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Biocomputational Prediction of Anticancer Activity of Ayurvedic Plants Inhibiting Cyclin D1: Molecular Docking Study of the Major Active Compounds of Licorice Root Extract (*Glycyrrhiza glabra*) in Inhibiting Oral Squamous Cell Carcinoma Proliferation

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ABSTRACT

Background: Oral squamous cell carcinoma (OSCC) reported for > 90% of oral cancer cases, causing 377,713 new cases and 177,757 deaths in 2020. Treatments like surgery, chemotherapy, and radiotherapy affect patients' lives. This study focuses on Licorice (*Glycyrrhiza glabra*) as an antineoplastic candidate targeting cyclin D1, crucial for cell proliferation in OSCC. It aims to predict licorice root extract (LRE) molecular mechanism against cyclin D1 and identify its most potent antineoplastic compound.

Method: The observational research employs a 2D biocomputational method. Ligand and enzyme require 2D isolation, human enzymes at 2–4 Å resolution, and >90% favorable regions. LRE and cyclin D1 are acquired from PubChem, RCSB PDB, PyMol, and Biovia. PyRx performs molecular docking, yielding quantitatively ΔGbind values in kcal/mol, which indicate anticancer potency (lower values signify better efficacy).

Results: All common active compounds of LRE that have negative ΔGbind values show that this compound can form bonds with the active site of cyclin D1 and inhibit its performance. The results of the molecular docking simulation also showed that 3 of the 9 LRE compounds had lower binding affinity values compared to the abemaciclib control, including glycyrrhetinic acid, liquiritin apioside, and 18β-glycyrrhetinic acid. These three compounds have binding affinity values of -5.5 kcal/mol, -5.3 kcal/mol, and -5.4 kcal/mol, respectively the most effective as an antineoplastic is glycyrrhetinic acid.

Conclusion: LRE had potential as antineoplastic against OSCC through cyclin D1 inhibition with the best being glycyrrhetinic acid.

INTRODUCTION

Oral Squamous Cell Carcinoma (OSCC) is a malignant form of cancer originating from the epithelium of the oral cavity. It is identifiable by observable indications such as plaque keratosis, persistent ulceration, indurated lesion edges, and redness [1]. OSCC is a multistage carcinogenesis process resulting from genetic mutations in cells, leading to hyperplasia, cell dysplasia, and irregular cell growth. The disease can affect various parts of the oral cavity, including the tongue, gingiva, lips, buccal, parotid, and oropharynx. Globally, OSCC reported for 90% of oral cancer cases reported over 377,713 new cases and 177,757 deaths in 2020 [2,3]. Treatment options for OSCC range from non-invasive to invasive methods, with ongoing research focusing on addressing challenges such as disease severity, poor prognosis, and drug resistance. Immunotherapy and targeted therapy are promising approaches, particularly for recurrent and metastatic cases. The prognosis of

OSCC is influenced by the disease stage, but it may not fully capture the complexity of tumor behavior, resulting in varied prognoses. Several biomarkers, including histopathological features, are being investigated for their potential in predicting prognosis in OSCC [4,5].

Cyclin D1 plays a crucial role in OSCC, influencing the cell cycle, survival, gene expression, and protein synthesis. Overexpression of cyclin D1 is associated with a poor prognosis in oral cancer, particularly in high-grade lesions. Immunohistochemistry studies have demonstrated a correlation between cyclin D1 and p53, with frequent expression observed in the palate, floor of mouth, and gingiva tumors. The role of cyclin D1 in OSCC suggests its potential as a marker for precancerous and cancerous conditions, and it may serve as a target for future interventions [6,7]. Ayurveda, an ancient system of medicine originating from India, aims to promote well-being by achieving harmony among the mind, body, and soul, thereby preventing diseases [8]. It utilizes a variety of medicinal plants to protect against different health issues, including those impacting digestion and mental health [9].

Glycyrrhiza glabra, commonly known as licorice root, is a popular herbal remedy in Ayurvedic medicine, recognized for its adaptogenic properties that aid in stress management. The plant contains sugars, bitters, resins, essential oils, tannins, and inorganic salts. Licorice is utilized as a natural sweetener and flavoring agent in various products and is incorporated into herbal formulations to treat conditions such as asthma, coughing, colds, sore throat, sinusitis, and allergic rhinitis [10–13].

Glycyrrhizin, a primary component of licorice, is a triterpenoid saponin that exhibits strong sweetness, approximately 50 times sweeter than sucrose. It comprises about 10% of the dry weight of licorice root and contains potassium, calcium, and magnesium salts of glycyrrhizic acid (2%–25%). The yellow color of licorice is attributed to flavonoids, including flavanones, flavones, chalcones, and others, with significant glycosides such as liquiritin and isoliquiritin [13]. Licorice, a traditional medicine staple, is being investigated for its potential in cancer treatment, particularly against OSCC. Research indicates that compounds such as 18β-glycyrrhetinic and glycyrrhizic acids induce apoptosis in tumor cells by modifying mitochondrial function. This research aims to predict LRE's molecular mechanism against cyclin D1 and identify its most potent antineoplastic compound using computational methods. Although licorice shows potential in inhibiting cancer proliferation in various types, a deeper understanding of its specific mechanism against OSCC's cyclin D1 pathway is needed [14–16].

METHODS

Research Design

This study employs an observational research approach with a biocomputational methodology using 2D and 3D materials virtually, also known as in silico research utilizing biological databases and programs. The research design incorporates in silico techniques with molecular docking and visualization of docking results.

Licorice root extract compound and protein target materials

In this research, the active compound from LRE was obtained and prepared in two dimensions by downloading it from the PubChem website (https://pubchem.ncbi.nlm.nih.gov/) (**Figure 1**). The active compounds featured in the Pharmacophore-based Virtual Screening (PPE) include liquiritin (CID 503737), isoliquiritin (CID 5318591), liquiritigenin (CID 114829), isoliquiritigenin (CID 638278), glycyrrhetinic acid (CID 10114), liquiritin apioside (CID 10076238), 18β-glycyrrhetic acid (CID 5702287), licochalcone A (CID 5318998), and glabridin (CID 124052). For comparison, abemaciclib (CID 46220502), was used as a comparator. The focal point of this study is the active conformation of the protein cyclin D1 (PDB ID 5VZU) attached in **Figure 2**, obtained and prepared for its three-dimensional structure from the RCSB Protein Data Bank web page (https://www.rcsb.org/). The selection of cyclin D1 as the target protein is based on its isolation from human enzyme sources, resolution exceeding 2Å, and a highly favorable region value of 90% (with this protein exhibiting 95.3%) within the Ramachandran range, making it well-suited for protein docking targets [17,18].

Research Tools

This investigation employs a bioinformatics methodology (in silico), leveraging database platforms and supportive tools executed through the Python program. Each phase of the in silico testing protocol involves distinct database platforms and tools. These include the utilization of Biovia and PyMol applications for the preparation of test materials and the visualization of docking outcomes. The Way2Drug page (http://www.way2drug.com/PASSOnline) is employed for predicting PASS, while the Lipinski Rule of Five page (http://www.scfbio-iitd.res.in/) is used for physicochemical assessments. The pkCSM website (https://biosig.lab.uq.edu.au) is utilized for predicting ADME (Absorption, Distribution, Metabolism, and Excretion) and toxicity parameters. The Uniprot website (https://www.uniprot.org/) aids in identifying active research target sites. Additionally, PyRx applications are employed for conducting molecular docking experiments [18,19].

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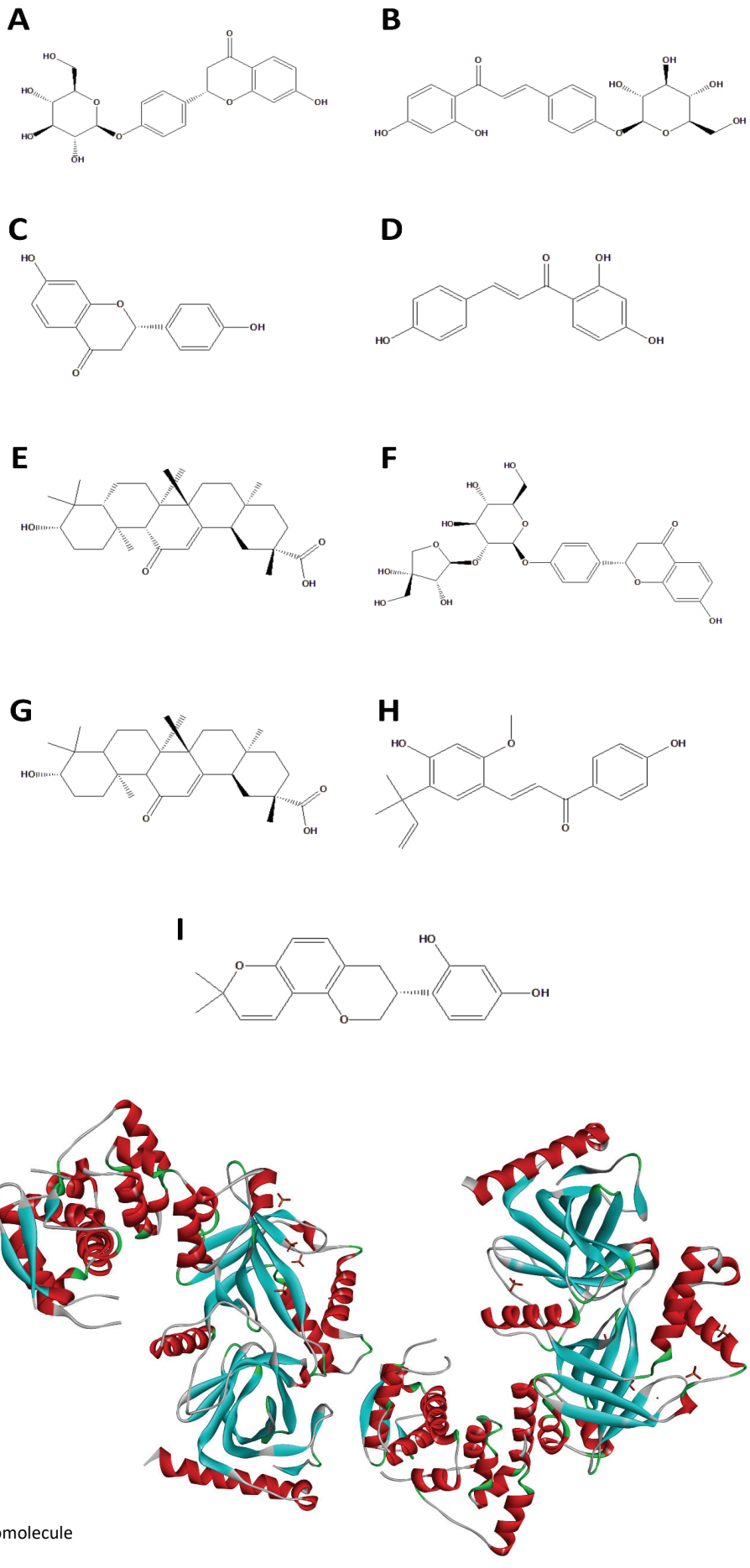

Figure 1. Ligand testing from licorice root extract's bioactive compound;
A) liquiritin (CID 503737),
B) isoliquiritin (CID 5318591),
C) liquiritigenin (CID 114829),
D) isoliquiritigenin (CID 638278),
E) glycyrrhetinic acid (CID 10114),
F) liquiritin apioside (CID 10076238),
G) 18β-glycyrrhetic acid (CID 5702287),
H) licochalcone A (CID 5318998), and
I) glabridin (CID 124052).

Figure 2. Visualisation of Cyclin-D1's Macromolecule (PDB ID: 5VZU).Research Tools

Preparation of ligand molecular and protein structure

The initial phase of test material preparation involves retrieving the test compound and targets from the PubChem and RCSB PDB databases. Upon download, the test and target compounds are labeled based on the compound name, as they are initially in CID number format. Subsequently, the active site of cyclin D1 (PDB ID 5VZU), crucial for neoplastic activity, is identified through the Uniprot site. Following the entry of the PDB ID code, the peptide chain sequence is obtained, necessitating isolation prior to the docking process. The target protein is then readied using the Biovia application, involving the removal of water molecules and native ligands, also sourced from the database. Post-preparation, the isolation of the peptide chain, constituting the active site of PI3K at the 286th position, is executed using the PyMol application [20].

Molecular docking test

The molecular docking test was executed by inputting the test compound, comparator compound, and target protein into the PyRx application. Following the upload, the PyRx program was executed to ascertain the results, encompassing binding affinity measured in kcal/mol, mode, and lower and upper bounds of root mean square deviation (RMSD). A compound is deemed to exhibit a propensity for binding with the target protein when it possesses a low binding affinity value. A lower binding affinity value implies reduced energy required for bond formation, signifying a heightened likelihood of bonding with the target protein. The mode parameter reflects the diversity of formed bonds, while the RMSD parameter gauges the accuracy and precision of the predictions. In general, compounds with low binding affinity values and optimal RMSD lower bounds and zero upper bounds are considered favorable [17,21–23].

Upon completion of the docking prediction test, the subsequent step involves visualization to validate the enzymatic reaction position concerning the active site. Visualization of the docking results is conducted to delineate the location, type, and quantity of bonds formed between the test compound and the target protein. This visualization process employs the PyMol and Biovia applications. The docked conformation, inserted into the target protein, is uploaded for visualization, revealing the spatial arrangement, nature, and count of formed bonds [24].

RESULTS

The results of the molecular docking test determine the ability and antineoplastic activity of LREs reviewed through their ability to inhibit cyclin D1 compared to standard drugs are shown in **Table 1** below.

Following the completion of the molecular docking simulation procedure, the simulation outcomes undergo visualization analysis to ascertain the precise positioning of the ligand binding to the cyclin D1 OSCC active site macromolecule, previously subjected to simulation (**Figure 3**). The findings reveal that each ligand from the LRE occupies the active site location of the LRE macromolecule. This observation indicates the appropriateness of the bond formed between LRE and cyclin D1 at the active site.

DISCUSSION

OSCC being a malignant cancer affecting the oral cavity, necessitates thorough treatment, ranging from precise examinations to appropriate and sufficient therapeutic interventions. Presently, chemotherapy and radiotherapy are administered as therapeutic modalities, both possessing antineoplastic capabilities [25,26].

Table 1. Molecular docking test result of LRE with comparative compound of abemaciclib

Protein Target	Compound	Binding Affinity (kcal/mol)	Mode	Root Mean Square Deviation (RMSD)	
				Lower Bound	Upper Bound
Cyclin D1 (PDB ID 5VZU)	Abemaciclib	-5.3	0	0	0
	Liquiritin	-5.1	0	0	0
	Isoliquiritin	-4.9	0	0	0
	Liquiritigenin	-4.4	0	0	0
	Isoliquiritigenin	-4.3	0	0	0
	Glycyrrhetinic acid	-5.5 (*)	0	0	0
	Liquiritin apioside	-5.3 (*)	0	0	0
	18β-Glycyrrhetic acid	-5.4 (*)	0	0	0
	Licochalcone A	-4.6	0	0	0
	Glabridin	-5.2	0	0	0

*Value lower or equal to comparison drugs abemaciclib

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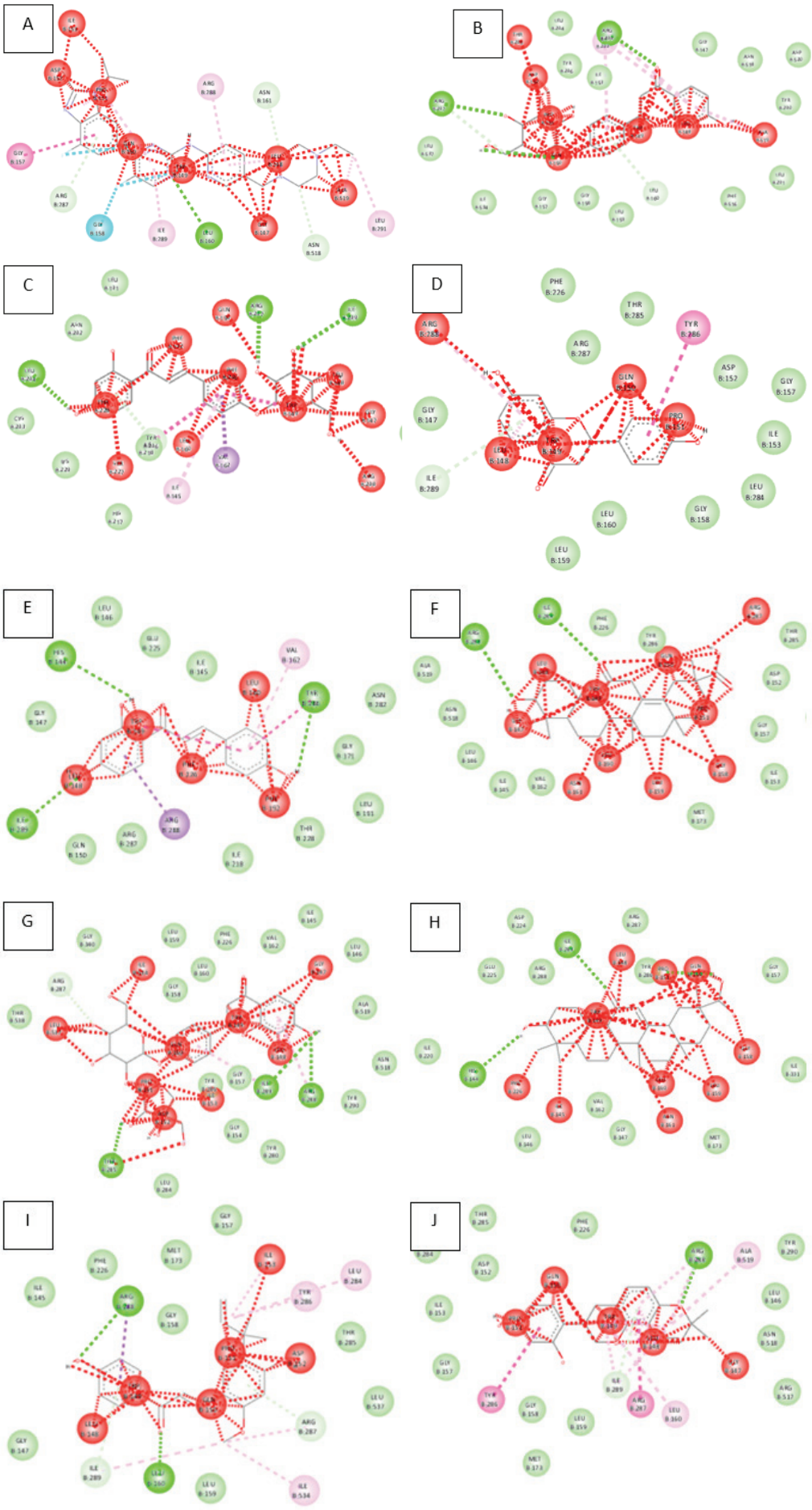

Figure 3.
Visualization of
(A) abemaciclib,
(B) liquiritin,
(C) isoliquiritin,
(D) liquiritigenin,
(E) isoliquiritigenin,
(F) glycyrrhetinic acid,
(G) liquiritin apioside,
(H) 18β-Glycyrrhetic acid,
(I) licochalcone A,
(J) and glabridin against cyclin D1 protein (PDB ID 5VZU).
Different colors and lines indicate the formation of the type of bond between the test compound and the enzyme peptide.
Light green indicates the formation of a pi-donor hydrogen bond, dark green indicates the formation of a van der Waals bond,
red indicates the formation of an unfavorable bump bond, dark purple indicates the formation of a π-σ bond, light purple indicates the formation of a π-π bond, yellow indicates the formation of a π-donor hydrogen bond. formation of π-sulfur bonds, and pink indicates the formation of π-alkyl bonds.

Among the antineoplastic agents utilized is abemaciclib, a kinase inhibitor recognized for its effective inhibition of cyclin D1, a protein crucial for cellular growth and division [27,28]. Operating as a selective CDK4/6 inhibitor, abemaciclib exhibits enhanced selectivity for CDK4/cyclin D1 over CDK6. This compound has demonstrated the inhibition of phosphorylation in key proteins such as Rb, cyclin E1, and cyclin D1, with greater potency observed against CDK4 than CDK6. The cyclin D1 pathway plays a pivotal role in the proliferation of OSCC, and its inhibition has been proven to induce apoptosis and cell cycle arrest in cancer cells [29]. Abemaciclib has also exhibited antitumor activity across various cancer types. The potential of abemaciclib as a cyclin D1 inhibitor has been explored in preclinical studies, revealing promise in targeting cyclin D1 to impede the proliferation of OSCC cells [30,31]. Previous studies indicate that inhibiting the active site of cyclin D1 specifically targets OSCC cells. In silico analysis revealed that pronethalol exhibits the highest binding affinity to Cyclin D1 compared to other compounds and the control, linoleic acid. Blocking the active site of cyclin D1 holds significance in cancer progression and serves as a target for anticancer treatments [32]. The cell cycle involves cell preparation and genome duplication, encompassing four successive phases: G1 phase (cell mass accumulation and metabolite preparation for DNA replication), S phase (DNA replication), G2 phase (essential for accurate DNA replication), and M phase (DNA and cell division). Most adult cells are in a quiescent state (G0 phase), but exposure to mitogenic stimuli can transition G0 phase cells into the G1 phase. Cyclin-D1, a key cell proliferation regulator, controls the cell cycle's progression in the nucleus and facilitates the transition from G0/G1 phase to the S phase. It acts as an allosteric regulator of cyclin-dependent kinase 4 (CDK) and CDK6 [7,29].

The outcomes of the study unveiled compelling evidence regarding the potential inhibitory effects of LRE compounds on the active site of cyclin D1. All nine compounds examined exhibited negative binding affinity, indicating their capability to impede the active site of cyclin D1. This negative value signifies a minimal energy requirement for the formation of a bond between the ligand and the active site of the cyclin D1 protein. Notably, three specific LRE compounds—glycyrrhetinic acid, liquiritin apioside, and 18β-Glycyrrhetic acid—displayed lower binding affinity values than the control compound abemaciclib, which had a value of -5.3 kcal/mol. The binding affinity values of these three compounds (-5.5 kcal/mol, -5.3 kcal/mol, and -5.4 kcal/mol, respectively) suggest their potential as competitive inhibitors, capable of hindering the active site of cyclin D1 when compared to abemaciclib. From a physiological standpoint, reactions or bond formations in the body typically require low binding energy. Comparing these three compounds with abemaciclib, which necessitates -5.3 kcal to bind every 1 mole of cyclin D1, indicates that the former compounds require an equivalent or lower energy level than the control. This implies that an inhibitory bond complex between the three LRE compounds and the active site of cyclin D1 is likely to be formed [17,21]. Additionally, six out of the nine primary LRE compounds identified through molecular docking research exhibited higher binding affinity values compared to the comparison compound abemaciclib. It is crucial to note that this doesn't imply an incapacity to inhibit the active site of cyclin D1 for these six compounds. Instead, it indicates a lower binding ability and tendency compared to the control compound.

In the assessment of these results, it is essential to consider RMSD values. Lower and upper bound RMSD values indicate the proximity of predicted in silico results to laboratory data, with values close to 0 signifying high accuracy in docking predictions. Remarkably, mefenamic acid, arachidonic acid, and all LRE compounds displayed lower and upper bound RMSD values of 0, indicating high accuracy in docking predictions, closely aligning with laboratory results [33]. Molecular docking test visualization further supported the notion that all LRE compounds share similar molecular activity with the compared compounds. This similarity arises from the identical binding locations to peptides in the cyclin D1 active site. The uniform molecular activity observed in this visualization underscores the robust antineoplastic abilities of LRE compounds. These research findings not only contribute valuable insights into the potential inhibitory effects of LRE compounds on cyclin D1 but also serve as a predictive reference for future investigations. Particularly, these results could guide further research into the potential applications of herbal medicine, with a specific focus on the field of dentistry. The implications of this research extend beyond the laboratory setting, providing a foundation for exploring the therapeutic potential of natural compounds in clinical contexts. This underscores the importance of continued research in unlocking the full spectrum of benefits that herbal medicine, such as LRE, may offer in the realm of cancer treatment and prevention [24,34,35].

Cyclin D1 stands as a pivotal protein in the intricate machinery governing cellular growth and division. Its role becomes particularly pronounced in OSCC, where the overexpression of cyclin D1 has been intricately linked with unfavorable prognoses and heightened resistance to chemotherapy. The significance of cyclin D1 inhibition becomes apparent, as studies have demonstrated its capacity to induce apoptosis and bring about cell cycle arrest in cancer cells, notably OSCC. Abemaciclib emerges as a promising kinase inhibitor, specifically designed to effectively impede cyclin D1. Mechanistically, the efficacy of abemaciclib is underscored by its ability to inhibit the phosphorylation of key

proteins such as Rb protein, cyclin E1, and cyclin D1. Positioned as a selective CDK4/6 inhibitor, abemaciclib not only hampers the growth of pediatric ependymomas but also showcases its inhibitory prowess by restraining RB, AKT, and ERK phosphorylation. Furthermore, it exerts control over the expression of genes intricately involved in cell cycle DNA replication and DNA repair [36–38]. The versatility of abemaciclib is further highlighted by its application in the treatment landscape, specifically in hormone receptor-positive, early and advanced breast cancer. Its deployment, whether in conjunction with other medications or as a standalone therapy, has yielded favorable outcomes. Beyond breast cancer, abemaciclib has exhibited noteworthy antitumor activity across various cancer types, broadening its therapeutic potential. In the realm of OSCC, where cyclin D1 overexpression complicates the prognosis, abemaciclib emerges as a potential game-changer. Studies indicate that heightened levels of cyclin D1 in OSCC cells can enhance chemosensitivity to TPF chemotherapeutic agents through the caspase-3 pathway. In this context, the inhibition of cyclin D1 by abemaciclib holds promise in augmenting the efficacy of chemotherapy in OSCC patients. As promising as these developments may seem, the intricate interplay between CDK4/6 and CDK2 in the context of abemaciclib's efficacy necessitates further exploration.

A more profound understanding of these relationships will not only deepen our comprehension of the drug's mechanisms but will also pave the way for its potential application in a broader spectrum of cancer types. As we navigate the complexities of cancer treatment, abemaciclib emerges as a beacon of hope, particularly in the challenging landscape of OSCC [39]. The pursuit of knowledge in this field becomes paramount, as we unravel the intricate relationships between key players like CDK4/6, CDK2, and abemaciclib. The potential implications of this research extend far beyond a singular type of cancer, opening doors to innovative therapeutic strategies that could revolutionize the way we approach cancer treatment across various contexts. The scientific journey delving into the intricacies of cyclin D1, abemaciclib, and their interplay in OSCC represents a critical frontier in cancer research. As we advance, it is not merely a pursuit of knowledge but a quest for groundbreaking solutions that can transform the landscape of cancer treatment. Abemaciclib, armed with its kinase inhibition capabilities, stands at the forefront of this scientific exploration, offering hope for enhanced efficacy and novel treatment avenues in the challenging terrain of oral squamous cell carcinoma and beyond [31]. The study's limitation lies in its focus solely on analyzing the inhibitory mechanism of licorice's active compound ligands on the active site of the cyclin D1 protein, a key player in OSCC cell proliferation. Utilizing a biocomputational approach serves as a preliminary step before conducting further research such as in vitro, in vivo, or clinical trials to assess the potential efficacy of LRE as an anticancer candidate. Researchers suggest conducting additional in vitro and in vivo observations in the future to comprehensively evaluate other anticancer parameters and ensure comprehensive results from the anticancer study.

CONCLUSIONS

The main active compounds from LRE are predicted to have good antineoplastic abilities against Cyclin-D1 protein with the best compounds in antineoplastic abilities being glycyrrhetinic acid. Researchers hope that this research can be developed comprehensively in vitro, and in vivo, as well as a systematic literature review and meta-analysis that can support the success of this innovative idea using ayurvedic medicine-based drugs.

DECLARATIONS

Competing interest

The authors declare no competing interest in this study.

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REFERENCES

1. Panarese I, Aquino G, Ronchi A, et al. Oral and Oropharyngeal squamous cell carcinoma: prognostic and predictive parameters in the etiopathogenetic route. Expert Rev Anticancer Ther. 2019 Feb 1;19(2):105–19.
2. Kementerian Kesehatan RI. Riset Kesehatan Dasar Nasional 2018 [Internet]. RISKESDAS RI. 2019. Available from: https://repository.badankebijakan.kemkes.go.id/id/eprint/3514/1/Laporan%20Riskesdas%202018%20Nasional.pdf
3. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May 4;71(3):209–49.
4. Sarode G, Maniyar N, Sarode SC, et al. Epidemiologic aspects of oral cancer. Dis Mon. 2020 Dec;66(12):100988.

5. Abati S, Bramati C, Bondi S, et al. Oral Cancer and Precancer: A Narrative Review on the Relevance of Early Diagnosis. Int J Environ Res Public Health. 2020 Dec 2;17(24):1–14.
6. Kakkar V, Sarin V, Chatterjee A, et al. Expression of Cyclin-D1 and p53 as Prognostic Markers in Treatment of Oral Squamous Cell Carcinoma. Indian J Otolaryngol Head Neck Surg. 2022 Dec;74(Suppl 3):6136–45.
7. Ramos-García P, González-Moles MÁ, González-Ruiz L, et al. Clinicopathological significance of tumor cyclin D1 expression in oral cancer. Arch Oral Biol. 2019 Mar 1;99:177–82.
8. Arnold JT. Integrating ayurvedic medicine into cancer research programs part 2: Ayurvedic herbs and research opportunities. J Ayurveda Integr Med. 2023 Mar 1;14(2):100677.
9. Imanu SF, Leginis SN, Iqbal M, Surboyo MDC. Pomegranate extract mechanism in inhibiting the development of oral cancer: A review. Indonesian Journal of Dental Medicine. 2023 May 15;6(1):37–42.
10. Sharma D, Namdeo P, Singh P. Phytochemistry and Pharmacological Studies of Glycyrrhiza glabra: A Medicinal Plant Review. Int J Pharm Sci Rev Res. 2021 Mar 21;67(1):187–94.
11. Kwon YJ, Son DH, Chung TH, Lee YJ. A Review of the Pharmacological Efficacy and Safety of Licorice Root from Corroborative Clinical Trial Findings. J Med Food. 2020 Jan 1;23(1):12–20.
12. Ding Y, Brand E, Wang W, Zhao Z. Licorice: Resources, applications in ancient and modern times. J Ethnopharmacol. 2022 Nov 15;298:115594.
13. Pastorino G, Cornara L, Soares S, et al. Liquorice (Glycyrrhiza glabra): A phytochemical and pharmacological review. Phytother Res. 2018 Dec;32(12):2323–39.
14. Tuli HS, Garg VK, Mehta JK, et al. Licorice (Glycyrrhiza glabra L.)-Derived Phytochemicals Target Multiple Signaling Pathways to Confer Oncopreventive and Oncotherapeutic Effects. Onco Targets Ther. 2022 Nov 30;15:1419–48.
15. Wang Y, Xia W, Tao M, Fu X. Oncopreventive and Oncotherapeutic Potential of Licorice Chalcone Compounds: Molecular Insights. Mini Rev Med Chem. 2023;23(6):662–99.
16. Khozeimeh F, Dehghan P, Yaghoobi N, et al. Effect of nystatin and licorice on yeasts isolated from the oral lesions of patients with cancer under chemotherapy (in vitro study). Dent Res J (Isfahan). 2022;19:61.
17. Pinzi L, Rastelli G. Molecular docking: shifting paradigms in drug discovery. Int J Mol Sci. 2019;20(18):4331.
18. Khoswanto C, Siswandono. Molecular Docking Analysis of Quercetin and Diclofenac as Cox-2 Potential Inhibitors. JIDMR. 2022;552–5.
19. Kusuma SMW, Utomo DH, Susanti R. Molecular Mechanism of Inhibition of Cell Proliferation: An In Silico Study of the Active Compounds in Curcuma longa as an Anticancer. J Trop Biodivers Biotechnol. 2022 Nov 14;7(3):74905.
20. Utomo DH, Kita M. Binding Mode of Actin–Aplyronine A–Tubulin Heterotrimeric Complex Revealed by Molecular Dynamics Simulation. Bull Chem Soc Jpn. 2023 Jan 13;96(2):120–6.
21. Pantsar T, Poso A. Binding Affinity via Docking: Fact and Fiction. Molecules. 2018 Jul 30;23(8):1899.
22. Saikia S, Bordoloi M. Molecular Docking: Challenges, Advances and its Use in Drug Discovery Perspective. Curr Drug Targets. 2019 Oct 25;20(5):501–21.
23. Ji D, Xu M, Udenigwe CC, Agyei D. Physicochemical characterisation, molecular docking, and drug-likeness evaluation of hypotensive peptides encrypted in flaxseed proteome. Curr Res Food Sci. 2020 Nov 1;3:41–50.
24. Burley SK, Bhikadiya C, Bi C, et al. RCSB Protein Data bank: Tools for visualizing and understanding biological macromolecules in 3D. Protein Sci. 2022 Dec 1;31(12):e4482.
25. Irani S. New insights into oral cancer—Risk factors and prevention: A review of literature. Int J Prev Med. 2020;11(1):202.
26. Nandini DB, Rao RS, Hosmani J, et al. Novel therapies in the management of oral cancer: An update. Dis Mon. 2020 Dec;66(12):101036.
27. Mosaddad SA, Beigi K, Doroodizadeh T, et al. Therapeutic applications of herbal/synthetic/bio-drug in oral cancer: An update. Eur J Pharmacol. 2021;890:173657.
28. Wong TSC, Wiesenfeld D. Oral Cancer. Aust Dent J. 2018 Mar 1;63 Suppl 1:S91–9.
29. Moharil RB, Khandekar S, Dive A, Bodhade A. Cyclin D1 in oral premalignant lesions and oral squamous cell carcinoma: An immunohistochemical study. J Oral Maxillofac Pathol. 2020 May-Aug;24(2):397.
30. Abdelmalak M, Singh R, Anwer M, et al. The Renaissance of CDK Inhibitors in Breast Cancer Therapy: An Update on Clinical Trials and Therapy Resistance. Cancers (Basel). 2022 Nov 1 [cited 2024 Jan 6];14(21):5388.
31. Palumbo A, Lau G, Saraceni M. Abemaciclib: The Newest CDK4/6 Inhibitor for the Treatment of Breast Cancer. Ann Pharmacother. 2019 Feb 1;53(2):178–85.
32. Listiyana A, Rachmawati YL, Susianti H, et al. Analysis of the Metabolite Compound of the Ethanol Extract of Chrysanthemum cinerariifolium Stem and Activity for inhibition of Oral Squamous Cell Carcinoma (OSCC) in silico study. Pharmacognosy Journal. 2023 Apr 30;15(2):393–8.

33. Velázquez-Libera JL, Durán-Verdugo F, Valdés-Jiménez A, et al. LigRMSD: A web server for automatic structure matching and RMSD calculations among identical and similar compounds in protein-ligand docking. Bioinformatics. 2020;36(9):2912–4.
34. Iqbal M, Kurniawan RV, Nurfani HDW, et al. Molecular docking analysis of major active compounds of pomegranate peel extract (Punica granatum L.) in inhibiting cyclooxygenase enzyme. WJARR. 2023 Dec 30;20(3):1824–42.
35. Berniyanti T, Iqbal M, Yaasir NI, et al. Anti-inflammatory ability of licorice (Glycyrrhiza glabra) root extract in cyclooxygenase-2 enzyme inhibition: In silico study. WJARR. 2024;21(1):1798–1804.
36. Khalesi S, Maleki L, Eskandari S, et al. Cyclin D1 and Ki-67 expression and its correlation with histopathological parameters and cervical lymph node metastasis in oral squamous cell carcinoma. Dent Res J (Isfahan). 2023 Oct 26;20:112.
37. Dar MS, Abbas R, Shah Z, et al. Immunohistochemical expression of E-Cadherin and Cyclin D1 in different grades of oral squamous cell carcinoma. J Oral Maxillofac Pathol. 2023 Jul-Sep;27(3):476–80.
38. Hu YJ, Sun WW, Zhao TC, et al. Cyclin D1 overexpression enhances chemosensitivity to TPF chemotherapeutic agents via the caspase-3 pathway in oral cancer. Oncol Lett. 2020 Nov;20(5):154.
39. Al-Rawi NH, Kawas SA, Ani MA, et al. Prediction of Lymphovascular and Perineural Invasion of Oral Squamous Cell Carcinoma by Combined Expression of p63 and Cyclin D1. Eur J Dent. 2023 Oct;17(4):1170–8.