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Research Article

MOLECULAR DOCKING OF STATINS AS *CASPASES* INHIBITOR IN THE REGIMEN OF TUMOUR

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ABSTRACT

R*ecently it has been approved by the US-FDA that statins are also known to exhibit activity in the treatment of cancers. The key effector molecule in apoptosis is Caspases, being potential targets for pharmacological modulation of cell death. The activity of Caspases increases at sites of cellular damage in a number of diseases. The objective of the present study is to understand the caspases (1, 2 and 3) inhibiting activity of statins; Mevinoline, Pitavastatin, Compactin and Fluvastatin by molecular docking studies. The ligands were docked with the protein by ARGUS LABS 12.0 software and were visualized using PyMOL viewer. The study carried out clearly indicated that statins have better binding pose and interaction with caspases 1, 2 and 3. Among the four statins, Mevinoline showed a best binding pose with least energy for the all Caspases. Mevinoline only inhibits Caspase 3 with lowest binding score -11.36; the active site residue at Tyr 361 and Arg 40. Compactin revealed -10.36 kcal/mol of binding affinity with only caspase 1 and key amino acid residue at Arg 371, Lys 372 and Tyr 360. The above study clearly indicates that statins have a better binding pose and interaction with caspases 1, 2 and 3.Compactin revealed a lower binding score with caspases 2 and it may help to control autoimmune diseases like Rheumatoid Arthritis, Myasthenia gravis, SLE et,. Mevinoline exhibited an excellent inhibitory activity with caspases 3 would be an approach in the treatment of cancer.*

KEYWORDS: *Caspases, Statins, Cancer, Mevinoline.*

INTRODUCTION

Statins are known to act as an anti-atherosclerotic agent. They are greatly involved in the reduction of the LDL Cholesterol present within the body and as a result reducing the risk of coronary heart diseases, both primarily and secondarily [1-3]. The inhibition of the HMG CoA *reductase* is found to have beneficial pleiotropic activities as there is the generation of a number of isoprenoids which are essential for various cellular functions which is obtained from the cholesterol synthesis where the control of cell growth and differentiation is found. They are even known to be involved in the formation of bones and prevent the formation of tumor [4,5]. Recently, according to the literature studies, statins have been known to possess the property of acting against cancer. Thus, due to it's already existence in the field, it has become a choice of drug in the diagnosis of malignancy in this concomitant world [6-9].

The inhibition of mevalonate, which is the product of HMG CoA reductase reaction, results in the pleiotropic effects and it is generally divided under two categories namely, intracellular signaling pathways and the other being the direct lipids [10]. As a result of these effects there would be many consequences like that of decrease in the secretion of lipoproteins, an inhibition of the cholesterol biosynthesis, more utilization and degradation of the low density lipoproteins, a halt in the oxidation of LDL cholesterol, etc [11]. The way that the statins are known to modulate the effects of these cholesterol is by causing a reduction in the accumulating of the esterified cholesterol into macrophages, a decrease in the inflammation process, the endothelial NO Synthetase is being increased, actions in the process of helping in the coagulation process and in the stabilization of atherosclerotic plaques. The activation of *caspases* selectively, would act as an approach in the treatment of tumour inflammatory actions and some of the long term viral infections within the body [12].

Under some of the beneficial activities of statins there has also been the reporting of a chemotherapy treatment by the inhibition of HMG CoA Reductase of the malignant cells where they are found to have increased activity [13, 14]. Thus the properties of acting against the tumor cells have been proved by both the *in-vitro* and *in-vivo* studies. So this inhibition of the growth of the tumor could be connected with the non-steroidal isoprenoids compound being reduced which causes an inhibition of the RAS dependent tumor cell growth due to the effect on RAS protein farnesylation. In rodents and rabbits it has also been proved that the risk of bone fractures are also decreased due to the increase in the mineral density of the bones [15].

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MATERIALS AND METHODS

Objective:

According to the recent findings of the US-FDA it has been come to know and approved by them that the statins, already acting as an anti-atherosclerotic and hypo-lipidemic agent, would undergo an activity even against malignancy. This particular activity could be seen as working out by the inhibition of the *caspases* enzyme by the statins. This is the main objective of this study and this is carried out through the use of molecular dockings. There is the uptake of four statins in this study which are, Mevinoline, Compactin, Fluvastatin, and Pitavastatin.

Experimental Work:

NCBI (National Centre for Biotechnological Information) was used in order to provide the *caspases* enzyme 1, 2 and 3 and then they were converted into the FASTA format. BLAST (BASIC LOCAL ALIGNMENT SEARCH TOOL) was made use of to check the alignments of the enzymes. The proteins were then taken from PDB (Protein Databank). 1RKW, 3RJM and 4RPY were the PDB codes of the caspases enzymes, Caspases 1, Caspases 2, and Caspases 3 respectively. The cross

checking of the active pockets present on the target proteins by the enzymes was done by the $CAST_p$ (Computer Atlas of Surface Topography of Protein) server. The designing of the ligands was done and Chem Sketch, ACD labs 12.0 was made use of in order to process and analyze the structures of Mevinoline, Pitavastatin, Compactin and Fluvastatin. Docking of the ligands along with the proteins was done with the ARGUS LAB 12.0 software and its visualization was done in the PyMOL viewer. Based upon the ligand-binding pockets of the templates, the selection of the binding sites of the molecules was done. The tools of Auto-Dock help in providing different methods for the analyzation of the docking stimulation results. Some of them to be listed could be that of visualization of the binding site, its energy, similarity by its conformation, and some of the other parameters like inhibition constant and intermolecular energy. For each of the four ligands the best poses in them were generated and the scores were attributed by the Auto dock 4.2 scoring functions. The score for the binding sites and the interaction of the protein and the enzymes are listed in the **Table 1.**

Table No. 1: Docking score and interaction of statin and Caspases

Drug name	PDB code	Docking score	Measurement of Interaction	Binding site
Mevinoline	1RWK	-9.55	2.3	Tyr 360
	3RJM	-9.834	2.7	Tyr 221
	4RPY	-11.36	2.4	Tyr 361
			2.5	Arg 40
Fluvastatin	3RJM	-7.729	2.3	Lys 480
			2.9	Lys 225
	4RPY	-9.03	3	Asn 28
	1RWK	-6.80	3	Arg 391
			3	Thr 389
Compactin	1RWK	-10.36	3	Arg 371
			2.4, 2.2	Lys 372
			2.8	Tyr 360
	3RJM	-10.86	-	-
	4RPY	-	-	-
Pitavastatin	1RWK	-7.65	2.7	Arg 374
			2.6	Arg 371
	3RJM	-9.49	3.2	Gln 129
			3	Arg 241
			3.1	Tyr 221
	4RPY	-	-	-

RESULTS AND DISCUSSION

Based upon the docking scores there is the ranking of the docking poses and the list of the docked ligands and their respective binding poses were tabulated. The ranking of the list was mainly based upon the energy of the binding of the proteins with the enzymes. Accordingly when the compounds possess lesser binding energy then they were found to be more active. This was the basic property inherited by the compounds in the docking studies.

The bonding of hydrogen with the other surrounding amino acids and the scoring function mentioned above lead to the affinity of the compounds for binding and there orientation in the active sites of the enzymes by the respective target compounds. The greater binding affinity of the enzyme with the ligand is analogous with the smaller score of dockings. There was the appearance of the best binding energy with all the caspases enzyme by the statin Mevinoline among all the other four where it showed the least binding energy when compared to the others. There was the inhibition of the caspases 3 enzyme by Mevinoline showing a least binding score of -11.36; the residues of the active site was seen at Tyr 361 and Arg 40. Compactin was found to show binding affinity only with Caspase 1 with a binding energy of -10.36 kcal/mol. Arg 371, Lys 372 and Tyr 360 were the key amino acids with which the binding poses were found for the Compactin statin. The resulting PyMOL view of the two statins, Mevinoline and Compactin along with their respective binding caspases are given in Fig 2.

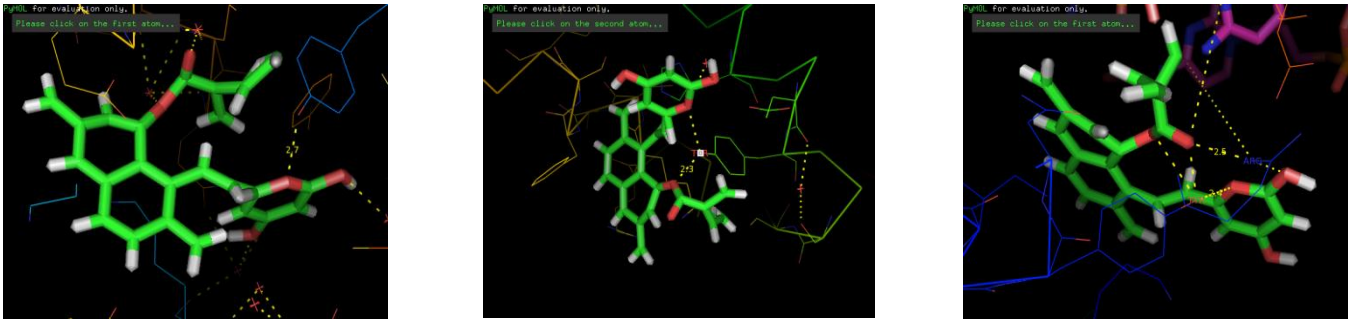

Fig. 1: PyMOL view of Mevinoline with 1RWK, 3RJM and 4RPY

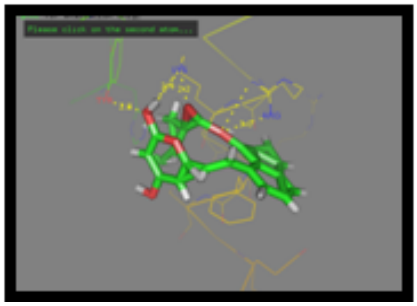

Fig. 2: PyMOL view of Compactin with 1RWK

CONCLUSION

It has been clearly viewed that among the four statins selected for the study, Mevinoline was found to see to expose least binding energy and show the best binding affinity with the enzyme caspases 1, 2 and 3. Among this caspases, the best inhibitory activity of Mevinoline was found to be with the caspases 3. Compactin showed a lower binding score only with Caspase 2. Then the study has been even continued with the other two statins with the three caspases enzyme. There has to be the more carrying out of the wet lab studies in this section to confirm this study. Thus statins already well known in the field of acting as a hypolipidemic and as an anti-atherosclerotic agent, each individually, could even act against tumor which was proved by studies. Thus it is found to be beneficial in the two way process.

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