Network Pharmacology and Molecular Docking-Based Identification of Key Therapeutic Targets of Solanum xanthocarpum in Lung Cancer

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ABSTRACT

Introduction:

The positive role of *Solanum xanthocarpum* in cancer has been proven in several studies. Still, the underlying molecular mechanisms are still unclear. In this study an effort has been made to understand the molecular basis of its action using network pharmacology.

Methods: The phytoconstituents of *Solanum xanthcarpum* were screened from various literatures and IMPPAT database. Then the target genes of effective compounds were screened by pharmacokinetic characteristics (ADMET) and drug likeness score. The target genes were predicted from Swiss Target Prediction. The genes of lung cancer were found in gene-card database and their related target genes were screened by comparison. Further, the related pathways and correlation analysis were explored by the KEGG database. Using Cytoscape_v3.10.4, the networks of compound-target, target-pathway and pathway-disease of *Solanum xanthcarpum* was constructed. Molecular docking was done using Autodock Vina and analysed through Discovery Studio Visualization (DSV).

Results: The effective phytoconstituents of *Solanum xanthocarpum* in lung cancer were Apigenin, Solasodine, Diosgenin, Chlorogenic acid and Esculetin. The network analysis showed the highly modulating proteins were AKT1, MTOR, SRC, HSP90AA1, ESR1, MDM2 and NFKB1 and act on the pathways like small cell lung cancer, MAPK signalling, mTOR signalling pathway, MicroRNAs etc Ligand preparation was done by Open Babel GUI and virtual screening was done by PyRx Software (Version 0.8).

Conclusion: The present study enables us to understand scientific evidence at the molecular level of understanding the action of *Solanum xanthocarpum* in Lung cancer.

Key words: *Solanum xanthocarpum*, Lung Cancer, Network Pharmacology, Molecular Docking, Apigenin, Solasodine, AKT1, mTOR Signalling Pathway; MAPK Signalling Pathway.

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INTRODUCTION:

Lung cancer continues to be one of the most common and deadly cancers around the world, causing a large share of cancer- related illness and deaths. The World Health Organisation reports that lung cancer kills about 1.8 million people each year and leads to 2.5 million new cases annually [1], making it top cause of cancer deaths worldwide. Among lung cancer types, Non-Small Cell Lung Cancer (NSCLC) represents about 85% of all cases, while Small Cell Lung Cancer (SCLC) makes up the rest [2]. The main risk factors that contribute to lung cancer include smoking, exposure to air pollution and carcinogens and having a genetic predisposition[3].

In clinical practice, lung cancer is asymptomatic in its early stages, which leads to delayed diagnosis. The symptoms include persistent cough, haemoptysis (coughing up blood), chest pain, breathing difficulty (dyspnoea), unexplained weight

loss and fatigue. As the disease advances, it can spread to distant organs like the brain, liver and bones, which makes the prognosis worse[4]. Even though diagnostic methods have improved with tools like computed tomography (CT) and positron emission tomography (PET), early detection remains a major hurdle.

Today, lung cancer treatment options include surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy. Targeted therapies have especially boosted patient outcomes, particularly those that target molecular markers like epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangements. Gefitinib and Erlotinib are two drugs used in targeted therapy [5]. Still, there are limitations such as drug resistance, adverse effects and high costs- which push researchers to look for alternative therapeutic options, especially those derived from natural sources.

Medicinal plants have been a fundamental of traditional healthcare systems for centuries including Ayurveda. *Solanum xanthocarpum,* commonly known as *Kantakari* or *Ringani* in India, belongs to the family Solanaceae and is widely used in Ayurvedic medicine [6]. It is one of the constituents of the classical formulation "*Dashamoola*," which is traditionally employed for the treatment of respiratory disorders such as asthma, bronchitis, and cough [7]. The plant is rich in bioactive compounds, including steroidal alkaloids such as solasodine, solasonine, and solamargine, which have demonstrated anti-inflammatory, antioxidant, and anticancer properties [8].

From an Ayurvedic perspective, *Solanum xanthocarpum* is described as having "*Katu*" (pungent) and "*Tikta*" (bitter) *rasa,* with *"Ushna virya"* (hot potency), and is known to pacify *Kapha* and *Vata* doshas [6]. Its therapeutic use in respiratory ailments suggests a potential role in lung-related disorders, including malignancies. Recent pharmacological studies have indicated that its phytoconstituents may induce apoptosis, inhibit tumour cell proliferation, and modulate oxidative stress pathways [8].

In recent years, computational methods have significantly transformed the drug discovery process by facilitating the rapid evaluation of bioactive compounds against selected molecular targets. In silico approaches, including molecular docking, ADMET prediction, and molecular dynamics simulations, offer valuable information regarding ligand–protein interactions and aid in the identification of promising lead molecules. These techniques help streamline the drug development process by reducing both the time and cost associated with traditional experimental investigations.

Accordingly, the present study was designed to evaluate the anticancer potential of phytoconstituents obtained from *Solanum xanthocarpum* against key lung cancer targets through in silico methodologies. This approach seeks to integrate traditional medicinal knowledge with contemporary computational techniques employed in drug discovery

Materials and methods:

Identification of *Solanum xanthocarpum* bioactives

The bioactive constituents of *Solanum xanthocarpum* were identified through an extensive review of the literature and relevant databases, including the IMPPAT database [9]. The structural information of the selected phytochemicals was subsequently retrieved from the PubChem database [10] in Structure Data File (SDF) format along with their phytochemical details. These compounds were then subjected to further analysis to evaluate their pharmacokinetic properties.

Drug likeness of Bioactives of *Solanum xanthcarpum*

The phytoconstituents were screened for its Drug likeness property on the basis of 'Lipinski's Rule of 5' [11] using SWISS-ADME [12] and pKCSM software [13]. The potential target genes of the selected bioactive compounds were identified using available databases and literature reports. Lung cancer associated genes were retrieved from disease databases. The common genes shared between bioactive targets and lung cancer-associated genes were considered overlapping genes and selected for further analysis.

Identification of Overlapping Genes

The overlapping genes were defined as the common genes present in both the disease target set and the drug target set. Identification of these shared targets was performed using Venny 2.1 mapping [14]. The screened disease-related genes were uploaded to List 1, whereas the drug-related targets were entered into List 2, resulting in the generation of a Venn diagram that illustrated the overlapping genes.

Protein-protein interaction

A Protein–Protein Interaction (PPI) network was constructed by submitting the overlapping genes/proteins to the STRING database [15] to identify potential interactions among the target proteins. The resulting network was analyzed to explore key protein interactions relevant to lung

cancer. Network visualization and subsequent analyses were performed using Cytoscape software [16], and the most influential hub genes were identified with the CytoHubba plugin.

Gene Ontology and KEGG Pathway Analysis:

The functional enrichment analysis of the overlapping genes was performed using the Shiny GO [17], DAVID database [18] and KEGG pathways database [19].Gene Ontology (GO) enrichment analysis was categorized into Biological Process, Cellular Component and Molecular Function was conducted to identify significantly enriched signalling pathways associated with lung cancer. The top enriched GO terms and KEGG pathways were selected based on FDR (false discovery rate) and enrichment scores. The graphical representation of GO enrichment and KEGG pathway analysis was generated using SR plot [20].

GEPIA Expression Analysis

Using GEPIA software [21], the expression profiling of selected hub genes in lung adenocarcinoma (LUAD) was analyzed which integrates the TCGA and GTEx datasets. Box plots were performed to compare the expression levels of selected target genes between normal and lung cancer tissues.

Docking Analysis

The Molecular docking was performed to evaluate the binding affinity between selected bioactive compounds and key target protein receptors associated with lung cancer. The 3D structure of target proteins was obtained from the RCSB Protein data Bank [22] while ligand structure retrieved from the Pub Chem. By using Auto Dock Tools [23] and Auto dock vina [24], the docking between protein receptors and ligands were done. For visualization and analysis of molecular docking we used BIOVIA Discovery Studio[25].

RESULTS:

Screening of Bioactive Compounds and Drug Likeness of *Solanum xanthocarpum*

By using IMPPAT Database and applying Lipinski's Rule we overall sorted the bioactive compounds.

Solanum xanthocarpum – 24 compounds

By using ADMET Report we selected 5 main bioactive compounds for further network pharmacology and molecular docking studies.

1. Apigenin
2. Chlorogenic acid
3. Diosgenin
4. Esculetin
5. Solasodine

ADME Report of above Phytochemicals

	Molecular weight	**LogP**	**H-Bond Donor**	**H-Bond Acceptor**	**Gastrointestinal absorption**
Apigenin	270.24	2.57	3	5	High
Chlorogenic acid	354.31	-0.61	6	9	Low
Diosgenin	414.63	4.29	1	3	High
Esculetin	178.14	1.46	2	4	High
Solasodine	413.64	3.97	2	3	High

Table 1. Evaluation of ADME characteristics of selected phytoconstituents

Lipinski's Rule of Five indicates that Apigenin and Esculetin exhibit optimal drug-likeness with zero violations and high gastrointestinal absorption, suggesting strong oral bioavailability. Even though Diosgenin and Solasodine each have one violation, they still show good absorption and lipophilicity, which confirms they are well suited for molecular docking and target interaction studies. Chlorgenic acid, on the other hand, has poor gastrointestinal absorption and is more polar which limits potential to serve as a lead compound.

Phytoconstituents	**Molecular Formula**	**Pubcem ID**	**Name of Targets**
Apigenin	$C_{15}H_{10}O_5$	5280443	AKT 1, ESR 1, SRC, MMP9
Solasodine	$C_{27}H_{43}NO_2$	442985	AKT 1, ESR 1, MDM2, SRC, BCL2L 1,

			HSP90 AA
Chlorogenic acid	$C_{16}H_{18}O_9$	17944 27	CASP3, APP, AKR1B 1, PYGL
Diosgenin	$C_{27}H_{42}O_3$	99474	MTOR, MDM2, SRC, AR, ALK
Esculetin	$C_9H_6O_4$	52814 16	AKT 1, ESR1, SRC, MMP9, NFKB1

Table 2: Selected Phytoconstituents of with its disease targets

Estimation of overlapping genes:

By overlapping genes between disease gene target and predicted target genes of ligand. 355 overlapping genes were identified with the help of Venny 2.1. Total 354 genes of bioactive compounds were overlapped with disease target genes.

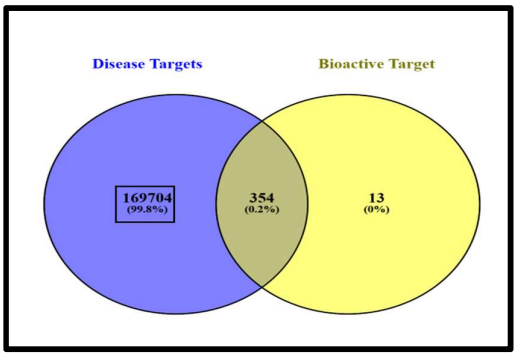
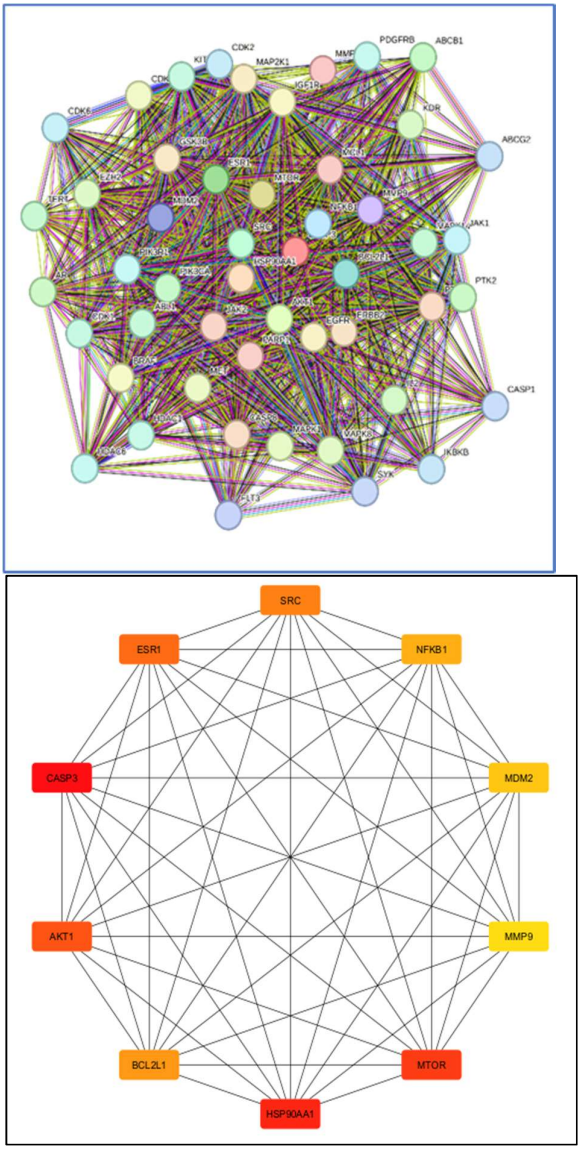


Fig.1 Venn diagram showing overlapping genes

Protein protein interaction

Solanum xanthocarpum overlapping targets and its metabolites was examined using STRING database to create a PPI network. It was done to determine top 10 genes with a confidence score 0.07. Top 10 hub genes out of 354 overlapped genes were selected by using cytohubba software. Through analysis of the protein-protein interaction network, protein receptors that are responsible for the Lung pathway are sorted. The protein receptors such as CASP3, HSP90AA1, MTOR, AKT1, ESR1, SRC, BCL2L1, NFKB1, MDM2, MMP9. This PPI network highlights key hub proteins and pathways involved in lung cancer, suggesting that targeting multiple interconnected proteins may provide an effective therapeutic strategy.



a

b

Fig 2. Protein–Protein Interaction (PPI) network of potential target genes associated with the active constituents of *Solanum xanthocarpum* in lung cancer.
a. PPI network illustrating the interactions among the identified target genes, where each node represents an individual gene.
b. Top 10 hub genes identified from the PPI network based on degree value. Darker node colours indicate higher degree scores and greater connectivity within the network

KEGG Pathway Analysis and Gene Ontology-

ID	Term	Count	P-Value	User IDs
hsa05222	Small cell lung cancer	16	4.45 E-07	PIK3CD, PIK3CB, PIK3R1, PTGS2, PTK2, NFKB1, IKBKB, CDK6, PIK3CA, CDK4, CASP3, AKT2, AKT3, CDK2, AKT1, BCL2L1
hsa04151	PI3K-Akt signaling pathway	45	7.57 E-14	EGFR, AKT1, JAK2, FGFR1, PIK3CB, MTOR, KIT, MAPK1, FLT4, BCL2L1, CSF1R, CDK4, IGF1R, AKT3, PDGFRB, NFKB1, PIK3CD, MET, TEK, HSP90AA1, JAK1, ERBB2, KDR, MDM2, FLT3, MAP2K1, CDK6, PRKCA, INSR, GSK3B, AKT2, SYK, PTK2, IKBKB, F2R, PIK3R1, IL2, JAK3, FGFR2, PKN1, MCL1, NOS3, CDK2, PIK3CA, PIK3CA.
hsa05235	PD-L1 expression and PD-1 checkpoint pathway in cancer	20	1.07 E-10	ALK, MAP2K1, CSNK2A1, PIK3CD, PIK3CB, PIK3R1, MAPK14, EGF, R, MTOR, NFKB1, IKBKB, PIK3CA, LCK, AKT2, AKT3, AKT1, MAPK1, PRKCQ, JAK2, JAK1
hsa04066	HIF-1 signaling pathway	22	8.21 E-11	CAMK2B, MAP2K1, PFKFB3, PRKCB, NOS3, INSR, PIK3CD, PRKCA, PIK3CB, PIK3R1, EGFR, MTOR, NFKB1, IGF1R, PIK3CA, AKT2, ERBB2, AKT3, PGK1, AKT1,

				MAPK1, TEK
hsa01521	EGFR tyrosine kinase inhibitor resistance	26	4.18 E-18	AKT1, AKT2, AKT3, AXL, BCL2L1, BRAF, EGFR, ERBB2, FGFR2, GSK3B, IGF1R, JAK1, JAK2, KDR, MAP2K1, MAPK1, MET, MTOR, PDGFRB, PIK3CA, PIK3CB, PIK3CD, PIK3R1, PRKCA, PRKCB, SRC.
hsa05205	Proteoglycans in cancer	33	2.34 E-13	EGFR, AKT1, ROCK2, FGFR1, MAPK1, PIK3CB, CASP3, SRC, MTOR, CAMK2B, MET, ESR1, PRKCA, SHH, AKT3, MMP9, PIK3CA, KDR, PTK2, MDM2, ROCK1, ERBB2, MAP2K1, SMO, PIK3CD, BRAF, IGF1R, CTSL, AKT2,
				PRKCB, MMP2, MAPK14, PIK3R1.
hsa05206	MicroRNAs in cancer	33	3.21 E-08	HDAC2, ABCB1, ROCK1, HDAC1, PIK3CD, PIK3CB, PIK3R1, PTGS2, EGFR, IKBKB, CASP3, ERBB2, ABL1, PIM1, CYP1B1, MAPK1, MCL1, PDGFRB, ABCC1, MAP2K1, PRKCB, PRKCA, MMP9, MTOR, NFKB1, CYP24A1, CDK6, MMP16, PIK3CA, MDM2, MDM4, MET, EZH2
hsa04150	mTOR signaling pathway	18	2.34 E-05	AKT1, AKT2, AKT3, BRAF, GSK3B, IGF1R, IKBKB, INSR, MAP2K1, MAPK1, MTOR, PIK3CA, PIK3CB, PIK3CD, PIK3R1, PRKCA, PRKCB,

				RPS6KA3
hsa04012	ErbB signaling pathway	23	5.07E-14	ABL1, AKT1, AKT2, AKT3, BRAF, CAMK2B, EGFR, ERBB2, GSK3B, MAP2K1, MAPK1, MAPK8, MAPK9, MAPK10, MTOR, PIK3CA, PIK3CB, PIK3CD, PIK3R1, PRKCA, PRKCB, PTK2, SRC.

Table 3. KEGG pathway analysis highlighting the shared target genes between *Solanum xanthocarpum* and lung cancer.

KEGG pathway enrichment analysis using the DAVID database demonstrated that the overlapping genes were significantly enriched in several cancer-associated pathways, including the HIF-1 signaling pathway, mTOR signaling pathway, pathways in cancer, ErbB signaling pathway, microRNAs in cancer, PD-L1 expression and PD-1 checkpoint pathway in cancer, proteoglycans in cancer, PI3K-Akt signaling pathway, and EGFR tyrosine kinase inhibitor resistance. The PI3K-Akt signaling pathway exhibited the highest enrichment, comprising 45 associated genes, indicating its prominent role in cancer cell proliferation, survival, and apoptosis. Furthermore, pathways in cancer and microRNAs in cancer were also found to be significantly enriched.

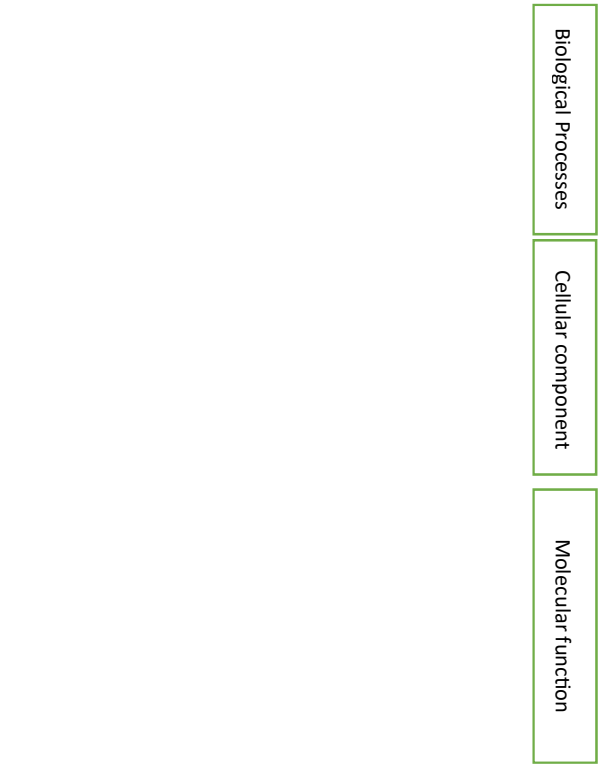


Fig 3. Gene Ontology (GO) enrichment analysis of candidate targets using the DAVID database.

To explore the biological relevance of the identified targets in lung cancer, Gene Ontology (GO) enrichment analysis was carried out using the DAVID database. The enriched GO terms were subsequently visualized as bar plots using the SR plot platform, facilitating the interpretation of the associated biological processes, cellular components, and molecular functions

Category	Term	Count	P-Value
Biological Processes	signal transduction	122	5.10E-32
Biological Processes	angiogenesis	26	1.19E-10
Biological Processes	cell migration	24	8.23E-09
Biological Processes	inflammatory response	34	3.17E-11
Biological Processes	positive regulation of apoptotic	18	1.17E-04
Biological Processes	protein phosphorylation	42	8.77E-27
Biological Processes	positive regulation of cell cycle	5	7.85E-03
Cellular Component	cytoplasm	215	1.53E-19
Cellular Component	plasma membrane	205	3.31E-31
Cellular Component	cytosol	179	8.09E-21
Cellular Component	membrane raft	22	2.29E-10
Cellular Component	extracellular exosome	71	3.18E-07
Cellular Component	mitochondrion	58	5.44E-06
Cellular Component	focal adhesion	17	3.51E-03
Cellular Component	nucleoplasm	100	8.11E-05
Molecular Function	protein kinase activity	81	1.4E-50
Molecular Function	protein tyrosine kinase activity	39	6.32E-34
Molecular Function	protein serine/threonine kinase	57	6.5E-32
Molecular Function	ATP binding	100	1.72E-29
Molecular Function	enzyme binding	37	1.42E-14
Molecular Function	identical protein binding	84	3.33E-15
Molecular Function	protein binding	304	6E-11
Molecular Function	MAP kinase activity	7	1.56E-06
Molecular Function	catalytic activity	22	3.1E-06

Table 4. Gene Ontology enrichment analysis of overlapping genes showing Biological Processes, Cellular Components, and Molecular Functions.

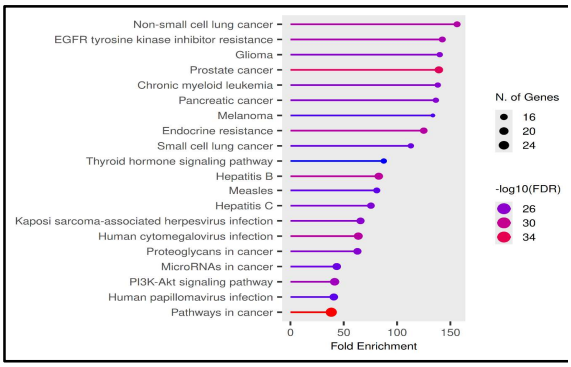


Fig 4. Significantly enriched KEGG pathways associated with the candidate targets of *Solanum xanthocarpum* in lung cancer treatment. The y-axis displays the enriched KEGG pathways, while the x-axis indicates the number of genes enriched within each pathway

KEGG pathway enrichment analysis of the overlapping target genes was performed using the ShinyGO web server to identify the major signaling pathways associated with the therapeutic mechanism of *Solanum xanthocarpum* against lung cancer. The enrichment analysis was significantly involved in several cancer-associated pathways. Among the enriched pathways, non-small cell lung cancer showed the highest fold enrichment, followed by EGFR tyrosine kinase inhibitor resistance, glioma, prostate cancer, chronic myeloid leukemia, pancreatic cancer, melanoma, endocrine resistance, and small cell lung cancer pathways. The key signaling pathways such as the PI3K-Akt signaling pathway, pathways in cancer, proteoglycans in cancer, microRNAs in cancer, and thyroid hormone signaling pathway were also significantly enriched. These pathways are known to regulate cancer cell proliferation, apoptosis, angiogenesis, metastasis, and therapeutic resistance.

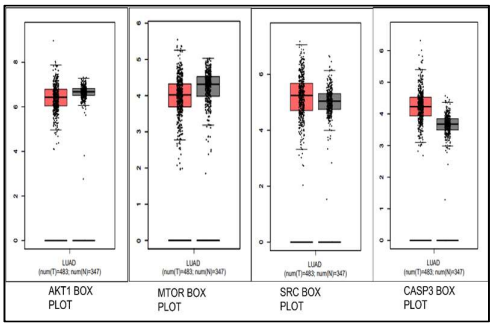


Fig. 5 -GEPIA BOX PLOT OF SELECTED RECEPTORS against lung adenocarcinoma (LUAD) / lung cancer

The clinical significance of the identified hub genes was further examined through gene expression profiling using the GEPIA platform, which incorporates data from both the TCGA and GTEx repositories. Differential expression analysis was performed using box plots to investigate variations in the expression levels of the selected target genes between lung adenocarcinoma (LUAD) samples and normal lung tissues

Among the identified hub genes, AKT1, MTOR, SRC, and CASP3 were selected for further analysis based on their high degree values in the PPI network, involvement in enriched KEGG pathways, and their previously reported role in lung cancer progression according to published studies.

The GEPIA box plot analysis revealed that these hub genes express differently in LUAD (lung adenocarcinoma) tissues compared to normal tissues, highlighting their significant role in the pathogenesis of lung cancer. AKT1, MTOR, and SRC showed relatively higher expression levels in cancer tissues, while CASP3 showed altered expression associated with apoptotic dysregulation.

Construction of Network & Analysis-

Using Cytohubba Software, we identified 6 receptor that are interconnected with each other and disease genes. We then built the network using Cytoscape version 3.10.4, which resulted in 26 nodes, 68 edges, including 10 pathways.

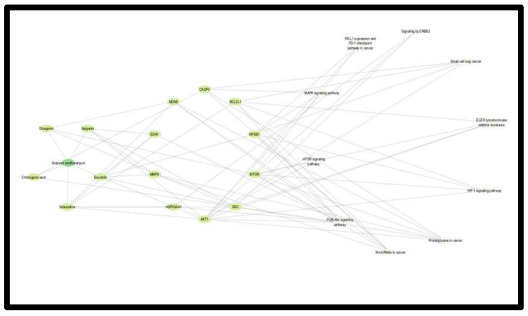


Fig. 6 Network Construction of *Solanum xanthocar*pum with bioactives-targets- pathways against lung cancer

Results of Molecular Docking:

Receptors-Ligands	Binding Energy (kcal/mol)	Hydrogen Bond Interaction	Hydrophobic Interaction

Interaction			
AKT1-Apigenin	-9.1	THR A:211, ASP A:292	ALA A:212, ASN A:53, LEU A:210, LEU A:264, LYS A:268, SER A:205, TRP A:80, TYR A:272, VAL A:270
AKT1-Chlorogenic acid	-9.3	ASP A:274, GLN A:203, THR A:82, TYR A:272, VAL A:271	ARG A:273, ASN A:204, ASP A:292, GLY A:294, LEU A:264, VAL A:270
AKT1-Diosgenin	-10.9	THR A:291, ASP A:292, THR A:211	ILE A:290, VAL A:270, ASN A:53
AKT1-Esculetin	-7.6	THR A:211, LYS A:268	SER A:205, LEU A:264, ASP A:292
AKT1-Solasodine	-10.9	THR A:211, TRP A:80, LEU A:210	VAL A:270, LEU A:264, SER A:205
MTOR-Apigenin	-8	GLU A:2032, PHE A:2039	TRP A:2102, TYR A:2105, SER A:2035
MTOR-Chlorogenic acid	-7	ALA D:2073, GLY D:2075, GLN D:2072, ASP D:2077, GLN D:2099	ARG D:2076, ASN D:2071, TYR D:2074, ARG D:2110, ASP D:2102
MTOR-Diosgenin	-9.3	ARG D:2086, LEU C:2103	LYS D:2090, HIS C:2106, ARG C:2109
MTOR-Esculetin	-6.4	PHE E:2039, TYR E:2105	TRP E:2101, LEU E:2031, PHE E:2108, GLU E:2032, SER E:2035
MTOR-Solasodine	-9.5	GLU C:2080, LEU C:2103, ARG D:2086, LYS D:2090	HIS C:2106, TRP C:2084, ASP C:2102, ARG C:2109
SRC-Apigenin	-7.9	GLN A:144, GLU A:147, LYS A:104	THR A:247, TYR A:149, PHE A:150, PRO A:246
SRC-Chlorogenic acid	-8	ARG A:160, SER A:522, GLU A:517, PHE A:520	LEU A:516, ASP A:365, VAL A:364, TYR A:519, ARG A:156, ASP A:518
SRC-Diosgenin	-9.7	TYR A:90, PHE A:150, ILE A:153, HIS A:319	GLU A:157, GLU A:320, LEU A:161, LYS A:321, SER A:372, THR A:247

SRC-Esculetin	-6.5	LEU A:89, TYR A:90	GLU A:147, THR A:247, PHE A:150, TYR A:149
SRC-Solasodine	-9.7	HIS A:319, ILE A:153, LYS A:321, PHE A:150, THR A:154	GLU A:157, GLU A:320, LEU A:161, LYS A:152, SER A:372, THR A:247, TYR A:90
CASP3-Apigenin	-7.1	ASP A:40, MET A:39	HIS A:277, HIS A:278, LYS A:38, SER A:36, TYR A:37, TYR A:276
CASP3-Chlorogenic acid	-6.8	ASP B:5, THR A:62, PHE A:256, VAL B:4	TYR A:204, THR A:166, GLY A:165, CYS A:163, TRP A:206, GLU B:3, MET A:61
CASP3-Diosgenin	-8.7	SER A:251, PHE A:256, VAL B:4, HIS A:121, MET A:61, PHE A:128	ASP A253, TYR A:204, ASP B:5, GLU B:3, THR A:166, THR A:62
CASP3-Esculetin	-5.9	SER A:251, PHE A:256, VAL B:4	TRP A:206, ASP A:253, GLU B:3, ASP B:2
CASP3-Solasodine	-8.5	HIS A:121, MET A:61, PHE A:128, PHE A:256, VAL B:4	ASP A:253, ASP B:5, GLU B:3, SER A:251, THR A:62, TYR A:204

Table no. 5 Binding affinity values of the modulated phytocompounds along with their corresponding targets

Results of Docking analysis:

The molecular docking study showed strong binding affinities between the selected bioactive compounds and key lung cancer targets, such as AKT1, MTOR, SRC, and CASP3**.** Binding energies ranged from −5.9 to −10.9 kcal/mol**,** which indicates meaningful ligand–receptors interactions.

Among all compounds tested, diosgenin and solasodine showed the highest binding affinity toward AKT1 (−10.9 kcal/mol)**,** followed by chlorogenic acid (−9.3 kcal/mol) and apigenin (−9.1 kcal/mol)**.** These strong interactions suggest that these compounds could effectively inhibit AKT1, a key regulator of the PI3K-Akt signaling pathway**,** which would suppress tumor cell survival and proliferation in lung cancer.

For the MTOR protein, solasodine (−9.5 kcal/mol**)** and diosgenin (−9.3 kcal/mol) displayed better binding than the other compounds, indicating their potential to modulate the mTOR signaling pathway, that plays a crucial role in cancer cell growth and metabolism.

In the case o**f** SRC**,** diosgenin and solasodine (−9.7 kcal/mol**)** demonstrated strong binding affinity, highlighting their capacity to interfere with tyrosine kinase-mediated signaling**,** which is frequently dysregulated in lung cancer.

For the apoptotic target CASP3**,** diosgenin (−8.7 kcal/mol) and solasodine (−8.5 kcal/mol) showed comparatively better interactions, suggesting their role in inducing apoptosis in cancer cells.

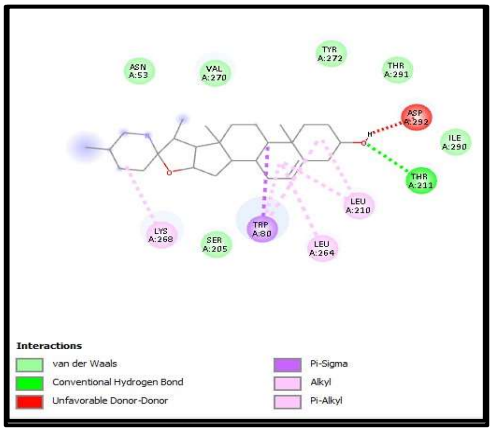


Fig. 7 3D & 2D structure of Solasodine – AKT1 Interaction Binding Affinity = -10.9kcal/mol

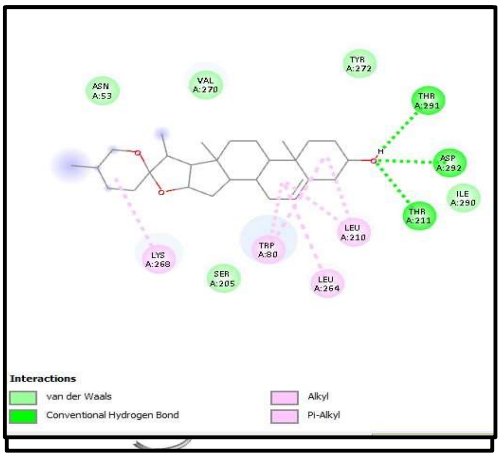


Fig. 8 3D & 2D structure of Diosgenin – AKT1 Interaction Binding Affinity = -10.9

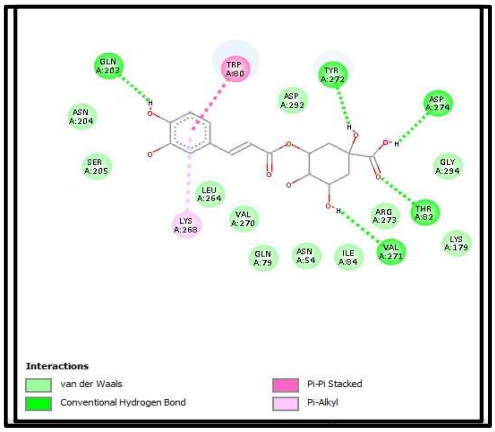


Fig. 9 3D & 2D structure of Chlorogenic acid – AKT1 Interaction Binding Affinity = -9.3kcal/mol

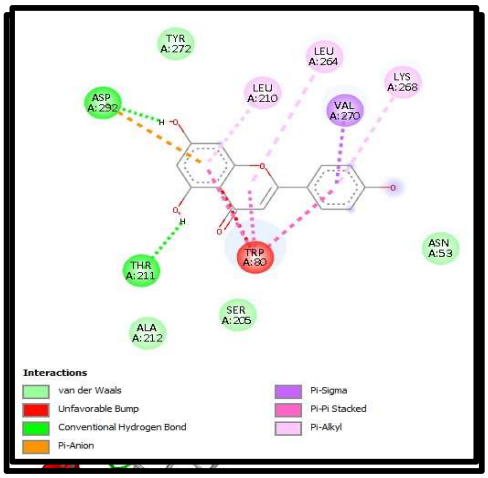


Fig. 10 3D & 2D Structure of Apigenin-AKT1 Interaction Binding Affinity = -9.1kcal/mol

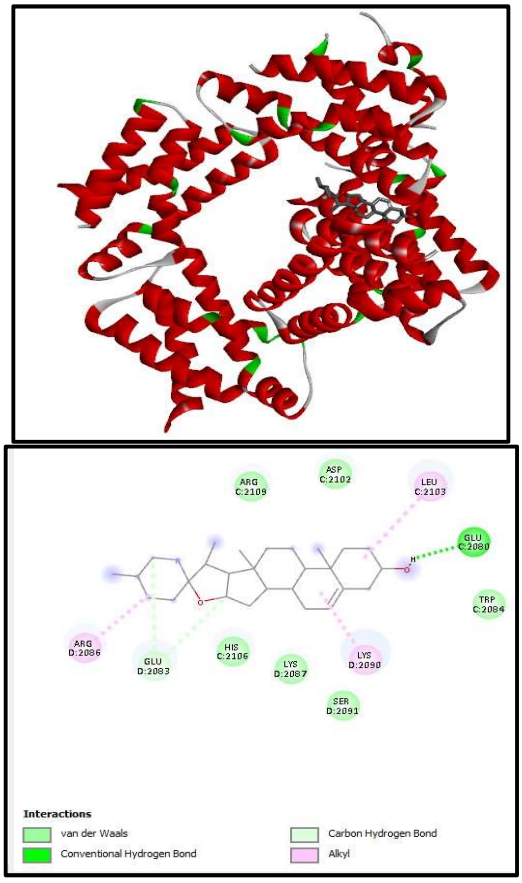


Fig. 11 3D & 2D structure of Solasodine-MTOR Interaction Binding Affinity = -9.5kcal/mol

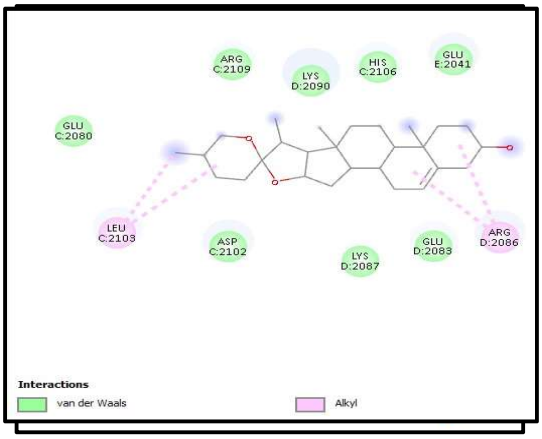


Fig. 12 3D & 2D structure of Diosgenin-MTOR Interaction Binding Affinity = -9.3kcal/mol

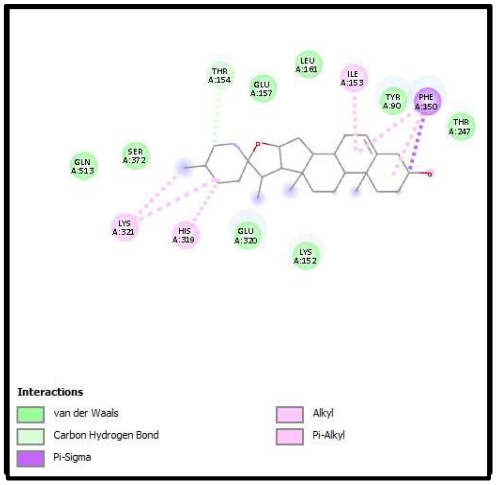


Fig. 13 3D & 2D structure of Solasodine-SRC Interaction Binding Affinity = -9.7kcal/mol

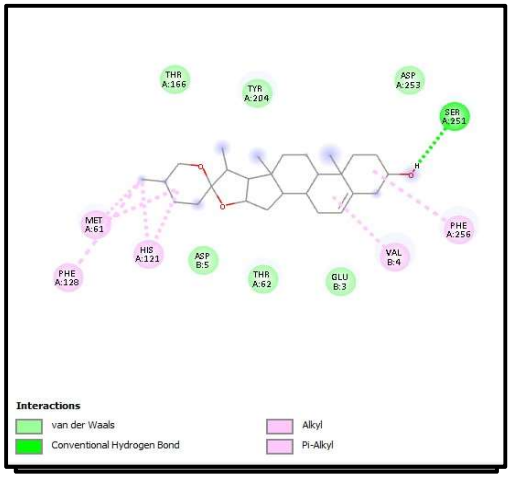


Fig. 14 3D & 2D structure of Diosgenin-CASP3 Interaction Binding Affinity = -8.7kcal/mol

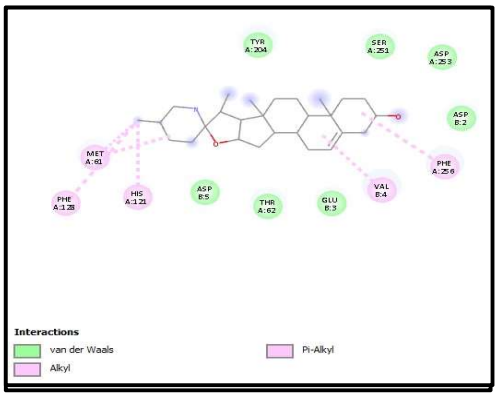


Fig. 15 3D & 2D structure of Solasodine-CASP3 Interaction Binding Affinity = 8.5kcal/mol

Discussion:

There is an urgent need in the advances of treatment of Lung cancer due to its increasing prevalence and higher mortality rates with small cell lung cancer exhibiting a more aggressive clinical course [26]. The primary cause is tobacco smoking, although environmental exposures such as radon, asbestos, air pollution and genetic mutations (e.g., EGFR, KRAS, ALK) contribute significantly [27]. However, several limitations persist, including late-stage diagnosis, limited accessibility and cost-effectiveness, therapeutic resistance, tumour heterogeneity and global disparities in healthcare access which continue to impede effective management and survival outcomes [28].Treatment of lung cancer such as chemotherapy, radiotherapy, targeted therapy and immunotherapy is commonly associated with side effects including fatigue, nausea, vomiting, mucositis, hair loss, myelosuppression and organ specific toxicities such as Pneumonitis [29]. Complementary approaches with Ayurveda may help in alleviating some of these symptoms along with dietary and lifestyle modifications that helps to improve the quality of life [30].

Solanum xanthocarpum belongs to *Dashamoola* and is widely used in respiratory ailments like *Kasa, Shwasa* and *Hridroga.* It is a *rasayana* drug and can be used both in preventive and therapeutics. Due to its *Ushna virya* (hot potency) it helps in pacifying *vata-kapha* and helps in reducing mucus secretion and airway obstruction. Phytochemical studies of *Kantakari* shows Phytoconstituents like Solasidine, flavonoids, saponins, Apigenin etc that contribute to its pharmacological effects [31].The plant has extensive pharmacological activities which include anti-inflammation, apoptosis inducing effect, anti-asthmatic effect, anti-oxidant activity and hepatoprotective activity [32].

Among the 24 phytoconstituents identified from *Solanum xanthocarpum* through the IMPPAT database, five compounds—Apigenin, Chlorogenic acid, Diosgenin, Esculetin, and Solasodine—were selected based on their drug-likeness characteristics and ADMET profiles. Apigenin and Esculetin demonstrated optimal pharmacokinetic properties with no violations of Lipinski's Rule of Five and high gastrointestinal absorption, suggesting favourable oral bioavailability. Furthermore, both compounds have been reported to exert anticancer effects through the modulation of key signalling molecules such as AKT1, ESR1, SRC, MMP9, and NF-κB, which are involved in tumour growth, invasion, and metastasis [33,34]. Diosgenin and Solasodine also exhibited high gastrointestinal absorption and acceptable lipophilicity despite a single Lipinski violation. Previous studies have demonstrated that these steroidal compounds exhibit significant anticancer activity by regulating apoptosis, cell-cycle progression, and oncogenic pathways, including the PI3K/AKT/mTOR and MDM2-mediated signaling pathways [35,36].

Although Chlorogenic acid showed comparatively low gastrointestinal absorption, it was included due to its well-established antioxidant, anti-inflammatory, and anticancer properties. Its ability to interact with apoptosis-related and metabolic targets such as CASP3, AKR1B1, and PYGL suggests it could play a role in tumour suppression and metabolic regulation [37]. Overall, the selected phytoconstituents showed favourable pharmacokinetic properties and multitarget therapeutic potential against cancer-associated proteins. Their documented biological activities and

interactions with crucial molecular targets supports their selection for subsequent network pharmacology, pathway enrichment, and molecular docking studies.

The GO enrichment analysis showed that the potential targets of *Solanum xanthocarpum* are primarily involved in biological processes linked to cell proliferation, apoptosis, protein phosphorylation, and oxidative stress response, all of which play critical roles the development and progression of Lung cancer. Cellular component analysis revealed enrichment in the cytoplasm, nucleus, and plasma membrane, while molecular function analysis highlighted protein kinase activity, ATP binding, and transcription factor binding. These findings indicate that the identified targets participate in key intracellular signaling mechanisms that regulate tumour growth, survival, and metastasis.

The KEGG pathway analysis showed significant enrichment of pathways related to non-small cell lung cancer, EGFR tyrosine kinase inhibitor resistance, small cell lung cancer, and several other cancer-associated pathways. Notably, the PI3K-Akt signaling pathway stood out as one of the most enriched pathways, suggesting its potential role in mediating the anticancer effects of *Solanum xanthocarpum* [38]. The enrichment of pathways in cancer, proteoglycans in cancer, and microRNAs in cancer further indicates that the selected phytoconstituents may produce therapeutic effects by regulating cell proliferation, apoptosis, angiogenesis, metastasis, and drug resistance.

Among the hub genes identified, AKT1, MTOR, SRC, and CASP3 were chosen for validation because of their central roles in the PPI network and cancer-related pathways. AKT1 and MTOR are key regulators of the PI3K/AKT/mTOR signaling pathway, which promotes tumour growth, survival, and therapeutic resistance [39]. SRC is involved in cancer cell proliferation, migration, and metastasis, and its elevated expression has been associated with poor clinical outcomes in lung cancer [40]. In contrast, CASP3 plays a critical role in apoptosis, and its altered expression reflects the disruption of programmed cell death mechanisms in cancer cells [41]. These findings suggest that the anticancer effects of *Solanum xanthocarpum* may be mediated through the modulation of multiple targets involved in tumour proliferation and apoptosis.

AKT1 is a key downstream effector of P13/AKT signaling pathway, which plays a pivotal role in regulating cell survival, proliferation and metabolism [42]. Dysregulation in this pathway is frequently observed in Non-small cell lung cancer which contributes to tumour initiation, progression and resistance to apoptosis [43]. Molecular docking showed Solasodine and diosgenin which are steroidal alkaloids may effectively interact with the active sites of AKT1, potentially leading to the inhibition of Kinase activity. These results are consistent with previous studies reporting that natural compounds with high binding affinity towards AKT1 can disrupt its phosphorylation and downstream signalling, thereby reducing cancer cell viability [44]. Similarly, chlorgenic acid and apigenin, though exhibiting slightly lower binding energies, still demonstrated substantial interaction with AKT1, supporting their potential role as modulators of this pathway.

Aberrant activation of mTOR is frequently driven by upstream molecular alterations, including mutations in EGFR or KRAS, as well as the loss of tumour suppressors such as PTEN. These changes result in persistent activation of the mTOR complexes, mTORC1 and mTORC2, which enhance protein synthesis, promote cell cycle progression, and suppress autophagy. Consequently, cancer cells acquire a proliferative advantage along with increased resistance to apoptosis [45]. Activation of mTORC1 further regulates downstream effectors, including S6 kinase (S6K) and 4E-BP1, thereby facilitating mRNA translation and protein synthesis necessary for rapid tumour growth [46]. In addition, mTORC2 activates AKT, reinforcing survival signalling pathways and contributing to therapeutic resistance. Clinically, elevated mTOR activity has been linked to poor prognosis and decreased overall survival in patients with lung cancer. As a result, mTOR has gained considerable attention as a therapeutic target, and several inhibitors, including rapamycin and its analogues, have been evaluated for the treatment of lung cancer. Nevertheless, the clinical benefits of these agents are often compromised by the activation of compensatory signalling pathways and the emergence of drug resistance.

The molecular docking suggested that solasodine and diosgenin exhibit strong binding affinities toward mTOR protein with -9.5 kcal/mol and -9.3 kcal/mol, respectively. These values indicate a higher likelihood of stable ligand-protein interaction. Such binding efficiency may be attributed to favourable hydrophobic interaction, hydrogen bonding and optimal conformational fitting within the active site of Mtor [47]. Further, the structural features of these steroidal compounds may facilitate their interaction with key residues in the mTOR active site, potentially leading to effective inhibition of Kinase activity [48]. Additional validation through molecular dynamics simulation, in vitro kinase assays and cellular studies is necessary to conform their inhibitory potential and biological efficacy.

The SRC gene is a well-characterized proto-oncogene that encodes a non-receptor tyrosine kinase involved in a variety of intracellular signaling processes [49]. Aberrant activation of SRC contributes to malignant transformation by promoting sustained downstream signaling through key pathways, including PI3K/AKT, RAS/MAPK, and STAT [50]. Molecular docking analysis revealed that Diosgenin and solasodine exhibited strong binding affinity towards SRC, with docking scores of -9.7kcal/mol. This high binding affinity suggests a stable interaction with the active or regulatory sites of SRC kinase domain, which could potentially inhibit its catalytic activity. These finding are especially significant for lung cancer, where SRC, diosgenin and solasidine may interfere with its phosphorylation activity, thereby dampening downstream oncogenic pathways like PI3K/AKT and MAPK. This could lead to reduced cell proliferation, survival, and metastatic potential. Additionally, previous studies have shown that natural compounds can function as kinase inhibitors by targeting ATP binding sites or allosteric regions of tyrosine kinase[51].

The observed binding affinity of diosgenin and solasodine in this study is comparable to, or on some cases exceeds, that of known SRC inhibitors, suggesting their potential as lead compounds for targeted therapy development. Additionally, the ability of these compounds to target SRC may also have implications for overcoming drug resistance in cancer and by its role in mediating resistance, it could enhance therapeutic sensitivity and improve treatment outcomes [52].

CASP3 encodes caspase-3, a crucial executioner protease in the apoptotic pathway that plays a major role in programmed cell death. Upon activation, caspase-3 cleaves multiple cellular substrates, resulting in DNA fragmentation, cytoskeletal degradation, and ultimately apoptosis. In lung cancer, particularly NSCLC, dysregulation of caspase-3 expression and activity has been connected to poor clinical outcomes and reduced responsiveness to chemotherapeutic agents, highlighting its importance in progression of cancer and its treatment [53].

Tumour cells often develop mechanisms to suppress apoptotic signaling upstream of caspase-3 activation, thereby preventing its proteolytic function[54]. Several studies have reported that activation of caspase-3 increases the sensitivity of lung cancer cells to anticancer treatments by facilitating apoptotic cell death, thereby enhancing the therapeutic effectiveness of these interventions. Thus, targeting CASP3 or its regulatory pathway remains a promising approach in cancer therapeutics [55]. In the present study, molecular docking revealed that diosgenin and solasodine exhibited favourable binding affinities toward CASP3, with docking scores -8.7 kcal/mol and -8.5 kcal/mol, respectively. The interaction of these compounds with CASP3 may facilitate conformational changes that promote enzyme activation or enhance substrate accessibility, thereby triggering apoptotic signaling. By potentially restoring or enhancing caspase-3 activity, diosgenin and solasodine may contribute to the induction of apoptosis and inhibition of tumour growth. It is also seen that diosgenin have been previously reported to induce apoptosis through activation pf caspase-dependent pathways, including caspase-3 [56].Similarly, solasodine has demonstrated pro-apoptotic effects in various cancer models by modulating mitochondrial pathways and activating downstream caspases [57]. Thus, the present docking results support these findings at a molecular level, providing structural evidence with CASP3.

The present findings are supported by previous experimental studies demonstrating the anticancer potential of *Solanum xanthocarpum*. Various extracts and phytoconstituent-based preparations of the plant have exhibited significant cytotoxic and antiproliferative activities against different cancer cell lines. Fruit extracts of *S. xanthocarpum* demonstrated notable cytotoxic activity, causing 70–91% growth inhibition in leukemia (THP-1) and lung cancer (HOP-62) cell lines. These findings suggest the presence of potent bioactive constituents that may effectively suppress tumour cell proliferation and contribute to the plant's anticancer potential [58].

Earlier research has also reported that sarsapogenin and diosgenin (steroidal components), derived from *S. xanthocarpum* and *Asparagus racemosus*, effectively induce programmed cell death in colon carcinoma cells, supporting the anticancer potential of these medicinal plants [59]. Additional evidence supporting the anticancer potential of Solanum xanthocaprum has emerged from studies employing gren nanotechnology-based approaches. Gold nanoparticles synthesized using leaf extracts of *S. xanthocarpum* demonstrated significant cytotoxic activity against the masopharyngeal carcinoma cell line C666-1. The synthesized nanoparticles were shown to induce apoptosis through a mitochondrial – dependent pathway while simultaneously promoting autophagy, leading to a marked reduction in cell viability and suppression of colony formation. These findings indicate that the phytoconstituents present can serve as effective bio-reducing and stabilizing agents during nanoparticle synthesis, thereby enhancing their overall anticancer activity [60].

The involvement of immunomodulatory pathways has also been proposed as an important mechanism underlying the anticancer activity of *S.*

xanthocarpum. Khandelwal et al. demonstrated that aqueous extracts of the plant significantly modulated Interleukin-2 (IL-2) expression in the N1S1 rat hepatocellular carcinoma cell line. Treatment with higher extract concentrations resulted in marked alterations in IL-2 production and gene expression, suggesting that the plant may influence tumour progression through immune-mediated pathways in addition to direct cytotoxic effects.

Collectively, the available evidence suggests that *S. xanthocarpum* exhibits significant anticancer potential through multiple mechanisms, including the induction of apoptosis, suppression of cancer cell proliferation, modulation of autophagy, and regulation of immune responses. These findings are in agreement with the present network pharmacology study and further support the potential of *S. xanthocarpum* as a valuable source of anticancer phytoconstituents. However, further preclinical and clinical studies are required to validate its activity and therapeutic applications in cancer management.

Conclusion:

This study demonstrated the potential anticancer activity of *Solanum xanthocarpum* against lung cancer using network pharmacology and molecular docking analyses. Solasodine, Apigenin, Diosgenin, and Chlorogenic acid were identified as the key bioactive compounds, while AKT1, MTOR, SRC, and CASP3 emerged as the major molecular targets. The findings suggest that *Solanum xanthocarpum* may act through multiple pathways involved in cancer progression and could serve as a promising adjunct to conventional chemotherapy. Furthermore, the study highlights the importance of in silico approaches in elucidating the molecular mechanisms of Ayurvedic drugs and provides a scientific basis for their further experimental and clinical validation.

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Ethics Approval

Not Applicable.

Consent to Participate

Not Applicable

Consent for Publication

Not Applicable

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