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Exploring the Anti-Cancer Mechanisms of Oxalis corniculata Through Integrated Network Pharmacology, Protein-Protein Interaction Network, and MCODE Cluster Analysis

Adiveppa Nashipudi[1], Mosin Karimkhan[2], Anbuselvam A[3], Yuvaraj Patil[4]

[1,2,3,4]Assistant Professor
[1]Department of Dravyaguna Vigyan, [2]Department of Rachana Sharira, [3]Kayachikitsa Department, [4]Samhita Siddhanta Department
[1,2,3,4]Dr. Ravi Patil Ayurvedic Medical College Hospital and Research Centre, Honaga, Belagavi – 591156.

Abstract

Oxalis corniculata Linn, commonly known as creeping wood sorrel, is a medicinal herb traditionally used for various ailments including inflammation, wounds, and gastrointestinal disorders. Recent studies have hinted at its potential anticancer activity, but the underlying molecular mechanisms remain largely unexplored. This study employs an integrated network pharmacology approach, protein-protein interaction [PPI] network construction, and MCODE cluster analysis to elucidate the possible anticancer mechanisms of O. corniculata. Twenty bioactive phytoconstituents including flavonoids, phenolic acids, terpenoids, and sterols were identified through literature mining and database retrieval. Digep pred database and GeneCards analysis revealed 85 overlapping targets between phytochemical-associated proteins and cancer-related genes. PPI network construction followed by MCODE clustering uncovered critical hub proteins such as KRAS, CDK4, EP300, MDM2, and NOTCH1 involved in cell cycle regulation, transcription, apoptosis, and oncogenic signaling pathways. Gene Ontology and KEGG enrichment analyses revealed modulation of biological processes including apoptosis, DNA damage response, signal transduction, and proliferation. Significantly enriched pathways included Pathways in cancer, MicroRNAs in cancer, and ErbB signaling pathway. A comprehensive compound–target–pathway [C–T–P] network identified Apigenin, KRAS, and the Pathways in cancer node as major hubs, while Cytohubba analysis highlighted p-hydroxybenzoic acid, Acacetin, Vanillic acid, and key signaling proteins as central regulators. These findings provide a systems level insight into the multi-targeted anti-cancer potential of O. corniculata, suggesting its promise as a phytopharmaceutical candidate for integrative oncology.

Keywords: Oxalis corniculata, Anti-cancer, Network pharmacology, Protein-protein interaction, MCODE, Systems biology

1. Introduction

Cancer remains one of the leading causes of mortality worldwide, accounting for nearly 10 million deaths annually [1]. Characterized by uncontrolled cellular proliferation, evasion of apoptosis, and potential metastasis, cancer encompasses a broad spectrum of diseases involving genetic, epigenetic, and environmental factors [2]. Among the various types, lung, breast, colorectal, prostate, and liver cancers constitute the majority of global cancer incidences [3]. Despite significant advancements in diagnostics and therapeutics, the global burden of cancer continues to rise, necessitating the exploration of alternative therapeutic strategies, including those derived from natural sources [4]. The etiology of cancer is multifactorial, involving both intrinsic factors such as mutations in oncogenes and tumor suppressor genes [TP53, BRCA1/2, RAS, MYC] and extrinsic factors including exposure to carcinogens, chronic inflammation, poor lifestyle, and infections [HPV, HBV, H. pylori] [5, 6]. These etiological agents trigger complex pathophysiological changes, including sustained proliferative signaling, resistance to cell death, angiogenesis, invasion, and immune evasion [7]. One of the hallmarks of cancer is the dysregulation of signaling pathways such as PI3K/Akt/mTOR, MAPK, Wnt/β-catenin, NF-κB, and JAK/STAT, which contribute to tumor growth and progression [8].

The current therapeutic landscape includes chemotherapy, radiotherapy, immunotherapy, targeted therapy, and hormonal therapy [9]. Chemotherapeutic agents such as paclitaxel, cisplatin, doxorubicin, and 5-fluorouracil are widely used in the treatment of various cancers [10]. Targeted therapies like tyrosine kinase inhibitors [imatinib, erlotinib], monoclonal antibodies [etrastuzumab, cetuximab], and immune checkpoint inhibitors [pembrolizumab, nivolumab] have revolutionized cancer treatment, providing improved survival benefits in specific cancer types [11-13]. However, despite these advancements, several limitations hinder their clinical efficacy [14].

The limitations of conventional therapies include drug resistance, non-specificity, high toxicity, severe adverse effects, and high cost. Chemotherapeutic agents, for example, often cause myelosuppression, gastrointestinal toxicity, nephrotoxicity, cardiotoxicity, and neurotoxicity, which can severely impact patient quality of life [15-17]. Moreover, tumor heterogeneity and the dynamic nature of cancer evolution contribute to therapy resistance, necessitating the need for alternative, safe, and multi-targeted therapeutic approaches.

In recent years, herbal medicines and plant-derived compounds have garnered significant attention due to their multi-targeted actions, lower toxicity, and cost-effectiveness [18, 19]. Plants are a rich source of secondary metabolites such as alkaloids, flavonoids, terpenoids, and phenolic compounds that possess anti-cancer properties through various mechanisms including apoptosis induction, cell cycle arrest, inhibition of angiogenesis, and suppression of metastasis [20, 21]. Several plant-derived drugs like vincristine, vinblastine, paclitaxel, camptothecin, and podophyllotoxin have already been integrated into clinical practice, demonstrating the therapeutic potential of phytochemicals [22, 23].

Oxalis corniculata [creeping wood sorrel] is a medicinal herb traditionally valued for its anti-inflammatory and antimicrobial properties [24]. Recent evidence suggests its anti-cancer potential,

linked to flavonoids, phenolic acids, and triterpenoids. However, its molecular mechanisms remain unclear. Network pharmacology, integrated with protein–protein interaction [PPI] analysis and MCODE clustering, enables a systems-level understanding of its multi-target actions. By leveraging phytochemical, gene-target, and pathway data, this approach reveals key targets and pathways involved in the anti-cancer effects of O. corniculata [25, 26].

This study aims to investigate the anti-cancer mechanisms of Oxalis corniculata using an integrated approach comprising network pharmacology, PPI network construction, and MCODE cluster analysis. The findings from this study will provide valuable insights into the molecular basis of its therapeutic action and support the development of plant-based alternatives for effective cancer treatment with reduced side effects.

2. Materials and Methods

2.1. Identification and Collection of Phytoconstituents of Oxalis corniculata

A comprehensive collection of phytoconstituents present in Oxalis corniculata was undertaken through a systematic review of the scientific literature and phytochemical databases. Peer-reviewed research articles were retrieved using keyword combinations such as "Oxalis corniculata phytochemicals", "Oxalis corniculata bioactive compounds", and "ethnomedicinal uses of Oxalis corniculata" from established electronic databases, including PubMed [https://pubmed.ncbi.nlm.nih.gov/], Scopus, and Google Scholar [https://scholar.google.com/]. Additionally, structured data were mined from specialized phytochemical and ethnobotanical databases such as Dr. Duke's [https://phytochem.nal.usda.gov/] Phytochemical and the Indian Medicinal Plants Phytochemistry and Therapeutics [IMPPAT] database [27]. The chemical identities of the bioactive constituents were confirmed using the PubChem database [https://pubchem.ncbi.nlm.nih.gov/], and their SMILES [Simplified Molecular Input Line Entry System] notations were retrieved to facilitate downstream in silico target prediction analysis.

2.2. Target Prediction of O. corniculata Phytoconstituents and Cancer-Associated Genes

The biological targets of each identified phytoconstituent were predicted using Digep pred database [https://www.way2drug.com/ge/], a reliable web-based tool that utilizes 2D and 3D molecular similarity to predict probable protein targets in Homo sapiens [28]. Only those targets with a probability score >0.5 were retained for further analysis to enhance prediction specificity. For disease relevance, cancer-associated genes were compiled using GeneCards [https://www.genecards.org/] database [29]. The keyword "cancer" was used to screen for relevant oncogenes and tumor suppressor genes. In the GeneCards database, a relevance score cut-off >17.50 was applied to filter genes with strong associations to cancer-related pathologies. The overlapping targets between the predicted phytoconstituent targets and the cancer-related genes were identified using Venny 2.1.0 [https://bioinfogp.cnb.csic.es/tools/venny/], a Venn diagram-based tool for intersection analysis. These common targets were subsequently selected for protein-protein interaction network construction and clustering analysis.

2.3. Construction of Compound–Target Interaction Network

The intersection of O. corniculata compound targets and cancer-associated genes formed the basis of the compound–target interaction network. This network was visualized and analyzed using Cytoscape version 3.10.3. Each node represented a compound or a gene/protein target, and edges denoted the interactions or associations between them. Topological parameters such as degree centrality [number of connections per node] and betweenness centrality [influence of a node over the flow of information] were calculated using the NetworkAnalyzer tool integrated within Cytoscape to identify key bioactive compounds and potential hub targets [30].

2.4. Construction of the Protein–Protein Interaction [PPI] Network

To understand the molecular interactions among the shared target genes, a Protein–Protein Interaction [PPI] network was constructed using the STRING database [https://string-db.org/]. The species was limited to Homo sapiens, and a minimum required interaction score of 0.400 [medium confidence] was applied. The resulting network was exported in tab-delimited format and imported into Cytoscape version 3.10.3 for advanced visualization and analysis. For the identification of highly interconnected regions within the PPI network, Molecular Complex Detection [MCODE] plugin in Cytoscape was employed. These clusters, or molecular complexes, often represent functionally significant modules or signaling hubs in biological systems. The MCODE analysis was carried out using the following optimized parameters: Degree Cutoff: 2, Node Score Cutoff: 0.2, K-Core: 2 and Max Depth: 100. The top-scoring clusters were selected for further enrichment analysis to identify the most functionally relevant gene modules involved in cancer pathways [31].

2.6. Gene Ontology and KEGG Pathway Enrichment Analysis

The core targets derived from the PPI network and significant MCODE clusters were subjected to functional enrichment analysis using the Kyoto Encyclopedia of Genes and Genomes [KEGG] database and Gene Ontology [GO] annotations. GO enrichment was conducted for three major categories: Biological Process [BP], Cellular Component [CC], and Molecular Function [MF]. KEGG pathway analysis was performed to uncover key signaling cascades and biological pathways implicated in cancer progression and therapy. Only pathways and GO terms with p-values < 0.05 were considered statistically significant. For graphical representation and easier biological interpretation, a Scatter Ratio [SR] plot was constructed to visualize enriched pathways and gene ontology terms. These visualizations provided insight into the functional roles of the target genes and the mechanistic pathways modulated by the phytoconstituents of Oxalis corniculata in the context of cancer [32].

Construction of network

To construct the interaction networks, two distinct files were prepared: [**i**] a compound-target file, containing the names of bioactive compounds from Oxalis corniculata and their corresponding predicted protein targets, and [**ii**] a pathway-target file, listing enriched KEGG pathways and the associated genes involved. These files were imported into Cytoscape [v3.10.3] for network visualization and analysis. Both networks were customized using the “Style” panel to apply specific visual mappings based on node attributes such as node type, size [based on degree centrality], and color [based on function or classification]. The “Merge Networks” feature in Cytoscape was optionally used to integrate both

networks into a comprehensive compound–target–pathway network, offering a systems-level view of how O. corniculata phytoconstituents potentially modulate cancer-related pathways. Topological parameters such as degree, closeness, and betweenness centrality were analyzed using the Networkanalyzer plugin to identify key regulatory nodes [hub genes or major compounds], thereby providing mechanistic insights into the multi-target and multi-pathway interactions underlying the anti-cancer potential of Oxalis corniculata [33].

Results and discussion

3. Results

3.1. Identification of Phytoconstituents from Oxalis corniculata

Through a comprehensive literature survey and phytochemical database mining, a total of 20 bioactive compounds were identified from Oxalis corniculata. These included major classes such as flavonoids [Apigenin, Isoorientin, Swertisin, Acacetin, Isovitexin, Vitexin and 5-Hydroxy-7,8-dimethoxyflavone], phenolic acids [P-hydroxy benzoic acid, Vanillic acid, Syringic acid, Tartaric acid and Citric acid etc.,], terpenoids, and sterols. The structures and SMILES notations of these compounds were retrieved from the PubChem database for use in target prediction analysis.

3.2. Prediction of Potential Targets for Phytoconstituents and Identification of Cancer-Associated Genes

Using Digep pred database [https://www.way2drug.com/ge/], approximately 725 unique human protein targets were predicted for the 20 phytochemicals, with each compound associated with multiple targets. After filtering using a probability threshold of >0.5, was retained. Simultaneously, a total of 915 cancer-associated genes were retrieved from GeneCards with filtered by a relevance score >17.50 to ensure strong cancer association. By comparing the compound-related targets with the cancer-associated gene set using Venny 2.1, a total of 85 overlapping targets were identified [**Figure 1**]. These common targets were considered to be potential mediators of the anti-cancer effects of O. corniculata and were selected for network and enrichment analyses.

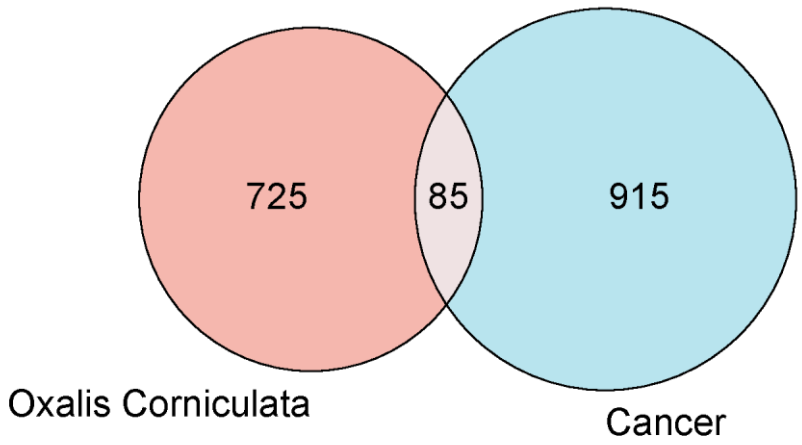

Figure 1: Intersection targets between oxalis corniculata and cancer

3.4. Protein–Protein Interaction [PPI] Network and MCODE Cluster Analysis

The 85 overlapping targets were submitted to the STRING database to construct the PPI network, which consisted of 84 nodes and 755 edges, expected number of edges 295, Avg node degree 18 and avg. local clustering coefficient 0.56. The network was visualized and analyzed in Cytoscape 3.10.3, revealing dense interconnectivity among key proteins involved in cancer-related signaling [**Figure 2**]. The MCODE cluster analysis reveals key functional modules involved in cancer pathogenesis based on the protein-protein interaction network of Oxalis corniculata target genes [**Figure 3**]. Cluster 1, the highest-scoring module [Score: 17.379], includes critical regulators such as AR, AURKA, CDK4, CTNNB1, EP300, KRAS, MAPK8, MDM2, and NOTCH1, which are central to pathways governing cell cycle progression, DNA repair, transcriptional regulation, epithelial–mesenchymal transition [EMT], and oncogenic signaling [MAPK, PI3K/Akt]. Aberrations in these genes are commonly associated with uncontrolled cell proliferation, apoptosis evasion, and tumor metastasis. Cluster 2 [Score: 6] contains pro-survival and apoptotic regulators like MCL1, CASP8, and STAT5A/B, implicating it in apoptosis dysregulation and immune evasion, common features in hematological and solid tumors. Cluster 3 [Score: 4] includes prostate cancer-associated genes such as RNASEL, ELAC2, and TMPRSS2, reflecting its involvement in androgen receptor signaling and prostate tumorigenesis. Lastly, Cluster 4 [Score: 3.3] comprises angiogenesis and fibrosis-related genes [FLT1, TGFB2, CCL5, FGFR1], pointing to roles in tumor vascularization, inflammation, and tumor microenvironment remodeling [**Table 1**]. Collectively, these clusters underscore the multi-target potential of Oxalis corniculata in modulating critical cancer pathways such as proliferation, apoptosis, angiogenesis, and metastasis.

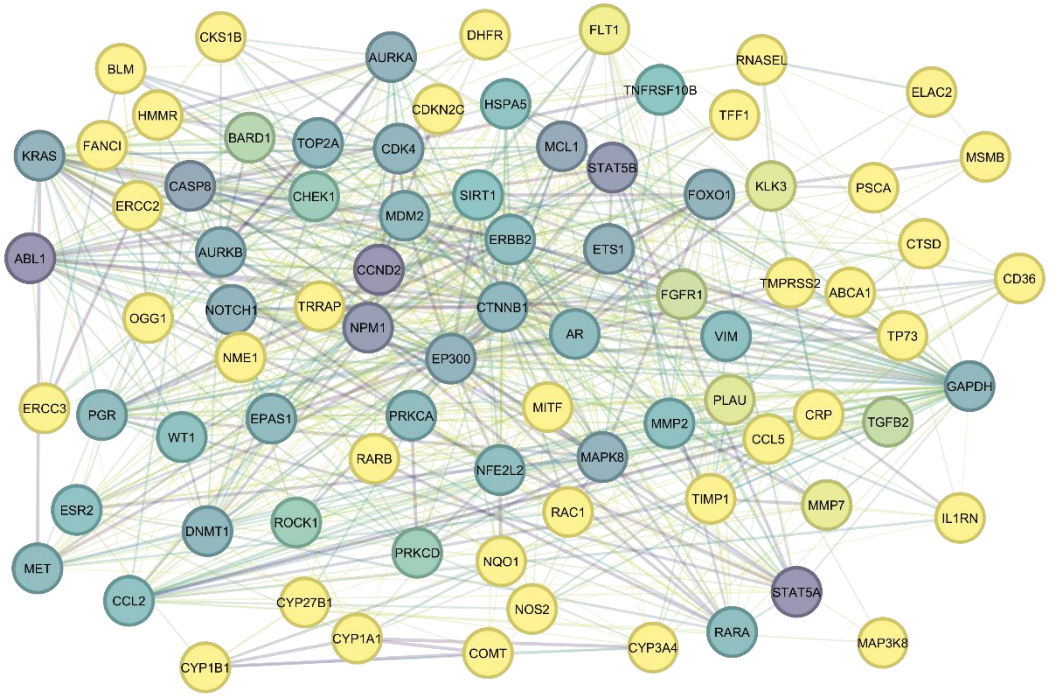

Figure 2: Protein-Protein Interaction [PPI] network.

Table 1: MCODE [Molecular Complex Detection] analysis

Cluster	Score	Nodes	Edges	Targets
1	17.379	30	252	AR, AURKA, AURKB, CCL2, CDK4, CTNNB1, DNMT1, EP300, EPAS1, ERBB2, ESR2, ETS1, FOXO1, GAPDH, HSPA5, KRAS, MAPK8, MDM2, MET, MMP2, NFE2L2, NOTCH1, PGR, PRKCA, RARA, SIRT1, TNFRSF10B, TOP2A, VIM, WT1
2	6	7	18	ABL1, CASP8, STAT5B, STAT5A, MCL1, CCND2, NPM1
3	4	4	6	RNASEL, ELAC2, TMPRSS2, MSMB
4	3.3	4	5	CCL5, FLT1, TGFB2, FGFR1

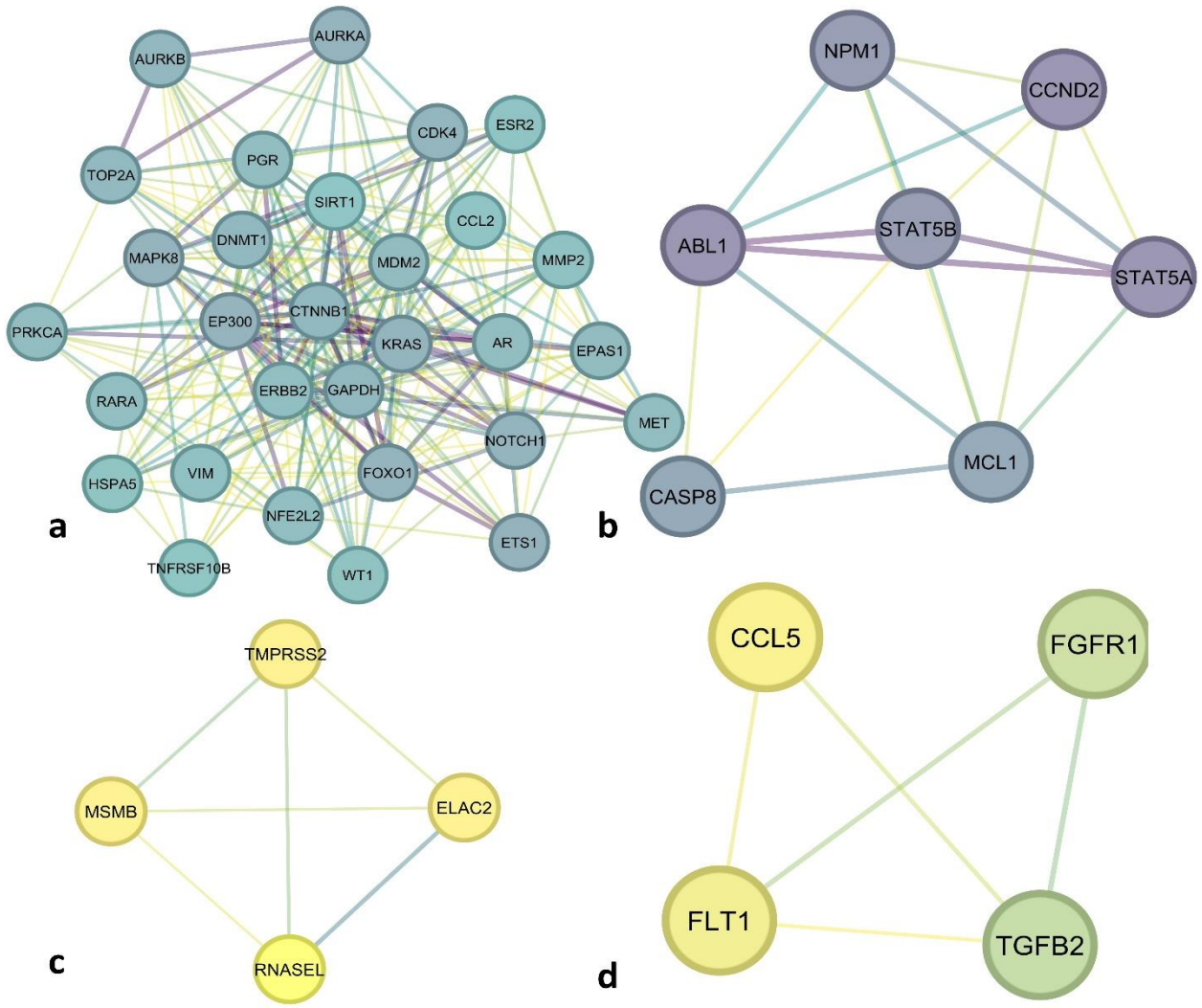

Figure 3: MCODE [Molecular Complex Detection] analysis

3.5. Gene Ontology [GO] and KEGG Pathway Enrichment Analysis

The Gene Ontology [GO] enrichment analysis of Oxalis corniculata target genes across biological processes, molecular functions, and cellular components reveals a multifaceted anti-cancer mechanism involving key hallmarks of cancer progression. In the biological process category, the targets were significantly involved in regulating apoptosis [GO:0042981] and programmed cell death [GO:0043068], through genes like SIRT1, AURKA, KRAS, and CASP8, indicating a role in restoring cancer cell death pathways. The regulation of signal transduction [GO:0009966] and gene expression [GO:0010468] further supports the compound's influence on transcriptional control and intracellular signaling, impacting oncogenes such as EP300, NOTCH1, and FOXO1. Enrichment in processes like response to stress [GO:0033554] and radiation [GO:0009314] highlights the potential role of these targets in enhancing DNA damage responses and overcoming chemoresistance. Additionally, the regulation of cell cycle [GO:0051726] and cell migration [GO:0030334] indicates inhibition of proliferation and metastasis via key genes such as CDK4, CCND2, and MET. From the molecular function perspective, the enriched terms such as protein binding [GO:0005515], kinase activity [GO:0016301], and catalytic activity [GO:0003824] illustrate how O. corniculata targets key proteins involved in phosphorylation, enzymatic regulation, and protein–protein interactions vital for tumor progression. Targets like KRAS, MAPK8, PRKCA, and EP300 suggest modulation of signal transduction, matrix remodeling, and transcription. Binding-related terms, including organic/heterocyclic compound binding and nucleotide binding, further imply the interaction versatility of phytoconstituents, potentially disrupting oncogenic molecular pathways. In the cellular component category, the enrichment of targets in the nucleus [GO:0005634], nucleoplasm, and chromatin underscores their roles in gene regulation and chromosomal stability. Localization in the cytosol, transcription regulator complexes, and intracellular organelle lumens reflects the involvement of these proteins in signaling hubs and regulatory machinery [**Figure 4**]. Together, these findings support that Oxalis corniculata exerts anti-cancer activity through a multi-target, multi-pathway mechanism, influencing apoptosis, transcriptional regulation, signal transduction, and stress responses making it a promising candidate for integrative cancer therapeutics.

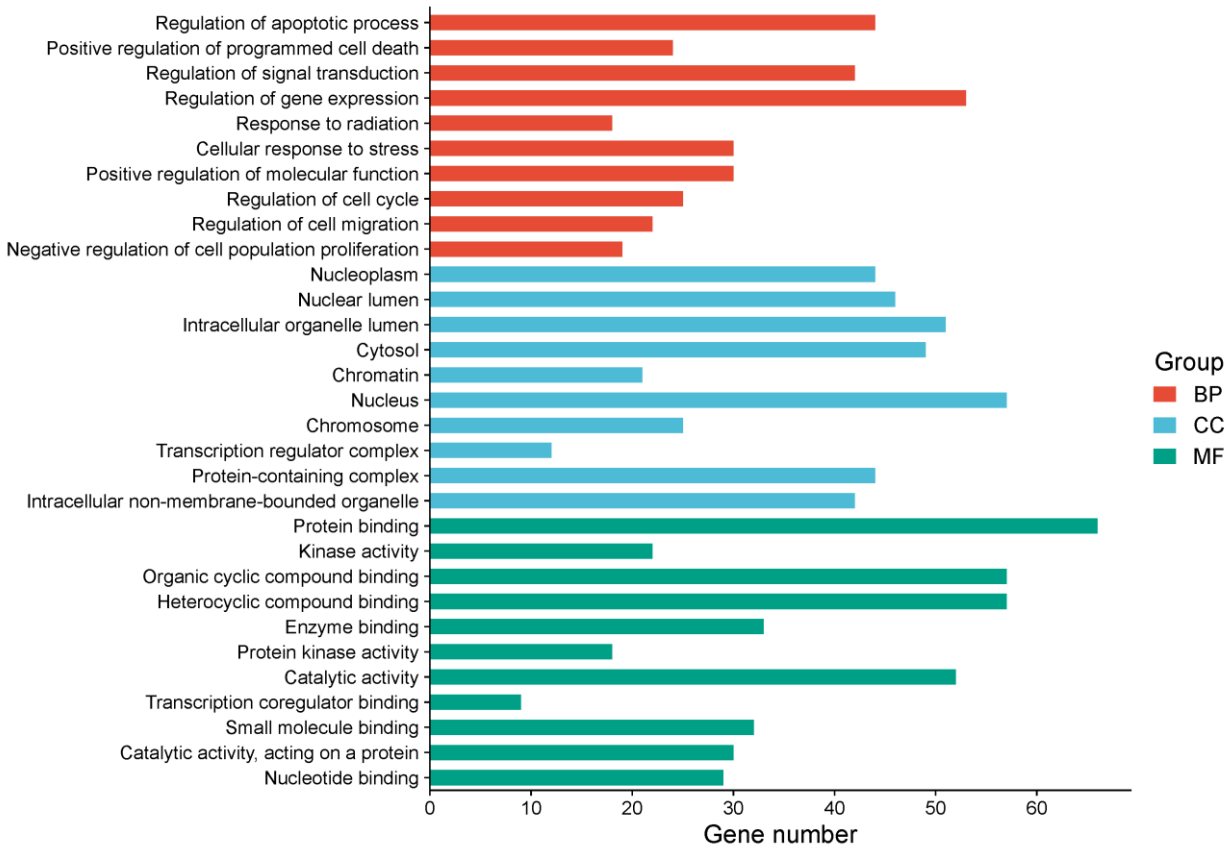

Figure 4: Gene ontology enrichment of analysis of Oxalis corniculata for treatment of cancer.

KEGG [Kyoto Encyclopedia of Genes and Genomes] pathway enrichment analysis

The KEGG pathway enrichment analysis of Oxalis corniculata target genes highlights its broad therapeutic potential in cancer treatment by modulating key oncogenic signaling networks. The most significantly enriched pathway, Pathways in cancer, involves 31 genes such as KRAS, CDK4, MDM2, ERBB2, FOXO1, MAPK8, and NOTCH1, which play central roles in cell proliferation, survival, metastasis, and angiogenesis. Other significantly enriched pathways include MicroRNAs in cancer, involving genes like SIRT1, MDM2, and DNMT1, indicating regulation at the post-transcriptional level that affects tumor suppression and oncogene expression. Specific cancer types, such as prostate, breast, bladder, and hepatocellular carcinoma, were represented with critical targets like AR, PLAU, FGFR1, and PRKCA, reflecting the phytoconstituents' relevance across diverse cancer phenotypes. Moreover, pathways like Transcriptional misregulation in cancer and Proteoglycans in cancer suggest effects on gene expression, extracellular matrix remodeling, and tumor microenvironment modification. The presence of KRAS, ERBB2, MAPK8, and FGFR1 in pathways such as EGFR tyrosine kinase inhibitor resistance, central carbon metabolism in cancer, and choline metabolism in cancer underscores the role of O. corniculata in targeting metabolic reprogramming and resistance mechanisms common in cancer therapy. Notably, the ErbB signaling pathway, enriched with 7 genes including KRAS, ERBB2, and STAT5B, further emphasizes the modulation of growth factor-driven tumorigenesis [**Figure 5**]. Collectively, these findings reveal that Oxalis corniculata may combat cancer through a multi-pathway, multi-target strategy, impacting genetic regulation, signaling cascades, metabolic adaptation, and

resistance mechanisms, thus presenting itself as a promising candidate for integrative and precision oncology approaches.

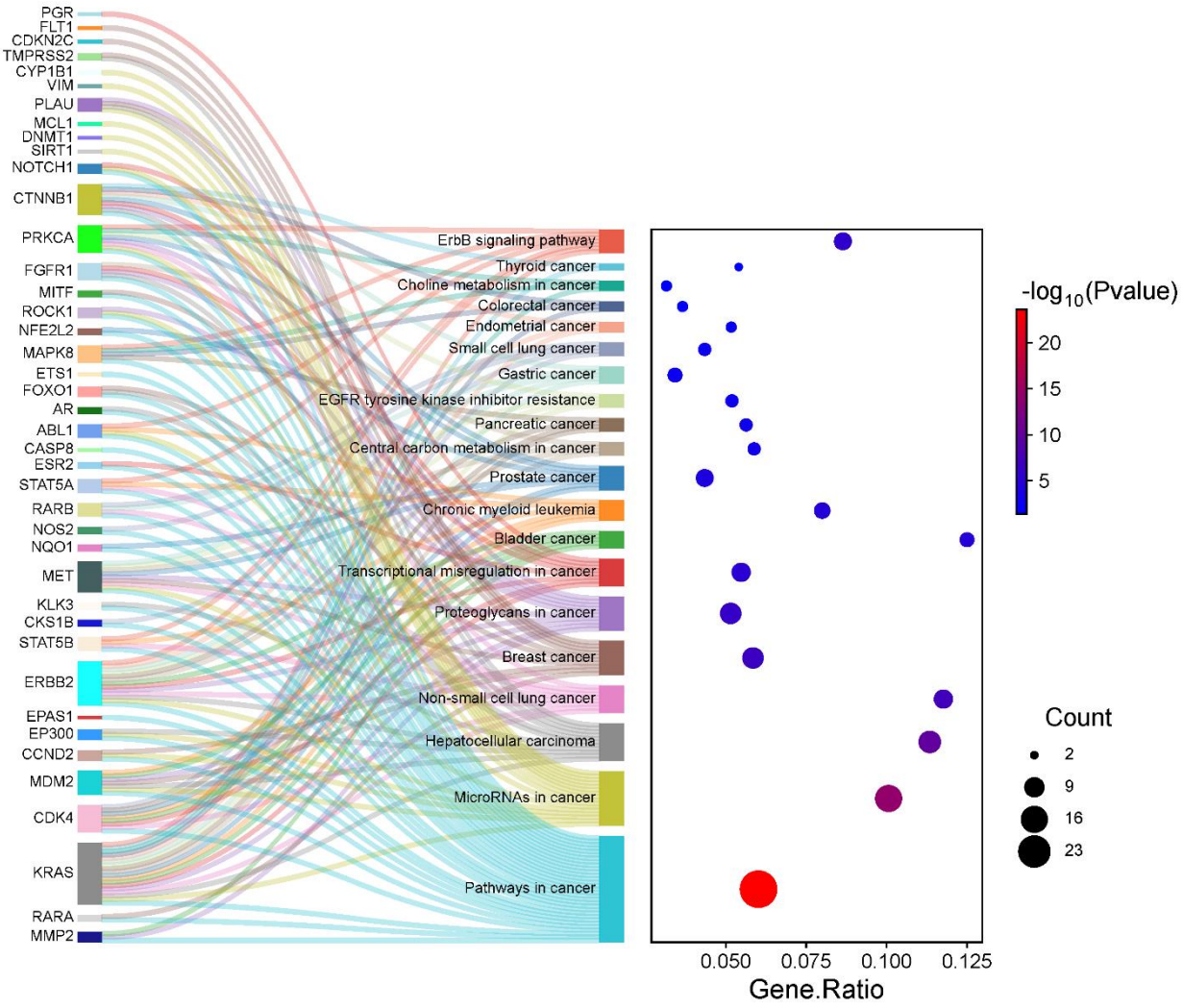

Figure 5: KEGG pathway analysis of selected signaling pathways involved in the treatment of lung cancer.

3.6. Integrated Compound–Target–Pathway Network Analysis

To gain a comprehensive understanding of the mechanistic interplay between phytoconstituents, molecular targets, and signaling cascades, an integrated compound–target–pathway [C–T–P] network was constructed using Cytoscape software by merging the individual compound–target and pathway–target interaction datasets [**Figure 6**]. The resultant network comprised 81 nodes-including bioactive compounds, target proteins, and KEGG pathways and 425 edges, illustrating a complex systems-level interaction map through which Oxalis corniculata phytochemicals potentially exert anti-cancer effects.

Network topology analysis revealed Apigenin, KRAS, and the "Pathways in cancer" module as the most central and influential nodes, indicating their pivotal roles in mediating therapeutic responses. Notably, Apigenin exhibited extensive polypharmacological interactions by targeting 29 key cancer-associated

proteins: NOTCH1, NQO1, PGR, EP300, SIRT1, MCL1, KRAS, AR, DNMT1, CDKN2C, EPAS1, PLAU, CKS1B, NOS2, CASP8, MET, MDM2, NFE2L2, CTNNB1, KLK3, FLT1, FGFR1, MMP2, MAPK8, RARB, MITF, ERBB2, ROCK1, and FOXO1. Further, hub node analysis performed using the Cytohubba plugin identified Apigenin, p-Hydroxybenzoic acid, Vanillic acid, Acacetin, 5-Hydroxy-7,8-dimethoxyflavone, "Pathways in cancer", KRAS, ERBB2, MET, and RARB as key regulatory nodes [**Figure 7**]. These central elements likely serve as major contributors to the observed multi-targeted anti-cancer potential of O. corniculata, underscoring the therapeutic relevance of its phytoconstituents in modulating diverse oncogenic signaling networks.

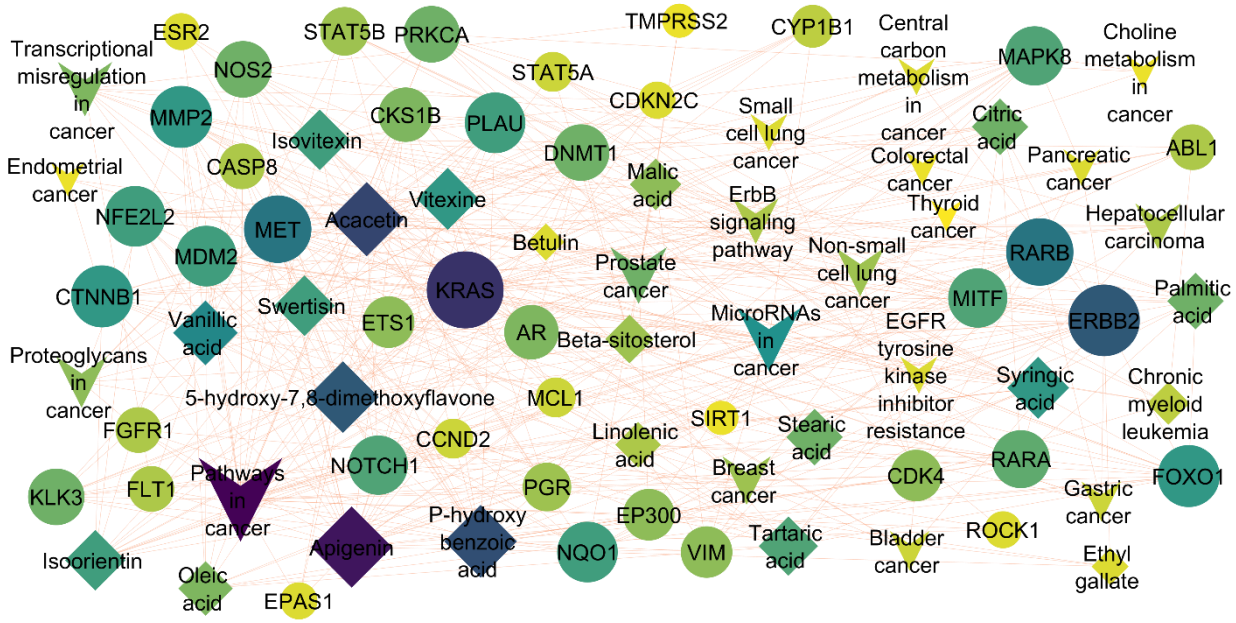

Figure 6: Network analysis oxalis corniculata involved in treatment of cancer.

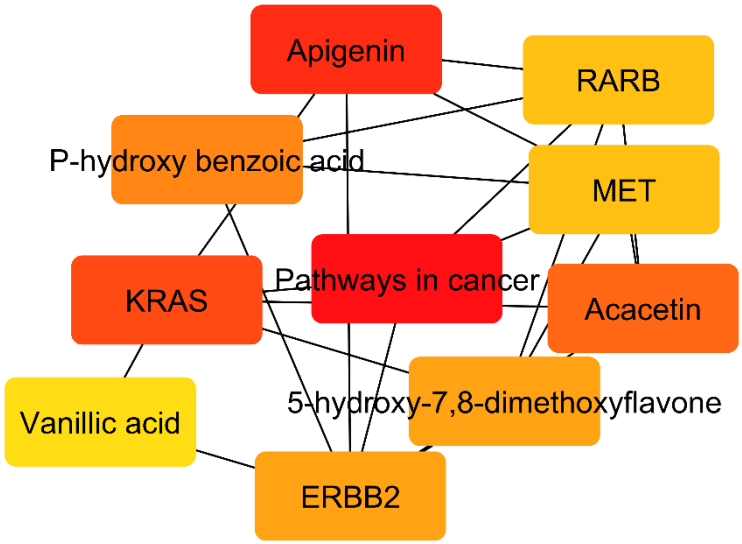

Figure 7: Cytohubba analysis of merged network.

Conclusion

This study elucidates the molecular basis of the anti-cancer activity of Oxalis corniculata through a systems biology framework integrating network pharmacology, PPI analysis, gene ontology, and pathway enrichment. The identification of 85 key protein targets at the intersection of compound–target predictions and cancer-associated genes supports the herb's polypharmacological nature. Functional clustering via MCODE highlighted core oncogenic regulators, while GO and KEGG analyses linked the targets to hallmark cancer processes such as apoptosis regulation, cell cycle control, transcriptional misregulation, and oncogenic signaling. The compound–target–pathway network identified Apigenin as a central compound interacting with multiple high-priority cancer targets, with supporting contributions from p-hydroxybenzoic acid, Acacetin, and Vanillic acid. Overall, the findings underscore O. corniculata's therapeutic potential in modulating multiple cancer-associated pathways, advocating further experimental validation and development of its phytoconstituents as candidates for multi-targeted cancer therapies.

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