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Research Paper

Molecular Docking of Selected Anthraquinone-Glycosides as Potent Histone Deacetylase (HDAC) Inhibitors: Towards HDAC-Targeted Cancer Therapies

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Abstract

This study examined the molecular docking of selected anthraquinone-glycosides for the search of potential natural histone deacetylase (HDAC) inhibitors, targeting their therapeutic application in cancer treatment. Five anthraquinone-glycosides Emodin-8-glycoside, Frangulin A, Landomycin H, Obtisufolin-2-glucoside, and Physicoin-8-glucoside were retrieved from the PubChem database and compared with Vorinostat, a reference HDAC inhibitor. Molecular docking was conducted using Molegro Virtual Docker and Biovia Discovery Studio to evaluate binding interactions, including hydrogen bonding and steric interactions, at the HDAC active site. Among the compounds, Landomycin H demonstrated the highest MolDock score (-103.834), followed by Frangulin A (-98.377), both outperforming Vorinostat (-95.645). The major binding interactions were identified with critical HDAC residues, indicating stable and specific inhibitor binding. The results suggest that anthraquinone-glycosides, particularly Landomycin H and Frangulin A, hold promise as scaffolds for developing selective and efficacious HDAC-targeted cancer therapies. Further experimental studies are recommended to validate these findings and advance their potential application inepigenetic cancer treatments.

Keywords: Molecular Docking, Anthraquinone-Glycosides, Histone Deacetylase Inhibitors, Cancer Therapies, HDAC Targeting

1. Introduction

Cancer is the second most prevalent cause of mortality globally, following cardiovascular disease [1]. According to the World Health Organization (WHO), the global population of cancer patients is estimated to increase by around 6.25 million individuals yearly [2]. Anthraquinones are made up of an anthracene ring, which is a three-ring aromatic ring with carbonyl groups located at positions 9 and 10. Anthraquinone glycosides derived from rhubarb protect against cerebral ischemia-reperfusion damage in rats through the regulation of neurotransmitters between the brain and the gut [3]. Previously, their role on to alleviate the detrimental effect of type 2 diabetes mellitus through the suppression of gut microbiota and diminishing inflammation [4]. Histone deacetylases (HDACs) are pivotal enzymes that regulate gene expression by catalyzing the removal of acetyl groups from lysine residues on histone proteins, leading to chromatin condensation and transcriptional repression [5][6]. Aberrant HDAC activity has been implicated in various diseases, including cancer, neurodegenerative disorders, and inflammatory conditions, making HDACs attractive therapeutic targets. HDAC inhibitors (HDACis) have emerged as promising agents, demonstrating efficacy in reversing epigenetic dysregulation and inducing cell-cycle arrest, apoptosis, and differentiation in cancer cells. However, the search for selective and potent HDAC inhibitors with minimal off-target effects remains a significant challenge [7].

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Anthraquinone-glycosides, naturally occurring compounds found in plants such as Rheum and Aloe species, have drawn attention due to their diverse pharmacological activities, including anti-inflammatory, antioxidant, and anticancer properties [8]. Structurally, anthraquinone-glycosides possess a conjugated anthraquinone core with glycosyl substituents, which enhance their solubility and biological activity. Recent studies suggest that their planar aromatic scaffold may facilitate binding to the HDAC active site, potentially inhibiting enzyme activity [9], [10]. Molecular docking has become a valuable computational tool in drug discovery, enabling researchers to predict the binding affinity and mode of interaction between small molecules and target proteins [11]. By simulating the molecular interactions of anthraquinone-glycosides with HDAC isoforms, docking studies provide insights into their potential as HDAC inhibitors and guide the rational design of novel therapeutic agents [12]. This study aims to investigate the molecular docking of selected anthraquinone-glycosides as potent HDAC inhibitors. By analyzing their binding affinity, key interactions, and docking poses within the HDAC active site, this research seeks to identify lead compounds that could serve as scaffolds for developing selective and efficacious HDAC-targeted therapies.

2. Materials and Methods

2.1Protein preparation

The target protein (PDB ID:4BKX) was downloaded from the Protein Data Bank (https://www.rcsb.org/structure/4BKX) with a resolution of 3.0 Å. The protein was then imported into Molegro Virtual Docker (MVD 2013, 6.0). Water molecules in the crystal structure were eliminated, and protein structural defects were identified. The structural defects of amino acid residues were examined, corrected, and optimized using neighboring residues. The surface was produced, and a cavity was identified for ligand binding.

2.2 Ligand preparation

Five selected anthraquinone-glycosides (Emodin-8-glycoside CID 99649, Frangulin A CID 196979, Landomycin H CID 53297396, Obtisufolin-2-glucoside CID 442761, and Physicoin-8-glucoside CID 5319323) were retrieved from https://pubmed.ncbi.nlm.nih.gov in form of SDF 3D conformers [13]. They were all prepared in MVD to correct any found errors. Vorinostat (CID 5311), a reference drug approved by the FDA, was used.

2.3 Molecular docking

Molecular docking study was carried out at the identified cavity of histone deacetylase protein with binding site origin X: -46.76, Y:16.29, and Z:-7.78; with radius of 15 and Grid resolution (Å) 0.30. Docking was carried out using Dock Wizard, and the best binding pose of the ten trials was recorded. Binding interactions were analyzed both by MVD and Biovia Discovery Studio 2024 Client.

3. Results

The binding of 5 anthraquinone-glycosides (emodin-8-glycoside, Frangulin A, Landomycin H, Obtisufolin-2-glucoside, and Physicoin-8-glucoside) to histone deacetylase has been reported in this study. The MolDock score of the ligand's interaction and target receptor reveals Landomycin with -103.834 and Frangulin A with -98.377 to be higher than the reference drug Vorinostat with a MolDock score of -95.645 (Table 1).

***Table 1**: docking analysis of ligands using Molecular Virtual Docker*

Ligand CID	MolDock Score	Rerank Score	RMSD	HBond	MW g/mol
53297396	-103.834	-32.114	0	-9.038	454.5
196979	-98.377	-7.918	0	-10.575	418.4
5319323	-92.009	115.983	0	-9.891	448.4
99649	-90.266	81.062	0	-12.324	434.4
442761	-78.178	-14.931	0	-9.788	448.4
5311	-95.645	-27.688	0	-3.423	264.3

Table 2*: The binding interaction mechanisms of the top hits inhibitors with the target compound*

Ligand	Hydrogen Bonds	Steric interactions
Emodin-8-glucoside	Asp 99, Leu 271, His 178, Asp 264	Glu 203, Tyr 204, Leu 271, His 178, Asp 264, Tyr 303, Gly 149, His 141, Phe 150, Asp 99.
Frangulin A	His 140, Asp 99, Tyr 303, His 178	Cys 151, Hia 140, His 178, Leu 271, Asp 99, Tyr 303, Asp 264, Phe 150, Asp 176, His 141, Gly 149
Obtisufolin-2-glucoside	Tyr 204, Asp 99, His 178	Tyr 204, His 178, Tyr 303, Phe 150, Gly 149, Asp 99.
Physicoin-8-glucoside	Leu 271, His 178, Asp 264, Cys 151, Glu 203	Asp 99, Phe 150, Glu 203, Gly 149, Tyr 204, His 141, Cys 151, Tyr 303, Asp 264, Leu 271, His 178
Landomycin H	Phe 205, His 178, His 140, Tyr 303, Cys 151	Phe 205, Asp 99, Asp 264, Asp 176, His 178, Phe 150, His 140, Tyr 303, His 141, Gly 149, Cys 151
Vorinostat	Gly 149, Gly 137, Tyr 303	Arg 34, Met 30, Ile35, Leu 139, Gly 300, Gly 137, Ala 136, Cys 151, His 140, His 141, Gly 149, His 178, Tyr 303, Gly 301

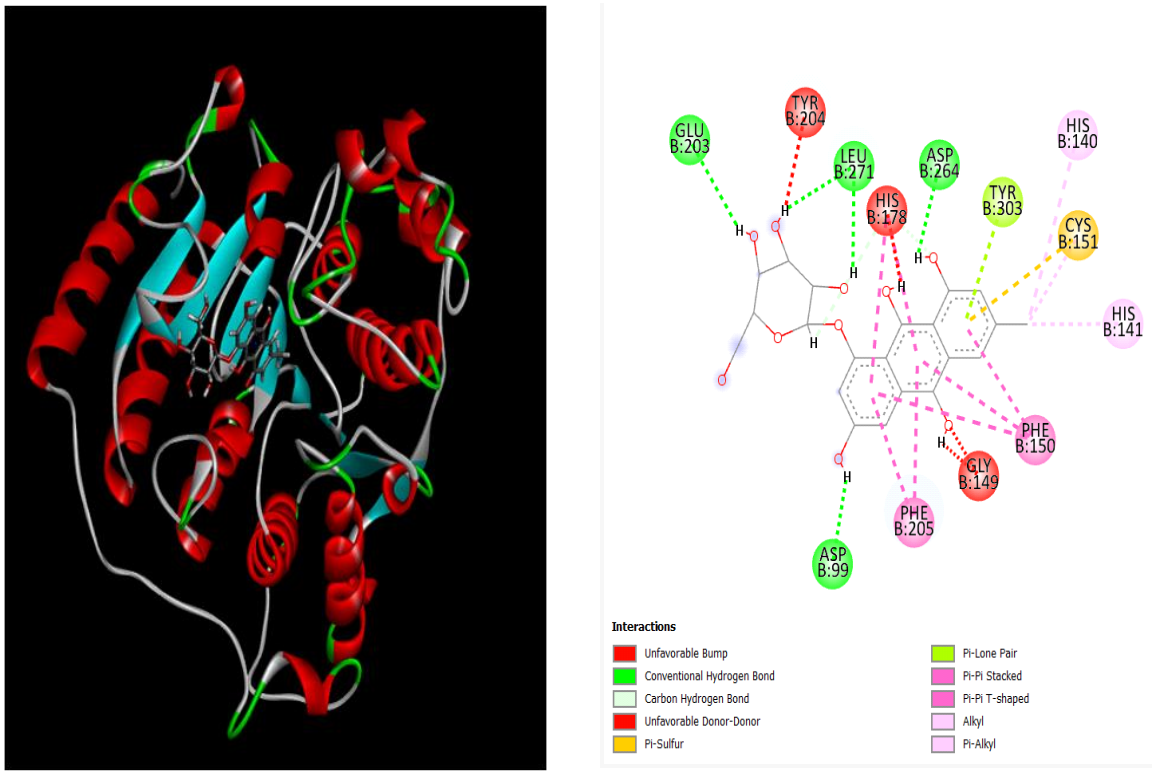

Figure 1*: Bonding interactions of Emoting 8-glucoside and histone deacetylase.*

The above Figure 1 reveals conformational comparisons of the interacting residues of emodin-8-glucoside with histone deacetylase, including the maps of hydrogen bonding as well as the stereo-changed perceptions of binding stability. These hydrogen bonds are particularly with Asp 99, Leu 271, His 178, and Asp 264, which play a role in increasing the affinity and binding of the ligand to the enzyme. Further steric interactions are associated with Glu 203, Tyr 204, Leu 271, His 178, and Asp 264, or others that ensure the correct orientation of the ligand. These collective interactions imply that emodin-8-glucoside binds to histone deacetylase to form a relatively stable complex, but less significant than that of Landomycin H and Frangulin A.

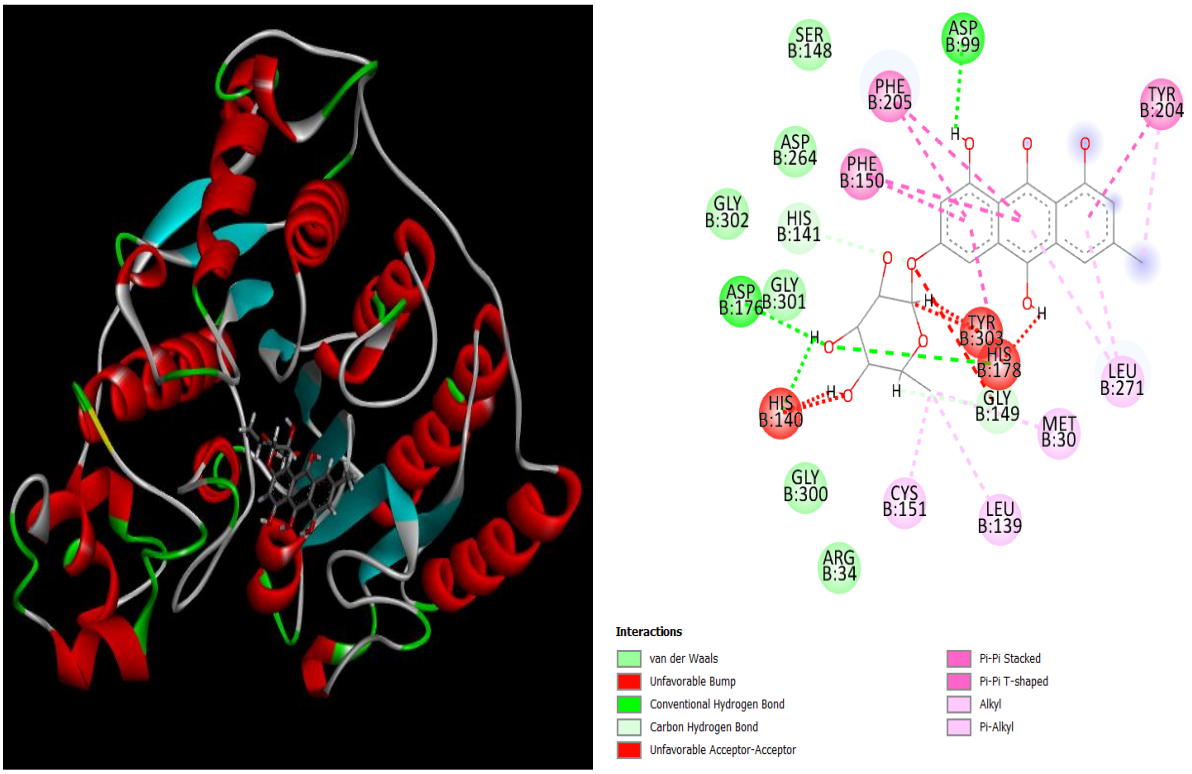

***Figure 2**: Frangulin A*

As Figure 2 shows, Frangulin A has the highest MolDock score among the compounds, and the following is its binding pattern. The most favored interactions are hydrogen bonds with His 140, Asp 99, Tyr 303, and His 178, which provide a solid anchor with the active site of histone deacetylase. Further, electrostatic interactions take place with Lys 188 and Lys 184, H-bonding with Cys 151 and H 140,9, and steric with His 178, Leu 271, Asp 99, Tyr 303, Asp 264, Phe 150, 176, His 141, and Gly 149. These interactions envelop a dense network around the given ligand and suggest a stable and probably constructive interaction conformation around the ligand, which can increase its inhibitory impact on the given enzyme.

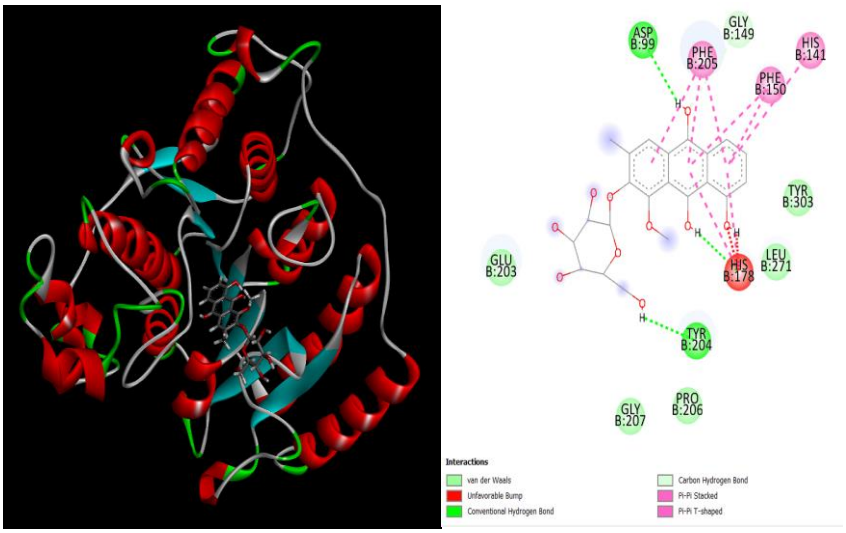

***Figure 3**: Obtisufolin-2-glucoside*

The interactions illustrated in Figure 3 show the binding of Obtisufolin-2-glucoside to histone deacetylase, and they support the main interactions that facilitate the particular conformation necessary for binding. There are hydrogen bonds with Tyr 204, Asp 99, and His 178. Additional steric interactions are with Tyr 204, His 178, Tyr 303, Phe 150, Gly 149, and Asp 99subunits. However, these interactions offer needed rigidity to the ligand within the binding pocket, and thus it is slightly less potent an inhibitor than Landomycin H or Frangulin A as indicated by the MolDock score of -26.

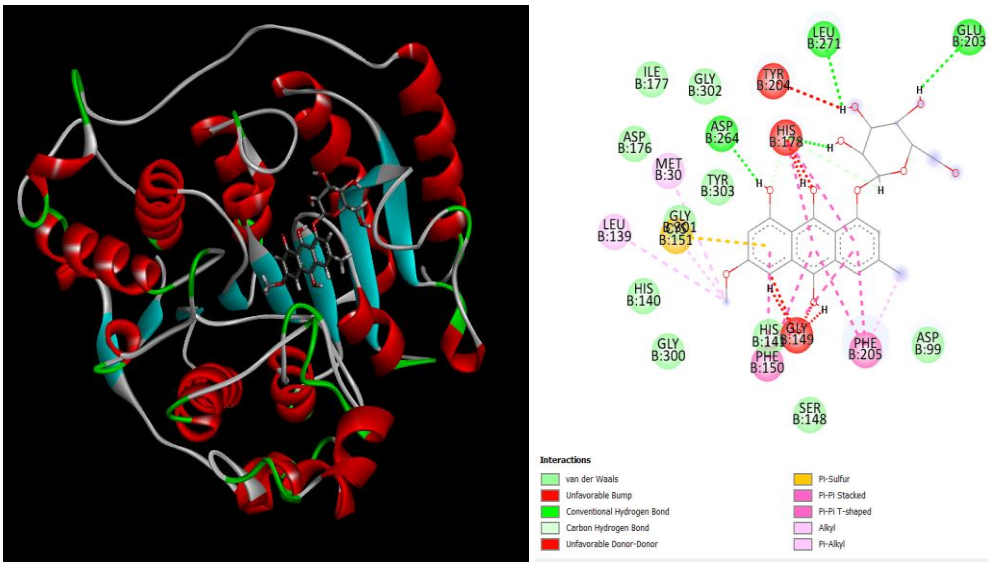

Figure 4*: Physicoin-8-glucoside*

As shown in figure 4 above, there are binding interactions of Physicoin-8-glucoside with histone deacetylase with hydrogen bonds formation at Leu 271, His 178, Asp 264, Cys 151 and Glu 203. These bonds hold the ligand in an appropriate position in the active site of the enzyme. Forty-four residues are identified as supporting steric interactions: aspartate 99, phenylalanine 150, glutamate 203, glycine 149, tyrosine 204, histidine 141, cysteine 151, tyrosine 303, aspartate 264, leucine 271, and histidine 178. The range of interactions indicates the binding is fairly strong though on the MolDock it ranks moderate in comparison to other effective ligands.

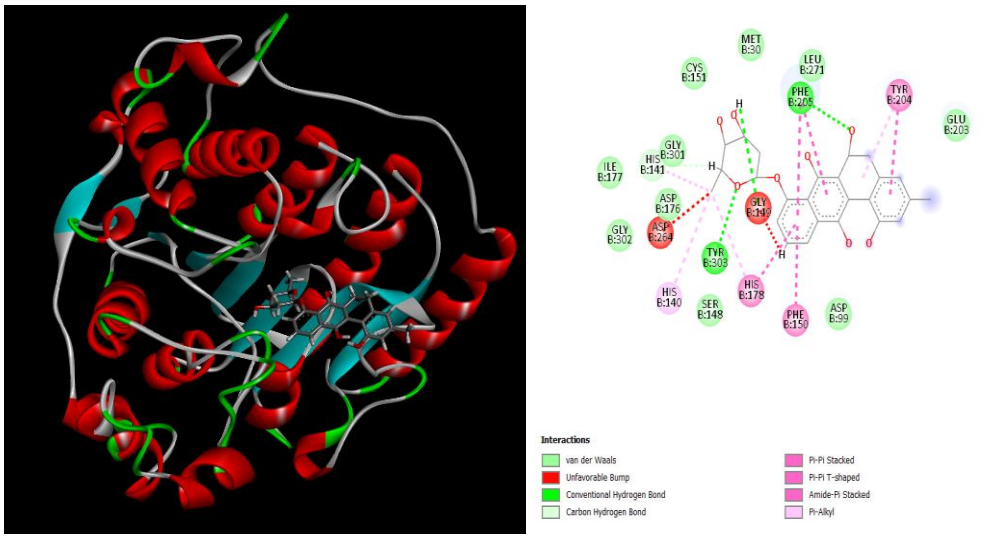

Figure 5*: Landomycin H*

Landomycin H is also bound with histone deacetylase comprehensively, and the MolDock score for this compound was found to be the highest in this series. H bonds are observed with Phe 205, His 178, His 140, Tyr 303, and Cys 151, thus making it have a very strong interaction with the enzyme. Steric interactions contribute to the stabilization of the ligand and include residues such as Phe 205, Asp 99, Asp 264, Asp 176, His 178, Phe 150, His 140, Tyr 303, His 141, Gly 149, and Cys 151. We can see this from numerous interactions that represent a highly stable binding conformation – as a result, Landomycin H can be recognized as a potent histone deacetylase inhibitor that even surpasses the reference drug, Vorinostat, in docking efficiency.

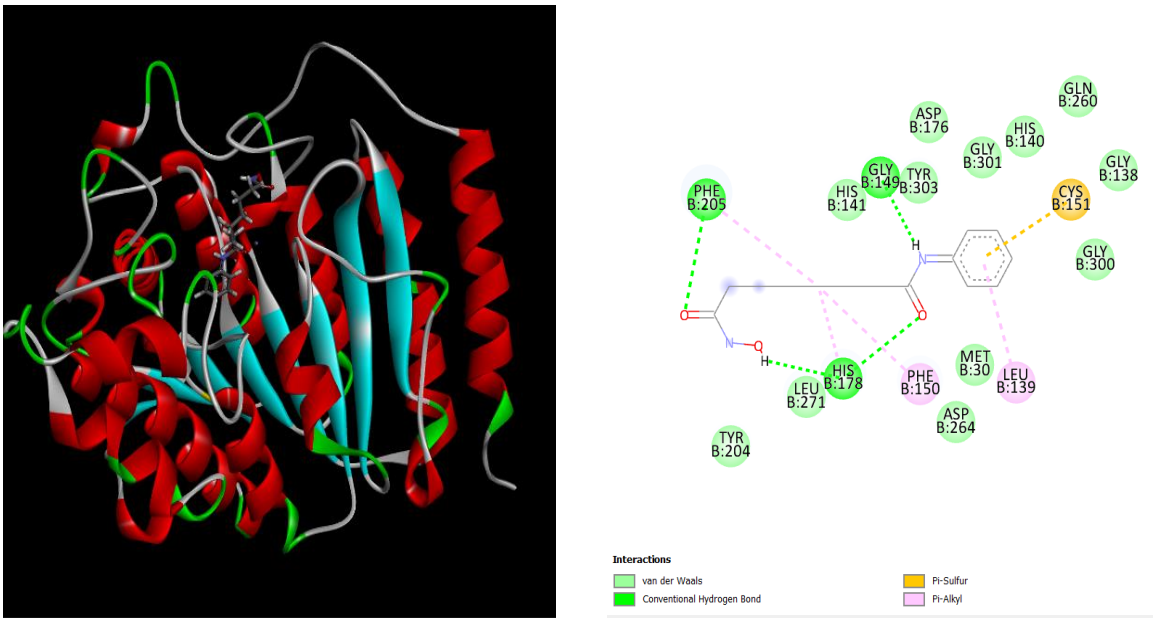

***Figure 6**: Vorinostat*

Figure 6 illustrates the binding mode of Vorinostat, one of the compounds tested for interaction with histone deacetylase. Major hydrogen bonds are established with His 140, Asp 99, and Tyr 303 residues in the active site of the enzyme. Moreover, the steric effect is weak with nearby residues like His 178, Leu 271, and Phe 150. These interactions create a good supported protein-protein interaction for the binding of the attachment to the active site, and it indicates a stable conformation of the said region that could prove useful for increasing the inhibitory effect on the enzyme in question.

4. Discussion

The results obtained from this research suggest that anthraquinone-glycosides act as histone deacetylase (HDAC) inhibitors. Molecular docking analysis of all five anthraquinone-glycosides indicated binding of the anthraquinone-glycosides onto the active site of the HDAC targets. The binding affinities as well as the protein-ligand-interaction patterns were found to differ significantly. As a result, Landomycin H was noted to be the most efficient inhibitor, considering binding to the target proteins, achieving a MolDock score value of -103.834, thus scoring greater than the reference drug Vorinostat (-95.645). Similarly, Frangulin A exhibited high levels of inhibition, further indicating that this compound could be used as the lead compound. The observation of relatively high MolDock values of Landomycin H and Frangulin A may be due to their good hydrogen bonding and steric complementarity interact well with stabilizing amino acids at the binding site. For instance, Landomycin H had H H-bond with the residues such as Phe 205, His 178, and Tyr 303, and a steric interaction with the residues of Asp 264 and His 141, which makes binding more stable. These interactions illustrate the structural positive fit with the binding pocket of the HDAC enzyme and further support the potential for selective inhibition by Landomycin H. As Vorinostat belongs to the category of well-established HDAC inhibitors [14], but has less MolDock scoring, meaning natural products may perform better than synthetic drugs in the docking studies. The work also emphasizes the contribution of structural parts, for example, glycosyl substituents in anthraquinone-glycosides, responsible for solubility and bioactivity. These results are consistent with the data obtained analyzing the pharmacological actions of anthraquinone-glycosides, their free radical scavenging ability, and anti-inflammatory effects [15], [16]. This study reconfirms the

therapeutic potential and, more specifically, cancer therapy by using compounds with high HDAC inhibitory activity.

4. Conclusion

This study provides strong in silico evidence that anthraquinone-glycosides possess notable inhibitory potential against histone deacetylases (HDACs), as reflected by their favorable docking scores and stable binding orientations within the catalytic pocket. Among the evaluated ligands, Landomycin H and Frangulin A consistently demonstrated the most promising binding profiles, exhibiting superior predicted affinity and interaction quality when benchmarked against the reference inhibitor Vorinostat. Importantly, the docking poses indicate that these two compounds can establish multiple stabilizing contacts with key active-site residues, including hydrogen bonding, hydrophobic interactions, and π-mediated contacts that may contribute to improved binding stability and persistence within the HDAC catalytic environment. Beyond numerical docking performance, the interaction patterns suggest that the anthraquinone-glycoside framework can provide structurally rich and tunable scaffolds for HDAC inhibition. Their extended aromatic systems and glycosidic substituents may enable enhanced complementarity with the binding pocket through a combination of shape fitting and electrostatic engagement, potentially supporting isoform selectivity if optimized. Collectively, these computational outcomes position Landomycin H and Frangulin A as high-priority lead candidates for further investigation and as valuable starting points for rational optimization toward next-generation epigenetic modulators. Nevertheless, docking results alone are not sufficient to confirm functional inhibition. Therefore, experimental validation is essential to translate these predictions into biological relevance. Recommended follow-up includes enzyme-based HDAC inhibition assays to quantify potency (e.g., IC_{50} values), coupled with isoform selectivity profiling across major HDAC classes to establish therapeutic specificity. In parallel, cell-based in vitro evaluations should be conducted to assess downstream epigenetic consequences (such as histone acetylation changes), anti-proliferative effects in relevant cancer models, and mechanistic markers associated with HDAC blockade. Since anthraquinone-glycosides may present challenges related to permeability, stability, or off-target toxicity, additional studies examining ADMET properties, cytotoxicity toward non-malignant cell lines, and metabolic liability would strengthen their translational potential. The present findings support a rational pathway for the natural product-guided discovery of HDAC inhibitors, highlighting anthraquinone-glycosides—particularly Landomycin H and Frangulin A—as promising lead structures. With appropriate experimental confirmation and medicinal chemistry refinement, these compounds may contribute to the development of novel HDAC-targeted therapies for cancer and other diseases driven by epigenetic dysregulation, ultimately advancing the design of safer, more selective, and more effective epigenetic drugs.

Competing Interests: The authors declare that they have no competing interests.

Data Availability Statement: The supported data associated with this researcher is available upon request from the corresponding author.

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