Open-Access Journal

Research Article

Volume 1, Issue 1, Year 2026 https://doi.org/10.5281/zenodo.21506225

Identification of novel GPX4 inhibitors from bioactive compounds of *Tinospora cordifolia*: An in-silico study

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Received: 06.07.2026 | Accepted: 20.07.2026 | Published: 24.07.2026

Abstract

In recent years, ferroptosis, a new form of regulated cell death mechanism, has attracted significant attention in cancer therapy. This pathway is negatively regulated by an enzyme glutathione peroxidase 4 (GPX4). Thus, targeting this enzyme offers an innovative approach for cancers which are resistant to conventional treatment. This study aims to identify selected alkaloid compounds of *Tinospora cordifolia* with excellent ADMET characteristics to find possible GPX4 inhibitors. The alkaloids of *T. cordifolia* were compiled from PubChem database and screened for drug likeliness and ADMET properties. ADMET analysis and Lipinski's rule of five showed that most of the compounds generally possess favorable pharmacokinetic properties. The CB Dock2 tool was used to evaluate the binding affinities of alkaloids with target protein GPX4. The binding free energies for berberine, palmatine, magnoflorine, jatrorrhizine, and tetrahydropalmatine were -7.0, -6.8, -7.1, -6.7, and -6.4 kcal/mol, respectively. Among the selected alkaloids of *T. cordifolia*, magnoflorine is the most effective GPX4 inhibitor with a binding affinity of -7.1 kcal/mol. These findings suggest that magnoflorine can be considered as a potential anticancer agent by targeting emerging targets like GPX4 but require further in-vitro and in-vivo experimental validation.

Keywords

Tinospora cordifolia; Ferroptosis; Glutathione peroxidase 4; Natural compounds; Anticancer agents

1. Introduction

Ferroptosis is a cell death regulation process that depends on iron levels and plays an important role in a variety of life-threatening diseases, including cancer [1]. Distinct from apoptosis and necrosis, ferroptosis is defined by the generation of lipid hydroperoxides (LOOHs) resulting from oxidative stress and the disruption of cellular antioxidant defense systems [2]. The complex molecular mechanisms of ferroptosis have attracted considerable academic attention due to their potential as therapeutic targets for innovative cancer therapies to address medication resistance [3]. Ferroptosis arises from cellular damage and dysfunction due to the breakdown of iron homeostasis and lipid peroxidation. Accumulated iron triggers the Fenton reaction, which in turn generates reactive oxygen species (ROS) and starts lipid peroxidation [4]. This process primarily impacts cellular membrane polyunsaturated fatty acids (PUFAs), which disrupts membrane integrity and thereafter leads to cell death. Moreover, the depletion of the cellular antioxidant glutathione (GSH) amplifies vulnerability to lipid peroxidation [5].

Targeting ferroptosis in several malignancies, including non-small cell lung cancer, ovarian cancer, breast cancer, and colorectal cancer, has been associated with the reduction of cancer cell proliferation [6], [7], [8], [9]. There is increasing evidence that the stimulation of ferroptosis is effective in addressing chemoresistance, targeting hypoxic tumor microenvironments, and enhancing the efficacy of immunotherapy [10], [11]. New covalent inhibitors of glutathione peroxidase 4 (GPX4) have demonstrated significant effectiveness in inhibiting cancer cell proliferation in xenograft models of triple-negative breast cancer, while exhibiting negligible damage towards normal cells [12].

Nature-Antioxidants obtained from diverse sources exhibit significant bioactivities with extensive applications in the prevention and/or treatment of disorders associated with oxidative stress. The mechanism of action of bioactive compounds is comprehensive and notably encompasses the reduction and scavenging of ROS, the prevention of lipid peroxidation, and the chelation of free metal ions. Moreover, numerous investigations have shown that various natural substances can modulate ferroptosis and may serve as potential therapeutics for ferroptosis-associated disorders [13], [14], [15].

Tinospora cordifolia (also known as Giloy or Guduchi) is a highly regarded medicinal herb in Ayurveda, Siddha, Unani, and traditional Chinese medicine. Numerous phytochemical studies have shown that *T. cordifolia* contains a variety of phytochemicals, including steroids, phenolics, glycosides, alkaloids, and carbohydrates [16]. The presence of phytochemicals supports the multiple pharmacological properties of *T. cordifolia*. Recent investigations reaffirm the anticancer efficacy of *T. cordifolia* across several carcinomas [17]. Although T. cordifolia is well recognized as a prolific source of bioactive phytochemicals with anticancer activity, a significant gap persists in understanding the molecular-level properties and interactions of its primary constituents, mainly alkaloids. Although, previous research has documented cytotoxic effects and preliminary findings, a thorough investigation focusing on novel developing cell death mechanisms, such as ferroptosis, has yet to be conducted [18]. Furthermore, a comprehensive assessment of binding interactions with ferroptosis-

associated targets, including GPX4, is yet to be conducted. This study systematically assesses the inhibitory efficacy of alkaloids phytoconstituents against the critical target GPX4 using molecular docking analyses, aiming to elucidate mechanistic insights and identify viable candidates for integrative cancer therapy.

2. Materials and Methods

2.1 Study design

This work examined the inhibitory effects of *T. cordifolia* alkaloids berberine, palmatine, magnoflorine, jatrorrhizine, and tetrahydropalmatine on a key ferroptosis molecular target. GPX4 is selected as a molecular target that is known for its role in facilitating cancer progression by inhibiting ferroptotic cell death. The present study evaluated the pharmacokinetics, binding interactions, and toxicity profiles of selected alkaloids to assess their therapeutic potential using in-silico methods such as molecular docking, Lipinski's rule of five, and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) analysis. In order to screen potential new drugs more efficiently and with less financial outlay, computational methods are being considered as an alternative to expensive experimental research. Additionally, it enables precise prediction of these compounds' medicinal potential and drug-likeness by providing atomic-level insights into chemical interactions. Figure 1 shows a schematic illustration of the impact of selected bioactive chemicals against the GPX4, a molecular target of ferroptosis.

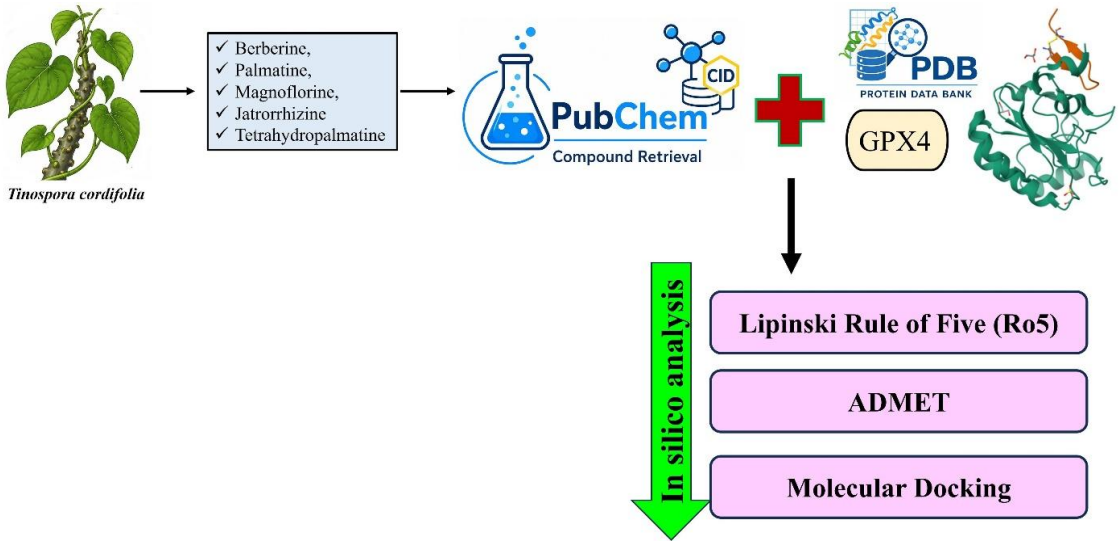

Figure 1. A schematic illustration of study design from bioactive compounds selection to in-silico analysis.

2.2 Target protein selection

Out of several important targets of ferroptosis in cancer progression, we have selected the highly studied protein GPX4 for present study. Inhibition of GPX4 resulted in ferroptosis induction through multiple mechanisms including ROS generation, lipid peroxidation and disruption of cell integrity. Thus, direct inhibition of GPX4 is one of the important methods to induce ferroptotic cell death in cancer. The three-dimensional structure of the GPX4 was obtained from Protein Data Bank (PDB) in the .pdb file format (PDB ID: 5H5Q).

2.3 Selected bioactive compounds as ligands

A total of five potent alkaloids from *T. cordifolia* were selected based on their potential anticancer activity, as evidenced by previous literature demonstrating their role in the modulation of oxidative stress mediated cell signaling pathways. The 3D structures of compounds were downloaded from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and saved in sdf files.

2.4 Drug likeliness and ADMET analysis

The ADMET properties of five alkaloids extracted from *Tinospora cordifolia* (berberine, palmatine, magnoflorine, jatrorrhizine, and tetrahydropalmatine) were assessed using the PkCSM tool (https://biosig.lab.uq.edu.au/pkcsm/) with the specific one-line canonical simplified molecular-input line-entry system (SMILES) for each phytocompound [19]. This parameter highlights the medicinal characteristics of selected compounds, which could lead to their advancement as anticancer medicines. Parameters, including the logarithm of the n-octanol/water partition coefficient (LogP), molecular weight (MW), hydrogen bond acceptors (HBAs), hydrogen bond donors (HBDs), molecular polar surface area (PSA), and the number of rotatable bonds (RotBs), were analyzed in accordance with Lipinski's rule of five and the Veber rule.

2.5 Molecular Docking

The Cavity detection-guided Blind Docking-2 (CB-Dock-2) tool (https://cadd.labshare.cn/cb-dock2/) was used to examine the interactions between the GPX4 protein and the alkaloids of *T. cordifolia*, specifically berberine, palmatine, magnoflorine, jatrorrhizine, and tetrahydropalmatine [20]. This online tool finds protein cavities automatically and figures out the centers and sizes of the top N cavities, where n=5 is the usual number of cavities. The lowest Vina score (kcal/mol) was picked for each ligand. The interactions involving the largest cavity and the ligand exhibiting the lowest Vina score are generally displayed at the top.

3. Results

3.1 Target protein and phytochemicals identification

For this study, an important target of ferroptosis pathway, GPX4, was selected and retrieved from the PDB. Additionally, five anticancer phytochemicals berberine, palmatine, magnoflorine, jatrorrhizine, and tetrahydropalmatine derived from *T. cordifolia* were identified for further investigation from PubChem (https://pubchem.ncbi.nlm.nih.gov/) (Table 1) (Figure 2).

Table 1: Target protein and phytochemicals (ligands) with their respective identification.

Target Protein	PDB ID	Alkaloids	PubChem CID
GPX4	5H5Q	Berberine	2353
		Palmatine	19009
		Magnoflorine	73337
		Jatrorrhizine	72323
		Tetrahydropalmatine	72301

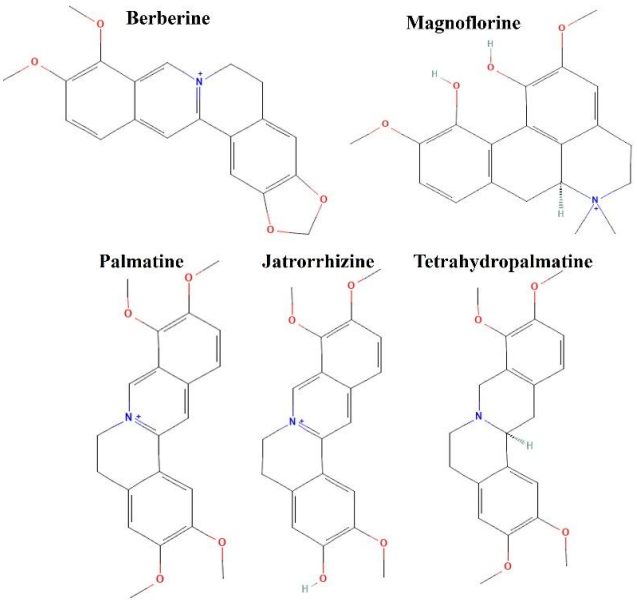

Figure 2. 2D structures of selected alkaloids of *T. cordifolia*

3.2 Drug likeliness and ADMET investigation

Using Lipinski's Rule of Five and ADME characteristics, the selected alkaloids of *Tinospora cordifolia* were examined. Initially, the PkCSM tool was used to determine whether the selected compounds comply with Lipinski's Rule of Five, a preliminary criterion for evaluating a chemical as a prospective therapeutic candidate. All identified compounds complied with Lipinski's Rule of Five without violating any condition (Table 2). Subsequently, the compounds were evaluated for their ADMET qualities using the PkCSM program to elucidate their pharmacokinetic characteristics. Comprehensive ADMET characteristics data for the compounds is provided in Tables 3-7. The investigation revealed that the chosen alkaloids fulfilled the criteria and had promising drug-like characteristics.

Table 2. Lipinski's Rule of Five analysis of selected alkaloids.

S. No.	Ligand	Molecular Weight (≤500Da)	cLogP (≤5)	H-Bond Donor (≤5)	H-Bond Acceptor (≤10)	Rotatable Bonds (≤10)
1.	Berberine	Yes	Yes	Yes	Yes	Yes
2.	Palmatine	Yes	Yes	Yes	Yes	Yes
3.	Magnoflorine	Yes	Yes	Yes	Yes	Yes
4.	Jatrorrhizine	Yes	Yes	Yes	Yes	Yes
5.	Tetrahydropalmatine	Yes	Yes	Yes	Yes	Yes

Table 3. Absorption properties of selected alkaloids.

S. No.	Alkaloids	Water Solubility (Log mol/L)	Caco2 Permeability (log Papp in 10-6 cm/s)	Intestinal Absorption (Human) (% Absorbed)	Skin Permeability (log Kp)	P-Glucoprotein Substrate	P-Glucoprotein-I Inhibitor	P-Glucoprotein-II Inhibitor
1.	Berberine	-3.973	1.734	97.147	-2.576	Yes	No	Yes
2.	Palmatine	-4.194	0.863	97.084	-2.554	Yes	Yes	Yes
3.	Magnoflorine	-3.924	1.575	96.107	-2.758	Yes	No	Yes
4.	Jatrorrhizine	-3.871	1.234	94.465	-2.741	Yes	No	Yes
5.	Tetrahydropalmatine	-3.049	0.679	93.104	-2.84	Yes	Yes	Yes

Table 4. Distribution properties of selected alkaloids.

S. No.	Ligand	VDss (Human) (log L/kg)	Fraction Unbound (Human) (log L/kg)	BBB Permeability (log BB)	CNS Permeability (logPS)
1.	Berberine	**0.58**	**0.262**	**0.198**	**-1.543**
2.	Palmatine	**0.641**	**0.245**	**-0.112**	**-1.535**
3.	Magnoflorine	**1.211**	**0.105**	**-0.651**	**-2.101**
4.	Jatrorrhizine	**0.539**	0.182	**-0.15**	**-2.142**
5.	Tetrahydropalmatine	**1.024**	**0.313**	**0.173**	**-1.827**

Table 5. Metabolic properties of selected alkaloids.

S. No.	Ligand	CYP-2D Substrate	CYP-3A4 Substrate	CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP2D6 Inhibitor	CYP3A4 Inhibitor
1.	Berberine	No	Yes	Yes	No	No	Yes	Yes
2.	Palmatine	No	Yes	Yes	No	No	Yes	No
3.	Magnoflorine	No	Yes	Yes	No	No	No	No
4.	Jatrorrhizine	No	Yes	Yes	No	No	Yes	No
5.	Tetrahydropalmatine	No	Yes	Yes	No	No	Yes	No

Table 6. Excretion properties of selected alkaloids.

S. No.	Ligand	Total Clearance (log ml/min/kg)	Renal OCT2 Substrate
1.	Berberine	1.27	No
2.	Palmatine	1.246	No
3.	Magnoflorine	1.083	No
4.	Jatrorrhizine	1.222	No
5.	Tetrahydropalmatine	**1.123**	No

Table 7. Toxicity prediction of selected alkaloids.

S. No.	Ligand	AMES toxicity	Max. Tolerated Dose (Human) mg/Kg	hERG-I Inhibitor	hERG-II Inhibitor	Oral Rat Acute Toxicity (LD_{50}) (mol/kg)	Oral Rat Chronic Toxicity (log mg/kg_bw/day)	Hepato Toxicity	Skin Sensitization	*T. pyriformis* Toxicity (log ug/L)	Minnow Toxicity (log mM)
1.	Berberine	Yes	0.144	No	No	2.571	1.89	Yes	No	0.354	-0.277
2.	Palmatine	Yes	0.231	No	Yes	2.551	1.536	Yes	No	0.388	-0.313
3.	Magnoflorine	No	0.198	No	Yes	2.274	1.748	No	No	0.659	0.954
4.	Jatrorrhizine	No	-0.613	No	No	2.494	2.122	No	No	0.286	2.725
5.	Tetrahydropalmatine	No	0.175	No	Yes	2.445	1.356	Yes	No	0.385	0.177

3.3 Molecular docking-driven investigation of alkaloids-GPX4 interactions

The GPX4 protein and selected alkaloids from *T. cordifolia* were docked blindly utilizing the web-based CB-Dock platform, which is based on the Auto-Dock-vina-algorithm. The three-dimensional structure of the GPX4 protein was individually deposited and docked with the

three-dimensional structure of each alkaloid. The best pose was chosen based on the Vina score, cavity size, grid map, and other factors. The CB-Dock results were obtained from the possible pose configurations of the GPX4 (receptor) and alkaloids (ligands). An interaction model was developed by projecting the predicted binding energies of alkaloids and GPX4 protein using a curvature-dependent surface-area model. Results from the binding energy calculations (vina score) were used to identify the interaction with the lowest binding energy (Table 8). The GPX4 protein displayed the lowest Vina score with magnoflorine at -7.1 kcal/mol whereas berberine, palmatine, jatrorrhizine and tetrahydropalmatine displayed lower Vina values of -7.0, -6.8, -6.7 and -6.4 kcal/mol, respectively (Fig. 3-7).

Table 8. Vina score and interacting amino acid residues facilitating interaction of alkaloids with GPX4 (assessed by CB-Dock2 tool).

Compound/Ligand	GPX4 (PDB ID: 5H5Q)	
	Vina score (kcal/mol)	Amino acid residues
Berberine PubChem CID:2353	-7	Chain A: TRP35, LYS47, SER131, LYS132, ILE133, GLU134, ASP138, ASP139, ALA140, HIS141, PRO142, LYS145 Chain B: LEU905, GLN906
Palmatine PubChem CID:19009	-6.8	Chain A: ASP34, TRP35, SER45, LYS47, MET53, SER102, ASN103, GLN104, LYS107, SER131, LYS132, ILE133, GLU134, ASP138, ASP139, ALA140, HIS141, PRO142, LYS145 Chain B: ARG902, VAL903, ASP904, LEU905, GLN906, GLY907, TRP908, ARG910
Magnoflorine PubChem CID:73337	-7.1	Chain A: PRO151, LYS152, GLY153, LYS154, GLY155, ILE156, LEU157, GLY158, ASN159, ALA160, LYS162, THR166, VAL177, LYS178, ARG179, TYR180, GLY181, PRO182, MET183, GLU184
Jatrorrhizine PubChem CID:72323	-6.7	Chain A: ASP34, TRP35, LYS47, ASN103, SER131, LYS132, ILE133, GLU134, VAL135, ASP138, ASP139, ALA140, HIS141, PRO142, LYS145, Chain B: LEU905, GLN906, GLY907, TRP908
Tetrahydropalmatine PubChem CID:72301	-6.4	Chain A: LYS75, LYS154, GLY155, ILE156, LEU157, GLY158, ALA160, ILE161, LYS162, TRP163, THR166, LYS178, ARG179, TYR180, GLY181, PRO182, MET183, GLU184

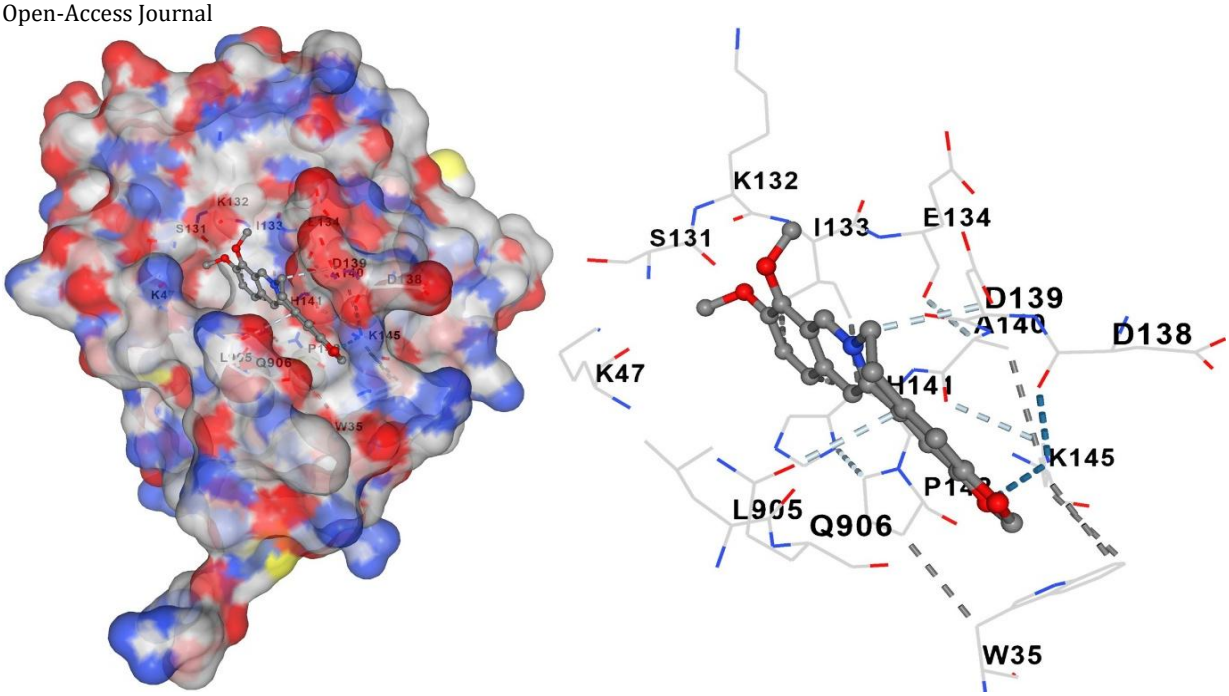

Figure 3. Molecular interaction of berberine with GPX4 by CB-Dock2 molecular docking analysis.

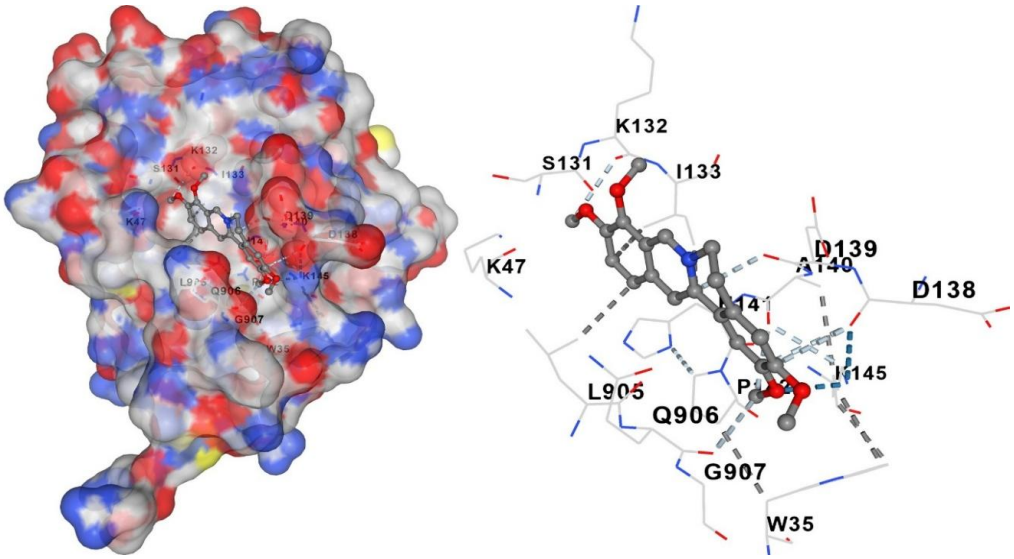

Figure 4. Molecular interaction of palmatine with GPX4 by CB-Dock2 molecular docking analysis.

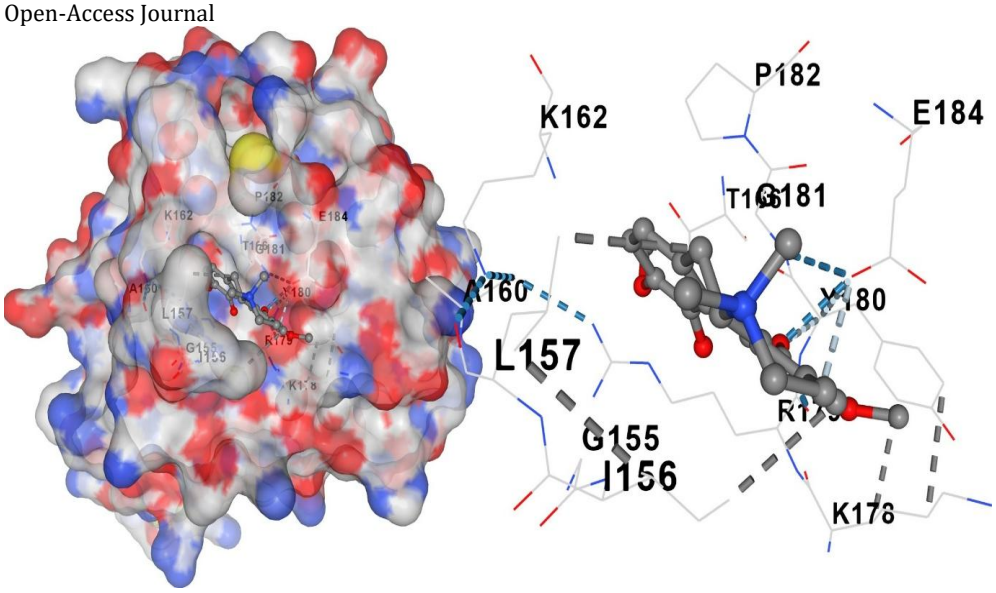

Figure 5. Molecular interaction of magnoflorine with GPX4 by CB-Dock2 molecular docking analysis.

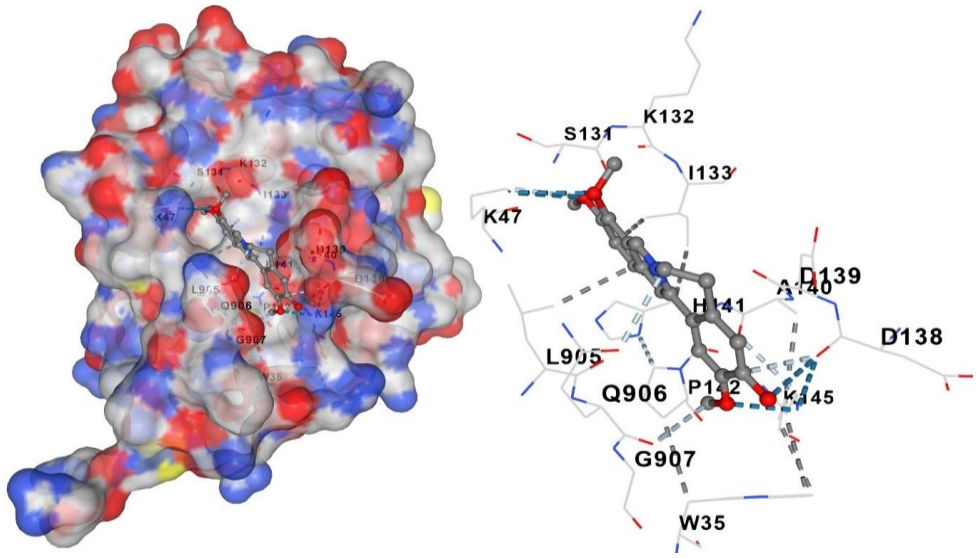

Figure 6. Molecular interaction of jatrorrhizine with GPX4 by CB-Dock2 molecular docking analysis.

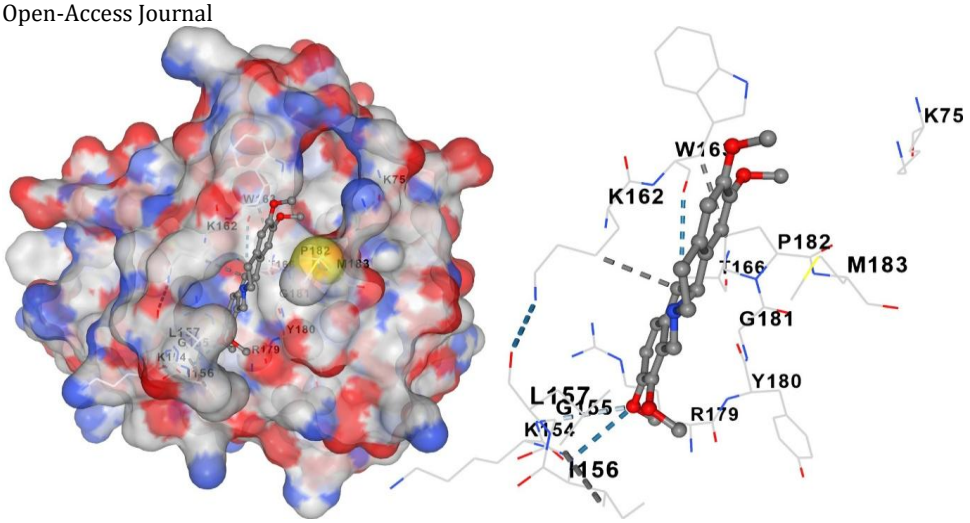

Figure 7. Molecular interaction of tetrahydropalmatine with GPX4 protein by CB-Dock2 molecular docking analysis.

4. Discussion

In recent years, significant progress has been made in treating various types of carcinomas by using different approaches. However, chemotherapy resistance and toxic adverse reactions are still serious problems that influence the prognosis of cancer patients [21]. It is imperative to develop novel strategies and therapies for cancer treatment. Ferroptosis, an innovative form of cell death characterized by iron-dependent lipid peroxidation, has emerged as a viable therapeutic approach [22]. Plant-derived natural products, recognized for their bioactive constituents that engage various targets and exhibit low adverse effects, serve as significant sources for the discovery of anticancer agents [23]. Consequently, it is highly important to investigate naturally occurring pharmacological compounds capable of inducing ferroptosis in cancer. *T. cordifolia* is a plant whose phytocomponents exhibit therapeutic efficacy against various disorders, including cancer. The bioactive phytochemicals of *T. cordifolia* comprise alkaloids, glycosides, steroids, aliphatic compounds, essential oils, a blend of fatty acids, calcium, phosphorus, proteins, and polysaccharides [24]. These phytocomponents elicited anticancer effects through mitochondrial-mediated apoptosis, cytotoxicity, mutagenicity, tumor size reduction, induction of reactive oxygen species, diminished gene expression related to the cell cycle, and effective inhibition of cancer proliferation [25], [26], [27]. This work aims to examine the anticancer potential of *T. cordifolia's* alkaloids by targeting the GPX4 protein inside the ferroptotic pathway through an in-silico approach.

The ADMET analysis indicated that the alkaloids generally complied with Lipinski's rule of five and exhibited favorable absorption, distribution, metabolism, excretion, and toxicity properties. However, some compounds were predicted to inhibit specific cytochrome P450 isoforms, particularly CYP1A2 and CYD2D6 and certain alkaloids showed potential toxicity alerts including AMES positivity and hepatotoxicity. While computation analysis supports the

potential translation relevance of these alkaloids, further in-vitro and in-vivo studies are necessary to comprehensively validate their pharmacokinetics and safety profiles before therapeutic utilization. The results of this work align with previous publications, indicating that computational screening of natural chemicals revealed various anticancer properties [28], [29].

Analysis of the CB dock indicated that alkaloids bind proficiently within the functional pocket of the ferroptotic pathway protein, GPX4. Among the selected alkaloids, magnoflorine exhibits greater binding affinity for GPX4 proteins. Stable protein-ligand interactions were enabled by low binding energies and many non-covalent interactions among critical amino acid residues of target proteins. These interactions suggest that these phytocompounds may operate as ferroptosis inducers, impairing anti-apoptotic signaling and facilitating apoptotic cell death. While these in-silico approaches exhibit potential molecular compatibility, they are inadequate to guarantee biological efficacy. Consequently, further experimental validation employing in-vitro techniques is essential. Comparable research has likewise highlighted the function of many natural compounds as inhibitors of GPX4 protein [30], [31].

5. Conclusion

In summary, this study provides a preliminary report of targeting a crucial enzyme of ferroptosis, GPX4, by plant derived bioactive compounds which could represent a promising cancer treatment strategy. The present work included in-silico analysis including ADMET, drug-likeness, and CB Dock2 molecular docking approach. The results demonstrated that out of five selected alkaloids, magnoflorine was recognized as a potent natural inhibitor of GPX4 with high binding affinity. However, this study was only based upon in-silico-based investigations, thus in-vitro and in-vivo studies are required to validate the repressive potential of magnoflorine against GPX4. This study will help future researchers in identifying novel targets to develop new generation therapeutics for chemo resistant tumors.

Author Contributions

Sahir Sultan Alvi performs conceptualization, methodology, analysis, and writing.

Ethics Statement

Not applicable.

Informed Consent

Not applicable.

Conflicts of Interest

Author declares that there are no conflicts of interest.

Abbreviations

Glutathione: GSH; Glutathione peroxidase 4: GPX4; Reactive oxygen species: ROS; Polyunsaturated fatty acids: PUFAs; Absorption, distribution, metabolism, excretion, and toxicity: ADMET; Protein Data Bank: PDB; Logarithm of the n-octanol/water partition

coefficient: LogP); Molecular weight: MW; Hydrogen bond acceptors: HBAs; Hydrogen bond donors: HBDs; Molecular polar surface area: PSA; Number of rotatable bonds: RotBs.

References

[1] F. Li and X. Chen, "Recent progress in understanding ferroptosis mechanisms in infectious diseases," Front. Cell. Infect. Microbiol., vol. 16, p. 1778721, Mar. 2026, doi: 10.3389/fcimb.2026.1778721.

[2] J. Zheng and M. Conrad, "Ferroptosis: when metabolism meets cell death," Physiological Reviews, vol. 105, no. 2, pp. 651–706, Apr. 2025, doi: 10.1152/physrev.00031.2024.

[3] Z. Chen, W. Wang, S. R. Abdul Razak, T. Han, N. H. Ahmad, and X. Li, "Ferroptosis as a potential target for cancer therapy," Cell Death Dis, vol. 14, no. 7, p. 460, Jul. 2023, doi: 10.1038/s41419-023-05930-w.

[4] J. Wang, D. Guo, S. Jiang, W. Wu, and X. Gao, "Targeting ferroptosis in cancer: from mechanistic insights to therapeutic approaches," Mol Biomed, vol. 7, no. 1, p. 20, Mar. 2026, doi: 10.1186/s43556-026-00416-5.

[5] M. Singh et al., "Ferroptosis in Cancer: Mechanism and Therapeutic Potential," IJMS, vol. 26, no. 8, p. 3852, Apr. 2025, doi: 10.3390/ijms26083852.

[6] L. Zhao et al., "Lactate dehydrogenase B noncanonically promotes ferroptosis defense in KRAS-driven lung cancer," Cell Death Differ, vol. 32, no. 4, pp. 632–645, Apr. 2025, doi: 10.1038/s41418-024-01427-x.

[7] R. Gong et al., "GPX4-AUTAC induces ferroptosis in breast cancer by promoting the selective autophagic degradation of GPX4 mediated by TRAF6-p62," Cell Death Differ, vol. 32, no. 11, pp. 2022–2037, Nov. 2025, doi: 10.1038/s41418-025-01528-1.

[8] J. Deng et al., "Histone lactylation enhances GCLC expression and thus promotes chemoresistance of colorectal cancer stem cells through inhibiting ferroptosis," Cell Death Dis, vol. 16, no. 1, p. 193, Mar. 2025, doi: 10.1038/s41419-025-07498-z.

[9] N. Jin et al., "Niraparib restricts intraperitoneal metastases of ovarian cancer by eliciting CD36-dependent ferroptosis," Redox Biology, vol. 80, p. 103528, Mar. 2025, doi: 10.1016/j.redox.2025.103528.

[10] Q. Hu et al., "A GPX4-targeted photosensitizer to reverse hypoxia-induced inhibition of ferroptosis for non-small cell lung cancer therapy," Chem. Sci., vol. 14, no. 34, pp. 9095–9100, 2023, doi: 10.1039/D3SC01597A.

[11] H. Liu et al., "Ferroptosis meets inflammation: A new frontier in cancer therapy," Cancer Letters, vol. 620, p. 217696, Jun. 2025, doi: 10.1016/j.canlet.2025.217696.

[12] J. Lee and J.-L. Roh, “Targeting GPX4 in human cancer: Implications of ferroptosis induction for tackling cancer resilience,” Cancer Letters, vol. 559, p. 216119, Apr. 2023, doi: 10.1016/j.canlet.2023.216119.

[13] S. M. D. L. Freitas et al., “Influence of plant-derived bioactive compounds on iron metabolism: mechanistic insights with translational relevance,” Critical Reviews in Food Science and Nutrition, vol. 66, no. 7, pp. 1231–1258, Mar. 2026, doi: 10.1080/10408398.2025.2540043.

[14] Y. Yang et al., “The potential of natural herbal plants in the treatment and prevention of non-small cell lung cancer: An encounter between ferroptosis and mitophagy,” Journal of Ethnopharmacology, vol. 346, p. 119555, Apr. 2025, doi: 10.1016/j.jep.2025.119555.

[15] D. Cao et al., “Pteris wallichiana bioactives induce ferroptosis via the SLC7A11-GSH-GPX4 axis to directly suppress colorectal cancer,” Phytomedicine, vol. 148, p. 157463, Nov. 2025, doi: 10.1016/j.phymed.2025.157463.

[16] S. S. Purewal, G. Garg, and A. Kaur, “Giloy (Tinospora cordifolia) enriched mead: a study on bioactive compounds and antioxidant efficacy,” Food Measure, vol. 19, no. 12, pp. 10135–10145, Dec. 2025, doi: 10.1007/s11694-025-03683-y.

[17] A. Rauf et al., “Bioactive Compounds of Tinospora Cordifolia: Implications for Cancer Treatment and Disease Management,” Saudi J. Med. Pharm. Sci., vol. 11, no. 03, pp. 159–177, Mar. 2025, doi: 10.36348/sjmps.2025.v11i03.004.

[18] M. K. M. et al., “Developing a formulation of Tinospora cordifolia, identifying its active components, and assessing its anticancer effects on breast cancer cell lines,” Med Oncol, vol. 42, no. 8, p. 312, Jul. 2025, doi: 10.1007/s12032-025-02777-3.

[19] D. Dey et al., “Amentoflavone derivatives significantly act towards the main protease (3CLPRO/MPRO) of SARS-CoV-2: in silico admet profiling, molecular docking, molecular dynamics simulation, network pharmacology,” Mol Divers, vol. 27, no. 2, pp. 857–871, Apr. 2023, doi: 10.1007/s11030-022-10459-9.

[20] Z. Song et al., “Network Pharmacology, Molecular Docking, and Molecular Dynamics Simulations to Elucidate the Potential Mechanism of Ermiao San in Osteoarthritis,” Food Science & Nutrition, vol. 13, no. 12, p. e71287, Dec. 2025, doi: 10.1002/fsn3.71287.

[21] D. Ajona, M. S. Cragg, and R. Pio, “The complement system in clinical oncology: Applications, limitations and challenges,” Seminars in Immunology, vol. 77, p. 101921, Mar. 2025, doi: 10.1016/j.smim.2024.101921.

[22] A. Wahida and M. Conrad, “Decoding ferroptosis for cancer therapy,” Nat Rev Cancer, vol. 25, no. 12, pp. 910–924, Dec. 2025, doi: 10.1038/s41568-025-00864-1.

[23] L.-Y. Yang et al., "Rising above: exploring the therapeutic potential of natural product-based compounds in human cancer treatment," Tradit Med Res, vol. 10, no. 3, p. 18, 2025, doi: 10.53388/TMR20240618001.

[24] H. Vaghasia, R. Patel, J. Prajapati, K. Shah, M. Saraf, and R. M. Rawal, "Cytotoxic and immunomodulatory properties of Tinospora cordifolia, Boerhaavia diffusa, Berberis aristata, and Ocimum basilicum extracts against HPV-positive cervical cancer cell line," BMC Complement Med Ther, vol. 25, no. 1, p. 59, Feb. 2025, doi: 10.1186/s12906-025-04817-x.

[25] H. Ali and S. Dixit, "Extraction Optimization of Tinospora cordifolia and Assessment of the Anticancer Activity of Its Alkaloid Palmatine," The Scientific World Journal, vol. 2013, no. 1, p. 376216, Jan. 2013, doi: 10.1155/2013/376216.

[26] P. Sharma, B. P. Dwivedee, D. Bisht, A. K. Dash, and D. Kumar, "The chemical constituents and diverse pharmacological importance of Tinospora cordifolia," Heliyon, vol. 5, no. 9, p. e02437, Sep. 2019, doi: 10.1016/j.heliyon.2019.e02437.

[27] A. Sharma, S. K. Saggu, R. Mishra, and G. Kaur, "Anti-brain cancer activity of chloroform and hexane extracts of Tinospora cordifolia Miers: an in vitro perspective," Annals of Neurosciences, vol. 26, no. 1, pp. 10–20, Jan. 2019, doi: 10.5214/ans.0972.7531.260104.

[28] G. Asha, S. Lekshmi, K. P. Najmathunnisa, T. Rajva, V. Krishnakumar, and K. P. S. Hussan, "Exploring the anticancer potential of Tinospora cordifolia with computational insights into EGFR inhibition," In Silico Pharmacol., vol. 13, no. 3, p. 208, Dec. 2025, doi: 10.1007/s40203-025-00468-5.

[29] S. Ahmad et al., "Exploring the potential mechanism of Tinospora cordifolia in cancer treatment: A network pharmacology and molecular docking approach," In Silico Research in Biomedicine, vol. 1, p. 100124, 2025, doi: 10.1016/j.insi.2025.100124.

[30] K. Tabti et al., "Computational investigation of pyrrolidin derivatives as novel GPX4/MDM2–p53 inhibitors using 2D/3D-QSAR, ADME/toxicity, molecular docking, molecular dynamics simulations, and MM-GBSA free energy," Struct Chem, vol. 33, no. 4, pp. 1019–1039, Aug. 2022, doi: 10.1007/s11224-022-01903-5.

[31] M. M. Mokhtari Tabar, A. Ghasemian, A. Kouhpayeh, and E. Behmard, "Computational discovery of novel GPX4 inhibitors from herbal sources as potential ferroptosis inducers in cancer therapy," Archives of Biochemistry and Biophysics, vol. 764, p. 110231, Feb. 2025, doi: 10.1016/j.abb.2024.110231.