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EXPLORING THE THERAPEUTIC POTENTIAL OF ROSUVASTATIN IN WOUND HEALING: A MOLECULAR DOCKING PERSPECTIVE

Dhilip S.[1], Dr. Pandian C.[2]* and Dr. Abdul Hasan Sathali A.[3]

[1]Department of Pharmaceutics, College of Pharmacy, Madurai Medical College, Madurai 625020, Tamil Nadu, India.
[2]Assistant Professor, Department of Pharmaceutics, College of Pharmacy, Madurai Medical College, Madurai-625020, Tamil Nadu, India.
[3]Principal, Professor and Head of the Department, Department of Pharmaceutics, College of Pharmacy, Madurai Medical College, Madurai-625020, Tamil Nadu, India.

***Corresponding Author: Dr. Pandian C.**

Assistant Professor, Department of Pharmaceutics, College of Pharmacy, Madurai Medical College, Madurai-625020, Tamil Nadu, India.

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ABSTRACT

Rosuvastatin, a synthetic HMG-CoA reductase inhibitor, has been shown in experiments to be beneficial in wound healing because it reverses the action of wound healing inhibitors like farnesyl pyrophosphate (FPP) and increases microvascular and endothelial activity, thereby improving wound healing processes. The work used molecular docking to analyze the interactions between rosuvastatin and nine wound healing-associated proteins (FGFR1, TGFR-β 1, VEGFR2 & 3, MMP9 & 12, ERB-β1, PDGFR, and RAGE). The molecular docking simulations were run with PyRx software, which predicted the binding relationships between rosuvastatin and the target proteins. Rosuvastatin's binding energies with each protein were computed to establish their affinity for the ligand. The docking studies showed that rosuvastatin had favourable binding interactions with all nine proteins, indicating that it has the ability to modulate their activity. MMP 9 proteins had the greatest binding energy among the target proteins, followed by TGFR-β1, ERB-β1, MMP-12, VEGFR 2, PDGFR, VEGFR 3, RAGE, and FGFR 1 in decreasing order of binding energies. In this study, we looked at the impact of Rosuvastatin (RSV) on nine proteins linked with poor wound healing. These nine proteins are linked and contribute to poor wound healing. The effect of RSV on these proteins was established utilizing molecular docking experiments. The PyRx application was used to conduct docking simulations between RC and the nine proteins related to poor wound healing. Visualizing the binding connections between rosuvastatin and the target proteins revealed molecular interactions and probable mechanisms of action. The findings highlight the rosuvastatin's therapeutic potential in targeting particular proteins involved in wound healing impairment, establishing it as a viable treatment for chronic wounds.

KEYWORDS: Rosuvastatin, molecular docking, wound healing FGFR1, TGFR-β 1,VEGFR2 & 3 , MMP9 & 12, ERB-β1, PDGFR and RAGE.

INTRODUCTION

The complex interplay between tiny molecules and proteins at the atomic level offers great potential for understanding the underlying processes of pharmaceutical treatments. Molecular docking emerges as an effective technique in this effort, providing insights into the complex interactions between drugs and target proteins.[1] In this work, we investigate the molecular dynamics of rosuvastatin, a synthetic HMG-CoA reductase inhibitor known for its many therapeutic uses beyond lipid control. The FDA has authorized the following indications: homozygous familial hypercholesterolemia, hyperlipidaemia, mixed dyslipidaemia, primary dysbetalipoproteinemia, hypertriglyceridemia, and cardiovascular disease prevention.[2]

Rosuvastatin inhibits the enzyme 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase. This enzyme is the rate-limiting step in cholesterol synthesis, slowing down the production of mevalonic acid from HMG-CoA. Furthermore, this increases the amount of low-density lipoprotein receptors on hepatocyte membranes, which promotes low-density lipoprotein catabolism. HMG-CoA reductase inhibitors also lower high-sensitivity C-reactive protein (CRP). They also exhibit pleiotropic properties, including as inhibition of platelet aggregation, anticoagulant effects, reduced inflammation at the site of a coronary plaque, and improved endothelial function.[2]

It has been experimentally proved to be useful in wound healing because it reverses the action of wound healing inhibitors such as farnesyl pyrophosphate (FPP) and

increases microvascular and endothelial activities, hence improving wound healing processes.[3] Furthermore, it inhibits the creation of certain proteins in bacteria by disrupting several cellular processes and metabolic pathways. This improves its capacity to inhibit the synthesis of important MRSA toxins, delaying the progression of septic skin sores.[4]

The wound healing process is a complicated and important part of restoring the skin's barrier function. It involves a complex interplay of components including blood cells, cytokines, and growth factors.[5] Wound healing may be separated into four stages: coagulation, inflammation, cell proliferation, and tissue regeneration. Each phase is intricately interrelated and requires precise synchronization to achieve optimal wound healing.[6] Dysregulation in any of these steps will results in impaired healing which subsequently leads to health and socioeconomic burden. Chronic wounds (diabetic ulcers and pressure ulcers) are difficult to treat because of inflammation, reduced oxygen supply, and bacterial development. Because of the complex metabolic dysfunction inside the wound environment, addressing these wounds remains an important medical requirement.[7] Receptor for advanced glycation end products is linked to delayed wound by increasing proapoptotic signalling, reactive oxygen species, TNF-α, IL 6, MMP-2, 3 & 9, and decreasing production of PDGF, VEGF.[8] Growth factors such as TGF-β, PDGF, FGF and EGF promote cell proliferation, granulation tissue formation, angiogenesis, and tissue healing.[9,10,11] VEGFR 2 and 3 are related with angiogenesis and lymphangiogenesis.[12] Matrix mettaloproteinases like MMP 9 & 12 also plays a role in wound healing by regulating cell migration and monitoring angiogenesis by producing angiostatin respectively.[13] This study attempts to explain the molecular processes by which rosuvastatin promotes wound healing. Using molecular docking simulations, we want to understand the complex interactions between rosuvastatin and important molecular targets involved in wound healing pathways. By deciphering these molecular complexities, we want to pave the path for the development of innovative treatment techniques that exploit the potential of rosuvastatin in wound care.

MATERIALS AND METHODS

Molecular docking is the process of fitting a molecule into a target structure while testing various locations, conformations, and orientations. Its purpose is to predict the formation of an intermolecular complex between two molecules.[14] PyRx 0.8 is an automated method for predicting the interactions of ligands with biomolecular targets. The protein and ligand starting structures determine the quality of the docking results. To achieve trustworthy docking data, the protein and ligand structures must be properly prepared, which involves operations like protein preparation, ligand preparation, receptor grid design, and docking itself.

Protein preparation

The three-dimensional structures of the PDGFR (PDB: 1H90), TGFR-β 1 (PDB ID: 1B6C), human Matrix metalloproteinase 9 (PDB: 1GKC), Human Epidermal growth factor receptor (ErRB1) (PDB:1IVO), and Fibroblast growth factor receptor 1 (PDB: 1AGW), Metalloelastase (PDB ID: 2POJ) Receptor of Advanced glycation end products (PDB ID: 6VXG) and VEGFR 2 & 3 (PDB ID:2XIW 4BSJ were downloaded from the RCSB Protein Data Bank in PDB format. Ligand and water molecules were removed using BIOVIA Discovery studio 2024. while polar hydrogen and Gasteiger charge were added to proteins to convert them into PDBQT format.[15,16,17,18]

Preparation of ligand

The compound Rosuvastatin (PubChem ID**:** 5282455) was loaded in 3D SDF format and the ligands were then minimized and turned to PDBQT format using PyRx tools to calculate the binding affinity in the targets.[15]

Docking of ligand and proteins

PyRx Autodock Vina was used to accomplish the binding interaction on the generated protein-ligand complexes. Docking experiments were conducted using PyRx's semiflexible docking device. The phytochemicals were converted to PDBQT formats using PyRx AutoDock tools. The stiffness of proteins and ligands was maintained throughout this investigation. Ligand molecules had provided ten degrees of freedom. During the transformation, a grid box with an active site in the centre was built. Finally, utilizing the BIOVIA Discovery Studio Visualizer 2024, docking sites for the best connection strategies were examined.[15,16,17,18]

RESULTS AND DISCUSSIONS

In this study, we looked at the effects of Rosuvastatin (RSV) on Nine proteins related with impaired wound healing. These nine proteins are linked together and contribute to impairment in wound healing. To determine the influence of RSV on these proteins, molecular docking analysis was used. PyRx software was used to do docking simulations between RC and the nine proteins linked to impaired wound healing. The docking findings were analysed using binding energy, and the average binding energy of RSV to the nine proteins was documented in a table 1. The findings revealed that RSV exhibited favourable binding to the receptor cavities of all nine proteins, indicating its potential to inhibit their activity. Among the docked proteins, the MMP9 proteins displayed the highest binding energy, suggesting a strong affinity between RC and the target ligand. Following TGFR-β 1, ERB-β1, MMP- 12, and VEGFR 2, PDGFR, VEGFR 3, RAGE and FGFR 1 in decreasing order of binding energies. In this work, we investigated the effects of rosuvastatin on nine proteins associated with poor wound healing. These nine proteins are related together and lead to poor wound healing. The impact of RSV on these proteins was determined using molecular docking studies. The PyRx program was used to perform

docking simulations between RSV and the nine proteins related to poor wound healing. The interaction between rosuvastatin and the target proteins was visually depicted in Figure 1.

Table 1: Binding energy of ligand with target protein.

SNO	PROTEINS	DOCKING ENERGY (Kcal)
1	ERB-β1	-7.1
2	FGFR 1	-5.9
3	MMP- 12	-6.8
4	MMP-9	-8.6
5	PDGFR	-6.3
6	RAGE	-6.1
7	TGFR-β 1	-8.3
8	VEGFR 2	-6.7
9	VEGFR 3	-6.2

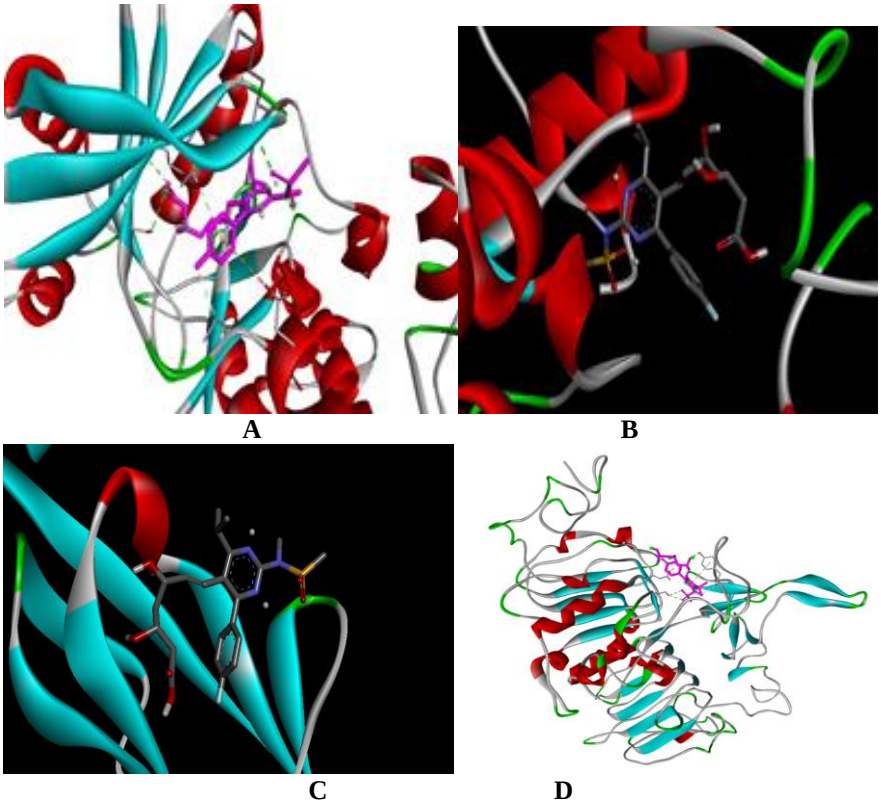

Figure 1: Visualizing ligand-protein interactions.

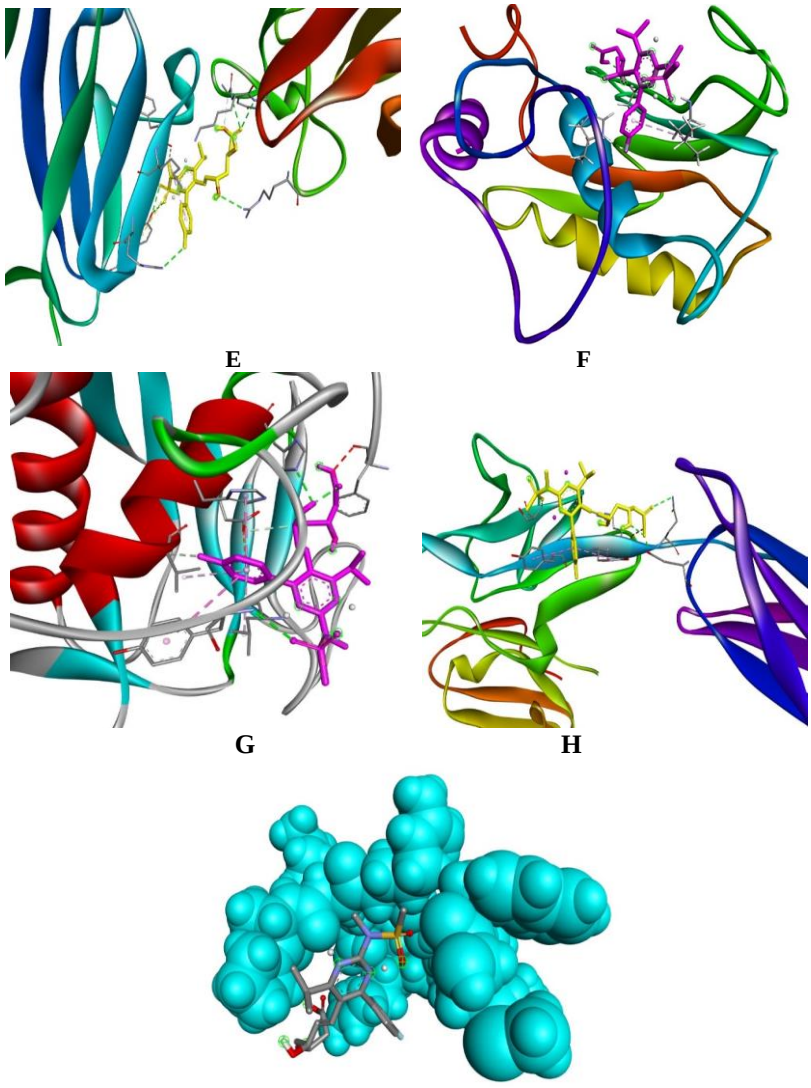

Figure 2: Visualizing ligand-protein interactions.

A) TGFR B1, B) VEGFR 2, C) VEGFR 3, D) ERBB1, E) FGFR1, F) MMP 12, G) MMP 9, H) PDGFR AND I) RAGE.

CONCLUSION

Finally, this study investigated the molecular docking interactions between rosuvastatin, a synthetic HMG-CoA reductase inhibitor, and nine proteins associated with impaired wound healing. The docking results revealed that rosuvastatin calcium had favourable binding interactions with all nine proteins, indicating its ability to modulate their activities and suggesting its potential as a therapeutic agent for chronic wounds. MMP 9 had the highest affinity for RC, followed by TGFR-β 1, ERB-β1, MMP-12, PDGFR, VEGFR 3, RAGE, and FGFR 1. These data imply that RC may exert wound healing benefits via regulating the activities of proteins implicated in wound repair impairment. The study's findings give important insights into the molecular processes behind rosuvastatin's wound healing characteristics. However, more experimental studies are required to corroborate these findings and investigate the usefulness of rosuvastatin as a therapeutic drug in both preclinical and clinical contexts. The use of computational methods such as molecular docking allows for a better understanding of the interactions between bioactive chemicals and target proteins, which aids in the discovery of prospective therapeutic candidates. Overall, this research demonstrates the prospective function of RSV in the treatment of wounds and emphasizes the significance of additional researches to completely understand its therapeutic potential and optimize its application in the development of novel therapies for chronic wounds.

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