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Protein-protein Interaction Studies between TSHR Protein in Human and Photosystem II Protein D1 of *Ulva fasciata* using *In silico* Protocols

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

The most prevalent mutation in Hypothyroid Protein, TSHR impacts the course and prognosis of Hypothyroidism in human. We employ 3D *in silico* drug docking techniques to make the possible mutant TSHR interact with Photosystem II Protein D1 of *Ulva fasciata*. To carry out drug docking techniques, the translated amino acid sequence and three-dimensional chemical compound were obtained from the NCBI database. The use of sophisticated 3D molecular visualization tools was employed in post-docking experiments. The use of sophisticated 3D molecular visualization tools was employed in post-docking experiments. The docking study results unequivocally show that Photosystem II Protein D1 directly suppresses amino acid mutational sites. TSHR and Photosystem II Protein D1's electrostatic force is depicted in a three-dimensional manner using notions from molecular dynamics techniques. In the end, we determined that Photosystem II Protein D1, a

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medicinal component of *Ulva fasciata*, helps in treating hypothyroidism. Hypothyroidism, being one of the major Endocrinological disorders, our research work helps to prove that the sea weed, *Ulva fasciata* can effectively act a novel therapeutic agent for treating this disorder.

Keywords: TSHR; Ulva fasciata; protein docking.

1. INTRODUCTION

A diverse range of illnesses, including hypothyroidism, hyperthyroidism, subclinical hypothyroidism (SH), subclinical hyperthyroidism, structural abnormalities, and malignancy, are collectively referred to as thyroid disorders (TD) [1]. Globally, the incidence of TD and associated impact have increased dramatically due to rising life expectancy, particularly in older persons. Different regions have different incidence and frequency of TD. However, some TD, like hypothyroidism, are thought to impact 5% of people worldwide [2], whereas hyperthyroidism affects 0.8% and 1.3% of people in Europe and the USA, respectively. Moreover, the age-standardized thyroid carcinoma (TC) rates for men and women worldwide are 3.1 and 10.1 per 100,000, respectively [3].

In 2012, the Keralan government launched the NBS for CH in a restricted way, encompassing 40% of government hospitals. By 2018, it had been expanded to 100% of government hospitals, covering 25% of all births in Kerala annually [4]. The remaining 75% of births take place in private hospitals, many of which test every newborn before releasing them at the point of care for thyroid function. The authors have observed a discernible improvement in the time to diagnosing CH following the implementation of partial NBS in 2012.Levothyroxine {LT4} is often used as a replacement for thyroid hormone in patients with hypothyroidism, or a combination of levothyroxine preparations is used instead [5]. Even though the primary hypothyroidism treatment plan has been one of the greatest "success stories" in medicine, a sizable percentage of patients who receive levothyroxine still experience ongoing side effects like fatigue, cognitive decline, musculoskeletal pain, weight gain, constipation, and lack of energy even after meeting their biochemical therapy targets. The unmet demands of patients with hypothyroidism may also be explained by the fact that the therapeutic targets of TSH {≤5 mIU/l} itself have been linked to numerous pathological problems, including lower cognitive function, anxiety, depression, and worse quality of life scores [6]. The entire *In silico* research study focuses on how the seaweed protein inhibits TSHR receptor, the protein responsible for human hypothyroidism, at 3D molecular level.

2. METHODOLOGY

2.1 Protein Selection

For the purpose of conducting molecular drug docking study, the data was used from the NCBI Genpept database (YP_009220463.1 photosystem II protein D1 (*Ulva fasciata*) and (AAI20973.1 TSHR protein (Human). Three-Dimensional structures were predicted using Discovery Studio, a potent molecular visualization program.

2.2 Protein Docking

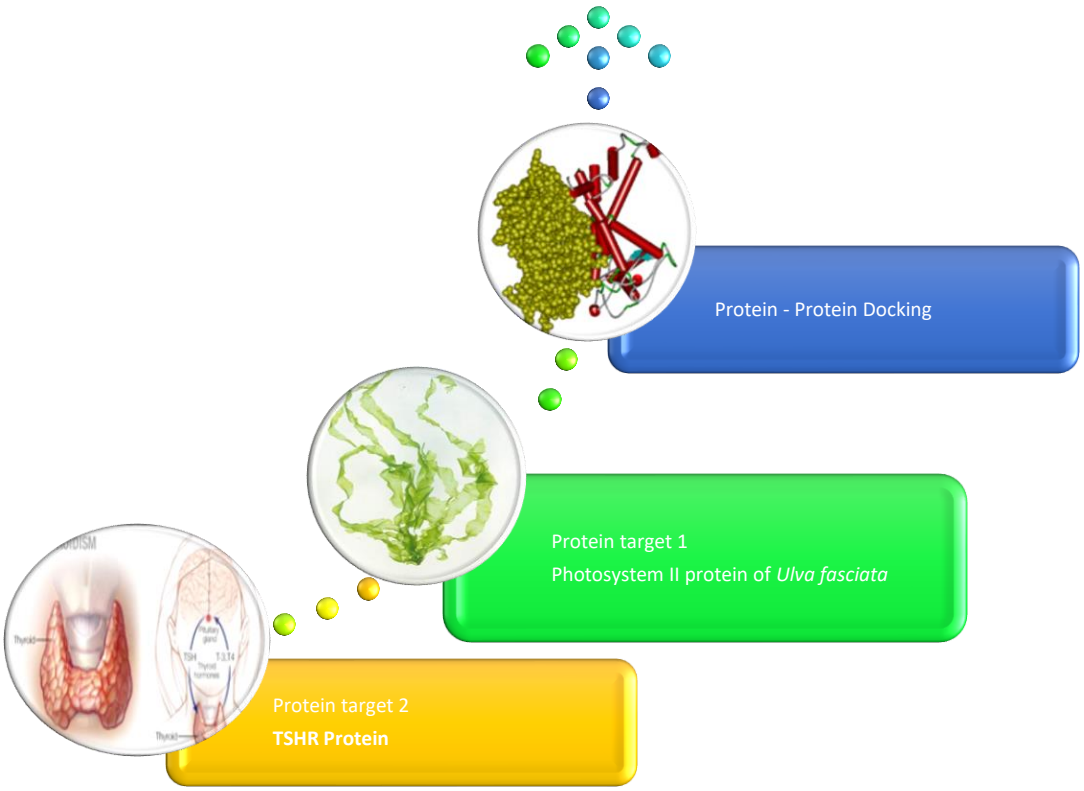
Molecular drug docking research have made use of HDOCK, an automated molecular drug docking service (http://hdock.phys.hust.edu.cn/) [7]. The molecular affinities of TSHR protein and photosystem II protein D1 (Ulva fasciata) in human hypothyroidism were determined by means of a 3D molecular dynamics technique.

2.3 H Bond Interactions

Post-docking experiments were carried out using the Discovery Studio program. A detailed analysis of the three-dimensional image based on the docking score (3D Electrostatic interactions) was conducted using the molecular dynamics concept.

3. RESULTS AND DISCUSSION

The amino acid sequences corresponding to the gene-coded proteins of photosystem II protein D1 (*Ulva fasciata*) and TSHR are 353aa and 231 aa, respectively (Figs. 1 and 2). In our research work, we use the potential inhibitor derived from algae (*Ulva fasciata*).



Picture 1. Diagrammatic depictions of the *in silico* research project overview

Macroscopic, multicellular, eukaryotic photosynthetic organisms that are part of the Plantae kingdom are referred to as marine macroalgae, or seaweed. These marine plants that live in salt can be found on the seabed or solid rock strata beneath it, as well as on rock surfaces, corals, shells, pebbles, and other plants. In areas of the water where light is most abundant, such as the tidal and subtidal zones, marine algae typically flourish. They can easily adjust to physiological changes by creating chemicals that can tolerate stress, which allows them to survive in extreme environments such as heat, cold, UV radiation, salinity, and desiccation [8]. They generate a wide range of primary and secondary metabolites as a result of their existence. Numerous physiologically active substances with a variety of medicinal uses can be found in marine algae [9].

The complex form of the TSHR protein retrieved via the H-Dock server and photosystem II protein D1 have a 3D docking score of -378.55 *kcal/mol*, (Fig. 3) as illustrated in Fig. 1. Using Discovery Studio software, the H-bond interactions between photosystem II protein D1 and the TSHR protein are displayed in detail (Figs. 4, 5, 6, 7, 8). It is clear from this image that the TSHR protein and the photosystem II protein D1 protein structure have interacted non-covalently. Therefore, it may be said that, as demonstrated by earlier research, the TSHR protein will be downregulated. Our docking studies are consistent with a number of prior investigations [10-16].

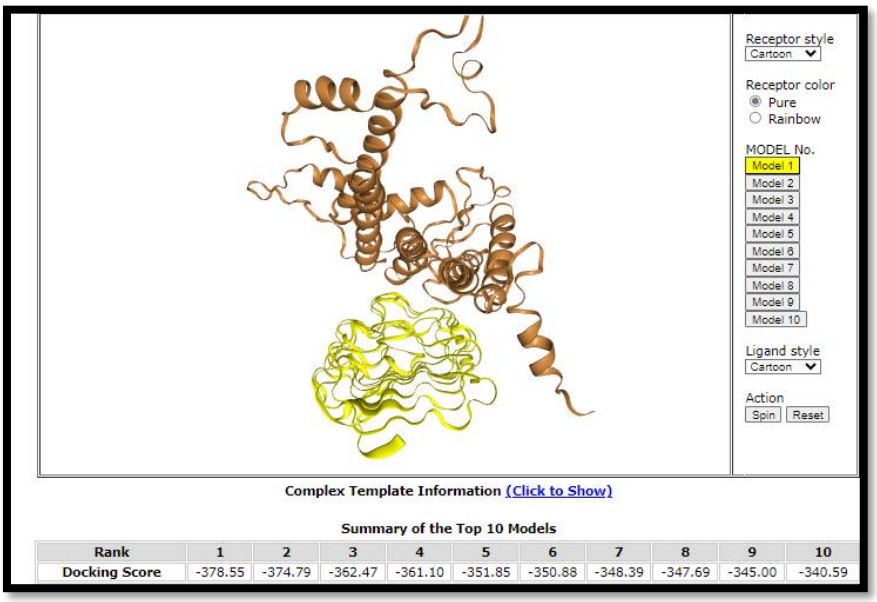
Our retrieved protein's functional domain area is the *Ulva fasciata* 213 ALA (208-213) N-myristoylation site (PS00008). Our research demonstrates that gentamicin, an antibiotic, interacts directly with the domain areas. Our study unequivocally demonstrated that the following amino acids are present at the drug-protein binding region: GLN: 113, HIS: 92, PHE: 119, ILE: 119, ALA: 213, THR: 227, SER: 232.

>YP_009220463.1 photosystem II protein D1 (chloroplast) [Ulva fasciata]
MTAILERREASSLWARFCEWVTSTENRLYVGWFGVIMIPTLLTAISVFIIAFVAAPPVDIDGIREPVSGS
LLYGNNIISGAVVPTSNAIGLHFYPIWEAASVDEWLYNGGPYQLIVCHFFLGVCAYMGREWELSFRLGMR
PWIAVAYSAPVAAASAVFIVYPIGQGSFSDGMPLGISGTFNFMIVFQAEHNILMHPFHMLGVAGVFGGSL
FSAMHGSLVTSSLIRETTENESANEGYKFGQEEETYNIVAAHGYFGRLIFQYASFNNSRSLHFFLAAWPV
VGIWFTALGISTMAFNLNGFNFNQSIVDSQGRVLNSWADIINRANLGMEVMHERNAHNFPLDLASVEAPS
ING

Fig. 1. Amino acid sequence of the sea weed, *Ulva fasciata*

>AAI20973.1 TSHR protein [Homo sapiens]
MRPADLLQLVLLLDLPRDLGGMGCSSPPCECHQEEDFRVTCKDIQRIPSLPPSTQTLKLIETHLRTIPSH
AFSNLPNISRIYVSIDVTLQQLESHSFYNLSKVTHIEIRNTRNLTYIDPDALKELPLLKFLGIFNTGLKM
FPDLTKVYSTDIFFILEITDNPYMTSIPVNAFQGLCNETLTLKLYNNGFTSVQGYAFNGTKLDAVYLNKN
KYLTVIDKDAFGGVYSGPSLL

Fig. 2. Amino acid sequence of human TSHR protein



Rank	1	2	3	4	5	6	7	8	9	10
Docking Score	-378.55	-374.79	-362.47	-361.10	-351.85	-350.88	-348.39	-347.69	-345.00	-340.59

Fig. 3. Complex form of human TSHR protein and photosystem II protein of *Ulva fasciata* viewed using H-Dock server with respective binding scores

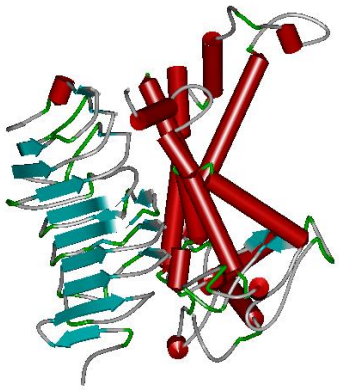


Fig. 4. 3D Complex form of human TSHR protein and photosystem II protein of *Ulva fasciata* viewed using discovery studio software

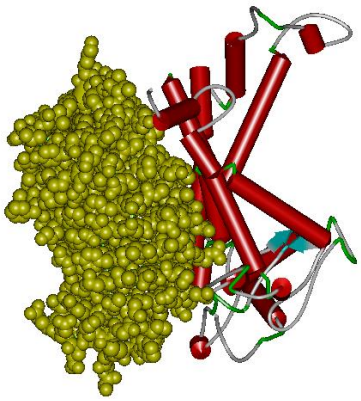


Fig. 5. Complex form of human TSHR protein and Photosystem II protein of *Ulva fasciata* viewed using Discovery Studio Software
Yellow coloured structure represents the TSHR protein

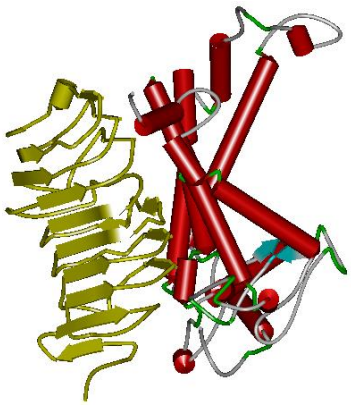


Fig. 6. 3D Complex form of human TSHR protein and Photosystem II protein of *Ulva fasciata* viewed using Discovery Studio software (Binding Interaction Mode).

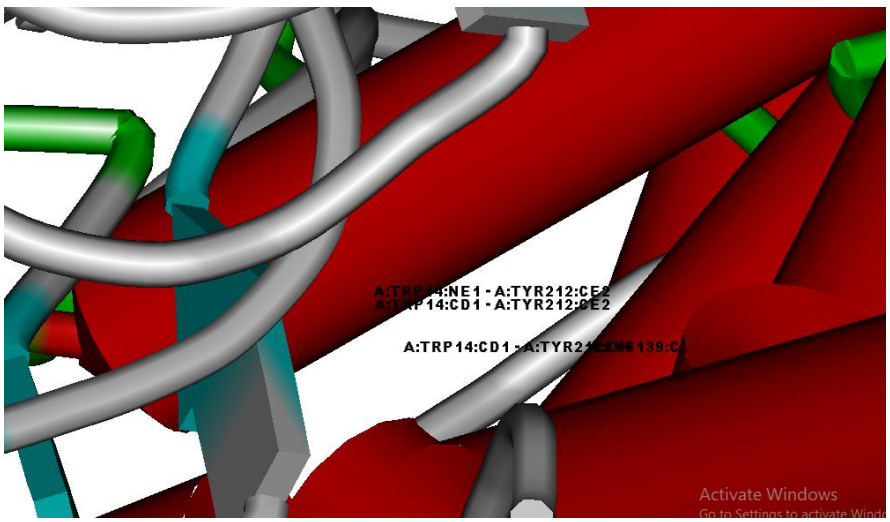


Fig. 7. 3D Complex form of human TSHR protein and Photosystem II protein of *Ulva fasciata* viewed using Discovery Studio software (Binding Interaction Mode with respective amino acid labels/positions)

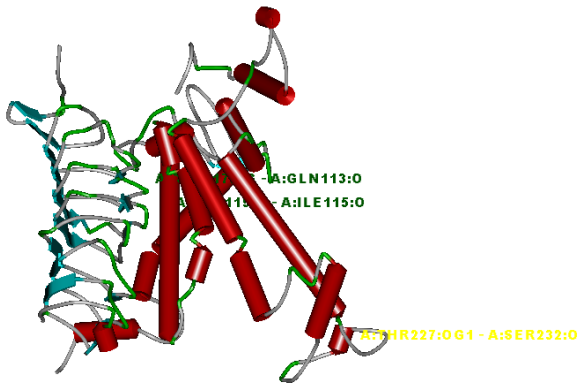


Fig. 8. 3D Complex form of human TSHR protein and Photosystem II protein of *Ulva fasciata* viewed using Discovery Studio software (Amino acids interacting at Domain and Motif)

4. CONCLUSION

Our study unequivocally demonstrates the interaction between the seaweed protein and the human hypothyroidism protein, TSHR. The *Ulva fasciata* Photosystem II protein binds efficiently to the TSHR protein's functional domain area, as demonstrated by our clear docking data. The H-bond interaction is clearly defined by the binding relationship between Photosystem II protein and TSHR protein, as assessed by docking scores. Therefore, we conclude that *Ulva fasciata* seaweed protein functions as a possible Endocrinological medication that lessens the symptoms of hypothyroidism in humans. Our *in silico* study clearly shows that the human TSHR protein may be pharmacologically affected by the Photosystem II protein.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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