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RESEARCH ARTICLE

In Silico Interaction Studies of Various Antioxidant Molecules with MAO-B Protein – A Potent Secondary Drug Target in Parkinson's Disease

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Abstract

Objective: Parkinson's Disease (PD) remains to be the second prominent neurodegenerative disorder affecting the oldster populace. Administration of dopamine is the existing therapeutic choice to treat PD disorder. Contradictorily, administrated dopamine is readily oxidised by monoamine oxidase type B (MAOB) protein. Thus, MAOB is a potent secondary drug target for treating PD. The main objective of this present investigation is to compare, analyse and conclude the best adjuvant drug for the PD therapy. **Methods:** Molecules with high antioxidant properties were shortlisted for this study. This in-silico study was carried out by utilising several bioinformatics tools such as Patch Dock, Discovery studio software and CPHmodels-3.0. **Findings:** Alpha Tocopherol and Essential long chain fatty acids exhibited a good affinity binding scores than the existing adjuvant therapy drugs. The atomic contact energy of the docked complex of Alpha Tocopherol - MAOB is -373.83 Kcal/Mol and Docosahexaenoic Acid (DHA) - MAOB is -322.77 Kcal/Mol. Alpha Tocopherol and DHA was more significant than the Safinamide-MAOB complex with the atomic energy of -302 Kcal/Mol. **Novelty:** The present study has comprehensively compared the in-silico interaction of various PD adjuvant drugs with the MAOB target and revealed the better MAOB inhibitor with their detailed interaction map and atomic contact energy.

Keywords: Parkinson's Disease; MAOB; Essential fatty acids; Selegiline; Tocopherol; MAOB inhibitors

1 Introduction

Parkinson's Disease (PD) is one of the most prominent neurodegenerative disorders. The term "Parkinson's Disease" is an eponym named after an English surgeon, James Parkinson. PD accounts 2nd common and crucial form of neuro disorder affecting the elderly populace. The cause of PD Incidence was majorly of idiopathic/sporadic (around

95%) and familial (around 5%) – induced by mutation/inheritance[1]. The progressive degeneration of dopaminergic neuron in the mesencephalon (mid brain) in association with misfolding of α-synuclein (α-syn) protein leading to deposition and formation of Lewis bodies in the stem of brain, paleomammalian cortex and sensory cortex of cerebrum is the cardinal pathological condition of PD[2,3]. These progressive aetiology results in the necrosis of neurons and consequently establish the shortage of dopamine. Dopamine is one of the most important neurotransmitters which is highly required for the co-ordinated motor function. Scarcity of dopamine leads to a series of motor dysfunctions and eventually ends up in the fracture of autonomic nervous system.

Levodopa is a traditional and Food and Drug Administration (FDA) approved potential prodrug which is used in the treatment of PD. Upon intake, this prodrug is readily converted to dopamine the therapeutic agent in treating the movement disorder[4]. Contrarily, Monoamine oxidase B a major monoamine metabolizing protein readily oxides the dopamine and making it insufficient for treating PD patients. Therefore, MAO B remains to be a potent secondary drug target in PD therapy[5–7].

Generally, neurological disorders are associated with oxidative stress. PD is no longer exception to this oxidative stress. In past two decades, several studies have identified and suggested various antioxidant molecules which are potential inhibitors of MAOB. Certain molecules like Rasagiline, Selegiline are clinically used in the PD treatment and have exhibited a beneficial effect by elevating the dopamine levels. Yet, the better adjuvant activity of all the identified drug molecules remains unclear. Thus, in this research the various antioxidant molecules and clinically prescribed MAOB inhibitors were docked with the target MAOB, respectively. This in-silico study has compared all the available drugs and antioxidant molecules. This docking studies was achieved by Patch dock. This computer aided drug docking tool remains much preferable as it provides a detailed interaction map between protein and drug.

2 Methodology

2.1. Retrieval of adjuvant therapy anti-PD drug data

In this study, several anti-PD adjuvant drugs used as MAOB inhibitors were retrieved from literature and drug bank databases (https://go.drugbank.com)The FDA approved drugs that were used as adjuvants to levodopa and also used as monotherapy drugs at initial stages of PD were chosen. The drug bank databases were utilized to gather complete information about the conventionally practised anti-PD adjuvant drugs. Several other naturally derived molecules with potential antioxidant properties were opted for this investigation. 3D forms of shortlisted antioxidant molecules and existing drugs were retrieved from NCBI(http://www.ncbi.nlm.nih.gov).

2.1.1 Modelling and visualization of target protein

The data base Ensembl, the prime source for human genome sequences were utilized to obtain the complete information about the target MAOB gene(http://www.ensembl.org/). This database was hyperlinked with the uniport database which provides the complete amino acid sequences in Fast Alignment Sequence Test for Application (FASTA) format(https://www.uniport.org/uniport). CPHmodels-3.0 was employed for protein modelling study(https://www.cbs.dtu.dk/services/CPHmodels). It is a high definition performing remote homology modelling server. This tool predicted an accurate and fault less three-dimensional model of MAOB. Discovery Studio software V 2.5, the molecular visualizer tool was used to visualize the 3D structure of MAOB protein.

2.1.2 Drug docking and 3D visualization

Patch Dock was adopted for easy and accurate docking(https://bioinfo3d.cs.tau.ac.il/patchdock). This molecular drug docking server is of full automated type. The clinically prescribed anti-PD adjuvant drugs and the opted antioxidant molecules were docked to obtain the drug binding scores. Discovery studio software was employed to generate the 3D form of protein-ligand interaction map.

3 Results and Discussion

The structural gene of human MAOB was present in chromosome X, band p11.3 designated with a gene ID 4129. Length of the gene transcript was 2570 bp long comprising 18 exon counts. It encodes amino oxidase B enzyme of length 520 amino acid sequences with a molecular mass of 59474$\pm$14 Da. An automated homology modelling server CPHmodels-3.0 predicted a flawless 3D form of the secondary structure of Mono amino oxidase type B protein. The predicted MAOB 3 D form was visualized through Discovery studio software (Figure 1a).

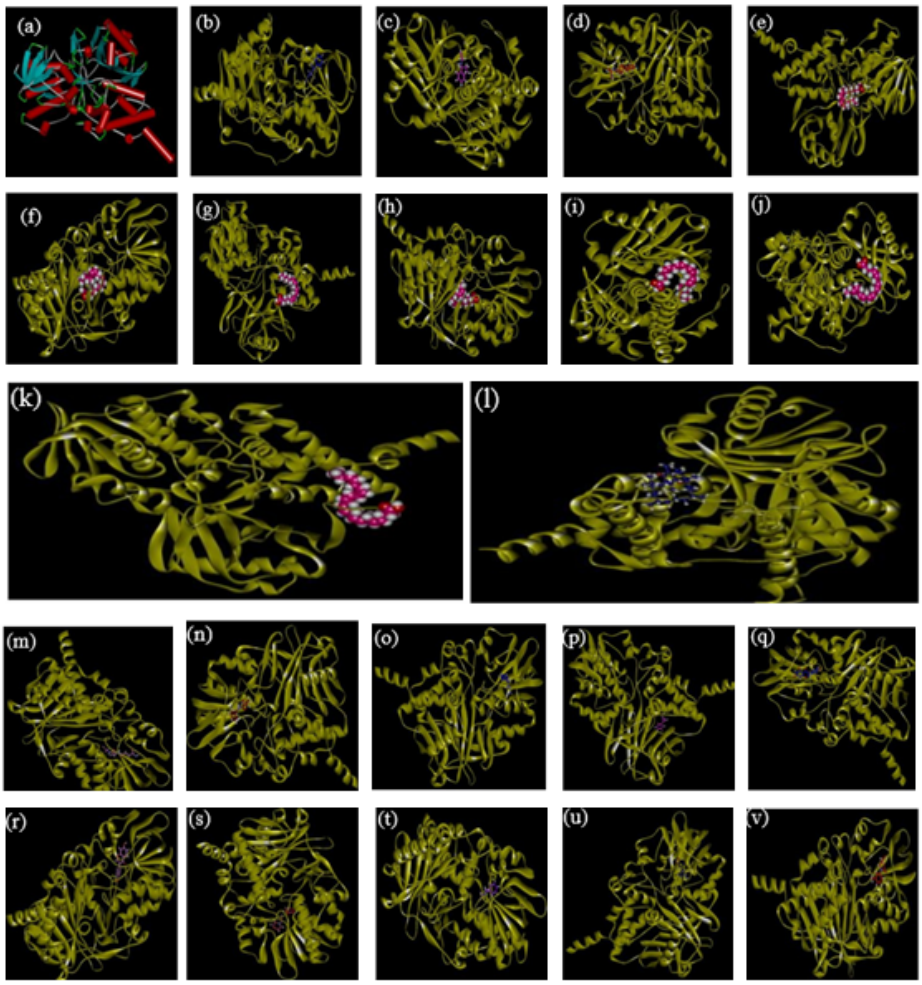

Fig 1. (a) 3 D form of the secondary structure of Mono amino Oxidase B (MAOB) protein.(b-v) 3-Dimensional form of docked complex of various MAOB inhibitors and MAOB protein. The compound name, Drug Bank Accession number and Atomic ContactEnergy (ACE) value (Kcal/Mol) for fig (b-v) are as follows. (b) Selegiline (DB01037) -233.91 (c) Rasagiline (DB01367) -251.96 (d) Safinamide (DB06654) -302 (e) Linoleic acid(LA) (DB14104) -240.46 (f) Alpha Linolenic acid (ALA) (DB00132) -269.60 (g)Gamma Linolenic acid (GLA) (DB13854) -222.00 (g) Di-hommo gamma Linolenic acid(DGLA) (DB00154) -314.60 (h) Arachidonic acid (ARA) (DB04557)-273.48 (i)Eicosapentaenoic acid (EPA) (DB00159)-294.01 (j) Docosahexaenoic acid (DHA)(DB03756) -322.77 (k) Alpha Tocopherol (DB1125)-373.83 (l) Glutathione(DB00143)-284.61 (m) Isocarboxazid (DB01247)-267.55 (n) Phenelzine (DB00780)-199.55 (o) Tranylcypromine (DB00752)-174.70 (p) Genistein (DB01645)-272.52(q) Daidzein (DB13182)-266.87 (r) Moclobemide (DB01171)-266.73 (s) Pargyline (DB01626)-203.89 (t) Safrazine (DB09253)-225.99 (u) Toloxatone (DB09245)-225.24

A new and eminent algorithm was used in patch dock server to dock the drug and the protein. In-silico docking results of MAOB with the existing adjuvant drugs and various antioxidant molecules that were analysed by Patch dock were keenly scrutinized. The interaction maps of the docked molecules were visualized in Discovery Studio software. 3D forms of the docked outputs provide a keen insight about the interactions between the docked molecules (Figure 1b-v). The Atomic Contact Energy (ACE) value refers to the binding affinity interaction scores between the Drug and the target protein. The docked complex of α-Tocopherol and MAOB (Figure 1k) exhibited the most stable conformation with the ACE value of -373.83Kcal/Mol. Following Tocopherol, Long Chain – Poly Unsaturated Fatty Acid (LC-PUFA) established a more stable conformation with good affinity binding values. ACE values of both ω-3 and ω-6 LC-PUFA were higher than the conventional drugs like Rasagiline, Selegiline, Pargyline, Toloxatone, Moclobemide, Phenelzine, Isocarboxazid and Tranylcypromine. The interaction map of tranylcypromine(Figure 1o), a conventionally used MAOB inhibitor showed the least conformation complex with the ACE value of -174.00Kcal/Mol. The complex of Safinamide and MAOB (Figure 1d) revealed the more stable conformation among

the conventionally using anti-PD adjuvant drug. It exhibited the ACE value of -302.00 Kcal/Mol, still its binding affinity is lesser than that of α- Tocopherol, Docosahexaenoic acid (DHA), and Di-hommo gamma Linolenic acid (DGLA). Many researchers have revealed the efficacy of α-Tocopherol in protecting the central nervous system [8] but the significance of Vitamin-E in connection with the MAOB protein was not investigated. Thus, α- Tocopherol has high potential in protecting the central nervous system.

Basically, brain is a lipid rich organ and LC-PUFA are well-known to protect the nervous system. Therefore, LC-PUFA were significantly considered and focused more in the present study. Among ω-6 fatty acids, DGLA, and MAOB protein (Figure 1g) showed a more stable conformation with ACE value of -314.60 Kcal/Mol. Amongst ω-3 fatty acid, DHA (Figure 1j) revealed an excellent binding affinity score of -322.77 Kcal/Mol. Considering LC-PUFA, the respective individual fatty acid (inclusive of ω-3 and ω-6) exhibit the affinity binding score in the following hierarchical order. DHA (-322.77) > DGLA (-314.60) > EPA (-294.01) > ARA (-273.48) > ALA (-269.60) > LA (-240.46) > GLA (-222.0).

LC-PUFA scavenges the oxygen free radicles and are the principal precursor for the leukotrienes, prostaglandins and so on. Deficiency of such inevitable molecules could be the root cause for the idiopathic incidence of PD. On the other hand, lack of such highly potential antioxidant molecules could be the underlying reason for the increased oxidative stress in nervous system leading to mutation induced PD. LC-PUFA serve as an efficient dietary supplement in the treatment of PD which effectively mitigated the PD development. Previous investigations have worked on various meta-analysis [9], in-vitro studies [10] and clinical trials [11] which has recommended the required consumption of omega 3 PUFA to reduce the PD risk. The molecular docking of PUFA and its binding scores with the MAOB was remained unknown. Therefore, the current investigation has shown the detailed comparison of the individual PUFA molecules with the target MAOB protein.

4 Conclusion

As the number of PD cases are increasing, the neurologists are looking for an effective drug therapy to ease the discomfort of patients. This study has compared both the natural and synthetic PD adjuvant drugs that are conventionally prescribed. This in-silico method has proved beneficial in comparing, predicting and to determine the better natural compound with excellent affinity binding scores. The molecular docking and ligand interaction evaluates the affinity scores between the various drugs and the MAOB target respectively. This research has concluded that α - Tocopherol and DHA are highly potent when compared to the miracle drug, Safinamide. Alpha Tocopherol exhibited 21.3% more affinity score and revealed the most stable conformation than Safinamide. DHA was 6.7% more efficient than Safinamide. Thus, Omega 3 PUFA and α- Tocopherol consumption has been considered to be safe and efficient in treating both initial and moderate stages of PD therapy. Results obtained from this in-silico studies has to be further correlated with analytical and in-vivo studies.

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