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In-Silico Investigation of Plant-Derived Natural Allosteric Compounds Towards Enhanced Drug-Protein Interaction of MOA Protein Complex in Depression Based on Molecular Docking and Molecular Dynamic Simulation Approaches

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Abstract

Allostery is an effective method of controlling the function of biological macromolecules and currently gaining more attention in the realm of drug development due to the unique characteristics of allosteric modulators, such as good selectivity and low toxicity. These qualities are critical for both the creation of the allosteric concept and the evaluation of allosteric interactions. Primarily, allosteric modulators are responsible for boosting efficacy and reducing the drug's catastrophic effects. Since the chemical compounds have always proven to cause side effects in the body. Hence, the discovery of an alternative natural allosteric compound instead of chemical allosteric compounds for enhancement of drug efficacy and regulating drug dosage is the major challenge in modern drug discovery, especially for diseases *i.e.,* cancer, Parkinson's, mental disorder, etc. where the long-term treatments are recommended. In this research paper *in-silico* based comparative interaction/molecular docking and dynamics study of FDA-approved Antidepressant drugs i.e., isocarboxazid Phenelzine, Selegiline, Tranylcypromine, etc with potential drug target protein [PDB ID: 2Z5X] MAO enzymes for major depressive disorder have been conducted. Various drug compounds complexed with protein have been analyzed by performing molecular docking. The site-directed docking /interaction energy for the Isocarboxazid drug complexed with protein target was performed with a docking score -8.6 kcal/mol using Autodockvina. The chemical allosteric compound (ID ASD01720151,) was retrieved from the Allosteric database (ASD) through virtual screening and docked at the predicted allosteric site by PASSER computational tool where the best docking/ interaction energy was found -11.8 kcal/mol. The final site-directed docking was performed on the complex (target protein-natural allosteric compound) with Isocarboxazid drug and the interaction energy was found better i.e., -8.7 kcal/mol. Finally, the simulation performed which reveals the stability of the final docked structure and supports the usage of the natural compound as an alternative allosteric compound for enhancement of drug binding. The work can be extended with wet lab-based experimentation for better understanding and validation

Keywords: Allosteric compound, Molecular docking, Homaline, Major Depressive Disorder, Molecular dynamic simulations

Introduction

Evolution has endowed organisms with intricate molecular mechanism networks that enable very effective reactions to environmental changes over billions of years. The majority of these processes rely on structure-switching biomolecules that change conformation in response to the stimulus.

Allostery is one of the most significant naturally occurring ways in which a stimulus causes the target biomolecule's structural alterations and functional modulation (1). Noncovalent events such as ion, small molecule, ribonucleic acid (RNA), deoxyribonucleic acid (DNA), or protein binding (2, 3, 4); covalent events such as phosphorylation, glycation,Rossetti, Marianna, and Alessandro Porchetta. "Allosterically regulated DNA-based switches: From design to bioanalytical applications." Analyticachimicaacta 1012 (2018): 30-41. nitration (5, 6, 7, 8) and light absorption (9) cause it. The allosteric disruption (such as the binding of an effector) usually happens at a position distant from the target biomolecule's active site (10). Allostery occurs in all dynamic proteins, multimolecular assemblies, RNA and DNA polymers, and multimolecular assemblies (11). Allosteric regulation is a common method in nature for controlling cellular activities by adjusting biomolecule affinities. To govern their activity, several important proteins use allosteric regulation. The negative allosteric regulation of hemoglobin by 2,3-bisphosphoglycerate (12) is one of the best examples. Allosteric modulators might be a new kind of medicine that is both effective and safe. The capacity of an allosteric modulator to modify the substrate/receptor affinity in a very predictable manner is one of its key advantages. As a result, large dosages of allosteric modulators can be given with minimal risk of harm dependent on the target (13). Furthermore, because the allosteric site is far from the receptor/substrate contact, allosteric modulation has no effect on the biomolecule's substrate specificity. Several effective allosteric modulators have been authorized as marketed medications by the US Food and Drug Administration (FDA) namely, Nevirapine, Maraviroc, Benzodiazepines, Cinacalcet, and more. These allosteric medications interact with important proteins such as ion channels, enzymes, and G protein-coupled receptors, among others (GPCRs) (13). Isocarboxazid is an antidepressant that is a non-selective and irreversible monoamine oxidase inhibitor known as MAOI, belonging to the hydrazine family (14). It is one of just three traditional MAOIs still accessible for therapeutic use in the treatment of depressive diseases in the United States, along with tranylcypromine and phenelzine, despite the fact that it is not as widely used as the others (15, 16). Isocarboxazidis mostly utilized to treat depression and anxiety. It is also being studied for the treatment of Parkinson's disease (17), schizophrenia, and other dementia-related conditions (18). The monoamine neurotransmitters norepinephrine, serotonin, and dopamine are elevated in the brain by isocarboxazid and other MAOIs (19). Some of the major pathways of MDD that are targeted by isocarboxazid are the Estrogen signaling pathway, Tryptophan metabolism, Folate biosynthesis, Metabolic pathways, and Serotonergic synapse (http://www.genome.ad.jp/kegg/). The (MAO) Monoamine oxidase enzymes regulate the catabolism of the biogenic trace amines and monoamine neurotransmitters as well as human behavior. The processes that control MAO, on the other hand, remain unknown. Many transcription factor proteins have been postulated to influence MAO gene transcription, although the evidence for these ideas is unclear (20). The (MAO-A, -B) Monoamine oxidases mediate and modify intracellular signal pathways that determine whether neuronal cells live or die. MAO-A has been linked to the formation of synaptic activity, neuronal architecture, and the emergence of mental diseases such as depression and antisocial-aggressive behavioral problems [21]. MAO-B is a protein that creates hydrogen peroxide and is involved in neuronal loss in neurodegenerative illnesses including Parkinson's and Alzheimer's (22). As with growing cases of depression-associated disorders, the need for efficient antidepressant drugs is increasing, and the number of young people diagnosed with depression has increased for unknown causes at this time. While environmental and genetic variables also play a significant part. Although there are some FDA-approved drugs in the market being used for treating patients with such conditions, these drugs come with devastating side effects such as hair loss, anemia, skin rashes, nausea, fatigue,

weakness, and diarrhea (23). Hence, there is an urgent need for a solution to overcome this problem and make the drug more efficient with fewer side effects.

Materials and Methods

Preparation of protein structure

The crystal structure of the human monoamine oxidase A with Harmine(2Z5X) was downloaded from the protein data bank www.rcsb.org (25). The total structure weight was 59.97 kDa while the total atom present was 4397.Complexes that were bound with protein molecules were removed and all the preprocessing of the protein structure was performed using Autodock software (version 4.2.6). Polar hydrogens were added, with no bond order, and gasteiger charges were added. After the preprocessing step, the appropriate formatting of the protein structure was formed for further analysis via autodockvina version 1.2.0 (26). Autodockvina is a command-line-based tool for performing molecular docking.

Preparation of ligand and allosteric structures

Preparation of ligand

The structure of different ligands was downloaded, after rigorous literature mining through Pubmed(https://pubmed.ncbi.nlm.nih.gov/30165565/). There were 4 ligands that were selected for further studies namely Isocarboxazid, Phenelzine, Selegiline, and Tranylcypromine.

Preparation of allosteric compound

The allosteric activators of oxidoreductase were downloaded from the allosteric database (22). ASD is a central repository that has offered complete information on allosteric control and regulation, which is available online at ASD database(24, 27). There were a total of 103 oxidoreductases available. Conversion of the allosteric compounds into suitable format was generated using open babel software (28)

Preparation of natural compounds

The activated natural compounds were taken from the Lotus natural database(29) with the Tanimoto similarity threshold score of 75. While the conversion of suitable format was generated using openbabel(28).

Identification of active site on protein

The active site prediction on the target protein was done by the castp server (30). CASTp is an online server-based prediction tool that provides resources for locating, delineating, and measuring concave surface regions on the 3d structure of the protein.

Identification of allosteric site on protein

The allosteric site was predicted on the target protein via passerCLI(31) which is a command-line interface-based package available on GitHub. It is a package based on the ensemble learning technique, consisting of a convolutional neural network and extreme gradient boosting. the algorithm used in identifying the allosteric site is FPocket algorithm

Molecular docking and its analysis

Molecular docking of protein-ligand was performed using the software autodock with center coordinate (X,Y,Z [A^0] = 38.8781, 26.2673, -19.7061) and center coordinates (31.3540, 35.3858, 34.5375). While that of the docking between protein and allosteric compound are also same(X,Y,Z [A^0]= 38.8781, 26.2673, -19.7061) and center coordinates (31.3540, 35.3858, 34.5375) with exhaustiveness 8.0 as both the active site and allosteric site lies nearby according to the prediction software. For better visualization of the docked structure PyMolsoftware(32) was used. Whereas, the two-dimensional interactions between both the docked compounds were identified using ligplot + software(33).

Admet property

ADMET stands for absorption, distribution, metabolism, excretion, and toxicity. These properties are used to identify

the likeliness of a drug. These properties are based on its pharmacokinetics calculations which act as a key feature to identify the activity of a drug inside the body. By the identification of these properties, one is able to find out the undesirable toxicity and features of a compound. The program ADMETSAR2.0 was used to do the ADMET analysis (34)

Pass analysis

The program PASS predicts the action of several ligands, allowing us to find an antiviral activity (35). PASS is a software that uses a computational technique to predict different sorts of physiological responses for distinct phytoconstituent molecules. It provides findings based on likely activity and probable inactivity, i.e. (Pa) and (Pa) (Pi). Those compounds with a higher Pa than Pi are the ones we can address for future medicinal uses.

Molecular dynamic simulation

For the molecular dynamic simulation iMODSserver(36) which is available online was explored.This server is used for the predictions of protein flexibility. The web server is comprised of a number of ASP, Java, PHP, JavaScript and Perl components. It is a powerful molecular dynamics modeling tool that could be used to examine the structural dynamics of protein complexes quickly and easily. It predicts deformability, eigenvalues, and other parameters. The ability of a complex or a protein to deform at each of its amino acid residues determines the deformability. The eigenvalue is proportional to the amount of energy required to distort (deform) a certain structure, and the lower the eigenvalue, the easier the complex is to deform. Furthermore, the eigenvalue also indicates the protein complex's motion stiffness.

Results and Discusion

Identification of the allosteric site

The allosteric sites was identified using Passer packages which show various poses and sites which can be an allosteric site of the protein. On the basis of the best pocket size and score, pocket 1 has been selected with the best pocket score of 0.866.

Identification of the active site

The active site of the protein was identified using the online tool CastP. The id of the protein structure was provided in the server and the server itself provides the best active site sites for further analysis.

Molecular docking and analysis of target prediction

The docking of the protein and ligand was performed by the software Autodock whereas virtual screening of the molecules was performed using the software pyrx.

Identification of suitable allosteric compound: -

The compounds that were downloaded from the allosteric database were thoroughly screened using Pyrx software and out of 103 downloaded activators the best allosteric activator identified was an isocitrate dehydrogenase with an ASD id ASD01720151, having the best affinity docking score -11.8.

Identification of suitable Ligand: - After performing molecular docking we were able to find that out of Isocarboxazid, Phenelzine, Selegiline, and Tranylcypromine, the ligand Isocarboxazid has the best docking score (-8.6 K cal/mol) and was suitable for further analysis as shown in table 1.

Table1. The docking score between different ligand compounds with Protein structure

S.no.	Pro-tein	Ligand	Pub-chem id	Docking score
1	2Z5X	Isocarbox-azid	3759	-8.6
2	2Z5X	Phenelzine	3675	-6.7
3	2Z5X	Selegiline	26757	-7.6
4	2Z5X	Tranylcy-promine	19493	-6.3

Identification of the natural compound

The natural compound was taken from the lotus database whereas the similarities score i.e., the Tanimoto similarity was set at 75%, there were 12 hits results were identified as having Tanimoto similarity of more than 75% on those 12 results a virtual screening have been performed and out of which the structure homaline, having lotus id LTS0214462 shows the best Docking score -10.1 and was taken for further experimentation.

Process of the experimentation

The Identification of a natural compound as a substitute for an allosteric compound was performed using molecular docking. In the initial step, the molecular docking was performed between chemical allosteric compounds and protein molecules, by using the virtual screening software Pyrx. The docking score obtained was -11.8kcal/mol of the allosteric compound with an id ASD01720151. Again molecular docking has been performed with the protein structure (2z5x) and different ligands in which the ligand Isocarboxazid shows the highest affinity with a score -8.6kcal/mol.

After performing docking between both the molecules a complex has been formed between protein and allosteric compound. This complex structure has been used for further experimentation, a molecular docking has been performed between complex and ligand isocarboxazid with a docking score of -9.0. From this score, we can identify that the allosteric compound performs its activity, and due to this better Docking score was obtained. But as the allosteric compound is a chemical compound, we have to find another compound that can be a good substitute for the chemical compound and have less toxicity.

So, for the identification of the natural compound, through literature mining and from various databases we were able to find out the best Tonimoto structure has the best structural similarity with the chemical compound. Again, performing molecular Docking with the same environment and coordinate file we were able to find that the Docking score between the protein and natural allosteric compound was -10.1. as we have earlier found out the Docking score between the protein and ligand was -8.6. Now again we made a complex structure between a protein and natural allosteric compound and performed docking between the complex structure and the ligand, the docking score was -8.7 kcal/mol as detailed in and table no.2,3. The pictorial representation of the docking is shown in fig1, fig 2 and interaction was shown in fig 3

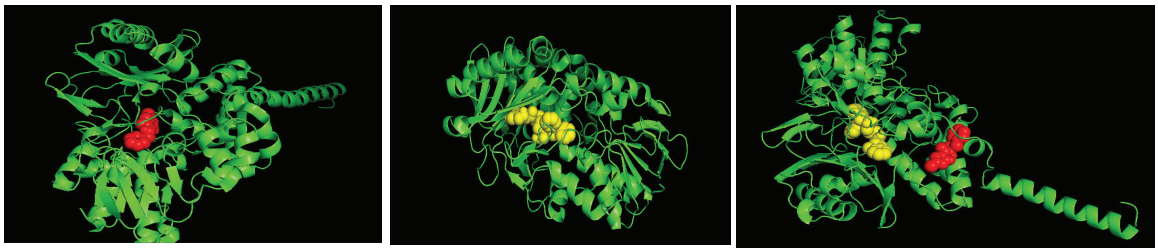
Table2: Docking between protein and ligands(chemical allosteric)

Protein	Ligand	Energy score	Method
2z5x	Isocarboxazid	-8.6 kcal/mol	Autodockvina
2z5x	ASD01720151	-11.8 kcal/mol	Autodockvina
Complex (2z5x+ ASD01720151)	Isocarboxazid	-9.0 kcal/mol	Autodockvina

Table3: Docking between protein and ligand(natural allosteric)

Protein	Ligand	Energy score	Method
2z5x	Isocarboxazid	-8.6 kcal/mol	Autodockvina
2z5x	Homaline	-10.1 kcal/mol	Autodockvina
Complex (2z5x+Homaline)	Isocarboxazid	-8.7 kcal/mol	Autodockvina

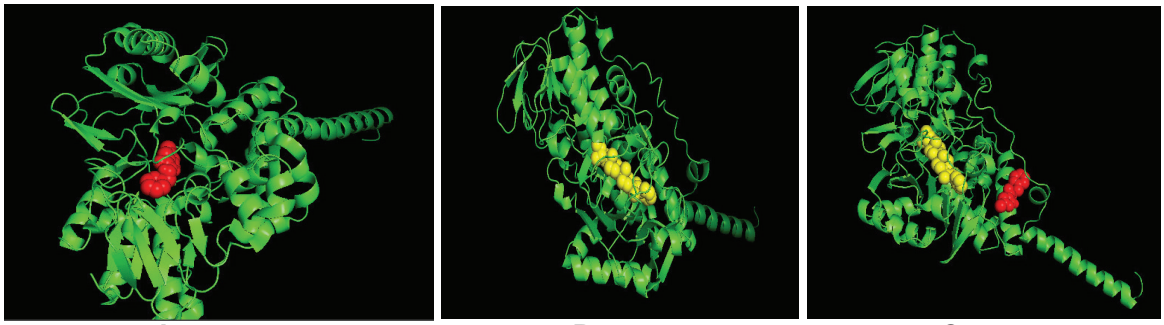
1.Below are the images of the docked compounds (chemical allosteric)



A B C

Fig1. illustrations of these images are as follows- (A) image shows the docking between the drug and the target protein, where red-colored molecule depicts the and green depicts the. (B) image shows the docking of the allosteric compound on the identified allosteric site of the target protein (C) Depicts the docking of the complex having the chemical allosteric compound and the target protein with the ligand molecule, where red-colored molecule depicts the and where the red-colored molecule depicts the and green depicts the, and the yellow, green depicts the, and the yellow.

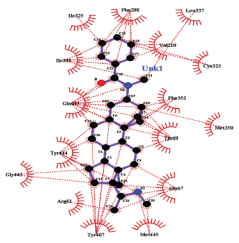
1.Below are the images of the docked compounds (chemical allosteric)



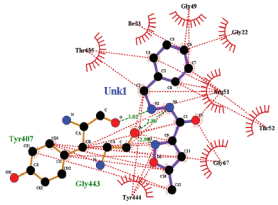
A B C

Fig2. illustrations of these images are as follows- (A) image shows the docking between the drug (red color) and the target protein (green color). (B)docking of the natural allosteric compound (yellow color) on the allosteric site of the target protein (green color). (c)Depicts the docking of the complex having the natural allosteric compound (yellow) and the target protein(green) with the ligand molecule (red color).

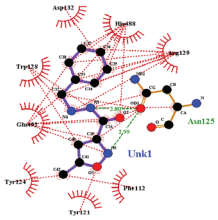
2D interaction between the docked protein, ligand, and natural allosteric compound



Protein-ligand interaction(allosteric)



Protein-ligand interaction(active compound)



Protein+allosteric+ligand interaction

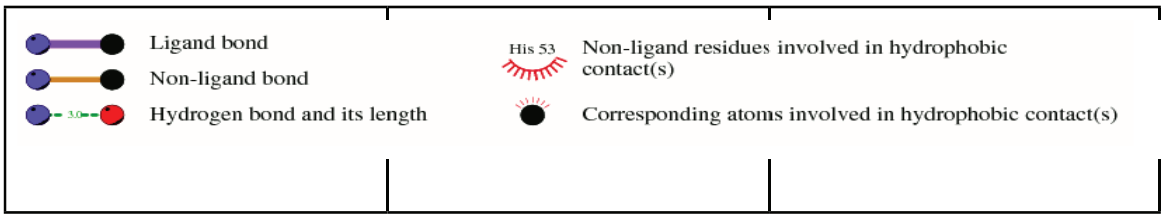


Fig 3. Two-dimensional representation of H-bonds and hydrophobic interactions between protein and allosteric compound, protein and ligand, protein and allosteric complex+ligand. Ligands are colored and represented in Purple color, H bonds are shown in green dotted lines, red stellations show hydrophobic interactions, and bonds of proteins are represented in brown color.

ADMET Properties of allosteric compound:-

ADMET properties are required to identify how a compound works as a ligand. After performing ADMET analysis the natural compound compounds follow the Lipinski rule and show good admit property but natural compounds showed better results and were also non-toxic in nature, also it does not penetrate the Blood-Brain Barrier as shown in table 4.

Table 4. Different ADMET properties of allosteric compounds where HIA stands for human intestinal absorption, BBB stands for Blood-Brain Barrier.

S.no.	Properties	Allosteric compound	Natural compound
1 Molecular weight, 484.280			450.360
2	Lipinski Rule	Accepted	Accepted
3	Caco-2 Permeability	-5.674	-4.695
4	BBB Penetration	Penetrate	Not penetrate
5	AMES Toxicity	Toxic	Non-toxic
6	HIA (Human intestinal absorption)	Low absorption	High absorption
7	Acute Toxicity Rule	0 alert	0 alert

Prediction of the antidepressant activity by Pass analysis

PASS is defined as Prediction of Activity Spectra for Substances. PASS analysis can be helpful In determining biologically active spectra of phyto-constituents. Here Pa is the probability of a compound to be active and shows chances of being an active compound whereas Pi represents the probability of a compound to be inactive which estimates that the compound belongs to the sub-class of the inactive compound. Here various activities have been shown in which PASS prediction of the natural compound shows a good response as shown in table 5

Table 5: Table shows the values of Pa, Pi with activities of compound

Pa	Pi	Activity
0,319	0,008	MAO inhibitor
0,106	0,018	MAO B inhibitor
0,071	0,044	MAO A inhibitor
0,591	0,127	Phobic disorders treatment
0,554	0,021	Neurodegenerative diseases treatment
0,275	0,179	Dementia treatment

Molecular dynamic simulation

The results of Molecular Dynamics Simulation are shown in Figure 4a and 4b. The

deformability graph indicates that the peaks in the graphs correlate to deformable regions in the protein (Figure 4a). In Figure 4b, the eigenvalue of the complex is shown. The eigenvalue of the docked complex was predicted to be 1.038932e-05.

According to the molecular dynamics simulation study of the docked complex, the complex Figure 4a has a lot of deformability potential as well as has a low eigenvalue of 1.038932e-05, which illustrates that the lower the eigenvalue, the easier the deformation of the complex would be Figure 4b, it also depicts the protein complex's motion stiffness.

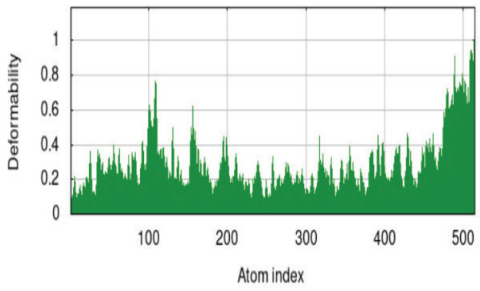


Figure 4a. Result of molecular dynamics simulation shows the graph of deformability

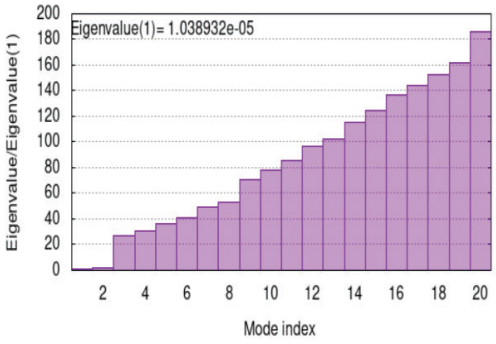


Figure 4b. Result of molecular dynamics simulation shows the graph of eigenvalue

Mental disorders are increasing rapidly and everyone in the entire world is suffering from one kind of mental disorder. There are many of the FDA approved drugs are available having good responses against mental disorders but are time-consuming and have low response rates for increasing the response rate allosteric compounds can be a good option, in this study we are able to identify the natural compound which can be used as an alternative of the chemical allosteric compound having an effect on the activity of the drug. In this approach, we have used different in silico methods like molecular docking, molecular simulation, etc., and on the basis of which the natural allosteric compounds were identified. The FDA-approved drug that has been used for this study is isocarboxazid while the chemical allosteric compound identified after performing virtual screening was an isocitrate dehydrogenase. This compound is further used to identify the natural compound as an alternative to the chemical allosteric compounds. With the growing scenario, the urgent need to replace chemical compounds with natural ones is increasing at a faster pace. Thus, in our study, we investigated an alternative of the chemical allosteric compound with a natural allosteric modulator**.**

Our study demonstrates that the natural allosteric compound could play a crucial role in increasing its efficacy and effectiveness.

Future direction or limitation

Biological screening of the natural allosteric compound is a key aspect of identifying and increasing the effect of the drug(37). The Monoamine oxidase(MAO) enzyme is a prevalent target for many depressive disorders. As this enzyme somehow plays a major role in various depressive disorders and neurodegenerative disorders. Potential therapeutics are required to suppress this enzyme activity. Isocarboxazid is such a drug which is an antidepressant(monoamine oxidase inhibitor), the activity of this drug can be enhanced by using an allosteric compound but outcomes and side effects of the allosteric could be a problem, To overcome the negative effects of the allosteric compound natural

compound can be an alternate. As the activity of the drug can be enhanced it could also be used in treating different diseases like parkinson's (38), and bipolar disorder(39) in which MAO is involved . one of the limitations of using the drug and allosteric compound is the amount of drug provided and its response rate. Wet lab-based experimentation would be required for proper validation.

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Conflict of Interest: Authors declares no conflict of Interest

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