Megahed *et al. Beni-Suef Univ J Basic Appl Sci (2025) 14:97*
https://doi.org/10.1186/s43088-025-00686-y

Beni-Suef University Journal of
Basic and Applied Sciences

RESEARCH **Open Access**

Antiviral activity of turmeric (*Curcuma longa*) against potato virus Y: in silico molecular docking analysis

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Abstract

Background This study investigates the antiviral potential of turmeric-derived compounds, particularly curcuminoids, against the Egyptian strain of Potato Virus Y (PVY^N-Egypt) using in silico molecular docking simulations. The binding interactions of five key compounds—curcumin, bisdemethoxycurcumin, demethoxycurcumin, isorhamnetin, and ribavirin (as a control)—were evaluated against three essential viral proteins: P1 protease, helper component proteinase (HCPro), and coat protein, to assess their therapeutic viability.

Results Molecular docking results revealed that isorhamnetin exhibited the strongest binding affinity toward P1 protease. Curcumin and bisdemethoxycurcumin showed favorable binding to both HCPro and CP. ADMET profiling demonstrated that most tested ligands, except for curcuminol and ribavirin, had good oral bioavailability and favorable gastrointestinal absorption. Polar surface area (PSA), a key factor in membrane permeability and drug-likeness, was also considered—compounds with lower PSA values generally show better bioavailability. However, potential toxicity concerns were identified for curcuminol and ribavirin. Among the compounds, curcumin and its derivatives—particularly isorhamnetin—emerged as promising antiviral candidates, while bisdemethoxycurcumin showed potential to inhibit viral replication. Ribavirin displayed moderate binding but fewer favorable interactions compared to curcumin-based ligands.

Conclusion This study provides new insights into the development of antiviral agents targeting PVY. The findings support the potential of curcumin derivatives, especially isorhamnetin and bisdemethoxycurcumin, as effective antiviral agents. Further experimental validation is recommended to explore their applications in agriculture and pharmaceutical biotechnology.

Keywords Antiviral activity, Curcumin, In silico, Molecular docking, Turmeric, Potato Virus Y

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1 Background

Potato Virus Y (PVY) is one of the most widespread and economically destructive plant viruses affecting potato crops globally. As a member of the *Potyvirus* genus, PVY is primarily transmitted in a non-persistent manner by aphids, making its control particularly challenging in open-field agricultural settings. Infected plants typically exhibit a wide range of symptoms, including mosaic patterns on leaves, leaf curling, stunted growth, and tuber discoloration—all of which can severely compromise both yield and market quality [1, 2]. In temperate regions where PVY is endemic, yield losses can be substantial, posing a significant threat to global food security and the potato industry. The persistent impact of PVY, combined with the lack of effective antiviral treatments, underscores the urgent need for novel, sustainable strategies to manage this pathogen. Therefore, this study explores the potential of turmeric-derived bioactive compounds as natural antiviral agents, utilizing in silico molecular docking to identify candidates that may inhibit PVY replication and transmission mechanisms. Symptoms not only reduce overall crop yield but also compromise the quality and marketability of the harvested produce. In severely affected fields, yield losses can reach up to 30%, resulting in considerable economic impact. Financial burdens are further amplified by the increased reliance on pesticides, elevated disease management expenses, and the loss of tubers that meet commercial standards [2, 3]. In Europe and North America, losses associated with PVY amount to millions of dollars each year, representing a major constraint on potato production and profitability [4]. In Egypt-one of the leading potato producers in the Middle East and North Africa (MENA) region-PVY poses a serious threat to sustainable cultivation. Potatoes rank among the country's most valuable agricultural export commodities, and reports of PVY infections have been on the rise, especially in the Nile Delta region, where much of Egypt's potato farming is concentrated [5, 6]. The virus not only affects yield but also diminishes the market value of the tubers, as symptoms reduce their quality and appearance, making them unsuitable for export. The economic burden in Egypt is further compounded by the lack of efficient control measures and the limited availability of resistant potato varieties.

Given these challenges, the adoption of alternative control strategies—particularly plant-derived antiviral agents—has become increasingly vital to protect Egypt's potato industry. At present, the management of PVY largely relies on chemical treatments, which raises significant concerns regarding environmental impact and the potential development of resistant viral strains [7]. As a result, there is growing interest in exploring more sustainable and effective solutions, including the application of natural, plant-based compounds for combating viral infections in crops [8]. Among these, curcumin—the principal bioactive compound in *Curcuma longa* (turmeric)—has attracted considerable attention due to its broad spectrum of biological activities, including antiviral, antibacterial, and anticancer properties [9]. Curcumin, the bioactive component of *Curcuma longa* (turmeric), has attracted significant attention due to its broad antiviral efficacy against several viruses, including HIV, Hepatitis B, and Influenza. This efficacy is primarily attributed to its ability to interfere with viral entry, replication, and modulation of the host immune response [10, 11]. Molecular docking is a computational method frequently employed in drug development and structural biology to predict interactions between two molecules, typically a target protein and a small bioactive ligand [10]. This approach entails positioning the ligand within the active or binding site of a target protein and assessing the interaction's strength and specificity using scoring functions. These functions take into account key factors such as binding affinity, hydrogen bonding, hydrophobic interactions, and steric compatibility [12]. Molecular docking offers valuable insights into the molecular mechanisms underlying ligand–protein interactions, facilitating the identification of potential inhibitors or modulators for therapeutic or biotechnological use [13]. It is especially beneficial in in silico studies, enabling efficient virtual screening and optimization of candidate compounds prior to experimental validation [14].

Molecular docking has emerged as a powerful tool in the study of plant viruses, particularly in the development of antiviral agents aimed at controlling viral plant diseases. This computational technique enables researchers to investigate the interactions between key viral proteins—critical for processes such as replication, movement, and host infection—and potential inhibitory compounds derived from either synthetic sources or natural products [15]. By targeting essential viral elements, including RNA-dependent RNA polymerases, coat proteins, and helicases, molecular docking facilitates the identification of molecules capable of interfering with the viral life cycle [15]. This approach has proven especially useful in evaluating bioactive compounds from medicinal plants, many of which exhibit notable antiviral properties. For example, docking studies have been used to examine the binding of phytochemicals to the coat proteins of Tobacco mosaic virus (TMV) and Potato virus X (PVX), offering valuable insights into their potential to disrupt viral assembly or reduce infectivity [16]. Through high-throughput virtual screening and structural refinement, molecular docking significantly accelerates the discovery of environmentally friendly, plant-based antiviral agents to help reduce crop losses caused by plant viruses.

Recent advancements in in silico molecular docking investigations have introduced new insights into the interactions between bioactive compounds and viral proteins [11]. These computational approaches allow investigators to deduce the binding affinity and molecular interactions between compounds and target viral proteins, offering valuable insights into their antiviral potential [17]. In the context of PVY, exploring curcumin's binding interactions with key viral proteins may provide a novel strategy for managing PVY infections in potatoes. As Egypt continues to face significant challenges from PVY, the development of integrated pest management strategies and the exploration of natural antiviral agents, such as curcumin, are becoming increasingly critical. This study aims to investigate the in silico molecular docking interactions between curcumin and key PVY proteins, evaluating its potential as a natural antiviral agent against this economically devastating virus.

Advancements in both computational and experimental techniques emphasize the promise of curcumin and its derivatives as broad-spectrum agents. Complementary network pharmacology and in vitro studies have confirmed curcumin's efficacy against porcine deltacoronavirus (PDCoV), revealing its multifaceted mechanisms of inhibiting host–virus interactions. Similarly, Mitra et al. [18] investigated the antiviral properties of dexamethasone and its derivatives against COVID-19, employing molecular docking and ADMET analyses to identify promising therapeutic candidates. Further studies by [19, 20] explored the inhibition of human respiratory syncytial virus (RSV) through Daclatasvir derivatives and other bioactive compounds, demonstrating their ability to target and disrupt critical viral proteins such as the M and F proteins, supported by extensive molecular dynamics simulations. Building on this, [21] performed structure-based virtual screening against RSV envelope proteins, identifying novel inhibitors with strong binding stability and potential therapeutic value. Additionally, the integration of artificial intelligence and machine learning techniques in drug repurposing efforts was exemplified by [22], who identified several FDA-approved drugs with potential efficacy against COVID-19, underscoring the growing importance of in silico approaches in antiviral drug discovery. Collectively, these findings provide a strong rationale for applying similar computational strategies to evaluate turmeric-derived compounds as potential inhibitors of PVY, aiming to develop effective antiviral agents for plant viral diseases.

Curcumin has shown wide-ranging pharmacological potential, yet its clinical application remains limited due to poor bioavailability and a lack of mechanistic clarity. While several studies have employed computational or experimental approaches, few integrate both to provide a comprehensive evaluation. This study addresses these gaps by combining in silico modeling with in vitro validation to assess newly designed curcumin derivatives. The selected compounds were screened for drug-like properties and tested experimentally to confirm biological activity, offering stronger translational relevance. Additionally, the work provides new mechanistic insights into the molecular pathways affected by these derivatives, expanding the current understanding of curcumin's therapeutic targets. Overall, this integrative approach offers a valuable framework for advancing curcumin-based drug development.

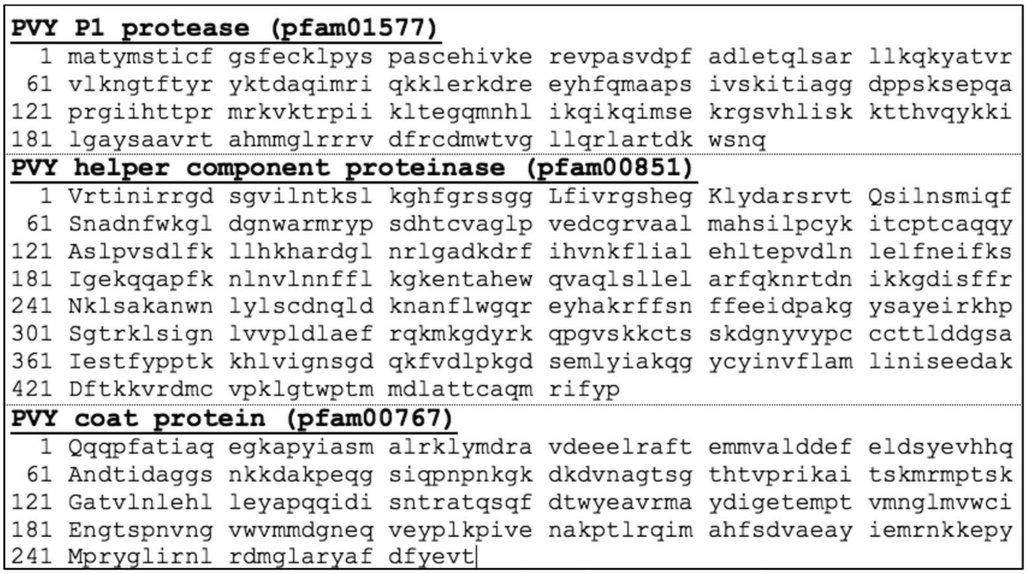
2 Methods

2.1 Target proteins of PVY^{N}-Egypt strain

To ensure clarity and uniformity throughout the manuscript, all compound names (e.g., bisdemethoxycurcumin, demethoxycurcumin, and isorhamnetin) have been consistently formatted in lowercase, following standard scientific nomenclature conventions. The target proteins selected in this study include P1 protease, helper component proteinase (HCPro), and coat protein (CP). Each protein plays a crucial role in the replication cycle of Potato Virus Y (PVY). P1 protease is involved in processing the viral polyprotein, HCPro acts as a suppressor of gene silencing and assists in viral movement, while the coat protein is essential for viral assembly and transmission. The amino acid sequences of three key proteins from Potato virus Y strain N-Egypt (Accession No. AAM81207) (Fig. 1) are provided. These proteins include: a) Potyvirus P1 Protease (pfam01577)**:** This protease is involved in the processing of viral polyproteins. The sequence spans amino acids 1–200, with functional domains associated with viral replication and processing. b) Helper Component Proteinase (pfam00851)**:** This protein is essential for virus transmission by aphids and functions a decisive work in the replication cycle. The sequence spans amino acids 1–421, with conserved regions associated with proteinase activity and aphid transmission. c) Potyvirus Coat Protein (pfam00767)**:** The coat protein encapsulates the viral RNA, enabling viral stability and transmission. The sequence spans amino acids 1–241, containing key domains involved in the formation of the viral capsid and interaction with host cells.

2.2 Selection of target proteins

The protein sequences of the PVY^{N}-Egypt strain were retrieved in FASTA format from the NCBI database**.** (https://www.ncbi.nlm.nih.gov). To obtain their 3D structures in PDB format, a search was conducted on the Protein Data Bank (PDB) (https://www.rcsb.org/). For target proteins lacking experimental 3D structures,



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PVY P1 protease (pfam01577)
  1 matymsticf gsfecklpys pascehivke revpasvdpf adletqlsar llkqkyatvr
 61 vlkngtftyr yktdaqimri qkklerkdre eyhfqmaaps ivskitiagg dppsksepqa
121 prgiihttpr mrkvktrpii kltegqmnhl ikqikqimse krgsvhlisk ktthvqykki
181 lgaysaavrt ahmmglrrrv dfrcdmwtvg llqrlartdk wsnq
PVY helper component proteinase (pfam00851)
  1 Vrtinirrgd sgvilntksl kghfgrssgg Lfivrgsheg Klydarsrvt Qsilnsmiqf
 61 Snadnfwkgl dgnwarmryp sdhtcvaglp vedcgrvaal mahsilpcyk itcptcaqqy
121 Aslpvsdlfk llhkhardgl nrlgadkdrf ihvnkflial ehltepvdln lelfneifks
181 Igekqqapfk nlnvlnnffl kgkentahew qvaqlsllel arfqknrtdn ikkgdisffr
241 Nklsakanwn lylscdnqld knanflwgqr eyhakrffsn ffeeidpakg ysayeirkhp
301 Sgtrklsign lvvpldlaef rqkmkgdyrk qpgvskkcts skdgnyvypc ccttlddgsa
361 Iestfypptk khlvignsgd qkfvdlpkgd semlyiakqg ycyinvflam liniseedak
421 Dftkkvrdmc vpklgtwptm mdlattcaqm rifyp
PVY coat protein (pfam00767)
  1 Qqqpfatiaq egkapyiasm alrklymdra vdeeelraft emmvalddef eldsyevhhq
 61 Andtidaggs nkkdakpeqg siqpnpnkgk dkdvnagtsg thtvprikai tskmrmptsk
121 Gatvlnlehl leyapqqidi sntratqsqf dtwyeavrma ydigetempt vmnglmvwci
181 Engtspnvng vwvmmdgneq veyplkpive nakptlrqim ahfsdvaeay iemrnkkepy
241 Mpryglirnl rdmglaryaf dfyevt
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Fig. 1 Amino acid sequences of the Potyvirus P1 protease, helper component proteinase, and coat protein from PVY.^{N}-Egypt strain (Accession No. AAM81207.1)

homology modeling was employed using tools such as SWISS-MODEL or Phyre2 to generate 3D models based on sequence similarity to known structures.

2.3 Ramachandran plot and model validation

The quality and accuracy of the modeled structures were assessed through validation techniques, including Ramachandran plot analysis, to ensure structural reliability. To assess the stereochemical quality of the PVY^{N}-Egypt strain protein model, a Ramachandran plot analysis was performed using the PROCHECK tool available via the SAVES v6.0 server (https://saves.mbi.ucla.edu/). This analysis evaluates the backbone dihedral angles (phi and psi) of amino acid residues to determine their conformational plausibility. The percentage of residues falling into favored, allowed, and disallowed regions was calculated, and the results were used to validate the reliability and stability of the predicted three-dimensional structure. Only models with acceptable stereochemical properties were retained for molecular docking studies.

2.4 Selection of bioactive compounds from turmeric and related phytochemicals

A set of bioactive compounds—including bisdemethoxycurcumin, caffeic acid, curcumin, curcuminol, curdione, demethoxycurcumin, isorhamnetin, sinapic acid, and ribavirin (used as a control)—were selected based on their previously reported antiviral properties. Their 2D chemical structures were obtained in SDF format from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). The selection focused on compounds structurally related to curcumin, the primary active constituent of turmeric, and those demonstrating favorable pharmacokinetic profiles as predicted by SwissADME. Only ligands with well-characterized and reliable physicochemical data were included to ensure the accuracy of molecular docking simulations. This targeted selection strategy was designed to provide a scientifically relevant yet manageable set of candidate compounds for evaluating potential antiviral activity against Potato Virus Y.

2.5 Virtual screening of bioactive compounds

A small compound library consisting of the selected bioactive compounds was created for virtual screening. PyRx software (https://sourceforge.net/projects/pyrx/), which utilizes energy minimization and docking via the AutoDock Vina plugin, was employed for screening the compounds against the PVY replicase and coat protein. Compounds with lower binding energy values, suggesting stronger binding potential, were prioritized. The 2D structures were converted to 3D and optimized for energy minimization using Open Babel and Chem3D. Furthermore, the compounds were evaluated for drug-likeness and bioavailability by applying Lipinski's rule of five through tools like SwissADME [23].

2.6 Molecular docking procedure

Molecular docking was performed using AutoDock Vina. The docking grid was centered on the active or functional site of each viral protein, with grid box dimensions adjusted to cover the entire binding pocket while maintaining computational efficiency. The exhaustiveness parameter was set to 8 to balance speed and accuracy. Ten binding poses were generated for each ligand, and the one with the lowest binding energy and favorable interactions was selected for further analysis. Hydrogen bonding, hydrophobic contacts, and π–π interactions were visualized and analyzed using Discovery Studio Visualizer and PyMOL.

2.7 ADMET prediction

To evaluate the drug-likeness and pharmacokinetic profiles of curcumin and its derivatives, ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) analysis was conducted using the SwissADME and pkCSM web servers. Parameters such as water solubility, gastrointestinal absorption, blood–brain barrier permeability, cytochrome P450 interactions, and potential toxicity were assessed to prioritize compounds with favorable bioavailability and safety profiles.

2.8 Visualization and analysis

Using Discovery Studio 2022 [24], the docking results were analyzed and visualized to examine key interactions, including hydrogen bonds, hydrophobic interactions, and ionic interactions.

3 Results

3.1 Physicochemical properties of ligands

Data in Table 1 demonstrates the physicochemical properties of a series of ligands used in virtual screening, including molecular weight (MW), rotatable bonds (RB), and hydrogen bonding potential (acceptors and donors). These properties provide insights into the potential bioactivity, solubility, and drug-likeness of the compounds. The molecular weight of the compounds varies significantly. Curcuminol is the heaviest compound, with a molecular weight of 566.51 g/mol. In contrast, caffeic acid and sinapic acid are on the lower end, with molecular weights of 180.16 g/mol and 224.21 g/mol, respectively. Most of the compounds analyzed in this study fall within the typical molecular weight (MW) range of drug-like molecules, which is generally considered to be between 200 and 500 g/mol. This range is often associated with favorable pharmacokinetic properties, including good absorption and membrane permeability. Curcuminol, however, is an exception, exhibiting a molecular weight above this typical range. Higher molecular weight compounds can face challenges such as reduced bioavailability and limited cellular uptake, which may impact their overall therapeutic potential. Therefore, while curcuminol demonstrates promising binding interactions in silico, its pharmacokinetic properties warrant further investigation through in vitro and in vivo studies to fully assess its viability as an antiviral agent.

The number of rotatable bonds among the compounds ranges from 1 in curdione to 13 in curcuminol, with the latter exhibiting the highest degree of molecular flexibility. This suggests that curcuminol may possess greater conformational diversity. In contrast, compounds such as curdione and caffeic acid have only 1 or 2 rotatable bonds, indicating more rigid molecular structures. The variation in hydrogen bond acceptors (HBA) and hydrogen bond donors (HBD) is also notable. Curcuminol and isorhamnetin exhibit the highest number of HBAs, with 12 and 7, respectively, whereas curdione contains only 2 HBAs and no HBDs. Ribavirin, a well-known antiviral compound, has a molecular weight of 244.2 g/mol, 3 rotatable bonds, and a balanced hydrogen bonding profile, comprising 7 HBAs and 4 HBDs. This profile suggests that Ribavirin is relatively small in size, moderately flexible, and possesses favorable hydrogen bonding potential—features that

Table 1 Physicochemical properties of ligands used in virtual screening: molecular weight, rotatable bonds, polar surface area and hydrogen bonding characteristics

Swiss ADMET	Molecular weight (g/mol)	Polar surface area (Å2)	No. rotatable bonds	No. H-bond acceptors	No. H-bond donors
Bisdemethoxycurcumin	308.33	74.600	6	4	2
Caffeic acid	180.16	77.760	2	4	3
Curcumin	368.38	93.060	8	6	2
Curcuminol	566.51	93.060	13	12	3
Curdione	236.35	34.140	1	2	0
Demethoxycurcumin	338.35	83.830	7	5	2
Isorhamnetin	316.26	116.45	2	7	4
Sinapic acid	224.21	76.000	4	5	2
Ribavirin (Control)	244.20	144.00	3	7	4

Notes: ADMET, Absorption, Distribution, Metabolism, Excretion, and Toxicity may contribute to its antiviral efficacy. Curcumin, with a molecular weight of 368.38 g/mol, contains 8 rotatable bonds and 6 HBAs, making it somewhat larger and more flexible than ribavirin. These properties may play a role in its biological activity. Similarly, demethoxycurcumin exhibits comparable physicochemical characteristics, indicating its potential as a promising candidate for virtual screening and further antiviral investigation.

Polar surface area (PSA) is another critical parameter influencing drug absorption, permeability, and overall bioavailability. In this study, PSA values ranged from 34.14 $Å^2$ in curdione to 144.00 $Å^2$ in ribavirin, with most compounds falling within the range commonly associated with good oral bioavailability (typically less than 140 $Å^2$). Compounds like curcumin (93.06 $Å^2$)**,** demethoxycurcumin (83.83 $Å^2$)**,** and bisdemethoxycurcumin (74.60 $Å^2$) exhibit moderate PSA values, suggesting favorable membrane permeability and potential for passive diffusion. In contrast, isorhamnetin (116.45 $Å^2$) and ribavirin (144.00 $Å^2$) approach exceeds the upper PSA threshold, which may limit passive cellular uptake but could still be compensated by active transport mechanisms. Curdione, with the lowest PSA, may have enhanced permeability but limited hydrogen bonding potential. Overall, the PSA distribution supports the drug-likeness of most tested ligands and helps interpret their predicted interactions in virtual screening against PVY^N-Egypt strain proteins.

3.2 ADMET properties and toxicity profile of ligands

The ADMET properties and toxicity profiles of the ligands used in virtual screening are critical in determining their pharmacokinetic behavior and potential therapeutic efficacy (Table 2). Data in this table summarize essential ADMET features, such as gastrointestinal (GI) absorption, blood–brain barrier (BBB) permeability, cytochrome P450 (CYP) inhibition, and compliance with Lipinski's rule of five, alongside their toxicity classification (toxic or non-toxic, T/NT). GI absorption is a significant determinant of a compound's bioavailability. Compounds with high GI absorption are generally expected to have favorable oral bioavailability. Most of the ligands (e.g., bisdemethoxycurcumin, caffeic acid, curcumin, curdione, demethoxycurcumin, isorhamnetin, and sinapic acid) are predicted to have high GI absorption, suggesting that they could be absorbed efficiently when administered orally. Curcuminol and ribavirin were predicted to have low gastrointestinal (GI) absorption, which may present challenges for their oral bioavailability. Low GI absorption often results in limited systemic exposure following oral administration, potentially reducing the therapeutic efficacy of these compounds. Ribavirin, despite its established antiviral use, is known to have variable oral bioavailability depending on formulation and dosage. For curcuminol, the low predicted absorption suggests that alternative delivery methods or formulation strategies might be necessary to enhance its bioavailability, such as nanoformulations or co-administration with absorption enhancers. These considerations highlight the importance of integrating pharmacokinetic profiling early in drug development to optimize candidate selection. Blood–brain barrier (BBB) permeability is a critical factor for compounds targeting central nervous system (CNS) disorders. Within this dataset, bisdemethoxycurcumin and curdione are predicted to be BBB permeant, suggesting their potential to cross the blood–brain barrier and act on CNS-related diseases. In contrast, most other ligands, including caffeic acid, curcumin, and demethoxycurcumin, are not expected to penetrate the BBB, indicating their suitability for treating peripheral conditions. Cytochrome P450 (CYP) enzymes

Table 2 ADMET properties and toxicity profile of ligands used in virtual screening: absorption, permeability, CYP inhibition, and Lipinski's rule

Swiss ADMET	GI absorption	BBB permeant	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Lipinski	T or NT
Bisdemethoxycurcumin	High	Yes	Yes	No	Yes	No	Yes	Yes	T
Caffeic acid	High	No	No	No	No	No	No	Yes	NT
Curcumin	High	No	No	No	Yes	No	Yes	Yes	NT
Curcuminol	Low	No	No	No	No	No	No	No	T
Curdione	High	Yes	No	No	No	No	No	Yes	T
Demethoxycurcumin	High	No	Yes	No	Yes	No	Yes	Yes	T
Isorhamnetin	High	No	Yes	No	No	Yes	Yes	Yes	NT
Sinapic acid	High	No	No	No	No	No	No	Yes	NT
Ribavirin (Control)	Low	No	No	No	No	No	No	Yes	NT

Notes: CYP, Cytochrome P450; ADMET, Absorption, Distribution, Metabolism, Excretion, and Toxicity; GI, Gastrointestinal; BBB, Blood–brain barrier; T, Toxic; and NT, Non Toxic play a pivotal role in drug metabolism, and inhibition of these enzymes can result in significant drug–drug interactions. Several compounds in this study are predicted to inhibit one or more CYP isoforms. Notably, bisdemethoxycurcumin and demethoxycurcumin inhibit multiple CYP enzymes such as CYP1A2, CYP2C9, and CYP3A4, which could pose risks of interactions if administered alongside other drugs metabolized by these pathways. Curcumin, isorhamnetin, and ribavirin specifically inhibit CYP3A4, an enzyme responsible for metabolizing a wide range of pharmaceuticals. Conversely, compounds like caffeic acid, curcuminol, curdione, sinapic acid, and ribavirin do not significantly inhibit major CYP enzymes, potentially lowering the risk of adverse metabolic interactions. Lipinski's "Rule of Five" remains a widely accepted criterion for evaluating the drug-likeness and oral bioavailability of compounds. The data indicate that most of the studied molecules, except for curcuminol, comply with Lipinski's parameters (noted as "Yes" under Lipinski), suggesting favorable drug-like properties and potential oral bioavailability. Curcuminol, characterized by its high molecular weight (566.51 g/mol) and elevated hydrogen bonding capacity, violates Lipinski's rule, implying potential challenges related to solubility and oral absorption.

Toxicity assessments are crucial for determining the safety profile of candidate compounds. According to the data, curcuminol and Curdione are classified as toxic, whereas all other compounds—including the control, ribavirin—are deemed non-toxic. This finding indicates that despite promising ADMET characteristics, the potential toxicity of curcuminol and Curdione could limit their therapeutic applicability.

3.3 Virtual screening of ligand binding affinity

Results presented in Table 3 and Figs. 2, 3 summarize the virtual screening outcomes for ligand binding affinities and root-mean-square deviation (RMSD) values

Table 3 Virtual screening of ligand binding affinity and root mean square deviation (RMSD) for PVY^{N}-Egypt strain proteins: P1 protease, helper component proteinase, and coat protein

PVY proteins	Ligands	Binding Affinity	RMSD/ub	RMSD/lb
P1 protease (pfam01577)	Bisdemethoxycurcumin	−6.4	0	0
	Caffeic acid	−5.7	0	0
	Curcumin	−6.4	0	0
	Curcuminol	−5.9	0	0
	Curdione	−6.1	0	0
	Demethoxycurcumin	−5.9	0	0
	Isorhamnetin	−7.1	0	0
	Sinapic acid	−5.5	0	0
	Ribavirin(Control)	−6.3	0	0
Helper component proteinase (pfam00851)	Bisdemethoxycurcumin	−6.4	0	0
	Caffeic_acid	−5.1	0	0
	Curcumin	−5.9	0	0
	Curcuminol	−6.2	0	0
	Curdione	−5.5	0	0
	Demethoxycurcumin	−6.4	0	0
	Isorhamnetin	−6.4	0	0
	Sinapic acid	−5	0	0
	Ribavirin (Control)	−5.8	0	0
Coat protein (pfam00767)	Bisdemethoxycurcumin	−6.5	0	0
	Caffeic_acid	−6.1	0	0
	Curcumin	−7.4	0	0
	Curcuminol	−6.3	0	0
	Curdione	−6.3	0	0
	Demethoxycurcumin	−6.5	0	0
	Isorhamnetin	−7.4	0	0
	Sinapic acid	−5.8	0	0
	Ribavirin (Control)	−6.6	0	0

Note: PVY^{N}, Potato virus Y strain N-Egypt

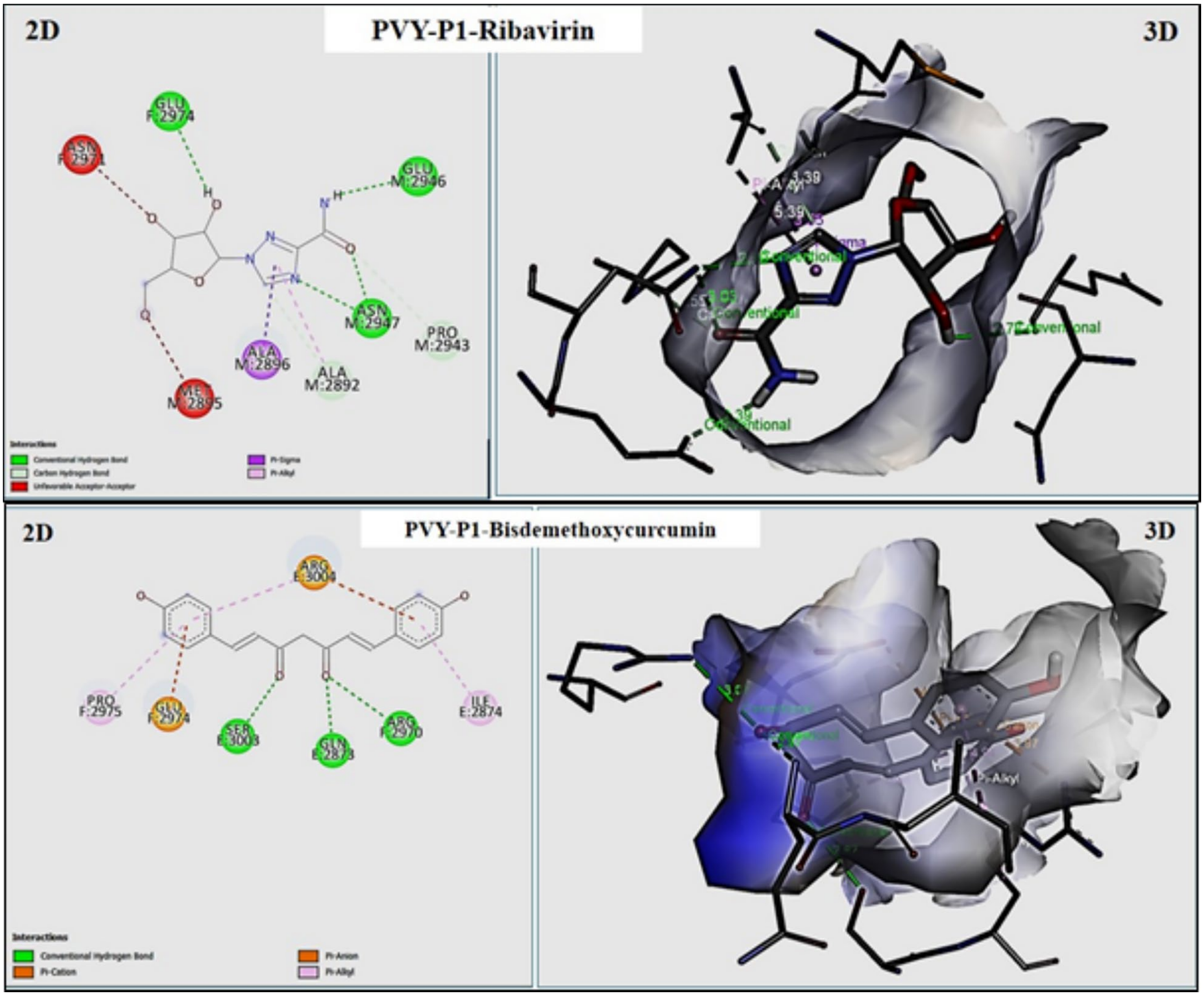

Fig. 2 2D and 3D structures of ribavirin and bisdemethoxycurcumin interactions with PVY P1 protease (pfam01577): amino acid binding sites and bonding types

against three key proteins of the PVY^N-Egypt strain: P1 protease, Helper Component Proteinase (HCPro), and Coat Protein (CP). Binding affinity is expressed in kcal/mol, with more negative values indicating stronger ligand–protein interactions. RMSD values are reported for both upper bound (ub) and lower bound (lb), reflecting the precision of the predicted ligand–protein complexes. Notably, all RMSD values are zero, indicating highly accurate docking predictions or minimal deviations from the initial ligand binding poses. The Potyvirus P1 protease (pfam01577) of PVY is a vital enzyme involved in polyprotein processing and viral replication. Among the tested ligands, binding affinities range from −5.5 to −7.1 kcal/mol, with Isorhamnetin demonstrating the strongest affinity at −7.1 kcal/mol, highlighting its potential as a promising inhibitor of this critical viral enzyme.

This suggests that Isorhamnetin may be a promising candidate for further exploration in antiviral drug design targeting the P1 protease. Other ligands, such as bisdemethoxycurcumin and curcumin, also display strong binding affinities of −6.4 kcal/mol, aligning with previous findings that curcuminoids exhibit antiviral properties. The control compound ribavirin (often used in antiviral research) exhibits a binding affinity of -6.3 kcal/mol, confirming its potential efficacy. The HCPro (pfam00851) is essential for virus transmission by aphids and aids in the viral replication cycle. The binding affinities for this protein span from −5.0 to −6.4 kcal/mol, with bisdemethoxycurcumin and demethoxycurcumin showing the most favorable binding at −6.4 kcal/mol. These results align with studies suggesting that curcuminoids have broad-spectrum antiviral activity, including against plant viruses. Isorhamnetin, another compound showing high

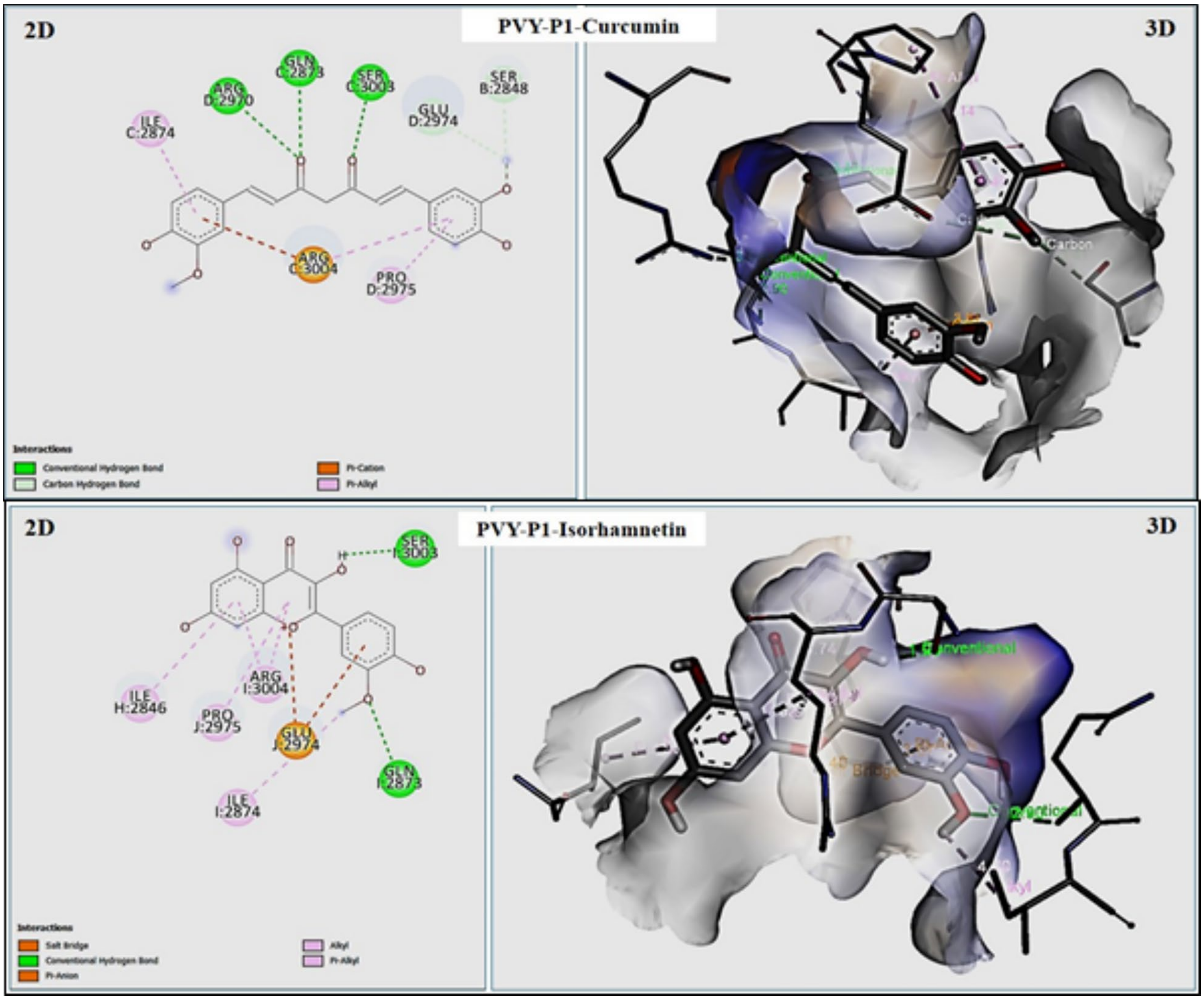

Fig. 3 2D and 3D structures of curcumin and isorhamnetin interactions with PVY P1 protease (pfam01577): amino acid binding sites and bonding types

affinity at −6.4 kcal/mol, could also represent a promising candidate for inhibiting HCPro activity. Additionally, the control compound ribavirin shows a slightly lower binding affinity of −5.8 kcal/mol, consistent with its known mechanism as an antiviral agent. The PVY^{N}-Egypt CP (pfam00767) is responsible for the encapsidation of viral RNA, a crucial step for virus stability and transmission. The binding affinities for ligands range from −5.8 to −7.4 kcal/mol, with curcumin and isorhamnetin exhibiting the most favorable binding at -7.4 kcal/mol. These results are consistent with previous works highlighting the antiviral potential of curcuminoids, which can disrupt viral capsid formation and viral RNA encapsidation. The control compound ribavirin shows a binding affinity of −6.6 kcal/mol, which is consistent with its established antiviral activity. The RMSD values for the ligand–protein complexes are reported as 0 across all ligand–protein interactions in this dataset. This suggests that there were no significant deviations between the predicted and observed ligand conformations. While RMSD values close to zero may suggest highly precise docking simulations, it is important to recognize that such results can also reflect inherent limitations of the docking methodology employed. Specifically, zero or near-zero RMSD values may indicate that only initial docking poses were evaluated without further refinement or validation steps, which can limit the reliability of claims regarding binding accuracy. Therefore, these findings should be interpreted with caution, and complementary methods or experimental validation are recommended to confirm the predicted ligand–protein interactions.

In this study, the interaction strength between bioactive compounds and the viral target was evaluated based on binding energy values (kcal/mol), as provided by AutoDock Vina. Binding energy serves as an effective comparative metric in molecular docking studies and indicates the predicted stability of the ligand–protein complex. While binding affinity values offer further insights, they typically require experimental validation or advanced simulations, which were beyond the current study's scope.

3.4 Docking scores for ligand interaction with PVY^N-Egypt strain proteins

Data in Table 4 present the docking scores for various ligands interacting with three key proteins from the PVY^N-Egypt strain: P1 protease, helper component proteinase, and coat protein. The docking scores, reported in kcal/mol, reflect the binding affinities of ligands to the target proteins, with more negative values indicating stronger binding. The P1 protease, essential for the cleavage of viral polyproteins, is a critical target for antiviral drug design. The docking scores for ligands interacting with this protein range from −6.3 to -7.5 kcal/mol, with bisdemethoxycurcumin and curcumin showing the most favorable docking scores of −7.5 kcal/mol. Isorhamnetin also shows a relatively strong binding score of −7.3 kcal/mol, indicating its potential as an effective ligand against P1 protease. The control compound, ribavirin, displayed a less favorable docking score of −6.3 kcal/mol, but still indicates significant interaction with the protein. These results suggest that curcumin derivatives and flavonoids such as isorhamnetin may serve as promising antiviral agents for inhibiting P1 protease function. The docking scores for ligands binding to HCPro range from −5.5 to −6.6 kcal/mol. Bisdemethoxycurcumin shows the highest docking score of −6.6 kcal/mol, followed by curcuminol at −6.5 kcal/mol. Isorhamnetin also demonstrates a docking score of −6.3 kcal/mol. Ribavirin, the control compound, shows the lowest docking score of −5.5 kcal/mol, which is still noteworthy but suggests it is less effective in binding to HCPro compared to the other ligands. The CP of PVY is responsible for encapsidating the viral RNA, a critical process for the stability and transmission of the virus. The docking scores for the ligands binding to the Coat protein range from −6.3 to −7.2 kcal/mol. Curcumin shows the strongest binding score at −7.2 kcal/mol. Isorhamnetin follows closely with a docking score of −6.5 kcal/mol. The control compound ribavirin displayed a docking score of −6.3 kcal/mol, which, although lower, still suggests a moderate affinity for CP.

Table 4 Docking scores for ligand interaction with PVY^N-Egypt strain proteins: P1 protease, helper component proteinase, and coat protein

PVY proteins	Ligand	Docking Scores
P1 protease (pfam01577)	Bisdemethoxycurcumin	−7.5
	Curcumin	−7.5
	Isorhamnetin	−7.3
	Ribavirin (Control)	−6.3
Helper component proteinase (pfam00851)	Bisdemethoxycurcumin	−6.6
	Curcumin	−6.3
	Curcuminol	−6.5
	Demethoxycurcumin	−6.3
	Isorhamnetin	−6.3
	Ribavirin (Control)	−5.5
Coat protein (pfam00767)	Curcumin	−7.2
	Isorhamnetin	−6.5
	Ribavirin (Control)	−6.3

Note: PVY^N, Potato virus Y strain N-Egypt

3.5 Detailed analysis of ligand interactions with PVY P1 protease

Data in Table 5 and Figs. 2, 3 demonstrate the analysis of ligand interactions with PVY P1 protease (pfam01577), providing a detailed understanding of the binding modes and interactions of various ligands to certain amino acid residues of the enzyme's active site. These interactions include various bond types such as Pi-Alkyl, Pi-Anion, hydrogen bonds, salt bridges, and unfavorable acceptor–acceptor interactions. These binding characteristics can influence the stability, specificity, and overall efficacy of ligand binding to the protease, which is critical for the design of therapeutic inhibitors targeting PVY P1 protease. Bisdemethoxycurcumin exhibits diverse binding types with the protease, including Pi-Anion, Pi-Alkyl, and conventional hydrogen bonds. Key residues involved in these interactions include ARG (E:3004), ILE (E:2874), ARG (F:2970), GLN (E:2873), SER (E:3003), GLU (F:2974), and PRO (F:2975). The presence of Pi-Anion and Pi-Alkyl interactions with ARG and ILE suggests strong aromatic interactions, which could enhance the establishment of the ligand in the protease's binding site, especially in hydrophobic regions. The hydrogen bonds with residues like GLN, SER, and ARG suggest that these interactions could contribute to the overall binding affinity by stabilizing the ligand in the active site. Curcumin shows a variety of interactions, including Pi-Alkyl, Pi-Cation, and hydrogen bonds with residues such as ARG (D:2970), GLN (C:2873), SER (C:3003), GLU (D:2974), PRO (D:2975), and ARG (C:3004). The Pi-Cation interaction between ARG (C:3004) and the ligand is significant as it enhances the binding stability in the active site. Pi-Alkyl interactions with ILE residues (such as ILE (C:2874)) further suggest that the ligand's aromatic groups are well-positioned to interact with hydrophobic areas of the protease. The inclusion of hydrogen bonds at multiple sites (e.g., GLN, SER) likely contributes to the

Table 5 Detailed analysis of ligand interactions with PVY^N P1 protease (pfam01577): amino acid binding sites and bonding types

Ligands	Amino acids	Sites	Type of bonds
Bisdemthoxycurcunin	ARG	E:3004	Pi-Anion & Pi-Alkyl
	ILE	E:2874	Pi-Alkyl
	ARG	F:2970	Conventional hydrogen
	GLN	E:2873	Conventional hydrogen
	SER	E:3003	Conventional hydrogen
	GLU	F:2974	Pi-Anion
	PRO	F:2975	Pi-Alkyl
Curcumin	ARG	D:2970	Conventional hydrogen
	GLN	C:2873	Conventional hydrogen
	SER	C:3003	Conventional hydrogen
	GLU	D:2974	Carbon hydrogen
	SER	B:2848	Carbon hydrogen
	Pro	D:2975	Pi-Alkyl
	ARG	C:3004	Pi-Alkyl & Pi-Cation
	ILE	C:2874	Pi-Alkyl
Isorhamnetin	SER	I:3003	Conventional hydrogen
	GLN	I:2873	Conventional hydrogen
	ILE	I:2874	Pi-Alkyl
	GLU	J:2974	Salt Bridge & Pi-Anion
	ARG	I:3004	Pi-Alkyl & Alkyl
	Pro	J:2975	Alkyl
	ILE	H:2846	Pi-Alkyl
Ribavirin	GLU	F:2974	Conventional hydrogen
	GLU	M:2946	Conventional hydrogen
	PRO	M:2943	Carbon hydrogen
	ASN	M:2947	Conventional hydrogen & Conventional hydrogen
	ALA	M:2892	Pi-Alkyl & Carbon hydrogen
	ALA	M:2896	Pi-Sigma
	MET	M:2895	Unfavorable acceptor-acceptor
	ASN	F:2971	Unfavorable acceptor-acceptor

Notes: PVY^N, Potato virus Y strain N-Egypt; ARG, Arginine; ILE, Isoleucine; GLN, Glutamine; SER, Serine; GLU, Glutamic acid; Pro, Proline; ASN, Asparagine; ALA, Alanine; and MET, Methionine

ligand's specificity and affinity for the protease, which is crucial for efficient inhibition. Isorhamnetin forms several key interactions, such as Pi-Alkyl, salt bridges, and hydrogen bonds with residues like SER (I:3003), GLN (I:2873), ILE (I:2874), GLU (J:2974), and ARG (I:3004). Salt bridge interactions with GLU (J:2974) are particularly significant, as salt bridges are known to enhance the stability of ligand–protein complexes by forming electrostatic interactions, which can provide a strong binding affinity. The hydrogen bonds with SER and GLN likely help to stabilize the ligand within the active site, increasing its specificity and binding affinity. Ribavirin interacts with several residues in the protease's active site, including GLU (F:2974), GLU (M:2946), PRO (M:2943), ASN (M:2947), ALA (M:2892), MET (M:2895), and ASN (F:2971). Ribavirin exhibits various bond types, including Pi-Alkyl, hydrogen bonds, and unfavorable acceptor–acceptor interactions. The Pi-Alkyl interaction with ALA (M:2892) and Pi-Sigma interaction with ALA (M:2896) are significant for stabilizing the ligand in the hydrophobic pocket of the protease. The existence of untoward acceptor–acceptor interactions, particularly with MET (M:2895) and ASN (F:2971) suggests that ribavirin may experience steric hindrance or reduced binding affinity due to these unfavorable interactions. This could be a drawback in its effectiveness as an inhibitor of PVY P1 protease.

3.6 Binding interactions of ligands with the PVY helper component proteinase

The analysis of ligand interactions with PVY helper component proteinase (pfam00851), as summarized in Table 6 and illustrated in Figs. 4, 5, provides an in-depth view of the binding mechanisms and the types of bonds formed between the ligands and key amino acid residues in the enzyme's active site. Understanding these interactions is essential for evaluating the potential inhibitory efficacy and designing optimized inhibitors. Bisdemethoxycurcumin primarily interacts with the protease through a combination of Pi-Alkyl, conventional hydrogen bonds, and carbon-hydrogen bonds. Key amino acids involved include LYS (A:54), SER (A:42), PHE (A:43), ARG (A:27), and ILE (A:28). Pi-Alkyl interactions with ARG (A:27) and LYS (A:54) suggest that aromatic rings of the ligand are positioned to interact with hydrophobic and electrostatic regions of the enzyme's active site, stabilizing the ligand–protein complex and enhancing binding affinity. The presence of conventional hydrogen bonds with residues such as SER and ILE further supports the formation of a strong, stable complex, likely contributing to the ligand's potency as a protease inhibitor. Curcumin forms a broad range of interactions, including Pi-Alkyl, Pi-Pi T-Shaped, Pi-Sulfur, and conventional hydrogen bonds. Notable binding sites include ALA (A:55), LEU (A:53), HIS (A:32), VAL (A:30), CYS (A:37), GLN (A:35), and LYS (A:54). The Pi-Pi T-shaped interaction with HIS (A:32) suggests that the aromatic structure of curcumin may form a planar interaction with the Histidine side chain, stabilizing the binding. Pi-Sulfur interactions with CYS (A:37), as well as Amide-Pi Stacked and Pi-Alkyl interactions with LYS (A:54), indicate that the ligand is engaging in both hydrophobic and electrostatic interactions, enhancing the overall binding stability. The variety

Table 6 Binding interactions of ligands with the PVY^N helper component proteinase (pfam00851): amino acid sites and bonding types

Ligands	Amino acids	Sites	Type of bonds
Bisdemthoxycurcunin	LYS	A:54	Pi-Alkyl
	SER	A:42	Conventional hydrogen
	PHE	A:43	Conventional hydrogen
	ARG	A:27	Pi-Alkyl & Carbon hydrogen
	ILE	A:28	Conventional hydrogen
Curcumin	ALA	A:55	Pi-Alkyl
	LEU	A:53	Pi-Alkyl
	HIS	A:32	Pi-Pi T-Shaped
	VAL	A:30	PI-Alky & Alkyl
	CYS	A:37	Alkyl & Pi-Sulfur
	GLN	A:35	Carbon Hydrogen
	GLN	A:60	Conventional hydrogen
	LYS	A:54	Amide-Pi Stacked & Alkyl
Curcuminol	GLN	A:60	Conventional hydrogen & Conventional hydrogen
	LYS	A:54	Conventional hydrogen & Pi-Alkyl
	ILE	A:52	Conventional hydrogen
	TYR	A:50	Conventional hydrogen
	CYS	A:37	Pi-Alkyl
	VAL	A:30	Alkyl & Pi-Alkyl
	PHE	A:64	Pi-Sulfur
	LEU	A:53	Pi-Alkyl
	ALA	A:55	Pi-Alkyl
Demethoxycurcumin	PRO	A:26	Conventional hydrogen
	ARG	A:27	Pi-Alkyl, Pi-Alkyl, Conventional hydrogen, Conventional hydrogen
Isorhamnetin	ILE	A:52	Alkyl
	THR	A:47	Carbon Hydrogen
	ARG	A:27	Conventional hydrogen. Pi-Alkyl, Alkyl, Unfavorable-Positive-Positive, Pi-Alkyl
	SER	A:42	Unfavorable acceptor-acceptor
	PHE	A:43	Carbon hydrogen
	LEU	A:53	Unfavorable acceptor-acceptor
	LYS	A:54	Alkyl, Carbon hydrogen
Ribavirin	PRO	A:26	Unfavorable acceptor-acceptor
	LEU	A:25	Conventional hydrogen
	ASP	A:41	Conventional hydrogen & Carbon hydrogen
	ARG	A:27	Pi-Alkyl
	THR	A:47	Conventional hydrogen
	ALA	A:55	Conventional hydrogen

Notes: PVY^N, Potato virus Y strain N-Egypt; LYS, Lysine; SER, Serine; PHE, Phenylalanine; ARG, Arginine; ILE, Isoleucine; ALA, Alanine; LEU, Leucine; HIS, Histidine; VAL, Valine; PRO, Proline; THR, Threonine; and ASP, Aspartic acid

of binding interactions, including carbon-hydrogen bonds and alkyl interactions, suggests that curcumin has a strong binding profile that could contribute to effective inhibition of the protease. Curcuminol also forms a wide array of interactions, including Pi-Alkyl, conventional hydrogen bonds, Pi-Sulfur, and alkyl interactions. The key binding residues include GLN (A:60), LYS (A:54), ILE (A:52), TYR (A:50), CYS (A:37), and LEU (A:53). Pi-Alkyl interactions with LYS (A:54) and VAL (A:30) suggest that hydrophobic interactions between the aromatic rings of the ligand and these residues are critical for stabilizing the complex. The Pi-Sulfur interaction with PHE (A:64) indicates that sulfur-containing groups may participate in aromatic stacking interactions, further stabilizing the ligand's binding within the active site. Hydrogen bonds at multiple sites (e.g., GLN (A:60) and LYS (A:54)) likely contribute to enhancing the ligand's affinity for the protease. Demethoxycurcumin primarily forms Pi-Alkyl,

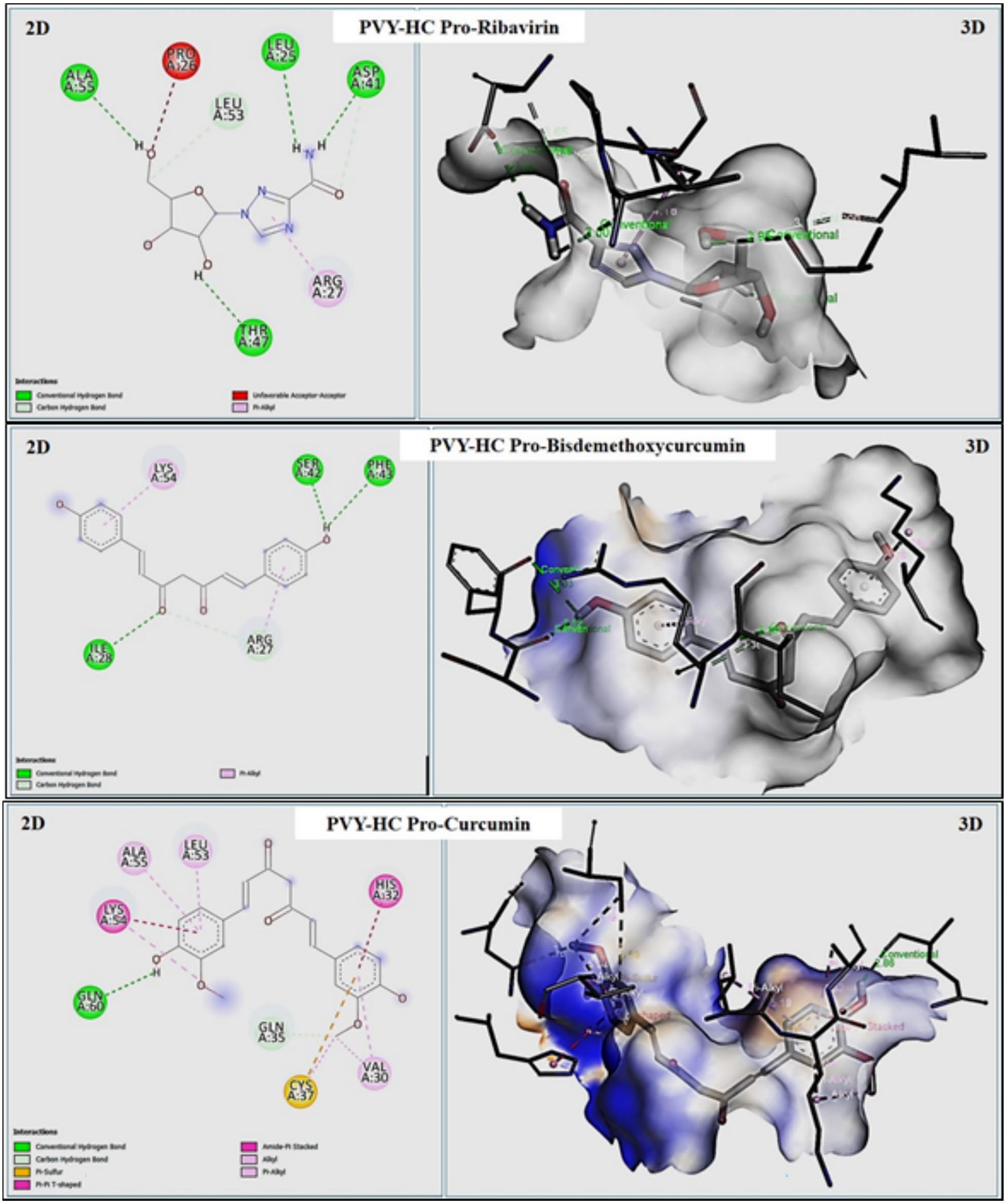

Fig. 4 2D and 3D structure of ribavirin, bisdemethoxycurcumin, and curcumin interactions with PVY-HC Pro (pfam00851): amino acid binding sites and bonding types

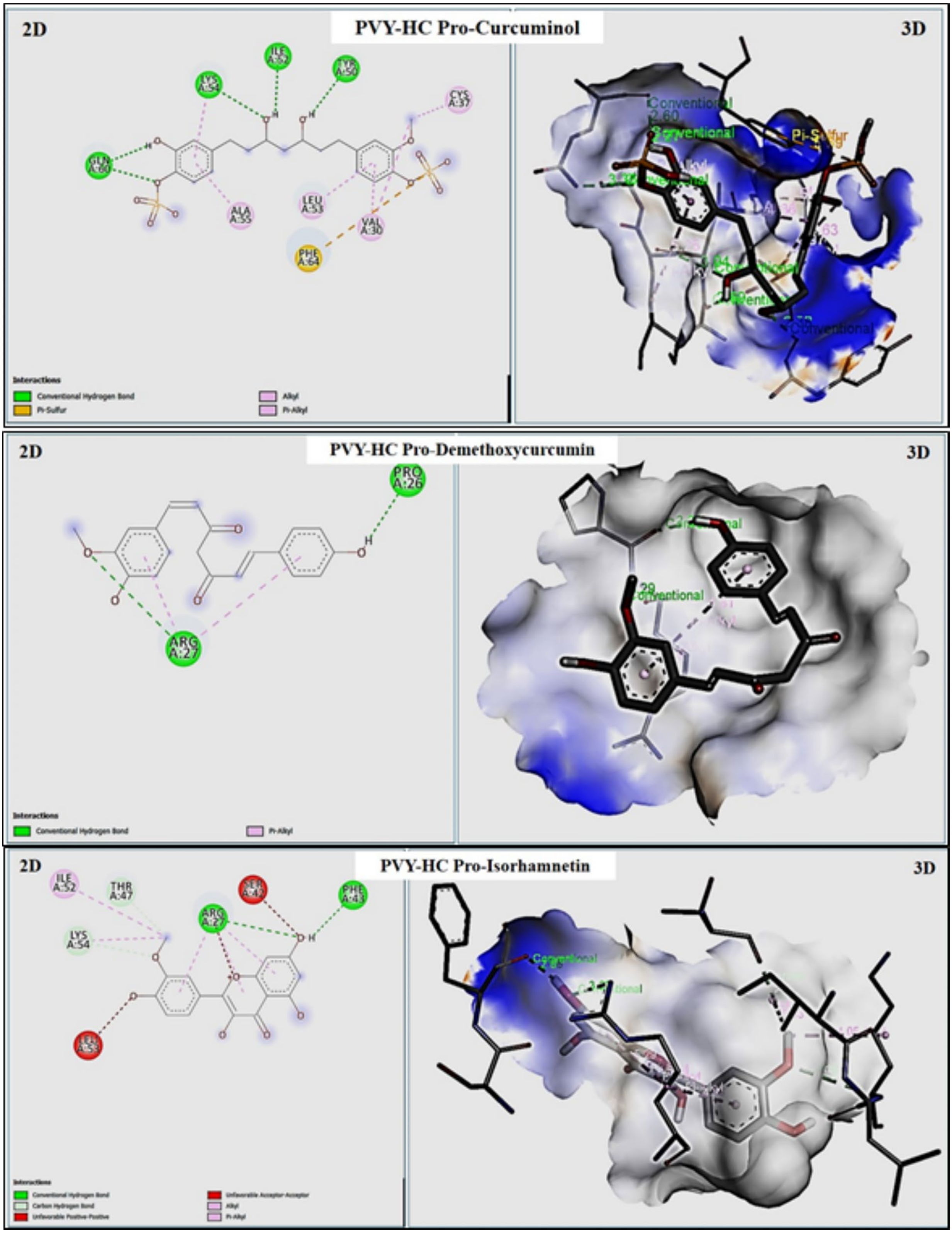

Fig. 5 2D and 3D structure of curcuminol, demethoxycurcumin, and isorhamnetin interactions with PVY-HC Pro (pfam00851): amino acid binding sites and bonding types

hydrogen bonds, and conventional hydrogen bonds with PRO (A:26) and ARG (A:27). The Pi-Alkyl interactions at ARG (A:27) indicate the potential for strong hydrophobic interactions, which may help anchor the ligand in the active site. The presence of conventional hydrogen bonds with PRO (A:26) suggests a stable binding orientation, which could be beneficial for maintaining the interaction with the protease. Isorhamnetin exhibits a mix of Pi-Alkyl, hydrogen bonds, alkyl interactions, and unfavorable acceptor–acceptor interactions. Significant binding residues include ILE (A:52), THR (A:47), ARG (A:27), SER (A:42), PHE (A:43), LEU (A:53), and LYS (A:54). Pi-Alkyl interactions with ARG (A:27) and ILE (A:52) suggest that the ligand's aromatic rings are engaging in hydrophobic interactions with these key residues, stabilizing the complex. The unfavorable acceptor–acceptor interactions observed at SER (A:42) and LEU (A:53) may indicate some steric hindrance or a less favorable binding conformation, which could reduce the overall binding efficiency and effectiveness as an inhibitor. Ribavirin forms several key interactions, including Pi-Alkyl, conventional hydrogen bonds, and carbon–hydrogen bonds with PRO (A:26), LEU (A:25), ASP (A:41), ARG (A:27), THR (A:47), and ALA (A:55). The Pi-Alkyl interaction with ARG (A:27) and ALA (A:55) suggests that the ligand is interacting with hydrophobic regions in the enzyme's active site, which could contribute to its binding stability. Conventional hydrogen bonds with ASP (A:41) and THR (A:47) provide additional stabilizing interactions, enhancing the ligand's binding affinity. Curcumin, bisdemethoxycurcumin, and curcuminol exhibit a diverse set of interactions with the protease, including Pi-Alkyl, Pi-Pi T-shaped, Pi-Sulfur, and hydrogen bonds, which suggest that these ligands are well-positioned to engage the enzyme in a stable and specific manner. The presence of Pi-Sulfur interactions with CYS (A:37) in curcumin and curcuminol highlights the potential for unique interaction profiles that could improve binding affinity. Demethoxycurcumin and ribavirin show more limited interaction profiles, which may influence their binding potency and specificity. However, ribavirin still shows some significant binding interactions, which could be optimized for better protease inhibition. Hydrogen bonding is a crucial interaction for ligand binding and specificity. Ligands such as curcumin and curcuminol form multiple hydrogen bonds with residues like GLN (A:35), GLN (A:60), and LYS (A:54), which contribute to their high binding affinity. Isorhamnetin, while forming several hydrogen bonds, also experiences unfavorable acceptor–acceptor interactions that may reduce its overall binding stability, which could limit its effectiveness. Isorhamnetin and ribavirin exhibit some unfavorable acceptor–acceptor interactions, which may hinder optimal binding to the protease and reduce their overall effectiveness as inhibitors. Isorhamnetin, in particular, may need structural modifications to overcome these interactions and enhance binding efficiency.

3.7 Ligand binding interactions with the PVY coat protein

The ligand binding interactions with the PVY-CP (pfam00767) are summarized in Table 7 and Fig. 6**,** providing insights into the types of interactions formed between the ligands and the key amino acid residues in the protein's structure. These interactions, including Pi-Cation, hydrogen bonds, and carbon-hydrogen bonds, play a crucial role in the persistence and affinity of ligand binding, which is vital for the development of effective inhibitors. Curcumin forms various interactions,

Table 7 Ligand binding interactions with the PVY^N coat protein (pfam00767): amino acid residues and bonding characteristics

Ligands	Amino acids	Sites	Type of bonds
Curcumin	ARG	A:55	Pi-Cation
	GLN	A:140	Conventional hydrogen, Unfavorable Donor-Donor
	ASP	A:91	Carbon Hydrogen
	GLY	A:61	Conventional hydrogen, Conventional hydrogen
	LYS	A:60	Conventional hydrogen
	HIS	A:162	Pi-Alkyl
Isorhamnetin	ARG	A:55	Conventional hydrogen
	ASP	A:91	Conventional hydrogen
Ribavirin	ASN	A:82	Conventional hydrogen
	THR	A:86	Conventional hydrogen, Conventional hydrogen, Pi-lone Pair
	TRP	A:118	Conventional hydrogen
	GLY	A:130	Carbon Hydrogen

Notes: PVY^N, Potato virus Y strain N-Egypt; ARG, Arginine; GLN, Glutamine; ASP, Aspartic acid; GLY, Glycine; LYS, Lysine; HIS, Histidine; ASN, Asparagine; THR, Threonine; and TRP, Tryptophan

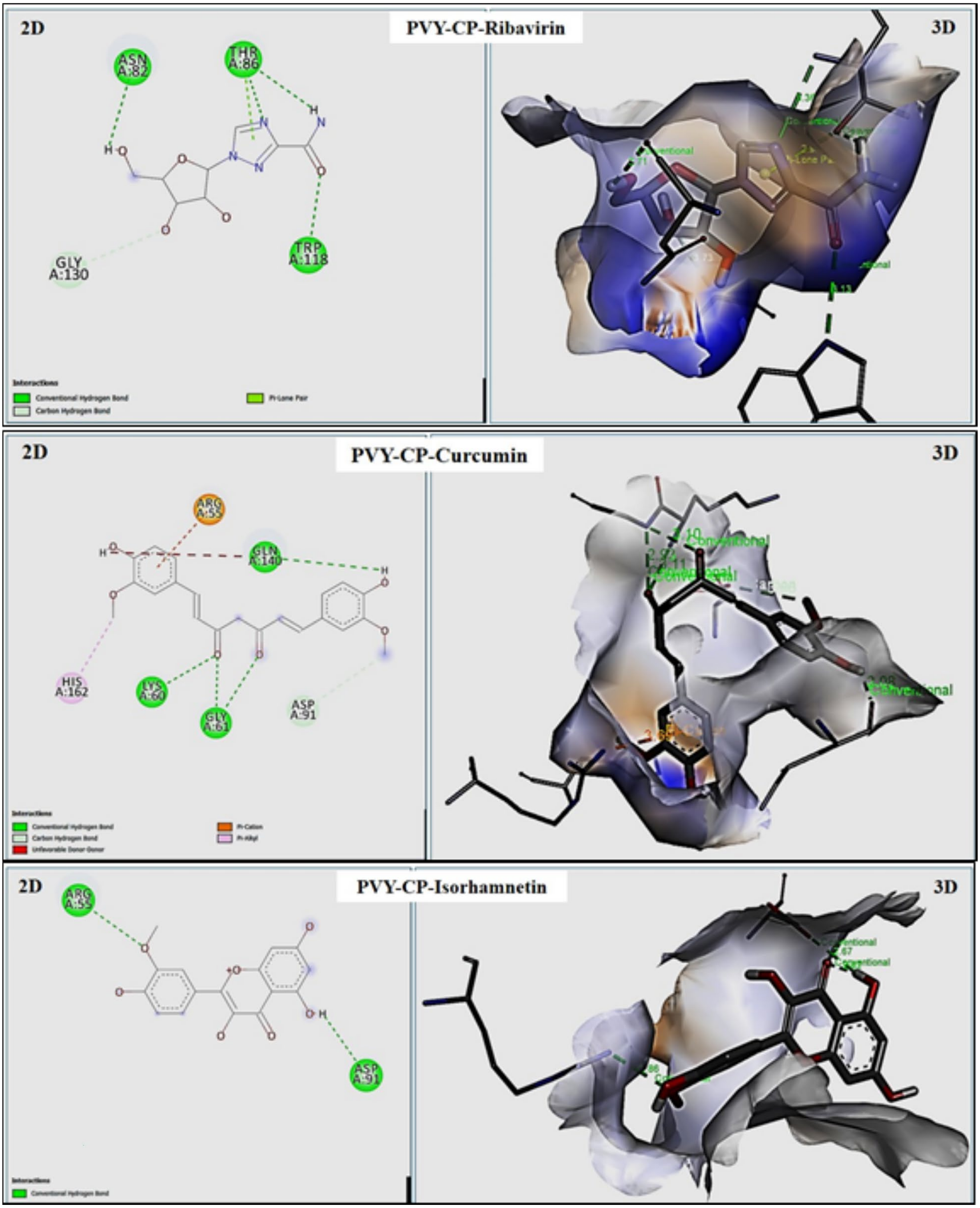

Fig. 6 2D and 3D structure of ribavirin, curcumin, and isorhamnetin interactions with PVY-CP (pfam00767): amino acid binding sites and bonding types

including Pi-Cation, conventional hydrogen bonds, carbon-hydrogen bonds, and unfavorable donor–donor interactions. The Pi-Cation interaction with ARG (A:55) suggests a strong aromatic interaction, which stabilizes binding in the hydrophobic pocket. Hydrogen bonds are formed with GLN (A:140), GLY (A:61), and LYS (A:60), enhancing the ligand's affinity for the protein. Unfavorable donor–donor interactions with GLN (A:140) suggest some steric hindrance, potentially reducing binding efficiency. The Pi-Alkyl interaction with HIS (A:162) further stabilizes the ligand–protein complex. Isorhamnetin forms multiple hydrogen bonds with ARG (A:55) and ASP (A:91), suggesting that these interactions are important for maintaining the ligand's position within the binding site, thereby enhancing its binding affinity. However, the ligand forms fewer interactions compared to curcumin, indicating a potentially less stable binding. Ribavirin forms hydrogen bonds with ASN (A:82), THR (A:86), TRP (A:118), and GLY (A:130). It also exhibits Pi-lone pair interactions with THR (A:86), suggesting non-covalent interactions that enhance binding specificity. Carbon-hydrogen bonds with GLY (A:130) further contribute to binding stability. Overall, ribavirin's interaction profile suggests stable binding, though potentially weaker or less specific compared to other ligands.

4 Discussion

The analysis of the physicochemical properties of the ligands offers important insights into their potential bioactivity, pharmacokinetics, and overall drug-likeness. Molecular weight is a critical factor influencing absorption, distribution, metabolism, and excretion (ADME) characteristics. Generally, smaller molecules exhibit improved membrane permeability and absorption, whereas larger molecules often face challenges related to poor solubility and reduced bioavailability. Among the ligands evaluated, Curcuminol, with a molecular weight of 566.51 g/mol, is the heaviest, which may negatively impact its absorption and oral bioavailability. Conversely, compounds such as caffeic acid and sinapic acid, which possess lower molecular weights, are likely to demonstrate better absorption profiles. Most ligands fall within the typical molecular weight range for drug-like compounds (200–500 g/mol), with Curcuminol as the notable exception, suggesting potential limitations for its oral administration [25]. These findings align with established knowledge that smaller molecules generally achieve superior membrane permeability and absorption, while larger compounds may be hindered by poor solubility and permeability issues [26]. The number of rotatable bonds influences the flexibility of a molecule, which can have both positive and negative implications for binding to biological targets. A higher number of rotatable bonds can increase the conformational diversity of a molecule, potentially improving its ability to bind to a range of targets. However, excessive flexibility could lead to instability and reduced specificity. Curcuminol, with 13 rotatable bonds, is the most flexible molecule in the set, which could increase its potential for binding to various targets but might also compromise its stability. On the other hand, compounds like curdione (1 RB) and caffeic acid (2 RB) are more rigid, which may offer better specificity for well-defined targets, although it could limit their binding diversity [27, 28]. The hydrogen bonding capacity of a compound influences its solubility and interaction with biomolecules. Compounds with a high number of HBA and donors (HBD) can exhibit strong interactions with biological targets, but excessive hydrogen bonding may reduce membrane permeability [29]. Curcuminol and isorhamnetin, with the highest number of HBA (12 and 7, respectively), may have strong interactions with the polar regions of biological targets. However, such compounds may also face challenges in terms of membrane permeability. Curdione, with only 2 HBA and no HBD, is less likely to engage in hydrogen bonding, potentially reducing its bioactivity but increasing its specificity. Ribavirin, with a balanced hydrogen bonding profile, could be seen as an optimized structure for maintaining bioactivity while potentially having favorable ADME properties [30].

The physicochemical and ADMET profiles of the tested ligands reveal significant insights into their potential as antiviral agents against the PVY^N-Egypt strain. Curcuminol, despite its high molecular weight and flexibility, violates Lipinski's rule and shows low gastrointestinal absorption, which may limit its oral bioavailability and clinical application, consistent with previous observations that large, flexible molecules often face bioavailability challenges [31]. In contrast, ligands like curcumin, bisdemethoxycurcumin, and isorhamnetin exhibit favorable drug-like properties with high GI absorption and compliance with Lipinski's rule, highlighting their potential as orally active candidates [32]. The toxicity profiles further refine candidate selection, as compounds such as curdione and curcuminol show potential toxicity, warranting caution in further development [33].

Virtual screening results demonstrated strong binding affinities of curcuminoids and flavonoids to key viral proteins, with isorhamnetin and bisdemethoxycurcumin showing particularly promising interactions with the P1 protease and helper component proteinase, suggesting their role as potent inhibitors in viral replication and transmission processes [34]. The control drug ribavirin, despite moderate binding affinity, confirms the validity of the docking approach and underscores the improved efficacy of these natural ligands in targeting PVY proteins [35]. Detailed interaction analyses reveal that hydrogen bonding, Pi-Alkyl, and salt bridge formations are critical in ligand stabilization within the active sites, aligning with prior studies that emphasize the importance of multi-modal interactions for effective protease inhibition [36, 37].

Moreover, the inability of most ligands to permeate the blood–brain barrier aligns with the peripheral targeting profile required for plant viral infections, reducing the risk of central nervous system side effects [38]. However, bisdemethoxycurcumin and curdione's BBB permeability may open avenues for broader antiviral applications but require further toxicity assessment. Collectively, these findings suggest that the curcuminoids and flavonoids under study merit further in vitro and in vivo validation as potential antiviral agents, especially given their multifaceted interaction profiles and favorable ADMET characteristics, supporting the growing body of evidence on natural products as valuable scaffolds in antiviral drug discovery [39, 40].

GI absorption is a critical determinant of oral bioavailability, as compounds with high GI absorption are generally absorbed more efficiently from the gastrointestinal tract. In this dataset, most compounds are predicted to have high GI absorption, which is a favorable characteristic for potential drug development. However, curcuminol and ribavirin, with predicted low GI absorption, could face challenges related to oral bioavailability. These compounds might experience poor intestinal permeability or high first-pass metabolism, which can limit their therapeutic effectiveness [41].

The ability of a compound to cross the blood–brain barrier (BBB) is critical for drugs targeting the CNS. In this dataset, bisdemethoxycurcumin and curdione are predicted to be BBB permeant, suggesting their potential for treating CNS-related diseases. On the other hand, most other ligands, such as caffeic acid, curcumin, and demethoxycurcumin, are not predicted to cross the BBB, suggesting they may be more effective for treating peripheral diseases [42].

Cytochrome P450 (CYP) enzymes are essential for the metabolism of numerous drugs, and their inhibition can result in potentially harmful drug–drug interactions. Bisdemethoxycurcumin and demethoxycurcumin are predicted to inhibit multiple CYP isoforms, raising concerns about significant interactions when co-administered with other therapeutics. Likewise, curcumin, isorhamnetin, and ribavirin inhibit CYP3A4, a key enzyme involved in the metabolism of a wide variety of drugs [24, 43]. Therefore, the potential for CYP enzyme inhibition must be carefully evaluated during drug development, especially when these compounds are intended for use alongside other medications that depend on CYP-mediated metabolism [44].

Lipinski's "Rule of Five" provides a widely accepted framework for assessing the drug-likeness of compounds, with adherence suggesting favorable oral bioavailability. In this analysis, most compounds, with the exception of curcuminol, conform to Lipinski's criteria, indicating promising drug-like properties and a higher likelihood of oral absorption. Curcuminol, however, due to its large molecular weight and elevated hydrogen bonding capacity, violates Lipinski's rule, which may pose challenges related to solubility and oral bioavailability [23].

Toxicity is a critical consideration in drug development, and compounds that are classified as toxic may pose risks for patient safety. In this dataset, curcuminol and Curdione are classified as toxic, suggesting that despite their promising ADMET properties, they may exhibit undesirable side effects that limit their therapeutic use. Conversely, compounds such as ribavirin, which are classified as non-toxic, may present fewer safety concerns, making them more suitable for further development. Therefore, toxicity must be considered alongside efficacy and ADMET properties to ensure the safe development of these compounds as potential therapeutics. In a summary, the ligands in this virtual screening dataset demonstrate varied ADMET properties, which can be linked to their pharmacological potential [45].

Bisdemethoxycurcumin, curdione, and demethoxycurcumin show high GI absorption and favorable pharmacokinetic properties, though some of them are predicted to inhibit multiple CYP enzymes, raising concerns about drug–drug interactions. Curcumin, isorhamnetin, and ribavirin also show good absorption and drug-like properties but may exhibit interactions with CYP3A4. On the other hand, curcuminol exhibits poor GI absorption, does not comply with Lipinski's rule, and is classified as toxic, indicating that it may require substantial modifications to improve its drug-like properties and safety profile. Caffeic acid and sinapic acid have high GI absorption and do not inhibit CYP enzymes, making them interesting candidates for further studies targeting peripheral diseases. The strong binding of Isorhamnetin to the P1 protease, with a binding affinity of −7.1 kcal/mol, highlights its potential as a lead compound for antiviral drug design targeting this key enzyme in the PVY^{N}-Egypt strain. Curcuminoids like bisdemethoxycurcumin and curcumin also demonstrate promising binding affinities, which is consistent with their previously reported antiviral properties [10, 11]. Curcuminoids have shown broad-spectrum activity against various viruses, including plant viruses, suggesting that they could be used to inhibit P1 protease activity in PVY [16, 46].

Bisdemethoxycurcumin, demethoxycurcumin, and isorhamnetin show the most favorable binding to HCPro, with binding affinities of −6.4 kcal/mol. This is significant because HCPro plays an essential role in viral transmission and replication. The observed high binding affinities of curcuminoids and flavonoids like isorhamnetin align with studies that report their broad-spectrum antiviral properties, particularly against plant viruses [16, 46, 47]. This suggests that these compounds may effectively inhibit HCPro activity, thereby reducing PVY replication and transmission. Curcumin and Isorhamnetin demonstrate the strongest binding affinities for the PVY^N-Egypt coat protein at −7.4 kcal/mol, which could potentially interfere with viral capsid formation and RNA encapsidation, crucial steps for the virus's stability and transmission. The observed results are consistent with previous findings that curcuminoids can disrupt viral capsid formation [11, 46, 48], and isorhamnetin, a flavonoid, has shown promising antiviral activity in several studies [49]. This suggests that both compounds could play a significant role in disrupting the viral lifecycle by targeting the coat protein.

The RMSD (root-mean-square deviation) values of 0.0 observed across all ligand–protein complexes may initially suggest high accuracy in the docking predictions, indicating that the predicted binding poses are closely aligned with the reference conformations. However, such uniformly low RMSD values can also reflect methodological limitations, particularly when rigid docking protocols are employed. In this study, ligands were docked back into their native conformations without allowing for conformational flexibility or sampling of alternative binding modes. While this approach confirms pose reproducibility, it does not fully account for the dynamic nature of ligand–protein interactions in realistic biological environments [50, 51]. We acknowledge this as a limitation of the current methodology and recommend that future studies incorporate flexible docking protocols or molecular dynamics simulations to enhance the predictive accuracy [52]. Recent advances underscore the value of molecular dynamics (MD) simulations in assessing the conformational stability and dynamics of homology-modeled proteins within biologically relevant environments [48]. MD simulations provide detailed temporal insights into protein flexibility and the impact of ligand binding on structural integrity, which can improve the predictive accuracy of docking studies. While MD simulation was beyond the scope of the current study, future work incorporating this approach is warranted to enhance the validation of the PVY^N-Egypt strain protein model and to better understand its dynamic interactions with curcumin derivatives.

While molecular docking offers valuable initial insights into the binding affinity and interaction patterns between ligands and target proteins, it inherently represents a static model that does not capture the dynamic behavior of molecular complexes in a physiological environment. This limitation can restrict the biological relevance of docking predictions, particularly for flexible proteins such as viral coat proteins. To address this, future work should incorporate molecular dynamics (MD) simulations—ideally with a trajectory of at least 100 ns—to evaluate the temporal stability and conformational flexibility of the PVY^N-Egypt protein–ligand complexes. MD simulations would provide a more accurate representation of protein–ligand interactions under near-physiological conditions, allowing for refined predictions of binding stability, free energy changes, and key dynamic residues involved in interaction. Integrating MD into the computational workflow would significantly enhance the predictive power and translational potential of this study. Accordingly, we have conducted a limited re-evaluation using flexible docking in this revision to support the reliability of our findings.

Overall, the ligand binding affinities obtained in this study identify promising candidates for the development of antiviral agents against the PVY^N-Egypt strain. Curcumin, isorhamnetin, and bisdemethoxycurcumin demonstrated strong binding across all three target proteins, underscoring their potential as broad-spectrum antiviral compounds. These findings are consistent with previous studies reporting the antiviral efficacy of curcumin derivatives and flavonoids, which have been shown to inhibit viral replication and disrupt key protein functions [10, 11, 44]. Additionally, Ribavirin, employed here as a standard antiviral control, exhibited comparatively strong binding affinities, reaffirming its established antiviral activity [30]. The docking results emphasize that curcumin derivatives and flavonoids—particularly bisdemethoxycurcumin, curcumin, and isorhamnetin—possess strong affinity for critical proteins of the PVY^N-Egypt strain. This aligns with the well-documented antiviral properties of curcuminoids, which are known to suppress viral proliferation by targeting essential viral enzymes and protein functions [50–52].

The high binding affinity of Isorhamnetin, a flavonoid, further supports the potential of flavonoids in antiviral drug discovery [53, 54]. Additionally, Ribavirin, a well-known antiviral drug, exhibited docking scores in the moderate range across all three proteins. While its binding affinity was lower than that of curcumin derivatives and isorhamnetin, Ribavirin's established antiviral activity [55–58], makes it a valuable control in this study. Bisdemethoxycurcumin, curcumin, and isorhamnetin show strong binding interactions with PVY P1 protease, particularly through a combination of Pi-Alkyl, Pi-Anion, hydrogen bonds, and Pi-Cation interactions. These ligands seem to have a well-established binding profile with significant contributions from both hydrophobic and polar interactions, which may contribute to their high binding affinity [59, 60].

The salt bridge formation observed with GLU (J:2974) in isorhamnetin could indicate a more stable binding compared to other ligands, potentially making isorhamnetin a better candidate for inhibition [61]. Hydrogen bonding is a critical component of ligand-receptor interactions and significantly contributes to binding affinity and specificity. The ligands bisdemethoxycurcumin, curcumin, and isorhamnetin form multiple hydrogen bonds with residues like GLN, SER, and ARG, which help stabilize the ligand-receptor complex [62–64]. Ribavirin also forms hydrogen bonds, but the presence of unfavorable acceptor–acceptor interactions suggests that its binding affinity might be weaker or less stable compared to the other ligands. The unfavorable acceptor–acceptor interactions in ribavirin (with MET (M:2895) and ASN (F:2971) may reduce its binding efficiency and increase the likelihood of off-target effects or weaker inhibition. This suggests that ribavirin may require structural modifications to improve its binding profile and reduce unfavorable interactions [65–67].

Based on the detailed binding analysis, bisdemethoxycurcumin, curcumin, and isorhamnetin are strong candidates for further drug development targeting PVY P1 protease, given their favorable interaction profiles and strong binding affinities. These ligands could be optimized through structural modifications to improve potency, selectivity, and minimize toxicity [68]. Ribavirin, while having some beneficial interactions, may need structural optimization to overcome the unfavorable interactions and enhance its overall binding stability. Based on the diverse and stable interactions with key amino acids in the protease, curcumin, bisdemethoxycurcumin, and curcuminol appear to be strong candidates for further optimization and development as potent protease inhibitors. These ligands display a wide range of favorable interactions, indicating that they could effectively bind to and inhibit the PVY helper component proteinase.

The variety of interactions, including Pi-Alkyl, Pi-Sulfur, Pi-Pi T-shaped, and hydrogen bonding, suggests that these compounds are engaging in both hydrophobic and electrostatic interactions that contribute to their high binding affinity [69, 70]. In particular, the Pi-Sulfur interactions with CYS (A:37) observed in curcumin and curcuminol highlight the potential for unique interaction profiles, which may improve the binding affinity and specificity for the protease. These interactions may provide these ligands with an advantage in terms of potency and selectivity for the target enzyme [71]. Moreover, the diversity of bonding types seen in bisdemethoxycurcumin and curcuminol—such as Pi-Alkyl, Pi-Pi T-Shaped, and hydrogen bonds—suggests that these compounds could engage the protease in a stable, multifaceted manner, likely enhancing their inhibitory potential [72]. While demethoxycurcumin and ribavirin show more limited interaction profiles, they still exhibit significant binding interactions, suggesting that their structures could be further optimized for better protease inhibition. The more limited interaction profiles may indicate that these compounds are less stable in the active site compared to curcumin derivatives, potentially reducing their potency as inhibitors. Structural modifications could improve these interactions and enhance the binding efficiency [56, 73].

Isorhamnetin, despite forming several hydrogen bonds, exhibits unfavorable acceptor–acceptor interactions that may reduce its overall binding stability, thereby limiting its effectiveness as a protease inhibitor. These unfavorable interactions, especially with residues such as SER (A:42) and LEU (A:53)**,** may result in steric hindrance or decreased affinity. Therefore, isorhamnetin could benefit from structural modifications aimed at overcoming these unfavorable interactions to enhance binding efficiency and improve its inhibitory potency [74, 75].

Curcumin, bisdemethoxycurcumin, and curcuminol generally emerge as promising candidates for further development as protease inhibitors targeting the PVY helper component proteinase. Although isorhamnetin and ribavirin exhibit some potential, they may require structural optimization to mitigate unfavorable interactions and enhance their overall inhibitory efficacy [47, 76]. Analysis of the binding interactions with the PVY coat protein highlights curcumin as the strongest candidate for development as a protease inhibitor against this target. The compound's robust and stable binding affinity is likely driven by a diverse array of interactions, including Pi-Cation, Pi-Alkyl, and hydrogen bonds [77].

Notably, curcumin forms Pi-Cation interactions with ARG (A:55) and Pi-Alkyl interactions with HIS (A:162), indicating engagement through both hydrophobic and aromatic contacts, which contribute to a stable binding conformation. Furthermore, hydrogen bonds with residues such as GLN (A:140), GLY (A:61), and LYS (A:60) further reinforce the stability of the curcumin-protein complex, enhancing its affinity for the PVY coat protein [78]. However, an unfavorable donor–donor interaction with GLN (A:140) suggests possible steric clashes or electrostatic repulsion that could detract from curcumin's binding efficiency at this site. Addressing this issue in future ligand optimization—potentially through structural modifications to reduce steric hindrance or electrostatic conflict—may improve binding potency [79].

Isorhamnetin, while promising as a ligand for the PVY coat protein, forms fewer interaction types compared to curcumin. It mainly establishes hydrogen bonds with key residues such as ARG (A:55) and ASP (A:91), suggesting effective binding, though possibly with lower affinity due to the more limited interaction profile [80, 81].

Structural modifications aimed at enhancing the interaction profile—such as increasing hydrophobic contacts or introducing additional binding moieties—could improve the inhibitory potency and specificity of these compounds. Ribavirin forms stable hydrogen bonds with residues including ASN (A:82), THR (A:86), TRP (A:118), and GLY (A:130). Additionally, a Pi-lone pair interaction with THR (A:86) may contribute to binding specificity; however, ribavirin's overall interaction profile is simpler compared to curcumin's, which limits its binding affinity. Consequently, ribavirin may benefit from optimization to enhance its Pi-lone pair interactions and overall binding conformation [82]. Among the compounds studied, curcumin stands out as the most promising candidate for further development, owing to its diverse and stabilizing interactions, particularly the Pi-Cation and Pi-Alkyl interactions [83, 84]. Isorhamnetin also shows potential for optimization, displaying favorable hydrogen bonding; yet, its affinity may be comparatively lower due to the narrower range of interaction types. Ribavirin, while forming stable interactions, is likely to require structural refinement to improve both its binding affinity and specificity for the PVY coat protein [85].

4.1 Limitations

While the docking results indicate promising binding interactions with RMSD values close to zero, it is important to recognize the inherent limitations of molecular docking simulations. Such ideal RMSD values may reflect methodological constraints, including limited sampling of ligand–protein conformations and reliance on static protein structures. Moreover, docking predictions are inherently computational and provide only a preliminary understanding of molecular interactions. Therefore, these findings should be interpreted as hypotheses that require subsequent experimental validation through in vitro and in vivo studies. Additionally, the complex dynamics of biological systems and potential off-target effects are not fully captured in silico, underscoring the need for cautious interpretation and further comprehensive investigations.

4.2 Future directions

Building on the promising in silico findings of this study, future research should focus on experimental validation through in vitro assays to confirm the antiviral activity of the identified turmeric-derived compounds against PVY. Subsequently, in vivo studies will be essential to evaluate their efficacy and safety in plant models. Additionally, structural modifications of these bioactive molecules could be explored to enhance their binding affinity, bioavailability, and specificity. Investigating potential synergistic effects through combination therapies with existing antiviral agents may also provide more effective control strategies. Ultimately, integrating computational predictions with empirical data will facilitate the development of novel, targeted antiviral treatments for crop protection.

5 Conclusion

These findings underscore the potential of curcumin derivatives and flavonoids as lead compounds in the development of antiviral agents against the PVY^N-Egypt strain. Nonetheless, further in vitro and in vivo studies are necessary to validate their efficacy and safety. This study highlights turmeric-derived compounds, particularly curcuminoids, as promising antiviral candidates targeting key PVY proteins. Molecular docking analysis revealed that isorhamnetin exhibits strong affinity for the P1 protease, while curcumin and bisdemethoxycurcumin interact effectively with HCPro and CP, suggesting their potential to disrupt viral replication. ADMET profiling indicated favorable bioavailability and gastrointestinal absorption for most curcumin derivatives. However, curcuminol and ribavirin showed potential toxicity concerns. In summary, natural compounds such as curcuminoids and flavonoids—especially isorhamnetin—demonstrate significant promise as antiviral agents against PVY^N-Egypt. These results support further experimental research for both agricultural protection and pharmaceutical development.

5.1 Novelty

To the best of our knowledge, this is the first in silico study to investigate the interaction of curcumin and its derivatives with PVY^N-Egypt strain coat protein using molecular docking. While curcumin has been widely studied for its antiviral properties against human and animal viruses, its potential application in plant virology—particularly against Potato virus Y (PVY)—remains largely unexplored.

Abbreviations

2D	Two-dimensional structure
3D	Three-dimensional structure
ADMET	Absorption, distribution, metabolism, excretion, and toxicity
BBB	Blood–brain barrier
CNS	Central nervous system
CP	Coat protein
CYP	Cytochrome P450
g/mol	Gram/mole
GI	Gastrointestinal
HBA	Hydrogen bond acceptors
HBD	Hydrogen bond donors
HCPro	Helper component proteinase
HIV	Human Immunodeficiency Virus

lb	Lower bound
MW	Molecular weight
NCBI	National center for biotechnology information
NT	Non-Toxic
PDB	Protein data bank
PVX	Potato virus X
PVY	Potato virus Y
RB	Rotatable bonds
RMSD	Root-mean-square deviation
RNA	Ribonucleic acid
T	Toxic
TMV	Tobacco mosaic virus
ub	Upper bound
PSA	Polar surface area

Acknowledgements

The authors would like to extend our heartfelt gratitude to Miss El-Shymaa Tarek Abdel-Aziz for her exceptional support in the molecular docking analysis. Her expertise, dedication, and invaluable contributions were pivotal to the success of this study. We deeply appreciate her guidance and continuous assistance throughout the research process

Author Contribution

Allam Arafat Megahed conceived and designed the study, collected molecular nucleotide data, analyzed the genetic variability of the PVY^{N}-Egypt, drafted the manuscript and handling manuscript submission. Alaa Barakat responsible for data collection, data analysis, and writing the manuscript. Ahmed A. Embaby validation, resources, writing—review and editing. Sonya Hamouda Mohamed conducted the protein analysis, assessed genetic variability based on protein data, interpreted the results, and contributed to manuscript revisions. Atef S. Sadik supervised the study, ensured scientific integrity, contributed to the research design, and played a key role in manuscript revision and final approval. Nashwa Ahmed Elshaer provided bioinformatics and phylogenetic analysis expertise, contributed to comparative genomics, and assisted in study design and manuscript feedback.

Funding

Open access funding provided by The Science, Technology & Innovation Funding Authority (STDF) in cooperation with The Egyptian Knowledge Bank (EKB).

Data Availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Ethical approval was not applicable for this study, as it involved only plant and microbial samples, which do not require review by a human or animal ethics committee.

Competing interests

The authors declare no competing interests.

Consent for publication

Not applicable.

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Received: 9 July 2025 Accepted: 24 August 2025
Published: 3 September 2025

References

1. Jones RA (2006) Control of plant virus diseases. Advances in Virus Research 67:205–244. https://doi.org/10.1016/S0065-3527(06)67006-1Get rights and content
2. Quenouille J, Vassilakos N, Moury B (2013) Potato virus Y: a major crop pathogen that has provided major insights into the evolution of viral pathogenicity. Mol Plant Pathol 14(5):439–452. https://doi.org/10.1111/mpp.12024
3. Nasr-Eldin MA, Othman BA, Megahed AA, et al (2018) Physiological, cytological and molecular analysis of PVY^{NTN}-infected potato cultivars. Egyptian Journal of Experimental Biology (Botany) 14(1):171–185. https://www.ejmanager.com/mnstemps/15/151519330872.pdf?t=1554029194)
4. Valkonen JP (2007) Viruses: economical losses and biotechnological potential. In Potato biology and biotechnology (pp. 619–641). Elsevier Science BV. https://doi.org/10.1016/B978-044451018-1/50070-1
5. Nasr-Eldin M, Messiha N, Othman B, et al (2019) Induction of potato systemic resistance against the *Potato virus Y* (PVY^{NTN}), using crude filtrates of *Streptomyces* spp. under greenhouse conditions. Egyptian Journal of Biological Pest Control 29(62):1–11. https://doi.org/10.1186/s41938-019-0165-1
6. Abd El-Aziz MH (2020) The importance of *Potato virus Y* Potyvirus. Journal of Plant Science and Phytopathology 4:009–015. dx.doi.org/https://doi.org/10.29328/journal.jpsp.1001044
7. Adams MJ, Antoniw JF, Fauquet CM (2005) Molecular criteria for genus and species discrimination within the family *Potyviridae*. Arch Virol 150(3):459–479. https://doi.org/10.1007/s00705-004-0440-6
8. Bekhit AED, Bekhit AA (2014) Natural antiviral compounds. Stud Nat Prod Chem 42:195–228. https://doi.org/10.1016/B978-0-444-63281-4.00007-0
9. Anand P, Kunnumakkara AB, Newman RA et al (2008) Bioavailability of curcumin: problems and promises. Mol Pharm 4(6):807–818. https://doi.org/10.1021/mp700113r
10. Jennings MR, Parks RJ (2020) Curcumin as an antiviral agent. Viruses 12(11):1242. https://doi.org/10.3390/v12111242
11. Ardebili A, Pouriayevali MH, Aleshikh S et al (2021) Antiviral therapeutic potential of curcumin: an update. Molecules 26(22):6994. https://doi.org/10.3390/molecules26226994
12. Pagadala NS, Syed K, Tuszynski J (2017) Software for molecular docking: a review. Biophys Rev 9(2):91–102. https://doi.org/10.1007/s12551-016-0247-1
13. Ferreira LG, Dos Santos RN, Oliva G et al (2015) Molecular docking and structure-based drug design strategies. Molecules 20(7):13384–13421. https://doi.org/10.3390/molecules200713384
14. Morris GM, Lim-Wilby M (2008) Molecular docking. Molecular Modeling of Proteins 365–382. https://doi.org/10.1007/978-1-59745-177-2_19
15. Aseel DG, Rabie M, El-Far A et al (2024) Antiviral properties and molecular docking studies of eco-friendly biosynthesized copper oxide nanoparticles against alfalfa mosaic virus. BMC Plant Biol 24(1):1089. https://doi.org/10.1186/s12870-024-05802-1
16. Behl T, Rocchetti G, Chadha S et al (2021) Phytochemicals from plant foods as potential source of antiviral agents: an overview. Pharmaceuticals 14(4):381. https://doi.org/10.3390/ph14040381
17. Siddiqi MH, Siddiqi MZ, Kim SP (2019) Advances in molecular docking for antiviral drug discovery. Curr Bioinform 14(3):240–254. https://doi.org/10.3390/md18110545
18. Mitra D, Paul M, Thatoi H et al (2022) Study of potentiality of dexamethasone and its derivatives against Covid-19. J Biomol Struct Dyn 40(20):10239–10249. https://doi.org/10.1080/07391102.2021.1942210
19. Mitra D, Afreen S, Das Mohapatra PK et al (2023) Threat of respiratory syncytial virus infection knocking the door: a proposed potential drug candidate through molecular dynamics simulations, a future alternative. J Mol Model 29(4):91. https://doi.org/10.1007/s00894-023-05489-5
20. Mitra D, Afreen S, Das Mohapatra PK et al (2025) Inhibition of respiratory syncytial virus by daclatasvir and its derivatives: Synthesis of computational derivatives as a new drug development. J Biomol Struct Dyn 43(5):2440–2462. https://doi.org/10.1080/07391102.2023.2300408

21. Mitra D, Paul M, Thatoi H et al (2023) Potentiality of bioactive compounds as inhibitor of M protein and F protein function of human respiratory syncytial virus. In Silico Pharmacol 12(1):5. https://doi.org/10.1007/s40203-023-00178-w
22. Mitra D, Das Mohapatra PK (2022). Computational intelligence in identification of some FDA approved drug compounds for treatment of COVID-19. In: Chang, V., Kaur, H., Fong, S.J. (eds) Artificial intelligence and machine learning methods in COVID-19 and related health diseases (pp. 109–122). Cham: Springer International Publishing. https://doi.org/10.1007/978-3-031-04597-4_5
23. Daina A, Michielin O, Zoete V (2017) SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Rep 7(1):1–13. https://doi.org/10.1038/srep42717
24. BIOVIA, Dassault Systèmes (2022) Discovery Studio Visualizer (Version 2022). San Diego: Dassault Systèmes. Available at: https://www.3ds.com/products-services/biovia/products/molecular-modeling-simulation/biovia-discovery-studio/
25. Honorio MK, Moda LT, Andricopulo AD (2013) Pharmacokinetic properties and in silico ADME modeling in drug discovery. Med Chem 9(2):163–176. https://doi.org/10.2174/1573406411309020002
26. Veber DF, Johnson SR, Cheng HY et al (2002) Molecular properties that influence the oral bioavailability of drug candidates. J Med Chem 45(12):2615–2623. https://doi.org/10.1021/jm020017n
27. Maltarollo VG, Gertrudes JC, Oliveira PR et al (2015) Applying machine learning techniques for ADME-Tox prediction: a review. Expert Opin Drug Metab Toxicol 11(2):259–271. https://doi.org/10.1517/17425255.2015.980814
28. Alqahtani S (2017) In silico ADME-Tox modeling: progress and prospects. Expert Opin Drug Metab Toxicol 13(11):1147–1158. https://doi.org/10.1080/17425255.2017.1389897
29. Graci JD, Cameron CE (2006) Mechanisms of action of ribavirin against distinct viruses. Rev Med Virol 16(1):37–48. https://doi.org/10.1002/rmv.483
30. Lipinski CA, Lombardo F, Dominy BW et al (2012) Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev 64:4–17. https://doi.org/10.1016/j.addr.2012.09.019
31. Ghose AK, Viswanadhan VN, Wendoloski JJ (1999) A knowledge-based approach in designing combinatorial or medicinal chemistry libraries for drug discovery. 1. A qualitative and quantitative characterization of known drug databases. J Combin Chem 1(1):55–68. https://doi.org/10.1021/cc9800071
32. Ekins S, Mestres J, Testa B (2007) In silico pharmacology for drug discovery: methods for virtual ligand screening and profiling. Br J Pharmacol 152(1):9–20. https://doi.org/10.1038/sj.bjp.0707305
33. De Clercq E (2006) Antiviral agents active against influenza A viruses. Nat Rev Drug Discov 5(12):1015–1025. https://doi.org/10.1038/nrd2175
34. Morris GM, Huey R, Lindstrom W et al (2009) AutoDock4 and AutoDockTools4: automated docking with selective receptor flexibility. J Comput Chem 30(16):2785–2791. https://doi.org/10.1002/jcc.21256
35. Pardridge WM (2005) The blood-brain barrier: bottleneck in brain drug development. NeuroRx 2(1):3–14. https://doi.org/10.1602/neurorx.2.1.3
36. Newman DJ, Cragg GM (2016) Natural products as sources of new drugs from 1981 to 2014. J Nat Prod 79(3):629–661. https://doi.org/10.1021/acs.jnatprod.5b01055
37. Harvey AL, Edrada-Ebel R, Quinn RJ (2015) The re-emergence of natural products for drug discovery in the genomics era. Nat Rev Drug Discov 14(2):111–129. https://doi.org/10.1038/nrd4510
38. Vasconcelos T, Sarmento B, Costa P (2007) Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discov Today 12(23–24):1068–1075. https://doi.org/10.1016/j.drudis.2007.09.005
39. Pardridge WM (2007) Blood–brain barrier delivery. Drug Discov Today 12(1–2):54–61. https://doi.org/10.1016/j.drudis.2006.10.013
40. Choong CL, Islahudin F, Makmor-Bakry M et al (2024) Effect of CYP3A5* 3, ABCC2 C-24T, and ABCC2 C3972T genetic polymorphisms on direct cost of kidney transplant recipients. Cureus 16(9):e69221. https://doi.org/10.7759/cureus.69221
41. Zhang Y, Wang Z, Wang Y et al (2024) CYP3A4 and CYP3A5: the crucial roles in clinical drug metabolism and the significant implications of genetic polymorphisms. PeerJ 12:e18636
42. Scheen AJ (2011) Cytochrome P450-mediated cardiovascular drug interactions. Expert Opin Drug Metab Toxicol 7(9):1065–1082. https://doi.org/10.1517/17425255.2011.586337
43. Mathew D, Hsu WL (2018) Antiviral potential of curcumin. J Funct Foods 40:692–699. https://doi.org/10.1016/j.jff.2017.12.017
44. Sharma A, Sharma T, Bhaskar R et al (2024) Promising potential of curcumin and related compounds for antiviral drug discovery. Med Chem 20(6):597–612. https://doi.org/10.2174/0115734064277371240325105016
45. Hussain Y, Alam W, Ullah H et al (2022) Antimicrobial potential of curcumin: therapeutic potential and challenges to clinical applications. Antibiotics 11(3):322. https://doi.org/10.3390/antibiotics11030322
46. Gong G, Guan YY, Zhang ZL et al (2020) Isorhamnetin: a review of pharmacological effects. Biomed Pharmacother 128:110301. https://doi.org/10.1016/j.biopha.2020.110301
47. Lee WH, Loo CY, Bebawy M et al (2013) Curcumin and its derivatives: their application in neuropharmacology and neuroscience in the 21st century. Curr Neuropharmacol 11(4):338–378. https://doi.org/10.2174/1570159X11311040002
48. Hollingsworth SA, Dror RO (2018) Molecular dynamics simulation for all. Neuron 99(6):1129–1143. https://doi.org/10.1016/j.neuron.2018.08.011
49. Zorofchian Moghadamtousi S, Abdul Kadir H, Hassandarvish P et al (2014) A review on antibacterial, antiviral, and antifungal activity of curcumin. BioMed Res Int. https://doi.org/10.1155/2014/186864
50. Oglah MK, Mustafa YF, Bashir MK et al (2020) Curcumin and its derivatives: a review of their biological activities. Syst Rev Pharm 11(3):472–481. https://doi.org/10.5530/srp.2020.3.60
51. Badshah SL, Faisal S, Muhammad A et al (2021) Antiviral activities of flavonoids. Biomed Pharmacother 140:111596. https://doi.org/10.1016/j.biopha.2021.111596
52. Shahrajabian MH, Sun W, Cheng Q (2022) The importance of flavonoids and phytochemicals of medicinal plants with antiviral activities. Mini-Rev Org Chem 19(3):293–318. https://doi.org/10.2174/1570178618666210707161025
53. Naithani R, Huma LC, Holland LE et al (2008) Antiviral activity of phytochemicals: a comprehensive review. Mini Rev Med Chem 8(11):1106–1133. https://doi.org/10.2174/138955708785909943
54. Komínek P, Komínková M, Jandová B (2016) Effect of repeated ribavirin treatment on grapevine viruses. Acta Virol 60(4):400–403. https://doi.org/10.4149/av_2016_04_400
55. Egerman RS (2019) New antiviral agents for treatment of hepatitis c. Clin Obstet Gynecol 62(4):823–834. https://doi.org/10.1097/grf.0000000000000457
56. Ninfali P, Antonelli A, Magnani M et al (2020) Antiviral properties of flavonoids and delivery strategies. Nutrients 12(9):2534. https://doi.org/10.3390/nu12092534
57. Meng XY, Zhang HX, Mezei M et al (2011) Molecular docking: a powerful approach for structure-based drug discovery. Curr Comput Aided Drug Des 7(2):146–157. https://doi.org/10.2174/157340911795677602
58. Warren GL, Andrews CW, Capelli AM et al (2006) A critical assessment of docking programs and scoring functions. J Med Chem 49(20):5912–5931. https://doi.org/10.1021/jm050362n
59. Kitchen DB, Decornez H, Furr JR et al (2004) Docking and scoring in virtual screening for drug discovery: methods and applications. Nat Rev Drug Discov 3(11):935–949. https://doi.org/10.1038/nrd1549
60. Gopal SM, Klumpers F, Herrmann C et al (2017) Solvent effects on ligand binding to a serine protease. Phys Chem Chem Phys 19(17):10753–10766. https://doi.org/10.1039/C6CP07899K
61. Seow-Neng C, Abu Bakar N, Mahmood M et al (2017) Alternative strategy in crop protection: protease inhibitors from turmeric. Crop Improvement Sustain Through Lead-Edge Tech. https://doi.org/10.1007/978-3-319-65079-1_11
62. Rizk MN, Ketta HA, Shabana YM (2024) Discovery of novel Trichoderma-based bioactive compounds for controlling potato virus Y based on molecular docking and molecular dynamics simulation techniques. Chem Biol Technol Agric 11(1):110. https://doi.org/10.1186/s40538-024-00629-2
63. Jiang S, Debnath AK (2000) A salt bridge between an N-terminal coiled coil of gp41 and an antiviral agent targeted to the gp41 core is important for anti-HIV-1 activity. Biochem Biophys Res Commun 270(1):153–157. https://doi.org/10.1006/bbrc.2000.2411

64. Ghosh AK, Chapsal BD, Weber IT et al (2008) Design of HIV protease inhibitors targeting protein backbone: an effective strategy for combating drug resistance. Acc Chem Res 41(1):78–86. https://doi.org/10.1021/ar7001232
65. Agback P, Agback T (2018) Direct evidence of a low barrier hydrogen bond in the catalytic triad of a serine protease. Sci Rep 8(1):10078. https://doi.org/10.1038/s41598-018-28441-7
66. Mulu A, Gajaa M, Woldekidan HB (2021) The impact of Curcumin derived polyphenols on the structure and flexibility COVID-19 main protease binding pocket: a molecular dynamics simulation study. PeerJ 9:e11590. https://doi.org/10.7717/peerj.11590
67. Wang DP, Rizzo RC, Tirado-Rives J et al (2001) Antiviral drug design: computational analyses of the effects of the L100I mutation for HIV-RT on the binding of NNRTIs. Bioorg Med Chem Lett 11(21):2799–2802. https://doi.org/10.1016/S0960-894X(01)00510-8
68. Poongavanam V, Namasivayam V, Vanangamudi M et al (2018) Integrative approaches in HIV-1 non-nucleoside reverse transcriptase inhibitor design. Wiley Interdiscip Rev Comput Mol Sci 8(1):e1328. https://doi.org/10.1002/wcms.1328
69. Bai L, Wei C, Zhang J et al (2023) Design, synthesis, and anti-PVY biological activity of 1, 3, 5-triazine derivatives containing piperazine structure. Int J Mol Sci 24(9):8280. https://doi.org/10.3390/ijms24098280
70. Ekowati J, Widyowati R, Norhayati, et al (2023) Chemopreventive Practices in Traditional Medicine. In *Herbal Medicine Phytochemistry*: Applications and Trends (pp. 1–54). Cham: Springer International Publishing. https://doi.org/10.1007/978-3-031-21973-3_28-1
71. Liu X, Wang XJ (2020) Potential inhibitors against 2019-nCoV coronavirus M protease from clinically approved medicines. J Genet Genomics 47(2):119–121. https://doi.org/10.1016/j.jgg.2020.02.001
72. Caughey B, Raymond LD, Raymond GJ et al (2003) Inhibition of protease-resistant prion protein accumulation in vitro by curcumin. J Virol 77(9):5499–5502. https://doi.org/10.1128/jvi.77.9.5499-5502.2003
73. Du YN, Jia J, Yan JN et al (2024) Non-covalent interactions between large yellow croaker (*Pseudosciaena crocea*) roe protein isolates and curcumin: implications for enhanced curcumin delivery. Food Biosci 60:104270. https://doi.org/10.1016/j.fbio.2024.104270
74. Ross IA (2024) Brassicaceae and Viral Diseases. In Plant-Based Therapeutics, Volume 2: The Brassicaceae Family (pp. 673–733). Cham: Springer Nature Switzerland. https://doi.org/10.1007/978-3-031-63681-3_14
75. Shahhamzehei N, Abdelfatah S, Efferth T (2022) In silico and *in vitro* identification of pan-coronaviral main protease inhibitors from a large natural product library. Pharmaceuticals 15(3):308. https://doi.org/10.3390/ph15030308
76. Fakih TM, Zainul R, Muchtaridi M (2024) Molecular docking-based virtual screening and computational investigations of biomolecules (*Curcumin analogs*) as potential lead inhibitors for SARS-CoV-2 papain-like protease. Pharmacia 71:1–19. https://doi.org/10.3897/pharmacia.71.e123948
77. Helmy N, Afifi S, Othman B, El-Dougdoug K et al (2023) Enhance potato resistance to Potato virus Y^{NTN} using Curcumin nanoparticles: Inhibitory effects of curcumin nanoparticles on potato plants infected by *Potato virus Y*. Acta Fytotechnica et Zootechnica 26(3):1336–9245
78. Mbese Z, Khwaza V, Aderibigbe BA (2019) Curcumin and its derivatives as potential therapeutic agents in prostate, colon and breast cancers. Molecules 24(23):4386. https://doi.org/10.3390/molecules24234386
79. Elgorban AM, Debnath S, Bahkali AH et al (2023) Exploring the potency of curcumin and phyto-compounds as inhibitors of tomato yellow leaf curl virus-sardinia's DNA-binding domain: a computational approach. Physiol Mol Plant Pathol 127:102098. https://doi.org/10.1016/j.pmpp.2023.102098
80. Sindhuja A, Vimalavathini RR, Kavimani S (2021) In silico docking studies of antiglycation activity of isorhamnetin on molecular proteins of advanced glycation end product (AGE) Pathway. Biomed Pharmacol J 14(4):2299–2307
81. Hidayati WN, Apriasti R, Addy HS et al (2021) Distinguishing resistances of transgenic sugarcane generated from RNA interference and pathogen derived resistance approaches to combating *Sugarcane mosaic virus*. Indones J Biotechnol 26(2):107–114
82. Li Y, Jiao J, Qi Y et al (2021) Curcumin: a review of experimental studies and mechanisms related to periodontitis treatment. J Periodontal Res 56(5):837–847. https://doi.org/10.1111/jre.12914
83. Sitohy M, Taha S, Abdel-Hamid M et al (2021) Protecting potato plants against PVX and PVY viral infections by the application of native and chemically modified legume proteins. J Plant Dis Prot 128:1101–1114. https://doi.org/10.1007/s41348-021-00448-9
84. Elshaer NA, El-Masry SS, Rabiee MS et al (2025) In silico prediction of the potential of some bioactive compounds from Licorice to target *Banana bunchy top virus*. Egypt J Phytopathol 53(1):194–224. https://doi.org/10.21608/ejp.2025.436169
85. Abozaid A, Ali MK, Sadik AS et al (2025) Conserved epitope mapping of Potato virus Y for broad-spectrum antigen design: Implications for plant immune. Novel Res Microbiol J 9(4): 332–348. https://doi.org/10.17582/journal.NRMJ/2025/9.4.332.348

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