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NETWORK PHARMACOLOGY INTEGRATED WITH MOLECULAR DOCKING REVEALS THE MULTI-TARGET MECHANISM OF *IPOMOEA BATATAS* AGAINST OROPHARYNGEAL CANCER

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ABSTRACT:
Oropharyngeal cancer (OC) is a rising subtype of head and neck squamous cell carcinoma driven by tobacco, alcohol and human papillomavirus infection, and its management remains constrained by treatment-related toxicity and acquired resistance to conventional chemotherapy and radiotherapy. Plant-derived phytochemicals with polypharmacological profiles are increasingly explored as complementary anticancer agents, yet the mechanistic basis of many ethnomedicinal species remains undefined. Ipomoea batatas (sweet potato), a widely consumed tuber rich in phenolic acids, flavonoids and coumarins, has documented antioxidant, anti-inflammatory and antiproliferative activity, but its molecular targets in oropharyngeal cancer have not been systematically mapped. Here we used an integrated network pharmacology and molecular docking strategy to decipher the multi-target mechanism of *I. batatas* against oropharyngeal cancer. Phytochemicals were retrieved from the IMPPAT database and their putative human protein targets were predicted using SwissTargetPrediction; disease-associated genes were obtained from GeneCards. Intersection of 473 phytochemical targets with 418 oropharyngeal-cancer-associated genes yielded 74 shared targets, which were mapped onto a protein–protein interaction network using STRING and Cytoscape. CytoHubba prioritised ten hub genes-CTNNB1, STAT3, BCL2, IL6, CCND1, MMP9, TNF, SRC, ESR1 and AKT1-with CTNNB1 (β-catenin) ranking highest. Gene Ontology and KEGG analyses implicated regulation of smooth-muscle-cell proliferation, gland development, the interleukin-6 receptor complex and nitric-oxide synthase regulatory activity, alongside enrichment of the prolactin signalling pathway, endocrine resistance, AGE–RAGE signalling and pathways in cancer. Molecular docking of the coumarin scopoletin against the crystal structure of CTNNB1 (PDB: 8Y0G) produced a binding energy of −5.47 kcal/mol (ligand efficiency, −0.39 kcal/mol). These findings provide systems-level and structural evidence that *I. batatas* phytochemicals, particularly scopoletin, may exert anti-oropharyngeal-cancer activity through modulation of the CTNNB1/Wnt signalling axis, offering a mechanistic rationale and candidate lead for future experimental validation.

KEYWORDS: Ipomoea batatas, oropharyngeal cancer, network pharmacology, molecular docking, Healthy Lives, Well-being, Quality Care.

1. INTRODUCTION

Head and neck squamous cell carcinoma is among the most common malignancies worldwide, and oropharyngeal cancer (OC) constitutes a biologically and epidemiologically distinct subset arising from the tonsils, base of tongue and soft palate [1,2]. According to recent global cancer burden estimates, cancers of the lip, oral cavity and pharynx together account for several hundred thousand new cases and deaths annually, with marked geographic variation attributable to differences in tobacco and alcohol use and, increasingly, to infection with high-risk human papillomavirus (HPV) [2,3]. In several high-income countries, the incidence of HPV-associated OC has risen sharply over the past two decades even as tobacco-related head and neck cancers have declined, reshaping the epidemiological and clinical landscape of the disease [3,4]. Regardless of aetiology, OC continues to carry a poor prognosis when diagnosed at advanced stage, and current standard-of-care regimens, comprising surgery, radiotherapy and platinum-based chemotherapy alone or in combination, are frequently associated with substantial locoregional morbidity, functional impairment of speech and swallowing, and treatment resistance, underscoring the continuing need for novel and better-tolerated therapeutic strategies [1,5].

Natural products remain a productive source of anticancer leads, and there is growing interest in the systematic evaluation of dietary and medicinal plants for their capacity to modulate the multifactorial signalling networks that

underlie carcinogenesis [6,7]. Unlike single-target synthetic agents, phytochemicals typically act on multiple nodes of interconnected pathways, a property well suited to network pharmacology, a discipline that integrates pharmacology, systems biology and bioinformatics to characterise the multi-component, multi-target and multi-pathway mode of action of complex natural mixtures [8,9]. This paradigm has been applied productively to elucidate the anticancer mechanisms of numerous medicinal plants and formulations, including their action against hepatocellular, colorectal, ovarian and leukaemic malignancies, by combining target prediction, protein–protein interaction network analysis, functional enrichment and molecular docking within a single analytical pipeline [10–14].

Ipomoea batatas (L.) Lam. (sweet potato, family Convolvulaceae) is among the most widely cultivated tuber crops globally and a staple component of diets across Asia, Africa and the Americas. Its tubers and leaves are rich in phenolic acids, anthocyanins, flavonoids and coumarins such as scopoletin, and the plant has a long history of use in traditional medicine for inflammatory and metabolic conditions [15,16]. Contemporary pharmacological studies have documented antioxidant, anti-inflammatory, antidiabetic, hepatoprotective and antiproliferative properties of *I. batatas* extracts and isolated constituents, with several bioactive compounds shown to suppress proliferation and induce apoptosis in cultured cancer cell lines [16–18]. Scopoletin in particular has been reported to exert anticancer effects in cervical, prostate and other tumour models through induction of apoptosis, cell-cycle arrest, inhibition of invasion and modulation of the PI3K/AKT signalling axis [19–22]. Despite this accumulating evidence, the specific molecular targets and signalling pathways through which *I. batatas* phytochemicals might act against oropharyngeal cancer have not been systematically characterised, and no study has yet examined the structural basis of ligand–target engagement for this indication.

Among the candidate oncogenic drivers relevant to head and neck carcinogenesis, the Wnt/β-catenin pathway, of which CTNNB1 is the central effector, has been repeatedly implicated in tumour proliferation, invasion and prognosis in head and neck squamous cell carcinoma, including HPV-positive and HPV-negative subtypes, making it an attractive node for phytochemical intervention [23–26]. Similarly, STAT3, BCL2, IL6, MMP9 and related hub proteins are well-established mediators of inflammation-driven tumour progression, epithelial–mesenchymal transition and chemoresistance in head and neck cancer [27,28]. In the context of the United Nations Sustainable Development Goals, this study supports SDG 3 (Good Health and Well-being) by advancing computational approaches for the discovery and evaluation of potential therapeutic candidates.

In this study, we applied an integrated network pharmacology and molecular docking framework to systematically identify the putative therapeutic targets of *I. batatas* phytochemicals in oropharyngeal cancer, to construct and analyse the resulting phytochemical–target–pathway network, to prioritise hub genes through topological analysis, and to evaluate the structural basis of interaction between the top-ranked hub target and its corresponding phytochemical through molecular docking. We hypothesised that *I. batatas* exerts polypharmacological activity against oropharyngeal cancer by converging on a limited set of hub oncoproteins, with CTNNB1 representing a structurally druggable target for its bioactive coumarin scopoletin. The results establish a mechanistic and structural rationale for the further preclinical development of *I. batatas*-derived phytochemicals as adjunct anticancer agents.

2. MATERIALS AND METHODS

2.1 Retrieval of phytochemical constituents and prediction of putative protein targets

The phytoconstituents reported for *I. batatas* were compiled from the Indian Medicinal Plants, Phytochemistry and Therapeutics (IMPPAT) database, a curated repository of phytochemical composition data for Indian medicinal plants [29,30]. For each retrieved molecule, the canonical Simplified Molecular Input Line Entry System (SMILES) notation was obtained from the PubChem compound database [31]. Each SMILES string was submitted to the SwissTargetPrediction webserver, which infers the most probable human protein targets of a small molecule on the basis of two- and three-dimensional similarity to a reference set of experimentally validated ligand–target pairs [32]. Predicted targets were retained above the platform's default probability threshold, duplicate entries were removed, and the resulting non-redundant list constituted the putative target set of *I. batatas* phytochemicals.

2.2 Identification of oropharyngeal-cancer-associated genes

Disease-related genes were retrieved from GeneCards, an integrative and searchable compendium of annotated and predicted human genes that consolidates information from more than 150 data sources [33]. The search term "oropharyngeal cancer" was used to extract associated gene entries, and to ensure specificity only genes with a GeneCards relevance score of ≥80 were retained for downstream analysis.

2.3 Determination of overlapping therapeutic targets

The putative phytochemical target set and the oropharyngeal-cancer gene set were intersected to identify candidate genes plausibly mediating the pharmacological action of *I. batatas* against the disease. The intersection was visualised using the Venny 2.1.0 web-based Venn diagram tool, which computes and displays overlaps among multiple gene lists [34]. Genes common to both sets were designated as candidate therapeutic targets and carried forward for network and enrichment analysis.

2.4 Construction of the protein–protein interaction network

The common target genes were submitted to the STRING database, using Homo sapiens as the reference organism, to generate a protein–protein interaction (PPI) network, with a minimum required interaction confidence score of 0.400 under full-network mode, which incorporates both predicted and experimentally validated associations [35]. The resulting network file was exported for topological analysis.

2.5 Hub-gene screening and network visualisation

The PPI network was imported into Cytoscape (version 3.10.4), an open-source platform for the visualisation and integrated analysis of molecular interaction networks [36]. Hub genes were identified using the cytoHubba plugin, applying the Maximal Clique Centrality (MCC) topological algorithm, which ranks nodes according to local network density and has been shown to outperform degree-based measures in identifying essential proteins [37]. A composite phytochemical–target–disease network, linking *I. batatas*, its constituent phytochemicals, the shared target genes and oropharyngeal cancer, was subsequently constructed in Cytoscape to visualise the polypharmacological architecture of the plant's putative mechanism of action.

2.6 Gene Ontology and KEGG pathway enrichment analysis

To characterise the biological functions of the shared target genes, Gene Ontology (GO) enrichment analysis, encompassing Biological Process, Cellular Component and Molecular Function categories, together with Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis, was performed using the ShinyGO 0.85 platform, a graphical gene-set enrichment tool [38]. A false-discovery-rate (FDR)-adjusted p-value threshold of ≤0.05 was applied to define statistically significant terms and pathways, and a pathway–target interaction network was constructed in Cytoscape to visualise the relationship between enriched pathways and their associated hub genes.

2.7 Molecular docking analysis

The top-ranked hub gene identified by MCC topological analysis was selected for structure-based validation. The three-dimensional crystal structure of the corresponding protein was retrieved from the RCSB Protein Data Bank, an internationally curated archive of experimentally determined macromolecular structures [39], while the two-dimensional structure of the corresponding phytochemical ligand was obtained from PubChem [31]. Molecular docking was performed using AutoDock 4.2.6, which employs a Lamarckian genetic algorithm to predict energetically favourable ligand-binding conformations within a defined receptor active site and to estimate the associated free energy of binding [40]. Following docking, the protein–ligand interaction profile of the lowest-energy binding pose, including hydrogen bonding and hydrophobic contacts, was analysed and visualised using BIOVIA Discovery Studio Visualizer [41].

3. RESULTS

3.1 Prediction of putative therapeutic targets

A total of 110 phytochemicals reported for *I. batatas* were screened through SwissTargetPrediction using a probability threshold >0.1, yielding 473 non-redundant human protein targets after removal of duplicates. Independently, mining of GeneCards using the search term "oropharyngeal cancer" and a relevance-score cut-off of ≥80 retrieved 418 disease-associated genes. Cross-referencing these two datasets by Venn diagram analysis revealed 74 overlapping genes, which were designated as the putative therapeutic targets through which *I. batatas* phytochemicals may exert activity against oropharyngeal cancer (Figure 1).

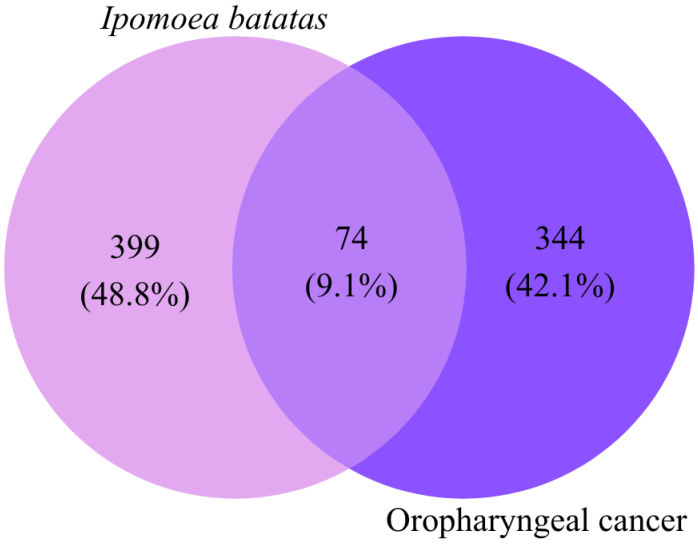

Figure 1. Venn diagram showing the common targets between predicted targets of *I. batatas* phytochemicals and oropharyngeal cancer genes.

3.2 Protein–protein interaction network and hub-gene prioritisation

Submission of the 74 shared targets to STRING generated a PPI network comprising 74 nodes interconnected by 1316 edges, an average node degree of 35.6, and a highly significant PPI enrichment p-value of $<1.0 \times 10^{-16}$ (Figure 2), indicating that the shared targets form a considerably more densely connected network than would be expected by chance and are therefore likely to participate in coordinated biological processes.

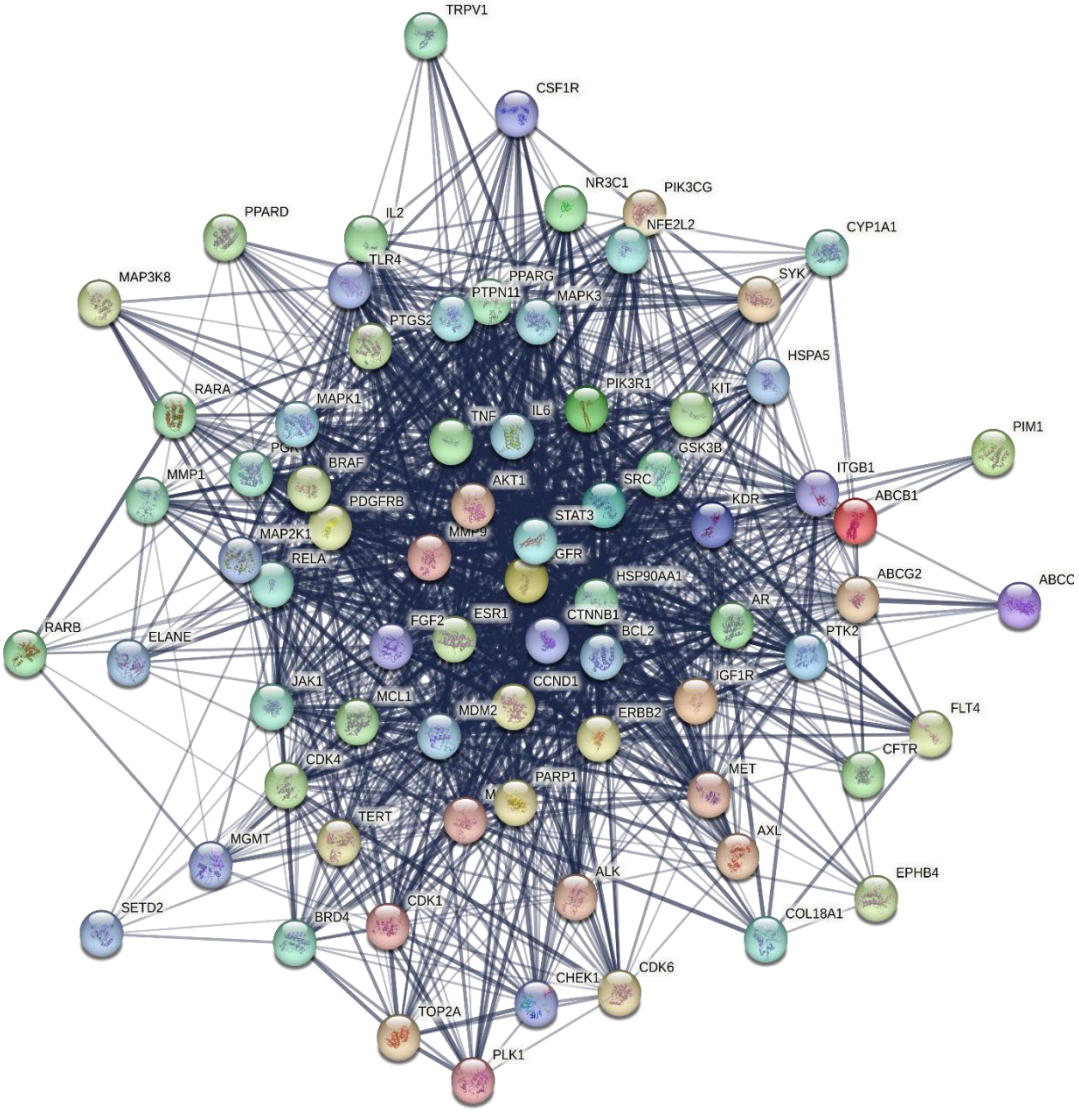

Figure 2. PPI interaction network of the overlapping targets generated using STRING.

Topological prioritisation using the cytoHubba MCC algorithm identified ten hub genes ranked in descending order of connectivity: CTNNB1, STAT3, BCL2, IL6, CCND1, MMP9, TNF, SRC, ESR1 and AKT1 (Figure 3). CTNNB1 (β-catenin) achieved the highest MCC score among all candidates and was accordingly selected as the primary target for structure-based validation.

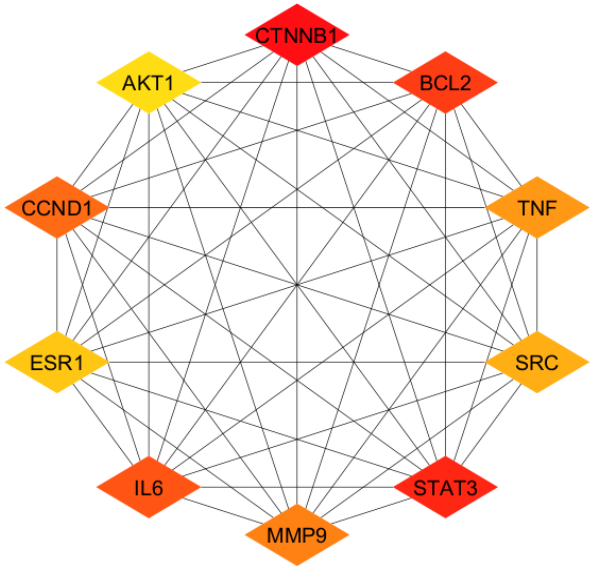

Figure 3. Ten top-ranked hub genes based on the MCC algorithm from the CytoHubba plugin.

A composite phytochemical–target–disease interaction network integrating *I. batatas*, its bioactive constituents, the 74 shared targets and oropharyngeal cancer was subsequently constructed (Figure 4), illustrating the extensively polypharmacological architecture underlying the plant's putative anticancer activity, in which several phytochemicals converge on overlapping target subsets.

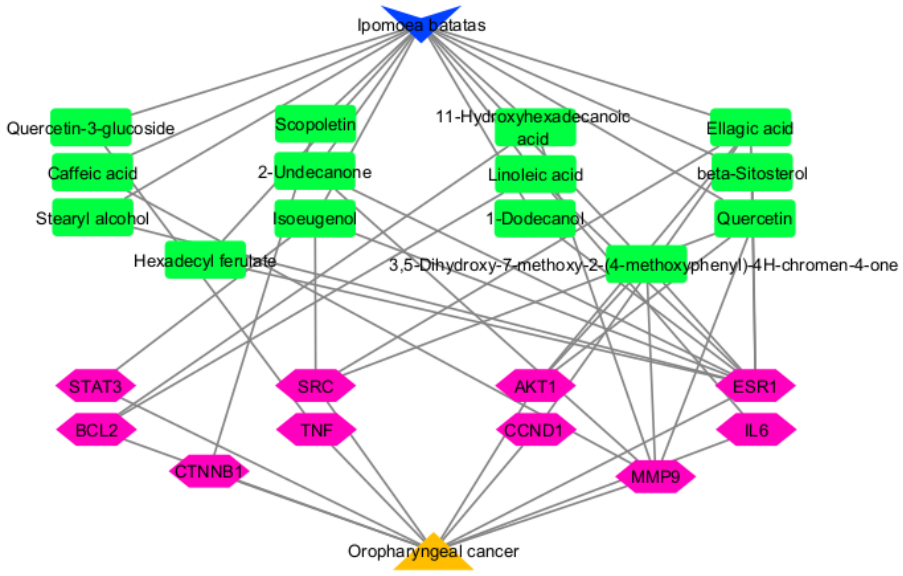

Figure 4. Network of plant-phytochemical-target-disease interactions created using Cytoscape. Nodes are represented in orange, pink, green and blue colours to denote oropharyngeal cancer, target proteins, phytochemicals and *I. batatas*, respectively, with edges representing their interactions.

3.3 Functional enrichment analysis

Gene Ontology annotation of the shared target genes distributed them across the three canonical GO domains (Figure 5). Within Biological Process, terms relating to the regulation of smooth-muscle-cell proliferation and gland development were significantly enriched; within Cellular Component, the interleukin-6 receptor complex emerged as the most significantly enriched term; and within Molecular Function, nitric-oxide synthase regulatory activity showed the strongest enrichment. KEGG pathway analysis (FDR ≤0.05) identified significant enrichment of the prolactin signalling pathway, endocrine resistance, the AGE–RAGE signalling pathway in diabetic complications, hepatitis B, fluid shear stress and atherosclerosis, proteoglycans in cancer, lipid and atherosclerosis, human cytomegalovirus infection, Kaposi sarcoma-associated herpesvirus infection, and pathways in cancer. The prolactin signalling pathway showed the most pronounced enrichment among these, with several hub genes mapping directly onto its core signalling components (Figure 6). A pathway–target network constructed in Cytoscape further delineated the interconnections between the enriched pathways and their constituent hub genes (Figure 7).

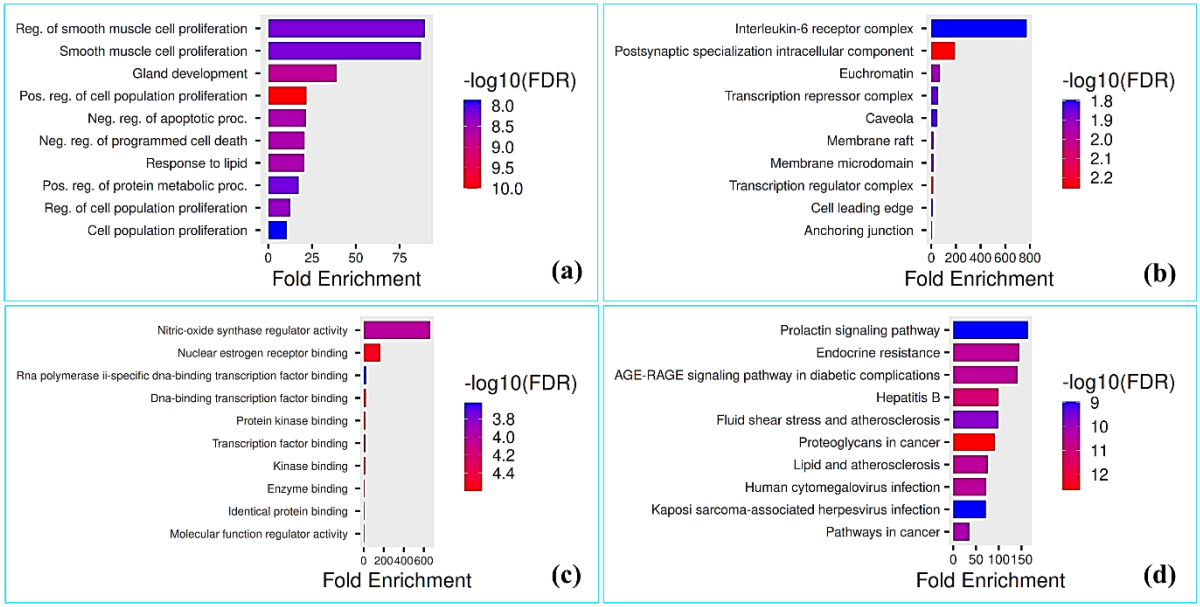

Figure 5. Enrichment analyses of gene ontology (GO) and KEGG pathways for hub genes. The panels represent (a) Biological Process, (b) Cellular Component, (c) Molecular Function, and (d) KEGG pathways of hub genes.

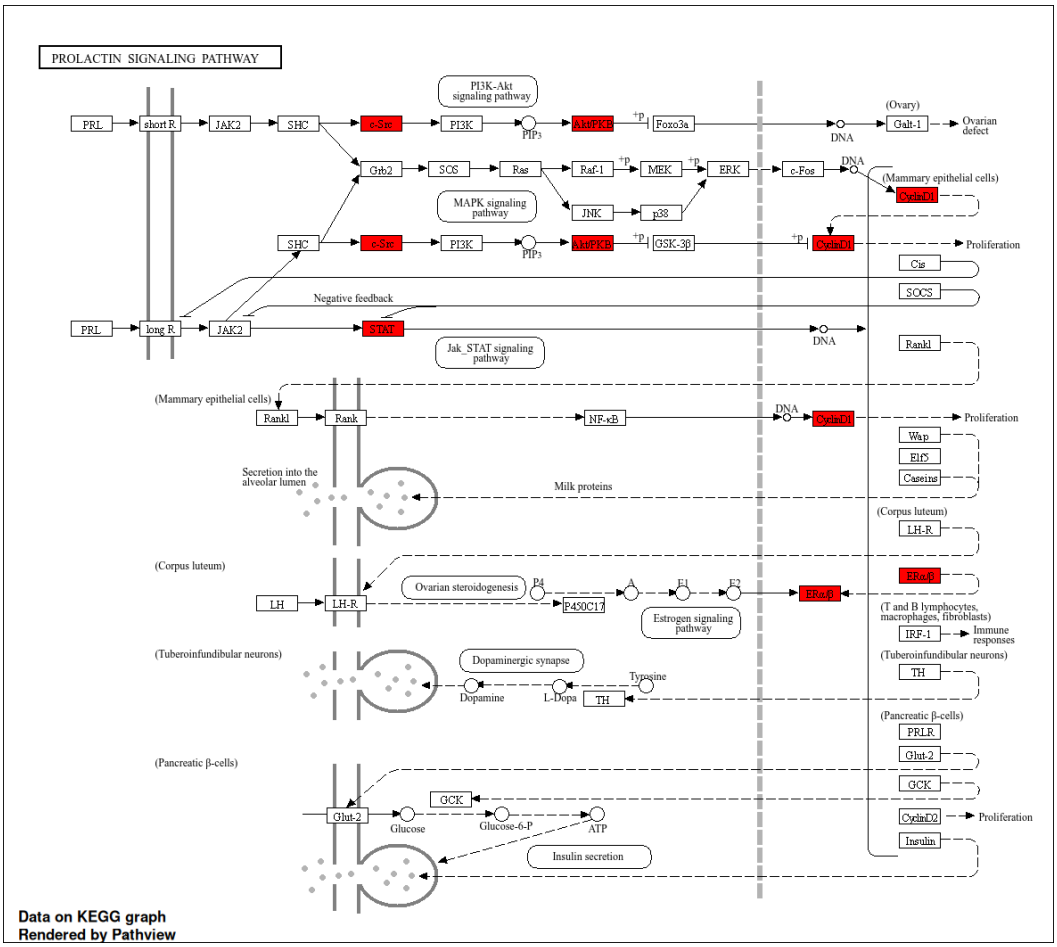

Figure 6. Prolactin signalling pathway, where the highlighted red colour denotes the hub gene involved in the pathway.

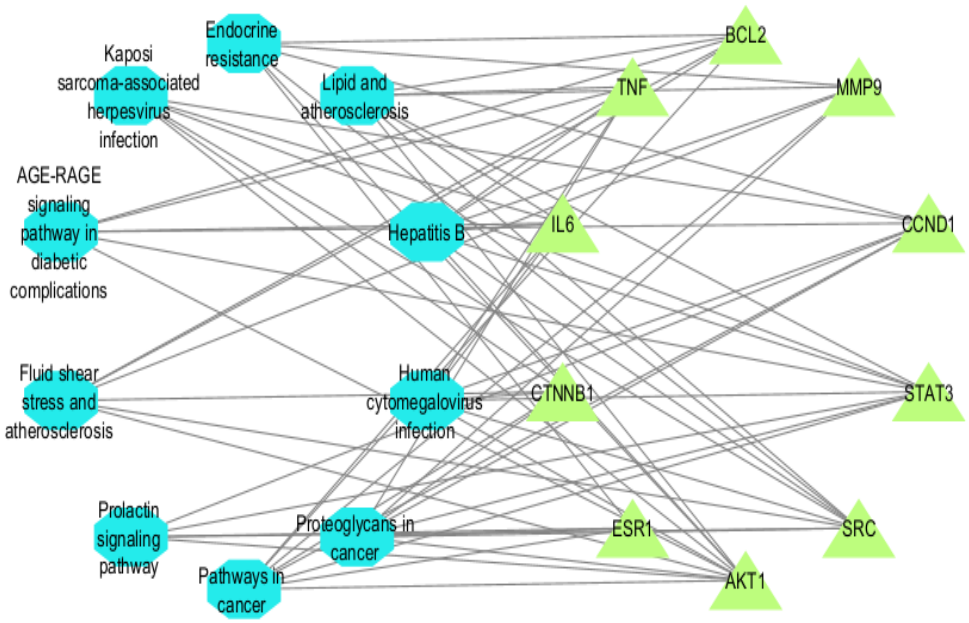

Figure 7. Pathway–target network generated using Cytoscape software, where the blue nodes represent the pathways and the green nodes represent the targeted genes, with edges representing the interaction between the pathway and the targets.

3.4 Molecular docking of CTNNB1 with scopoletin

To evaluate the structural plausibility of CTNNB1 as a druggable target of *I. batatas*, molecular docking was performed between the crystal structure of CTNNB1 (PDB ID: 8Y0G) and scopoletin, one of the plant's characteristic phytochemical constituents mapping to this target in the network analysis. The docked complex exhibited a binding energy of −5.47 kcal/mol and a ligand efficiency of −0.39 kcal/mol (Figure 8), indicative of a thermodynamically favourable and per-atom efficient interaction.

Analysis of the docking pose revealed an extensive, multivalent interaction network stabilising scopoletin within the CTNNB1 binding pocket. Five hydrogen bonds were resolved, involving the residues Gly307, Lys312, Lys345 and Val346: Gly307 engaged scopoletin at a bond distance of 1.85 Å, Lys312 formed a comparable contact at 1.84 Å, Lys345 contributed two discrete hydrogen bonds at 2.73 Å and 1.99 Å, and Val346 formed an additional hydrogen bond with a ligand oxygen atom at 3.58 Å. In parallel, the docked pose was reinforced by hydrophobic contacts involving Tyr306, Val346, Val349 and Lys345, with interaction distances spanning approximately 3.7–5.4 Å; Val346 and Val349 in particular participated in multiple non-polar contacts, consistent with a substantial contribution of these residues to ligand accommodation within the binding cleft. Collectively, Gly307, Lys312, Lys345, Val346, Tyr306 and Val349 constituted the principal residues mediating the CTNNB1–scopoletin interaction (Table 1), with the combination of short-range hydrogen bonding and complementary hydrophobic packing supporting a structurally stable protein–ligand association.

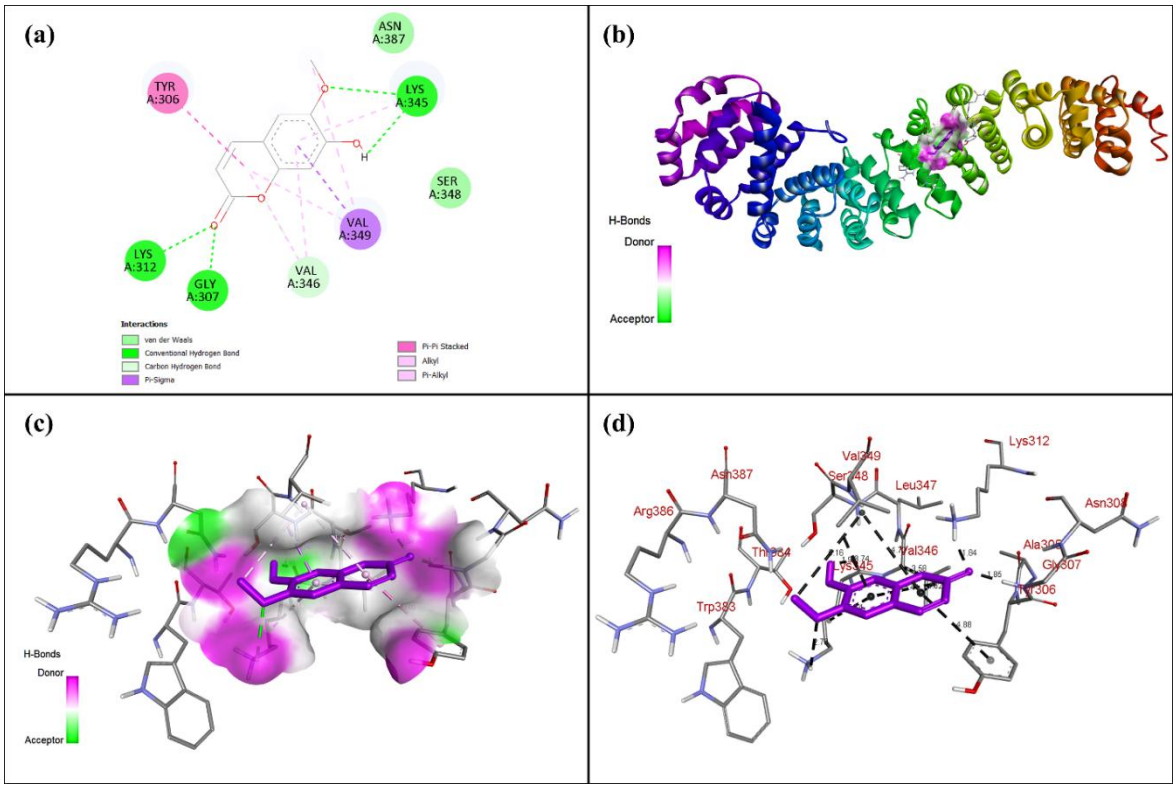

Figure 8. Molecular docking analysis of CTNNB1 with scopoletin showing (a) 2D interaction map, (b) 3D ribbon representation of the protein–ligand complex, (c) hydrogen bond donor and acceptor interactions around the bound ligand, and (d) amino acid interaction profile with bond distances.

Table 1. Inter-molecular interactions between CTNNB1 (PDB: 8Y0G) and scopoletin identified in the docking complex.

Complex	Interacting residue…ligand atom	Interaction type	Distance (Å)
CTNNB1–Scopoletin	Gly307(HN)…LIG(O)	Hydrogen bond	1.85
	Lys312(HZ1)…LIG(O)	Hydrogen bond	1.84
	Lys345(HZ1)…LIG(O)	Hydrogen bond	2.73
	Lys345(O)…LIG(H)	Hydrogen bond	1.99
	Val346(CA)…LIG(O)	Hydrogen bond	3.58
	Val349(CG1)…LIG	Hydrophobic	3.74
	Tyr306…LIG	Hydrophobic	4.88
	Val349…LIG(C)	Hydrophobic	5.16
	Val346…LIG	Hydrophobic	4.82
	Val349…LIG	Hydrophobic	4.72
	Lys345…LIG	Hydrophobic	5.14
	Val346…LIG	Hydrophobic	5.41

Binding energy: −5.47 kcal/mol; ligand efficiency: −0.39 kcal/mol.

4. DISCUSSION

The present study integrates network pharmacology with structure-based molecular docking to provide a systems-level characterisation of the mechanism by which *I. batatas* phytochemicals may act against oropharyngeal cancer. By intersecting 473 predicted phytochemical targets with 418 oropharyngeal-cancer-associated genes, we identified 74 shared targets forming a densely interconnected protein interaction network, a topology consistent with the polypharmacological mode of action characteristic of plant-derived natural products and previously reported for other medicinal species evaluated against cancer through analogous network pharmacology pipelines [10–14,42]. Rather than acting through a single dominant target, *I. batatas* phytochemicals appear to converge on a coordinated module of oncogenic effectors, among which CTNNB1, STAT3, BCL2, IL6, CCND1, MMP9, TNF, SRC, ESR1 and AKT1 emerged as the topologically most influential hub genes. Several of these hub proteins have well-documented roles in head and neck carcinogenesis: IL6-driven STAT3 activation promotes epithelial–mesenchymal transition and metastatic dissemination in head and neck squamous cell carcinoma [27,28], BCL2 overexpression confers resistance to apoptosis and to conventional cytotoxic therapy, and MMP9 facilitates extracellular matrix degradation and local invasion, together supporting the biological plausibility of these nodes as points of pharmacological convergence for a multi-target natural intervention.

Functional enrichment reinforced this mechanistic picture. The prominent enrichment of the interleukin-6 receptor complex among Cellular Component terms, together with KEGG enrichment of the prolactin signalling pathway and endocrine resistance, is consistent with the established role of cytokine- and hormone-receptor-driven signalling in sustaining proliferative and anti-apoptotic programmes in epithelial malignancies, including through cross-talk between prolactin receptor signalling and growth-factor pathways implicated in tumour progression [43,44]. The additional enrichment of pathways in cancer and proteoglycans in cancer further supports the involvement of the shared targets in canonical oncogenic circuitry rather than in a disease-nonspecific background process, while enrichment of nitric-oxide synthase regulatory activity is compatible with the recognised contribution of nitric oxide signalling to angiogenesis and tumour microenvironment remodelling in head and neck cancer.

The central focus of this study is the structural validation obtained through molecular docking of the highest-ranked hub gene, CTNNB1, with scopoletin, a coumarin constituent of *I. batatas*. CTNNB1 encodes β-catenin, the principal transcriptional effector of canonical Wnt signalling, a pathway whose dysregulation, through altered protein stability, nuclear translocation and downstream activation of proliferative target genes such as cyclin D1 and MYC, has been repeatedly implicated in the initiation, progression and prognosis of head and neck squamous cell carcinoma, including both HPV-positive and HPV-negative tumours, and has been proposed as a rational therapeutic target in this malignancy [23–26,45]. Our docking analysis showed that scopoletin engages CTNNB1 with a binding energy of −5.47 kcal/mol, mediated by five discrete hydrogen bonds with Gly307, Lys312 and Lys345, together with complementary hydrophobic packing involving Tyr306, Val346 and Val349. Several of these interacting residues, notably the basic lysine residues Lys312 and Lys345, lie within regions of the β-catenin armadillo-repeat domain that mediate protein–protein interactions with TCF/LEF transcription factors and other Wnt pathway partners, suggesting that ligand occupancy at this site could plausibly interfere with the protein-interaction surfaces required for β-catenin-driven transcriptional activity, although this inference is necessarily preliminary in the absence of functional assays. The magnitude of the predicted binding affinity, while moderate in comparison with high-affinity synthetic inhibitors, is comparable to that reported for other phytochemical-oncoprotein docking studies conducted through similar network pharmacology pipelines and is considered indicative of a biologically meaningful interaction warranting experimental follow-up [11,13,46].

Scopoletin itself has an emerging, independently documented anticancer pharmacology: it has been shown to induce apoptosis and cell-cycle arrest in prostate and cervical cancer cell lines, to suppress invasive capacity, and to modulate PI3K/AKT signalling, alongside broader anti-inflammatory and antioxidant activities relevant to tumour microenvironment modulation [19–22,47]. The convergence of these independent lines of evidence, namely cell-based anticancer activity of scopoletin in other tumour types, network-level prioritisation of CTNNB1 as a hub target of *I. batatas* phytochemicals in oropharyngeal cancer, and direct structural evidence of a stable scopoletin–CTNNB1 complex, provides a coherent, mechanistically plausible rationale for the further investigation of scopoletin as a Wnt-pathway-directed candidate against oropharyngeal cancer. Similar convergent network pharmacology–docking strategies have identified structurally analogous coumarin and flavonoid ligands as candidate inhibitors of hub oncoproteins in other malignancies, supporting the generalisability of this approach for the rational prioritisation of natural-product leads [12,14]. Computational approaches such as network pharmacology and molecular docking provide an integrated framework for systematically exploring the molecular targets and interaction profiles of plant-derived phytochemicals. By linking phytochemical constituents with disease-associated targets and evaluating their potential ligand–protein interactions, these approaches can facilitate the identification and prioritisation of promising bioactive candidates for further investigation [48,49,50,51,52,53].

5. CONCLUSION

This study applied an integrated network pharmacology and molecular docking approach to elucidate the multi-target mechanism through which Ipomoea batatas phytochemicals may exert therapeutic activity against oropharyngeal cancer. Analysis of 74 shared targets between *I. batatas* phytochemicals and oropharyngeal-cancer-associated genes revealed a densely interconnected protein interaction network converging on ten hub genes, with CTNNB1 emerging as the

topologically dominant node. Functional enrichment implicated interleukin-6 receptor signalling, prolactin signalling, and broader cancer-associated pathways as key biological processes mediating this activity. Molecular docking demonstrated a structurally stable, multivalent interaction between the phytochemical scopoletin and the Wnt-pathway effector CTNNB1, characterised by an energetically favourable binding pose stabilised by hydrogen bonding and hydrophobic contacts. Collectively, these findings identify the CTNNB1/Wnt signalling axis as a plausible molecular basis for the anti-oropharyngeal-cancer activity of *I. batatas* and nominate scopoletin as a promising natural lead compound. Future work incorporating molecular dynamics simulation, binding free-energy calculation, and in vitro and in vivo functional validation will be essential to confirm these findings and to advance scopoletin and related *I. batatas* phytoconstituents toward rational, mechanism-based anticancer drug development.

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