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EGFR-Pathway Inhibiting Anticancer Mechanisms of Pteridophytic Bioactive Compounds: A Network Pharmacology and Molecular docking Approach

RAJNI SAWANNY, KRISHAN KANT, PRIYA BANSAL, SURYA PRAKASH, SIDDHI GUPTA and ABHISHEK KUMAR*

KIET School of Pharmacy, KIET Group of Institutions, Delhi-NCR, Ghaziabad-201206, U.P., India.
*Corresponding author E-mail: imabhishek12321@gmail.com

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ABSTRACT

This study used network pharmacology and molecular docking to assess the anticancer potential of Polypodiaceae pteridophytes. Key bioactive compounds were discovered and assessed for pharmacokinetics, target prediction, and pathway involvement. A compound-target network identified 246 common targets with substantial interaction patterns. Enrichment analysis identified EGFR signaling as a key route. Docking demonstrated the high binding of drugs to targets such as AKT1, SRC, and EGFR. The findings show that Polypodiaceae components offer potential as anticancer drugs, which justifies additional experimental confirmation.

Keywords: Polypodiaceae, Network pharmacology, Molecular docking, Skin cancer.

INTRODUCTION

One in four individuals will likely receive a cancer diagnosis at some point in their lives, making it a significant global health concern. Every year, more than 1.1 million new cases are recorded in India alone. Cancer is categorized according to the origin of the impacted cells or tissues, such as melanoma, leukemia, or carcinoma, and can be caused by either internal or external sources. Sun ultraviolet (SUV) radiation is the main risk factor for skin cancer, which is the most prevalent kind and is mostly classified as either squamous cell carcinoma (SCC) or basal cell carcinoma (BCC)[1-2]. Cancer development involves several signaling pathways, including EGFR, SRC, PI3K/AKT/mTOR, MAPK, Wnt/β-catenin, p53, TGF-β, Notch, Hedgehog, JAK/STAT, and VEGF. Early identification makes cancer extremely curable, generally with surgery, chemotherapy, radiation, or targeted treatments[3,4].

[1]In addition to synthetic cancer therapies, herbal, Compounds produced from plants, and herbs are extensively studied for their anticancer qualities; they frequently provide a variety of mechanisms that might boost immune responses, stop tumor development, and trigger apoptosis. Polyphenols, flavonoids, and alkaloids—found in plants like garlic, green tea, and turmeric—are often-researched substances. These natural compounds

are considered promising therapeutic agents in cancer treatment due to their cost-effectiveness and lower toxicity profile than traditional chemotherapy[5]. Numerous potent anticancer treatments currently in use are found in nature, including some medications derived from plants as well as medications with microbial origins, including doxorubicin, dactomycin, and bleomycin. Of these, the USFDA has authorized many plant-derived anticancer agents. Taxol (Paclitaxel), Taxotere (Docetaxel), Vincristine, Navelbine, Etoposide, Teniposide, Topotecan, and Irinotecan are a few examples of anticancer agents obtained from nature.[6]

Pteridophytes, particularly ferns, are emerging as important sources of bioactive molecules with anticancer properties. They include flavonoids, alkaloids, terpenoids, and other metabolites that have antioxidative, anti-inflammatory, antiproliferative, and pro-apoptotic properties. These plants, particularly Himalayan species, have long been utilized in India for a variety of reasons and offer promising natural chemicals for cancer prevention and treatment[7].

A systems biology approach called network pharmacology combines biological networks and multi-target drug discovery to better understand the mechanisms of drug actions. Network pharmacology is very useful for complicated diseases like cancer, diabetes, and neurodegenerative disorders because it focuses on multi-target, multi-pathway interactions rather than the conventional "one drug, one target" approaches. On the other hand, a computational technique for forecasting how a ligand (drug or chemical) will interact with a target protein is called molecular docking, used to predict binding affinity, drug discovery, and rational drug design. When it comes to drug discovery and development, network pharmacology and molecular docking be a potent combo. The current study investigates the anticancer potential of some Pteridophytic bioactive constituents via computational techniques.

MATERIAL AND METHODS

Retrieval Criteria and Prediction

Six Himalayan pteridophytes were found using literature sources such as Google Scholar, PubMed, Taylor & Francis, MEDLINE, NCBI, Elsevier, and Science Direct. Bioactive constituents reported in the literature were retrieved, and their canonical smiles and molecular structure were obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/)[8–10]. Screening of compounds was done by using SwissADME [http://www.swissadme.ch] with two parameters (Lipinski rule of five with 0 and 1 violation and bioavailability score≥0.55)[11-13] Click or tap here to enter text. ProTox 3.0 (Tox-Prediction) [https://tox.charite.de/protox3/] and Way 2 Drug https://www.way2drug.com/adverpred/ were utilized to screen compounds based on Organ Toxicity, toxicity endpoints[14] and the adverse effects of compounds, respectively.

Drug and Skin Cancer Targets

The Swiss target prediction database [http://www.swisstargetprediction.ch/] was used to predict the drug targets having a probability>0.DisgeNet [https://disgenet.com/], Genecard [https://www.genecards.org/], Omim [https://www.omim.org/], and Uniprot [https://www.uniprot.org/] databases were explored for screening of potential skin cancer targets by utilizingkeywords “skin cancer” and “Melanoma”. Combined targets of all the databases are considered as SC linked targets and further utilized in network analysis. Swiss Target Prediction identifies probable biological targets for small compounds based on chemical structure. Useful for determining compound-target interactions. DisGeNET provides gene-disease correlations. Helps discover genes associated with certain illnesses, like as cancer, which aids with target validation. Gene Cards provides a comprehensive database of human genes. Used to find gene functions, expressions, and illness relationships that are important to drug-target networks. The OMIM (Online Mendelian Inheritance in Man) database provides thorough information on genetic illnesses and gene-phenotype correlations. Helps to understand the genetic basis of illnesses in the network. UniProt is a protein sequence and function database. Used to gather precise protein data, which is required for the development of protein-protein interaction (PPI) networks.

Protein-Protein Interaction Network (PPI)

Drug and skin cancer-associated common targets were obtained with the help of Venny (v2.10) (https://bioinfogp.cnb.csic.es/tools/venny/). These genes represent potential therapeutic targets. PPI network (protein-protein interaction network (ppi) was formed with String 12.0 [https://string-db.org/]. Nodes in the PPI network mainly represent proteins, and edges represent interactions. Cytoscape, an open-source bioinformatics tool [https://cytoscape.org/], was used to analyze key drug targets,

functional pathways, and protein-protein interactions (PPI). Plugin CytoHubba in Cytoscape for identifying the top 10 hub genes and key targets. It assists in analyzing protein-protein interaction (PPI) networks and pinpointing possible drug targets by evaluating network topology, and also shows the top nodes in order of degree.

GO and KEGG Pathway Analysis in David Database

The David database online bioinformatics tool [https://david.ncifcrf.gov/] is utilized for GO enrichment (Gene Ontology), functional annotation, and KEGG pathway analysis (Kyoto Encyclopedia of Genes and Genomes). Biological processes (BP), cellular components (CC), and molecular functions (MF) are critical for elucidating disease mechanisms and drug actions. KEGG pathway analysis aids in identifying relevant pathways and associated proteins, facilitating the selection of potential targets for molecular docking studies. A total of 05 BP, CC, MF, and 10 KEGG pathways were used for further analysis.

Virtual Screening (Multiple Ligands Docking)

Using PyRx [https://pyrx.sourceforge.io/] Python Prescription–Virtual Screening Tool for this computational binding study of ligands and targeted proteins, navigate to the PyRx workspace. Target proteins are selected from the Hub gene present in key skin cancer pathways retrieved from the KEGG pathway for molecular docking, and also to predict how target proteins interact with small molecules and their binding affinity. 3D Structures of target proteins are retrieved from RCSB PDB (Research Collaboratory for Structural Bioinformatics Protein Data Bank) in PDB format [https://www.rcsb.org] is AKT1 (PDB ID:4EKL), which is prepared in BIOVIA Discovery Studio Visualizer 2024 by expunging water molecules, heteroatoms, reference ligands, extra amino acid chains which are unwanted and inclusion of polar hydrogen atoms via biovia, After that, the prepared proteins were saved in PDB format.[15] "SMILES CODES" are taken straight out from PubChem (Public Chemical Database) for ligands 2D structure construction using ChemDraw Ultra 12.0 Fig. 1. A user-friendly interface for in-depth 2D and 3D protein-ligand interaction visualization and analysis is provided by BIOVIA Discovery Studio Visualizer 2024 [https://www.3ds.com/products/biovia/discovery-studio][16].

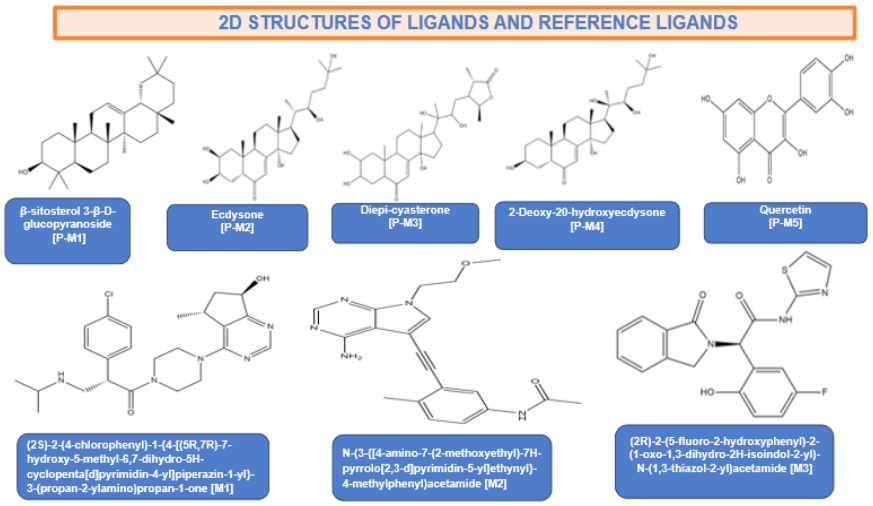

Fig. 1. 2D structures of bioactive constituents and reference ligands [M1, M2, M3].

RESULTS

Retrieval Criteria and Prediction

From PubChem, smile codes are retrieved for all 91 compounds of six plants after screening of these compounds via SWISSADME, only 5 compounds of four Polypodiaceae plants followed the Lipinski rule of five 0 and 1 (MW>500) violation, and bioavailability score ≥0.55 violation. Further, 58 molecules were screened using ProTox 3.0 (Tox-Prediction) based on organ toxicity and toxicity endpoints. Additionally, Adverse Effects Prediction was employed to refine the selection, resulting in five compounds with either no adverse effects or minimal toxicity. These five compounds were chosen for further *in-silico* studies are β-sitosterol 3-β-D-glucopyranoside, Ecdysone, 2-Diepi-cyasterone, and Quercetin.

Table 1: List of Bioactive Constituents

Plant name	Bioactive constituents	Mol Id	Molecular formula	Lipinski voilation	Bioavailability score
Drynaria quercifolia	β-sitosterol 3-β-D-glucopyranoside	P-M1	$C_{36}H_{62}O_6$	1	0.55
Phymatosorus scolopendria	Ecdysone	P-M2	$C_{27}H_{44}O_6$	0	0.55
	Diepi-cyasterone	P-M3	$C_{29}H_{44}O_8$	1	0.55
Microsorum punctatum	2-Deoxy-20-hydroxyecdysone	P-M4	$C_{27}H_{44}O_6$	0	0.55
Pyrrosia lingua	Quercetin	P-M5	$C_{15}H_{10}O_7$	0	0.55

Drug and Skin Cancer Targets

251 potential drug targets were identified from five molecules derived from four different plants of the Polypodiaceae family. For skin cancer targets, after eliminating duplicates from the total 21,458 entries, 20,580 unique targets were obtained. These were compiled from multiple databases: DisGeNet (261), GeneCards (19,440), OMIM (244), and UniProt (1,513).

Protein-Protein Interaction Network (PPI)

Narrowing down the most relevant common targets for further analysis by Venny2.1.0. 246 intersected gene targets between drug and skin cancer targets identified, depicted in Fig. 2. STRING is a computational tool designed for predicting and visualizing protein-protein interaction (PPI) networks with an average node degree of 22.6 and 246 nodes and 2816 edges. Network visualization and top 10 Hub gene (AKT1, IL6, TNF, STAT3, SRC, EGFR, ESR1, PPARG, MAPK3, PTGS2) revealed from CytoHubba within Cytoscape software 3.10.3 version. Color coding to highlight the top 10 hub genes red for the highest centrality, yellow for lower applied based on topological analysis, specifically the degree centrality of a gene Fig. 3. There are more interactions with other genes when the degree value is higher, signifying the biological importance of these targets within the network.

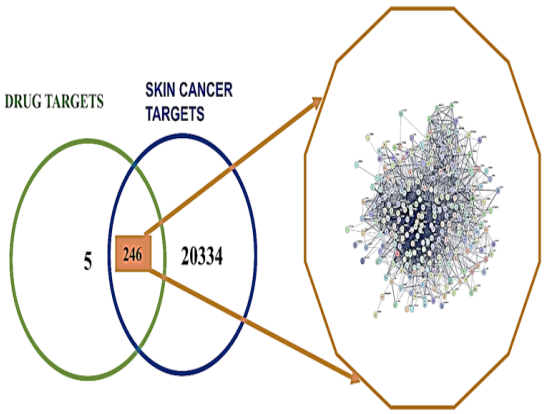

Fig. 2. Venn diagram with PPI network via STRING database

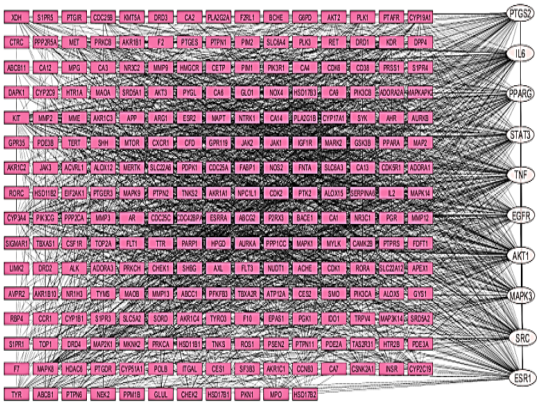

Fig. 3. The PPI network was analyzed and validated using Cytoscape, identifying hub genes through topological parameters to reveal key molecular targets

GO and KEGG Pathway Analysis in David Database

GO analysis of the top 10 hub genes revealed 149 biological processes (BP), 21 cellular components (CC), and 29 molecular functions (MF). This analysis aids in understanding the biological mechanisms of the bioactive constituents of Polypodiaceae plants against skin cancer (SC). The top five BP, CC, and MF terms are visualized as a bubble plot in Fig. 4. KEGG pathway analysis identified 116 pathways, including several associated with skin cancer (SC).

The pathway enrichment results indicate that five bioactive constituents of the Polypodiaceae family may potentially target skin cancer cells, as these pathways are linked to apoptosis, cancer progression, the immune system, and other biological functions. A bubble plot was implemented to display the top ten pathways of KEGG Fig. 4. Among the Top 10 KEGG pathways, the key cancer-related pathway is EGFR tyrosine kinase inhibitor resistance, was prominently identified, which is associated with Hub genes (AKT1, SRC, EGFR). To further investigate their therapeutic role and molecular mechanisms in skin cancer treatment, docking analysis was conducted on these proteins.

Virtual Screening (Multiple Ligands Docking)

Docking of all 5 constituents was done with AKT1 (PDB ID-4EKL), SRC (PDB ID-6WIW), and EGFR (PDB ID-5ZWJ) were carried out and molecular scaffold and amino acid interactions are depicted in Fig. 5-7 respectively. The binding affinity of selected bioactive constituents has a higher value than reference ligands. The results (shown in Table 2) suggest that these molecules may have good anticancer potential and may be further investigated for the exact mechanism.

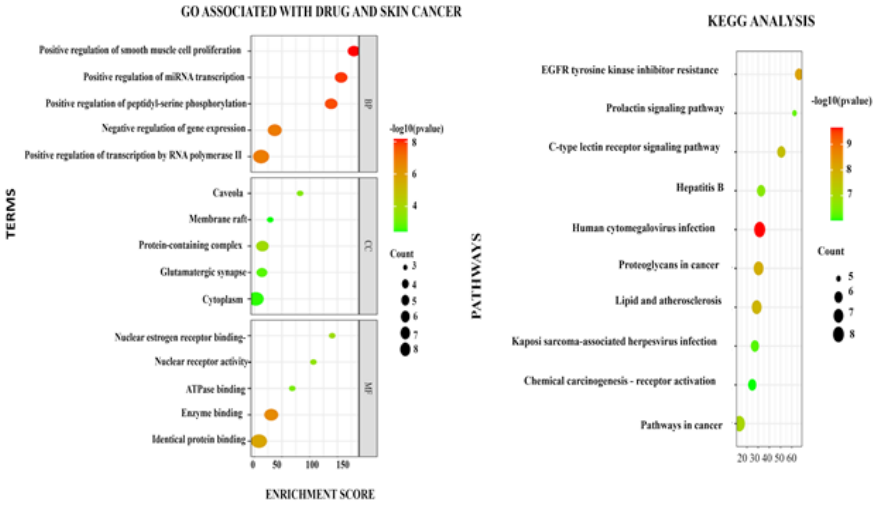

Fig. 4A). Bubble Plot of Top 5 BP, CC, MF Associated with Polypodiaceae Constituents and Skin Cancer, B) Top 10 KEGG Pathways

Table 2: Details of the computational docking model and docking outcomes

Mol. Id Reference Ligand	AKT1[PDB ID-4EKl] M1[-8.1]	SRC[PDB ID-6WIW] M2[-7.3]	EGFR[PDB ID-5ZWJ] M3 [-7.6]
P-M1	-8.9	-10.1	-10.5
P-M2	-9.2	-8.2	-8.5
P-M3	-8.9	-8.8	-8.4
P-M4	-8.2	-8.1	-8.1
P-M5	-8.7	-8.8	-8.1

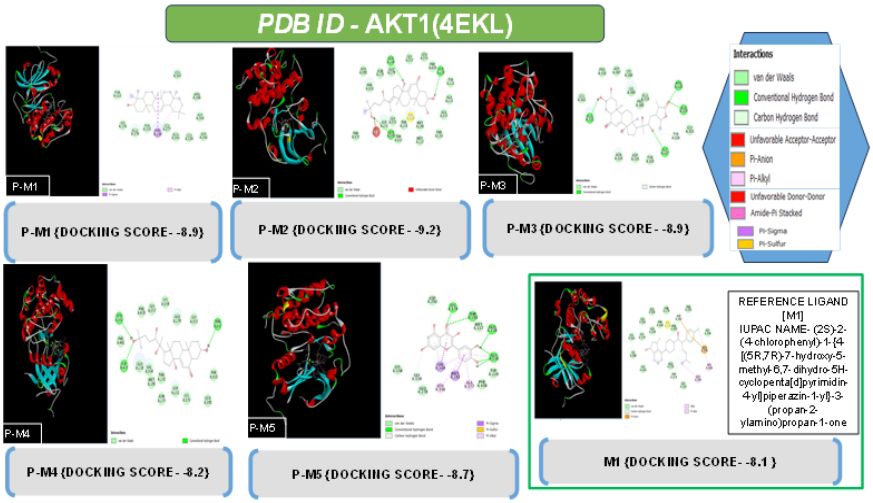

Fig. 5. Molecular interactions and binding conformations of phytoconstituents (P-M1 to P-M5) were analyzed through amino acid interaction with AKT1 protein

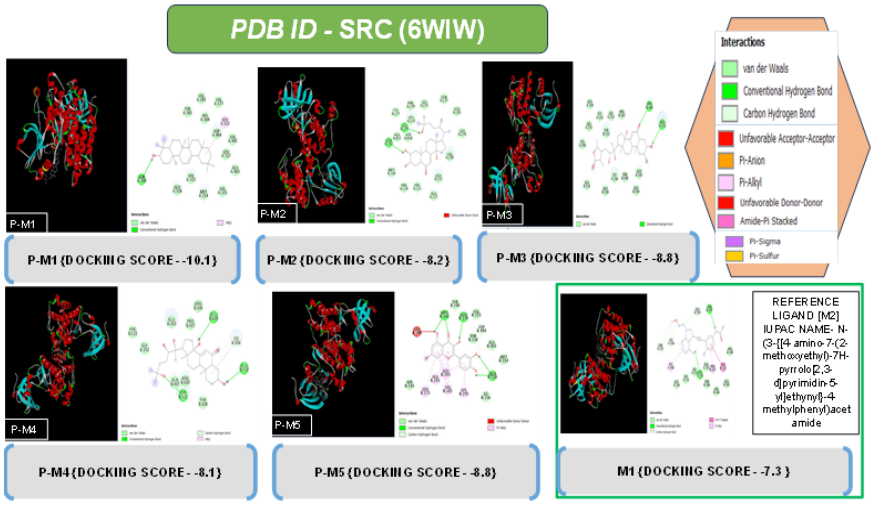

Fig. 6. Molecular interactions and binding conformations of phytoconstituents (P-M1 to P-M5) were analyzed through amino acid interaction with the SRC protein

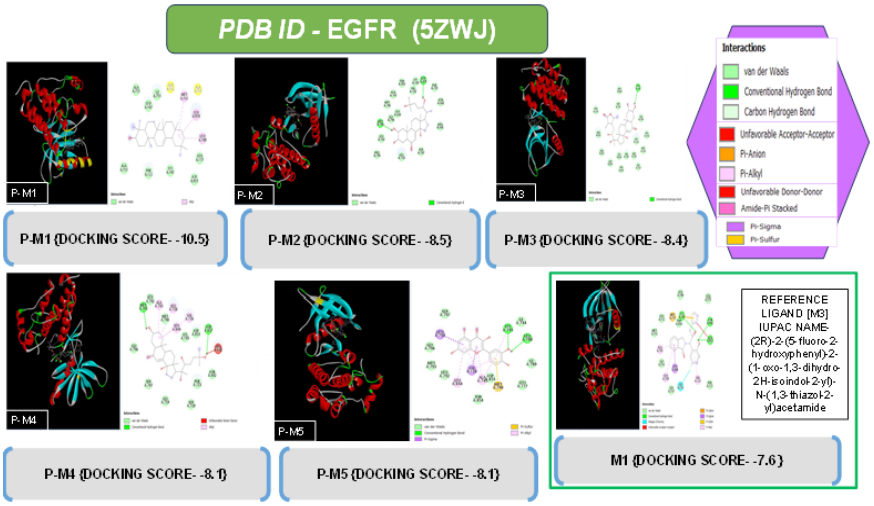

Fig. 7. Molecular interactions and binding conformations of phytoconstituents (P-M1 to P-M5) were analysed through amino acid interaction with the EGFR protein

DISCUSSION

Skin cancer is a critical area of research due to its widespread occurrence and seriousness. The current standard approach for treating skin cancer is the combination of surgery and chemotherapy. Polypodiaceae family bioactive constituents have shown significant promise in treating skin cancer, offering numerous advantages over conventional synthetic treatments and surgical approaches. These plants are rich in bioactive components, including flavonoids, polyphenols, and terpenoids, that have anti-inflammatory, antioxidant, and anti-cancer properties. According to studies, compounds obtained from plants in the Polypodiaceae family may hinder the formation of tumors, stop them from spreading, and strengthen the body's defences against cancerous cells. The natural substances derived from these plants provide a more beneficial therapeutic alternative to manufactured medications, which frequently have a variety of negative consequences. Only five of the 91 phytocompounds were chosen to use network pharmacology and virtual screening to examine their possible mechanism of action against the treatment of skin cancer. According to the study's findings, certain compounds have a high affinity for binding to proteins implicated in the EGFR signaling pathways, which suggests that they could serve as targets for anticancer treatment.

Initially, we identified 5 bioactive molecules from a set of 91 based on Swiss ADME, PROTOX, and Adverse Effect way to prediction parameters. The drug targets of these 5 molecules were obtained from the Swiss Target Prediction database, and after eliminating duplicates, a total of 251 targets were gathered. A total of 20580 skin cancer targets were collected from four databases, such as DisGenet, Gene Card, OMIM, and UniProt. Using Venn analysis, a total of 246 common targets between the drug and skin cancer were identified. To construct a PPI network of these 246 common venny targets STRING database is utilized as nodes (246), edges (2816), and average node degree (22.6). As a result, 10 hub genes [AKT1, IL6, TNF, STAT3, SRC, EGFR, ESR1, PPARG, MAPK3, PTGS2] with the highest degree values were identified from CytoHubba within Cytoscape. For in-depth analysis to explore the functions, roles, and signaling pathways with the Hub genes are retrieved from the David database, which led to the identification of 315 terms categorized into different groups, such as (BP-149), (CC-21), (MF-29), KEGG PATHWAYS (116). The top 5 BP, CC, MF terms and top 10 KEGG signaling pathways are displayed as bubble plots Figure 4.

In BP's top five terms play a crucial role in cancer progression, in which negative regulation of gene expression, positive regulation of peptidyl-serine phosphorylation, positive regulation of miRNA transcription, positive regulation of smooth muscle cell proliferation, and positive regulation of transcription by RNA polymerase II-can all lead to cancer when they are dysregulated. Uncontrolled growth is a characteristic of tumors and is caused by overactive cell proliferation. Oncogenes can be enhanced or tumor-suppressor genes suppressed by abnormal miRNA transcription. Signaling pathways that promote growth and survival can become hyperactivated due to elevated peptidyl-serine phosphorylation. Important tumor suppressor genes may be silenced by negative control of gene expression. Finally, genes that support invasion, angiogenesis, and proliferation-all important processes in the development of cancer-can be upregulated by excessive transcription activation by RNA polymerase II[17-19].

Other Top five terms of CC (protein-containing complex, caveola, glutamatergic synapse, cytoplasm, membrane raft) are also related to cancer progression. Caveolae are small membrane structures that organize and concentrate signaling molecules, impacting different cellular functions. Their involvement in cancer progression is intricate, as they have the potential to either inhibit or encourage tumour growth depending on the circumstances[20]. Glutamatergic synapses, which use glutamate as their main neurotransmitter, have been associated with different factors in cancer development. The glutamate system, encompassing receptors and transporters, contributes to the formation of tumours, infiltration, and metastasis. Glutamate receptors (NMDA) receptors, participate in neuronal signaling and have been connected to the advancement of cancer[21]. The cytoplasm is essential in cancer development, as it enables processes such as autophagy, lysosomal activity, and nucleo-cytoplasmic transport, all of which contribute to tumor growth and spread[22]. Lipid rafts in membranes serve as lipid-centric structures that modulate the organization and activity of various cellular signaling pathways, including those associated with cancer, such as tumor cell proliferation, adhesion, migration, invasion, and programmed cell death[23].

Moreover, top MF terms are also involved in cancer progression. In the advancement of cancer, crucial molecular interactions involving estrogen receptor alpha (ERα) play an important role in tumor formation and spread. The enzyme binding capacity of ERαallows it to modulate gene expression through interactions with enzymes, affecting cellular processes such as proliferation and survival[24]. Furthermore, the binding of identical proteins promotes the dimerization of ERα, increasing its transcriptional activity, which is essential for fostering tumor growth. ERα also interacts with nuclear estrogen receptors inside the cell, specifically targeting estrogen response elements (EREs) in the DNA, thereby regulating genes that are critical for pathways involved in cell proliferation and survival, which are necessary for cancer progression. Functioning as a nuclear receptor, ERα operates as a ligand-activated transcription factor, promoting the expression of genes that further enhance cancer cell growth and spread. Additionally, the ATPase binding ability of ERα engages with ATPases, affecting energy-dependent processes and cellular metabolism, which contributes to the rapid proliferation and viability of cancer cells. These interconnected functions highlight the significant

role of ERα in cancer progression, establishing it as a potential focus for therapeutic strategies[24]. Among the leading 10 KEGG pathways, the EGFR signaling pathway is significantly associated with cancer progression due to its critical function in oncogenic signaling. Following ligand binding, EGFR experiences autophosphorylation, which activates Src kinase, an essential mediator in tumorigenic activities. Src then contributes to the phosphorylation and activation of downstream effectors, including AKT1, which is a vital regulator of cell survival, growth, and metabolic adaptation in cancerous cells. The EGFR–Src–AKT1 signaling pathway is instrumental in fostering malignant transformation, creating resistance to apoptosis, and increasing metastatic potential, thus making it an important target for cancer treatment strategies[25-27]. Based on the findings obtained from network pharmacology and molecular docking it can be anticipated that (P-M1, to P-M5) are the main constituents to work against the AKT1, Src, and EGFR which are found to be the primary targets of skin cancer Fig. 8. It has been determined that the EGFR signaling pathway is the main mechanisms implicated in the therapy among top 10 KEGG pathways. The binding affinity of the key compounds to the primary targets of skin cancer appears to be promising, suggesting that these compounds could have a positive impact on the development of melanoma or skin cancer cells.

CONCLUSION

The EGFR signaling pathway significantly influences the development of cancer. Five compounds out of the 91 bioactive ingredients found in four distinct pteridophyte species showed substantial anticancer potential and higher binding affinities with important EGFR pathway proteins (AKT1, Src, EGFR) than the reference compound AKT1 (PDB ID-4EKL), SRC (PDB ID-6WIW), and EGFR (PDB ID-5ZWJ). These chosen targets' essential roles in the EGFR cancer pathway were validated by molecular docking analysis, indicating their potential therapeutic value in the management of skin cancer. By focusing on these mechanisms, skin cancer therapy approaches may become more innovative. To confirm their effectiveness, more *in-vivo* and *in-vitro* research must be conducted. These substances have great potential for both medicinal uses and cancer research.

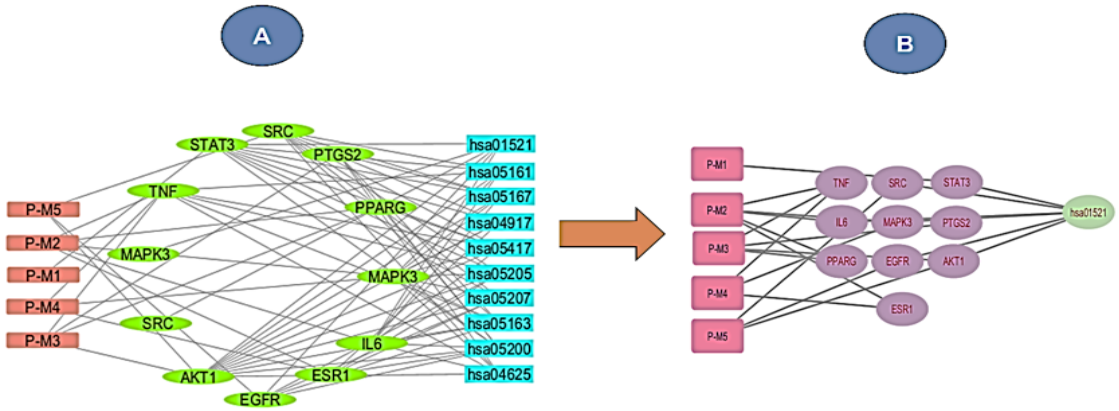

Fig. 8A. Constituent-target-pathways B) Bioactive constituent-target network with EGFR Signalling pathway (hsa01521)

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Conflict of interest

The author declare that we have no conflict of interest.

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