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In Silico Exploration of Multi-Target Neuroprotection: Phytocompounds Addressing Thyroid Hormone-Induced Challenges

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ARTICLE DETAILS

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ABSTRACT

The thyroid gland, a small butterfly-shaped organ located in the neck, plays a crucial role in various body functions by producing hormones that regulate mood, body temperature, heart rate, and metabolism. Dysfunction of the thyroid can lead to numerous health issues due to its key role in controlling these physiological processes. The primary hormones produced by the thyroid are thyroxine (T4) and triiodothyronine (T3), which exert their effects through complex molecular and cellular mechanisms. Key proteins involved include the thyroid hormone receptor alpha and dopamine beta-hydroxylase, with Levothyroxine and Propylthiouracil as the respective drugs targeting these proteins. In this study, 3D structures of these proteins were retrieved from the Protein Data Bank (PDB). Additionally, 50 neuroprotective natural compounds were identified using the PubChem database. The binding efficacy of these compounds was evaluated through an integrated computational approach, combining molecular docking and molecular dynamics (MD) simulations. Furthermore, ADME (Absorption, Distribution, Metabolism, and Excretion) predictions were conducted to assess the oral absorption potential of the most promising compounds identified in this study.

1. Introduction

The thyroid gland produces thyroid hormones within its follicles, where tyrosine residues in the glycoprotein thyroglobulin are iodinated to form these hormones (Zimmermann, 2009). The thyroid-stimulating hormone (TSH) acts directly on the TSH receptor (TSH-R), located on the basolateral membrane of thyroid follicular cells. Released by the anterior pituitary in response to feedback from circulating thyroid hormones (Chiamolera *et al*., 2009), TSH regulates iodide uptake through the sodium/iodide symporter, initiating a series of events essential for the proper production and secretion of thyroid hormones (Brent *et al*., 2012).

Our project focuses on molecular docking in the context of thyroid hormones. Molecular docking is a fast and cost-effective technique widely used in both academic and professional environments to determine the optimal binding modes of ligands to target proteins. The primary aim of ligand-protein docking is to explore the orientation and conformation of molecules within the binding site of a macromolecular target. Search algorithms generate potential poses, which are then ranked using scoring functions. The docking process involves two main steps: posing and scoring, which together produce a prioritized list of potential complexes between ligands and targets (Torres *et al*., 2019). Molecular docking is particularly relevant in addressing

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thyroid diseases, such as hypothyroidism and hyperthyroidism, which affect a significant portion of the population and present a major public health challenge. By applying docking technology to monitor thyroid function, researchers and healthcare professionals can meet the critical need for efficient and accessible diagnostic tools. Docking enables continuous monitoring of thyroid hormone fluctuations, providing clinicians with actionable insights for timely intervention and complication prevention. In this project, we utilized Schrödinger software, which offers a user manual designed to assist in performing ligand database screening and high-accuracy docking using Glide. Glide operates primarily through the Maestro graphical user interface, but can also be run from the command line. High-speed computational methods can now enhance the identification of suitable lead candidates from a chemical database, significantly boosting productivity (Yoshihara *et al.,* 2019). Dopamine-β-hydroxylase [3, 4-dihydroxyphenylethylamine, ascorbate: oxygen oxidoreductase (3-hydroxylating)] is the enzyme responsible for catalyzing the biosynthesis of noradrenaline, a catecholamine neurotransmitter. Norepinephrine, the product of this reaction, is biochemically and pharmacologically significant because these monoamines serve as key intracellular messengers, functioning as neurotransmitters and hormones that regulate behavior, emotion, and neuronal processes in higher animals. Dopamine-β-hydroxylase (DBH), which requires both copper (Cu++) and ascorbic acid (Vitamin C) for its activity, is classified as a mixed-function copper oxygenase (Levine *et al*., 2001).

The enzyme's activity can be enhanced by the addition of fumaric acid and other dicarboxylic acids. DBH is an intraneuronal enzyme of the sympathetic nervous system, with activity observed in the adrenal medulla, brain, and various sympathetically innervated organs, such as the heart. It has been quantified in plasma of humans and laboratory animals, and more recently, in cerebrospinal fluid (CSF). The source of DBH in plasma is the sympathetic nervous system and adrenal medulla. As a primary enzyme involved in neurotransmitter regulation, DBH has attracted considerable interest from researchers in pharmacology and clinical medicine as a potential marker of sympathetic nervous system activity. Dopamine deficiency is linked to several neurological conditions, most notably Parkinson's disease, while pheochromocytoma is associated with a marked increase in DBH activity (Levin *et al*., 2001).

2. Materials and methods

2.1 Protein Data Bank

The Protein Data Bank (PDB) is a crystallographic database for the three dimensional structure data of large biological molecules, such as proteins and nucleic acids. The data typically obtained by x-ray crystallography or NMR spectroscopy and submitted by biologists and biochemists from around the world. The PDB is a key resource in areas of structural biology and structural genomics. Most major scientific journals and some funding agencies, now require scientists to submit their structure data to the PDB. The file format initially used by the PDB was call PDB file format. The file may be viewed using one of several open source computer programs including Jmol, PyMOL and Rasmol.

2.2 PubChem database

PubChem is a database of chemical molecules and their activities against biological assays. The system is maintained by the national center for biotechnology information, a component of the national library of medicine, which is part of the United States national institutes of health. PubChem can be accessed for free through a web user interface, millions of compound structures and descriptive datasets can be freely downloaded via FTP. PubChem contains substance descriptions and small molecules with fewer than 1000 atoms and 1000 bonds. More than 80 database vendors contribute to growing PubChem database (www.pubchem.ncbi.nlm.nih.gov).

2.3 Drug Bank

The Drug Bank database is a unique bioinformatics and cheminformatics resource that combines detailed drug data with comprehensive drug target information. The database contains 7759 drug entries including 1602 FDA approved small molecule drugs, 161 FDA approved biotech drugs. Drug bank has been widely used to facilitate in silico drug target discovery, drug design, drug docking or screening, drug metabolism prediction, drug interaction prediction and general pharmaceutical education (http://www.drugbank.ca).

2.4 Schrodinger

Schrödinger user manual is intended to help you perform ligand database screening and high accuracy docking with glide. Glide is run primarily from the Maestro graphical user interface, but can also be run from the command line. The widespread use of combinational chemistry and high through screening in the pharmaceutical and biotechnology industries means that large numbers of compounds can now routinely be investigated for biological activity. High speed computational methods can now enrich the fraction of suitable lead candidates in a chemical database, thereby creating the potential to greatly enhance productivity and dramatically reduce drug development costs. With an ever increasing number of drug discovery project having access to high resolution crystal structures of their targets, high performance ligand-receptor docking is the clear computational strategy of choice to augment and accelerate structure based drug design

(http://www.schrodinger.com/Glide).

2.5 Gromacs

GROMACS (GROningen Machine for Chemical Simulations) is a molecular dynamics package primarily designed for simul.ations of protein, lipids and nucleic acids that have a lot of complicated bonded interactions, but since GROMACS is extremely fast at calculating the nonbonded interactions many groups are also using it for research on non-biological systems. The GROMACS was originally started in 1991 at Department of Biophysical chemistry. GROMACS supports all the usual algorithms you expect from a modern molecular dynamics implementation (www.gromacs.org/About_Gromacs).

2.6 ADME database

ADME (Absorption, Distribution, Metabolism and Excretion) describes the deposition of a pharmaceutical compound within an organism. The four criteria all influence the drug levels and kinetics of drug exposure to the tissues and hence influence to tissues and hence influence the performance and pharmacological activity of the compound. It is designed for use in drug research and development, including drug-drug interactions. The information was categorized as drug name, enzyme, reaction and type. ADME database is supported by chemical/metabolite structures as well as kinetic values found in the literature. The database is available to support investigational studies on drug-drug interaction. ADME database contains more than 25,500 substances, a number of natural products and preparations, as well as other factors influencing drug metabolizing enzymes activity. Data was collected from more than 10,300 citation(www.fqs.pl/chemistry_materials_life_science/products/adme_db).

3. Methodology

3.1 ADME screening

A computational analysis was performed to assess the Absorption, Distribution, Metabolism, and Excretion (ADME) properties of various plant compounds.

3.2 Selection of promising plant candidates

Based on the ADME evaluation, 23 plant compounds were identified as potential candidates for further investigation.

3.3 Acquisition of 3D structures

The three-dimensional (3D) structures of the shortlisted plant compounds were retrieved in SDF format from the PubChem database.

3.4 Induced-fit docking simulations

Molecular docking simulations were conducted using Schrodinger software to predict the binding modes of the plant compounds within the target protein's binding pocket. This docking approach incorporates protein flexibility to account for potential conformational changes upon ligand interaction.

3.5 Molecular dynamics simulations

The docked complexes were subjected to molecular dynamics simulations to evaluate their stability and refine the binding poses over time. These simulations provide insights into the dynamic behaviour of the complex at an atomic level.

3.6 Ligand selection based on comprehensive analysis

The results from the molecular simulations were meticulously analysed to identify the ligand with the most favourable binding characteristics. Key factors considered during this selection process include binding affinity, target specificity, complex stability, and potential pharmacological properties.

3.7 Prioritizing optimal candidates

Particular emphasis was placed on ligands that demonstrate strong and specific interactions with the target molecule while exhibiting minimal off-target effects or undesirable properties. This prioritization ensures the selection of the most promising candidate for further development.

3.8 Selection of best ligand:

Particular emphasis was placed on ligands that demonstrate strong and specific interactions with the target molecule while exhibiting minimal off-target effects or undesirable properties. This prioritization ensures the selection of the most promising candidate for further development.

4. Results

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

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 Human dopamine beta-hydroxylase - 4ZEL

In Table: 2, the study utilized computational methods to investigate the interactions between certain plant compounds and a specific protein, Human Dopamine Beta Hydroxylase (DBH). Initially, a group of over 23 different plant compounds was selected. Each compound was individually tested or docked against its respective target proteins using computational docking techniques. This initial screening identified which plant compounds exhibited the most promising interactions with specific proteins. These selected compounds were then subjected to molecular docking simulations specifically targeting the DBH protein.

Of the selected Phytocompounds, only top ten compounds (- 5.298 to - -4.821 kcal/mol) (Tab.2) were having G.Score less than the drug Propylthiouracil (-4.070 kcal/mol) . The drug interacted with the residues Lys 181, Glu 186, Lys 218. The Top three compounds donepezil, Carnosine, had lower G.Score of -5.298 and - -5.465 (kcal/mol), respectively than the drug and interacted with the residues Lys 181, Glu 186, Lys 218 of which the latter is important for the Metabolic activity (Table 2).

Table 2: Molecular docking results for Human dopamine beta-hydroxylase - 4ZEL

S.no	Compound Id	Compound Name	G score Kcal/mol	G energy	Interacting residues
			Compounds		
1	3152	Donepezil	-5.298	-23.732	Lys 181, His 185, Lys 218, Thr 219
2	439224	Carnosine	-5.503	-27.834	Lys 181, Glu 186, Lys 218
3	65064	Alpha Lipoicacid	-5.465	-33.528	Lys 181, His 185, Lys 218, Thr 219
4	9064	Apigenin	-5.106	-41.939	Glu 186, His 195, Lys 218
5	5282032	Astaxanthine	-5.437	-30.551	Gly 143, Thr 182, Lys 218
6	5281727	Bacillus	-4.268	-33.13	Tyr 177(2), Lys 181(2), Thr 182
7	854026	Huperzine A	-4.209	-25.087	Leu 141, Tyr 177, Lys 218
8	5280445	Luteolin	-4.841	-29.859	Thr 182, Lys 218
9	896	Lycopene	-4.09	-35.931	Lys 181, Thr 182
10	4309557	Magnolol	-4.821	-27.639	Thr 182, Lys 218
			Drugs		
11	657298	Propylthiouracil	-4.07	-28.953	Lys 181, Glu 186, Lys 218

In the table below, Induced Fit Docking (IFD) is highlighted as an advanced computational technique used in molecular docking studies to account for the dynamic flexibility of both the ligand (small molecule compound) and the receptor (typically a protein) during the binding process. When conducting molecular docking of compounds against human Dopamine Beta Hydroxylase (DBH) using IFD, a wide range of plant-derived compounds were screened.

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 3: IFD results for Human dopamine beta-hydroxylase - 4ZEL

S.No	Compound Name	Compound Name	IFD score (Kcal/mol)	Prime Energy	Interaction Residues
			Compounds		
1	439224	Carnosine	-7.7	-3945.38	Tyr 177, Glu 186, His 195, Glu 199, Thr 219
2	65064	Alpha lipoicacid	-6.0	-3812.20	Lys 181, Glu 186, Lys 218
3	3152	donepezil	-5.0	-3827.20	Lys 181, His 185, Lys 218, Thr 219
			Drug		
4	657298	Propylthiouracil	-4.4	-3392.62	Lys 181, Glu 186, Lys 218

Fig.2. Complex structure of Human dopamine beta-hydroxylase with the compound Carnosine

Fig.3. Complex structure of Human dopamine beta-hydroxylase with the compound Alpha lipoicacid

Fig.4. Complex structure of Human dopamine beta-hydroxylase with the compound donepezil

Fig.5. Complex structure of Human dopamine beta-hydroxylase with the Drug Propylthiouracil

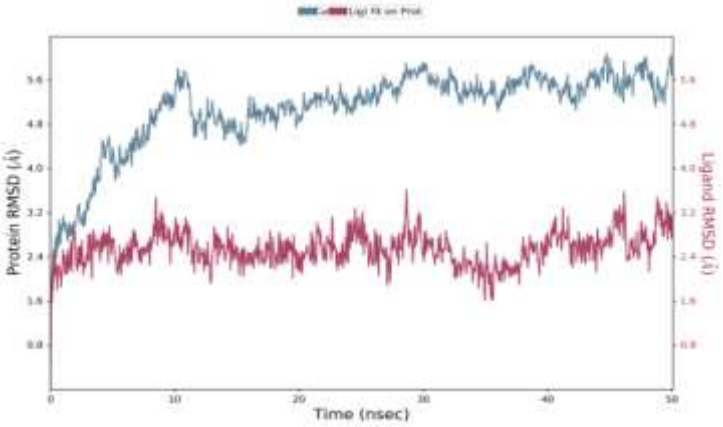

Fig.6. RMSD Graph complex structure of Human dopamine beta-hydroxylase with the compound Carnosine and Drug Propylthiouracil

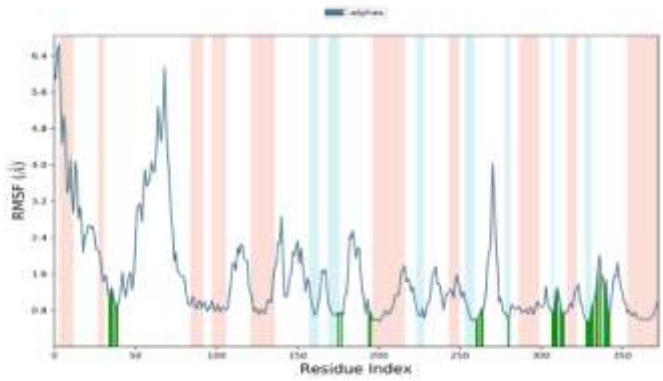

Fig.6. RMSD Fluctuation Graph of Human dopamine beta-hydroxylase with the compound Carnosine and Drug Propylthiouracil

GROMACS (GROningen Machine for Chemical Simulations) is a molecular dynamics package specifically designed for simulating proteins, lipids, and nucleic acids, particularly those with complex bonded interactions. The observation that both the protein-ligand complex and the protein-neuroprotective compound complex remained aligned and stable over a period of 10 to 50 nanoseconds indicates that these interactions are energetically favorable and robust over time. This stability is a critical factor, suggesting the potential effectiveness of these compounds.

5. Discussion

The graph analysis comparing how proteins interact with propylthiouracil (PTU) versus certain neuroprotective compounds reveals something significant. Both interactions, between the protein and PTU and between the protein and neuroprotective compounds, show stability within a critical timeframe of 10 to 50 nanoseconds. This stability suggests that these interactions are strong and potentially impactful within this short time frame. Given this finding, it prompts us to consider using neuroprotective compounds instead of PTU to treat thyroid disease. The idea is that certain neuroprotective compounds, which demonstrate stability and effectiveness similar to PTU in their interactions with proteins, could serve as viable alternatives for managing thyroid conditions.

The advantages of using neuroprotective compounds over PTU are quite compelling. Neuroprotective compounds are believed to have fewer side effects, making them potentially safer for patients. Additionally, they are more readily available and less expensive, making them a more practical choice for widespread use in healthcare settings. The fact that these compounds are naturally occurring adds to their appeal, aligning with the trend towards natural remedies in medicine.This Study suggests exploring neuroprotective compounds as a new approach for treating thyroid disease based on their observed stability and therapeutic potential in protein interactions. This could lead to improved treatment options and underscores the importance of leveraging scientific insights to drive innovative medical interventions (Kumar, 2006).

Use of Neuroprotective plant compounds presents a promising alternative for the treatment of thyroid disease, offering a natural and potentially more accessible option compared to conventional English medicines. The prohibitive cost and often significant side effects associated with mainstream pharmaceutical treatments underscore the urgent need for viable alternatives rooted in nature's own resources. Moreover, the neuroprotective qualities of these plant compounds highlight their potential to support not only thyroid health but also overall neurological wellness, offering a multifaceted approach to health management (Alevizaki *et al*., 2006). Embracing these natural remedies not only addresses the immediate challenges posed by thyroid disease but also embodies a proactive stance towards cultivating a healthier, more resilient population. As we navigate towards a future of personalized medicine, the integration of plant-based compounds into mainstream therapeutic approaches holds great promise. Through continued research and innovation in this field, we can optimize treatments for thyroid disorders and pave the way for a more sustainable and inclusive healthcare landscape. 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 *et al*., 2010)

6. Conclusion

Carnosine, Alpha lipoicacid, donepezil are suggested to be the best compounds which can be evaluated as Human dopamine beta-hydroxylase. The neuroprotective compound Carnosine exhibited very good docking results with the selected Human dopamine beta-hydroxylase 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. Ongoing research and innovation in this field will enhance treatment options for thyroid disorders and contribute to a more sustainable and inclusive healthcare landscape.

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