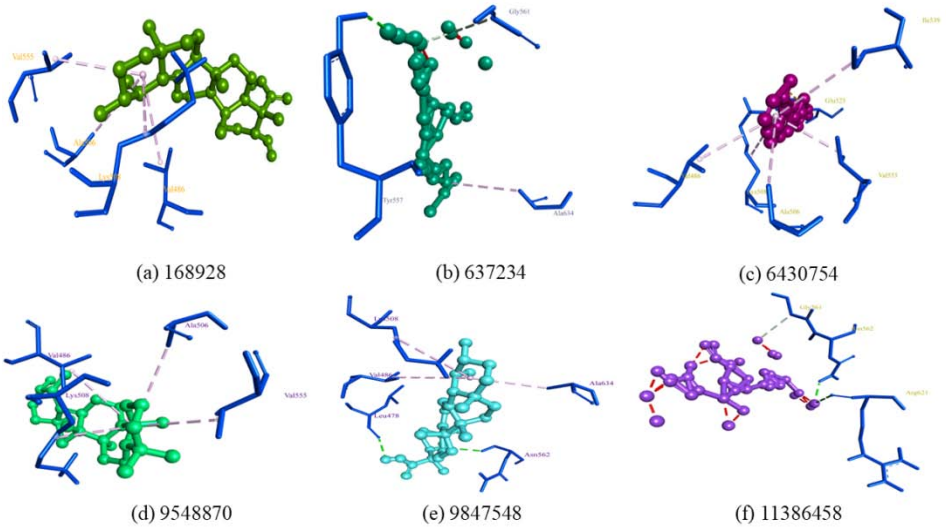

Fig. 8: Molecular interactions of *Boswellia serrata* phytocompounds with target FGFR

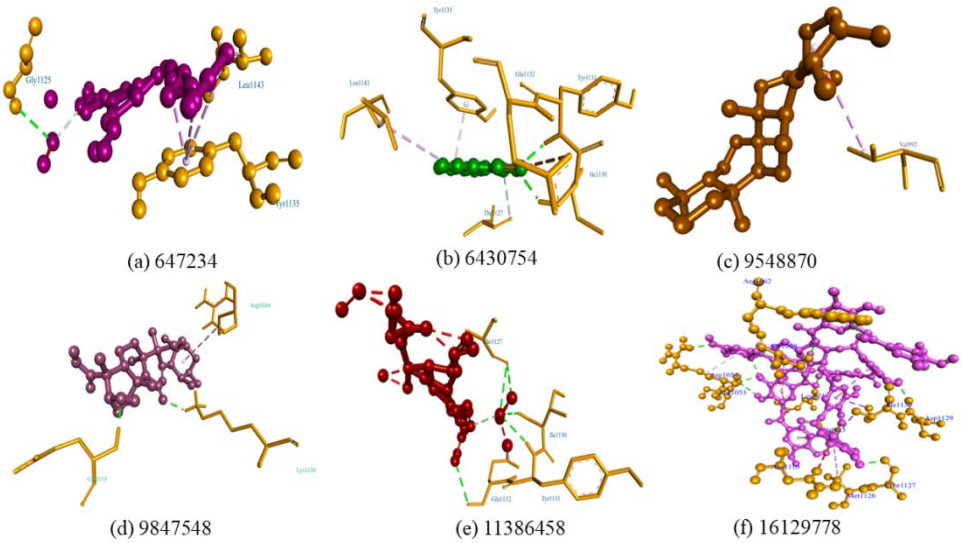

Fig. 9: Molecular interactions of *Boswellia serrata* phytocompounds with target ILGFR

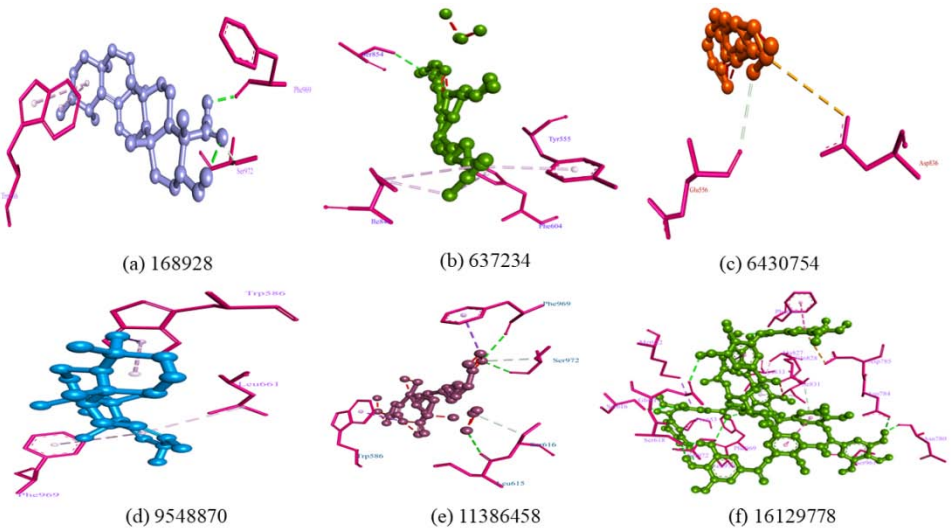

Fig. 10: Molecular interactions of *Boswellia serrata* phytocompounds with target PDGFR

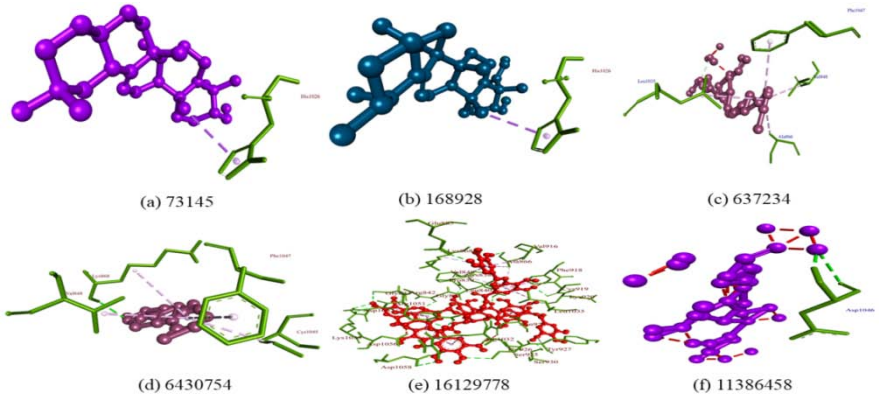

Fig. 11: Molecular interactions of *Boswellia serrata* phytocompounds with target VEGFR

Table 3: Physicochemical properties of anti-cancer *Boswellia serrata* phytocompounds

S. No.	PubChem CID	MW	VOLUME	nHD	nHA	n-Rot	n-Ring	n Het	Flex	TPSA	Log S
1	6430754	222.2	257.037	1	1	1	2	1	0.091	20.23	-3.232
2	9847548	470.34	511.905	2	4	1	5	4	0.036	74.6	-4.721
3	11168203	512.35	552.651	1	5	3	5	5	0.103	80.67	-5.083
4	11386458	498.37	546.497	1	4	3	5	4	0.107	63.6	-5.263
5	102021630	456.36	511.671	2	3	5	4	3	0.227	57.53	-4.014
6	637234	456.36	505.751	2	3	1	5	3	0.037	57.53	-4.278
7	73145	426.39	490.807	1	1	0	5	1	0	20.23	-6.142
8	168928	456.36	505.751	2	3	1	5	3	0.037	57.53	-4.62
9	222284	414.39	482.068	1	1	6	4	1	0.3	20.23	-7.052
10	12312921	414.42	493.21	0	0	5	4	0	0.25	0	-7.577
11	16129778	1700.17	1527.82	25	46	31	11	46	0.408	777.98	1.308
12	9548870	412.41	484.654	0	0	0	5	0	0	0	-7.422

MW: Molecular weight; nHA: Number of hydrogen bond acceptors; nHD: Number of hydrogen bond donors; nRot: Number of rotatable bonds; nRing: Number of rings; nHet: Number of heteroatoms; nRig: Number of rigid bonds: Flex: Flexibility; TPSA: Topological polar surface area; logS: The logarithm of aqueous solubility value

Table 4: Absorption properties of anti-cancer *Boswellia serrata* phytocompounds

S. No.	PubChem CID	Caco-2 permeability	MDCK permeability	Pgp-inhibitor	Pgp-substrate	HIA	F(20%)
1	6430754	-4.489	1.45E-05	0.057	0	0.004	0.144
2	9847548	-5.385	1.71E-05	0.079	0.001	0.029	0.003
3	11168203	-5.14	1.88E-05	0.227	0	0.012	0.033
4	11386458	-5.063	1.56E-05	0.003	0	0.01	0.005
5	102021630	-5.248	1.38E-05	0.026	0	0.013	0.123
6	637234	-5.26	1.17E-05	0.001	0	0.023	0.007
7	73145	-5.034	6.76E-06	0.049	0	0.03	0.257
8	168928	-5.207	1.39E-05	0.002	0	0.013	0.008
9	222284	-4.756	8.63E-06	0.341	0.001	0.004	0.01
10	12312921	-5.045	5.06E-06	0.029	0	0.008	0.084
11	16129778	-7.722	6.22E-06	0.532	0	1	1
12	9548870	-5.114	5.03E-06	0.037	0	0.016	0.343

Caco-2: Caco-2 Permeability; MDCK: Madin–Darby Canine Kidney cells (MDCK) Permeability; Pgp-inh/Pgp-sub: the inhibitor and substrate of P-glycoprotein; HIA: Human intestinal absorption; F(20%): the human oral bioavailability 20%

Table 5: Distribution properties of anti-cancer *Boswellia serrata* phytocompounds

S. No.	PubChem CID	PPB	VD	BBB permeation	FU
1	6430754	94.22%	2.06	0.758	3.24%
2	9847548	97.02%	0.785	0.899	2.71%
3	11168203	99.54%	0.628	0.191	2.93%
4	11386458	100.02%	0.722	0.563	1.99%
5	102021630	96.05%	0.918	0.554	1.88%
6	637234	99.24%	0.869	0.802	3.15%
7	73145	99.78%	1.82	0.749	2.52%
8	168928	99.38%	0.821	0.777	2.25%
9	222284	98.31%	1.963	0.84	1.48%
10	12312921	98.69%	2.892	0.566	1.56%
11	16129778	97.82%	-0.338	0	99.01%
12	9548870	100.12%	2.559	0.369	1.82%

BBB: Blood-brain barrier; PPB: Plasma protein binding; VDss: Volume Distribution; Fu: fraction unbound in plasma

Table 6: Medicinal chemistry properties of anti-cancer *Boswellia serrata* phytocompounds

S. No.	PubChem CID	QED	SA Score	Fsp3	Lipinski rule	PAINS
1	6430754	0.663	3.788	0.867	Accepted	0
2	9847548	0.434	5.168	0.867	Accepted	0
3	11168203	0.41	4.975	0.844	Rejected	0
4	11386458	0.313	4.907	0.875	Accepted	0
5	102021630	0.42	4.708	0.833	Accepted	0
6	637234	0.409	4.745	0.9	Accepted	0
7	73145	0.387	4.56	0.933	Accepted	0
8	168928	0.414	4.869	0.9	Accepted	0
9	222284	0.436	4.388	0.931	Accepted	0
10	12312921	0.42	4.305	1	Accepted	0
11	16129778	0.02	6.542	0.079	Rejected	1
12	9548870	0.372	4.623	1	Accepted	0

QED: A measure of drug-likeness based on the concept of desirability; PAINS: Pan Assay Interference Compounds; Lipinski Rule of 5: Molecular weight less than 500 daltons, nHD<5, nHA<10, and lipohilicity<4.15; Fsp3: the number of sp3 hybridized carbons/total carbon count; SAScore: Synthetic accessibility score were accounted.

Table 7: Metabolism and excretion properties of anti-cancer *Boswellia serrata* phytocompounds

S. No.	PubChem CID	CPYP1A2 inhibitor	CYP1A2 substrate	CYP3A4 inhibitor	CYP3A4 substrate	CL	T (1/2)
1	6430754	0.073	0.554	0.11	0.285	9.095	0.162
2	9847548	0.004	0.7	0.317	0.82	9.864	0.031
3	11168203	0.005	0.55	0.203	0.692	1.636	0.04
4	11386458	0.008	0.421	0.136	0.612	2.325	0.021
5	102021630	0.009	0.464	0.039	0.122	16.249	0.02
6	637234	0.006	0.463	0.109	0.305	4.578	0.024
7	73145	0.021	0.402	0.2	0.522	15.308	0.009
8	168928	0.008	0.609	0.122	0.601	8.354	0.021
9	222284	0.044	0.491	0.202	0.784	16.686	0.013
10	12312921	0.026	0.32	0.187	0.444	11.084	0.007
11	16129778	0.464	0	0	0	12.869	0.998
12	9548870	0.026	0.553	0.173	0.717	15.307	0.008

CL: Clearance rate; T1/2: Half-life of the small molecules.

Table 8: Toxicity endpoints of anti-cancer *Boswellia serrata* phytocompounds

S. No.	PubChem CID	hEGR Blockers	DILI	AMES Toxicity	Carcinogenicity	IGC50	LC50 FM
1	6430754	0.007	0.02	0.004	0.073	3.098	3.276
2	9847548	0.002	0.071	0.043	0.028	4.661	5.436
3	11168203	0.001	0.03	0.023	0.043	5.271	6.39
4	11386458	0.001	0.031	0.014	0.063	5.132	6.174
5	102021630	0.011	0.008	0.01	0.028	4.404	5.413
6	637234	0.002	0.009	0.024	0.061	5.028	5.79
7	73145	0.004	0.008	0.018	0.017	5.442	6.786
8	168928	0.001	0.014	0.014	0.058	5.049	5.849
9	222284	0.049	0.203	0.026	0.047	4.984	5.365
10	12312921	0.104	0.134	0.028	0.007	5.566	6.431
11	16129778	0.001	0.961	0.007	0.001	4.107	4.04
12	9548870	0.026	0.029	0.035	0.008	5.579	6.743

hERG: The human ether-a-go-go related gene; DILI: Drug-induced liver injury; AMES: The Ames test for mutagenicity; LC50 FM: 96-hour fathead minnow LC_{50} were examined.

Table 9: Evaluation of the bioactivity of anti-cancer *Boswellia serrata* phytocompounds

S. No.	Pubchem ID	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1	6430754	-0.29	0.2	-0.81	0.53	-0.32	0.4
2	9847548	0.23	-0.04	-0.63	0.84	0.36	0.36
3	11168203	0.15	-1.1	-0.67	0.74	0.31	0.59
4	11386458	0.16	-0.02	-0.49	0.69	0.28	0.56
5	102021630	0.18	-0.04	-0.36	0.82	0.09	0.59
6	637234	0.24	-0.01	-0.35	0.67	0.25	0.58
7	73145	0.22	-0.05	-0.31	0.67	0.11	0.56
8	168928	0.24	0.02	-0.44	0.79	0.33	0.62
9	222284	0.14	0.04	-0.51	0.73	0.07	0.51
10	12312921	0.17	0.07	-0.35	0.55	0.02	0.4
11	16129778	-4.06	-4.07	-4.08	-4.08	-4.04	-4.05
12	9548870	0.08	0.04	-0.31	0.44	-0.01	0.29

DISCUSSION

Growth factors are fundamental to the development and proliferation of cancerous cells. These signaling molecules bind to distinct receptor proteins on the surface of cells to promote cell growth, reproduction, and viability. To sustain homeostasis in normal cells, the expression of growth factors is strictly controlled and counterbalanced by other signaling pathways such as tumor suppressor genes and apoptotic pathways. Nevertheless, growth factor activity is dysregulated in cancer cells, resulting in unchecked cell proliferation and division [7].

Many cancer subtypes have been identified to have abnormal activation of growth factor receptors, including EGFR [2], FGFR [3], ILGFR [4], PDGFR [5], and VEGFR [6]. Many processes, including the overexpression of receptors, mutations in the receptor genes, or activation of downstream signaling cascades, can lead to this dysregulation. Angiogenesis, metastasis, persistent cell proliferation, and apoptosis evasion can all result from the aberrant engagement of these receptors. Targeting growth factor signaling has consequently emerged as a possible strategy for chemotherapeutic agents. Drugs that block growth factors have proven effective in the treatment of malignancy, but their administration has a multitude of disadvantages and constraints. Development of drug resistance through changes in the receptor or downstream signaling pathways, activation of compensatory pathways, or overexpression of alternative receptors is a significant deterrent while devising chemotherapeutics. Drugs that block growth factors also have the propensity to be poisonous and have negative consequences. These medications have the potential to disrupt biological and cell signaling processes, resulting in undesirable effects like skin infections, constipation, vertigo, and drug-induced liver toxicity. Several medications, including VEGF inhibitors, can potentially worsen hypertension, thromboembolism, and wound healing. Moreover, growth factor inhibitor drugs are not affordable and need to be administered regularly, which imposes a tremendous financial burden on both patients and healthcare systems [7]. Drugs that suppress growth factors may also have an adverse effect on healthy cells and tissues. Growth factors are essential for many physiological functions, such as tissue regeneration and repair. These procedures may be hampered by growth factor signaling inhibition, which could harm healthy cells and tissues. Moreover, certain malignancies or patient populations may not respond to growth factor inhibitor medications due to the genetic diversity and heterogeneity of cancer cells [2-7].

Plant-based medicines and phytocompounds have demonstrated promise in addressing cancer growth factors. Growth factor inhibitors include several substances derived from natural sources, such as EGFR, FGFR, and VEGFR. In comparison to synthetic pharmaceuticals, plant-based medications and phytocompounds have a lower potential for toxicity and side effects. These substances may also be more readily available and less expensive because they can be obtained from plants or by growing crops. Moreover, plant-based medications sometimes target several pathways at once, which results in a more thorough prevention of cancer cell growth and progression [8].

Boswellia serrata, popularly known as Indian frankincense, is a plant indigenous to India and the Middle East that has long been valued for its anti-inflammatory and anti-cancer effects in traditional medicine [11]. Boswellic acids are among the major phytocompounds found in the resin of the *Boswellia serrata* tree, and research has indicated that they may be useful in preventing cancer by targeting GFRs [20, 23]. Hence, we are currently focusing on EGFR, FGFR, ILGFR, PDGFR, and VEGFR targets with *Boswellia serrata* secondary compounds. According to previous scientific studies, the protein EGFR, which is found on the surface of cells, is abundantly expressed in several cancers, which results in continuous stimulation of signaling pathways that support cell survival, proliferation, and invasion [2]. Angiogenesis and uncontrolled cell proliferation can result from abnormally activated FGFR signaling, which supports the growth and progression of tumors [3]. It has been demonstrated that blocking IGF1R signaling decreases tumor development and improves chemotherapy sensitivity. PDGFR is a family of two subtypes (PDGFR-α and PDGFR-β) that are activated by platelet-derived growth factors. Many cancers, including glioblastoma, gastrointestinal stromal tumors, and chronic myeloid leukemia, have been linked to the dysregulation of PDGFR signaling [5]. Angiogenesis, the process by which new blood vessels are generated to deliver nutrition and oxygen to tumor cells, is predominantly mediated by VEGFR signaling pathways [6].

Therefore, owing to the indispensable functional roles of growth factors in cancer pathogenesis, the growth factor receptors were appraised as potential targets in the present study. It was found that the *Boswellia serrata* phytocompounds, including 10-epi-gamma-Eudesmol (6430754), 11-Keto-beta-boswellic acid (9847548), 3-Acetyl-11-keto-beta-boswellic acid (11168203), 3-Acetyl-beta-boswellic acid (11386458), 3-Hydroxytirucalla-8,24-diene-21-oic acid (102021630), Alpha-Boswellic acid (637234), Beta-Amyrin (73145), Beta-Boswellic acid (168928), Beta-Sitosterol (222284), Euphane (12312921), Tannic acid (16129778), and Ursane (9548870) were among the top phytocompounds that have demonstrated better binding (table 2) (fig. 7-11) and advantageous pharmacological properties (Tables 3-9) with the target protein. Among the *Boswellia serrata* phytocompounds, the boswellic acids and their derivatives were the major class of compounds that significantly inhibited the GFRs. From the results of the present study, it is evident that the compound Alpha-boswellic acid displayed significantly better inhibition than the other compounds. The findings from past research have corroborated the fact that Alpha-boswellic acids have the potential to alleviate cancer-associated clinical symptoms as they have anti-inflammatory potential and could be administered as an analgesic with cancer chemotherapy [20, 24]. Additionally, they can modulate multiple signaling pathways governed by GFRs and cytokines, induce apoptosis, and inhibits angiogenesis. Therefore, Alpha-boswellic acid could be a novel candidate to address GFRs mediated cancers.

CONCLUSION

Growth factors and their receptors are significant components in the initiation and progression of malignancy, and aberrant functioning of these pathways can result in unrestrained cell division and expansion. Targeting GFRs has emerged as a viable strategy for cancer treatment, and preclinical and clinical investigations have shown tremendous promise for the development of medicines that suppress GFRs and their downstream signaling pathways. The use of *Boswellia serrata* in Ayurveda highlights the importance of traditional herbal medicine in promoting health and treating illness. Scientific research has shown the potential health benefits of this ancient remedy, which has led to increased interest in its use in modern medicine. The current research presents Alpha-boswellic acid as a potential anti-cancer agent as it may also be beneficial in alleviating cancer-related symptoms and related disorders. However, additional study is required to completely comprehend its mechanisms of action and possible clinical uses.

LIST OF ABBREVIATIONS

WHO-World Health Organization, GFRs-Growth Factor Receptors, EGFR-Epidermal Growth Factor Receptor, FGFR-Fibroblast Growth Factor Receptor, ILGFR-Insulin-like Growth Factor 1 Receptor, PDGFR-Platelet-Derived Growth Factor Receptor, VEGFR-Vascular Endothelial Growth Factor Receptor, SMILES-Simplified Molecular Input Line Entry System, SDF-Standard Data Files, GPF-Grid Parameter Files, RMSD-Root Mean Square Deviation, ProSA-Protein Structure Analysis.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest

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