ORIGINAL RESEARCH

Examining the modulatory function of diosgenin in oral cancer signalling: evidence from in vitro and in silico studies

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Abstract

Background: Oral squamous cell carcinoma (OSCC) is still a major global health concern, especially in developing countries, because of delayed diagnosis, treatment resistance, and the unfavourable effects of traditional treatment methods. Research on bioactive compounds derived from plants as alternative treatment approaches has increased. By altering multiple signalling pathways, diosgenin, a steroidal saponin derived from Dioscorea species, has demonstrated encouraging anticancer effects.

Aim: Investigating diosgenin's anticancer potential against OSCC using a combination of in vitro and in silico approaches, with an emphasis on its pro-apoptotic mechanisms, molecular targets, and pathways.

Materials and Methods: Diosgenin's chemical structure was obtained from PubChem, energy-minimized, and then examined for ADME characteristics and drug-likeness using SwissADME and pkCSM. CTD and GeneCards were used to identify targets associated with OSCC. AutoDock Vina was used for molecular docking, STRING and Cytoscape were used to build protein-protein interaction networks, and GO and KEGG were used for functional enrichment analyses. The in vitro cytotoxicity against KB-1 oral cancer cells was evaluated using the MTT assay, morphological evaluation, and AO/EtBr dual staining.

Results: Diosgenin exhibited favourable pharmacokinetics, which were marked by increased gastrointestinal absorption and bioavailability. Nineteen common OSCC targets were found to be enriched in the PI3K-Akt, MAPK, and p53 pathways. Docking showed strong interactions with KEAP1 and NRF2, with binding energies of -8.8 kcal/mol and -9.2 kcal/mol, respectively. In vitro, diosgenin significantly decreased KB-1 cell viability, increased apoptotic cell populations, and induced apoptotic morphology (IC_{50} = 18.26 ± 0.94 µM).

Conclusion: Diosgenin modulates important oncogenic pathways and induces apoptosis to provide multi-targeted anticancer efficacy in OSCC. These results support its potential as a therapeutic adjuvant candidate, thereby calling for additional in vivo and pharmacokinetic studies.

Keywords: ADME, Apoptosis, Diosgenin, Molecular Docking, Natural Anticancer Agents Oral Squamous Cell Carcinoma.

Introduction

Oral cancer is one of the leading ten tumours with respect to incidence and mortality and is one of the most prevalent cancers in the world.[1] It is a significant risk to public health, particularly in developing countries such as India, where consumption of tobacco and alcohol and exposure to the human papillomavirus (HPV) can lead to 30–40% of all cancers.[2] Many cases are still found at a late stage with poor prognosis and five-year survival rates of less than 50%, despite improved cancer screening and public awareness. Improved preventive, diagnostic, and therapeutic strategies need to be developed due to the high morbidity and mortality associated with oral cancer.[3]

The most common diagnostic techniques for oral cancer include imaging studies such as CT, MRI, and PET scans, examination of the eyes, and histological verification via biopsy. Although these techniques are pivotal in making accurate diagnoses and staging, their ability to identify early diseases and forecast treatment outcomes is limited. Treatment usually includes the use of chemotherapy, radiation, and surgery either individually or combined.[4] While these methods have improved survival, they often

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come with severe side effects, such as infection, xerostomia, mucositis, and a compromised quality of life. In addition, the repetitive nature of therapeutic resistance and relapse highlights the ineffectiveness of traditional drugs to maintain long-term management of the disease.[5] As a result of these limitations, currently more attention is focused on complementary and alternative treatments derived from naturally occurring bioactive molecules that are capable of simultaneously targeting multiple cancer pathways with potentially fewer toxic effects.[6,7]

Diosgenin is a naturally occurring steroidal saponin found in medicinal plants such as Rhizoma polygonati and Dioscorea species. It has received much attention due to its broad variety of pharmacological activities, ranging from anti-inflammatory, antioxidant, and anticancer properties.[8,9] Diosgenin has been found to modulate key molecular pathways associated with tumour initiation, development, and metastasis in cancer therapies.[10,11] Its capacity to induce apoptosis, inhibit cell proliferation, and inhibit angiogenesis in numerous cancers, such as those of the mouth, breast, pancreas, liver, and colon, has been confirmed by preclinical studies.[12] Diosgenin affects oral cancer by inducing apoptotic cell death, evidenced by dose-dependent reductions in cell viability and characteristic morphological changes such as nuclear condensation and cell shrinkage.[13] In addition, in silico studies have shown that diosgenin has a high degree of interaction with molecular targets implicated in cancer development, highlighting its potential as a lead compound for therapy. In light of these findings, diosgenin could be an effective ancillary treatment for oral cancer.

The aim of this study is to exhaustively evaluate diosgenin's effect on oral cancer via in vitro and in silico approaches. By combining computational modelling and cell-based assays, this research will elucidate the molecular mechanisms involved in diosgenin's anticancer activity and its relationship with key cancer-related proteins. The novel two-step approach of this study brings together experimental verification with bioinformatics knowledge to bridge bench research to clinical application. The results are expected to contribute to the design of successful treatments based on natural products, which may be used to complement current therapies and enhance patient response for oral cancer.

Materials and Methods

Compound Acquisition, Preparation, and In Silico Evaluation

The identification number (ID) and chemical structure of diosgenin were obtained from the PubChem (Public Chemical Database) database. The canonical SMILES (Simplified Molecular Input Line Entry System) of diosgenin was utilized to generate an energy-minimized three-dimensional (3D) ligand structure using OpenBabel. Polar hydrogens were added, Gasteiger charges were assigned, and the final ligand structure was saved in PDBQT (Protein Data Bank, Partial Charge [Q], Torsional degrees of freedom [T]) format for molecular docking analyses. ADME (Absorption, Distribution, Metabolism, and Excretion) properties and drug-likeness were predicted using SwissADME, which included the assessment of gastrointestinal absorption, blood-brain barrier permeability, compliance with Lipinski's rule of five, bioavailability score, and physicochemical parameters. Additionally, pkCSM was employed to evaluate the toxicological profile of diosgenin.

Identification of Targets

Putative diosgenin targets were identified through public resources, such as GeneCards and the Comparative Toxicogenomics Database (CTD). Oral cancer genes were retrieved using the search terms "oral cancer", "oral squamous cell carcinoma", and "head and neck squamous cell carcinoma". Target lists were normalised to official HGNC symbols, and Venn diagram analysis was used to determine the common targets of diosgenin and oral cancer.

Functional Enrichment Assessment

The intersecting targets went through Gene Ontology (GO) enrichment analysis for Biological Processes (BP) and Molecular Functions (MF) and pathway analysis using the KEGG and Reactome databases. Enrichment was performed using a hypergeometric test with Benjamini–Hochberg false discovery rate (FDR) correction, with FDR < 0.05 being significant.

Building Protein–Protein Interaction (PPI) Networks

Common target proteins were queried into the STRING database (Homo sapiens; interaction score > 0.7) to construct a PPI network. Cytoscape software was used to visualise and analyse the network, and hub genes were identified using the CytoHubba plugin by describing topological features such as degrees and MCC scores.

Preparation of Protein Structure

Crystal structures of key target proteins, including CASP3, ERK4, IRS2, KEAP1, and NRF2, were obtained from the Protein Data Bank (PDB). Protein architectures were created by removing non-essential water molecules and heteroatoms, adding polar hydrogens, and assigning Kollman charges. Active site grids for docking were determined with reference to cocrystallized ligands or binding residues reported in the literature.

Molecular Docking

Molecular docking was performed through AutoDock Vina. Diosgenin was treated as a flexible ligand, while proteins were treated as rigid. The docking simulations generated numerous binding conformations to every target protein, and the best of these was selected on the basis of binding affinity and interaction analysis. Protein-ligand interactions, such as hydrogen bonding, hydrophobic interactions, and van der Waals interactions, were visualised with Discovery Studio Visualiser and LigPlot+.

Cell Line and Culture Parameters

The human oral cancer cell line (KB-1) was obtained from the National Centre for Cell Science (NCCS), Pune, India. The cells were cultured in Dulbecco's modified Eagle's medium (DMEM), supplemented with 10% foetal bovine serum (FBS) and a 1% antibiotic-antimycotic solution. Cultures were maintained at a humidified incubator temperature of 37°C with 5% CO_2 levels. Cells were subcultured at 80–90% confluence

with trypsin-EDTA. The study used diosgenin (Catalogue No. 41131; Diosgenin extrapure, 95%; (25R)-5-Spirosten-3β-ol, 3β-Hydroxy-5-Spirostene), which was acquired from SRL Chemicals, India.

MTT Cytotoxicity Assay

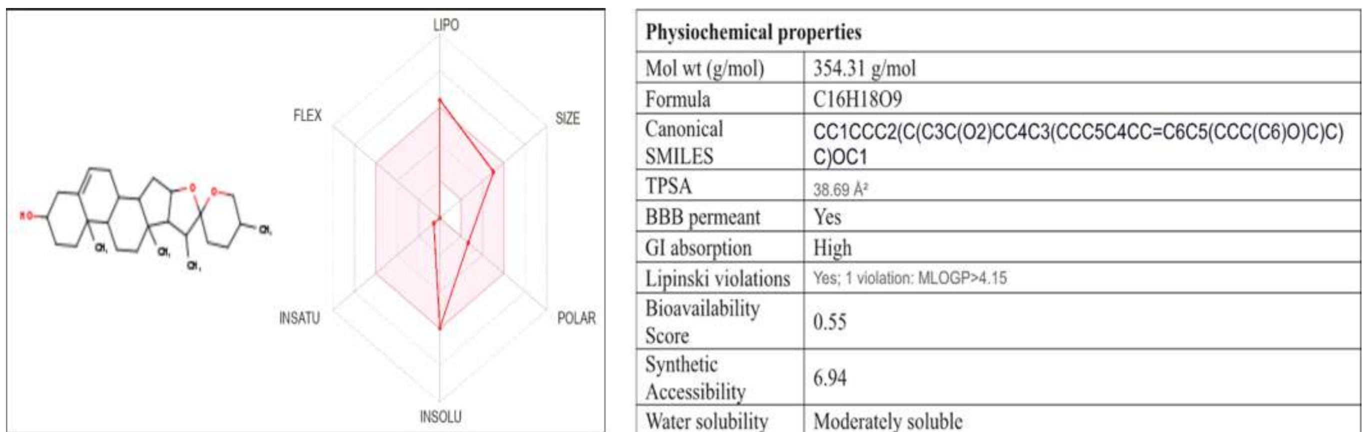
Cell viability was assessed through the MTT test. KB-1 cells (5×10^3 cells/well) were seeded into 96-well plates and allowed to incubate overnight. Cells were treated with various concentrations of diosgenin (2.5–25 μM/ml) for 24 hours. After treatment, 20 μL of MTT reagent (5 mg/mL in PBS) was added to every well and incubated at 37°C for 4 hours. The resulting formazan crystals were solubilised in 150 μL of dimethyl sulfoxide (DMSO), and the absorbance was measured at 570 nm on a microplate reader. Cell viability percentages were determined in comparison to control wells, and IC_{50} values were determined.

Morphological Examination

Morphological changes induced by diosgenin were investigated through an inverted phase-contrast microscope. KB-1 cells (2×10^5 cells/well) were seeded in 6-well plates and treated with the IC_{50} dose of diosgenin for 24 hours. Cells were then examined for changes in morphology, cytoplasmic shrinkages, and membrane blebbing compared to vehicle-treated controls.

Apoptotic features were assessed by AO/EtBr dual staining

KB-1 cells were treated with diosgenin at a dose of 18 μM/ml for 24 hours. Cells were harvested after treatment, washed with ice-cold PBS, and stained with 1 μL of acridine orange (100 μg/mL) and 1 μL of ethidium bromide (100 μg/mL). The stained cells were put on glass slides and observed under a fluorescence microscope. Viable cells showed green fluorescence, while apoptotic and necrotic cells gave yellow,



Physiochemical properties	
Mol wt (g/mol)	354.31 g/mol
Formula	C16H18O9
Canonical SMILES	CC1CCC2(C(C3C(O2)CC4C3(CCC5C4CC=C6C5(CCC(C6)O)C)C)C)OC1
TPSA	38.69 Å²
BBB permeant	Yes
GI absorption	High
Lipinski violations	Yes; 1 violation: MLOGP>4.15
Bioavailability Score	0.55
Synthetic Accessibility	6.94
Water solubility	Moderately soluble

Fig. 1. 3D structure, physicochemical properties, and ADME/drug-likeness prediction of diosgenin. The figure illustrates the 3D chemical structure of diosgenin, its physicochemical parameters including Lipinski's rule compliance and bioavailability radar, along with SwissADME predictions showing high gastrointestinal absorption, blood–brain barrier permeability, and a bioavailability score of 0.55.

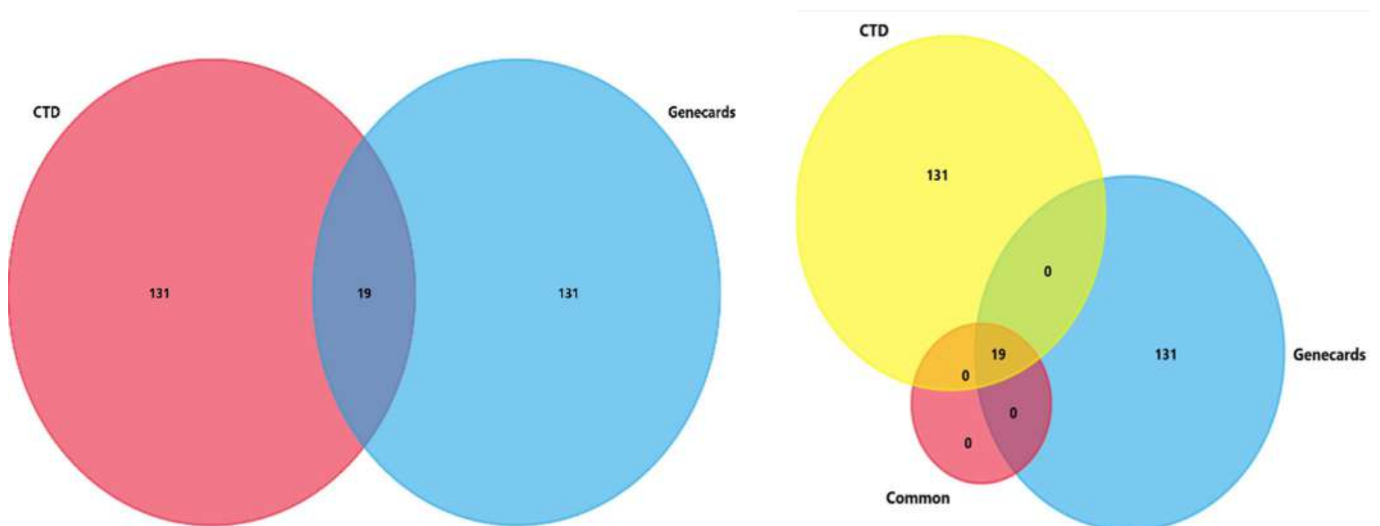


Fig. 2: Venn diagram showing common targets between diosgenin and oral cancer-related genes.

orange, or red emissions. Statistical Analysis. The experiments were all done in triplicate, and the results were expressed as mean ± SD. Statistical analysis employed a one-way ANOVA followed by a Student's t-test, where $p < 0.05$ was statistically significant.

Results

Compound Retrieval, Preparation, and ADME/Drug-Likeness Prediction

The molecular structure of diosgenin was retrieved from

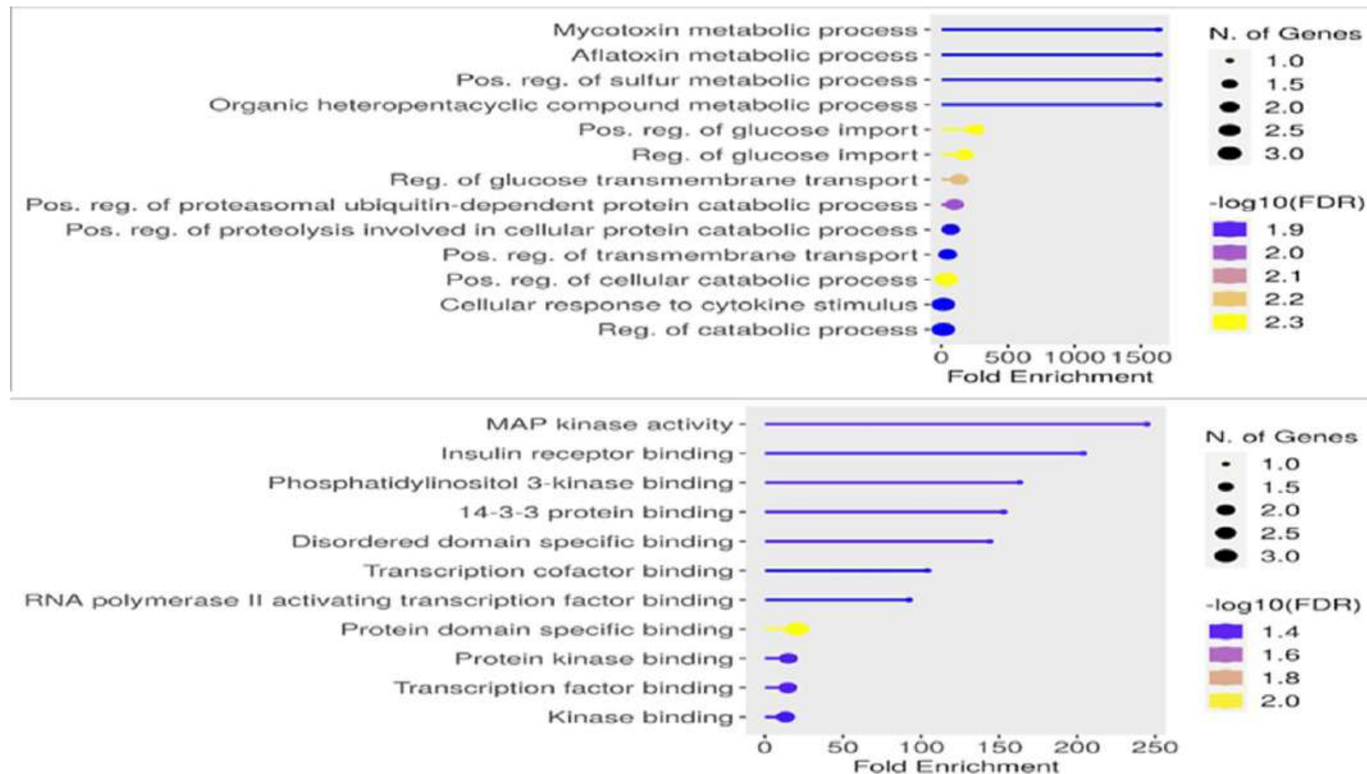


Fig. 3a: Top 10 enriched GO Biological Processes and Molecular Functions.

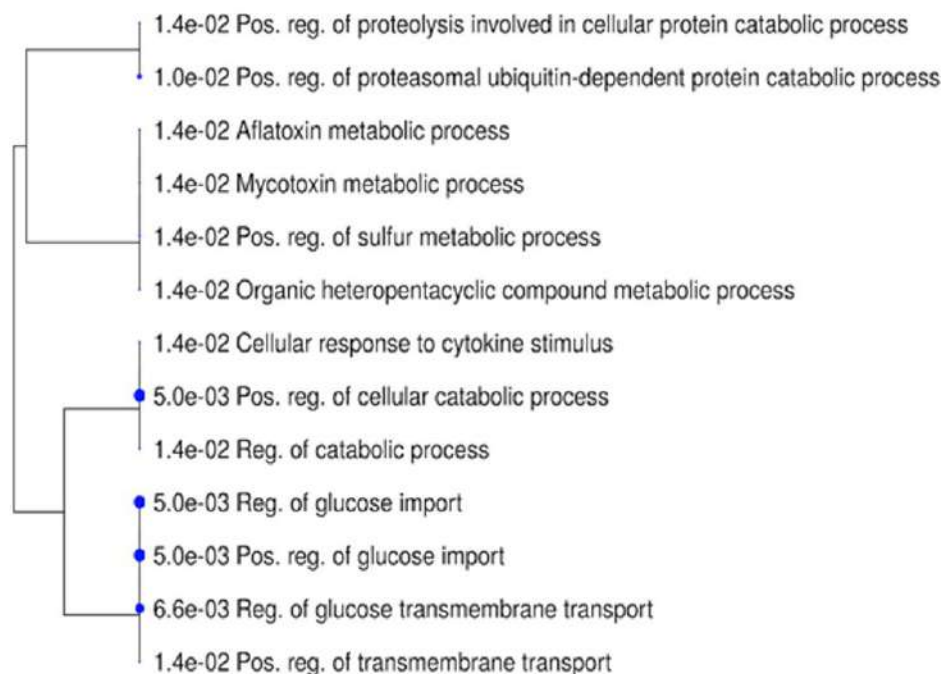


Fig. 3b: KEGG pathway enrichment highlighting apoptosis-related signaling pathways.

the PubChem database (CID: 99474). A 3D ligand model was generated, energy minimized, and visualized. Diosgenin exhibited a steroidal backbone with polar functional groups, indicating its suitability for interaction with target proteins. SwissADME analysis further revealed high gastrointestinal absorption and blood–brain barrier permeability. The compound complied with Lipinski's rule of five, with only a minor violation (MLOGP > 4.15), and showed a bioavailability score of 0.55, supporting its favorable pharmacokinetic and drug-like properties (Figure 1).

Target Identification

Using GeneCards and CTD, 150 oral cancer-associated genes and 121 diosgenin-associated targets were identified. Venn diagram analysis revealed 19 overlapping targets potentially mediating diosgenin's effects against oral cancer (Figure 2).

Functional Enrichment Analysis

GO enrichment analysis indicated that common targets were significantly enriched in biological processes such as regulation of apoptosis, glucose import, and response to cytokine stimulus. Molecular function analysis revealed enrichment in kinase binding, transcription factor binding, and MAP kinase activity. KEGG pathway analysis highlighted the PI3K-Akt, MAPK, and p53 signaling pathways as major pathways modulated by diosgenin (Figure 3a-c).

Protein–Protein Interaction (PPI) Network Construction

The PPI network comprised 19 nodes and 112 edges, indicating strong interconnectivity among identified targets. Hub gene analysis identified TP53, AKT1, BCL2L1, MAPK8, and CCND1 as central regulators (Figure 4).

Protein Structure Preparation and Molecular Docking

Key proteins (CASP3, ERK4, IRS2, KEAP1, NRF2) were prepared for docking. AutoDock Vina docking revealed strong binding affinities, with diosgenin showing the highest affinity for CASP3 (-9.2 kcal/mol) and KEAP1 (-8.8 kcal/mol). Interactions involved multiple hydrogen bonds and

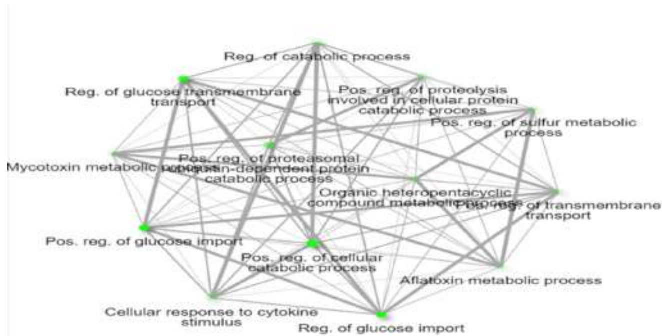


Fig. 3c: Network of GO terms and pathways associated with overlapping targets.

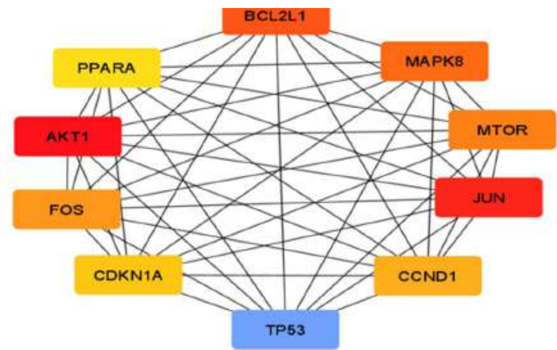


Fig. 4: PPI network of common targets visualized in Cytoscape, with hub genes highlighted in red.

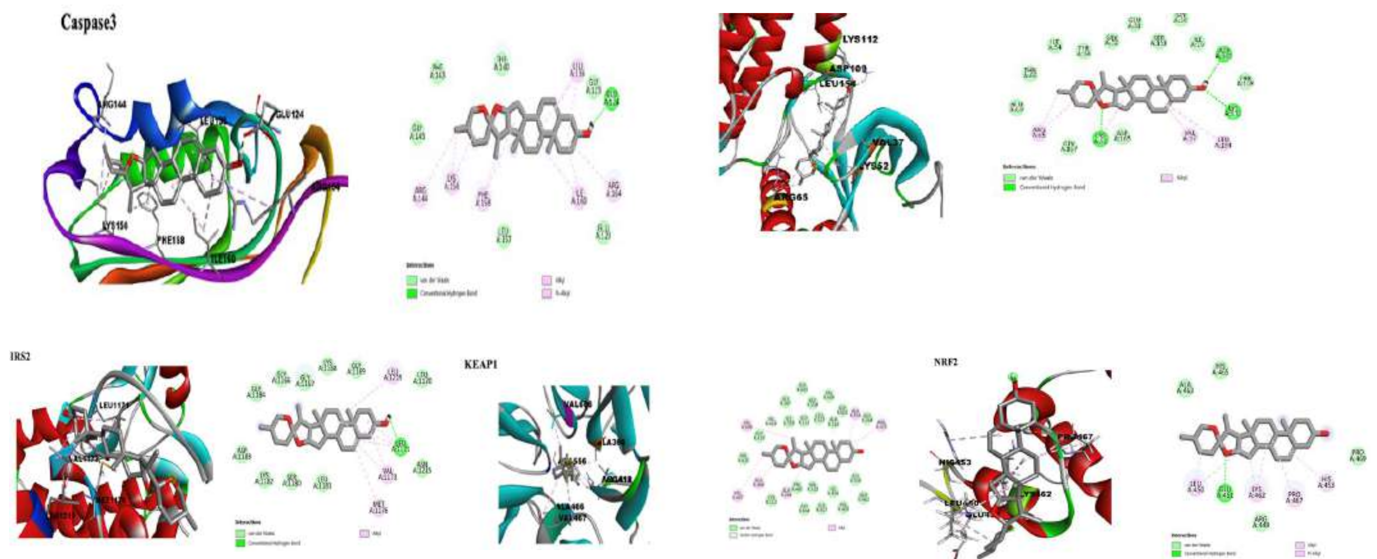


Fig. 5a–e: Docked complexes of diosgenin with CASP3, ERK4, IRS2, KEAP1, and NRF2, showing key binding interactions.

hydrophobic contacts with critical active site residues (Table 1 and Figure 5a-e).

MTT Cytotoxicity Assay

Diosgenin significantly reduced KB-1 cell viability in a dose-dependent manner. The IC_{50} value was calculated as 18.26 ± 0.94 μM, confirming its cytotoxic potential against oral cancer cells (Figure 6).

Morphological Analysis

The phase-contrast microscopy revealed pronounced morphological changes in diosgenin-treated cells, including cell shrinkage, detachment, and membrane blebbing, compared to healthy, elongated control cells (Figure 7).

Acridine Orange/Ethidium Bromide (AO/EtBr) Dual Staining

Fluorescence microscopy demonstrated increased apoptotic cell populations in diosgenin-treated groups. Control cells displayed uniform green fluorescence, while treated cells exhibited yellow, orange, and red signals indicating early and late apoptosis (Figure 8).

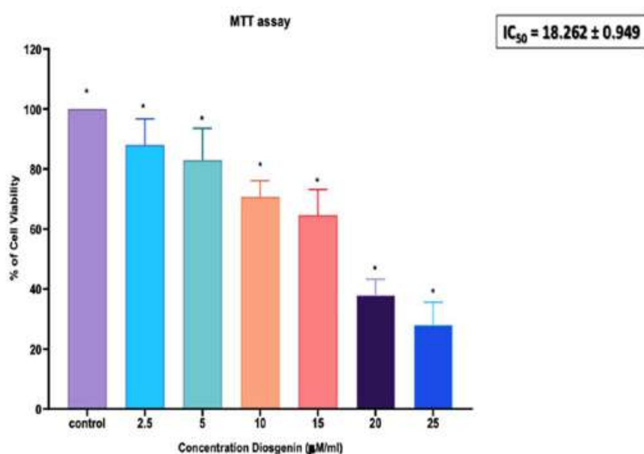


Fig. 6: MTT assay showing percentage cell viability of KB-1 cells treated with different concentrations of diosgenin. Data represent mean ± SD (n = 3). *p < 0.05 vs. control.

Discussion

Oral squamous cell carcinoma (OSCC) is one of the most common cancers in the world, particularly among developing nations, with high morbidity and mortality due to delayed presentation and the modest success of conventional treatment methods. Despite their effectiveness, chemotherapy agents often cause serious side effects, drug resistance, and decreased patient compliance. This concern has led to exploring naturally occurring chemicals that have potential anticancer activity.[14] Diosgenin, a steroidal saponin extracted from Dioscorea species, emerged as a potential candidate due to its multi-targeted activity against a variety of cancers.[15] This article investigated the anticancer activity of diosgenin against oral cancer both in silico and in vitro, highlighting its molecular mechanisms of action.

Our target identification and enrichment analysis indicated that diosgenin targets various oral cancer-associated genes, 19 of which were shared targets as per Venn analysis. These targets were significantly enriched by pathways such as PI3K-Akt, MAPK, and p53 signalling, which are known to play roles in modulating cell survival, proliferation, and death. Similar multi-target actions of diosgenin have been reported in breast and liver cancers, where it suppressed carcinogenesis by targeting the NF-κB and STAT3 pathways.[16] This multi-modal targeting emphasises diosgenin's potential as a therapeutic compound that can overcome the limitations of single-target chemotherapies.

Protein–protein interaction (PPI) network analysis pinpointed hub genes like TP53, AKT1, MAPK8, and BCL2L1 as essential regulatory nodes. TP53, the master tumour suppressor, and AKT1, the master survival kinase, play crucial roles in oral cancer progression. The crosstalk between diosgenin and these proteins points towards its ability to modulate critical checkpoints in tumour biology. The previous studies validate these findings, demonstrating diosgenin-mediated TP53 activation and AKT phosphorylation inhibition in prostate and colon cancer models.[17] The mechanism of diosgenin involves downregulation of anti-apoptotic proteins (Bcl-2, Bcl-xL) and upregulation of pro-apoptotic mediators (Bax, Caspase-3), which reveals its potential to induce apoptosis.[18]

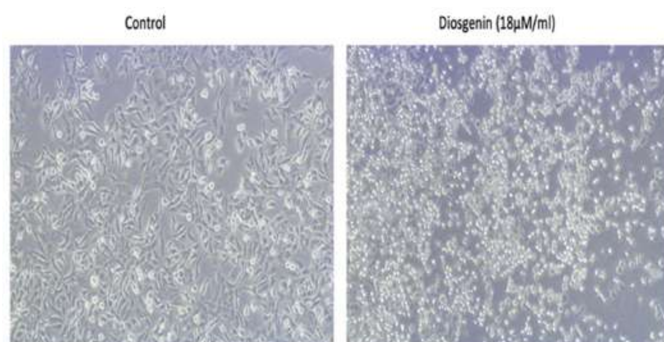


Fig. 7: Morphological changes of KB-1 cells under control and diosgenin-treated conditions observed under phase-contrast microscopy (20× magnification).

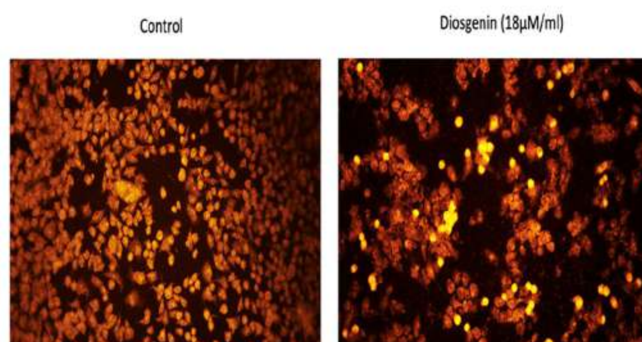


Fig. 8: AO/EtBr dual staining of KB-1 cells showing induction of apoptosis following diosgenin treatment.

The molecular docking experiments supported diosgenin's strong binding affinity for key apoptotic and oxidative stress-related proteins, namely CASP3, KEAP1, and NRF2. CASP3, the executioner caspase, plays a pivotal role in apoptosis, while KEAP1 and NRF2 regulate oxidative stress responses. Diosgenin's high binding potential with CASP3 supports its pro-apoptotic action, as evidenced in hepatocellular carcinoma, where diosgenin prompted caspase-mediated apoptosis.19 Additionally, the KEAP1-NRF2 interaction points towards a regulatory role in oxidative stress, a feature of cancer progression. Diosgenin triggers NRF2-dependent antioxidant defences in addition to inducing oxidative stress in cancer cells, leading to selective apoptosis.[20]

The in vitro cytotoxicity assessment demonstrated a dose-dependent reduction in the viability of KB-1 oral cancer cells with an IC_{50} of 18.26 μM. This is consistent with previous studies showing that diosgenin exhibited cytotoxic activity in breast (IC_{50} = 12 μM) and colon (IC_{50} = 15 μM) cancer cells.21,22 The observed cytotoxicity can be attributed to diosgenin's ability to disrupt mitochondrial membrane potential, increase reactive oxygen species (ROS) levels, and activate intrinsic apoptotic pathways.

A morphological study supported these observations, showing that cells treated with diosgenin showed typical apoptotic features, including cell shrinkage, rounding, and membrane blebbing. Morphological changes are in accordance with mitochondrial-mediated apoptosis, were cytochrome c release triggers caspase activation. Similar morphological findings have been reported in leukaemia cells exposed to diosgenin, where mitochondrial dysfunction was a major driver of death.[23]

Acridine orange/ethidium bromide (AO/EtBr) double -labelling confirmed apoptotic induction, showing high numbers of early and late apoptotic cells after treatment. The yellow, orange, and red fluorescence pattern of the nuclei is indicative of chromatin condensation and DNA fragmentation. Findings were also observed in lung cancer cells treated with diosgenin, where double labelling confirmed apoptosis through mitochondrial and caspase-mediated pathways.[24] Diosgenin mechanistically suppresses survival pathways like PI3K/AKT/mTOR and induces death receptors, thereby enhancing apoptosis.[25]

Overall, these results demonstrate diosgenin's remarkable anticancer activity against oral cancer by regulating numerous molecular targets and signalling pathways. Its ability to interact with key oncogenic proteins, trigger mitochondrial failure, and induce apoptosis suggests a dual role in both direct cytotoxicity and modulation of tumour-engendering mechanisms. Additionally, its beneficial ADME properties and drug-likeness indicate translational potential as a therapeutic agent.

Conclusion

This research provides significant evidence for the anticancer activity of diosgenin in oral cancer. By incorporating the use of in-silico target prediction, molecular docking, and in-vitro confirmation, we demonstrate that diosgenin exhibits multi-targeted action, inducing apoptosis by activating

Table 1

S.No	Name of the Protein	Binding affinity (kcal/mol)	Hydrogen Interaction	Amino acid residues
1	Caspase3	−9.2	1. Van der Waals 2. Conventional Hydrogen Bond 3. Alkyl	1. GLY A:145, PHE A:143, THR A:140, GLY A:125, GLU A:123, LEU A:157 2. GLU A:124 3. ARG A:146, LYS A:136, PHE A:158, ILE A:160, ARG A:164, LEU A:136
2	ERK4	-6.3	1. Van der Waals 2. Conventional Hydrogen Bond 3. Alkyl	1. GLU A:69, THR A:66, ILE A:54, TYR A:34, GLY A:32, GLU A:31, SER A:151, GLY A:30, ILE A:29, THR A:108, ASP A:165, GLY A:167 2. ASP A:109, LYS A:112, LYS A:52 3. ARG A:65, VAL A:53, LEU A:154
3	IRS2	-6.8	1. Van der Waals 2. Conventional Hydrogen Bond 3. Alkyl	1. ASP A:183, GLY A:184, GLY A:1166, GLY A:1167, LYS A:1168, GLY A:1169, LEU A:1170, ASN A:1215, LYS A:1182, SER A:1180, LEU A:1181
4	KEAP1	−8.8	1. Van der Waals 2. Conventional Hydrogen Bond 3. Alkyl	1. ALA A:463, HIS A:465, ARG A:449, PRO A:469 2. GLU A:451 3. LEU A:450, LYS A:462, PRO A:467, HIS A:453
5	NRF2	-6.9	1. Van der Waals 2. Conventional Hydrogen Bond 3. Alkyl	1. ALA A:463, HIS A:465, ARG A:449, PRO A:469 2. GLU A:451 3. LEU A:450, LYS A:462, PRO A:467, HIS A:453

caspases and modulating the PI3K-Akt, MAPK, and p53 pathways. These results validate the therapeutic potential of diosgenin and enable its progression as an adjuvant or second-line treatment for oral cancer. Follow-up studies with a focus on in vivo efficacy and pharmacokinetics will be required to translate these findings into therapy.

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