Exploring potential inhibitors for colorectal cancer targeting aldehyde dehydrogenase X (ALDH1B1) using molecular docking

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ABSTRACT

Background: Colorectal cancer (CRC) is a major global health concern, demanding continuous exploration of novel therapeutic avenues. Aldehyde dehydrogenase X (ALDH1B1) has surfaced as a promising CRC target due to its involvement in cancer progression and resistance to conventional treatments. This study integrates insights from scientific literature, incorporating prevalence data, current treatments, highlighting the need for innovative therapeutic strategies.
Methods: Facing challenges in efficacy and side effects, a paradigm shift towards targeted therapies is crucial for CRC. Molecular docking, a robust computational tool, systematically identifies potential inhibitors by simulating ligand-protein interactions. The study aims to contribute to more effective and targeted therapeutic approaches for CRC by exclusively focusing on ALDH1B1, informed by prevalence data and insights from the current treatment landscape.
Results: The assessment using molecular docking revealed β-sitosterol as the top affinity ligand among twenty-one compounds targeting ALDH1B1. Validation with the original ligand NAD ensures the computational predictions' reliability. Two-dimensional representations offered insights into ligand-receptor interactions, emphasizing β-sitosterol's dynamic engagement with ALDH1B1 through hydrogen bonds and hydrophobic interactions. The study showcased the interaction between ALDH1B1 and irinotecan, unraveling intricate hydrogen bonds. Three-dimensional visualizations further elucidated complex interactions within the system.
Conclusion: β-sitosterol has anticancer features such as apoptosis induction, cell cycle arrest, anti-angiogenic actions, and anti-inflammatory effects. As an antioxidant, it protects cells from oxidative stress, suggesting CRC treatment potential. Molecular docking suggests CRC ALDH1B1 targeted treatments. Clinical validations, molecular mechanisms, combination therapy, bioactive molecule exploration, and precision medicine should be the emphasis of future research to improve therapeutic outcomes.

Keywords: Colorectal cancer, ALDH1B1, molecular docking, bioactive compounds, molecular mechanisms

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INTRODUCTION

Colorectal cancer stands as a formidable global health concern, posing a substantial burden on public health systems worldwide [1]. This malignancy arises from the uncontrolled growth of cells in the colon or rectum, segments of the large intestine [2]. The complexity of colorectal cancer is reflected in its diverse molecular subtypes and the challenges associated with its diagnosis and treatment [3].

In the complex terrain of colorectal cancer, aldehyde dehydrogenase X (ALDH1B1) has surfaced as a significant contributor [4]. ALDH1B1 is a member of the ALDH superfamily, a group of enzymes crucial for detoxifying aldehydes generated during cellular metabolism [5]. Beyond its conventional role in cellular detoxification, ALDH1B1 has garnered attention for its involvement in cancer progression and its potential impact on treatment resistance [6].

Research indicates that ALDH1B1 is implicated in promoting cancer cell survival and proliferation [7]. Its overexpression has been associated with aggressive phenotypes in various cancers, including colorectal cancer. In the context of CRC, heightened ALDH1B1 levels have been linked to tumor progression, emphasizing its role as a potential therapeutic target [8].

Moreover, ALDH1B1 has been correlated with resistance to conventional cancer treatments. The ability of cancer cells to overexpress ALDH1B1 is believed to contribute to their resilience against chemotherapy, making the enzyme an

intriguing focus for therapeutic intervention [9].

The integration of ALDH1B1 into the broader landscape of colorectal cancer research signifies a shift toward more innovative therapeutic strategies [10]. Recognizing the significance of ALDH1B1 in cancer biology opens avenues for targeted therapies that specifically address the molecular intricacies associated with this enzyme [11].

Current research endeavors leverage insights from scientific literature, incorporating prevalence data and current treatment modalities. Molecular docking, a potent computational tool, plays a pivotal role in these studies by systematically identifying potential inhibitors that could disrupt the actions of ALDH1B1 [12]. The identification of bioactive molecules, exhibiting high affinity for ALDH1B1 in molecular docking studies, presents promising prospects for future therapeutic developments [13]. The aim of this study was to investigate the possibility of developing inhibitors for colorectal cancer by focusing exclusively on ALDH1B1. Through the utilization of prevalence data and the gleaned insights from the existing landscape of colorectal cancer treatment methods, to make a contribution to the creation of therapeutic approaches that are more effective and more specifically targeted.

MATERIALS AND METHODS

Materials

The aldehyde dehydrogenase X (ALDH1B1) complex, was obtained from the Protein Data Bank Repository (PDB) with the ID Code 7MJD [11]. The files associated with it were downloaded in .pdb format. Furthermore, a 3D conformer file of the anticancer drug agent irinotecan was acquired from the original ligand nicotinamide adenine dinucleotide (NAD) in the 3D protein structure. Additionally, a total of 15 ligand files were obtained 3,4-dimethoxybenzoic acid, 4-terpineol, β-caryophyllene oxide, β-ocimene, β-phellandrene, β-pinene, β-sitosterol, camphor, caryophyllene, curcumin, furanodienone, germacrone, kaempferol, sabinene, vanillic acid, zerumbone, sesquiphellandrene from the PubChem database [14]. The ligand files were saved in the .sdf format.

Protein preparation

Following the elimination of initial ligands and water molecules using Discovery Studio Visualizer [15], the .pdb files of protein are obtained. Several critical stages are required to prepare a protein structure for molecular docking with PyRx [16] and guarantee that the protein is suitable for docking simulations. The process consists of several stages: acquiring the protein structure in a format that is compatible with PyRx, inputting the structure into the program, eliminating water molecules, if required, supplementing missing residues with hydrogen atoms, designating atom types to the residues, optimizing the structure, and ultimately saving the prepared protein structure. Researchers can ensure that their protein structures are sufficiently prepared for precise and dependable docking simulations by adhering to the subsequent procedures.

Molecular docking

The protein and ligand were prepared using the PyRx Tools software, which also converted them to the.pdbqt format. To conduct molecular docking simulations, adhere to the subsequent procedures: Import the protein structure into PyRx after obtaining it from a database such as the Protein Data Bank (PDB). In order to assemble the protein, it is necessary to remove water molecules, supplement any absent residues, and introduce hydrogen atoms. An alternative approach to improve precision is to allocate atom types and optimize the structure. Save the protein structure that has been prepared in PDB or PDBQT format. Subsequently, acquire the ligand structure through computational means or obtain it from a chemical database, guaranteeing its compatibility with PDB or SDF formats. Assign atom types, load the ligand into PyRx, supplement with hydrogen atoms as necessary, and convert to PDBQT format if necessary. Ensure that the ligand structure is saved in an appropriate format.

Protein and ligand interaction

Protein and ligand docking data were generated in accordance with.pdb files. The data integration process utilized the PyRx program in order to guarantee a consistent and standardized representation that could be built upon in subsequent analyses. Furthermore, a 3D structure visualization was performed using PyMOL [17], which allowed for a thorough examination of conformational changes, binding interfaces, and spatial arrangements. In addition, the binding energy (ΔG) value was employed to compute the magnitude of the ligand-target interaction during molecular docking. Using the formula $Ki = e^{-RT/\Delta G}$, the inhibition constants (Ki) were also calculated to determine the degree of binding affinity between a ligand and a target enzyme or receptor.

RESULTS

Protein and ligand interaction

The assessment employed a PyRx gridbox, which functioned as an intuitive interface to establish a personalized receptor docking gridbox for the purpose of molecular docking. The inhibition constant and binding energy of the interaction between the ligand inhibitors and aldehyde dehydrogenase X (ALDH1B1) are depicted in Figures 1 and 2, respectively. Of the twenty-one compounds examined, β-sitosterol exhibited the highest degree of affinity for binding to the ALDH1B1 receptor. The original ligand nicotinamide adenine dinucleotide (NAD), which was extracted from the three-dimensional structure of the protein-ligand complex, was utilized to validate the docking.

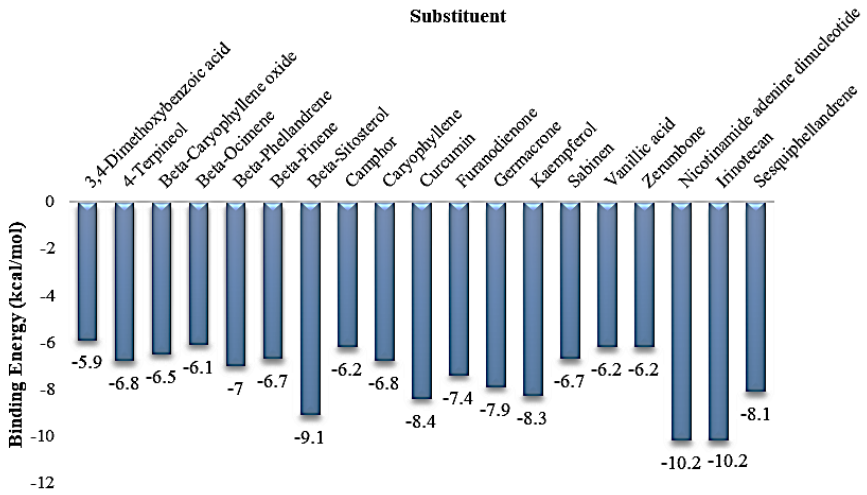

Figure 1. Binding energy between natural compounds towards aldehyde dehydrogenase X (ALDH1B1).

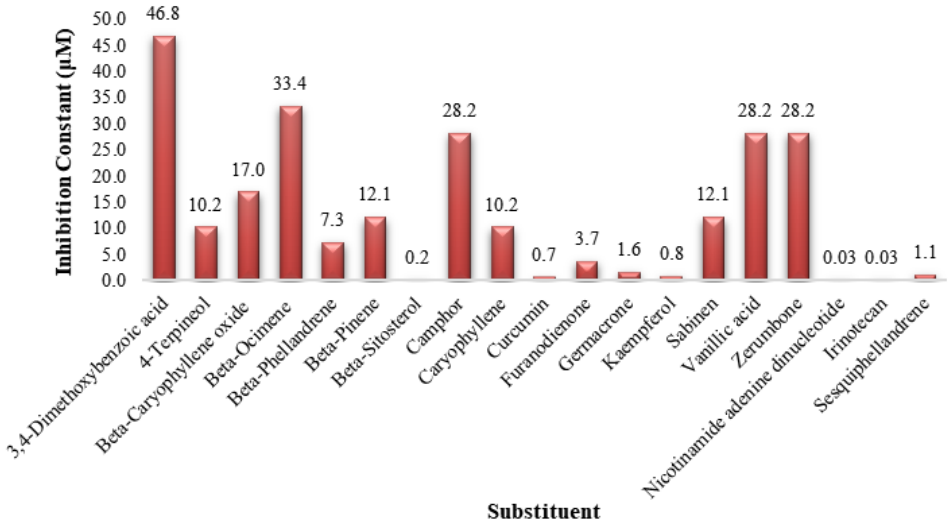

Figure 2. Inhibition constant value (Ki) of natural compounds towards aldehyde dehydrogenase X (ALDH1B1).

Figure 3 illustrated a two-dimensional representation of receptor-ligand interactions, specifically the formation of complexes among various entities. The dynamic interaction between β-sitosterol and the receptor ALDH1B1 was depicted in Figure 3A. Three hydrogen bonds were formed during this interaction with Leu-120, Phe-170, Gln-289, and eleven hydrophobic interactions with Glu-124, Asp-121, Val-173, Trp-177, Met-174, Val-459, Ile-458, Phe-296, Asn-457, Glu-292, Glu-288. A comprehensive illustration of the interaction between the ALDH1B1 receptor and the anticancer agent irinotecan was presented in Figure 3B. The illustration depicted ten hydrogen bonds with: Val-249, Gly-225, Pro-226, Ala-230, Leu-252, Phe-243, Ile-165, Ala-194, Glu-195, Trp-168. Finally, the intricate interaction between the ligand NAD and the ALDH1B1 receptor was depicted in Figure 3C. This analysis offers a holistic viewpoint on the molecular connections present in the system, encompassing seven hydrogen bonds with Pro-226, Val-249, Gln-196, Glu-348, Phe-401, Glu-399, Gly-245. In addition, the 3D visualization of complex interactions between the following substances was presented in Figure 4: A. ALDH1B1 receptor and β-sitosterol; B. ALDH1B1 receptor and irinotecan drug; and C. ALDH1B1 receptor and the original ligand.

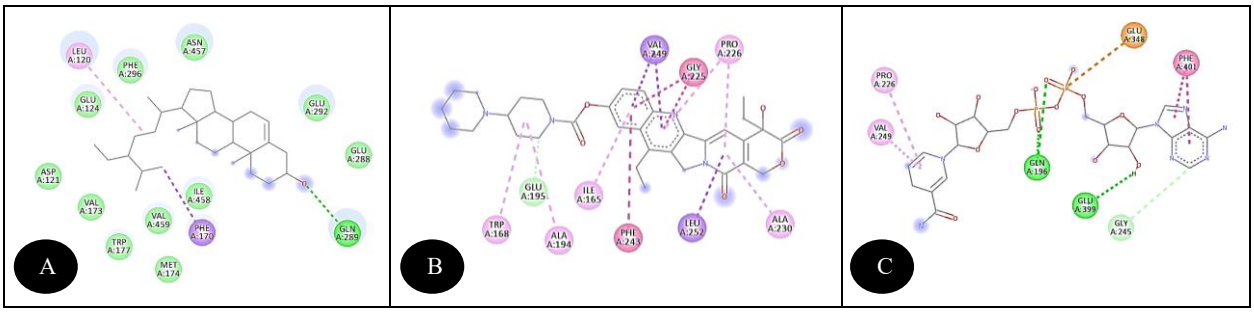

Figure 3. The 2D visualization of interactions complex between: A. ALDH1B1 receptor and β-sitosterol, B. ALDH1B1 receptor and irinotecan drug, ALDH1B1 receptor and the original ligand.

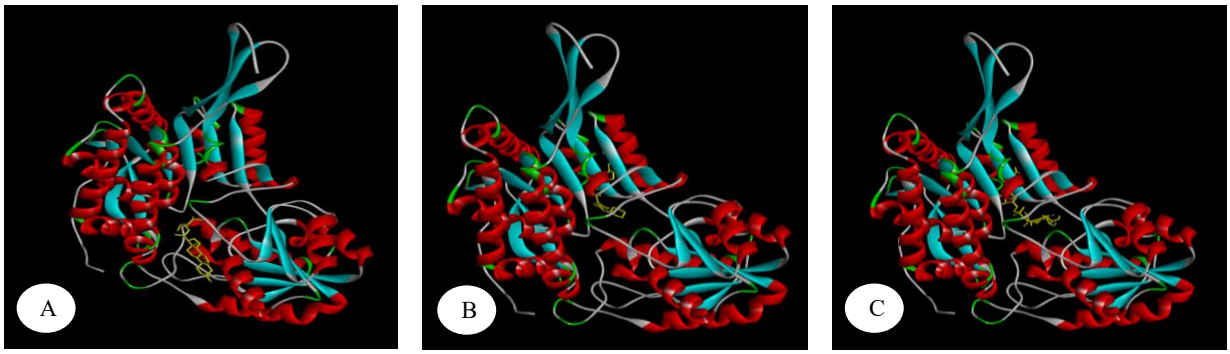

Figure 4. The 3D visualization of interactions complex between: A. ALDH1B1 receptor and β-sitosterol, B. ALDH1B1 receptor and irinotecan drug, ALDH1B1 receptor and the original ligand.

DISCUSSION

Current treatment approaches for CRC encounter challenges such as limited efficacy and adverse side effects, necessitating a shift toward targeted therapies [18]. The paradigm shift is crucial to enhance treatment outcomes and minimize undesirable consequences. Molecular docking, as a robust computational tool, provides a systematic approach for identifying potential inhibitors. This technique simulates interactions between ligands and target proteins, enabling the screening of diverse compounds to identify those with high binding affinity and therapeutic potential [19].

The assessment of inhibition acitivites to the targeted ALDH1B1 using molecular docking showed that β-sitosterol demonstrated the highest affinity for binding to the ALDH1B1 receptor among the twenty-one ligands. Validation of docking with the original ligand nicotinamide adenine dinucleotide (NAD) ensures the reliability of the computational predictions. The two-dimensional representation of receptor-ligand interactions in Figure 3 provides insights into the formation of complexes among various entities. Notably, β-sitosterol's dynamic interaction with the ALDH1B1 receptor involves hydrogen bonds and hydrophobic interactions with specific amino acid residues. A comprehensive illustration in Figure 3B showcases the interaction between the ALDH1B1 receptor and the anticancer agent irinotecan, revealing intricate hydrogen bonds. Additionally, the 3D visualization in Figure 4 further elucidates the complex interactions between ALDH1B1 and β-sitosterol, irinotecan, and the original ligand, offering a holistic perspective on the molecular connections within the system.

β-sitosterol has multifaceted ability to target multiple cellular processes involved in tumor development and progression, such as induction of apoptosis by triggering programmed cell death in cancer cells through various pathways, including activation of caspases, downregulation of anti-apoptotic proteins, and mitochondrial dysfunction. β-sitosterol has the ability to the cell cycle arrest by disrupting the normal cell cycle progression, preventing cancer cells from replicating and dividing uncontrollably. This can be achieved through inhibition of cyclin-dependent kinases (CDKs) and modulation of cell cycle regulatory proteins. Moreover, anti-angiogenic activity of β-sitosterol hinders the formation of new blood vessels, a crucial step in tumor growth and metastasis. This can be mediated by downregulating pro-angiogenic factors like vascular endothelial growth factor (VEGF) and upregulating anti-angiogenic molecules [20]. β-sitosterol has anti-inflammatory properties which plays a key role in tumorigenesis [21]. β-sitosterol exhibits anti-inflammatory effects by suppressing the activity of pro-inflammatory cytokines and enzymes, creating a less favorable environment for cancer cell growth [22]. Lastly, β-sitosterol acts as an antioxidant, scavenging ROS and protecting cells from oxidative stress inducing DNA damage and tumor progression [20].

The integration of molecular docking as a computational tool for identifying potential inhibitors against ALDH1B1 in colorectal cancer (CRC) marks a significant stride in the quest

for targeted therapies. As we navigate the future landscape of cancer treatment, several promising directions emerge from the current findings.

CONCLUSION

The molecular docking analysis provides valuable insights into potential inhibitors for CRC targeting ALDH1B1. The identified compounds, such as β-sitosterol, exhibit promising binding affinities, laying the groundwork for further experimental validation. These findings hold the potential to contribute to the development of targeted therapies for CRC, addressing the global health burden associated with this prevalent and challenging disease.

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