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In Silico Investigation of Betalaine Compounds from *Hylocereus polyrhizus* Peel as Antiplasmodial Agents

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ABSTRACT

Introduction: *Malaria is a parasitic infection that continues to pose a global health challenge, largely because of the rise of medication resistance. Researchers were concentrating on discovering novel medicines that specifically target critical parasite proteins to address this issue. The peels of Hylocereus polyrhizus (dragon fruit) contain betalains which exhibit antiplasmodial activity. Due to many proteins correlated with malaria, in silico techniques were the best method to screen the efficacy of six betalains derived from H. polyrhizus peels in inhibiting specific Plasmodium falciparum proteins.*
Methods: *The protein structures were acquired from the Protein Data Bank (PDB) and processed by eliminating non-protein molecules. The 3D structures of the betalaine ligands were obtained from PubChem and optimized with Avogadro 1.2.0. Using the Pyrx 0.8 system with Autodock Vina, the ligands were docked to the proteins. The research assessed ADMET characteristics of the ligands utilizing the SwissADME and ProTox-II platforms, respectively.*
Results: *The molecular docking data indicated that Phyllocactin had the lowest binding affinity of -10.7 kcal/mol to PfPNP. Hylocerenin had the lowest binding affinity to PfDHFR-TS at -9.4 kcal/mol. The investigation of amino acid interactions indicated that Hylocerenin engaged with essential residues, specifically Lys27 and Lys28, in PfDHFR-TS. Regarding ADMET characteristics, all six betalaines exhibited minimal gastrointestinal absorption and lacked permeability across the blood-brain barrier. Moreover, Hylocerenin was anticipated to be non-immunotoxic, presenting a notable benefit over other substances such as Betacyanin and Phyllocactin, which were forecasted to have immunotoxic effects.*
Conclusions: *Hylocerenin and Phyllocactin were the most promising antiplasmodial possibilities among the examined betalaine compounds. Hylocerenin was a primary candidate for the inhibition of PfDHFR-TS, whereas Phyllocactin was a prominent candidate for the inhibition of PfPNP. The results indicated that betalaine compounds derived from H. polyrhizus peels merit more research as a novel category of antimalarial medicines.*

Introduction

Malaria is a multifaceted parasite illness that continues to pose a significant global health burden, with the rise of drug-resistant forms highlighting the pressing necessity for novel therapeutic approaches (Li et al., 2025). To address this, researchers have concentrated on discovering and targeting critical parasite proteins. A broad range of targets encompasses vital metabolic enzymes, notably PfDHFR-TS (Dihydrofolate Reductase-Thymidylate Synthase), a

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bifunctional enzyme vital for DNA synthesis. Antifolate medicines such as pyrimethamine target this enzyme, but resistance has emerged due to point mutations in the gene that encodes the enzyme (Chaianantakul et al., 2013). PfLDH (Lactate Dehydrogenase) is an essential enzyme that facilitates the parasite's energy production via glycolysis in the hypoxic milieu of red blood cells. Its distinctive structure relative to its human equivalent renders it an optimal candidate for selective inhibition (Sama-ae et al., 2025). The enzymes PfDHODH (Dihydroorotate Dehydrogenase) and PfENR (Enoyl-ACP Reductase) are crucial therapeutic targets as they regulate the production of essential cellular components necessary for the parasite's rapid proliferation. PfDHODH is a pivotal, rate-limiting enzyme in the pyrimidine synthesis pathway of the parasite, which is crucial for *P. falciparum* due to its absence of a pyrimidine salvage pathway, unlike humans. PfENR serves as the rate-limiting enzyme in the apicoplast's fatty acid biosynthesis pathway (FAS) and is structurally distinct from its human counterpart, rendering both PfDHODH (e.g., DSM265 in clinical trials) and PfENR optimal targets for the development of species-selective pharmaceuticals that inhibit parasite proliferation without impacting the host (Gehlot & Vyas, 2023).

In addition to metabolic pathways, the parasite depends on many proteins for its survival and cellular regulation. Plasmepsins (I, II, III, and IV) are a diverse group of aspartic proteases found in the Plasmodium parasite, demonstrating remarkably diverse roles that include hemoglobin breakdown and the processing of secretory proteins vital for parasite egress and invasion (Nasamu et al., 2020). This mechanism is a quintessential target for antimalarial agents such as chloroquine. PfATP6 (Calcium-dependent ATPase 6) is a sarco/endoplasmic reticulum Ca^{2+}-ATPase that plays a role in the regulation of calcium homeostasis. The parasite depends on the chaperone PfHsp90 (Heat Shock Protein 90) to properly fold and stabilize critical client proteins, including those associated with stress response and drug resistance processes, but its role as the primary target of artemisinins remains contentious. Inhibiting PfHsp90, which new studies indicate disrupts the 26S proteasome and exhibits anti-Plasmodium effects at various stages, undermines the parasite's resistance, rendering it a prime target for combination therapy to re-sensitize it to established medications such as chloroquine (Mansfield et al., 2024).

Inhibition of the enzyme PfCDPK4 (Calcium-Dependent Protein Kinase 4) is a critical transmission-blocking approach, as this kinase is required for male gamete exflagellation, the process by which the parasite must differentiate for transmission to the mosquito vector. By inhibiting and deactivating this enzyme, novel pharmaceuticals can entirely disrupt the parasite's life cycle, thereby averting the transmission of the disease from an infected individual (Oduselu et al., 2024a). The essence of novel malaria drug development focus on inhibiting PfPrx1 (1-cysteine peroxiredoxin), an essential enzyme that supports the parasite's robust antioxidant defense. By inactivating this protein, drugs hinder the survival of *Plasmodium falciparum* against the reactive oxygen species generated within the host's red blood cells. This technique undermines the parasite's essential redox equilibrium, rendering it highly vulnerable to oxidative stress and presenting a viable method for the development of innovative antimalarial medicines (Orozco et al., 2023a).

The parasite's dependence on salvage and synthesis pathways presents numerous possibilities for innovative pharmaceuticals. PfHAD1 (Haloacid Dehalogenase 1) is a sugar phosphatase that modulates a vital metabolic pathway for isoprenoid biosynthesis. Its role in the resistance to the antimalarial agent fosmidomycin has underscored its significance and potential as a therapeutic target (Park, Guggisberg, John, et al., 2015). The malaria parasite, being a purine auxotroph, cannot synthesize purines and must acquire them from the host. Thus, it utilizes the purine salvage route, wherein Purine Nucleoside Phosphorylase (PfPNP) serves as a crucial

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enzyme. The significance of PfPNP is heightened by its unique dual role, which encompasses supplying purines for DNA/RNA synthesis and recycling a byproduct of the polyamine synthesis pathway, including Spermidine Synthase (PfSpdS). Thus, blocking PfPNP is a principal objective in pharmacological research, since it concurrently deprives the parasite of purines and interrupts its vital polyamine metabolism, ultimately impairing the cell's ability to grow and divide (Holanda et al., 2020).

Hylocereus polyrhizus, usually referred to as dragon fruit, is a vine cactus from the Cactoideae subfamily of cacti (Safira et al., 2021). The genus of this species originates from Central and South America and has been a significant crop in Southeast Asia especially Indonesia in the sixteenth century. Numerous bioactive phytochemicals in pitaya, including betalains, polyphenolic compounds, and polysaccharides, have demonstrated health benefits such as scavenging reactive oxygen species, protecting low-density lipoprotein from oxidation, preventing DNA damage, and inducing antioxidative and anti-inflammatory activities (Luu et al., 2021; Yu et al., 2023). Furthermore, crude methanol, n-hexane, dichloromethane, and ethyl acetate extracts of *H. polyrhizus* peels show various antiplasmodial activities against chloroquine-sensitive 3D7 and chloroquine-resistant W2 strains of *P. falciparum* (Hendra et al., 2021). However, there were no reports about targeting various specific *P. falciparum* proteins using betalains from *H. polyrhizus*. Therefore, this research will focus on betalains, including betacyanin, betanine, phyllocactin, 17-decarboxy-betanin, gomphrenin, and hylocerenin.

In silico techniques were used in this research to screen the most promising betalain compounds in *H. polyhizus*. Furthermore, this method also reduces the amount of time needed to test individual compounds against many proteins correlated with *P. falciparum*, reducing the cost and time needed to find a potential compound.

Methods

Molecular docking technique was mainly used in this in silico investigation using 64 GB of random-access memory (RAM), a single Intel Core i7-13900K processor, an NVIDIA RTX 3090 graphics processing unit (GPU). All ligands with 3D .sdf format were retrieved from https://pubchem.ncbi.nlm.nih.gov/ and optimized further using Avogadro 1.2.0 with MMFF94s and cojugate gradients algorithm (Rajendran et al., 2023). The optimized structures were converted to .pdb format with the same program.

The crystal structure of PfLDH (1UO4), PfDHFR-TS (1J3K), PfENR (3AM3), Plasmepsin II (1M43), PfATP6 (ma-cies5), PfDHODH (7WYF), PfCDPK4 (4RGJ), PfHsp90 (3IED), PfHAD1 (4ZEV), PfPrx1 (2C0D), PfSpdS (4CWA), and PfPNP (1NW4) were sourced from the Protein Data Bank (https://www.rcsb.org). The receptor was prepped for docking by eliminating non-protein molecules and its native ligand utilizing Discovery Studio Visualizer 2025.

The protein and ligand were optimized further using Pyrx 0.8. Blind docking method was employed in this research by maximizing the grid box size of Autodock Vina embedded in Pyrx system (Dallakyan & Olson, 2015). All proteins and ligands were docked using Autodock Vina with exhaustiveness level of 16. Both 2D and 3D visualization were generated using Pymol 2.6 and Discovery Studio Visualizer 2025.

The ADMET properties of ligands were obtained from http://www.swissadme.ch/ server by inserting their SMILES identifiers. Those identifiers were also subjected to https://tox.charite.de/protox3/ to investigate their toxicities (Setlur, 2023).

Results

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The molecular docking results in **Table 1** indicated that the betalaine compounds from *H. polyrhizus* peels exhibited different levels of binding affinity to the twelve individual *P. falciparum* proteins evaluated. Binding affinity quantified the strength of interaction between a ligand and a protein target. A lower binding affinity value indicated a stronger binding relationship (Du et al., 2016). Phyllocactin exhibited the lowest binding affinity to PfPNP at -10.7 kcal/mol, indicating its potential as a powerful inhibitor of this enzyme. This is significant because PfPNP is an essential enzyme in the parasite's purine salvage pathway, which it depends on for growth and division, as it is incapable of synthesizing purines independently.

Notably, Hylocerenin exhibited the lowest binding affinity to PfDHFR-TS at -9.4 kcal/mol. This enzyme is a recognized target for antifolate medications such as pyrimethamine; nevertheless, resistance has emerged as a result of genetic changes. The robust affinity of Hylocerenin indicated its potential as a candidate for a novel therapeutic agent to address this resistance. Conversely, several betalaine compounds exhibited comparatively lower binding affinities to specific proteins, shown as Gomphrenin's affinity of -7.2 kcal/mol for PfDHODH and Hylocerenin's affinity of -7.1 kcal/mol for PfATP6. These findings underscore the varied inhibitory efficacy of distinct betalaine molecules against many parasite targets, with certain compounds demonstrating greater potential than others.

Table 1. Binding affinity values of betalains against specific proteins of *P. falciparum*.

Ligands	Binding Affinity (kcal/mol)											
	PfLDH	PfDHFR-TS	PfENR	Plasmepsin II	PfATP6	PfDHODH	PfCDPK4	PfHsp90	PfHAD1	PfPrx1	PfSpdS	PfPNP
Betacyanin	-8.4	-8.8	-8.1	-8.9	-8.2	-8.1	-8.2	-8.0	-9.7	-8.2	-7.8	-8.6
Betanine	-8.5	-9.0	-8.2	-8.1	-8.4	-8.0	-8.7	-7.5	-8.2	-8.7	-7.9	-8.7
Phyllocactin	-8.4	-9.1	-7.6	-8.5	-8.0	-7.8	-8.9	-8.1	-9.4	-7.7	-8.0	-10.7
17-decarboxy-betanin	-8.3	-8.8	-8.0	-9.2	-8.7	-8.4	-8.1	-7.7	-8.2	-7.7	-7.5	-8.6
Gomphrenin	-7.5	-8.5	-7.9	-8.8	-8.2	-7.2	-8.3	-7.2	-9.0	-8.8	-7.8	-8.5
Hylocerenin	-8.1	-9.4	-8.2	-9.0	-7.1	-7.8	-8.2	-7.6	-9.0	-7.7	-8.6	-8.9

Hylocerenin and Phyllocactin are two potential inhibitors of PfDHFR-TS due to their low binding affinity values, revealing unique yet intersecting patterns of amino acid interactions with their corresponding protein targets. Hylocerenin exhibited a significant binding affinity of -9.4 kcal/mol to PfDHFR-TS, interacting with many amino acids such as Val20, Ser22, Lys27, Lys28, Val31, Thr36, Arg38, Thr190, Tyr596, and His598 (**Table 2**). An intriguing observation was the common interaction with Lys27 and Lys28 among various betalaine compounds such as Betanin and 17-decarboxy-betanin, while Hylocerenin's supplementary interactions enhance its binding efficacy. This indicates that the lysine residues are essential anchor sites for the betalaine scaffold within the PfDHFR-TS binding pocket. The varied amino acids interacted with by Hylocerenin demonstrated the intricacy of its binding, especially eight hydrogen bond interaction formed in the complex strengthen their interaction (Rasyid et al., 2019).

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Table 2. Amino acid interactions of betalains against six specific proteins of *P. falciparum*.

Ligands	Amino acid Interactions					
	PfLDH	**PfDHFR-TS**	**PfENR**	**Plasmepsin II**	**PfATP6**	**PfDHODH**
Betacyanin	His195, Asn197, Thr232, Ala236, Pro246	Glu21, Ser22, Lys27, Lys28, Lys373, Leu376	Arg293, Thr410, Gln409, Asn418	Asp34, Ser79, Ala117, Asp214, Phe241	Lys6, His9, Ser182, Glu206, Lys211, Asn231, Glu237	Ser202, Asp204, Ser205, Asn547, His548
Betanine	Ile31, Asp53, Gly99, Asn140, Arg171, His195, Ser245	Val20, Lys27, Lys28, Glu30, Leu374, Leu376, Ile593, His598	Glu97, Asp98, Lys257, Gln259, Ser396, Leu399, Arg401, Glu402, Glu402	Asn13, Lys163, Glu271, Tyr272, His276, Pro304, Arg307	Thr80, Glu96, Ile291, His292, Tyr297, Ser1121, Phe1181	Asp216, Phe217, Ile218, Leu238, Gly241, Ser304, Lys559
Phyllocactin	Gly29, Ile31, Asp53, Thr101, Lys102, Val138, Arg171, His195, Ser245	Arg345, Glu382, Arg402, Ile403, Cys490, Asp513, Asn521, His551, Arg470	Gln271, Glu289, Arg293, Thr410, Tyr412, Asn418, Thr410, Tyr412	Gly36, Tyr192, Gly216, Thr217, Lys238, Ile290, Ser79	Asn59, Val66, Leu104, Asn107, Ala108, Gln114	Ser205, Asn547, His548, Tyr555, Tyr556
17-decarboxy-betanin	Ile31, Gly99, Arg171, His195	Lys19, Ser22, Lys27, Glu30, Thr36, Arg38, Thr190	Glu289, Gln409, Asn418, His268, Arg293, Gln409, Thr410, Tyr412, Asn418	Ser79, Gly216, Thr221, Pro243, Gln275, Asn288, Ile289, Pro240	Asn283, His286, Asp289, Tyr302, Gly994, Cys1110	Ser202, Asp204, Val540, Arg544, Tyr555
Gomphrenin	Ile31, Asp53, Gly99, Thr101, Arg109	Lys19, Lys27, Leu374, Ile593, Asn595, Tyr596	Asp98, Arg122, Ser400, Glu402, Arg122	Asp34, Val78, Ser79, Asp214, Gly216, Ala219	Ser76, Thr80, Phe94, Glu96, His292, Lys304, Gln1003, Ile1180	Asn211, Ile500, Ser523, Asn557, Lys559, Ile562
Hylocerenin	Gly29, Asp53, Thr97, Phe100, Asn140, Arg171, His195, Ser245, Pro246	Val20, Ser22, Lys27, Lys28, Val31, Thr36, Arg38, Thr190,	His268, Arg293, Val294, Gln409, Thr410, Tyr412, Asn418, Arg293,	Gly36, Tyr192, Gly216, Thr217, Lys238, Ile290, Ser79	Lys51, Glu115, Leu122, Thr323, Val340, Arg341, Leu343	Thr201, Asp204, Asp216, Phe217, Asn219, Lys305, His306, Lys543, Lys559

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		Tyr596, His598	Gly408, Ile419			

Phyllocactin's strong binding affinity for PfPNP, calculated at -10.7 kcal/mol, is due to its interactions with a distinct array of amino acids. **Table 3** indicated that Phyllocactin interacts with Asp24, Arg27, Arg88, Ser91, Met159, Tyr160, Met183, Asp206, Trp212, and Asn219 in PfPNP. Like Hylocerenin, the strong binding of Phyllocactin is probably due to these many hydrogen bond interactions that form a highly stable complex. The amino acid interactions of Phyllocactin with PfDHFR-TS, including Arg345, Glu382, and Arg402, differ from those of Hylocerenin, underscoring the notion that each ligand possesses a distinct binding mechanism despite targeting the same protein.

Table 3. Amino acid interactions of betalains against the last six specific proteins of *P. falciparum*.

Ligands	**Amino acid Interactions**					
	PfCDPK4	**PfHsp90**	**PfHAD1**	**PfPrx1**	**PfSpdS**	**PfPNP**
Betacyanin	Ser51, Glu377, Tyr405, Glu427, Lys456, Arg463	Asn133, Asp136, Gly206, Glu211, Asn215, Gly223, Gly245	Leu28, Asp29, Tyr148, Lys171, Thr201, Glu207, Lys215, Glu240, Asn241	Asn159, Asn166, Gln168, Glu169, Arg172, Thr173, Ser176	Gln72, Gly125, Ser197, Gln229	Val129, Asp131, Phe132, Asp133, Met189, Thr199
Betanine	Ser51, Lys52, Leu53, Pro55, Glu377, Glu414, Asp420, Lys456, Arg463	Asn133, Asp136, Lys140, Gly206, Glu211, Asn215, Gly245	Asn37, Gly62, Asn90, Glu207, Asp238, Asn273	Asn159, Asn166, Gln168, Glu169, Arg172, Glu169, Arg172, Thr173, Ser176	Gln72, Asp89, Val91, Gln93, Gly126, Asp127, Glu147, Asp196, Ser197	Arg116, Arg169, Arg116, Leu120, Gly124
Phyllocactin	Ser51, Lys52, Glu83, Ser102, Thr373	Glu129, Asn133, Ser222, Gly245	Leu28, Asp29, Gly62, Tyr148, Glu152, Lys171, Thr201, Asp238, Glu240, Ser259	Asn159, Gly164, Asn166, Glu169, Ser176	Leu88, Gln93, Glu147, Ser180, Ser197, Gln229, Tyr264	Asp24, Arg27, Arg88, Ser91, Met159, Tyr160, Met183, Asp206, Trp212, Asn219, Arg45
17-decarboxy-betanin	Ser51, Lys52, Glu377, Lys456	Asn133, Asp202, Gln221, Gly245, Gly247, Thr299	Leu28, Asp29, Asn37, Thr61, Gly62, Phe202, Lys215, Asp238, Asn241	Asn166, Gln168, Arg172, Gly164	Lys70, Glu150, Glu150, Lys157, Glu168, Val172, Asn173, Val174	Gly152, Asn177, Val129, Asp131, Thr193, Lys198, Thr199

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Gomphrenin	Val44, Ser51, Lys52	Asn133, Ala137, Lys140, Asp202, Asn215, Gln221, Ser222	Asp29, Leu33, Ser35, Asn37, Asp238, Asn241, Ser259, Asn273	Gly164, Arg165, Glu169, Glu169, Arg172, His179, Pro188, Ile189	Lys157, Glu168, Asp169, Lys170, Val172, Tyr65, Thr67, Ser69, Lys70, Asp149, Thr151, Glu154	Asn109, Tyr135, Gly130, Asp131, Asp133, Thr193, Val197
Hylocerenin	Gly82, Glu83, Ser102, His105, Leu408, Leu409, Asp420	Ser132, Asn133, Ser135, Asp139, Lys140, Glu211, Asn215	Asn34, Asn37, Gly62, Arg63, Lys171, Asp238, Gly239	Asn159, Asn166, Gln168, Glu169, Asn166, Glu169, Thr173, Ser176	Glu150, Glu154, Lys157, Lys161, Val172, Val174, Tyr65, Glu154, Lys157	Arg169, Arg116, Arg116, His123, Arg169, Arg116, His119, His123, Arg169

Table 4 elucidates the ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) and toxicity characteristics of the betalaine compounds, providing substantial insights into their viability as therapeutic candidates. All six betalaines had minimal gastrointestinal absorption and were impermeable to the blood-brain barrier. This indicates that they are not readily assimilated into the bloodstream from the digestive system and are improbable to penetrate the central nervous system, potentially advantageous for reducing neurological adverse effects. Furthermore, none of the substances are anticipated to inhibit prevalent cytochrome P450 enzymes (CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4), which is advantageous as it diminishes the likelihood of harmful drug-drug interactions when provided concurrently with other medications. All chemicals have low skin permeability, meaning they are not easily absorbed or penetrate slowly through the skin's layer. Therefore, those compounds were not suitable for topical application (Souto et al., 2022).

The chemicals exhibit a varied yet predominantly favorable toxicological profile. None of the betalaines are anticipated to exhibit hepatotoxicity, carcinogenicity, mutagenicity, or cytotoxicity. Nonetheless, there are significant disparities in their anticipated immunotoxicity. Betanine is the sole compound anticipated to be non-immunotoxic, while Betacyanin, Phyllocactin, 17-decarboxy-betanin, and Gomphrenin are all expected to have immunotoxic effects. Hylocerenin is anticipated to be non-immunotoxic. A significant discovery is that Hylocerenin is the sole chemical anticipated to be a P-glycoprotein (P-gp) substrate, potentially influencing its bioavailability and cellular efflux. From their molecular weight (MW), all compounds have a hard time to be absorbed and distributed across biological membranes due to their high MW. The betalaine compounds are classified as soluble or highly soluble. The elevated solubility guarantees that, despite their high molecular weight, the chemicals can easily dissolve in the gastrointestinal tract. The capacity to dissolve is the essential initial step that facilitates passive diffusion or facilitated transport, optimizing the potential concentration accessible for absorption (Dahan et al., 2016).

Table 4. ADMET properties of studied betalains.

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Parameter	Compounds					
	Betacyanin	Betanine	Phyllocactin	17-decarboxy-betanin	Gomphrenin	Hylocerenin
Formula	$C_{24}H_{26}N_2O_{13}$	$C_{24}H_{26}N_2O_{13}$	$C_{27}H_{29}N_2O_{16}^+$	$C_{23}H_{27}N_2O_{11}^+$	$C_{24}H_{26}N_2O_{13}$	$C_{30}H_{34}N_2O_{17}$
Molecular weight (g/mol)	550.47	550.47	637.52	507.47	550.47	694.59
Num. H-bond acceptors	13	14	16	11	13	18
Num. H-bond donors	8	8	9	8	8	9
TPSA (Å^2)	249.38	247.11	289.92	209.25	249.38	310.71
WLOGP	-4.46	-2.55	-3.10	-2.58	-4.46	-2.39
Water Solubility	Very soluble	Soluble	Soluble	Soluble	Very soluble	Very soluble
Bioavailability	0.11	0.11	0.11	0.11	0.11	0.11
Pharmacokinetics						
GI absorption	Low	Low	Low	Low	Low	Low
BBB permeant	No	No	No	No	No	No
P-gp substrate	No	No	No	No	No	Yes
CYP1A2 inhibitor	No	No	No	No	No	No
CYP2C19 inhibitor	No	No	No	No	No	No
CYP2C9 inhibitor	No	No	No	No	No	No
CYP2D6 inhibitor	No	No	No	No	No	No
CYP3A4 inhibitor	No	No	No	No	No	No
Log K_p (skin permeation)	-10.73 cm/s	-10.55 cm/s	-11.46 cm/s	-11.46 cm/s	-10.73 cm/s	-12.12 cm/s
Toxicities						
Hepatotoxicity	-	-	-	-	-	-
Carcinogenicity	-	-	-	-	-	-

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Immunotoxicity	+	-	+	+	+	-
Mutagenicity	-	-	-	-	-	-
Cytotoxicity	-	-	-	-	-	-

Discussion

Three essential amino acids involved in the biochemical conversion of pyruvate to lactate in PfLDH are Asp168, Arg171, and His195 (Chen et al., 2024). **Table 2** illustrates that all ligands, with the exception of betacyanin, directly bind with the essential catalytic residues of PfLDH, indicating their ability to limit the activity of this enzyme (**Figure 1A**). The amino acids in the DHFR domain of PfDHFR-TS that are essential for inhibition and confer drug resistance upon mutation include Ala16, Asp54, Phe58, Arg59, Ser108, and Arg122 (Seetin et al., 2023). Although all compounds in this investigation exhibit strong binding affinities, they lack selectivity for interaction with particular amino acids. Consequently, those compounds require additional investigation through in vitro study to validate their efficacy in suppressing PfDHFR-TS. Inhibitors of PfENR usually bind to the protein's active site, especially on Ala217 and Asp218 (A R Oliveira et al., 2024). All ligands in this study do not interact directly with those two crucial amino acids that are inhibited by other inhibitors. However, the low binding affinity values of betalains from this study offer a different inhibition mechanism that shows a high potential to inhibit PfENR.

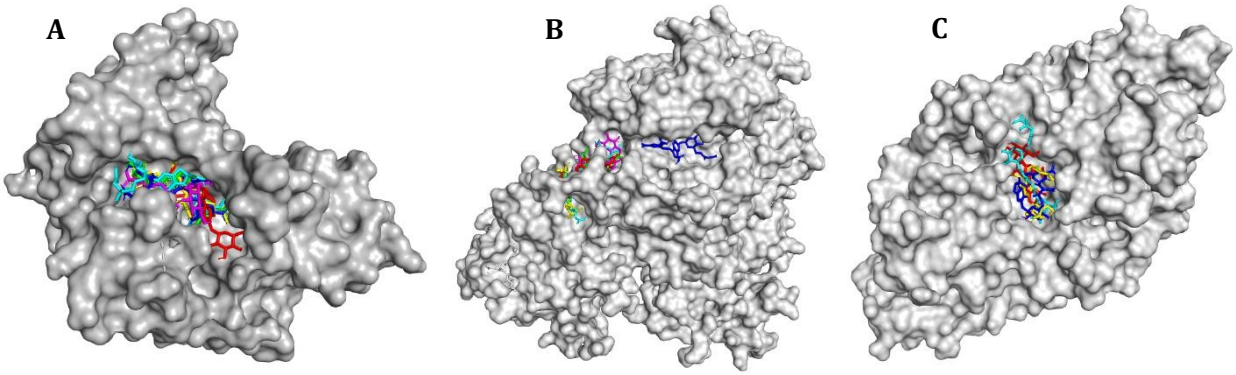

Figure 1. The 3D visualization of betacyanin (red), betanine (green), phyllocactin (blue), 17-decarboxy-betanin (yellow), gomphrenin (magenta), and hylocerenin (cyan) against PfLDH (A), PfDHFR-TS (B), and PfENR (C).

Plasmepsin II, like other aspartic proteases, has a catalytic active site containing important residues, including Asp34 and Asp214. Inhibitors like pepstatin A and peptidomimetic compounds are designed to interact with this catalytic dyad, disrupting the catalytic mechanism (Syed et al., 2025). Betacyanin (-8.9 kcal/mol) and gomphrenin (-8.8 kcal/mol) are potent inhibitors because they interact with those amino acids (**Figure 2A**). For PfATP6, key amino acids involved in this protein are Leu263, Ala217, and Ser769. Leu263 mutation is the most studied amino acid due to its drug resistance (N. et al., 2016). Looking at **Table 2**, there are no ligands interact with this specific amino acid. Clinical drug named DSM265 inhibits PfDHODH by interacting with His185, Phe188, Arg265, and Cys276 (Alzain et al., 2022). Betalains from *H.*

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polyrhizus that shows the best binding affinity is 17-decarboxy-betanin (-8.4 kcal/mol). However, this ligand does not inhibit the same active site as suggested by study about DSM265.

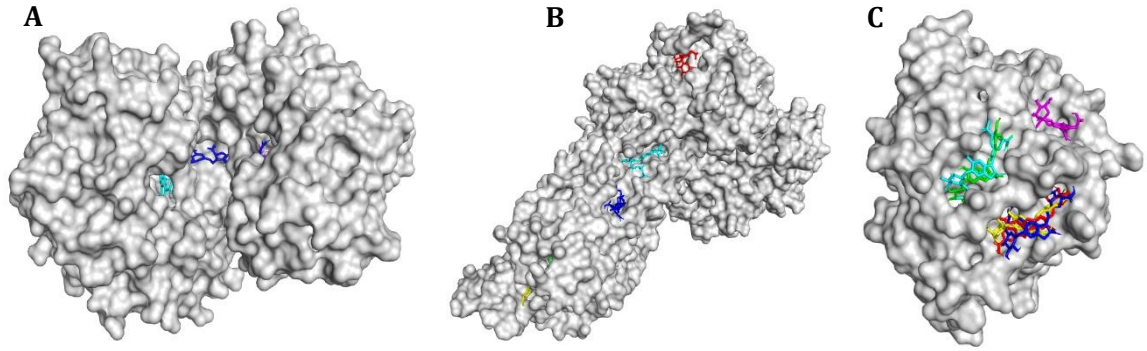

Figure 2. The 3D visualization of betacyanin (red), betanine (green), phyllocactin (blue), 17-decarboxy-betanin (yellow), gomphrenin (magenta), and hylocerenin (cyan) against Plasmepsin II (A), PfATP6 (B), and PfDHODH (C).

PfCDPK4 is a protein kinase with an ATP-binding cleft suitable for targeted inhibition. A small serine gatekeeper residue at position 147 (Ser147) within this pocket is strategically utilized by a category of geometrically altered drugs called bumping kinase inhibitors (BKIs), providing significant parasite-specific selectivity (Oduselu et al., 2024b). From amino acid interactions, there are no ligands having interaction with Ser147 because betalains have high molecular weight. PfHsp90 inhibitors largely target the ATP-binding pocket within its N-terminal domain, mainly near Asn37, Gly100, Thr101, Phe104, and Tyr125 (Ojo et al., 2014). All compounds inhibit the N-terminal domain (**Figure 3B**). The function of PfHAD1 is dependent on a specific amino acid (Asp27) that acts as a nucleophile in its catalytic mechanism (Park, Guggisberg, Odom, et al., 2015). Even though all ligands inhibit the catalytic site, none of them interact with Asp27 (**Figure 3C**).

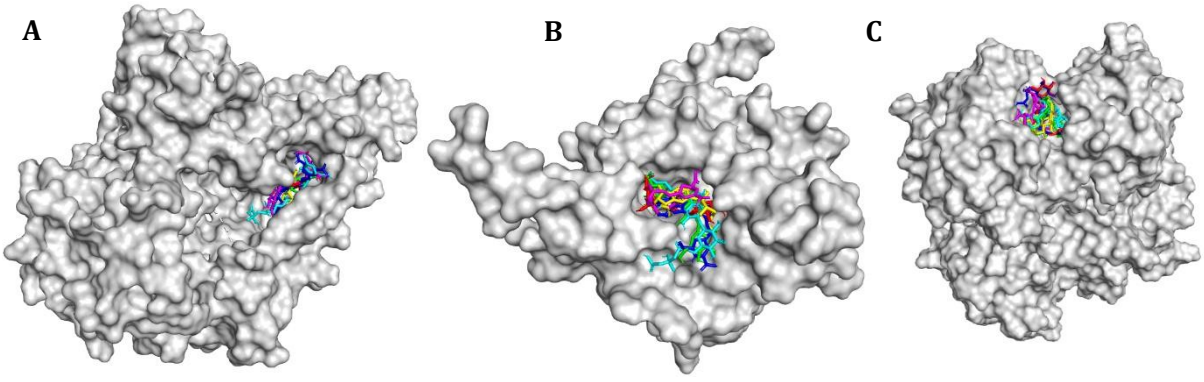

Figure 3. The 3D visualization of betacyanin (red), betanine (green), phyllocactin (blue), 17-decarboxy-betanin (yellow), gomphrenin (magenta), and hylocerenin (cyan) against PfCDPK4 (A), PfHsp90 (B), and PfHAD1 (C).

Betanine (-8.7 kcal/mol) and Gomphrenin (-8.8 kcal/mol) show promise as PfPrx1 inhibitors due to their potent binding affinity values. The structures of those ligands show

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similarity with UV802, which shows highly potent antimalarial activity (Orozco et al., 2023b). Putrescine binding site is an important active pocket of PfSpdS. Specific amino acids implicated in binding the putrescine substrate are Tyr102, Asp196, and Ser197 (Sprenger et al., 2015). Betacyanin, betanine, and phyllocactin inhibits the same active site because all of them interact with Ser197 as an key amino acid of PfSpdS. Lastly, specific mutation at Met183 and Tyr160 interfere with both catalysis and the binding of inhibitor DADMe-ImmG. Betalain from this study that shows similar inhibition mechanism is Phyllocactin.

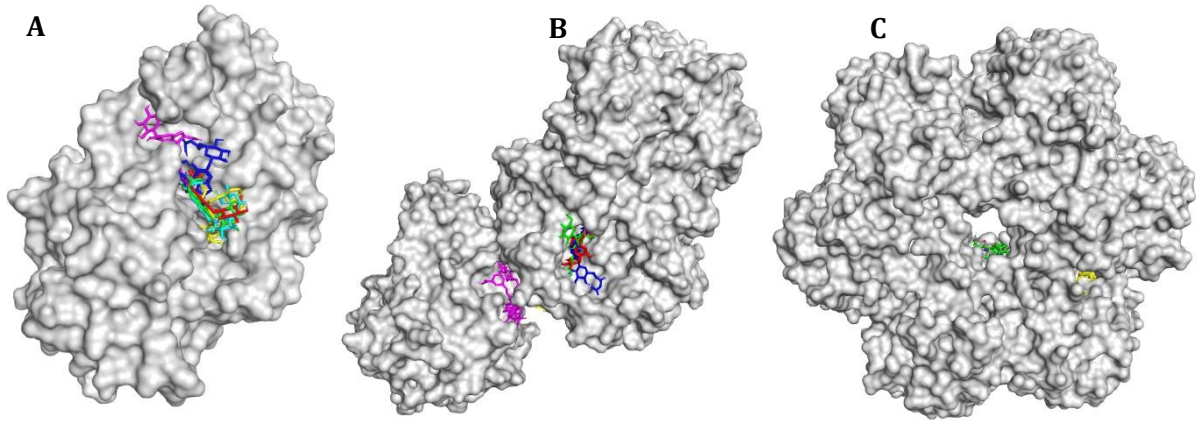

Figure 4. The 3D visualization of betacyanin (red), betanine (green), phyllocactin (blue), 17-decarboxy-betanin (yellow), gomphrenin (magenta), and hylocerenin (cyan) against PfPrx1 (A), PfSpdS (B), and PfPNP (C).

According to the aggregated data from binding affinities, particular amino acid interactions, and ADMET characteristics, Hylocerenin and Phyllocactin are identified as the most promising candidates among the examined betalaine compounds. This is due to their robust inhibitory capacity coupled with a comparatively advantageous safety profile. Hylocerenin is the leading choice for targeting PfDHFR-TS, owing to its significant binding affinity of -9.4 kcal/mol and its capacity to engage with essential amino acid residues such as Lys27 and Lys28. The lysine residues serve as shared contact sites with other betalaine compounds, indicating they establish a common "anchor" for this class of molecules. From a safety standpoint, Hylocerenin exhibits a positive ADMET profile, characterized by low gastrointestinal absorption, absence of blood-brain barrier permeability, and a non-toxic profile for hepatotoxicity, carcinogenicity, mutagenicity, and cytotoxicity. It is anticipated to be non-immunotoxic, presenting a considerable benefit over substances such as Betacyanin and Phyllocactin. The one potential issue is that Hylocerenin is a substrate of P-glycoprotein (P-gp), which may influence its overall bioavailability, a consideration that must be examined in subsequent research.

In contrast, Phyllocactin emerges as the most promising option for suppressing PfPNP, with the highest binding affinity among all molecules at -10.7 kcal/mol. The robust binding is ascribed to interactions with essential amino acids in the PfPNP active site, such as Asp24, Arg27, Arg88, Ser91, Met159, and Tyr160, among others. The connection between Met183 and Tyr160 is crucial, as mutations at these loci are known to disrupt the binding of inhibitors such as DADMe-ImmG, indicating that Phyllocactin may be effective against drug-resistant strains. Although Phyllocactin's ADMET profile is predominantly advantageous, exhibiting minimal gastrointestinal absorption and non-toxic characteristics akin to other betalaines, its anticipated

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immunotoxicity need additional scrutiny. Its remarkable binding affinity and interactions with a recognized resistance-associated region render it an optimal option for PfPNP inhibition.

According to the molecular docking and ADMET investigation, hylocerenin and phyllocactin were identified as the most promising antiplasmodial possibilities, with each targeting a distinct protein. Hylocerenin is the premier inhibitor of PfDHFR-TS, demonstrating a notable binding affinity of -9.4 kcal/mol and engaging with critical residues like Lys27 and Lys28. The ADMET profile is exceptionally advantageous, marked by minimal gastrointestinal absorption, absence of blood-brain barrier permeability, and crucially, the expectation of non-immunotoxicity, which distinguishes it from other substances such as phyllocactin. In contrast, phyllocactin is the most promising inhibitor of PfPNP with the lowest binding affinity of -10.7 kcal/mol among all tested compounds. The robust binding is ascribed to interactions with essential PfPNP active site residues, specifically Asp24, Arg27, Met159, and Tyr160, with the latter two being pivotal, as mutations in these residues are recognized to impart drug resistance. Phyllocactin's advantageous ADMET characteristics (poor gastrointestinal absorption, impermeability to the blood-brain barrier) are partially mitigated by its expected immunotoxicity.

Although all compounds not adhere to Lipinski's guidelines for oral medicines, the strong binding affinity of hylocerenin and phyllocactin for specific targets warrants additional investigation. One approach involves utilizing a nanoemulsion technology to enhance their solubilities and dissolution rates. Moreover, nanoemulsion provides additional absorption paths for these drugs and safeguards them from degradation once reaching their targets (Preeti et al., 2023).

Conclusion

The molecular docking analysis indicated that betalaine compounds derived from Hylocereus polyrhizus peels possess significant promise as antiplasmodial drugs. Specifically, Hylocerenin displayed the highest binding affinity for PfDHFR-TS, a crucial enzyme in DNA synthesis, which is a known target for antimalarial medicines. Phyllocactin had the highest binding affinity for PfPNP, a crucial enzyme in the purine salvage cycle of the parasite. The research indicated that the binding of these betalaine molecules entails unique amino acid interactions, implying their potential efficacy against drug-resistant bacteria. The ADMET analysis revealed that Hylocerenin possesses a favorable safety profile, positioning it as a promising candidate for further research and development as a possible antimalarial medication.

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