



Exploring the GSTP1 inhibition potential of photosensitizer compounds for enhanced cancer treatment in photodynamic therapy

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Abstract

Photodynamic therapy (PDT) has gained considerable attention in cancer treatment due to its non-invasive nature and the ability of photosensitizers to generate reactive oxygen species upon light activation, leading to tumor destruction. Glutathione S-transferase P1 (GSTP1) is a key enzyme in chemotherapy resistance, often overexpressed in various cancers, and its inhibition of GSTP1 presents a promising strategy to enhance cancer treatment. This study is aimed at assessing the potential of prominent photosensitizers as GSTP1 inhibitors through molecular docking analysis to strengthen the efficacy of PDT. The photosensitizers were docked into the active site of GSTP1, and their binding affinities, inhibition constants (K_i), and molecular interactions were assessed. Among the tested photosensitizers, zinc phthalocyanine, hypericin, and temoporfin emerged as the top candidates, exhibiting binding energies of -10.8 , -10.2 , and -9.8 kcal/mol, along with K_i values of 0.012 , 0.033 , and 0.064 μM , respectively. These compounds outperformed the reference inhibitor ethacrynic acid, which had a binding energy of -6.6 kcal/mol and a K_i of 14.35 μM . These findings suggest that the dual action of these photosensitizers provides a promising strategy for combating cancer and overcoming treatment resistance.

Keywords Photosensitizers · Photodynamic therapy · Glutathione S-transferase P1 · Drug resistance · Molecular docking

Introduction

Since the late 1970s, photodynamic therapy has become an effective cancer treatment, approved in countries like the USA, UK, France, Germany, and Japan (Szeimies et al. 2001). Hermann von Tappeiner coined the term “photodynamic” in 1904 to differentiate photo-oxidation from the sensitization process in photography (Babilas et al. 2005). In 1903, the first report was made on the killing of cancer cells by irradiating tumors coated with eosin. Following this study, numerous hematoporphyrin derivatives were applied to PDT (Cengel et al. 2016; Railkar and Agarwal 2018). Essential PDT components include photosensitizers, oxygen, and a light source, which together initiate reactive oxygen

species (ROS) production through complex energy transitions, generating free radicals that damage cancer cells and other cellular structures (Mroz et al. 2011).

GSTP1 is the most studied member of the GST family (Brockmöller et al. 1996). In humans, GSTP1 typically consists of two identical dimeric subunits, each composed of 210 amino acids and two binding sites, G and H. Different residues in the G and H regions of GST may play distinct roles. GSTP1 specifically binds to GSH or GSH analogs through the G site and catalyzes the interaction between GST amino acid residues in the H site and GSH thiols with conventional electrophiles. Therefore, modification of the G site often contributes to the development of specific GSTP1 inhibitors (Laborde 2010). There is a strong relationship between GSTP1 expression and tumor progression. In various types of cancer, GSTP1 expression is significantly higher compared to normal tissues. High levels of GSTP1 have been observed in colorectal, esophageal, lung, bladder, thyroid, and breast cancers (Cui et al. 2020). Particularly in colorectal cancer, GSTP1 overexpression is present at various stages of the disease, and this protein is considered a potential target for cancer treatment. In esophageal cancer, high GSTP1 expression

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can reduce the chemosensitivity of cancer cells (Cui et al. 2020).

Protoporphyrin IX is a widely used photosensitizer in photodynamic therapy. Upon light activation, it generates high levels of reactive oxygen species. Protoporphyrin IX is a naturally occurring precursor of heme in cells and is known for its accumulation in cancer cells. This accumulation provides selective phototoxicity (Lyles et al. 2020). Temoporfin is another powerful photosensitizer used in clinical photodynamic therapies. It is activated by light at longer wavelengths (e.g., infrared light), allowing deeper tissue penetration (Yakavets et al. 2019). Methyl aminolevulinate is a photosensitizer clinically used, particularly in the treatment of skin lesions such as actinic keratosis (Zhang et al. 2023). Chlorin e6 is another potent photosensitizer frequently used in photodynamic therapy applications. It generates ROS under red light, making it suitable for deep tissue penetration (Liao et al. 2023). Photofrin attacks and destroys tumor cells by generating ROS following light activation like other photosensitizers (Abrahamse and Hamblin 2016; Bartusik-Aebischer et al. 2023). Hypericin is a naturally occurring polycyclic aromatic naphthodianthrone. The utilization of hypericin-mediated photodynamic therapy has been shown to effectively impede the proliferation of a wide range of tumor cells, spanning from bladder, colon, breast, and cervical cancers to glioma, leukemia, hepatic, melanoma, lymphoma, and lung cancers (Dong et al. 2021). Phthalocyanines are also highly desirable for the therapy of colorectal cancer because of their versatile molecular structure, outstanding photochemical properties, and multifunctional nature (Janas et al. 2021). Curcumin that is biologically safe appears to fulfill many requirements for a promising and “druggable” photosensitizer (Kazantzis et al. 2020). Additionally, the exploration of novel curcumin derivatives for antimicrobial photodynamic therapies and surface decontamination presents an encouraging approach to improve the efficiency and broaden the range of curcumin's use as a photosensitizer (Dias et al. 2020). Another photosensitizer called rose bengal is used in both anti-cancer and anti-bacterial photodynamic therapy (Dhaini et al. 2022).

Each of these photosensitizers not only holds strong properties for use in PDT but also has the potential to inhibit the GSTP1 enzyme, a key enzyme in chemotherapy resistance mechanisms. Targeting GSTP1 holds promise for enhancing cancer treatment outcomes, as it could reduce the cell's defense mechanisms while amplifying ROS-induced cytotoxic effects of PDT. This study examines the interactions between key photosensitizers and GSTP1 through molecular docking to assess their potential as GSTP1 inhibitors and enhance the effectiveness of photodynamic therapy. The dual action of these photosensitizers presents a promising strategy to combat cancer and overcome treatment resistance.

Materials and methods

Preparation of ligands

The molecular structures of several photosensitizer compounds and the GSTP1 inhibitor ethacrynic acid were retrieved from the PubChem database for use in this study (Kim et al. 2023). The compounds included protoporphyrin IX with PubChem compound ID 4971, temoporfin with ID 60751, methyl aminolevulinate with ID 157922, chlorin e6 with ID 5479494, photofrin with ID 3086257, hypericin with ID 3663, zinc phthalocyanine with ID 2735172, curcumin with ID 969516, rose bengal with ID 25474, and ethacrynic acid with ID 3278. Before the docking procedures, energy minimization of these compounds was performed using Avogadro software to ensure that they adopted optimal conformations conducive to the docking process (Hanwell et al. 2012).

Docking analysis

The crystal structure of the Glutathione S-transferase P1 protein was retrieved from the Protein Data Bank (PDB) under the code 2GSS, featuring a resolution of 1.9 Å, R-factor of 0.209, and R-free of 0.229 (Oakley et al. 1997). Before initiating the docking procedure, all water molecules and non-protein structures were systematically removed from the crystal structure. Subsequently, hydrogen atoms were incorporated into the protein structure, and Gasteiger charges were assigned to facilitate accurate docking. The active site of the GSTP1 crystal structure was determined based on the binding site of ethacrynic acid, a known ligand for this protein. The coordinates for the active site were established as x : 9.2316, y : 3.21369, and z : 28.8571, with the active site defined within a cubic region measuring $20 \text{ Å} \times 20 \text{ Å} \times 20 \text{ Å}$. Docking operations were carried out using AutoDock Vina version 1.2.5 (Trott and Olson 2010; Eberhardt et al. 2021). The binding affinities of the ligands to the active site of GSTP1 were calculated, and the docking process utilized the default parameters of the Lamarckian Genetic Algorithm.

Determination of molecular interactions

Following the completion of the docking analysis, the molecular interactions between GSTP1 and the photosensitizer compounds were further analyzed. Visualization and in-depth analysis of these interactions were conducted using Discovery Studio software. The analysis focused on identifying hydrogen bonds, hydrophobic interactions,

and other relevant binding interactions, which provided insights into the molecular dynamics and binding characteristics between GSTP1 and the various photosensitizers.

Statistical analysis

Energy minimization of the compounds was conducted using Avogadro, which utilizes the default MMFF94 force field to optimize molecular geometries, ensuring stable conformations before docking. This process incorporates default statistical methods to evaluate the stability and energy profiles of the minimized structures. Docking analyses were performed using AutoDock Vina, which employs its default Lamarckian Genetic Algorithm to calculate binding affinities based on energy and geometric complementarity. The docking process also integrated default statistical methods to assess the reliability and significance of the calculated binding affinities. Visualization of the docking results was carried out using Discovery Studio, which offers default features for evaluating binding affinities and interaction frequencies. This software facilitates the identification of key interactions, such as hydrogen bonds and hydrophobic contacts, while employing default statistical analyses to provide insights into the distribution and significance of these interactions.

Results

Evaluation of molecular docking analysis

The molecular docking analysis revealed varying binding affinities between the GSTP1 protein and the photosensitizer compounds, as summarized in Table 1. The binding energies, presented in kcal/mol, provide insights into the strength of the interactions, with lower (more negative) values indicating stronger binding. Additionally, the inhibition constant (K_i) is an important metric that quantifies the effectiveness of the photosensitizer compounds in inhibiting GSTP1 activity. A lower K_i value suggests a more potent inhibitor, reflecting a higher affinity for the target protein.

The three compounds with the strongest binding energies were zinc phthalocyanine, hypericin, and temoporfin. Zinc phthalocyanine exhibited the highest binding affinity with a binding energy of -10.8 kcal/mol, indicating a highly stable and robust interaction with GSTP1. Similarly, hypericin, with a binding energy of -10.2 kcal/mol, demonstrated a strong interaction, closely following zinc phthalocyanine. Temoporfin also showed significant affinity with a binding energy of -9.8 kcal/mol, placing it among the most effective photosensitizers in terms of binding to GSTP1. These three compounds are the most promising candidates, as their

strong interactions suggest a high potential for inhibiting GSTP1 activity in photodynamic therapy. Following these top three compounds, a group of photosensitizers exhibited moderate binding affinities to GSTP1. Photofrin had a binding energy of -8.6 kcal/mol, followed by rose bengal at -8.2 kcal/mol, and protoporphyrin IX at -8.0 kcal/mol. While these binding energies are not as strong as the top three compounds, they still reflect notable interactions with GSTP1, indicating their potential role as moderately effective inhibitors in therapeutic applications. Chlorin e6 and curcumin, with binding energies of -7.8 kcal/mol and -7.3 kcal/mol, respectively, also fall within this mid-range group. Though their affinities are lower, these compounds still exhibit the ability to interact with GSTP1 moderately.

On the other hand, methyl aminolevulinate displayed the weakest binding affinity to GSTP1, with a binding energy of -4.4 kcal/mol, suggesting a comparatively limited interaction. This lower binding energy indicates that methyl aminolevulinate may be less effective in modulating GSTP1 activity, especially when compared to the stronger binding compounds in the study. As a reference point, ethacrynic acid, a known GSTP1 inhibitor, had a binding energy of -6.6 kcal/mol. Although this value is lower than the top three photosensitizers, it provides a benchmark for comparing the effectiveness of the new compounds in inhibiting GSTP1.

Spatial arrangement of compounds

The docking process of GSTP-1 with ethacrynic acid was performed using a grid box containing the active site of GSTP1 (H-site), as shown in Fig. 1. The grid box was positioned around the site where the crystal structure of ethacrynic acid was previously identified in a complex with GSTP-1. A cubic grid box of $20 \text{ \AA}$ was created around this site, accommodating the molecular size of the photosensitizer compounds. Subsequently, all photosensitizer compounds were docked within this grid box.

Furthermore, the spatial arrangement of each photosensitizer compound within the active site of GSTP1 is illustrated in Fig. 2. This figure provides a visual overview of the docking results, highlighting how each compound is positioned in relation to the active site. These binding patterns provide insight into how each photosensitizer compound may interact with GSTP1, impacting their potential efficacy in photodynamic therapy applications targeting this enzyme.

Interaction profiles

The molecular docking results highlight zinc phthalocyanine, hypericin, and temoporfin as the top three compounds with the highest docking scores against GSTP1, indicating

Table 1 Binding energies and inhibition constant of photosensitizer compounds and ethacrynic acid to GSTP1

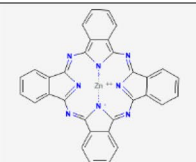
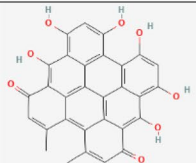
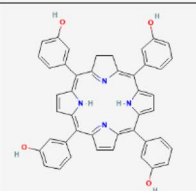
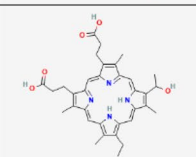
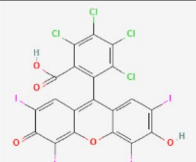
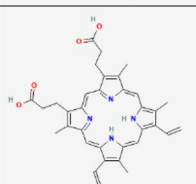
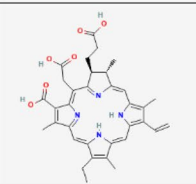
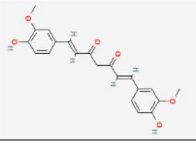
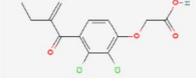
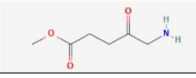
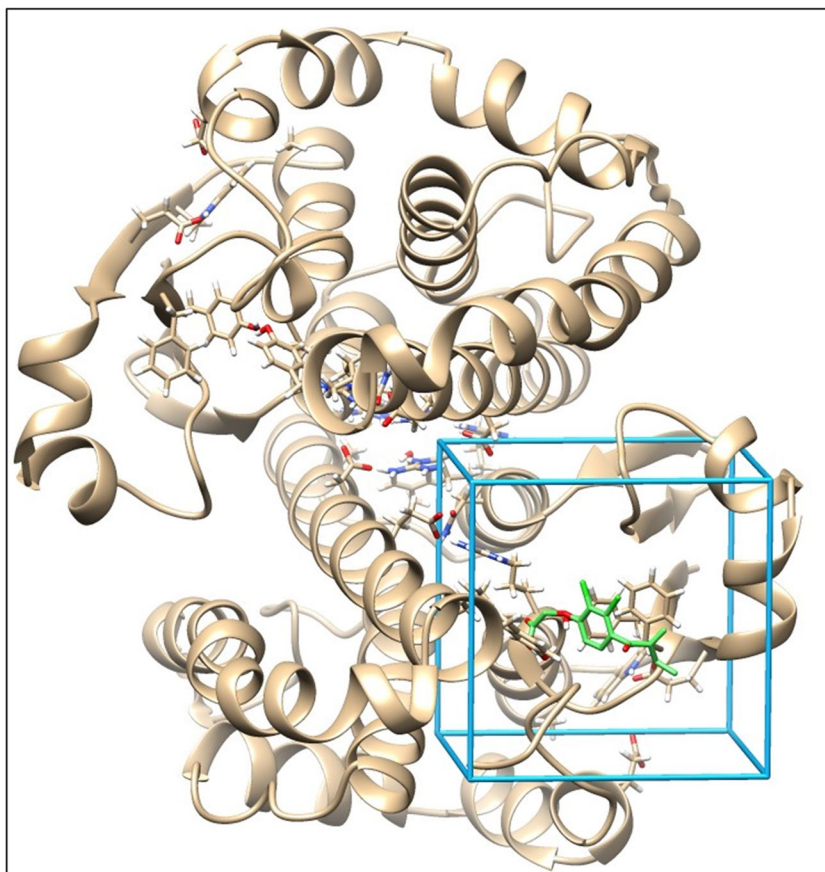
Compounds	Molecular structure	Binding energy (kcal/mol)	Inhibition constant (μM)
Zinc phthalocyanine		-10.8	0.012
Hypericin		-10.2	0.033
Temoporfin		-9.8	0.064
Photofrin		-8.6	0.489
Rose bengal		-8.2	0.961
Protoporphyrin IX		-8.0	1.347
Chlorin e6		-7.8	1.889
Curcumin		-7.3	4.397
Ethacrynic acid		-6.6	14.35
Methyl aminolevulinate		-4.4	590.5

Fig. 1 3D Binding pose of ethacrynic acid within the active site of GSTP-1 with a 20 Å cubic grid box. The GSTP1 protein structure is depicted in brown while the structure of ethacrynic acid is shown in green



their potential as strong binders to the active site (Fig. 3). Zinc phthalocyanine, the top hit, exhibits robust hydrophobic interactions, particularly van der Waals and alkyl interactions with key residues such as Phe (A:8), Tyr (A:108), and Val (A:10), which stabilize its binding within the active site (Fig. 3a). Hypericin, ranking second, engages in both π -anion interactions with Phe (A:8) and Tyr (A:108), and conventional hydrogen bonds with Val (A:10) and Gly (A:7), demonstrating a balanced interaction profile that includes both hydrophobic and charge-based interactions (Fig. 3b). Temoporfin, the third most potent compound, forms van der Waals and carbon-hydrogen bond interactions with Phe (A:8), Val (A:35), and Arg (A:13). However, an unfavorable donor-donor interaction with Arg (A:100) may slightly diminish its binding efficiency, although its overall interactions still support a strong binding potential (Fig. 3c). On the other hand, ethacrynic acid, a known inhibitor of GSTP1 used as a reference in this study, exhibited a lower docking score compared to the top hits. While it formed conventional hydrogen bonds with residues like Gly12 and Arg13, its binding was primarily driven by polar interactions, including π -anion interactions with Phe8 (Fig. 3d). Despite its established inhibitory role, ethacrynic acid displayed a weaker binding affinity in comparison to the newly identified top-hit compounds.

Discussion

Photodynamic therapy has evolved as an innovative technique for treating various types of cancer due to its ability to target tumor cells with minimal damage to surrounding healthy tissue. The essential components of PDT include light, oxygen, and a photosensitizer, which, upon light activation, produce reactive oxygen species (Mroz et al.) that induce cell death. The role of photosensitizers in cancer treatment has been extensively studied, yet their potential to inhibit proteins involved in drug resistance, such as glutathione S-transferase P1, remains underexplored. GSTP1 is highly expressed in many cancers, including colorectal, lung, breast, and esophageal cancers, where its elevated levels contribute to chemotherapy resistance by detoxifying anticancer drugs (Cui et al. 2020). Thus, targeting GSTP1 can enhance the efficacy of cancer treatments, including PDT.

This study was aimed at assessing the inhibitory potential of several well-established photosensitizers against GSTP1 through molecular docking simulations. Our results demonstrated that compounds like zinc phthalocyanine, hypericin, and temoporfin exhibited strong binding affinities to GSTP1, with binding energies surpassing that of ethacrynic acid, a recognized GSTP1 inhibitor (Oakley et al. 1997; Schultz

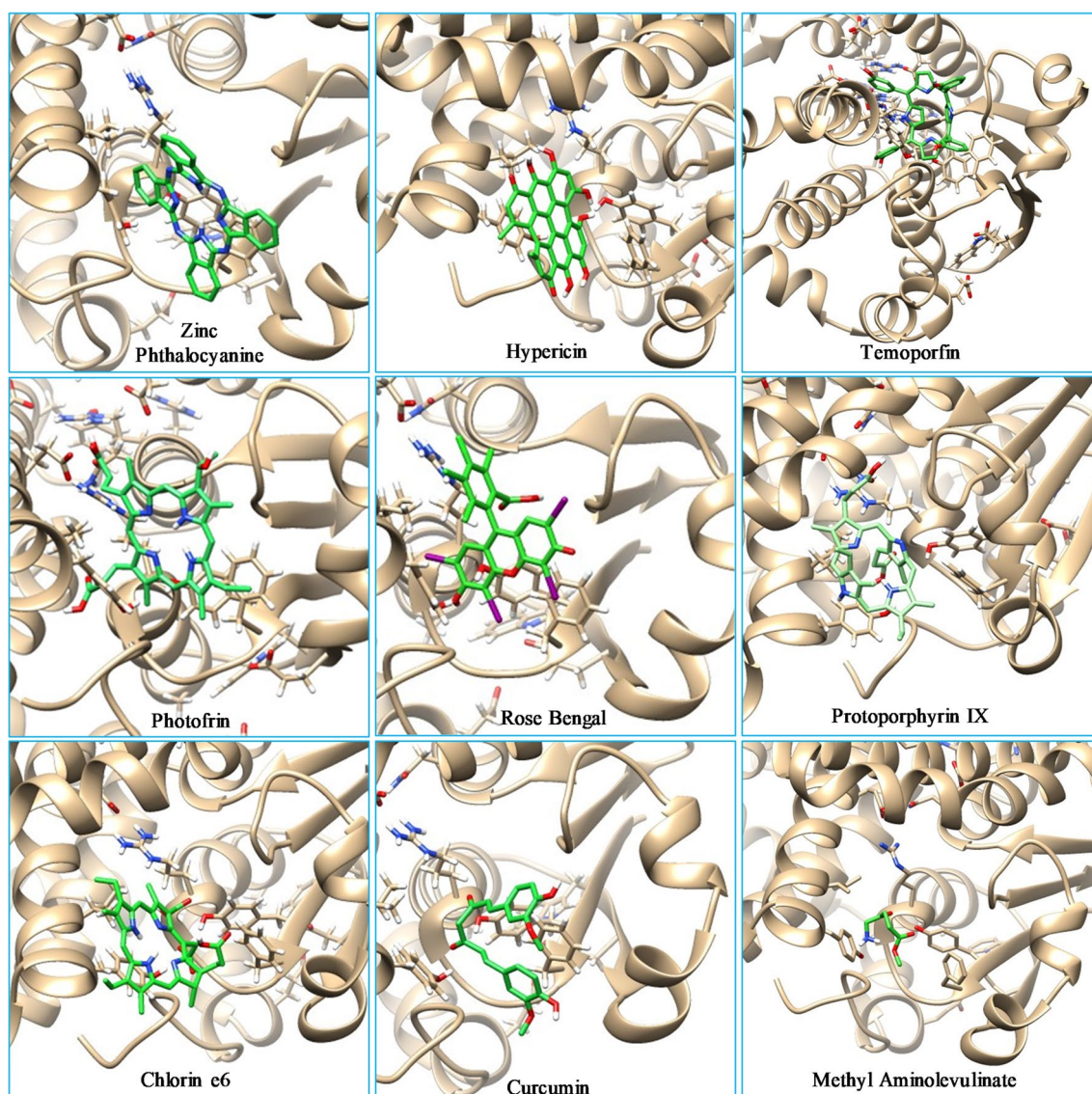


Fig. 2 The spatial positioning of photosensitizer compounds within the active site (H-site) of GSTP1. The GSTP1 protein structure is depicted in brown, while the structures of the photosensitizer compounds are shown in green

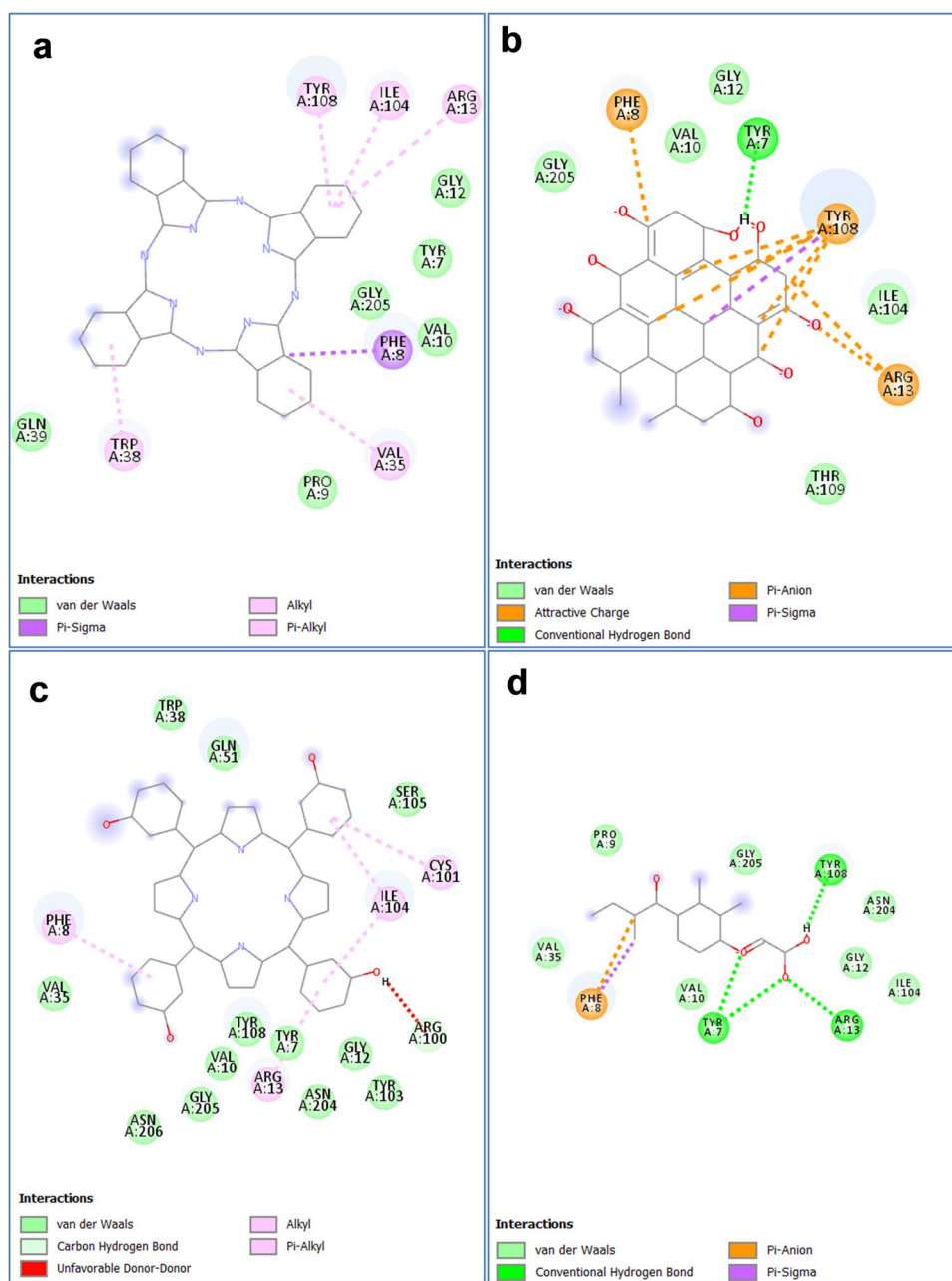
et al. 1997). These findings are particularly promising, suggesting that certain photosensitizers, beyond their ROS-generating properties, may modulate also the activity of GSTP1, potentially mitigating one of the major mechanisms of drug resistance in cancer.

Supporting this, one study has shown that a molecular construct combining a brominated BODIPY photosensitizer with ethacrynic acid as a GSTP1 inhibitor was able to overcome hypoxia-induced resistance in preclinical PDT models (Won et al. 2021). This highlights that using GSTP1 inhibitors in addition to photosensitizers or the use of only GSTP-1 inhibitors may increase the success rate in PDT. This property aligns with our study's aim to improve photodynamic therapy (PDT) efficacy by increasing ROS production and

inhibiting GSTP1. Thus, selecting photosensitizers for PDT with both hypoxia-tolerant ROS generation capabilities and GSTP1 inhibition may offer a promising strategy to mitigate drug resistance.

The photosensitizers analyzed, including zinc phthalocyanine, temoporfin, photofrin, rose bengal, protoporphyrin IX, chlorin e6, and methyl aminolevulinate, have not been reported in the literature as GSTP1 inhibitors. However, hypericin and curcumin have previously been reported to exhibit GSTP1 inhibition (Lu and Atkins 2004; Appiah-Opong et al. 2009). Consistent with these reports, our analysis revealed a strong binding energy of -10.2 kcal/mol and an inhibition constant (K_i) of 0.033 μM for hypericin, while curcumin showed a weaker binding energy of -7.3 kcal/

Fig. 3 2D Interaction diagrams of top hits and reference compound with GSTP1 protein: **a** zinc phthalocyanine, **b** hypericin, **c** temoporfin, and **d** ethacrynic acid



mol with a K_i of 4.397 μM . These findings align with earlier studies demonstrating hypericin's strong inhibitory effect, with a nanomolar-scale IC_{50} value of 190 nM (Lu and Atkins 2004), and curcumin's relatively lower inhibition effect, with an IC_{50} value of 15.1 μM (Appiah-Opong et al. 2009).

Previous studies have demonstrated that hypericin and phthalocyanines exhibit strong anticancer activity, primarily through ROS generation and apoptosis induction (Janas et al. 2021). Our study is the first to reveal their potential to inhibit GSTP1, highlighting their dual-functional capabilities. With binding affinities surpassing that of the traditional GSTP1 inhibitor ethacrynic acid, these photosensitizers may

offer significant advantages in both potency and specificity for cancer treatment. These findings open new avenues for exploring hypericin and phthalocyanines as promising agents that combine ROS-mediated anticancer effects with GSTP1 inhibition, offering a novel approach to overcoming drug resistance.

Furthermore, the high photodynamic efficacy of zinc phthalocyanines in melanoma treatment has been well-documented, with our results identifying zinc phthalocyanine as the compound with the greatest inhibition potential among the tested photosensitizers (Castro et al. 2022). The longer absorption wavelength of zinc(II)-phthalocyanine enables deeper light penetration into human tissue compared to

photofrin II, which may account for its superior effectiveness in photodynamic therapy applications (Ochsner 1996). Its role as a powerful dual-action agent in cancer therapy, combining ROS generation with strong GSTP1 inhibition, may explain why zinc phthalocyanines are more effective in photodynamic therapy. In a reported study, the application of hypericin-containing photodynamic therapy in combination with chemotherapy agents or targeted therapies is more effective in inhibiting the growth of tumor cells (Dong et al. 2020). When compared with the molecular docking results we obtained, hypericin seems to be the second most potent compound that can inhibit GSTP-1. This suggests that the mechanism behind hypericin's effective cancers response may perhaps be due to GSTP-1 inhibition.

On the other hand, hypericin among potential photosensitizers is particularly attractive due to its strong PDT response. This, combined with its low toxicity in the absence of light, selectivity for certain tumors, and rapid clearance from the human body, suggests that hypericin is a promising photosensitizer for cancer PDT (Karioti and Bilia 2010; De Souza et al. 2022). Another study reported that hypericin-based photodynamic therapy showed greater selectivity and phototoxicity against melanoma and squamous cell carcinoma compared to normal keratinocytes in vitro, aligning with our findings (Woźniak and Nowak-Perlak 2023).

Ferroptosis is an iron-dependent modality of programmed cell death that is closely associated with excessive accumulation of intracellular reactive oxygen species and the related lipid peroxide (Li et al. 2020). Convincing evidence suggests that the use of ferroptosis inducers can effectively suppress tumor growth (Wu et al. 2022). When cellular damage is induced by PDT, excessive GSH production in tumor cells will counteract oxidative stress in an attempt to maintain redox homeostasis. Inhibition of GSTP1 activity initiates ferroptosis. Molecular docking studies have shown that photosensitizers inhibit GSTP1. The mechanism behind the success of these photosensitizers may be that they initiate ferroptosis by inhibiting GSTP1.

Glutathione peroxidase 1, like GSTP1, is an enzyme that neutralizes free radicals. In particular, it protects cell membranes from oxidative damage by converting harmful oxygen derivatives such as hydrogen peroxide into water (Lei et al. 2007; Ozcan et al. 2021, 2024). In the reported study, glutathione peroxidase 1 inhibitors were used in combination with temoporfin (Lange and Bednarski 2021). In the results obtained, the use of glutathione peroxidase 1 inhibitors increased the effect of temoporfin-based photodynamic therapy. In this combination, it was hypothesized that ROS accumulation resulting from inhibition of glutathione peroxidase 1-catalyzed H_2O_2 degradation during PDT would lead to increased PDT-induced phototoxicity. Molecular docking results showed that temoporfin strongly inhibits GSTP1. Consistent with the literature, the mechanism underlying the

effect of temoporfin may be due to its strong inhibition of GSTP1.

In a study, it was reported that LD_{50} values were used to assess the efficiency of various photosensitizers on human epidermoid carcinoma cells (A431 cell line) (Berlanda et al. 2010). The LD_{50} value represents the concentration needed to achieve a cytotoxic effect on cancer cells under light exposure; a lower LD_{50} indicates higher efficacy, as the desired effect can be reached with a smaller concentration. Among the photosensitizers, hypericin demonstrated the highest effectiveness, with the lowest LD_{50} value. Temoporfin (foscan), hypericin, photofrin, and protoporphyrin IX had LD_{50} values of 0.03 μ M, 0.31 μ M, 1.94 μ M, and 393.07 μ M, respectively. Temoporfin (Foscan), hypericin, and photofrin may yield more effective results compared to other photosensitizers, possibly due to their GSTP1 inhibition potentials. It is important to note that these findings are based on LD_{50} data and require further validation in animal and human studies.

While this study provides a valuable foundation for exploring the potential of photosensitizers as GSTP1 inhibitors, certain limitations should be considered. The molecular docking approach, although useful, may not fully capture the dynamic interactions that occur in a cellular environment. Future research could explore the GSTP1 inhibitory effects of various derivatives of these compounds, which may help clarify the mechanisms underlying their therapeutic potential. Additionally, in vitro and in vivo studies would be important to further assess the GSTP1 inhibitory effects of these photosensitizers under biological conditions. Exploring their potential as adjuvants in combination with traditional chemotherapeutic agents may also enhance their effectiveness against multidrug-resistant cancers. Lastly, while GSTP1 overexpression is prevalent in cancer cells, it also contributes to the antioxidant defense in normal cells. Therefore, selectively targeting GSTP1 in cancer cells without affecting healthy cells will be crucial for clinical applications. Advances in targeted drug delivery and the development of cancer-specific photosensitizers may help address these challenges.

Conclusion

This study identifies zinc phthalocyanine, hypericin, and temoporfin as promising dual-function photosensitizers for photodynamic therapy. By targeting GSTP1, these compounds could provide a synergistic approach to enhancing cancer treatment, combining ROS-mediated cytotoxicity with GSTP1 inhibition to overcome resistance mechanisms. These findings lay the groundwork for future research exploring the therapeutic potential of photosensitizers in targeting drug resistance, ultimately contributing to more

effective and comprehensive cancer therapies. Further experimental validation and clinical studies will be essential to realize the full potential of these compounds in enhancing the efficacy of photodynamic therapy and improving outcomes for patients with drug-resistant cancers.

Authors contributions M.O. conceptualized work. M.O., C.C., and M.G. designed and wrote the initial manuscript draft. M.O. prepared the figures and tables. M.O., C.C., and M.G. edited and revised the manuscript critically. The final manuscript has been approved by all the authors. The authors declare that all data were generated in-house and that no paper mill was used.

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Data availability All source data for this work (or generated in this study) are available upon reasonable request.

Declarations

Ethics approval Not applicable.

Competing interests The authors declare no competing interests.

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