International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 20s, 2025
https://theaspd.com/index.php

In Silico Molecular Structure Based Screening Of Glycyrrhiza Glabra Identifies Potential Inhibitors Of Breast Cancer Target Nudt5

Chithra Shanmugam[1], Ramani Mani[2], Meenakshi Chandrasekaran[3] Malarvizhi Shanmugam[4], Tamil Muhil Madhavan Karthikeyan[5], Selvakumar S[6]

[1]Professor, Sri Sairam Siddha Medical College and Research Centre, West Tambaram, Chennai, Tamilnadu, India – 600044

[2]Research Scholar, Department of Siddha, The Tamil Nadu Dr. M. G. R. Medical University, Guindy, Chennai, Tamilnadu, India –600032

[3]Associate Professor, Post graduate department of Siddhar yoga maruthuvam, Government Siddha Medical College, Arumbakkam, Chennai, Tamilnadu, India – 600106

[4]Siddha Physician, Perambur, Chennai, Tamilnadu, India – 600011

[5]Siddha Consultant, Puliyur PHC, Cuddalore, Tamilnadu, India – 606107

[6]Assistant Professor, Department of Physiology, JR Medical College and Hospital, Tindivanam, Villupuram Dt, Tamilnadu.

Abstract

Background: *In worldwide, breast cancer is the leading type of cancer especially in women. Breast cancer is nothing but a lump in breast, changes in breast shape, dimpling of the skin and fluid coming from the nipple, inverted nipple or a red or scaly patch of skin. NUDT5 has been recognized for its significant involvement in the regulation of the G1-S transition in mammalian organisms. NUDT5 enzyme is associated with the regulation of hormone-dependent gene expression and cell proliferation in breast cancer cells.*

Aim & Objective: *The present study, we retrieved 3 bioactive Compounds such as Glabridin, Glycyrrhizin and Liquiritin which inhibit the target NUDT-5 may act as a potential therapeutic agent for management of Breast cancer.*

Materials and methods: *Docking simulations were performed by using the Lamarckian genetic algorithm (LGA) and the Solis & Wets local search method. Initial position, orientation, and torsions of the ligand molecules were set randomly.*

Results: *Total of 3 bioactive lead compounds were retrieved from Glycyrrhiza glabra, the phytochemicals such as Glabridin and Liquiritin possess maximum of four to five interactions with the core active amino acid residues present on the target NUDT-5 followed by which other compound such as Glycyrrhizin ranked second with the maximum of three interactions with the core active amino acid residues present on the target NUDT-5.*

Conclusion: *Binding of phyto-components with the core amino acids against the target NUDT5 which is associated with the regulation of hormone dependent gene expression and cell proliferation in breast cancer cells. Thereby phyto-components which inhibit the target NUDT5 may act as a potential therapeutic agent for management of breast cancer condition.*

Keywords: *Glycyrrhiza glabra, Breast cancer, NUDT-5, Molecular docking.*

BACKGROUND:

In worldwide, breast cancer is the leading type of cancer especially in women. 2nd leading cause of cancer related deaths in the United States. Global breast cancer incidence is increasing at an annual rate of 3·1%.[1,2]In Indian women,breast cancer is the most common with age adjusted rate as high as 25.8 per 1,00,000 women and a mortality rate of 12.7 per 1,00,000 women.[3] Globally age-adjusted incidence rate of carcinoma of the breast was 42.3 new cases per 1,00,000 population by using 2000 World Standard Population.The World Health Organization (WHO) released a Global Breast cancer initiative framework in February 2023. It is a map to attain the target to save 2.5 million lives from breast cancer by 2040. Countries need to ensure that this framework engages and integrates into primary health care for universal health coverage.

Breast cancer is nothing but a lump in breast, changes in breast shape, dimpling of the skin and fluid coming from the nipple, inverted nipple or a red or scaly patch of skin.[4] Survival rates in the developed countries are high, 80% and 90% in England and the United States alive for at least 5 years.[5,6] The

enzyme NUDT5 (nucleotide diphosphate hydrolase type 5) catalyzes the ADP (Adenosine diphosphate) ribose derived from hydrolysis of poly (ADP-Ribose) and pyrophosphate are converted to ATP. It is known that NUDT5 is an upstream regulator of tumor drivers and are a biomarker for cancer stratification, as well as a target for drug discovery towards the treatment of aggressive cancer types and metastasis.[7] It is also known as NUDT5 protein plays noteworthy roles in regulating the G1-S transition in mammalian. [8] NUDT5 (also referred as NUDIX5) has been linked to hormone dependent gene regulation andproliferation in the breast cancer cells. The NUDIX hydrolases are acore family of nucleotide metabolizing enzymes that have critical roles in health and disease. Thus, NUDT5 is an attractive target for drug design against breast cancer.[9]

List of Phytocomponents Selected for docking[10]

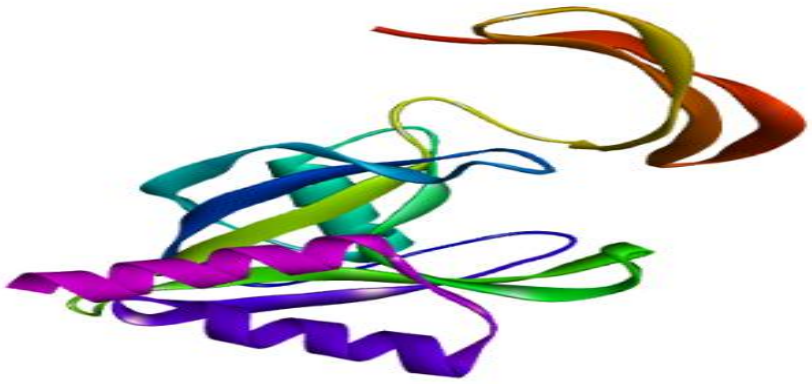
Herbs	Phytochemicals
Glycyrrhizaglabra	❖ Glabridin ❖ Liquiritin ❖ Glycyrrhizin

Objective:

Binding of phyto-components with the core amino acids (TRP28, VAL29, ARG51, ALA96, GLY97, LEU98, MET132, ILE141) of the target NUDT5 by forming hydrogen bond will hinder the function of the enzyme and thereby inhibits the NUDT5 mediated metabolism of ADP ribose and subsequent cell proliferation in breast cancer cells.Thereby phyto-components which inhibit the target NUDT5 may act as a potential therapeutic agent for management of breast cancer condition.

PDB	Name of the Target
3L85	NUDT-5 (Nudix- nucleoside diphosphate linked moiety X hyrolase)

NUDT-5 (Nudix- nucleoside diphosphate linked moiety X hyrolase)-PDB 3L85



RECEPTOR STRUCTURE

Crystalline structure of the target protein NUDT-5 was retrieved from protein data bank and protein clean-up process was done and essential missing hydrogen atoms were being added. Different orientation of the lead molecules with respect to the target protein was evaluated by Auto-dock program and the best dock pose was selected based on the interaction study analysis.

Protein preparation

Three dimensional protein structure of the target protein NUDT-5 (Nudix- nucleoside diphosphate linked moiety X hyrolase) with PDB 3L85 were retrieved from the online repository of Protein Data Bank and subjected to protein clean prior to docking simulation.

Ligand Preparation

Phytochemical subjected to the investigation were retrieved from the herbs listed in the table based on the literature survey and 3D structure of the same were built using Chem Draw prof online tool version 12.0. Ligands prepared through geometry optimization method (MMFF94). [11, 12]

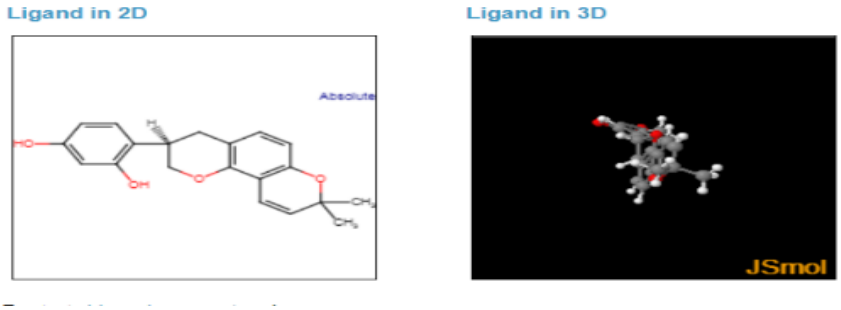
International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 20s, 2025
https://theaspd.com/index.php

MATERIALS AND METHODS

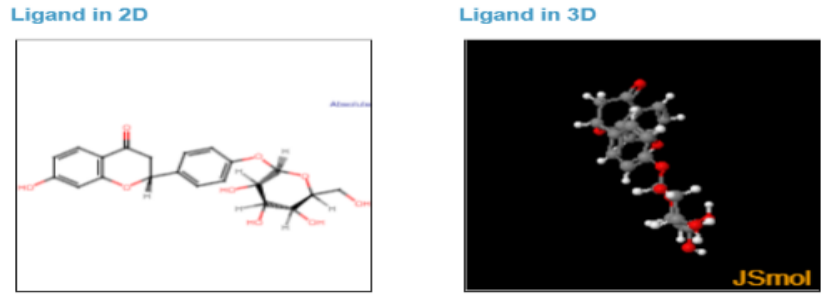
Docking calculations were carried out for retrieved phytocomponents against target protein. Essential hydrogen atoms, Kollman united atom type charges, and solvation parameters were added with the aid of AutoDock tools (Morris, Goodsell et al., 1998). Affinity (grid) maps of ×× Å grid points and 0.375 Å spacing were generated using the Autogrid program (Morris, Goodsell et al., 1998).[13] Auto Dock parameter set and distance dependent dielectric functions were used in the calculation of the van der Waals and the electrostatic terms, respectively. Docking simulations were performed using the Lamarckian genetic algorithm (LGA) and the Solis & Wets local search method (Solis and Wets, 1981).[14] Initial position, orientation, and torsions of the ligand molecules were set randomly. All rotatable torsions were released during docking. Each docking experiment was derived from 2 different runs that were set to terminate after a maximum of 250000 energy evaluations. The population size was set to 150. During the search, a translational step of 0.2 Å, and quaternion and torsion steps of 5 were applied.[15]

2D and 3D Structure of Phytocomponents

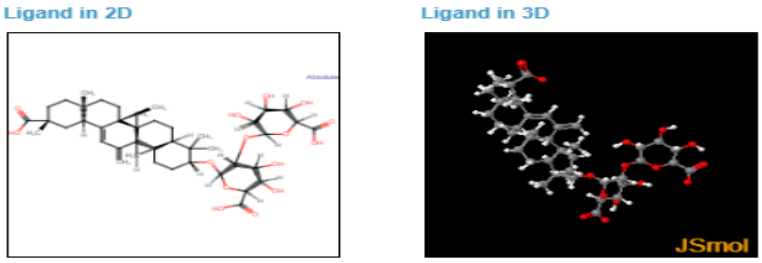
Glabridin



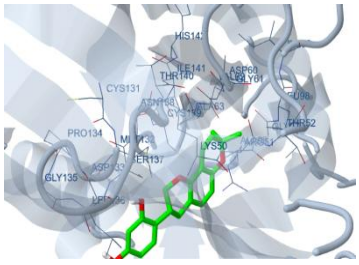
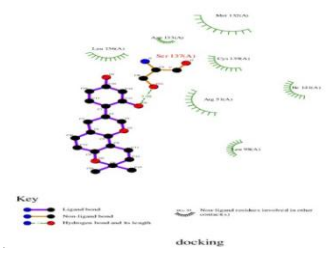
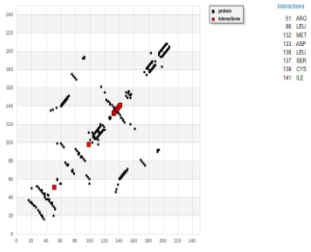
Liquiritin

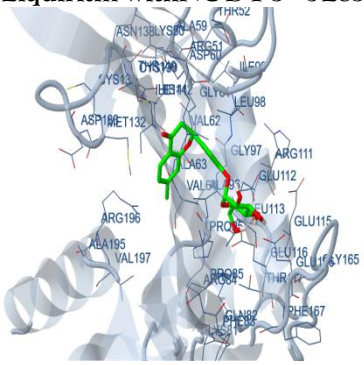
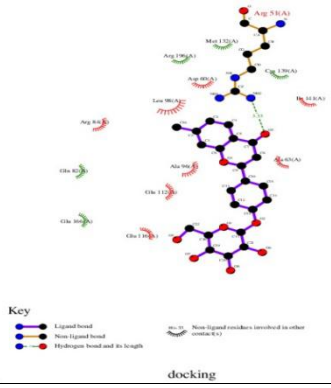
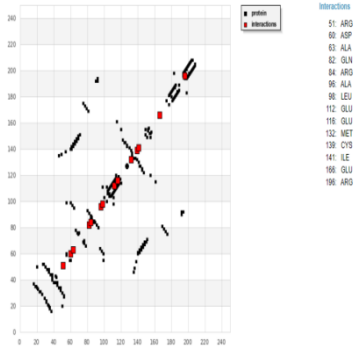
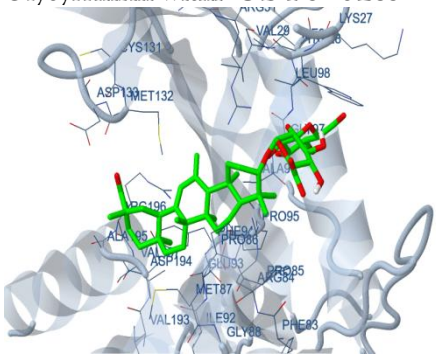
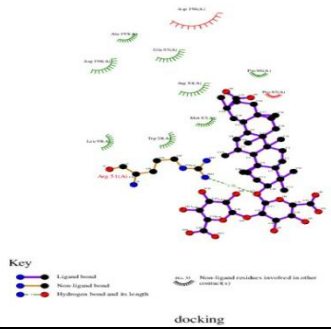
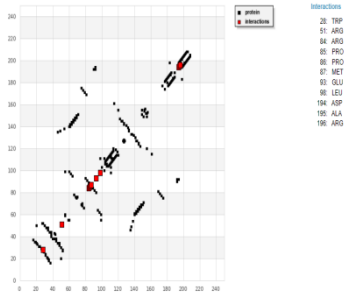


Glycyrrhizin



Docking Pose

Glabridin withNUDT-5 - 3L85	2D Interaction Plot Analysis	Hydrogen bond plotting with core amino acid Analysis
		

Liquiritin withNUDT-5 - 3L85 	**2D Interaction Plot Analysis** 	**Hydrogen bond plotting with core amino acid Analysis** 
Glycyrrhizin withNUDT-5 - 3L85 	**2D Interaction Plot Analysis** 	**Hydrogen bond plotting with core amino acid Analysis** 

Ligand Properties of the Compounds Selected for Docking Analysis

Compound	Molar weight g/mol	Molecular Formula	H Bond Donor	H Bond Acceptor	Rotatable bonds
Glabridin	324.4 g/mol	$C_{20}H_{20}O_4$	2	4	1
Liquiritin	418.4 g/mol	$C_{21}H_{22}O_9$	5	9	4
Glycyrrhizin	822.9 g/mol	$C_{42}H_{62}O_{16}$	8	16	7

Summary of the molecular docking studies of compounds against Amino acid Residue Interaction of Lead against NUDT-5 -PDB 3L85

Compounds	Est. Free Energy of Binding	Est. Inhibition Constant, Ki	Electrostatic Energy	Total Intermole c. Energy	Interact. Surface
Glabridin	-4.84 kcal/mol	282.57 uM	-5.41 kcal/mol	-0.39 kcal/mol	675.836
Liquiritin	-6.40 kcal/mol	20.37 uM	-6.27 kcal/mol	-0.41 kcal/mol	784.25

Glycyrrhizin	-7.85 kcal/mol	1.75 uM	-8.42 kcal/mol	-1.05 kcal/mol	1308.081

Amino acid Residue Interaction of Lead against NUDT-5 (Nudix- nucleoside diphosphate linked moiety X hyrolase)- PDB 3L85

Compounds	Interactions	Amino acid Residues													
Glabridin	4	51	98	132	133	136	137	139	141						
		ARG	LEU	MET	ASP	LEU	SER	CYS	ILE						
Liquiritin	5	51	60	63	82	84	96	98	112	116	132	139	141	166	196
		ARG	ASP	ALA	GLN	ARG	ALA	LEU	GLU	GLU	MET	CYS	ILE	GLU	ARG
Glycyrrhizin	3	28	51	84	85	86	87	93	98	194	195	196			
		TRP	ARG	ARG	PRO	PRO	MET	GLU	LEU	ASP	ALA	ARG			

RESULTS AND DISCUSSION

Total of 3 bioactive lead compounds were retrieved from the herb Glycyrrhiza glabra, the phytochemicals such as Glabridin and Liquiritin possess maximum of four to five interactions with the core active amino acid residues present on the target NUDT-5 followed by which other compound such as Glycyrrhizin ranked second with the maximum of three interactions with the core active amino acid residues present on the target NUDT-5. It is of interest to design inhibitors for the breast cancer target NUDT5 using molecular docking based virtual screening followed by molecular docking.The binding analysis indicates that these molecules can bind to the drug target efficiently and would be potential drugs for NUDT5. The molecular docking was applied to explore the binding mechanism and studies on the novel ligand against the NUDT5 protein and the ligand binds favorably to the binding site. The ligand was observed as the best inhibitor candidate, which may be considered as a potential ligand for treatment of Breast cancer. Therefore, this study helps to focus on in silico drug design for breast cancer based on its essential protein, NUDT5

CONCLUSION

Design and development of potential inhibitors to NUDT5 is of interest in the treatment of breast cancer. Based on the results of the computational analysis it was concluded that all the bio-active compound's like Glabridin and Liquiritin revels significant binding affinity against the target NUDT-5 by interacting with active amino acid present on the active site thereby it was concluded that these compounds may exerts anti-cancer activityagainst breast cancer conditionby limiting the cell proliferation potential of the enzyme NUDT-5.

Acknowledgements

We would like to thank Sri Sairam Siddha Medical College and Research Centre, West Tambaram, Chennai, and Noble Research Solutions, Perambur, Chennai for supporting this research.

Author's contribution

Dr.Malarvizhi designed the work, Dr.Chithra and Dr.Ramani carried out the bench work and the above authors wrote the manuscript and Dr.Tamilmuhil and Dr.Meenakshi edited the manuscript. Dr Selvakumar assisted for publication.

Conflict of interest

The authors declare that there are no conflicts of interest.

Funding

Self-funded research work

REFERENCES

1. Page BDG et al. Nat Commun. 2019, 10:5050. [PMID: 29343827]
2. De la Mare JA et al. Recent Pat Anticancer Drug Discov. 2014, 9:153. [PMID: 24171821]
3. Veronesi U et al. Lancet. 2005, 365:1727. [PMID: 15894099]
4. Merino Bonilla JA et al. Radiologia. 2017, 59:368. [PMID: 28712528]
5. Anastasiadi Z et al. Updates Surg. 2017, 69:313. [PMID: 28260181]
6. Bray F et al. CA Cancer J Clin. 2018, 68: 394.[PMID: 30207593]
7. Pickup KE et al. Cancers (Basel). 2019, 10:11. [PMID: 31510016]
8. Zhang LQ et al. Mol Cell Biochem. 2012, 36:377. [PMID: 22200976]
9. Zha M et al. J Mol Biol. 2006 364:1021. [PMID: 17052728]
10. Pastorino G, Cornara L, Soares S, Rodrigues F, Oliveira MBPP. Liquorice (Glycyrrhizaglabra): A phytochemical and pharmacological review. Phytother Res. 2018; 32(12):2323-2339.
11. Bikadi, Z., Hazai, E.Application of the PM6 semi-empirical method to modeling proteins enhances docking accuracy of AutoDock. J. Cheminf.(2009), 1, 15.
12. T. A. Halgren. Merck molecular force field. I. Basis, form, scope, parametrization, and performance of MMFF94. Journal of Computational Chemistry, (1998), 17 (5-6), 490-519.
13. G. M. Morris, D. S. Goodsell, et al. Automated docking using a Lamarckian genetic algorithm and an empirical binding free energy function. Journal of Computational Chemistry,(1998), 19 (14), 1639-1662.
14. Solis, F.J. and Wets, R.J.B. Minimization by Random Search Techniques. Mathematics of Operations Research,(1981),6, 19-30.
15. Sultana, R., Islam, M., Haque, M. A., Evamoni, F. Z., Imran, Z. M., Khanom, J., &Munim, M. A. Molecular docking based virtual screening of the breast cancer target NUDT5. Bioinformation, (2019), 15(11), 784–789.