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Research article

Systems Pharmacology and Molecular Docking Investigation of Zingerone and Ellagic Acid as Potential Therapeutics for Oral Carcinogenesis

Shingare Shailesh, Shaikh Zaid Rashid, Shaikh Mehmood Dawood*

Aurangabad Pharmacy College, Mitmita, City- Chhatrapati Sambhajinagar, Maharashtra, Country – India.

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***Corresponding Author: Dr. Shaikh Mehmood Dawood**, Aurangabad Pharmacy College, Mitmita, City- Chhatrapati Sambhajinagar, Maharashtra, Country – India.
Email id: mehmoodpharma99@gmail.com

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Abstract

Oral carcinogenesis is a complex multistep pathological process that includes oxidative stress, chronic inflammation, aberrant cell proliferation, apoptosis resistance, angiogenesis, and metastatic development. Despite advancements in chemotherapy and targeted medicines, oral cancer treatment remains difficult due to systemic toxicity, drug resistance, and a poor prognosis. As a result, naturally occurring phytochemicals with multitarget therapeutic potential have received significant interest in anticancer research. The current study sought to assess the synergistic therapeutic potential of Zingerone and Ellagic Acid against oral carcinogenesis by integrated computational techniques. A network pharmacology analysis was used to identify common molecular targets linked with oral cancer, followed by protein-protein interaction, Gene Ontology enrichment, and KEGG pathway studies to clarify the underlying molecular mechanisms. The integrated study demonstrated considerable involvement of pathways linked with oxidative stress, inflammation, apoptosis, angiogenesis, and tumor growth, such as the PI3K/Akt and ERBB signaling pathways. Ellagic Acid has a higher binding affinity to EGFR (-8.6 kcal/mol) and ERBB2 (-7.5 kcal/mol) than the conventional medication Erlotinib, demonstrating persistent ligand-protein interactions. Zingerone also demonstrated good binding interactions with both target proteins. The results show that the synergistic combination of Zingerone and Ellagic Acid could be a promising multitarget treatment strategy against oral carcinogenesis.

1. Introduction

Oral cancer is a well-known invasive malignant tumor that kills many people and often recurs. It is projected that mouth cancer (including lip cancer) would account for 2.0% of all malignancies (377,713 new cases) and 1.8% of all carcinoma fatalities (177,757 deaths) worldwide in 2020, with an annual increase. Cancer is usually caused by cigarette carcinogens, excessive alcohol intake, or both [1-3]. Betel nut, like alcohol and tobacco, is one of the most common causes of oral cancer. Epidemiological study results show that various Chinese provinces, including Hunan, Hainan, and Taiwan, have a high prevalence of oral cancer. Oropharyngeal cancers are usually associated with human papillomavirus (HPV) infection, primarily HPV-16 but also, to a lesser extent, HPV-18, HPV-52, and other strains. Oral cancer incidence is also closely related to the patient's oral hygiene, residual roots, crowns, sharp tooth points, dental calculus, and poor restorations. Poor oral hygiene can turn the mouth into a breeding ground for bacteria and mold, cause stomatitis, promote cell proliferation, and make cells more susceptible to carcinogens, resulting in the development of oral cancer. Long-term stimulation from lingering dental crowns, roots, tooth edges, and poor restorations can result in an incurable ulcer those progresses to cancer. Furthermore, precancerous lesions or states exist in oral mucosal illnesses such as oral

leukoplakia, erythema, and oral mucosal fibrosis, all of which can proceed to mouth cancer [5-6].

At the moment, the most common techniques of treating oral cancer are surgical resection, followed by radiation, chemotherapy, immunotherapy, targeted therapy, and so forth. The majority of early mouth cancer patients respond favourably to surgical treatment. However, certain dangers include severe face symmetry and attractiveness loss, high surgical trauma, and low postoperative patient quality of life and happiness scores. Radiation kills tumor cells in the same way as it kills normal biological tissue cells. It will cause significant adverse effects while treating conditions such as radiation jaw and bone marrow suppression, xerostomia, osteomyelitis, and so on. Systemic chemotherapy is ineffective in treating oral cancer patients, and drug resistance typically limits its effectiveness. Although immunotherapy dramatically lowers the incidence of oral cancer, it is costly, has severe side effects, and has no effect on people who do not get platinum treatment [7-12]. Natural chemicals originating from food and medicinal plants have considerable pharmacological activity and comparably low toxicity profiles. Zingerone (4-(4-hydroxy-3-methoxyphenyl)-2-butanone) is an active phenolic ingredient of ginger (*Zingiber officinale*) that has powerful antioxidant, anti-inflammatory, antibacterial, and anticancer activities. Previous research has shown that ginger-derived phytoconstituents can affect numerous cancer-related signaling pathways, inhibiting tumor growth, invasion, and metastasis. Network pharmacology investigations have shown the role of ginger bioactives in modulating molecular targets implicated in carcinogenesis [9]. Ellagic acid, a naturally occurring polyphenolic molecule found in pomegranates, berries, walnuts, and various medicinal plants, has also been identified as a potential anticancer agent. Extensive data demonstrates that ellagic acid has antioxidant, anti-inflammatory, antiproliferative, and pro-apoptotic properties against a variety of malignancies. Mechanistically, ellagic acid has been shown to influence PI3K/Akt signaling, inhibit oncogenic kinases, regulate apoptosis-related proteins, and disrupt tumor metabolic pathways. Molecular docking and systems pharmacology investigations have shown that ellagic acid interacts strongly with a variety of cancer-related receptors, indicating that it has multitarget therapeutic potential [10-11]. Recent *in silico* studies have notably emphasized ellagic acid's therapeutic potential against oral cancer by modulating the PI3K/Akt pathway, suggesting positive binding interactions and good pharmacokinetic properties. However, the synergistic potential of zingerone and ellagic acid against oral carcinogenesis has yet to be fully studied. Given their complimentary pharmacological actions, utilizing these phytocompounds to target several oncogenic pathways simultaneously may give increased therapeutic efficacy against oral cancer development [12]. In recent years, network pharmacology has developed as an efficient systems biology technique for understanding the intricate relationships between phytochemicals, targets, genes, and signaling pathways linked to illness. Network pharmacology, when combined with molecular docking, allows for the discovery of new therapeutic targets as well as the molecular confirmation of ligand-protein interactions. This integrated approach is especially useful for investigating multitarget natural chemicals against complicated disorders like cancer [13-14]. The current study aims to evaluate the synergistic therapeutic potential of zingerone and ellagic acid against oral carcinogenesis utilizing integrated network pharmacology and molecular docking techniques.

2. Materials and methods

2.1 Chemical Candidates and Compound Related Targets

The literature was used to aid the chemical selection process. The selected bioactive compounds were then searched in the PubChem database to obtain their chemical structures and SMILES notations. Potential target proteins linked with these chemicals, with potential scores higher than zero, were then predicted using the Swiss Target Prediction Database.

Identification of Oral Cancer-related targets

We searched the GeneCards database for possible targets related with oral cancer. This database combines data from several sources to provide complete information on human genes. The selected targets were collated for additional study and classified as oral cancer-related targets [33].

2.2 Venn diagram

Venn diagram was developed to assess the overlap between oral cancer-associated targets and possible targets for Zingerone and Ellagic acid.

2.3 Protein-Protein Interaction (PPI) Network

The STRING database (https://string-db.org/) collects known and projected protein-protein interactions, including functional and physical correlations. For this study, we utilized STRING [33] to look at the connections between the chemicals in our analysis and the targets associated with oral cancer, finding potential therapy targets. To build a reliable protein-protein interaction (PPI) network for these targets, we employed the "Homo sapiens" organism with a confidence level of 0.4. This confidence score is commonly employed because it strikes a good balance between sensitivity and specificity, resulting in a credible criteria for interaction prediction. As a consequence, only proteins with interaction scores of 0.4 or higher were included to the PPI network, increasing the accuracy of our potential target identification.

2.4 Functional Enrichment and Pathway Analysis

To identify key pathways and related Gene Ontology (GO) concepts, all potential therapeutic targets were analyzed using pathway and GO enrichment analyses in the String

database [33] (https://string-db.org/). This investigation shed light on the biological processes (BP), molecular functions (MF), and cellular components (CC) connected with the targets. Pathways and GO keywords having a significance level of $p < 0.05$ were chosen for further study.

2.5 Building a Compound-Target Network

The compound-target interaction network was created by linking the targets associated with each chemical. Cytoscape 3.10.2 (Cytoscape Consortium, San Diego, CA, USA) was used to visualize the network [33]. Nodes in the network represent drugs and their targets, while edges show their interactions.

2.6 Molecular Docking

Molecular docking investigations were carried out in accordance with the previously published approach described by Ahmad *et al.* (2024). The three-dimensional structures of target proteins were obtained from the Protein Data Bank, while ligand structures were obtained from PubChem. AutoDock Vina was used to investigate binding affinity and protein-ligand interactions. The docked complexes with the lowest binding energy were chosen and visualized using PyMOL and Discovery Studio, following the previously defined computational process [22-24].

3. Result and Discussion

3.1 Potential Therapeutic Targets of Compounds Used to Treat Hypertension

Employing oral cancer as a keyword, data were gathered from the GeneCards database, resulting in 9457 target genes. Among these, 111 targets were identified as shared by the chemicals and oral cancer-related genes, indicating prospective therapeutic targets for compounds used to treat mouth cancer. A Venn diagram (Figure 1) depicts these overlapping targets.

3.2 Construction of the Compound-Target Network

To analyze the signaling pathways and functional functions of the identified target genes, we used Cytoscape data analysis. This strategy made it easier to create a sophisticated compound-target network, as seen in Figure 2. The network demonstrates the pharmacological methods by which the drugs may impact the therapy of oral cancer, with a focus on 134 target proteins. Network analysis shows that different components are converging across numerous targets, implying that these bioactive chemicals may have synergistic effects. These interactions may improve the therapeutic efficacy of these drugs not just in the treatment of oral cancer, but also in other associated disorders.

3.3 PPI network Visualization and Analysis

The STRING database was used to investigate interactions between 111 putative medicinal targets. The final protein-protein interaction (PPI) network included 111 nodes and 122 edges, with an average node degree of 2.2 and a local clustering coefficient of 0.401 (Figure 3). In this network, nodes represent individual proteins, while edges represent the relationships between them. A higher degree value indicates a more important involvement for the protein in the network. Following a filtering procedure using the defined criteria, numerous hub genes were found, including SRC, PTK2, EGFR, HSP90AA1, JAK2, ESR1, ERBB2, IGF1R, KDR, and AKT1. These proteins, which include biological enzymes and cytokines, play critical roles in a variety of regulatory processes such as signal transduction and protein phosphorylation. The top five nodal targets were identified as SRC, PTK2, EGFR, JAK2, and ERBB2. The substantial connections between these genes and other possible therapeutic targets highlight their significance in the context of oral cancer therapy.

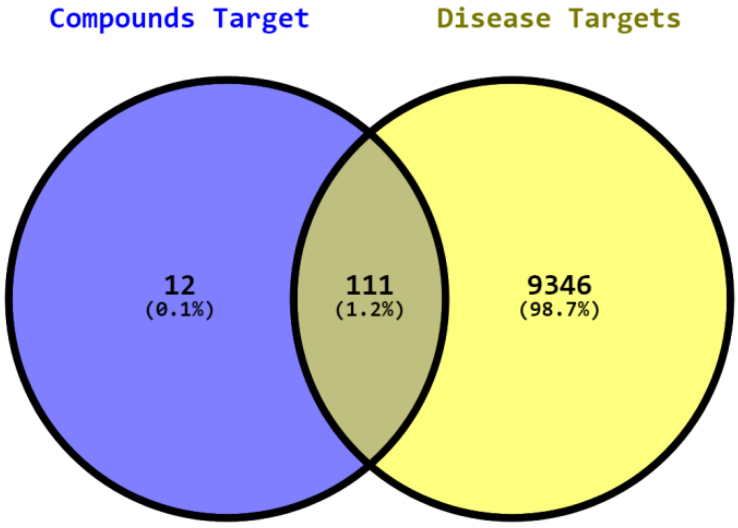


Figure 1. Venn Plot.

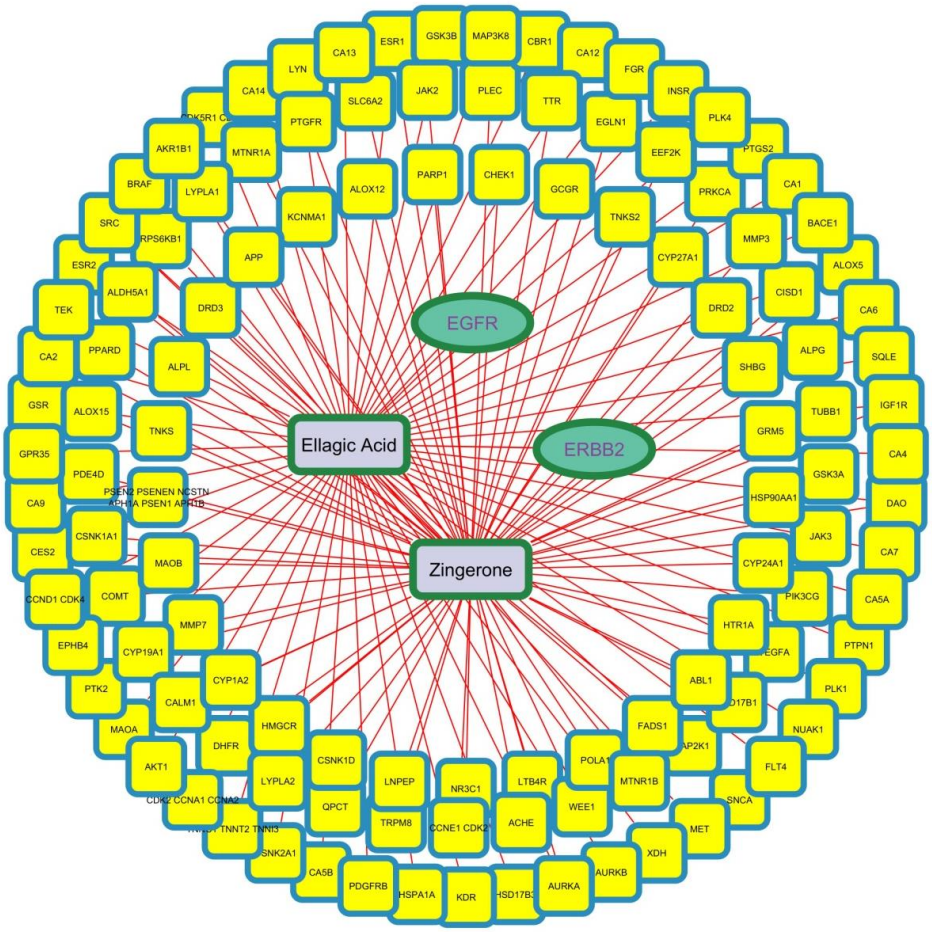


Figure 2. Compound Target Network.

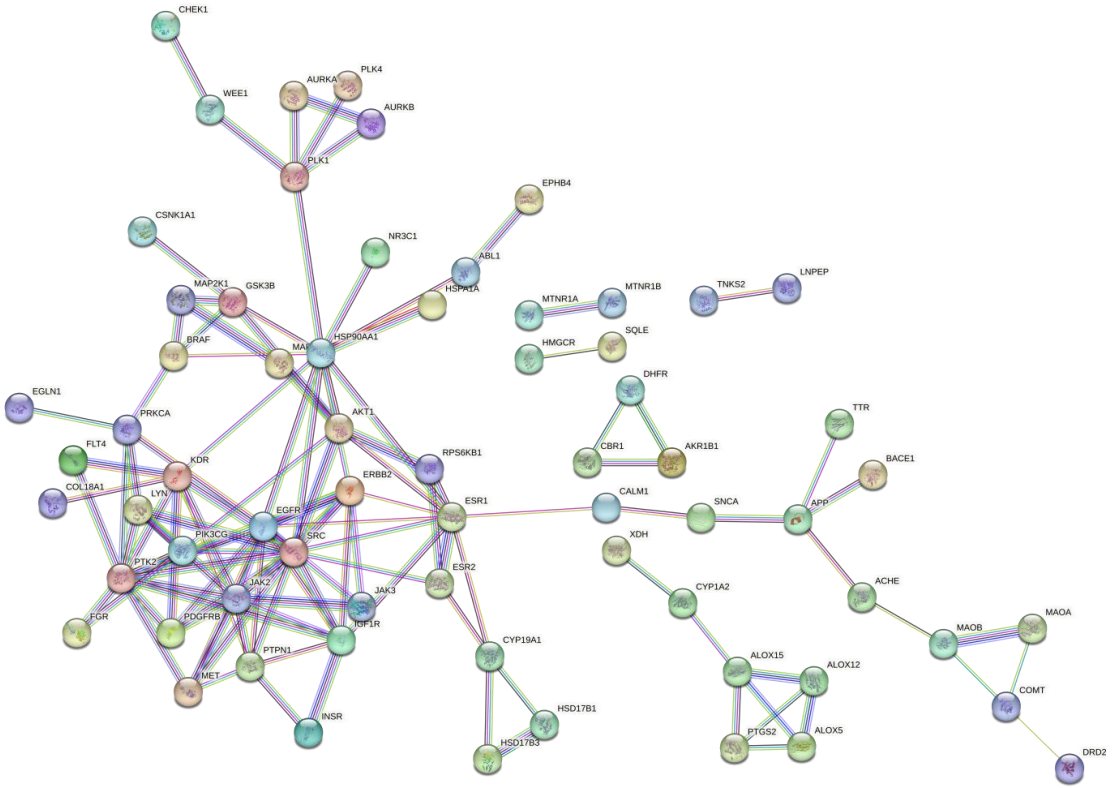


Figure 3. PPI Network.

3.4 GO enrichment analyses

To further understand the molecular processes by which drugs affect oral cancer, we performed Gene Ontology (GO) enrichment analysis on 111 possible therapeutic targets linked with these compounds using the string database. This study divided into three categories: biological process (BP), molecular function (MF), and cellular component. The top ten GO keywords found in each category are displayed in a bar plot, with data described in Tables 1 (BP), 2 (MF), and 3 (CC), as well as Figure 4A, 4B, and 4C. In the illustrations, the size of each bar correlates to the number of enriched genes linked with that GO word, while the color gradient indicates the importance of the p value, with deeper colors representing lower p values. A higher bar indicates a greater number of enriched therapeutic genes inside the associated GO word, implying a stronger link with hypertension therapy than the other terms.

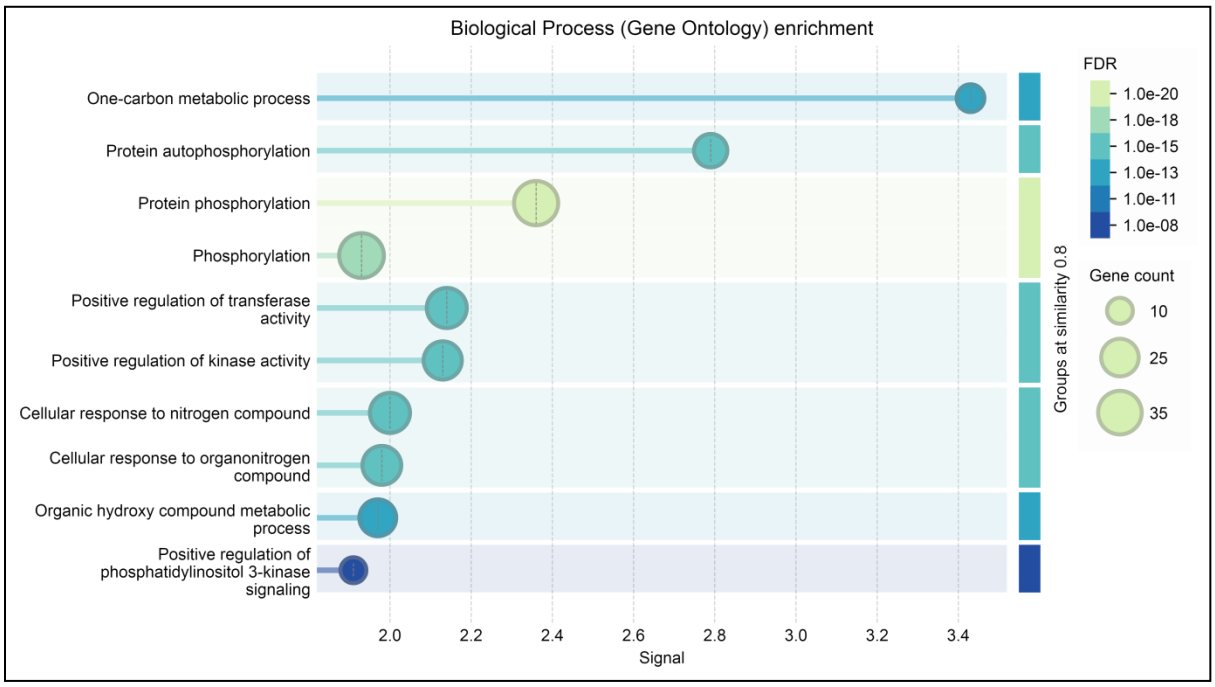


Figure 4A. Biological Process.

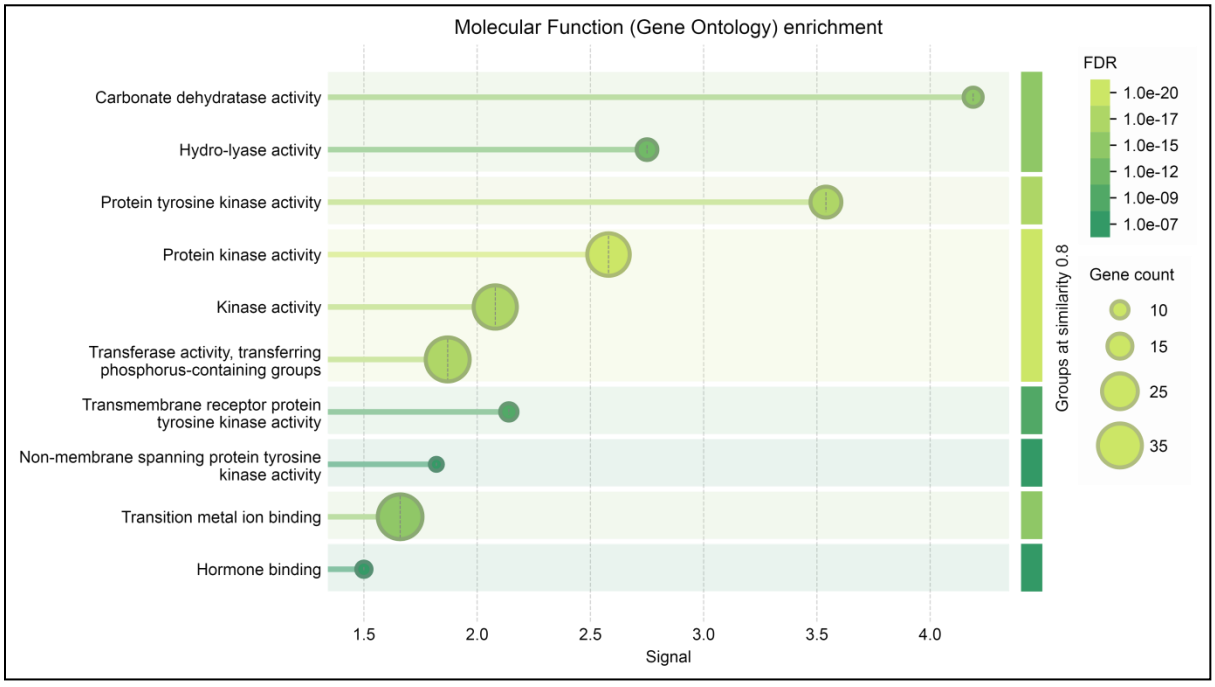


Figure 4B. Molecular Function.

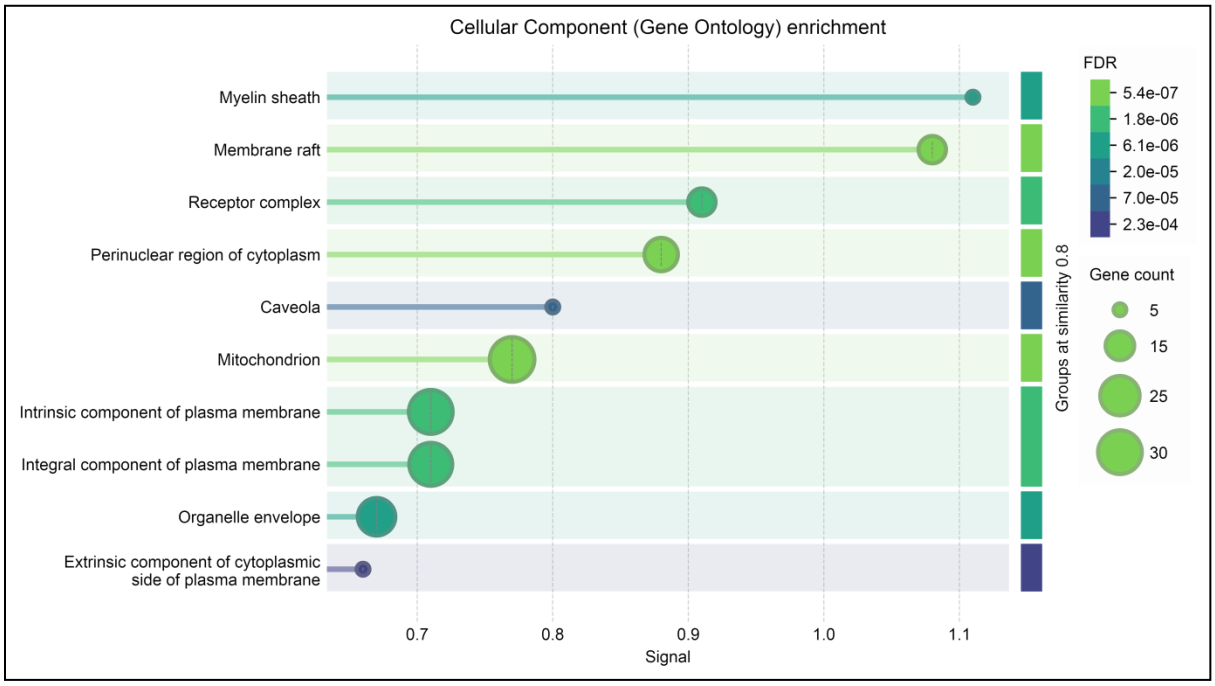


Figure 4C. Cellular Components.

Table 1. Biological Process.

Description	Observed gene count	False discovery rate
Cellular metabolic process	93	1.74E-23
Metabolic process	99	1.39E-22
Protein phosphorylation	36	5.21E-20
Phosphate-containing compound metabolic process	49	1.22E-17
Response to oxygen-containing compound	45	1.32E-17
Phosphorylation	37	1.44E-17

Table 2. Molecular Function.

Description	Observed gene count	False discovery rate
Catalytic activity	88	3.89E-25
Ion binding	91	3.89E-25
Protein kinase activity	33	2.38E-20
Protein tyrosine kinase activity	20	2.87E-18
Kinase activity	34	8.54E-18
Transferase activity, transferring phosphorus-containing groups	35	1.17E-16

Table 3. Cellular Components.

Description	Observed gene count	False discovery rate
Mitochondrion	31	5.44E-06
Plasma membrane	61	5.44E-06
Membrane raft	14	5.44E-06
Cell periphery	64	5.44E-06
Cytoplasm	95	5.91E-06
Perinuclear region of cytoplasm	19	9.15E-06

3.5 KEGG Pathway Enrichment Analyses

The pathways associated with potential therapeutic targets for oral cancer treatment were identified through KEGG pathway enrichment analysis. Signaling pathways were obtained via the string database. The top 10 signaling pathways were then visualized in a bar graph (Table 4 and Figure 5), organized by their P values in ascending order. The analysis indicated that the key targets were notably enriched in the ERBB signaling pathway (Figure 5A).

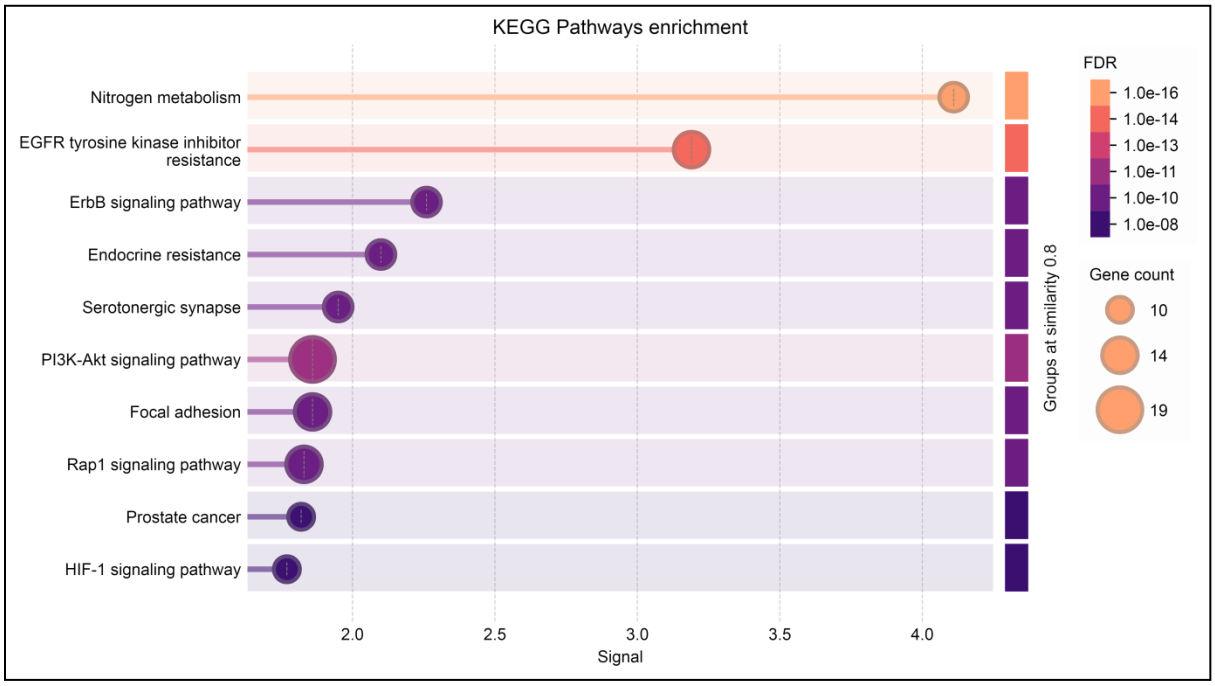


Figure 5. KEGG Pathway.

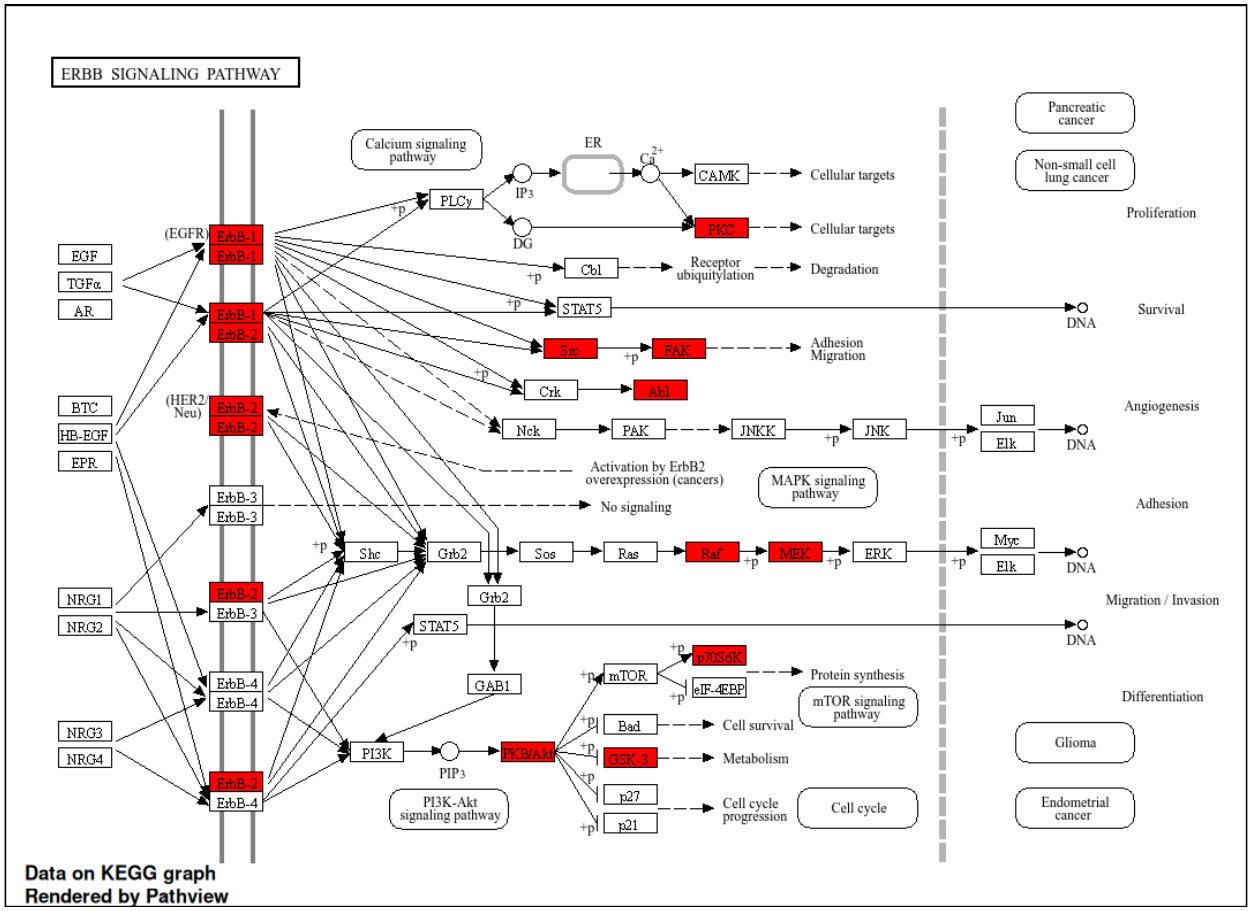


Figure 5A. ERBB Signaling Pathway.

Table 4. KEGG Pathway.

Description	Observed gene count	False discovery rate
EGFR tyrosine kinase inhibitor resistance	14	1.62E-14
Metabolic pathways	38	3.30E-14
PI3K-Akt signaling pathway	19	1.68E-11
Pathways in cancer	22	1.68E-11
ErbB signaling pathway	11	2.12E-10
Nitrogen metabolism	11	6.85E-16

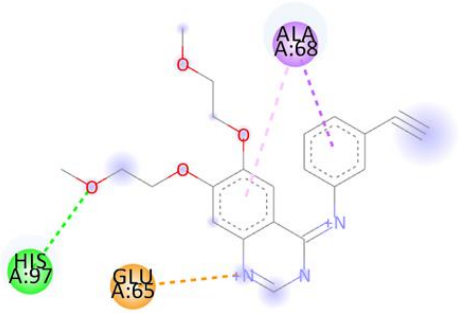
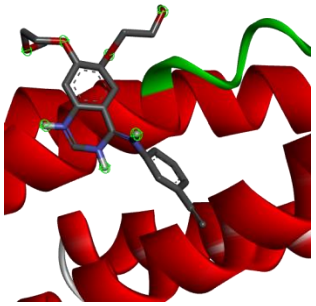
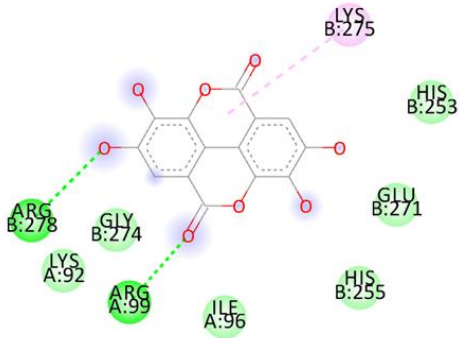
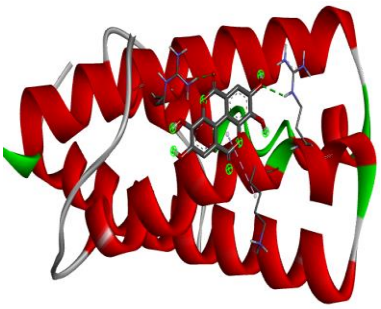
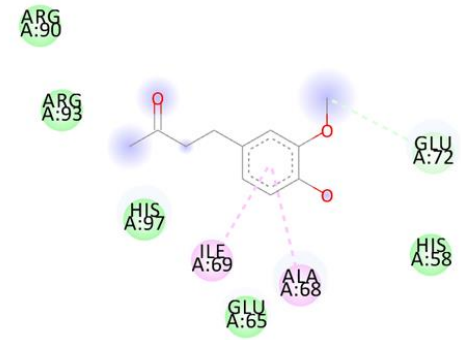
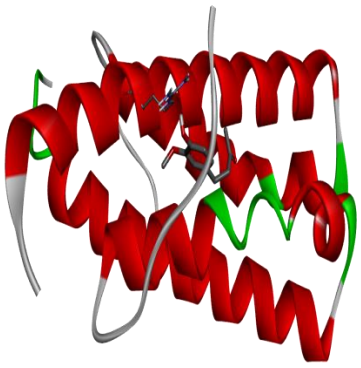
Compound/Targets	2D	3D
Erlotinib -(5WB7)		
Ellagic Acid -(25WB7)		
Zingerone -(5WB7)		

Figure 6. Illustrates 2D and 3D docking poses of Erlotinib, Ellagic Acid and Zingerone with protein EGFR (5WB7).

Table 5. Molecular Docking Analysis.

Sr. No.	Compound	Target Protein	PDB ID	Binding Energy (kcal/mol)	Interpretation
1	Erlotinib	EGFR	5WB7	-6.9	Erlotinib exhibited good binding affinity toward EGFR, indicating effective interaction with the active binding pocket of the receptor.
2	Ellagic Acid	EGFR	5WB7	-8.6	Ellagic Acid demonstrated the strongest binding affinity against EGFR among the tested compounds, suggesting potential inhibitory activity and stable protein–ligand interaction.
3	Zingerone	EGFR	5WB7	-5.5	Zingerone showed moderate binding affinity toward EGFR, indicating possible interaction with the receptor active site.
4	Erlotinib	ERBB2	3H3B	-6.5	Erlotinib demonstrated favorable binding interaction with ERBB2, supporting its inhibitory potential against receptor signaling pathways.
5	Ellagic Acid	ERBB2	3H3B	-7.5	Ellagic Acid exhibited strong binding affinity toward ERBB2, indicating potential multitarget anticancer activity.
6	Zingerone	ERBB2	3H3B	-5.6	Zingerone showed moderate interaction with ERBB2, suggesting possible inhibitory effects against receptor-mediated signaling.

3.6 Molecular Docking

Molecular docking (MD) studies of zingerone and ellagic_acid with key oral cancer-associated targets, including EGFR (node degree = 12) and ERBB2 (node degree = 8), were performed using AutoDock Vina to evaluate binding affinities and interaction profiles. The docking analysis assessed parameters include binding affinity (kcal/mol), interacting amino acid residues. The obtained docking results demonstrated favorable ligand-protein interactions and are summarized in Table 5 and illustrated in Figure 6.

The molecular docking analysis was performed to evaluate the binding affinity and interaction profile of Ellagic Acid and Zingerone against important oral carcinogenesis-associated target proteins including EGFR and ERBB2. The standard anticancer drug Erlotinib was used as the reference compound for comparative analysis. Binding affinity was evaluated based on docking scores expressed in kcal/mol, where lower binding energy indicates stronger ligand-protein interaction and greater binding stability. Among the tested compounds, Ellagic Acid demonstrated the highest binding affinity toward EGFR (PDB ID: 5WB7) with a docking score of -8.6 kcal/mol, which was comparatively stronger than the reference drug Erlotinib (-6.9 kcal/mol). Similarly, Ellagic Acid also exhibited significant interaction with ERBB2 (PDB ID: 3H3B) showing a binding energy of -7.5 kcal/mol compared with Erlotinib (-6.5 kcal/mol). These findings suggest that Ellagic Acid may possess strong inhibitory potential against receptor tyrosine kinases involved in tumor cell proliferation, angiogenesis, and metastasis during oral carcinogenesis. Zingerone showed moderate binding affinity toward EGFR and ERBB2 with docking scores of -5.5 kcal/mol and -5.6 kcal/mol, respectively.

Although the binding affinity was comparatively lower than Ellagic Acid and Erlotinib, the observed interactions indicate that Zingerone may still contribute to anticancer activity through modulation of receptor-mediated signaling pathways and antioxidant mechanisms. Previous studies have reported that Zingerone possesses antioxidant, anti-inflammatory, and antiproliferative properties that may synergistically enhance its therapeutic potential when combined with other phytochemicals.

The strong interaction of Ellagic Acid with EGFR and ERBB2 suggests its possible role in inhibiting downstream oncogenic signaling pathways such as PI3K/Akt, MAPK, and NF-κB pathways, which are critically associated with cell proliferation, survival, inflammation, and tumor progression. The combined use of Zingerone and Ellagic Acid may therefore provide multitarget therapeutic effects against oral carcinogenesis through synergistic modulation of oxidative stress, apoptosis, inflammation, and growth factor signaling pathways. The molecular docking findings indicate that Ellagic Acid exhibited superior binding affinity against oral cancer-associated targets compared to Zingerone and the reference drug. These results support the potential application of these phytochemicals as promising natural therapeutic candidates for oral carcinogenesis and provide a scientific basis for further *in vitro* and *in vivo* experimental validation studies.

3.7 Conclusion

The current integrated computational analysis found that Zingerone and Ellagic Acid have great therapeutic potential against oral carcinogenesis by modulating many pathways involved in oxidative stress, inflammation, apoptosis, angiogenesis, and tumor growth. Network pharmacology

research showed numerous critical molecular targets and signaling pathways involved in oral cancer growth, whereas molecular docking experiments demonstrated Ellagic Acid has a high binding affinity for EGFR and ERBB2 proteins when compared to the conventional treatment Erlotinib. These findings indicate that the synergistic combination of Zingerone and Ellagic Acid could be a potential multitarget treatment approach for oral carcinogenesis, providing a scientific foundation for further experimental and clinical validation research.

Author Contribution

Shingare Shailesh performed the literature review and network pharmacology analysis. Shaikh Zaid Rashid conducted molecular docking studies and interpretation of the findings. Dr. Shaikh Mehmood Dawood supervised the overall study and reviewed the manuscript for final submission.

Funding Statement

The authors declare that no financial support or funding was received for this study.

Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

Ethics Approval and Consent to Participate

This study was entirely based on computational and *in silico* methodologies including network pharmacology and molecular docking approaches. Therefore, ethical approval and informed consent were not required as no human participants or experimental animals were involved in the study.

Consent for Publication

All authors have read and approved the final version of the manuscript for publication.

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Declaration of Generative AI

During the preparation of this manuscript, generative artificial intelligence (AI)-assisted tools were utilized only for language refinement, grammatical correction, and improvement of scientific readability.

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