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Letter to editor

Dear Editor,

I wish to submit a letter in response to your previous mail and letter sent by

Ardavan Abiri (Corresponding author)

Department of Medicinal Chemistry, Faculty of Pharmacy, Kerman University of Medical Sciences, Kerman, Iran.

a.abiri@kmu.ac.ir

ard.abiri@ymail.com

addressing my article entitled "In silico molecular docking of astaxanthin and sorafenib with different apoptotic proteins involved in hepatocellular carcinoma" published in 6th of March 2019 on Biocatalysis and Agricultural Biotechnology. (BAB 2018 820. Special Issue E & B. Managing Editor: MubarakAli).

Ref: "Eschatological Scrutiny of Unprofessional Usage of Molecular Docking; How Unreliability in Computational Methods Arises from Amateurish Mistakes?" for consideration in *Biocatalysis and Agricultural Biotechnology*.

I wish to bring to your notice that the research work submitted as manuscript to BAB was a special issue pertaining to the conference proceeding. This insilico work was part of doctoral degree in Biochemistry. The intention was to find out the variation in binding potential of Astaxanthin with various growth factors and apoptotic proteins involved in hepatocellular carcinoma.

The letter addressed by him showcased the pitfalls of insilico methods among biologist which is more common now a days. Though it is acceptable, as researcher he should understand that the perception and hypothecation of science definitely varies with individual. That too, the field of molecular modelling and docking involves interdisciplinary knowledge on biology of proteins, chemistry of atoms, biophysics, molecular and quantum mechanics. Moreover, the results will also vary as per the configuration of working system, accuracy of software and visualisation tools used.

Hence, I suggest he can give a common review article on the purpose, methodology and usage of insilico tools in biology without targeting my article which is already being published. Anyhow I have given following references as evidence to my paper. As a good gesture, he would have mailed me directly denoting the mistakes which would be considered and taken care during the forthcoming projects.

Thanks and Regards

Dr.Anuradha.

1. Molecular docking of astaxanthin and sorafenib was carried out using online docking site (https://www.dockingserver.com/web) (Bikadi and Hazai, 2009) which is the basic docking method for primary researchers. This method is used just to check the binding affinity of the compound and not to confirm or to prove the binding site. It also explains only the interaction between astaxanthin and apoptotic protein with minimum binding energy.

Docking server was designed with 3 steps:

The proteins are uploaded as a pdb file, or can directly be downloaded (after keyword search) from Protein Data Bank (www.rcbs.org). Small molecules present in the pdb files are added to the ligand folder. More accurate protein partial charge calculation using quantum chemical methods were applied.

The ligand can be directly downloaded from PubChem database, uploaded or drawn in. beside singe ligand multiple ligand was also downloaded in sdf files format to enable high throughput docking of ligand libraries.

In the docking window multiple ligands and dockings are done and individual docking calculation are carried out with high throughput screening. The docking calculationswas started with default parameters moreover it is also allowed to set manual docking parameters for more advanced users. Finally, docking results are automatically processed in different ways. Reverse docking was not performed since it is useful for organic chemists which are not dealing with the biological activity of molecules.

2. Proteins used in this article are downloaded from RCSB PDB (Protein Data Bank) which is ready for molecular docking purposes. Since many compounds are found for similar protein based on their resolution and X-ray diffraction method we have selected different proteins from homo sapiens species.

Example: We have selected Bcl-2 i.e 2W3L protein for docking purpose with resolution of 2.1 Å. Anti-apoptotic Bcl-2 protects cells from apoptosis by binding to pro-apoptotic members of the Bcl-2 family thereby playing a role in tumor survival in response to chemo- or radiation therapy. A series of phenyl pyrazoles that have high affinity for Bcl-2 and rationalise the observed SAR by means of an X-ray crystal structure was described by Porter et al., 2009).

3. Caspase 9: PDB ID: 2AR9.

The docking analysis was carried out between astaxanthin and 2AR9 and the results were tabulated in **Table 13**. The minimum binding energy between these two compounds was −4.62 kcal/mol. The results showed that the seven hydrophobic bonds of 2AR9 was interacted with astaxanthin compound that involves phe348, phe351, ile396, tyr397, met400, cys402, ile403 residues. The binding mechanism of sorafenib with 2AR9 was also studied using molecular docking method. The docking results show that sorafenib forms hydrogen bonds with ser175, polar bonds with arg178, hydrophobic bonds with leu177 and halogen bonds with asp254, gly255 of 2AR9 receptor (**Table 14**). Interference with the docking interaction by small molecules could potentially prevent the inhibition of caspase-9 activation by phosphorylation at Thr^{125} and therefore promote apoptosis, for instance in cancer cells in which classical MAPKs are constitutively activated. The inhibition of caspases represents a highly promising avenue for intervention in a number of conditions involving apoptosis-mediated cell and tissue damage in acute and chronic diseases (O'Brien and Lee, 2004). Many potent caspase inhibitors have been synthesized based on the structures of caspase peptide substrates. 12 human

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caspases are known and they demonstrate a stringent specificity for an aspartic acid residue in the P1 position. They use their active-site thiol to cleave peptide/protein targets exclusively C-terminal to an aspartic acid residue. Furthermore, caspases are selective for residues in the S4 and S1′ subsites (Ganesan et al., 2006a,b). Active caspases are $(\alpha\beta)_2$ heterotetramers that can be described as homodimers of heterodimeric subunits with two active sites located in close proximity to the dimer interface (Ganesan et al., 2006a,b). Thermodynamic analysis and NMR experiments revealed that residues from the dimer interface are critical for stabilizing the active-site loops (Keller et al., 2009, 2010).

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V. Suganya, V. Anuradha*

PG and Research Department of Biochemistry, Mohamed Sathak College of Arts & Science, Sholinganallur, Chennai, Tamil Nadu, India

E-mail address: vanuradha2712@gmail.com (V. Anuradha).

* Corresponding author. Tel.: +91 9841751450.