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Exploring Multitarget Neuroprotection: In Silico Identification of Phytocompound against Thyroid Hormone Challenges

Navya.A.S[1]; Shahananasli.K[1] and Dr. V. Sharmila2[1]
[1]-M.Sc. Biotechnology Student, Nehru Arts and Science College, Coimbatore , India.
[2] Assistant Professor, Department of Biotechnology, Nehru Arts and Science College, Coimbatore, India.

ARTICLE DETAILS

Corresponding Author:
Dr. V. Sharmila

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ABSTRACT

The thyroid gland is a tiny, butterfly-shaped gland in the neck that is vital to numerous body functions. It generates hormones that control your mood, body temperature, heart rate, and metabolism. Thyroid dysfunction can result in a number of different health issues. By producing and releasing thyroid hormones, the thyroid gland is essential for controlling a number of physiological functions. The primary thyroid hormones are thyroxine (T4) and triiodothyronine (T3). The mechanism of action of thyroid hormones involves a complex interplay of molecular and cellular processes. Thyroid hormone receptor, alpha and Dopamine beta- hydroxylase are the two main proteins present. The drugs responsible for the proteins are Levothyroxine and Propylthiouracil respectively. Using the Protein Data Bank (PDB) protein 3D structures were retrieved. 50 Neuroprotective natural compounds were retrieved using Pubchem Database. The binding efficacy of the compounds was analyzed using an integrated computational protocol that combines Molecular docking and Molecular dynamics (MD) simulation. Finally, ADME prediction was carried out to find the oral absorption level of the best compounds from the results of this study.

1. Introduction

The thyroid gland is the organ that makes thyroid hormone. Thyroid hormone is produced by iodinating the tyrosine residues in the glycoprotein thyroglobulin in follicles *(Zimmermann and Rubio, 2009).*TSH acts directly on the basolateral membrane of thyroid follicular cells, where it binds to the TSH receptor (TSH-R). The anterior pituitary releases TSH in reaction to the thyroid hormone that is in the blood *(Chiamoler et al.,2009).*According to TSH regulates iodide through the sodium/iodide symporter, which sets off a series of processes necessary for normal thyroid hormone production and secretion.*(Brent, 2010)*.

Here, the focus of our investigation is docking in thyroid hormones. Molecular docking is a fast, low-cost technique that is frequently applied in academic and professional contexts. The main objective of ligand protein docking is to determine which ligand binding modalities work best for the target protein. A method for examining the orientation and conformation of molecules inside a macromolecular target's binding site is called "molecular docking (Tan *et al*., 2004). "Possibilities are generated by search algorithms and then ranked using scoring methods. The two primary phases in molecular docking computations are posing and scoring, which result in a prioritized list of potential complexes between ligands and targets *(Torres et al.,2019).* Molecular docking projects find thyroid disease, Conditions like hypothyroidism and hyperthyroidism impact a large number of people, thus posing a significant public health issue (Chen *et al.,* 2015). Through the utilization of docking technology in monitoring thyroid function, researchers and healthcare professionals can effectively address the urgent requirement for efficient and easily accessible diagnostic tools. Docking allows for continuous tracking of these fluctuations, providing clinicians with actionable insights to intervene promptly and prevent

[1]Author can be contacted at: *Assistant Professor, Department of Biotechnology, Nehru Arts and Science College, Coimbatore, India.*
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complications. Focusing on thyroid disease in docking projects brings numerous advantages, such as enhanced patient care, advancements in medical research, and innovation in wearable sensor technology (Kumar, 2006).

The goal of the Schrödinger user handbook is to assist you in using glide for high precision docking and ligand database screening. Although it can also be launched from the command line, Glide is mainly operated through the Maestro graphical user interface. With the use of high-speed computational techniques, it is now possible to increase the proportion of viable lead candidates in a chemical database, potentially leading to significant cost savings and productivity gains in the drug development process.

2. Materials and Methods

The target proteins 3D structures were retrieved using PDB and Ligand compounds were retrieved using Pubchem database. The docking was carried out using the commercial software Schrödinger version 9.8. The docking analysis was performed with "Xtra Precision" (XP) mode of Glide 9.8v. The MD simulations and calculations were performed Workstations from Supermicrowith configurations of Intel(R), Core(TM)i72600 CPU @ 3.40 GHz force field and the particle mesh Ewald summation method (Schuler *et al*., 2001). Using pdb2gmx, the topology of the protein was created. All of the details on the bonded and unbounded parameters are contained in the file. For ligand topology generation, the PRODRG2 server is employed. (Schuttelkopf and van Aalten, 2004).

It was created a cubic box with a single point solvent model. By introducing sodium or chloride counter ions, charges were neutralized. Before running the simulation, we used the steepest descent technique to expose the system to an energy minimization procedure (maximum number of steps of 4,000). Leap frog algorithm was used for the system equilibration, bringing the temperature and pressure to 300 K and 1 bar, respectively. The protein-ligand combination underwent a 10 ns molecular dynamic simulation following equilibration at the required temperature and pressure. The LINCS algorithm was used to restrict the bond length (Hess *et al*., 1997) and trajectories were analyzed was carried for 10ns. ADME was calculated for the compounds exhibiting best results.

3. Methodology

1. Examining ADME characteristics and choosing plant-based compounds.
2. Following the ADME qualities, 23 plant substances were chosen, and proteins and medications were then used.
3. From the PubChem database, a 3D structure of plant chemicals in SDF format was retrieved.
4. Schrodinger software was utilized to carry out the molecular docking process.
5. It therefore goes through induced fit docking. Carry out the simulation of molecules.
6. Make use of computational techniques to forecast structure dynamics, binding affinities, and other pertinent characteristics.
7. Choosing the most effective ligand based on Determine which ligands have the most promising binding properties by analyzing the simulation findings. Take into account elements like stability, specificity, binding affinity, and pharmacological characteristics.
8. Give top priority to ligands that exhibit ideal interactions with the target molecule while reducing any negative attributes or off-target consequences.

4. Results

In below Table 1, 23 plant compounds are selected, under the characterization of Adsorption, Distribution, Metabolism, Excretion (ADME) using ADME database.

Of the selected Phytocompounds, only top ten compounds (- 7.757 to - 4.125 kcal/mol) (Tab.2) were having G.Score less than the drug Levothyroxine (- 4.953 kcal/mol).

The drug interacted with the residues Gln 92 (H--O), His 94 (Pi--Pi), Thr 199 (H--O). The Top three compounds Rivastigmine, Triclosan, Magnolol had lower G.Score of -7.757 and - 7.479 (kcal/mol), respectively than the drug and interacted with the residues Gln 92 and His 94 of which the latter is important for the enzyme activity (Table 2).

The IFD results of Thyroid Hormone receptor exhibited variation in positions of the top three compounds and the dock scores. In the top position was Rivastigmine with dock score of -13.091 kcal /mol and it had 1Hbond and 1 pi-pi interaction with Phe 131, Thr 200 (Table. 3).

The second compound Magnolol which was in the third position in XP docking had dock score of 12.605 kcal/mol and 3H-bonds with Asn 67 (H--O)Gln 92 (H--O), Thr 200 (O--H). The third compound is Triclosan had the dock score of -11.202 kcal /mol and the interactions are His 64 (Pi--Pi), Asn 67 (O--H). The Drug had the dock score with -7.801 kcal/mol it was less when compare with the compounds and it had 3 interactions (Fig 2-5).

Table 1: ADMET Result

S.no	Compound Name	MW	QPlogPo/w	QPlogS	QPPMDCK	HOA%
1	Alpha Lipoicacid	206.317	2.561	-5.812	407.099	84.365
2	Apigenin	270.241	1.624	-3.317	52.038	73.955
3	Astaxanthine	596.848	8.324	-10.86	97.51	91.78
4	Bacillus	149.207	-2.609	0.525	24.003	43.59
5	Cannabidiol	314.467	5.377	-6.155	1357.982	100
6	Carnosine	226.235	-2.36	0.434	1.783	20.073
7	Celecoxib	381.372	3.271	-5.697	810.167	92.053
8	Centella Asiatica	488.706	4.172	-5.148	37.322	84.755
9	Dha	222.151	-1.939	-6.045	0.339	19.291
10	Donepezil	379.498	4.328	-4.429	478.693	100
11	Egcg	458.378	-1.37	-5.269	0.264	80
12	Green Tea Catechin	290.272	1.427	-4.608	25.125	60.111
13	Huperzine A	242.32	1.436	-4.116	87.259	75.845
14	Luteolin	286.24	2.941	-3.039	33.333	62.05
15	Lycopene	536.882	5.447	-16.908	5899.293	100
16	Magnolol	266.339	4.965	-4.219	850.365	100
17	Mematine	179.305	1.684	-1.384	466.746	89.353
18	N Acetyl Cysteine	163.191	0.494	-4.124	137.402	61.427
19	Phosphatidylserine	792.084	4.776	-17.552	59.085	52.601
20	Pqq	330.21	-1.546	-5.381	45.007	82
21	Pterostilbene	256.301	3.842	-5.996	1628.862	100
22	Rivastigmine	250.34	2.366	-2.043	665.338	95.899
23	Sulforaphane	177.279	1.431	1.05	6525.796	66.189

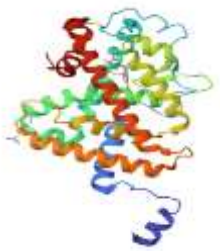

Fig.1: 3D Structure of Thyroid hormonereceptor, alpha - 3ILZ

Table 2: Molecular docking results for Thyroid hormonereceptor, alpha - 3ILZ

S.no	Compound Id	Compound Name	G score (Kcal/mol)	G energy	Interactions
		Compound Results			
1	77991	Rivastigmine	-7.757	-40.821	Phe 131 (Pi--Pi) Thr 200 (H--O)
2	5564	Triclosan	-7.341	-34.832	His 64 (Pi--Pi) Asn 67 (O--H)
3	72300	Magnolol	-7.479	-21.794	Asn 67 (H--O) Gln 92 (H--O) Thr 200 (O--H)
4	10275	Amiphenazole	-6.077	-24.188	Thr 199 (Pi--Pi) His 94 (Pi--Pi)
5	5280460	Scopoletin	-4.344	-23.697	Phe 131 (H--O) Thr 199 (H--O)
6	10275	Amiphenazole	-5.605	-22.758	His 94 (Pi--Pi) Phe 131 (Pi--Pi) Thr 199 (H--O)
7	5350	Sulforaphane	-3.662	-28.196	Asn 67 (H--O) Gln 92 (H--O)
8	6137	L-methionine	-3.418	-18.549	Tyr 124 (H--O) Trp 286 (Pi--Pi) Ser 293 (H--O)

9	5280460	scopoletin	-4.485	-20.87	Trp 286 (Pi-Pi) Ser 293 (O--H)
10	439224	Carnosine	-4.125	-19.57	His 94 (Pi--Pi) Phe 131 (H--O) Thr 199 (H--O)
		Drug Result			
1	5819	Levothyroxine	-4.953	-37.599	Gln 92 (H--O) His 94 (Pi--Pi) Thr 199 (H--O)

Table 3: IFD results for Thyroid Hormone receptor, alpha 3ILZ

S.No	Compound ID	Compound Name	IFD score (Kcal/mol)	Prime Energy	Interaction residues
			Compounds		
1	77991	Rivastigmine	-13.091	-3655.18	Phe 131 (Pi--Pi) Thr 200 (H--O)
2	72300	Magnolol	-12.605	-3586.40	Asn 67 (H--O) Gln 92 (H--O) Thr 200 (O--H)
3	5564	Triclosan	-11.202	-3576.94	His 64 (Pi--Pi) Asn 67 (O--H)
1	5819	Levothyroxine	-7.801	3100.65	Gln 92 (H--O) His 94 (Pi--Pi) Thr 199 (H--O)

Fig.2. 3D structure of Thyroid Hormone receptor with the compound Rivastigmine

Fig.3. 3D structure of Thyroid Hormone receptor with the compound Magnolol

Fig.4. 3D structure of Thyroid Hormone receptor with the compound Triclosan

Fig.5. 3D structure of Thyroid Hormone receptor with the Drug Levothyroxine

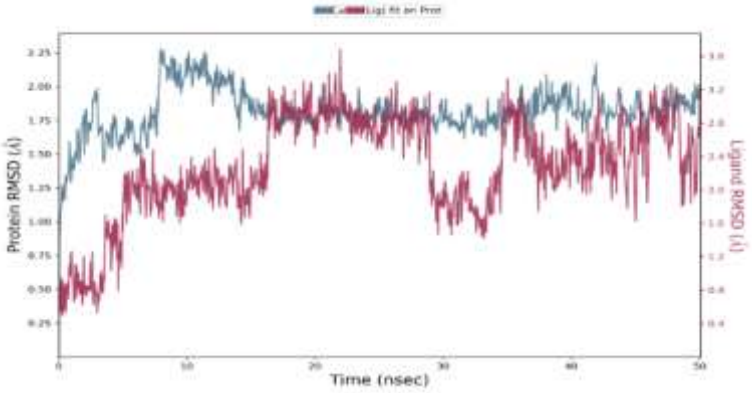

Fig.6. RMSD Graph complex structure of Thyroid Hormone receptor with the compound Rivastigmine and Drug Levothyroxine

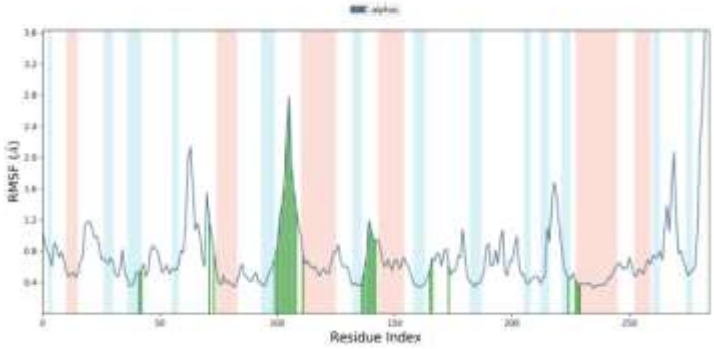

Fig. 7. RMSD Fluctuation Graph of Thyroid Hormone receptor with the compound Rivastigmine and Drug Levothyroxine

By using GROMACS methods from the graph observed from 15 to 50 nanosecond both protein and ligand , protein and neuroprotective plant compound both are aligned in same , which means both are more stable. GROMACS (GROningen Machine for Chemical Simulations) is a molecular dynamics package primarily designed for simulations of protein, lipids and nucleic acids that have a lot of complicated bonded interactions.

5. Discussion

Something important is shown by the graph analysis that contrasts the interactions of proteins with levothyroxine with specific neuroprotective drugs. Within a crucial window of 15 to 50 nanoseconds, both interactions—between the protein and neuroprotective substances and between the protein and levothyroxin—show stability. This stability shows that these interactions are potent and could have an effect in this brief amount of time (Alevizaki *et al.,* 2006). This conclusion leads us to think about treating thyroid disease with neuroprotective chemicals rather than levothyroxine. It is proposed that several neuroprotective substances, whose interactions with proteins show stability and efficacy akin to that of levothyroxine, may be useful substitutes for treating thyroid disorders. When compared to levothyroxine, neuroprotective substances have a lot of advantages. Neuroprotective substances may be safer for patients because they are thought to have fewer adverse effects. They are also more affordable and easily accessible, which makes them a more sensible option for general usage in healthcare settings (Cheng *et al.,* 2010). These substances are more appealing because they are naturally occurring, which is in line with the medical trend towards using natural therapies. Based on their demonstrated stability and therapeutic potential in protein interactions, this study proposes investigating neuroprotective chemicals as a novel treatment approach for thyroid illness (Rousset *et al*., 2015). This highlights the significance of using scientific knowledge to drive creative medical solutions and may result in better treatment alternatives. *(kumar V 2006).* This

paradigm shift underscores the importance of exploring diverse sources of healing and expanding our understanding of the intricate connections between human health and the natural world . *(Iriti M et al.,2010).*

Utilizing neuroprotective plant compounds as an alternative treatment for thyroid disease offers a natural and potentially more accessible option compared to conventional pharmaceuticals (Kudlaoui and Levine, 2014). The high cost and significant side effects associated with mainstream medications emphasize the need for effective alternatives rooted in nature's resources. By tapping into the power of naturally occurring plant compounds, we explore treatment avenues that are not only economically feasible but also potentially safer for individuals with thyroid disorders. This shift towards plant-based therapies aligns with broader trends in healthcare towards holistic and sustainable practices, recognizing the inherent healing properties of botanicals that have long been used in traditional medicine (Fagin *et al.,* 2004). Furthermore, the neuroprotective qualities of these plant compounds highlight their potential to support not only thyroid health but also overall neurological well-being, providing a comprehensive approach to health management. Embracing these natural remedies addresses immediate challenges posed by thyroid disease and demonstrates a proactive stance towards cultivating a healthier, more resilient population (Knobel, 2016). As we progress towards personalized medicine, integrating plant-based compounds into mainstream therapeutic approaches holds great promise.

6. Conclusion

Rivastigmine, Magnolol, Triclosan are suggested to be the best compounds which can be evaluated as Thyroid Hormone receptor. The neuroprotective compound Rivastigmine exhibited very good docking results with the selected Thyroid Hormone receptor target which are better than the drugs suggesting its efficacy as a drug with multi- targeting potential or as a lead compound for synthesizing a multi- targeting drug to combat Thyroid. Continued research and innovation in this area will optimize treatments for thyroid disorders and contribute to a more sustainable and inclusive healthcare landscape.

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