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Rutin as a Potential Multi-Target Agent for Diabetic Wound Healing: A Molecular Docking Study on AKR1B1, COX-2, and MMP-9

Theodorus Rexa Handoyo[1*]

[1] Faculty of Pharmacy, Universitas 17 Agustus 1945 Jakarta, DKI Jakarta, Indonesia, 13450
*Corresponding author: theodorus.rexa@uta45jakarta.ac.id

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Abstract

Diabetic wound healing is hindered by the interplay of oxidative stress, chronic inflammation, and excessive extracellular matrix degradation, which collectively delay tissue repair. Conventional treatments often address only single pathological pathways, resulting in suboptimal outcomes. This study aimed to evaluate the multitarget potential of rutin, a natural flavonoid, against key proteins implicated in diabetic wound pathology, such as aldose reductase (AKR1B1), cyclooxygenase-2 (COX-2), and matrix metalloproteinase-9 (MMP-9) using molecular docking analysis. The three-dimensional structures of rutin and the target proteins were obtained from the PubChem and Protein Data Bank databases, respectively, and docking simulations were performed using Molegro Virtual Docker 6.0. Rutin exhibited favorable binding affinities toward all targets, with the strongest predicted interaction observed for COX-2 (MolDock score -184.339), followed by AKR1B1 (-169.803) and MMP-9 (-160.330). Hydrogen bond analysis indicated significant contributions to complex stability, particularly for COX-2 and MMP-9. These findings suggest that rutin may modulate oxidative stress, inflammation, and extracellular matrix remodeling simultaneously. Overall, rutin demonstrates promising multitarget potential for diabetic wound healing, warranting further validation through molecular dynamics and experimental studies.

Keywords: Rutin; Molecular docking; Aldose reductase (AKR1B1); Cyclooxygenase-2 (COX-2); Matrix metalloproteinase-9 (MMP-9)

Introduction

Diabetic wound healing remains a major clinical challenge due to the complex pathophysiological mechanisms involved, including persistent inflammation, oxidative stress, impaired angiogenesis, and excessive extracellular matrix degradation. Chronic hyperglycemia alters multiple biochemical pathways that collectively delay tissue repair and increase the risk of infection and amputation. Conventional therapies are often

insufficient to fully address these multifactorial processes, highlighting the need for novel therapeutic strategies that can simultaneously modulate several molecular targets associated with diabetic wound pathology [1-4].

Among the key proteins involved in diabetic wound progression, aldose reductase (AKR1B1) plays a central role in the polyol pathway, contributing to osmotic stress and oxidative damage under hyperglycemic conditions. Cyclooxygenase-2 (COX-2, PTGS2) is a major mediator of inflammation, which is often prolonged and dysregulated in diabetic wounds. Meanwhile, matrix metalloproteinase-9 (MMP-9) is responsible for extracellular matrix degradation and tissue remodeling, and its overexpression has been associated with delayed wound closure and impaired healing. Dysregulation of these targets collectively contributes to the chronic and non-healing nature of diabetic wounds [5-8].

Natural products have long been recognized as valuable sources of bioactive compounds with multitarget therapeutic potential. Rutin, a flavonoid glycoside widely found in medicinal plants including *Anredera cordifolia*, has been reported to exhibit antioxidant, anti-inflammatory, and wound-healing activities. However, the molecular mechanisms underlying its potential role in diabetic wound healing, particularly in relation to specific protein targets such as AKR1B1, COX-2, and MMP-9, remain insufficiently characterized. Computational approaches such as molecular docking offer a powerful and cost-effective strategy to predict ligand-protein interactions and explore possible mechanisms of action at the molecular level. Docking studies can provide insights into binding affinity, binding mode, and interaction patterns, thereby supporting the rational design of multitarget therapeutics prior to experimental validation. In this context, structure-based docking can help elucidate whether rutin is capable of interacting with multiple pathological targets involved in diabetic wound healing [8-11].

Therefore, the present study aims to investigate the binding interactions of rutin with AKR1B1, COX-2, and MMP-9 using molecular docking techniques. By evaluating the predicted binding affinities and interaction profiles, this study seeks to provide mechanistic insights into the potential multitarget role of rutin in diabetic wound healing and to support its further exploration as a candidate therapeutic agent.

Materials and Method

This study was conducted as an in silico investigation to evaluate the interaction of rutin with key protein targets involved in diabetic wound healing, namely aldose reductase (AKR1B1), cyclooxygenase-2 (COX-2/PTGS2), and matrix metalloproteinase-9 (MMP-9), using molecular docking and network analysis approaches.

Ligand Preparation

The three-dimensional structure of rutin was obtained from the PubChem database (PubChem CID: 5280805). The structure was downloaded in SDF format and imported into the docking software. Prior to docking, the ligand was prepared by assigning proper atom types, adding hydrogen atoms, and optimizing its geometry to ensure a stable conformation for molecular interaction analysis.

Protein Structure Prepatarion

The crystal structures of the target proteins were retrieved from the Protein Data Bank (PDB). The human aldose reductase (AKR1B1), cyclooxygenase-2 (COX-2), and matrix metalloproteinase-9 (MMP-9) structures were selected based on high resolution and biological relevance. All crystallographic water molecules, buffer components, and co-crystallized ligands were removed prior to docking. Essential cofactors required for enzymatic activity, such as the catalytic Zn^{2+} ion in MMP-9, were retained. Protein structures were prepared by adding missing hydrogen atoms and optimizing side-chain orientations to ensure proper interaction geometry.

Molecular Docking

Molecular docking simulations were performed using Molegro Virtual Docker 6.0. Binding cavities were identified using the built-in cavity detection algorithm, and the most relevant cavity corresponding to the active site region was selected for docking. Rutin was docked into the selected binding pockets using the MolDock scoring function with default search parameters. For each protein-ligand complex, multiple docking poses were generated, and the best pose was selected based on the lowest MolDock score and favorable interaction geometry.

Docking Analysis

Docking results were evaluated using MolDock score, Rerank score, and hydrogen bond contribution values. The predicted binding modes and key amino acid interactions were visualized and analyzed using Discovery Studio Visualizer v21.1.0.20298. Interactions such as hydrogen bonds, hydrophobic contacts, and metal coordination (where applicable) were examined to interpret the stability and specificity of ligand binding.

Result and Discussion

Molecular docking simulations were performed to investigate the binding affinity and interaction profiles of rutin toward three protein targets associated with diabetic wound healing, namely aldose reductase (AKR1B1), cyclooxygenase-2 (COX-2/PTGS2), and matrix metalloproteinase-9 (MMP-9). These proteins were selected based on their

established roles in oxidative stress regulation, inflammatory response, and extracellular matrix remodeling, respectively.

Table 1. Result of Molecular Docking

Target	Moldock Score	Rerank Score	H-Bond
AKR1B1	-169.803	-138.333	-8.51311
COX 2	-184.339	-148.128	-22.9697
MMP9	-160.330	-79.1975	-18.5493

The docking results are summarized in Table 1. Rutin exhibited favorable binding affinities toward all three targets, as reflected by the negative MolDock and Rerank scores. Among the tested proteins, the strongest predicted binding was observed with COX-2, followed by AKR1B1 and MMP-9. Specifically, the MolDock scores for rutin were -184.339 for COX-2, -169.803 for AKR1B1, and -160.330 for MMP-9, indicating stable ligand–protein complex formation across all targets. The Rerank scores, which incorporate more detailed energy terms including electrostatics and steric interactions, followed a similar trend.

Hydrogen bond contributions further supported the stability of these interactions. The strongest hydrogen bonding contribution was observed for COX-2 (-22.97), followed by MMP-9 (-18.55) and AKR1B1 (-8.51). These values suggest that hydrogen bonding plays a particularly important role in stabilizing rutin within the active sites of COX-2 and MMP-9, whereas hydrophobic and van der Waals interactions may contribute more substantially to the binding with AKR1B1.

Overall, the docking results indicate that rutin is capable of interacting with multiple molecular targets relevant to diabetic wound pathology, supporting its potential as a multitarget modulator.

Interaction of rutin with AKR1B1

Aldose reductase (AKR1B1) is a key enzyme in the polyol pathway, catalyzing the reduction of glucose to sorbitol under hyperglycemic conditions. Excessive activation of this pathway contributes to osmotic stress, oxidative damage, and delayed wound healing in diabetic tissues [12,13].

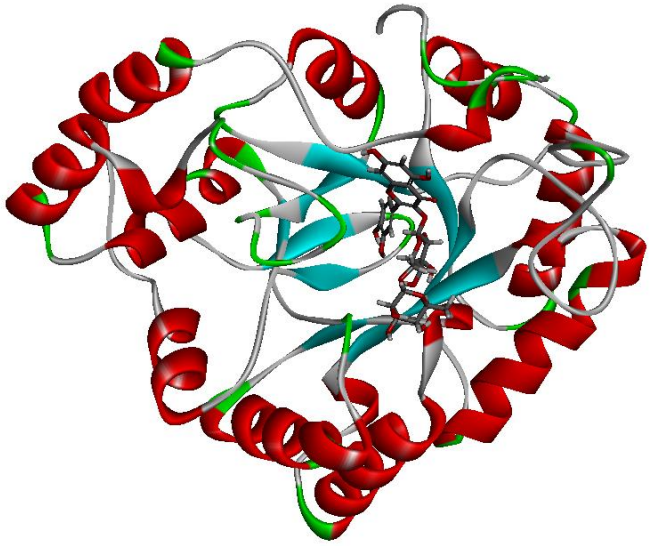

Figure 1. Interaction of rutin with the active site of aldose reductase (AKR1B1) as predicted by molecular docking.

Docking analysis showed that rutin binds within the catalytic pocket of AKR1B1, forming multiple stabilizing interactions with residues located in the active site region. The predicted binding pose revealed that the polyphenolic moiety of rutin is oriented toward the catalytic center, allowing the formation of hydrogen bonds with polar residues and electrostatic interactions with charged amino acids. Although the hydrogen bond contribution was lower than that observed for COX-2 and MMP-9, the overall binding score indicates a stable complex supported by a combination of van der Waals and electrostatic interactions.

These results suggest that rutin may partially inhibit AKR1B1 activity by occupying its active site, thereby reducing flux through the polyol pathway and mitigating hyperglycemia-induced oxidative stress. Such an effect would be beneficial in the context of diabetic wound healing, where oxidative stress is a major factor impairing fibroblast function, keratinocyte migration, and angiogenesis.

Interaction of rutin with COX-2

Cyclooxygenase-2 (COX-2) is an inducible enzyme responsible for the conversion of arachidonic acid into pro-inflammatory prostaglandins. In diabetic wounds, prolonged COX-2 expression contributes to chronic inflammation, which interferes with the normal progression of the wound healing process from the inflammatory phase to the proliferative phase [14].

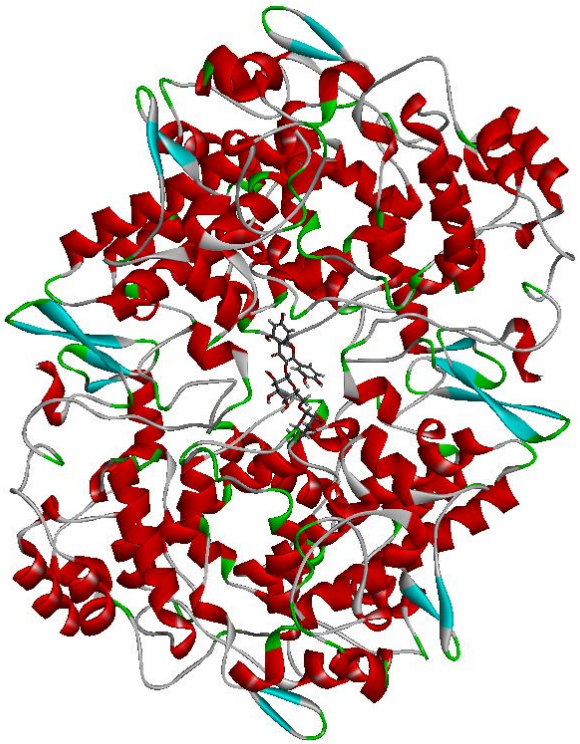

Figure 2. Interaction of rutin with the active site of cyclooxygenase-2 (COX-2) as predicted by molecular docking.

Rutin showed the strongest predicted binding to COX-2 among the three targets, as evidenced by the most negative MolDock and Rerank scores. The docking pose revealed that rutin occupies the COX-2 active site channel, forming multiple hydrogen bonds with residues lining the binding pocket. The flavonoid backbone of rutin allows extensive π–π and hydrophobic interactions with aromatic and nonpolar residues, while its hydroxyl groups participate in hydrogen bonding, contributing to the high binding affinity.

This strong interaction suggests that rutin may function as a COX-2 inhibitor, potentially reducing excessive prostaglandin production and alleviating persistent inflammation in diabetic wounds. This mechanism is consistent with previous reports describing the anti-inflammatory activity of rutin and related flavonoids.

Interaction of rutin with MMP-9

Matrix metalloproteinase-9 (MMP-9) plays a crucial role in extracellular matrix (ECM) degradation. While controlled ECM remodeling is necessary for normal wound healing, excessive MMP-9 activity in diabetic wounds leads to degradation of growth factors and structural proteins, impairing tissue regeneration and angiogenesis [5,15].

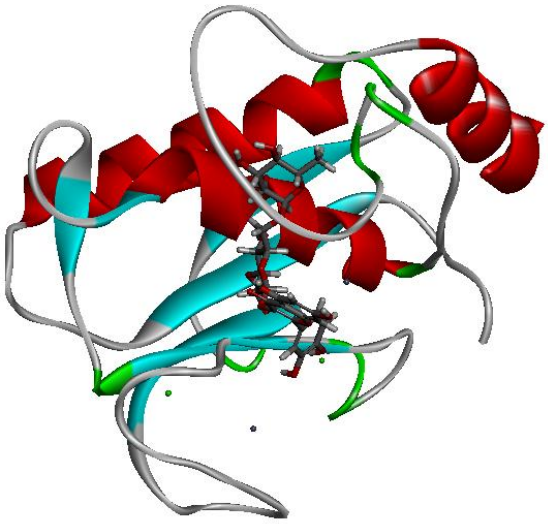

Figure 3. Interaction of rutin with the active site of matrix metalloproteinase-9 (MMP-9) as predicted by molecular docking.

Docking results showed that rutin binds within the catalytic region of MMP-9 with a favorable binding score and substantial hydrogen bond contribution. The predicted binding pose indicated that rutin interacts near the zinc-containing catalytic site, forming hydrogen bonds and stabilizing interactions with residues involved in substrate recognition.

These interactions suggest that rutin may act as a partial MMP-9 inhibitor, potentially preventing excessive ECM degradation and preserving the structural scaffold necessary for cell migration and tissue repair. This mechanism further supports the potential role of rutin as a regulator of multiple pathological processes in diabetic wound healing.

Multitarget Implications in Diabetic Wound Healing

Diabetic wound healing is characterized by the simultaneous dysregulation of multiple biological pathways, including oxidative stress, inflammation, and extracellular matrix turnover. Conventional therapies often target only one aspect of this complex pathology, which may explain their limited efficacy [5,16].

The present docking study suggests that rutin can interact with multiple key proteins involved in these pathways. By potentially inhibiting AKR1B1, rutin may reduce oxidative stress; by inhibiting COX-2, it may attenuate chronic inflammation; and by modulating MMP-9 activity, it may preserve ECM integrity. This multitarget profile positions rutin as

a promising candidate for the development of adjunctive therapies aimed at restoring balance across several pathological processes simultaneously.

Limitations and Future Perspectives

Although molecular docking provides valuable insights into potential ligand–protein interactions, it represents a simplified model that does not fully capture the dynamic nature of biological systems. The present study is limited by the absence of molecular dynamics simulations and experimental validation, such as enzyme inhibition assays or cell-based wound healing models.

Future studies should incorporate molecular dynamics simulations to assess the stability of the predicted complexes under physiological conditions and experimental assays to validate the inhibitory effects of rutin on AKR1B1, COX-2, and MMP-9 activities. Additionally, in vitro wound healing assays using diabetic fibroblasts or keratinocytes would provide further evidence of the therapeutic relevance of rutin in diabetic wound repair.

Conclusion

This study demonstrates that rutin exhibits favorable binding affinities toward three key proteins involved in diabetic wound pathology, namely AKR1B1, COX-2, and MMP-9. The docking results suggest that rutin may simultaneously modulate oxidative stress, inflammation, and extracellular matrix remodeling, supporting its potential as a multitarget agent for improving diabetic wound healing. These findings provide a computational basis for further experimental investigation and the potential development of rutin-based therapeutic strategies.

Conflict of Interest Statement

The authors declare no conflict of interest related to this work.

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