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# Molecular Docking Study of White Radish (*Raphanus sativus* L.) Active Compounds on Progesterone Receptor (PRG) as Anti-Cancer Agents

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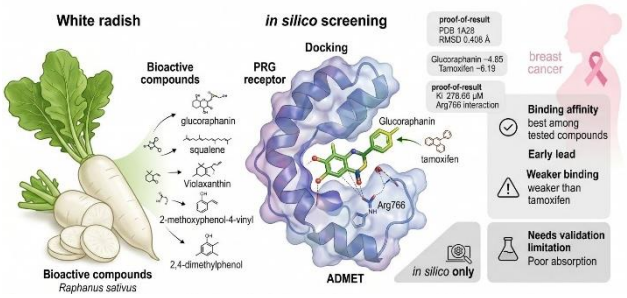
## ABSTRACT




White radish (*Raphanus sativus* L.) contains various bioactive compounds that may contribute to different biological activities. This study aimed to evaluate the interaction of selected white radish compounds with the progesterone receptor (PRG) using an in silico molecular docking approach as a preliminary step for anticancer screening. Molecular docking was performed using AutoDock 4, BIOVIA Discovery Studio, and PyMOL to assess binding affinity, Root Mean Square Deviation (RMSD), and amino acid interactions. Among the five tested white radish compounds, glucoraphanin had the best docking score (–4.8 kcal/mol) for the progesterone receptor. However, this binding affinity remained weaker than that of the control ligand tamoxifen (–6.19 kcal/mol). Molecular interaction analysis indicated that glucoraphanin formed interactions with several key amino acid residues within the receptor binding site. Docking validation produced an RMSD value of <2 Å, indicating acceptable docking reliability. These findings suggest that glucoraphanin from white radish may interact with the progesterone receptor and warrant further investigation. Nevertheless, further experimental studies are required to confirm its potential biological activity.

**Keywords:** *molecular docking; progesterone receptor; glucoraphanin; white radish; breast cancer screening*

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## INTRODUCTION

Cancer remains one of the leading causes of death worldwide, accounting for approximately 10 million deaths in 2020, according to the World Health Organization (WHO) [1] . Among various cancer types, breast cancer is the most frequently diagnosed malignancy in women and represents a major global public health concern, with an estimated 2.3 million new cases reported annually [2][3]. The development and progression of breast cancer are strongly influenced by hormonal signaling pathways, particularly those involving estrogen and progesterone receptors [4][5].

The progesterone receptor (PRG) plays an important role in regulating cell proliferation and differentiation in hormone-dependent breast cancer [6-8]. PRG expression has been reported in approximately 60–70% of invasive breast cancer cases, highlighting its

significance as both a prognostic biomarker and a therapeutic target [9][10]. Hormone-based therapies such as tamoxifen have been widely used in the treatment of receptor-positive breast cancer and have significantly contributed to reducing mortality rates [11][12]. However, long-term use of tamoxifen may cause several adverse effects, including mood changes, nausea, hypertension, and cardiovascular complications [13-15], which necessitate the exploration of alternative compounds with potentially improved safety profiles.

Plant-derived bioactive compounds represent a promising source of new therapeutic candidates. One plant of interest is white radish (Raphanus sativus L.), a member of the Brassicaceae family that contains various phytochemicals such as glucosinolates, flavonoids, tannins, and other secondary metabolites [16-18]. Previous studies have reported that extracts of white radish exhibit antioxidant and anticancer activities against several cancer cell lines, which are attributed to compounds such as sulforaphane and other glucosinolate derivatives [19-21]. Despite these findings, the potential interaction of specific white radish compounds with the progesterone receptor (PRG) has not been widely explored.

Molecular docking has emerged as an important computational tool in early-stage drug discovery because it enables the prediction of ligand–receptor interactions and binding affinities before experimental validation [22--25]. This approach has been widely applied to screen plant-derived compounds against various therapeutic targets, including hormone receptors involved in breast cancer progression. In addition to docking analysis, the evaluation of pharmacokinetic and toxicity properties through in silico ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) prediction has become increasingly important to assess the drug-likeness and safety profile of candidate compounds at an early stage [26-28].

Studies investigating the interaction of specific bioactive compounds from white radish with the progesterone receptor (PRG) are still limited. Furthermore, comparative evaluations involving these compounds alongside native ligands and established therapeutic agents such as tamoxifen within a unified computational framework, including both docking and ADMET analysis, remain scarce.

This study aims to perform an initial computational screening of selected bioactive compounds from white radish (Raphanus sativus L.) against the progesterone receptor (PRG) using molecular docking and ADMET analysis. The study evaluates binding affinity, inhibition constants, molecular interaction patterns, and pharmacokinetic properties to identify compounds that may interact with the receptor and serve as candidates for further investigation.

## METHODS

### 1. Materials and Software

The three-dimensional structure of the progesterone receptor (PRG) (PDB: 1A28) was obtained from the Protein Data Bank. The structure was selected due to its high resolution (1.80 Å), allowing accurate atomic-level analysis. The receptor contains two chains (chain A and chain B), each bound to the native ligand progesterone. Ligand structures of active compounds from white radish (Raphanus sativus L.) were retrieved from public chemical

databases. The ligands used in this study included 2-methoxyphenol-4-vinyl, 2,4-dimethylphenol, violaxanthin, squalene, and glucoraphanin, with tamoxifen used as the reference ligand. Ligand structures were retrieved from the PubChem database. Tamoxifen was included as the pharmacological reference ligand. Computational analysis was performed using BIOVIA Discovery Studio 2024 Client, AutoDock Tools, AutoDock 4, Avogadro, ChemDraw 3D, Notepad, pkCSM, and PyMOL

**2. Receptor Ligand Screening Using Lipinski's Rule of Five**

Drug-likeness screening of the selected white radish (*Raphanus sativus* L.) bioactive compounds was conducted using Lipinski's Rule of Five before molecular docking analysis, as summarized in Table 1. This screening aimed to identify compounds with favorable oral drug-likeness properties based on molecular mass, lipophilicity, hydrogen bond donor capacity, hydrogen bond acceptor capacity, and molar refractivity.

All candidate compounds were pre-screened using Lipinski's Rule of Five to evaluate their oral drug-likeness before docking. Parameters evaluated included molecular weight (MW ≤ 500 Da), lipophilicity (Log P ≤ 5), hydrogen bond donors (HBD ≤ 5), hydrogen bond acceptors (HBA ≤ 10), and molar refractivity (MR: 40–130). Compounds satisfying these criteria were considered suitable for further computational analysis. Squalene was retained for docking despite its elevated Log P to allow comparative analysis, with its pharmacokinetic limitations explicitly noted in the ADMET evaluation.

**Table 1.** Results of Lipinski's Rule of Five Evaluation for Bioactive Compounds of White Radish (*Raphanus sativus* L.)

| Ligand | Molecular mass | Log P | HBD | HBA | MR |
|---|---|---|---|---|---|
| 2-methoxyphenol-4-vinyl | 150.00 | 2.043 | 1 | 2 | 44.74 |
| 2,4-dimethylphenol | 122.00 | 2.009 | 1 | 1 | 37.58 |
| Squalene | 410.00 | 10.60 | 0 | 0 | 140.06 |
| Glucoraphanin | 435.00 | 0.271 | 5 | 11 | 94.04 |
| Violaxanthin | 312.00 | -0.053 | 5 | 6 | 77.14 |

**3. Receptor Preparation**

The receptor structure was prepared using BIOVIA Discovery Studio by removing water molecules and native ligands to prevent interference during docking simulations. The cleaned structure was saved in ".pdb" format. The PRG structure consists of two chains (chain A and chain B), each bound to progesterone. One chain was selected as the primary reference based on redocking validation results, particularly the lowest RMSD value, ensuring consistency and reliability in subsequent docking analysis.

**4. Ligand Preparation and Optimization**

Ligand structures downloaded from PubChem in .sdf format were first converted to .pdb format. Optimization was performed sequentially as follows: (1) hydrogen atoms were added and initial geometry was set using Avogadro; (2) energy evaluation and geometry optimization were then performed using the MMFF94 force field in ChemDraw 3D, yielding the lowest-energy conformation for each ligand; (3) the optimized structures were saved in .pdb

format; and (4) the .pdb files were converted to .pdbqt format using AutoDock Tools, which assigns Gasteiger partial charges and defines rotatable bonds. The same preparation procedure was applied uniformly to all test ligands and to the native ligand (progesterone) to ensure methodological consistency.

## 5. Redocking Validation

The reliability of the docking protocol was validated by redocking the native ligand (progesterone) back into the binding site of each receptor chain. The grid box was defined based on the spatial coordinates of the co-crystallized progesterone molecule to accurately represent the active binding site. Grid dimensions were set to 20 × 20 × 20 grid points with a spacing of 1.0 Å. Docking accuracy was evaluated using the root mean square deviation (RMSD) between the redocked pose and the original crystallographic pose, with RMSD ≤ 2 Å accepted as a valid reproduction of the experimental binding mode. Chain A produced an RMSD of 0.408 Å and was selected for all subsequent analyses. Full grid box coordinates for both chains are reported in Table 2.

**Table 2.** Grid box parameters and redocking validation results

| Ligand | Native Ligand (PRG) | Chain A | Chain B |
|---|---|---|---|
| ***Number Grid Point*** | **X** | 20 | 20 |
| | **Y** | 20 | 20 |
| | **Z** | 20 | 20 |
| ***Coordinate Grid Point*** | **X** | 22,853 | 36.380 |
| | **Y** | 10.139 | 33.660 |
| | **Z** | 60.282 | 42.749 |
| ***Spacing Grid Point*** | | 1.000 Å | 1.000 Å |
| **RMSD** | | 0.408 Å | 0.588 Å |
| **ΔG** | | -11.48 kcal/ mol | -11.50 kcal/ mol |

## 6. Docking Protocol

Molecular docking was performed using AutoDock 4 with the Lamarckian Genetic Algorithm (LGA) to predict ligand–receptor interactions. AutoDock4 employs a physics-based scoring function to estimate binding affinity and identify optimal ligand conformations [29]. The docking protocol was carried out using 100 genetic algorithm runs to enhance conformational sampling and improve the reliability of the results. This approach is consistent with commonly applied molecular docking procedures and has been widely used in structure-based drug discovery studies [30]. These parameters were selected to ensure sufficient conformational sampling and reproducibility of the docking results. The docking protocol followed standard procedures commonly applied in molecular docking studies [31-33] and established AutoDock methodologies [34][35]. All ligands were docked using the same grid box configuration centered on the active site to ensure consistency and comparability of the results.

## 7. Visualization and Superimposition

Docking results were visualized using BIOVIA Discovery Studio and PyMOL in both 2D and 3D formats. Interaction analysis was conducted to identify hydrogen bonds, hydrophobic interactions, and other non-covalent interactions between ligands and receptor residues. Structural superimposition between the best-performing ligand, glucoraphanin, and the native ligand was also performed to evaluate binding mode similarity within the PRG binding pocket. This step was used to assess whether glucoraphanin occupied a comparable binding region and interacted with key amino acid residues

involved in ligand recognition. The similarity of binding orientation and residue interaction patterns was considered as supporting evidence for the potential relevance of glucoraphanin as a candidate ligand for PRG.

### 8. ADMET Prediction

For further evaluation of the drug-likeness of the screened compounds, ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) prediction was conducted using pkCSM. Parameters analyzed included solubility, lipophilicity, gastrointestinal absorption, blood–brain barrier permeability, cytochrome P450 interactions, and toxicity profiles. This analysis was performed to complement the docking results by providing insight into the pharmacokinetic properties and safety profiles of the compounds.

## RESULTS AND DISCUSSION

### 1. Receptor Preparation

The progesterone receptor (PRG) with PDB code 1A28 was obtained from the RCSB PDB database. This receptor contains two chains (A and B), with the natural ligand progesterone, which binds via hydrogen bonding and hydrophobic interactions. The structure was chosen because it is suited for docking analysis and has a high resolution (1.80 Å), which allows for thorough atomic visualization. At the molecular level, PRG is one of the estrogen target genes that contributes to breast cancer cell proliferation and also acts as a prognostic marker [36][37]. Meanwhile, in clinical practice, PRG and estrogen receptors are used as international standard biomarkers for diagnosis, hormone status evaluation, and breast cancer therapy determination, as recommended in the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) Guideline update [38]. Receptor preparation was carried out using Biovia Discovery Studio by eliminating water molecules and the native ligand to prevent interference with test ligand interactions.

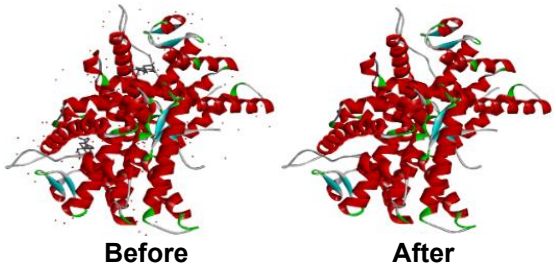



**Figure 1**. Structure of the progesterone receptor (PRG) with PDB ID: 1A28

### 2. Ligand and Native Ligand Preparation

Ligand preparation incorporated energy minimization to obtain the most thermodynamically stable conformation for each compound, thereby improving the reliability of predicted binding poses [39]. The preparation process also included the native ligand (progesterone) to guarantee that the observed interactions originated solely from the test ligands, without interference from existing bonds that could affect docking results [40]. The docking protocol was validated through redocking, yielding an RMSD value of 0.408 Å. This validation ensured that the parameters used could accurately reproduce the ligand's original position [41]. A grid box was defined as the binding region, adjusted through grid size and grid center (coordinates along the x, y, and z axes) to ensure docking simulations were focused on the receptor's active site [42].

The accuracy of the method was confirmed by calculating the Root Mean Square Deviation (RMSD), with values ≤ 2 Å considered valid [43][44], confirming that the AutoDock 4

protocol reliably reproduces the crystallographic binding pose under the defined grid box parameters. Although progesterone is bound to both chains A and B in the crystal structure, subtle differences in ligand orientation between the two chains result in distinct grid coordinates and different redocking outcomes (RMSD: chain A = 0.408 Å; chain B = 0.588 Å). Chain A was therefore selected as the sole reference receptor to ensure consistency of the binding site definition across all docking simulations.

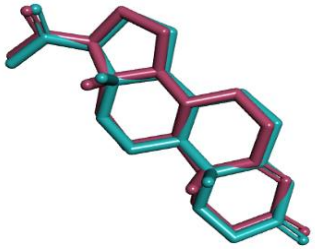


**Figure 2.** Validation Results of the Native Ligand (Progesterone) in the PRG (Blue: before re-docking & Pink: after re-docking)

### 3. Docking Performance and Comparative Analysis

The docking data were analyzed according to each compound's binding affinity, where lower binding free energy indicates easier ligand-receptor binding and greater interaction stability [45]. The binding affinities and inhibition constants (Ki) obtained from molecular docking of all ligands against the PRG active site are summarized in Table 3.

The molecular docking results demonstrated that all tested compounds were able to interact with the progesterone receptor (PRG), with varying binding affinities (Table 3). Among the screened ligands, glucoraphanin showed the most favorable binding affinity compared to other compounds derived from white radish. However, its binding energy remained weaker than that of the native ligand and the control drug tamoxifen, indicating that its interaction strength is still limited.

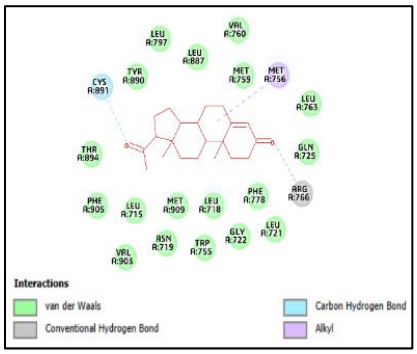
**Table 3.** Docking results of bioactive compounds with the progesterone receptor (PRG).

| Ligand | Binding Affinity | Inhibition constant (Ki) |
|---|---|---|
| Native ligand 1 | -11.18 kcal/mol | 6.39 nM |
| Tamoxifen | -6.19 kcal/mol | 29.25 µM |
| 2-methoxyphenol-4-vinyl | -4.27 kcal/mol | 739.12 µM |
| 2,4-dimethylphenol | -4.44 kcal/mol | 556.56 µM |
| Squalene | -4.50 kcal/mol | 504.37 µM |
| Glucoraphanin | -4.85 kcal/mol | 278.66 µM |
| Violaxanthin | +1.18e+003 | - |

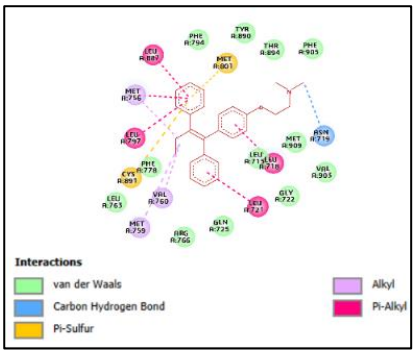
The estimated inhibition constant (Ki) further supported this finding, where glucoraphanin was in the micromolar range, whereas effective ligand–receptor interactions are typically associated with nanomolar values. This suggests that, although glucoraphanin is the best among the tested natural compounds, it cannot yet be considered a strong binder to the PRG receptor.

Violaxanthin showed a highly positive binding energy, indicating an unstable interaction with the receptor. This may be attributed to steric incompatibility or an inability to fit properly within the binding pocket, resulting in unfavorable docking poses. Squalene, on the other hand, demonstrated moderate binding affinity but exhibited high lipophilicity, which may affect its solubility and bioavailability. These findings highlight that favorable docking results alone do not guarantee drug-like properties.

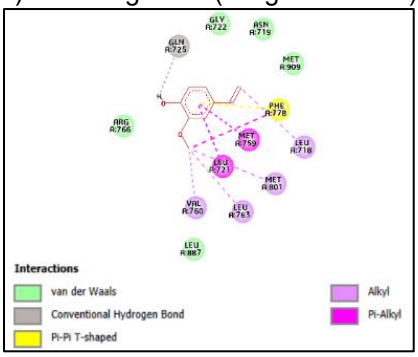
This finding indicates that while glucoraphanin demonstrates relatively better interaction compared to other tested natural compounds, its binding strength is still considerably weaker than established ligands. As binding affinity reflects the stability of ligand–receptor interactions, more negative values correspond to stronger binding due to lower free energy states [46][47].



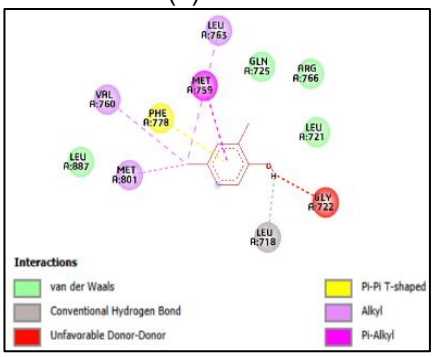

(a) Native ligand 1 (Progesterone A)



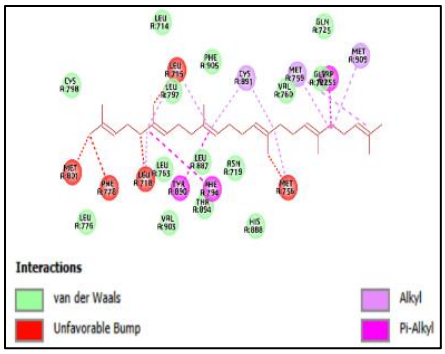

(b)Tamoxifen



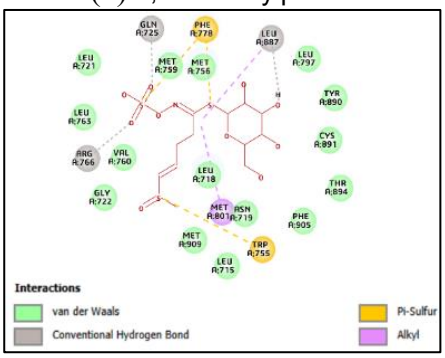

(c)2-methoxyphenol-4-vinyl



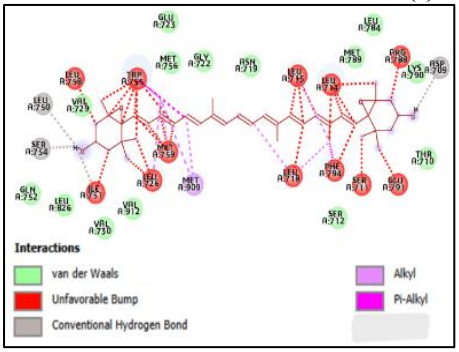

(d) 2,4-dimethylphenol




(e) Squalene




(f) Glucoraphanin




(g) Violaxanthin

**Figure 3.** 2D Visualization of Molecular Docking Results

**Table 4.** Frequency of amino acid residues interacting with ligands

| Residue | Type of interaction | Number of ligands | Ligands involved |
|---|---|---|---|
| Arg766 | H-bond | 2 | Native ligand 1 (Progesteron A), Glucoraphanin. |
| | Hydrophobic | 3 | Tamoxifen, 2-methoxyphenol-4-vinyl, 2,4-dimethylphenol. |
| Leu718 | H-bond | 1 | 2,4-dimethylphenol. |
| | Hydrophobic | 5 | Native ligand (Progesteron A), Tamoxifen, Squalene, Glucoraphanin, Violaxanthin. |
| Met801 | Hydrophobic | 4 | Tamoxifen, 2,4-dimethylphenol, Squalene, Glucoraphanin. |
| Leu763 | Hydrophobic | 6 | Native ligand 1 (Progesterone A), Tamoxifen, 2-methoxyphenol-4-vinyl, 2,4-dimethylphenol, Squalene, Glucoraphanin. |
| Phe794 | π–π stacking | 3 | Tamoxifen, Squalene, Violaxanthin. |
| Asp590 | H-bond | 1 | Violaxanthin |
| Ser754 | H-bond | 1 | Violaxanthin |

## 4. Binding Interaction and Residue Analysis

Interaction analysis revealed that several amino acid residues contributed to ligand binding within the PRG active site. Among these, Arg766 was consistently observed in interactions involving both the native ligand and glucoraphanin. This residue is known to contribute to binding stabilization through hydrogen bonding, suggesting that glucoraphanin partially mimics the interaction pattern of the native ligand. However, it is important to note that the presence of shared residues does not necessarily indicate identical binding mechanisms. Instead, it reflects only partial overlap in binding interactions, which may not fully translate into comparable biological activity.

The molecular interaction analysis demonstrated that glucoraphanin showed binding activity, showing partial similarity with the native ligand, particularly through its interaction with the Arg766 residue of the progesterone receptor. This similarity suggests that glucoraphanin adopts a binding mode resembling that of the native ligand, highlighting its potential to interact with the receptor. These results align with previous soaking studies on progesterone receptors. For example, Mathew et al., [48] reported that reference ligands interacted with residues Arg766, Val760, and Phe778. Similarly, Shahab et al., [49] emphasized the role of Arg766 in stabilizing the ligand-receptor complex through hydrogen bonding, thereby enhancing ligand affinity. Moreover, Khan et al., [50] demonstrated that conserved residues among steroid receptors interact with the steroid A-ring, influencing the transcriptional activity of progesterone.

Interaction analysis revealed that several ligands shared common amino acid residues with the native ligand, including key residues such as Arg766. The presence of shared residues suggests partial similarity in binding location; however, this does not necessarily indicate an identical binding mechanism. Superimposition analysis

showed that glucoraphanin partially overlaps with the native ligand within the binding pocket, although differences in overall conformation indicate that the binding mode is not identical. This suggests that similarity in interacting residues alone is insufficient to confirm comparable biological activity. This finding highlights that similarity in interacting residues alone is insufficient to confirm comparable biological activity, as ligand conformation and interaction geometry also play crucial roles in receptor binding.

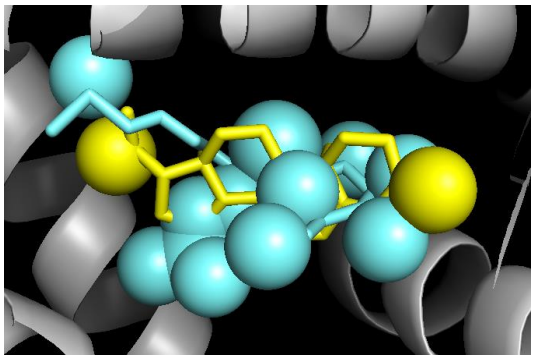


**Figure 4.** Superimposition of glucoraphanin (blue) and native ligand (yellow) within PRG binding pocket.

## 5. ADMET Analysis and Pharmacokinetic Evaluation

ADMET analysis was used to assess the pharmacokinetic characteristics of the selected ligands in order to supplement the docking results, including acceptable molecular weight, hydrogen bond donors and acceptors, and good predicted solubility. Glucoraphanin exhibited low membrane permeability and extremely low intestinal absorption, indicating poor oral bioavailability. This limitation is likely associated with its high polarity, which restricts passive diffusion across biological membranes [51]. The compound also demonstrated a favorable safety profile, with no significant indications of hepatotoxicity or mutagenicity based on in silico predictions.

In contrast, squalene demonstrated better membrane permeability due to its lipophilic nature but showed poor aqueous solubility, indicating a trade-off between permeability and solubility. This highlights a common challenge in drug development, where improving one physicochemical property may negatively affect another [52]. Additionally, several compounds were predicted to be substrates of P-glycoprotein (P-gp), suggesting that efflux mechanisms may further reduce intracellular drug accumulation and overall bioavailability. This illustrates the classical solubility permeability trade-off that must be managed during lead optimization.

Furthermore, the Lipinski rule of five analysis suggested that glucoraphanin is within an acceptable range for oral bioavailability, although slight deviations related to polarity may occur. Overall, these findings suggest that glucoraphanin possesses acceptable pharmacokinetic and safety characteristics, supporting its potential for further investigation as a bioactive compound.

## 6. Comparative Evaluation of Key Compounds

The combined analysis of docking and ADMET results indicates that glucoraphanin is the most promising compound among the screened white radish constituents in terms of receptor interaction. However, its pharmacokinetic limitations, particularly poor absorption and low permeability, significantly reduce its potential as an orally active drug candidate. Conversely, squalene exhibited

better membrane permeability but insufficient solubility, which may limit its application without formulation optimization.

These findings suggest that none of the tested compounds fully satisfy both binding affinity and pharmacokinetic requirements. Therefore, they should be positioned as early-stage lead compounds rather than fully developed drug candidates. This study has several limitations. The docking approach employed a rigid receptor model, which does not account for protein flexibility. In addition, ADMET predictions were based on computational models and require experimental validation. Furthermore, no molecular dynamics simulations were performed to evaluate the stability of ligand–receptor complexes over time.

**Table 5.** ADMET prediction results of all ligands using pkCSM

| Name Model | Gluco-raphanin | 2Methoxy phenol-4vinyl | 2,4-Dimethyl phenol | Squalene | Violaxanthin | Tamoxifen |
|---|---|---|---|---|---|---|
| A1 | -2.338 | -1.958 | -1.224 | -8.401 | -6.461 | -5.929 |
| A2 | -0.681 | 1.499 | 1.611 | 1.193 | 0.384 | 1.065 |
| A3 | 0 | 91.965 | 92.865 | 89.002 | 90.257 | 96.885 |
| A4 | -2.735 | -2.262 | -1.763 | -2.763 | -2.855 | -2.737 |
| A5 | Yes | No | No | No | No | Yes |
| A6 | No | No | No | No | Yes | Yes |
| A7 | No | No | No | Yes | Yes | Yes |
| D1 | -0.564 | 0.118 | 0.302 | 0.35 | -0.444 | 0.83 |
| D2 | 0.692 | 0.322 | 0.459 | 0 | 0 | 0.093 |
| D3 | -1.761 | 0.289 | 0.339 | 0.965 | -0.175 | 1.329 |
| D4 | -3.913 | -2.0442 | -1.944 | -0.935 | -1.561 | -1.473 |
| M1 | No | No | No | No | No | No |
| M2 | No | No | No | Yes | Yes | Yes |
| M3 | No | Yes | No | No | No | Yes |
| M4 | No | No | No | No | No | No |
| M5 | No | No | No | No | No | No |
| M6 | No | No | No | No | No | Yes |
| M7 | No | No | No | No | No | No |
| E1 | 0.39 | 0.233 | 0.227 | 1.791 | 0.511 | 0.556 |
| E2 | No | No | No | No | No | No |
| T1 | No | Yes | No | No | No | Yes |
| T2 | 1.225 | 1.067 | 0.458 | -0.533 | -0.85 | 0.313 |
| T3 | No | No | No | No | No | Yes |
| T4 | No | No | No | Yes | No | Yes |
| T5 | 2.197 | 2.076 | 2.204 | 1.893 | 2.259 | 2.285 |
| T6 | 3.136 | 2.019 | 2.046 | 0.911 | 1.991 | 0.41 |
| T7 | No | No | No | No | No | No |
| T8 | No | Yes | Yes | No | No | No |
| T9 | 0.285 | 0.071 | 0.169 | 0.483 | 0.304 | 0.316 |
| T10 | 5.557 | 1.957 | 1.654 | -3.275 | -2.227 | 0.6 |

## CONCLUSION

This study demonstrated that active compounds from white radish are capable of interacting with the progesterone receptor, although with relatively weaker binding affinity compared to the native ligand and tamoxifen. Among the tested compounds, glucoraphanin showed the most favorable docking results; however, ADMET analysis revealed significant pharmacokinetic limitations, particularly poor absorption and low membrane permeability. Therefore, glucoraphanin may serve as an early-stage lead compound for further investigation, but additional optimization and experimental validation are required before it can be further evaluated as a viable drug candidate.

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