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Evaluation of Emetogenic Mechanisms of Antineoplastic Drugs on 5-HT3A Receptor Using a Structure-Based Computational Approach

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ABSTRACT

Objective: Chemotherapy-induced nausea and vomiting (CINV) following antineoplastic drug administration in cancer patients significantly affects their quality of life and treatment adherence. The 5-hydroxytryptamine type 3A receptor (5-HT3A) (serotonin) is a key target involved in emetic signaling. Understanding the molecular interactions between chemotherapeutic agents and this receptor may aid in the development of more effective antiemetic therapies. This study aims to investigate the binding potential of commonly used chemotherapeutic drugs to the serotonin receptor to better understand their role in triggering emetic responses.

Materials and Methods: A computer-aided protein-ligand docking analysis was performed using AutoDock4 and PyMol software to evaluate drug-receptor binding affinities. Frequently used chemotherapeutic agents (azacitidine, carboplatin, cyclophosphamide, dacarbazine, doxorubicin, lomustine, melphalan, and streptozocin) and standard antiemetics were analyzed in experimental groups, with serotonin used as a control in the computational study.

Results: The chemotherapeutic agents demonstrated significantly higher binding potential compared to antiemetics and serotonin. Notably, these antineoplastic drugs were shown, for the first time, to interact with common amino acids, compared to antiemetics, and serotonin, suggesting that chemotherapy drugs might compete with them for binding to the 5-HT3A receptor and thereby exacerbate nausea and vomiting during chemotherapy administration.

Conclusion: Chemotherapy-induced nausea and vomiting are known to result indirectly from serotonin released by damaged intestinal cells in response to the toxic side effects of chemotherapy drugs. However, this study remarkably proposes an alternative mechanism for CINV and presents the first evidence of a direct interaction between certain antineoplastic drugs and the serotonin receptor.

Keywords: Antiemetics, chemotherapy, CINV, docking, emesis, 5-HT3R ligands.

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INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) is one of the most frequent side effects of anticancer drugs, significantly reducing patients' quality of life and potentially discouraging them from adhering to their treatment plans. CINV remains a clinical problem, particularly for patients undergoing highly emetogenic chemotherapy.[1] This multifactorial condition includes several distinct types (acute, delayed, anticipatory, breakthrough, and refractory), each characterized by different temporal patterns and underlying mechanisms, highlighting the need for personalized management strategies.[2]

The interaction between the gastrointestinal (GI) tract and the central nervous system (CNS) plays a key role in the pathogenesis of CINV.[3] The 5-hydroxytryptamine type 3 (5-HT3A) receptor, located in both the brain and GI tract, serves as a critical mediator of the emetic response. When intestinal epithelial cells are damaged by antineoplastic agents, enterochromaffin cells in the GI mucosa release serotonin (5-hydroxytryptamine or 5-HT).[4,5] Serotonin then binds to 5-HT3A receptors (5-HT3AR) on vagal afferent nerve terminals, triggering signals that are transmitted to the chemoreceptor trigger zone (CTZ) and the brainstem vomiting center.[3,6] The 5-HT3A receptor is a Cys-loop ligand-gated ion channel and is also classified among the G-protein-coupled receptors (GPCRs).[3,4] Its ligand-binding site is located in the extracellular domain (ECD). Upon serotonin binding to the ECD, a conformational change occurs, opening the pore domain and allowing the influx of cations such as calcium and sodium. This leads to neuronal depolarization and the transmission of emetic signals.[7] From this molecular perspective, 5-HT3 receptor antagonists, also known as setrons, have become prominent in preventing acute-phase CINV. These drugs competitively inhibit serotonin binding to its receptors, thereby alleviating emetic stimuli. Ondansetron, granisetron, dolasetron, ramosetron, and palonosetron are well-documented antiemetics that effectively control acute CINV by maintaining the 5-HT3AR in a closed, inactive state.[8,9] Nonetheless, these drugs are not fully effective in eliminating nausea and vomiting, suggesting that distinct molecular mechanisms may underlie the interaction between chemotherapeutic agents and the emetic pathway.

Although antineoplastic agents are known to indirectly induce CINV through serotonin release, there is currently no evidence that these drugs directly activate the emetic signaling pathway by interacting with 5-HT3A receptors. In this study, we hypothesize that certain chemotherapeutic agents may also bind directly to 5-HT3A receptors, similar to serotonin, and synergistically initiate emetic signaling in cells. To explore this possibility, we aimed to assess the binding potential of various chemotherapy agents to 5-HT3AR, in comparison with antiemetic drugs, using an in silico molecular docking approach.

KEY MESSAGES

- Certain chemotherapeutic drugs analyzed in this study may interact directly with the human 5-HT3A receptor.
- The findings suggest that chemotherapeutic agents may compete with both antiemetic medications and serotonin for binding to the 5-HT3A receptor.
- This research presents an intriguing proposal and introduces a novel hypothesis regarding the cause of CINV, based on computational data.

This study has provided several intriguing insights for the first time in the literature. First, our analyses showed that the chemotherapy drugs examined can interact with the extracellular domain of the human 5-HT3A receptor. The binding region overlapped with the serotonin-binding site, suggesting that these drugs may directly contribute to the activation of emetogenic signaling in nerve cells, in addition to the effects of serotonin released from damaged GI tract cells. Second, our study offered new insights into the molecular binding mechanisms of various setrons to the human 5-HT3 receptor, compared to serotonin, through computational methods. Third, our results revealed that the binding affinities of the chemotherapy drugs were comparable to those of the antiemetics. This finding led us to speculate that these drugs may compete for binding to the serotonin receptor when administered concurrently, which could help explain the limited effectiveness of antiemetics in fully preventing CINV.

MATERIALS AND METHODS

3D Structure Files

The experimentally determined three-dimensional structure model of the human 5-HT3A receptor (PDB ID: 8AXD) was obtained from the RCSB Protein Data Bank (https://www.rcsb.org/). All five peptide chains (chains A, B, C, D, and E) were retained and included in the docking analysis. Conformer structure files of all drugs, including serotonin, were acquired from the PubChem chemical database maintained by the National Institutes of Health (NIH).[10]

Structure-Based Molecular Docking

Three-dimensional structures were processed, and in silico molecular docking was performed using AutoDock 4.2.6 (version 1.5.7).[11] As previously described,[12,13] the receptor (protein structure) was prepared by removing heteroatoms and water molecules, adding polar hydrogens, and assigning

Kollman charges. The Lamarckian Genetic Algorithm (LGA), a widely used method in computer-aided protein-ligand docking,[14,15] was employed due to its foundation in principles of genetic evolution and Mendelian genetics.[16] A population size of 300 was chosen, as population sizes of 200 or 400 have been reported to be sufficient for reliable results.[17] A total of 100 conformations were run to explore the best binding pose. The grid box was centered on the protein at the x-, y-, and z-coordinates (146.779, 146.166, 187.126). The dimensions of the grid box along the x-, y-, and z-axes were set to 126, 126, and 64, respectively, with a spacing of 0.569 Angstroms, to cover the ECD of the receptor.

Analysis and Graphical Interpretation

The conformation with the best binding energy was selected for further analysis. The structure file of each drug-receptor complex (best docking pose) was exported to examine molecular interactions. After identifying intermolecular interactions (covalent or non-covalent) using the Protein-Ligand Interaction Profiler (PLIP) tool,[18] interaction diagrams were generated and interpreted using PyMOL 3.1 software (Schrödinger, LLC).

Heat maps and XY scatter plots were created using GraphPad Prism 9.5.

Statistical Analysis

As this study involved computational data (e.g., calculated binding energies and estimated inhibition constants), traditional statistical analysis was not applicable.

RESULTS

The binding potential of eight commonly used chemotherapy drugs in oncology clinics (azacitidine, carboplatin, cyclophosphamide, dacarbazine, doxorubicin, lomustine, melphalan, and streptozocin),[19] to the human 5-HT3A receptor was evaluated computationally and compared to well-documented antiemetic drugs (dolasetron, granisetron, ondansetron, palonosetron, and ramosetron). Serotonin (5-HT), the natural ligand of the 5-HT3AR, was also included as a reference in the molecular docking analysis. As expected, the antiemetics showed high binding affinities, ranging from -7.94 to 9.41 kcal/mol. Notably, the calculated binding energies of the antineoplastic drugs against the extracellular domain of the 5-HT3AR were also significant (Table 1). Lomustine (-6.76 kcal/mol), doxorubicin (-6.55 kcal/mol), and streptozocin (-6.19 kcal/mol) exhibited the highest binding potential among the chemotherapeutic agents, while melphalan (-1.43 kcal/mol) showed the lowest (Table 1, Fig. 1). The binding energies of azacitidine, carboplatin, cyclophosphamide, and dacarbazine were relatively moderate. Interestingly, the computed binding affinity of serotonin (-5.30 kcal/mol) was lower than that of the antiemetics (setrons) but very similar to the chemotherapy drugs in this analysis (Table 1). The binding affinities of the setrons were clearly superior to all other molecules tested. Dolasetron showed the strongest binding, with a free binding energy of -9.41 kcal/mol, while granisetron had a binding energy of -7.94 kcal/mol in this group, as summarized in Table 1.

Table 1. Computed binding energies, root mean square deviation (RMSD) values, and inhibition constant (Ki) scores for drug/ligand-receptor complexes

Drug/Ligand	Binding energy (kcal/mol)	RMSD (A°)	Estimated Ki (μM)
Azacitidine	-5.07	262.697	192.51
Carboplatin	-4.28	308.125	723.14
Cyclophosphamide	-5.44	263.442	102.10
Dacarbazine	-5.05	263.766	198.74
Doxorubicin	-6.55	266.986	15.85
Lomustine	-6.76	285.567	11.14
Melphalan	-1.43	260.794	88820
Streptozocin	-6.19	262.281	29.13
Dolasetron	-9.41	262.619	0.1276
Granisetron	-7.94	258.294	1.51
Ondansetron	-8.14	261.830	1.08
Palonosetron	-9.38	262.916	0.1332
Ramosetron	-8.20	266.146	0.9779
Serotonin (5-HT)	-5.30	263.215	131.15

RMSD: Root mean square deviation; A°: Ångström; Ki: Inhibition constant.

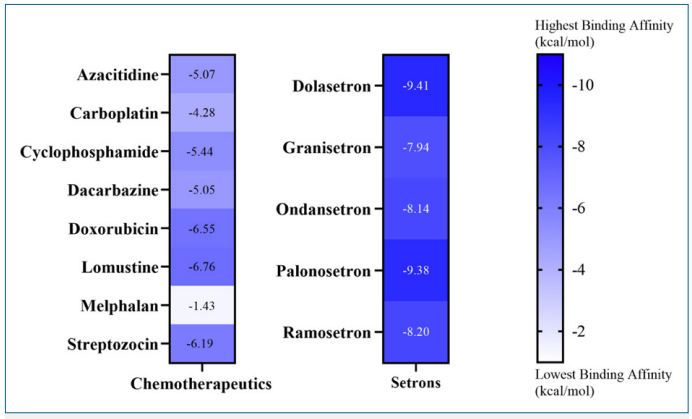

Figure 1. Heatmap comparing the binding energies of antiemetics and chemotherapeutic agents.

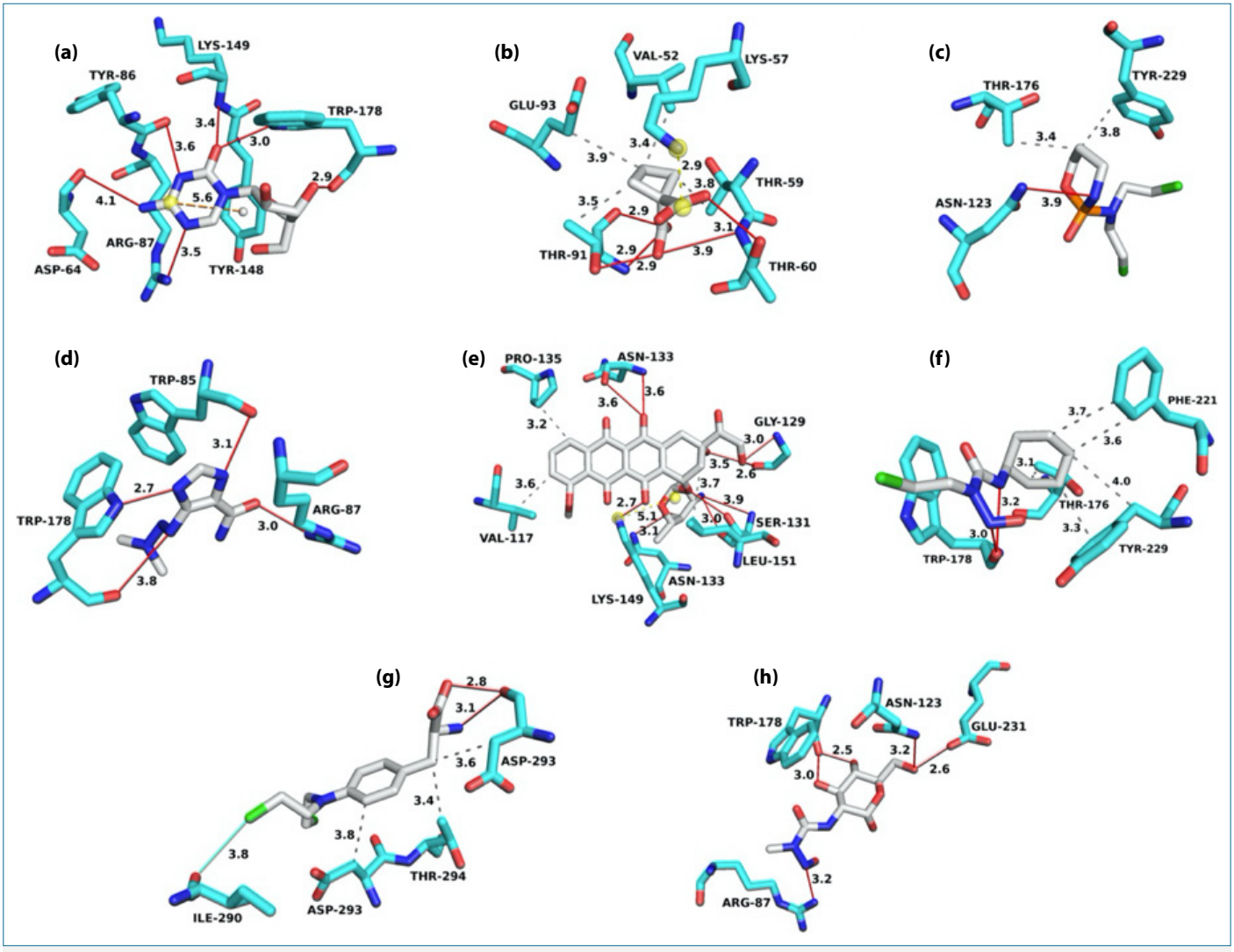

Figure 2. Amino acids surrounding the binding pockets of azacytidine **(a)**, carboplatin **(b)**, cyclophosphamide **(c)**, dacarbazine **(d)**, doxorubicin **(e)**, lomustine **(f)**, melphalan **(g)**, and streptozocin **(h)**.

Furthermore, we examined the binding regions and molecular interactions of these drugs (Fig. 2, 3), as well as serotonin (Fig. 4) on the receptor protein. All chemotherapy drugs, except for melphalan and carboplatin, interacted with similar amino acids on the 5-HT3AR, such as Arg87, Asn123, Thr176, and Trp178, primarily through hydrogen bonding (Fig. 2, Table 2). In contrast, melphalan and carboplatin interacted with unrelated amino acid residues (Table 2). Specifically, the N-terminal amino acids Val52, Lys57, Thr59, and Thr60 were involved in carboplatin-receptor binding, while melphalan interacted with amino acids located more centrally in the protein (namely Asp293, Thr294, Asp293, and Ile290) (Fig. 2).

Meanwhile, granisetron, ondansetron, and palonosetron bound to a common binding pocket on the receptor, including Ile66, Trp85, Arg87, Asn133, Thr176, and Trp178. In contrast, dolasetron and ramosetron were located in distinct regions in silico, primarily surrounded by amino acids between 119-129 and 70-77, respectively (Fig. 3).

Similarly, serotonin was also located in a region overlapping with those of the chemotherapy and antiemetic agents (Fig. 4, Table 2). Notable interacting residues for serotonin included Asn123, Thr176, Trp178, and those between positions 221-231 on the ECD (Fig. 4).

DISCUSSION

Chemotherapeutic agents are both life-sustaining and highly invasive drugs used in the treatment of cancer. However, many antineoplastic regimens are associated with nausea

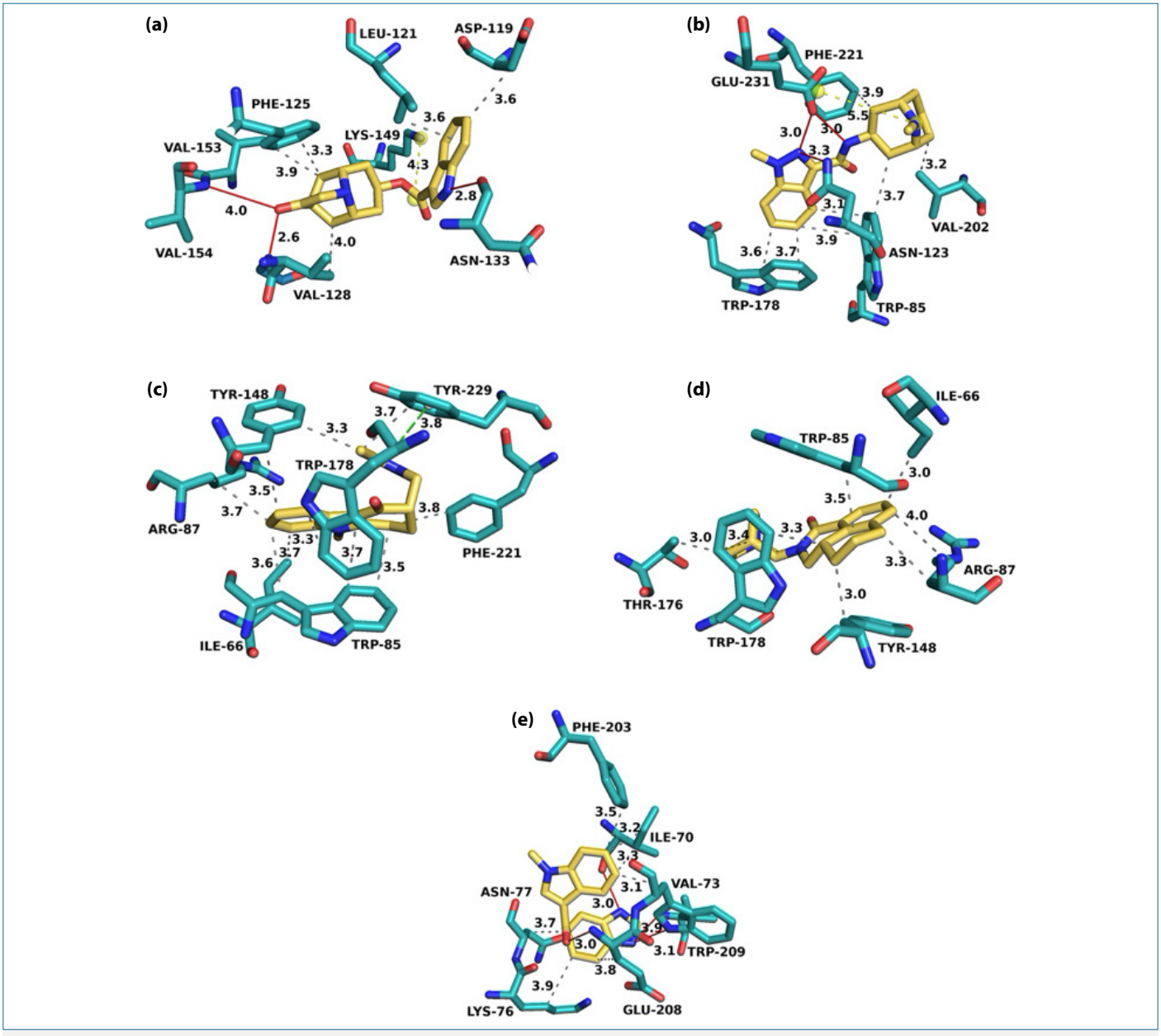

Figure 3. Amino acids surrounding the binding pockets of dolasetron **(a)**, granisetron **(b)**, ondansetron **(c)**, palonosetron **(d)**, and ramosetron **(e)**.

and vomiting during the course of treatment, often severely affecting patients' quality of life and adherence to therapy.[20] Unfortunately, numerous studies have reported that antiemetic drugs are often suboptimal in fully preventing emesis during chemotherapy regimens.[21–23] Therefore, a deeper understanding of how chemotherapy drugs induce these side effects, particularly through the coordination between the nervous and digestive systems, is essential to enhance the effectiveness of antiemetic drugs. According to the literature, the primary cause of chemotherapy-induced nausea and vomiting is the excessive release of serotonin from intestinal epithelial cells. Serotonin, the natural ligand of the 5-HT3A receptor, initiates emetogenic signaling via vagal neurons.[24] However, there has been no prior evidence suggesting that chemotherapeutic drugs directly induce CINV through binding to the human 5-HT3A receptor.

In the present study, azacitidine, carboplatin, cyclophosphamide, dacarbazine, doxorubicin, lomustine, and streptozocin

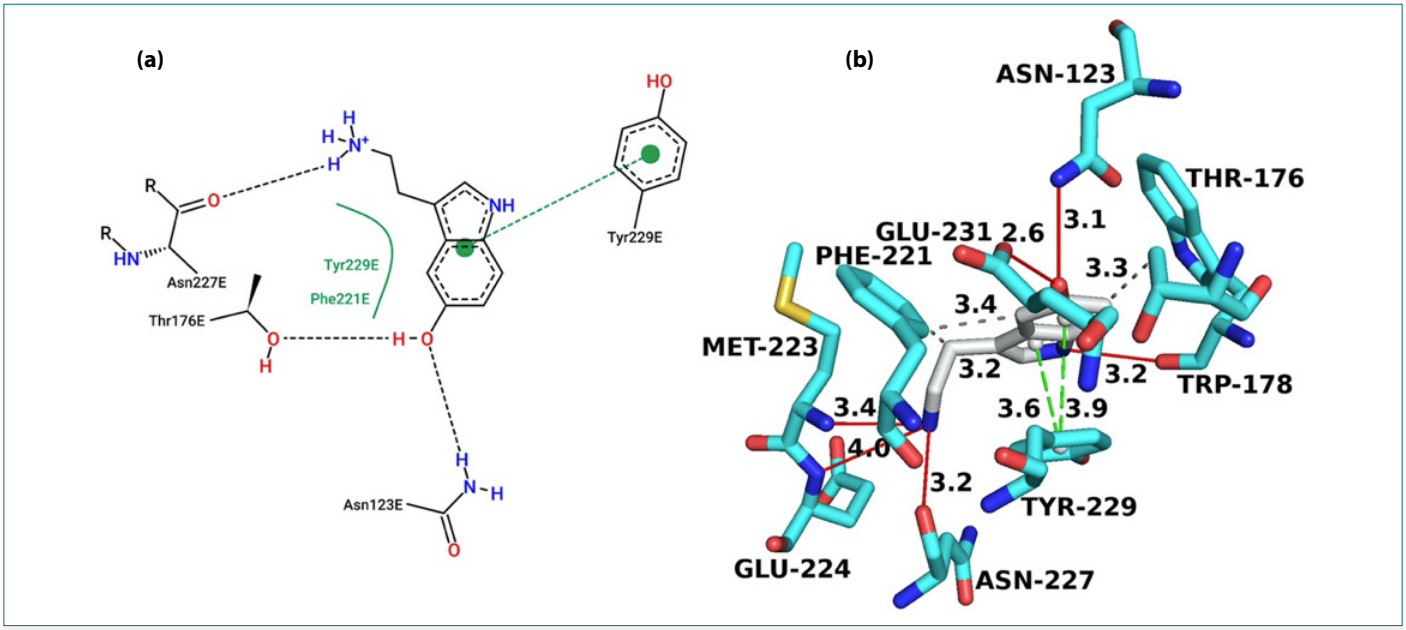

Figure 4. Two-dimensional (2D) diagram **(a)** and three-dimensional (3D) illustration **(b)** of the serotonin binding pocket *in silico*.

demonstrated notable binding potential to the 5-HT3A receptor when compared to its natural ligand, serotonin. Remarkably, lomustine, doxorubicin, streptozocin, and cyclophosphamide exhibited better computed binding energies than serotonin itself. The average binding energies for chemotherapeutics, serotonin, and antiemetics were calculated as -5.1 kcal/mol, -5.3 kcal/mol, and -8.6 kcal/mol, respectively (Fig. 5a). As expected, the binding affinities of setrons were higher than that of serotonin (Table 1), as they function as pharmacological antagonists of serotonin.[25] Palonosetron has been reported to have a stronger receptor affinity than other setrons.[26] The in silico docking scores appear consistent and credible, as ondansetron and palonosetron showed the best binding energies in our analysis. Additionally, Bigaud et al.[27] reported that dolasetron was more effective at lower doses than ondansetron, granisetron, and tropisetron. In line with this, the estimated inhibition constant (Ki) values in Table 1 indicate that dolasetron had the lowest Ki (0.1276 μM) among all tested compounds, suggesting that a smaller amount of dolasetron was sufficient to bind the receptor effectively in our model. Taken together, our computational findings align well with previously reported empirical results.

5-HT3A receptor is a pentameric ligand-gated ion pump composed of five peptide chains: A, B, C, D, and E. Upon serotonin binding to the ECD of the resting receptor, a conformational change occurs, allowing the channel to open.[28] Basak et al.[29] reported that the amino acids W63, Y64, R65, Y126, W156, F199, and Y207 constitute the serotonin-binding pocket in mouse 5HT-3A receptors. When protein sequences

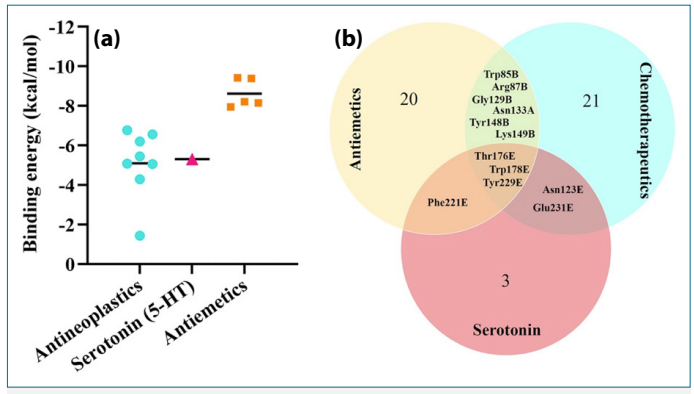

Figure 5. Average binding energies **(a)** and shared amino acids in the binding pockets **(b)** of serotonin, chemotherapy drugs, and setrons.

were aligned (data not shown), those residues corresponded to Trp85, Tyr86, Arg87, Tyr148, Trp178, Phe221, and Tyr229 in the human homolog, respectively. As listed in Table 2, the amino acids Trp178, Phe221, and Tyr229 were also identified in our docking analysis. Electron microscopy imaging has revealed the crystal structures of granisetron-, palonosetron-, and ondansetron-bound mouse 5-HT3A receptors.[30,31] In addition to the serotonin-binding residues, various interacting amino acids have been detected in drug-receptor complexes,[30–34] as shown in Table 3. When comparing Table 2 and Table 3, it is evident that analogous or adjacent amino acids were identified for each drug-receptor complex in the study, supporting the

Table 2. Interacting amino acids and types of chemical bonds between 5-hydroxytryptamine (5-HT), antineoplastic agents, and antiemetic drugs

Drug/Ligand	# of hydrogen bonds[a]	# of hydrophobic interactions[b]	# of π-stacking/ cation[c]	# of salt bridges[d] or halogen bonds[e]	Interacting amino acids
Azacitidine	6	–	1	–	Asp64B[a], Tyr86B[a], Arg87B[a], Tyr148B[c], Lys149B[a], Trp178E[a]
Carboplatin	5	4	–	1	Val52D[b], Lys57D[d], Thr59D[b], Thr60D[a], Thr91D[a,b], Glu93D[b]
Cyclophosphamide	1	2	–	–	Asn123E[a], Thr176E[b], Tyr229E[b]
Dacarbazine	4	–	–	–	Trp85B[a], Arg87B[a], Trp178E[a]
Doxorubicin	10	3	–	1	Asn133A[a], Val117B[b], Gly129B[a], Ser131B[a], Asn133B[a], Pro135A[b], Lys149B[a,d], Leu151B[b]
Lomustine	2	5	–	–	Thr176A[b], Trp178A[a], Phe221A[b], Tyr229A[b]
Melphalan	2	3	–	1	Asp293C[b], Thr294C[b], Asp293D[a,b], Ile290E[e]
Streptozocin	6	–	–	–	Arg87B[a], Asn123E[a], Trp178E[a], Glu231E[a]
Dolasetron	3	5	–	1	Asn133A[a], Asp119B[b], Leu121B[b], Phe125B[b], Val128B[b], Gly129B[a], Lys149B[d], Val153B[b], Val154B[a]
Granisetron	3	7	–	1	Trp85A[b], Val202A[b], Asn123B[a], Trp178B[b], Phe221B[b], Glu231B[a,d]
Ondansetron	–	10	–	1	Ile66B[b], Trp85B[b], Arg87B[b], Tyr148B[b], Trp178E[b], Phe221E[b], Tyr229E[b,d]
Palonosetron	–	8	–	–	Ile66B[b], Trp85B[b], Arg87B[b], Tyr148B[b], Thr176E[b], Trp178E[b]
Ramosetron	4	7	–	–	Lys76C[b], Asn77C[b], Ile70E[b], Val73E[a], Phe203E[b], Glu208E[a,b],Trp209E[a,b]
Serotonin (5-HT)	7	3	2	–	Asn123E[a], Thr176E[b], Trp178E[a], Phe221E[b], Met223E[a], Glu224E[a], Asn227E[a], Tyr229E[c], Glu231E[a]

reliability of the in silico data. As depicted in Figure 5, Thr176, Trp178, Phe221, and Tyr229 were common interacting amino acids for both antiemetic drugs and serotonin, aligning well with previously reported serotonin-binding residues (Table 3). Notably, in our analysis, chemotherapeutic drugs were surrounded by amino acids such as Trp85, Arg87, Tyr148, and Trp178, (Table 2), which were also reported to be involved in the mouse 5-HT3AR-serotonin interaction.[29] This suggests that the tested antineoplastic drugs may substantially occupy the serotonin-binding pocket in the human 5-HT3A receptor. Furthermore, these residues emerged as shared interacting amino acids between the antiemetic and chemotherapeutic drugs (Fig. 5b). Taken together, these findings indicate that chemotherapeutic agents may compete with both serotonin and antiemetic drugs for binding to the 5-HT3A receptor.

Chemotherapy drugs are categorized based on their emetogenic risk. Azacitidine, cyclophosphamide, and dacarbazine are classified as highly emetogenic, while carboplatin, doxorubicin, lomustine, and streptozocin exhibit moderate to high emetogenicity in patients.[1,35–36] The estimated binding affinities and interacting residues were also consistent with this classification. For instance, all docking residues of azacitidine (Asp64, Tyr86, Arg87, Tyr148, and Trp178) (Table 2), classified as a highly emetogenic chemotherapy drug, matched the serotonin-binding amino acids mentioned above.[29] In contrast, melphalan has minimal emetogenic potential. Consistently, melphalan exhibited the lowest binding energy (Table 1) and interacted with a binding pocket unrelated to that of serotonin (Fig. 2g).

Table 3. Amino acids in the mouse 5-hydroxytryptamine type 3A receptor (5-HT3A) involved in antiemetic drug-receptor interactions reported in the literature

Drug/Ligand	Interacting amino acids in mouse 5-HT3AR	References
Alosetron	Asp42 (***h***Asp64), Ile44 (***h***Ile66), Arg65, (***h***Arg87), Asn101 (***h***Asn123), Tyr126 (***h***Tyr148), Ser155 (***h***Ser177), Trp156 (***h***Trp178), Tyr207 (***h***Tyr229)	25, 29
Granisetron	Asp42 (***h***Asp64), Val43 (***h***Val65), Ile44 (***h***Ile66), Trp63 (***h***Trp85), Tyr64 (***h***Tyr86), Arg65 (***h***Arg87), Asn101 (***h***Asn123), Tyr126 (***h***Tyr148), Ser155 (***h***Ser177), Trp156 (***h***Trp178), Arg169 (***h***Arg191), Phe199 (***h***Phe221), Ile201 (***h***Met223), Tyr207 (***h***Tyr229)	25, 26, 28
Ondansetron	Asp42 (***h***Asp64), Ile44 (***h***Ile66), Trp63 (***h***Trp85), Arg65 (***h***Arg87), Asn101 (***h***Asn123), Tyr126 (***h***Tyr148), Ser155 (***h***Ser177), Trp156 (***h***Trp178), Tyr207 (***h***Tyr229)	25, 26
Palonosetron	Ile44 (***h***Ile66), Trp63 (***h***Trp85), Tyr64 (***h***Tyr86), Arg65 (***h***Arg87), Trp156 (***h***Trp178), Ile201 (***h***Met223), Tyr207 (***h***Tyr229)	25, 26
Tropisetron	Asp42 (***h***Asp64), Arg65 (***h***Arg87), Asp97 (***h***Asp119), Phe103 (***h***Phe125), Tyr126 (***h***Tyr148), Trp156 (***h***Trp178), Asp202 (***h***Glu224), Phe199 (***h***Phe221), Tyr207 (***h***Tyr229)	27

Corresponding residues in the human 5-HT3AR receptor are indicated by the prefix 'h.'

Furthermore, evaluating the estimated Ki values of chemotherapy drugs can help us to understand how different doses of chemotherapy influence the proposed CINV mechanism. Ki refers to the concentration of a ligand required to occupy half of the receptor population. This implies that even small amounts of a ligand with a low Ki can produce significant biological effects. As shown in Table 1, doxorubicin, lomustine, and streptozocin (classified as highly emetogenic drugs) had relatively low Ki values of 15.85 µM, 11.14 µM, and 29.13 µM, respectively. In contrast, melphalan exhibited a much higher Ki of 88.82 mM. These findings suggest that highly emetogenic antineoplastic agents may exacerbate CINV even at lower doses by triggering the proposed receptor-binding mechanism. In contrast, drugs with relatively higher Ki values, such as melphalan, may cause milder CINV due to their reduced ability to bind to the 5-HT3AR and activate this mechanism. Nevertheless, the concurrent operation of both mechanisms: the release of serotonin (as per the established model) and the direct binding of chemotherapy drugs to the receptor (as proposed in this study) may contribute to the stronger CINV observed in moderately to highly emetogenic chemotherapy regimens.

These findings imply that highly emetogenic chemotherapy drugs may exert their effects by mimicking serotonin and binding to the same amino acids. In summary, this study proposes an alternative mechanism for CINV, in addition to the established model, which may also explain the limited effectiveness of antiemetic drugs during highly emetogenic chemotherapy regimens.

CONCLUSION

Until now, CINV has primarily been attributed to indirect damage in the GI tract. However, the present study offers a novel perspective by highlighting the potential direct effects of chemotherapy drugs on the emetogenic signaling pathway. Thus, our study presents a novel and compelling hypothesis about the cause of CINV, based on computational findings. Accordingly, redesigned agents with physicochemical properties capable of competing with chemotherapy drugs, rather than conventional antiemetics that compete with serotonin, should be developed to alleviate CINV, based on the novel perspective introduced in this study. In this context, we have hypothesized for the first time, using computational methods, that chemotherapy drugs themselves may act directly as emetogenic agents. Consequently, these findings provide a foundational basis for further experimental and *in vivo* studies to investigate the interaction between chemotherapy drugs and the 5-HT3AR receptor. Moving forward, research building on this study will help clarify the potential direct effects of chemotherapy drugs on the emetic signaling pathway.

Ethics Committee Approval: No ethical approval is required for this computational study because no human material or data were utilized. Thus, the current study does not conflict with the Declaration of Helsinki.

Conflict of Interest: The author have no conflict of interest to declare.

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