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Original Research Article

Exploring the Therapeutic Axis of Antioxidant Alkaloids Against Sickle β-globin Mutation with Binding Site Engineering and Bioavailability

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Abstract

Background: Sickle cell anemia is a monogenic hemoglobinopathy caused by a mutation in the β-globin gene (hemoglobin subunit beta, HBB), leading to the production of hemoglobin S (HbS). Under deoxygenated conditions, HbS polymerizes abnormally, causing red blood cells to adopt a sickled shape. This results in vaso-occlusion, hemolysis, and chronic organ damage. Current treatment options remain limited, necessitating the identification of novel therapeutic agents that can target the molecular mechanisms underlying the disease.

Objectives: This study aimed to investigate the therapeutic potential of 12 antioxidant alkaloids for targeting mutant HbS through a computational approach. The primary goal was to evaluate binding interactions, drug-likeness, and pharmacokinetic profiles to identify lead candidates for further development in sickle cell anemia therapy.

Materials and Methods: Target validation of the HBB gene was performed using the STRING database to confirm its relevance in disease pathology. The three-dimensional structure of mutant HbS (Protein Data Bank ID: 2HBS) was retrieved and used to evaluate interactions with selected antioxidant alkaloids. Molecular interaction simulations were conducted to determine binding affinities, followed by drug-likeness screening based on Lipinski's rule of five. Pharmacokinetic and bioavailability profiling was carried out using absorption, distribution, metabolism, excretion, and toxicity-based prediction tools.

Results: The selected compounds exhibited binding affinities ranging from −5.5 to −10.7 kcal/mol, with rutaecarpine, harmine, and vindoline showing the strongest interactions with HbS. In total, 10 of the 12 compounds complied with drug-likeness criteria. Pharmacokinetic modeling predicted favorable gastrointestinal absorption for most compounds, with no predicted blood–brain barrier penetration. Radar plot analysis revealed that vindoline, capsaicin, and harmine displayed optimal bioavailability profiles across key physicochemical parameters, indicating their suitability for oral administration.

Conclusion: The study identified vindoline, harmine, and rutaecarpine as top candidate alkaloids with strong binding affinity, favorable pharmacokinetics, and bioavailability for therapeutic targeting of HbS. These findings support the continued exploration of natural antioxidant alkaloids as viable leads for developing novel interventions in sickle cell anemia, pending further *in vitro* and *in vivo* validation.

Keywords

Hemoglobin S, β-globin mutation, sickle cell anemia, antioxidant alkaloids, molecular interaction, phytochemicals, sustainable development goals (SDGs), good health and well-being (SDG 3), *in silico* analysis, drug-likeness, ADMET profiling, molecular docking

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Introduction

Sickle cell anemia is a genetically inherited hematological disorder that arises from a single point mutation in the β-globin gene (hemoglobin subunit beta, HBB), resulting in the substitution of valine for glutamic acid at the sixth position of the hemoglobin β-chain. This seemingly minor change significantly alters the physicochemical properties of hemoglobin, leading to the formation of hemoglobin S (HbS).[1,2]

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Under deoxygenated conditions, HbS polymerizes abnormally, distorting red blood cells into a characteristic sickle shape. These deformed cells are prone to hemolysis and vaso-occlusion, which lead to recurrent pain episodes, organ damage, and reduced life expectancy in affected individuals.[3]

Despite the severity of the disease, current treatment strategies, such as hydroxyurea therapy, chronic blood transfusions, and bone marrow transplantation, are either palliative, limited in availability, or associated with serious complications. Furthermore, emerging gene therapies are promising but remain inaccessible to the majority of patients due to high cost and logistical challenges. Hence, there is a pressing need to develop safer, cost-effective, and accessible therapeutics that target the root cause of the disease while minimizing adverse effects.[4,5]

Oxidative stress plays a critical role in the exacerbation of sickle cell anemia by contributing to membrane damage, inflammation, and endothelial dysfunction. Given this, the use of natural antioxidant compounds has emerged as a potential adjunct or alternative therapeutic approach. Among these, plant-derived alkaloids have shown promising pharmacological activities, including free radical scavenging, anti-inflammatory, and anti-sickling effects. Their natural origin, structural diversity, and bioactivity make them attractive candidates for drug development.[6,7]

The integration of computational tools into early-phase drug discovery allows for high-throughput screening and rational design of bioactive molecules.[8] *In silico* methods, such as molecular docking, pharmacokinetic modeling, and protein–protein interaction (PPI) analysis, offer a time- and cost-efficient means to evaluate the interaction potential, drug-likeness, and systemic behavior of candidate compounds. By simulating molecular interactions and predicting absorption, distribution, metabolism, and excretion (ADME) properties, researchers can prioritize the most promising compounds for experimental validation.[9,10]

The aim of this study is to screen a panel of 12 antioxidant alkaloids using an *in silico* approach to evaluate their therapeutic potential against mutant HbS. The study begins with target validation of the HBB gene using the STRING database, followed by molecular docking to assess binding affinity and drug-likeness evaluation using Lipinski's rule of five. Further, pharmacokinetic profiling is performed to assess bioavailability and blood–brain barrier (BBB) permeability. The ultimate objective is to identify lead compounds with strong binding affinity, favorable pharmacokinetics, and oral bioavailability as potential candidates for the treatment of sickle cell anemia.

Materials and Methods

Target Validation of HBB Using STRING-based PPI Network

The STRING database was used to validate the HBB as a key target in sickle cell disease. The PPI network revealed 11 nodes and 48 edges, indicating strong functional connectivity. HBB showed direct associations with other hemoglobin subunits and regulatory proteins. This confirmed its central role in disease pathology and justified its selection for molecular docking studies.

Compound Selection

In total, 12 antioxidant alkaloids were selected for the study based on a comprehensive review of existing scientific literature. These compounds were chosen due to their established antioxidant properties, which are crucial for counteracting the oxidative stress associated with sickle cell anemia. The selection process focused on natural phytochemicals known to modulate redox balance and reduce free radical activity, with the intention of identifying candidates that could potentially alleviate or inhibit the pathological polymerization of HbS.

Target Protein Identification and Validation

The target protein for this study was the mutant form of HbS, a structurally altered variant responsible for the clinical manifestations of sickle cell anemia. The three-dimensional structure of the protein was retrieved from the Protein Data Bank (PDB), under the accession code 2HBS. The docking studies specifically focused on chain B of the HbS structure, which was oriented at spatial coordinates $X = 17.234461$, $Y = 42.224132$, and $Z = 28.235829$ to ensure accurate simulation of binding sites. To validate the biological relevance of HbS in disease progression, the STRING database was utilized, confirming its central role in the pathophysiology of sickle cell anemia and reinforcing its validity as a therapeutic target.

Molecular Docking Analysis

Molecular docking was conducted to evaluate the binding interactions between the selected alkaloids and the HbS protein. The docking simulations aimed to predict the orientation and binding strength of each compound within the active site of the protein. Binding affinities were calculated in terms of Gibbs free energy (kcal/mol), with more negative values indicating stronger and more stable interactions. This computational modeling provided preliminary insight into how well each alkaloid could potentially inhibit or modulate the activity of mutant HbS by occupying its key interaction sites.

Drug-likeness Evaluation

To assess the suitability of the alkaloids as oral drug candidates, drug-likeness properties were evaluated using Lipinski's rule of five. This rule examines essential physicochemical parameters, including molecular weight, lipophilicity (logP), hydrogen bond donors, and hydrogen bond acceptors. Compounds that adhered to these guidelines were

considered to have favorable oral bioavailability and systemic absorption potential. This step was critical in filtering out molecules with suboptimal drug-like characteristics before advancing to pharmacokinetic modeling.

Pharmacokinetic and Bioavailability Profiling

Pharmacokinetic properties of the alkaloids were predicted using *in silico* absorption, distribution, metabolism, excretion, and toxicity (ADMET) analysis tools. This included the evaluation of parameters such as BBB permeability, gastrointestinal (GI) absorption, and potential metabolic liabilities. The focus was on identifying compounds that would demonstrate acceptable bioavailability and minimal systemic toxicity. Special attention was given to BBB permeability since a non-neurological target was being addressed, and compounds with no BBB penetration were deemed preferable to minimize central nervous system (CNS)-related side effects.

Results

Target Validation via STRING Interaction Network

The PPI network retrieved from the STRING database validates the HBB gene as a critical target in the context of sickle cell anemia. In this network, HBB appears as the central node, indicating its pivotal role, and is connected to 10 other proteins, forming a total of 11 nodes and 48 edges. These nodes include structurally and functionally related proteins, such as HBA1, HBA2, HBD, HBZ, HBM, AHSP, HP, and the regulatory protein BCL11A. The edges represent predicted and experimentally supported interactions, visualized through color-coded connections denoting various evidence types, such as co-expression, curated databases, and experimental validation. The dense interconnectivity underscores HBB's functional centrality within the hemoglobin complex, and its disruption is likely to affect multiple associated pathways, reinforcing its relevance as a therapeutic target in sickle cell disease (Figure 1a and 1b).

Binding Affinity Analysis

The molecular docking analysis yielded a range of binding affinities for the 12 selected antioxidant alkaloids against mutant HbS. The calculated docking scores spanned from −5.5 to −10.7 kcal/mol, with lower (more negative) values indicating stronger and more stable ligand–protein interactions. Among these, rutaecarpine and harmine demonstrated the most favorable binding profiles, suggesting their high potential to interact with the active site of HbS and potentially disrupt its pathological polymerization. These results establish a foundational understanding of the structure–activity relationship between natural alkaloids and mutant hemoglobin. The overall docking pattern highlighted multiple hydrogen bonding and hydrophobic interactions at the target site, strengthening the potential efficacy of the top-ranking compounds (Figure 2; Table 1).

Drug-likeness Evaluation

Assessment of the selected alkaloids using Lipinski's rule of five indicated that 10 out of 12 compounds met all the criteria required for optimal oral bioavailability. These

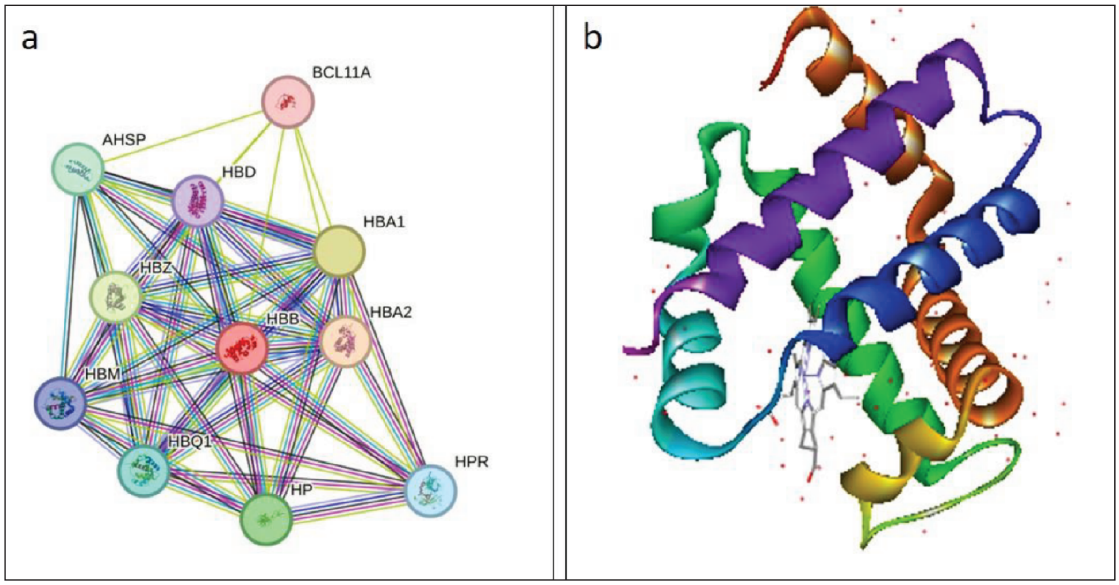


Figure 1. (a) STRING Network Analysis Depicting the Interactions Among Genes Associated with Hemoglobin S Mutation. (b) Three-dimensional Structural Representation of Mutant Hemoglobin S (HbS).

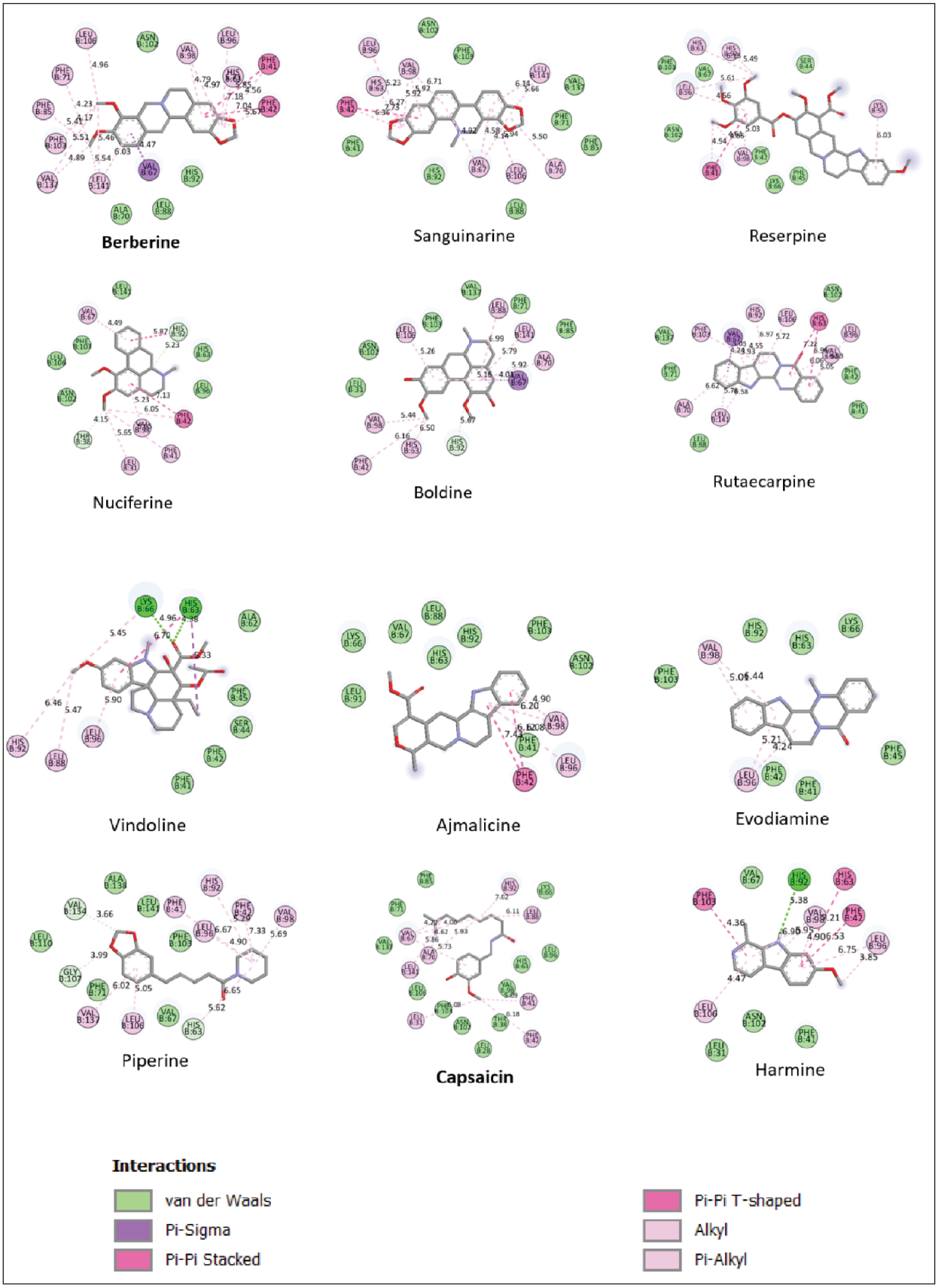


Figure 2. Three-dimensional Molecular Docking Interaction Diagrams of Rutaecarpine and Harmine with Hemoglobin S (HbS).

Table 1. Binding Affinity Values (kcal/mol) for All 12 Alkaloids.

Sl. No.	Compounds	Binding Affinity (kcal/mol)	Interacting Amino Acids
1	Berberine	−9.3	Phe42, Phe41, His73, Leu96, Val98, Asn102, Leu106, Phe71, Phe85, Phe103, Val137, Leu141, Ala70, Val67, Leu88, His93
2	Sanguinarine	−9.9	Phe103, Asn102, Val98, Leu96, His63, Phe42, Phe41, His92, Val67, Leu106, Leu88, Ala70, Phe85, Phe71, Val137, Leu141
3	Piperine	−8.3	Val98, Phe42, His92, Leu96, Phe103, Phe41, Leu141, Ala138, Val134, Leu110, Gly107, Phe71, Val137, Leu106, Val67, His63
4	Capsaicin	−7.2	Phe85, Phe71, Val67, Val137, Ala70, Leu141, Leu106, Phe103, leu31, Asn102, Leu28, Thr38, Phe42, Phe41, Val98, His63, Leu96, Leu88, Lys66, His92
5	Reserpine	−7.1	Lys59, Ser44, His92, His63, Val67, Phe103, Leu96, Asn102, Phe41, Val98, Phe42, Lys66, Phe45
6	Vindoline	−5.5	His92, Leu88, Leu96, Phe41, Phe42, Ser44, Phe45, Ala62, His63, Lys66
7	Ajmalicine	−7.6	Leu91, Lys66, Val67, Leu88, His63, His92, Phe103, Asn102, Val98, Leu96, Phe41, Phe42
8	Harmine	−7.5	Leu96, Phe42, His63, Val98, His92, Val67, Phe103, Leu106, Leu31, Asn102, Phe41
9	Rutaecarpine	−10.7	Leu141, Leu88, Ala70, Phe71, Val137, Phe103, Val67, His92, Leu106, His63, Asn102, Leu96, Phe42, Phe41
10	Evodiamine	−8.3	Lys66, His63, His92, Val98, Phe103, Leu96, Phe42, Phe41, Phe45
11	Boldine	−8	His92, His63, Phe42, Val98, Leu31, Asn102, Leu106, Phe103, Val137, Leu88, Phe71, Leu141, Phe85, Ala70, Val67
12	Nuciferine	−8	Leu141, Val67, Phe103, Leu106, Asn102, Thr38, Leu31, Val98, Phe41, Phe42, Leu96, His63, His92

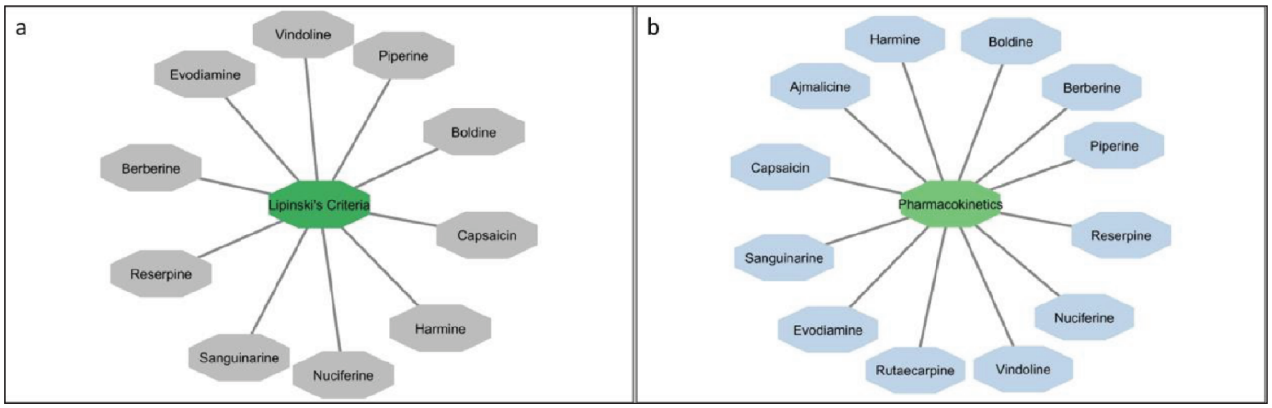


Figure 3. (a) Drug-likeness Evaluation of the Selected Compounds Based on Lipinski's Rule of Five. (b) Pharmacokinetic Profiling of the Same Compounds, Highlighting Absorption, Distribution, Metabolism, and Excretion (ADME) Characteristics.

parameters included molecular weight under 500 Da, logP under 5, fewer than 5 hydrogen bond donors, and fewer than 10 hydrogen bond acceptors. The remaining two compounds showed only minor violations, such as marginally higher lipophilicity or molecular weight, which do not entirely rule out their drug-likeness but may require structural optimization. The high level of compliance among the majority of compounds confirms their favorable physicochemical profiles, supporting their candidacy for further preclinical development (Figure 3a).

Pharmacokinetics and Bioavailability

Pharmacokinetic modeling revealed that none of the alkaloids were predicted to cross the BBB, which is advantageous for the treatment of sickle cell anemia, as CNS penetration is neither required nor desired. This reduces the risk of potential neurotoxicity and off-target CNS effects. Most compounds showed favorable GI absorption predictions and acceptable metabolic stability profiles, indicating a strong likelihood of systemic circulation when administered orally. Although the

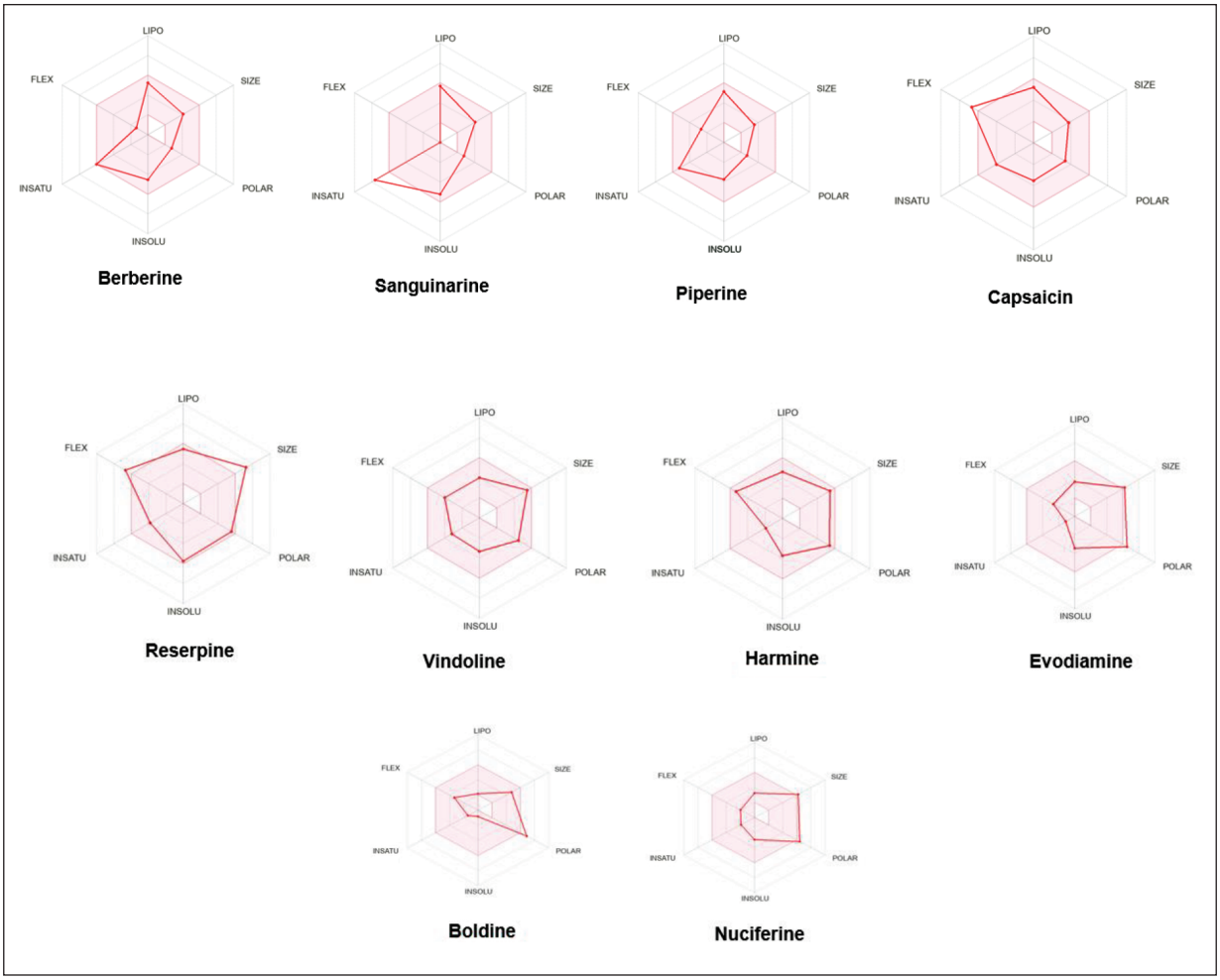


Figure 4. Radar Plot Showing Lead Compounds and Their Properties.

Note: FLEX: Flexibility; INSATU: Unsaturation; INSOLU: Insolubility; LPO: Lipophilicity; POLAR: Polarity; SIZE: Size.

exact bioavailability values were not quantified in this *in silico* model, the ADMET profile for the top-performing alkaloids suggested compatibility with drug development requirements (Figure 3b).

Identification of Lead Compounds

The radar plot analysis of the lead antioxidant alkaloids provides a comprehensive view of their oral bioavailability based on six key physicochemical properties: lipophilicity (LIPO), size (SIZE), polarity (POLAR), insolubility (INSOLU), unsaturation (INSATU), and flexibility (FLEX). These compounds were initially shortlisted through docking studies, drug-likeness evaluations, and pharmacokinetic profiling, which identified 10 promising candidates—berberine, sanguinarine, piperine, capsaicin, reserpine, vindoline, harmine, evodiamine, boldine, and nuciferine (Figure 4).

Each demonstrated strong binding affinity toward HbS and favorable pharmacokinetic behavior. The radar plots confirmed that most compounds displayed favorable bioavailability profiles, with parameters largely falling within the optimal range for drug-like behavior. Berberine and harmine showed well-balanced characteristics with moderate polarity and lipophilicity, supporting good absorption and stability (Figure 4). Capsaicin exhibited an especially strong profile with ideal size, polarity, and flexibility, suggesting efficient absorption and distribution. Vindoline emerged as the most bioavailable compound, displaying nearly perfect alignment across all six parameters, indicating excellent drug-likeness and oral efficacy. Piperine and sanguinarine had slightly elevated lipophilicity and rigidity, which may affect solubility and metabolic processing but remain within tolerable limits. Reserpine and boldine showed higher flexibility or reduced solubility, potentially limiting bioavailability unless optimized. Nuciferine and evodiamine presented moderately strong profiles, though their lower unsaturation and solubility may require formulation enhancement. Notably, harmine and rutaecarpine stood out not only for their docking strength but also for their overall molecular profile. Overall, vindoline, capsaicin, and harmine are identified as the most

promising candidates in terms of oral bioavailability for further therapeutic development against sickle cell anemia.

Discussion

The present *in silico* study explored the potential of selected antioxidant alkaloids to interact with mutant HbS as a therapeutic strategy for sickle cell anemia. Our molecular docking results demonstrated strong binding affinities of several compounds, particularly rutaecarpine, harmine, and vindoline, with docking scores ranging from −5.5 to −10.7 kcal/mol. These values indicate a high likelihood of stable interactions between the ligands and the HbS active site, suggesting possible inhibitory effects on hemoglobin polymerization. Such interactions are critical since inhibition of HbS polymerization can directly reduce red cell sickling and the downstream pathophysiological consequences of the disease.

Several studies have supported the application of plant-based compounds in sickle cell disease management. A similar *in silico* study by Alao et al. reported that alkaloids such as piperine and berberine displayed notable binding interactions with HbS, reinforcing our findings regarding the therapeutic relevance of these compounds.[11] Moreover, harmine has been previously reported to exert antioxidant and neuroprotective effects through modulation of oxidative pathways, supporting its multifaceted potential in hemoglobinopathies.[12] These congruencies validate the effectiveness of *in silico* methodologies in the early stages of drug discovery and strengthen confidence in our screening approach.

The assessment of drug-likeness through Lipinski's rule of five revealed that 10 out of 12 compounds complied fully, indicating their potential suitability for oral administration. This aligns with previous findings by Olubiyi et al., who reported high compliance of natural alkaloids with oral drug-likeness parameters, thereby justifying their inclusion in early drug development pipelines.[13] However, two compounds in our study exhibited minor violations, suggesting the need for structural optimization to enhance their pharmacokinetic properties. This limitation highlights the importance of balancing molecular potency with physicochemical attributes to ensure clinical viability.

Pharmacokinetic modeling revealed that none of the alkaloids were predicted to cross the BBB, a favorable attribute in the context of sickle cell anemia, where CNS penetration is unnecessary and potentially undesirable. This aligns with the work of Yang et al., who emphasized the reduced risk of neurotoxicity in non-CNS drugs when BBB impermeability is ensured.[14] On the other hand, some studies argue that CNS effects in sickle cell disease, such as stroke and cognitive dysfunction, may benefit from compounds capable of CNS penetration.[15] Thus, while BBB impermeability is advantageous for safety, it may limit the broader neuroprotective scope in severe complications of the disease.

One of the most promising findings of this study was the identification of vindoline as a compound exhibiting nearly ideal physicochemical and pharmacokinetic properties. Previous research by Singh et al. also highlighted vindoline's potential in modulating oxidative stress and inflammation, mechanisms central to the progression of sickle cell disease.[16,17] The compound's balance in lipophilicity, polarity, solubility, and molecular flexibility suggests a high potential for systemic availability and target-specific action. Its performance, along with that of capsaicin and harmine, underscores the importance of considering both binding efficiency and oral bioavailability in selecting lead candidates.

However, it is important to recognize the limitations of this study. *In silico* docking and pharmacokinetic modeling, although powerful, do not replicate the full complexity of biological systems. Factors such as metabolic biotransformation, active transport, and protein binding, which influence drug efficacy and safety, require *in vitro* and *in vivo* validations. Moreover, the accuracy of docking predictions is influenced by the quality of protein structures and the limitations of scoring functions used in computational models. Future research must integrate experimental validation, including enzyme inhibition assays, erythrocyte sickling tests, and animal models, to confirm the predicted therapeutic effects.

In conclusion, this study identifies several plant-derived antioxidant alkaloids with promising anti-sickling potential, particularly vindoline, harmine, and rutaecarpine. These compounds demonstrated strong interactions with mutant HbS, favorable drug-likeness, and desirable pharmacokinetic profiles. The findings support the rationale for using natural phytochemicals in treating sickle cell anemia and justify further preclinical evaluation. While computational approaches provide valuable initial insights, a multidisciplinary strategy combining *in silico, in vitro*, and *in vivo* methods will be essential for advancing these candidates toward clinical development.

Conclusion

This study successfully identified and evaluated 12 antioxidant alkaloids for their potential therapeutic application against mutant HbS in sickle cell anemia using an *in silico* approach. Through molecular docking, drug-likeness assessment, and pharmacokinetic profiling, several compounds demonstrated strong binding affinities, favorable drug-like properties, and acceptable oral bioavailability. Vindoline, harmine, and rutaecarpine emerged as the top-performing candidates, exhibiting both structural compatibility with the HbS binding site and suitable physicochemical profiles. These findings reinforce the potential of natural plant-based alkaloids as promising leads for anti-sickling drug development and validate the utility of computational tools in preclinical screening.

Study Limitations and Future Directions

While this study provides valuable insights into the therapeutic potential of antioxidant alkaloids against mutant HbS, it is not without limitations. The findings are derived entirely from *in silico* simulations, which, though efficient and cost-effective,

cannot fully replicate the complex dynamics of biological systems. Molecular docking predictions may not accurately capture all physiological interactions, and pharmacokinetic modeling based on ADMET parameters assumes idealized conditions that can differ *in vivo* due to metabolic transformations, protein binding, or active transport mechanisms. Moreover, the current study did not evaluate toxicity or off-target effects, which are crucial before clinical translation. To strengthen these findings, future research should incorporate *in vitro* assays, such as hemoglobin polymerization inhibition, red blood cell sickling reversal, and antioxidant activity testing, to validate the predicted bioactivity of the top lead compounds. Subsequently, *in vivo* studies using animal models should assess their efficacy, safety, pharmacodynamics, and pharmacokinetics under physiological conditions. Structural optimization and formulation enhancements may further improve bioavailability, particularly for compounds with borderline pharmacokinetic profiles. Additionally, exploring the integration of these natural alkaloids with existing or emerging therapeutic regimens could reveal synergistic benefits. If experimentally validated, these compounds hold strong promise as the foundation for developing novel, affordable, and plant-derived therapeutic interventions for sickle cell anemia, especially in resource-limited regions.

Abbreviations

HBB: Hemoglobin subunit beta; **HbS:** Hemoglobin S; **kcal/mol:** Kilocalories per mole; **PDB:** Protein Data Bank.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval and Informed Consent

Ethical approval and informed consent were not applicable to this study, as it was based exclusively on *in silico* computational analyses using publicly available databases.

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References

1. Ingram VM. A specific chemical difference between the globins of normal human and sickle-cell anemia hemoglobin. *Nature* 1956; 178(4537): 792–794.
2. Wood KC, Granger DN. Sickle cell disease: role of reactive oxygen and nitrogen metabolites. *Clin Exp Pharmacol Physiol* 2007; 34(9): 926–932.
3. Nurain IO, Bewaji CO and Olaleye TM, et al. Potential of three ethnomedicinal plants as antisickling therapy in sickle cell disease management. *J Ethnopharmacol* 2016; 190: 190–198. DOI:10.1016/j.jep.2016.05.054
4. Yembeau NL, Omam JP, and Ngoule CC, et al. Ethnopharmacological study of medicinal plants used to treat sickle cell patients in West Cameroon. *J Ethnopharmacol* 2022; 291: 115150. DOI:10.1016/j.jep.2022.115150
5. Tian KM, Li JJ and Xu SW. Rutaecarpine: a promising cardiovascular-protective alkaloid from *Evodia rutaecarpa*. *Pharmacol Res* 2019; 141: 541–550. DOI:10.1016/j.phrs.2019.01.043
6. Choi JH, Park SY, Oh DS, et al. Rutaecarpine protects against acetaminophen-induced acute liver injury in mice by activating antioxidant enzymes. *Antioxidants (Basel)* 2021; 10(1): 86. DOI:10.3390/antiox10010086
7. Gong, M and Jia, J. Rutaecarpine mitigates cognitive impairment by balancing mitochondrial function via AMPK/PGC-1α pathway. *Mol Neurobiol* 2023; 60(4): 2058–2071. DOI:10.1007/s12035-022-03179-3
8. Agarwal T, Manivannan HP, and Gayathri R, et al. Selective plant alkaloids as potential inhibitors of PARP in pancreatic cancer: an *in silico* study. *Indian J Biochem Biophys* 2023; 60(7): 555–566. DOI:10.56042/ijbb.v60i7.90
9. Priyadarshini G, Sukumaran G, Dilipan E, et al. Targeting oral cancer: *in silico* docking studies of phytochemicals on oncogenic molecular markers. *Asian Pac J Cancer Prev* 2024; 25(6): 2069–2075. DOI:10.31557/APJCP.2024.25.6.2069
10. Krishna KN, Krishnamoorthy K, Veeraraghavan VP, et al. *In vitro* biological properties and *in silico* studies on *Tinospora cordifolia* stem aqueous extract. *J Pharm Bioallied Sci* 2024; 16(Suppl 2): S1317–S1320. DOI:10.4103/jpbs.jpbs_598_23
11. Alao PG, Oyewole AO, Olubiyi OO. *In silico* molecular docking of plant alkaloids as potential anti-sickling agents. *J Mol Model* 2020; 26(7): 182. DOI:10.1007/s00894-020-04415-1
12. Herraiz T and Guillén H. Monoamine oxidase-A inhibition and antioxidant properties of harmine and other β-carboline alkaloids. *Food Chem Toxicol* 2018; 111: 679–685. DOI:10.1016/j.fct.2017.12.026
13. Olubiyi OO, Olagunju, MO, Olubiyi TM. Computational evaluation of anti-sickling potential of selected plant-derived alkaloids. *J Appl Pharm Sci* 2019; 9(4): 51–57. DOI:10.7324/JAPS.2019.90408
14. Yang H, Lou C, Sun L, et al. admetSAR 2.0: web-service for prediction and optimization of chemical ADMET properties. *Bioinformatics* 2019; 35(6): 1067–1069. DOI:10.1093/bioinformatics/bty707
15. DeBaun MR, Armstrong FD, McKinstry RC, et al. Silent cerebral infarcts: a review on a prevalent and progressive cause of neurologic injury in sickle cell anemia. *Blood* 2012; 119(20): 4587–4596. DOI:10.1182/blood-2011-02-272682
16. Singh A, Singh DK, Verma A, et al. Vindoline and other indole alkaloids: potential agents in antioxidant and anti-inflammatory therapy. *Phytochem Rev* 2017; 16(5): 857–869. DOI:10.1007/s11101-017-9491-4
17. Brandow AM, Liem RI. Advances in the diagnosis and treatment of sickle cell disease. *J Hematol Oncol* 2022; 15: 20. DOI:10.1186/s13045-022-01237-z