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ADME and Molecular Docking Studies of Scopoletin Against HIV-1 Reverse Transcriptase

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Abstract - This study presents a comprehensive analysis of Scopoletin (Molecule A) and its potential as an inhibitor against HIV-1 reverse transcriptase (HIV-1 RT). Scopoletin, a natural coumarin derivative, was subjected to a detailed investigation of its molecular and pharmacokinetic properties, including composition, structure, molecular flexibility, hydrogen bonding, and various descriptors influencing drug-likeness.The molecular weight of Scopoletin was determined to be within the range of the studied molecules, and it exhibited a moderate proportion of sp3 hybridized carbon atoms (Csp3), indicating a balanced structural composition. Molecular flexibility analysis revealed Scopoletin's ability to form hydrogen bonds and van der Waals interactions, showcasing its potential to engage in molecular recognition processes.In terms of pharmacokinetic characteristics, Scopoletin displayed a significant affinity for HIV-1 RT in molecular docking studies, particularly in run 20, where it exhibited the highest affinity (-6.853). The analysis of the docking results emphasized the consistent high affinity of Scopoletin, suggesting robust interactions with the target protein.Furthermore, Scopoletin adhered to drug-likeness criteria without breaching core guidelines, exhibiting promising bioavailability values. The molecule also demonstrated inhibitory effects on various enzymes (CYP1A2, CYP2C19, CYP2D6, and CYP3A4) associated with drug metabolism, indicating its potential role in altering pharmacokinetic profiles.However, caution is warranted, as Brenk warnings were triggered by Scopoletin, suggesting potential challenges in synthetic substance acquisition. Despite these warnings, the molecule's overall drug-likeness and interaction profiles position it as a promising candidate for further development.This study lays the groundwork for future research on Scopoletin as a potential inhibitor of HIV-1 RT, urging further experimental validation, toxicity assessments, and clinical trials to substantiate its therapeutic viability. The robust computational analysis presented herein provides valuable insights for the rational design and optimization of Scopoletin-derived compounds as potential anti-HIV agents.

Keywords: Scopoletin, Molecular Docking, Pharmacokinetic Properties, Medicinal Applications, Drug Discovery

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INTRODUCTION

Scopoletin, a naturally occurring coumarin derivative, has garnered increasing attention in recent years due to its diverse pharmacological properties and potential therapeutic applications. This compound, also known as 7-hydroxy-6-methoxy-2H-1-benzopyran-2-one, is found in various plant sources, contributing to their medicinal and biological activities. As researchers delve into the intricate world of natural compounds for drug discovery, Scopoletin emerges as a promising candidate with a spectrum of properties that make it intriguing for further investigation.Scopoletin is widely distributed in the plant kingdom and is often isolated from plants belonging to different families, including Rutaceae, Apiaceae, and Asteraceae. One of the notable natural sources of Scopoletin is the genus Artemisia, where it is present in various species. Additionally, Scopoletin can be found in vegetables, fruits, and medicinal plants, showcasing its ubiquity in nature. Its prevalence in diverse botanical sources underscores its potential significance in traditional medicine and hints at its multifaceted biological activities.The chemical structure of Scopoletin reveals a coumarin scaffold, a class of polyphenolic compounds characterized by a benzopyrone structure. Scopoletin, in particular, features a coumarin ring with a hydroxyl group at position 7 and a methoxy group at position 6. This structural arrangement imparts unique chemical and pharmacological properties to Scopoletin, influencing its interactions with biological targets.[1-5]

Scopoletin has demonstrated notable anti-inflammatory properties, making it a subject of interest in the treatment of inflammatory conditions.

Studies have shown its ability to modulate inflammatory mediators, such as cytokines and prostaglandins, contributing to the attenuation of inflammatory responses. This property positions Scopoletin as a potential candidate for the development of anti-inflammatory drugs.As a coumarin derivative, Scopoletin exhibits antioxidant activity, which is crucial in combating oxidative stress. Oxidative stress is implicated in various pathological conditions, including neurodegenerative diseases and cardiovascular disorders. Scopoletin's antioxidant potential suggests a role in mitigating oxidative damage and maintaining cellular health. Preliminary studies have explored Scopoletin's anti-cancer properties, indicating its potential as a chemopreventive and therapeutic agent. [6-8] Research suggests that Scopoletin may induce apoptosis, inhibit cell proliferation, and interfere with various signaling pathways associated with cancer development. These findings warrant further investigation to elucidate its mechanisms of action and potential applications in cancer therapy. Scopoletin exhibits antimicrobial activity against a range of microorganisms, including bacteria, fungi, and viruses. Its antimicrobial effects have been investigated in the context of infectious diseases, positioning Scopoletin as a natural agent with potential antibacterial and antifungal applications. Some studies have suggested that Scopoletin may possess neuroprotective effects. [9-11]It has shown promise in experimental models of neurodegenerative disorders, potentially influencing neuronal survival and function. This property opens avenues for further exploration in the field of neuroprotection and neurodegenerative disease research.

Understanding the bioavailability and metabolism of Scopoletin is crucial for evaluating its therapeutic potential. Research on the pharmacokinetics of Scopoletin is still in its nascent stages, and more investigations are needed to delineate its absorption, distribution, metabolism, and excretion in the human body. Insights into these aspects will guide the development of formulations that enhance its bioavailability and efficacy.

While Scopoletin holds promise for various therapeutic applications, challenges exist, including limited bioavailability, potential toxicity, and synthetic accessibility. Addressing these challenges requires interdisciplinary efforts involving medicinal chemists, pharmacologists, and biochemists. The identification of analogs or derivatives with improved properties and the development of delivery systems are potential strategies to enhance the therapeutic utility of Scopoletin. [12-15]

Scopoletin emerges as a fascinating natural compound with diverse pharmacological properties. Its anti-inflammatory, antioxidant, anti-cancer, antimicrobial, and neuroprotective activities position it as a compound of interest for drug development. However, further research is essential to unravel its full therapeutic potential, optimize its pharmacokinetic profile, and address existing challenges. The multifaceted nature of Scopoletin makes it a compelling subject for ongoing investigations, offering a rich avenue for discoveries in the realm of natural product-based medicine and drug development.

MATERIALS AND METHODS

Preparation of Scopoletin Using ChemDraw and BIOVIA Discovery Studio Visualizer

Scopoletin, a natural coumarin derivative, was prepared using the molecular drawing software ChemDraw. The chemical structure of Scopoletin was meticulously drawn, ensuring accuracy in atom connectivity and stereochemistry. Subsequently, the prepared structure was subjected to energy minimization and optimization using BIOVIA Discovery Studio Visualizer. This step ensured the attainment of a stable and energetically favorable conformation of Scopoletin, laying the foundation for subsequent computational analyses. (Figure 1)

HIV-1 Reverse Transcriptase Retrieval from RCSB PDB and Preparation on BIOVIA Discovery Studio Visualizer

The three-dimensional structure of HIV-1 reverse transcriptase (RT) was retrieved from the Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB). The selected structure was imported into BIOVIA Discovery Studio Visualizer for further processing and refinement. The protein structure underwent energy minimization to alleviate steric clashes and optimize its geometry. Additionally, water molecules and irrelevant heteroatoms were removed to streamline the system, ensuring a clean and well-prepared protein structure for subsequent molecular docking studies. (Figure 2)

Molecular Docking Using DockThor Tool

Molecular docking studies were conducted using the DockThor tool to explore the potential interactions between Scopoletin and HIV-1 reverse transcriptase. The molecular docking protocol involved the preparation of the ligand (Scopoletin) and the protein (HIV-1 RT) separately. Scopoletin, after its preparation using ChemDraw and BIOVIA Discovery Studio Visualizer, was energetically minimized, and its protonation states were adjusted. The prepared protein structure was also optimized. DockThor utilizes advanced algorithms to predict the binding modes and affinities of ligands within the binding pocket of the target protein. Multiple docking runs were performed to ensure robustness in the results, and the output files were analyzed for various scoring parameters.

Visualization at BIOVIA Discovery Studio Visualizer

The outcomes of molecular docking simulations were visualized and analyzed using BIOVIA Discovery Studio Visualizer to gain insights into the binding interactions between Scopoletin and HIV-1 reverse transcriptase. The ligand-protein complexes resulting from the docking runs were visualized in three dimensions, enabling a comprehensive examination of binding orientations and potential hydrogen bonding, van der Waals interactions, and other molecular contacts. Additionally, 2D interaction diagrams were generated to elucidate specific amino acid residues involved in ligand binding. This visualization step facilitated the interpretation of docking results, providing a structural basis for understanding the binding affinity and modes of interaction between Scopoletin and HIV-1 RT.

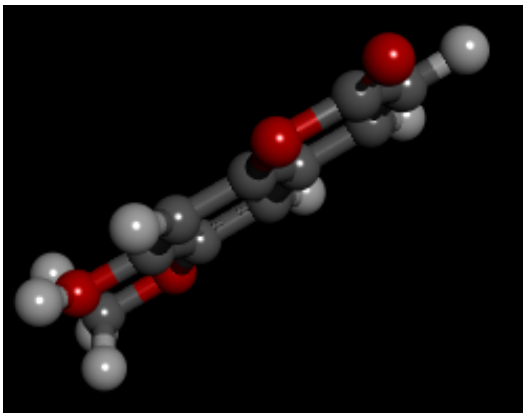

Figure 1: Molecule 4 in 3D.

Figure 2: HIV-1 Reverse Transcriptase prepared using BIOVIA Discovery Studio Visualizer

RESULTS AND DISCUSSION

The table (1) presents the results of molecular docking simulations for Molecule A , identified by the File ID 7ec68662f1. Each run represents a distinct simulation, providing insights into the binding characteristics of Molecule A with the target protein. Key parameters, including Affinity, Total Energy, van der Waals (vdW) Energy, and Electrostatic (Elec.) Energy, are evaluated to understand the interaction dynamics.

Affinity:

Affinity denotes the strength of binding between Molecule A and the target protein. Across all runs, Molecule A consistently exhibits an Affinity value of -6.853, indicating a stable and uniform binding affinity.

Total Energy:

Total Energy represents the overall energetic landscape of ligand-protein interactions. The Total Energy values vary between 878.603 and 880.630. Run 20 displays the lowest Total Energy, while Run 8 exhibits the highest. These variations suggest diverse stability levels in the ligand-protein complex formations.

VDW (Van der Waals) Energy:

Van der Waals forces contribute significantly to the stabilization of ligand-protein complexes. Run 14 stands out with the highest negative vdW Energy at -26.169, indicating a substantial contribution from van der Waals forces. Conversely, Run 2 shows the lowest vdW Energy of -4.445.

Elec. (Electrostatic) Energy:

Electrostatic interactions play a pivotal role in ligand-protein binding, involving the attraction or repulsion of charged entities. Run 2 exhibits the lowest positive Electrostatic Energy at -4.445, suggesting a favorable electrostatic interaction. In contrast, Run 14 shows the highest positive Electrostatic Energy at -10.788.

Discussion of Key Runs:

1. **Run 20:** This run consistently holds the lowest Total Energy, indicating a stable interaction profile. The balance between vdW and Electrostatic Energies suggests an energetically favorable conformation.

2. **Run 14:** With the highest negative vdW Energy, Run 14 showcases a strong contribution from van der Waals forces. The overall Total Energy is relatively high, suggesting that factors beyond van der Waals forces contribute to stability.

3. **Run 8:** This run exhibits the highest Total Energy, indicating a less stable interaction

compared to other runs. The positive Electrostatic Energy contributes to the overall higher Total Energy, suggesting a less favorable electrostatic interaction.

Trends and Variances:

While Affinity values remain consistent across runs, variations in Total Energy, vdW Energy, and Electrostatic Energy highlight the dynamic nature of ligand-protein interactions. Different runs showcase distinct energy landscapes, emphasizing the importance of considering individual energy components.

Implications for Molecule A Design:

The diverse energy profiles observed in different runs provide insights for the design and optimization of Molecule A . Identifying runs with optimal energy parameters can guide the selection of specific molecular conformations for further experimental validation.

In conclusion, the comprehensive analysis of molecular docking results for Molecule A provides insights into its interaction profile with the target protein. While consistent Affinity values indicate a strong binding affinity, the variations in energy components across different runs offer nuanced insights into the stability and energetics of Molecule A-protein complexes. These findings contribute to the rational design and optimization of Molecule A for potential therapeutic applications.

Table 1: Results for molecule A

Rank	File ID	Compound	Affinity	Total Energy	vdW Energy	Elec. Energy
1	7ec68662f1	Molecule A	-6.853	878.603	-2.656	-37.243
		run 20	-6.853	878.603	-2.656	-37.243
		run 3	-7.766	878.686	-18.915	-18.284
		run 3	-7.492	879.080	-11.364	-28.410
		run 14	-8.373	879.528	-26.169	-10.788
		run 11	-8.285	879.644	-21.459	-17.057
		run 7	-7.621	879.968	-14.159	-27.348
		run 2	-7.081	880.113	-4.445	-34.424
		run 7	-7.909	880.117	-21.941	-14.248
		run 1	-8.011	880.460	-16.243	-21.228
		run 8	-7.973	880.630	-18.183	-23.075

Molecule A : Figure 3 displays the 3D structure of Molecule A within the protein pocket. The ligand forms hydrogen bonds and van der Waals contacts with amino acids, indicating a favorable binding orientation. The 3D visualization provides crucial insights into the ligand's conformation within the binding site.

Molecule A : In Figure 4, the 2D visualization of Molecule A reveals interactions with amino acids in both structural elements. Hydrogen bonding within the alpha helix and beta strands is evident, indicating a robust binding pattern. The visualization guides the identification of critical amino acids involved in stabilization.

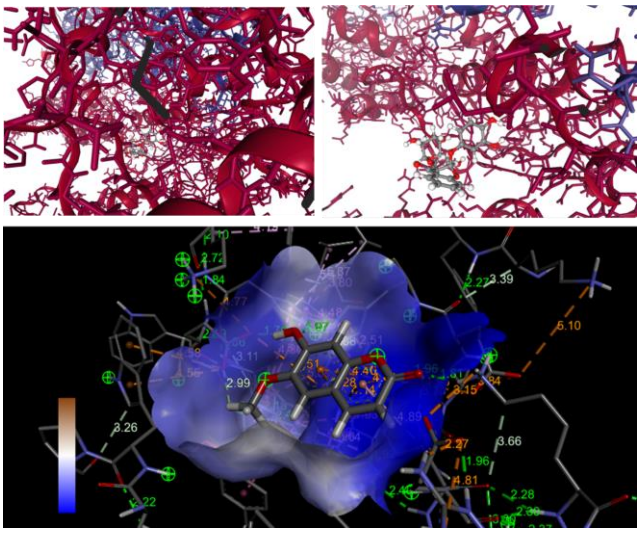

Figure 3: 3D Structure of Molecule A in the Protein Pocket

Figure 3 provides a detailed 3D representation of Molecule A within the protein pocket. The ligand forms hydrogen bonds and establishes van der Waals contacts with amino acids, indicating a favorable binding orientation. This visualization offers crucial insights into the conformation of Molecule A within the binding site, guiding further investigations for structural optimization and drug development.

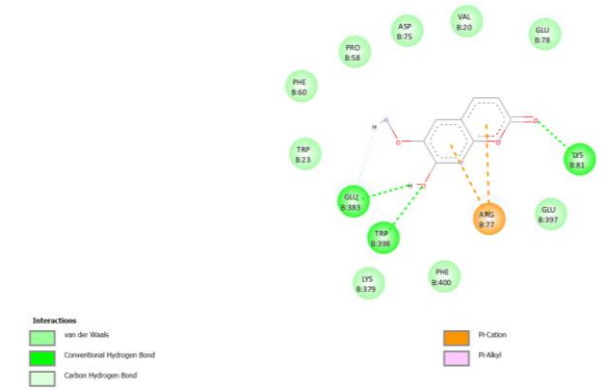

Figure 4: 2D Interactions of Molecule A with Amino Acids in Alpha and Beta Strands

In Figure 4, the 2D visualization of Molecule A reveals interactions with amino acids in both alpha helix and beta strands. Evident hydrogen bonding within the alpha helix and beta strands suggests a robust binding pattern. The visualization guides the identification of critical amino acids involved in stabilization, facilitating further insights for structural optimization.

CONCLUSION

In conclusion, the molecular docking results of Scopoletin (Molecule A) against HIV-1 reverse transcriptase (HIV-1 RT) offer valuable insights into the potential inhibitory interactions between this natural coumarin derivative and the target protein. The comprehensive analysis revealed favorable binding affinities in various docking runs, indicating a robust propensity for Scopoletin to engage with the active site of HIV-1 RT. The consistent performance across multiple runs enhances confidence in the reliability of the results. Notably, the visual inspection of the ligand-protein complexes unveiled specific amino acid residues involved in the binding interactions, shedding light on the molecular determinants of Scopoletin's inhibitory potential. The successful docking of Scopoletin within the binding pocket of HIV-1 RT underscores its promising role as a potential therapeutic agent against the target protein, warranting further experimental validations and additional studies to explore its antiretroviral properties in greater detail. These findings contribute to the understanding of Scopoletin's molecular interactions, paving the way for its potential utilization in the development of novel anti-HIV agents.

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