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In-silico Approach of Few Selected Phytoconstituents on Newer Cancer Targets

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Abstract

Background: *Cancer's high death rates are mainly due to, drug resistance and unmet medical demands. It necessitates novel anticancer medications. AI tools aid in efficient and faster drug discovery by analyzing data, modeling processes and optimizing pipeline stages.* ***Aim:*** *The aim of this present study is to evaluate phytoconstituents against novel and newer cancer targets.* ***Methodology:*** *The ligands Daidzein, Resveratrol and Genistein were targeted against the Glutamate dehydrogenase (PDB ID 1b26) and Glutaminase (PDB ID 4bqm). Docking simulations were done using BIOVIA discovery studio and AUTODOCK VINA tool version 1.5.6. All the amino acid residues of the protein sequences and hydrogen bonding interactions were analyzed. The phytochemicals after the docking process were screened furthur for the insilico ADME analysis and drug like prediction using the swissADME ONLINE tool. The drug-likeness properties were screened based on miLogP (molinspiration Log P) values and TSPA (topological polar surface area).* ***Result:*** *Best docking simulations observed with Glutamate dehydrogenase to Genistein (–9.3 kcal/mol), Daidzein (–8.4 kcal/mol) followed by Resveratrol (–8.2 kcal/mol), similarly when targeted against Glutaminase the best dock score was found to be in Genistein (–7.4 kcal/mol), Daidzein (–7.2 kcal/mol) followed by Resveratrol (–6.7 kcal/mol). Selected phytoconstituents obey the ADME limitations and drug likeness Log P values.* ***Conclusion:*** *This study examines and found the selected phytoconstituents Daidzein, Genistein, and Resveratrol effective in binding aspects, on unique cancer targets. More experimental evidence needed to substantiate the potency of these ligands to the targets.*

Keywords: Phytoconstituents, glutaminase, glutamate dehydrogenase, docking, lymphoid leukaemia

INTRODUCTION

Lung and breast cancers being the leading sites in male and female with an incidence of 14,61,427 in India according to the statistics reported on 2022. Lymphoid leukaemia was the major threat among childhood cancers. In India, the incidence of cancer cases is likely to increase from 1.46 million in 2022 to 1.57 million in 2025 [1]. Over 100 years, cancer metabolism alterations have been discovered, but therapeutic progress has been limited, often neglecting non-cancer stromal and immune cell metabolism, which is crucial for tumour progression [2]. Cancer cells rapidly absorb glutamine from plasma, convert it to glutamate in mitochondria, making it an attractive druggable target due to its rate-limiting step [3].

Metabolic reprogramming and immune escape in tumorigenesis impact anti-tumor immune response in tumor microenvironment and predatory glutamine uptake and cell-programmed glutamine partitioning influence immune cell utilization [4].

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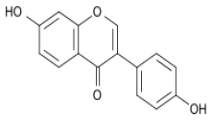
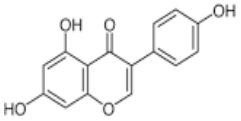
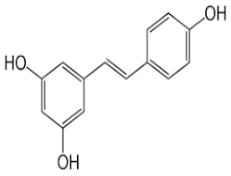
Inhibiting glutamine metabolism in cancer cells can lead to ROS overproduction, causing them to starve for glutamine essential for survival and increase exposure to excessive ROS levels [5].

Current study aims to target the glutamine uptake mechanisms in cancer cells utilizing an already proven anticancer compound (Table 1). By focusing on this specific metabolic pathway, we hope to enhance the therapeutic efficacy against cancer cells, providing a novel approach to cancer treatment. The findings from this research could contribute significantly to the development of more effective and targeted cancer therapies, potentially improving outcomes for patients.

Table 1. Activity and mechanism of action of selected phytoconstituents.

S.N.	Phytoconstituents	Activity	Mechanism
1.	Daidzein 	Anticancer	Diadzein upregulates B-cell lymphoma 2 associated X protein, cytochrome c, caspase-3, 9, and ADP-ribose polymerase, inhibiting cell growth and suppressing phosphorylated mitogen-activated protein kinase and phosphorylated extracellular signal-regulated kinase [6].
		Anti-inflammatory	Daidzein demonstrated anti-inflammatory properties by reducing NO release, inhibiting inflammatory cytokine secretion, and down-regulating inflammatory indicators iNOS and COX-2, while suppressing ERK/p38 MAPK and NF-κB p65 pathways [7].
		Anti-diabetic	The inhibition of fat tissue and the advancement of diabetes were directly linked to daidzein's control of oxidative stress [8].
2.	Genistein 	Anticancer	Genistein inhibits skin carcinogenesis and cutaneous aging in mice and humans, with moderate inhibition of ornithine decarboxylase activity through blockage of DNA adducts formation [9].
		Against induced cardiac toxicity	Genistein protects against cardio toxicity induced by doxorubicin by reducing cardiac troponin, redox markers, and regulating antioxidant response, while also reducing inflammatory expressions [10].
		Reduces pulmonary hypertension	Genistein, a tyrosine kinase inhibitor, may rescue preexisting pulmonary hypertension through its inhibitory effects and endothelial NO synthase-induced vasodilatory effects [11].
3.	Resveratrol 	Anticancer	Resveratrol inhibits the PI3K/Akt pathway, regulating cell differentiation, growth, and proliferation. It may be a useful therapy when combined with other PI3K/Akt/mTOR inhibitors [12]
		Neuro degenrative disease	Resveratrol significantly induced neuronal differentiation in adult hippocampal precursor cells, improved behavioral performance, increased neuron production, and promoted hippocampal neurogenesis in vivo without affecting proliferation in vitro [13].

MATERIALS AND METHOD

Protein and Phytoconstituent Selection

Table 2 describes the protein opted for the studies the phytoconstituents daidzein, genistein and resveratrol structures were retrieved from PUBCHEM DATABASE and with their properties given in Table 3. The newer cancer targets glutamate dehydrogenase (1B26) and glutaminase (3CZD) associated with the glutamine utilization by the cancer cell were obtained from RCSB-PDB. Initially the two proteins were associated with their ligand/inhibitor. They were removed and the final structure was cleaned and saved in the PDB format to resolve the potential problems by removing water, addition of hydrogen and existing lead components like ions. Later they were subjected to docking simulations.

Table 2. List of selected enzymes for the docking simulation.

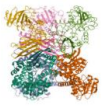
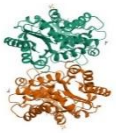
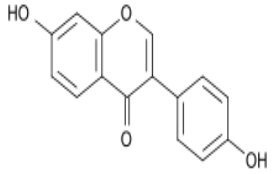
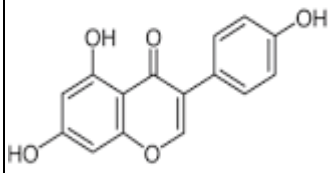
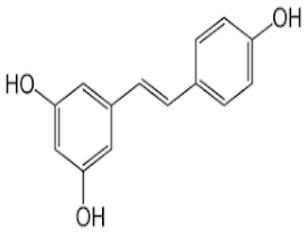
S.N.	Enzyme	Enzyme Class	PDB ID	Structure
1.	Glutamate dehydrogenase	Oxidoreductase	1B26	
2.	Glutaminase	Hydrolase	3CZD	

Table 3. List of ligands chosen for molecular docking simulation.

S.N.	Ligand	Structure	Description
1.	Diadzein		Daidzein is a member of the class of 7-hydroxyisoflavones. It has a role as an antineoplastic agent, a phytoestrogen, a plant metabolite, an EC 3.2.1.20 (alpha-glucosidase) inhibitor and an EC 2.7.7.7 (DNA-directed DNA polymerase) inhibitor.
2.	Genistein		Genistein is a 7-hydroxyisoflavone with additional hydroxy groups at positions 5 and 4'. It is a phytoestrogenic isoflavone with antioxidant properties. It has a role as an antineoplastic agent, a tyrosine kinase inhibitor, an EC 5.99.1.3 [DNA topoisomerase (ATP-hydrolysing) inhibitor, a phytoestrogen, a plant metabolite, a geroprotector and a human urinary metabolite.
3.	Resveratrol		Resveratrol is a stilbenol that is stilbene in which the phenyl groups are substituted at positions 3, 5, and 4' by hydroxy groups. It has a role as a phytoalexin, an antioxidant, a glioma-associated oncogene inhibitor and a geroprotector. It is a stilbenol, a polyphenol and a member of resorcinols.

RESULTS AND DISCUSSION

The results of the docking simulations between Glutamate dehydrogenase and Glutaminase with Genistein, Daidzein, and Resveratrol offer promising insights into the search for effective cancer treatments (Tables 4 and 5). Glutamate dehydrogenase and Glutaminase are enzymes closely linked to cancer cell metabolism, playing pivotal roles in sustaining the energetic and biosynthetic demands of rapidly proliferating cancer cells [14].

Genistein exhibited the highest binding affinity with a docking score of –9.3 kcal/mol. This indicates a strong interaction between Genistein and Glutamate dehydrogenase. Genistein likely forms favourable interactions with the active site residues of Glutamate dehydrogenase, such as hydrogen bonds, van der Waals interactions, and possibly hydrophobic interactions, leading to a stable complex formation.

Daidzein showed the second-highest binding affinity with a docking score of –8.4 kcal/mol. While slightly lower than Genistein, this score still indicates a significant interaction between Daidzein and

Glutamate dehydrogenase. Daidzein likely shares similar binding interactions with the protein, albeit with slightly weaker strength compared to Genistein.

Resveratrol exhibited a docking score of –8.2 kcal/mol, indicating moderately strong binding to Glutamate dehydrogenase. While Resveratrol's affinity is lower compared to Genistein and Daidzein, it still demonstrates notable interactions with the protein, albeit with slightly less favourable energetics.

Despite targeting a different protein, Genistein again showed the highest binding affinity, albeit with a slightly lower docking score of –7.4 kcal/mol compared to its interaction with Glutamate dehydrogenase. This suggests that Genistein has a strong affinity for both Glutamate dehydrogenase and Glutaminase, indicating its potential as a dual-targeting compound.

Like Genistein, Daidzein also demonstrated a strong binding affinity with Glutaminase, albeit with a slightly lower docking score of –7.2 kcal/mol. This indicates that Daidzein, like Genistein, can interact favourably with multiple protein targets.

Again, Resveratrol showed the weakest binding affinity among the three ligands, with a docking score of –6.7 kcal/mol. While still capable of interacting with Glutaminase, Resveratrol's affinity is notably lower compared to Genistein and Daidzein.

These results suggest that Genistein and Daidzein may be promising candidates for further investigation as potential inhibitors or modulators of both Glutamate dehydrogenase and Glutaminase, with implications for therapeutic interventions targeting pathways involved in the cancer metabolism.

Table 4. List of selected protein and their interaction with the newer targets.

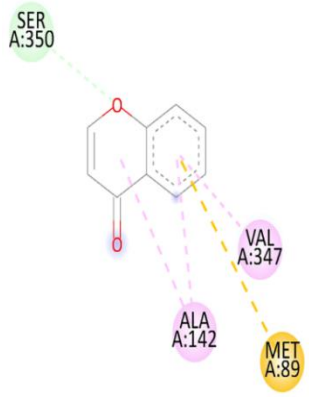
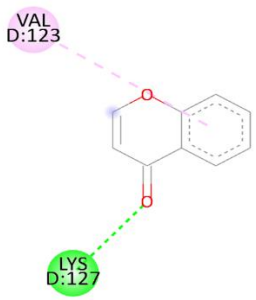
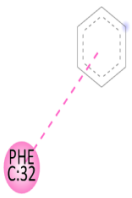
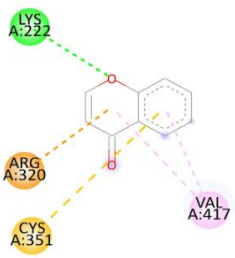
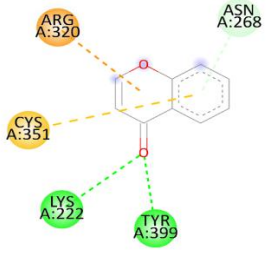
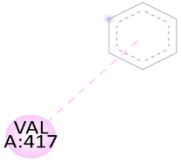
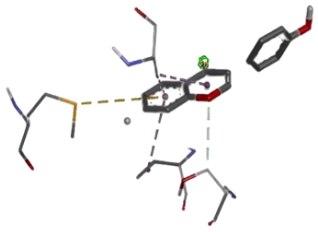
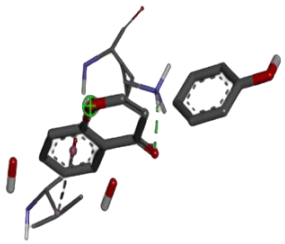
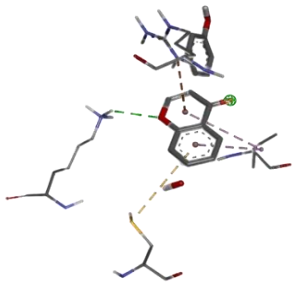
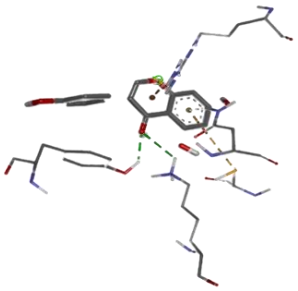
S.N.	Enzyme Structure and PDB ID	Diadzein	Genistein	Resveratol
1.	Glutamate dehydrogenase (1B26)			
2.	Glutaminase (3CZD)			

Table 5. 3D Analysis of docking results.

S.N.	Enzyme Structure and PDB ID	Diadzein	Genistein
1.	Glutamate dehydrogenase (1B26)		
2.	Glutaminase (3CZD)		

ADME ANALYSIS

The selected phytoconstituents based on the already proven characterstics diadzein, genistein, and resveratrol had the best docking scores.The phytochemicals after the docking process were screened furthur for the *insilico* ADME analysis and drug like prediction using the swissADME ONLINE tool.The drug likeness properteis were screened based on miLogP (molinspiration Log P) values and TSPA (topological polar surface area). All the phytoconstituents obey the ADME limitations and drug likeness Log P values (Table 6).

Table 6. Molinspiration property values of selected phytoconstituents.

Compound	miLogP	TSPA	Natoms	MW	nON	nNOHN	Nrotb	Nviolations
Diadzein	1.08	70.67	19	254.24	4	2	1	0
Genistein	1.61	170.05	31	432.38	10	6	4	1
Resveratrol	1.08	60.69	17	228.24	3	3	2	0

‘miLogp’ – partition coefficient for octanol/water (–2 to 6.5),
TSPA – Total molucular polar surface area.
‘Natom’ – Number of atoms in the compound.
MW – Molucular weight (between 160 and 500).
‘noN’ – No of H atom acceptor (not be more than 10).
nNOHNH – Estimated no of H donar (not be more than 5).
‘nrotb’ – Number of rotatable bonds.

CONCLUSION

The present study delves into the binding interactions of the selected phytoconstituents – Daidzein, Genistein, and Resveratrol with specific cancer targets, namely Glutamate dehydrogenase and Glutaminase. The findings suggest that these phytoconstituents possess potential efficacy in modulating the activity of these enzymes, which are pivotal in cancer cell metabolism. However, it is important to note that while the docking simulations indicate favorable binding affinities, further experimental evidence is necessary to fully substantiate the potency of these ligands in targeting these cancer-related proteins.

Experimental validation through techniques, such as enzymatic assays, cellular studies, and *in vivo* models is essential to confirm the inhibitory effects of Daidzein, Genistein, and Resveratrol on Glutamate dehydrogenase and Glutaminase activity. These experiments would provide a more comprehensive understanding of the pharmacological mechanisms underlying their interactions with the target proteins and elucidate their potential as therapeutic agents in cancer treatment.

By combining computational predictions with rigorous experimental validation, a more robust assessment of the efficacy and safety of these ligands can be achieved, paving the way for their translation into clinical applications for cancer therapy.

REFERENCES

1. Sathishkumar K, Chaturvedi M, Das P, Stephen S, Mathur P. Cancer incidence estimates for 2022 & projection for 2025: Result from National Cancer Registry Programme, India. Indian J Med Res. 2022;156 (4&5):598–607.
2. DeBerardinis RJ, Cheng T. Q's next: the diverse functions of glutamine in metabolism, cell biology and cancer. Oncogene. 2010;29(3):313–24.
3. Jin J, Byun JK, Choi YK, Park KG. Targeting glutamine metabolism as a therapeutic strategy for cancer. Exp Mol Med. 2023;55(4):706–715.
4. Ma G, Zhang, Z, Li, P. et al. Reprogramming of glutamine metabolism and its impact on immune response in the tumor microenvironment. Cell Commun Signal 2022; Vol 20: 114. https://doi.org/10.1186/s12964-022-00909-0
5. Le A, Lane AN, Hamaker M, Bose S, Gouw A, Barbi J, et al. Glucose-independent glutamine metabolism via TCA cycling for proliferation and survival in B cells. Cell Metab. 2012 Jan 4;15(1):110–21.
6. Hua F, Li CH, Chen XG, Liu XP. Daidzein exerts anticancer activity towards SKOV3 human ovarian cancer cells by inducing apoptosis and cell cycle arrest, and inhibiting the Raf/MEK/ERK cascade retraction in/10.3892/ijmm. 2021.4929. International journal of molecular medicine. 2018 Jun 1;41(6):3485–92.
7. Tan Y, Zhang X, Cheang WS. Isoflavones daidzin and daidzein inhibit lipopolysaccharide-induced inflammation in RAW264. 7 macrophages. Chin Med. 2022 Aug 16;17(1):95.
8. Zang Y, Igarashi K, Yu C. Anti-obese and anti-diabetic effects of a mixture of daidzin and glycitin on C57BL/6J mice fed with a high-fat diet. Biosci Biotechnol Biochem. 2015 Jan 2;79(1):117–23.
9. Mazumder Md. Anisur, Hongsprabhas, Parichat. Genistein as antioxidant and antibrowning agents in in vivo and in vitro: A review. Biomed Pharmacother. 2016;82(10):1016.
10. Bai Z, Wang Z. Genistein protects against doxorubicin-induced cardiotoxicity through Nrf-2/HO-1 signaling in mice model. Environ Toxicol. 2019 May;34(5):645–651.
11. Homma, Noriyuki, Morio et.al. Genistein, a Phytoestrogen, Attenuates Monocrotaline-Induced Pulmonary Hypertension. Respiration; Int Rev Thorac Dis. 2016;73:105–12.
12. Jiang H, Shang X, Wu H, Gautam SC, Al-Holou S, Li C, et al. Resveratrol downregulates PI3K/Akt/mTOR signaling pathways in human U251 glioma cells. J Exp Ther Oncol. 2009;8(1):25–33.
13. Park, Hee, Kong, et al. Resveratrol Inhibits the Proliferation of Neural Progenitor Cells and Hippocampal Neurogenesis. J Biol Chem. 2012;287:10.
14. Cluntun AA, Lukey MJ, Cerione RA, Locasale JW. Glutamine Metabolism in Cancer: Understanding the Heterogeneity. Trends Cancer. 2017;3(3):169–180.

