



Molecular mechanics of caffeic acid in food profilin allergens

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Abstract

Vegetable profilins are considered potent allergens for their cross-reactivity as a result of the high sequence identity. Nowadays an attractive attention is focused to find new ligands to inhibit the active site of allergenic profilins. Some studies have shown that caffeic acid may have a certain inhibitory effect on some allergens. For this reason, we studied caffeic acid as an important ligand and its interaction between seven vegetable profilins. We applied molecular dynamic simulations methods and binding free energy analysis by MM–PBSA. We found that caffeic acid had a favorable behavior, and their coupling was mediated by hydrophobic interactions. Furthermore, the analysis of epitopes showed an important contribution of the secondary structure after docking simulations.

Keywords Profilin · Allergy · Molecular mechanics · Caffeic acid

1 Introduction

Allergies have been become a global health problem, with high prevalence rates that are increasing [1]. An important part of this disease group is food allergies, caused by intake of a specific food containing proteins that our body recognizes as antigens [2]. Their severity is multifactorial and variable among people, and there are no specific evaluations to determine the intensity of allergic reaction; nevertheless, foods have key elements with high allergenic potential, called allergens [3]. One of these allergens is profilin; they are proteins present in all living organism (including plants and animals) and have functions associated with actin polymerization in cellular cytoplasm.

Vegetable profilins produce an activation of the immune system when they get into our organism; this reaction is part of type 1 hypersensitivity response. Not all profilins

enter through food, and some do it by inhalation through the pollen of some plants. In 1992, birch pollen allergen was reported by Valenta et al. [4] as the first allergenic profilin; less than 20 years had passed since the discovery of these proteins [5, 6]. The World Health Organization (WHO) and International Union of Immunological Societies (IUIS) have registered and recognized 48 profilins as allergens. Cross-reactions can occur among profilins from pollen and food (vegetables and/or fruits) because they have residue regions with high homology [7]. For this reason, they are also considered pan-allergens.

Structural alteration of proteins to modify their function is a methodology that has been used since the discovery of proteins [8]. Allergenic profilins also have been subjected to several processes to reduce their allergenic potential to alter their molecular structure, configuration, and properties through physical–chemical treatments or adding compounds that reduce their allergenicity [9]. A thermal treatment process as high temperature in food processing can modify the native structure in different ways: denaturation, restructuring of the disulfide bonds, and generation of new bonds [10]. Structural changes can modify profilin epitopes, which directly interact with allergen receptors, altering their binding capacity to the antibody; nevertheless, this could generate the formation of new allergenic compounds [11]. Epitopes are identified by the IgE; by changing the structural form between the proteins, these sites change, varying their epitopes, which can be altered by different reactions such

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Table 1 Features of studied profilins

Profilin	Species	Common name	PDB code	UniProt access code	AA*
Api g 4	<i>Apium graveolens</i>	Celery	*	Q9XF37	134
Ara h 5	<i>Arachis hypogaea</i>	Peanut	4ESP	D3K177	131
Cit s 2	<i>Citrus Sinensis</i>	Orange	*	P84177	131
Gly m 3	<i>Glycine max</i>	Soybean	*	O65809	131
Mus a 1	<i>Musa acuminata</i>	Banana	*	Q94JN3	131
Sola l 1	<i>Solanum lycopersicum</i>	Tomato	*	Q93YG7	131
Zea m 12	<i>Zea mays</i>	Maize	5FEF	Q9FR39	131

*AA number of amino acids; structures obtained by homology modeling

**Fig. 1** Multiple sequence alignment of the seven profilin protein sequences

as increased temperature, radiation. It has been seen that the enzymatic hydrolysis on the allergens Ara h 1, Ara h 2, and Ara h 3 is effective, deactivating its allergenic capacity; however, this process is expensive, which would affect its overcrowding [12]. The high-pressure processing has been effective against the apple profilin (Mal d 3) in 30% [13]. The use of adjuvant substances is not very frequent; however, it is shown that in allergens it is very effective.

Different compounds have been used to decrease the allergenic potential of profilins in food processing; Oleic acid reduces the allergenic properties of peanuts by binding to allergic proteins such as profilins Ara h 1 and Ana o 2 from cashew [14]. Polyphenol oxidase and caffeic acid can reduce the allergenic potential of Ara h 1 and Ara h 2 (peanut profilins), through a cross-reaction with these proteins

[15]. Food processing with caffeic acid can improve the functional properties of soy protein, increase the thermal stability of milk proteins, and improve the antimicrobial effect of lysozyme [16, 17]. Caffeic acid reduces the capacity of binding to the IgE of the profilin Pru av 1 (sweet cherry) [18]. It has been seen that other polyphenols such as ferulic acid and chlorogenic acid have shown similar properties [19]; also, tannic acid removes peanut allergens [20].

The only treatment for allergy is the avoidance or withdrawal of the food that has the allergen, being a factor causing the decrease in the quality of the patient. Accidental consumption of these allergens is frequent, mainly in children [21]. The computational methods for the evaluation of potential allergens and their allergenicity have been increasing during the last years. This method has been

Fig. 2 **a** Plot of RMSD of the seven profilins during 300 ns MD simulation. **b** Plot of RG of the seven profilins during 300 ns MD simulation

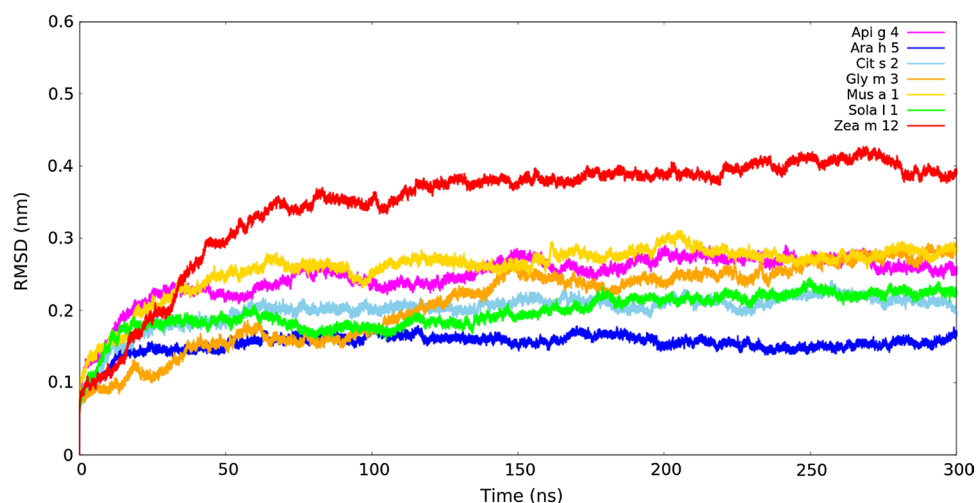


Table 2 Average values of RMSD and RG of profilins

Profilin	RMSD (nm)	RG (nm)
Api g 4	0.25 ± 0.031	1.42 ± 0.006
Ara h 5	0.15 ± 0.014	1.35 ± 0.003
Cit s 2	0.20 ± 0.024	1.38 ± 0.005
Gly m 3	0.21 ± 0.056	1.35 ± 0.0003
Mus a 1	0.26 ± 0.035	1.39 ± 0.0005
Sola l 1	0.20 ± 0.025	1.40 ± 0.008
Zea m 12	0.35 ± 0.079	1.46 ± 0.004

RMSD root-mean-square deviation, RG radii of gyration

recommended by FAO/WHO. Therefore, the objective of the present investigation is to evaluate the interaction properties of caffeic acid and different vegetable profilins reported as allergic by computational techniques, with guidance in the search for a solution for the treatment of food.

2 Computational details

The molecular structure of caffeic acid (CID = 2519) was obtained from PubChem database (<http://pubchem.ncbi.nlm.nih.gov/>). For its geometry optimization, we used the density functional theory (DFT) method with the GEN-A2 auxiliary function and the DVZP basis set in deMon2k software [22–24]. Topologies for OPLS-AA were obtained from TPPMKOP (<http://erg.biophys.msu.ru/tp/>).

We selected profilins corresponding to *Apium graveolens* (Api g 4), *Arachis hypogaea* (Ara h 5), *Citrus sinensis* (Cit s 2), *Glycine max* (Gly m 3), *Musa acuminata* (Mus a 1), *Solanum lycopersicum* (Sola l 1), and *Zea mays* (Zea m 12). UniProt (Universal Protein Resource) (<http://www.uniprot.org/>) and PDB (Protein Data Bank) (<https://www.rcsb.org/>) were employed to obtain their amino acid sequence and protein structure coordinates, respectively. MODELLER software was used to find the molecular structures of the profilins without crystal structure [25].

Fig. 3 Binding energy plot of the seven complexes

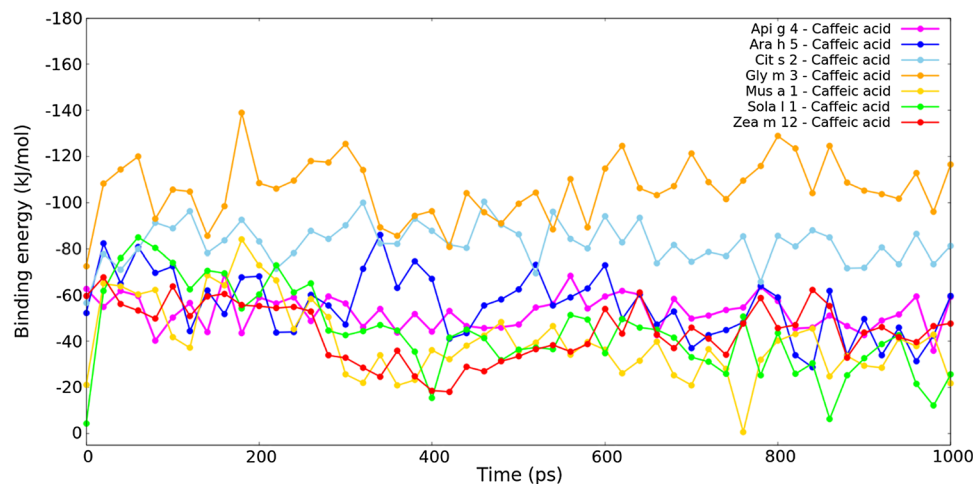


Table 3 Binding free energy components of profilin–caffeic acid complex (protein–ligand), using MM–PBSA calculation method

Profilin	Van der Waals energy	Electrostatic energy	Polar solvation energy	SASA energy	Binding energy
Api g 4	-101.67 ± 0.95	-9.21 ± 0.47	70.21 ± 1.15	-12.18 ± 0.11	-52.79 ± 1.03
Ara h 5	-80.34 ± 1.36	-36.31 ± 3.15	71.56 ± 2.04	-10.58 ± 0.07	-55.72 ± 1.90
Cit s 2	-95.16 ± 1.26	-17.78 ± 0.79	41.47 ± 0.63	-10.94 ± 0.09	-82.56 ± 1.24
Gly m 3	-136.41 ± 1.34	-38.57 ± 1.03	79.96 ± 0.85	-11.00 ± 0.07	-106.02 ± 1.81
Mus a 1	-51.18 ± 2.32	-47.95 ± 2.66	67.91 ± 3.59	-8.88 ± 0.22	-40.06 ± 2.27
Sola l 1	-60.13 ± 2.88	-22.07 ± 1.97	47.27 ± 3.46	-8.83 ± 0.30	-43.79 ± 2.52
Zea m 12	-56.49 ± 2.41	-18.77 ± 1.11	40.14 ± 1.12	-8.99 ± 0.25	-44.26 ± 1.71

All values are in kJ/mol

We performed 300 ns molecular dynamic (MD) simulations of the profilins in the OPLS-AA (Optimized Potential for Liquid Simulation-All Atom) force field using Gromacs v.2016 software with canonical ensemble [26]. These simulations have been solvated with an explicit solvent, using SPC (Simple point charge) as water model in a cubic box (6 Å). The net charge was neutralized by adding Cl and Na ions. The temperature was regulated with Nose–Hoover thermostat (300 K). Energy was minimized for 20,000 steps using the steepest descent integer. The integration time step was 1 fs. Long-range electrostatic interactions were evaluated using the standard Ewald summation, with a real-space cutoff of 1.9 nm. The short-range non-bonded interactions were calculated using a cutoff of 1.0 nm. Periodic boundary conditions were used to keep the number of solvent molecules constant.

PatchDock server was employed to carry out molecular docking (<https://bioinfo3d.cs.tau.ac.il/PatchDock>) [27]. The binding pockets for the ligand were analyzed by PockDrug (<http://pockdrug.rpbs.univ-paris-diderot.fr/cgi-bin/index.py?page=home>) [28]. Additionally, we considered MD simulations of complexes, with an isobaric–isothermal ensemble by 1 ns at the same previous conditions, without restriction. Binding free energy was calculated using MM/PBSA method by a 1 ns NPT simulation. Epitopes were calculated to analyze the active site from IgE by Ellipro server, and the visualization was in VMD [29] and Chimera UCSF [30].

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3 Results and discussion

We analyzed seven vegetable profilins (Table 1). The sequences had a homology higher than 75%, showing a high similarity between them. In Fig. 1, we present the alignment

of the profilin protein sequences. It is important to note that high homology is a cause of cross-reactivity in this species, and it is one of the most important features of vegetable profilins [31]. Three-dimensional structure of vegetable profilins was explored. In this work, five of seven profilins did not have the crystal structure. For these reasons, we modeled their structures using Bet v 2 (*Betula pendula*) as a template. This template was selected based on a high homology (> 80%) and a good resolution of 2.4 Å [32, 33].

3.1 RMSD, RMSF, and RG analyses

The MD simulation was analyzed through root-mean-square deviation (RMSD), root-mean-square fluctuation (RMSF) per residue, and radii of gyration (RG) (Fig. 2). The RMSD plot analyzed the protein structure stabilization through time, in all cases, the stabilization started at 50 ns, and the most stable structure was Ara h 5 with average RMSD of 0.15 ± 0.014 nm value, shown in Table 2. The RG analysis shows us the molecular structure compactness along the simulations, and the results indicated similar behavior for each profilin (Table 2). Details of RMSD, RMSF, and RG of each protein are in Supporting Information (Figs. S1–S7).

3.2 Docking analysis

In the present study, caffeic acid has been seen having the potential to bind with seven vegetable profilins. We selected the top score solution of PatchDock server. The evaluation of the ΔG bind was performed through the MM–PBSA approach (Fig. 3). The snapshots were extracted from all MD trajectories (1 ns) for binding free energy analysis. The binding affinity of the ligand followed the order: Gly m 3 (-106.02 ± 1.81 kJ/mol) > Cit s 2 (-82.56 ± 1.24 kJ/mol) > Ara h 5 (-55.72 ± 1.90 kJ/mol) > Api g 4 (-52.79 ± 1.03 kJ/mol) > Zea m 12 (-44.26 ± 1.71 kJ/mol) > Sola l 1 (-43.79 ± 2.52 kJ/mol) > Mus a 1 (-40.06 ± 2.27 kJ/mol). Additional information about the binding energy is in Supporting

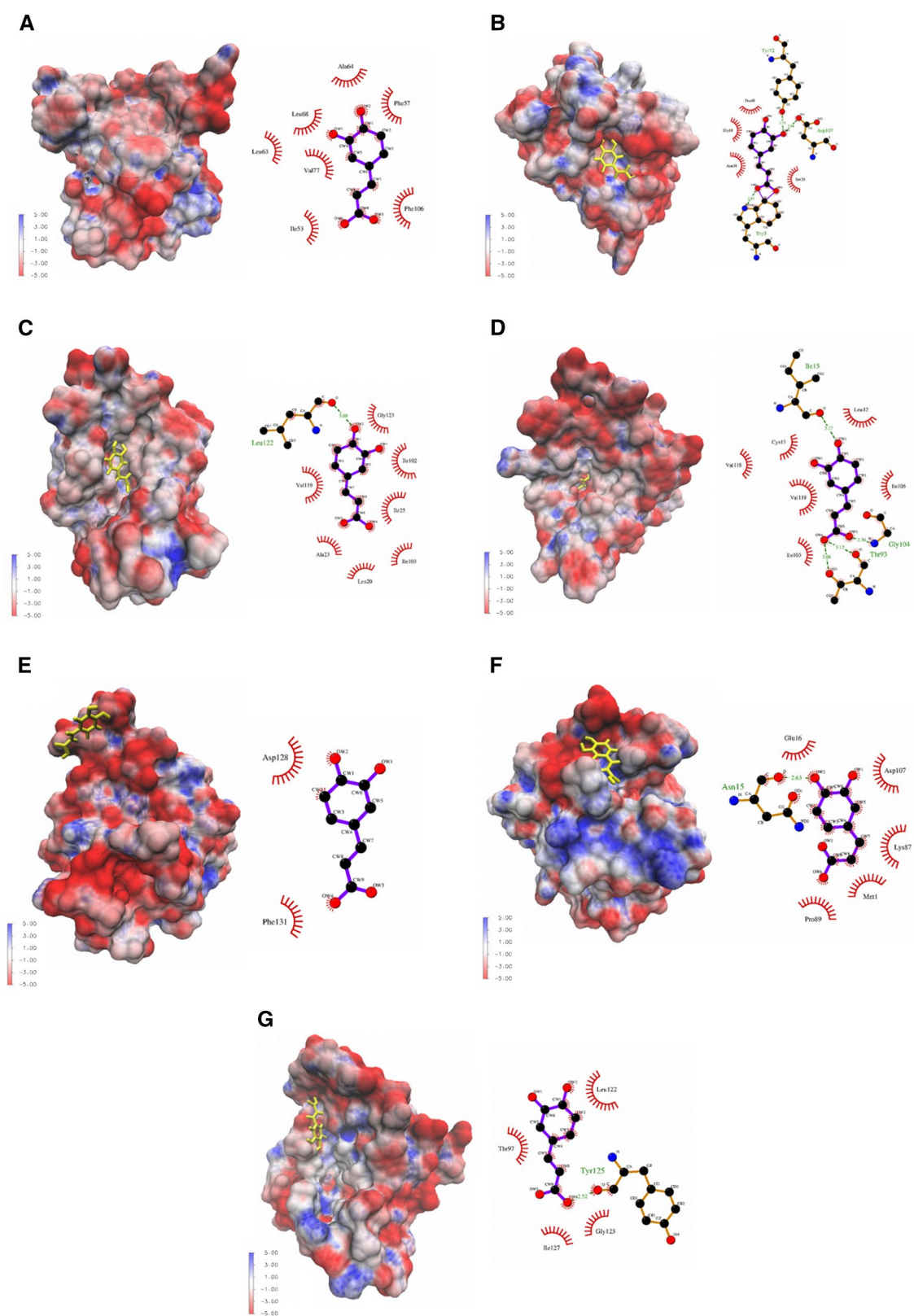


Fig. 4 Interaction between receptor and ligand of the last frame MD simulation. **a** Apg 4. **b** Ara h 5. **c** Cit s 2. **d** Gly m 3. **e** Mus a 1. **f** Sola l 1. **g** Zea m 12

Table 4 Comparison of predicted profilin epitope (with and without ligand–caffeic acid) after MD simulation

	Non-docked protein			Docked protein		
	Start	End	Score	Start	End	Score
Api g 4	126	134	0.734			
	1	22	0.71	126	134	0.788
	110	118	0.687	1	22	0.683
	43	51	0.635	43	67	0.636
	53	83	0.558	110	118	0.613
	90	93	0.519			
Ara h 5	2	10	0.81	120	131	0.822
	120	131	0.731	2	10	0.776
	56	59	0.698	12	19	0.659
	13	19	0.649	87	90	0.594
	107	112	0.596	28	33	0.576
	40	52	0.581	40	52	0.543
	86	90	0.578	56	77	0.543
	62	80	0.506	107	112	0.531
Cit s 2	1	10	0.798	1	6	0.816
	120	131	0.696	107	113	0.749
	12	19	0.623	121	131	0.74
	107	114	0.616	13	17	0.667
	52	73	0.611	28	31	0.668
	28	32	0.577	36	46	0.668
	86	90	0.563	54	64	0.607
				86	90	0.6
Gly m 3				67	80	0.542
	1	6	0.816	121	131	0.82
	107	113	0.749	107	113	0.702
	121	131	0.74	1	11	0.675
	13	17	0.667	28	33	0.626
	28	31	0.668	68	73	0.613
	36	46	0.668	13	18	0.611
	54	64	0.607	54	64	0.595
	86	90	0.6	36	48	0.582
	67	80	0.542	86	90	0.544
Mus a 1	123	131	0.814	120	131	0.726
	1	11	0.719	1	11	0.71
	40	46	0.668	13	19	0.675
	13	19	0.648	39	47	0.664
	51	80	0.564	51	64	0.628
	28	33	0.534	27	31	0.586
	97	100	0.525	107	110	0.574
	112	118	0.522	87	90	0.563
Sola l 1	1	19	0.725	3	17	0.782
	107	131	0.646	107	125	0.717
	76	81	0.628	28	6	0.551
	40	45	0.588	40	6	0.538
	28	34	0.506	54	19	0.515

Information (Fig. S8). The van der Waals energy was higher than other energies with a significant contribution to the binding free energy, suggesting hydrophobic

interaction was important during the binding process. The polar solvation energy was contrary to the binding free energy and in a high level in Api g 4, Ara h 5, Mus a 1,

and Sola l 1, and this might be due to the high volume of the binding pocket, thereby exposing the ligand to solvent (Table 3).

The docking results suggested that no hydrogen bonding takes place between caffeic acid with Api g 4 and Mus a 1. Interaction between Api g 4–caffeic acid is mediated mainly by hydrophobic interactions since the energy of van der Waals is very high, unlike the electrostatic energy. Apolar amino acids dominate the active site of Api g 4. On the other hand, caffeic acid is not attracted to Mus a 1, which is because the energy contribution and free energy binding were worst. The coupling that occurs between the profilins: Ara h 5, Cit s 2, Gly m 3, Sola l 1, and Zea m 12, with caffeic acid showed the formation of hydrogen bonds, especially Gly m 3 and Ara h 5 profilins presenting more hydrogen bonds. In Fig. 4, it is observed that interactions do not seem to be mediated by electrostatic interactions in the active site.

3.3 Epitope analysis

We compared the epitopes conformation between the profilins that were not docked with caffeic acid and the docked profilins (Table 4). There is variation in the conformation of epitopes due to caffeic acid; however, there is no pattern of variation among all profilins. In some cases, it can be inferred that caffeic acid had a direct effect on the conformation of the epitope. Additionally, a possible effect of the ligand on the protein can be observed in the variations of the secondary structure conformation and consequently alter the epitope conformation (Figs. S9–S15). Api g 4 had modifications on its secondary structure (decreasing two helices), where the interaction area (protein–ligand) is closely involved. Gly m 3 also had modifications on its secondary structure, decreasing the helices at the beginning of the structure and increasing at the opposite end; the interaction zone could be associated with the disarticulation of the helix. Mus a 1 secondary structure and epitopes did not suffer relevant changes after the interaction with caffeic acid.

Epitopes in the profilin structures conformed at least 48.1% of the structure and at most 62.7%. In the structures, those interacted with caffeic acid were similar, which fluctuated between 50.4 and 61.5%. The interaction with the caffeic acid showed a reduction of amino acid that conformed linear epitopes: Api g 4 (↓14.2%) and Mus a 1 (↓11.5%). The discontinuous epitope reduction was observed in the profilins: Api g 4 (↓3%), Cit s 2 (↓7.6%), Ara h 5 (↓3.8%), and Sola l 1 (↓1.5%).

4 Conclusions

In this study, seven vegetable profilins reported as allergens were modeled using 300 ns molecular dynamic simulations, and these molecular structures were used for docking prediction with the caffeic acid as a ligand. The last frame of MD simulations of complexes showed us that six of seven profilins had a strong attraction to caffeic acid in their active site. The MM–PBSA decomposition of the binding energy into electrostatic, van der Waals, polar solvation, and SASA energies allowed us to analyze the coupling of caffeic acid between vegetable profilins. This analysis indicated that the binding of the ligand is mediated mainly by van der Waals interaction as a predominant contributor to the whole free binding energy. Finally, epitopes analysis demonstrated the favorable action of caffeic acid in profilins and assumed epitopes reduction by modification of the secondary structure.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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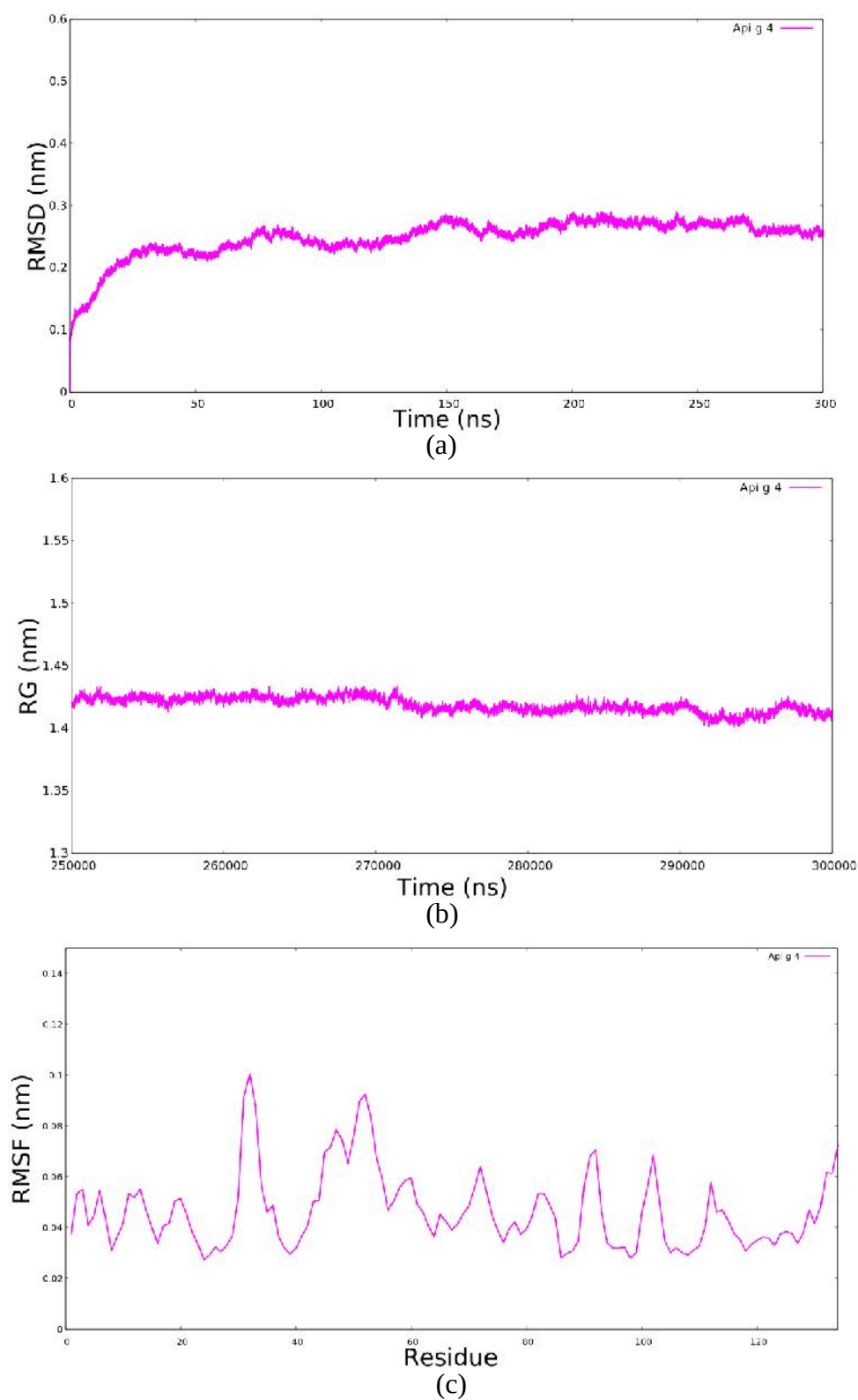


Figure S1. Analysis of RMSD, RMSF, and RG of Api g 4 profilin at 300ns. (a) RMSD of the backbone atoms in the trajectory of Api g 4 over the entire simulation. (b) RG of the protein backbone over last 50ns. (c) RMSF of the residues in the protein from 250 ns.

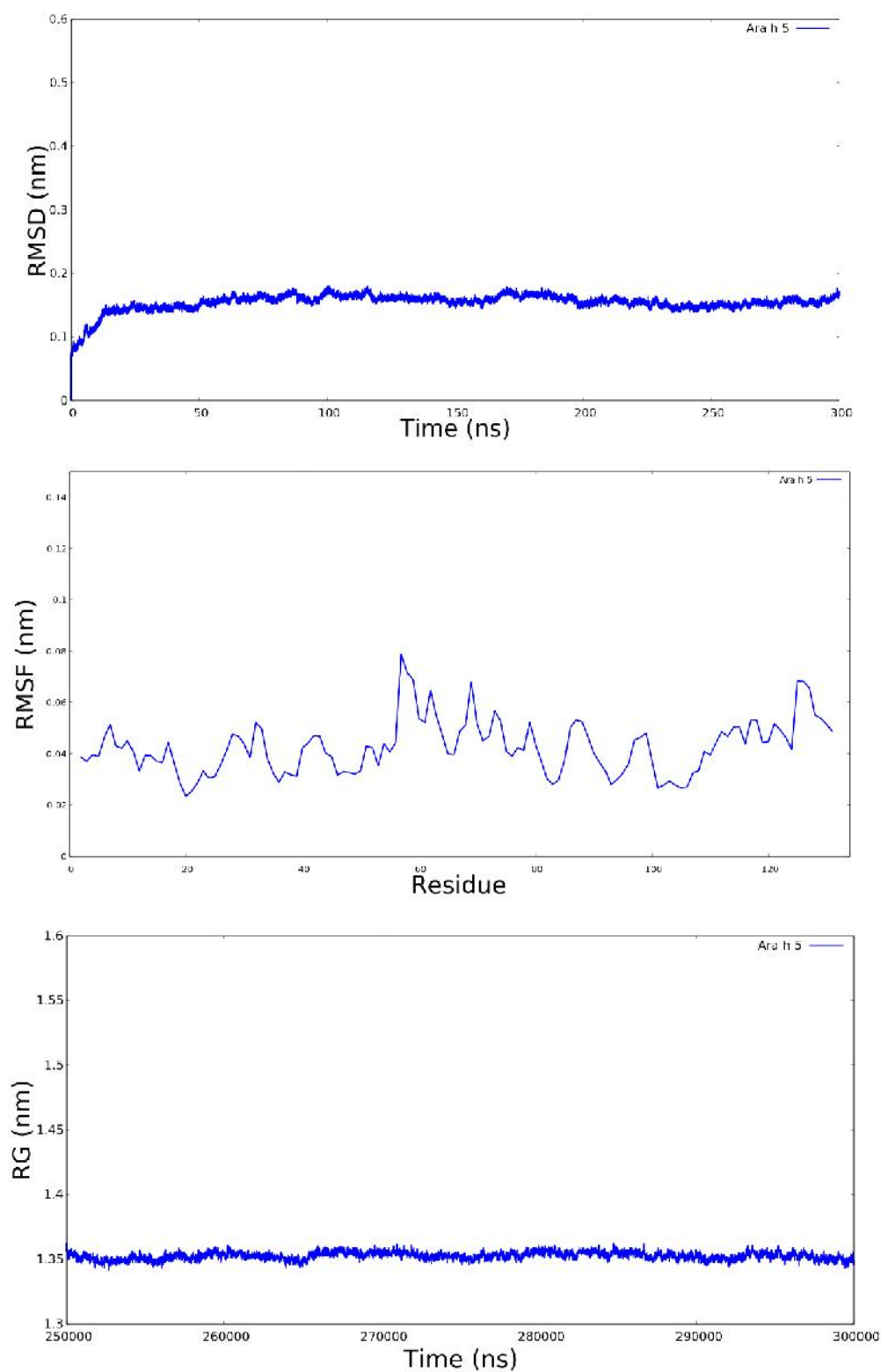


Figure S2. Analysis of RMSD, RMSF, and RG of Ara h 5 profilin at 300ns. (a) RMSD of the backbone atoms in the trajectory of Ara h 5 over the entire simulation. (b) RG of the protein backbone over last 50ns. (c) RMSF of the residues in the protein from 250 ns.

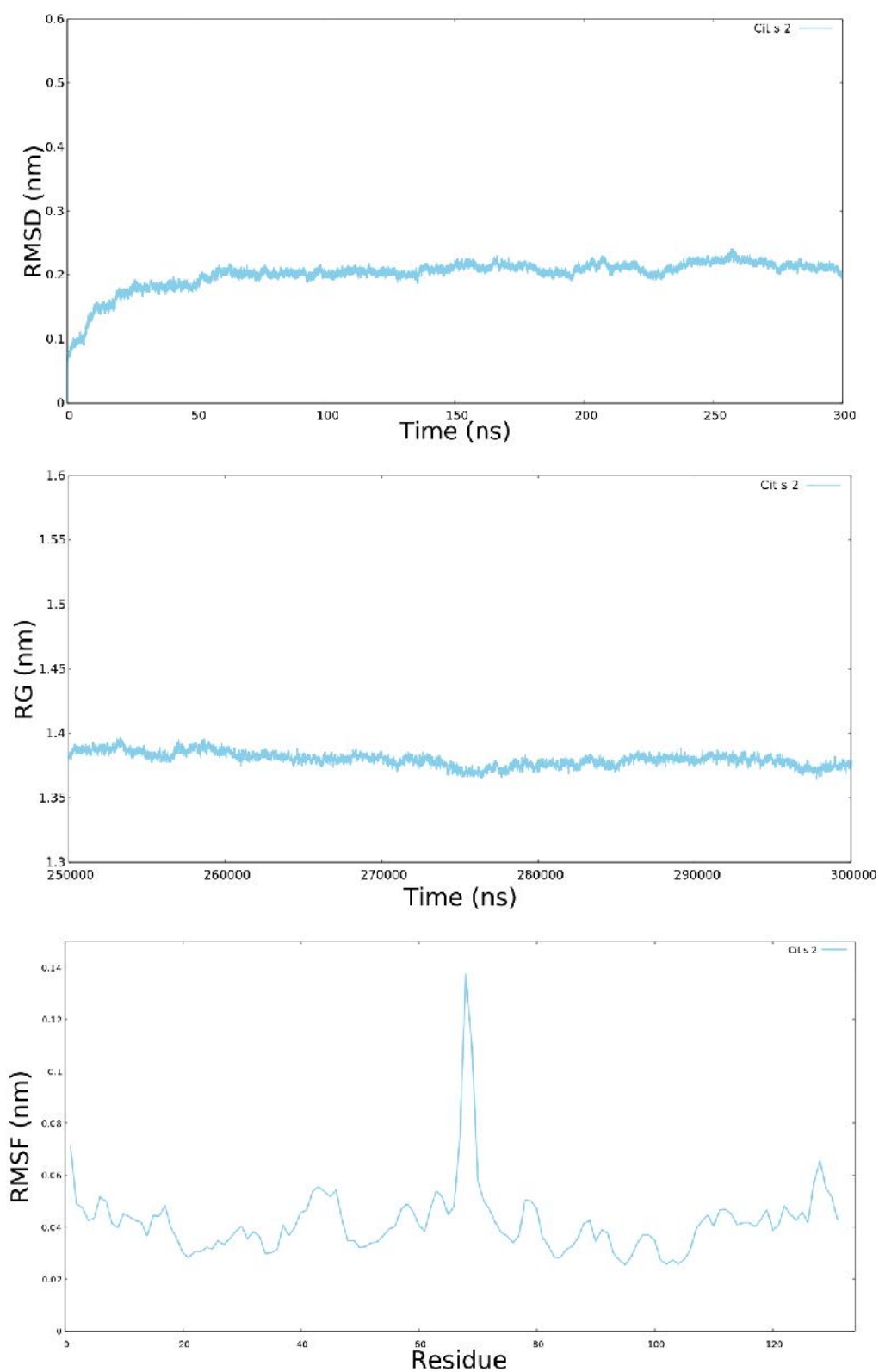


Figure S3. Analysis of RMSD, RMSF, and RG of Cit s 2 profilin at 300ns. (a) RMSD of the backbone atoms in the trajectory of Cit s 2 over the entire simulation. (b) RG of the protein backbone over last 50ns. (c) RMSF of the residues in the protein from 250 ns.

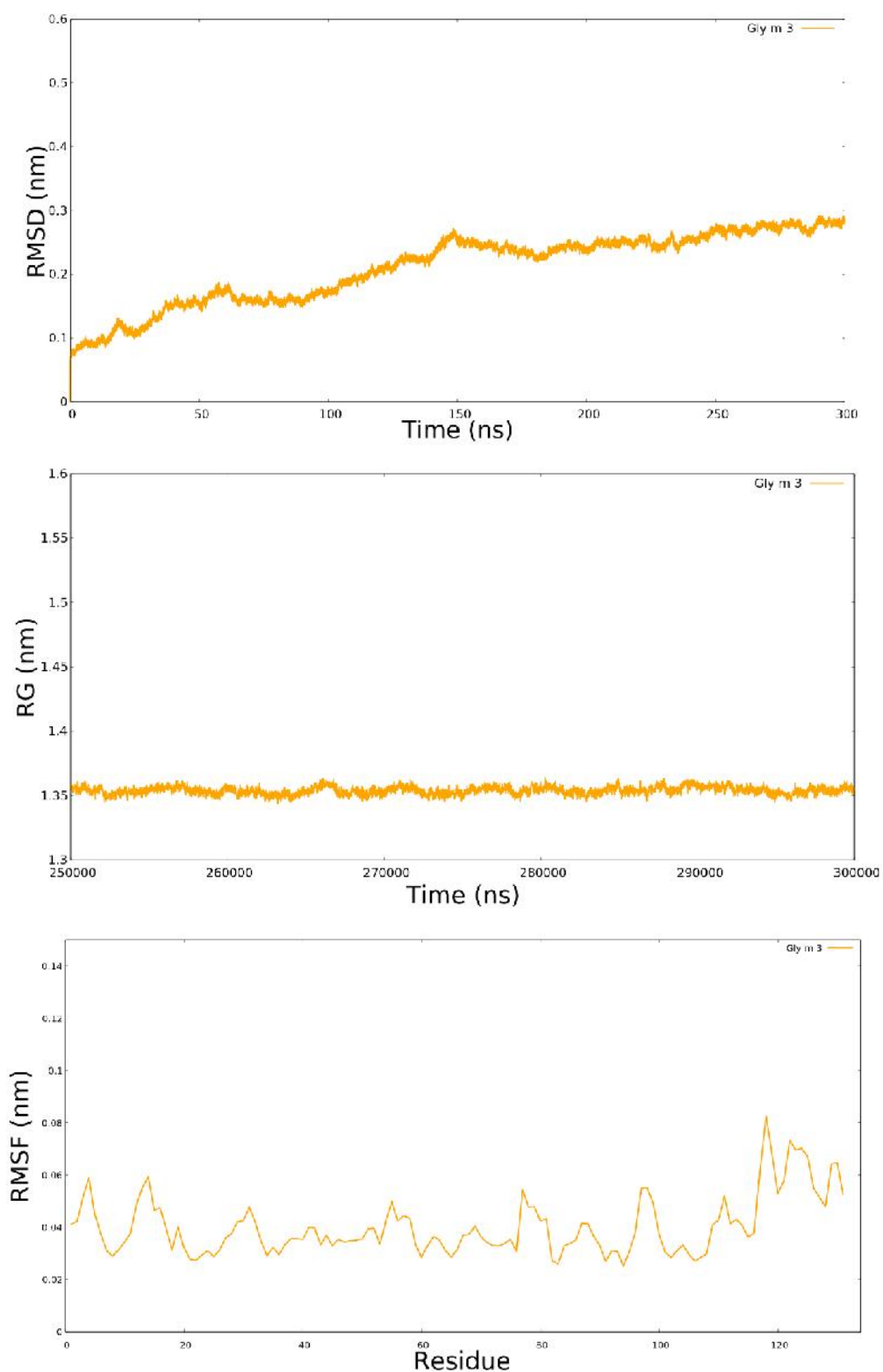


Figure S4. Analysis of RMSD, RMSF, and RG of Cit s 2 profilin at 300ns. (a) RMSD of the backbone atoms in the trajectory of Cit s 2 over the entire simulation. (b) RG of the protein backbone over last 50ns. (c) RMSF of the residues in the protein from 250 ns.

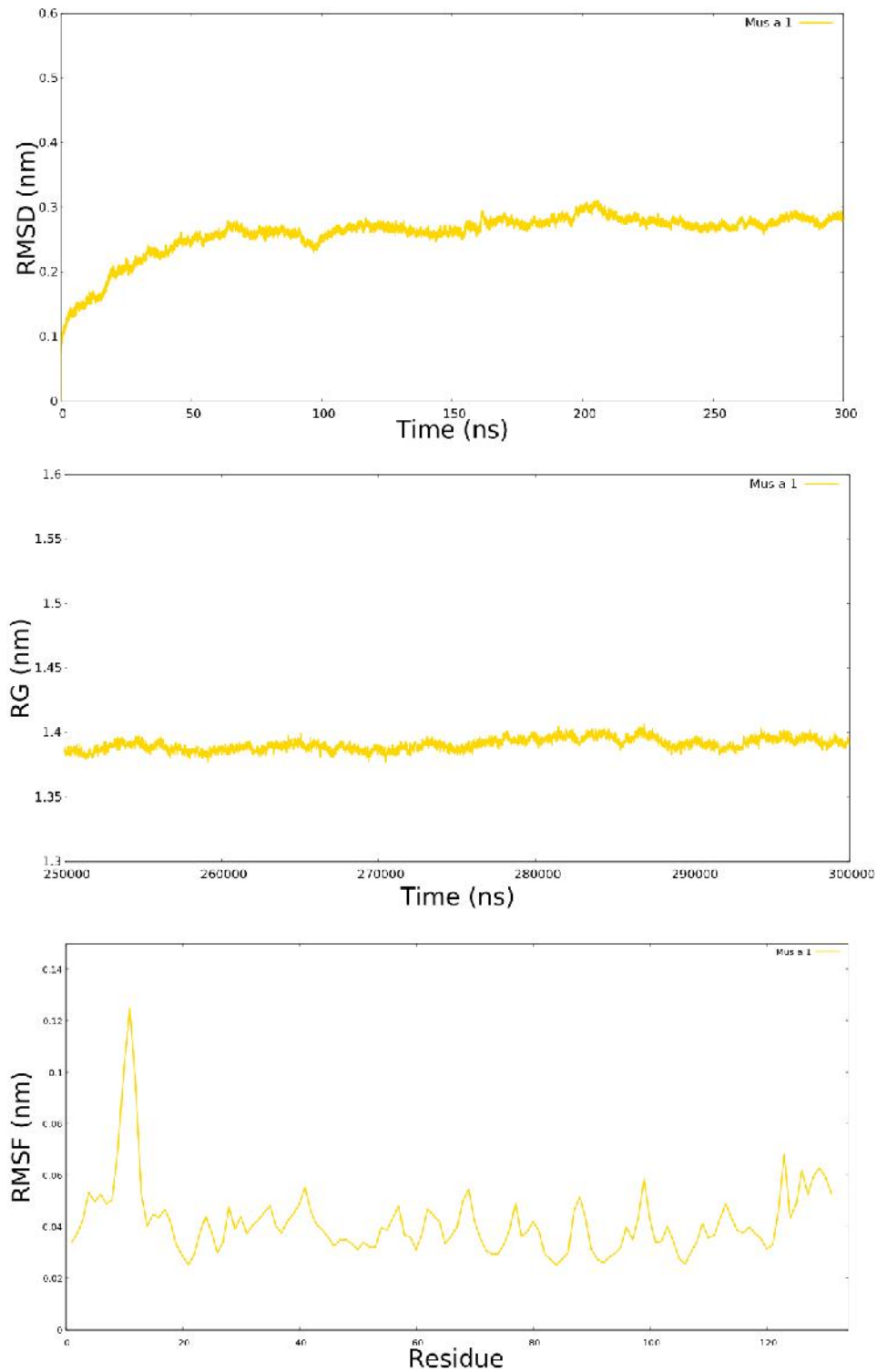


Figure S5. Analysis of RMSD, RMSF, and RG of Mus a 1 profilin at 300ns. (a) RMSD of the backbone atoms in the trajectory of Mus a 1 over the entire simulation. (b) RG of the protein backbone over last 50ns. (c) RMSF of the residues in the protein from 250 ns.

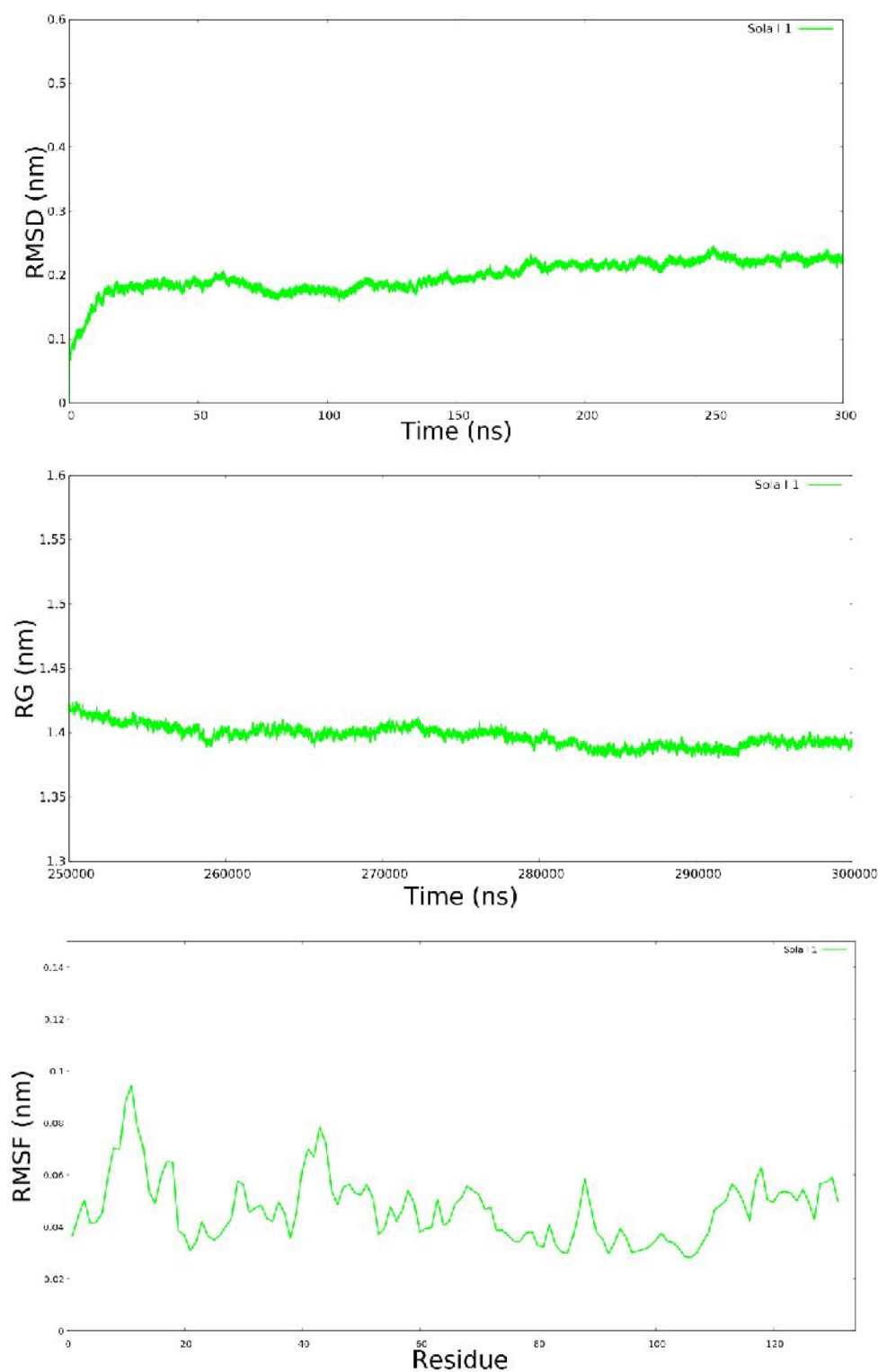


Figure S6. Analysis of RMSD, RMSF, and RG of Sola l 1 profilin at 300ns. (a) RMSD of the backbone atoms in the trajectory of Sola l 1 over the entire simulation. (b) RG of the protein backbone over last 50ns. (c) RMSF of the residues in the protein from 250 ns.

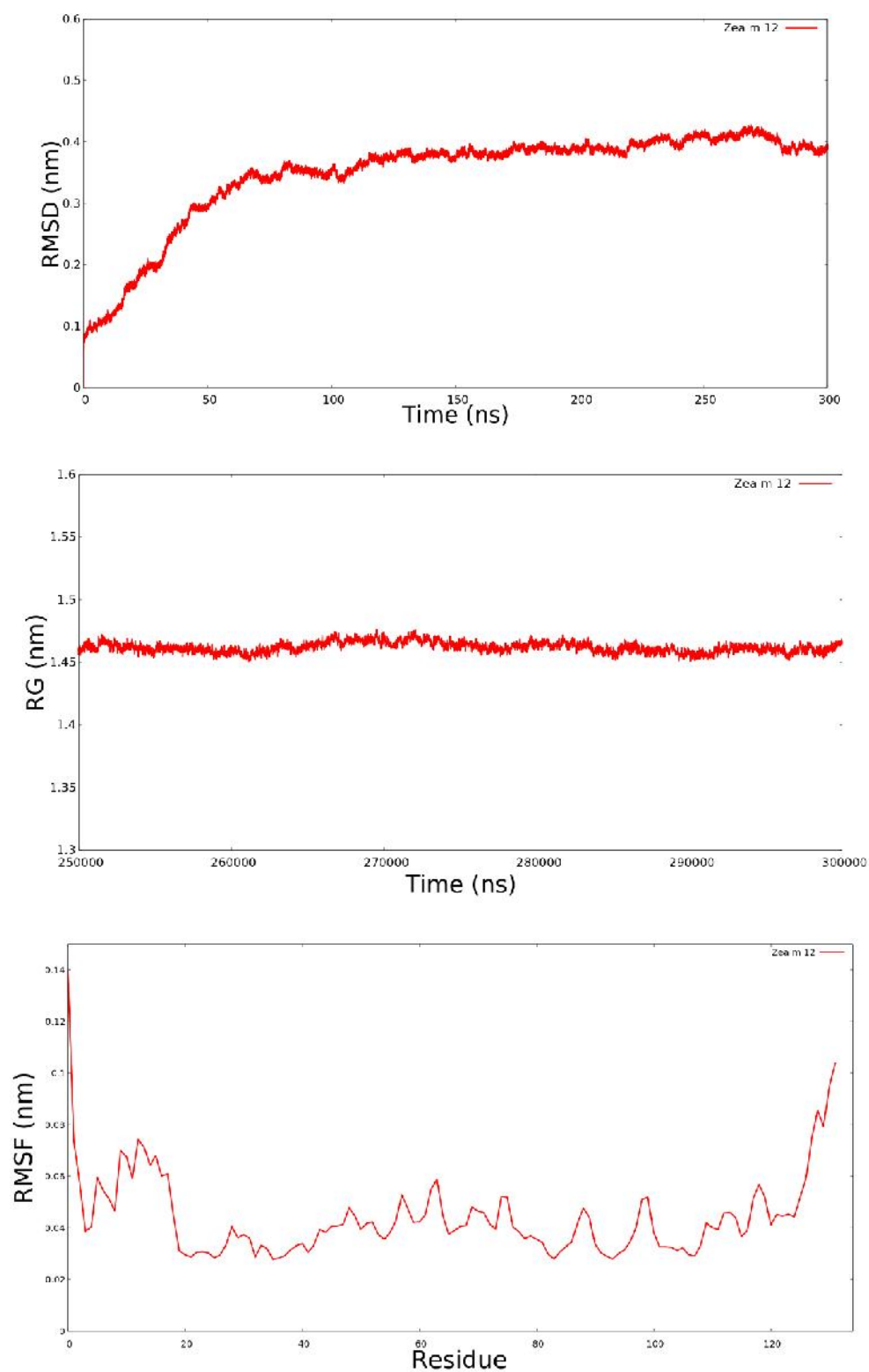


Figure S7. Analysis of RMSD, RMSF, and RG of Sola l 1 profilin at 300ns. (a) RMSD of the backbone atoms in the trajectory of Sola l 1 over the entire simulation. (b) RG of the protein backbone over last 50ns. (c) RMSF of the residues in the protein from 250 ns.

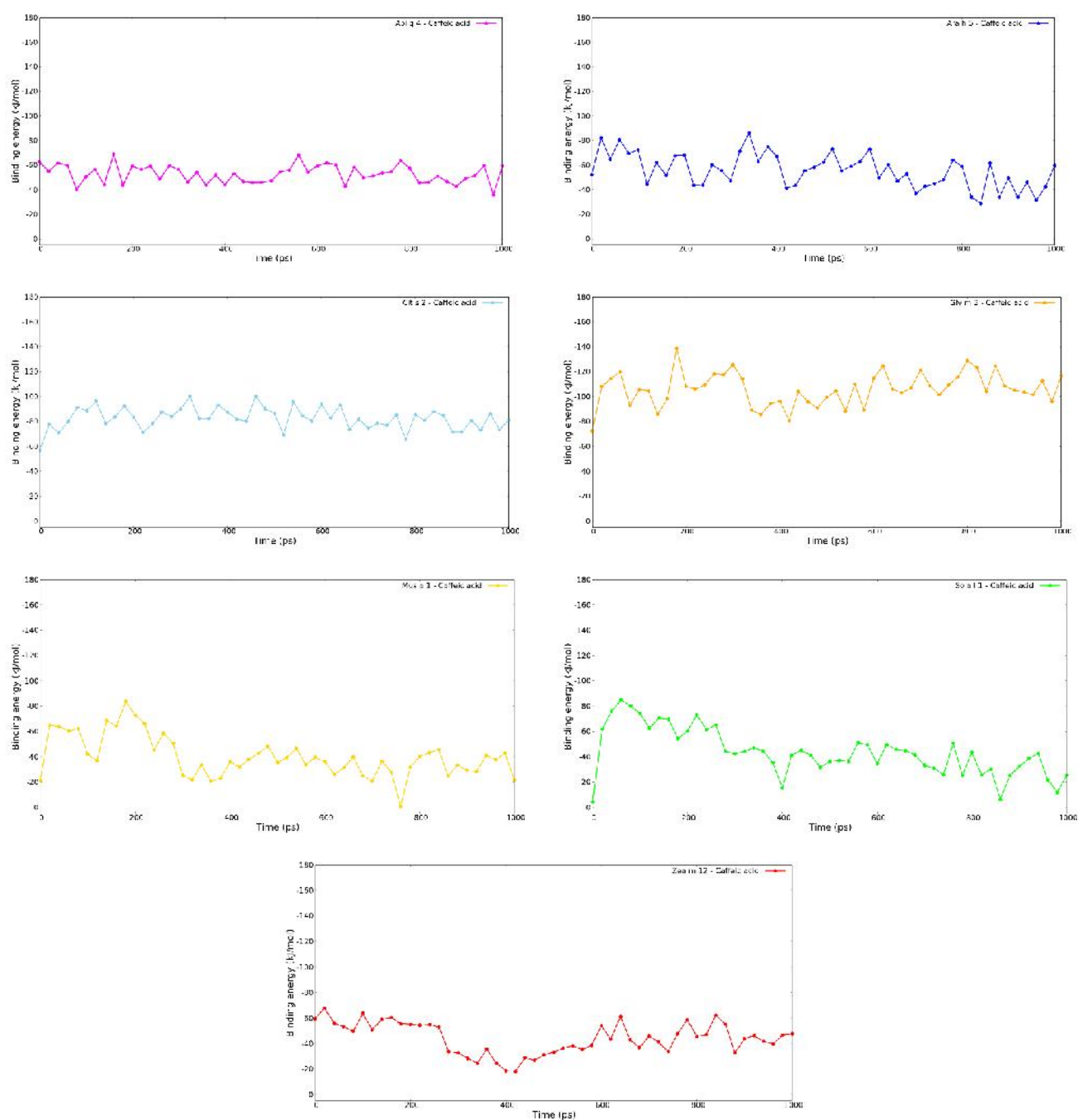


Figure S8. MM-PBSA binding free energy fluctuation with respect to time of simulation for each of the profilin-caffeic acid complex. (a) Api g 4, (b) Ara h 5, (c) Cit s 2, (d) Gly m 3, (e) Mus a 1, (f) Sola l 1, and (g) Zea m 12

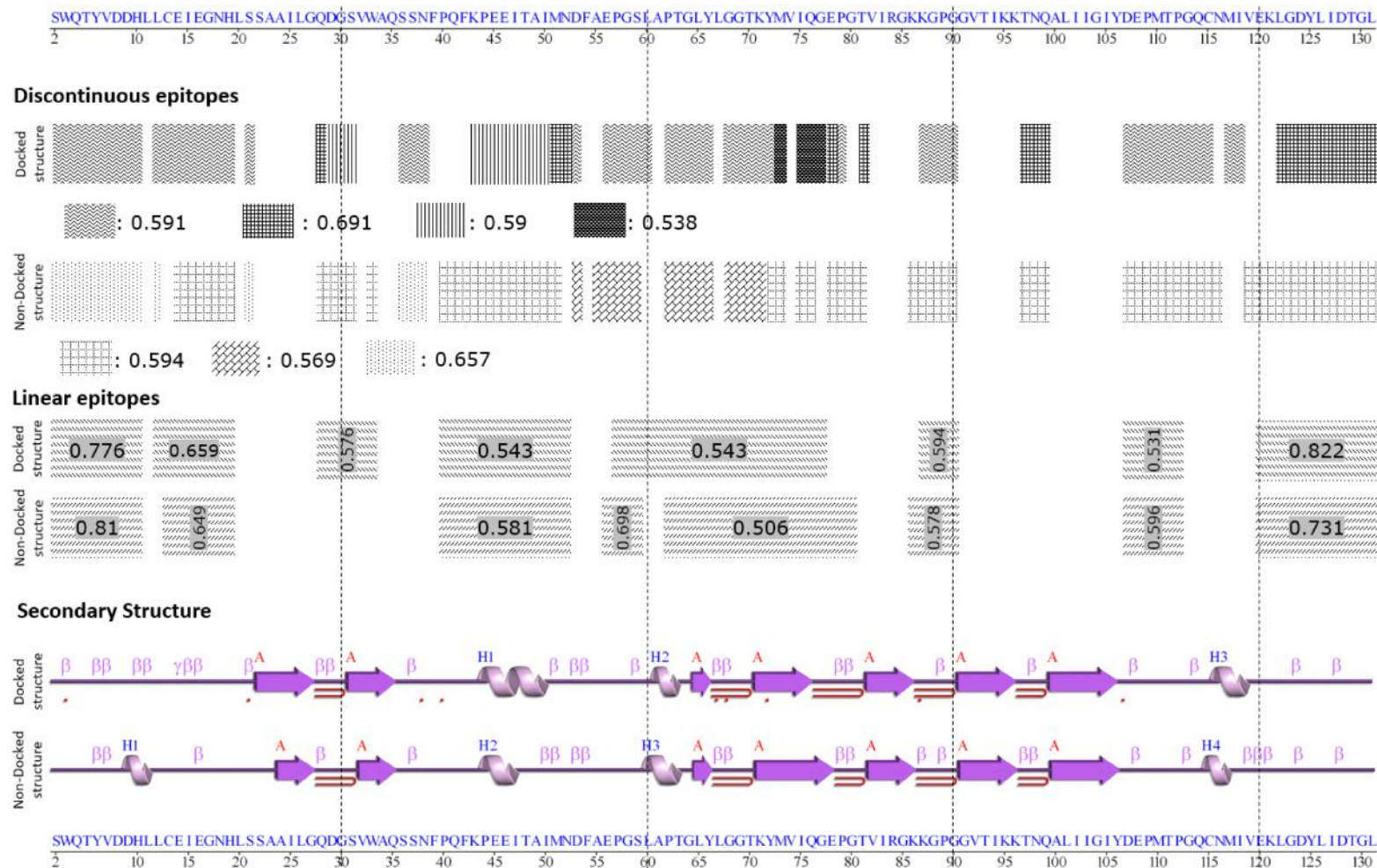


Figure S10. Analysis of secondary structure, linear epitopes, and discontinuous epitopes in Ara h 5.

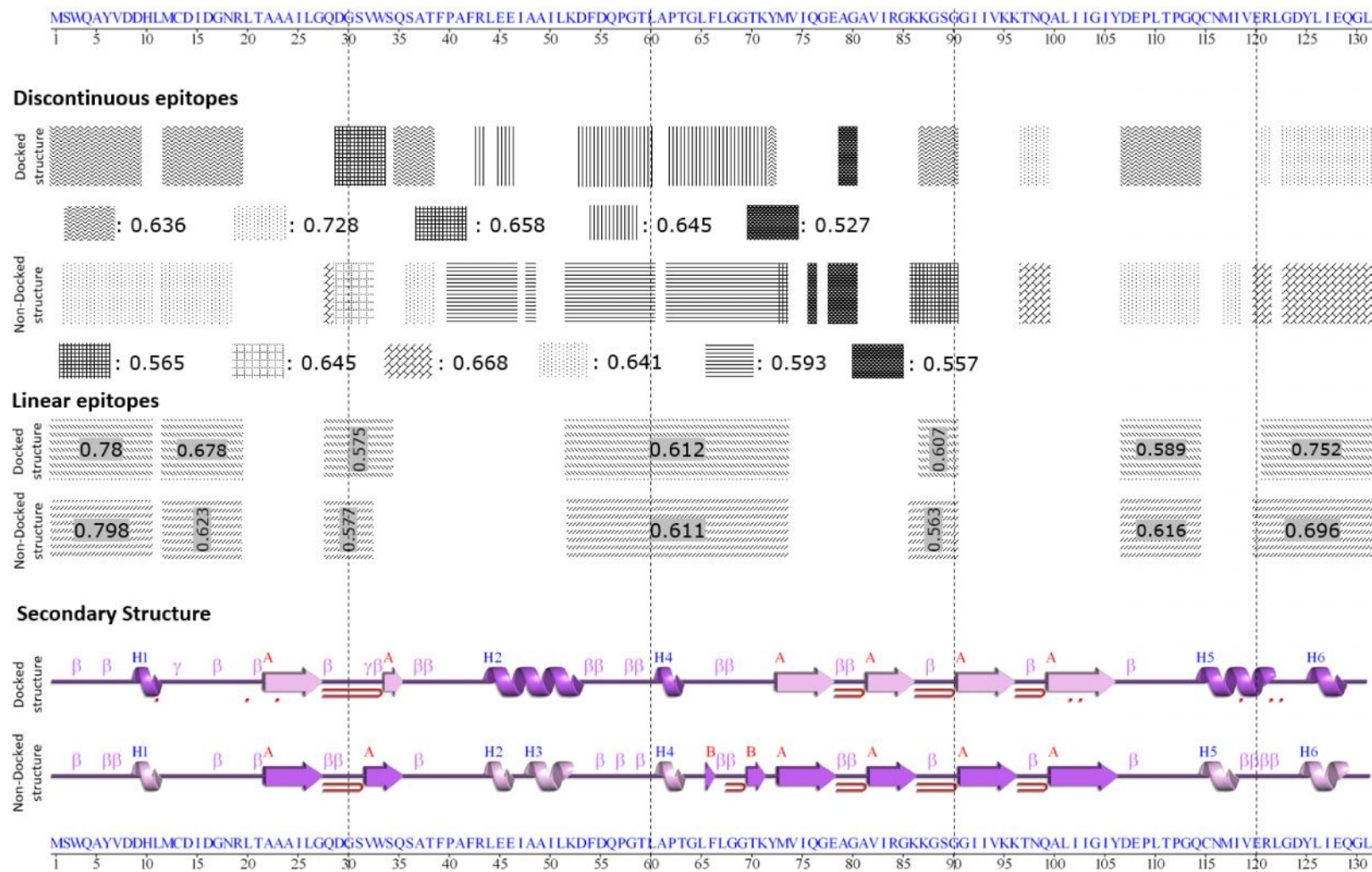


Figure S11. Analysis of secondary structure, linear epitopes, and discontinuous epitopes in Cit s 2.

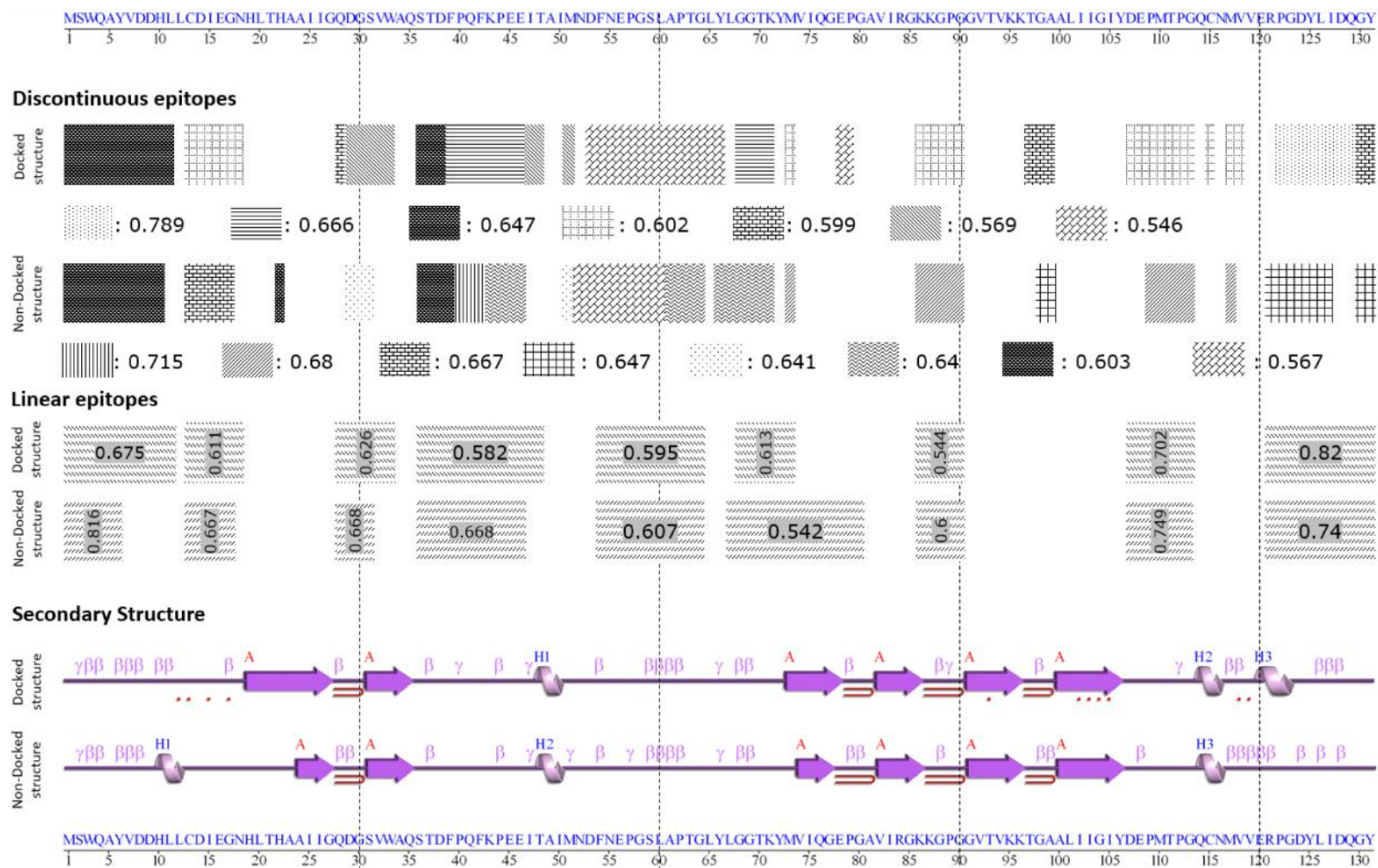


Figure S12. Analysis of secondary structure, linear epitopes, and discontinuous epitopes in Gly m 3.

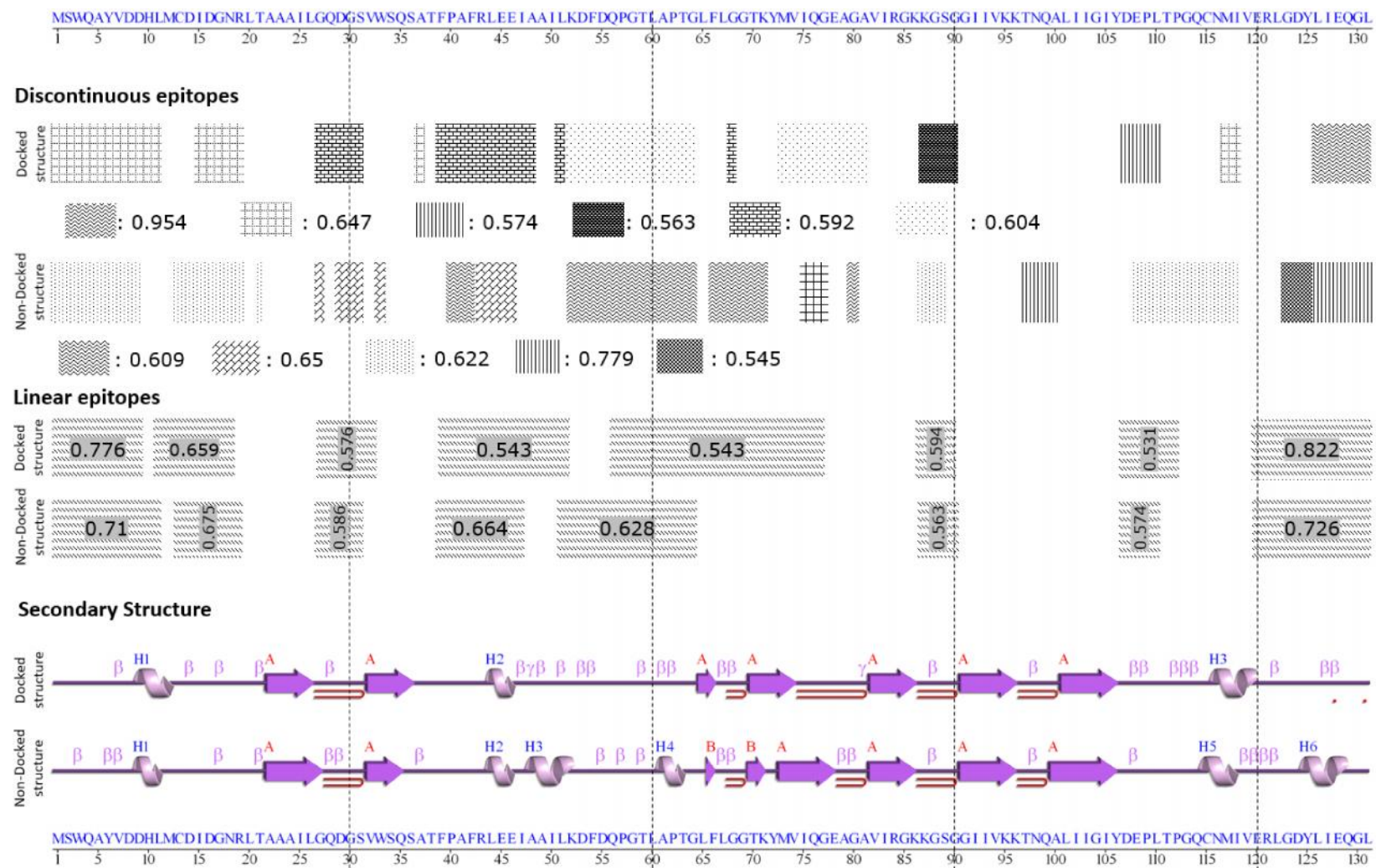


Figure S13. Analysis of secondary structure, linear epitopes, and discontinuous epitopes in Sola l 1.

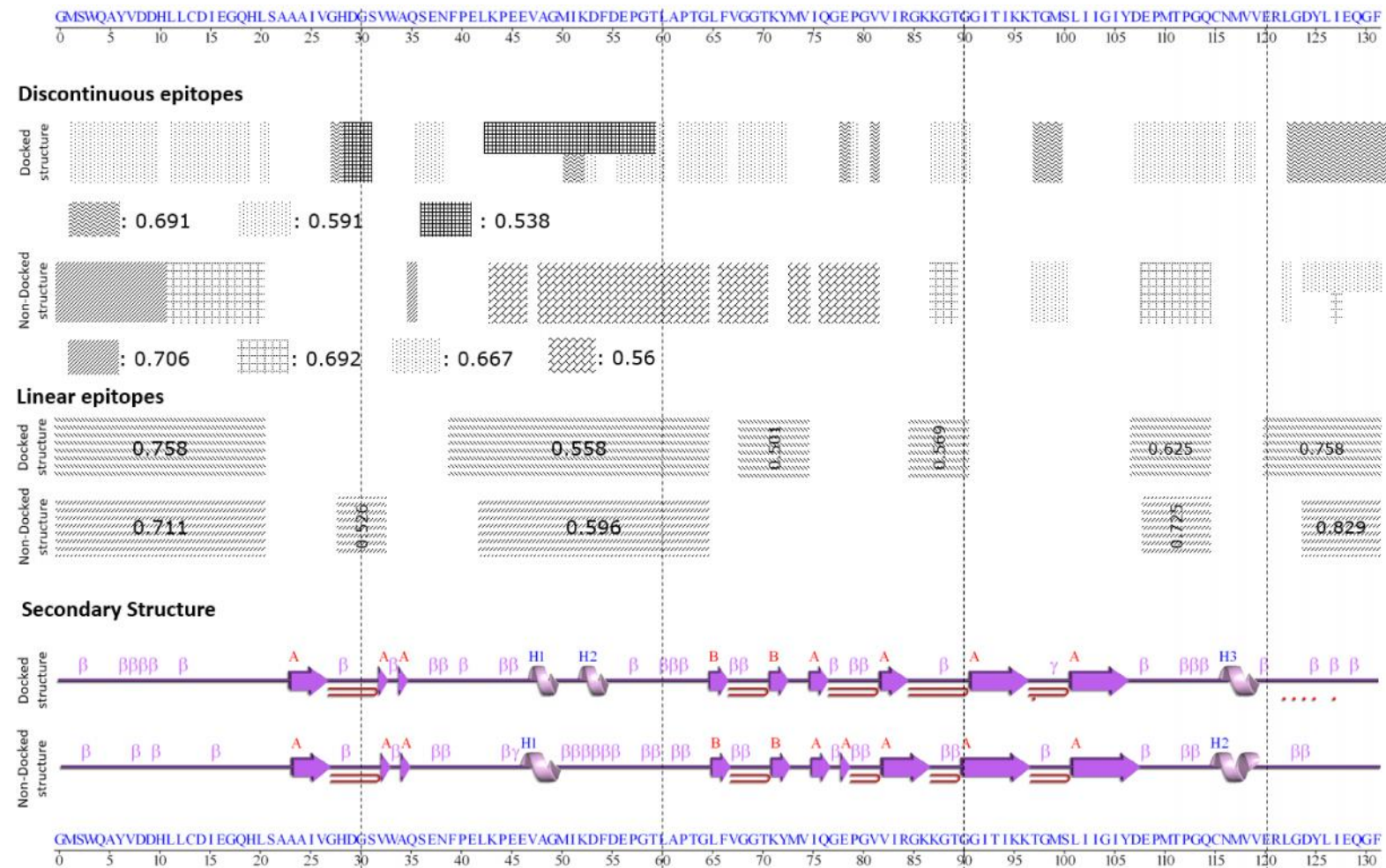


Figure S13. Analysis of secondary structure, linear epitopes, and discontinuous epitopes in Zea m 12.