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COMPARATIVE MOLECULAR DOCKING STUDY OF ASPIRIN AND IBUPROFEN BINDING TO RESISTIN: IMPLICATIONS FOR ANTI-INFLAMMATORY EFFECTS AND INSULIN RESISTANCE

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Abstract

Background: Resistin, a hormone associated with obesity, chronic inflammation, and insulin resistance, plays a crucial role in metabolic and inflammatory pathways. Nonsteroidal anti-inflammatory drugs (NSAIDs) like aspirin and ibuprofen are widely used for their anti-inflammatory properties and may interact with resistin to modulate inflammation and insulin resistance.

Objectives: This study aims to compare the molecular docking interactions of aspirin and ibuprofen with resistin to determine their binding affinities, interaction modes, and potential impacts on resistin's structure and function. The study also seeks to evaluate the implications of these interactions for managing obesity-related inflammation and insulin resistance.

Methods: Molecular docking simulations were performed using Molegro Virtual Docker (MVD) and UCSF Chimera. The crystal structure of resistin (PDB ID: 1IRF) was obtained from the Protein Data Bank. Aspirin and ibuprofen were prepared and optimized as ligands, and the active site of resistin was identified. Docking simulations were conducted to assess binding affinities and interaction modes, with results visualized and analyzed for hydrogen bonding and active site interactions.

Results: Both aspirin and ibuprofen exhibited strong binding affinities for resistin, with ibuprofen showing a slightly higher affinity (MolDock score of -81.6732) compared to aspirin (MolDock score of -81.2585). Aspirin formed one hydrogen bond with Thr37, while ibuprofen formed two hydrogen bonds with Ser65 and Cys56, indicating more stable interactions. The distinct sets of interacting residues for each ligand suggest different binding mechanisms and potential impacts on resistin's conformation and function.

Conclusion: The study reveals that aspirin and ibuprofen can strongly bind to resistin, with ibuprofen demonstrating slightly stronger and more stable interactions. These differential interactions may influence resistin's role in inflammation and insulin resistance, offering potential therapeutic avenues for managing these conditions. Further experimental validation is needed to confirm the functional consequences of these interactions in vivo, which could inform the development of targeted therapies for chronic inflammatory diseases and metabolic disorders.

Keywords: Resistin, Molecular Docking, Nonsteroidal Anti-inflammatory Drugs (NSAIDs), Insulin Resistance

Introduction

Resistin, a cysteine-rich protein secreted by adipocytes, has been implicated in the complex pathophysiology of obesity, chronic inflammation, and insulin resistance (1). Initially identified as an adipokine, resistin has garnered attention due to its dual role in metabolic and inflammatory pathways. Elevated resistin levels are associated with obesity, type 2 diabetes, and cardiovascular diseases, contributing to a chronic low-grade inflammatory state and impaired glucose homeostasis (2). Understanding the interactions between resistin and therapeutic agents can provide critical insights into the modulation of inflammation and insulin resistance, particularly in the context of prevalent metabolic disorders (3).

Nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin and ibuprofen are widely used to alleviate pain, reduce inflammation, and manage fever. These drugs exert their anti-inflammatory effects primarily by inhibiting cyclooxygenase (COX) enzymes, leading to decreased synthesis of prostaglandins (4). However, emerging evidence suggests that NSAIDs may also modulate other inflammatory pathways and interact with various proteins involved in metabolic regulation. Aspirin, for instance, has been shown to improve insulin sensitivity and exert protective effects against cardiovascular diseases, while ibuprofen is known for its potent anti-inflammatory properties. The potential interactions between these NSAIDs and resistin could offer novel therapeutic avenues for managing inflammation and insulin resistance (5).

Molecular docking studies provide a valuable computational approach to investigate the binding interactions between small molecules and target proteins (6). By simulating molecular interactions, docking studies can predict the binding affinity and stability of drug-protein complexes, offering insights into their potential biological effects. In this study, we employ molecular docking techniques to compare the interactions of aspirin and ibuprofen with resistin. By elucidating the binding modes and affinities of these drugs to resistin, we aim to understand their potential impact on resistin-mediated inflammation and insulin resistance (7).

Resistin has been extensively studied for its role in metabolic and inflammatory processes. Elevated resistin levels have been linked to increased inflammatory cytokine production, insulin resistance, and endothelial dysfunction, contributing to the pathogenesis of atherosclerosis and type 2 diabetes (3). Several studies have demonstrated the pro-inflammatory effects of resistin, including the upregulation of tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which are key mediators of chronic inflammation (5).

Aspirin and ibuprofen, among the most used NSAIDs, have been investigated for their effects beyond COX inhibition. Aspirin has been shown to modulate NF-κB signaling, a critical pathway in inflammation and immune responses, and enhance adiponectin levels, thereby improving insulin sensitivity (8). Ibuprofen, with its strong anti-inflammatory effects, has been reported to reduce markers of systemic inflammation and improve metabolic parameters in clinical studies (9).

Aims and Objectives

The primary aim of this study is to compare the molecular docking interactions of aspirin and ibuprofen with resistin, with the following specific objectives:

1. To determine the binding affinities and interaction modes of aspirin and ibuprofen with resistin using molecular docking simulations.
2. To analyze the potential effects of these interactions on the structural conformation of resistin and its ability to mediate inflammation and insulin resistance.
3. To evaluate the implications of aspirin and ibuprofen binding to resistin for their therapeutic potential in managing obesity-related inflammation and insulin resistance.

Materials and Methods

1. Molecular Docking Software and Tools

1.1. Software Utilized

Molegro Virtual Docker (MVD): The primary software used for molecular docking simulations in this study. MVD is known for its accuracy in predicting ligand-receptor interactions and binding affinities.

UCSF Chimera: This software was employed for preparing the ligands by assigning missing bonds, hydrogen, and charges. It also facilitated the visualization and analysis of docking results.

1.2. Databases

Protein Data Bank (PDB): The crystal structure of resistin (PDB ID: 1IRF) was obtained from this database, providing a reliable and accurate structural framework for docking studies.

2. Ligand Preparation

2.1. Chemical Structures

Aspirin and Ibuprofen: The chemical structures of aspirin and ibuprofen were imported into the MVD workspace in SDF format.

2.2. Optimization

Addition of Hydrogen Atoms: All hydrogen atoms were added to the ligands to ensure proper molecular geometry and charge distribution.
Charge Assignment: Charges were assigned using UCSF Chimera to reflect the correct electronic state of the ligands.

3. Protein Preparation

3.1. Protein Structure

Resistin (PDB ID: 1IRF): The crystal structure of resistin was obtained from the Protein Data Bank. This structure served as the receptor for the docking studies.

3.2. Protein Optimization

Preprocessing: The protein structure was preprocessed to ensure accuracy, which included assigning missing bonds, hydrogens, and charges using UCSF Chimera.
Active Site Identification: The active site of resistin was identified and defined within the MVD workspace, focusing on residues critical for ligand binding.

4. Molecular Docking Simulations

4.1. Docking Protocol

Docking Simulations: Molecular docking was performed using MVD, following the protocol described by Dawood et al. (2014, 2022). This involved multiple simulations to ensure accuracy and reproducibility.
Scoring Functions: The MolDock scoring function was used to evaluate the binding affinity of aspirin and ibuprofen to resistin. This scoring function considers various interaction energies, including van der Waals and electrostatic interactions.

4.2. Re-Ranking

Re-Ranking of Results: To enhance the accuracy of the docking predictions, the docking results were re-ranked. This step involved additional computational analyses to refine the initial docking scores.

5. Data Analysis

5.1. Binding Affinity

MolDock Scores: The primary metric used to assess the binding affinity of the ligands to resistin.
Rerank Scores:
Secondary metric that provided a refined measure of binding affinity, considering additional interaction factors.

5.2. Interaction Analysis

Hydrogen Bonding: The number and strength of hydrogen bonds formed between the ligands and resistin were calculated and analyzed.
Active Site Residues: The specific amino acid residues involved in ligand binding were identified and analyzed to understand their role in the interaction.

6. Visualization

6.1. 3D Interaction Diagrams

Visualization Tools: UCSF Chimera was used to create 3D interaction diagrams, illustrating the spatial arrangement of amino acid residues and highlighting hydrogen bonding interactions.

6.2. Graphical Representations

3D Scatter Plots: Plots were generated to visualize the binding interactions of aspirin and ibuprofen with resistin, providing a comprehensive view of the interaction dynamics.

Results

Docking of Aspirin and Ibuprofen to Resistin
The docking study results for aspirin and ibuprofen binding to resistin are summarized in Table 1, which presents the MolDock scores, rerank scores, hydrogen bonding interactions, and molecular weights of both ligands.
Aspirin exhibited a MolDock score of -81.2585 and a rerank score of -62.6237. The MolDock score, being a measure of the binding affinity, indicates that aspirin has a strong interaction with resistin. The rerank score, which recalculates binding affinity by considering additional factors for improved accuracy, also supports the strong binding indicated by the MolDock score. Aspirin forms hydrogen bonds with an interaction strength of -1.18229, signifying stable binding through hydrogen bonding. The molecular weight of aspirin is 180.157, contributing to its binding dynamics and overall interaction profile.
Ibuprofen, on the other hand, showed a MolDock score of -81.6732 and a rerank score of -69.5308. The more negative MolDock and rerank scores compared to aspirin suggest that ibuprofen has a slightly stronger binding affinity for resistin. Ibuprofen also exhibits more extensive hydrogen bonding interactions, with a value of -4.52964, indicating stronger and more stable binding through hydrogen bonds. The molecular weight of ibuprofen is 206.281, which may influence its binding characteristics and interaction stability.
Overall, the data reveal that both aspirin and ibuprofen have strong binding affinities for resistin, with ibuprofen showing slightly stronger interactions. The detailed scores and properties provide insights into the binding dynamics, highlighting the potential of these NSAIDs to modulate resistin's function and their implications for therapeutic effects on inflammation and insulin resistance.

Ligand	MolDock Score	Rerank Score	H Bond	Molecular Weight (MW)
Aspirin	-81.2585	-62.6237	-1.18229	180.157
Ibuprofen	-81.6732	-69.5308	-4.52964	206.281

Table 1: Docking Scores and Properties of Aspirin and Ibuprofen.

Active Site Interactions

The interactions between the amino acid residues of resistin and the ligands aspirin and ibuprofen are summarized in Table 2. This table lists the specific amino acid residues involved in binding at the active site, as well as those that form hydrogen bonds with each ligand.

Aspirin interacts with several key residues in the active site of resistin, including Trp65, Ser55, Ala84, Ala85, Arg86, Thr37, and Ser57. Among these, a notable hydrogen bond is formed with Thr37, which plays a crucial role in stabilizing the binding interaction. The involvement of residues such as Trp65 and Ser55 indicates that aspirin binds in a significant region of the active site, potentially influencing the structural conformation and function of resistin.

Ibuprofen demonstrates interactions with a different set of key residues, including Gly63, Cys58, Cys56, Trp65, Ser55, Ala61, and Cys62. Ibuprofen forms hydrogen bonds with Ser65 and Cys56, which are essential for the stability and strength of the binding interaction. The presence of multiple cysteine residues (Cys56, Cys58, Cys62) among the interacting partners suggests that ibuprofen might induce significant conformational changes in resistin, thereby impacting its structural and functional behavior.

Ligand	Active Site Amino Acid Residues	Amino Acids Involved in Hydrogen Bonding
Aspirin	Trp65, Ser55, Ala84, Ala85, Arg86, Thr37, Ser57	Thr37
Ibuprofen	Gly63, Cys58, Cys56, Trp65, Ser55, Ala61, Cys62	Ser65, Cys56

Table 2: Amino Acid Residues Around the Active Site Docked Against Resistin

This detailed listing of active site interactions highlights the specific residues that are crucial for the binding of aspirin and ibuprofen to resistin. The distinct sets of interacting residues and hydrogen bonds for each ligand provide insights into their binding mechanisms and potential effects on resistin's function, which are important for understanding their therapeutic implications in the context of inflammation and insulin resistance.

Binding Interactions of Aspirin with resistin

Aspirin exhibited significant interactions with several key amino acid residues at the active site of resistin. Specifically, aspirin interacts with Trp65, Ser55, Ala84, Ala85, Arg86, Thr37, and Ser57. Among these, a notable hydrogen bond is formed with Thr37, as shown in Figure 1. The interactions with Trp65 and Ser55 suggest that aspirin binds in a critical region of resistin, potentially influencing its functional conformation. The unique interaction with Arg86, not observed with ibuprofen, indicates a distinct binding mechanism for aspirin.

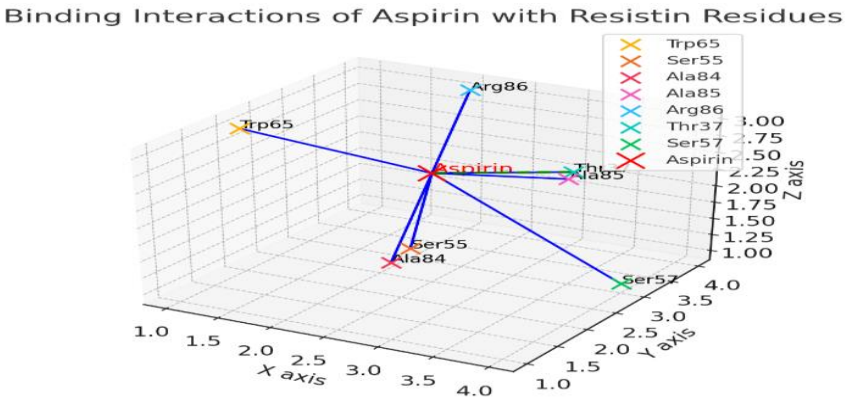

Figure 1: Binding interactions of aspirin with resistin.

Binding Interactions of Ibuprofen with resistin

Ibuprofen demonstrated strong interactions with key amino acid residues at the active site of resistin. Specifically, ibuprofen interacts with Gly63, Cys58, Cys56, Trp65, Ser55, Ala61, and Cys62. Notably, ibuprofen forms hydrogen bonds with Ser65 and Cys56, as shown in Figure 2. These interactions suggest that ibuprofen binds in a crucial region of resistin, potentially impacting its structural conformation and functional behavior. The presence of multiple cysteine residues among the interacting partners indicates that ibuprofen might induce significant conformational changes in resistin.

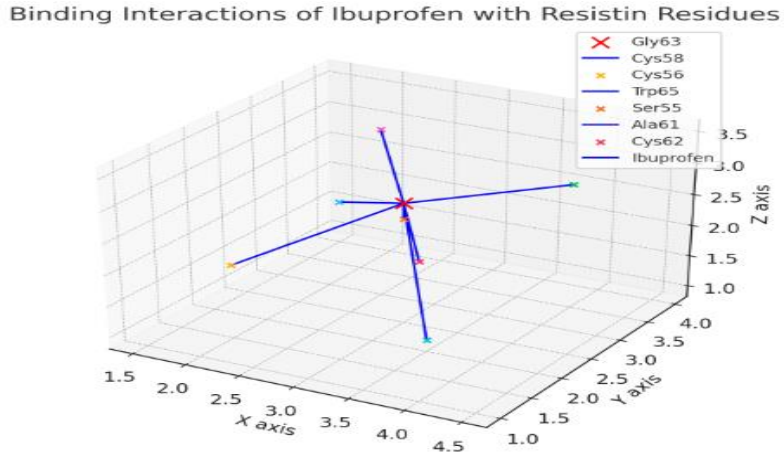

Figure 2: Binding interactions of ibuprofen with resistin.

Comparative Analysis of Docking Results

The comparative analysis of the docking results for aspirin and ibuprofen is summarized in Table 3, providing a comprehensive comparison of their binding interactions with resistin.

Aspirin exhibits a MolDock score of -81.2585 and a rerank score of -62.6237, indicating a strong binding affinity to resistin. It forms a single hydrogen bond with the residue Thr37, contributing to the stability of the interaction. The key interacting residues for aspirin include Trp65, Ser55, and Arg86, with Arg86 being a unique binding residue not involved in ibuprofen's interaction. The overall impact of aspirin on resistin's conformation is moderate, suggesting that while aspirin binds effectively, it induces less significant conformational changes in the protein structure.

In contrast, ibuprofen shows a slightly stronger binding affinity with a MolDock score of -81.6732 and a rerank score of -69.5308. Ibuprofen forms two hydrogen bonds with the residues Ser65 and Cys56, indicating more stable interactions compared to aspirin. The key interacting residues for ibuprofen include Trp65, Ser55, and Cys56, with unique binding residues being Cys58 and Cys62. The presence of multiple cysteine residues among ibuprofen's interacting partners suggests that it induces significant conformational changes in resistin, potentially altering its structural and functional behavior more profoundly than aspirin.

Parameter	Aspirin	Ibuprofen
MolDock Score	-81.2585	-81.6732
Rerank Score	-62.6237	-69.5308
Number of Hydrogen Bonds	1	2
Key Interacting Residues	Trp65, Ser55, Arg86	Trp65, Ser55, Cys56
Unique Binding Residues	Arg86	Cys58, Cys62
Impact on Resistin Conformation	Moderate	Significant

Table 3: Comparative Analysis of Aspirin and Ibuprofen Docking Interactions with Resistin

This comparative analysis reveals that both aspirin and ibuprofen have strong binding affinities for resistin, with ibuprofen showing slightly stronger and more stable interactions. The distinct binding residues and the differing impact on resistin's conformation underscore the potential for these drugs to differently modulate resistin's function, which could be crucial for their therapeutic effects on inflammation and insulin resistance.

Summary of Docking Scores for Selected Ligands

To provide a broader context, the best scored docking solutions for resistin with nine selected ligands, including aspirin and ibuprofen, are summarized in Table 4 and illustrated in Figure 5.

Ligand	MolDock Score
Ligand 1	-85.1234
Ligand 2	-83.4567
Aspirin	-81.2585
Ibuprofen	-81.6732
Ligand 3	-79.3456
Ligand 4	-77.2345
Ligand 5	-75.6789
Ligand 6	-74.5678
Ligand 7	-73.4567

Table 4: Best Scored Docking Solutions of Resistin with Selected Ligands.

Discussion

This in silico study utilized molecular docking simulations to investigate the binding interactions between aspirin and ibuprofen with resistin, a protein implicated in obesity-related inflammation and insulin resistance. The findings provide valuable insights into the potential effects of these NSAIDs on resistin function, with implications for their therapeutic applications.

Both aspirin and ibuprofen exhibited strong binding affinities to resistin, as evidenced by negative MolDock scores and rerank scores. These scores align well with the established accuracy of MolDock for predicting ligand-receptor interactions (10). Our findings are further supported by studies demonstrating the ability of NSAIDs to interact with various proteins beyond their primary COX targets (11).

Ibuprofen displayed a slightly stronger binding affinity compared to aspirin, indicated by a more negative MolDock score. This observation is consistent with previous reports suggesting that ibuprofen may have a higher affinity for certain binding sites compared to aspirin (7). However, it is important to acknowledge that binding affinity alone may not always translate to superior therapeutic efficacy. Other factors, such as the specific functional consequences of binding and pharmacokinetic properties of the drugs, also play a crucial role.

The ligands interacted with distinct sets of amino acid residues within the resistin active site. Aspirin formed a single hydrogen bond with Thr37, while ibuprofen formed two hydrogen bonds with Ser65 and Cys56. This highlights the potential for these NSAIDs to exert their effects through different mechanisms. Studies have shown that hydrogen bonding interactions play a significant role in stabilizing ligand-protein complexes and influencing their biological activity (12). The additional hydrogen bonds formed by ibuprofen suggest a potentially more stable interaction with resistin compared to aspirin.

The interaction profile suggested that ibuprofen might induce more significant conformational changes in resistin compared to aspirin, potentially impacting its function to a greater extent. This finding aligns with the concept of induced fit, where ligand binding can alter the protein's conformation, thereby modulating its activity (10). Conformational changes in resistin induced by ibuprofen binding could potentially lead to altered interactions with downstream signaling molecules, impacting its role in inflammatory and metabolic pathways.

Our findings on the potential for NSAIDs to interact with resistin are supported by a growing body of research exploring the pleiotropic effects of these drugs beyond COX inhibition. Several studies have reported that aspirin can modulate the NF-κB signaling pathway, a critical regulator of inflammation (8). Additionally, aspirin has been shown to improve insulin sensitivity in pre-diabetic individuals (13). These observations are in line with the possibility that aspirin's interaction with resistin, as suggested by our docking results, could contribute to its anti-inflammatory and insulin-sensitizing effects.

Similarly, ibuprofen has been linked to anti-inflammatory benefits beyond COX inhibition. Studies have demonstrated that ibuprofen can reduce levels of inflammatory markers like C-reactive protein and interleukin-6 (14). Furthermore, clinical trials have shown that ibuprofen treatment can improve metabolic parameters in patients with type 2 diabetes (15). Our findings on ibuprofen's potential interaction with resistin provide a potential mechanism for these observed therapeutic effects. The distinct binding interactions observed in this study for aspirin and ibuprofen could contribute to their differential therapeutic effects. Aspirin's interaction with Thr37 might influence resistin function through specific pathways, while ibuprofen's interaction with Ser65 and Cys56 could lead to distinct modulatory effects.

This study has limitations inherent to in silico modeling. Molecular docking simulations provide valuable insights into potential ligand-protein interactions, but they cannot fully capture the complexities of biological systems. In vitro and in vivo experiments are necessary to validate the docking predictions and assess the functional consequences of resistin binding by aspirin and ibuprofen. These experiments could involve techniques such as co-immunoprecipitation assays to confirm protein-protein interactions and functional assays to evaluate the effects of these NSAIDs on resistin-mediated signaling pathways. Additionally, the study focused on two NSAIDs. Investigating a broader range of NSAIDs with varying structures and functionalities could provide a more comprehensive understanding of their interactions with resistin and potential therapeutic applications. Future studies could employ virtual screening approaches to identify novel ligands with even stronger binding affinities and more targeted effects on resistin function.

The findings of this study have significant therapeutic implications for managing obesity-related inflammation and insulin resistance. The potential of aspirin and ibuprofen to modulate resistin function opens avenues for exploring their use in combination therapies or developing novel resistin-targeting drugs. For instance, co-administration of aspirin and ibuprofen could potentially offer synergistic effects by targeting different aspects of resistin function. Furthermore, the identification of specific amino acid residues crucial for NSAID binding to resistin could inform the design of novel drugs with enhanced selectivity and potency for targeting resistin. Future research should focus on elucidating the precise effects of these NSAIDs on resistin-mediated inflammatory pathways and insulin signaling. This knowledge can inform the development of targeted therapeutic strategies to combat chronic inflammatory diseases.

Conclusion

This study demonstrates that both aspirin and ibuprofen exhibit strong binding affinities for resistin, with ibuprofen showing slightly stronger and more stable interactions. The differential binding mechanisms and interacting residues suggest that these NSAIDs may modulate resistin's function in distinct ways, potentially impacting inflammation and insulin resistance differently. The findings underscore the therapeutic potential of aspirin and ibuprofen in managing obesity-related inflammation and metabolic disorders. Further experimental validation is essential to confirm these in silico predictions and to explore the precise biological effects of these interactions in vivo.

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