ORIGINAL ARTICLE

Integrative Network Pharmacology and *In vitro* Evaluation of *Dictyota bartayresiana* Bioactives as Potential Therapeutics for Oral Cancer

S. A. Keerthi Shivani[1], P. Sanjay[2], Lavanya Panchatcharam[3], Vijayaraj Radha[4], M. Kavitha[5], Syed Shahid Afridi[6], Mukesh Kumar Dharmalingam Jothinathan[7], Remya Rajan Renuka[8]

[1]Center for Global Health Research, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India, [2]Department of Sports Medicine, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India, [3]Department of Paediatrics, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India, [4]Department of Marine Biotechnology, AMET University, Chennai, Tamil Nadu, India, [5]Department of Information Technology, Karpagam Institute of Technology, Coimbatore, Tamil Nadu, India, [6]Centre for Stem Cell Mediated Advanced Research Therapeutics, Saveetha Dental College and Hospital, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India, [7]Department of Biochemistry, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India, [8]Centre for Integrative Medical Research, Sree Balaji Medical College and Hospital, Bharath Institute of Higher Education and Research, Chennai, Tamil Nadu, India

Abstract

Dictyota bartayresiana is a brown seaweed and known to contain potent diterpenoids that are proven to possess anti-cancer activity. The nutritional composition and cytotoxic effect of water, ethanol and methanolic extracts of *D. bartayresiana* on KB cells was evaluated. Based on Lipinski 0 violation rule, 2 bioactives of *D. bartayresiana* were selected and screened for gene targets. Meanwhile oral cancer (OC) related gene targets were also determined. On combining, 63 gene targets were identified and subjected to protein-protein interaction network analysis, and 5 nodes referred to as hub genes with the highest degree were selected, that is, Tumor Protein 53 (TP53), CTNNB1, epidermal growth factor receptor (EGFR), AKT1, and MYC. Top 3 hub genes were further evaluated for interactions with bioactive compounds using Molecular docking studies. Network pharmacology and molecular docking analysis show TP53, CNNTB1, and EGFR as key targets involved in initiation, progression and metastasis of OC.

Key words: Brown seaweed, cytotoxicity, *Dictyota bartayresiana*, hub genes, molecular docking, network pharmacology, oral cancer

INTRODUCTION

Oral cancer (OC) is cancer of oral cavity and is among the 6th most occurring malignancies in world, two-third of which occur in Asia. Among all, oral squamous cell carcinomas account for 90% of OCs.[1] Risk factors include alcohol consumption, betel nut chewing, tobacco, chronic inflammation and poor oral hygiene. OC has poor prognosis with 5 years survival rate of 40% and initiates as asymptomatic painless white lesions that

Address for correspondence:
Remya Rajan Renuk, Centre for Stem Cell Mediated Advanced Research Therapeutics, Saveetha Dental College and Hospital, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India.
E-mail: remya.praveen5@gmail.com

Received: 19-02-2026
Revised: 24-03-2026
Accepted: 31-03-2026

gradually thicken into red spots and become ulcerative lesions often diagnosed at advanced stages.[2]

Natural products have been historically in use owing to their therapeutic potential. Around 60% of approved anticancer drugs are either influenced by or derived from nature. Marine derived compounds have gained attention owing to diverse species and potent biological compounds making them desirable candidates for anticancer drug discovery (Alves *et al*., 2018). At present, Cytarabine, Trabectidine, Eribulin mesylate and Brentuximab vedotin are approved marine derived drugs for various cancer treatments.[3]

Despite tremendous advancement in cancer therapy limitations such as high toxicity, drug resistance, limited effect on certain aggressive cancers and off target effects result in failure of conventional treatment.[4] Tumor heterogeneity and dynamic evolutionary nature of cancer are accounted for these results. This has necessitated need for novel, less toxic therapeutic agents for improved clinical outcomes.[5]

Dictyota bartayresiana is a multicellular member spread across southeast coast of India, tropical western central Pacific Ocean, Gulf of Mexico, and Tropical western Atlantic Ocean.[6] This brown seaweed produces cyclic diterpenes – dolabellanes and high sulfated polysaccharides – fucans and fucoidans that possess potent immunomodulatory, anti-tumor, anti-protozoal, anti-viral and anti-microbial activities.[7]

In recent years drug discovery has accelerated due to *in silico* method implementation and has reduced cost that is put into laborious experiments. These methods anticipate effectiveness of compounds against number of illnesses.[8] The use of network pharmacology in anticipation of "protein-compound," "disease-gene" networks, compound toxicity and drug classification has drawn attention. Molecular docking is an important tool in predicting interactions between compound and target proteins, thus aiding optimization of drug screening process.[9]

The current study aims to explore potential *D. bartayresiana* derived compounds as alternative for OC treatment and hasten drug discovery by network pharmacology approach and predicting compound-protein interactions by molecular docking.

MATERIALS AND METHODS

Sample collection

D. bartayresiana was collected from coastal area of Mandapam, Tamil Nadu, India. The samples were washed, shade dried for 10 days and stored in powder form.

Preparation of extract

10 g of powdered *D. bartayresiana* was dissolved in 100 mL of d. H_2O, methanol and ethanol. Each mixture was heated to 80°C for 1 hr. After cooling, the mixture was filtered followed by concentration in a rotary evaporator. The water, methanolic and ethanolic extracts were stored at 4°C for further use.[10]

Nutritional profiling of *D. bartayresiana*

Moisture, Ash, crude protein, lipid, fiber and carbohydrate contents were determined by Harakeh *et al*.[11] Each experiment was performed in triplicate and average results were noted.

Determination of moisture content

The percentage of moisture was determined using the standard AOAC method (Equation 1). 1 g of *D. bartayresiana* sample (DS) was weighed in a crucible and dried at 100°C for 3 h. The sample was cooled in a desiccator and reweighed. The samples were dried for another round until they attained a consistent weight.

$$\text{Percent Moisture} = [(w_2 - w_3)/(w_2 - w_1)] \times 100 \quad (1)$$

w_1 – Empty crucible weight
w_2 – (crucible + sample) weight before drying
w_3 – Final (crucible + sample) weight after drying

Determination of ash content

1 g of DS was weighed in a dry crucible and dried until consistent weight achieved. The DS was ashed in muffle furnace for 12 h at 500°C until white powdery ash and reweighed. Equation (2) was used to determine Percent Ash content.

$$\text{Percent Ash} = (\text{Weight of Ash}/\text{Weight of Sample}) \times 100 \quad (2)$$

Determination of crude protein

Crude protein content was estimated by Kjeldahl method. 5 g of DS was weighed into digestion flask along with Kjeldahl catalyst (2 g) and Sulfuric acid (200 mL). The mixture was boiled until bubbles free clear solution is obtained. Once the mixture is cooled, 60 mL of d. H_2O and 6 drops of mixed indicator were aliquoted. After heating solution untilall N_2 was evaporated and titrated against Sodium Hydroxide. Equation (3) was used to determine the percent crude protein.

$$\text{Percent crude protein} = [(A\text{-}B) \times N \times \text{Atomic weight of Nitrogen} \times 6.25]/W \quad (3)$$

A – Volume of 0.25 N HCl used for sample titration

B - Volume of 0.25 N HCl used for blank titration

N – Normality of NaOH

W – Weight of DS (in g)

6.25 – protein- nitrogen conversion factor

Determination of lipid content

Soxhlet extraction was performed 5 g of DS in 250 mL of petroleum ether at 85°C until the solvent is evaporated entirely and reweighed after cooling in a desiccator. Percent Lipid determined by equation (4).

$$\text{Percent Lipid} = [(w_2 - w_1)/w_3] \times 100 \quad (4)$$

w_1 – Empty bottle weight

w_2 – (Bottle + Fat) weight

w_3 – Sample weight.

Determination of fiber content

A solution containing 2 g of DS and 200 mL of Sulfuric acid was boiled for 30 min and filtered. The residue was washed with hot d. H_2O thrice. 100 mL of 2% Sodium Hydroxide was added to the residue and boiled for 30 min until the acid is neutralized. The neutral residue is dried in an oven overnight at 105°C, and the residual weight is recorded. Then ashed at 550°C in a muffle furnace for 3 h till grey ash is formed. Equation (5) was used to determine the percent fiber content.

$$\text{Percent crude fiber} = [(w_1 - w_2)/w_3] \times 100 \quad (5)$$

w_1 - Sample weight before heating

w_2 –Sample weight after heating

w_3 –Original sample weight

Determination of carbohydrate content

Percent carbohydrate was calculated by equation (6)

$$\text{Percent carbohydrate} = 100 - [\%\text{ Moisture} + \%\text{Ash} + \%\text{Crude Protein} + \%\text{ Lipid} + \%\text{ Fiber}] \quad (6)$$

Cytotoxicity assay

The cytotoxic activity of *D. bartayresiana* extract was assessed by MTT colorimetric assay. The KB cells were procured from NCCS, Pune, and cultured in Dulbecco's modified eagle medium supplemented with 10% Fetal Bovine Serum and 1% Penstrep at 37°C and 5% CO_2. The media was changed every 24 h. Cells were observed for adherence and confluency, and trypsinized at 80% confluency with trypsin-EDTA and sub-cultured.

For the MTT assay, 1×10^5 cells are seeded into 96-well plates and grown overnight for adherence and confluency. Then treated with water, methanolic, and ethanolic extracts of *D. bartayresiana* and incubated for 48 h, followed by washing with complete media. After aliquoting 200 µL of MTT solution (3 mg/mL) into each well, cells were incubated for 2 h followed by adding 100 µL of MTT dissolving solution (Dimethyl sulfoxide) and shaker incubation for 15 min, and absorbance measurement at 570 nm.[12]

Network pharmacology analysis

Screening for active lead compounds from D. bartayresiana

Active compounds were collected from Seaweed Metabolite Database (SWMD) (https://www.swmd.co.in/) and screened for potential leads in Swiss ADME database based on ADME indices. The active compounds with 0 Lipinski violations were selected for further analysis. The chemical structures of selected bioactive compounds were obtained from SWMD.[13]

Profiling of D. bartayresiana and OC targets

Target profiling is a preliminary step to understand the interaction framework of bioactive compounds that have been used in the treatment of various disease conditions. The target genes that are interacting with the selected bioactive compounds of *D. bartayresiana* were assessed by "Comparative Toxicogenomics Database (CTD) (https://ctdbase.org/)," a database that has integrated toxicological information of chemicals with genes, phenotypes, and diseases to understand the impact on human health.

OC related targets were retrieved from "Genecards database (https://www.genecards.org/)" using keywords "Oral cancer," "oral squamous cell carcinoma," and "neck carcinoma." Genecards provides information on all annotated human genes automatically combined from about 150 web sources.[14]

Finally, the target genes for *D. bartayresiana* in OC were mapped using a Venn diagram to identify potential targets (www.bioinformatics.org). These mapped genes served as a foundation for network analysis.

Protein-protein interaction (PPI) network construction and analysis

The relationship analysis between mapped therapeutic targets common to *D. bartayresiana* and OC was carried out through "STRING database (https://string-db.org/)," which includes integrated data of all known and predicted associations between proteins. PPI network was constructed based on two conditions: species *Homo sapiens* and medium confidence ≥0.4. Isolated points in the constructed network were deleted and imported to Cytoscape v3.8.0 software for analysis to obtain topological parameters of nodes in the network, including degree value, betweenness centrality, and closeness centrality. The key targets referred to as Hub genes are identified by using CytoHubba, a Cytoscape plugin.

These Hub genes may serve as potential therapeutic targets that might be involved in disease pathways.[15]

Molecular docking studies

The binding sites of screened *D. bartayresiana* bioactive compounds and potential therapeutic targets identified by network pharmacology analysis were anticipated by molecular docking studies. Before docking, Ligand and Protein was prepared. The 3D structure of target proteins was accessed through "Protein Data Bank (PDB) (https://www.rcsb.org/)." The protein was prepared using Autodock Tools by removing water molecules, heteroatoms, and co-crystallized ligands, and by the addition of polar hydrogens and Gasteiger charges. The 3D structure of ligands 12-hydroxydolabella-3, 7-dien-9-one and 5-acetoxy-12-hydroxydolabell-3,7E-dienon were obtained from SWMD and converted to PDB file format by "Open Babel tool (https://openbabel.org/docs/Installation/install.html)." Ligand preparation made by optimizing geometry and energy minimization using PyRx. Autodock Vina (https://vina.scripps.edu/) was employed for docking with grid box dimensions set to 90 × 90 × 90 Å to allow unrestricted movement of ligand with respect to the binding site. Docking was performed in triplicate, and docked complex was visualized via BIOVIA Discovery Studio Visualizer 2021.[16]

RESULTS

Nutritional profiling of *D. bartayresiana*

The nutritional profiling revealed a high amount of nutritional components, including carbohydrates, proteins, lipids, and fibers. It also has a high moisture content of 45.82% and an ash content of 19.87%. The complete profile is listed in Table 1.

Table 1: Nutritional profiling of *D. bartayresiana* extract

S. No.	Content	% nutritional content
1.	Moisture	48.82±2.4
2.	Ash	19.87±1.3
3.	Protein	12.47±3.6
4.	Lipid	4.80±0.9
5.	Fiber	10±0.5
6.	Carbohydrate	6.91±3.6

Cytotoxicity analysis

The cytotoxicity assay of water, ethanol, and methanolic extracts of *D. bartayresiana* on KB cells reveals a dose-dependent inhibition of cell growth after 48 h of treatment, as shown in Figure 1. All extracts show excellent cytotoxicity against KB cells, with the methanolic extract exhibiting the highest effect with IC_{50} 52.78 mg/mL as compared to ethanolic and water extracts with IC_{50} 82.37 mg/mL and 99.78 mg/mL, respectively. The treatment shows characteristic cell damage and membrane blebbing, indicating apoptosis.

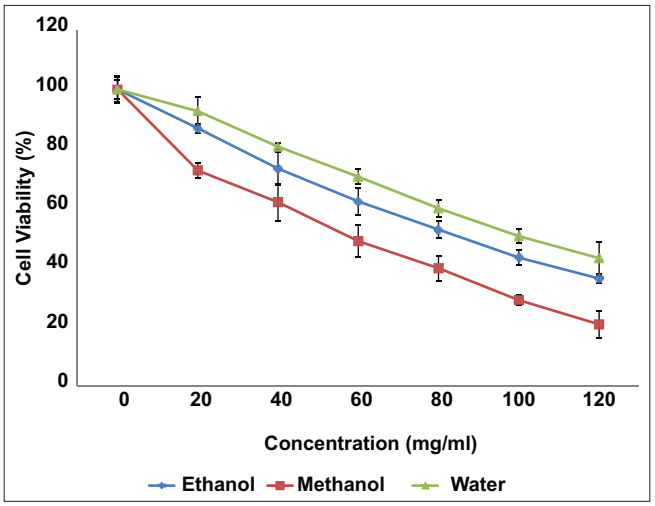

Figure 1: Cytotoxicity of *Dictyota bartayresiana* extract on KB cells after 48 h of treatment

Network pharmacology analysis

Screening for active lead compounds from D. bartayresiana

A Total of 7 active compounds were selected that are deposited in SWMD. The Swiss ADME prediction of these compounds revealed 2 active compounds 12-hydroxydolabella-3, 7-dien-9-one and 5-acetoxy-12-hydroxydolabella-3,7E-dienon, that satisfy Lipinski 5 rule formula (0 Lipinski violations) as represented in Table 2. These compounds were used for further analysis.

Profiling of D. bartayresiana and OC targets

Target prediction by CTD screening revealed 569 gene targets that are interacting with the selected active compounds of *D. bartayresiana,* that is, 12-hydroxydolabella-3, 7-dien-9-one and 5-acetoxy-12-hydroxydolabell-3,7E-dienon. Likewise, Genecards Database predicted 300 gene targets associated with OC. Subsequently, a Venn diagram was plotted to predict potential gene targets that are overlapping between *D. bartayresiana* and OC, as shown in Figure 2. A total of 63 target genes were identified as potential targets and subjected to subsequent investigations.

PPI network analysis

PPIs mediate most of the signaling pathways in an organism. A PPI network was constructed to understand the functional mechanism of 63 overlapped potential targets found by Venn diagram analysis. The network contains 63 nodes, 994 edges, with an average node degree of 31.6. Target genes were closely related to each other, and the network was found to be significant. Network was visualized in Cytoscape and

Table 2: ADME prediction of screened bioactive compounds from SWMD

S. No.	Bioactive compounds	SWMD accession number	Number of Lipinski violation/s
1.	9-acetoxydolabella-3,7,12-trien-16-al	BD075	1
2.	12-hydroxydolabella-3,7-dien-9-one	BD078	0
3.	9-acetoxydolabella-3E,7E-dien-12-ol	BD079	1
4.	49-hydroxydolasta-1,3-dien-6-one	BD080	1
5.	5-acetoxy-12-hydroxydolabell-3,7E-dienon	BD081	0
6.	9-hydroxydolabelladien-6-one	BD072	1
7.	Trihydroxydolasta-2-en-6-one	BD073	1

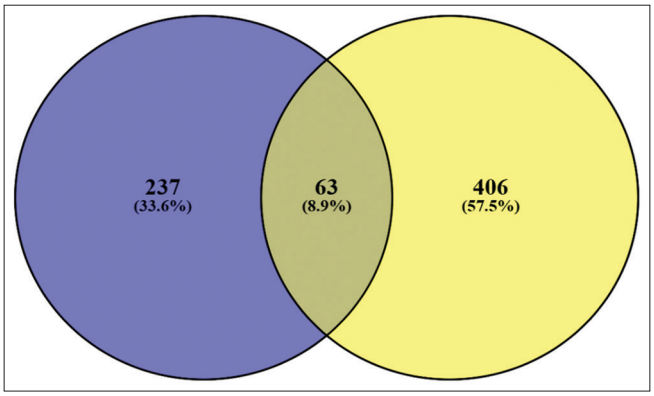

Figure 2: Venn diagram representing overlapping genes between Gene card and Comparative Toxicogenomics Database

demonstrated the presence of 62 nodes and 1988 edges. The degree of protein is measured by node size, and the greater the degree between targets, the greater is the linkage and potential for contribution in disease development. Further, Cytoscape plugin CytoHubba predicted hub genes based on the degree parameter and found that Tumor Protein 53 (TP53) (59), CTNNB1 (58), epidermal growth factor receptor (EGFR) (57.5), AKT1 (57.5), and MYC (57.5) to be top 5 Hub genes in core target subnetwork with highest degree values in descending orders as shown in Figure 3.

Molecular docking studies

Molecular docking predicts interactions between potential drug candidates and target proteins and plays key role in drug discovery. The top three potential targets identified by Hub gene analysis for the bioactives from *D. bartayresiana* were screened using molecular docking. Strong binding affinities between bioactives and the binding pockets of hub gene protein products were predicted. The stronger is ligand affinity for the target, more negative is its binding energy (BE). The bioactive compounds showed BE for CTNNB1 (1JDH). 12-hydroxydolabella-3, 7-dien-9-one showed a BE of −6.2 kcal/mol, making 1 hydrogen bond with Asg-342 of the binding site, and 5-acetoxy-12-hydroxydolabell-3,7E-dienon did not have any interactions. The BE of bioactive compounds with TP53 (1A2B) was −6 kcal/mol and −6.1 kcal/mol, respectively. Both compounds made two identical H-bonds with Lys-162 and Ala-161. The BE for compound interaction with EGFR (1M17) is −7.6 kcal/mol and -6.6 kcal/mol for 12–hydroxy and 5-acetoxy, respectively. 5-acetoxy shows higher binding affinity with the lowest BE as compared to 12-Hydroxy. Although the latter made 3 H-bonds with amino acids in the binding site, that is, Ala-317, Lys-851, and Glu-734, whereas former made 1 H-bond with Asp-831. The 2D and 3D docked protein structures of 12-Hydroxy –cnntb1, 12-Hydroxy –p53, 5-acetoxy –p53, 12-Hydroxy –EGFR, and 5-acetoxy –EGFR are given in Figure 4. An examination of interplay between target proteins and bioactive compound ligands also shed light on the influence of hydrogen bonding, C-H bonding, alkyl interactions, and pi-alkyl interactions.

DISCUSSION

OC is an evolving concern, especially in areas where betel nut chewing, intoxication, and tobacco use are prevalent. Genetic mutations and environmental cues also account for OC occurrence. The disease usually goes unnoticed until advanced stages, resulting in delayed diagnosis and aggressive progression.[17] Current treatment modalities include primary tumor resection, radiation, chemotherapy, and brachytherapy. Among chemotherapeutic drugs, cisplatin, carboplatin, and 5- fluorouracil are traditionally in use.[18] Recently, targeted therapy has gained traction due to its targeted effect on tumor. The onset of OC is a result of the accumulation of mutations in the genome. The most affected genes are EGFR and TP53.[19] Mutation in EGFR results in overexpression of the receptor, which continuously activates phosphoinositide 3-kinase (PI3K)/Protein Kinase B (AKT)/Mechanistic Target of Rapamycin (mTOR) pathway that promotes cell proliferation.[20] TP53 is a tumor suppressor gene and produces protein p53 and is involved in cell maintenance. Mutation in TP53 results in loss of function, resulting in the initiation and progression of OC. Current targeted therapies include Cetuximab, an anti-EGFR monoclonal antibody that targets EGFR overexpression in OC, and tyrosine kinase inhibitors such as Gefitinib and Erlotinib are in clinical use.[21] Bevacizumab, an anti-vascular endothelial growth factor monoclonal antibody, targets the PI3K/AKT/mTOR pathway and angiogenesis, thereby cutting down the blood supply to tumor. Immune checkpoint inhibitors such as Pembrolizumab and Nivolumab against programmed

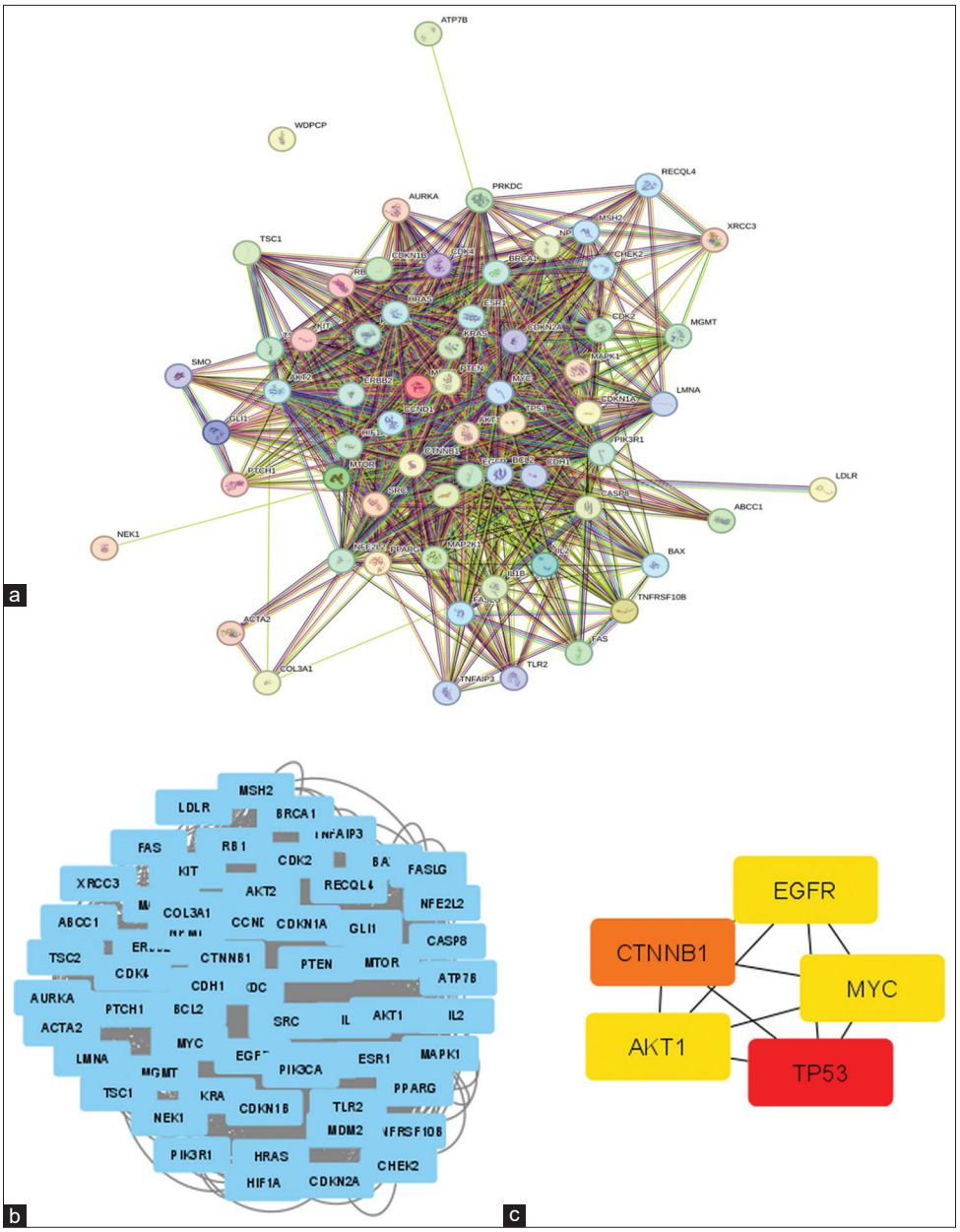

Figure 3: Protein-protein interaction (PPI) analysis. (a) PPI Network from STRING, (b) PPI visualization in Cytoscape, (c) Top 5 Hub genes predicted from CytoHubba

cell death 1 and programmed death ligand 2 proteins are also in use.[22]

The proximate analysis of *D. bartayresiana* shows various amounts of nutrient composition. Moisture content being the highest (48.82 ± 2.4%) among all, followed by ash, protein, fiber, carbohydrate, and lipid. Seaweeds have been reportedly low lipid content, whereas high amount of fiber and protein are part of a dietary supplement.[23] Although the protein and lipid components are consistent with species found in other coastal parts of India, the nutritional composition varies among species that are located at different depths. Environmental factors such as nutrient level in seawater, salinity, and temperature also affect the overall nutritional profile.[24,25]

D. bartayresiana has been reported to contain numerous active substances such as phenol and alkaloids. In the current study, the extracts of this marine alga have exhibited profound effects on KB cells. After 48 h of treatment, we found that all three extracts show the highest cytotoxic effect at 100 mg/mL and 120 mg/mL. This result is agreement with previous reports on anti-cancer activity of *D. bartayresiana* against HT-29 colon cancer cells[26] and MDA-MB-23 triple negative breast cancer cells.[27] The ethyl acetate extract of this alga has also been reported to decrease hyperglycemia in a rat model.[28]

To understand the genes involved in OC, network pharmacology was employed. We predicted mechanisms underlying the therapeutic effects of *D. bartayresiana*

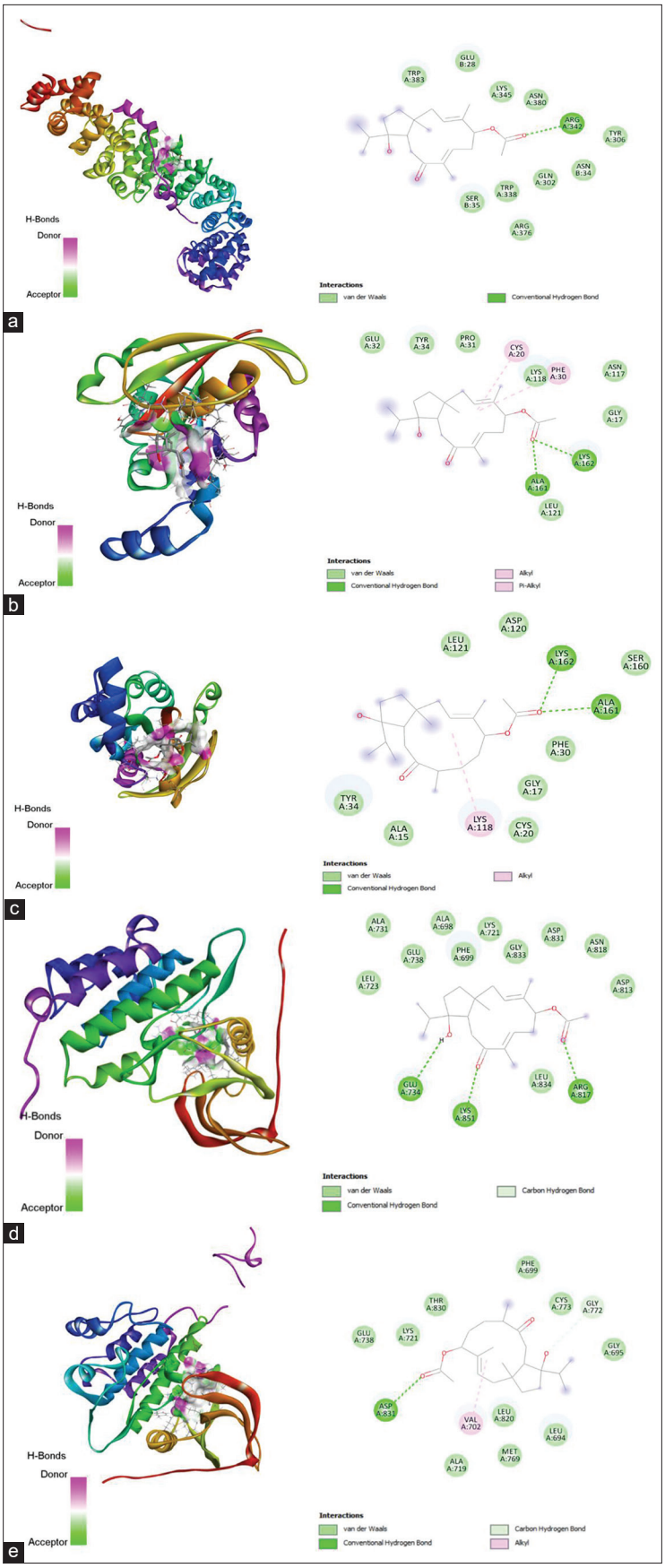

Figure 4: Molecular docking studies of selected *Dictyota bartayresiana* bioactives on the top 3 Hub genes. 3D and 2D interactions of (a) 12-Hydroxy – CNNTB1, (b) 12-Hydroxy – Tumor Protein 53 (TP53), (c) 5-acetoxy – TP53, (d) 12-Hydroxy – epidermal growth factor receptor (EGFR), (e) 5-acetoxy – EGFR

compounds for treating OC and identified 2 base antitumor compounds and genes that are targeted by these compounds. We found 63 interrelated common targets. By analyzing the interactions between potential therapeutic targets, it was concluded that these targets are clustered in five protein modules, and genes relevant to these proteins are referred to as hub genes. In particular, TP53, CTNNB1, EGFR, AKT1, and MYC play synergistic role in OC. CTNNB1 encodes β –catenin, protein localized to plasma membrane and maintain cell-cell adhesion. When mutated, β –catenin accumulates in cytoplasm and nucleus, constitutively activating Wnt pathway, leading to activation of oncogenic drivers that promote tumor initiation and progression. EGFR plays a key role in normal growth and development of tissue by responding to Epidermal Growth factor and activating downstream signaling by tyrosine kinase activity of cytoplasmic domain. When mutated, overexpression of EGFR drives cancer initiation and proliferation. One such signaling of EGFR is stabilization of β –catenin in nucleus by phosphorylation and induction of mesenchymal cell morphology promoting neoplastic growth.[29] AKT1 takes part in various cellular processes, and phosphorylation of AKT1 by membrane receptors results in downstream activation of mTOR signaling pathway. In cancer, AKT1 activity is enhanced, impairing the downstream protein cascade, thereby inhibiting pro-apoptotic proteins Bad and Bax. According to a study by Roy *et al*., AKT1 and AKT2 isoform silencing with siRNAs caused cell cycle arrest at G2/M phase in SAS cells by reducing the expression of corresponding genes by 90%.[30]

Overall, our results based on cytotoxic assay, network pharmacology, and molecular docking studies shed light on the potential anti-cancer mechanism of 12-hydroxydolabella-3, 7-dien-9-one and 5-acetoxy-12-hydroxydolabella-3,7E-dienon of *D. bartayresiana* on OC by highlighting its ability to interact with many gene targets involved in OC initiation and progression.

CONCLUSION

This research demonstrates foundation for determining the efficacy of active compounds from *D. bartayresiana* against gene targets involved in OC. These targets and pathways provide a pharmacological basis for development of new drugs using seaweeds for OC. However, current research has some constraints since further chemical constituents and investigations are required to validate our findings.

REFERENCES

1. Abati S, Bramati C, Bondi S, Lissoni A, Trimarchi M. Oral cancer and precancer: A narrative review on the relevance of early diagnosis. Int J Environ Res Public Health 2020;17:9160.
2. Agrawal AG, Hande AH, Bansod A, Goenka Y, Panchabhai A. Role of epidermal growth factor (EGFR) in oral cancer. J Pharm Res Int 2021;33:78-84.
3. Alves C, Silva J, Pinteus S, Gaspar H, Alpoim MC, Botana LM, *et al*. From marine origin to therapeutics: The antitumor potential of marine algae-derived compounds. Front Pharmacol 2018;9:777.
4. Antonysamy JMA, Thangiah S, Irulappan R. Green synthesis of silver nanoparticles using *Dictyota bartayresiana* JV Lamouroux and their cytotoxic potentials. Int Biol Biomed J 2016;1:112-8.
5. Bandaru N, Patil YP, Ekghara SD, Patil KS, Bonthu MG. Exploring marine-derived compounds as potential anti-cancer agents: Mechanisms and therapeutic implications. Cancer Pathog Ther 2025;4:192-207.
6. Bharathi DS, Raja AB, Nachimuthu S, Thangavel S, Kannan K, Shanmugan S, *et al*. Exploration of bioactive compounds, antioxidant and antibacterial properties, and their potential efficacy against HT29 cell lines in *Dictyota bartayresiana*. Mar Drugs 2025;23:224.
7. Bharathi SD, Raja BA, Deshpande MN, Chakrapani IS, Priyadarshini IA, Anbazhagan A. New record of *Dictyota bartayresiana*, a marine brown algal species revealed from rich seaweed diversity area of South India. J Coast Life Med 2023;11:825-30.
8. Chakraborty S, Bhattacharya T. Nutrient composition of marine benthic algae found in the Gulf of Kutch coastline, Gujarat, India. J Algal Biomass Util 2012;13:32-8.
9. Chellamanimegalai P, Deshmukhe G, Balange AK, Layana P. Unveiling the nutritional and antioxidant properties of brown algae resources (Dictyota J.V. Lamouroux) from the Bay of Bengal and Arabian Sea, Indian coast. Heliyon 2025;11:e40693.
10. Gondak RO, Mariano FV, De Sousa SF, Siqueira EC, Díaz KP, Martins LA, *et al*. CTNNB1 and APC mutations in odontogenic carcinoma with dentinoid. Oral Surg Oral Med Oral Pathol Oral Radiol 2020;129:e249-56.
11. Harakeh S, Niyazi HA, Niyazi HA, Abdalal SA, Mokhtar JA, Almuhayawi MS, *et al*. Integrated network pharmacology approach to evaluate bioactive phytochemicals of *Acalypha indica* and their mechanistic actions to suppress target genes of tuberculosis. ACS Omega 2024;9:2204-19.
12. Harsha C, Banik K, Ang HL, Girisa S, Vikkurthi R, Parama D, *et al*. Targeting AKT/mTOR in oral cancer: Mechanisms and advances in clinical trials. Int J Mol Sci 2020;21:3285.
13. Harshini SS, Ameya KP, Usman PP, Sekar D. Elucidating the role of TP53 in oral squamous cell carcinoma: A cross-sectional observational study of integrated analysis of expression patterns and functional importance. Indian J Med Paediatr Oncol 2025.
14. Hu M, Yan H, Li H, Feng Y, Sun W, Ren Y, *et al*. Use of network pharmacology and molecular docking to explore the mechanism of action of curcuma in the treatment of osteosarcoma. Sci Rep 2023;13:9569.
15. Imran M, Iqbal A, Badshah SL, Sher AA, Ullah H,

Ayaz M, *et al*. Chemical and nutritional profiling of the seaweed *Dictyota dichotoma* and evaluation of its antioxidant, antimicrobial and hypoglycemic potentials. Mar Drugs 2023;21:273.
16. Inchingolo F, Santacroce L, Ballini A, Topi S, Dipalma G, Haxhirexha K, *et al*. Oral cancer: A historical review. Int J Environ Res Public Health 2020;17:3168.
17. Islam SI, Ahmed SS, Habib N, Ferdous MA, Sanjida S, Mou MJ. High-throughput virtual screening of marine algae metabolites as high-affinity inhibitors of ISKNV major capsid protein: An analysis of *in-silico* models and DFT calculation to find novel drug molecules for fighting infectious spleen and kidney necrosis virus (ISKNV). Heliyon 2023;9:e16383.
18. Jason AS, Gidean Arularasan S, Krishnan M, Kumar MP, Lakshmanan S. Survivin in the malignant transformation of oral potentially malignant disorders to oral squamous cell carcinoma: A systematic review. Cuest Fisioter 2025;54:2564-75.
19. Mir MA, Banik BK. Sustainable healing: Natural compounds facilitating the future cancer treatment. World Dev Sustain 2025;6:100215.
20. Mohideen NS, Rao A, Begum SM. Anti-cancer potential of crude extracts from *Dictyota bartayresiana* in triple-negative breast cancer. Bangladesh J Pharmacol 2024;19:114-21.
21. Noor F, Tahir ul Qamar M, Ashfaq UA, Albutti A, Alwashmi AS, Aljasir MA. Network pharmacology approach for medicinal plants: Review and assessment. Pharmaceuticals 2022;15:572.
22. Ramachandran S. Oral cancer: Recent breakthroughs in pathology and therapeutic approaches. Oral Oncol Rep 2024;12:100678.
23. Roy NK, Monisha J, Padmavathi G, Lalhruaitluanga H, Kumar NS, Singh AK, *et al*. Isoform-specific role of Akt in oral squamous cell carcinoma. Biomolecules 2019;9:253.
24. Rushdi MI, Abdel-Rahman IA, Attia EZ, Saber H, Saber AA, Bringmann G, *et al*. The biodiversity of the genus *Dictyota*: Phytochemical and pharmacological natural products prospectives. Molecules 2022;27:672.
25. Saberian E, Jenča A, Petrášová A, Jenčová J, Jahromi RA, Seiffadini R. Oral cancer at a glance. Asian Pac J Cancer Biol 2023;8:379-86.
26. Shahzadi Z, Yousaf Z, Anjum I, Bilal M, Yasin H, Aftab A, *et al*. Network pharmacology and molecular docking: Combined computational approaches to explore the antihypertensive potential of *Fabaceae* species. Bioresour Bioprocess 2024;11:53.
27. Singh S, Cojandaraj L, Suttee A, Kumar A. *In vitro* evaluation of natural extracts as potential anticancer agents: A study on KB cell lines. Afr J Biomed Res 2024;27:285-94.
28. Tan Y, Wang Z, Xu M, Li B, Huang Z, Qin S, *et al*. Oral squamous cell carcinomas: State of the field and emerging directions. Int J Oral Sci 2023;15:44.
29. Thomas P, Ramani P, Ramasubramanian A, Sekar D. Characterizing miR-20a-3p expression in the progression of oral squamous cell carcinoma. J Adv Oral Res 2025;16:34-42.
30. Zhang M, Liang J, Yang Y, Liang H, Jia H, Li D. Current trends of targeted drug delivery for oral cancer therapy. Front Bioeng Biotechnol 2020;8:618931.

Source of Support: Nil. **Conflicts of Interest:** None declared.