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Exploring the Anticancer Potential of Some Commonly used *Tectaria* Plants through Network Pharmacology and Molecular Docking

Neha Jangid, Muskan Mall, Mohit Sengar, Shivang Mishra, Priya Bansal, Surya Prakash, Krishan Kant, Abhishek Kumar*

KIET School of Pharmacy, KIET Group of Institutions, Delhi-NCR, Ghaziabad-201206, U.P., India

***Corresponding Author:** Dr. Abhishek Kumar*

KIET School of Pharmacy, KIET Group of Institutions, Delhi-NCR, Ghaziabad-201206, U.P., India

Email: imabhishek12321@gmail.com

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ABSTRACT

Objective: To evaluate the anticancer potential of four *Tectariaceae* plants using a network pharmacology approach and identify key molecular mechanisms involved.

Methods: Bioactive compounds were screened via SWISS ADME; targets were predicted using public databases. Overlapping cancer-related targets were analyzed using PPI networks, GO, KEGG, and molecular docking were done to evaluate the mechanism of action.

Result and discussion: Out of 27 compounds, 15 met drug-likeness criteria. 348 overlapping targets were identified; IL-17 and TNF pathways emerged as key anticancer mechanisms. Several compounds showed strong binding affinity (≥ -6 kcal/mol) against targets like 6ESM, 51KV, 2ZOQ, and 1RE1, indicating promising anticancer activity.

Conclusion: The study highlights *Tectariaceae* plants as potential anticancer agents, with multiple bioactive compounds targeting inflammation and immune-related pathways, supporting their role in future drug development.

Keywords: *Anticancer Potential, Tectaria Plants, Network Pharmacology, Molecular Docking*

1. INTRODUCTION

Cancer represents a major global health issue, responsible for one in every six fatalities worldwide. In 2020, it was estimated that there were 19.3 million new cancer cases and around 10 million deaths attributed to the disease across the globe. (1). Cancer is a systemic condition characterized by a gradual disruption of immunological, metabolic, neuroendocrine, and possibly microbial elements, thereby impacting the overall ecosystem of the body (2). As of 2020, skin cancer ranks as the fifth most frequently diagnosed cancer globally, as reported by the World Health Organization. In 2022, the American Academy of Dermatology (AAD) revealed that around 9,500 individuals in the United States receive a skin cancer diagnosis each day.(3) Existing treatment options, including surgery, radiotherapy, traditional chemotherapy, targeted therapy, and immunotherapy, encounter various challenges such as high costs, toxicity, and bioavailability issues, which contribute to reduced effectiveness in treating skin cancer and lower patient adherence to treatment (4). Among the nine primary signaling pathways associated with cancer, seven have been linked to both cancer and stem cells. These pathways include the JAK/STAT pathway, NOTCH signaling pathway, MAP-Kinase/ERK pathway, PI3K/AKT pathway, NFkB pathway, Wnt pathway, and TGFβ pathways (5). Additionally, TH17 cells that secrete IL-17 and TNF have been shown to be abundant in colon and prostate tumors. (6). The utilization of plants for the prevention and treatment of various diseases is prevalent globally. Recent research by the World Health Organization (WHO) indicates that approximately 80% of the global population depends on traditional medicine. (7) Traditional medicine encompasses the utilization of plant along with their active compounds. In fact, numerous anti-cancer agents sourced from plants have been identified over the past few decades. (8). Plants have been crucial in providing effective anti-cancer agents, with more than 60% of the anti-cancer medications in use today originating from natural sources, such as plants, marine life, and microorganisms. The quest for anti-cancer compounds derived from plants began in earnest during the 1950s, marked by the discovery and advancement of vinca alkaloids, specifically vinblastine and vincristine, along with the extraction of cytotoxic podophyllotoxins. The swift discovery of novel proteins that play crucial regulatory roles in the progression of the tumor cell cycle, along with their transformation into targets for high-throughput screening, highlights the importance of compounds derived from plants and other natural sources. These molecules are emerging as a significant reservoir of innovative inhibitors that can modulate the activity of these essential proteins, offering promising avenues for the development of selective anti-cancer therapies.(9)

Pteridophytes are non-flowering plants that reproduce through spores (10). The medicinal properties of pteridophytes have been recognized by humans for over 2000 years, with individuals worldwide employing various parts of these plants to address a range of health issues (11). In recent years, there has been an increasing interest in the exploration of phytochemicals that possess antioxidant, antimicrobial, or anti-inflammatory properties, owing to their potential applications in the treatment of a range of chronic and infectious diseases (12). Tectaria is a terrestrial herb that ranges from medium to large in size. It typically thrives along the cut edges of hills, hillocks, or riverbanks. This plant features an erect, suberect, or creeping rhizome, which can be either short or long, as observed in species such as T. coadunata, T. impressa, T. wightii, and T. herpetocaulos (13). T. coadunata exhibits notable anticancer properties against human leukemic cancer cell lines, suggesting its potential as an effective anticancer agent (14). The rhizome of Tectaria coadunata is utilized in the treatment of gastrointestinal disorders, stomach pain, and for its anthelmintic properties in children. Additionally, fresh rhizome and fronds are effective remedies for insect bites and various other conditions. This study was conducted based on the frequency of applications of the rhizomes of Tectaria coadunata (15). In Ayurveda, the rhizomes of Tectaria cicutaria are utilized to address a diverse range of ailments, including respiratory issues, sprains, rheumatic pain, burns, venomous bites, dental pain, gum problems, and diarrhea. Additionally, in traditional folk medicine, it is employed for conditions such as tonsillitis, mental health issues, and obesity. Both decoctions and infusions are applied in Ayurvedic practices to treat various gynecological disorders and inflammatory conditions (16). Tectaria wightii is utilized for treating insect bites and alleviating discomfort from centipede stings. The extract from its dried rhizome is also employed for its anthelmintic properties, addressing stomach pain, gastrointestinal issues, and the elimination of worms in childrenFresh rhizomes and fronds are utilized for treating insect bites and alleviating discomfort from centipede stings. Additionally, the extraction of dried rhizomes, stems, and stipes is employed in managing respiratory issues such as colds, coughs, asthma, and bronchitis (J. Malviya et al., 2012). A decoction of T. wightii has also been found beneficial for colitis (Upreti et al., 2009). Phytochemical analysis of different extracts from the rhizomes of Tectaria wightii (C. B. Clarke) Ching revealed the presence of various bioactive compounds, including alkaloids, which supports the traditional use of T. wightii rhizomes in treating a range of ailments. (17). T. paradaxa demonstrated a range of biological activities, including anti-ulcer, anti-bacterial, anti-fungal, anti-viral, anti-rheumatic, antioxidant, anti-inflammatory, and anti-cancer properties (18). In this study, the mechanism and bioactive components involved in the treatment of skin cancer were examined through the application of network pharmacology and molecular docking techniques (19). Network pharmacology, which integrates pharmacology and pharmacodynamics, represents an innovative area of research that enables researchers to elucidate the synergistic effects and fundamental mechanisms of various compounds by promoting the assessment of their complex multilevel interactions. Molecular docking is a computational simulation method employed to forecast the binding orientation and strength of interaction between molecules and proteins, in addition to evaluating the nature of these binding interactions. This method is noted for its exceptional precision, affordability, and primary application in drug development and the clarification of biochemical pathways. Numerous research efforts have combined network pharmacology with molecular docking techniques. For example, Network pharmacology and molecular docking techniques were employed to investigate the potential of naringenin as a treatment for cervical cancer. The findings indicated that naringenin could effectively reduce the migration and invasion of cervical cancer cells. (20)

Network pharmacology enables the direct identification of drugs and disease targets from extensive datasets, facilitating an understanding of the mechanisms and pathways that connect them. Commonly utilized tools in network pharmacology include the Protein Data Bank, such as RCSB, as well as databases for drug molecules associated with active ingredients, including PubChem and KEGG. Additionally, there are target databases and gene-related resources like OMIM, DisGeNET, GeneCards, and UniProt, along with protein-related databases such as STRING (21). Molecular docking offers insights into the potential formation of a stable complex between the ligand and receptor. In this study, the molecular mechanisms by which the tecteria plant may contribute to the treatment of skin cancer were assessed using an in silico methodology. The interactions of the target proteins were validated through the application of the molecular docking technique (22). This study aimed to identify the key therapeutic targets and signaling pathways linked to skin cancer, in order to explore how tecteriacea may act as an anticancer agent for this condition. (23)

2. MATERIAL AND METHODS:

The data regarding the phytoconstituents found in *Tectariacea*e leaves were gathered from various literature sources like PubMed, Sci-Hub, Research Gate, Google Scholer.. The canonical SMILES and PubChem ID for each phytoconstituent were sourced from the PubChem database. For those phytoconstituents not listed in the PubChem database, their structures were created using a molecular sketcher based on ChemAxon's Marvin JS. The analysis of ADMET predictions for the compounds was performed utilizing the Swiss ADME database (http://www.swissadme.ch/) and the Lipinski Rule modules. The main aim was to evaluate the pharmacokinetic and pharmacodynamic characteristics of these compounds, focusing on two essential ADME parameters: gastrointestinal absorption and drug likeness (24). The gastrointestinal absorption index reflects the capacity of a drug to be digested and absorbed in the stomach and intestines following oral administration. Meanwhile, the drug likeness index evaluates the potential of a molecule to function as an oral medication in terms of

bioavailability. Consequently, only those compounds exhibiting a high gastrointestinal absorption rate and advantageous drug-likeness were deemed suitable candidates. (25)

Predicting Potential Targets of Bioactives of Tectariaceae:
The canonical SMILES for each phytoconstituent of *Tectariaceae* were utilized to predict their protein targets through the Swiss Target Prediction web tool, available at http://www.swisstargetprediction.ch/. This approach allows us to comprehend these compounds and examine their therapeutic potential by investigating specific targets. These target proteins are instrumental in identifying essential compounds and their biological functions.. (26).

Screening of Disease Target:
Genecards, OMIM, DisGeNET, and UniProt databases were utilized to identify potential disease targets. Duplicate protein targets related to phytoconstituents and skin cancer were eliminated. (27).

Construction of Protein-protein Interaction (PPI) Network:
The overlapping targets of phytoconstituents and disease targets were identified, leading to the creation of a Venn diagram. The intersecting proteins were subsequently uploaded to the STRING database version 12.0 (https://string-db.org). The species selection was restricted to "Homo sapiens," and the resulting file was then exported to Cytoscape software version 3.10.1 to visualize the protein-protein interaction network. (28).

Function Enrichment Analysis:
The drug and skin cancer targets were added to the David database to facilitate GO (Cellular Component, Molecular Function, Biological Process) and KEGG pathway enrichment analyses. The top twenty most significant biological functions and pathways were selected based on gene enrichment and presented through either a histogram or a bubble chart. (29).

Molecular Docking Analysis:
The three-dimensional structures of the proteins have been submitted to the Protein Data Bank (PDB) (https://www.rcsb.org). The corresponding PDB codes are: MMP9-6ESM, CAS93-1RE1, MAPK3-2ZOQ, and PTGS2-51KV. (30).
The three-dimensional structure of the ligand was obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov) in SDF format. The Openbabel graphical user interface was employed to convert the SDF format into PDBQT format. For the visual examination of docking poses, BIOVIA Discovery Studio software was utilized. (31). The process of protein preparation was conducted in the following manner: Ligands and water molecules were removed, polar hydrogens and Kollman charges were incorporatedThe protonation states of the ionizable residues were modified to align with physiological conditions. and subsequently, the proteins were saved in PDB+ format. The conformation of the ligand exhibiting the lowest binding energy was deemed the most stable among the phytoconstituents. Interactions between the proteins and ligands were further analyzed using Discovery Studio, focusing on the docked poses of the ligands at the designated binding sites of the proteins. (32). After conducting docking simulations with the BIOVIA Discovery Studio tool, the complexes were evaluated and ranked according to several criteria, such as binding energy, van der Waals forces, hydrogen bonds, hydrophobic interactions, and other intermolecular forces. The analysis of these complexes aimed to pinpoint potential ligands exhibiting a high binding affinity. (33)

3. RESULT:

Predicting Potential Targets of Bioactives of Tectariaceae:
Total of 4 plants are selected from Tectariaceae family, total 27 bioactive constituents are obtained out of which only 15 follow criteria of oral bioavailability and Lipinski rule. Total of 356 potential target from 15 bioactive constituent were obtained from swiss target prediction.[34]

Table:1 Active constituents with their OB and R05 criteria

S. No.		Mol Code	Name of active constituent	Smile ID	OB Value	R05
1		MTC01	2-propanone	CC(=O)C	0.55	Yes
2		MTC02	dihydroxydimethylsilane	C[Si](C)(O)O	0.55	Yes
3		MTC03	phthalic acid	C1=CC=C(C(=C1)C(=O)O)C(=O)O	0.85	Yes

4		MTC04	Phthalic acid, dibutyl ester	CCCCOC(=O)C1=CC=CC=C1C(=O)OCCCC	0.55	Yes
5		MTC05	Oleic acid, Methyl ester	CCCCCCCC/C=C\CCCCCCCC(=O)OC	0.55	Yes; 1 violation: MLOGP>4.15
6		MTC06	n-Hexadecanoic acid	CCCCCCCCCCCCCCCC(=O)O	0.85	Yes; 1 violation: MLOGP>4.15
7		MTC07	9-Octadecenoic acid	CCCCCCCC/C=C/CCCCCCCC(=O)O	0.85	Yes
8		MTC08	l3-Octadecenal	CCCCCCCCCCCCCC/C=C/CC=O	0.55	Yes
9		MTC09	Heptadecane	CCCCCCCCCCCCCCCCC	0.85	Yes
10	T. coudnate	MTCo01	methyl sterate	CCCCCCCCCCCCCCCCCC(=O)OC	0.85	Yes
11		MTCo02	Decanediol	CCCCCCCCCC(O)O	0.55	Yes
12		MTCo03	Octanoic acid	CCCCCCCC(=O)O	0.17	No; 2 violations: MW>500, MLOGP>4.15
13		MTCo04	Pentadecanoic acid	CCCCCCCCCCCCCCC(=O)O	0.85	Yes; 1 violation: MLOGP>4.15
14		MTCo05	Dihydroagarofuran (cis)	C[C@@H]1CCC[C@]2([C@]13C[C@@H](CC2)C(O3)(C)C)C	0.55	Yes; 1 violation: MLOGP>4.15
15	T. wightii	MTW01	5-Hexen-2-one, 5-methyl-3-methylene	CC(=C)CC(=C)C(=O)C	0.55	Yes
16		MTW02	3, 5-Heptadien-2-one, 6-methyl-, (E)	CC(=C/C=C/C(=O)C)C	0.55	Yes
17		MTW03	Methyl-à-d-ribofuranoside	CO[C@H]1[C@@H]([C@@H]([C@H](O1)CO)O)O	0.55	Yes
18		MTW04	Propanal, 2, 3-dihydroxy-, (S)	C(C(C=O)O)O	0.55	Yes
19		MTW05	á-D-Glucopyranose, 1, 6-anhydro	C1[C@@H]2[C@H]([C@@H]([C@H]([C@H](O1)O2)O[C@@H]3[C@@H]([C@H]([C@@H]([C@H](O3)CO)O)O)O)O)O	0.55	Yes; 1 violation: NHorOH>5

20		MTW06	3-(1-Methylhept-1-enyl)-5-methyl-2, 5- dihydrofuran-2-one	CCCCC/C=C(\C)/C1=CC(OC1=O)C	0.55	Yes
21		MTW07	Hexadecanoic acid, 15-methyl-, methyl ester	CC(C)CCCCCCCCCCCCCC(=O)OC	0.55	Yes; 1 violation: MLOGP>4.15
22		MTW08	9, 12-Octadecadienoic acid, methyl ester, (E,E)-	CCCCC/C=C/C/C=C/CCCCCCCC(=O)OC	0.55	Yes; 1 violation: MLOGP>4.15
23		MTW09	Phytol	C[C@@H](CCC[C@@H](C)CCC/C(=C/CO)/C)CCCC(C)C	0.55	Yes; 1 violation: MLOGP>4.15
24	T. subtriphylla	MTS01	eriodictyol-8-D-glucopyranoside	C1[C@@H](OC2=C(C(=CC(=C2C1=O)O)O)[C@H]3[C@@H]([C@H]([C@@H]([C@H](O3)CO)O)O)O)C4=CC(=C(C=C4)O)O	0.55	Yes
25		MTS02	gallic acid	C1=C(C=C(C(=C1O)O)O)C(=O)O	0.56	Yes
26		MTS03	ellagic acid	C1=C2C3=C(C(=C1O)O)OC(=O)C4=CC(=C(C(=C43)OC2=O)O)O	0.55	Yes
27		MTS04	epicatechin	C1[C@H]([C@H](OC2=CC(=CC(=C21)O)O)C3=CC(=C(C=C3)O)O)O	0.55	Yes

Screening of Disease Target:
19213 disease target genes associated with skin cancer were retrieved using GeneCards, OMIM and DisGeNET platforms. 348 shared common target genes were identified between drug target and disease target by using venny 2.0, list of both disease target and drug target is entered and common target were obtained. This tool is usefull for for creating simple visual comparisons [35]

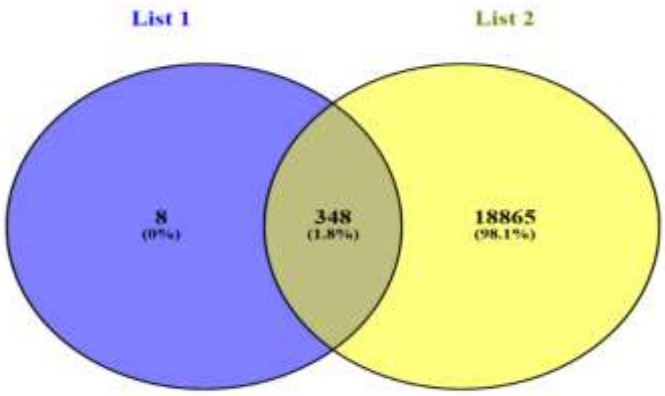


FIG.1: Venny common targets

Construction of Protein-protein Interaction (PPI) Network:
These drug and disease target are used in venny to calculate common targets came out to be 348, These common targets were then entered into the STRING database to analyse the protein-protein interactions, which comprise direct (physical) and indirect (functional) associations, obtained via computational prediction, inter-organismal knowledge transfer, and

associations culled from other databases . The PPI network included 135 nodes connected by 371 edges. The network of string of is visualized using cytoscape (A tool designed to visualize data from a variety of genomic data). The top 10 targets (hereafter referred to as core targets) in the PPI network were identified based on degrees, betweenness, and closeness parameters, following the analysis of the network with the CytoHubba algorithm. [36]

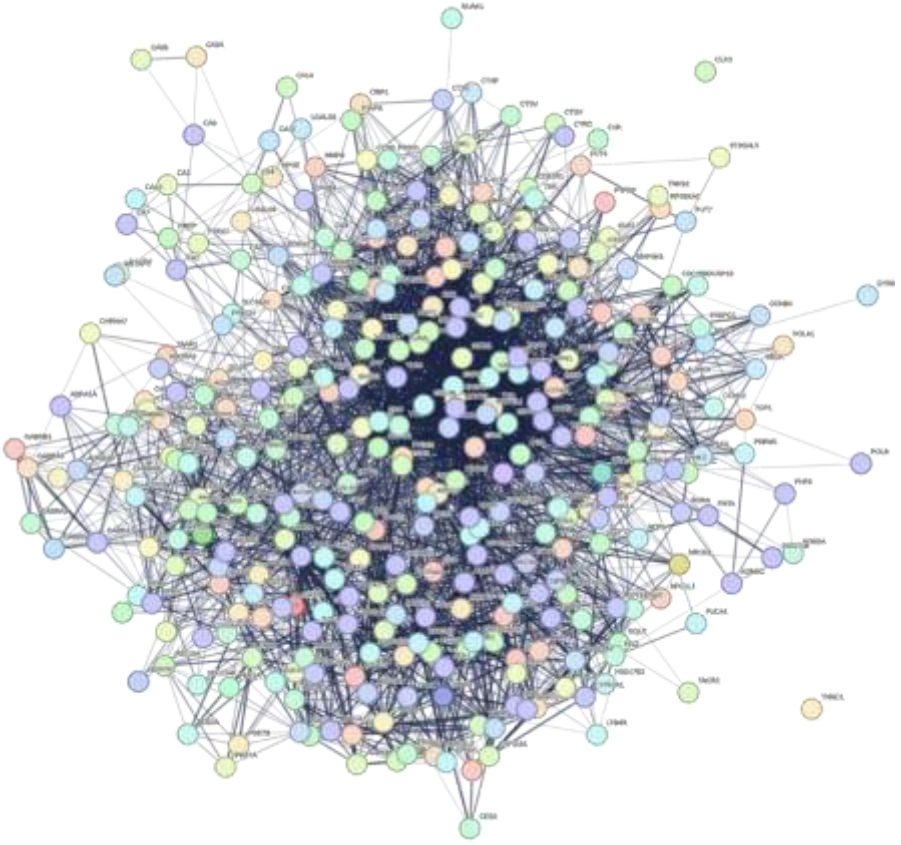


Fig.2: STRING database PPI Network

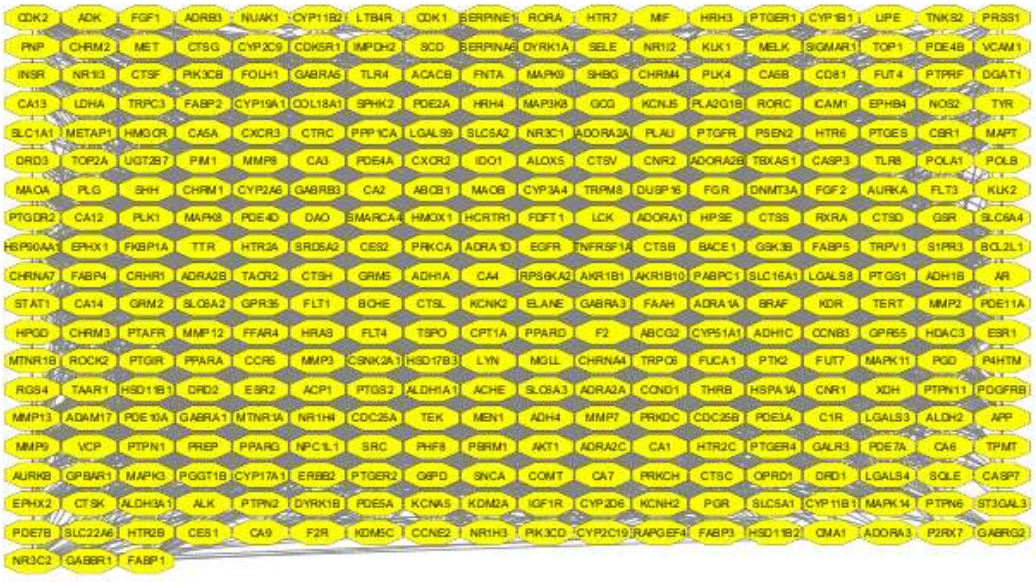


Fig.3: Cytoscape PPI network

Function Enrichment Analysis:

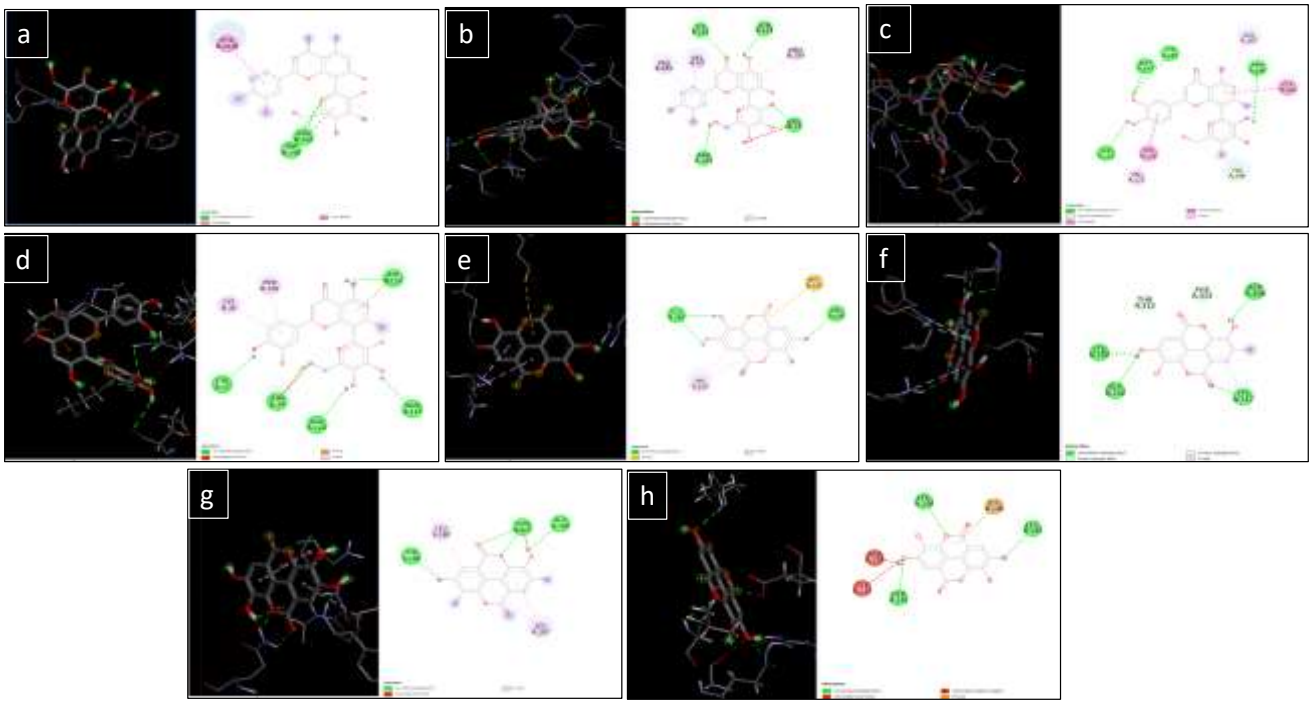
Now by using david database, gene ontology is identified, 90 BP, 19 CC, 27 MF found and targets were found to affect 87 biological pathways by the KEGG pathway enrichment analysis. Enrichment analysis results indicate the significant potential of targets on cancer disease.[37]

Molecular Docking Analysis:

Molecular docking aims to predict the ligand-receptor complex through computer-based methods. The process of docking involves two main steps which include sampling the ligand and utilizing a scoring function [38], Detailed insights into the docking scores and conformations, interactions with MMP9-6ESM, CASP3-1RE1, MAPK3-5UP3, PTGS2-5IKV [39] Molecular analysis confirmed that 13 molecule showed binding affinity equal to or more than -6kcal/mol for 6ESM, 6 molecules showed more than -6kcal/mol for 51KV, 5 molecules showed equal or more than 6kcal/mol for 2ZOQ and 2 molecules showed equal or more than 6kcal/mol for 1RE1.

Table:2 Binding affinity of active constituents

Phytoconstituents	Source	MMP9 – 6ESM Docking score (kcal/mol)	PTGS2-51KV Docking score (kcal/mol)	MAPK-2ZOQ Docking score (kcal/mol)	CASP3 – 1RE1 Docking score (kcal/mol)
MTC03	*T.circuteria*	-7.1	-6.2	-5.7	-5.1
MTC04	*T.circuteria*	-6.8	-6.1	-6.6	-4.6
MTC07	*T.circuteria*	-7.2	-5.3	-5.7	-3.9
MTC08	*T.circuteria*	-6.6	-4.5	-4.7	-3.7
MTC09	*T.circuteria*	-6.1	-5.7	-4.9	-3.8
MTCo01	*T.coadunate*	-6.4	-4.5	-5	-3.6
MTCo02	*T.coadunate*	-6.4	-4.8	-5	-4.4
MTW01	*T.wightii*	-5.7	-5.6	-5.2	-4.1
MTW02	*T.wightii*	-6.2	-4.8	-5.3	-4.1
MTW03	*T.wightii*	-6.2	-5.8	-5.1	-5.2
MTW04	*T.wightii*	-4.1	-4.1	-3.8	-3.2
MTW06	*T.wightii*	-7.8	-6.9	-6.4	-5.4
MTS01	*T.subtriphylla*	-9.4	-8.9	-8.1	-7
MTS02	*T.subtriphylla*	-7	-6.4	-6	-4.9
MTS03	*T.subtriphylla*	-6	-8.9	-8.6	-7.8



(a) MTS01 1RE1 (b) MTS01 2ZOQ (c) MTS01 6ESM (d) MTS01 51KV
(e) MTS03 1RE1 (f) MTS03 2ZOQ (g) MTS03 6ESM (h) MTS03 51KV

4. DISCUSSION:

In this study, we used network pharmacology to investigate the anticancer potential of four *Tecteria* species (T. subtriphylla, T. circuteria, T. wightii and T. coaduntate) against modulating the cancer signal pathway. The main advantage of this approach is that it would allow for the collection of respective biological information on the bioactive components from database such as SWISS ADME, on drug targets and diseases from OMIM, DisGeNet, Gene Cards , and Uniprot database, as well as interaction with a protein-protein database STRING.Consideration of ADME profiling of compounds was treated as an important factors for drugs development. Skin Permeability was chosen to screen ADME properties of compounds. Here to predict toxicity, we used parameters like Mutagenic, Tumorigenic, Irritant, Reproductive effective, Druglikness and Drug score.[40]

Out of the 27 bioactive compounds screened from the potential Tectaria plants from our results, 15 were confirmed to comply with the oral bioavailability criteria and Lipinski's rule. 356 target genes related to drugs were mapped to the above compounds, and 19,213 cancer-associated targets were retrieved. The PPI network analysis was then performed by incorporating drug targets and cancer targets, resulting in a final compound of 348 common targets. This analysis highlighted biological processes, molecular functions, and cellular components associated with the therapy of skin cancer. In GO and KEGG pathway analyses, we found 90 biological processes, 19 cellular components, 27 molecular functions and 87 pathways associated with cancer inhibition.[41]

Matrix metalloproteinases (MMPs), commonly referred to as matrixins, are a group of over 20 metalloenzymes that are structurally and functionally interconnected. These proteinases are essential for various biological functions, including embryonic development, tissue remodeling, wound healing, and the formation of new blood vessels (angiogenesis). They play a significant role in the development of various severe and chronic conditions, including osteoarthritis, rheumatoid arthritis, vascular diseases, and the spread of cancer. MMPs are zinc dependent metalloenzymes. The conserved catalytic domain comprises a catalytic Zn2+ ion, a structural Zn2+ ion, and between one to three structural Ca2+ ions that are essential for the stability of the enzyme. Among the various matrix metalloproteinases (MMPs), gelatinases (MMP-2 and MMP-9) and metalloelastase (MMP-12) play a crucial role in the progression of various significant diseases. Notably, MMP-2 and MMP-9 are especially implicated in the pathogenesis and advancement of cancer. (42). Numerous pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), play a significant role in the development of atherosclerotic plaques and vascular or tissue damage through the overexpression of MMP-9, the downregulation of TIMP-1, and the transcytosis of LDL. To our knowledge, both TNF-α and IL-6 have the capacity to activate transcription factors, particularly the PPAR-γ and NF-κB pathways. This activation can initiate the transcytosis of LDL across the endothelial barrier, thereby contributing to the advancement of atherosclerosis. Additionally, it may lead to the activation of reactive oxygen species (ROS) and inflammasomes (43). Significant upregulation of gene expression and MMP activity, particularly MMP9, has been noted in numerous cancers. Research indicates that increased levels of MMP9 are associated with a negative prognosis for cancer patients, leading to the proposal of MMP9 as a potential biomarker for cancers such as breast, colorectal, ovarian, and non-small cell lung cancer. In this regard, targeting MMP9 activity presents a promising approach for anticancer therapy. (44)

Caspases are a type of cysteine protease that selectively cleave bonds at the Asp-Xxx sites. They play a crucial role in processes such as inflammation and apoptosis, making them promising targets for therapeutic interventions in conditions like inflammation, neurodegeneration, ischemia, and cancer. Caspases represent promising targets for therapeutic strategies in various diseases due to their crucial involvement in apoptosis. Unregulated and excessive apoptosis is associated with several conditions that currently have no effective treatments, including neurodegenerative diseases, ischemia-reperfusion injuries, and autoimmune disorders. This indicates that inhibiting caspases could provide a valuable avenue for therapeutic intervention. Caspases can be categorized into two primary subfamilies based on the homology of their amino acid sequences, a classification that is indicative of their biological functions and substrate specificities. The first family, which includes caspases-1, -4, and -5, is linked to inflammatory processes, while the second family, comprising caspases-3, -8, and -9, is crucial for the process of apoptosis. Within this latter group, caspases function as either initiators or effectors of apoptosis. Initiator caspases, such as caspase-8 and -9, are activated in response to apoptotic signals and subsequently move within the cell to activate effector caspases like caspase-3 (45). In mixed primary septo-hippocampal cultures, TNF-α (0.3–500 ng/ml) induced apoptotic cell death, which was marked by several distinct features: membrane blebbing, nuclei that were shrunken and condensed, an irregular distribution of DNA staining, the formation of apoptotic bodies, and DNA fragmentation. These features are characteristic of the apoptotic process. Furthermore, the broad-spectrum protein synthesis inhibitor, cycloheximide, significantly inhibited cell death. Our prior research has demonstrated that protein synthesis is essential for the activation of caspase-3 and the occurrence of apoptotic cell death in this particular culture system during staurosporine-induced apoptosis. (46) The role of caspases in programmed cell death has been examined numerous times [47]. It is widely recognized that in mammals, the activation of the caspase cascade primarily occurs through two key pathways: the mitochondrial pathway (also known as the intrinsic pathway) and the death receptor pathway (referred to as the extrinsic

pathway). The intrinsic pathway is initiated by various internal death signals, including oncogene activation and DNA damage. The disruption of this pathway is commonly regarded as a characteristic feature of cancer. (48)

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Cyclooxygenases, specifically COX-1 and COX-2, facilitate the transformation of arachidonic acid (AA) into prostaglandin H2 (PGH2) (1). PGH2 is then converted by specific synthases in various tissues into powerful signaling molecules that are essential for maintaining physiological balance and are also involved in disease conditions like inflammation and cancer. Endocannabinoid signaling is crucial in numerous physiological functions and has been associated with a range of disorders, including anxiety, depression, multiple sclerosis, Parkinson's disease, and cancer (51). The presence of tumor-associated PTGS2 did not seem to influence the overall survival of patients, and measuring specific gPTGS2 levels in tissue lysates did not provide a clear distinction in patient outcomes. It is possible that tumor epithelial PTGS2 is less responsive to physiological stimuli due to the impact of certain oncogenic mechanisms on its expression. For instance, PTGS2 is often downregulated in microsatellite instability colorectal cancer (MSI CRC), whereas mutations in PIK3CA may enhance PTGS2 activity (52). Colorectal cancer (CRC) often develops through the gradual buildup of dysregulation in essential genes, such as oncogenes and tumor suppressor genes. Focusing on the key driver pathways could enhance the potential for creating more effective therapeutic strategies for CRC. In the present report, our shRNA silencing experiments validated the oncogenic role of PTGS2 in colorectal cancer (CRC). Additionally, we identified RUNX1 as a significant transcription factor that activates PTGS2 expression in CRC cells. Consequently, we present evidence that the increased expression of PTGS2, driven by RUNX1, plays a role in the development of colorectal tumors. It has been noted that the heightened expression of intestinal PTGS2 occurs early in the process of colorectal tumorigenesis. Furthermore, the upregulation of PTGS2 is linked to reduced survival rates specific to CRC. As a result, PTGS2 is considered a promising target for both the prevention and treatment of CRC (53).

MMP9-6ESM (Matrix Metalloproteinase 9) plays a crucial role in the degradation of extracellular matrix components and is significant in processes related to inflammation and tissue remodeling. The production of MMP9 is stimulated by TNF and IL-17. Inhibiting MMP9 can help mitigate inflammation by limiting tissue damage and promoting the healing of wounds. CAS93-1RE1 (presumably a chemical or molecular compound): This can be a molecule that blocks MAPK3 or MAPK pathway, involved in inflammatory processes such as IL-17 and TNF pathways. MAPK3 (or ERK pathway) can be recruited into both IL-17 and TNF pathways to activate inflammatory cytokines. MAPK3-2ZOQ (MAPK3/ERK): MAPK3 (ERK) is responsible for signaling IL-17 and TNF. ERK activation is the one that triggers inflammation and immune processes. Inhibition of MAPK3 (ERK) signaling would downregulate IL-17 and TNF pathways through inhibition of NF-kB and AP-1 transcription factor activation, which induce the expression of inflammatory cytokines. PTGS2-51KV (Cyclooxygenase-2, COX-2): COX-2 is an enzyme involved in prostaglandin synthesis, which is involved in inflammation and immunity. Both

TNF and IL-17 are able to induce expression of COX-2. Inhibition of COX-2 expression (e.g., with selective COX-2 inhibitors like celecoxib) can inhibit IL-17 and TNF-induced inflammatory responses.

5. CONCLUSION:

This research highlights the promising anticancer potential of *Tectaria* plants—*T. subtriphylla*, *T. circuteria*, *T. wightii`*, and *T. coadunate*—in the treatment of skin cancer, particularly in targeting key signalling pathways such as IL-17 and TNF. Network pharmacology proved to be a powerful tool for identifying bioactive compounds and understanding the molecular mechanisms through which these plants might exert their therapeutic effects.

Out of the 27 bioactive constituents studied, 15 were found to meet the necessary criteria for bioavailability score and pharmacokinetic properties, with the identification of 348 common drug-cancer targets offering a foundation for further exploration. The PPI network analysis revealed critical pathways linked to cancer progression, and the GO and KEGG pathway analysis suggested that these plants could influence immune regulation, inflammation, and cell proliferation in ways that support their anticancer activity.

The findings from this study contribute to the growing body of evidence supporting the use of traditional plant-based therapies in modern cancer treatment. Further research, particularly in vivo studies and clinical trials, is needed to validate the effectiveness of these plants and their bioactive compounds as novel therapeutic agents against skin cancer. Through network pharmacology, we have not only uncovered potential targets for anticancer therapy but also provided a methodological framework that could be applied to explore the anticancer activity of other traditional medicinal plants.

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Declaration of Competing Interest:
None

REFERENCES

1. Debela, D. T., Muzazu, S. G., Heraro, K. D., Ndalama, M. T., Mesele, B. W., Haile, D. C., ... & Manyazewal, T. (2021). New approaches and procedures for cancer treatment: Current perspectives. *SAGE open medicine*, *9*, 20503121211034366.
2. Kroemer, G., Chan, T. A., Eggermont, A. M., & Galluzzi, L. (2024). Immunosurveillance in clinical cancer management. *CA: A Cancer Journal for Clinicians*, *74*(2), 187-202.
3. Zeng, L., Gowda, B.H.J., Ahmed, M.G. *et al.* Advancements in nanoparticle-based treatment approaches for skin cancer therapy. *Mol Cancer* **22**, 10 (2023). https://doi.org/10.1186/s12943-022-01708-4
4. Zeng, L., Gowda, B.H.J., Ahmed, M.G. *et al.* Advancements in nanoparticle-based treatment approaches for skin cancer therapy. *Mol Cancer* **22**, 10 (2023). https://doi.org/10.1186/s12943-022-01708-4
5. Dreesen O, Brivanlou AH. Signaling pathways in cancer and embryonic stem cells. Stem Cell Rev. 2007 Jan;3(1):7-17. doi: 10.1007/s12015-007-0004-8. PMID: 17873377.
6. Wang, X., Yang, L., Huang, F., Zhang, Q., Liu, S., Ma, L., & You, Z. (2017). *Inflammatory cytokines IL-17 and TNF-α up-regulate PD-L1 expression in human prostate and colon cancer cells. Immunology Letters, 184, 7–14.* doi:10.1016/j.imlet.2017.02.006
7. Hu, M., Yan, H., Li, H. *et al.* Use of network pharmacology and molecular docking to explore the mechanism of action of curcuma in the treatment of osteosarcoma. *Sci Rep* **13**, 9569 (2023). https://doi.org/10.1038/s41598-023-36687-z
8. 3. Rekha Y. Halayal, Zabin K. Bagewadi, Raju B. Maliger, Salim Al Jadidi, Sanjay H. Deshpande, Network pharmacology based anti-diabetic attributes of bioactive compounds from Ocimum gratissimum L. through computational approach, Saudi Journal of Biological Sciences, Volume 30, Issue 9, 2023, 103766, ISSN 1319-562X , https://doi.org/10.1016/j.sjbs.2023.103766
9. Cragg, G. M., & Newman, D. J. (2005). *Plants as a source of anti-cancer agents. Journal of Ethnopharmacology, 100(1-2), 72–79.* doi:10.1016/j.jep.2005.05.011
10. Praveen, A., & Pandey, V. C. (2019). *Pteridophytes in phytoremediation. Environmental Geochemistry and Health.* doi:10.1007/s10653-019-00425-0
11. Sureshkumar, J., Silambarasan, R., Bharati, K. A., Krupa, J., Amalraj, S., & Ayyanar, M. (2018). *A review on ethnomedicinally important pteridophytes of India. Journal of Ethnopharmacology, 219, 269–287.* doi:10.1016/j.jep.2018.03.024

12. Baskaran, X., Geo Vigila, A., Zhang, S., Feng, S., & Liao, W. (2018). *A review of the use of pteridophytes for treating human ailments. Journal of Zhejiang University-SCIENCE B, 19(2), 1–35.* doi:10.1631/jzus.b1600344
13. Patil SM, Kachhiyapatel RN, Rajput KS. Review on the genus Tectaria Cav. from India. Plant Science Today 2019;6(2):170-182. https://doi.org/10.14719/pst.2019.6.2.511
14. Reddy MN, Adnan M, Alreshidi MM, Saeed M, Patel M. Evaluation of Anticancer, Antibacterial and Antioxidant Properties of a Medicinally Treasured Fern Tectaria coadunata with its Phytoconstituents Analysis by HR-LCMS. Anticancer Agents Med Chem. 2020;20(15):1845-1856. doi: 10.2174/1871520620666200318101938. PMID: 32188388. (00)
15. Venkata Samy Manivannan, Marimuthu alias Antony Samy Johnson, Ray S. Almeida, Henrique D.M. Coutinho, Chemical profiling of Tectaria paradoxa (Fee.) Sledge and Bolbitis Appendiculata (Willd.) K. Iwats using UHPLC, Biocatalysis and Agricultural Biotechnology, https://doi.org/10.1016/j.bcab.2021.102043 (20)
16. Karade, P. G., & Jadhav, N. R. (2017). *In vitro studies of the anticancer action of Tectaria cicutaria in human cancer cell lines: G 0 /G 1 p53-associated cell cycle arrest-Part I. Journal of Traditional and Complementary Medicine.* doi:10.1016/j.jtcme.2017.07.003 (21)
17. Hu, M., Yan, H., Li, H. *et al.* Use of network pharmacology and molecular docking to explore the mechanism of action of curcuma in the treatment of osteosarcoma. *Sci Rep* **13**, 9569 (2023). https://doi.org/10.1038/s41598-023-36687-z
18. Manivannan, Johnson, M. alias A., Almeida, R. S., & Coutinho, H. D. M. (202*1). Chemical profiling of Tectaria paradoxa (Fee.) Sledge and Bolbitis appendiculata (Willd.) K. Iwats using UHPLC. Biocatalysis and Agricultural Biotechnology, 34, 102043.* https://doi.org/10.1016/j.bcab.20. *(23)*
19. Zhou M, Li J, Luo D, Zhang H, Yu Z, Chen Y, Li Q, Liang F, Chen R. Network Pharmacology and Molecular Docking-Based Investigation: *Prunus mume* Against Colorectal Cancer via Silencing *RelA* Expression. Front Pharmacol. 2021 Nov 19;12:761980. doi: 10.3389/fphar.2021.761980. PMID: 34867383; PMCID: PMC8640358. (111)
20. Jin, L., Guan, Y., Li, X., Wang, M., Shen, Y., Wang, N., & He, Z. (2025). Combining Network Pharmacology, Molecular Docking and Experimental Validation to Explore the Effects and Mechanisms of Indirubin on Acute Lymphoblastic Leukemia. *"Drug Design, Development and Therapy*, *19*, 1083–1103
21. Zhou, Z., Chen, B., Chen, S., Lin, M., Chen, Y., Jin, S., … Zhang, Y. (2020). *Applications of Network Pharmacology in Traditional Chinese Medicine Research. Evidence-Based Complementary and Alternative Medicine*, *2020*, *1–7.* doi:10.1155/2020/1646905 (19)
22. *Emel Akbaba (2024). Molecular Mechanisms of Melatonin for Treating Medullary Thyroid Cancer Using in silico Analysis. Advances in Pharmacology and Pharmacy, 12(4), 430 - 442. DOI: 10.13189/app.2024.120415. (27)*
23. Hu, M., Yan, H., Li, H. *et al.* Use of network pharmacology and molecular docking to explore the mechanism of action of curcuma in the treatment of osteosarcoma. *Sci Rep* **13**, 9569 (2023). https://doi.org/10.1038/s41598-023-36687-z
24. https://doi.org/10.1016/j.jksus.2024.103134
25. Hu, M., Yan, H., Li, H. *et al.* Use of network pharmacology and molecular docking to explore the mechanism of action of curcuma in the treatment of osteosarcoma. *Sci Rep* **13**, 9569 (2023). https://doi.org/10.1038/s41598-023-36687-z
26. Suvarna P. Ingale, Anagha M. Joshi, Pramod L. Ingale (2024). Network Pharmacology-Based Evaluation of Therapeutic Potential of Passiflora edulis Leaves in Alzheimer's Disease. Advances in Pharmacology and Pharmacy, 12(3), 186 - 198. DOI: 10.13189/app.2024.120304.
27. Emel Akbaba (2024). Molecular Mechanisms of Melatonin for Treating Medullary Thyroid Cancer Using in silico Analysis. Advances in Pharmacology and Pharmacy, 12(4), 430 - 442. DOI: 10.13189/app.2024.120415.
28. Mohammad Ibrahim, Ganesh R Pawar, Shabina Khan, Mohd Mazhar, Sanchita Pathak , "Therapeutic Lead Identification from Ginkgo biloba against Enzyme Causing Alzheimer's Disease Using in-vitro Studies Integrated Network Pharmacology and Molecular Docking," Advances in Pharmacology and Pharmacy, Vol. 12, No. 3, pp. 248 - 255, 2024. DOI: 10.13189/app.2024.120309.
29. Zhou, J., Li, H., Wu, B. *et al.* Network pharmacology combined with experimental verification to explore the potential mechanism of naringenin in the treatment of cervical cancer. *Sci Rep* **14**, 1860 (2024). https://doi.org/10.1038/s41598-024-52413-9
30. Emel Akbaba (2024). Molecular Mechanisms of Melatonin for Treating Medullary Thyroid Cancer Using in silico Analysis. Advances in Pharmacology and Pharmacy, 12(4), 430 - 442. DOI: 10.13189/app.2024.120415.
31. Premkumar, B & Yesuraj, Samson & Mohan, Santhosh & Chandran, Savitha. (2024). Molecular docking studies for NPACT ligands for the treatment of melanoma skin cancer. International Journal of Pharmaceutical Chemistry and Analysis. 11. 51-54. 10.18231/j.ijpca.2024.007.
32. Mohammad Ibrahim, Ganesh R Pawar, Shabina Khan, Mohd Mazhar, Sanchita Pathak , "Therapeutic Lead Identification from Ginkgo biloba against Enzyme Causing Alzheimer's Disease Using in-vitro Studies Integrated

Network Pharmacology and Molecular Docking," Advances in Pharmacology and Pharmacy, Vol. 12, No. 3, pp. 248 - 255, 2024. DOI: 10.13189/app.2024.120309.

33. https://doi.org/10.1016/j.jksus.2024.103134
34. Jin, L., Guan, Y., Li, X., Wang, M., Shen, Y., Wang, N., & He, Z. (2025). Combining Network Pharmacology, Molecular Docking and Experimental Validation to Explore the Effects and Mechanisms of Indirubin on Acute Lymphoblastic Leukemia. *"Drug Design, Development and Therapy*, *19*, 1083–1103. https://doi.org/10.2147/DDDT.S500249 (30)
35. Emmanuel I. Ugwor, Adewale S. James, Adekunle I. Amuzat, Emmanuel O. Ezenandu, Victory C. Ugbaja, Regina N. Ugbaja,Network pharmacology-based elucidation of bioactive compounds in propolis and putative underlying mechanisms against type-2 diabetes mellitus,Pharmacological Research - Modern Chinese Medicine,Volume 5,2022,100183,ISSN 2667-1425, https://doi.org/10.1016/j.prmcm.2022.100183 (S2)
36. Emmanuel I. Ugwor, Adewale S. James, Adekunle I. Amuzat, Emmanuel O. Ezenandu, Victory C. Ugbaja, Regina N. Ugbaja,Network pharmacology-based elucidation of bioactive compounds in propolis and putative underlying mechanisms against type-2 diabetes mellitus,Pharmacological Research - Modern Chinese Medicine,Volume 5,2022,100183,ISSN 2667-1425, https://doi.org/10.1016/j.prmcm.2022.100183 (S2)
37. 3. Rekha Y. Halayal, Zabin K. Bagewadi, Raju B. Maliger, Salim Al Jadidi, Sanjay H. Deshpande, Network pharmacology based anti-diabetic attributes of bioactive compounds from Ocimum gratissimum L. through computational approach, Saudi Journal of Biological Sciences, Volume 30, Issue 9, 2023, 103766, ISSN 1319-562X , https://doi.org/10.1016/j.sjbs.2023.103766
38. 4. JOUR Agu, P. Afiukwa, C. aOrji, O. Ezeh, E. M.Ofoke, I. H. Ogbu, C. O. Ugwuja, E. I. Aja, P. M. 20232023/08/17TMolecular docking as a tool for the discovery of molecular targets of nutraceuticals in diseases management Scientific Reports - 13398 - 13- 1 https://doi.org/10.1038/s41598-023-40160-2
39. https://doi.org/10.1038/s41598-024-58877-z JOUR- Vikhar Danish Ahmad, Ansari - Khan, Subur W.- Ali, Syed Ayaz - Yasar, Qazi- 2024 2024/04/29- Network pharmacology combined with molecular docking and experimental verification to elucidate the effect of flavan-3-ols and aromatic resin on anxiety - Scientific R eports - 9799 141
40.] Gogoi, Barbi, Saikia, S. P., Virtual Screening and Network Pharmacology-Based Study to Explore the Pharmacological Mechanism of *Clerodendrum* Species for Anticancer Treatment, *Evidence-Based Complementary and Alternative Medicine*, 2022, 3106363, 17 pages, 2022. https://doi.org/10.1155/2022/3106363
41. [3]Zhou, Zhuchen, Chen, Bing, Chen, Simiao, Lin, Minqiu, Chen, Ying, Jin, Shan, Chen, Weiyan, Zhang, Yuyan, Applications of Network Pharmacology in Traditional Chinese Medicine Research, *Evidence-Based Complementary and Alternative Medicine*, 2020, 1646905, 7 pages, 2020. https://doi.org/10.1155/2020/1646905
42. Elisa Nuti, Doretta Cuffaro, Elisa Bernardini, Caterina Camodeca, Laura Panelli, Sílvia Chaves, Lidia Ciccone, Livia Tepshi, Laura Vera, Elisabetta Orlandini, Susanna Nencetti, Enrico A. Stura, M. Amélia Santos, Vincent Dive, and Armando Rossello.*Journal of Medicinal Chemistry* **2018** *61* (10), 4421-4435. DOI: 10.1021/acs.jmedchem.8b00096
43. Akbari T, Kazemi Fard T, Fadaei R, Rostami R, Moradi N, Movahedi M, Fallah S. Evaluation of MMP-9, IL-6, TNF-α levels and peripheral blood mononuclear cells genes expression of MMP-9 and TIMP-1 in Iranian patients with coronary artery disease. J Cardiovasc Thorac Res. 2023;15(4):223-230. doi: 10.34172/jcvtr.2023.31844. Epub 2023 Dec 30. PMID: 38357561; PMCID: PMC10862034.
44. Augoff, K.; HryniewiczJankowska, A.; Tabola, R.; Stach, K. MMP9: AToughTarget for Targeted Therapy for Cancer. Cancers 2022, 14, 1847. https://doi.org/10.3390/ cancers14071847
45. Becker, J. W., Rotonda, J., Soisson, S. M., Aspiotis, R., Bayly, C., Francoeur, S., … Zamboni, R. (2004). *Reducing the Peptidyl Features of Caspase-3 Inhibitors: A Structural Analysis. Journal of Medicinal Chemistry, 47(10), 2466–2474.* doi:10.1021/jm0305523
46. Zhao, X., Bausano, B., Pike, B. R., Newcomb-Fernandez, J. K., Wang, K. K. W., Shohami, E., … Hayes, R. L. (2001). *TNF-? stimulates caspase-3 activation and apoptotic cell death in primary septo-hippocampal cultures. Journal of Neuroscience Research, 64(2), 121–131.* doi:10.1002/jnr.1059 .
47. Zhou, Zhuchen, Chen, Bing, Chen, Simiao, Lin, Minqiu, Chen, Ying, Jin, Shan, Chen, Weiyan, Zhang, Yuyan, A pplications of Network Pharmacology in Traditional Chinese Medicine Research, *Evidence-Based Complementary and Alternative Medicine*, 2020, 1646905, 7 pages, 2020. https://doi.org/10.1155/2020/1646905
48. Noor ZM, Ahmad H, Ain Q, Anjum T, Malik ZS, Hussain Z, et al. Caspase 3 and Its Role in the Pathogenesis of Cancer. Clin Oncol. 2022; 7: 1941. ISSN: 2474-1663
49. Cargnello M, Roux PP. Activation and function of the MAPKs and their substrates, the MAPK-activated protein kinases. Microbiol Mol Biol Rev. 2011 Mar;75(1):50-83. doi: 10.1128/MMBR.00031-10. Erratum in: Microbiol Mol Biol Rev. 2012 Jun;76(2):496. PMID: 21372320; PMCID: PMC3063353.
50. Lee S, Rauch J, Kolch W. Targeting MAPK Signaling in Cancer: Mechanisms of Drug Resistance and Sensitivity. Int J Mol Sci. 2020 Feb 7;21(3):1102. doi: 10.3390/ijms21031102. PMID: 32046099; PMCID: PMC7037308.

51. Orlando, B. J., & Malkowski, M. G. (2016). *Substrate-selective Inhibition of Cyclooxygeanse-2 by Fenamic Acid Derivatives Is Dependent on Peroxide Tone. Journal of Biological Chemistry, 291(29), 15069–15081*. doi:10.1074/jbc.m116.725713.
52. Venè R, Costa D, Augugliaro R, Carlone S, Scabini S, Casoni Pattacini G, Boggio M, Zupo S, Grillo F, Mastracci L, Pitto F, Minghelli S, Ferrari N, Tosetti F, Romairone E, Mingari MC, Poggi A, Benelli R. Evaluation of Glycosylated PTGS2 in Colorectal Cancer for NSAIDS-Based Adjuvant Therapy. Cells. 2020 Mar 11;9(3):683. doi: 10.3390/cells9030683. PMID: 32168749; PMCID: PMC7140631.
53. Zheng, W., Guo, Y., Kahar, A. *et al.* RUNX1-induced upregulation of PTGS2 enhances cell growth, migration and invasion in colorectal cancer cells. *Sci Rep* **14**, 11670 (2024). https://doi.org/10.1038/s41598-024-60296-z