ISSN: 0975-766X
CODEN: IJPTFI
Available Online through *Research Article*
www.ijptonline.com

IN SILICO ANALYSIS OF OMEGA-3-FATTYACID FOR SUPERIOR REGULATION OF GLUCOSE HOMEOSTASIS

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Received on: 18.10.2016 *Accepted on: 11.11.2016*

Abstract

Omega-3 fatty acid has a significant role as anti-inflammatory sensors and control lipid metabolism. Thus, it is considered to be a precaution agent to control hyper-cholesterol, depression, diabetes, and Alzheimer. It binds to protein PPARγ/GPR120 and inhibits phosphorylation NFκB protein of IKKβ and other inflammatory precursor. In the current work, nine omega-3 fatty acid and PPARgama/GPR120 protein were taken to study binding affinity and complex omega-3 fatty acids with both PPAR Gama and Gpr120; respectively. This was docked to NFκB in order to predict the minimum energy configuration and the best lead of all omega-3 fatty acid. The simulation results predicted ETE (Eicosatrienoic acid), ETA (Eicosatetraenoic acid) and DPA Docosapentaenoic acid) based on geometric shape configuration as well as the α-linolenic acid having minimum energy when interact with both Gpr120–omega-3 complex bind to NFκB having energy of -102.21 kcal/mol and PPARγ–omega-3 complex bind to NFκB having energy of - 53.53 kcal/mol. Lower binding energy of native complex indicates better interaction and good compatibility with the flavopiridol compound.

Keywords: Omega-3, Glucose Homeostasis, PPARγ–omega-3 complex bind, NFκB

1. Introduction

Drug innovation is significant for health care improvement and for organizations engaged in drug discovery development and research. In silico studies are carried out through the computer simulation, which have a challenging task and have the potential in medicine to speed the drugs' discovery rate while reducing the need for expensive lab work and clinical

trials. There are five in silico methods in drug discovery, namely the Molecular docking, Virtual High through put screening, QSAR (Quantitative structure-activity relationship), Pharmacophore mapping, and the Fragment based screening.

Docking in the Molecular docking is the computational determination of binding affinity between molecules (protein structure and ligand). Given a protein and a ligand find out the binding free energy of the complex formed by docking them. Docking or Computer aided drug designing can be broadly classified as "Receptor based methods". It uses the target protein structure and "Ligand based methods" [1] by employing the 3D structure of the target receptor to search for the potential candidate compounds that can modulate the target function. These involve molecular docking of each compound in the chemical database into the binding site of the target and predicting the electrostatic fit between them. The compounds are ranked using an appropriate scoring function, where the scores correlate with the binding affinity. In the absence of the target structural information, ligand based method make use of the information provided by known inhibitors for the target receptor. Structures similar to the known inhibitors are identified from chemical databases by variety of methods, such as similarity and substructure searching, pharmacophore matching and the 3D shape matching method. Virtual High Throughput Screening is a computational method, where large libraries of compounds are assessed for their potential to bind specific sites on target molecules such as proteins, and well-matched compounds tested. Virtual screening (VS) is a computational technique used in drug discovery research by using computers. It deals with the quick search of large libraries of chemical structures in order to identify those structures which are most likely to bind to a drug target, typically a protein receptor or enzyme.

The QSAR is a statistical approach that attempts to relate physical and chemical properties of molecules to their biological activities. It is applied to predict the molecular properties from their structure without performing the in-vitro or in-vivo experiments, thus it saves time and resources [2].Various descriptors such as the molecular weight and the number of rotatable bonds LogP are commonly used. Many QSAR approaches are in practice based on the data dimensions. A pharmacophore is a set of features together with their relative spatial orientation that capable to interact with a particular biological target such as Hydrogen bond donors and acceptors, positively and negatively charged groups, hydrophobic regions and aromatic rings. It depends on atomic properties rather than element types. It does not depend on specific chemical connectivity. Pharmacophore mapping is the process of deriving a 3D pharmacophore that

developed by specifying the nature of the key pharmacophoric features and the 3D distance map among all the key features. Creative data mining may provide useful knowledge on protein-ligand interactions from these databases, with potential use in the design of docking algorithms or scoring functions. Testing of docking algorithms, on the other hand, requires a particular processing of both the protein and ligand structures, so that the given docking program has all the required data to perform the simulation. Several databases containing information on ligand molecules found in the Protein Data Bank (PDB), and on protein-ligand interactions (PDB-ligand [3], PLD [4], PDBsum [5], Hic-Up [6], Relibase [7,8] and MOAD [9]) have been released. Furthermore, a few databases collecting data on protein binding sites found in the PDB have been recently reported [10,11,12,13].

Typically, the atomic contacts between two molecules are determined based on a distance criterion. Thus, in several reports a contact between two atoms is registered if the distance between them is below a fixed cut-off value. For example, in Relibase [7,8], a value of 7 Å was used. In a previous work, a cut-off of 4.3 Å was used to collect protein-small ligand interactions [14]. In a stricter approach, a contact is postulated if the distance between the two atoms is not larger than the sum of their van der Waals radii, plus certain tolerance value (generally in the range of 0.5 – 1.0 Å) [4, 7, 8, 14]. For the prediction of the proteins' tertiary structure, three approaches can be used, namely Homology modeling (Comparative Modeling), Threading, and the Ab initio structure prediction. The Homology Modeling is the simplest and most reliable approach. It has been observed that even proteins with 25% sequence identity fold into similar structures. This method does not work for remote homologs (< 25% pair wise identity). The homology modeling algorithm states that "given a query sequence Q, and a sequence database of known protein structures, find a protein P such that P has high sequence similarity to Q and return P's structure as an approximation to Q'structure". The homology modeling main steps are: i) finding known structures (templates) related to the query sequence whose structure has to be modeled, ii) aligning the query sequence to the template(s), iii) constructing variable side-chains and main-chains (loops, insertions and deletions), and iv) modeling refinement, assessing the model(s) built and selecting the most native conformations. Threading is a method for fold recognition that used for sequences with sequence identity ≤30%. For a given sequence and a set of folds that available in the PDB, this approach aims to investigate if the sequence can adopt one of the folds of known structure or no. Fold assignment and alignment are achieved by threading the sequence through each of the structures in a library of all known folds. The homology modeling and threading techniques require

knowledge of known structures, while the Ab initio (de novo) structure prediction has no such limitations. It starts with the assumption that the native structure of a protein is at the global free energy minimum. Moreover, the Virtual Screening results are highly dependent on the database and target preparation. Databases need to be tuned, thus a considerable effort should be put into filtering out molecules with undesirable physical properties and chemical functionalities such as high molecular weight, reactive groups, too many rotating bonds and unsuitable lipophilicity. Servers for Homology (Comparative) Modeling: RAMP [15] and http://software.compbio.washington.edu/ramp/.SWISSMODEL: http://swissmodel.expasy.org [16]. Servers for threading (fold recognition) are 3-D PSSM http://www.sbg.bio.ic.acuk/~3dpssm [17].

Protein-ligand docking is a widely used computational tool that tries to predict the most favorable structure of the complex formed between a given protein-target (often an enzyme) and a small-molecule ligand. It can be considered as part of the molecular docking domain to predict the most favorable structure of the intermolecular complex formed between two or more generic constituent molecules, a definition which also encompasses the field of protein-protein docking [18,19]. Molecular recognition events are essential in many bio-logical processes, including signal transduction, cell regulation and other macromolecular association actions. These processes rely on a variety of atomic-level scale events including enzyme-substrate, drug-protein, drug-nucleic acid and protein-protein recognition [20] that are of great therapeutic importance. Docking offers a relatively fast and economic alternative to standard experimental techniques, allowing the prediction in silico (i.e. computationally) of the binding modes and affinities for molecular recognition events such as the ones outlined above [21]. 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 [18, 19, 22, 23]. In terms of scoring functions the number of available alternatives is also quite vast, even though the availability of some scoring functions is sometimes restricted to specific software packages. The most common scoring functions normally applied can be divided into three major classes: force-field-based, empirical, and knowledge-based scoring functions. In addition to good accuracy, an important condition for scoring functions is that they should be fast enough to allow their application to a large number of potential solutions, a feature that implies a number of simplifications that end to reduce the complexity and computational cost of the scoring functions at the cost of accuracy. Popular examples of scoring functions include ChemScore [24], DrugScore [25,26], D-Score [27], Fresno [28], F-Score

[29], G-Score [27], GoldScore [30], SMoG score [31], and X-SCORE [32]. Omega-3 fatty acids (ω-3 Fas or n-3 FAs) belong to the PUFA family [33]. They are considered to be source for glucose regulation, lowering the increased blood fats level and depression. The n-3 FAs acts as anti-inflammatory and anti-depression [34]. They influence the cell and tissue behavior through changing the concentration of hormone/metabolite as well as direct/indirect association to various receptors such as PPARγ (peroxisome proliferator activated receptor- γ) and GPR120 via NFKB [35, 36]. The PPARα, β/δ, &γ are differentiated by growth expression, distribution in cell/ tissue, having specific ligands and belong to family of nuclear receptor PPAR/GPR120 (G-protein coupled receptor). Researchers observed that both PPAR γ and GPR120 protein are activated by n-3 fatty acid that play major role in lipid metabolism and glucose homeostasis [36,37]. Furthermore, high level of circulating insulin is due to secretion of glucagon by GPR120 via binding of n-3 fatty acids [38]. Studies depicted that n-3 fatty acid binds PPARgama and NFKB, also PPARgama binds to NFKB which inhibits.

The PPARs act as physiological sensors and regulator for the genes in lipid metabolism. Ligand activated PPAR acts as transcription factor and activated by fatty acids. The n-3 Fatty acids and PPARa are keys regulator for biosynthesis of acetylcholine and support in development of cognitive function. Research established that low concentration of omega-3diet leads to behavior impairment and high concentration of saturated fatty acid, which increases blood pressure and cholesterol.

Omega-3 maintains cellular signaling, membrane compositional changes, permeability selection and fluidity. It helps PPAR to protect neuron and inflammation in the central nervous system [39]. Furthermore, n-3 supplement also reduces hypertension, ischemia growth and help in proper functioning of blood brain barrier and spatial memory improvement. Moreover, a study on obese mice [40] given dietary omega-3 proved a loss of energy homeostasis when changed in GPR120, which confirmed it as receptor for omega-3.Omega-3 diet support GPR120 to activate stimulates anti-inflammatory activity. Additionally, anti-inflammatory activity GPR120 stimulate by various signaling pathway [41]. In the current study, it is assumed that N-3 FA binds to PPARgama & GPR120 and complex bind NFKB and studying binding affinity and energy of complex to predict superior leads from omega-3 fatty acids and natural therapeutic. This can incorporate in diet that regulates glucose and can prevent various diseases, such diabetes, Alzheimer, hyper cholesterol, reduce depression etc. Further study can also help to identify novel leads similar to best ligands by performing virtual screening, phamarcophore modeling and computer aided drug design. The remaining sections are

organized as follows. Section 2 presents the methodologies used in the proposed approach. Section 3 reports the obtained results with discussion and analysis. Section 4 includes the conclusion of the present work.

2. Material and Methods

2.1. Data Mining and Ligand Structure

Ligand structures of nine Omega-3 fatty acids, namely Hexadecatrienoic acid (HTA), Alpha-linolenic acid (ALA), Stearidonic acid (SDA), Eicosatrienoic acid (ETE), Eicosatetraenoic acid (ETA), Eicosapentaenoic acid (EPA), Heneicosapentaenoic acid (HPA), Docosapentaenoic acid (DPA) and Docosahexaenoic acid (DHA). The structure file and properties were retrieved from PubChemdatabase and converted to PDB file using Open Babel software.

2.2. Protein Structure and Modeling

Receptor Protein crystal structure Human Peroxisome Proliferator-Activated Receptor Gama ligand binding domain (PPARγ) PDB ID: 2ZK0 and Protein crystal IKAPPABALPHA/NF-KAPPAB complex (PDB ID: 1IKN) retrieved from protein data bank RCSB (Research Collaboratory for Structural Bioinformatics). In the current work, protein modeling of GPR120 by Swiss model using template 4GRV.1.A (Neurotensin receptor type 1, lysozyme chimera) homology 30% and resolution 2.80 A^0. Refinement and validate using SAVES and ModLoop.

2.3. Protein –ligand and Complex Docking

The PatchDock and Firedock are employed to study binding crystal structure of PPARgama with the nine ligands omega-3 fatty acid and complex ofPPARgama and omega-3 fatty acid with NFKB. Moreover, the GPR120 was docked with nine ligands omega-3 fatty acid and complex of GPR120 and omega-3 fatty acid with NFKB. Finally, the best docked was and analyzed based on Geometric shape complementarity score, which approximated the interface area of the complex and Atomic contact energy.

2.4. The PatchDock User Interface

The PatchDock [21] and Firedock [42] are employed to study binding crystal structure of PPARgama with the nine ligands omega-3 fatty acid and complex of PPARgama and omega-3 fatty acid with NFKB. FireDock method for flexible refinement and scoring of protein–protein docking solutions was developed by Andrusier *et al*. [42]. In the current work, the web server is presented to provide a user-friendly interface for running this protocol online. It includes a side-chain optimization component. It allows a high-throughput refinement of up to 1000 solution candidates. The

method simultaneously targets the problem of flexibility and scoring of solutions produced by fast rigid-body docking algorithms. The output provides a list of refined complexes, sorted by a binding energy function, and a 3D visualization for observing and comparing between the refined complexes.

1. The PatchDock user interface includes several actions such as i) the request form of PatchDock. The receptor molecule and the ligand molecule are given either by the PDB code of the molecule (chain IDs are optional) or by uploading a file in PDB format, and ii) the solution page to present the geometric score, interface area size and desolvation energy of the 20 top scoring solutions. The user can use the 'show next 20' button to view solutions of lower score. The user can download each solution by pressing the solution link in the rightmost column or download an archive file (ZIP format) of the best solutions using the action button at the bottom of the page. Figures 1 through 3 illustrate the structure of the PPARγ, omega-3 fatty acid, GPR120 and IKAPPABALPHA/NF-KAPPAB and their model structure.

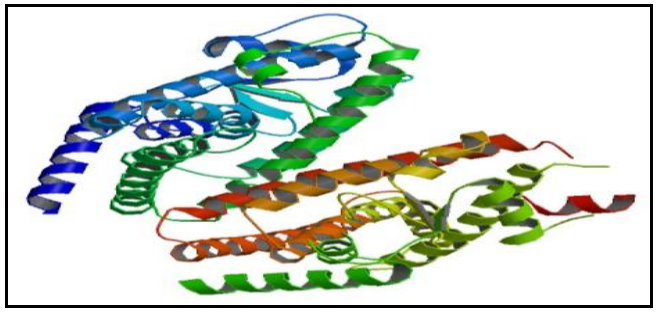

Figure1: Crystal Structure of Human peroxisome proliferator-activated receptor gamma(PPARγ) ligand binding domain (PDB ID:2ZK0)

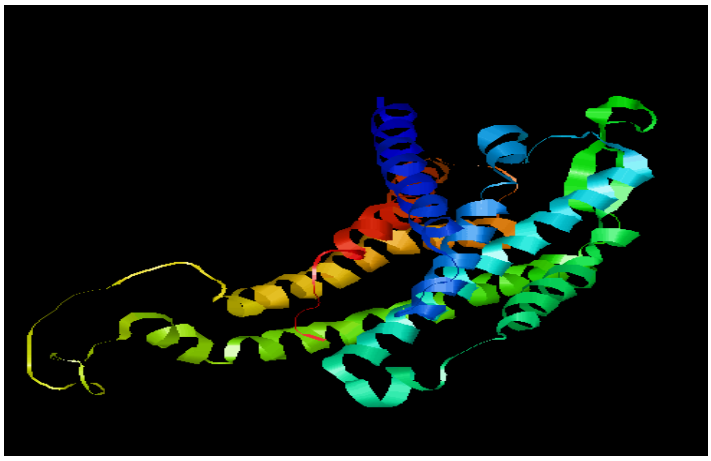

Figure2: Modeled structure of GPR120 template 4GRV (30%)

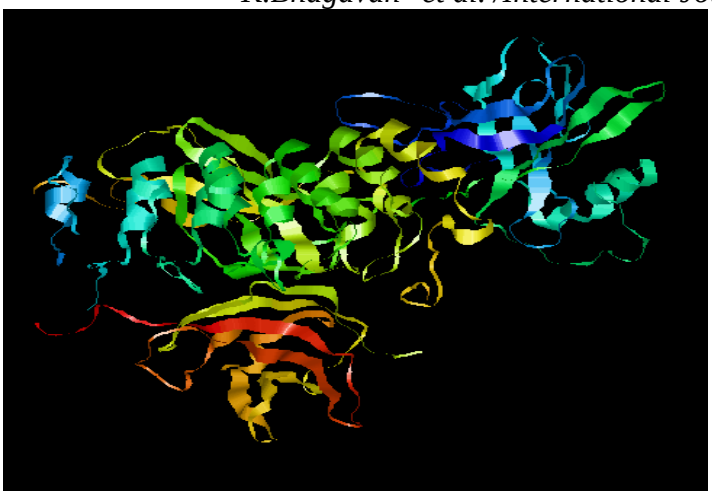

Figure3: Crystal Structure of IKAPPABALPHA/NF-KAPPAB COMPLEX (PDB ID: 1IKN).

3. Results and Discussion

In order to perform the docking analysis, the PPARγ receptor and omega-3 fatty acid ligand (1-9) complex binding sites residue and interaction type (i.e. bump, alkyl, pi alkyl, carbon, conventional and donor donor) are employed. The docking result of PPARγ receptor and omega-3 fatty acid ligands is as follows, where the input is two molecules in the PDB format. The molecules are either uploaded to the server or retrieved from the PDB or the user has only to enter the PDB code. In order to dock a certain chain or chains, the user should specify the desired chain ID or IDs. The *Complex Type* is used for the docking analysis in the current proposed method. PatchDock has different sets of parameters that optimized for different types of complexes. In the case of the enzyme–inhibitor complex type, the algorithm restricts the search space to the cavities of the enzyme molecule. In the case of the antibody–antigen complex type, the algorithm automatically detects the complementarity-determining regions (CDRs) of the antibody and restricts the search to these regions. In the case of protein–small ligand docking, the algorithm uses an optimized parameter set for small-size molecules.The output consists of automatically generated top 20 solutions. The geometric score, the desolvation energy [43], the interface area size and the actual rigid transformation of the solution are shown. Based on the results in [44], the CAPRI and other benchmarks [45] indicate that a near-native result is found among the top 100, and very often among the top 10 solutions. The PatchDock output is a list of candidate complexes between the user's specified receptor and ligand molecule which illustrated in Table 1.

Table 1: Docking analysis and Geometric shape complementarity score, approximate interface area of the complex and Atomic contact energy of omega-3fatty acid and PPARγ

Table 1: includes the Score that provides the geometric shape complementarily score, where the solutions are sorted according to this score. The Area gives the approximate interface area of the complex, while the ACE represents the atomic contact energy according to Zhang *et al*. [50] as shown in Figure 4. Lower binding energy of native complex indicates better interaction and good compatibility with the flavopiridol compound.

Simulation results predicted that ETE (Eicosatrienoic acid), ETA (Eicosatetraenoic acid) and DPA Docosapentaenoic acid) based on geometric shape configuration as well as the α-linolenic acid having minimum energy when interact with both Gpr120–omega-3 complex bind to NFκB having energy of -102.21 kcal/mol and PPARγ–omega-3 complex bind to NFκB having energy of - 53.53 kcal/mol.

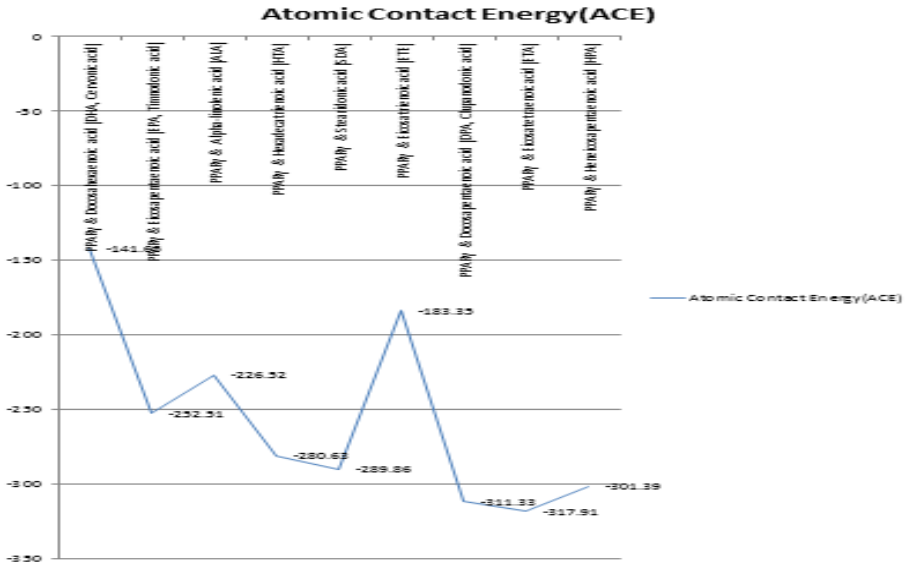

Figure 4: The ACE line plot between omega-3 fatty acid and PPARγ showing.

Figure 4 depicts that the ACE line plot between omega-3 fatty acid and PPARγ shows DPA and ETA with -3.17 and -3.11 values; respectively. Figure 5 illustrates the geometric shape complementary histogram.

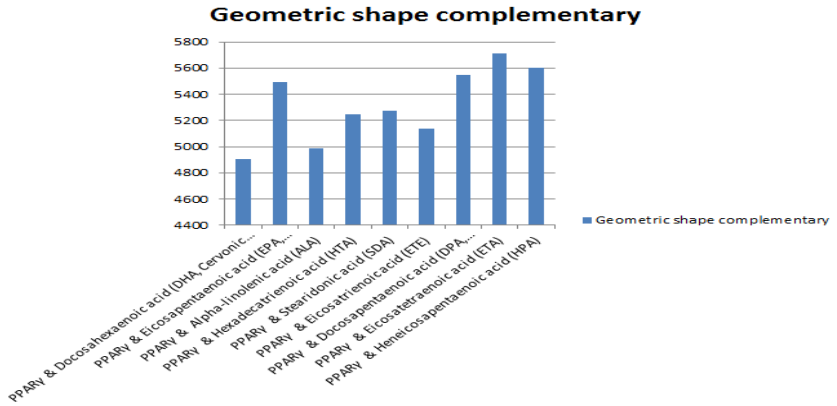

Figure 5: Geometric shape complementary histogram.

Figure 5 depicts shows the high score for ETA and DPA out of nine omega-3 fatty acid and PPARγ complex. The server output is a table of all the input solutions, where each row corresponds to a single input complex as illustrated in Table 2, where the table is sorted by the global energy values. Table 2 shows the PPARγ receptor and omega-3 fatty acid ligands complex docked with protein I-KAPPA-B-ALPHA/NF-KAPPAB complex PDB ID:1IKN for the Human Peroxisome Proliferator-Activated Receptor Gama ligand binding domain (PPARγ)PDB ID: 2ZK0.

Table 2: Docking analysis of PPARγ and omega-3 fatty acid complex docked with protein I-KAPPA-B-ALPHA.

Docked complex Receptor Ligands Complex	**Global Energy**	**ACE**	**HB**
Docosahexaenoic acid (DHA, Cervonic acid)	-49.33	-2.56	-3.94
Eicosapentaenoic acid (EPA, Timnodonic acid)	-49.33	-2.56	-3.94
Alpha-linolenic acid (ALA)	-53.53	-8.78	-0.97
Hexadecatrienoic acid (HTA)	-43.00	-6.69	-1.92
Stearidonic acid (SDA)	-49.33	-2.56	-3.94
Eicosatrienoic acid (ETE)	-49.33	-2.56	-3.94
Docosapentaenoic acid (DPA, Clupanodonic acid)	-51.87	-6.51	-0.75
Eicosatetraenoic acid (ETA)	-43.00	-6.69	-1.92
Heneicosapentaenoic acid (HPA)	-43.00	-6.69	-1.92

The docking analysis depicted in Table 2 consists of the global energy, atomic contact energy (ACE), and the Hydrogen and disulphide (HB) energy of PPARγ/omega-3 fatty acid complex docked with protein I-KAPPA-B-ALPHA. Table 2 illustrates that the refined complex structures are generated for up to 100 lowest energy candidates. Different complexes can be viewed simultaneously for comparison and the 3D structures. Table 2 can be sorted by different energy terms, such as the attractive and repulsive van der Walls forces, the ACE and the contribution of the hydrogen bonds (HB) to the global binding energy.

The final ranking stage attempts to identify the near-native refined solutions. The ranking is performed according to a binding energy function that includes a variety of energy terms, such as the desolvation energy (ACE), van der Waals interactions, partial electrostatics, hydrogen and disulfide bonds, π-stacking/aliphatic interactions, and rotamer's probabilities. The ranking output is a table of all the input solutions that ranked by the global energy value. The refined complex structure is generated for up to 100 low-energy candidates. Figure 6 demonstrates the global energy line plot between omega-3 fatty acid-PPARγ complex NFκB.

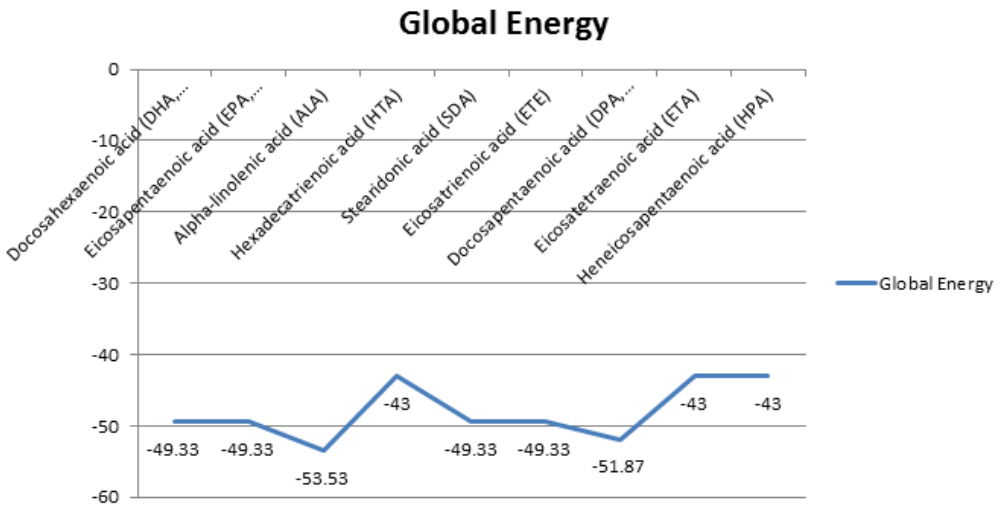

Figure 6: The global energy line plot between omega-3 fatty acid-PPARγ complex.

Figure 6 depicts that the values of the DPA and α-linolenic acid are -51.87, and -53.53; respectively. Moreover, the docking result of GPR120 (FFAR4) free fatty acid receptor and omega-3 fatty acid ligands is demonstrated in Table 3, where the receptor is Model GPR120 of human FFAR4.

Table 3: Docking analysis consisting of the Geometric shape complementarily score.

Ligands	Score	Area	Pen	ACE
Docosahexaenoic acid (DHA, Cervonic acid)	5692	626.8	-1.86	-276.52
Eicosapentaenoic acid (EPA, Timnodonic acid)	5574	619.2	-1.86	-227.67
Alpha-linolenic acid (ALA)	4954	529.3	-1.71	-193.49
Hexadecatrienoic acid (HTA)	5696	606.3	-1.47	-203.53
Stearidonic acid (SDA)	5486	652.6	-2.32	-259.59
Eicosatrienoic acid (ETE)	5872	670.4	-1.71	-327.36

Docosapentaenoic acid (DPA, Clupanodonic acid)	5586	612.2	-1.92	-296.5
Eicosatetraenoic acid (ETA)	6148	685.9	-1.78	-276.92
Heneicosapentaenoic acid (HPA)	6164	672.1	-1.89	-276.24

Table 3 includes the docking analysis that consists of the Geometric shape complementarity score, approximate interface area of the complex and atomic contact energy of GPR120 (FFAR4) free fatty acid receptor and omega-3 fatty acid ligand. Figure 7 illustrates the geometric shape complementary histogram. Furthermore, Figure 8 illustrates the ACE line plot between omega-3 fatty acid and GPR120.

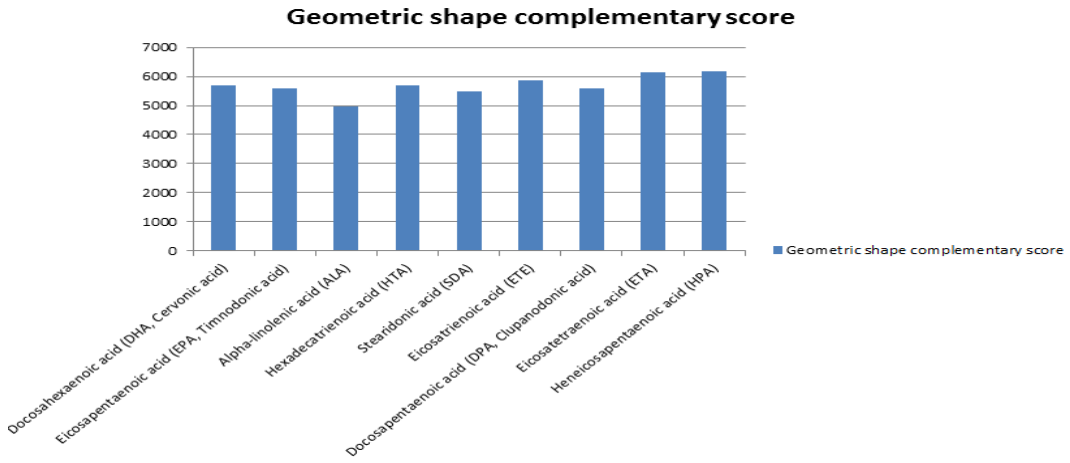

Figure 7: Geometric shape complementary histogram represents.

Figure 7 represents the high score for ETA and HPA out of nine omega-3 fatty acid and GPR120 complex.

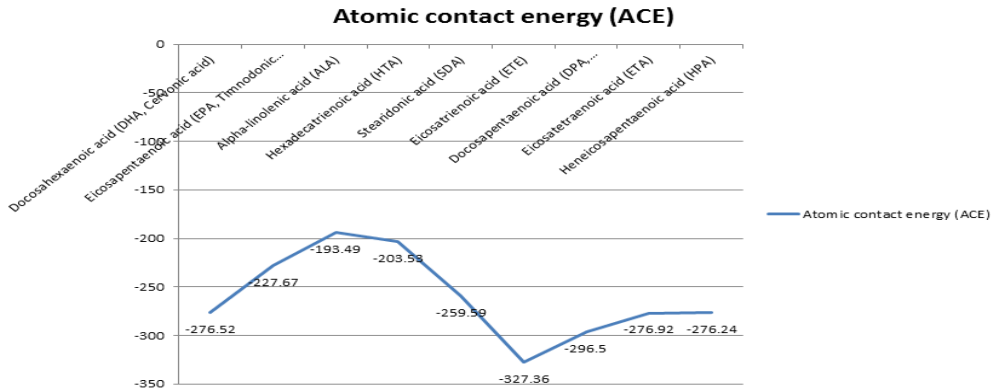

Figure 8: ACE line plot between omega-3 fatty acid and GPR120.

Figure 8: Illustrates the values of ETE and ETA are -327.36 and -293.36; respectively. Table 4 includes the docking analysis consisting of the Global energy, ACE, and HB of the GPR120 and omega-3 fatty acid complex docked with protein I-KAPPA-B-ALPHA/NF-KAPPAB Complex PDB ID:1IKN for model GPR120 of human FFAR4.

Table 4: Docking analysis of the GPR120 and omega-3 fatty acid complex docked with protein I-KAPPA-B-ALPHA

Docked complex Receptor Ligands Complex	**Global Energy**	**ACE**	**HB**
Docosahexaenoic acid (DHA, Cervonic acid)	-46.49	-3.09	-2.46
Eicosapentaenoic acid (EPA, Timnodonic acid)	-98.80	-17.96	-0.76
Alpha-linolenic acid (ALA)	-102.21	-22.26	-1.74
Hexadecatrienoic acid (HTA)	-100.82	-16.13	-4.58
Stearidonic acid (SDA)	-99.45	-18.24	-1.08
Eicosatrienoic acid (ETE)	-99.17	-17.32	-0.83
Docosapentaenoic acid (DPA, Clupanodonic acid)	-101.24	-16.30	-4.83
Eicosatetraenoic acid (ETA)	-102.70	-15.09	-4.34
Heneicosapentaenoic acid (HPA)	-103.75	-17.92	-3.66

Table 4 reports that the mechanism through which metabolites of PUFAs mediates GPR120 activity. It is obvious that the LXA4, which is an endogenously synthesized nonclassic eicosanoid has highest binding affinity for GPR120 in comparison to the PUFAs. Furthermore, the metabolites considered in the study have a binding energy of -102.21 kcal/mol and PPARγ–omega-3 complex bind to NFκB with energy of - 53.53 kcal/mol. Figure 9 demonstrates the global energy plot for the GPR120 and omega-3 fatty acid complex docked with protein I-KAPPA-B-ALPHA.

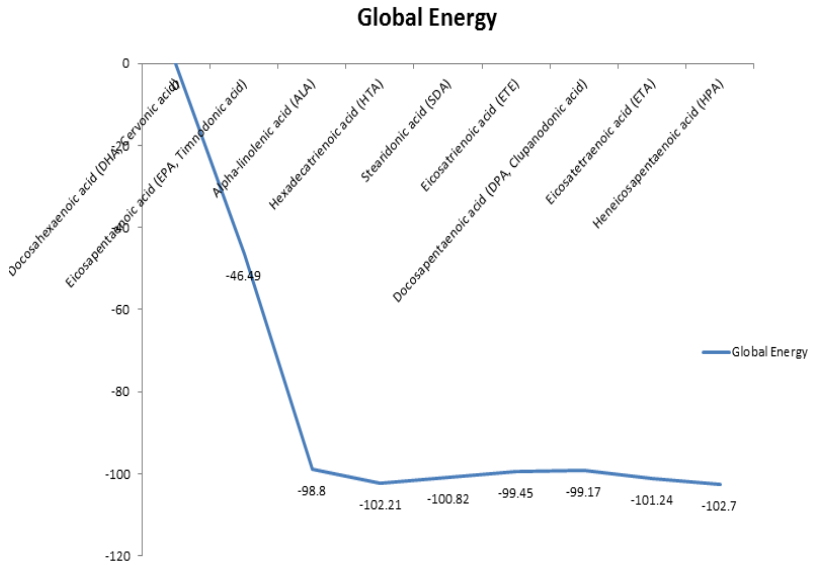

Figure 9: Global energy plot for the GPR120 and omega-3 fatty acid complex docked with protein I-KAPPA-B-ALPHA

Figure 9 reports that the HTA and the α-linolenicacid have values of -100.82 and -102.21; respectively. The preceding results established that the proposed Insilico design and analysis of the Omega-3-Fatty acid based PPARg & GPR120 complexes exhibits higher binding affinities for better regulation of Glucose Homeostasis. The results of the present study are consistent with the hypothesis that PUFAs and their metabolites such as lipoxins, resolvins and protectins interact with BDNF and possibly, other neurotrophic factors and thus bring about their beneficial actions both in diabetes mellitus and neurological conditions such as depression Alternatively, the beneficial actions of BDNF in these clinical conditions could also be attributed to its interaction with PUFAs.

Thus, a better understanding of the close interaction(s) between BDNF and PUFAs and their metabolites may pave way for the development of newer therapeutic strategies in diabetes mellitus, depression and other clinical conditions in which they are believed to play a significant role.

However, there are some limitations that can be addressed as follows. A major problem in structure-based virtual screening applications is the appropriate selection of a single or even multiple protein structures to be used in the virtual screening process.

Nevertheless, A priori software can provide superior results in a virtual screening experiment of the protein structure(s). Scoring functions implemented in docking programs make various assumptions and simplifications in the modeled complexes evaluation without considering the number of physical phenomena that determine molecular recognition in entropic effects. Free-energy simulation techniques have been developed for quantitative modeling of protein–ligand interactions and the prediction of binding affinity. The calculation of shape complementarity implicitly takes hydrophobic effects into account; however, a large (and sometimes the largest) contribution to the hydrophobic effect comes from desolvation of hydrophobic ligands (such as in HIV protease), which is insufficient accounted for in docking scores. It can be significantly underestimated relative to other scoring terms in some active sites.

Furthermore, precise modeling and scoring of electrostatic interactions continues to be a major challenge for contemporary scoring functions. As mentioned above, simple Coulombic models are still applied for these purposes in a number of cases and have the tendency to grossly overestimate charge–charge interactions or create artificial ones. The fairly unspecific inhibition by such compounds can be attributed to dominating hydrophobic character and aggregation effects that tend to favor their detection in both docking simulations and screening assays.

3. Conclusion

Omega-3 fatty acids are polyunsaturated fatty that have a significant role for normal metabolism. In the current study, the N-3 FA was docked to PPARgama & GPR120 and complex bind NFKB to study binding affinity and global energy of complex. The experimental results established minimum energy configuration with NFκB which is -53.53 as well as the GPR120-αlinolenic acid proved minimum energy configuration with NFκB of -102.21 value, from the binding energy of PPAR Gama –α-linolenic acid.

Furthermore, from the prediction based on minimum energy configuration, both PPAR Gama and GPR120 demonstrated effective binding with α-linolenic acid. Moreover, based on the geometric shape configuration, it was reported that both PPAR Gama and GPR120 had the ETE, ETA, and DPA as the best lead for omega-3 fatty acid. Consequently, based on the proposed study this omega-3 fatty acid can be added as substitute diet to regulate lipid, glucose and other metabolic pathway. Further studies are recommended to validate these as leads using intelligent bioinformatics tools.

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