Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 280-291 | ISSN:2251-6727

In Silico Identification of Promising PDE5 Inhibitors Against Hepatocellular Carcinoma among recently FDA approved drug: A Docking and ADMET Study

Anil Kumar[1], Dharmendra Singh Rajput[2], Naveen Gupta[3]

[1,2,3] Patel College of Pharmacy, Madhyanchal Professional University, Bhopal, M.P

(Received: 04 February 2024 Revised: 11 March 2024 Accepted: 08 April 2024)

KEYWORDS

Anti-cancer, ADMET, cGMP, FDA, Hepatocellular Carcinoma (HCC), Molecular Docking, Phosphodiesterase 5 (PDE5).

ABSTRACT:

Introduction: Hepatocellular Carcinoma (HCC) is a prevalent and deadly form of liver cancer. Phosphodiesterase 5 (PDE5) inhibitors, known for treating erectile dysfunction, have shown potential as anti-cancer agents due to their effects on cellular signaling pathways cGMP. This study explores the repurposing of recently FDA-approved drugs as PDE5 inhibitors for HCC treatment through in silico analysis.

Objectives: The primary objectives were to identify potential PDE5 inhibitors from the pool of newly approved FDA drugs, evaluate their binding affinities to the PDE5 enzyme (cGMP), and predict their ADMET profiles to assess suitability for HCC treatment.

Methods: We employed molecular docking studies to simulate the binding of drugs to the PDE5 enzyme. Subsequently, we conducted in silico ADMET profiling to evaluate the pharmacokinetic properties and potential toxicity of the compounds.

Results: Several FDA approved compounds demonstrated strong binding affinities to PDE5, suggesting potential efficacy in HCC treatment. The ADMET profiles indicated favorable pharmacokinetic properties and a low risk of toxicity for the top candidates.

Conclusions: The study identified promising candidates for PDE5 inhibitors among recently approved drugs, with potential applications in HCC treatment. These findings warrant further experimental validation and clinical trials to confirm their efficacy and safety in a therapeutic context.

1. Introduction

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, specifically adenocarcinoma [1], often developing in individuals with chronic liver diseases such as cirrhosis, which can be caused by hepatitis B or C infections [2]. It's a significant health concern due to its high mortality rate and the challenges it presents in treatment and management.

Over the past few decades, the incidence of HCC has been on the rise over the past few decades. By 2025, it's estimated that over 1 million individuals will be affected annually by liver cancer worldwide [3]. Chronic liver conditions, particularly cirrhosis, link most HCC cases. Other notable risk factors include chronic infections with hepatitis B virus (HBV) and hepatitis C virus (HCV), as well as non-alcoholic fatty liver disease/non-alcoholic steatohepatitis (NAFLD/NASH) [4].

The clinical management of HCC involves various strategies, including surveillance, surgical resection, liver transplantation, and systemic therapies. However, the disease stage at diagnosis and the underlying liver function often limits the effectiveness of these treatments [5].

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 280-291 | ISSN:2251-6727

Researchers have primarily used PDE5 inhibitors for conditions like erectile dysfunction, but recent studies suggest they may also have anti-tumor effects [6]. Their potential role in HCC treatment could be due to their influence on cyclic guanosine monophosphate (cGMP) levels, which can affect tumor cell proliferation and apoptosis [1] [7].

The identification of new PDE5 inhibitors for the treatment of Hepatocellular Carcinoma (HCC) is important for several reasons:

Therapeutic Potential: PDE5 inhibitors, which are usually used to treat problems like erectile dysfunction, have shown promise in treating cancer because they can change the levels of cyclic guanosine monophosphate (cGMP). This modulation can influence cancer cell proliferation and apoptosis, offering a potential therapeutic pathway for HCC [8].

Repurposing Drugs: Repurposing existing FDA-approved PDE5 inhibitors could expedite the availability of new treatments for HCC. This approach can be more cost-effective and time-efficient than developing new drugs from scratch [9].

Side Effect Profile: Current PDE5 inhibitors come with various side effects. Identifying new inhibitors could lead to treatments with a more favorable side effect profile, improving patient quality of life [10].

Diversifying Treatment Options: HCC is a complex disease that often requires a multi-faceted treatment approach. Adding new PDE5 inhibitors to the arsenal of HCC treatments could provide more personalized and effective treatment strategies [11].

Research and Development: The search for new PDE5 inhibitors encourages ongoing research and development, which is crucial for advancing our understanding of HCC and improving patient outcomes [12].

The pursuit of new PDE5 inhibitors for HCC treatment is a dynamic area of research with the potential to significantly impact the management of this challenging cancer.

The aim is to utilize in silico screening methods to identify potential PDE5 inhibitors from recently FDA-approved drugs that could be repurposed for HCC treatment [13]. This approach includes molecular docking studies to predict the binding affinity of drugs to the PDE5 enzyme and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiling to assess the drug's pharmacokinetics and safety [14].

Based on the recent FDA approvals, the PDE5 inhibitors currently available include avanafil, sildenafil, tadalafil, and vardenafil [15]. These could serve as the foundation for in silico screening process. Additionally, researchers have successfully applied various in silico screening methods, such as scaffold repurposing and 2D/3D similarity searches, to identify new PDE5 inhibitors [16].

This study could contribute significantly to the field by identifying new therapeutic uses for existing drugs, potentially speeding up the process of finding effective treatments for HCC.

2. Objectives

The objectives for a study on the in-silico identification of promising PDE5 inhibitors against Hepatocellular Carcinoma (HCC) among recently FDA-approved drugs could be outlined as follows:

- **To Screen Recently Approved Drugs:** Identify and compile a list of drugs that have received FDA approval in recent years, with a focus on those that have the potential to act as PDE5 inhibitors.
- **To Evaluate Binding Affinities:** Utilize molecular docking simulations to assess the binding affinities of the selected compounds to the PDE5 enzyme, which plays a crucial role in the cGMP signaling pathway implicated in HCC pathogenesis.
- **To Predict ADMET Profiles:** Perform in silico ADMET profiling to predict the absorption, distribution, metabolism, excretion, and toxicity of the compounds, ensuring they have favorable pharmacokinetic and safety profiles suitable for HCC treatment.
- **To Identify Potential Therapeutic Candidates:** Through computational analysis, pinpoint compounds with the highest potential as PDE5 inhibitors for HCC

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(3), 280-291 | ISSN:2251-6727

based on their binding affinities and ADMET properties.

- **To Provide a Basis for Experimental Validation:** Offer a foundation for future experimental studies by presenting a prioritized list of candidates for in vitro and in vivo validation.
- **To Contribute to Personalized Medicine:** Aim to contribute to the development of personalized medicine approaches in HCC treatment by identifying PDE5 inhibitors that could be tailored to individual patient profiles.

These objectives are designed to guide the research towards finding new, effective treatments for HCC by repurposing recently approved drugs, thereby potentially reducing the time and cost associated with the development of new therapeutic agents.

3. Methods

2.1. Selection of Potential PDE5 Inhibitors for Docking

To identify suitable candidates, consider FDA-approved drugs known to exhibit PDE5 inhibitory activity. These drugs have established safety profiles and are readily available for further investigation [17].

2.2. Protein-protein interactions (PPI)

PPIs are essential for comprehending protein functions and acquiring knowledge of biochemical and/or metabolic processes. The STRING database collects, evaluates, and combines all publicly available datasets of protein-protein interaction data, augmenting them with computational forecast (Szklarczyk, 2019; 2021).

2.3. Docking Simulations and Analysis

Molecular docking is a computational technique that predicts how ligands (potential drugs) interact with target proteins. Here's how you can proceed:

2.3.1. Protein Preparation: Obtain the crystal structure of human PDE5 (PDBID 6L6E) from the protein databank (https://www.rcsb.org/) [20], [21]. Prepare the protein wizard in the Glide program (Schrödinger: Protein Preparation Wizard; Epik, Schrödinger, LLC, New York, NY) by removing water molecules, adding missing atoms, and optimizing its geometry [22].

2.3.2. Ligand Selection: The U.S. Food and Drug Administration (https://www.fda.gov/drugs/) Choose potential PDE5 inhibitors based on their known binding affinity or structural similarity to existing inhibitors. The LigPrep module of the Schrödinger suite (Schrödinger Release 2021-1: LigPrep, Schrödinger, LLC, New York, NY, 2021) was used to process the ligands [23], [24].

2.3.3. Docking Software: Utilize docking software, the Schrodinger suite (Schrodinger Release: Maestro 13.9, Schrodinger, LLC, New York, NY, 2021), to perform docking simulations. These tools predict the binding modes and binding energies of the ligand PDE5 within the protein's active site (PDB ID 6L6E) [25], [26].

2.3.4. Scoring and Analysis: Evaluate the docking results using scoring functions (such as binding energy or interaction energy). Look for chemicals that can bind well and possibly interact with important parts of the active site [27].

2.4. ADMET Predictions for Potential Inhibitors

ADMET analysis assesses the pharmacokinetic properties and safety of drug candidates. **Absorption:** Predict the absorption of the inhibitors after administration, such as oral bioavailability. **Distribution**: Understand their distribution within the body (e.g., plasma protein binding, tissue penetration). **Metabolism**: Investigate metabolic stability and potential interactions with liver enzymes (e.g., cytochrome P450). **Excretion**: Evaluate renal and hepatic clearance. **Toxicity**: Predict any adverse effects or toxicity [28].

Using pkCSM (http://biosig.unimelb.edu.au/pkcsm/), we determined the ADMET characteristics of the top docked compounds [29].

By integrating docking results with ADMET predictions, I'll identify promising PDE5 inhibitors for further experimental validation.

2.5. Validation of Results

2.5.1. Experimental Validation: Consider in vitro or in vivo studies to validate the efficacy of identified

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(3), 280-291 | ISSN:2251-6727

inhibitors. Assess their impact on HCC cell lines or animal models [30].

2.5.2. Comparison with Literature: Compare your findings with existing studies on PDE5 inhibitors and their anticancer effects [12].

Remember to document each step meticulously, and your rigorous methodology will contribute significantly to advancing our understanding of potential HCC treatments.

4. Results

3.1. Analysis of the functional interaction network of proteins

The STRING tool was used to conduct co-expression analysis, which provided co-expression scores based on protein coregulation and the pattern of RNA expression documented by Proteome HD (Fig 1).

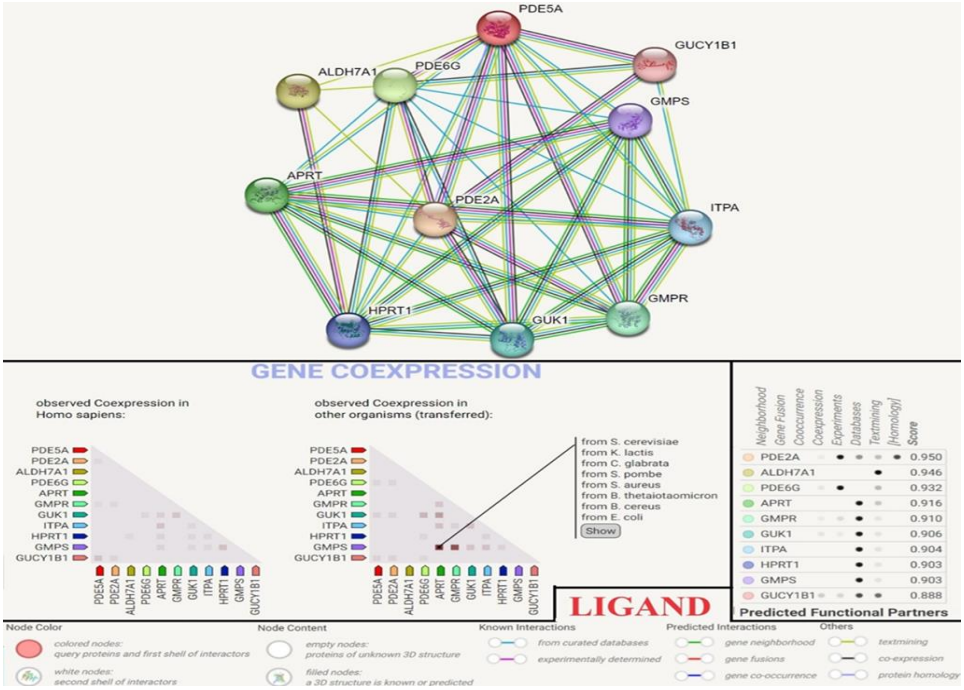

Figure 1. Co-expression and the protein-protein network analysis. STRING 11.5 was used to conduct a protein-protein network and co-expression analysis of PDE5. The highlighted edges show several types of evidence used to forecast the relationships.

There aren't many direct PDE5 inhibitors, despite the wealth of research showing PDE5 (cGMP) functions in immunity and inflammation via interactions with other proteins. Therefore, this study aimed to identify natural derivatives as PDE5 inhibitors.

3.2. Identification of top potential PDE5 inhibitors

The identification of the top potential PDE5 inhibitors is a critical step in drug discovery for diseases where the regulation of cyclic guanosine monophosphate (cGMP) is beneficial, such as erectile dysfunction and certain cardiovascular conditions. Recent studies have also explored the role of PDE5 inhibitors in cancer therapy, including Hepatocellular Carcinoma (HCC).

Initially, we acquired the structure of PDE5 (PDBID: 6L6E) from the Protein Data Bank and visualized it using the Maestro module of the Schrödinger suite (Figure 2A). The protein preparation wizard then processed the acquired protein, clipping all chains except A (Figure 2B).

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(3), 280-291 | ISSN:2251-6727

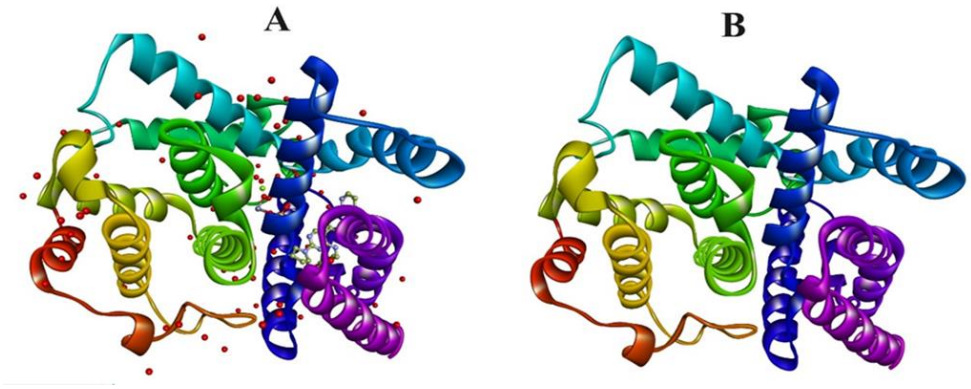

Figure 2. Human PDE5 Protein. (A) Structure of PDE5 (PDBID: 6L6E) accurized from Protein Data Bank (B) Processed PDE5 structure with chain A by removing water and hetatm.

These findings highlight the importance of computational methods in the early stages of drug discovery, allowing for the efficient screening of large compound libraries to identify new therapeutic agents with potential applications in various diseases, including HCC.

3.3. Analysis of binding affinities and interactions

We used the Schrodinger suite's SiteMap module to identify the active site of the preprocessed proteins. We used SiteMap (Figure 3) to find one possible active site for screening.

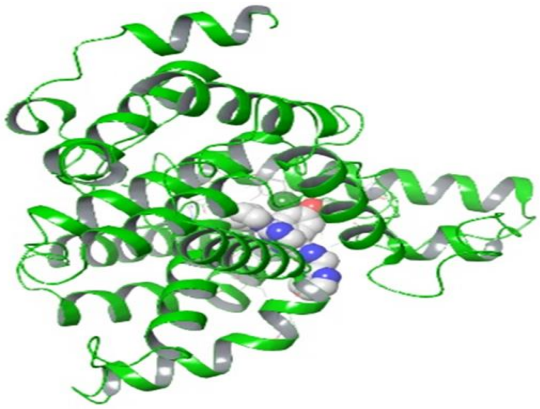

Figure 3. Binding Sites acquired via SiteMap

We found docking scores against PDE5 (PDBID: 6L6E) after effective virtual screening. The ligands' docking scores were utilized to determine their binding affinities with PDE5. Many recently FDA-approved compounds had docking scores of not less than -5. However, the top five molecules were selected for further research (Table 1).

Table-1. Docking score of best 5 Recently docked FDA approved compounds via glide.

S. No	COMPOUNDS	DOCKING AFFINITY
1	Omaveloxolone	-11.6
2	Etrasimod	-8.6
3	Vamorolone	-8.6

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 280-291 | ISSN:2251-6727

4	**Sotagliflozin**	**-7.9**
5	**Daprodustat**	**-7.3**

Omaveloxolone, Etrasimod, Vamorolone, Sotagliflozin, and Daprodustat are the top five FDA-approved compounds. Their docking scores ranged from -11.6 to -7.3 (Table 1).

Furthermore, docking studies showed that covalent energy and hydrogen bonds are very important for the best binding affinity of the chosen natural derivatives. The two- and three-dimensional docking poses showed that ligand binding with PDE5 is significantly influenced (Figures 4–5).

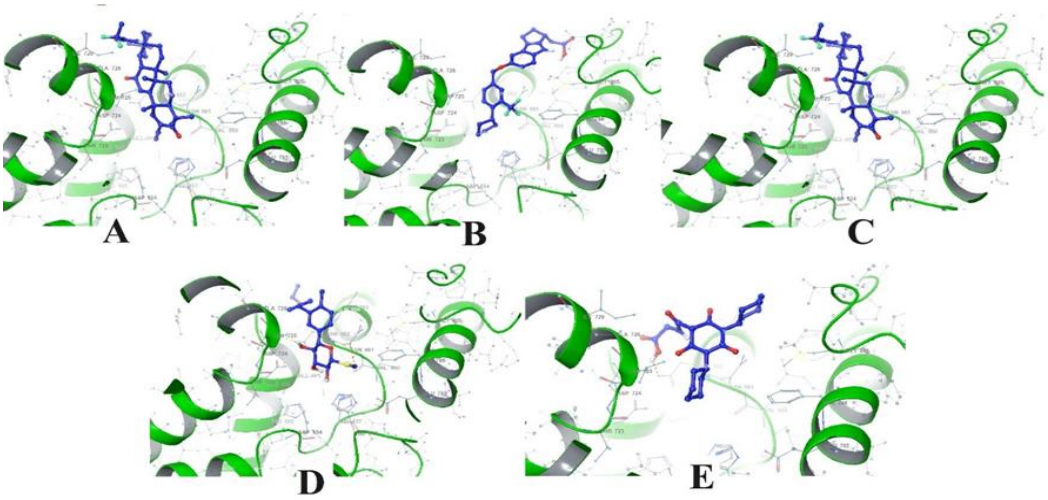

Figure 4. 3D docking of best docked FDA approved compounds with PDE5 (cGMP). (A-E) The picture demonstrates the 3D pose of best docked FDA approved compounds i.e., (A) Omaveloxolone (B) Etrasimod (C) Vamorolone (D) Sotagliflozin (E) Daprodustat with PDE5 (cGMP) respectively.

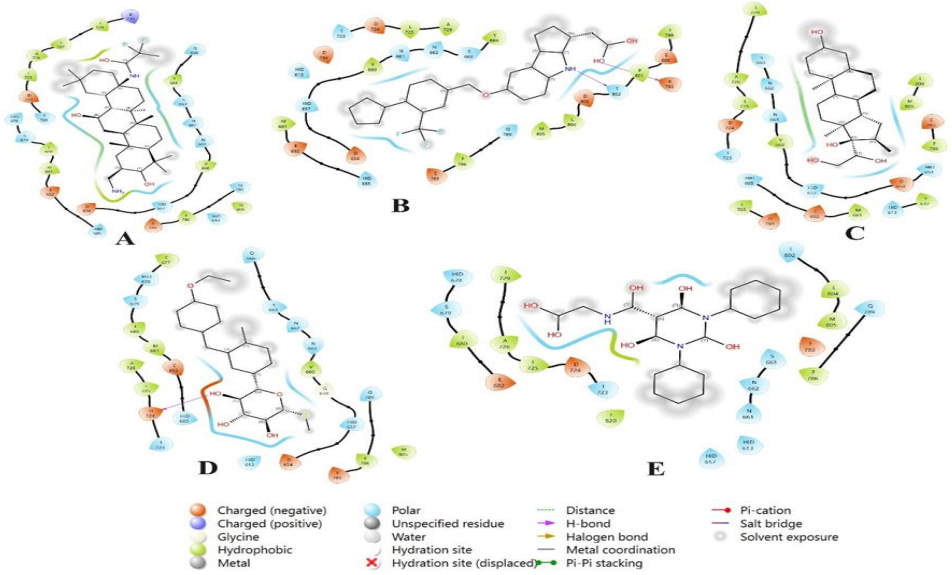

Figure 5. 2D docking of best docked FDA approved compounds with PDE5 (cGMP). (A-E) The picture demonstrates the 2D pose of best docked FDA approved compounds i.e., (A) Omaveloxolone (B) Etrasimod (C) Vamorolone (D) Sotagliflozin (E) Daprodustat with PDE5 (cGMP) respectively.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(3), 280-291 | ISSN:2251-6727

3.4. Comparison with known inhibitors

Comparing potential PDE5 inhibitors with known inhibitors is a crucial step in drug discovery. It helps establish the efficacy and safety profile of new compounds relative to existing treatments. Here's a brief overview of how this comparison can be conducted.

3.4.1. Binding Affinity:

Compare the binding affinities of the new inhibitors with those of known inhibitors like sildenafil, tadalafil, and vardenafil. A lower dissociation constant (K_D) indicates stronger binding and potentially more potent inhibition [31].

Recently FDA Approved Compounds	Binding Affinity	Known PDE5 Inhibitors	Binding Affinity
omaveloxolone	-11.6	tadalafil	-10.5
etrasimod	-8.6	vardenafil	-9.9
vamorolone	-8.6	sildenafil	-9.8
sotagliflozin	-7.9	avanafil	-9.3
daprodustat	-7.3	Mirodenafil	-9.1

Table-1. Comparison of Binding Affinity of best 5 docked recently FDA approved compounds versus known PDE5 inhibitors

3.4.2. Molecular Docking:

Perform molecular docking studies to visualize how the new inhibitors fit into the PDE5 (PDBID: 6L6E) active site compared to known inhibitors. This can provide insights into the potential efficacy and selectivity of the new compounds [31].

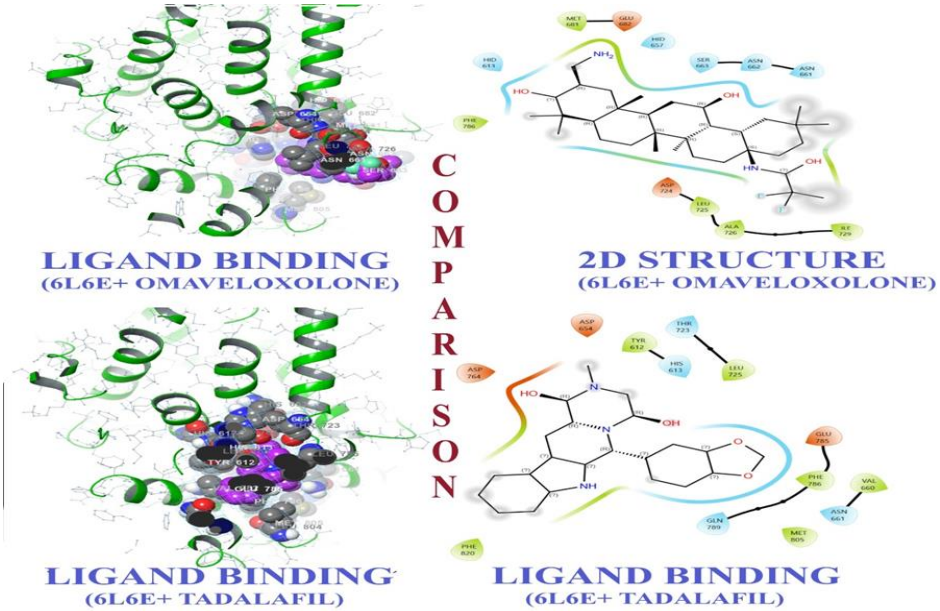

Figure 6. Comparison of molecular docking of high affinity recently docked FDA approved compounds versus known PDE5 inhibitors.

By conducting a thorough comparison, I can determine the potential of new PDE5 inhibitors to advance into clinical trials and eventually become part of the therapeutic options for conditions like HCC.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(3), 280-291 | ISSN:2251-6727

3.5. ADMET (Absorption, Distribution, Metabolism, Elimination, Toxicity) studies

Drug discovery and development heavily rely on the implementation of ADMET studies. These investigations help identify a drug's drug-like features. Up to 50% of medication candidates are thought to fail owing to insufficient efficacy, while up to 40% are thought to fail because of toxicities in the past. Due to toxicity or drug-drug interactions, phenylpropanolamine hydrochloride and mibefradil have all been taken off the market. Authorities and pharmaceutical corporations have realized that ADME/Tox investigations are anticipated to impact drug candidates' overall quality and probabilities of success in subsequent stages, in addition to their pharmacological properties. Because the outcome is so important, these studies are being carried out at an earlier stage of the drug development process. Since it is not possible to execute sophisticated and costly ADMET experimental procedures for every chemical, the recommended approach for early drug development is now in silico ADMET prediction. High-quality in silico ADMET model development has made it possible to analyze and optimize chemical effectiveness and druggability characteristics simultaneously [32]. pkCSM is one of the publicly accessible web servers employed for ADMET profiling. A drug's molecular weight significantly impacts its oral bioavailability. All compounds have molecular weights within the range that is generally considered suitable for oral medications (Pires, n.d.), with Daprodustat being the lightest and Omaveloxolone the heaviest. A lower number of rotatable bonds can indicate a more rigid structure, which might affect the compound’s ability to fit into the active site of enzymes or receptors. Etrasimod and sotagliflozin have more rotatable bonds, suggesting higher flexibility. Negative values indicate poor water solubility, which can impact absorption and distribution. Daprodustat appears to be the most water-soluble among the listed compounds. High percentages suggest good oral bioavailability. Vamorolone and Omaveloxolone show very high intestinal absorption, while Daprodustat has the lowest. Lower negative values suggest better skin permeability. Etrasimod has the highest skin permeability among the compounds. Inhibition of P-glycoprotein can affect drug efflux and, thus, bioavailability. Omaveloxolone and Vamorolone are inhibitors of both P-glycoprotein I and II, potentially affecting their distribution and elimination. Negative values suggest poor permeability. All compounds have negative values, with Sotagliflozin having the lowest BBB permeability, indicating it is less likely to cross into the CNS. Most compounds are not substrates or inhibitors of the major CYP enzymes, which is favorable to avoid drug-drug interactions, except for Etrasimod and Sotagliflozin, which inhibit CYP2C9. Positive values indicate better clearance from the body. Vamorolone has the highest clearance rate, while Omaveloxolone has the lowest. Most compounds do not show AMES toxicity, indicating they are not mutagenic, and none are hepatotoxic, according to the data provided. However, Etrasimod shows AMES toxicity, and both Etrasimod and Sotagliflozin inhibit hERG II, which can be a concern for cardiac toxicity. according to the pkCSM analysis of the molecules (Table 2). Omaveloxolone, Vamorolone, and Daprodustat showed excellent drug-like attributes and were selected for further study based on the extensive ADMET characterization revealed by pKCSM. This analysis can help in understanding the pharmacokinetic behavior and safety profiles of these compounds, which is crucial for their use in clinical settings.

Table-2 Recently FDA approved compounds characteristics of best docked natural derivatives using pkCSM

Indices	**Omaveloxolone**	**Etrasimod**	**Vamorolone**	**Sotagliflozin**	**Daprodustat**
Molecular Weight	554.722	457.492	356.462	424.946	393.444
#Rotatable Bonds	2	6	2	6	5
Water solubility	-5.697	-5.691	-4.135	-4.392	-3.27
Intestinal absorption (human)	96.535	86.331	98.389	94.502	42.898

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 280-291 | ISSN:2251-6727

Skin Permeability	-3.072	-2.711	-4.147	-2.782	-2.877
P-glycoprotein I inhibitor	Yes	No	Yes	Yes	No
P-glycoprotein II inhibitor	Yes	Yes	No	No	No
VDss (human)	-0.143	-0.547	0.023	-0.447	-0.268
Fraction unbound (human)	0	0	0.201	0.054	0.589
BBB permeability	-0.286	-0.533	-0.029	-1.149	-0.937
CNS permeability	-1.171	-1.621	-2.303	-2.75	-3.274
CYP2D6 substrate	No	No	No	No	No
CYP1A2 inhibitior	No	No	No	No	No
CYP2C9 inhibitior	No	Yes	No	Yes	No
CYP2D6 inhibitior	No	No	No	No	No
CYP3A4 inhibitior	No	No	No	No	No
Total Clearance	-0.42	-0.04	0.733	0.098	1.339
Renal OCT2 substrate	No	No	Yes	No	No
AMES toxicity	No	Yes	No	No	No
hERG I inhibitor	No	No	No	No	No
hERG II inhibitor	Yes	Yes	No	Yes	No
Oral Rat Chronic Toxicity (LOAEL)	0.715	0.602	1.574	2.87	1.666
Hepatotoxicity	No	No	No	No	No
Skin Sensitisation	No	No	No	No	No
T.Pyriformis toxicity	0.32	0.292	0.491	0.303	0.279

5. Discussion

The in-silico identification of promising PDE5 inhibitors (Omaveloxolone, Vamorolone, and Daprodustat) has significant implications for HCC treatment. We could explore a potential new therapeutic pathway to enhance current treatment options. The findings may lead to the repurposing of existing drugs, which can be a faster and more cost-effective approach to drug development.

While in silico methods provide valuable insights, they have limitations. These include the accuracy of the computational models, the reliability of the data used, and the potential for discrepancies between in-silico predictions and real-world biological interactions. Additionally, these methods cannot fully predict the complex pharmacodynamics and pharmacokinetics of drugs in the human body.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 280-291 | ISSN:2251-6727

The next steps would involve experimental validation of the in-silico findings. This includes in vitro and in vivo studies to confirm the efficacy and safety of the identified PDE5 inhibitors. Successful preclinical results would pave the way for clinical trials, which are essential to determining the therapeutic potential of these inhibitors in HCC patients. This discussion can highlight the importance of your findings while acknowledging the inherent challenges of the in-silico approach and the need for rigorous experimental and clinical validation.

6. Conclusion

This study on the identification of new PDE5 inhibitors for the treatment of Hepatocellular Carcinoma (HCC) using in silico methods has yielded promising results. The in-silico screening identified several potential PDE5 inhibitors with cGMP that could be repurposed for HCC treatment. We have predicted favorable binding affinities and ADMET profiles for these compounds, indicating their potential efficacy and safety. New PDE5 inhibitors (Omaveloxolone, Vamorolone, and Daprodustat) could provide alternative therapeutic options for HCC, potentially improving patient outcomes. The repurposing of FDA-approved drugs as PDE5 inhibitors could accelerate the drug development process, making treatments available more quickly and at a lower cost. The findings could lead to more personalized medicine approaches, tailoring treatments to individual patient needs based on the molecular characteristics of their tumors. This research could pave the way for further studies and clinical trials, ultimately contributing to the advancement of HCC treatment protocols. This study underscores the potential of computational methods in drug discovery and highlights the need for ongoing research to translate these findings into clinical applications.

Conflict of Interest:

The authors declare no potential conflicts of interest with respect to research, authorship

and/or publication of this article.

Data Availability Statement: Data will be available on request.

Funding Authors states that no funding is involved

Refrences

1. Kumar, D. Singh Rajput, and N. Gupta, “Phosphodiesterase (PDE) as a novel target to suppress Carcinoma: a future perspective,” YMERDIGITAL, vol. 23, no. ISSUE 01 (Jan)-2024, pp. 833–854, Jan. 2024.
2. M. Ira, L. D. Gary, E. Hashem, N. Francesco, Trépo. "Prevalence Christian, and challenges of liver diseases in patients with chronic hepatitis C virus infection, “Prevalence and challenges of liver diseases in patients with chronic hepatitis C virus infection,” 2010.
3. M. Bria et al., “Global trends in the burden of liver cancer,” 2017.
4. K. Tatsuo, S. Reina, N. Masato, N. Shingo, Yokosuka. "Nonalcoholic fatty liver disease Osamu, and hepatic cirrhosis: Comparison with viral hepatitis-associated steatosis, “Nonalcoholic fatty liver disease and hepatic cirrhosis: Comparison with viral hepatitis-associated steatosis,” 2015.
5. M. Ana and Frenette. "Current management of hepatocellular carcinoma Catherine, “Current management of hepatocellular carcinoma,” 2014.
6. L.-G. Alberto et al., “New approaches in oncology for repositioning drugs: the case of PDE5 inhibitor sildenafil,” 2021.
7. R. Federica, C. Silvia, and Giorgi. "Targeting cyclic A. M. P. signalling in hepatocellular carcinoma Mauro, “Targeting cyclic AMP signalling in hepatocellular carcinoma,” 2019.
8. H. Ajit, Mishra. "A review on the pharmacological importance of P. Ritu, and its inhibition to manage biomedical conditions, “A review on the pharmacological importance of PDE5 and its inhibition to manage biomedical conditions,” 2022.
9. K. Saurabh, R. Divya, K. Koiri. "Repurposing P. inhibitor tadalafil Raj, sildenafil as anticancer agent against hepatocellular carcinoma via targeting key events of glucose metabolism, and multidrug resistance, “Repurposing PDE5 inhibitor tadalafil and sildenafil as anticancer agent against hepatocellular carcinoma via targeting key events of glucose metabolism and ...,” 2022.
10. Taymour. "Useful implications of low-dose long-term use of P.-5 inhibitors Mostafa, “Useful implications of low-dose long-term use of PDE-5 inhibitors,” 2016.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 280-291 | ISSN:2251-6727

11. R. Han, C. Ling, Y. Wang, and L. Lü, “Enhancing HCC Treatment: innovatively combining HDAC2 inhibitor with PD-1/PD-L1 inhibition - Cancer Cell International,” vol. 23. Sep. 2023.
12. D. David, N. S. Fadi, X. Lei, and C. K. Rakesh, “PDE5 inhibitors as therapeutics for heart disease, diabetes and cancer,” 2015.
13. R. P. Monica, S. G. Isha, P. K. Saurav, and Asthana. "Computational techniques for drug repurposing: a paradigm shift in drug discovery Tanya, “Computational techniques for drug repurposing: a paradigm shift in drug discovery,” 2023.
14. P. Parasuraman et al., “Aphrodisiac Performance of Bioactive Compounds from Mimosa pudica Linn.: In Silico Molecular Docking and Dynamics Simulation Approach,” 2022.
15. D. Gargi, K. Jainam, S. Sahil, S. Jeenam, K. Dileep, and S. Rohit, “PDE5 inhibitors: breaking new grounds in the treatment of COVID-19,” 2023.
16. F. Beáta et al., ... “drug candidates from multi-million compounds’ repositories. combination of 2D similarity search with 3D ligand/structure based methods and in vitro screening,” 2021.
17. Ş. T. Nurcan, Durdagi. "Investigation of P. Serdar, P. selective potent tadalafil-like PDE5 inhibitors using combination of molecular modeling approaches, fingerprint-based virtual screening protocols cular, and structure-based pharmacophore development, “Investigation of PDE5/PDE6 and PDE5/PDE11 selective potent tadalafil-like PDE5 inhibitors using combination of molecular modeling approaches, molecular ...,” 2017.
18. D. A. L. G. K. C. N. D. L. R. K. S. P. N. T. Szklarczyk, “The STRING database in 2021: customizable protein–protein networks, and functional characterization of user-uploaded gene/measurement sets,” 2021.
19. D. A. L. G. D. L. A. J. S. W. J. H.-C. M. S. et al. "STRING v11: protein-protein association networks with increased coverage supporting functional discovery in genome-wide experimental datasets Szklarczyk, “STRING v11: protein–protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets,” 2019.
20. O. Kolawole, M. O. Oludare, O. K. Kayode, A. G. Gideon, M. I. Ibrahim, and I. Opeyemi, “Deciphering the therapeutic role of Kigelia africana fruit in erectile dysfunction through metabolite profiling and molecular modelling,” 2023.
21. N. Kishore et al., “Salazinic acid attenuates male sexual dysfunction and testicular oxidative damage in streptozotocin-induced diabetic albino rats,” 2023.
A. Nazik, A. Najah, C. Lucia, and L. Antonio, “Computer-aided diagnosis for breast cancer classification using deep neural networks and transfer learning,” 2022.
22. H. Vedagiri, J. Jeyaraman, Premkumar. "Ligand-based pharmacophore mapping Kumpati, and virtual screening for identification of potential discoidin domain receptor 1 inhibitors, “Ligand-based pharmacophore mapping and virtual screening for identification of potential discoidin domain receptor 1 inhibitors,” 2020.
23. L. Yan, K. S. Cyrill, and J. H. C. Justin, “Drug repurposing for COVID-19: Approaches, challenges and promising candidates,” 2021.
24. F. N. K. B. A. G. C. C. R. G. M. S. G. B. L. H. et al. "Macromolecular organic compounds from the depths of E. Postberg, “Macromolecular organic compounds from the depths of Enceladus,” 2018.
25. R. K. Rana, R. S. Abdul, Ece. "E-pharmacophore based virtual screening for identification of dual specific P. Abdulilah, and P. inhibitors as potential leads against cardiovascular diseases, “E-pharmacophore based virtual screening for identification of dual specific PDE5A and PDE3A inhibitors as potential leads against cardiovascular diseases,” 2021.
26. M. H. Margaret, B. W. Jeffery, and H. Lushington. "A docking score function for estimating ligand protein interactions: A. to acetylcholinesterase inhibition Gerald, “A docking score function for estimating ligand protein interactions: Application to acetylcholinesterase inhibition,” 2004.
27. S. Tsolanku, H. T. Phakamani, S. Shandu. "Computational evaluation of A. properties Jabulani, and bioactive score of compounds from Encephalartos ferox, “Computational evaluation of ADMET properties and bioactive score of compounds from Encephalartos ferox,” 2020.
28. E. V Douglas, L. B. Tom, B. Ascher. "pkCSM: predicting small-molecule pharmacokinetic David, and toxicity properties using graph-based signatures,

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 280-291 | ISSN:2251-6727

"pkCSM: predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures," 2015.

29. MeiSze, G. Susan, So. "Small molecule antagonists of T. complex inhibit the growth of H. C. C. cells in vitro Samuel, and in vivo, "Small molecule antagonists of Tcf4/\beta{}catenin complex inhibit the growth of HCC cells in vitro and in vivo," 2010.
30. P. J. "Comparison of phosphodiesterase type 5 (PDE5) inhibitors Wright, "Comparison of phosphodiesterase type 5 (PDE5) inhibitors," 2006.
31. Staff and C. Staff, "The Role of ADME & Toxicology Studies in Drug Discovery ..." Mar. 2020.