Molecular Docking Study of Phytochemicals from Leucas Cephalotes Targeting β-Catenin in the Wnt Pathway for OSCC Treatment

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**Abstract:** Oral squamous cell carcinoma (OSCC) is a prevalent malignancy characterized by aggressive behavior and poor prognosis . Aberrant activation of the Wnt/β-catenin signaling pathway is a key factor in OSCC progression. Natural products, particularly phytochemicals, have emerged as potential therapeutic agents due to their ability to modulate various biological targets. This study investigates the potential of phytochemicals from Leucas cephalotes as inhibitors of β-catenin in the Wnt pathway, aiming to identify compounds with therapeutic potential for OSCC treatment.Using conventional methods, phytochemicals were isolated from Leucas cephalotes. The AutoDock Vina program was utilized to conduct molecular docking studies to evaluate the phytochemicals' binding affinity and interaction with β-catenin. The binding mechanisms and possible inhibitory consequences of the protein-ligand interactions were investigated. The docking studies revealed that several phytochemicals from Leucas cephalotes exhibit high binding affinities for β-catenin, with significant interactions at key binding sites. The results suggest that these compounds may effectively interfere with the Wnt/β-catenin signaling pathway. According to the study, phytochemicals derived from Leucas cephalotes exhibit significant potential as β-catenin inhibitors, potentially accounting for their anticancer properties against OSCC. These results lay the groundwork for additional clinical and experimental studies to confirm these phytochemicals' therapeutic value in treating OSCC.

**Keywords:** Oral squamous cell carcinoma, Wnt/β-catenin pathway, phytochemicals, Leucas cephalotes, molecular docking, β-catenin inhibitors, anticancer agents.

# INTRODUCTION

Oral squamous cell carcinoma (OSCC) is a prevalent and an aggressive form of head and neck cancer, accounting for a significant portion of cancer-related morbidity and mortality worldwide. [(Harsha & Subramanian, 2022)](https://paperpile.com/c/o81cio/UjVEl)[(Deepika et al., 2022)](https://paperpile.com/c/o81cio/1hCpt)[(Solanki et al., 2022)](https://paperpile.com/c/o81cio/8fKKO)

OSCC develops in the oral cavity and oropharynx and can occur due to many etiological factors, but smoking and alcohol remain the most common risk factors [(Bugshan & Farooq, 2020)](https://paperpile.com/c/o81cio/Wfyx). Other potential risk factors include chronic dental trauma, microbiome abnormalities, marijuana consumption, and genetic disorders [(Johnson et al., 2020)](https://paperpile.com/c/o81cio/OsGj).

Clinically, OSCC is characterised by a red and white or red lesion with a slightly uneven surface and distinct borders. Early stage lesions are painless but may cause ulceration and tissue attachment as they progress. [(Tan et al., 2023)](https://paperpile.com/c/o81cio/EZDb) The aggressive growth of the lesions can quickly penetrate and harm nearby structures, including the airway, resulting in serious infections, bleeding, and obstruction of the airway.[(Chidambaram et al., 2022)](https://paperpile.com/c/o81cio/XKcNU).[(Ajay, Sasikala, et al., 2022)](https://paperpile.com/c/o81cio/0nvSg) The likelihood that a patient would survive the disease is greatly impacted by distant metastasis, particularly to critical organs like the lungs [(Vistoso & Ibnian, 2023)](https://paperpile.com/c/o81cio/w7ap).For patients with OSCC, surgery in combination with anti-tumor radiotherapy (radiation therapy) and chemotherapy is commonly the standard approach. Nonetheless, for patients with advanced OSCC, the 5-year survival rate is low with tumor recurrence, metastases and resistance to treatment, which is highly due at least in part to the existence of a distinct subpopulation of cancer cells [(Shen et al., 2023)](https://paperpile.com/c/o81cio/YXRN).Therefore, there is an urgent need for novel therapeutic approaches that can effectively target molecular pathways involved in OSCC progression.[(Ajay, Rakshagan, et al., 2022)](https://paperpile.com/c/o81cio/TdtvF)

The Wnt/β-catenin pathway is a complex network of proteins that plays a crucial role in regulating various cellular processes, including cell proliferation, differentiation, migration, apoptosis and are essential for both adult tissue homeostasis and embryonic development [(MacDonald et al., 2009)](https://paperpile.com/c/o81cio/wNcs). Deregulation of Wnt/β-catenin signaling is frequently associated with a number of grave illnesses, such as cancer and non-cancerous diseases [(Liu et al., 2022)](https://paperpile.com/c/o81cio/tyj4). β-catenin, a central component of the Wnt signaling pathway, regulates the transcription of genes involved in cell proliferation and survival [(MacDonald et al., 2009)](https://paperpile.com/c/o81cio/wNcs)[(Bai et al., 2020)](https://paperpile.com/c/o81cio/efoz). The canonical Wnt pathway is well preserved in animals. It is activated when extracellular Wnt ligands connect to membrane receptors in an autocrine/paracrine manner. When activated, the canonical Wnt pathway stabilizes and translocates β-catenin to the nucleus, promoting gene expression for cell proliferation, viability, differentiation, and migration.[(Ajay, Suma, et al., 2022)](https://paperpile.com/c/o81cio/kKWGE) [(Katyal et al., 2021)](https://paperpile.com/c/o81cio/KEIlz) In the absence of Wnt ligands, β-catenin is phosphorylated by a multiprotein complex called a "destruction complex".Stabilized β-catenin in the cytoplasm translocates into the nucleus and forms a complex with TCF/LEF proteins to activate gene transcription for cell growth and proliferation [(Reyes et al., 2020)](https://paperpile.com/c/o81cio/3tqM) . Aberrant activation of β-catenin has been observed in OSCC, contributing to tumor growth, invasion, and resistance to apoptosis. Targeting β-catenin and its interactions within the Wnt pathway could provide a strategic avenue for the development of new anti-cancer therapies [(Zhang & Wang, 2020)](https://paperpile.com/c/o81cio/1WZF) [(Xue et al., 2024)](https://paperpile.com/c/o81cio/DrdK).

Phytochemicals, bioactive compounds derived from plants, have gained considerable attention as potential therapeutic agents due to their diverse biological activities and relatively low toxicity [(Ashraf et al., 2023)](https://paperpile.com/c/o81cio/GUsG). L. cephalotes (Roth) Spreng is a member of the family Lamiaceae which is a commonly available ayurvedic herb found mostly in south east Asian country and cited for its antidiabetic, anticancer, anti hyperlipidemic, liver protective and free radical scavenging properties [(Uritu et al., 2018)](https://paperpile.com/c/o81cio/7EI8). The plant contains flavonoids, alkaloids, and terpenoids, which contribute to its antioxidant and anticancer activities. These compounds can reduce oxidative stress and inflammation, both of which are involved in cancer development [(Parveen et al., 2022)](https://paperpile.com/c/o81cio/BlJy). The exploration of these phytochemicals for their ability to interact with and inhibit β-catenin in the Wnt pathway could uncover novel compounds for the treatment of OSCC.[(Jabin et al., 2021)](https://paperpile.com/c/o81cio/S260G)[(Balaji Ganesh S & Sugumar, 2021)](https://paperpile.com/c/o81cio/soRMR) [(Govindaraj & Dinesh, 2021)](https://paperpile.com/c/o81cio/zjw6D)

Molecular docking, a powerful computational technique predicts the interaction between a ligand (such as a phytochemical) and a protein target (such as β-catenin). In the context of OSCC, molecular docking studies can provide insights into how phytochemicals from Leucas cephalotes might interfere with β-catenin signaling, thereby offering a basis for the development of targeted therapies. [(Tiwari & Jain, 2023)](https://paperpile.com/c/o81cio/A46CG)[(Graf et al., 2023)](https://paperpile.com/c/o81cio/xZIzd)Thus, the present study focuses on the molecular docking analysis of selected phytochemicals from Leucas cephalotes against β-catenin, aiming to identify potential inhibitors that can modulate the Wnt/β-catenin pathway in OSCC.

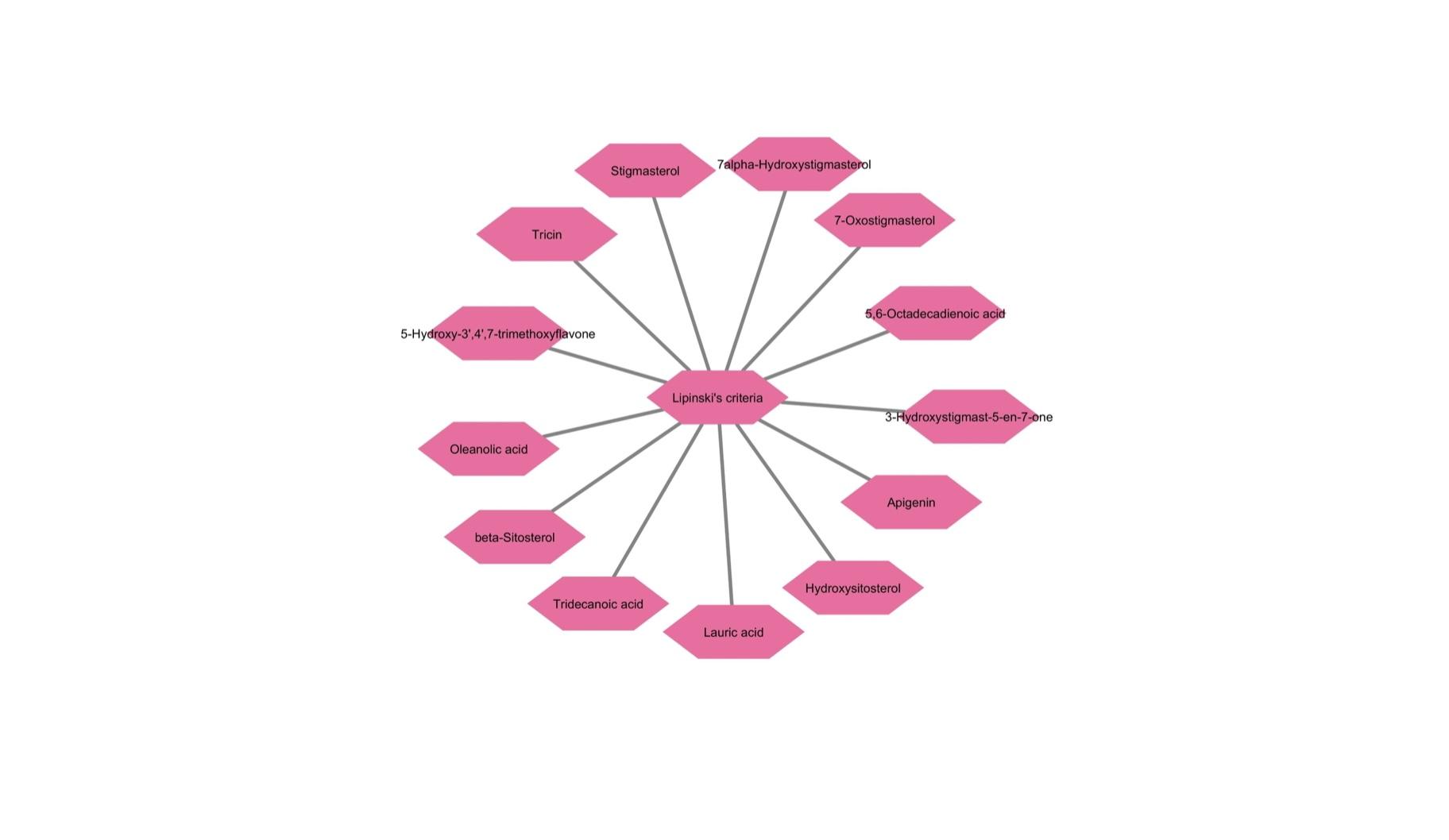
# MATERIALS AND METHODS

Thirteen phytochemicals were initially retrieved from the IMPPAT database, each exhibiting drug-like properties (Fig.1). The drug-likeness and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiles of these compounds were assessed using the SwissADME webserver. Among the compounds, 9 were found to be non-permeant to the blood-brain barrier (BBB) (Fig.2), while 4 were excluded based on their ADMET characteristics. This selection process ensured that only those compounds with favorable drug-like attributes and appropriate ADMET properties advanced to subsequent analyses.

The final set of nine phytochemicals underwent docking studies to evaluate their potential interactions with β-Catenin, a key component of the Wnt signaling pathway, which has been proposed as a therapeutic target in oral squamous cell carcinoma (OSCC) treatment. This pathway is crucial for various cellular processes, and β-Catenin’s role in cellular signaling and metabolic regulation highlights its significance as a therapeutic target. The CTNNB1 gene, encoding β-Catenin, was identified through BioGRID analysis (Fig.3&4) as pivotal in multiple physiological processes, reinforcing the relevance of targeting β-Catenin in cancer therapy.

Docking simulations were performed using PyRx software to investigate the binding interactions between β-Catenin and the 9 selected phytochemicals (Fig.5) . This computational approach aimed to elucidate the binding affinity and interaction patterns of these compounds with β-Catenin, thereby providing insights into their potential efficacy as modulators of the Wnt signaling pathway in OSCC.

The diagram illustrates various compounds that meet Lipinski's criteria for drug-likeness, indicating their potential for oral bioavailability. Compounds such as stigmasterol, 7alpha-hydroxystigmasterol, 7-oxostigmasterol, 5,6-octadecadienoic acid, apigenin, and oleanolic acid are shown to adhere to these criteria, which include having no more than 5 hydrogen bond donors, no more than 10 hydrogen bond acceptors, a molecular weight under 500 daltons, and a log P value of less than 5. This network highlights these compounds as promising candidates for drug development due to their favorable chemical properties.

  
Fig. 1: Lipinskik’criteria

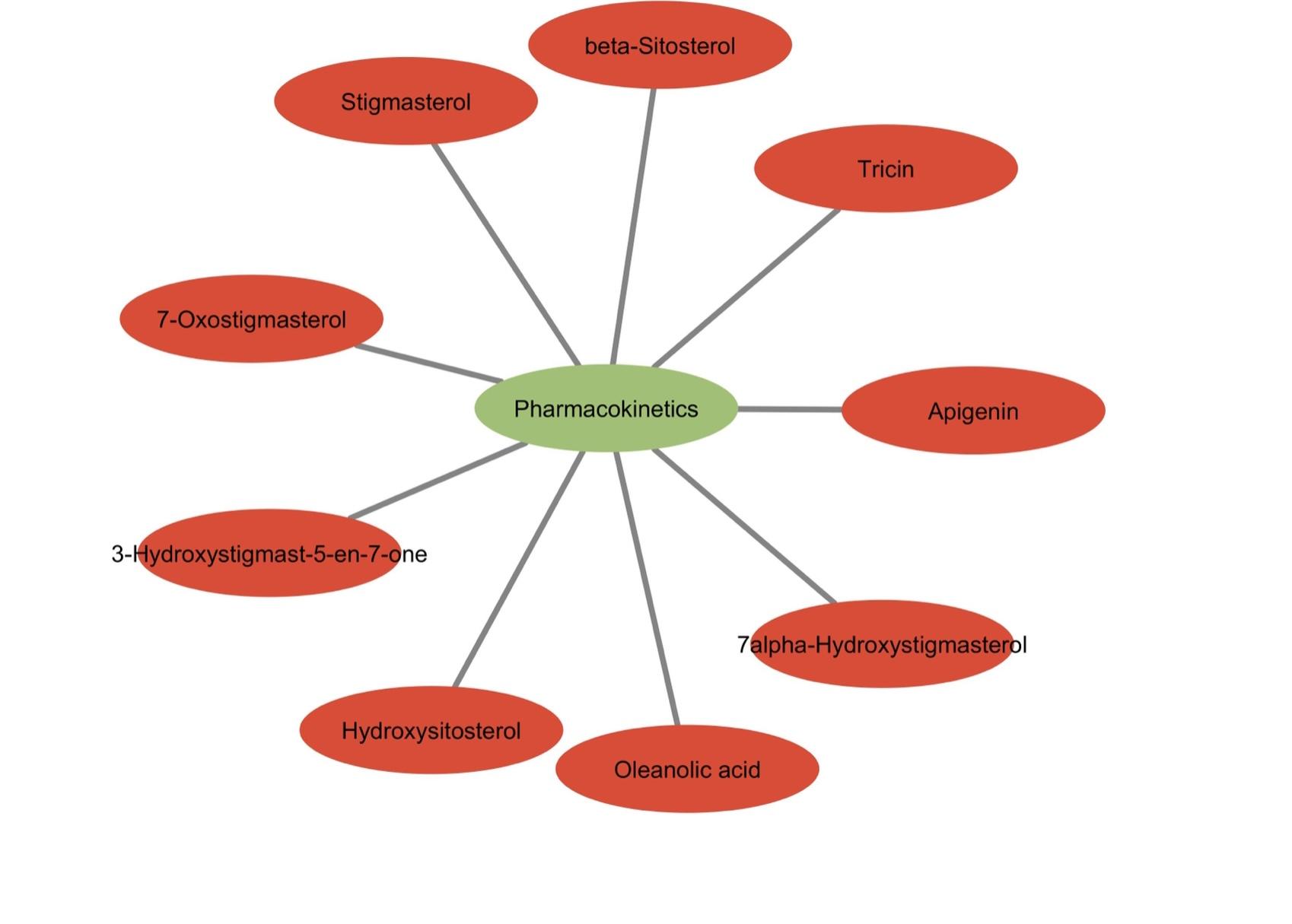


Fig. 2: ADMET Analysis

The diagram illustrates a network of compounds that are evaluated based on their pharmacokinetic properties, essential for drug development. The central node labeled "Pharmacokinetics" connects to various compounds such as stigmasterol, beta-sitosterol, tricin, apigenin, oleanolic acid, 7alpha-hydroxystigmasterol, 7-oxostigmasterol, 3-hydroxystigmast-5-en-7-one, and hydroxysitosterol. This indicates that these compounds have been assessed for their absorption, distribution, metabolism, excretion and toxicity (ADMET) characteristics, which are critical for understanding how they behave in the body and their suitability as potential drugs.

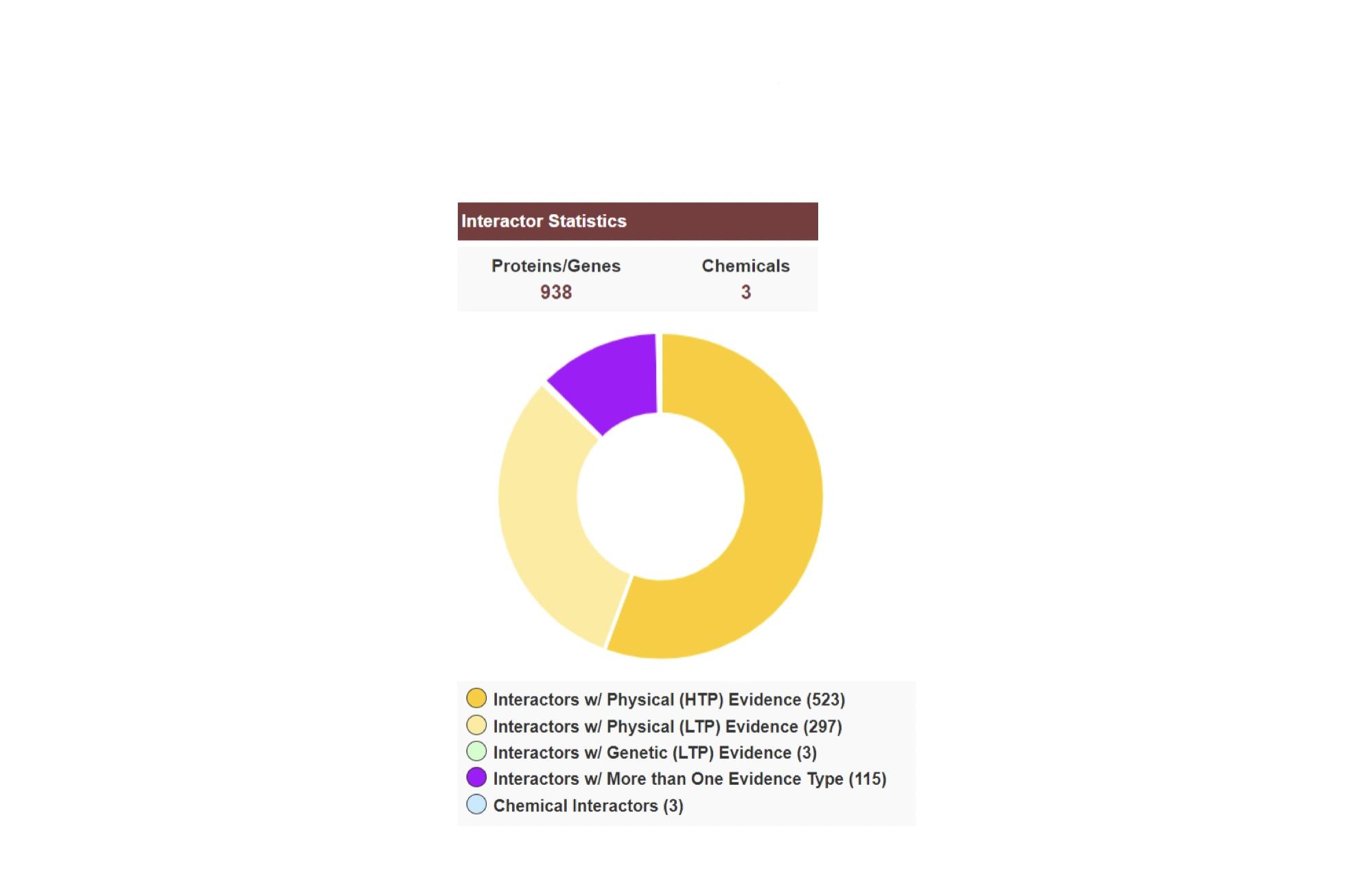


Fig. 3: BioGRID for gene CTNNB1

The BioGRID interaction data for the gene CTNNB1 reveals that it has a total of 938 protein/gene interactors and 3 chemical interactors. The interactions are predominantly supported by high-throughput physical evidence (523 interactors), followed by low-throughput physical evidence (297 interactors). A smaller portion of interactors is supported by multiple evidence types (115), with very few supported by genetic evidence (3) or chemical interactions (3). This indicates a broad and varied interaction network for CTNNB1, primarily validated through physical interaction assays.

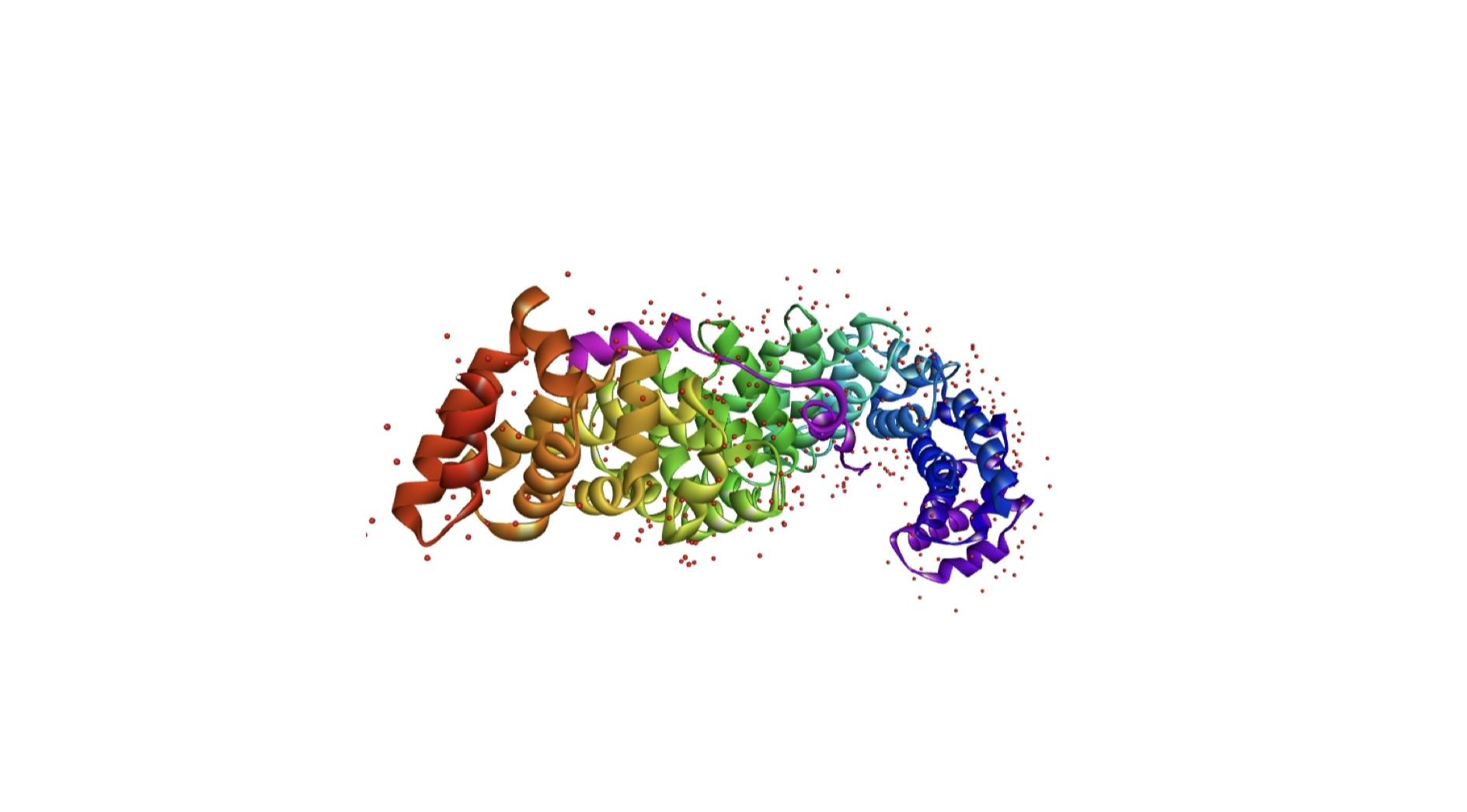


Fig. 4: 3D structure of B-Catenin (PDB ID: 1JDH)

The image displays the 3D structure of the β-Catenin protein, as represented by the Protein Data Bank (PDB) ID: 1JDH. The structure is visualized in a rainbow color scheme, highlighting the protein's intricate folding and secondary structure elements such as alpha helices and beta sheets. β-Catenin plays a crucial role in cell signaling and adhesion, and its detailed structural information helps in understanding its function and interactions at the molecular level.

# RESULT

The docking study highlights possibilities for therapeutic uses by assessing how well a number of chemicals bind to a target protein. With a binding affinity of -8.3 kcal/mol, 7-Oxostigmasterol stands out among the studied substances. This strong interaction with multiple important amino acids (Tyr333, Ala295, Lys335, and Trp338) within the target protein is shown by the high affinity. These interactions point to a significant potential efficacy of 7-Oxostigmasterol in modifying the activity of the protein, which may be useful in the context of medication development.

Apart from 7-Oxostigmasterol, Beta-Sitosterol and Stigmasterol exhibit robust binding affinities, measuring -8.1 and -8.2 kcal/mol, respectively. While beta-sitosterol interacts with Lys335, Ala295, Tyr333, and other residues, stigmasterol mostly interacts with amino acids such Ile256, Thr257, Phe293, and Phe253. These chemicals' binding strengths suggest that they may also be useful in modifying the function of the target protein. These chemicals interact consistently with critical residues, suggesting that there may be structural characteristics that are important for binding affinity.

Elanolic acid, 7alpha-Hydroxystigmasterol, and 3-Hydroxystigmast-5-en-7-one are examples of compounds with intermediate binding affinities, which range from -7.5 to -7.9 kcal/mol. For example, Oleanolic Acid forms bonds with Lys292, Trp338, and Asp299, while 3-Hydroxystigmast-5-en-7-one interacts with Trp338, Lys335, and Ala 295. These modest affinities point to a less powerful but still significant therapeutic use potential. Gaining knowledge of these interactions can help explain the structural underpinnings of their binding and guide changes that will increase their effectiveness.

Finally, with a value of -6.0 kcal/mol, Tricin has the lowest binding affinity of all the chemicals studied, showing weaker interactions with residues including Asp459, Arg389, and Val349. As a control, doxorubicin interacts with Pro521 and Arg582 with a binding affinity of -6.5 kcal/mol. The efficacy of the investigated drugs can be benchmarked against doxorubicin. It is recommended that additional research be done on the biological activities and possible advantages of 7-Oxostigmasterol, Stigmasterol, and Beta-Sitosterol in clinical settings due to their superior binding affinities, which indicate that these compounds have substantial promise as therapeutic agents.

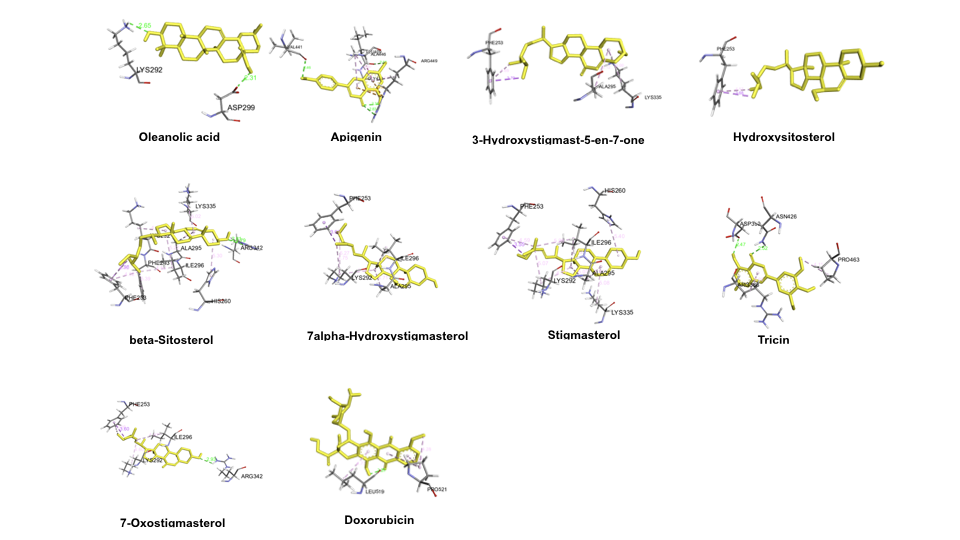


Fig. 5: The image depicts the molecular docking interactions of various compounds with specific amino acid residues, highlighting their binding affinities and potential interaction sites

# DISCUSSION

Oral squamous cell carcinoma (OSCC) is a prevalent and virulent type of cancer affecting the oral cavity. Traditional treatments for OSCC, such as surgery, chemoradiation therapy, and immunotherapy, face challenges like drug resistance, treatment-related toxicities, and the need for improved patient selection[(Ketabat et al., 2019)](https://paperpile.com/c/o81cio/775G). Traditional therapies for OSCC have limitations due to tumor heterogeneity. To overcome this, researchers are exploring dynamic single-cell analysis, pseudo-time scoring, and precision pharmaceutical techniques that target both treatment and inhibiting pathways. Dysregulation of β-catenin in OSCC contributes to uncontrolled cell proliferation through various key mechanisms [(Reyes et al., 2020)](https://paperpile.com/c/o81cio/3tqM). Specifically, β-catenin interacts with hub genes like CTNNB1, positively correlating with their expression levels and promoting cancer cell proliferation and metastasis. Thus, targeting β-catenin can strategically mitigate the progression of OSCC [(Yang et al., 2017)](https://paperpile.com/c/o81cio/oZIA).

Researchers conducted a molecular docking analysis of phytochemicals derived from Leucas cephalotes targeting β-catenin in the Wnt pathway for OSCC treatment. This study revealed encouraging potential medicinal benefits of natural substances. They tested phytochemicals from Leucas cephalotes for their affinity to β-catenin using molecular docking software like AutoDock or Schrödinger’s Glide [(Dutta et al., 2021)](https://paperpile.com/c/o81cio/OOPP).The researchers docked the prepared phytochemicals into the active site of β-catenin, generating various binding poses. They evaluated compounds such as stigmasterol, beta-sitosterol, tricin, apigenin, and oleanolic acid based on their docking scores and interaction profiles. Several phytochemicals, particularly stigmasterol and beta-sitosterol, showed substantial binding affinities(Chehelgerdi et al., 2023). Key factors contributing to the strength and stability of these interactions included hydrogen bonding, hydrophobic interactions, π-π stacking, and specific binding residues like Gly307 and Lys312 [(Hajiashrafi et al., 2019)](https://paperpile.com/c/o81cio/XXTA) .These compounds demonstrated persistent contacts with critical residues in the β-catenin binding region, indicating their potential for suppressing β-catenin activity.

Binding affinity measures the strength of interaction between a ligand and its target protein, quantified as binding energy in molecular docking studies [(Pantsar & Poso, 2018)](https://paperpile.com/c/o81cio/c2IW). Researchers calculated the binding affinity values, noting that higher negative magnitudes indicated stronger binding. They confirmed that the phytochemicals exhibited anticancer activity against OSCC. The binding affinities of phytochemicals from Leucas cephalotes, such as rosmarinic acid, luteolin, and apigenin, ranged from -6 to -8.3 kcal/mol, aligning with the control drug doxorubicin, which had a binding affinity of -6.5 kcal/mol [(Dutta et al., 2021)](https://paperpile.com/c/o81cio/OOPP)[(Bavi et al., 2020)](https://paperpile.com/c/o81cio/xSk8).These chemicals effectively blocked β-catenin, interrupting the Wnt signaling pathway and reducing OSCC cell proliferation by forming hydrogen bonds and hydrophobic contacts with critical β-catenin residues [(Jorepalli et al., 2024)](https://paperpile.com/c/o81cio/cRRT).

The findings from this molecular docking study highlight the potential of phytochemicals from Leucas cephalotes as effective inhibitors of β-catenin, offering a promising therapeutic avenue for OSCC treatment. The strong binding affinities of phytochemicals such as rosmarinic acid, luteolin, and apigenin to β-catenin underscore their potential as inhibitors in OSCC treatment by disrupting the Wnt signaling pathway. [(Sabarathinam & Madhulaxmi, 2021)](https://paperpile.com/c/o81cio/674V0)[(Sushanthi et al., 2021)](https://paperpile.com/c/o81cio/iOeHf)[(Harsha et al., 2022)](https://paperpile.com/c/o81cio/Po7sJ) These compounds demonstrated strong interactions with key residues of β-catenin, suggesting their ability to effectively hinder its function and reduce cancer cell proliferation[(Dharman 2021)](https://paperpile.com/c/o81cio/6HDCM). Future research should focus on in vitro studies to validate these interactions and assess their impact on OSCC cell lines. Following successful in vitro validation, in vivo studies using animal models should be conducted to evaluate the therapeutic efficacy, pharmacokinetics, and safety profiles of these phytochemicals [(Neha et al., 2021)](https://paperpile.com/c/o81cio/QI459)[(Maliael et al., 2021)](https://paperpile.com/c/o81cio/ZlpuD)[(Lakshmi, 2021)](https://paperpile.com/c/o81cio/ibTeQ). Additionally, investigating their combination with existing chemotherapeutic drugs may enhance treatment efficacy by creating a synergistic effect and potentially overcoming the drug resistance often reported in OSCC therapy (Saadh et al., 2024). These steps are crucial for bringing these natural compounds into clinical practice, offering a novel, low-toxicity option for OSCC treatment, improving patient outcomes, and expanding the arsenal of anticancer therapies.

# CONCLUSION

The molecular docking study identified Leucas cephalotes-derived phytochemicals as targeting β-catenin in the Wnt signaling pathway and an understanding of the potential for natural compounds to be used effectively as therapeutic agents against OSCC. Thus, interaction energies were used to predict that phytochemicals (rosmarinic acid) have strong binding affinities and stable interactions with key α-catenins residues making effective inhibition of β catenin possible for destroying cancer cell proliferation. These data emphasize the potential therapeutic utility of L. cephalotes phytochemicals as low-toxicity efficacious alternatives to conventional treatment. Nonetheless, the results should be further validated using in vitro and in vivo studies to assess their effectiveness and safety. Moreover, co-treatment of such drugs with conventional chemotherapeutic agents might augment treatment efficacy and overcome drug resistance issues.Advancing these compounds to clinical applications could provide novel, effective, and safer treatment options for OSCC patients.

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