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Research Article

COMPUTATIONAL ANALYSIS OF NARINGENIN AS AN ANTIDEPRESSANT

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ABSTRACT

Objective: This works aims at analyzing the potential of Naringenin (NAR) as an antidepressant drug by computational methods.

Methods: The database Protein Data Bank and PubChem were used to retrieve the three-dimensional structures of the protein and the compound. The software Discovery Studio was used to study the interactions between the protein and the ligand.

Results: NAR, one of the flavanone, which has strong anti-inflammatory and antioxidant activities, is studied for its antidepressant and neuroprotective effects through *in silico* approach. Interaction study and pharmacophore analysis using Discovery Studio show that the molecule NAR interacts with the protein at different sites. The interaction has a maximum dock score at position B.

Conclusion: The compound NAR shows to have antidepressant quality from the computational study. The docking studies show promising result that NAR can be explored further as a potential drug.

Keywords: Naringenin, Antidepression, Neuroprotection, Pharmacophore, Docking.

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INTRODUCTION

Depression is one of the most prevalent mental ailment defined by pathological variation in mood. The general symptoms exhibited are loss of interest in life, lack of concentration, confidence, self-esteem, appetite, and disturbed sleep. According to the World Health Organization, by 2020, around 350 million individuals would suffer from depression and would be the second most dynamic reason for drawback globally [1]. The etiology of depression is multifactorial ranging from genetic and environmental components to biochemical and endocrine factors such as hypothyroidism and Cushing's syndrome. Biochemical manifestation of depression occurs when there is a decrease in brain biogenic amines which act as neurotransmitter this may be due to excess secretion of cortisol or particularly low concentration of brain-derived neurotrophic factor (BDNF) [2]. In addition, it may be caused due to the impairment of noradrenaline (NE), serotonin (5-HT), and dopamine (DA) signaling [3].

Recently, various studies have revealed dietary flavanones exhibit antidepressant and neuroprotective activity. Citrus fruits such as oranges, mandarins, grapefruit, and acid citrus fruits, namely, lemons, bergamots, and limes, are notably rich in flavonoid content and possess various bioactivities. Flavonoids are naturally occurring molecules abundant in fruit, vegetables, nuts, seeds, and beverages, such as tea and wine [4]. A number of studies have investigated the ability of flavonoids to act as antioxidants [5]. Accumulating evidence suggests that neuroinflammation is closely associated with the pathogenesis of neurodegenerative disorders such as Parkinson's disease and Alzheimer's disease. The hallmark of neuroinflammation is considered to be microglial activation in the central nervous system [6]. Flavonoids comprise a large family of secondary plant metabolic intermediates that exhibit a wide variety of antioxidant and human health-related properties [7]. Naringenin (NAR), a flavonoid found in high concentrations in grapefruit, has been reported to have antimicrobial, antioxidant, anti-atherogenic, anti-inflammatory, anticancer, and antidepressant effects [8]. Due to these biological properties, researchers recommend the usage of NAR for controlling various diseases such as cardiovascular, neurological, rheumatological, metabolic, and gastrointestinal disorder [9]. Moreover, the ameliorated behavioral alterations of NAR through the central serotonergic and noradrenergic systems have been demonstrated in mice [10]. The antidepressant-like effect of NAR has been discussed and reviewed on different perspectives [11]. NAR has been notified as a strong scavenger of free radicals [12]. To study, the effect of Naringenin computationally different poses is generated by a search algorithm, which ideally should sample the degrees of freedom of the protein-ligand complex adequately enough as to include the true binding modes [13]. The author has worked on the interaction of small molecules, both of natural origin and synthetic ligands with proteins [14,15]. Within the molecular docking field, protein-ligand docking represents a particularly important and well-established methodology and a relevant part of the current drug discovery process [16-19].

Molecular docking targets at achieving optimized conformation for protein and ligand so as to arrive at a complex of the protein and ligand with the whole system acquiring minimum energy [20]. Receptor-ligand interactions are central to numerous biological processes such as signal transduction, physiological regulation, gene transcription, and enzymatic reactions [21]. The term receptor is usually used as a synonym for any biological target that binds specifically with a small molecule, that is, ligand and, as a result of this interaction, some biological response is observed [22]. Ligand (or drug if we emphasize its pharmacological effect) is most often an inhibitor or substrate and has low molecular weight. The aim of molecular docking [23] is to predict the structure of the intermolecular complex formed by two or more molecules. Most methods concentrate on docking of ligand to macromolecular binding sites [23]. The potential of the flavonoid NAR as an antidepressant has been analyzed using a computational approach.

METHODS

Target protein

The structure of the target protein Fig. 1 was retrieved from the protein data bank (PDB). It is the structure of the chimeric protein 5HT1. Its structure has been solved by X-ray crystallographic technique with a

resolution of 2.7 A° units and bears the PDB id 4IAR. It is a complex with ergotamine. Fig. 1 shows the secondary structure of the target protein.

Protein preparation

The raw protein from the protein databank with PDB ID 4IAR is further prepared for docking studies. Initially, all the Het atoms were removed and subsequently subjected to energy minimization to remove the bad steric clashes using tool smart minimizer for 1000 steps at RMS gradient of 0.1 and 0.03, respectively, by applying the suitable force field CHARMm available through Accelrys life science software [24]. The possible binding sites of the protein were analyzed using the binding site analysis feature available in the Accelrys Discovery Studio 2.1.

Ligand molecule

The structure of NAR was retrieved from PubChem compound database. Fig. 2 shows the structure of the ligand NAR. It bears the PubChem id of CID 439246.

Structure-based drug design

Docking of known protein with known ligands constitutes the method of structure-based drug design. This is a common method of the receptor-ligand interactions between the active site of the protein and the ligand molecules. In this present study, the protein with PDB id 4IAR is docked with NAR and analyzed for the possible potential of NAR to unravel its antidepressant activity.

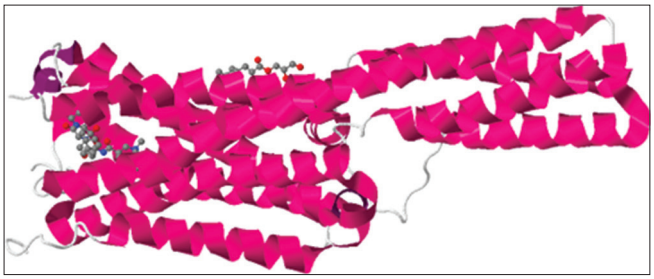

Fig. 1: Secondary structure of the target protein 4IAR

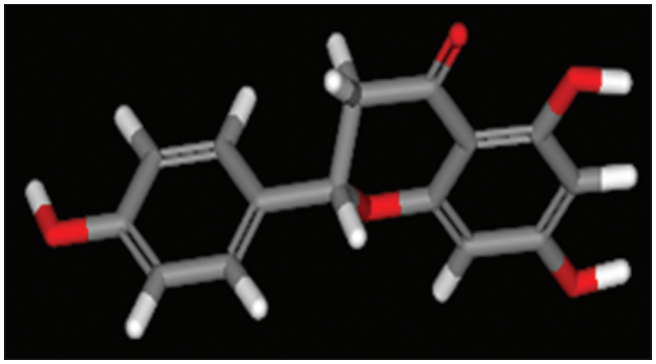

Fig. 2: Structure of naringenin

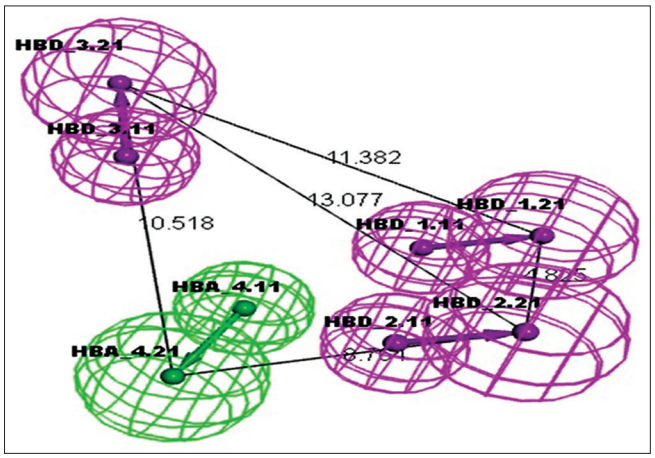

Fig. 3: Pharmacophore of the ligand naringenin

RESULTS

Pharmacophore analysis of the ligand

The following Fig. 3 shows that the pharmacophores present in the ligand. "A pharmacophore is the ensemble of steric and electronic features that are necessary to ensure the optimal supramolecular interactions with a specific biological target to trigger (or block) its biological response [25,26]." It shows the presence of one hydrogen bond acceptor and three hydrogen bond donors in the ligand. The coordinates of the pharmacophore groups were also determined. Table 1 and Table 2 show the coordinates of the pharmacophores present in NAR and the distance between the pharmacophores.

Receptor ligand interactions

Docking is frequently used to predict the binding orientation of small molecule drug candidates to their protein targets to predict the affinity and activity of the small molecule. Hence, docking plays an important role in the rational design of drugs [20]. The drug target protein was initially prepared by applying the CHARMM force field to avoid the steric clashes and non-bonded interaction, followed by defining the appropriate binding site for the lead molecule to go and bind with the active site of the drug target protein, the binding sites of the protein are predicted by flood filling algorithm. Binding site analysis of the protein revealed 13 sites. All these sites were analyzed for possible interaction between the protein and the ligand. The ligand could be seen to interact with the protein at three different sites.

DISCUSSION AND CONCLUSION

Depression is one of the most prevalent mental ailment which is often undiagnosed and under evaluated. As a result, it causes serious adverse effect to the well being of a person. Brain- derived neurotrophic factor is an essential neurotrophic factor which provides neuroprotection. Decreased level of Brain-derived neurotrophic factor (BDNF) is one of the crucial factor in the expression of depression [27]. The current scenario of antidepressant drugs available in market involves various inhibitors like monoamine oxidase inhibitors, norepinenephrine inhibitors, serotonin inhibitors. [28] Flavonoids which are widely distributed in many plants such as ,naringenin, rutin, liquiritin, quercetin, vitexin and isoliquiritin have been researched

Table 1: Coordinates of the pharmacophores present in the ligand

Feature	X	Y	Z	Radius in Angstrom
HBD_1.11	−4.191	0.83	−1.893	1.7
HBD_1.21	−6.72	−0.72	−2.38	2.3
HBD_2.11	−5.197	0.919	2.826	1.7
HBD_2.21	−7.72	−0.64	2.34	2.3
HBD_3.11	2.983	−1.79	0.534	1.7
HBD_3.21	4.46	−2.8	−1.9	2.3
HBA_4.11	−1.15	2.955	1.203	1.7
HBA_4.21	−0.68	4.36	3.84	2.3

Table 2: Distance between the pharmacophore groups in the ligand

Name	X	Y	Z	Distance in angstrom
Distance1	−1.11	−1.619	−1.999	11.382
Distance2	−1.56	−1.587	0.353	13.077
Distance4	2.064	0.849	1.039	10.518
Distance5	−7.028	−0.64	0.02	4.825
Distance6	−4.309	1.978	3.208	8.764

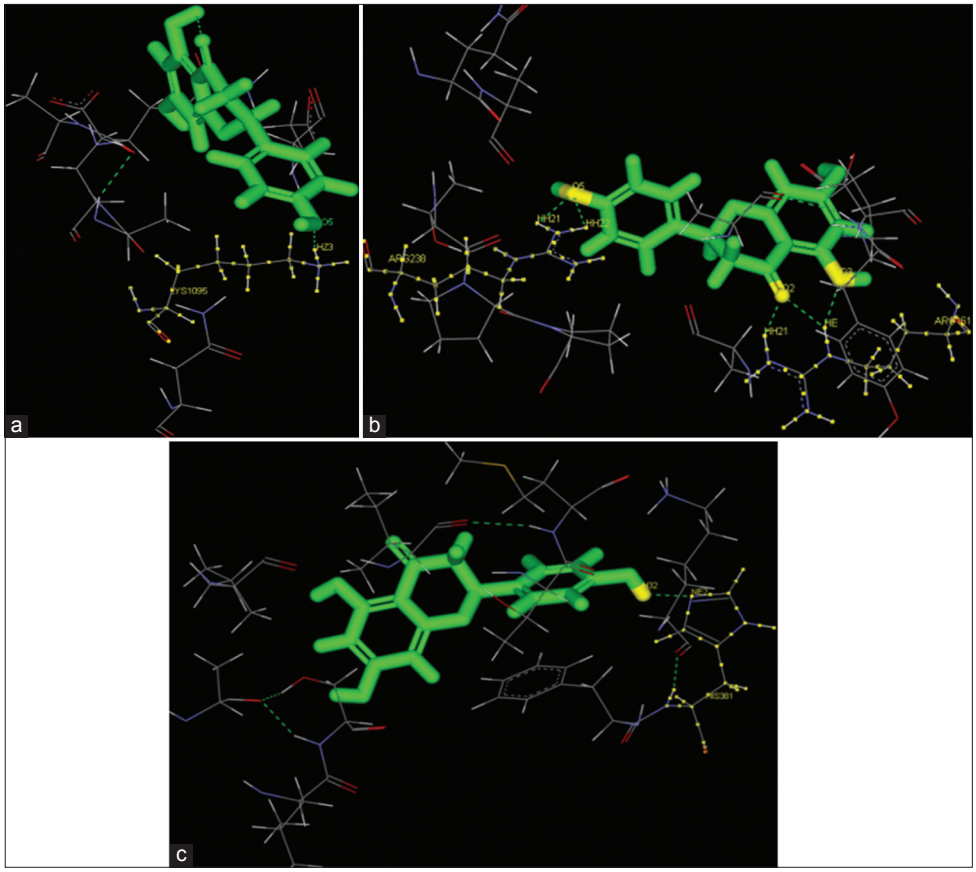

Fig. 4: Binding interactions of the ligand with the target protein. (a) Binding site 8-A and its interactions with naringenin, (b) binding site B and its interaction with the ligand, and (c) binding site C and its interaction with naringenin

for its potential antidepressant effects .The antidepressant effect of these flavanoids may be due to their involvement in various signalling pathyways such as by serotonergic, adrenergic, opioid, and NO pathways [28].

Analyzing the docking of the target protein with the natural ligand NAR shows that the ligand molecule binds to the target at three different sites Fig. 4. As for the binding Sites A and C, both show only one interaction. It interacts with the hydrogen of 1095th residue of the sequence, which is lysine at Site A with a dock score of 26.99 and Site C, it is between the hydrogen of histidine which is the 381th residue and the N of the ligand and showing a dock score of 37.125. The docking at the B position shows five interactions, two of which are with the same residue arginine at the 161th position with two different oxygen in the ligand. Again the other three interactions are with two arginine residues, one at the 161th position with oxygen of the ligand and the other two interactions at 238th position with the oxygen of the ligand with a dock score of 36.512.

As shown from the interaction studies, the antidepressant effect of NAR depends on its interaction with serotonergic 5-HT1A receptors. The present result is in accordance with the findings, that serotonergic mechanism is the most important general mode of action as an antidepressant[28]. The probable mechanism may be that NAR binds to 5-HT1A receptors and inhibits the activity of monoamine oxidases, thereby increasing the biogenic amine level in the brain, which, in turn, brings about the upregulation of BDNF signaling [12].

The present study shows that NAR could be used as a potent antidepressant agent. Further, clinical studies are warranted to better address NAR safety, effectiveness, distribution, and bioavailability in humans to achieve feasible NAR-based clinical formulations.

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AUTHORS' CONTRIBUTIONS

All authors have contributed equally to the manuscript.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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