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Computational identification of insecticide candidates targeting vitellogenin receptor in *Bemisia tabaci* using docking and ADMET analysis

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Abstract

Bemisia tabaci (whitefly) is a major agricultural pest responsible for significant crop losses worldwide, primarily due to its high reproductive capacity and resistance to conventional insecticides. The vitellogenin receptor (VgR), a key protein involved in yolk uptake during oocyte development, represents a promising molecular target for disrupting insect reproduction. In this study, a structure-based in silico workflow was employed to identify potential small-molecule inhibitors of the VgR of *B. tabaci*. The three-dimensional structure of VgR was obtained using AlphaFold and functionally annotated, identifying the β-propeller domain as the primary ligand-binding region. A library of bioactive compounds, including known insecticides and plant-derived flavonoids, was screened using molecular docking. The top-ranking compounds were further evaluated using in silico ADMET and toxicity prediction tools. Docking analysis revealed that afidopyropen exhibited the highest binding affinity (−9.2 kcal/mol), while several flavonoids, including quercetin (−8.8 kcal/mol), isorhamnetin (−8.7 kcal/mol), and genkwanin (−8.4 kcal/mol), showed comparable interaction strengths. Toxicity profiling, incorporating predicted acute oral LD_{50} values, indicated that genkwanin (LD_{50} ≈ 3,919 mg/kg) and isorhamnetin (LD_{50} ≈ 5,000 mg/kg) possessed relatively favorable safety profiles with low acute toxicity (toxicity class 5). In contrast, afidopyropen (LD_{50} > 2,000 mg/kg) and quercetin (LD_{50} ≈ 159 mg/kg) showed multiple predicted organ toxicities, with quercetin indicating higher acute toxicity (toxicity class 3). Among all candidates, genkwanin demonstrated the most balanced profile, combining strong binding affinity with lower predicted acute toxicity and fewer organ-specific risks. Overall, this study highlights the vitellogenin receptor as a viable target for reproductive interference in *B. tabaci* and identifies genkwanin as a promising lead compound for further experimental validation. The findings support the use of integrated in silico screening strategies in the rational development of safer, more sustainable insect control agents.

Keywords: Bemisia tabaci; Vitellogenin receptor; Afidopyropen; In-silico studies; ADMET analysis

1. Introduction

Bemisia tabaci, commonly known as whitefly, is a sap-sucking insect that threatens global food security if not properly managed (Abubakar et al., 2022). It infects many important crops such as tomatoes, peppers, watermelons, cassava, and cowpeas, causing vegetative damage and spreading diseases, which leads to higher pesticide costs (Li et al., 2021). With high reproductive capacity, one female can lay up to 320 eggs quickly, leading to rapid population growth within a few generations (Abubakar et al., 2022; Musa & Ren, 2005). Whiteflies are found worldwide. Currently, control methods

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include integrated pest management strategies, primarily involving chemical insecticides that target essential insect proteins (Abubakar et al., 2022; Saleem et al., 2022).

In oviparous insects such as Bemisia tabaci, the Vitellogenin receptor (VgR) a low-density protein- plays a crucial role in reproductive development by mediating the uptake of vitellogenin into developing oocytes (Lian et al., 2022). At the molecular level, VgR is composed of several domains; The **low-density lipoprotein class A repeats (LDLa)**, located in the extracellular region, are responsible for calcium-dependent ligand binding and contribute to the initial recognition of vitellogenin molecules. Adjacent to these repeats are epidermal growth factor **(EGF)-like domains**, which participate in receptor folding, stability, and conformational changes during endocytosis. A central and functionally critical component of the receptor is the **β-propeller domain**, which plays a key role in ligand release and receptor recycling (Han et al., 2022). Following ligand binding, the Vg-VgR complex clusters in clathrin-coated pits on the oocyte surface and undergoes clathrin-mediated endocytosis. Upon internalization of the Vg-VgR complex via clathrin-mediated endocytosis, acidification of the endosomal environment induces conformational changes in the β-propeller domain, facilitating dissociation of vitellogenin from the receptor (Lei et al., 2025).

The significance of vitellogenin receptor for insect reproduction and survival is well-established; however, its exploitation as a target for specific chemical inhibition remains largely under-explored, particularly through rational in silico methods. Currently, the traditional methods of insecticide discovery are augmented by computer-aided drug design (CADD), which offers a cost-effective path to identifying novel bioactive compounds for insect control (Sabe et al., 2021). In this context, the integration of molecular docking and ADMET profiling is highly effective for the high-throughput virtual screening of chemical libraries against insect protein targets, enabling the rapid identification of high-affinity ligands (Bhardwaj et al., 2021). This methodology is not only efficient but critical for early prioritization of lead compounds, as in silico ADMET analysis filters candidates based on predicted pharmacokinetics, bioavailability, and ecotoxicity, which are key determinants of downstream success and environmental safety (Ancuceanu et al., 2025). Although this computational pipeline has been successfully applied to other *Bemisia tabaci* targets (Gahalyan et al., 2025), and validated in integrated discovery workflows (Da Costa et al., 2022). A targeted computational search for small-molecule inhibitors specifically designed to bind and disrupt *B. tabaci*. VgR has not been conducted. This strategy was subsequently applied to VgR to identify and prioritize drug-like lead compounds with high potential for subsequent experimental validation.

Accordingly, this study aims to employ a structure-based in silico workflow to identify possible VgR inhibitors in *Bemisia tabaci*. To achieve this, a reliable three-dimensional model of the target VgR protein will be constructed through homology modeling, followed by the prediction of its primary ligand-binding site. Subsequently, a library of bioactive compounds was screened using molecular docking to compare their binding modes and affinities. Finally, a comparative ADMET analysis of the top-ranking compounds was performed to evaluate their pharmacokinetic and toxicity profiles.

2. Methodology

2.1. Retrieval of Target Protein Sequence

The amino acid sequence of the vitellogenin receptor (VgR) from *Bemisia tabaci* was retrieved from UniProt (UniProt ID: A0A6J1HVE9) and saved in FASTA format (Muhammed & Aki-Yalcin, 2024). The protein sequence, comprising over 1800 amino acids, was modeled using the AlphaFold Protein Structure Database (Jumper et al., 2021). The top-ranked model was selected based on the AlphaFold ranking score. Structural confidence was assessed using predicted Local Distance Difference Test (pLDDT) scores, yielding an overall value of 70.34, with higher confidence in the β-propeller domain (residues 1340–1660; pLDDT = 74.40). Additional metrics included pTM (0.49), iPTM (0.49), and a disordered residue fraction of 0.14 (Abramson et al., 2024). Although the global pLDDT indicates moderate confidence, pLDDT varies across large multi-domain proteins, often providing reliable local predictions even when overall scores are lower; the elevated confidence in the β-propeller ligand-binding region supports the model's suitability for structure-based analyses (Cazals & Sarti, 2024).

The prepared AlphaFold model was submitted to the PrankWeb server for structure-based ligand-binding site prediction (Jendele et al., 2019; or appropriate PrankWeb citation). The top-ranked pocket, is identified by the highest probability score (0.901), had); the following center coordinates: x = 16.7081, y = -19.6875, z = 12.7643. The predicted binding pocket residues (chain A) were: A_1375, A_1377, A_1378, A_1381, A_1419, A_1420, A_1421, A_1424, A_1461, A_1463, A_1464, A_1465, A_1466, A_1468, A_1511, A_1512, A_1513, A_1514, A_1515, A_1517, A_1553, A_1554, A_1555, A_1556, A_1557, A_1601, A_1602, A_1603, A_1604, A_1609, A_1610, A_1611. This pocketThe location was verified to lie within the β-propeller domain annotated by InterPro (Polák et al., 2025).

Functional domains in the VgR sequence were annotated using InterPro, confirming the presence and boundaries of the conserved β-propeller domain, designated as the primary target for inhibitor screening (Blum et al., 2025). annotated by InterPro (Polák et al., 2025).

The three-dimensional coordinates of the selected PrankWeb pocket were used to define the docking search space. A grid box (center x = 15.9900, y = -20.9980, z = 14.4455) encompassing the pocket with a 5 Å margin in all directions was constructed using AutoDock Tools.

A chemical library of 60 compounds was prepared for virtual screening, including: the known insecticide afidopyropen (PubChem CID: 131676375) as a positive control; plant-derived flavonoids genkwanin (CID: 5281617) and isorhamnetin (CID: 5281654); and 57 additional structurally diverse compounds from natural product databases (e.g., PubChem, COCONUT) selected for reported insect growth regulatory effects. Canonical SMILES for all ligands were obtained from PubChem and COCONUT. Ligands were prepared using PyRx, involving conversion to PDBQT format, addition of Gasteiger charges, rotatable bond assignment, and energy minimization with the Universal Force Field (UFF) (Dallakyan & Olson, 2015; Diedrich et al., 2023; Muhammed & Aki-Yalcin, 2024).

Molecular docking was performed using PyRx with the prepared protein (PDBQT format) and ligand library as inputs. Docking employed the predefined grid box, with exhaustiveness set to 82 for thorough sampling (Dallakyan & Olson, 2015). For each compound, the conformation with the most negative binding free energy (ΔG, kcal/mol) was retained. The top 8 compounds with the strongest affinities were selected as primary hits. Protein-ligand interactions (hydrogen bonds, hydrophobic contacts, ionic interactions) were analyzed and visualized using PyMOL 2.5 and PoseEdit (Dallakyan & Olson, 2015; Diedrich et al., 2023).

Top-ranked compounds were evaluated for toxicity and environmental safety using ADMETlab 2.0 and ProTox-II. Acute toxicity (oral LD_{50} in rodents and toxicity classes) and organ-specific toxicities (hepatotoxicity, neurotoxicity, nephrotoxicity, respiratory toxicity, cardiotoxicity, carcinogenicity, immunotoxicity, mutagenicity, cytotoxicity) were predicted with ProTox-II (Banerjee et al., 2018). Ecotoxicological risks, including toxicity to aquatic organisms (e.g., *Daphnia magna*, fish), persistence, and bioaccumulation, were assessed via ADMETlab 2.0 (Xiong et al., 2021).

These evaluations enabled the identification of compounds balancing strong binding affinity with favorable safety profiles, supporting rational lead selection for further experimental validation.

3. Results and Discussion

Table 1 Binding Affinities of Eight Compounds to the Beta Propeller Domain of VgR Protein

S/N	Compound Name	Compound Id	Binding Affinity
1	**pentoxifylline**	cnp0155893.0	-7.3
2	**Genkwanin**	cnp0145919.0	-8.4
3	**Isorhamnetin**	cnp0304008.0	-8.7
4	Gossypol	cid3503	-7.4
5	Quercetin	cid5280343	-8.8
6	Azadirachtin	cid5281303	-5.9
7	Suramin	cid5361	-8
8	Afidopyropen	cid54589430	-9.2

Molecular docking analysis revealed variable binding affinities of the screened compounds toward the β-propeller domain of the vitellogenin receptor. Afidopyropen exhibited the strongest binding affinity (−9.2 kcal/mol), indicating the highest predicted binding stability within the target pocket. Among the plant-derived compounds, quercetin (−8.8 kcal/mol), isorhamnetin (−8.7 kcal/mol), and genkwanin (−8.4 kcal/mol) showed strong binding affinities comparable to the reference compound suramin (−8.0 kcal/mol). Moderate binding interactions were observed for gossypol (−7.4 kcal/mol) and pentoxifylline (−7.3 kcal/mol), while azadirachtin displayed the weakest interaction with the target protein (−5.9 kcal/mol). Overall, the docking results suggest that afidopyropen and selected flavonoids, particularly

quercetin, isorhamnetin, and genkwanin, possess favorable binding characteristics toward the vitellogenin receptor β-propeller domai

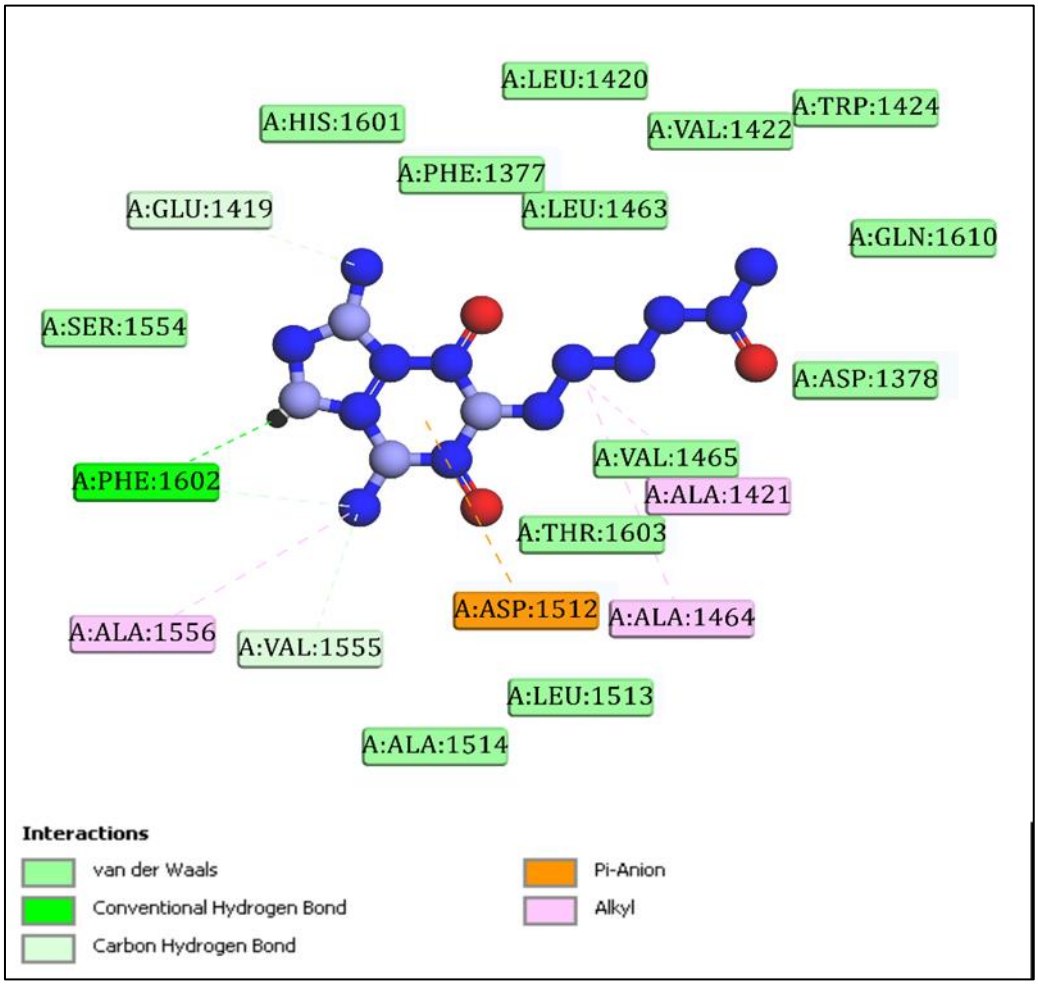

Figure 1 2D Molecular Interaction Map of Genkwanin Bound to the β-Propeller Domain of the Vitellogenin Receptor

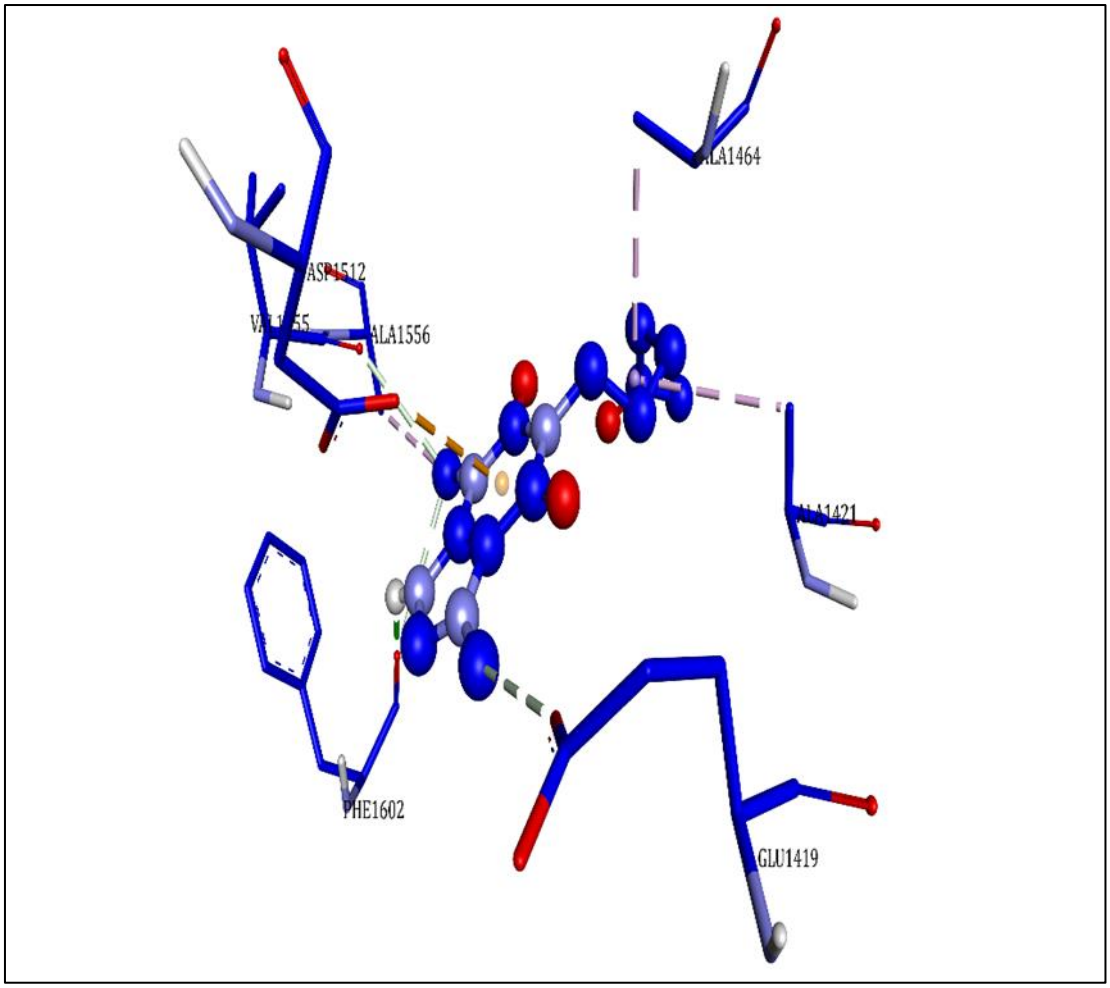

Figure 2 3D Binding Interaction of Genkwanin within the β-Propeller Domain of the Vitellogenin Receptor

The predicted acute toxicity and organ-specific safety profiles of the screened compounds revealed notable differences in toxicological behavior (table 2). Based on LD_{50} values and toxicity class assignments, suramin exhibited the lowest acute toxicity (LD_{50} = 10,000 mg/kg; class 6), indicating a high margin of safety. Genkwanin and isorhamnetin also demonstrated low acute toxicity, with LD_{50} values of 3,919 mg/kg and 5,000 mg/kg, respectively, both classified under toxicity class 5. In contrast, quercetin (LD_{50} = 159 mg/kg; class 3) and gossypol (LD_{50} = 325 mg/kg; class 4) showed relatively higher acute toxicity, suggesting narrower safety margins.

Organ-specific toxicity predictions indicated that hepatotoxicity was absent across all compounds. Neurotoxicity was predicted for pentoxifylline alone, whereas nephrotoxicity and respiratory toxicity were commonly predicted across several compounds, including genkwanin, isorhamnetin, gossypol, quercetin, and afidopyropen. Cardiotoxicity was predicted for isorhamnetin and afidopyropen, while carcinogenicity and immunotoxicity were observed sporadically among the compounds. Mutagenicity and cytotoxicity predictions were generally absent, suggesting low genotoxic and cellular toxicity risks for most candidates.

Suramin demonstrated the most favorable safety profile overall combining low acute toxicity with minimal predicted organ toxicity. Among the plant-derived compounds, genkwanin and isorhamnetin exhibited comparatively safer toxicity profiles relative to quercetin and gossypol, supporting their consideration as promising lead candidates despite not being the strongest binders in docking analysis. Afidopyropen, although exhibiting the highest binding affinity, displayed multiple predicted organ toxicities, highlighting a trade-off.

Table 2 Predicted acute and organ toxicity endpoints for candidate vitellogenin receptor inhibitors targeting *Bemisia tabaci*.

s/n	compound	LD50/ mg/kg	Toxicity class	Hepatotoxicity	Neurotoxicity	Nephrotoxicity	Respiratory toxicity	Cardiotoxicity	Carcinogenicity	Immunotoxicity	Mutagenicity	Cytotoxicity	Clinical toxicity	Nutritional toxicity
1	pentoxifylline	780mg/kg	4	Inactive	Active	Inactive	Active	Inactive	Inactive	Inactive	Inactive	Inactive	Active	Inactive
2	Genkwanin	3919mg/kg	5	Inactive	Inactive	Active	Active	Inactive	Active	Inactive	Active	Inactive	Active	Inactive
3	Isorhamnetin	5000mg/kg	5	Inactive	Inactive	Active	Active	Active	Inactive	Active	Inactive	Inactive	Inactive	Active
4	Gossypol	325mg/kg	4	Inactive	Inactive	Active	Active	Inactive	Inactive	Active	Inactive	Inactive	Active	Inactive
5	Quercetin	159mg/kg	3	Inactive	Inactive	Active	Active	Inactive	Active	Inactive	Active	Inactive	Inactive	Active
7	Suramin	10000mg/kg	6	Inactive	Inactive	Active	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Active	Inactive
8	Afidopyropen	1213mg/kg	4	Inactive	Inactive	Active	Active	Active	Inactive	Active	Inactive	Inactive	Active	Active

4. Discussion

The maintenance and continuation of insect populations rely on female reproductive capacity. Therefore, any disruption of female fertility pathway can have considerable impact on population growth and reduce the economic losses caused by insect pests. The VgR facilitates the uptake of vitellogenin into developing oocytes, making it a strategic molecular target for reproductive interference strategies in pest management (Guo et al., 2025; Miccoli & Randazzo, 2025). In this study insilico methods were employed to identify potential inhibitors of VgR in *bemesia tabacci* with emphasis on the β propeller domain, which is associated with ligand dissociation and receptor recycling (Miccoli & Randazzo, 2025).

Molecular docking analysis revealed a wide range of binding affinities among the screened compounds, with values ranging from −5.9 to −9.2 kcal/mol (Alruwaili et al., 2025; Muhammed & Aki-Yalcin, 2024). Afidopyropen exhibited the strongest predicted binding affinity, followed closely by quercetin, isorhamnetin, genkwanin, and suramin. The narrow differences observed among the top-ranking compounds, particularly within the −8.4 to −8.8 kcal/mol range, suggest comparable binding potentials and fall within the typical uncertainty limits of docking-based scoring functions (Muhammed & Aki-Yalcin, 2024; Shirali et al., 2025). As a result, binding affinity alone was not sufficient to define the most suitable lead compound which underscored the importance of integrating interaction analysis and toxicity profiling into the lead selection process(ref).

Detailed inspection of ligand–receptor interaction patterns provided additional insights. Genkwanin showed a compact and well-lining the functional core of the domain (Wang et al., 2025).This binding mode suggests a higher likelihood of interfering with conformational changes required for ligand release and receptor recycling. In contrast, although isorhamnetin exhibited a marginally higher docking score, its binding orientation was comparatively more surface-exposed, potentially resulting in reduced stability within the pocket (Park et al., 2025). These qualitative interaction features support the prioritization of genkwanin for detailed structural illustration despite its slightly lower binding affinity.

Toxicity profiling played a decisive role in refining lead selection(Bo et al., 2023) (Qin et al., 2026) Acute toxicity predictions indicated that several compounds, including quercetin and gossypol, fell into more toxic classes with lower LD_{50} values, raising concerns regarding mammalian safety. Afidopyropen, despite its superior binding affinity, was associated with multiple organ-specific toxicity alerts, including cardiotoxicity and immunotoxicity, which limit its suitability as a lead agrochemical candidate (Sangaraju et al., 2024). In contrast, genkwanin and isorhamnetin exhibited relatively high LD_{50} values and comparable toxicity classes; however, isorhamnetin showed additional cardiotoxic and immunotoxicity alerts. Genkwanin demonstrated fewer critical organ toxicity predictions, suggesting a more favorable safety margin.From an agrochemical development perspective, safety considerations are particularly important, as compounds intended for pest control must minimize risks to non-target organisms and the environment (Shekhar et al., 2024). Natural flavonoids such as genkwanin offer additional advantages, including structural simplicity, biodegradability, and prior evidence of bioactivity in plant–insect interactions (Pereira et al., 2024; Riddick, 2024). The balanced profile of genkwanin, characterized by strong binding affinity, a well-defined interaction pattern, and comparatively lower predicted organ toxicity, supports its designation as the most promising lead compound among those evaluated.

Comparatively, previous in silico studies on *Bemisia tabaci* have largely focused on other molecular targets involved in hormone regulation, detoxification, or nervous system signaling (Indu et al., 2025). The present study differs in that it targets the vitellogenin receptor, a reproductive protein that has received limited attention in structure-based insecticide discovery. Moreover, the integration of molecular docking with acute toxicity, organ-specific toxicity, and ecotoxicity prediction represents a comprehensive screening strategy that enhances early-stage lead prioritization and aligns with modern sustainable pest management goals (Sampaio de Sousa et al., 2025). Despite the strengths of this study, certain limitations should be acknowledged. Molecular dynamics simulations were not performed to further evaluate the stability of ligand–receptor complexes over time, and all toxicity assessments were based on predictive computational models (Kovalishyn et al., 2025). While these approaches are well-established for preliminary screening, experimental validation through biochemical binding assays and in vivo bioassays in *B. tabaci* will be necessary to confirm the predicted inhibitory effects. Future studies may also explore structural optimization of genkwanin to enhance specificity and potency while further reducing potential toxicity.

5. Conclusion

This study identified the β-propeller domain of the *Bemisia tabaci* vitellogenin receptor as a viable target for small-molecule inhibition. It demonstrated the importance of structure-based in silico screening workflow for agrochemical

discovery. Among the screened compounds, genkwanin emerged as the most balanced lead candidate based on its favorable binding characteristics, interaction profile, and predicted safety. These findings provide a foundation for subsequent experimental validation and contribute to the rational development of novel, reproduction-targeted control strategies for *Bemisia tabaci*.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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