EVALUATION OF INHIBITORY POTENTIAL OF PUFAs FROM FISH OIL AGAINST MONOAMINE OXIDASE-B: A MOLECULAR DOCKING STUDY

Maria Masroor, Erum Shireen and Sadaf Naeem*

Department of Biochemistry, University of Karachi, Karachi 75270, Pakistan
*Corresponding Author: snaeem@uok.edu.pk

ABSTRACT

Fish oil (FO) is a rich source of poly-unsaturated fatty acids (PUFAs). The present research aimed to evaluate the inhibitory potential of PUFAs from FO against enzyme monoamine oxidase B (MAO-B). The MAO-B enzyme is a target of interest for several neurological disorders because of its potential to oxidize dopamine and other neurotransmitters.

Docking of PUFAs was performed to discover the binding mode and their interaction within the active site of MAO-B by using MolegroVirtual Docking (MVD) Software. The results show that docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA) exhibit lowest docking score and form hydrogen bonds with Tyr 435, Tyr 326 and Gln 206, respectively.

To the best of our knowledge, this is the first study describing the interaction of PUFAs with MAO-B. Our results demonstrate that PUFAs successfully interact with the active site residues that are known to have a key role in the enzyme's catalytic activity, that are Tyr 435, Tyr 326 and Gln 206 thus, can be used as MAO-B inhibitors. Therefore, these PUFAs could help to normalize the levels of dopamine and other amine neurotransmitters in the brain. These findings are helpful in employing the use of FO for treating various neurological diseases linked with MAO-B's increased activity. However, further preclinical studies will be required to validate the current findings.

Key Words: Docking; Fish Oil; MAO-B; MAO- B inhibitors; PUFAs.

LIST OF ABBREVIATIONS

1. Adrenic acid = ADA
2. Arachidonic acid = AA
3. Dihomo-gamma-linolenic acid = DGLA
4. Docosahexaenoic acid = DHA
5. Docosapentaenoic acid = DPA
6. Eicosadienoic acid = EDA
7. Eicosapentaenoic acid = EPA
8. Fish oil = FO
9. Flavin adenine dinucleotide= FAD
10. Gamma- linolenic acid = GLA.
11. Human Monoamine oxidase B = hMAO-B
12. Monoamine oxidase B = MAO-B
13. Poly Unsaturated Fatty Acids = PUFAs
14. Protein Data Bank = PDB

INTRODUCTION

Growing body of evidences shows that fish oil (FO) supplementation could offer significant neuroprotection in models of animals for neurodegeneration (Bousquet *et al.*, 2008; Flores-Mancilla *et al*., 2014). FO is a rich source of omega-3 PUFAs including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) (Shinto *et al.*, 2014). Omega-3 PUFAs have been proposed to be involved in the pathophysiology of variety of psychiatric disorders including schizophrenia, attention deficit and hyper activity disorders, Alzheimer's disease and dementias (Calon and Cole, 2007; Sinn *et al*., 2008; Colangelo *et al.*, 2009). Moreover, clinical studies have also shown that the red cell membranes of some schizophrenics' patients, especially those with negative symptoms have depleted levels of arachidonic acid that is the major PUFA from the (omega-6) family and similarly the major PUFA from the (omega-3) family, DHA, respectively (Kaiya *et al.*, 1991; Peet *et al*., 1996).

Monoamine Oxidases (MAOs) (MAO-A and MAO-B), flavin containing enzymes are located on outer mitochondrial membranes and catalyze the oxidative deamination of monoamines resulting in the generation of hydrogen peroxide as a by-product (Trettel *et al.,* 2000). Among these enzymes, MAO-B is involved in the metabolism of dopamine and other amines, therefore, involved in the pathological conditions such as Alzheimer's disease, a neurodegenerative disorder, along with that it is also involved in many neurological disorders, for example, an attention deficit disorder, depression, schizophrenia and anorexia nervosa (Youdim *et al*., 2006; Carradori and Silvestri, 2015). Therefore, MAO-B inhibitors may decrease the production of potentially dangerous by-products of dopamine metabolism in the brain, hence employing a neuroprotective effect (Youdim and Bakhle, 2006). For this reason, a number of inhibitors are used clinically to inhibit the activity of MAO-B while others are in development (Binda *et al*., 2003).

Considering the protective effects of PUFAs on numerous neurodegenerative diseases, we hypothesized that PUFAs from fish oil could possibly play a preventive role in brain disorders and or neurodegenerative diseases by inhibiting the activity of enzyme MAO-B. Therefore, the aim of this present study is to evaluate the binding affinity of PUFAs from fish oil with MAO-B, in order to find out their potential inhibitory effects on the enzyme by using the molecular docking method.

Molecular docking is used to predict the intermolecular complex's structure, formed between two or more molecules, the two molecules are often a target protein and a small ligand (Prasanthi and Harasreeramulu**,** 2014)**.**

MATERIALS AND METHODS

In the present research, PUFAs from FO have been studied in order to assess their inhibitory activity against the MAO-B for the reversal and/or inhibition of neuroleptics induced motor and neurological disorders using molecular docking studies. During this study, molecular docking of omega-3 and omega-6 PUFAs against the MAO-B enzyme has been performed using the Molegro Virtual docker (MVD) software. To perform docking, a three dimensional crystal structure of the protein MAO-B (Homo sapiens) bound with antidiabetic drug, pioglitazone (PDB ID: 4A79) has been selected, as it is non- mutated and resolved at a relatively low resolution (1.89 Å). Various Omega -3 and omega -6 PUFAs that are found in fish oil were compiled from a review conducted by Osman and colleagues, in which fatty acid composition of variety of FOs has been demonstrated (Osman *et al.*, 2001). Table 1 enlists the omega-3 and omega-6 PUFAs selected here for docking studies against the MAO-B. The structures of these constituent fatty acids of FO were downloaded from PubChem (Wang *et al*., 2014) and Chemspider (Pence and Williams, 2010) (http://www.chemspider.com) databases. In order to perform docking, at first, protein was imported in to the work space and all the water molecules were removed as they can severely weaken the intermolecular electrostatic interactions, therefore, causes a reduction in the affinities by solvating polar or charged groups, and imparting hydrophobic effects that contribute to binding (Rush *et al.*, 2004).

The MVD software, detect the possible binding sites of a protein through cavity prediction algorithm. The binding site was set within a sphere of radius 10 Å, after which, ligands were imported into the work space and docked them against the target protein, MAO-B (PDB ID: 4A79). To obtain a high docking accuracy, for each ligand, 10 docking runs were performed, therefore, after the execution of docking simulation, 10 poses for each ligand were returned. The ligand interactions as well as hydrogen bond energies were taken into account to sort out the best pose for each ligand.

RESULTS

In the present study, six of the omega-3 PUFAs (Table 1) were docked into the active site of MAO-B. Table 2 summarizes the docking results of these omega-3 PUFAs, out of which docking results of two of the PUFAs with lowest energy and maximum interactions are presented in Figure 1 a and 1b.

Among the six of the docked omega-3 fatty acids, Docosahexaenoic acid (DHA) exhibited the highest MVD score with a binding energy of -162.588 Kcal/ mol (Fig. 1a). The binding site of MAO-B consists of amino acids Tyr 326, Tyr 435, Gln 206, Cys 172 and Phe 168. The carboxylic group of DHA formed only one hydrogen bond with the OH group of Tyr 435. The present docking results show that, among the six of the omega-3 PUFAs, EPA and stearidonic acid have formed two hydrogen bonds within the enzyme's active site, where, EPA formed hydrogen bonds with OH of Tyr 326 and with amide group of Gln 206, whereas, Stearidonic acid (-139.864 Kcal /mol) was successful in forming bonds with Gln 206 and Leu 171 (Table 2). Remaining three of the docked omega 3 PUFAs , 6,9,12,15,18-Henicosapentaenoic acid (Fig. 1b) , 11,14,17-eicosatrienoic acid (-151.357 Kcal/mol), α-Linolenic acid (-135.938) tend to bind within the active site through a single hydrogen bond with residues Cys 172, Tyr 60, Tyr 326, respectively (Table 2).

The docking results of omega -6 PUFAs are summarized in Table 3. It is revealed from the results that Docosopentaenoic acid (DPA) binds with the highest moldock score within the pocked of MAO-B with a binding energy of -181.608 Kcal/mol. Figure 2(a) shows the binding of DPA with the enzyme. It could be observed that the active site residues surrounding DPA includes Cys 172, Tyr 326, Gln 206, Tyr 398, and Tyr 435. The carboxylic moiety of DPA formed two hydrogen bonds with the OH group of Tyr 326 and an amide group of Gln 206. A similar pattern of hydrogen bond interaction has also been exhibited by Dihomo-gamma-linolenic acid (DGLA) and Gamma- linolenic acid (GLA), both forming hydrogen bonds with Tyr 326 and Gln206 of the enzyme's active site. Among the rest of the four docked omega- 6 PUFAs, arachidonic acid (AA) and adrenic acid (ADA) both were found to bind in the similar manner within the active site of the enzyme by forming hydrogen bonds with amino acid residues Tyr 435 and Cys172, whereas, upon docking, Eicosadienoic acid (EDA) formed only one hydrogen bond with Tyr 435 (Fig. 2b).

Table 1. List of Omega-3 and Omega- 6 PUFAs found in fish oil.

	Omega-3 PUFAs	Omega-6 PUFAs
01	α-Linolenic acid	Arachidonic acid
02	Docosahexaenoic acid	Adrenic acid
03	Eicosapentaenoic acid	Docosapentaenoic acid
04	11-14-17 -eicosatrienoic acid	Dihomo-gamma-linolenic acid
05	6,9,12,15,18- Henicosapentaenoic acid	Eicosadienoic acid
06	Stearidonic acid	Gamma- linolenic acid
07		Linolenic Acid

Table 2. Docking results of Omega-3 PUFA with docking score and interacting amino acids.

	Omega- 3 PUFA	MolDck Score	Hydrogen bond energy	Interacting amino acids
1	Docosahexaenoic acid	-162.588	0	Tyr-435
2	6,9,12,15,18-Henicosapentaenoic acid	-162.03	0	Cys-172
3	Eicosapentaenoic acid	-153.053	-0.38198	Tyr-326, Gln-206
4	11,14,17-eicosatrienoic acid	-151.357	-1.57504	Tyr-60
5	α-Linolenic acid	-135.938	-2.5	Tyr-326
6	Stearidonic acid	-139.864	0	Gln-206, Leu-171

Table 3. Docking results of omega-6 PUFA.

	Omega-6 PUFA	MolDock score	Hydrogen bond energy	Interacting amino acids
1	Docosapentaenoic acid	-181.608	-0.12026	Tyr-326, Gln-206
2	Eicosadienoic acid	-180.216	0	Tyr-435
3	Arachidonic acid	-153.967	-0.18264	Tyr-435, Cys-172
4	Adrenic acid	-150.352	-0.46822	Tyr-435, Cys-172
5	Dihomo-gamma-linolenic acid	-149.774	-0.48487	Tyr-326, Gln-206
6	Gamma- linolenic acid	-143.609	-0.01884	Tyr-326, Gln-206
7	Linolenic Acid	-134.815	-3.5576	Tyr-326

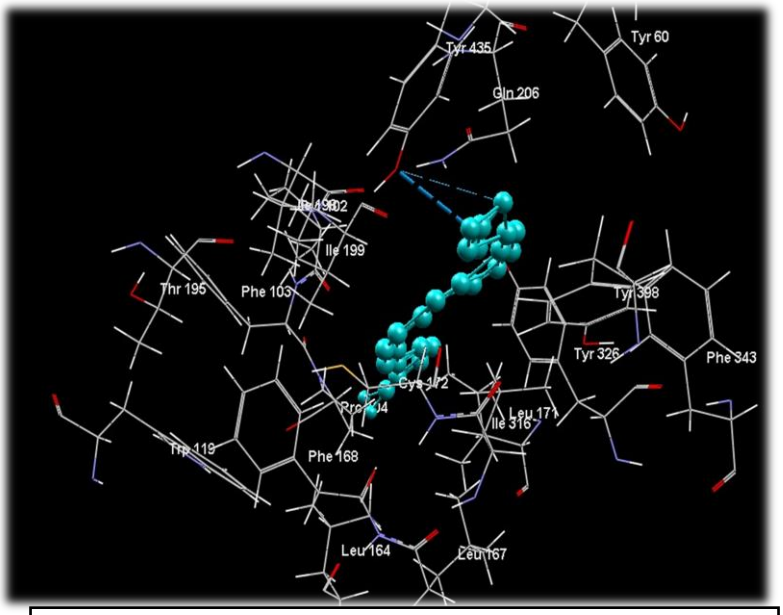

Fig 1 (a). Docosohexaenoic acid.

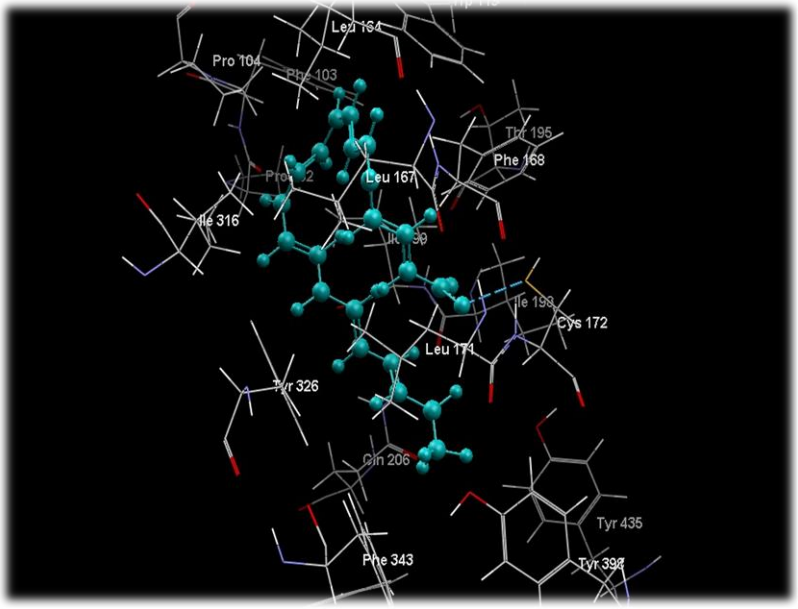

Fig 1 (b). 6,9,12,15,18-Henicosapentaenoic acid.

Fig. 1 (a- b). Shows the docking results of omega-3 PUFA with human MAO-B. Hydrogen bonds are indicated by blue dashed lines and ligand molecules are shown with ball and sticks with blue color.

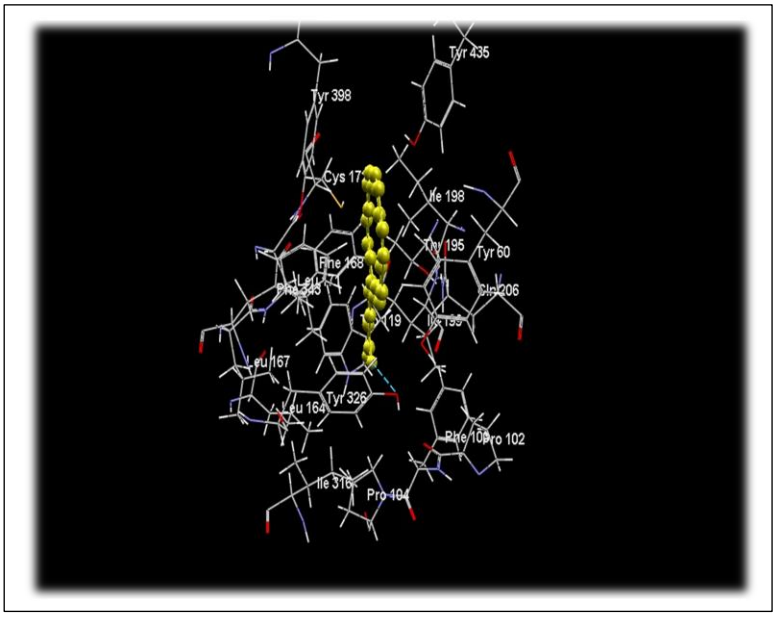

Fig. 2 (a). Docosapentaenoic acid.

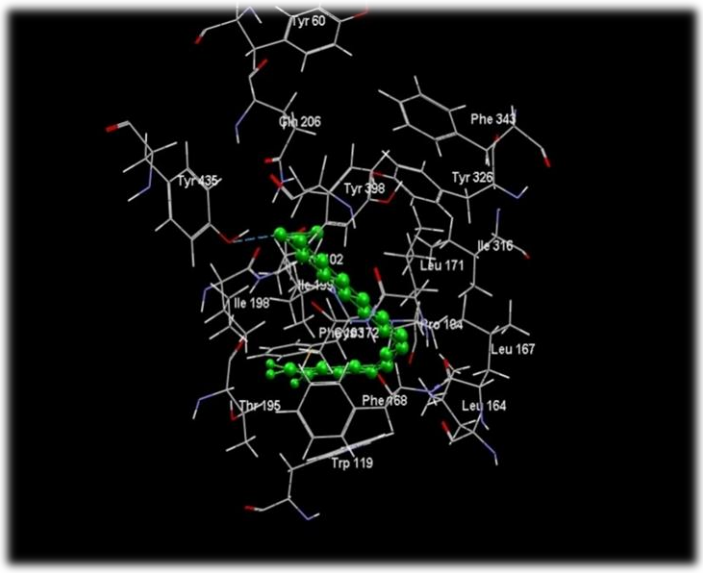

Fig 2 (b). Eicosadienoic acid.

Fig. 2 (a-b). Shows the docking results of omega- 6 PUFA with human MAO- B. hydrogen bonds are indicated by blue dashed lines and ligand molecules are shown with ball and sticks with yellow and light green colors.

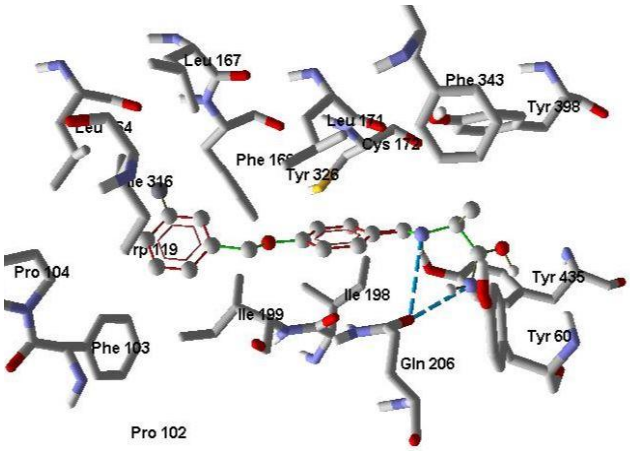

Fig. 3. The binding of Safinamide in the MAO B cavity. Hydrogen bonds are indicated by blue dashed lines.

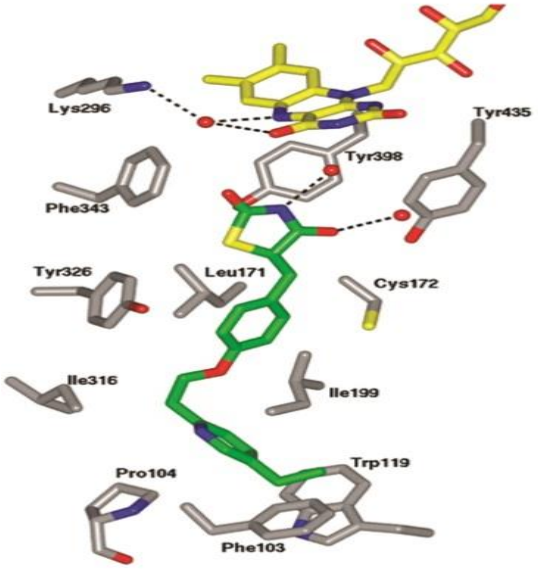

Fig. 4. Binding of pioglitazone within the active site of human MAO B. Hydrogen bonds is presented by dashed lines. Pioglitazone is in green (Binda *et al*., 2011).

DISCUSSION

The oval shaped active site of human monoamine oxidase B (hMAO-B) is lined by amino acid residues Tyr 60, Tyr 188, Tyr 326, Tyr 398, Tyr 435, Leu 171, Cys 172, Ile 198, Ile 199 and Phe 343 (Binda *et al.*, 2004; Li *et al.*, 2006), two of which, Ile199 and Tyr326, function as gate and creates two cavities with a volume ~400 and 290 $Å^3$. One of the cavities act as the substrate binding cavity while the other act as an entrance cavity (Milczek *et al.*, 2011). Figure 3 and 4 demonstrates the binding of Safinamide and Pioglitazone within the active site of MAO-B respectively, indicating important amino acid residues including Tyr 435, Tyr326, Gln 206 and Tyr 398 for the catalytic activity of the enzyme. Structural analysis of several flavin adenine dinucleotide (FAD) dependent amine-oxidizing enzymes, including hMAOs, suggests that two of the aromatic residues, namely Tyr 398 and Tyr 435, are perpendicular to the flavin ring in the binding site, and thus form an opening of a "cage", toward the entrance. These two residues were proposed to involve in the placement of substrate towards the flavin coenzyme (Akyüz *et al.*, 2007) along with that, these residues also have a role in the proton transfer reactions. Furthermore, the aromatic residues present within the active site of the enzyme also have a role in cation π interactions (Pless *et al*., 2007).

Comparing the present docking results with the control ligand, Pioglitazone (Fig. 4), it could be observed that Eicosadienoic acid, (EDA) Arachidonic acid (AA) and Adrenic acid (ADA) from omega -6 PUFAs share fairly the

similar binding pattern within the enzyme's active site as do Pioglitazone, that is evident by the involvement of Tyr 435 of enzyme's active site in the formation of hydrogen bonds with these compounds. The amino acid Tyr 435 has been suggested to play a key role in substrate binding, as suggested by the mutagenesis studies targeting Tyr 435 and Tyr 398 (Geha *et al.*, 2002).

On the other hand, investigation of binding modes of omega-3 PUFAs within the MAO-B cavity didn't reveal any binding similarities with Pioglitazone, except for Docosahexaenoic acid (DHA) that also formed hydrogen bond with Tyr 435. Along with Tyr 435, amino acid Tyr 326 along with Ile 119 has also been suggested to play an important role in determining the substrate affinity for an enzyme's active site (Milczek *et al.*, 2011). The results of the present research revealed that, four of the omega - 6 PUFAs (Docosapentaenoic acid,Dihomo-gamma-linolenic acid, Gamma- linolenic acid and Linolenic acid) and ecosapentanoic acid (EPA) and α Linoleic acid (omega -3 PUFA) forms hydrogen bonds with Tyr 326. The study conducted by Milczek and collogues, also shows that the removal of the Ile199 and Tyr 326 side chains from the substrate cavity of MAO-B, results reduction of enzyme's affinity for ligand binding within the MAO-B active site.

Similar reported studies on binding of safinamide, an antileptic drug, with MAO-B shows the involvement of Gln 206 in formation of H-bonding (Binda *et al*., 2011) (Fig. 3). In the present docking studies, Gln 206 is also found to involve in hydrogen bonding with many of the selected PUFAs including Eicosapentaenoic acid, stearidonic acid, the omega-3 PUFAs, along with, Docosapentaenoic acid,Dihomo-gamma-linolenic acid, and Gamma- linolenic acid, the omega-6 PUFAs.

Experimental studies, in animals have shown that substantial disturbances in neural functions are associated with a diet lacking in omega-3 PUFAs, in most cases that can be restored by taking a diet rich in omega-3 PUFAs (Sinclair *et al.*, 2012). Moreover, omega-3 PUFAs are linked to prevention or attenuation of neuro-inflammation, neuronal cell death and also involved in cognitive development. (Hussain *et al*, 2013). Alike omega-3 PUFAs, omega-6 PUFAs also influence the development, function and growth of brain, hence playing a major role in brain (Simopoulos, 2011). Dietary deficiency of omega-6 result in reduce concentration of omega-6 PUFAs that is related to decreases levels of dopamine and serotonin both (Owens and Innis, 1999). From this finding, the role of omega-6 PUFA in the regulation of synthesis of the neurotransmitters, dopamine and serotonin is evident, therefore, they are also involved in the normal functioning of the brain (Fernandes *et al*., 2017). The role of omega -3 and omega-6 PUFAs as potential inhibitors of enzyme MAO- B was evaluated in this present research. The results of this research demonstrates that omega-3 and omega -6 PUFAs fits well within the active site of MAO-B through interactions with the amino acid residues Tyr 326, Tyr 435, Gln 206, that are proven to be critical for enzyme's catalytic activity (Geha *et al.*, 2001; Li *et al*., 2006). This is the first study clarifying the binding potentials of PUFAs within the active site of enzyme MAO-B. It is, therefore, suggested that PUFAs that are present in fish oil could possibly attenuate MAO-B catalytic activity and elicit neuro-protective effects in the treatment of neurodegenerative and mental disorders.

Conclusion

The results of present docking studies shed light on the binding mode of omega-3 and omega-6 PUFAs present in fish oil within the active site of human MAO-B. It was demonstrated from the results of current research that omega-3 PUFAs differ in their mode of interaction within the active site of MAO-B, each omega -3 PUFA forming a bond with a different residue. On the other hand, omega-6 PUFAs mainly interact with residues Tyr 326, Tyr 435, and Gln 206 of the enzyme's active site by forming hydrogen bonds. It has been reported previously that these residues are involved in determining the functionality of the enzyme. Based on our findings, we propose that fish oil could confer defense against neuropathologies and/ or neurodegeneration by inhibiting the activity of MAO-B mainly through omega-6 PUFAs. Thus, incorporation of fish oil in daily life can be of great impact in the deterrence and treatment of neurodegenerative diseases. However, further preclinical behavioral and biochemical investigations are required to demarcate the beneficial effects of fish oil rich in PUFAs.

Conflict of Interest

Authors declare no conflict of interest

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