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RESEARCH ARTICLE

Dual Targeting of Transferrin and Ferritin by Chemical Constituents from *Hagenia abyssinica* in Iron Overload Disorders

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Abstract

Background: Hereditary Hemochromatosis (HH) is a genetic iron overload disorder characterised by progressive accumulation of iron in vital organs, leading to cirrhosis, diabetes, and cardiomyopathy. Current therapies, including phlebotomy and synthetic chelators, are limited by invasiveness, poor compliance, and systemic toxicity. Plant-derived phytochemicals, such as those from *Hagenia abyssinica*, offer a promising natural alternative due to their iron-chelating and bioactive properties. **Aim:** To evaluate the iron-chelating potential of six phytochemicals from *H. abyssinica* by targeting transferrin and ferritin through molecular docking and ADMET profiling. **Methods:** Molecular docking was performed using AutoDock Vina against transferrin (PDB ID: 1A8F) and ferritin (PDB ID: 3AJO). Binding affinities and key protein-ligand interactions were analysed. Drug-likeness was assessed using Lipinski's Rule of Five, and pharmacokinetics/toxicity were predicted via *in silico* ADMET tools. **Results:** Kosotoxin and alpha-kosin showed strong dual binding affinities with transferrin (-6.6 and -5.7 kcal/mol) and ferritin (-6.1 and -7.0 kcal/mol). Both interacted with iron-coordinating residues, indicating inhibitory potential on iron transport and storage. ADMET profiling demonstrated favourable gastrointestinal absorption, low predicted toxicity, and blood-brain barrier permeability for kosotoxin, suggesting potential application in neurological manifestations of iron overload. **Conclusion:** Kosotoxin and alpha-kosin emerge as promising natural iron chelators with dual-target activity, favourable pharmacokinetics, and safety profiles. These findings provide a strong rationale for experimental validation and further development in the management of hereditary hemochromatosis and related iron dysregulation disorders.

Major Finding: Kosotoxin and alpha-kosin from *H. abyssinica* showed potent dual binding to transferrin and ferritin with favourable pharmacokinetics, highlighting their potential as safe and effective natural chelators in iron overload disorders.

Keywords: Alpha-kosin, Ferritin, *Hagenia abyssinica*, Hereditary Hemochromatosis, Iron Overload, Kosotoxin, Transferrin

1. Introduction

Iron plays an indispensable role in various physiological processes, including oxygen transport, enzymatic activity, and cellular respiration. However, its redox-active nature also renders it potentially toxic when present in excess[1]. The human body tightly regulates iron levels through a complex network involving key proteins such as transferrin, which transports iron in the bloodstream, and ferritin, which stores it intracellularly. Disruption of this balance can lead to iron overload, a condition implicated in numerous pathological states[2].

Hereditary Hemochromatosis (HH) is a genetic disorder characterised by excessive intestinal iron absorption and progressive iron accumulation in vital organs, including the liver, pancreas, and heart. Most

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commonly associated with mutations in the HFE gene, HH can result in complications such as liver cirrhosis, diabetes mellitus, cardiac dysfunction, and increased risk of hepatocellular carcinoma. Despite being treatable, current therapeutic options like phlebotomy and synthetic iron chelators often suffer from limitations including invasiveness, poor compliance, adverse side effects, and systemic toxicity[3,4].

These challenges have sparked interest in identifying safer and more effective alternatives, particularly from natural sources. Plant-derived compounds offer a chemically diverse and biologically active pool of molecules with potential therapeutic applications. Their intrinsic properties—such as metal chelation, antioxidant activity, and anti-inflammatory effects—make them especially attractive candidates for managing disorders involving iron dysregulation. In this context, phytochemicals provide not only functional diversity but also enhanced biocompatibility and lower toxicity profiles compared to synthetic agents[5].

Hagenia abyssinica, a traditional medicinal plant native to East Africa, has long been used for its anthelmintic and anti-inflammatory properties[6,7]. Recent phytochemical studies have revealed that this plant contains a variety of biologically active compounds, including kosotoxin and alpha-kosin. Although their therapeutic potential has been explored in other contexts, their application as iron chelators in managing iron overload disorders remains largely underexplored[8,9].

Advances in computational drug discovery, particularly *in silico* approaches such as molecular docking and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) modelling, have revolutionised the early stages of therapeutic development. These tools allow for high-throughput screening of compounds based on their ability to bind to target proteins and predict pharmacokinetic behaviour, thus reducing the time, cost, and risk associated with experimental methods[10,11].

This study aims to leverage these computational tools to evaluate the iron-chelating potential of six phytochemicals derived from *H. abyssinica*. Using molecular docking, we assess their binding affinity toward transferrin and ferritin, the two primary proteins involved in iron transport and storage. Complementary ADMET profiling is conducted to predict the drug-likeness and safety of these compounds. The ultimate goal is to identify promising lead molecules that can be further developed into effective, plant-based therapeutics for the treatment of hereditary hemochromatosis and related iron overload conditions.

2. Materials and Methods

2.1 Selection of Phytochemicals

Six phytochemicals derived from *H. abyssinica* were selected for analysis based on their reported biological activity and iron-chelating potential, relevant to the pathophysiology of hereditary hemochromatosis. The selected compounds were retrieved from the Traditional Chinese Medicine (TCM) database, ensuring credible phytochemical sourcing from validated ethnobotanical records.

2.2 Protein Target Identification

Two essential human proteins implicated in iron metabolism were chosen as molecular targets—Transferrin (TF), which regulates iron transport, and Ferritin Heavy Chain 1 (FTH1), which is responsible for intracellular iron storage. The 3D crystallographic structures of these proteins were sourced from the RCSB Protein Data Bank using the following PDB IDs: 1A8F for human transferrin and 3AJO for human ferritin. These high-resolution structures facilitated accurate and reliable docking simulations[12].

2.3 Molecular Docking Studies

2.3.1 Preparation of Proteins and Ligands

The protein structures were pre-processed by eliminating water molecules and heteroatoms to optimise the binding site for ligand interactions. Phytochemical ligands underwent energy minimisation using molecular mechanics-based force fields to achieve stable conformations. All structural files were converted into the PDBQT format using AutoDockTools for compatibility with the docking software.

2.3.2 Docking Procedure

Molecular docking was carried out using AutoDock Vina, selected for its reliable scoring functions and computational efficiency. Docking simulations were performed for each compound against both transferrin and ferritin, generating binding affinity scores and predicted interaction poses. The results were further

visualised using molecular modelling tools to examine the nature of ligand-protein interactions, including hydrogen bonding, hydrophobic contacts, and spatial orientation within the binding pocket.

2.4 Binding Affinity Analysis

Binding affinities, measured in kcal/mol, were analysed to determine the strength of ligand-protein interactions. For transferrin, docking scores ranged from -1.6 to -6.6 kcal/mol, whereas ferritin binding affinities ranged from -4.5 to -7.5 kcal/mol. These values were graphically represented to compare and rank the binding efficiency of each phytochemical with respect to both protein targets.

2.5 Drug-likeness Evaluation

To evaluate the oral bioavailability of the selected compounds, drug-likeness was assessed using Lipinski's Rule of Five. Key parameters, including molecular weight, hydrogen bond donors and acceptors, and lipophilicity (LogP), were examined. Three compounds were found to violate one or more of Lipinski's criteria, suggesting limitations in their drug-like behaviour and potential challenges in formulation development.

2.6 Pharmacokinetics and ADMET Analysis

ADMET profiling was conducted to predict the pharmacokinetic behaviour and safety of the phytochemicals. Parameters such as gastrointestinal absorption, blood-brain barrier permeability, and potential interaction with P-glycoprotein were analysed. One of the compounds exhibited predicted ability to cross the blood-brain barrier, implying potential central nervous system activity. Overall, the analysis helped to identify compounds with favourable pharmacokinetic and toxicity profiles.

2.7 Identification of Lead Compounds

Based on an integrated assessment of docking performance and ADMET characteristics, kosotoxin and alpha-kosin emerged as the most promising lead compounds. These phytochemicals demonstrated strong binding affinities with both transferrin and ferritin and possessed favourable iron-chelating capabilities. Their drug-like and pharmacokinetic profiles support their candidacy for further development as therapeutic agents for managing hereditary hemochromatosis.

3. Results and Interpretation

3.1 Molecular Docking Analysis

To evaluate the potential of *H. abyssinica* phytochemicals as therapeutic iron chelators, molecular docking studies were conducted against two critical proteins involved in iron metabolism—transferrin (TF) and ferritin (FTH1). These targets are central to the pathology of hereditary hemochromatosis, with transferrin mediating iron transport and ferritin functioning as an intracellular iron reservoir (Table 1).

Table 1. PDB ID of selected compounds

S. No.	Target	Gene	PDB ID
1	Transferrin	TF	1A8F
2	Ferritin	FTH1	3AJO

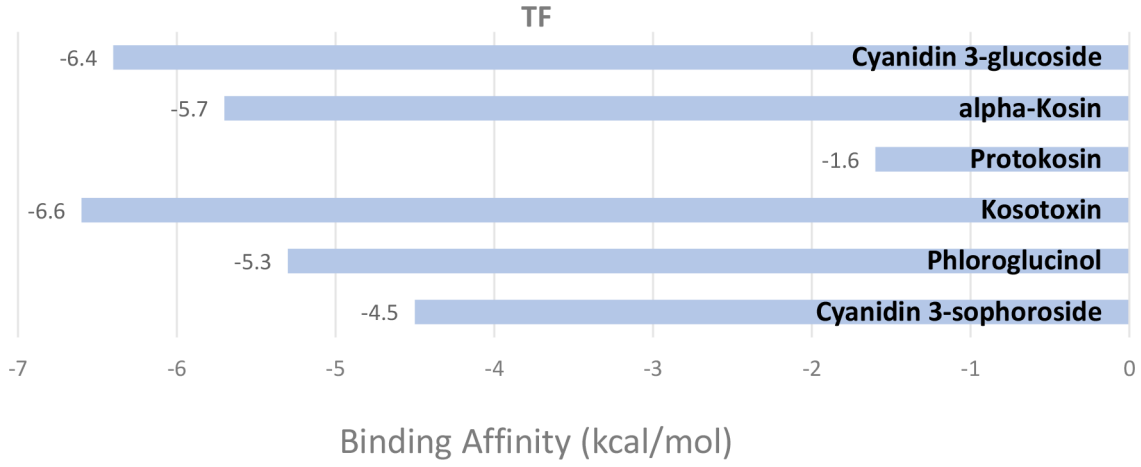


Figure 1. Binding affinity of transferrin.

Table 2. The binding affinity of transferrin

S. No.	Compounds	Binding affinity (Kcal/mol)	Interacting amino acids
1	Cyanidin 3-sophoroside	-4.5	Gln184, Ser189, Asp292, Tyr188, Gly190, Arg124, Gly187, Phe186, Thr181, Lys291, Leu293, His14, His289, Gly290, Pro288, Asn213, Lys196, Asp197, Phe192, Lys193
2	Phloroglucinol	-5.3	Glu15, Leu294, Thr61, Glu83, Phe295, His249, Lys296, Asp292, Arg124, Tyr188, Phe186
3	Kosotoxin	-6.6	Lys196, Phe192, Asn213, Ser189, Lys193, His289, His14, Leu293, Gly290, Lys291, Thr181, Gly187, Phe186, Asn183, Gln184, Gly190, Tyr185
4	Protokosin	-1.6	Ser208, Phe211, His207, Tyr238, Glu212, Tyr85, Ser298, Gln92, Asp297, Lys276, His300, Gly86, Ser87
5	alpha-kosin	-5.7	Lys196, Lys193, Phe192, Asn213, His289, Gly290, Lys291, His14, Gln184, Thr181, Gly190, Gly187, Asp292, Phe186, Ser189
6	Cyanidin 3-glucoside	-6.4	Phe192, Lys196, Asn213, Lys193, Ser189, Gly190, Lys291, Tyr188, Asp292, Gly187, Phe186, Asn183, Tyr185, Thr181, Gln184, Gly290, His289

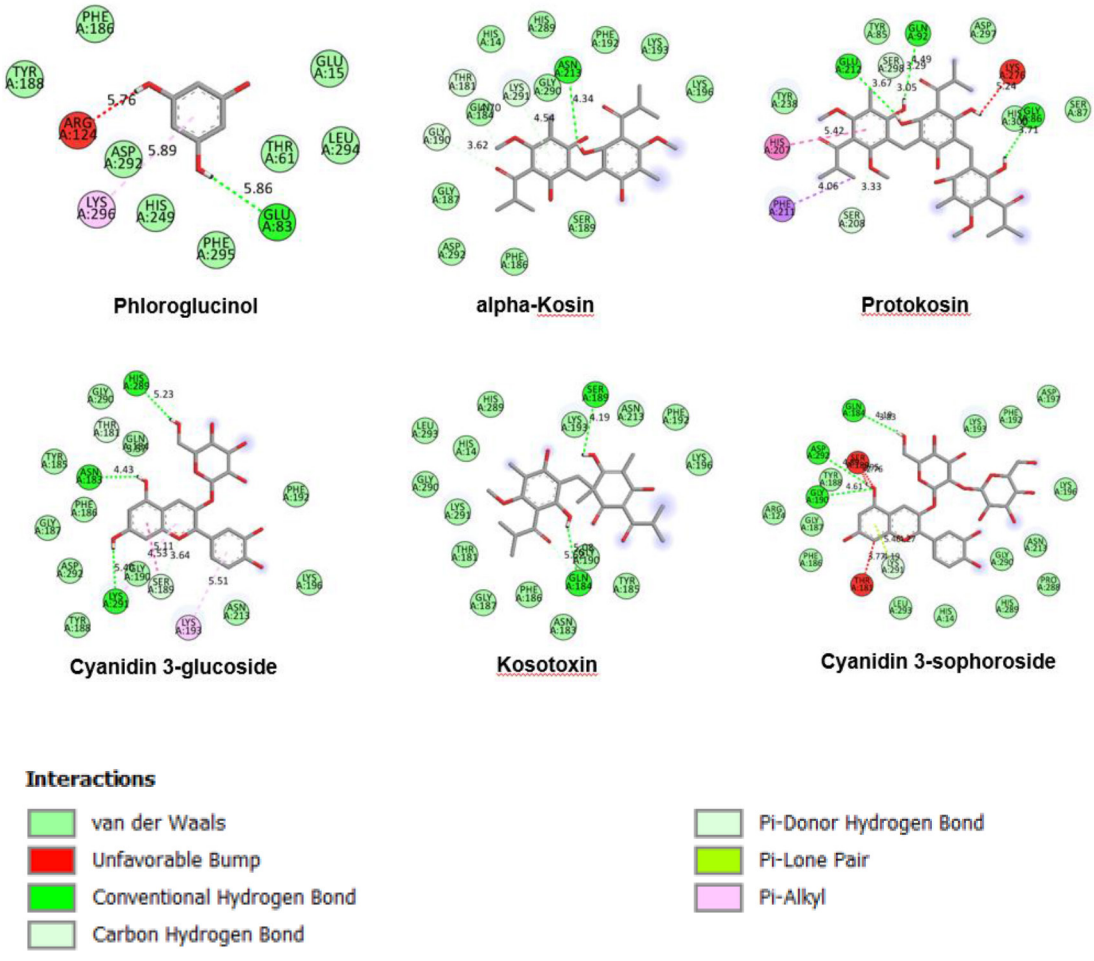


Figure 2. Molecular docking of TF.

3.1.1 Interaction with Transferrin

The binding affinities of the six phytochemicals toward transferrin (PDB ID: 1A8F) ranged from -1.6 to -6.6 kcal/mol. Kosotoxin exhibited the most favourable binding affinity (-6.6 kcal/mol), followed by cyanidin 3-glucoside (-6.4 kcal/mol) and alpha-kosin (-5.7 kcal/

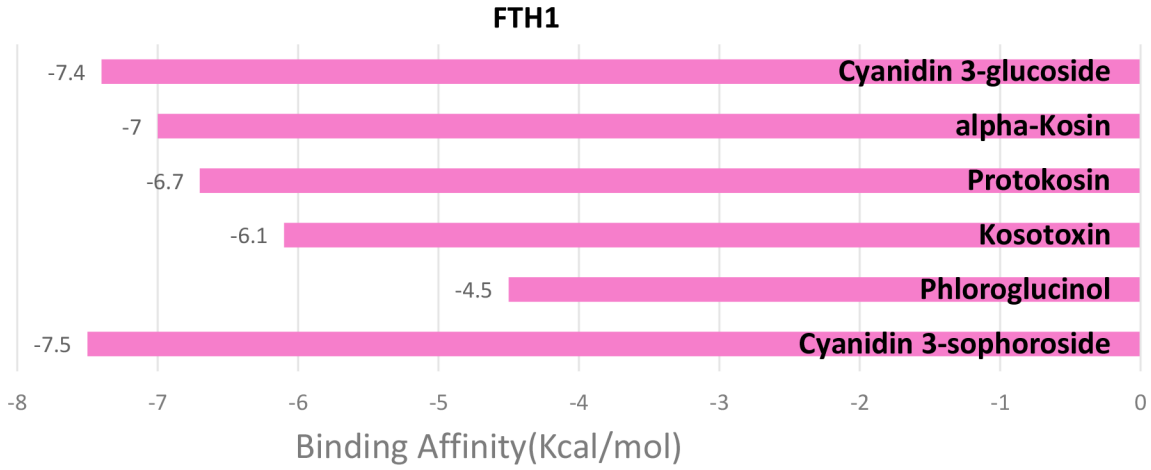


Figure 3. Binding affinity of ferritin.

mol). These values reflect a high likelihood of stable interactions between the ligands and the protein's iron-binding clefts (Figures 1 and 2, Table 2).

The stronger binding of kosotoxin and alpha-kosin to transferrin suggests their potential to inhibit or modulate the iron-carrying function of this glycoprotein. This modulation could reduce the systemic iron load, making these compounds promising candidates for therapeutic intervention in hereditary hemochromatosis. Additionally, the nature of hydrogen bonding and hydrophobic interactions observed in docking poses supports the specificity and stability of these ligand-protein complexes.

3.2 Interaction with Ferritin

Ferritin (PDB ID: 3AJO) displayed even more favourable binding interactions. The binding energies ranged from -4.5 to -7.5 kcal/mol, with cyanidin 3-sophoroside showing the highest affinity (-7.5 kcal/mol), followed closely by cyanidin 3-glucoside (-7.4 kcal/mol) and alpha-kosin (-7.0 kcal/mol). Notably, kosotoxin also exhibited a strong interaction at -6.1 kcal/mol (Figures 3, 4, Table 3).

The enhanced binding to ferritin, particularly by alpha-kosin and kosotoxin, indicates a promising mechanism to interfere with intracellular iron storage. In hereditary hemochromatosis, where iron accumulation within tissues contributes to disease pathology, the disruption of ferritin-iron interactions could offer therapeutic benefit. These findings emphasise the dual-target capability of the lead phytocompounds.

3.3 Structural Validation of Docking Poses

High-resolution three-dimensional structures of transferrin and ferritin were utilised to confirm ligand orientation within the active or allosteric binding sites. Structural validation revealed that all top-performing phytochemicals aligned within functional regions known for iron coordination, thereby affirming the biological relevance of the docking results.

The spatial alignment and fit of kosotoxin and alpha-kosin within the iron-binding domains provide further support for their mechanistic role as iron chelators. Such interactions may enable functional inhibition through direct competition or allosteric modulation (Figure 5).

3.4 Drug-Likeness and Physicochemical Properties

Drug-likeness was assessed using Lipinski's Rule of Five. While some phytochemicals showed minor deviations—primarily due to high molecular weight or hydrogen bond donors—kosotoxin fully complied, and alpha-kosin demonstrated only one borderline violation.

The compliance of kosotoxin and near-compliance of alpha-kosin with key drug-likeness parameters underscores their potential for oral bioavailability and systemic distribution. These physicochemical traits are essential for progression into pharmacological testing and clinical development (Figure 6).

3.5 Pharmacokinetic and Toxicological Profiling (ADMET)

To evaluate the clinical potential of the identified compounds, ADMET profiling was conducted. The

Table 3. The binding affinity of ferritin

S. No.	Compounds	Binding affinity (Kcal/mol)	Interacting amino acids
1	Cyanidin 3-sophoroside	-7.5	Gln112, Val110, Asn109, Ser113, Gln23, Arg22, Glu116, Asp89, His105, Leu106, Tyr29, Lys86, Ile85, Asp84, Asn25
2	Phloroglucinol	-4.5	Ser113, Gln23, Arg22, Glu116, Leu120, Ala19, Leu117
3	Kosotoxin	-6.1	Tyr29, Asn109, Leu26, Gln112, Glu116. Ser113, Arg22, Gln83, Asn25, Lys86
4	Protokosin	-6.7	Tyr29, Lys86, Asn25, Leu26, Gln83, Lys119, Leu120, Glu116, leu117, Ala19, Arg22, Gln112, Ser113, Asn109, val110
5	alpha-kosin	-7	Arg22, Leu26, Asn25, Lys86, Tyr29, Asn109, Ser113, Gln23, Ala19, Glu116, Leu117
6	Cyanidin 3-glucoside	-7.4	Gln83, Asn25, Arg22, Leu26, Ala19, Leu117, Gln23, Ser113, Glu116, Gln112, Asn109

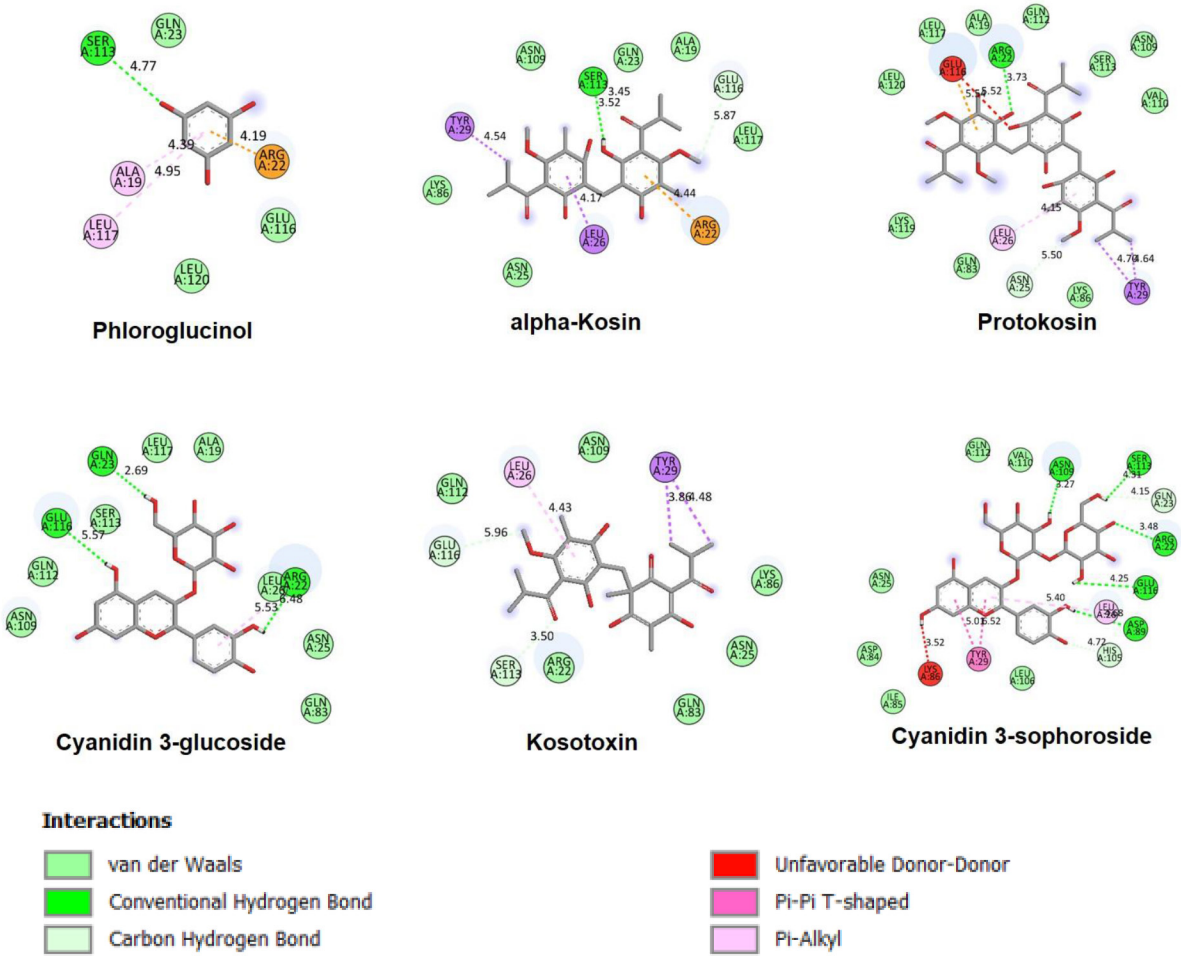


Figure 4. Molecular docking with FTH1.

analysis revealed that kosotoxin demonstrated the ability to cross the blood-brain barrier, highlighting its potential application in managing neurodegenerative disorders associated with iron dysregulation. Most of the compounds, including kosotoxin and alpha-kosin, exhibited favourable gastrointestinal absorption, supporting the feasibility of oral administration. Furthermore, *in silico* toxicity predictions indicated

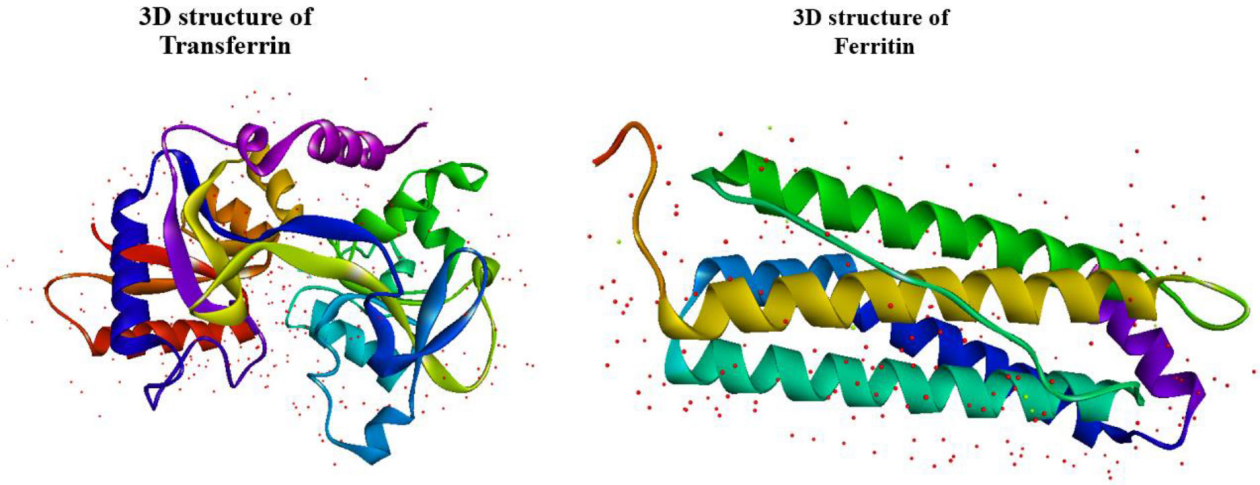


Figure 5. 3D structure of transferrin and ferritin.

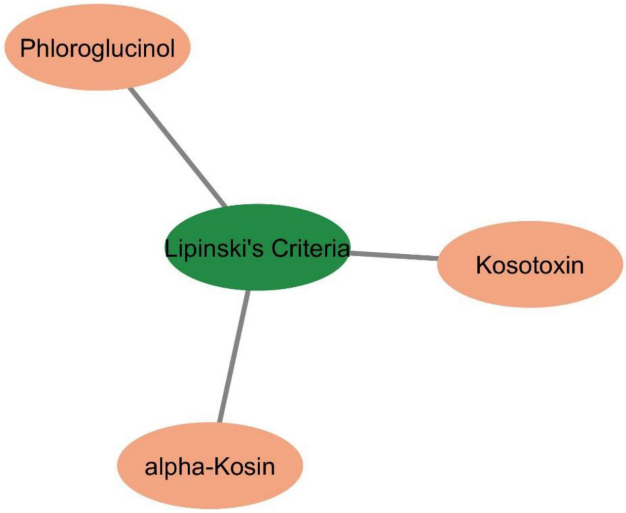


Figure 6. Compounds showing Lipinski criteria.

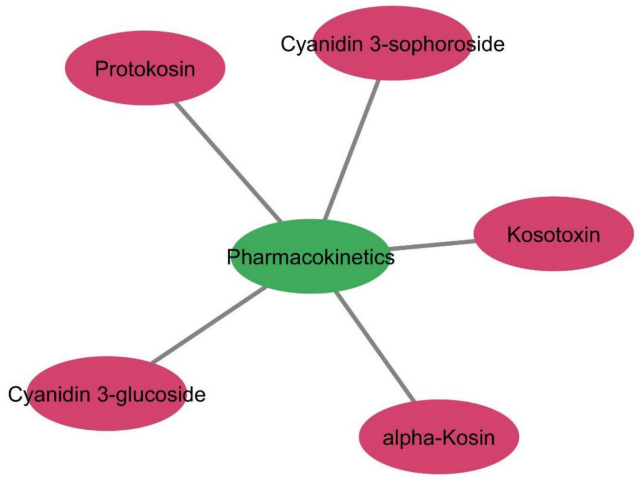


Figure 7. Pharmacokinetics of *H. abyssinica* compounds.

that none of the top-ranking compounds displayed mutagenic or hepatotoxic effects, thereby suggesting a favourable safety profile (Figure 7).

The ADMET results highlight kosotoxin and alpha-kosin as strong candidates not only due to their dual protein-targeting capabilities but also because of their acceptable pharmacokinetic and safety parameters. Kosotoxin's ability to cross the BBB adds a unique therapeutic dimension, potentially extending its utility to neurological manifestations of iron overload.

3.6 Prioritisation of Lead Compounds

Integrative analysis of docking performance, drug-likeness, and ADMET characteristics led to the prioritisation of kosotoxin and alpha-kosin as the most viable lead compounds for further development. Both compounds demonstrated strong, specific binding to transferrin and ferritin, alongside suitable physicochemical and pharmacokinetic properties (Figure 8).

These compounds meet essential early-phase criteria for drug discovery and should be advanced to *in vitro* validation for confirmation of biological activity and cytotoxicity. Their performance in dual protein interaction positions them as promising multitarget therapeutics for hereditary hemochromatosis and related iron overload disorders.

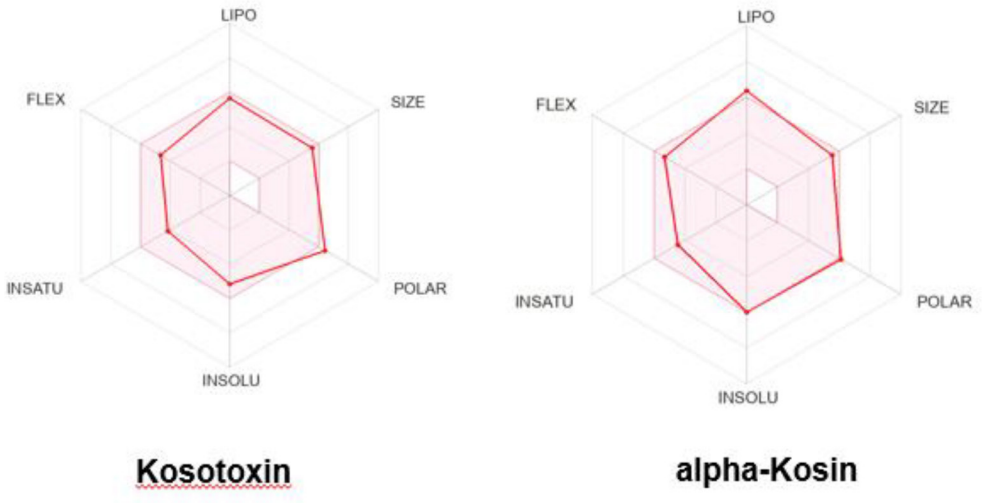


Figure 8. Radar plot of Kosotoxin and alpha kosin.

4. Summary of Key Findings (Table 4)

Table 4. Summary of key findings

Parameter	Kosotoxin	Alpha-kosin
Transferrin Affinity	-6.6 kcal/mol	-5.7 kcal/mol
Ferritin Affinity	-6.1 kcal/mol	-7.0 kcal/mol
Lipinski's Compliance	Full compliance	1 minor violation
BBB Permeability	Yes	No
GI Absorption	High	High
Predicted Toxicity	Low	Low

5. Discussion

The current study provides a comprehensive evaluation of six phytochemicals derived from *H. abyssinica* as potential iron chelators targeting transferrin and ferritin, the principal proteins regulating systemic and intracellular iron homeostasis. Through molecular docking and pharmacokinetic profiling, kosotoxin and alpha-kosin emerged as promising candidates for further development in the management of HH, a disorder characterised by progressive iron accumulation and associated organ damage.

The strong binding affinities of kosotoxin (-6.6 kcal/mol for TF, -6.1 kcal/mol for FTH1) and alpha-kosin (-5.7 kcal/mol for TF, -7.0 kcal/mol for FTH1) suggest their ability to interfere with both iron transport and storage mechanisms. These results are consistent with prior studies showing that flavonoids and polyphenols, due to their hydroxyl groups, effectively bind ferritin and transferrin proteins. Wang *et al.*,[11] demonstrated that natural flavonoids such as quercetin and rutin exhibit significant binding potential with ferritin, supporting their use in iron modulation therapies[12]. Gupta et al. also reported the iron-chelating abilities of plant-based compounds, highlighting the relevance of specific structural features such as catechol and hydroxyl groups for effective metal binding[13].

Mechanistically, dual inhibition of transferrin and ferritin is an advantageous therapeutic strategy, offering a two-pronged approach to controlling both systemic and intracellular iron levels. Kang *et al.*[14] emphasised the benefit of dual targeting in iron overload disorders, suggesting improved outcomes over monotherapy approaches. Compared to conventional chelators like deferoxamine, which are limited by narrow target specificity and administration challenges, phytocompounds offer a multitarget profile with potentially fewer side effects and better patient compliance[15,16].

The ADMET analysis provided further support for the drug-like characteristics of kosotoxin and alpha-kosin. Kosotoxin demonstrated high gastrointestinal absorption and the ability to cross the Blood-Brain Barrier (BBB), which may extend its therapeutic application to neurological manifestations of iron overload. Pretorius *et al.*,[17] linked iron dysregulation to neurodegeneration in diseases such as Alzheimer's and Parkinson's, underscoring the therapeutic value of CNS-permeable chelators. The observed pharmacokinetic properties position kosotoxin as a candidate for addressing both peripheral and central iron overload.

Despite one minor violation of Lipinski's Rule of Five, alpha-kosin still demonstrated strong drug-likeness. Veber *et al.*,[18] noted that many pharmacologically active plant-derived molecules fall outside traditional drug-likeness parameters yet remain clinically viable due to their favourable biological profiles. Therefore, alpha-kosin's borderline deviation does not preclude its candidacy as a lead compound, particularly in combination therapies or novel formulations.

It is important to note, however, that computational predictions alone are not definitive indicators of biological activity. Naqvi *et al.*,[19] highlighted discrepancies between docking predictions and *in vivo* efficacy due to protein flexibility and metabolism-related changes in ligand structure. Therefore, the current findings must be validated through *in vitro* and *in vivo* assays to assess bioactivity, specificity, and safety in biological systems. Toxicological studies, enzymatic interaction profiling, and cell-based iron assays will be crucial in translating these preliminary findings into clinically actionable outcomes.

Thus, the present study demonstrates the potential of kosotoxin and alpha-kosin as natural iron chelators with dual-target efficacy and favourable pharmacokinetic properties. Their multitarget interactions and predicted safety profiles support their advancement into experimental models. By combining traditional medicinal knowledge with modern drug design approaches, this research contributes to the emerging paradigm of plant-based therapeutics for complex metabolic disorders such as hereditary hemochromatosis.

6. Conclusion

The findings of this study provide compelling evidence for the therapeutic potential of phytochemicals derived from *H. abyssinica*, particularly kosotoxin and alpha-kosin, as natural iron chelators. Through robust molecular docking analysis, these compounds demonstrated strong and stable interactions with transferrin and ferritin, the two key proteins involved in systemic and intracellular iron regulation. Their high binding affinities suggest a promising dual mechanism of action—targeting both iron transport and storage pathways—which is highly desirable in managing complex iron overload disorders such as hereditary hemochromatosis. Moreover, the compounds exhibited favourable pharmacokinetic characteristics, including good gastrointestinal absorption and, in the case of kosotoxin, the ability to cross the blood-brain barrier. Compliance with key drug-likeness criteria further strengthens their viability as lead compounds. Overall, this study underscores the value of integrating plant-based pharmacophores into modern therapeutic strategies for chronic iron dysregulation.

7. Future Perspective

While the current findings offer a strong preliminary foundation, the true translational potential of kosotoxin and alpha-kosin can only be realised through experimental validation. Future research should focus on conducting comprehensive **in-vitro** assays to assess iron-chelating efficacy, cytotoxicity, and interaction kinetics with target proteins under physiological conditions. Additionally, *in vivo* studies in relevant animal models of hereditary hemochromatosis will be critical to evaluate bioavailability, tissue distribution, metabolic stability, and therapeutic effectiveness over time. Given kosotoxin's predicted ability to penetrate the blood-brain barrier, its role in addressing neurodegenerative conditions associated with iron accumulation—such as Parkinson's and Alzheimer's diseases—also warrants investigation. Expanding this research to include Structure-Activity Relationship (SAR) studies, semi-synthetic derivatives, and formulation development may further enhance the pharmacological performance and clinical applicability of these compounds. The integration of ethnopharmacological knowledge with molecular drug design thus presents a promising path forward in the treatment of iron-related disorders.

8. Limitations

Despite its strengths, this study is limited by its exclusive reliance on computational modelling and virtual screening techniques, which, while highly predictive, do not account for the dynamic complexity of biological systems. The absence of experimental validation means that binding affinities, ADMET profiles, and drug-likeness predictions remain theoretical until corroborated by laboratory data. Furthermore, the docking simulations do not consider factors such as protein flexibility, metabolic transformation of compounds, and off-target effects, all of which could influence therapeutic efficacy and safety in

real-world applications. Therefore, empirical studies are essential to confirm and extend the current findings.

9. Author Contribution

HS: Performed data collection, literature review, and drafted the initial version of the manuscript. NK: Conceived and designed the study, supervised the research process, critically reviewed, and finalised the manuscript. SS: Contributed to methodology, data validation, and provided critical inputs during manuscript preparation. RR: Assisted in study design, data analysis, and interpretation; contributed to manuscript editing. SP: Contributed to drafting, proofreading, and intellectual content revision of the manuscript. All authors have read and agreed to the published version of the manuscript.

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